FORMULATION AND DISSOLUTION ASSESSMENT OF A NOVEL REPEAT ACTION TABLET CONTAINING A DECONGESTANT AND AN ANTIHISTAMINE

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ABSTRACT

Controlled and sustained release dosage forms are the focus of worldwide research. These dosage forms facilitate patient compliance by simplifying the dosage regimen, and decrease the risk of adverse effects by reducing large fluctuations in the plasma concentration of the drug. The objective of this study was to formulate a repeat-action tablet to provide a sustained release dose of pseudoephedrine sulfate (PSS), and an immediate release dose of both PSS and loratadine.

The release profile was compared to that of a commercially available preparation, Clarityne-D®. This formulation developed presents a novel mechanism of sustaining the release of PSS. The prototype tablet consisted of a sustained release core coated with an ethylcellulose dispersion to introduce a lag phase into the release profile and a second outer film coat incorporating PSS and loratadine. The core comprised an ethylcellulose granulation of PSS compressed into a hydroxypropyl methylcellulose matrix.

The release of PSS from prototypes was assessed using USP Apparatus 3, as this apparatus was more representative of *in vivo* conditions and discriminated more effectively between the different tablet compositions produced during development. All dissolution samples were analysed for PSS and loratadine using validated high-performance liquid chromatographic methods.

The prototype sustained release cores were found to be more resistant than the reference product to elevated temperature and humidity (40°C/87% RH) with fewer observed changes to the release profiles following storage for up to six months.

This study was a feasibility study to obtain proof of concept. The release profile obtained from the prototype tablets was similar (f_2 = 50.0) to that of the reference product. Further development and optimisation of this dosage form is necessary, including evaluation of the choice of hydrophobic polymer, the effect of compression force and tablet geometry and characterisation of the release mechanism from the coated matrix. Assessment of these factors is necessary in order to optimise the formulation with respect to the desired therapeutic objectives.

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STUDY OBJECTIVES

Pseudoephedrine is a commonly used decongestant used primarily in the treatment of allergic rhinitis. The use of pseudoephedrine in combination with the antihistamine loratadine provides an enhanced therapeutic effect as compared to either drug alone. It is desirable to formulate a combination formulation with a simple regimen in order to facilitate patient compliance and maximise the therapeutic effect. As a rapid onset of action followed by a sustained effect is desirable, a repeat action dosage form provides an effective means of achieving the desired release profile. Loratadine has a long half-life, and a sustained release component of this drug is not required. However, pseudoephedrine sulfate is eliminated rapidly, and it is desirable to administer the dose in two components: an immediate release component to provide rapid relief from congestion, and a sustained release component to maintain this effect for a reasonable effect.

The objectives of this study were therefore:

1. To develop a repeat action dosage form using a novel method of sustaining the release of pseudoephedrine sulfate.
2. To utilise an appropriate dissolution method to assess the release of pseudoephedrine sulfate from the developed prototype tablet.
3. To compare the release of the developed prototype to a commercially available product.
4. To identify key aspects of the prototype dosage form for further study.

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1.1 PSEUDOEPHEDRINE

1.1.1 INTRODUCTION

Pseudoephedrine (PS) is a sympathomimetic agent used as a decongestant primarily in over-the-counter preparations. It was first isolated in 1926 from the Chinese plant Ma Huang (*Ephedra vulgaris*) [1], while its diastereomer ephedrine was isolated from the same plant in 1887 [2]. It also occurs in other members of the *Ephedra* species, namely *E. sinica and E. equisetina* [3]. The hydrochloride (PSH) and sulfate (PSS) salts are used in both liquid and solid oral dosage forms, although the hydrochloride is more widely used [4,5]. No parenteral dosage form is available for either salt [6].

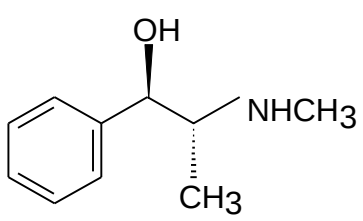
1.1.2 PHYSICO-CHEMICAL PROPERTIES

1.1.2.1 DESCRIPTION

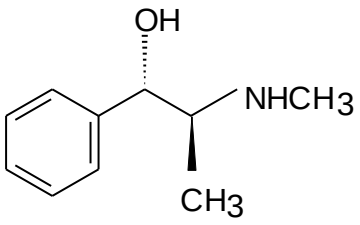
The chemical structure of pseudoephedrine is shown in Figure 1.1. It is described by several chemical names.

1. DL-threo-2-(methylamino)-1-phenylpropan-1-ol [3]
2. Benzenemethanol α-(1-(methylamino)ethyl)-(S-(R*,R*) [7]
3. (1SR,2SR)-2-methylamino-1-phenylpropan-1-ol [6,8]

Figure 1.1 Structure of Pseudoephedrine



(1R, 2R)



(1S, 2S)

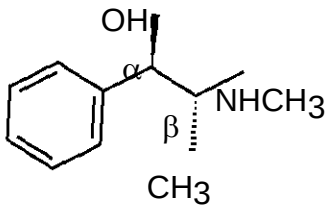
Pseudoephedrine hydrochloride salt has the empirical formula $C_{10}H_{15}NO.HCl$ and has a molecular weight of 201.70 g/mol [6]. It occurs as fine white to off-white crystals or powder with a faint odour. The crystals have an orthorhombic structure [9]. The sulfate salt has the empirical formula $(C_{10}H_{15}NO)_2.H_2SO_4$, and a molecular weight of 428.5 g/mol [2], and occurs as an odourless fine white crystalline hygroscopic powder [4]. Pseudoephedrine has a rhombic crystal structure [3].

1.1.2.2 STEREOCHEMISTRY

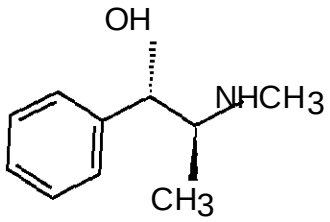
Pseudoephedrine is DL-threo-2-(methylamino)-1-phenylpropan-1-ol. The active isomer is d-pseudoephedrine, which is L-(+)-pseudoephedrine [3,10] or (1S,2S)-2-methylamino-1-phenylpropan-1-ol [6,8].

The erythro pair of isomers is DL-ephedrine. The naturally occurring isomers are d-pseudoephedrine and l-ephedrine [3]. The chemical structures of the ephedrine and pseudoephedrine isomers are given in Figure 1.2.

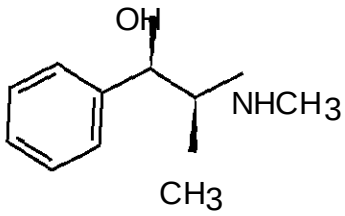
Figure 1.2 The Isomers of Pseudoephedrine and Ephedrine



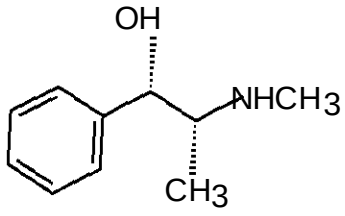
(1R, 2R) pseudoephedrine



(1S, 2S) pseudoephedrine



(1R, 2S) ephedrine



(1S, 2R) ephedrine

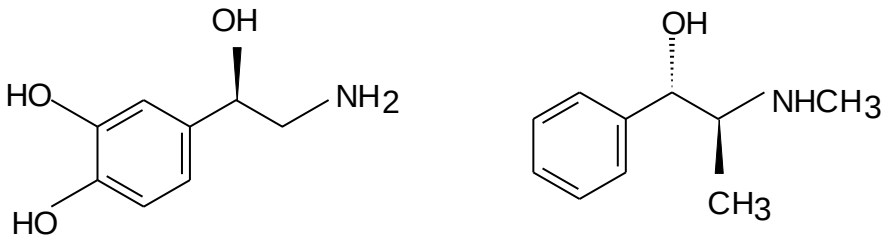
There are chiral carbons in the alpha and beta positions, as marked on Figure 1.2. The (1R, 2R) and (1S, 2S) forms form the pseudoephedrine enantiomers, while the (1R, 2S) and (1S, 2R) forms are the ephedrine enantiomers [9]. The (1S, 2S) form is the commercially marketed form [6,8,10], and unless otherwise specified, all references to pseudoephedrine and its salt are for this enantiomer (d-pseudoephedrine).

The naturally occurring isomers are d-pseudoephedrine and l-ephedrine [3].

1.1.2.3 STRUCTURE-ACTIVITY RELATIONSHIP

Pseudoephedrine resembles norepinephrine, an endogenous neurotransmitter substance of the sympathetic nervous system, as shown in Figure 1.3.

Figure 1.3 Structures of Norepinephrine and d-Pseudoephedrine



Norepinephrine d-Pseudoephedrine

Pseudoephedrine comprises a benzene ring linked with an ethylamine derivative, a structural requirement for sympathetic activity [11]. The methyl group on the alpha carbon inhibits the metabolism of pseudoephedrine by monoamine oxidase, particularly in the gastro-intestinal tract [11]. The configuration at this carbon is important, as the (2R) isomer has predominantly indirect activity while the (2S) isomer has more direct activity [2]. The hydroxyl group at the beta carbon increases hydrophilicity and reduces the penetration of pseudoephedrine into the central nervous system [11]. The lack of catechol hydroxy groups (as are found on epinephrine) reduce pseudoephedrine metabolism by catechol -O-methyl transferase, enabling it to be administered orally [2].

1.1.2.4 SYNTHESIS

Pseudoephedrine is synthesised by a Welsh re-arrangement of l-ephedrine hydrochloride with acetic anhydride, followed by deactylation with hydrochloric acid [9]. l-Ephedrine is resolved from d-ephedrine with l-mandelic acid.

1.1.2.5 DISSOCIATION CONSTANT AND PARTITION COEFFCIENT

The partition coefficients between n-octanol and aqueous solutions of pH 1.2 and pH 6.0 are 0.010 and 0.049 respectively [9]. The Hansch hydrophobicity constant for pseudoephedrine (log P) is given as 0.92 [12], indicating that the molecule is relatively hydrophilic.

In three different studies, the dissociation constant for the free base was reported as 9.4 [10], 9.8 [13] and 9.9 [12]. The K_a value for the hydrochloride is given as 9.8 [6] and 9.22 [9]. The latter value applies to a solution in 80% aqueous methylcellosolve. To date the K_a for the sulfate salt has not been reported.

1.1.2.6 SOLUBILITY

Pseudoephedrine is sparingly soluble in water as the free base, although its diastereomer ephedrine is water-soluble [3]. It is freely soluble in alcohol and ether. Pseudoephedrine hydrochloride and sulfate are soluble in water and alcohol [4]. Solubility of the hydrochloride salts in various solvents is listed in Table 1.1. Little data is available pertaining to the sulfate salt.

Table 1.1 Solubility of Pseudoephedrine Hydrochloride

Solvent	Solubility	Reference
Water	0.625 g/mL 0.5 g/mL	6 9
Ethanol	0.25 g/mL 0.278 g/mL	6 9
Chloroform	0.011 g/mL	9
Ether	1.4×10^{-4} g/mL	9

1.1.2.7 PH OF SOLUTION

The pH of a 1 in 20 aqueous solution of pseudoephedrine hydrochloride ranges between 4.6 and 6.0, while a 1 in 20 solution of the sulfate salt ranges between pH 5.0 and 6.5 [7]. The pH of a 1 in 200 solution of the hydrochloride is 5.9, while a 1 in 200 aqueous solution of the free base has a pH of 10.8 [3].

1.1.2.8 OPTICAL ROTATION

The optical rotation for the hydrochloride salt is +61.0° to +62.5° [7] or +62° (at 20°C for the sodium line) [3]. The optical rotation for the sulfate salt is +56.0° to +59.0° [7]. The free base has an optical rotation of +51° at 20°C for the sodium line [3].

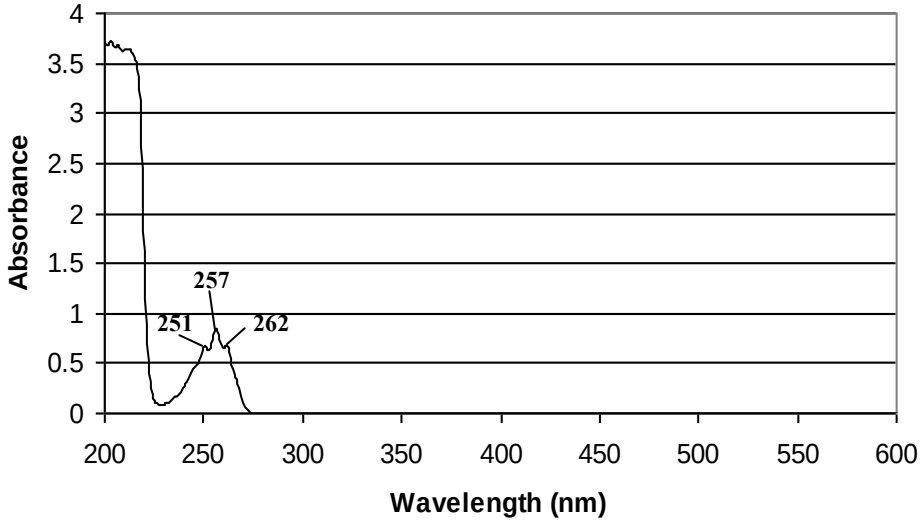
1.2.2.9 MELTING POINT

The melting range of the hydrochloride salt is 182-186°C, where complete melting occurs within a 2°C range [7] or 185°C [9]. The sulfate salt has a melting range of 174-179°C, where complete melting occurs within 2° [7]. The racemic mixture pseudoephedrine melts at 118°C, while d-pseudoephedrine melts at 119°C [3]. In addition, the heat of fusion for the hydrochloride is 6.4 kcal/mol [9].

1.1.2.10 ULTRA-VIOLET ABSORPTION SPECTRUM

Pseudoephedrine sulfate has an absorption maximum at 257 nm [7] while pseudoephedrine hydrochloride has absorption maxima at 208,251,257 and 264 nm in ethanol [3,9]. The UV spectrum of PSS in water was determined using a Cary 500 Scan (Varian) and the spectrum is given in Figure 1.4.

Figure 1.4 The Ultra-violet Absorption Spectrum of PSS in Water



1.1.2.11 INFRARED SPECTRUM

The reference infrared absorption spectra for the hydrochloride is given in Figure 1.5 [14], and summarized in Table 1.2. An infrared scan was performed on PSS using a Perkin-Elmer Spectrum 2000 TG-IR (Perkin-Elmer, UK) and is illustrated in Figure 1.6.

Table 1.2 Infrared Spectrum data for Pseudoephedrine HCl [9]

Wavelength (cm^{-1})	**Bond**
3270	OH stretch
3010	CH stretch (asymmetric)
2930	CH stretch (symmetric)
2700	NH^{+} stretch
1587, 1490	OH bend (secondary alcohol)
762, 702	CH bend (mono-substituted benzene)

Figure 1.5 Infrared Reference Spectrum for Pseudoephedrine HCl

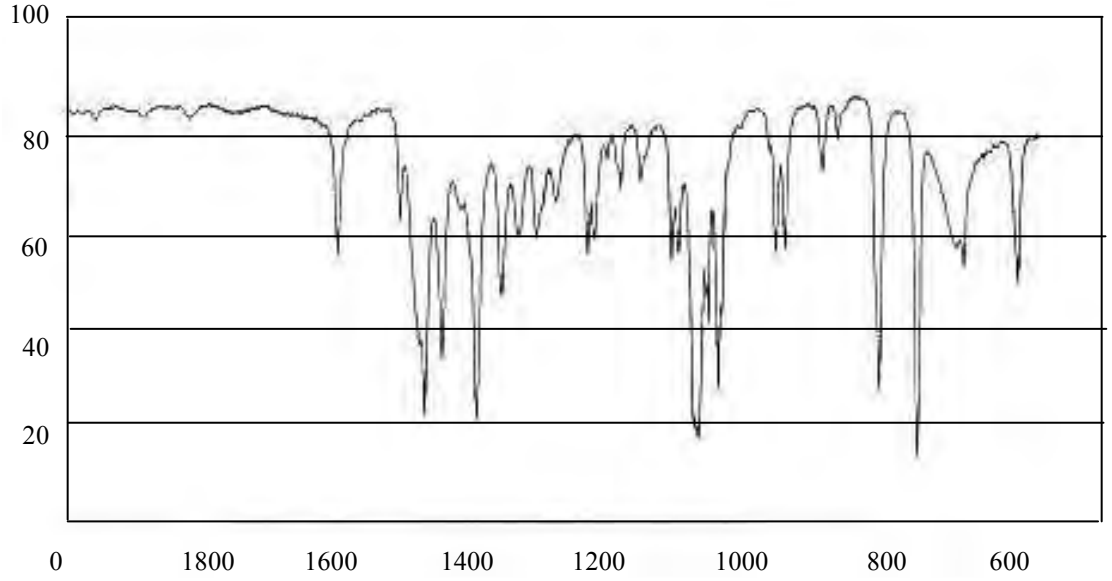
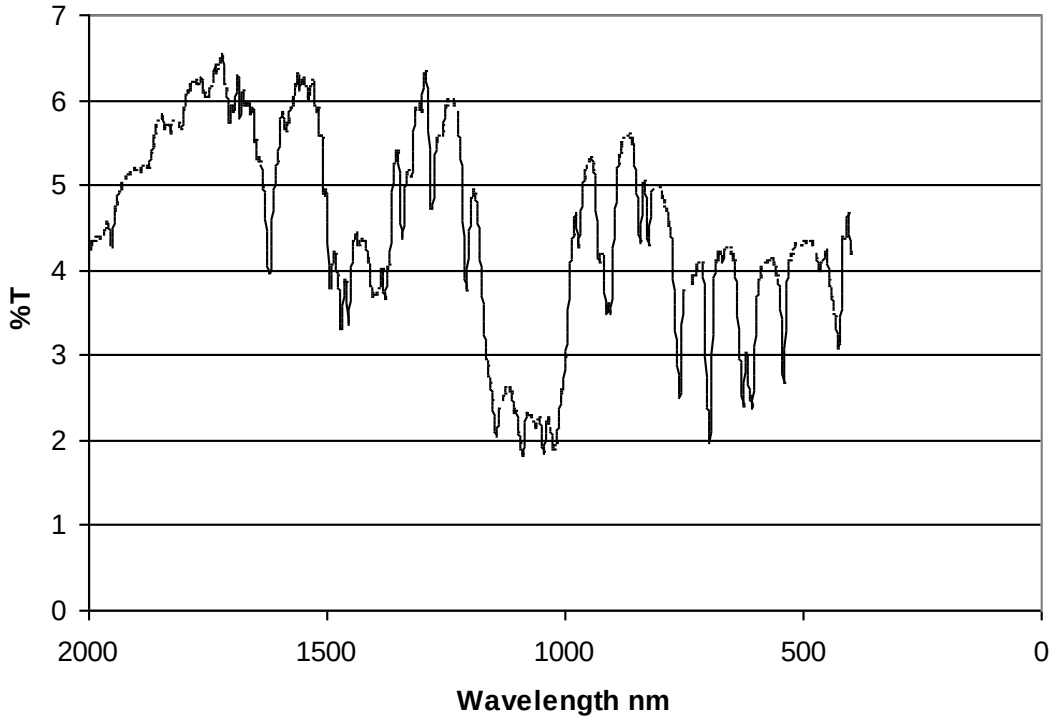


Figure 1.6 Infrared Spectrum for Pseudoephedrine Sulfate



1.1.3 STABILITY

Pseudoephedrine is a relatively stable compound, and although certain texts recommend that both salts be protected from light [4,7], the hydrochloride salt has been found to be stable to light (both UV and fluorescent) and temperature for 3 to 6 months [9]. Tablets and syrups containing pseudoephedrine hydrochloride have been shown to undergo no appreciable degradation when stored for 5 years at 15 – 30°C [9]. Pseudoephedrine hydrochloride is also stable in aqueous solution under drastic temperature conditions [15]. No data pertaining to the stability of the sulfate is available. However, in the absence of this information, and as the two salts have similar properties, the stability characteristics of PSH could be extrapolated to PSS, until evidence to the contrary is revealed.

1.1.4 CLINICAL PHARMACOLOGY

1.1.4.1 MODE OF ACTION

Pseudoephedrine is a sympathomimetic agent with both indirect and direct effects [6]. It exerts direct effects primarily at peripheral α_1 receptors and at cardiac β receptors (where it is a weak agonist). As the peripheral α_1 receptors are concentrated in post-capillary venules, which are capacitance vessels, agonist action at these receptors causes vasoconstriction [11]. Pseudoephedrine also acts as an agonist at the α_1 receptors of the trigone and sphincter muscles of the bladder, causing constriction and urinary retention [11,16,17].

Pseudoephedrine has minimal β activity, with approximately one quarter of the effect of ephedrine on the cardiovascular system, and minimal bronchodilatory action [18,19]. Pseudoephedrine may also antagonise certain effects of norepinephrine [20].

l-Pseudoephedrine has negligible direct sympathomimetic activity, but is capable of binding norepinephrine re-uptake sites, preventing the re-uptake of norepinephrine and thereby potentiating its effects [21]. l-Pseudoephedrine has some ability to antagonise the pressor effects of norepinephrine [21].

1.1.4.2 INDICATIONS

Pseudoephedrine is primarily indicated as a decongestant for the symptomatic treatment of allergic rhinitis. It is not particularly effective in infective rhinitis [22]. Pseudoephedrine is frequently formulated in combination with antihistamines, expectorants and bronchodilators [4,23,24], and has been found to be more effective in these combinations than when used alone [18,25].

Pseudoephedrine is also indicated as the drug of choice for the treatment of stress incontinence with or without sphincter weakness in females [16,17,26].

In addition, pseudoephedrine is a useful adjunct in the treatment of chronic, serous otitis media [18,27] and nasal polyposis [28]. The results of two clinical trials have revealed that pseudoephedrine is effective in reducing the risk of barotrauma during air travel (aerotitis media) and it has been suggested that this be an additional indication for the compound [13,29].

Despite encouraging results, a relatively unexplored use is in the treatment of aspermia following testicular lymphadectomy. [30].

Pseudoephedrine is abused amongst the general population for its central nervous system (CNS) stimulant effect (although this is small) and amongst athletes, where its stimulant effect is thought to enhance competitiveness and decrease fatigue [31].

1.1.4.3 CONTRA-INDICATIONS

Pseudoephedrine is contra-indicated in patients with cardiovascular disease because of the potential for pseudoephedrine to elevate blood pressure and increase heart rate by virtue of its sympathomimetic action [6,11].

Patients suffering from glaucoma may not take pseudoephedrine as it causes contraction of the iris and consequent mydriasis, which decreases the drainage of aqueous humor, raising intra-ocular pressure [11].

As pseudoephedrine can cause urinary retention, it is contra-indicated in patients with prostatic hypertrophy [6,11,32].

The sympathomimetics all exert effects on the endocrine system, with alterations in insulin release and uptake, and pseudoephedrine is thus contra-indicated in diabetes mellitus, as symptoms similar to hypoglycaemia may be observed [6,11,32].

Hyperthyroid individuals should avoid pseudoephedrine as these individuals are more sensitive to adrenergic stimulation, and thyroid storm may be precipitated if there is underlying thyrotoxicosis [6,33].

1.1.4.4 HIGH RISK PATIENT GROUPS

The elderly are more sensitive to the effects of pseudoephedrine and have a larger incidence of adverse drug reactions. In particular, hypertension is most prevalent [32]. Paediatric patients also have increased sensitivity to pseudoephedrine, with greater end-organ effects [34] and pseudoephedrine should be used with caution in these groups.

Pseudoephedrine is known to cross the placenta, and its use in pregnancy should be

avoided [6,32], although no evidence has been found of teratogenicity in humans [35] or of adverse effects on the neonate [36]. Pseudoephedrine is also excreted in breast milk, with 0.4 to 0.6 percent of the oral dose present in the milk [37]. The use of pseudoephedrine by lactating mothers is therefore discouraged, despite the fact that no effects on infants have been demonstrated [38].

The use of pseudoephedrine in hypertensive patients should be minimized because of the potential of pseudoephedrine to elevate blood pressure and heart rate. The cardiovascular effects of pseudoephedrine appear to be unrelated to plasma concentration and are therefore difficult to predict [39]. No clinically significant increase in blood pressure or heart rate has been demonstrated [39,40], although one study found a trend for both parameters to increase slightly during treatment with pseudoephedrine [39]. A study on the effects of pseudoephedrine on blood pressure and heart rate during exercise found that neither parameter was affected significantly, nor was there any alteration in blood glucose or insulin when pseudoephedrine was administered [41]. A decrease in blood pressure has been observed with chronic dosing of pseudoephedrine, suggesting that blood pressure changes are an indirect effect of pseudoephedrine, which disappear as the displaced norepinephrine is depleted [42]. However, pseudoephedrine is usually used for acute therapy, and this effect is of little clinical significance. It has been reported that effects on blood pressure are only observed at doses greater than those recommended for therapy [11].

Patients suffering from renal tubular acidosis require careful monitoring should pseudoephedrine be administered, as there is a tendency for pseudoephedrine accumulation as it is subject to tubular reabsorption and this will be more significant in this patient population [43].

1.1.4.5 DRUG INTERACTIONS

Pseudoephedrine is predisposed to drug interactions with other drugs acting on the sympathetic nervous system. It may precipitate a hypertensive crisis if given with mono-amine oxidase inhibitors by virtue of its indirect effects [5,6,32]. It may reduce the efficacy of anti-hypertensive therapy through its actions on the cardiovascular system, which tend to elevate blood pressure [32]. Concurrent use with beta-blockers may lead to hypertensive reactions [5]. Concomitant use with other sympathomimetics will cause potentiation of cardiovascular effects such as tachycardia and hypertension [32]. Pseudoephedrine may also interact with tricyclic antidepressants, leading to cardiac arrhythmias and hypertension [5].

1.1.4.6. ADVERSE DRUG REACTIONS

1.1.4.6.1 Common Side Effects

Pseudoephedrine has several side effects, all of which are readily explained by its mode of action. As pseudoephedrine is a sympathomimetic agent it has anti-cholinergic effects in the autonomic nervous system by enhancing sympathetic relative to parasympathomimetic activity. In addition, pseudoephedrine has some activity in the central nervous system (CNS), where it acts as a stimulant and weak anoretic.

The most commonly reported adverse reaction is dry mouth [29,42,44]. Other frequently reported side effects include transient hypertension, insomnia, nausea, anorexia, anxiety, tension, tremor, palpitations and restlessness [6,29,42,44]. Dry eyes have also been reported [45]. A reduced incidence of insomnia has been found with a controlled release, once-daily formulation [46].

1.1.4.6.2 Adverse Reactions

In general, adverse reactions to sympathomimetic amines are rare [47], and pseudoephedrine is no exception, with a paucity of adverse reactions at the recommended dosages [6,18].

Several cases of non-pigmenting fixed drug eruptions caused by pseudoephedrine have been reported in the literature [47,48,49,50]. These are usually symmetrical, with erythematous, swollen tender plaques on the limbs, trunk and neck, which subsequently undergo extensive desquamation [47,48]. One report has been made of a solitary eruption of similar nature [48]. A case of pseudoephedrine-induced stereospecific cutaneous eruption has also been reported [8]. Similar reactions have been reported which are accompanied by angioedema of the tongue and altered sensation in the extremities, where plaques appear, followed by extensive desquamation after two weeks [49,50]. Pseudoephedrine has also been known to cause a recurrent toxic shock syndrome with no mucous membrane involvement [23]. Recurrent pseudoscarlatinia has also been reported [50].

Pseudoephedrine may precipitate thyroid storm in thyrotoxic individuals, usually patients suffering from Graves disease [33].

Pseudoephedrine has the potential to cause seizures by virtue of its CNS activity [51], and has been linked to visual hallucinations in a toddler administered an overdose [34]. Abuse of pseudoephedrine may result in psychosis and cardiovascular effects [18], and other reported reactions include intracranial haemorrhage and manic depression [34].

1.1.5 PHARMACOKINETICS

1.1.5.1 DOSAGE

The conventional dose for relief from congestion is 60 mg every 6 hours or 120 mg every 12 hours for adults [4,5,6,31], and doses greater than this are no more effective in relieving nasal congestion [18]. Children between 6 and 12 years should receive 30 mg every 6 hours and children from 2 to 6 years 15 mg every six hours. Patients should not receive more than 240 mg in 24 hours [5,6,32,53]. Therapy should be discontinued after 2 to 3 days to reduce the risk of rebound congestion [32]. It is recommended that children under 2 years of age not be given pseudoephedrine [32].

The dose for urinary incontinence is 15 to 30 mg every 6 to 8 hours [16,17, 53]. While dosages greater than 2 g in adults [6] or 200 mg in children under 13 years [18] are fatal. Therapeutic doses generally yield plasma concentrations of 0.5 to 0.7 μg/mL and urinary concentrations of 4 to 50 μg/mL, while lethal doses are associated with plasma concentrations greater than 20 μg/mL and urinary concentrations greater than 100 μg/mL [54], although therapeutic doses may yield urinary concentrations as high as 130 μg/mL [22].

1.1.5.2 ABSORPTION

Pseudoephedrine is well absorbed from the gastro-intestinal tract (GIT) and undergoes negligible pre-systemic metabolism [10,24,37]. A decrease in nasal congestion is evident after 15 to 30 minutes and lasts for approximately 4 hours [10,32,37]. The maximal effect corresponds to peak plasma concentration 1 to 2 hours after administration, with a 50 to 60 percent reduction in nasal resistance [32,37]. The absorption half-life of immediate release pseudoephedrine has been reported as 35.8 minutes [43].

The presence of food has no clinically significant effect on the absorption of pseudoephedrine [44,55,56,57,58,59], although the time to reach peak plasma concentration may be delayed [57,58]. The relative bioavailability of pseudoephedrine in the fed relative to the fasted state is reported as 91 percent [44]. Several authors have studied the effect of food on C_{max}, $t_{1/2}$ and AUC for immediate and controlled release preparations. A summary of their findings is listed in Table 1.3.

Absorption is facilitated by aluminium hydroxide, as the increase in gastric pH facilitates pseudoephedrine transport across the stomach epithelium [60,61]. Kaolin may adsorb pseudoephedrine, leading to a delayed absorption, but there is no change in the total amount of pseudoephedrine absorbed [61]. Sodium bicarbonate is expected to increase the absorption of pseudoephedrine, but any effects are confounded by the effect that the sodium bicarbonate (which is absorbed) has on urinary pH, which leads to altered pseudoephedrine excretion [61]. Absorption may be increased in the elderly [58].

1.1.5.3 DISTRIBUTION

The disposition of pseudoephedrine can be described by a one-body compartment model with no lag phase [10,52]. Steady state is achieved in 3 days with conventional dosing [10] or 5 days for controlled release products [62], although if an estimate of 3.32 half lives is used, steady state should be reached within 24 hours. The volume of distribution is 2.64 to 3.51 L/kg [6,10,42], although it is generally higher in children (2.83 to 3.33 L/kg) [63]. There is no evidence of plasma protein binding [6]. Table 1.4 presents reported data on the effect of single versus multiple dosing on various pharmacokinetic parameters.

Pseudoephedrine crosses the placenta and is found in the central nervous system [37]. Pseudoephedrine also enters the breast milk, with 0.4 to 0.6 percent of the dose found in the breast milk of lactating mothers [6,12,37].

Table 1.3 The Influence of Food on the Pharmacokinetic Parameters of Pseudoephedrine

A: Controlled Release Dosage Forms

Dose	Dosage Form	State	C_{max} (ng/mL)	t_{max} (h)	k_{el} (h^{-1})	AUC_0^t (ng/mL/h)	AUC_0^∞ (ng/mL/h)	Reference
240mg stat	60 mg IR, osmotic CR core	fed	246.3	6.6	0.081	6554	6862	44
240 mg stat	GITS (gastro-intestinal therapeutic system)	fed	314	11.2	0.091	7486	8153	56
		fasted	298	13.6	0.091	7332	8064	57
240 mg stat	2 GITS	fasted	267	13.3	0.113	6214	6322	58
240 mg stat	Matrix	fed	411	6.9			7122	57
		fasted	383	6.7			7236	57
120 mg bd	GITS	fasted	278	17.5	0.121	5889	5989	56
120 mg stat	2 capsules (coated polystirex particles)	fed	314	4.5	0.11	4483		58
		fasted	310	5.44	0.117	4066		58
120 mg stat	Suspension (coated polystirex particles)	fed	304	4.13	0.112	3911		55
		fasted	297	4.5	0.117	4201		55
120 mg stat	Capsule (coated polystirex particles)	fasted	392	4.16		3442		59

B: Immediate Release Dosage Forms

Dose	Dosage Form	State	C_{max} (ng/mL)	t_{max} (h)	k_{el} (h^{-1})	AUC_0^t (ng/mL/h)	AUC_0^∞ (ng/mL/h)	Reference
120 mg stat	20 mL syrup	fed	422	1.97	0.123	4883		58
		fasted	401	2.66	0.13	4438		58
120 mg stat	Solution	fed	372	2.53	0.137	4074		55
		fasted	397	1.84	0.122	4341		55
120 mg stat	Syrup	fasted	392	1.39		3582		59
60 mg qid	Syrup	fasted	278	1.71	0.135	6421	6491	56

Table 1.4 Changes in Pharmacokinetic Parameters at Steady State for two Pseudoephedrine Formulations

Dose	Number of doses	C_{max1} (ng/mL)	C_{max2} (ng/mL)	C_{min1} (ng/mL)	C_{min2} (ng/mL)	t_{max1} (h)	t_{max2} (h)	AUC_0^t (ng/mL/h)	AUC_0^{12} (ng/mL/h)	AUC_0^{∞} (ng/mL/h)	Reference
240 mg d	single	348				6.43		7353		7664	46
120 mg bd	single	7.8				7.22		4036		4239	46
240 mg d	multiple (10 days)	520		208		6.96		8987			46
120 mg bd	multiple (10 days)	474	482	313	274	4.43	4.17	9213	4562		46

1.1.5.4 METABOLISM

Less than one percent of the oral dose undergoes hepatic metabolism by N-demethylation to form the active metabolite nor-pseudoephedrine [6,10]. This percentage is increased to up to 25 percent if urinary pH is controlled with an alkalinising agent such as sodium bicarbonate [9,22].

Nor-pseudoephedrine exerts its activity primarily in the CNS, where it acts as a stimulant and anoretic agent [37], but also has some peripheral sympathomimetic activity.

1.1.5.5 EXCRETION

Pseudoephedrine undergoes renal excretion, with 43 to 96 percent of the oral dose being excreted unchanged in the urine within 24 hours as pseudoephedrine and 1 to 6.2 percent as the active metabolite [6,17,37,57]. Typical serum half-lives following administration of immediate release dosage forms are in the range of 4.3 to 8 hours. This variation can be attributed to differences in urinary pH, which is typically between 5 and 8 [10,57, 64, 65,66]. The elimination rate constant is also affected by the formulation used [55]. Clearance is slower in geriatrics, with a half-life value of 8.1 hours reported [10].

Pseudoephedrine accumulates in renal failure, and is not readily removed by dialysis [64].

Clearance is typically 0.44 L/h/kg [10], or 15.5 L/hr [43], but values are higher in children [63].

Both pseudoephedrine and nor-pseudoephedrine are subject to extensive tubular reabsorption in the proximal tubule [10,22]. As only the unionized fraction is reabsorbed, urinary pH plays an important role in determining the excretion rate, with elimination being more rapid in acidic urine [24]. In alkaline urine (pH > 7), the urinary flow rate becomes an important factor in determining elimination rate as this affects the time for which the pseudoephedrine is present at the reabsorption sites [18,43].

The use of diuretics reduces the urinary concentration by 4 to 6 fold for the first 4 hours after the diuretic is administered, but there is no change in the total amount excreted or metabolised, except for a 200 mg dose of acetazolamide, where the amount recovered in the first 4 hours is reduced [22].

A summary of reported values for the half-life of pseudoephedrine in immediate and controlled preparations and at various urinary pH values is given in Table 1.5.

Table 1.5 Variations in the Half-Life of Pseudoephedrine with Urinary pH

Dose	Serum $t_{1/2}$	Urine pH	Reference
120 -180 mg	9.2-16	7.9-8.1	37,57,66
	5.2-8	5.6-6.0	37,58, 66
	3.0-6.4	5.0-5.4	37,59,66

1.2 LORATADINE

1.2.1 INTRODUCTION

Loratadine is a long-acting anti-histamine used to relieve the symptoms of hypersensitivity reactions [67]. It was introduced onto the European market in the late 1980's and was approved by the FDA in 1993. Loratadine is marketed as a syrup or as tablets, either alone or in combination with pseudoephedrine [5].

1.2.2 PHYSICO-CHEMICAL PROPERTIES

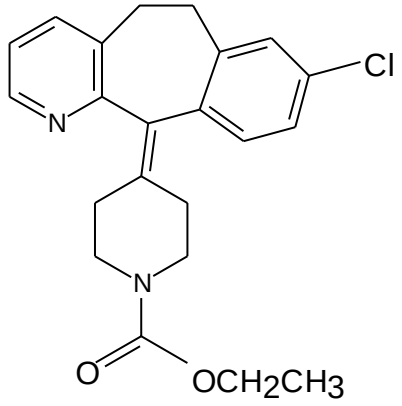
1.2.2.1 DESCRIPTION

Loratadine is 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2b]pyridin-11-ylidene)-1-piperidincarbocylic acid ethyl ester.

The empirical formula is $C_{22}H_{23}ClN_2O_2$ and it has a molecular weight of 382.89 g/mol.

Loratadine occurs as a fine white to off-white powder.

Figure 1.7 Structure of Loratadine



1.2.2.2 STRUCTURE-ACTIVITY RELATIONSHIP

Loratadine is an antihistamine of the piperidine group. It is less basic than its parent compound azatadine, decreasing its ability to penetrate the CNS [68]. The chlorine substituent increases its potency as well as increasing the duration of action [68].

1.2.2.3 SYNTHESIS

Loratadine is synthesized from azatadine, another histamine-1 (H_1) receptor antagonist. Azatadine is treated with a chloroformate on benzene and the phenylcarbamate obtained is subsequently treated with sodium ethoxide in toluene. This product is then halogenated to yield the chloro-derivative, which is loratadine [69].

1.2.2.4 DISSOCIATION CONSTANT AND PARTITION COEFFICIENT

The pKa of loratadine is 4.58 and that of its metabolite descarboethoxyloratadine is 8.65 [70].

The octanol water partition coefficient (log P) has been experimentally determined as 4.40 [70] or calculated as 5.37 [71] for loratadine and 1.29 -2.56 for descarboethoxyloratadine, depending on pH [70].

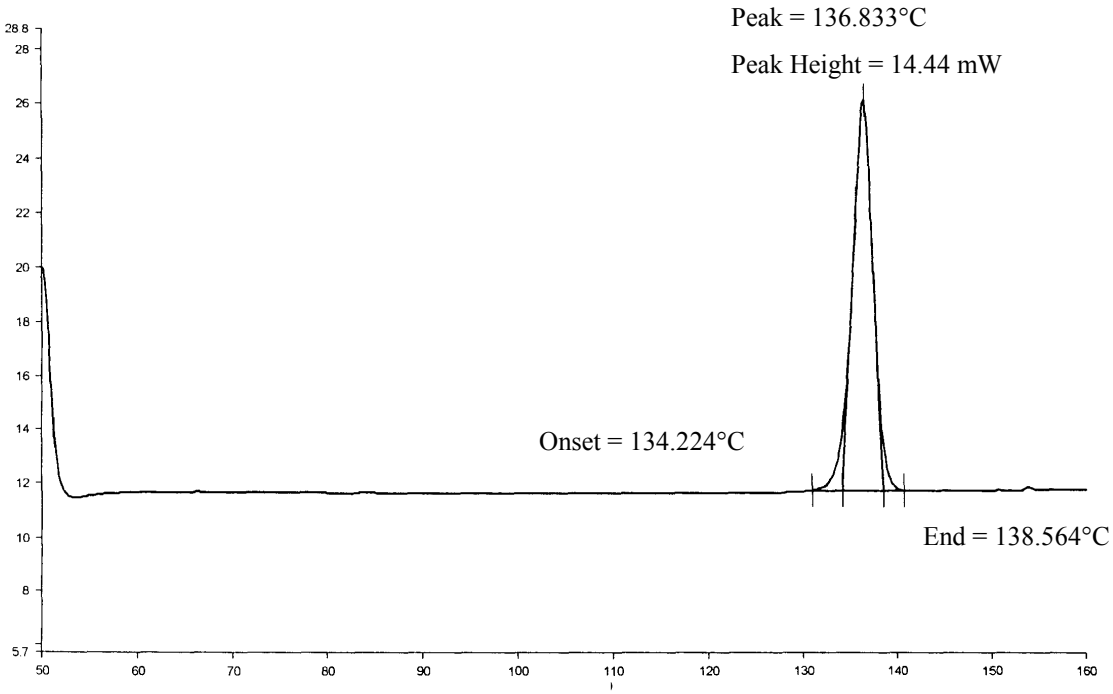
1.2.2.5 SOLUBILITY

Loratadine is relatively hydrophobic. It is insoluble in water, but highly soluble in ethanol, acetone and chloroform [4].

1.2.2.6 MELTING POINT

The melting point was assessed by differential scanning calorimetry (DSC), using a Perkin Elmer DSC 7 apparatus (Perkin-Elmer, UK). Loratadine has a melting range of 134 – 138°C, with a melting point of 136.8°C. The scan is depicted in Figure 1.8. The molar heat of fusion is 28.42 kJ/mol.

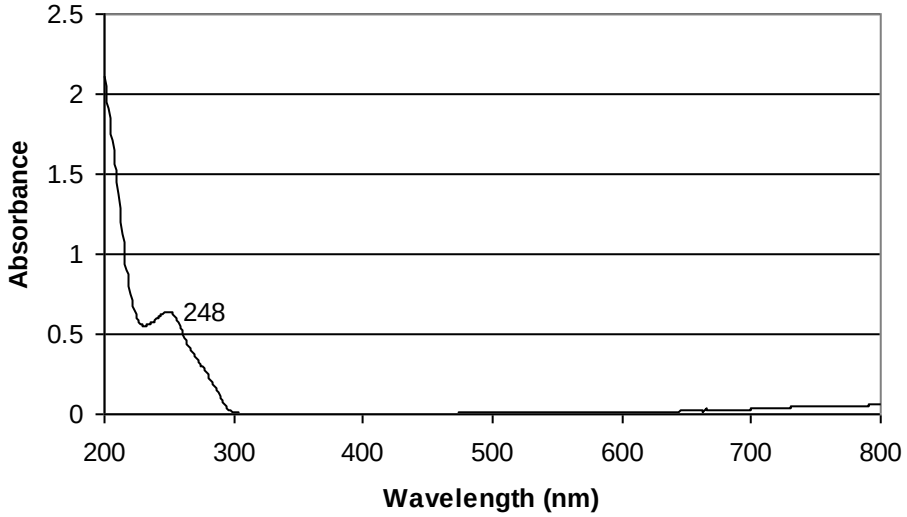
Figure 1.8 DSC Scan of Loratadine



1.2.2.7 ULTRAVIOLET ABSORPTION SPECTRUM

Loratadine has an absorption maximum at 247 nm in acetonitrile-water (50:50). The UV scan is illustrated in Figure 1.9.

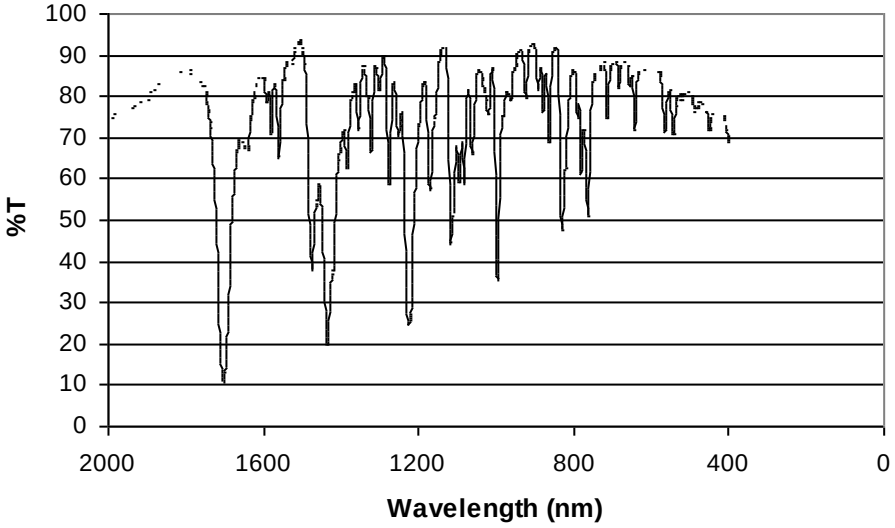
Figure 1.9 UV Absorption Spectrum of Loratadine



1.2.2.8 INFRARED SPECTRUM

The infrared spectrum was assessed using a Perkin-Elmer Spectrum 2000 TG-IR (Perkin-Elmer, UK), and is illustrated in Figure 1.10.

Figure 1.10 Infrared Absorption Spectrum of Loratadine



1.2.3 STABILITY

No data pertaining to the stability of loratadine is available. Loratadine was found to be stable in acidic solution for periods of one week (§4.2.5.6)

1.2.4 CLINICAL PHARMACOLOGY

1.2.4.1 MODE OF ACTION

Loratadine is a long-acting H_1 receptor antagonist. It also has a weak affinity for cholinergic and adrenergic α receptors [72]. It has a low affinity for CNS H_1 receptors and is partially selective for peripheral H_1 receptors [73]. It has weak anti-serotinergic activity [74] and some anti-inflammatory activity, including mast cell stabilizing effects and the inhibition of eosinophil chemotaxis [75].

1.2.4.2 INDICATIONS

Loratadine is indicated for the relief of hypersensitivity reactions, particularly allergic rhinitis and chronic urticaria [76,77,78]. It is formulated alone and in combination with pseudoephedrine, which gives a better therapeutic response than either drug alone [79]. It has been proposed as an alternative to sodium cromoglycate for the prophylaxis of mild to moderate allergic asthma in children [75,80], where it exhibits a similar efficacy to cromolyn, but has the advantage of once daily versus four times daily dosing. It has also proven useful to reduce symptoms of pruritis in atopic dermatitis [80,81].

1.2.4.3 CONTRA-INDICATIONS

Loratadine is contra-indicated in children under 2 years of age as little data is available pertaining to its use in this patient population [82].

1.2.4.4 HIGH-RISK PATIENT GROUPS

Loratadine should be used with caution in pregnant or lactating women. Although there is no evidence of teratogenicity of harmful effects on the neonate, little data is available and use in these patients is best avoided. Loratadine is excreted in breast milk [5].

Individuals with hepatic impairment may experience reduced loratadine clearance and possible accumulation. The use of loratadine in these patients must be carefully monitored and these individuals should begin therapy at a lower dose than the usually recommended one [78].

1.2.4.5 DRUG INTERACTIONS

Erythromycin, ketoconazole and cimetidine have been shown to decrease the metabolism of loratadine. There is no evidence of cardiac effects as seen with other long-acting antihistamines administered concurrently with erythromycin [73]. Steady-state pharmacokinetic studies on loratadine in the presence of clarithromycin showed that although the concentrations of loratadine and descarboethoxyloratadine in plasma increases, there are no cardiac effects or evidence of an interaction [83]. There has been one reported case of a prolonged QT interval with asssociated ventricular tachycardia in a patient on quinidine and loratadine, where this appeared to be a result of a drug interaction [84].

Concomitant administration with pseudoephedrine increases the anticholinergic effects of both drugs, leading to more pronounced side-effects [73].

1.2.4.6 ADVERSE DRUG REACTIONS

1.2.4.6.1 Common Adverse reactions

The most commonly reported adverse effects of loratadine therapy are headache [85], fatigue, dry mouth and sedation. Nervousness, hyperkinesia and gastro-intestinal disturbances have been reported in children weighing less than 30 kgs. Sedation and antimuscarinic effects are rare at therapeutic doses [86,87]. Somnolence is dose-related and occurs at doses greater than 10 mg per day [72].

1.2.4.6.2 Adverse reactions

Alopecia and anaphylaxis have been reported since loratadine was approved for sale.

Loratadine may cause hepatotoxicity and subfulminant liver failure, particularly with long-term use. Two patients with no evidence of other causative factors have developed

hepatotoxicity while taking loratadine, and one required liver transplantation [88].

Loratadine has been reported as promoting tumour growth in mice after intravenous administration, with this effect being maximal at human-equivalent doses [89]. Further studies are necessary to determine whether this effect is of any significance in humans.

1.2.5 PHARMACOKINETICS

Loratadine exhibits dose-independent pharmacokinetics [90], with a biexponential decline, indicating a two-body compartment model [90,91].

1.2.5.1 DOSAGE

Loratadine is administered as a daily 10 mg dose or twice daily 5 mg dose in adults or 5 mg daily for children aged between 2 and 12. Children under 2 years or weighing less than 30 kilograms should not be given loratadine [92,93].

1.2.5.2 ABSORPTION

Loratadine is rapidly and well absorbed [4,72,94]. Absorption of loratadine appears to be enhanced in the presence of food [57], probably because of the associated decrease in hepatic blood flow. The maximum plasma concentration following a 10 mg once daily dose has been reported as 3.42 μg/mL and following a 5 mg twice-daily dose has been reported as 1.54 - 1.56 μg/mL [82]. The time to reach maximum concentration ($\mathbf{t_{max}}$) is 1.5 - 2 hours for a 10 mg dose, 1 hour for 20 mg and 1.3 hours for 40 mg and 2.2 - 2.6 hours after twice daily dosing with 5 mg [46]. Some pharmacokinetic parameters after single and multiple doses are listed in Table 1.6.

Table 1.6 Some Pharmacokinetic Parameters for Loratadine and its Active Metabolite, Descarboethoxyloratadine [46]

A: Single dose Study

Compound	**Dosage Form**	$t_{1/2}$	C_{max}	t_{max}	AUC_0^t	AUC_0^∞
Loratadine	10 mg daily		1.9	2	5.84	
	5 mg twice daily		1.02	2.09	3.33	
Descarboethoxyloratadine	10 mg daily	18.1	2.67	2.43	43.4	42.4
	5 mg twice daily	17.5	1.44	2.61	21.7	24.6

B: Multiple Dose Study

Compound	**Dosage Form**	C_{max1}	C_{max2}	C_{min1}	C_{min2}	t_{max1}	t_{max2}	AUC_0^{24}	AUC_0^{12}
Loratadine	10 mg daily	3.42		0.09		2		13.6	
	5 mg twice daily	1.54	1.56	0.14	0.17	2.26	2.61	13.4	6.25
Descarboethoxyloratadine	10 mg daily	4.13		1.4		2.61		54.1	
	5 mg twice daily	3.14	2.77	1.83	1.79	2.61	2.78	53.9	28.3

1.2.5.3 DISTRIBUTION

Loratadine is extensively bound to plasma proteins, with 97 - 99% being bound [73, 80], mainly by a saturable mechanism [70]. Descarboethoxyloratadine is 73 -77% bound [80]. Loratadine has a relatively low affinity for α_1 acid glycoprotein [70]. The estimated volume of distribution is 119 L/kg and the half-life of distribution for loratadine has been given as 0.9 to 1 hour [73,90,91], while that of descarboethoxyloratadine is 2.1 hours [90]. Steady state is achieved in 5 to 10 days [46,94]. There is little distribution to the central nervous system as the log P value for loratadine is high, indicating extensive hydrophobicity. It has been found that for compounds to cross the blood brain barrier a log P value of between 2 and 3 is required [70].

1.2.5.4 METABOLISM

Loratadine undergoes extensive first pass metabolism in the liver to form the active metabolite descarboethoxyloratadine [57]. It is metabolised by N-deacetylation by P450 CYP3A4 and to a lesser extent by P450 CYP2D6 [80], and metabolism is reduced in liver disease [72]. The secondary metabolic pathway may account for the reduced incidence of drug interactions with P450 enzyme inhibitors, most of which interact with the CYP3A4 subtype [80].

Descarboethoxyloratadine is four times more active than loratadine [68].

1.2.5.5 ELIMINATION

Loratadine is excreted in both the urine and faeces, with approximately 44 percent of an oral dose excreted in the faeces and 40 percent in the urine. A total of 27 percent is excreted within 24 hours [82,95]. Loratadine is also present as a conjugated metabolite in the urine [82]. The elimination half-life of loratadine ranges from 7.8 to 11 hours from a single dose, or 14.4 hours at steady state [80,82,90], although the half-life may be prolonged in the elderly [72]. The half-life of descarboethoxyloratadine is 28 hours [90]. Neither loratadine nor descarboethoxyloratadine are appreciably removed by dialysis, and the plasma concentration of descarboethoxyloratadine is raised in patients with compromised renal function, although this appears not to be clinically significant [91].

Pharmacokinetics in adolescents and the elderly are not substantially different from the general adult population [95], although the ratio of AUC to maximum concentration is frequently raised in younger patients [80].

A small percentage of the dose (0.03 percent) is excreted into breast milk [76,95,96], with

the concentration versus time curves for milk closely paralleling those for plasma for both loratadine and descarboethoxyloratadine [96]. The maximal possible dose received by the infant has been extrapolated at 1.1 % of the adult dose on a mg per kg basis [96].

CHAPTER 2
FORMULATION OF A CONTROLLED RELEASE CORE

2.1 CONTROLLED RELEASE ORAL DOSAGE FORMS

2.1.1 INTRODUCTION

There has been an increased interest in controlled release oral dosage forms in recent years [97]. As patients become more knowledgeable and assertive about their health it has become necessary to design therapeutic regimens that are simple and convenient, facilitating patient compliance. Controlled release dosage forms hold a number of advantages over traditional immediate release formulations, including a less complex dosage regimen, reduced fluctuations of the drug concentration in the blood, thereby minimising the possibility of toxic effects and prolonged periods of subtherapeutic concentrations in the body [98].

The oral route is the most commonly used route of drug administration although the development of controlled release dosage forms has not been limited to oral delivery. The oral route presents a challenge to the formulator owing to physiological constraints (for example gastric transit time, varying pH and ionic strength), which impose limits on dosage form design, and the necessity of designing a dosage form which is readily administered. The most commonly used types of controlled release oral dosage forms are matrix systems and coated tablets [99], while alternate technologies include the use of osmotic tablets, multiparticulate dosage forms, ion-exchange resins, bioadhesives, devices with altered density and combinations thereof [97].

The absorption of drugs administered orally is affected by the nature of the delivery system (whether it is multiparticulate or monolithic, disintegrating or non-disintegrating) and the influence of physiological variables [99]. Physiological variables of particular

importance include gastric emptying rate, small intestinal fluid flow rate, and the transformation processes or transport mechanisms and pathways which are required for the successful absorption of some chemical entities [100,101]. Drugs that are absorbed by an active process may exhibit or undergo site-specific absorption within the gastro-intestinal tract (GIT), depending on the distribution of the necessary enzymes or carrier molecules. As different dosage forms are affected differently, the temporal and spatial placement of the drug within the GIT will vary with the dosage form, thereby affecting absorption. Modified release dosage forms usually have an inherent release-controlling component, which enable a variety of interactions with physiological absorption variables [100]. These formulation additives influence either the gastric transit, transportation, transformation processes whereby the active is absorbed or a combination of these.

The drug release profile obtained from any dosage form is a function of the properties of its components and the manufacturing procedures used, and any interaction between these variables [102]. In addition, the geometry, size and density of the dosage form will influence the gastric retention time and may thus contribute to a sustained or delayed release effect [100,103]. The release of a drug compound can be slowed either chemically (by alteration of the properties of the dosage form constituents including the active) or physically (by manipulating the choice of constituents and/or the manufacturing procedures) [97]. Most controlled release formulations rely to some extent on the use of polymers to delay or control drug release [97,99].

Controlled release delivery systems can be broadly classified into three types [99], which are illustrated schematically in Figure 2.1

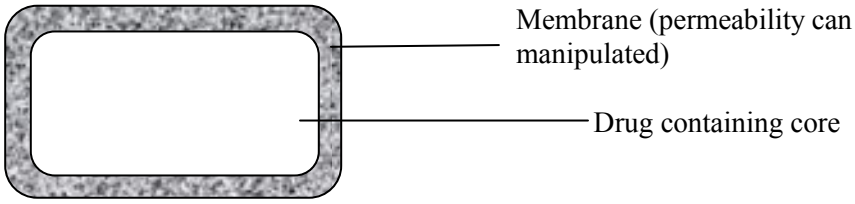
1. Membrane systems: These comprise a drug core surrounded by a rate-controlling membrane, as illustrated in Figure 2.1.A.
2. Matrix systems: These usually comprise a solution or suspension of drug in a carrier matrix, usually a polymer, as illustrated in Figure 2.1.B.

3. Hybrid systems: These dosage forms have properties of both membrane and matrix systems, as illustrated in Figure 2.1.C.

All three systems can exist as multi-particulate or single entity systems. Membrane systems are usually non-disintegrating, but matrix and hybrid systems can be either disintegrating or non-disintegrating. The type of system will determine the release-controlling mechanism, and each is characterized by typical drug release profiles.

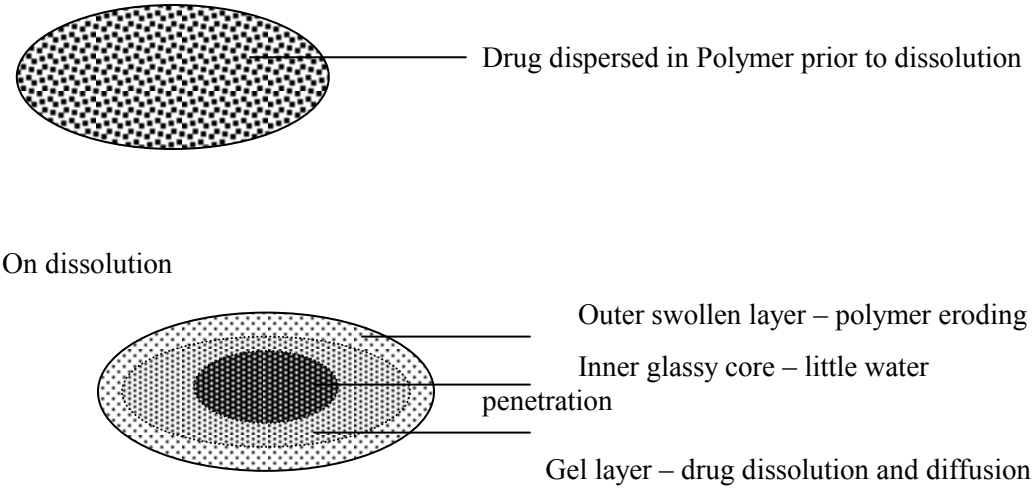
Figure 2.1 Schematic Representations of the Principal Types of Controlled Release Dosage Forms

A: Membrane systems

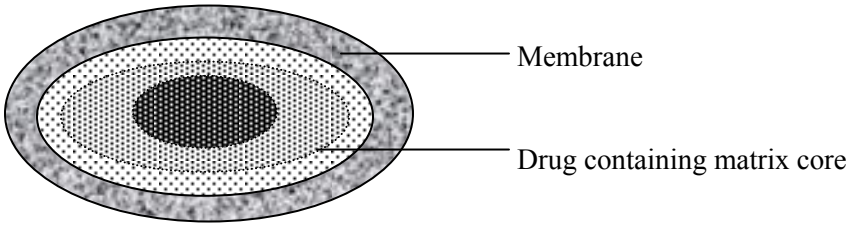


Drug diffuses through pores created in the membrane by dissolution of membrane components.

B: Matrix type system



C: Hybrid system



2.1.2 RELEASE-CONTROLLING MECHANISMS

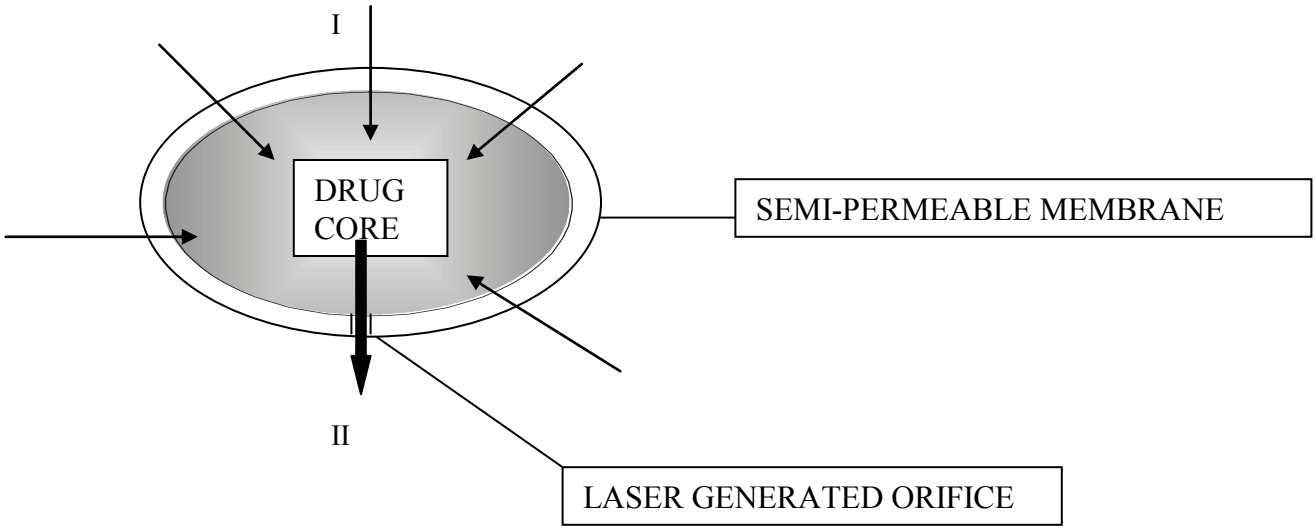
2.1.2.1 MEMBRANE SYSTEMS

2.1.2.1.1 Osmotic pumping

On contact with fluid, the membrane is wetted and water enters the dosage form by osmosis. After water has entered, a solution is formed on the interior, but as the membrane is semi-permeable, the solution cannot diffuse out, and thus an osmotic pressure gradient is generated across the semi-permeable membrane. Dissolved drug is expelled through an orifice, usually laser-generated, in the membrane as a result of this pressure gradient [99]. The system can be modified to include a swellable polymer, such as polyethylene oxide, in the reservoir. As water enters, the polymer swells and forces a suspension of drug through the orifice into the GIT. This process is illustrated in Figure 2.2. Osmotic pumping is only possible in membrane systems. A constant release rate is achieved provided there is a constant osmotic gradient across the membrane and the concentration of drug in the reservoir is greater than its saturation solubility. In formulations where a swellable polymer is used, a constant rate will be maintained if the swelling rate of the polymer is constant.

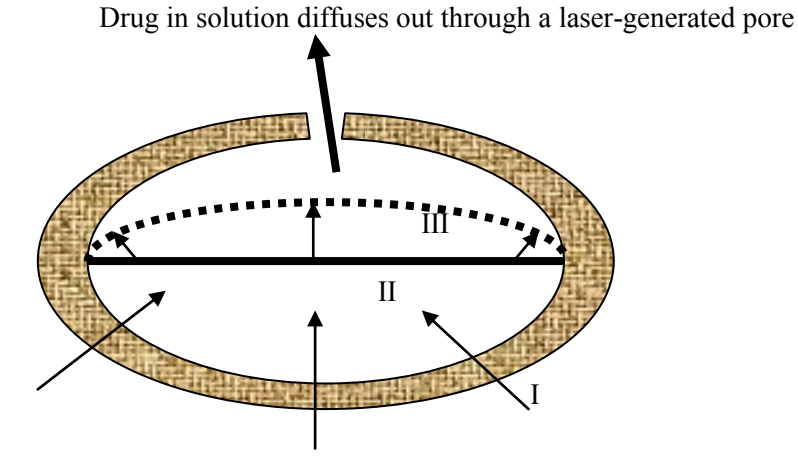
Figure 2.2 Release by Osmotic Pumping

A. Conventional osmotic release



I: Surrounding medium penetrates the semi-permeable membrane
II: Drug exits through the orifice in solution

B. Push-pull modification for osmotic pumping



I: The entry of water causes the swelling of the polymer contained in this separated region of the core.
II: The swelling polymer expands against the barrier dividing it from the drug-containing portion.
III: The expansion of polymer increases the pressure within the dosage form, and drug is expelled in solution or suspension through the laser-generated orifice.

2.1.2.1.2 Solution-diffusion

This is the most common mechanism of drug release from membrane systems, although osmotic effects frequently contribute [99,104,105]. Water penetrates the dosage membrane and dissolves the drug within the core. The dissolved drug then partitions into the membrane and diffuses down a concentration gradient in accordance with Fick's first law of diffusion (Equation 2.1).

$$J = -D \frac{\delta C}{\delta x} \qquad (2.1)$$

Where J is the flux (amount of drug moving through a unit cross-sectional area of membrane per unit time)

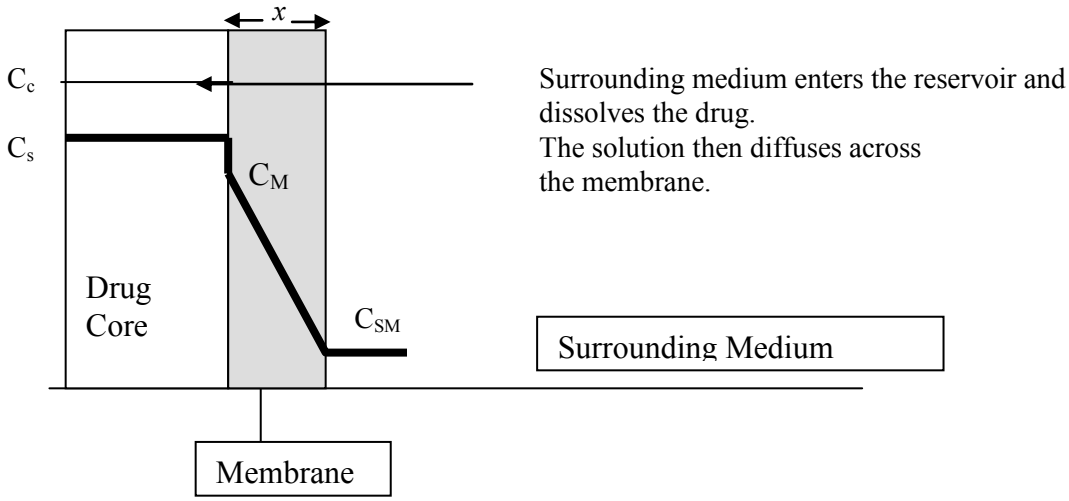
D is the diffusion coefficient of the drug

C is the drug concentration in the reservoir

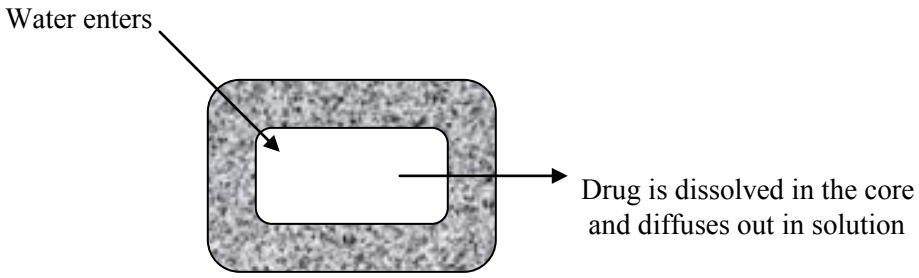
x is the perpendicular distance travelled (usually the thickness of the membrane is used).

The diffusion coefficient incorporates the partition coefficient between the drug and the membrane and is affected by the viscosity, tortuosity and binding ability of the membrane. In addition, the crystalline structure and the extent to which the drug is subjected to attractive bonding forces within the membrane will impact on the partitioning of the drug. A constant rate of release is attained when the drug concentration in the core exceeds saturation solubility [99]. The drug release process is illustrated in Figure 2.3.

Figure 2.3 Solution-diffusion across a Membrane

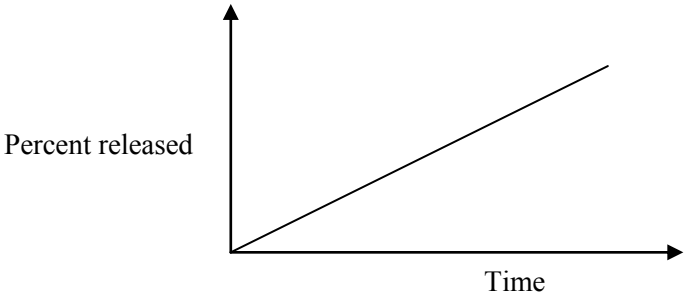


C_c: The concentration of drug contained in the core
C_s: The saturation concentration of drug in the water or the dissolution medium
C_m: The saturation concentration of drug in the membrane
C_{sm}: The concentration of drug in the surrounding medium
X: The diffusional distance, equal to the thickness of the membrane



The diffusional distance does not change as the membrane does not erode. Thus constant release is maintained provided that the concentration of drug in the core exceeds the saturation solubility of the drug.

Typical Dissolution Profile for Solution Profile for Solution-Diffusion



2.1.2.2 MATRIX SYSTEMS

2.1.2.2.1 Diffusion-control

Diffusion control refers to passive diffusion from matrix systems. Water penetrates the matrix dissolving the drug, which then diffuses down a concentration gradient to the receptor phase. Release from these systems is usually first-order with square-root time dependence and can be described by Fick's second law of diffusion [99,106], given in Equation 2.2.

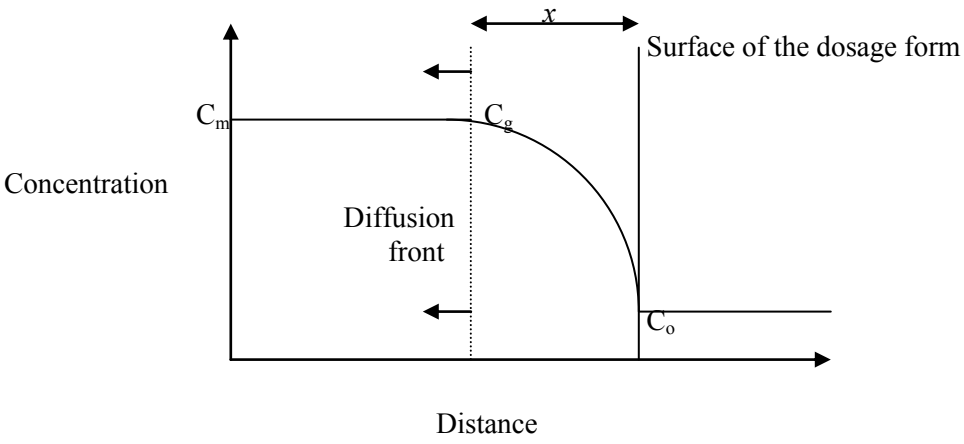
$$\frac{\delta C}{\delta x} = -D \frac{\delta^2 C}{\delta x^2} \qquad (2.2)$$

The increasing diffusional distance within the matrix accounts for the continuously decreasing rate of drug release, as the outer surface is depleted of drug and the surface area available to the penetrating water front is reduced [99], as illustrated in Figure 2.4. It is unusual for matrix systems to have release purely controlled by diffusion, and other mechanisms, such as those described below (§ 2.1.2.2.2, 2.1.2.2.3) frequently contribute to the release pattern[3]. In addition to these mechanisms, which predominate in hydrophilic matrices, hydrophobic matrices exhibit counter-current diffusion as a primary mechanism of release [107].

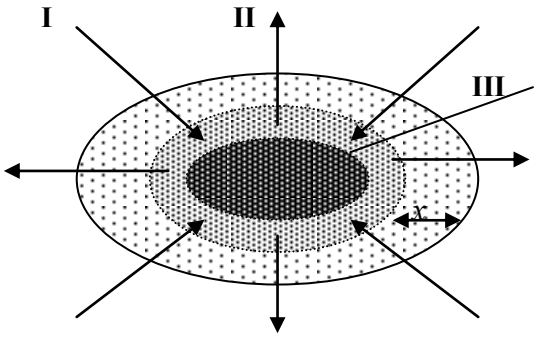
2.1.2.2.2 Dissolution-control

Dissolution-controlled drug release applies to matrix systems containing poorly water-soluble drug or high loads of water-soluble drug [99]. Water uptake is followed by dissolution of the drug and subsequently diffusion of the solution, but for these systems dissolution is significantly slower than diffusion. While the depletion zone remains small, linear release is obtained, but as this increases, the diffusional distance increases and the contribution of diffusion to the release of drug becomes significant.

Figure 2.4 Diffusion Controlled Release in a Matrix System

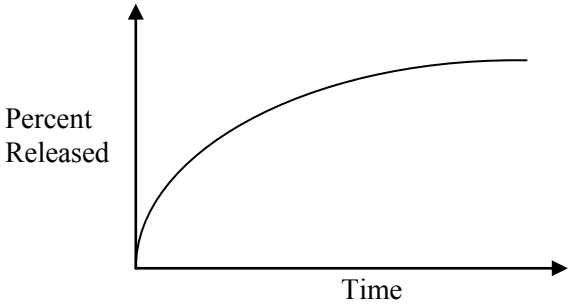


C_m : The concentration of drug in the matrix
C_g : The concentration of drug at the diffusion front
X : The diffusional distance, which is equivalent to the thickness of the gel layer
C_o: The concentration of drug at the interface of the dosage form and receptor fluid.



I: Water enters the matrix and dissolves the drug
II: Drug in solution diffuses through the matrix
III : As the outer layer of the matrix is depleted of drug, the penetrating water has a smaller exposed area of drug for dissolution, and the diffusional distance (*x*) has increased, and the rate of release is reduced.

Typical release profiles for Diffusion-controlled dosage forms

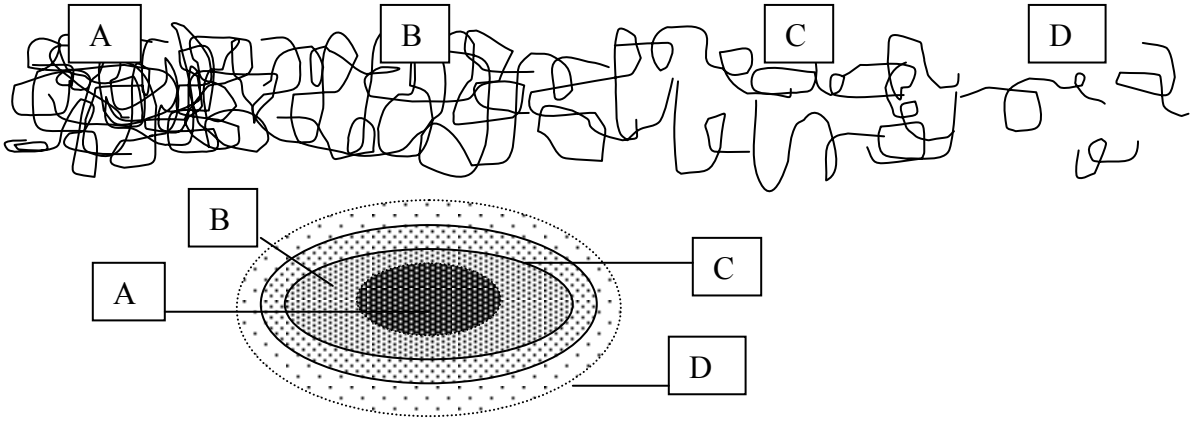


A : Water enters the matrix and dissolves the drug
B : Drug in solution diffuses through the matrix
C : As the outer layer of the matrix is depleted of drug, the penetrating water has a smaller exposed area of drug for dissolution, and the diffusional distance (*x*) has increased, and the rate of release is reduced.

2.1.2.2.3 Swelling and erosion control

This is a common mechanism of control for hydrophilic matrix systems. The polymer forms a viscous gel on contact with water through which the drug must diffuse. The entry of water causes polymer plasticisation and swelling, which continues until the outer surface has a polymer concentration too small to maintain entanglement of the polymer chains. At this point the polymer chains become disentangled and dissolve, leading to erosion of the matrix. Three phases can be identified in these systems. An initial swelling period with formation of a gel layer is followed by a period where the erosion and swelling processes are synchronised and the gel layer thickness remains constant. An illustration is provided in Figures 2.5 and 2.6. Eventually the erosion rate predominates and the gel layer is depleted. However, not all polymers conform to this, and hydroxypropyl methylcellulose has a swelling rate far greater than its erosion rate, leading to a swelling-controlled diffusion process for release of water-soluble drugs and an erosion-dissolution controlled mechanism for poorly water-soluble drugs. Polyvinyl acetate has a swelling rate which is altered in the presence of salts, and so the release rate can be manipulated by altering the amount and type of salt included in the formulation [108].

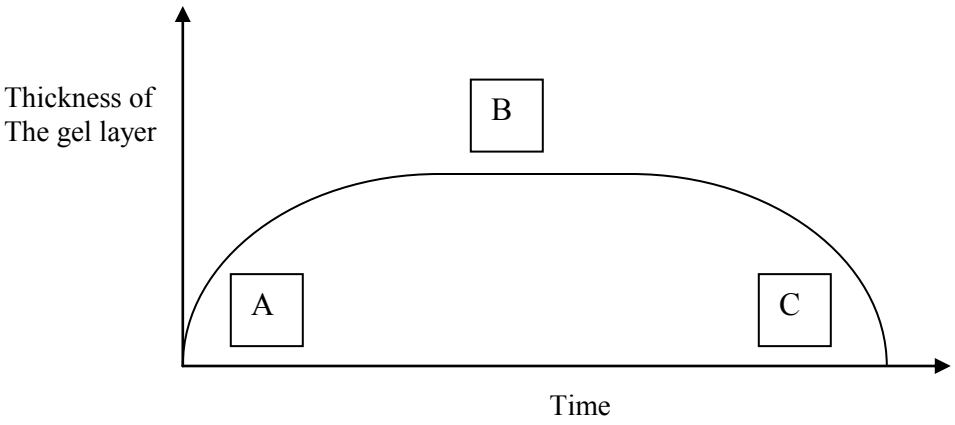
Figure 2.5 Swelling and Erosion Control



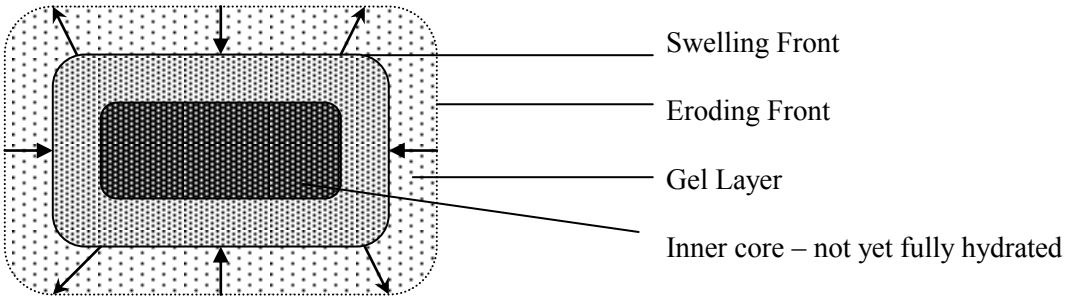
A: Dry glassy core: unhydrated and frozen
B: Swollen glassy layer: some hydration but very strong polymer chain entanglement
C: Gel layer: extensively hydrated with strong polymer chain entanglement
The swelling front moves outwards to form the gel layer.
D: Diffusion Layer: polymer chain concentration is insufficient to maintain entanglement

The erosion front moves inwards from the edge of the gel layer.

Figure 2.6 Swelling and Erosion Kinetics



A: Swelling phase. The swelling rate is far greater than that of erosion, and the thickness of the gel layer increases rapidly.
B: Synchronous phase. The swelling rate and erosion rate are equal**;** gel layer thickness remains constant as swelling is compensated for by erosion.
C: Erosion phase. The erosion rate is greater than that of swelling and the gel layer thickness decreases rapidly as erosion occurs.



The gel layer is bounded by the swelling and erosion fronts. The thickness of the layer is thus determined by the relative rates of erosion and swelling, and will be thick for swelling-controlled release (swelling rate predominates), and thin for erosion controlled-release (erosion rate predominates). Release from these systems may be zero-order, particularly if erosion predominates, but the kinetics are usually complex, as diffusion also contributes to the release profile.

Constant release may be obtained for systems where the drug release is controlled predominantly by erosion or where the polymer has a rapid dissolution rate and the synchronous phase begins early. However, matrix systems generally exhibit release with square-root time dependent kinetics as described by Higuchi [109] (Equation 2.3).

$$Q = [D(2A-C_s)C_st]^{0.5} \quad (2.3)$$

Where Q is the amount of drug released

D is the diffusion coefficient of the drug in the matrix,

A is the total amount of drug in the matrix

C_s is the saturation solubility of the drug in the matrix

t is time

This model was developed for homogenous, non-eroding matrices. A modification of the Higuchi equation, which includes terms for porosity of the matrix and tortuosity of the diffusion path, has been developed to describe release from an eroding matrix (Equation 2.4).

$$Q=\left[\frac{D\varepsilon}{\tau}(2A-\varepsilon C_s)C_st\right]^{0.5} \quad (2.4)$$

Where τ is tortuosity, and refers to the degree of convolution and bending of the channels

ε refers to porosity, and can be approximated by dividing the amount of drug (A) by its density and expressing this as a percentage of matrix volume

D is the diffusion coefficient of the drug in the fluid-filled channels, and is modified by τ.

The effective diffusion coefficient is expressed by D/τ.

The diffusion coefficient, D, differs from that of Fick's law as it refers to diffusion through the fluid in the pores rather than the polymer material of the matrix.

Several other models have been developed to describe release from matrix formulations.

1. The Fessi model, a modification on Higuchi's principle applied to non-eroding matrices[110], was developed as the Higuchi model is only applicable to inert matrices that are not completely wetted. Once complete wetting occurs there is a change in the slope of the percent released versus root time profile. Fessi's model is used to determine the amount of drug remaining in the tablet at which the release rate will change, and the equation is given in Equation 2.5.

$$J = e\ S\ h\ r\ \frac{(3.1416)}{6} \qquad (2.5)$$

where J is the amount remaining
e is porosity
S is the solubility of the drug
h is the thickness
r is the radius

2. The Hopfenberg equation, given in Equation 2.6, [111] assumes that the release occurs from a primary surface area (for instance only from the axial surfaces of a tablet) and that erosion is the rate-limiting process.

$$M_t = 1 - \left[1 - \frac{k_0 t}{C_0 a_0}\right]^n \qquad (2.6)$$

3. The Korsemeyer equation [98] relates fraction of drug released to potency time and can be applied to Fickian diffusion and zero-order release systems. The Korsemeyer equation is given by

$$\frac{M}{M_\infty} = kt^n \qquad (2.7)$$

4. The Hopfenberg equation can be modified to account for axial and radial erosion rates in eroding matrices [112, 113], as shown in Equation 2.8.

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_0 a_0}\right)^2 \left(1 - \frac{2k_0 t}{C_0 b_0}\right) \qquad (2.8)$$

2.1.2.2.4 Geometry and area changes

Release from matrices can also be controlled by manipulating the exposed area or the area available for swelling. Donut shapes [114] and tablets with multiple central holes [115], cylinders and partial coatings [114] have been investigated to assess their efficiency in maintaining a near-constant surface area for release, but these dosage forms are frequently impractical to manufacture on a industrial scale and are primarily of research and not commercial interest. Changes in the surface area to volume ratio may also alter release as the smaller this ratio, the smaller the amount of exposed drug relative to the total amount of drug present, and the slower the release [116].

2. 2 MATRIX SYSTEMS

Matrix systems are widely used to control release as they are relatively simple and economical to manufacture, but the release rate is difficult to control as the diffusional distance in these dosage forms is constantly changing [117]. Matrices can be classified as hydrophilic and eroding, inert, lipidic, mineral or biodegradable [98]. In general, currently used oral matrix formulations are either inert or hydrophilic and eroding. The resistance to drug transport in these systems is largely dependent on the composition and structure of the matrix [118]. Where the dosage form is a single matrix system with one polymeric component, it is referred to as a monolithic delivery system.

The release of a drug from hydrophilic matrix systems is dependent on several properties of the polymer used, including composition [97], particle size, viscosity and rate and extent of hydration [119]. The proportion of polymer to drug [98] and any interactions

between the polymer and the drug are also influential factors deserving consideration. These factors may influence each other, for example, the polymer particle size of HPMC has been shown to alter the amount of water absorbed [120].

Polymer branching is an additional factor that may contribute to a delay in drug release. Extensive branching reduces the ability of the polymer to create voids through which the drug can move, thereby increasing tortuosity and decreasing the drug's diffusivity coefficient [107]. The diffusion rate is also affected by the nature of the polymer, as more crystalline polymers are heterogeneous in nature, making diffusion tortuous and slower [121]. Rubbery polymers do not have regions of crystallinity and do not hinder dissolution to the same extent. Release from ethylcellulose inert matrices is affected by the polymer content, viscosity and particle size [122]. Polymers with smaller particle size exhibit slower release as diffusion is inhibited more than in matrices comprising larger sized particles [123], while increasing ethylcellulose content decreases the release rate to a 30% polymer content, after which there is no significant effect on release rates [123]. Vargas and Ghaly found that this principle is also true for hydrophilic HPMC matrices [124].

The aqueous solubility and particle size of the drug also influence diffusion and subsequent release rates. Solubility determines the extent to which diffusion occurs [112,125,126] and particle size influences the rate of diffusion through the polymer, with larger particles exhibiting slower diffusion as the drug must move through voids created within the matrix, and smaller voids are formed more readily [121]. The amount of drug may also be an important consideration as loss of carrier control has been reported for systems containing more than 20% drug [127]. This has an impact on the size of the dosage form, which in turn may affect the ease and feasibility of oral administration.

The length of the polymer chain influences the dissolution rate of the polymer, as long chains exhibit a greater degree of entanglement, and in turn a greater extent of water

penetration is necessary for disentanglement and subsequent dissolution [118]. The increase in water penetration will require a longer time period and thus the swelling rate will be reduced and the rate of drug release altered [127]. Rapid swelling and gel-layer formation is desirable, as the diffusion of drug across the gel layer is frequently the rate limiting step in the drug release process [118]. The rate of erosion for HPMC is influenced by various factors including the polymer viscosity, the drug concentration, the tablet geometry and the inclusion of polyethylene glycols [112]. PEGs have been shown to increase the erosion rate of both hydrophilic and hydrophobic polymers [112], possibly by increasing the water solubility of the polymer through a cosolvent action, which may also occur with other similar additives.

The presence of any plasticisers, their type (hydrophilic or hydrophobic) and their concentration [125,128], will affect the release rate from polymer matrices by altering their water permeability and flexibility. Peh and Yuen [129] demonstrated that glyceryl monostearate decreased the release rate from microcrystalline cellulose matrices. The presence of other additives, such as lubricants or waxes, may alter the extent of channel formation within a matrix [129,130]. The effect of lubricants has also been observed by Lee *et al* [119], who found that the release from hydroxypropyl methyl cellulose (HPMC) matrices depended on the choice of lubricant and glidant. Katikaneni *et al* [131] found that the amount of magnesium stearate included in an ethylcellulose matrix altered the release rate, with increasing magnesium stearate concentration retarding release. Durig *et al* [132] found that the proportion of magnesium stearate altered the ratio of the axial to radial erosion rate constants, altering release. The inclusion of lipids [133,134] has also been found to delay release, as has the inclusion of waxes, which gave a flexible matrix with pore diffusion release mechanisms in addition to matrix effects [135]. The choice of excipients in matrices with low polymer content may have a profound effect on the release rate of the active, depending on their water solubility [124].

Matrices can be manufactured by several methods including direct compression [136],

wet granulation [137], roller compaction [138], freeze-drying [139] and extrusion-spheronization [137]. The method of manufacture and processing variables, such as compaction pressure [140] and spheronization speed, affect the rate of drug release from the matrix.

Matrices formed by wet granulation prior to compression may show slower release with increasing amounts of granulation fluid used and increased kneading time [137], although release may not be affected after tableting [138].

The change in diffusion path length may be offset to some extent by incorporating the drug to give a high concentration in the centre of the dosage form [102], facilitating the manufacture of a dosage forms with zero-order release patterns. Vandelli *et al* [114] designed a coated ethylene vinyl acetate copolymer matrix with a central uncoated hole which gave time-independent release. The central-hole principle (donut tablets) is used to minimise changes in exposed surface area as erosion then takes place on two fronts [115]. These dosage forms are difficult to manufacture and have limited applicability. The rate of change in the exposed surface area of a tablet can be manipulated by altering the radius to thickness ratio, thereby changing the geometry of the tablet. As longitudinal and axial erosion occur at different rates, the initial geometry of the tablet will affect the overall rate of erosion and the changes in surface area exposed to the medium with time [112].

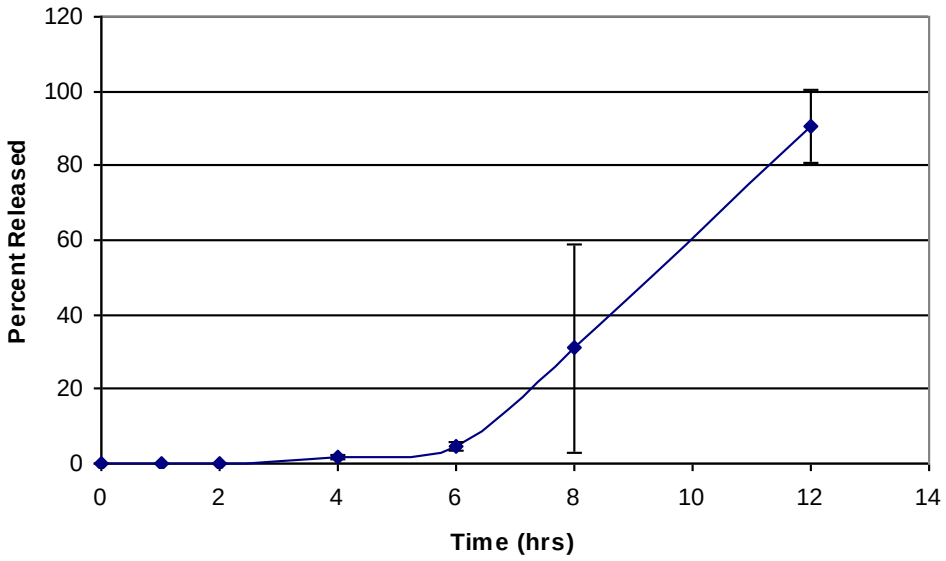
Some matrix-forming polymers are sensitive to prandial effects, with slower erosion if taken after food, possibly as a result of increased gel-layer strength [141]. Therefore dosage regimen design is a further factor to consider for the successful development and use of eroding matrices.

2.3 INITIAL DOSAGE FORM DEVELOPMENT

2.3.1 PROPOSED DESIGN

The proposed dosage form is a repeat action tablet containing both an antihistamine (loratadine) and decongestant (PSS) in combination. The term 'repeat action' refers to the use of two drug release components, one of which releases the drug immediately whilst the second exhibits sustained or controlled drug release characteristics. The rationale behind this design is the development of a dosage form that provides extended periods of symptom relief for the patient, but has a rapid initial action, and has an easily followed dosage regimen to facilitate compliance. As loratadine has an extended half-life (refer to § 1.2.5), a lasting effect is obtained with an immediate release dosage form, and controlled release is not necessary. Conversely, PSS has a relatively short half-life (§ 1.1.5) and requires multiple daily dosing. The proposed release profile is based on that of Clarityne D® (Schering-Plough), which is a coated tablet with a twice daily regimen. This tablet contains an outer sugar coating that incorporates the loratadine dose and half of the PSS dose to achieve a rapid onset of action and relief from congestion. This coating is applied over a tablet previously coated with an insoluble proteinaceous polymer, zein. This zein-coated tablet contains the other half of the PSS dose, and exhibits a controlled drug release profile, with a lag phase of approximately four hours followed by zero-order release over an eight-hour period, as depicted in Figure 2.7.

Figure 2.7 Dissolution Profile of Clarityne-D® Cores



2.3.2 PRELIMINARY STUDIES

In order to establish the desired drug release characteristics of the dosage form, preliminary dissolution rate studies were performed on two commercial preparations: an immediate release dosage form of pseudoephedrine hydrochloride (Adco-Sufedrin®, Adcock-Ingram), and Clarityne-D® (Schering-Plough). Schering-Plough has four identical repeat action dosage forms on the market: Demazin NS®, Polaratyne-D®, Clarityne-D and Loratyne-D®. Clarityne-D® was the product used as a reference. The dissolution test procedure is discussed in Chapter 3. All analysis was performed using the HPLC method described in Chapter 4.

The preliminary dissolution studies provided a projected prototype release profile summarized as follows:

The controlled release portion should exhibit an initial lag phase of four to five hours, followed by zero-order release until 12 hours. This would allow the immediate release portion of the dose to be eliminated sufficiently before release from the core begins, avoiding excessive release and consequent absorption of PSS, with possible toxicity and

associated adverse effects.

Based on these initial studies, it was decided to use a matrix formulation for the sustained release core, which could be coated with an insoluble coat to induce a lag phase and obtain zero-order release of PSS. Matrix formulations are relatively facile to manufacture and are suitable for scale-up procedures, and a coat can be added to further control or manipulate release characteristics.

2.4 FORMULATION OF THE MATRIX CORE

Pseudoephedrine sulfate is a highly water-soluble drug, and as such difficulties in sustaining its release for eight to twelve hours were expected. The initial matrix formulations were manufactured by direct compression, as this is the most facile manufacturing procedure. Hydroxypropyl methylcellulose (HPMC) was chosen as the matrix-forming polymer, and three different grades were evaluated (§ 2.4.1.1.2). Eudragit® RSPO, a polymethacrylate, was evaluated as a hydrophobic matrix-forming polymer. As the resultant delay in release from these direct compression matrices was not appropriate, the feasibility of wet granulation using hydrophobic polymers as the granulation fluids was evaluated. Klinger *et al* [142] found that for ethylcellulose matrices, a double granulation was necessary to achieve sustained release for water-soluble drugs, although a single granulation step was sufficient for poorly water-soluble drugs, and in light of this, both single and double granulations using ethylcellulose were manufactured. In addition, a single granulation with an insoluble polymethacrylate was formulated. These granulations were then tableted with or without other excipients. These formulations also exhibited some sustained release properties, but the release of PSS was not sustained for the desired length of time of at least eight hours.

As both the hydrophilic matrix and hydrophobic granulations did exhibit sustained release

characteristics, the two procedures were then combined, and granules using either ethylcellulose or polymethacrylates as the granulation fluid were manufactured and blended with HPMC and other excipients before compression. All formulations were assessed with respect to hardness, friability and weight uniformity. Summaries of these tests and the release profiles can be found in Appendix I.

2.4.1 DIRECT COMPRESSION MATRICES

2.4.1.1MATERIALS USED

2.4.1.1.1 Drug compound

Pseudoephedrine hydrochloride (BASF Knoll, Germany), which has very similar properties to PSS (§ 1.1.2) was used in the initial work-up batches. This was later replaced with pseudoephedrine sulfate (BASF Knoll, Germany).

2.4.1.1.2 Matrix forming materials

Various grades of hydroxypropyl methylcellulose, HPMC, (Methocel® K4M, K15M and K100M, Colorcon, Kent, UK) were evaluated as a hydrophilic matrix. HPMC in combination with ethylcellulose as a hydrophobic matrix-forming component was also evaluated. Eudragit® RSPO (Röhm, Germany) was also evaluated.

2.4.1.1.3 Excipients

Excipients used included Avicel® PH102 and PH200 (FMC, PA, USA), Emcocel® 90M (Mendell, NY, USA), Microquick® WC595, a dispersing agent, (FMC, PA, USA) and Magnesium stearate. All excipients used are listed in Appendix II, with the supplier and the purpose for which they were used.

2.4.1.2 METHOD OF MANUFACTURE

The method of manufacture is outlined in Figure 2.8. Powder blends containing pseudoephedrine hydrochloride, microcrystalline cellulose, with or without Microquick® and ethylcellulose, and HPMC (the matrix-forming excipient) were blended for 20 minutes in a V-blender (capacity of 1.5 L). The magnesium stearate was then added and blended with the powders for 3 minutes, after which the mixture was compressed using a Manesty F3 single-punch tablet press to a target hardness of 8-10 kp. The formulations for these batches are given in Table 2.1.

Figure 2.8 Flow diagram of Direct Compression Process Used

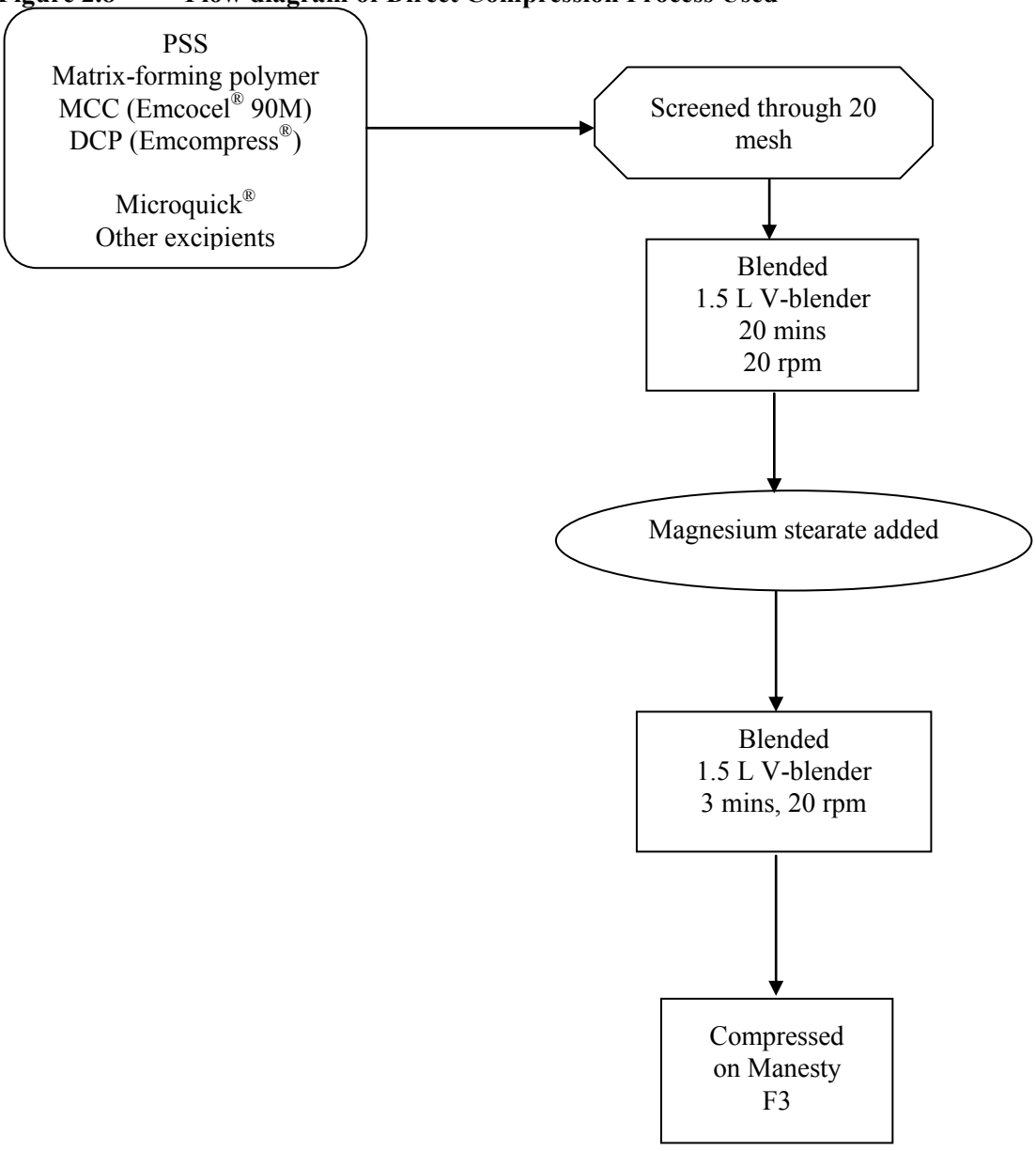


Table 2.1 Formulations for Direct Compression Tablets

Batch Number	PSS or PSH	Matrix Forming Polymer	Excipients
01026001	PSH	Methocel® K4M	Avicel® PH102 Avicel® PH200 Magnesium stearate
01028001	PSH	Methocel® K4M	Avicel® PH102 Avicel® PH200 Microquick® WC595 (5%) Magnesium stearate
01030001	PSH	Methocel® K4M	Avicel® PH102 Magnesium stearate
01031001	PSH	Methocel® K15M	Emcocel® 90M Magnesium stearate
01032001	PSH	Methocel® K100M	Emcocel® 90M Magnesium® stearate
01034001	PSH	Methocel® K4M	Emcocel® 90M Microquick® WC595 (5%) Magnesium stearate
01034002	PSH	Methocel® K4M	Emcocel® 90M Microquick® WC595 (10%) Magnesium stearate
01034003	PSH	Methocel® K4M	Emcocel® 90M Microquick® WC595 (15%) Magnesium stearate
01038001	PSH	Methocel® K100M	Emcocel® 90M Ethylcellulose N22 Magnesium stearate
02002002	PSS	Eudragit® RSPO	Emcocel® 90M Magnesium stearate

2.4.1.3 TABLET EVALUATION

Of the matrix materials evaluated, it was found that the high viscosity grade HPMC, Methocel K100M, gave the most promising release profiles, as may be expected as it has the highest molecular weight and viscosity, enabling greater water absorption with rapid formation of a strong gel layer [111]. The hydrophobic matrix was difficult to compress, and disintegrated during dissolution, and was thus unsuitable. Although sustained release characteristics were observed for some formulations, the release was not sustained for the desired length of time. This is in accordance with the literature, where direct compression matrices have been found to be subject to high variability [143] and unsuitable for the manufacture of sustained release dosage forms [144].

2.4.2 GRANULATIONS

2.4.2.1 MATERIALS USED

2.4.2.1.1 Drug Compound

Pseudoephedrine sulfate (BASF Knoll, Germany) was used as the drug candidate in all further developmental studies.

2.4.2.1.2 Granulating fluids

Eudragit® NE30D, an aqueous dispersion of a polymethacrylate (Röhm, Germany), and ethylcellulose were used as hydrophobic binders. Ethylcellulose (Hercules, VA, USA) was used as an extemporaneously prepared solution in either 90% ethanol or isopropyl alcohol, or as a commercially available aqueous suspension, Surelease® grade E-7-19010 (Colorcon, Kent, UK).

2.4.2.1.3 Excipients

All granules contained both dibasic calcium phosphate (DCP) as Emcompress® (Mendell, NY, USA) and microcrystalline cellulose (MCC) as Emcocel® 90M in addition to pseudoephedrine sulfate. Selected batches were blended with Emcocel® 90M and colloidal silica or Emcompress®, and all granules were blended with magnesium stearate as a lubricant prior to compression.

2.4.2.3 METHOD OF MANUFACTURE

An outline of the manufacturing process is given in Figure 2.9. The PSS, MCC and DCP were blended together in a Kenwood Major planetary mixer (Kenwood, UK). Granulating fluid was added gradually until a wet powder mass was formed. This was then screened using an oscillating granulator (Erweka, Germany) with a 20-mesh screen. The granules were then dried and re-screened. Certain batches were then re-granulated using the same

granulating fluid as before. The dried granules were then blended with any other excipients in the V-blender for 15 minutes, and subsequently with magnesium stearate for 3 minutes before compression on a Manesty F3 or B3B press with 1, 2 or 4 punches to a target hardness of 10- 12 kp. Table 2.2 describes the composition of each formulation and gives the press used. Some formulations contain the same excipients, although the proportions differ, as may be seen in Appendix I.

Figure 2.9 Flow diagram of the Wet Granulation Process

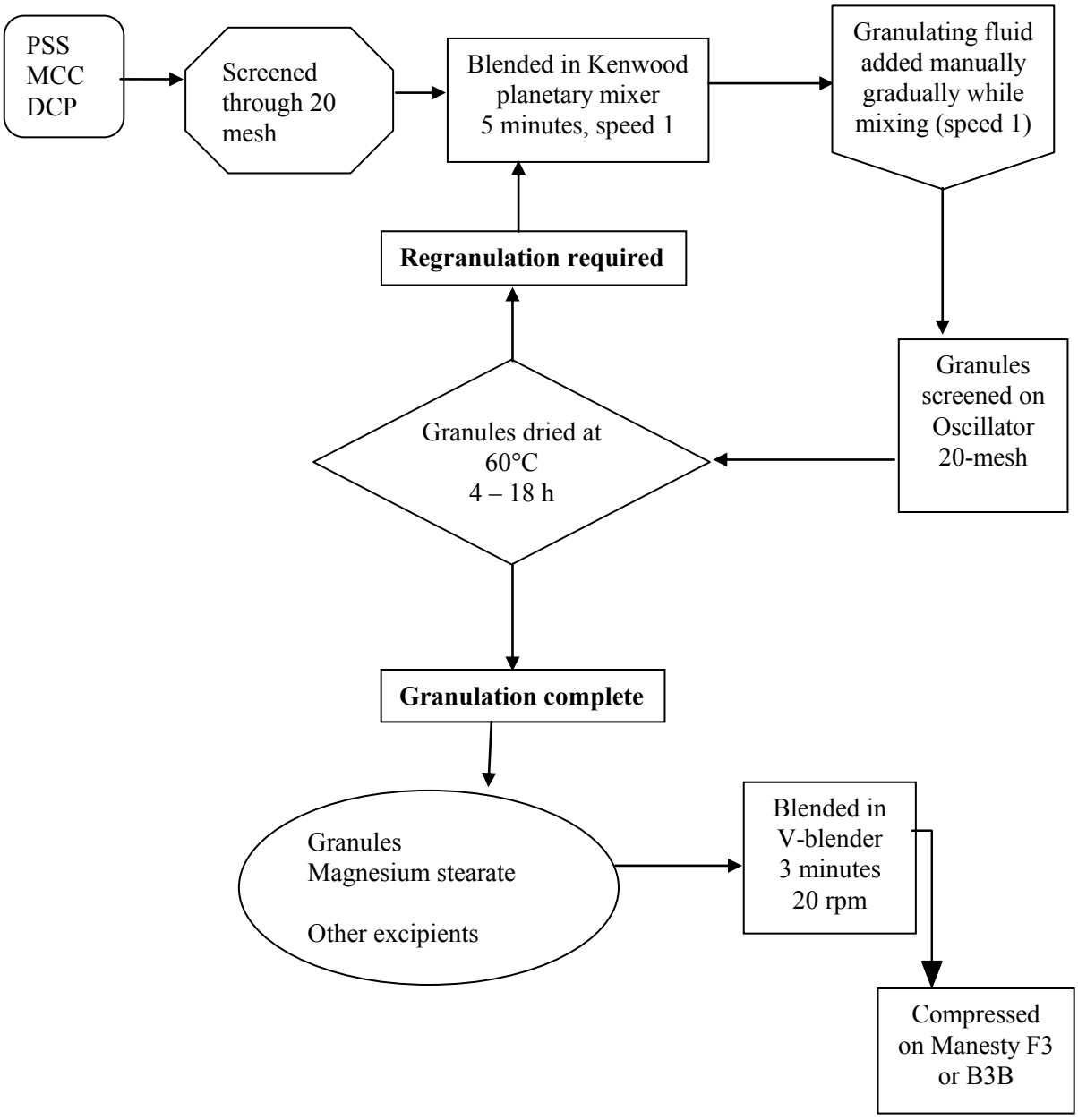


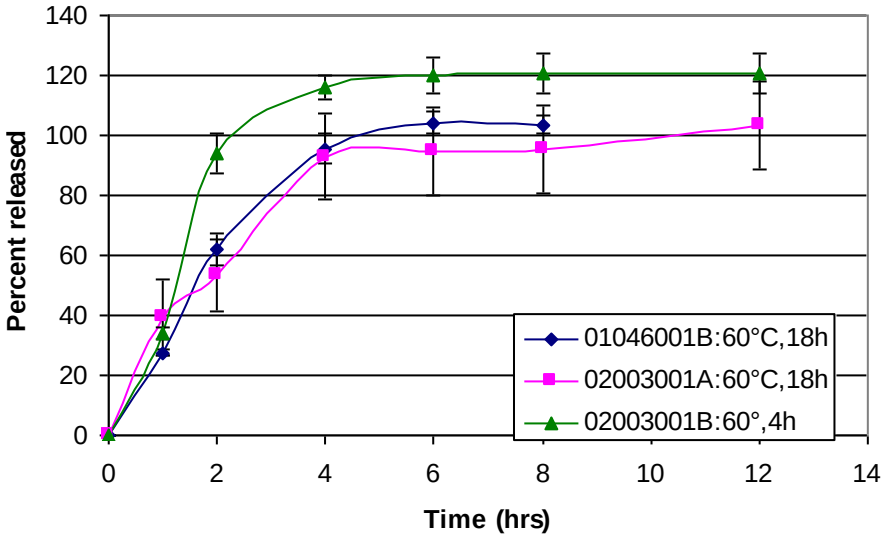
Table 2.2 Formulations of Hydrophobic Granulations

Batch Number	Granulation Fluid	Single/ Double granulation	Granulation excipients	Tableting excipients	Press Used
01040001	Ethylcellulose N7 in ethanol	Single	Emcocel® 90M Emcompress®	Magnesium stearate	Manesty F3
01041001	Ethylcellulose N22 in IPA	Single	Emcocel® 90M Emcompress®	Magnesium stearate	Manesty F3
01043001A	Ethylcellulose N7 in IPA	Single	Emcocel® 90M Emcompress®	Magnesium stearate	Manesty F3
01043001B	Ethylcellulose N7 in IPA	Double	Emcocel® 90M Emcompress®	Magnesium stearate	Manesty B3B
01044001	Ethylcellulose N7 in IPA	Double	Emcocel® 90M Emcompress®	Magnesium stearate	Manesty B3B
01046001A	Surelease®	Single	Emcocel® 90M Emcompress®	Emcompress® Magnesium stearate	Manesty B3B
01046001B	Surelease®	Double	Emcocel® 90M Emcompress®	Emcocel® 90M Colloidal Silica Magnesium stearate	Manesty B3B
01047001	Ethylcellulose N7 in IPA	Double	Emcocel® 90M Emcompress®	Emcocel® 90M Colloidal Silica Magnesium stearate	Manesty B3B
01047002	Ethylcellulose N7 in IPA	Double	Emcocel® 90M Emcompress®	Emcompress® Magnesium stearate	Manesty B3B
01048001	Eudragit® NE30D	Single	Emcocel® 90M Emcompress®	Emcocel® 90M Colloidal Silica Magnesium stearate	Manesty B3B
02003001	Surelease®	Double	Emcocel® 90M Emcompress®	Emcocel® 90M Colloidal Silica Magnesium stearate	Manesty B3B

2.4.2.4 TABLET EVALUATION

The most promising release rates were obtained with double granulations of ethylcellulose, both as a solution in IPA and as the aqueous dispersion, and a single granulation of Eudragit® NE30D, but the release rate was not sustained for the desired eight to twelve hours. In addition, the drying time was found to affect the release rate, with a tendency for the tablets to split if dried for long periods, as seen in Figure 2.10.

Figure 2.10 Effect of Drying Time on PSS Release from Granulations



2.4.3 GRANULE-CONTAINING MATRICES

2.4.3.1 MATERIALS USED

2.4.3.1.1 Granulation Fluids

Ethylcellulose and polymethacrylate dispersions were once again used as granulating fluids. Ethylcellulose was used in solution with IPA as a solvent or in dispersion in the form of Surelease® E-7-19010 (Colorcon, Kent, UK). Acetyl triethyl citrate (ATEC) was used as a hydrophobic plasticiser in two of the Surelease® formulations at 10% w/w of the solids content. The polymethacrylates used were Eudragit® NE30D and Eudragit® RS30D (Röhm, Germany). Eudragit® NE30D is a neutral dispersion of a polymer containing no reactive functional groups, which forms water-insoluble films with limited swelling characteristics. It is particularly suited to granulation processes, and does not require additional plasticisers [145]. Eudragit® RS30D forms water-insoluble films and exhibits limited swelling on contact with fluid, owing to the limited amount of quaternary groups present [145].

2.4.3.1.2 Granulation Excipients

Emcompress® and Emcocel® 90M were used in all granule formulations. In addition, Methocel® K4M was used as an excipient in two of the granule formulations granulated with Surelease® (one containing ATEC (01068001) and one containing no ATEC (01065001)) in order to impart a matrix-like quality to the individual granules and confer some degree of flexibility.

2.4.3.1.3 Matrix forming Excipients

Methocel® K100M was used as the matrix-forming polymer in all but one case as it showed the most promising release-retarding effect in the initial formulations. The remaining formulation used Eudragit® RSPO as the matrix forming polymer.

2.4.3.1.4 Tableting Excipients

All batches contained magnesium stearate as a lubricant and Emcocel® 90M as a tableting excipient. Two Surelease® batches, one containing ATEC and one without, were tableted with Emcompress® in addition to the Emcocel® 90M. The batches containing the Eudragits® and four Surelease® batches (01068002; 02001001; 02002001; 02001002) were tableted with colloidal silica in addition to the Emcocel® 90M, which was included to absorb excess moisture.

Table 2.3 describes the composition of the composite batches not selected for further study, while Table 2.4 describes the formulations for those batches placed on stability testing.

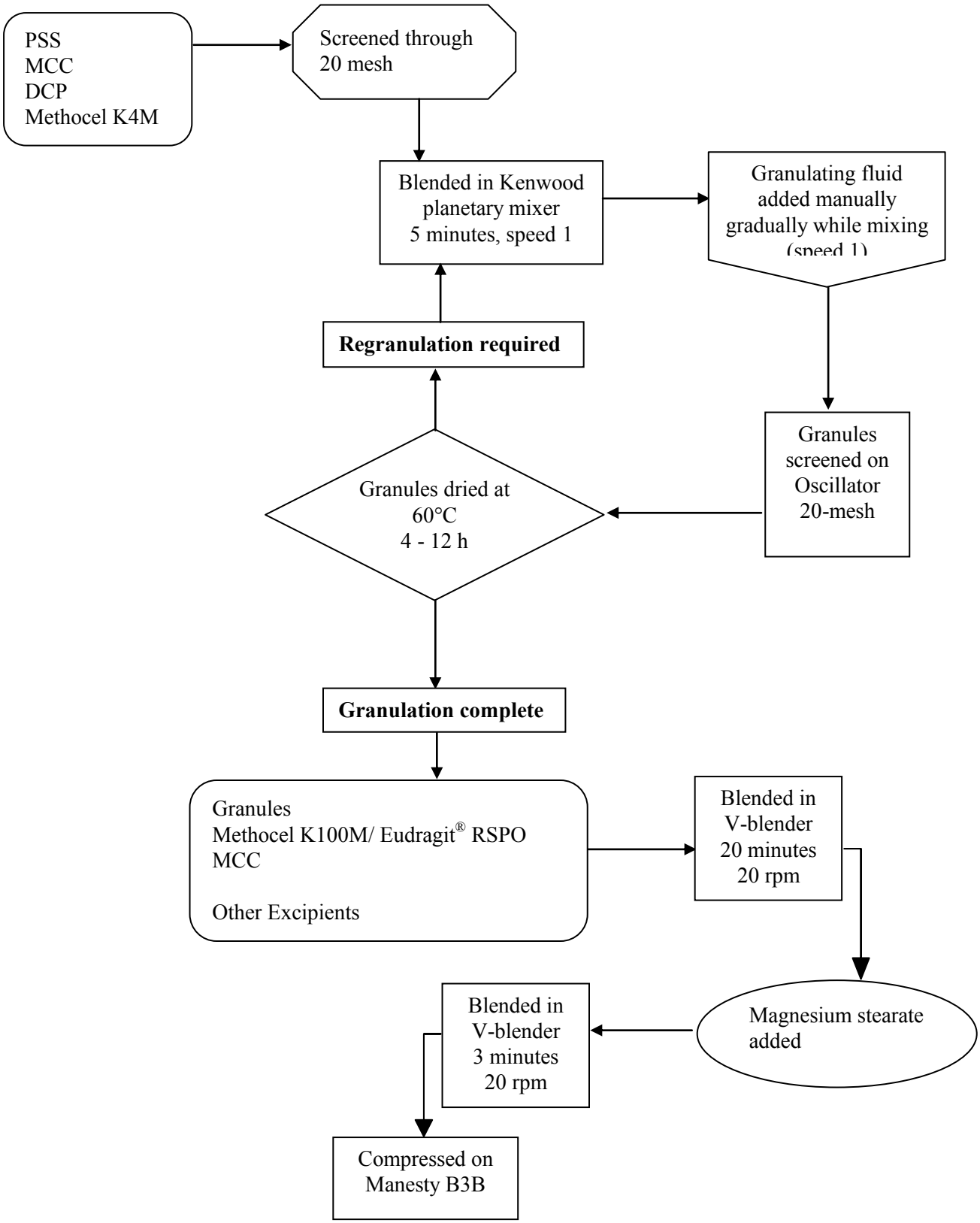
Table 2.3 Compositions of Composite Formulations

Batch Number	Granulation Fluid	Granulation Excipients	Tableting Excipients	Matrix forming polymer	Time for 50% release	Time for 100% release
01045001	Ethylcellulose N7 in IPA (double)	Emcompress® Emcocel® 90M	Emcocel® 90M Magnesium stearate	Methocel® K100M	2 h	8 h
01050001	Ethylcellulose N7 in IPA (double)	Emcompress® Emcocel® 90M	Emcocel 90M Magnesium stearate	Methocel® K100M	1.5 h	6 h
02001001	Surelease®	Emcompress® Emcocel® 90M	Emcocel® 90M Colloidal silica Magnesium stearate	Methocel® K100M	1 h	8 h
02001002	Surelease® (double)	Emcompress® Emcocel® 90M	Emcocel® 90M Colloidal silica Magnesium stearate	Methocel® K100M	3 h	12 h
02002001	Surelease®	Emcompress® Emcocel® 90M	Emcocel® 90M Colloidal silica Magnesium stearate	Eudragit® RSPO	0.5 h	2 h

2.4.3.2 METHOD OF MANUFACTURE

An outline of the manufacturing process is illustrated in Figure 2.11. All powders for granulation were blended in a Kenwood Major planetary mixer (Kenwood, UK) and the granulating fluid was added gradually. The wet powder mass was screened as described earlier and dried. The batches containing ethylcellulose in IPA were re-granulated, as was one of the batches containing Eudragit® NE30D and one of the batches containing Surelease®. After re-screening, the dried granules were blended with the tableting excipients for 15 minutes in a V-blender and then with the magnesium stearate for 3 minutes before compression on a Manesty B3B press to a target hardness of 10-12 kp.

Figure 2.11 Manufacturing Process for Composite Formulations



2.4.3.3 TABLET EVALUATION

The incorporation of the granules into the matrices provided a means to retard the release substantially, with all batches taking longer than 2 hours to release 50% of the pseudoephedrine sulfate content.

The incorporation of Emcompress® as an excipient prior to tableting appeared to have more effect on retarding the release rate than the use of Emcocel® 90M with Aerosil®, possibly as a result of its insoluble nature, as opposed to the hygroscopic nature and wicking capability of microcrystalline cellulose, which would promote tablet wetting. Microcrystalline cellulose has been found to give a significantly faster release rate then dibasic calcium phosphate when used in HPMC and other matrices, an effect more pronounced at low polymer content (and high excipient content) [124,146]. The inclusion of colloidal silica could also be expected to increase the release rate as colloidal silica is hygroscopic and swells, and can be used as a tablet disintegrant [147].

Three formulations were identified as promising and selected for initial stability assessments at ambient and accelerated conditions. Three additional batches with minor variations were placed on accelerated stability testing. These formulations are listed in Table 2.4, with the time taken to release 50 and 100% of the drug during initial tests. Batches 01046002, 01049001 and 01049002 were remanufactured on a larger scale with a slight decrease in PSS content. A peristaltic pump (Masterflex Easyload, Cole-Palmer Instrument C^{o}, IL, USA) was used to add the granulating fluid. Two of these remanufactured batches showed increased release rates relative to the initial batches of similar formulation. This is probably a result of the lower amount of granulating fluid used in the remanufacture, as the peristaltic pump in combination with the planetary mixer facilitated better mixing during fluid addition and consequently less fluid was used. Batch 01065001 was also placed on stability testing, although batches 01066001 and 01067001 were not, as the increase in release rate observed with these batches was

greater.

Table 2.4 Promising Formulations Selected for Further Study*

Batch Number	Granulation Fluid	Granulation Excipients	Tableting Excipients	Time for 50% release	Time for 100% release
01046001 *(01065001)*	Surelease®	Emcocel® 90M Emcompress® Methocel® K4M	Emcocel® 90M Emcompress® Magnesium Stearate	3.5 h (3 h)	10.3 h (12 h)
01049001 (*01066001)*	Eudragit® NE30D	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Silica	3 h (3 h)	11 h (9 h)
01049002 (*01067001*)	Eudragit® NE30D (double)	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Silica	5 h (1.5 h)	12 h (7 h)
01068001	Surelease® - 10% ATEC	Emcocel® 90M Emcompress® Methocel® K4M	Emcocel® 90M Emcompress® Magnesium Stearate	3.2 h	12 h
01068002	Surelease® - 10% ATEC	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Silica	3 h	12 h
01069001	Eudragit® RS30D	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Silica	2 h	9 h

* Batches denoted in italics refer to batches remanufactured on a larger scale with a decrease in PSS content.

2.5 DEVELOPMENT OF SELECTED PROTOTYPE

Based on the dissolution and stability studies, Batch 01046002 was selected for further development. The batch was remanufactured on a large scale as batch 02008001, as described above, with the use of the peristaltic pump for granulation. The production records for this batch and its subsequent derivations are contained in Appendix III. The formula for batches 01046002 and 02008001 is shown in Table 2.5.

Table 2.5 Formulae for Selected Developmental Batches

Excipient	Quantity (%w/w)
Pseudoephedrine sulfate	20
Methocel® K4M	10
Emcompress® (DCP)	40
Emcocel® 90M (MCC)	30
Surelease® (g suspension/g powder blend)	0.69g Batch 01046002 0.21g Batch 02008001
Granules	**69**
Methocel® K100M	15
Emcocel® 90M	5
Emcompress®	10
Magnesium stearate	1

As the batch was to be coated, it was compressed to a target hardness of 12-14 kp. The initial dissolution profile and results from the physical tests are shown in Figure 2.12. The manufacture of a larger batch appeared to improve weight and hardness uniformity. This may have been a function of the compression process, as four stations on the Manesty B3B as opposed to one were used. The pressure exerted on the upper punches is likely to have been more consistent than when only one punch is used.

Preliminary coating studies led to an investigation of the effects of small changes in the formulation, and three modified batches were manufactured, as described in Table 2.6. Batch records for these batches are contained in Appendix III. Batch 02010001 contained double the PSS content as compared with 02008001. This allowed the assessment of the effect of drug loading on the release profile, and the feasibility of manufacturing a once-daily dosage form. Batch 02009001 contained sodium chloride within the granules, while 02011001 contained sodium chloride within the matrix. Sodium chloride was included as an osmotic agent, and the effect of an osmotic agent on the release profile both before and after coating could therefore be assessed. In addition, the effect of the location of the osmotic agent could be determined.

Figure 2.12 Summary for Batch 02008001: Physical tests and Dissolution Profile

Date of Manufacture	25 May 2000
Press	Manesty B3B

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	527.44 ± 6.35	1.20
Hardness (kp)	13.58 ± 0.35	2.58

Friability	passed
Weight before (20 tablets)	11.41 g
Weight after 100 drops	11.41 g
Percent lost	0.0

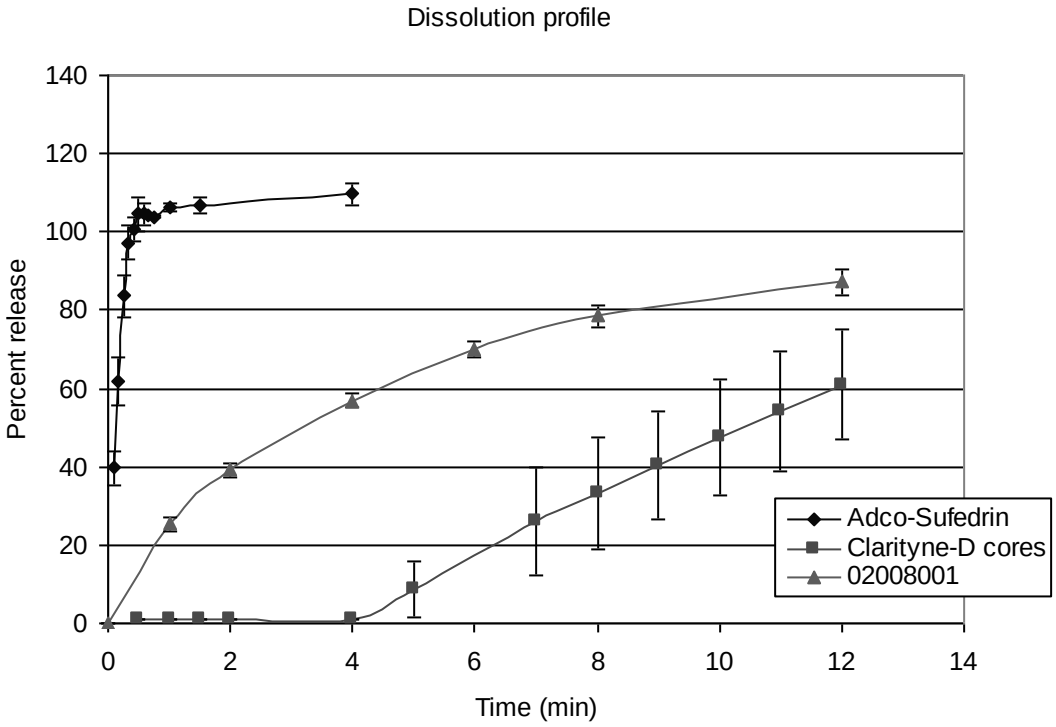
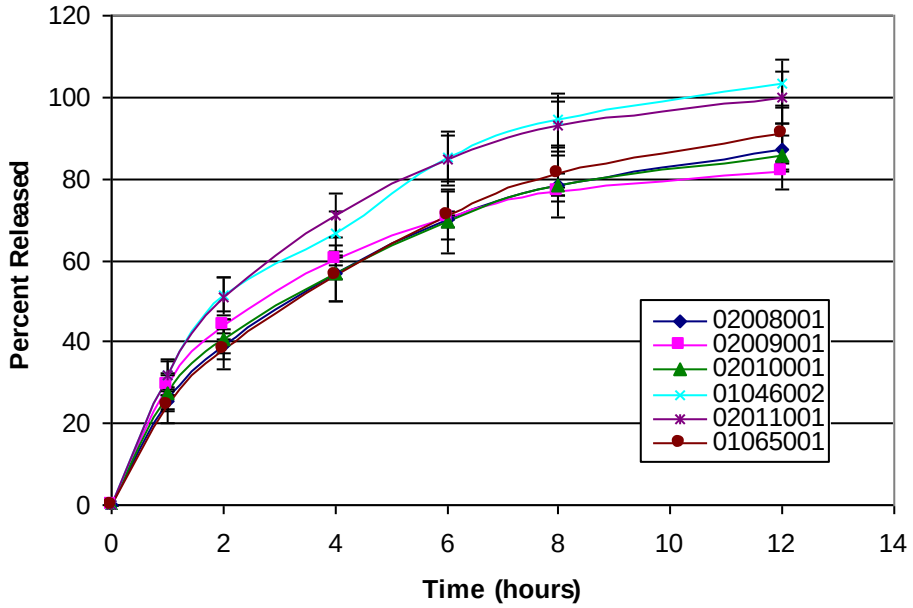


Table 2.6 Formulations of Modified Developmental Batches

Excipient	Quantity %			
	02008001	02010001	02009001	02011001
PSS	20	40	20	20
HPMC	10	10	10	10
MCC	30	30	35	30
DCP	40	20	30	40
Sodium chloride	0	0	5	0
Surelease® (g suspension/g powder blend)	0.21g	0.24g	0.23g	0.44g
Granules	**69**	**79**	**69**	**67**
HPMC	15	15	15	15
MCC	5	5	5	7
DCP	10	0	10	5
Sodium Chloride	0	0	0	5
Magnesium stearate	1	1	1	1

Batch 02008001 exhibited slower release of PSS than 01046002, the parent batch, despite a lower proportion of Surelease®. This is probably the result of a more efficient manufacturing process and greater tablet hardness. It is interesting to note that 02011001, the batch containing sodium chloride in the matrix, exhibited the most similar dissolution profile to 01046001, and had the most similar proportion of Surelease®. The dissolution profiles are illustrated in Figure 2.13.

Figure 2.13 Comparative Release Profiles for Developmental Batches



2.6 CONCLUSIONS

The release of PSS, a highly water-soluble drug, can be retarded by matrix type dosage forms. The greatest effect on release is obtained when PSS is granulated with a hydrophobic polymer and these granules incorporated into a hydrophilic matrix. Although direct compression matrices and ordinary granulations with hydrophobic polymers do alter the release of PSS, the effect is not adequate for the manufacture of twice-daily dosage forms. The use of hydrophobic polymethacrylates as the matrix-forming material appears to lead to compression problems, and limited or no sustained release effects. The higher viscosity grades of HPMC are more effective in retarding the release of PSS in matrix dosage forms. This is in line with published reports on the effects of polymer viscosity on drug release from hydrophilic matrices [111, 148].

CHAPTER 3
THE *IN VITRO* RELEASE OF PSEUDOEPHEDRINE SULFATE

3.1 INTRODUCTION

Dissolution testing is a means of assessing the rate at which the drug leaves the dosage form and is dissolved when the dosage form is placed in contact with a fluid. The pharmacological activity of a drug *in vivo* requires that it be released from the dosage form prior to absorption into the systemic circulation. In order for absorption to occur, the drug must be present in the dissolved state, and must therefore have been released from the dosage form. Sustained and controlled-release products seek to control the release of the drug from the dosage form in order to limit the amount of drug available for absorption at any time. The release characteristics of a dosage form *in vitro* are thus of paramount importance in predicting the behaviour of the dosage form *in vivo.*

In addition to providing the manufacturer with a rational basis on which to predict *in vivo* behaviour, dissolution testing is a valuable quality control tool, and provides a basis for dosage form improvement or assessing minor changes to the manufacturing process [149,150]. Dissolution testing is thus a vital tool with respect to dosage form development and assessment in the pharmaceutical industry.

3.1.1 VARIABLES AFFECTING DISSOLUTION

Numerous variables play a role in dissolution and the choice of optimal conditions will depend on the properties of the compound being tested [151]. It is desirable to select dissolution test conditions that are relevant to the *in vivo* condition in order to obtain meaningful results. For this reason, aqueous media are most frequently used, and may enable the establishment of *in vitro* - *in vivo* correlations (IVIVC), precluding the need for

costly and time-consuming clinical trials during the development of generic formulations.

An active ingredient will have an intrinsic dissolution rate dependent on its solubility and particle size [151,152]. The properties of the active may influence the choice of dissolution medium, particularly with respect to pH as many drugs are weak acids or bases, which are more soluble in basic or acidic solutions respectively [151]. The particle size of the drug present in the formulation is also an important parameter for consideration [152,153].

Once the drug has been incorporated into a dosage form, the rate at which the active is released into the external environment, and consequently the rate of dissolution, will be altered, often intentionally. In particular, the concentration and type of binder and lubricants used may significantly affect the rate of dissolution [153,154]. The presence of coatings, the compression force and the method chosen for granulation may also alter the rate of drug release from the formulation [153,154]. The size and shape of the dosage form [155], mechanical strength [156] and the compression force used [140] will also influence drug release.

The rate of drug release may also be affected by variables independent of the dosage form. The temperature of the dissolution media may alter the rate of dissolution [153,157], and dissolution experiments are usually carried out at temperatures representing the physiological temperatures they would be exposed to *in vivo*. In addition the pH of a medium, its ionic strength and the inclusion of other additives will affect the dissolution rate of an active, which is frequently dependent on the pH of the medium into which it dissolves [153,158,159,160]. The agitation to which the dosage form is subjected will also influence the rate of release, as will the hydrodynamics of the system, which will affect the formation of a stagnant boundary layer and sink conditions [150,157,161,162].

HPMC and other hydrophilic matrices have been found to exhibit dissolution behaviour

which varies with the apparatus selected [163] as the altered hydrodynamic conditions in Apparatus 3 may increase the erosion rate of the polymer, and increase the contribution of erosion to the release rate. High pH values together with high osmotic and ionic strength tend to reduce dissolution rates from HPMC matrices, while low pH values are associated with an increase in dissolution rates in media with high osmotic and ionic strength [164].

The dissolution profile obtained will also be influenced by the choice of time points for analysis [165]. It is necessary to ensure that sufficient time points are used to characterize the profile adequately. For characterization of controlled or extended release systems and for comparative purposes, at least 3 time points should be used [166], and when performing comparisons, only one time point after 85% release should be included [149,167]. It is important to realise that although the dissolution profile of a dosage form is useful in postulating *in vivo* behaviour, it does not always provide an accurate prediction, and unless an IVIVC has been established, dissolution results should not be assumed to represent *in vivo* performance [149]. Differences in behaviour between dosage forms are more pronounced *in vitro* than *in vivo* [150,168], but absorption *in vivo* is frequently slower than release *in vitro* [168].

3.1.2 DISSOLUTION APPARATUS

The USP has a number of official apparatus, some of which have specialized and limited application [7]. The two most commonly used apparatus are Apparatus 1, commonly known as the Basket, and Apparatus 2, commonly referred to as the paddle. These two apparatus are similar, but in Apparatus 1 the dosage form is placed in a basket attached to a rotating shaft, whereas for Apparatus 2 the dosage form is placed at the bottom of the dissolution vessel and a rotating paddle provides medium agitation. Apparatus 3, or the Bio-Dis, is used for extended-release applications [7]. Apparatus 4, or the flow-through, is mainly applicable to poorly water-soluble drugs [161]. The choice of apparatus may

influence the results of the dissolution test [157] and consequently this choice is critical. Other apparatus are listed, but were not of concern in the present study or are applicable to formulations designed for other routes of administration.

3.2 DISSOLUTION PROFILE COMPARISON

Comparisons of dissolution profiles from different batches of tablets, before and after a change in manufacturing processes or formulation, or pre-and post-storage provide useful information for dosage form development and optimisation. Any changes that occur need to be evaluated in terms of their relevance. Several methods have been used to compare the release profiles, including the Rescigno Index, ANOVA, model-independent similarity and difference factors and ratio tests. [149,165,167,169,170,171,172,173,174]. Currently the f_1 and f_2 equations developed by Moore and Flanner [167], which appear in the FDA guidance to industry for Scale-up and post-approval changes [149] are most frequently cited [165,166,172,173,174,175]. Most pair wise tests and model dependent methods have been reported to give meaningful results [173].

Dissolution profile similarity depends on the similarity between the profiles at each time point and the similarity between the overall profiles [174]. The similarity between overall profiles is particularly important for sustained release dosage forms, while a single time point comparison may be appropriate for immediate release formulations [172]. When comparing dissolution profiles it is important to ensure that the test conditions were identical [172] and that the sample times used are representative of the profile [170]. Both the Rescigno Index and the f_1 and f_2 equations are influenced by the choice of sample time points included in the comparison [165,169,172], as neither accounts for the time scale used. In addition, a similarity limit should be set [170]. This is frequently set at an arbitrary difference of not more than 10% between the profiles [170], which equates to an f_2 value of 50 or greater, as given by the FDA [149,167,170]. The number of units used in the test is another consideration, and for the use of the f_2 equation, 12 units are

recommended [149,172], although 3 units have been used in studies [176]. If wide variation is evident, a bootstrap analysis may be of value [172,174] with the f_2 equation, although some authors have found that an f_2 limit for similarity of not less than 50 conservative [165,173]. It is also possible to use weighting factors if desired [167,169]. Any bias in the method used for comparison should also be noted, for example the Rescigno Index gives more weight to the magnitude of any differences than to the duration for which the difference is observed [169], whereas the f_1 and f_2 equations allow for the use of a weighting factor [167], and the f_2 equation gives higher similarity values if more than one time point after 85% dissolution is included in the comparison [172]. Comparisons done in this study were performed using the f_1 and f_2 equations, as these are recommended by the FDA [149]. The two equations are given below.

$$f_1 = \{[\sum_{t=1}^{n} R_t - T_t]/[\sum_{t=1}^{n} R_t]\} \bullet 100 \qquad (3.1)$$

$$f_2 = 50 \bullet \log\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100 \qquad (3.2)$$

3.3 CHOICE OF APPARATUS

As PSS is highly water-soluble, Apparatus 4 is not suitable. Apparatus 1 and 2 are the most commonly used dissolution apparatus in the industry [132,157,162,177,178]. Apparatus 1, 2 and 3 were considered. Apparatus 1 is mainly utilised for floating dosage forms, and as the prototype formulations evaluated in this study were swellable matrices, Apparatus 1 was deemed unsuitable as the swelling could be restricted by the basket, and both Apparatus 1 and 2 are significantly affected by the rotation speed used [132,150, 162], and by the presence of air bubbles. In addition, there is limited scope for changing the dissolution media to simulate the range of pH values to which an extended release dosage form would be exposed during its passage through the GIT.

Apparatus 3 holds several advantages over Apparatus 1 and 2, particularly for evaluating sustained release dosage forms of a matrix type [178]. Hydrophilic matrices frequently adhere to the base of the dissolution vessel in Apparatus 2, resulting in a reduction of exposed surface area, altered hydrodynamics and a slower release rate [132,158,179]. The initial surface area exposed to the dissolution medium may influence the total amount released [180] and thus sticking may lead to erroneous results. Coning is a problem often encountered with Apparatus 2, where the tablet erodes predominantly at the surface nearer the paddle, while the bottom of the tablet remains unexposed to any hydrodynamic stress [178]. In addition, there is a stagnant region at the base of the vessels and below the paddles [132]. Apparatus 3 provides a dissolution testing system particularly suited to extended release dosage forms, as it allows the dosage form to be sequentially exposed to a variety of dissolution media [178]. In addition, the dosage form is contained in reciprocating tubes, which move in a vertical plane within the media, and this mechanical influence provides a better approximation of the *in vivo* condition. In addition, it gives an indication of the susceptibility of the dosage form to erosion by mechanical force, an important consideration for sustained release single entity dosage forms, which must remain intact throughout the release process [178]. Apparatus 3 is not affected by differences in the geometry of the dissolution vessels or by the presence of air bubbles [178].

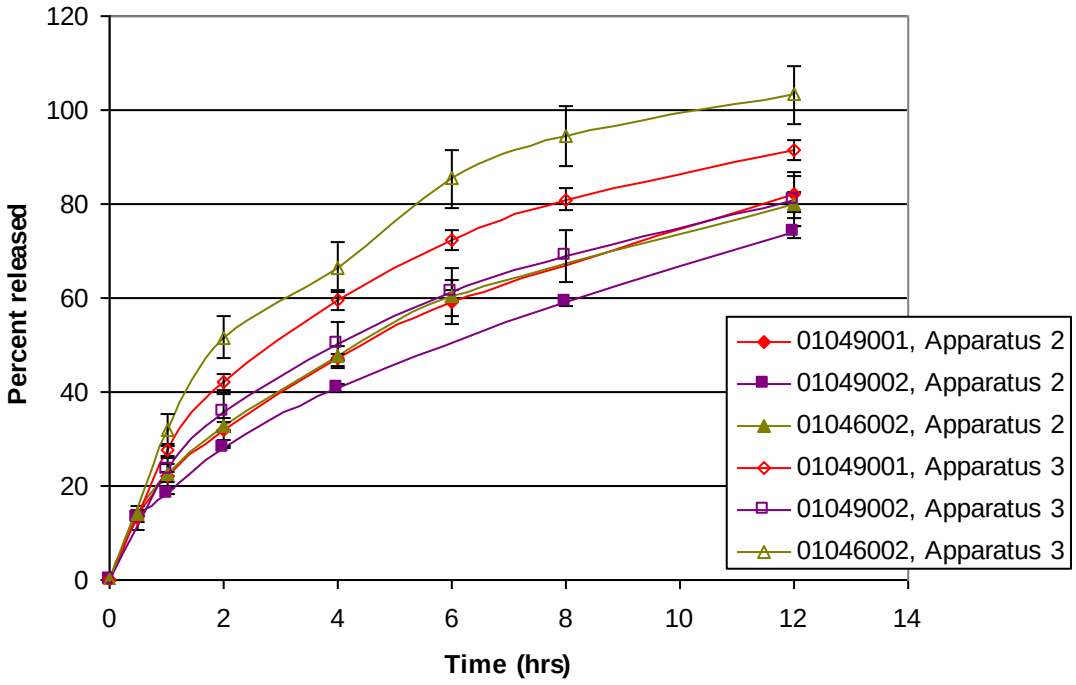
For the initial prototype batches, dissolution was assessed using both Apparatus 2 and 3. From these experiments, it was found that Apparatus 3 discriminated between the dosage forms more effectively than Apparatus 2 when the dissolution curves were compared [181]. The dissolution profiles for these batches are illustrated in Figure 3.1 and the results of the f_1 and f_2 equations used to compare them are shown in Table 3.1. In addition, it was felt that the ability of Apparatus 3 to provide exposure to a range of media was valuable.

Table 3.1 Effect of Dissolution Apparatus on f_1 and f_2 Results

Comparison	Apparatus 2		Apparatus 3	
	f_1	f_2	f_1	f_2
Batch D versus E	11.2	64	18.1	51.9
Batch D versus F	2	91.5	14.3	49.7
Batch E versus F	11.1	65.6	26	35.3

Acceptance criteria: $f_1 < 15$ and $f_2 > 50$ [149]

Figure 3.1 Effect of Dissolution Apparatus on the Release Profile of PSS



The use of Apparatus 3 did impose some limitations. The duration and pattern of the test had to be chosen from five pre-set programmes, and for the purposes of this study either a 12- or 22- hour duration was selected, with exposure times programmed as shown in Table 3.2. The second limitation was that sampling could only be performed when the dosage form had completed its cycle in the particular medium and moved to the next row. This limited the sampling intervals to six, but for an extended release dosage form this was not deemed to be critical.

Table 3.2 Exposure Times to the Various Dissolution Media in Apparatus 3

Row	Exposure Time (hours)	
	12 hour test	*22 hour test*
1	1	1
2	1	1
3	2	4
4	2	4
5	2	4
6	4	8

3.4 CHOICE OF DISSOLUTION TEST CONDITIONS

All tablet formulations were subjected to dissolution studies, and the dissolution rate profile compared to that of both Adco-Sufedrin®, an immediate release tablet containing pseudoephedrine hydrochloride, and Clarityne-D®, to assess the success of the prototype in sustaining the release of PSS.

The temperature chosen for the dissolution studies was 37° C, as this is representative of internal body temperature, to which a tablet would be exposed *in vivo*.

The initial conditions used were those specified for the dissolution of pseudoephedrine hydrochloride tablets in the USP, as listed in Table 3.3 [7].

Table 3.3 Dissolution Conditions for Pseudoephedrine Hydrochloride Tablets

Apparatus	2
Rotation Speed	50 rpm
Medium	900 mL water

All initial batches were assessed under these conditions. The USP specifies that not less than 75% should be released within 45 minutes for immediate release tablets, and this

specification was met for the Adco-Sufedrin® used.

However, when Clarityne-D® cores were assessed under these conditions, the release profile was much slower than expected. In order to ascertain whether this was a realistic result, whole tablets were evaluated in Apparatus 3, using the conditions given in Table 3.4 and a second set of cores was evaluated in Apparatus 2, but replacing the water with 0.1 molar phosphate buffer at pH 7.2.

Table 3.4 Dissolution Test Conditions in USP Apparatus 3

Parameter	**Setting**	
Medium	175 mL of 0.1 M phosphate buffer	
	Row	*pH*
	1	1.6
	2	3.4
	3	4.7
	4	6.8
	5	7.2
	6	7.2
Agitation	20 dips/min	
Temperature	37 ± 0.5°C	

The dissolution in Apparatus 3 was more rapid than that obtained in Apparatus 2, possibly because of the increased agitation, while the dissolution in Apparatus 2 using the buffer was more rapid than that using the water, as shown in Figure 3.2. A prototype formulation was then evaluated in both water and buffer in Apparatus 2. This formulation showed slightly slower dissolution in the buffer than in the water, as shown in Figure 3.3, but the difference was not as great as that of Clarityne-D®. It has been reported that the presence of buffer solutions or increased ionic strength may decrease polymer swelling in matrix systems and thus decrease the release rate [182]. Apparatus 2 was used for initial assessments using the phosphate buffer for the early prototype batches, despite the differences observed with Clarityne-D®. Three prototype batches showed promising results and were selected for further development. These batches were assessed in both

Apparatus 2 and 3, and Apparatus 3 was found to discriminate more effectively between the batches, as described in § 3.3. Apparatus 3 was used for all further dissolution studies, using the conditions shown in Table 3.4.

Figure 3.2 Effect of Dissolution Medium and Apparatus on the Release Profile of PSS from Clarityne-D®

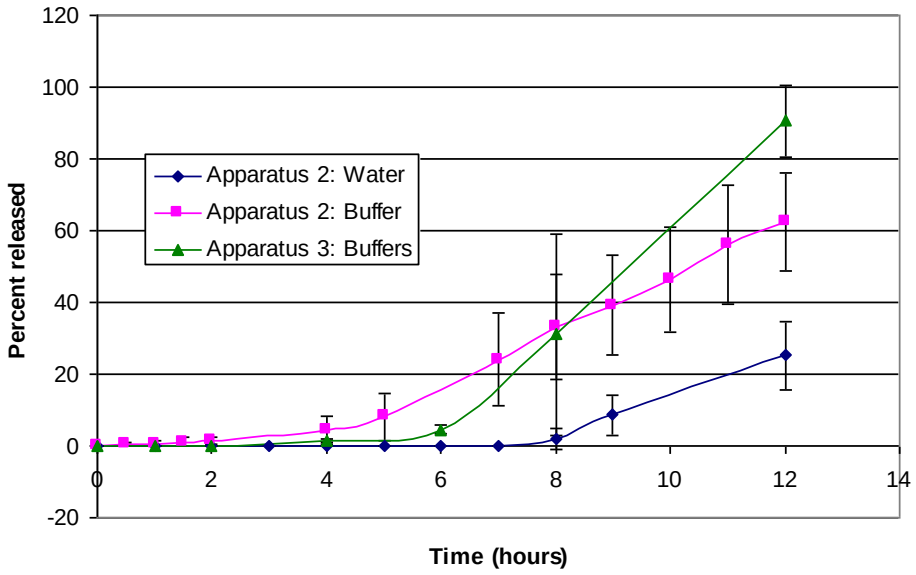
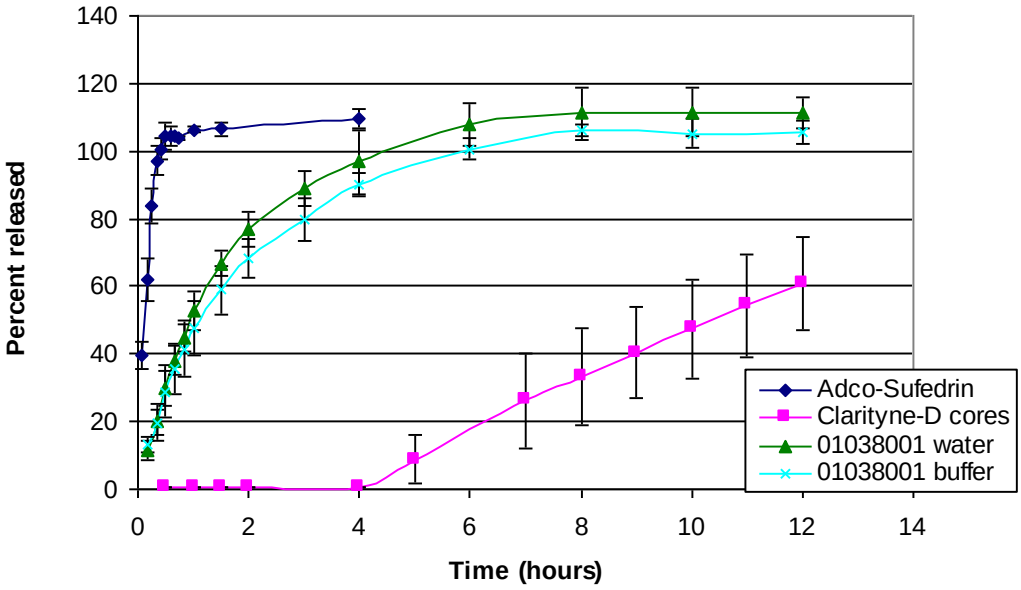


Figure 3.3 The Effect of Buffer on the Release of PSS from a Matrix Formulation



The pH values of the dissolution media were chosen to represent the range of pH values found in the GIT. As the dosage form is a single entity sustained release system, it is expected to release PSS throughout the GIT, and thus a system of this kind is most representative of the *in vivo* condition, which is desirable [183]. 20 dips/minute was chosen as being within the physiologically representative range of 10 – 30 dips/minute [163,178].

3.5 MATERIALS AND METHODS

Clarityne-D, batch 9JRPA6B, Demazin NS (batch JRPA), Polaratyne-D cores (batch 8JRPA58DA) (all Schering Plough, Johannesburg) and Adco-Sufedrin® (Adcock-Ingram, Johannesburg) were evaluated. Orthophosphoric acid (PAL Chemicals, South Africa) and sodium hydroxide (BDH, Poole, England) were used in the preparation of the dissolution media.

3.5.1 BUFFER PREPARATION

The buffers were prepared as follows:
31 mL of 85% orthophosphoric acid was pipetted into a 5 L A-grade volumetric flask and made up to volume with distilled water. The pH of the solutions were then adjusted to the required values using sodium hydroxide pellets, after which the solutions were filtered through a 0.44 μm filter (Millipore, MA, USA) and degassed under vacuum before use.

3.6 MECHANISMS OF RELEASE FROM HYDROPHILIC MATRICES

The fundamental release mechanisms from matrix systems have been discussed in § 2.1.2. As HPMC matrices were used in this study, factors affecting this type of dosage form are discussed in more detail here.

The release kinetics from HPMC matrices depend on the variables of polymer erosion, drug diffusion through the polymer, drug dissolution (and solubility) and polymer relaxation [184]. The interplay of these variables and the movement of the swelling, eroding and diffusion fronts confer complex release kinetics on HPMC matrix systems [163,184]. However, the diffusive process is usually predominant [184]. Hydrophilic polymers generally exhibit homogenous erosion throughout the matrix, leading to diffusion controlled kinetics rather than erosion controlled zero-order kinetics [185].

HPMC polymer swelling is influenced by the polymer structure and the drug properties [186], particularly the particle size and viscosity of the polymer [134,148,187], as these influence the water-absorbing capacity of the polymer, with more viscous, larger polymer molecules absorbing more water. The molecular weight of the polymer also appears to influence the diffusion coefficient of the drug [188]. The gel layer formed on swelling plays an active role in drug release by altering drug distribution in the polymer [184]. HPMC forms a strong gel layer [189], which is not readily eroded. Electrolytes may interact with the polymer in the gel layer region to form layers of different textures at the swelling interface [190]. The size, shape and degree of ionisation of the drug will influence its interactions with the polymer, and hence its diffusion rate through the gel layer, and mass transfer into the bulk fluid [156,191]. Excipients, such as microcrystalline cellulose and dibasic calcium phosphate, may also influence the release kinetics, by contributing to channel formation [102,130,148] or altering the rates of diffusion and erosion. MCC also absorbs water, enhancing water uptake by the matrix and promoting swelling and release [192]. PS has been found to alter the hydration characteristics and increase the resistance to erosion of HPMC in combination with PVP [193]. The dissolution rate of PS has been found to be relatively unaffected by excipients [194].

3.7 INITIAL STUDY: CLARITYNE-D®

3.7.1 ISOLATION OF THE CONTROLLED RELEASE CORE

In order to characterize the release profile of PSS from the controlled release portion of Clarityne-D®, it was necessary to remove the outer coating. This was achieved by placing the Clarityne-D® tablets in a humidity chamber consisting of a saturated solution of potassium nitrate, which gives a relative humidity of 93% at 22°C, for a total of 48 hours. This was the minimum period necessary to sufficiently soften the sugar coat to facilitate its removal whilst avoiding damage to the zein coat beneath.

After 24 hours in the chamber the outer coating had started to soften and was partially removed by wiping with paper towel. The tablet was replaced in the chamber for a further 24 hours after which the remainder of the coat was sufficiently softened to enable its removal. Six tablet cores (Clarityne-D, batch 9JRPA6B) were weighed and were found to have a mean weight of 347.30 ± 6.97 mg.

The impact of humidity on the release was not assessed at this point, as the period of exposure was short. However, stability assessments with respect to the effects of temperature and humidity were carried out on Clarityne-D®, and the results are discussed in Chapter 5.

3.7.2 DISSOLUTION PROCEDURE

The dissolution assessment was initially performed in USP Apparatus 2 (Pharmatest, PTWS, Germany), using the conditions listed in Table 3.3.

Aliquots of 2 mL were taken and filtered through a 10 μm sintered polyethylene filter before analysis using the validated HPLC method described in Chapter 4. The results

reveal a lag phase of 8 hours with less than 30% released in 12 hours. The release profile is illustrated in Figure 3.2. As Clarityne-D® is prescribed as a twice-daily regimen, this profile is unlikely to be representative of the *in vivo* condition, and a more suitable dissolution procedure was desirable. In view of this, the dissolution test was performed using USP Apparatus 3 (Bio-Dis, GB Caleva, England) under the conditions listed in Table 3.4 to assess whether the release of PSS from the zein coat is affected by pH. The results obtained using this method provided a more probable release pattern for PSS. After the initial immediate release of PSS there was a lag phase of approximately 5 hours before PSS was released from the core. The resulting profile is presented in Figure 3.2. The release of PSS from the core appeared to follow zero order kinetics, with 100% release after a total of 12 hours in the dissolution medium. It is apparent that the pH, presence of ions or increased agitation may affect the release of PSS from this formulation.

In order to assess whether this effect was dependent on the presence of ions or on agitation, the test was repeated in Apparatus 2 the Clarityne-D cores (batch 9JRPA6B), under the same conditions as described in Table 3.3, with the exception of the dissolution medium, which was altered to 900 mL deaerated 0.1 M phosphate buffer at pH 7.2. The results from this test show a 5-hour lag phase followed by a zero-order release profile. The r^2 value for the linear portion of the release profile was 0.999, and a total of 60% of the nominal PSS dose was released after 12 hours. This represents an increase of approximately two-fold when compared to the release of PSS in apparatus 2 using water, indicating that the presence of ions affects the release from the core.

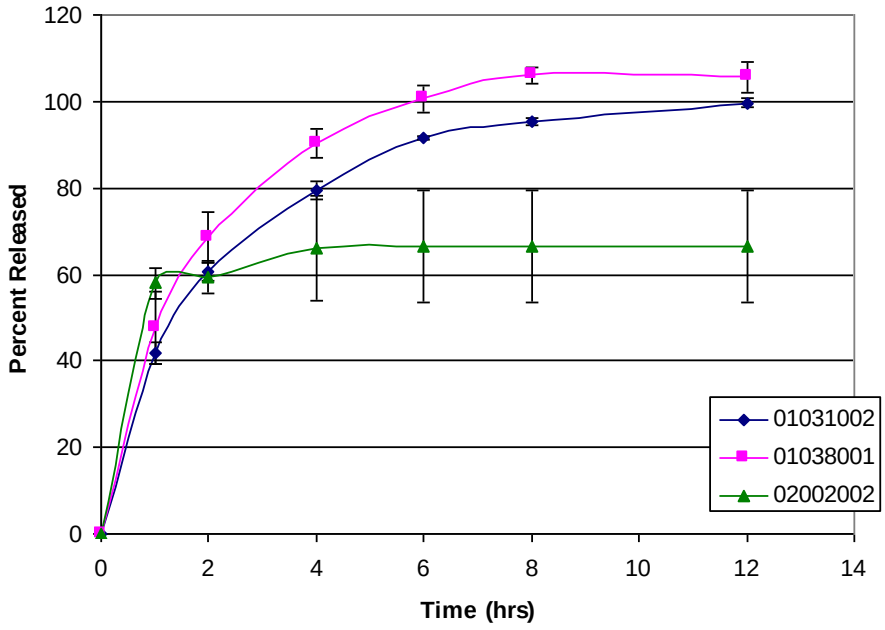
It was noticed that after 4-6 hours the zein coat around the core split along the tablet edges, but there was no alteration in release kinetics despite the loss of integrity. At the conclusion of the dissolution test the coat retained its shape, although split and was present as a ghost.

3.8 DISSOLUTION STUDIES: PROTOTYPE MATRICES

3.8.1 DIRECT COMPRESSION MATRICES

All initial prototype formulations were evaluated using Apparatus 2, with a dissolution medium of 0.1 M phosphate buffer (pH 7.2), and the profiles compared to those of Adco-Sufedrin® and Clarityne-D®. These profiles are depicted in the batch summaries in Appendix 1, and representative profiles are illustrated in Figure 3.4.

Figure 3.4 Typical Release Profiles for Direct Compression Matrices



The direct compression HPMC matrices retarded the release of PSS, but the effect was insufficient. A representative profile (batch 01032001) is illustrated in Figure 3.4. The inclusion of ethylcellulose, a hydrophobic polymer in the matrices (batch 01038001) increased the release rate, as depicted in Figure 3.4, possibly as a result of retarding the wetting and therefore the subsequent swelling rate of the HPMC, which would hinder the

formation of the gel layer. The hydrophobic matrix tablet (batch 02002002) manufactured by direct compression using an insoluble polymethacrylate proved to have no retarding effect, and the tablets laminated early during the dissolution process. This was unexpected, as some methacrylates and polymethacrylates have been used as inert matrices [195], resulting in first-order release profiles where the release rate was dependent on the amount of polymer used [196].

The initial matrix formulations exhibited predominantly diffusion-controlled release. The correlation coefficients for these direct compression matrices are listed in Table 3.5.

Table 3.5 Correlation Coefficients for Direct Compression Matrices

Batch Number	Correlation Coefficient (r^2)	Linearity	Time Period (hours)
01026001	0.992	Square root time	0 – 6
01028001	0.995	Square root time	0 – 4
01030001	0.977	Square root time	0 – 4
01031001	0.986	Square root time	0 – 4
01031002	0.981	Square root time	0 – 6
01034001	0.978	Square root time	0 – 8
01034002	0.981	Square root time	0 – 9
01034003	0.993	Square root time	0 – 6
01038001	0.960	Square root time	0 – 8
02002002	Disintegrated	-	-

The use of Avicel PH200, which has a larger particle size than Emcocel 90M or Avicel PH102 tended to increase the release rate as illustrated in Figure 3.5. This effect may be attributable to increased tablet porosity. The use of the dispersing agent increased the release rate with increasing concentration, although it appeared to delay release slightly at the 5% level, as illustrated in Figure 3.6.

Figure 3.5 The Effect of Microcrystalline cellulose Particle Size on PSS Release

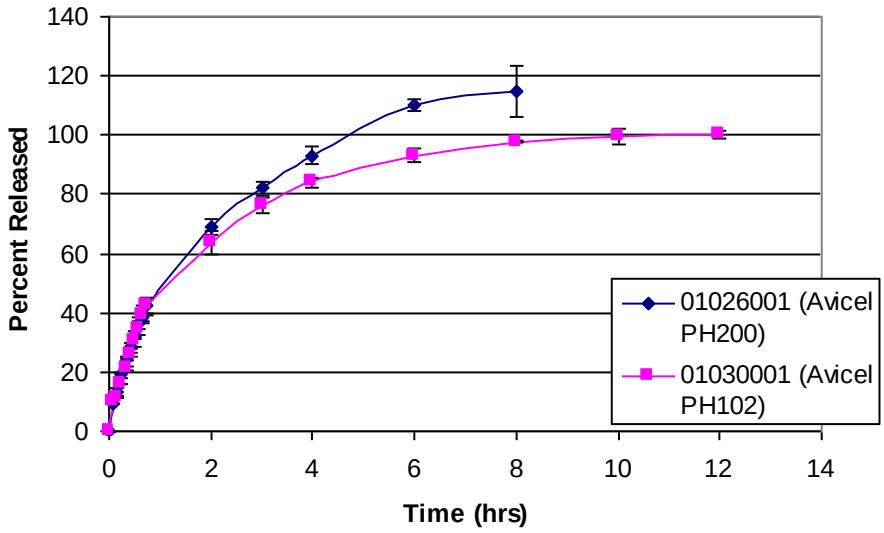
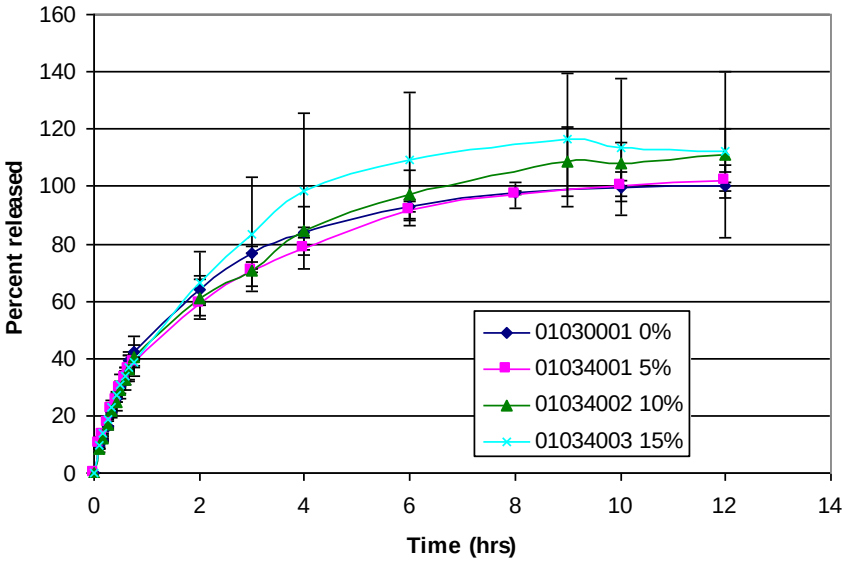


Figure 3.6 The Effect of a Dispersing Agent on PSS Release



3.8.2 GRANULATIONS

The granulations also exhibited some rate-retarding properties, but once again, the effect was not deemed suitable. The most promising release rates from granulations were obtained with double granulations of ethylcellulose, both as a solution in IPA and when used an aqueous dispersion, and a single granulation of Eudragit® NE30D. All of these formulations released 50% of the pseudoephedrine dose in 1.5 hours and 100% in 4 - 6 hours, as illustrated in Figure 3.7. The double granulations with ethylcellulose, tended to exhibit slower release than the single granulations, as previously reported in the literature [131]. The release profiles are illustrated in Figure 3.8.

Certain batches exhibited zero-order release, and others split early in the dissolution testing, with a resultant burst effect. Correlation coefficients are presented in Table 3.6. An example of the release profile for PSS from a split tablet is illustrated in Figure 3.9. This phenomenon was observed for batches containing Surelease® as the granulation fluid where neither HPMC nor acetyl triethylcitrate was present in the granulation. This suggests that additional plasticiser was required to maintain the integrity of the dosage form.

Table 3.6 Correlation Coefficient for Granulations

Batch Number	Correlation coefficient (r^2)	Linearity	Time Period (hours)
01040001	0.992	Time	0 – 2
01041001	0.953	Time	0 – 3
01043001A	0.982	Square root time	0 – 6
01043001B	0.999	Square root time	0 - 8
01044001	*	-	-
01046001A	*	-	-
01046001B	*	-	-
01047001	0.984	Square root time	0 – 4
01047002	0.991	Square root time	0 – 4
01048001	0.980	Time	0 – 4
02003001A	*	-	-
02003001B	*	-	-

* Tablets split, and therefore correlation coefficients could not be calculated.

Figure 3.7 Typical Release Profiles for Granulations

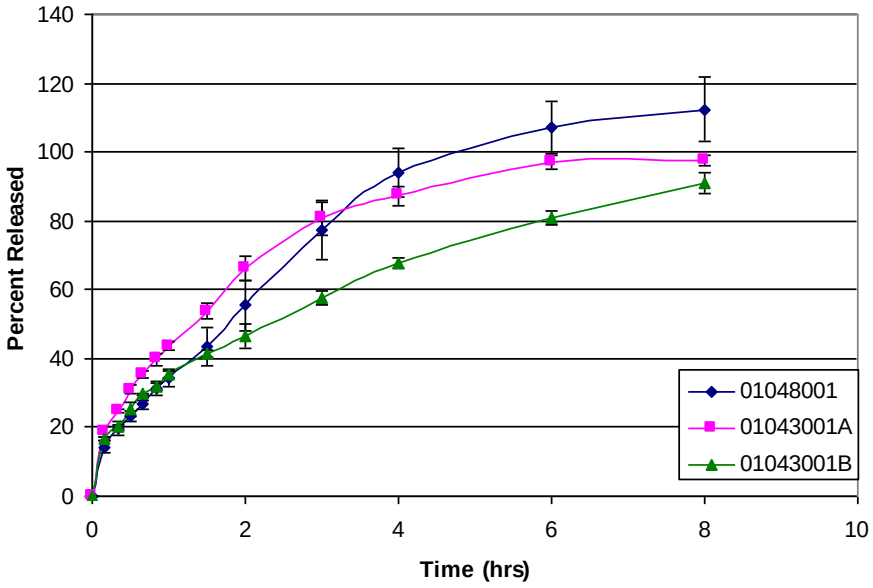


Figure 3.8 Release Profiles of Single versus Double Granulation with Ethylcellulose

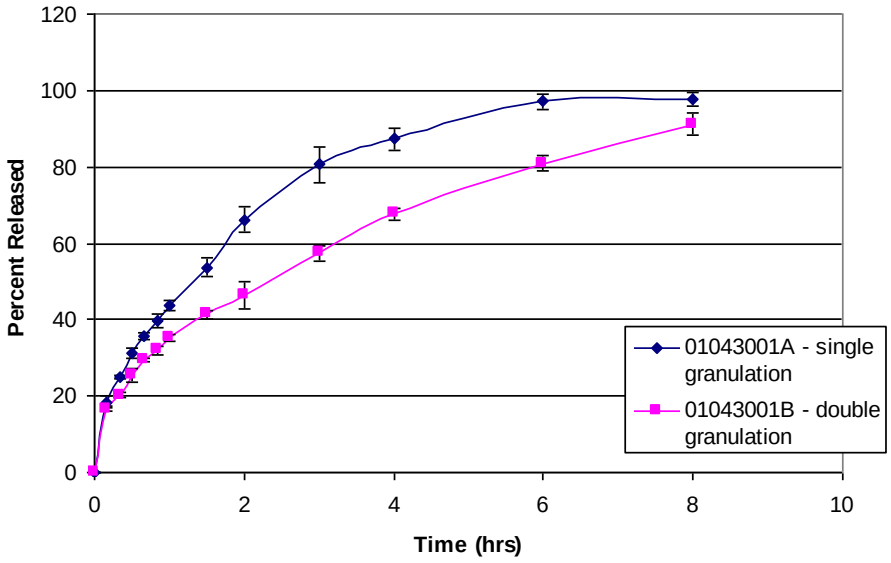
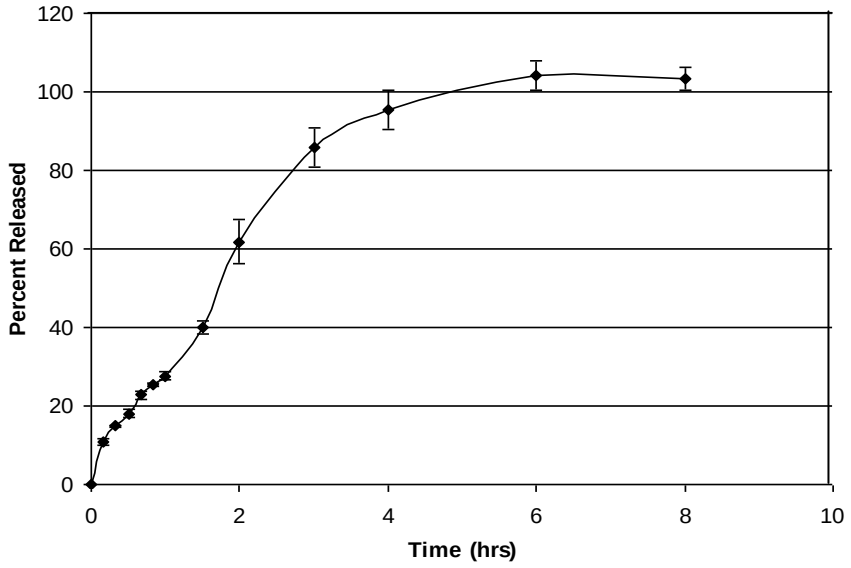


Figure 3.9 PSS Release Profile Obtained from Split Tablets (Batch 01046001B)



3.8.3 COMPOSITE FORMULATIONS

The formulations containing granules within a matrix exhibited the best sustained-release characteristics, as depicted in Figure 3.10. As expected, the release rate was retarded more effectively than for tablets produced by either direct compression or granulation alone. An increase in compression force and hence in tablet hardness decreased the dissolution rate. The release profiles are shown in Figure 3.11. The slower release rate is expected as the tablet would be less porous, and dissolution medium penetration into the dosage form would be retarded. Diffusion control was evident from the plots of percent released versus square root time, as depicted in Figure 3.12. The correlation coefficients are listed in Table 3.7.

Figure 3.10 Typical Release Profiles for All Formulation Types

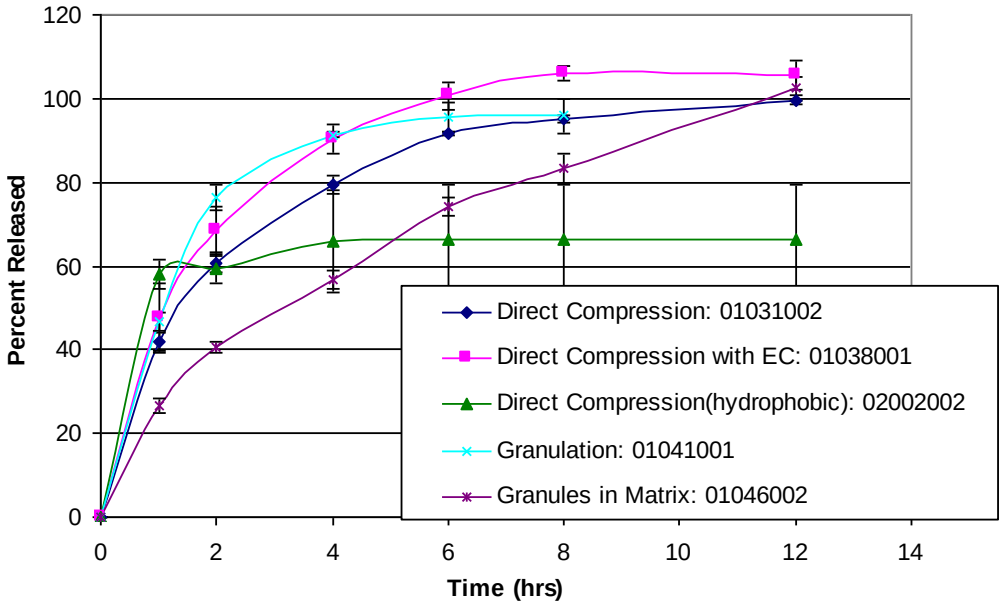


Figure 3.11 The Effect of Tablet Hardness on PSS Release from Composite Formulations

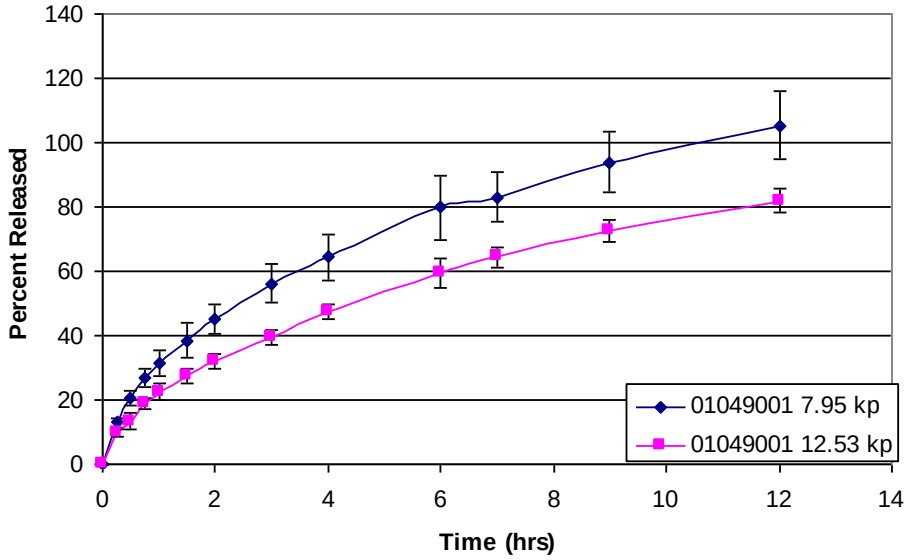


Table 3.7 Correlation Coefficients for Composite Batches

Batch Number	Correlation Coefficient (r^2)	Apparatus	Linearity	Time Period (hours)
01045001	0.991	2	Square root time	0 – 6
01050001	0.977	2	Square root time	0 – 6
02001001	0.990	3	Square root time	0 - 8
02001002	0.994	3	Square root time	0 – 12
02002001	*	3	-	-
01049001	0.987 0.998	3 2	Square root time	0 – 8 0 - 8
01066001	0.990	3	Square root time	0 – 8
01049002	0.996 0.999	3 2	Square root time	0 – 12 0 - 12
01067001	0.993	3	Square root time	0 – 8
01069001	0.992	3	Square root time	0 – 8
01046002	0.989 0.996	3 2	Square root time	0 – 8 0 - 12
01065001	0.997	3	Square root time	0 – 8
01068001	0.992	3	Square root time	0 – 8
01068002	0.999	3	Square root time	0 – 8
02008001	0.998	3	Square root time	0 - 8
02009001	0.992	3	Square root time	0 – 8
02010001	0.999	3	Square root time	0 – 8
02011001	0.994	3	Square root time	0 – 8

* Tablet disintegrated.

Apparatus 3 was used for the assessment of the release profiles of 01046002, the selected prototype. More rigorous assessments of the release profiles were performed on batch 01046002, 02008001, 02009001, 02010001 and 02011001, as the chosen formulations for development. Korsemeyer-Peppas plots were performed, as illustrated in Figure 3.13, and the values obtained for n, were approximately 0.5, and are listed in Table 3.8, indicating diffusion-controlled release [186,189].

Figure 3.12 Square-root Time plots for the Release Rate of PSS from Promising Formulations

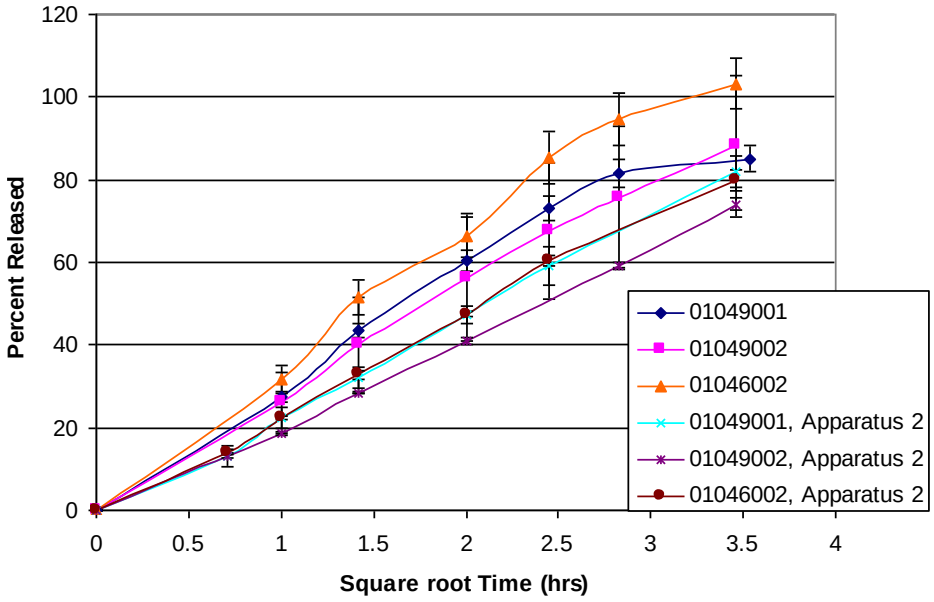


Figure 3.13 Korsemeyer-Peppas Plots for Developmental Batches

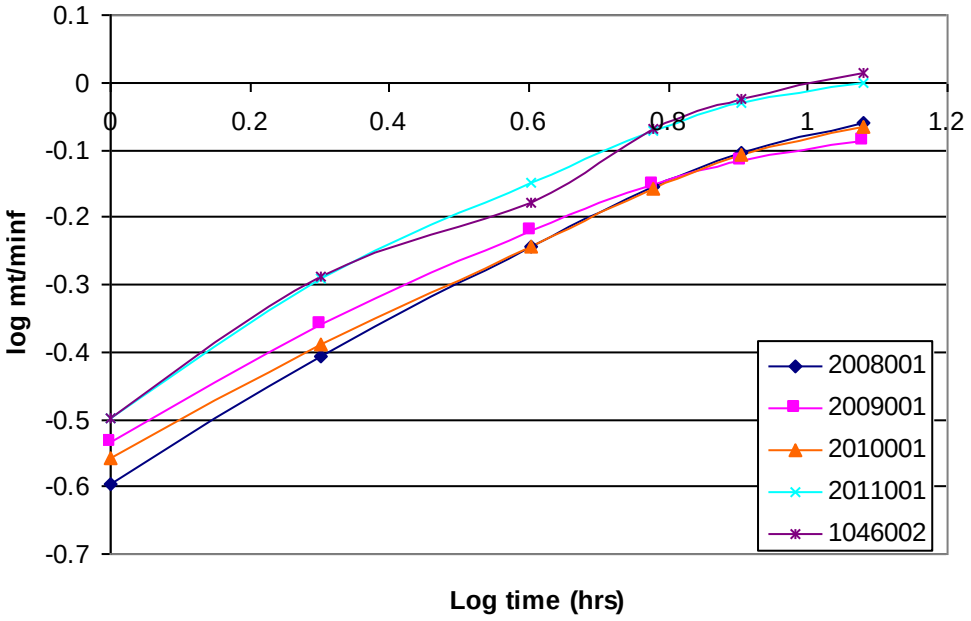


Table 3.8 Korsemeyer-Peppas 'n' values

Batch Number	Value for n	Time period (hours)
01046002	0.51	0 – 8
02008001	0.55	0 – 8
02010001	0.50	0 – 8
02009001	0.46	0 – 8
02011001	0.51	0 – 8

3.8.4 EFFECT OF DISSOLUTION VARIABLES

As agitation rate and ionic strength have been found to affect the dissolution rate from HPMC matrices [164] the effect of ionic strength and agitation rate on the release rate of PSS from Batch 020080001 in apparatus 3 was also assessed. The effect of ionic strength was assessed using phosphate buffers of 0.05 M, 0.1 M and 0.2 M. The effect of agitation rate was assessed using dip rates of 10, 20 and 30 dips per minute with the 0.1 M buffers. The control condition in both studies was 20 dips/minute in 0.1 M buffers, which was the condition used in the initial assessment of this batch. All other variables, including pH, were unaltered from the initial assessment (§3.4, Table 3.4). Six tablets were assessed for each condition.

The resulting release profiles are illustrated in Figures 3.14 and 3.15.

The curves obtained were compared using the f_1 and f_2 equations, and the results are listed in Table 3.9. All comparisons gave f_1 and f_2 values indicating curve similarity. This suggests that effect of buffer molarity and agitation rate on the rate of PSS release from this formulation is negligible.

Table 3.9 Results of Dissolution Profile Comparisons using the f_1 and f_2 Equations

Effect of Agitation Rate		
Conditions (dips/minute)	f_1	f_2
10 versus 20	12.0	53.8
10 versus 30	9.2	59.9
20 versus 30	4.1	72.4
Effect of Buffer Molarity		
0.05M versus 0.10M	4.7	73.0
0.05M versus 0.20M	7.2	63.7

0.10M versus 0.20M	11.5	54.2

Figure 3.14 The Effect of Buffer Molarity on PSS Release from Batch 02008001

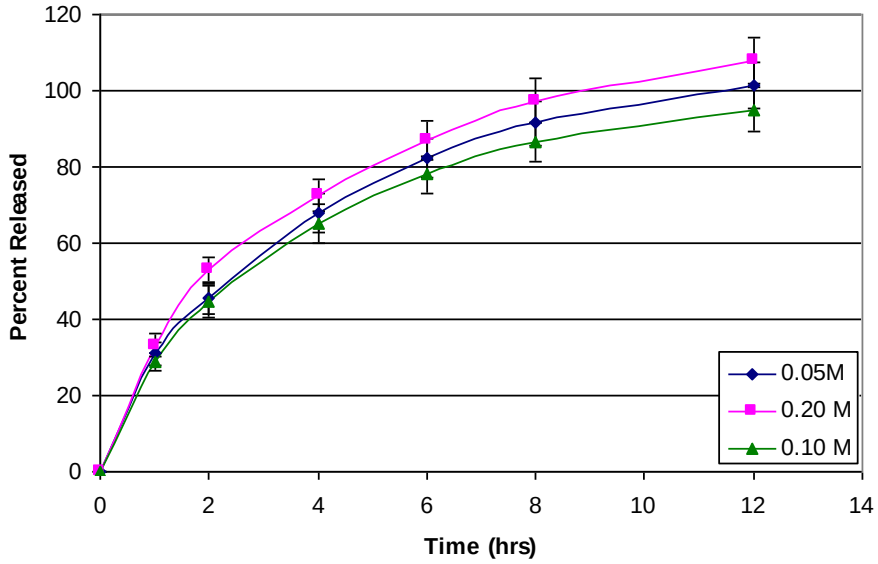
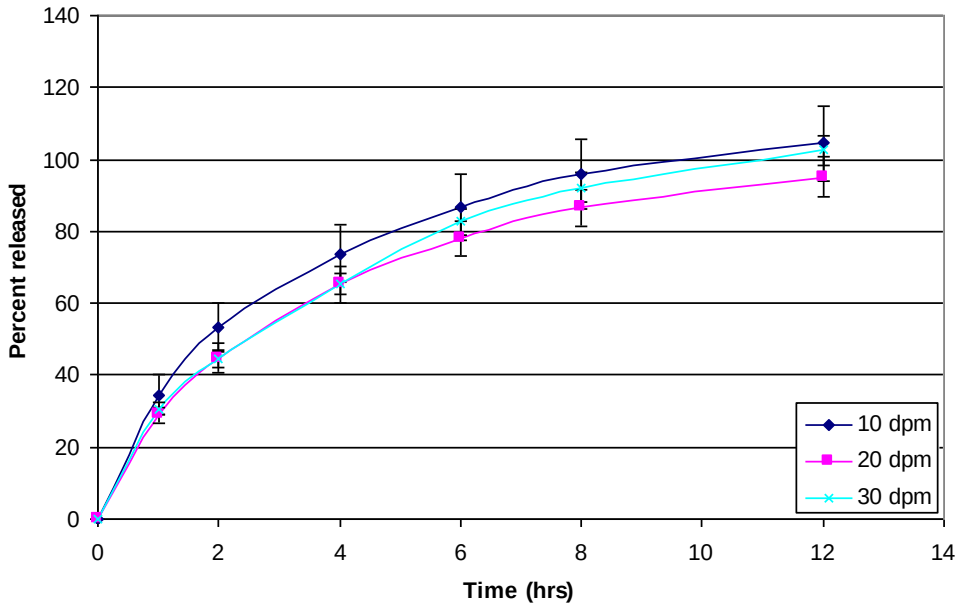


Figure 3.15 The Effect of Agitation Rate on PSS Release from Batch 02008001



It is interesting to note that the slowest agitation rate resulted in the fastest release rate of PSS. This result was unexpected, as higher agitation rates would be expected to produce

higher release rates by more effectively reducing any stagnant layer surrounding the tablet and promoting tablet erosion. In addition, the weakest buffer molarity gave the fastest release rate of PSS, followed by the highest buffer molarity. More rapid release of PSS is expected with the low molarity buffer, as reduced ionic strength is associated with increased release rates. However, the 0.20 M buffer would be expected to give the lowest release rates, an effect which is not observed. No trends are evident for either the effect of ionic strength or agitation rate, and there is no substantial alteration in the release rate of PSS from this formulation with changes to either of these variables within the ranges evaluated.

The resistance of the dosage form to the effect of buffer molarity may be a result of the inclusion of ethylcellulose in the granules before compression into the matrix. The inclusion of the granulation step for these formulations did alter the release as opposed to the direct compression of matrices (§ 3.8.3), and therefore must contribute to the sustained-release effect. This contribution may counteract any effect of ionic strength on the HPMC.

Apparatus 3 subjects the dosage form to greater mechanical agitation than apparatus 2, and has different hydrodynamic conditions. Dissolution rates are frequently affected by agitation rate (stirring speed) in apparatus 2, as any increase in stirring speed has an impact on the hydrodynamics of the system and reduces the stagnant layer at the surface of the tablet (§ 3.3). The alteration of the agitation rate in apparatus 3 does not substantially alter the hydrodynamics of the system, nor is there likely to be any effect on a stagnant layer, as even low agitation rates are likely to provide sufficient agitation to prevent the formation of a stagnant layer. The most likely effect of agitation rate in apparatus 3 is to increase the resistance of the dosage form to erosion. No increase in erosion was visually observed. PSS has been reported to alter the rate of hydration of hydroxypropyl methylcellulose (HPMC) and polyethelene glygol (PEG) matrices, thus increasing their resistance to erosion [193], and this is likely to be a contributing factor in this instance. In addition, the high viscosity of Methocel® K100M, the matrix-forming

polymer would result in a reduced susceptibility as compared to lower viscosity grades of HPMC.

3.9 CONCLUSIONS

The results of the dissolution testing facilitated the selection of a prototype tablet for further development. It was found that while neither granulations with hydrophobic fluids nor direct compression matrices retarded the release adequately, a satisfactory decrease in the release rate could be obtained with a formulation in which granules were incorporated into a hydrophilic matrix. A double granulation procedure appeared to retard drug release to a greater extent than a single granulation. Compression force also appeared to affect the release rate of PSS from the composite formulations.

The preliminary dissolution studies revealed the importance of the choice of dissolution apparatus and media. Apparatus 3 was found to be more appropriate for dissolution profile characterization of this type of dosage form, and provided better discrimination between formulations. The mechanism of release of PSS from these dosage forms was found to be diffusion-controlled in all cases in which release was sufficiently retarded. This has implications for sustained release formulation as diffusion control in matrix systems will not give zero-order release as the diffusional distance is constantly changing, as discussed in §2.1.2. These findings provided a basis for the choice of coating material for the rate-retarding coat, as discussed in § 6.3. The dosage form developed was robust with respect to alterations in the dissolution test conditions, which reduces the likelihood of variations in release arising from analytical variables during the dissolution test.

This study was essentially a feasibility study in order to select an appropriate core formulation for coating and to characterize the release profile for this type of dosage form. Further evaluation of larger batches was not performed in this study, but is necessary for

further development and optimisation of the dosage form.

CHAPTER 4
THE *IN VITRO* ANALYSIS OF PSEUDOEPHEDRINE SULFATE AND LORATADINE

4.1 PSEUDOEPHEDRINE SULFATE

4.1.1 METHOD DEVELOPMENT

4.1.1.1 INTRODUCTION

High Performance Liquid Chromatography (HPLC) is an effective and widely used analytical technique, which is frequently superior to gas chromatography for the analysis of ionic species [197]. Pseudoephedrine has previously been analysed using several techniques, including HPLC [9,198,199,200,201,202,203,204], gas-liquid chromatography [198,199], gas chromatography [200], radiolabel techniques [200], electro-chemical detection [201] and ultraviolet spectrophotometry [198].

Several methods for the analysis of pseudoephedrine by HPLC have been published, and a summary is listed in Table 4.1. Most of these methods pertain to the analysis of the hydrochloride salt, but as the properties of the sulfate are similar, the conditions for analysis are expected to be similar. Many of the published methods have been developed for the analysis of multiple components of various cold and flu preparations, and thus are not specifically optimised for the quantitation of pseudoephedrine. Some shortcomings of these methods include the use of extreme pH values (pH 3.5 [7,205] and 8.9 [9,200]), which may reduce column life [9,200,204], and the use of an ion-pairing reagent [199,206,207]. For the purpose of this investigation, a simple, rapid and sensitive method with a relatively simple and robust sample preparation was required to analyse dissolution, stability and content uniformity of batches. Previously published methods were used as a starting point for the development of a rapid and specific HPLC method

for pseudoephedrine sulfate in prototype dosage forms.

Table 4.1 HPLC Methods used for the Analysis of Pseudoephedrine

Reference	Stationary Phase	Mobile Phase	Wavelength	Internal standard
9	C_{18} /C_8	Ethanol: 0.4% ammonium acetate 85:15		-
9	C_{18}/C_8	Methanol: sodium dihydrogen phosphate: phosphoric acid 195:50:2		
9	Anion-exchange	0.02 M dibasic ammonium phosphate: dioxane 64:36		
9	Phenyl/C_{18}	Acetonitrile: 0.1% ammonium carbonate 9:1 pH = 8.9		
9	Phenyl/C_{18}	Acetonitrile: 1% ammonium carbonate 6:4, pH = 7.4		
202	C_8	Methanol: 25mM phosphate buffer 70:30, pH = 6.5	257nm	Lidocaine
203	C_{18}	Acetonitrile: methanol: 0.001M sodium nitrate 35:40:25 with 0.001M heptane sulfonic acid, pH = 5	254 nm	Chlorpromazine
207	C_{18}	Actonitrile: water: acetic 40:60:1, with 0.01M octane sulfonic acid sodium and 0.05 M potassium nitrate	265 nm	
206	Polybutadiene	Water: methanol: diammonium phosphate 25:75:0.1, pH = 8.5	257 nm	
199	C_{18}	Methanol: water: glacial acetic acid 45:55:2, with 0.005M octane sulfonic acid	254 nm	
201	C_{18}	Ethanol: 0.015M aqueous ammonium acetate 70:30	257 nm	
7	Phenyl	Water: acetonitrile: methanol: tetrahydrofuran 550:320:80:50, with 4.33g sodium lauryl sulfate and 1 mL phosphoric acid, pH 3.5	254 nm	Azoline hydrochloride
200	C_{18}	0.03 heptane sulfonic acid: acetonitrile 73:23, pH = 3	220 nm	
204	C_{18}	Water:acetonitrile:TEA: phosphoric acid 50:50:0.1:0.1	210 nm	Dextropropoxyphene
199	Cation exchange	Dibasic ammonium phosphate dioxane, water	Not given	Phenylpropanolamine

4.1.1.2 EXPERIMENTAL

4.1.1.2.1 Reagents

All reagents used were at least of analytical grade. Acetonitrile and methanol (HPLC grade, distilled in glass) were purchased from Burdick and Jackson (Michigan, USA). Phosphoric acid (85%, analytical grade) was obtained from PAL Chemicals and sodium hydroxide was purchased from BDH Chemicals (UK). All chemicals were used without further purification. Pseudoephedrine sulfate was donated by BASF Knoll (Germany). Purified water was obtained using a Milli-Ro®-15 water purification system (Millipore, Bedford, USA). This system consists of a Super-C® carbon cartridge, two Ion-X® ion exchange cartridges and an Organex-Q® cartridge in series. The water was filtered through a 0.22µm Millipak® filter stack before use.

4.1.1.2.2 High Performance Liquid Chromatography (HPLC) System

System A

The modular HPLC system comprised a P100 pump (Thermo Separation Products, USA), a WISP 710B autosampler (Waters Associates, USA), a Prodigy® (150mm x 4.6 mm i.d.) 5 µm column (Phenomenex, USA), a SSI 500 UV-Vis variable wavelength detector (Linear Instruments), a Spectrum amplifier and a Perkin-Elmer 561 chart recorder (Hitachi, Japan).

System B

An independent second system (system B) was used to assess the ruggedness of the method. This system consisted of a second P100 pump and an AS1000 auto sampler with a 20 µL fixed loop injection, both from Thermo Separation products (Florida, USA), a Prodigy® 5 µm column (Phenomenex, California, USA), a Spectrochrom UV-100 UV detector (Linear Instruments Corporation) and a Perkin-Elmer 561 chart recorder (Hitachi, Japan).

The differences between the systems apart from the apparatus included a variable volume injection system (system A), with the injection volume set at 10 µL, while system B used a 20 µL fixed loop injector. Analytical signal enhancement was achieved using an amplifier (system A) with the UV detector sensitivity set at 0.01 absorbance units full scale (AUFS) and the amplifier at a gain of 2. System B did not include an amplifier and consequently the AUFS was set to 0.02.

4.1.1.2.3 Detection

Detection by ultra-violet absorption is a convenient and effective technique that is readily combined with HPLC. It is the most commonly described method for the analysis of pseudoephedrine in the literature [198,199,200,201,202,203,204,206]. Pseudoephedrine exhibits absorption maxima at 251, 257 and 263nm [201](§ 1.2.10), with maximal absorption at 257nm. Published methods for the analysis of pseudoephedrine vary considerably, from 210 to 265 nm, but many of these methods are optimised for the detection of multiple compounds. In order to minimize interference from commonly used HPLC solvents and natural compounds, it is desirable to use the longer wavelengths. The ability of the UV source to generate the required wavelength is important, particularly if impurities related to the analyte are present, and any error in wavelength may not be consistent over the range of the detector [208].

4.1.1.2.4 Column Selection

The choice of column will influence the retention time of the compound of interest and the performance of the system as the separation in HPLC depends on the interaction of the solute with the stationary phase and the partitioning between the stationary and the mobile phases [197]. Column packings are usually primarily composed of silica, which can be present in one of several forms, although ion exchange columns may be packed with polymeric gels. Large, porous silica beads exhibit slow mass transfer properties and are not frequently used. Pellicular packings, where porous beads of silica are embedded in layers on an inert support surface are most commonly used for guard columns or ion-

exchange columns, as they have a limited sample capacity as the surface area is reduced. The most commonly used form of silica is spherical or irregular nanoparticles, either 5 or 10 μm in diameter, which is referred to as multiparticulate packing, and which gives columns with high efficiency and a large surface area available for interaction with the analyte [197]. Multiparticulate silica can be used as a substrate for bonded phases, support for stationary liquid phases or for adsorbent chromatography. Bonded phase columns are the most commonly used, and these can be polar or non-polar. Non-polar bonded phases are used for reversed-phase HPLC, with polar solvents such as water, buffers, methanol and acetonitrile, while polar bonded phases are used in normal phase HPLC, usually with non-polar mobile phases. Non-polar bonded silica is frequently used as it is extremely stable, and octadecasilane (C_{18}) is the most common bonded phase.

The choice of the bonded phase will depend on the properties of the analyte. As the separations obtained in HPLC depend on the interactions between the analyte, the stationary (bonded) phase and the mobile phases, the polarity of all three must be considered. Polar compounds are readily analysed by reversed-phase HPLC, and their retention time will depend on the degree to which they interact with the stationary phase, which is influenced by molecular weight, ionisable groups and solubility of the analyte. Compounds with highly ionisable groups may require the use of ion-exchange columns, but compounds with weakly ionisable groups can usually be analysed using reversed-phase HPLC using ion-suppression or ion-pairing techniques. PSS is a relatively polar weak base, and can be analysed using ion-suppression or ion pairing with a reversed phase column.

The most commonly used columns reported for the analysis of PSH are octadecasilyl (C_{18}) [9,198,200,201,203,204,207] and octylsilane (C_8) [9,202], and all columns used were either reversed-phase HPLC columns or ion-exchange columns.

Reversed phase HPLC allows the separation of compounds with a wide range of

polarities, and exhibits better reproducibility than normal phase chromatography [197]. The mobile phases used are also frequently less hazardous, consisting primarily of aqueous buffers with small amounts of organic modifiers rather than comprising primarily organic solvents. The limitations of reversed phase HPLC include the potential for the bonded phase to be hydrolysed if mobile phases with pH values greater than 8 are used, and interactions of unreacted silanols with the analyte, particularly with basic compounds such as PSS [205]. Despite these limitations, reversed-phase HPLC is a versatile and widely used analytical technique and was selected for the analysis of PSS and PSH.

4.1.1.2.5 Mobile Phase Selection

The composition of the mobile phase will have a profound effect on the retention time of any analyte and the selectivity of a method. The mobile phase is used to transport the analyte through the column, and the relative affinity of the analyte for the mobile phase versus the stationary phase will determine the extent to which it is retained on the column [197,205]. In addition to any interactions with the analyte, the mobile phase may also interact with the stationary phase. The relative extent of these three-way interactions will determine the efficiency and efficacy of the method used. The flexibility of HPLC, which allows the analyst to alter the mobile and stationary phases in order to manipulate these interactions, makes HPLC a powerful analytical and separation technique. If the analyte is highly soluble in the mobile phase, it will undergo limited partitioning onto the stationary phase, and retention times will be short. Conversely, if the analyte displays limited solubility in the mobile phase, it will partition readily into the stationary phase and thus retention time will be long. Changes in the pH of the mobile phase of reversed-phase systems will modify the retention time of weak acids and bases, as the unionised species is retained longer, being less polar. The use of organic modifiers in predominantly aqueous mobile phases will also alter the retention characteristics of the compound. The choice and amount of modifier required will depend on the properties of the analyte and the stationary phase.

The use of a mobile phase that interacts with the selected stationary phase can alter the properties or integrity of the stationary phase. This precludes or limits the use of mobile phases with pH values outside the range of 3 – 9, as hydrolysis of the bonded phase or dissolution of silica may occur. In addition, the mobile phase must not interfere with the detection of the analyte. This is of particular importance when using UV detection, as many solvents exhibit some degree of UV absorbance, usually at lower wavelengths. In general, wavelengths above 210 nm can be used with limited interference. It is important that the UV cut-off values for the solvents used are known and evaluated.

The effect of the mobile phase on the HPLC system must also be considered. All mobile phases should be filtered through at least a 2 μm filter prior to use to prevent build up of particulate matter on the column and subsequent blockages [197]. In addition, all mobile phases should be degassed to ensure that dissolved air is removed. The presence of air may interfere with detection and also, if trapped in the pump, with flow rate and pressure, causing untoward pressure fluctuations, which will ultimately affect performance. Dissolved carbon dioxide may alter the pH, while dissolved nitrogen may cause baseline drift and aberrant peaks [209]. All solvents used should be clean and chemically pure to ensure that there is no build up of impurities on the column or in the system, and that no impurities interfere with the analysis. HPLC grade solvents with low UV cut-offs are available, and were used in these studies. The viscosity of the solvent used is also important as this can influence column backpressure. More viscous solvents and solvent combinations generally give rise to higher back pressures. As the column ages and particles accumulate at the inlet, the maximum pressure the system can withstand may be reached, and the column life will be reduced. High concentrations of buffer salts are also undesirable as there is a potential for precipitation with subsequent damage to pump heads, seals and pistons and blockages with consequent increases in back pressure.

The initial mobile phases used were based on those published or were modifications of

published mobile phases. The analytical column used was a C_{18} column, as described in published methods. As the methods published are not optimised for PSS, manipulations were required to achieve a rapid and effective method, and an original method was developed. The mobile phases used during development and the corresponding retention times of PSS are reported in Table 4.2.

Table 4.2 The Effect of Mobile Phase on PSS Retention Time

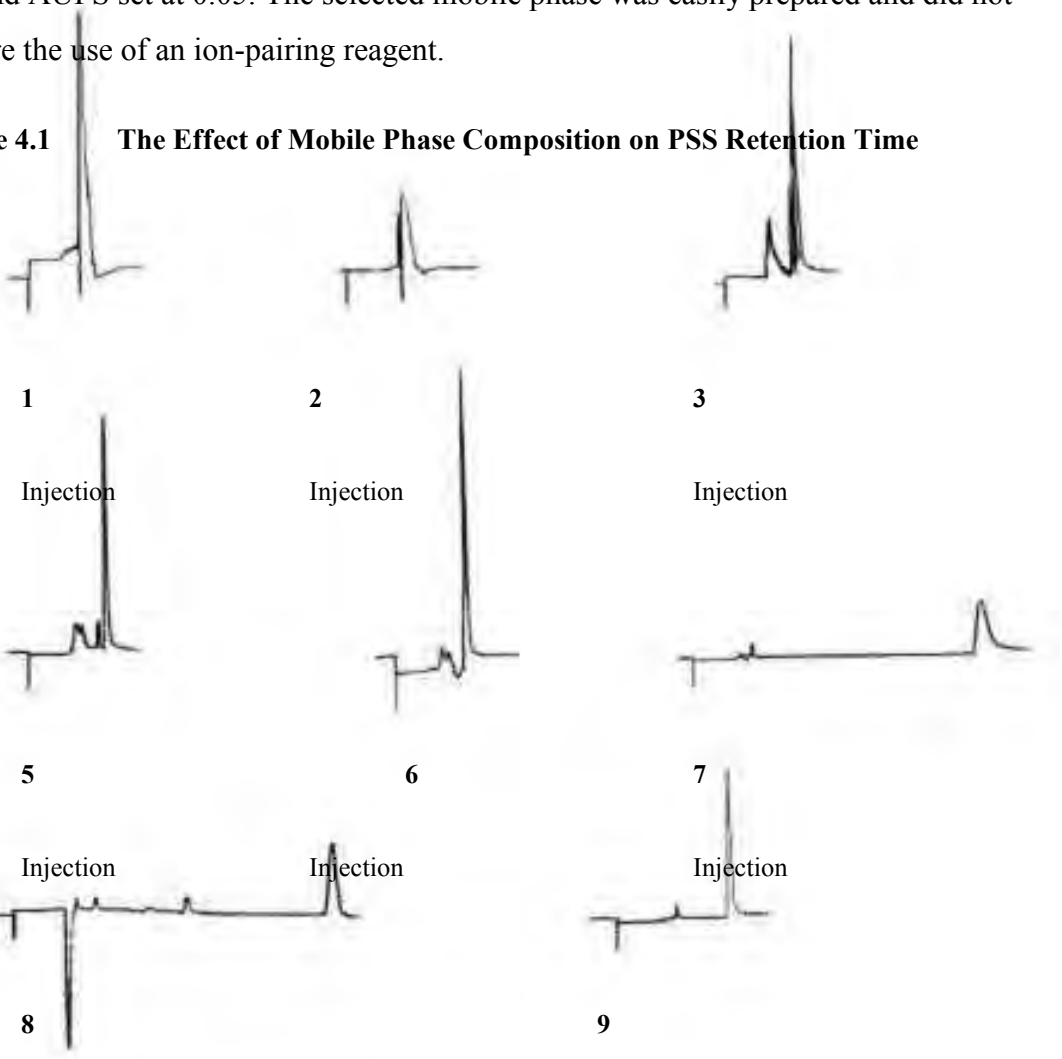
Mobile Phase Number	Mobile Phase Composition	Reference	PSS Retention Time
1	Acetonitrile: Methanol: 0.05 M potassium nitrate 35:40:25	*[203]	Unresolved from solvent front
2	Acetonitrile: Methanol: 0.05 M Potassium nitrate containing 0.001 M octane sulfonic acid 35:40:25	*[203]	Unresolved from solvent front
3	Acetonitrile: 0.025M Phosphate buffer (pH 6.25) 25:75		Unresolved from solvent front
4	Acetonitrile: 0.025M Phosphate buffer (pH 6.25) containing 0.005 M octane sulfonic acid 25:75		No peak eluted by 35 minutes
5	Acetonitrile: 0.05M Phosphate buffer (pH 6.24) 25:75		2.4 minutes, barely resolved from solvent front
6	Acetonitrile: 0.1M Phosphate buffer (pH 6.24) 25:75		2 minutes, barely resolved from solvent front
7	Methanol: 0.05 M Phosphate buffer (pH 6.24) 25:75		Broad peak, 8.6 minutes
8	Methanol: Water: Glacial Acetic Acid 45:55:2 with 0.005 M octane sulfonic acid	[198]	Small, broad peak, 9.8 minutes
9	Acetonitrile: Methanol: 0.05 M Phosphate buffer (pH 6.24) 25:25:150		Sharp peak, 3.4 minutes, well resolved from solvent front

*Refers to a mobile phase modified from the corresponding reference in Table 4.1.

A mobile phase comprising acetonitrile, methanol and 0.05 M phosphate buffer (pH 6.24) in a ratio of 25:25:150 gave sharp peaks at a retention time of 3.4 minutes, which ensured good resolution from the solvent front, and this mobile phase was selected for further

development and validation. Two other mobile phases yielded PSS peaks at 8.6 and 9.8 minutes that were well resolved from the solvent front but broad. These retention times were deemed longer than required. Figure 4.1 depicts the chromatographic separation of PSS from these different mobile phases with an on-column load of 2 µg, detection at 257 nm and AUFS set at 0.05. The selected mobile phase was easily prepared and did not require the use of an ion-pairing reagent.

Figure 4.1 The Effect of Mobile Phase Composition on PSS Retention Time



* Numbers refer to Table 4.2, which gives the compositions for the mobile phases

4.1.1.2.6 Preparation of Selected Mobile Phase

The buffer solution was prepared as follows:
6.2 mL of 85% orthophosphoric acid was accurately pipetted into a 1L A-grade volumetric flask and made up to volume with HPLC grade water. The pH was then adjusted to 6.24 using sodium hydroxide pellets. A Crison pH meter (Crison, LASEC, South Africa) was used for pH measurements.

The buffer solution was then combined with acetonitrile and methanol in a ratio of 25:25:150 and filtered through a 0.45 μm HVLP filter (Millipore, MA, USA) before use.

4.1.1.2.7 Preparation of Stock Solutions

Stock solutions of PSS were prepared in the following manner:
Approximately 1.00g (1.00258g) of PSS (USP reference standard) was accurately weighed into an A-grade 100 mL volumetric flask and made up to volume with HPLC grade water or 0.1 M phosphate buffer (pH 7.2) prepared with HPLC grade water.

Standards ranging in concentration from 3 to 150 μg/mL were prepared by serial dilution of this stock solution using A-grade glassware.

4.1.1.3 OPTIMISATION OF THE CHROMATOGRAPHIC CONDITIONS

4.1.1.3.1 Detector Wavelength (λ)

The most frequently reported wavelengths for the detection of pseudoephedrine in dosage forms are 257 nm [201,202,206] and 254 nm [7,198,203]. The λ_{max} of PSS is 257 nm (§ 1.1.2.10), with secondary maxima occurring at 263 and 251 nm [3]. Consequently, the effect of different wavelengths on the PSS peak height was investigated. As expected, peak height was affected by the wavelength used. The data are listed in Table 4.3 and illustrated in Figure 4.2. The results indicate that absorption was optimal at 257 nm, with decreasing absorbance through 263 nm, 254 nm, 251 nm and 248 nm. The wavelength

248 nm was included in the experiment as it is the λ_{max} of loratadine (§1.2.2.7) and the effect of this wavelength was assessed in order to ascertain whether a single wavelength would be suitable for the simultaneous analysis of both compounds using a single method. The wavelength chosen should correspond to a maximum, minimum or shoulder of the solute's absorption spectrum to ensure that the Beer-Lambert law is obeyed as many UV sources emit a band of light of varying wavelength rather than a single wavelength [197].

Table 4.3 Effect of Wavelength on the Peak Height of PSS

Concentration (µg/mL)	248 nm	251 nm	254 nm	257 nm	263 nm
5.013	61.54	92.31	92.31	100	92.31
10.025	61.54	80.77	92.31	100	100
40.102	61.54	78.85	88.46	100	94.23
60.155	59.49	76.58	85.44	100	91.14
100.258	60.94	78.13	87.5	100	93.75
Mean	**61.01**	**81.33**	**89.20**	**100**	**94.29**
Standard Deviation	0.89	6.32	3.04	0	3.42
% RSD	1.45	7.77	3.40	0	3.63

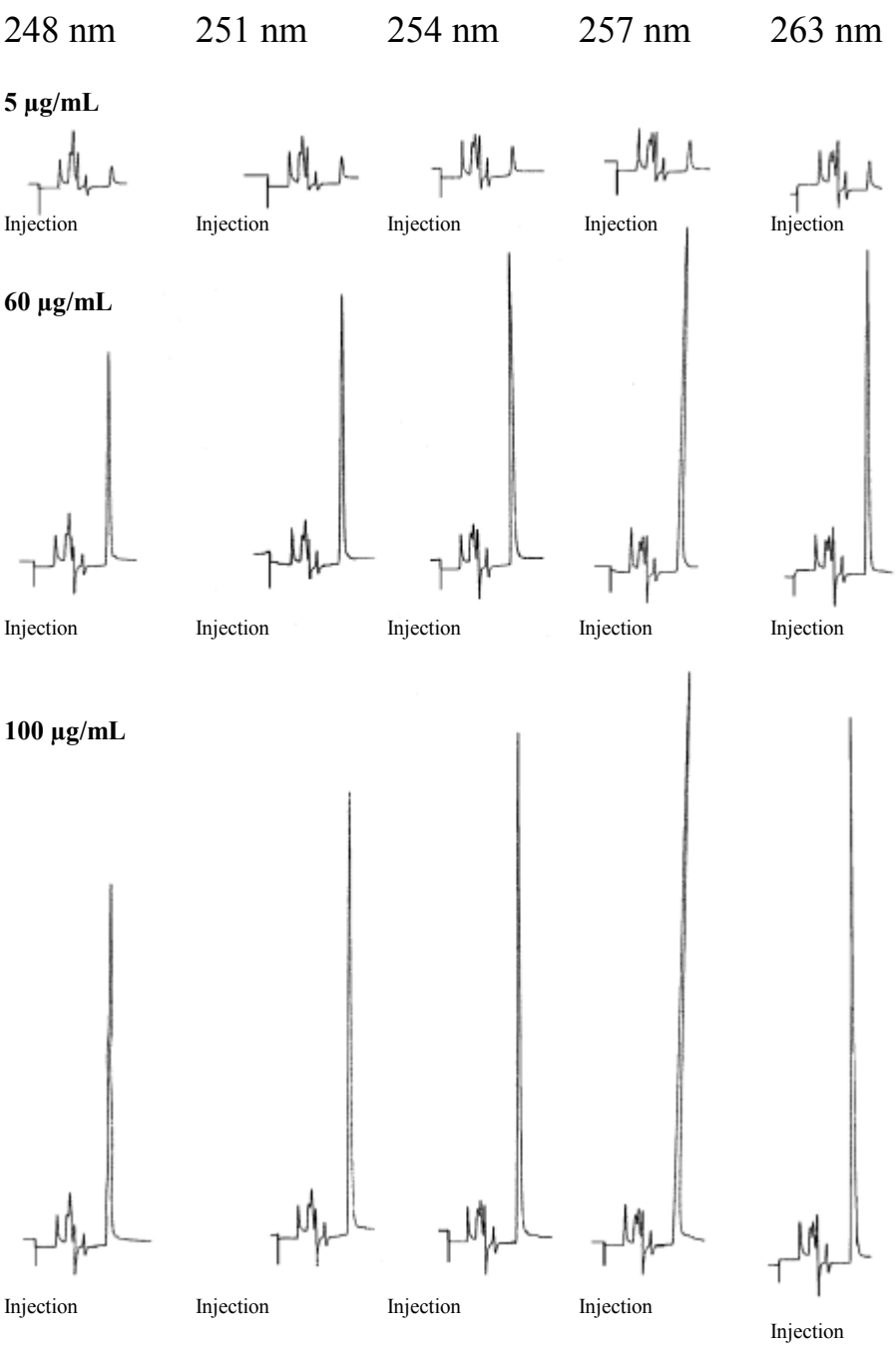
(Results are shown as a percentage of peak height obtained with the 257 nm wavelength)

Based on the results of this experiment, 257 nm was chosen as the wavelength of detection. The results obtained with 248 nm are consistent, with a relative standard deviation of 1.45%, and a joint analysis of PSS and loratadine with detection at 248 nm may be feasible.

4.1.1.3.2 Choice of Column

A C_{18} column was selected for the analysis of PSS. PSS is a weak base and is highly water soluble, thus retention times are expected to be short with a non-polar stationary phase, as PSS will partition preferentially into the mobile phase. This is desirable as rapid and selective analysis of PSS in single component dosage forms was required.

Figure 4.2 The Effect of Wavelength on PSS Peak Height



4.1.1.3.3 Mobile Phase Composition

There are several difficulties associated with the HPLC analysis of basic compounds, including peak broadening and tailing [205]. These phenomena are usually a function of unreacted silanol groups rather than by the bonded non-polar stationary phase, as silanol groups are capable of ion-exchange reactions with basic compounds [205]. This results in the creation of 'slow sites', which are the sites at which the compound is interacting with the silanol groups rather than bonded phase and causes peak tailing. The problem of tailing can be minimized through various manipulations of the mobile phase as described below:

1. The pH of the mobile phase can be buffered to ensure that ionisation of the base is suppressed. This was not feasible for PSS, as the mobile phase would have to be at a pH greater than 9, which would lead to hydrolysis of the bonded phase [197,205].
2. The use of a mobile phase of low pH may decrease the incidence of tailing as the silanol groups will be ionised, however pH values less than 3 may decrease column life, and the pKa of silanol groups may be less than 3 [197, 205].
3. The use of organic modifier may reduce the extent of protonation of the base, and therefore its tendency to interact with silanol groups [205].
4. Increasing the concentration of buffer often decreases retention time and improves peak symmetry. Potassium is a more effective buffer cation than sodium [205], but this effect was not assessed for this method.

As mentioned previously (§ 4.1.2.5), the mobile phase selected for development comprised acetonitrile and methanol with a 0.05 M phosphate buffer (pH 6.24). This mobile phase gave a satisfactory retention time and resolution. From the initial experiments it was observed that an increase in the acetonitrile component decreased retention time, while an increase in the methanol component increased retention time, but also caused peak broadening.

The effect of buffer concentration independent of pH on PSS retention time and peak height was assessed and the results are listed in Table 4.4. A buffer concentration of 0.05 M appears to be optimal as peak height decreased with both an increase and a decrease in buffer concentration.

Table 4.4 The Effect of Buffer Molarity on Retention Time and Peak Height

Buffer Molarity	Retention Time (min)	Mean Peak Height (n=5) (expressed as a percentage of peak height obtained with 0.05 M buffer)
0.025	3.95	85.86 ± 1.14
0.05	3.4	100 ± 0
0.075	3.16	92.71 ± 3.01

4.1.1.4 CHROMATOGRAPHIC CONDITIONS

The optimal chromatographic conditions established during the method development are listed below.

HPLC System	System A
Mobile Phase	Acetonitrile: Methanol: 0.05 M Phosphate buffer (pH 6.24) 25:25:150
Flow Rate	1.0 mL/min
Detection Wavelength	257 nm
AUFS (Attenuation)	0.01
Gain	x2
Injection volume	10 µL
Retention time	3.4 minutes
Temperature	Ambient

4.1.1.5 CONCLUSION

The effects of altering system variables on the elution of PSS were established in these preliminary investigations to enable the choice of mobile phase, detection wavelength and analytical column for the rapid analysis of PSS in controlled release dosage forms. The impact of changes in these variables was assessed, and it was found that alterations in wavelength and buffer concentrations affected peak height, although linearity was not compromised. The chromatographic conditions were optimised for the analysis of PSS, providing a method that yielded well-resolved, sharp peaks at a suitable retention time.

4.1.2 METHOD VALIDATION

4.1.2.1 INTRODUCTION

Method validation is an essential and critical process in determining the applicability and value of an analytical method for its intended purpose. The Food and Drug Administration requires that methods of analysis reported in new drug applications be validated in order to establish analytical methods which can be used in regulatory affairs [210]. Despite the wide acceptance of the need for method validation and its importance, few formal guidelines are available on how such validation should be performed [211]. There are however several parameters which have been outlined by various organizations as requiring investigation during method validation. Current Good Manufacturing Practice (cGMP) in the USA require that methods used by a company must be evaluated with respect to accuracy, sensitivity, specificity and reproducibility, and documentation proving adequate performance in these areas must be on file [210]. The International Conference on Harmonization (ICH) guidelines recommend that accuracy, repeatability, intermediate precision, reproducibility, specificity, linearity, range, system suitability and robustness be evaluated and the limit of detection (LOD) and limit of quantitation (LOQ) be characterised [211]. The United States Pharmacopoeia outlines eight components of method validation: precision, accuracy, LOD, LOQ, specificity, linearity and range, ruggedness and robustness [211]. A limitation of these guidelines is that they give requirements for analytical methods designed to determine content uniformity, and therefore are focussed on a relatively narrow concentration range of analyte, and give few recommendations as to what is expected from methods used to determine a wide range of concentrations, such as determining the amount of drug released at various time points during a dissolution test. Analytical methods developed for use with biological samples may also require demonstration of recovery [212], which may be applicable to dosage form assessment, in particular controlled or sustained release preparations, although it is not required.

It is important to realise that method validation is not a stand-alone process, and is rather a part of an overall validation process, which includes the validation of the hardware and software being used (installation, operation and performance qualifications should be performed for all equipment being utilized), and the verification of system suitability and performance [208,211].

4.1.2.2 SPECIFICITY

Specificity is defined as the ability to measure the analyte in the presence of other expected compounds [213]. Specificity was assessed by analysing samples after dissolution of a placebo tablet and an active tablet and comparing these to the chromatogram obtained from a standard solution of PSS, as shown in Figure 4.3. The peaks obtained were well resolved from the solvent front and no interference was observed, indicating that the method was specific for PSS. A typical chromatogram for each HPLC system (Systems A and B) is shown in Figure 4.4.

Figure 4.3 Comparison of Chromatograms of Dissolution Samples of a Placebo (A) and an Active Tablet (B)

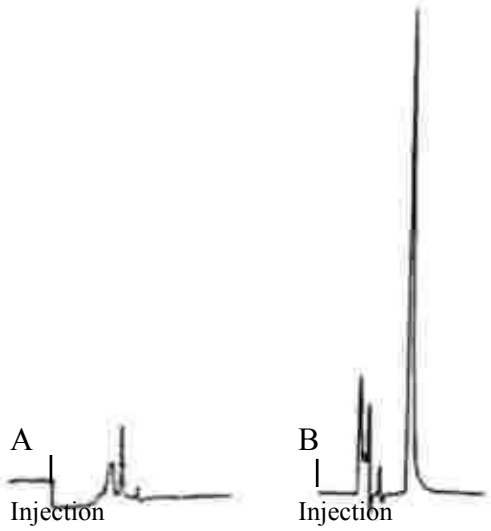
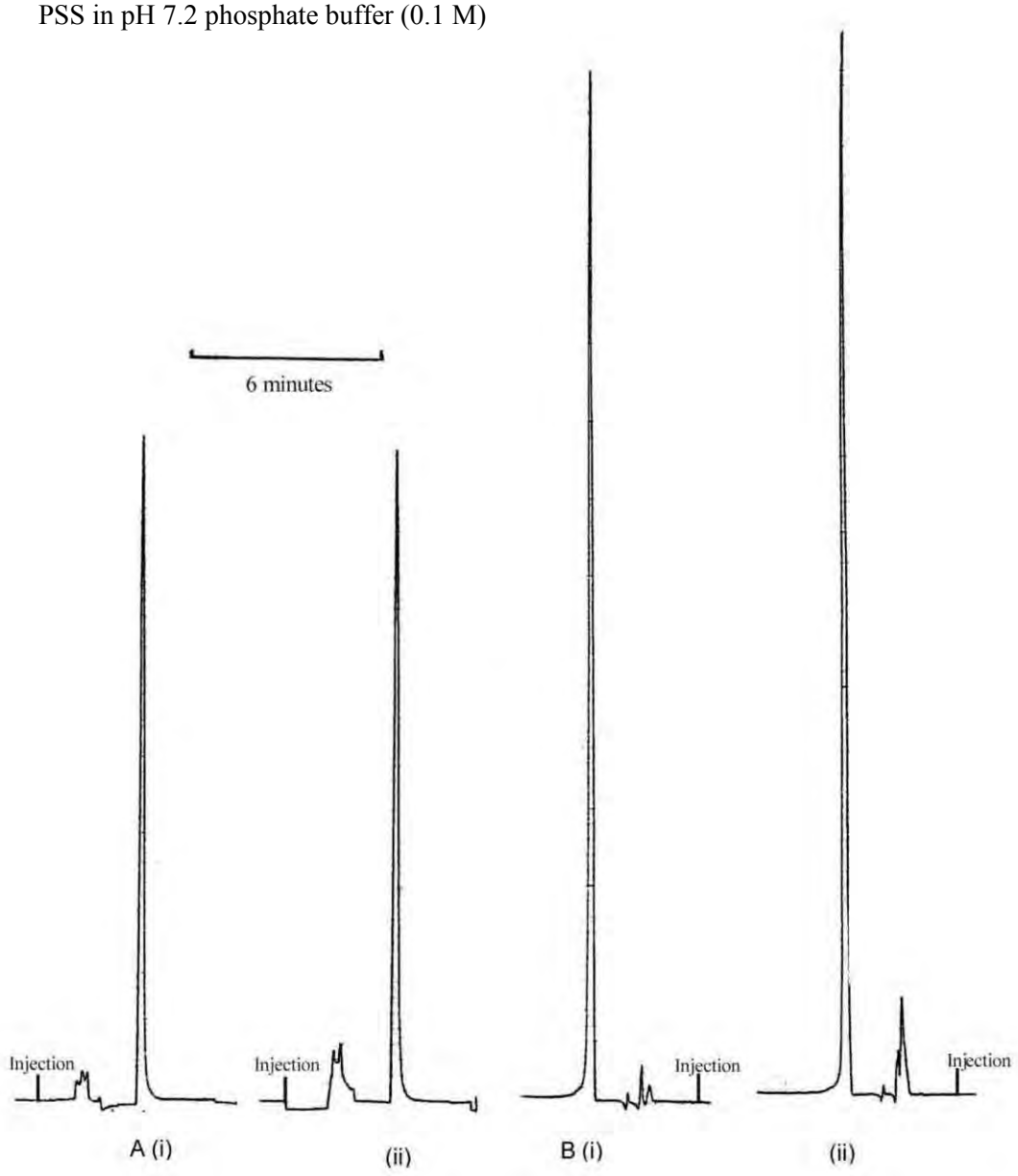


Figure 4.4 Typical Chromatograms Obtained with System A and B.

(i) PSS in Water
(ii) PSS in pH 7.2 phosphate buffer (0.1 M)

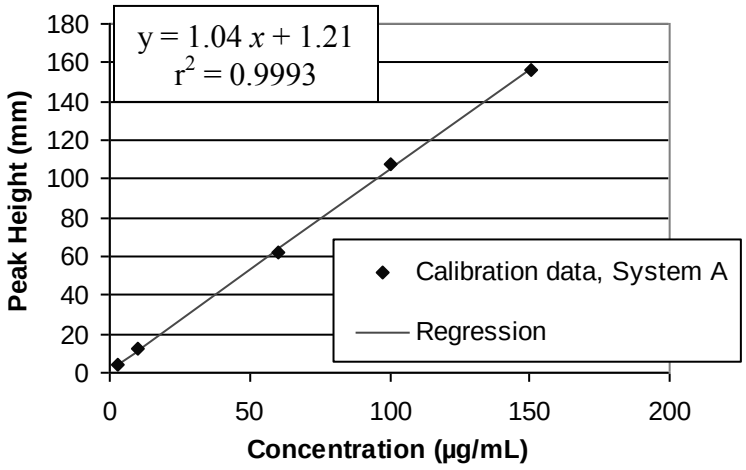


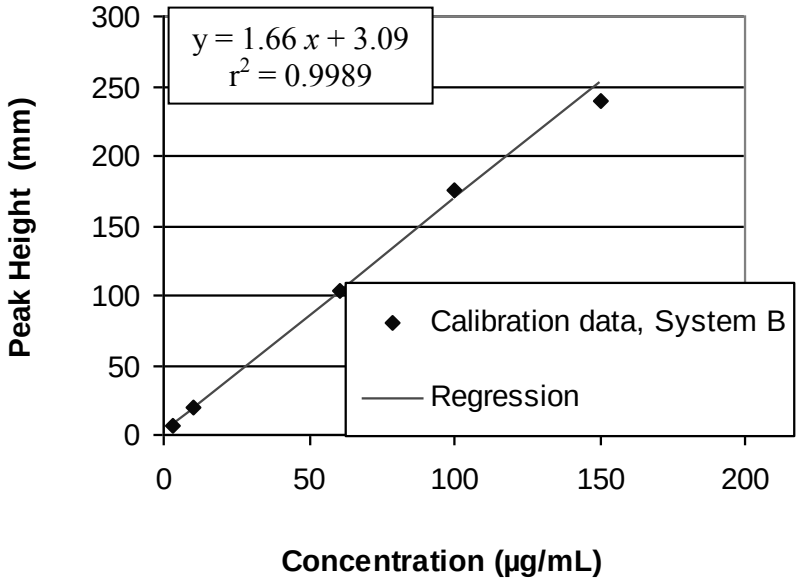
4.1.2.3 LINEARITY

Linearity refers to the capability of the system to produce results proportional to the concentration of the analyte [213]. The ICH guidelines recommend that five concentrations spanning the concentration range to be studied be used [211]. It has been found that a total of twenty assays (four duplicate assays for each concentration) are necessary for statistical validity [213]. It has also been recommended that two data sets compiled from separately prepared samples be used [213].

A calibration curve was constructed over the concentration range of 3 - 150 µg/mL by linear regression of the peak heights obtained versus the concentration. Four replicate injections of each of six concentrations were used, providing twenty-four assays. The calibration curve was linear over the concentration range studied, with $r^2 = 0.9996$ and 0.9988 for systems A and B respectively. The equations of the regression lines are $y = 1.04x + 1.21$ and $y = 1.66x + 3.10$ for systems A and B respectively. A typical calibration curve is shown in Figure 4.5.

Figure 4.5 Typical Calibration Curves Obtained with System A and B





4.1.2.4 PRECISION

Precision refers to the degree of repeatability obtained with replicate assays and is expressed as percent relative standard deviation (%RSD). Three types of precision can be defined, and should all be assessed, as described below.

4.1.2.4.1 Repeatability

Repeatability expresses the degree of variation arising during replicate assays performed consecutively and non-consecutively, but on the same day. Consecutive measurements were defined as consecutive injections of the same concentration from different sample vials, while non-consecutive measurements are defined as measurements of the same concentration where the sample vials are interspersed with those of other concentrations. The repeatability for this system was assessed by repeat measures of the 3 µg/mL and the 100 µg/mL calibrating solutions. Consecutive analysis (n=5) of the standards gave a %RSD of 5.7% and 6.3% for the 3 µg/mL sample on systems A and B respectively, and 1.01% (system A) and 0.95% (system B) for the 100 µg/ml calibrator. Repeated analysis of the 3 µg/mL and the 100 µg/mL calibration samples injected in a non-consecutive sequence (n=5) produced %RSD values of 10.4% and 8.6% for the low calibration standard for systems A and B respectively, and 1.2% and 2.4% for the high calibration standard. These data are shown in Table 4.5.

Table 4.5 Repeatability with respect to High and Low Calibration Solutions

Consecutive measurements (n=5)

System	Concentration (µg/mL)	Mean Peak Height (mm)	Standard deviation	Precision (R.S.D.)
A	3.0	3.9	0.2	5.7
	100.4	107.4	1.1	1.0
B	3.0	6.6	0.4	6.3
	100.4	169.8	1.6	0.9

Non-consecutive measurements (n=5)

System	Concentration (µg/mL)	Mean Peak Height (mm)	Standard deviation	Precision (R.S.D.)
A	3.0	4.3	0.5	10.4
	100.4	107.7	1.3	1.2
B	3.0	6.4	0.6	8.6
	100.4	167.2	3.9	2.4

4.1.2.4.2 Intermediate Precision (Ruggedness)

Intermediate precision refers to the variation arising from intra-laboratory changes, such as a change of analyst, system hardware or ambient conditions, and as such is concerned with changes in external variables. Inter-day precision of the calibration standards over a one week period, showed a %RSD of less than 6.5 % for the dilute samples (3 µg/ml – 10 µg/ml) and less than 4% for the high standards (40 µg/ml - 150µg/ml) for both systems. These results are shown in Tables 4.6 and 4.7. The degree of variation between the two systems was small, as can be seen in Tables 4.5, 4.6 and 4.7. A direct comparison of peak heights between the two systems was not possible as one system included an amplifier while the other did not. Comparisons of the percent released during dissolution assessment exhibited no significant variation, as illustrated in Figure 4.6.

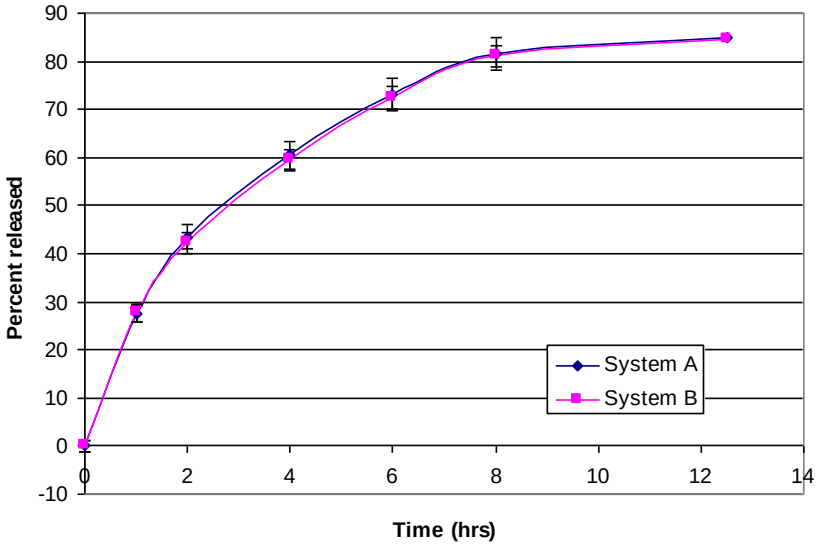
Table 4.6 Intermediate Precision of System A

Concentration (µg/mL) n=4	Mean Peak Height (mm)	Standard deviation	Precision (R.S.D.)
3.0	3.9	0.3	6.5
10.0	12.3	0.5	4.1
40.2	42.6	0.9	2.2
100.3	107.4	1.3	1.2
150.6	156.5	2.5	1.6

Table 4.7 Intermediate Precision of System B

Concentration (µg/mL) n=4	Mean Peak Height (mm)	Standard deviation	Precision (R.S.D.)
3.0	6.3	0.3	4.6
10.0	19.5	0.6	2.9
40.1	69.3	1.3	1.9
100.3	171.5	5.3	3.1
150.6	244.4	6.2	2.5

Figure 4.6 Comparison of Dissolution Curve Results Obtained Using Systems A and B



The effect of the pH of the dissolution medium on the analysis of pseudoephedrine was assessed using standard solutions ranging from 5 µg/mL to 100 µg/mL prepared in the previously mentioned buffers (§3.5.1). There was no discernible effect of pH on the calibration standards, with the RSD% between the measurements, 9.6% for the 5µg/mL sample and less than 5% for the other concentrations, for system A. The RSD% was less than 5% for all concentrations analysed on system B. These data are listed in Table 4.8. These values are comparable to those obtained for the inter-day repeatability (Tables 4.5 and 4.6) and the repeatability of measuring low calibrators in water alone (Table 4.7), and thus it appears as though sample pH has a negligible effect on pseudoephedrine analysis.

Table 4.8 Effect of Buffer on PSS Peak Height

System	Concentration (µg/mL)	Peak Height (mm)							Standard deviation	Precision (%R.S.D.)
		pH 1.6	pH 3.4	pH 4.7	pH 6.8	pH 7.2	Water	Mean		
A	5.0	6	6.5	6	5.5	5.5	7	6.1	0.6	9.6
	10.0	10.5	11	11	11	10.5	12	11.0	0.6	4.9
	40.2	43	42	43	43	43	42.5	42.8	0.4	0.9
	100.4	111	109	107	108	105	108	108.0	2.0	1.9
B	5.0	10	10	9.5	10	10	11	10.1	0.5	4.9
	10.0	18.5	18	18	17.5	18	19	18.2	0.5	2.8
	40.2	71	70	70	70	70.5	69.5	70.2	0.5	0.7
	100.4	178	170	171	170	172	173.5	172.4	3.0	1.8

The analysis of blank water and different pH buffers showed no baseline changes for pH 3.40 - 7.20 or water for both chromatographic systems. Analysis of the blank pH 1.65 solution did reveal background noise with both systems A and B. This did not, however affect the signal to noise ratio of the peak of interest when the calibration and dissolution samples were analysed. These results indicate good system suitability.

4.1.2.4.3 Reproducibility

Reproducibility is an indication of the ability of the method to be transferred from one laboratory to another, and was not assessed.

4.1.2.5 LOQ and LOD

The limit of quantitation refers to the lowest concentration that can be accurately analysed, while the limit of detection refers to the lowest concentration which yields an identifiable peak. Several methods are used to determine the LOD and LOQ [214], and it has been suggested that there is a 100% inherent uncertainty in the LOD and 30% in the LOQ [214]. The four commonly used methods yield similar results, and no trends dependent on the method used have been identified [214]. The first method states the

LOQ is the lowest concentration with a %RSD of less than 10% on multiple injections, and that the LOD is 30% of the LOQ. The second method uses a plot of standard deviation versus concentration. The y-intercept is then multiplied by 3 to obtain the LOD and multiplied by 10 to obtain the LOQ. The third method utilises the 95% confidence interval of the best-fit line of the calibration curve. The y-intercept of the upper confidence interval line is joined horizontally to the lower intercept line and the corresponding concentration interpolated. This concentration represents the LOD, and can be multiplied by 3.3 to give the LOQ. The fourth method is perhaps the most often used. Here the criterion assessed is the signal to noise ratio. The LOQ has a signal to noise ratio of 10 : 1, while the LOD yields a signal to noise ratio of 3 : 1. Of these, the first and last methods are most applicable to experimental determination, and the first method was used in this validation. The limit of quantitation was found to be 2 µg/mL, which had a RSD % of less than 10% for both system A and B, and the limit of detection at 1 µg/mL, which showed a RSD % of more than 15% for both systems. Previously published methods for the analysis of pseudoephedrine hydrochloride, list the limit of quantitation as 24-84 µg/mL for dosage form analysis [201] and 5 ng/mL for plasma analysis [200] and several of the published papers do not give any values for this limit [198,203,204,206,207].

4.1.2.6 ACCURACY AND BIAS

Accuracy refers to the ability of the method to measure concentration, and is expressed as percent error [213]. Bias assesses the influence of the analyst on the performance of the method. The accuracy and bias of the system was evaluated by making repeated measurements of three blinded samples varying in concentration. The measurements were performed in triplicate, in consecutive and in non-consecutive sequences. The percent error in determining the concentration of the blinded unknowns varied from -4.9% to 1.5% for system A for both sets of measurements, and -5.1% to -1.3% for system B. The data are summarised in Table 4.9.

Table 4.9 Percent Error Obtained during Determination of Blinded Unknowns

System	Theoretical concentration (µg/mL)	Mean Determined concentration (µg/mL) (n=3)	Standard deviation	Precision (%R.S.D.)	Percent error
A	14.5	14.2	0.3	1.9	-1.9
	9.0	8.6	0	0	-4.9
	70.3	71.3	0.7	1.0	+1.5
B	14.5	14.1	0.2	1.2	-2.9
	9.0	8.6	0.2	2.0	-5.1
	70.3	69.4	0.4	0.5	-1.3

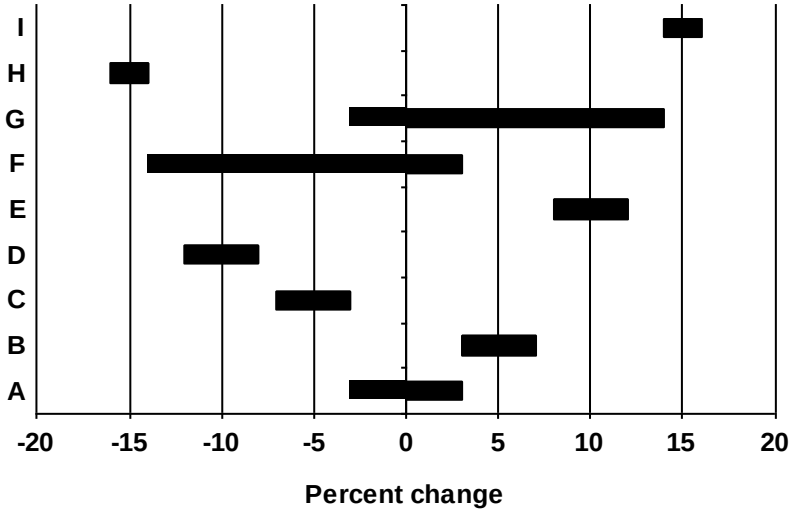
4.1.4.7 ROBUSTNESS

The robustness of the method refers to the capacity to withstand deliberate manipulation of system variables (internal factors) and is discussed in § 4.1.1.3.1and 4.1.1.3.3.

4.1.4.8 STABILITY OF ANALYTE

It is important to ensure that the analyte remains stable in solution during the duration of the analysis and under the conditions of an analytical run. PSS remained stable throughout the analytical procedure, as samples reanalysed in triplicate after three month's storage at 18°C and at the end of a run showed no differences in detector response when compared to the initial analysis. The method developed by Timm *et al* [215] was used to assess the results to determine whether any differences observed constituted a relevant and significant change. This method is particularly useful as it accounts for the influence of the analytical method and any error associated with it [215]. It involves the calculation of 90% confidence intervals for the difference between two data sets. The change is regarded as significant if the confidence interval does not include zero change, but the change is not considered relevant unless both the upper and lower limits of the confidence interval are either greater than 10% or less than –10% [215]. This concept is illustrated in Figure 4.7

Figure 4.7 Determination of Significant and Relevant Changes in Response



The bars represent the confidence intervals for nine possible scenarios:

A – The change is neither significant nor relevant

B – There is a significant, but not relevant increase in response

C – There is a significant, but not relevant decrease in response

D – There is a significant and possibly relevant decrease in response

E – There is a significant and possibly relevant increase in response

F – There is a possibly relevant, but not significant decrease in response

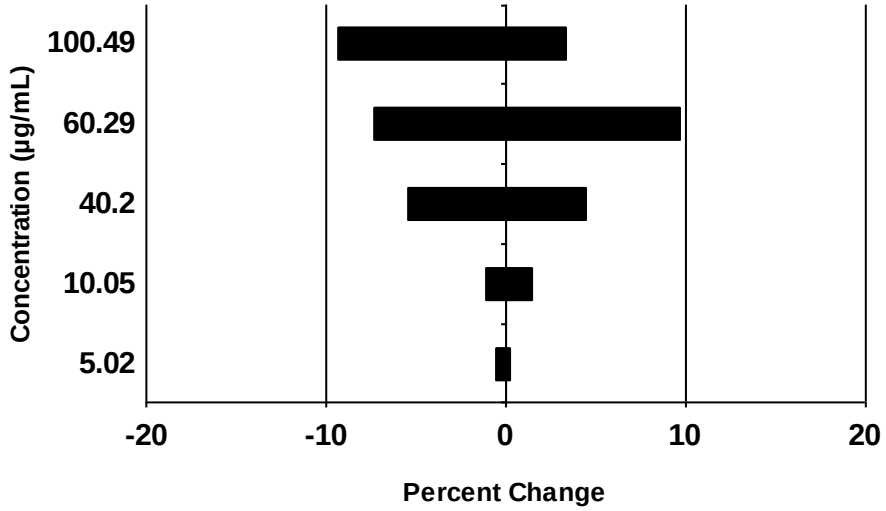
G – There is a possibly relevant, but not significant increase in response

H – There is a significant and relevant decrease in response

I – There is a significant and relevant increase in response

The results obtained following the analysis of PSS solutions after storage reveal that the observed differences were neither relevant nor significant for all calibration solutions. These data are depicted graphically in Figure 4.8.

Figure 4.8 90% Confidence Intervals for Differences in Response for PSS Solutions Stored for 3 Months



4.1.4.9 CONCLUSION

The results obtained with this analytical method show that it is both rapid and sensitive when compared with previously published methods for the analysis of PS from dosage forms, while avoiding the use of pH extremes and/or ion-pairing reagents. It has proved useful both for the characterisation of dissolution profiles. In addition, the results obtained using the different pH's show that the pH of the sample has no discernible effect on the analytical results. This is particularly valuable when assessing the dissolution behaviour of dosage forms using USP Apparatus 3, as several different buffers may be used. The results suggest that the use of one set of calibration standards is possible during analysis rather than standards prepared in buffers of each pH.

The method developed here is more sensitive than previously reported methods for the analysis of PSS from dosage forms, with a reduced LOQ (2 µg/mL as opposed to 24 µg/mL), and has the advantage of being optimised for pseudoephedrine sulfate. It is

particularly applicable to the analysis of dissolution samples of sustained release dosage forms because of the increased sensitivity. The apparent robustness of this method to pH changes of the sample makes it valuable in analysing dissolution samples, particularly where the dissolution media is changed or consists of multiple buffers of different pH values.

4.2 LORATADINE

4.2.1 INTRODUCTION

Few methods have been published concerning the analysis of loratadine in either dosage forms or plasma. The paucity of available literature is expected as loratadine is still under patent protection, and not widely used, Papers concerning the characterization of loratadine's pharmacokinetics give few details of the analytical methods, but indicate that the determination of loratadine in biological fluids is usually carried out by radio-immunoassay [[90,91,94,96]. One article states that an HPLC method was used in conjunction with mass spectrometry for the analysis of loratadine, but state that the method is unpublished [83]. Other analytical techniques that have been used for the analysis of loratadine in plasma are gas chromatography [46] and gas-liquid chromatography [57]. Two published methods for the analysis of loratadine by HPLC were found, and are listed in Table 4.10. As loratadine is hydrophobic, it was difficult to analyse it simultaneously with PSS, and a separate method was therefore used.

Table 4.10 Published Methods for the HPLC Analysis of Loratadine

Reference	Column	Mobile Phase	Detection and Wavelength	Internal standard	Flow rate	Retention Time	Matrix
216	C_{18} 10µm, 250 x 4.6 mm	Acetonitrile: Diethylamine/glacial acetic acid buffer 85:15 with 0.005 M OSA	UV 249 nm	sulfanilamide	1.5 ml/min	< 5 minutes	Dosage forms
217	C_{18} 7 µm, 250 x 4.6 mm	Acetonitrile: Water 1100:1500 with 15 g ammonium dihydrogen phosphate, 8 mL phosphoric acid	Fluorescence Excitation: 290 nm Emission: 460 nm		1.5 ml/min		Plasma

4.2.2 METHOD DEVELOPMENT

An analytical method was required in order to quantitate the loratadine released from the outer immediate release coat applied to the sustained release cores. This enabled the amount of loratadine transferred to the core during coating to be quantitated. A simple, rapid and quantitative method was therefore required. As a specific concentration range for loratadine was of interest, high sensitivity was not required. The method used for the analysis for loratadine was that described by Chandrashekar *et al* [216], with minor modifications. This method was developed for the determination of loratadine in tablets, and only minor changes were necessary to optimise the method for the system used here before it was validated.

4.2.2.1 HPLC SYSTEM

The system used was System A (§ 4.1.2.2).

4.2.2.2 REAGENTS

All reagents were of at least analytical grade (§ 4.1.2.1). In addition, diethylamine was obtained from Merck Chemicals (Germany) and glacial acetic acid was obtained from Saarchem (Krugersdorp, South Africa). Sodium octane sulfonic acid was obtained from Sigma-Aldrich (South Africa). Loratadine was obtained from Reddy-Cheminor (Hyderbad, India). No USP reference standard is available for loratadine.

4.2.2.3 DETECTION

The two published methods used either UV detection [216] or fluorescence detection [217]. UV detection is convenient and effective, and was the method chosen for the analysis of PSS. Loratadine has a λ_{max} of 248 nm (§ 1.2.2.10), and this wavelength was

used for the analysis.

4.2.2.4 COLUMN

The column selected was a C_{18} column (Prodigy®, Phenomenex, USA), which is a reversed-phase column. Chandrashekar *et al* [216] used a C_{18} column, but dimensions of the column used in this study differed from that of the published method, as described in Table 4.11.

Table 4.11 Differences in Column Dimensions

Dimension	**Published Method**	**Prodigy®**
Size of silica beads	10 µm	5 µm
Length	250 mm	150 mm

4.2.2.5 MOBILE PHASE SELECTION AND PREPARATION

As loratadine is hydrophobic, a high proportion of organic modifier is required in order to achieve short retention times. Loratadine is a weak base (§1.2.2.4), and is ionised below pH 4.58. Consequently the use of ion-pairing reagents in an acidic mobile phase may facilitate its separation. The mobile phase described by Chandrashekar *et al* [216] was used, and was prepared as described below.

The buffer component was prepared by pipetting 4 mL of diethylamine and 4 mL of glacial acetic acid into a 1000 mL A-grade volumetric flask. Approximately 500 mL of HPLC grade water was then added, and the solution shaken. Approximately 1.08 g of sodium octane sulfonic acid was accurately weighed and then added to the solution. The solution was made up to 1000 mL with HPLC grade water.

The buffer solution was added to acetonitrile in a ratio of 15 parts buffer to 85 parts

acetonitrile, and degassed and filtered through a 0.45 μm HVLP filter (Millipore, MA, USA) prior to use.

4.2.2.6 PREPARATION OF STOCK SOLUTIONS

Stock solutions of loratadine were prepared as follows:
Approximately 0.100 g (0.10033 g) of loratadine was accurately weighed and transferred to a 100 mL volumetric flask and made up to volume with a 50:50 mixture of methanol and 0.1 M phosphate buffer of pH 3. Serial dilutions of this solution were prepared to yield solutions in the concentration range of 5 – 100 μg/mL.

4.2.3 OPTIMISATION OF THE CHROMATOGRAPHIC CONDITIONS

As the column used differed slightly in properties from the column described in the published method, certain changes were necessary to effect a separation, and are listed in Table 4.12.

Table 4.12 Alterations in HPLC Parameters

Parameter	Published Method	Present Study
Flow rate	1.5 mL/min	1.0 mL/min
Injection volume	10 μL	10 μL
Detection wavelength	249 nm	248 nm
AUFS	1.0	0.1
Attenuation	-	x2

The retention time for loratadine was reported as less than 5 minutes [216], while the retention time obtained here was 2.9 minutes, illustrating that these changes in settings compensated for the differences in column dimensions. An injection volume of 5 μL without attenuation was evaluated, but gave high variability between injections, which was reduced by using an injection volume of 10 μL with an attenuation value of x2. These data are listed in Table 4.13.

Table 4.13 Effect of Injection Volume on Variability

Concentration	5 µL		10 µL	
	Mean ± Standard Deviation	% RSD	Mean ± Standard Deviation	% RSD
5.0165	8.33 ± 3.66	43.93	7.33 ± 0.58	7.87
10.033	17.83 ± 5.21	29.21	15.5 ± 0.5	3.23
25.083	46.17 ± 15.53	33.65	41.5 ± 0.5	1.2
50.165	93.33 ± 25.86	27.71	83.33 ± 3.51	4.21
75.248	141.5 ± 26.46	18.7	124.67 ± 5.51	4.42
100.33	189.67 ± 26.86	14.16	181.16 ± 8.19	4.53

4.2.4 CHROMATOGAPHIC CONDITIONS

HPLC System	System A (§ 4.1.1.2.2)
Mobile Phase	Acetonitrile: Diethylamine/Glacial Acetic Acid Buffer 85:15
Flow rate	1.0 mL/min
Detection Wavelength	248 nm
AUFS	0.1
Attenuation	x2
Injection volume	10 µL
Retention Time	2.9 minutes
Temperature	Ambient

4.2.5 METHOD VALIDATION

4.2.5.1 SPECIFICITY

Specifity was assessed by analysing dissolution samples of tablets with and without loratadine, and comparing these to the chromatograms obtained with loratadine alone. No interference was observed, as illustrated in Figure 4.9, indicating specificity for

loratadine. The peaks obtained were well resolved from the solvent front. A typical chromatogram for loratadine is illustrated in Figure 4.10.

Figure 4.9 Comparison of Chromatograms of Dissolution Samples from tablets containing only PSS (A), PSS in combination with Loratadine (B) and a Loratadine Solution (C)

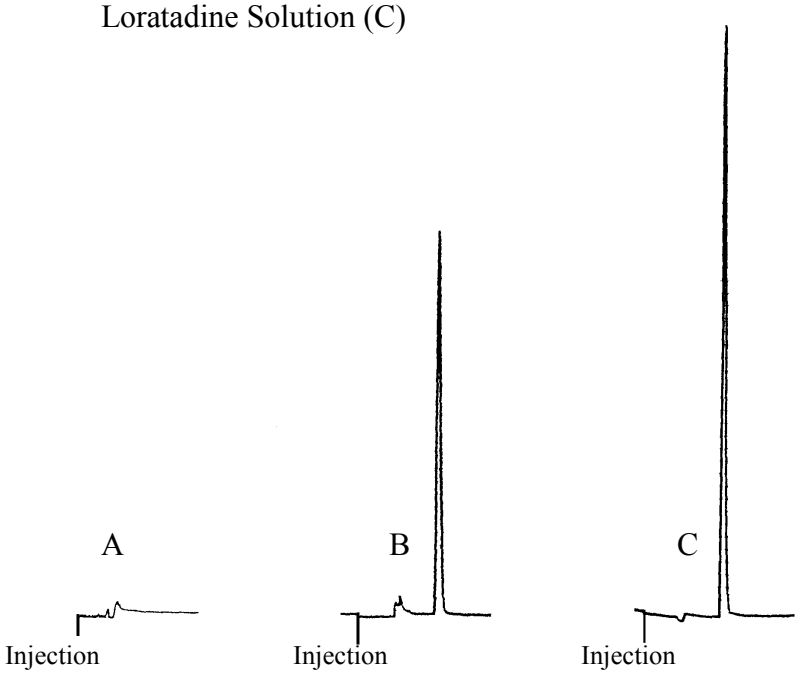
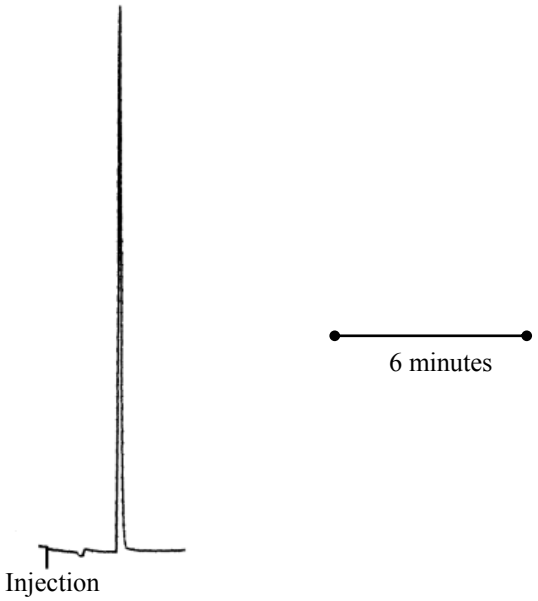


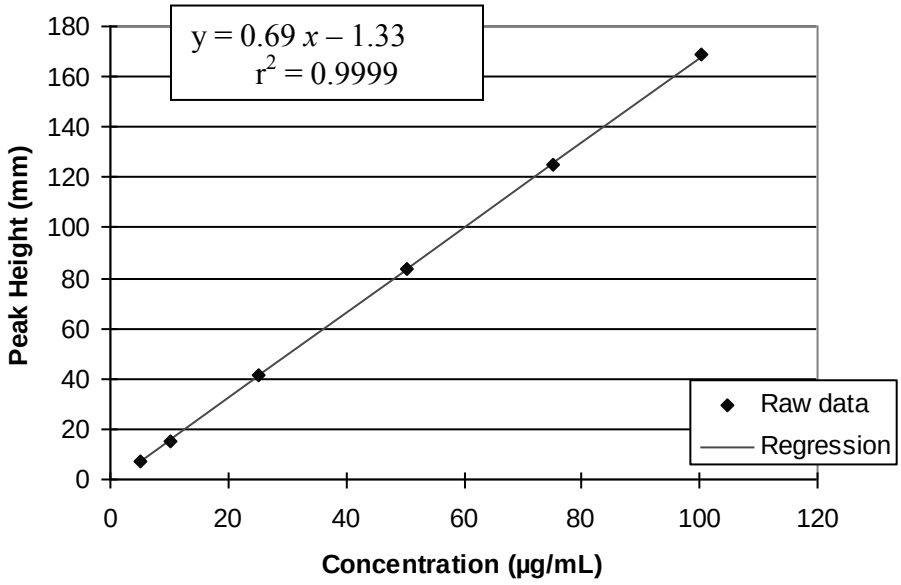
Figure 4.10 A Typical Chromatogram for Loratadine



4.2.5.2 LINEARITY

Linearity was assessed for the concentration range 5 to 100 µg/mL, using four duplicate assays of each of six different concentrations, giving more than the minimum total of twenty assays [213]. The calibration curve was constructed by linear regression of the peak heights obtained with concentration. The curve was linear over the concentration range studied, with a correlation coefficient (r^2) of 0.9999. A typical calibration curve is illustrated in Figure 4.11. The equation for the line is $y = 1.69\,x - 1.33$.

Figure 4.11 Typical Calibration Curve for Loratadine



4.2.5.3 PRECISION

4.2.5.3.1 Repeatability

The repeatability was assessed by repeated measurements of the standard solutions. The measurements were done consecutively, non-consecutively and as replicates on the same day. Consecutive measurements were done sequentially from different sample vials containing solutions of the same concentration, while replicate injections were sequential injections from a single vial for each concentration. The results are summarised in Table 4.14. The relative standard deviations are all less than 5%, which is within the limit of 10% set in our laboratory for this parameter, indicating good repeatability.

Table 4.14 Repeatability

Consecutive Measurements (n=3)

Concentration (µg/mL)	Mean Peak Height (mm)	Standard Deviation	Precision (%RSD)
5.0165	7.83	0.29	3.69
10.033	16.5	0.5	3.03
25.083	44.17	0.29	0.65
50.165	81.17	0.29	0.36
75.248	124.17	1.89	1.52
100.33	167.67	0.58	0.34

Non-consecutive Measurements (n=3)

Concentration (µg/mL)	Mean Peak Height (mm)	Standard Deviation	Precision (%RSD)
5.0165	8.17	0.35	4.33
10.033	17.17	0.35	2.06
25.083	45.5	1.06	2.33
50.165	88.33	2.12	2.4
75.248	135	1.41	1.05
100.33	180	12.73	7.07

Replicate Injections (n=3)

Concentration (µg/mL)	Mean Peak Height (mm)	Standard Deviation	Precision (%RSD)
5.0165	7.83	0.29	3.69
10.033	17.17	0.29	1.68
25.083	45.17	0.29	0.64
50.165	84.83	0.29	0.34
75.248	131.67	0.58	0.44
100.33	174.5	0.5	0.29

4.2.5.3.2 Intermediate Precision

The variation between the results obtained over a one-week period was assessed, and the results are shown in Table 4.15. The relative standard deviations are all less than 7%, which is less than the 10% limit set in our laboratory, indicating good intermediate precision for this modular system. This also indicates that the system used was suitable for the analysis.

Table 4.15 Intermediate Precision

Concentration (µg/mL)	Mean Peak Height (mm)	Standard Deviation	Precision (%RSD)
5.0165	7.88	0.38	4.79
10.033	16.5	0.93	5.63
25.083	44.08	3.04	6.89
50.165	84.58	4.76	5.63
75.248	131.13	8.44	6.43
100.33	171.21	5.63	3.29

4.2.5.3.3 Reproducibility

Reproducibility refers to the transferability of the method to other laboratories. This was not assessed.

4.2.5.4 LOD and LOQ

As this analysis was developed in order to assess a specific concentration range, the LOD and LOQ were not of particular concern, and the sensitivity of this method could easily be increased by altering the AUFS and attenuation, should greater sensitivity be required. For this application and these settings, the LOD was found to be 1 µg/mL and the LOQ was 3 µg/mL, which was the lowest concentration exhibiting a relative standard deviation of less than 10%.

4.2.5.5 ACCURACY AND BIAS

The accuracy and bias of the method were assessed by performing repeated measurements of three samples of different concentrations prepared by an independent analyst. The measurements were performed in triplicate as consecutive and replicate sequences. The data are summarised in Table 4.16.

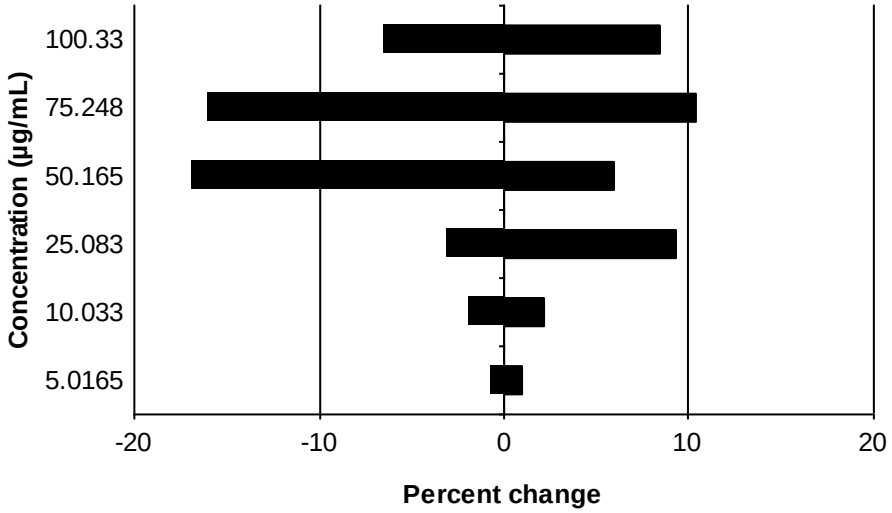
Table 4.16 Percent Error Obtained during Determination of Blinded Unknowns

Measurement	Theoretical concentration (µg/mL)	Mean determined Concentration (µg/mL) n= 3	Standard Deviation	Precision (%RSD)	% Error
Consecutive	20.066	19.7	1.0	4.8	-1.08
	60.198	57.4	1.5	2.6	-4.3
	75.248	75.0	1.0	1.4	0.0
Replicate					
	20.066	20.0	0.2	0.8	-0.2
	60.198	58.3	0.5	0.8	-2.9
	75.248	76.8	0.7	0.9	+2.4

4.2.5.6 ANALYTE STABILITY

In order to ascertain whether the samples remained stable, samples were stored at 18°C for one week and re-analysed. These showed no difference in detector response, indicating that loratadine remained stable for storage periods of one week in the refrigerator. Samples analysed at the beginning and end of a run also showed no change in response, indicating that loratadine is stable under the conditions of an analytical run. Confidence intervals were constructed and are depicted in Figure 4.12. The results of these indicate that, the changes observed are neither significant nor relevant, and although the changes observed for the more concentrated solutions are fairly large, the relative standard deviations for these measurements are less than 7%, falling within the limit of 10% set in our laboratory.

Figure 4.12 90% Confidence Intervals for the Difference in Response for Loratadine Solutions Stored for 1 Week



4.2.2.6 CONCLUSION

The method proposed by Chandrashekar *et al* was found to be suitable for the analysis of loratadine from tablets following slight modification. It provided rapid, sensitive and quantitative analysis for loratadine. The sensitivity can be increased should the quantitation of lower concentrations of loratadine be required.

CHAPTER 5
DISSOLUTION STABILITY ASSESSMENT

5.1 INTRODUCTION

Drug compounds are usually chemically reactive entities with functional groups which provide the reactive sites necessary to produce a therapeutic effect. However, the presence of these functional groups also increases the susceptibility of the molecule to chemical reactions outside the body, which may lead to degradation and a subsequent loss of the therapeutic effect. In addition, excipients used during dosage form manufacture may be sensitive to factors such as temperature, humidity or may undergo oxidation, causing a change in dosage form appearance (and patient acceptability), behaviour, safety, ease of use or efficacy [218]. This is of particular importance with respect to sustained release dosage forms, as any loss of sustained release characteristics will lead to dose-dumping with consequently elevated levels of drug in the body, and an associated risk of adverse or toxic effects. Preformulation studies provide the manufacturer with an indication of the reactions to which a drug and the excipients used in a dosage form may be sensitive. Precautions can be taken to minimize the influence of these variables.

Drug compounds are susceptible to degradation by four principal mechanisms: hydrolysis, photolysis, oxidation and thermolabile reactions. These reactions may occur in isolation or in combination, and the susceptibility of a drug compound to each reaction type will determine its overall susceptibility to degradation. Chemical stability can be seen as the ability of a drug compound to withstand the effects of moisture, light, air and heat, and as such depends on the physical and chemical properties of the dosage form components and on the packaging or containers used for storage [219]. Physical, chemical and microbial changes should all be assessed [219], although chemical stability does not necessarily imply that the drug release profile will remain unchanged [220]. During the manufacturing process the manufacturer is able to control the temperature and humidity

to which the dosage form and its constituents are exposed, and if necessary can limit the exposure to UV radiation or oxygen. However, the manufacturer has very little control over any variables encountered once the dosage form leaves the manufacturing plant. In order to minimize the potential hazards to which the dosage form may be exposed, the choice of packaging becomes critical, and can do much to reduce the influence of external variables such as humidity, oxygen and light. However, the protection provided by packaging against humidity is limited, and may alter on prolonged exposure of the product to elevated temperatures and humidities [221]. Packaging also provides no protection against the effects of elevated temperature. The evaluation of the resistance of the drug compound alone and within a dosage form to temperature excursions is thus of critical importance [218]. Exposure of dosage forms to elevated temperature may alter the shelf life of the product, and may even result in physical changes in the product [222]. Product shelf life can be defined as the period of storage during which the product retains the properties and characteristics it possessed at the time of manufacture within specified limits [7]. The shelf life varies for different compounds, and usually 10% degradation is the maximum degradation is allowed. The effect of temperature excursions may differ depending on the duration and number of deviations from the set temperature [222]. The climatic conditions of the country for which the drug is destined must also be considered [223]. Factors such as customs delays or mishandling and transport delays, particularly in hot or tropical countries where the cold chain is not well-established are variables over which the manufacturer has no control, but nevertheless must consider, and therefore should conduct studies which provide an indication of the resilience of the dosage form to heat and humidity. In South Africa, exposure to elevated temperature is likely during drug distribution, and exposure to elevated humidity is probable. In particular, the coastal regions frequently record annual average relative humidity (RH) values of above 75 - 80% [224].

In order to minimize the incidence of unforeseen effects it is important to assess the stability of the dosage form under both ambient and accelerated conditions. Although

laboratory scale data may not provide an adequate prediction of dosage form susceptibility [225] it does provide an indication of dosage form resilience and a rational basis for a more thorough and widespread investigation. The International Conference for Harmonization (ICH) has divided the world into five climatic zones according to prevailing climatic conditions. South Africa and most of the Western world fall under Zone I or Zone II [226]. Stability testing recommendations for these zones have been made in the ICH guidelines, which stipulate that dosage forms should be evaluated at 25 ± 2° C and 60 ± 5 % RH to represent ambient conditions, and at 40 ± 2° C and 75 ± 5 % RH to represent accelerated conditions [219,220]. Table 2.1 summarises the ICH requirements for Zones I and II. In addition, it has been estimated that 6 weeks at 40°C is equivalent to 3 months at 25°C [220].

Table 5.1 ICH Stability Assessment Guidelines for Solid Oral Dosage Forms in Zones I and II

Assessment Type	Temperature	Humidity
Accelerated	40° C	75% RH
Intermediate	30° C	60% RH
Long term	25° C	60% RH

5.2 EXPERIMENTAL

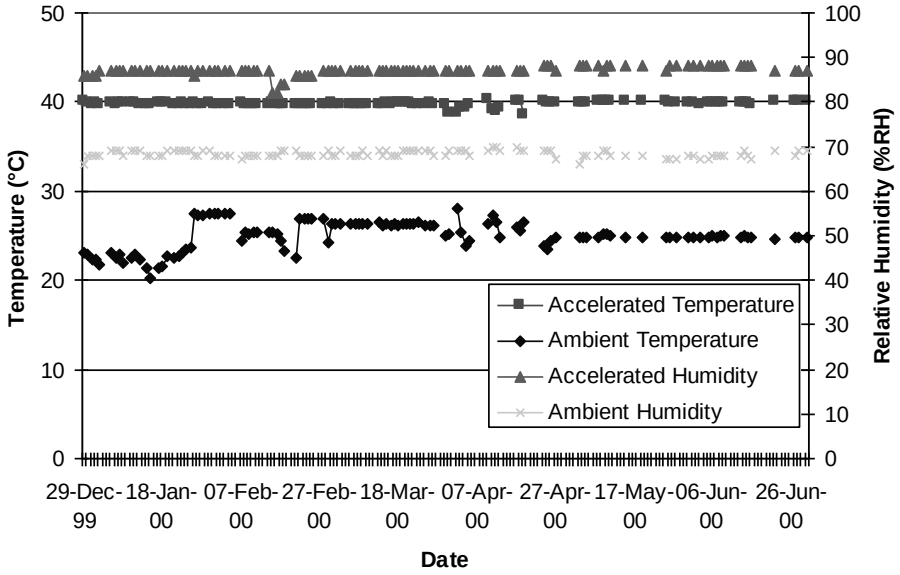
5.2.1 METHOD

Preliminary stability studies were performed on some prototype formulations for the core matrix tablets as listed in Table 5.2, as well as on Clarityne D® (Batch 9JRPA30A). These studies were conducted as feasibility studies to provide relevant data for the selection of one of the prototypes for further development. As pseudoephedrine is known to be stable in solid state and solution at elevated temperature (see§ 1.1.3), chemical stability of the drug compound was not assessed. This study was carried out to determine the ability of the selected dosage forms to retain their sustained release characteristics under the storage

conditions used.

The study was conducted over a six-month period, and as no stability chambers were available, two humidity chambers were prepared in desiccators, using saturated salt solutions. These chambers were then placed in ovens and maintained at 25 ± 2°C and 40 ± 2°C. Sodium chloride was used to obtain a relative humidity of 75%, as it is reported to produce a relative humidity of 76% at 20° and 75% at 37° [147]. Sodium nitrite, which is reported to produce a relative humidity of 66% at 20° and 62% at 37° [147], was used to provide a humidity of approximately 60%. The chambers were allowed to equilibrate before the tablets were stored for the study. After equilibration, the relative humidities obtained in the chambers were 67 and 87% respectively. For this study, ambient and accelerated conditions were designated by 25°C/ 67% RH and 40°C/ 87% RH respectively. The temperature and humidity were monitored weekly using thermohygropens (Control Company, China), which were also stored in the chambers. The temperature and humidity graphs are shown in Figure 5.1.

Figure 5.1 Temperature and Stability Records for Stability Chambers



The humidity in both chambers remained within 5% of their initial values, which is the variation allowed by ICH. However, the temperature showed more variability, and only the accelerated condition complied with the required variation of 40 ± 2°C. The ambient condition showed variation between 20.3 and 28.0°C, which is outside the allowed variation of 25 ± 2°C. The temperature of this oven was difficult to control at the low temperature range, and the internal temperature did show some variation with ambient temperature outside the chamber.

Tablets from seven experimental batches as well as Clarityne-D® (batch 9JRPA30A) were used in the study. The tablets were placed in unsealed glass jars, which were then placed inside the desiccators, which were then placed inside the ovens. Clarityne-D® was assessed in three forms:

1. As the whole tablets, exposed to the atmosphere (§ 5.2.2.1)
2. As the controlled release core, after stripping the outer immediate release portion (referred to as Clarityne-D® cores) (§ 5.2.2.2)
3. In the commercial blister packaging, in order to assess the protection afforded by the packaging versus humidity. (§ 5.2.2.3)

The prototype batches assessed are listed in Table 5.2.

Tablets from three experimental batches were stored under both accelerated and ambient conditions, while tablets from the remaining four experimental batches were only assessed under accelerated conditions. Although tablets would not usually be directly exposed to atmospheric humidity in this way, it was felt that this would provide a good indication of whether the dosage forms could resist humidity related effects. Three tablets from each batch were sampled at 1, 2, 3 and six months under accelerated conditions, and 1, 3 and 6 months under ambient conditions, as recommended by the World Health Organisation [225]. All batches were evaluated before storage to provide an initial release profile, which was used as a reference profile. The release of PSS from the tablets was assessed using the dissolution method described in Chapter 3 to monitor whether the

release profile had altered. The dissolution samples were analysed using the validated HPLC method described in § 4.1.4.

Table 5.2 Prototype Batches Selected for Stability Assessment

Batch	Granulation Fluid	Granulation Excipients	Tableting Excipients	Storage Conditions
01046001	Surelease®	Emcocel® 90M Emcompress® Methocel® K4M	Emcocel® 90M Emcompress® Magnesium Stearate	Ambient Accelerated
01049001	Eudragit® NE30D	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Colloidal Silica	Ambient Accelerated
01049002	Eudragit® NE30D (double)	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Colloidal Silica	Ambient Accelerated
01065001	Surelease®	Emcocel® 90M Emcompress® Methocel® K4M	Emcocel® 90M Emcompress® Magnesium Stearate	Accelerated
01068001	Surelease® - 10% ATEC	Emcocel® 90M Emcompress® Methocel® K4M	Emcocel® 90M Emcompress® Magnesium Stearate	Accelerated
01068002	Surelease® - 10% ATEC	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Colloidal Silica	Accelerated
01069001	Eudragit® RS30D	Emcocel® 90M Emcompress®	Emcocel® 90M Magnesium Stearate Colloidal Silica	Accelerated

5.2.2 RESULTS

5.2.2.1 CLARITYNE D®: OPEN CONTAINERS

5.2.2.1.1 Ambient Conditions

Visual Appearance

No visual changes were observed at any sample times.

Release Profile

The results for the tablets stored in open glass containers are presented in Figure 5.2. The dissolution profile remained unchanged over the six-month period, both in terms of the rate of release and the shape of the release profile.

Figure 5.2 Dissolution Profiles for Clarityne-D® After Storage (Ambient Conditions)

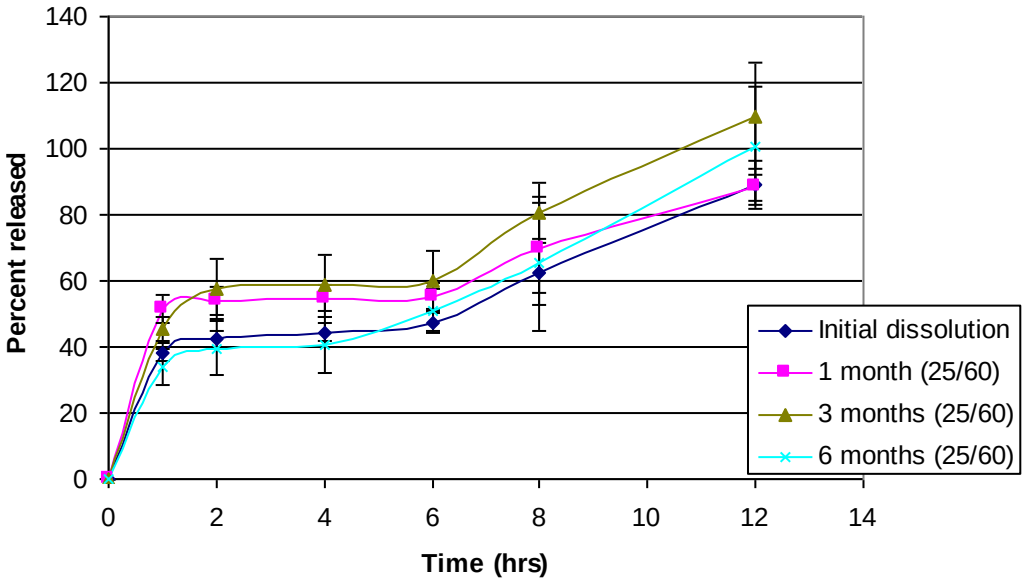
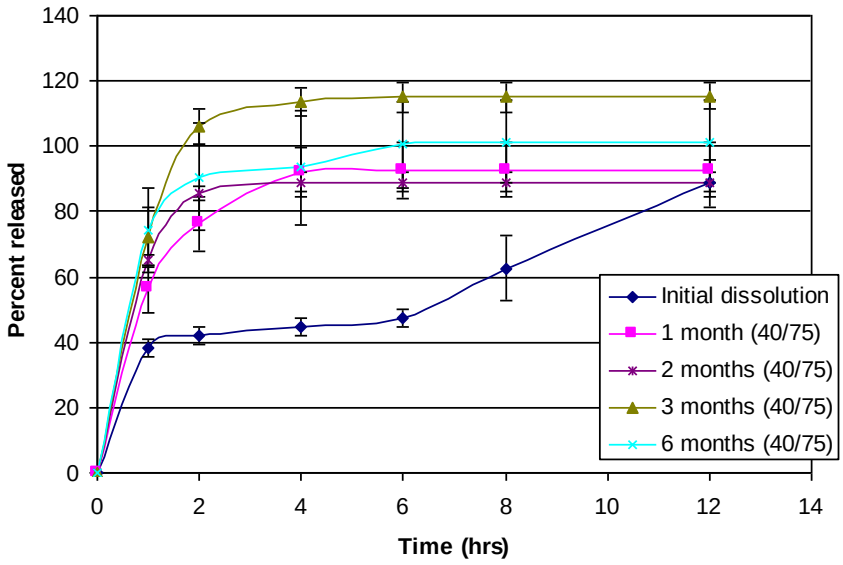


Figure 5.3 Dissolution Profiles for Clarityne-D® After Storage (Accelerated Conditions)



5.2.2.1.2 Accelerated Conditions

Visual Appearance

After one month's exposure, the outer coat was found to be tacky and was easily damaged. In addition, the tablets adhered to the container. The coat became increasingly sticky over the six-month period of storage, and after three months a greyish hue rather than the original pristine white was observed. The surface of the tablet had also developed a pitted, orange-peel type appearance. These changes are unacceptable in terms of patient use. However, the effects of high humidity were expected as the removal of the outer coat was performed in this way (§ 3.7.1). These previous experiments showed that a short period of exposure to high humidity had no effect on the release profile of the core. This lack of effect is expected as this coat contains the immediate release portion, and does not contribute to the release retarding effect.

Release Profiles

A marked change in the release profile was observed after one month's exposure. As illustrated in Figure 5.3, the release characteristics were altered substantially, with a considerable change in the shape of the profile and the rate of release. After one month 100% of the PSS dose was released after 4 hours, while after two, three and six months, 100% was released after 2 hours, as shown in Figure 5.3. This constitutes a considerable loss of sustained release properties, and would hold serious implications for therapeutic efficacy and safety of this dosage form, as the patient would effectively receive a double dose of PSS within two hours, with probable adverse effects.

5.2.2.1.3 Discussion and Recommendations

Clarityne-D® appears to be relatively stable at moderate temperature and humidity levels, but is sensitive to elevated temperature and humidity. The rate controlling component of Clarityne-D® is a zein coat, which surrounds the inner core. Zein is reported to be stable to elevated temperature up to 200°C in dry heat [147], but no published data concerning its stability in moist heat was found. As zein is a proteinaceous polymer, some sensitivity

to temperature could be expected, but this may be moisture dependent, and this instability needs to be investigated further. The package insert recommends that Clarityne-D® be protected from excessive moisture.

The zein coat appeared to undergo physical changes, as its behaviour on dissolution was altered after storage under accelerated conditions. Prior to storage, the zein coat was observed to split along the tablet edge, but otherwise remained intact, and was present as a ghost at the end of dissolution testing. However, after one month's storage, the coat fragmented into small flakes after 1 to 2 hours in the dissolution medium.

5.2.2.2 CLARITYNE D®: CORES

5.2.2.2.1 Ambient Conditions

Visual Appearance

A slight, mottled discolouration of the zein was observed after one month's exposure, but there was no increase in the intensity of this change over the remainder of the six-month storage period.

Release Profiles

The dissolution profiles for the exposed cores stored under ambient conditions are shown in Figure 5.4. No remarkable changes in the shape of the release profile or the rate of release were observed over the six-month storage period.

Figure 5.4 **Dissolution Profiles for Clarityne-D® Cores After Storage (Ambient Conditions)**

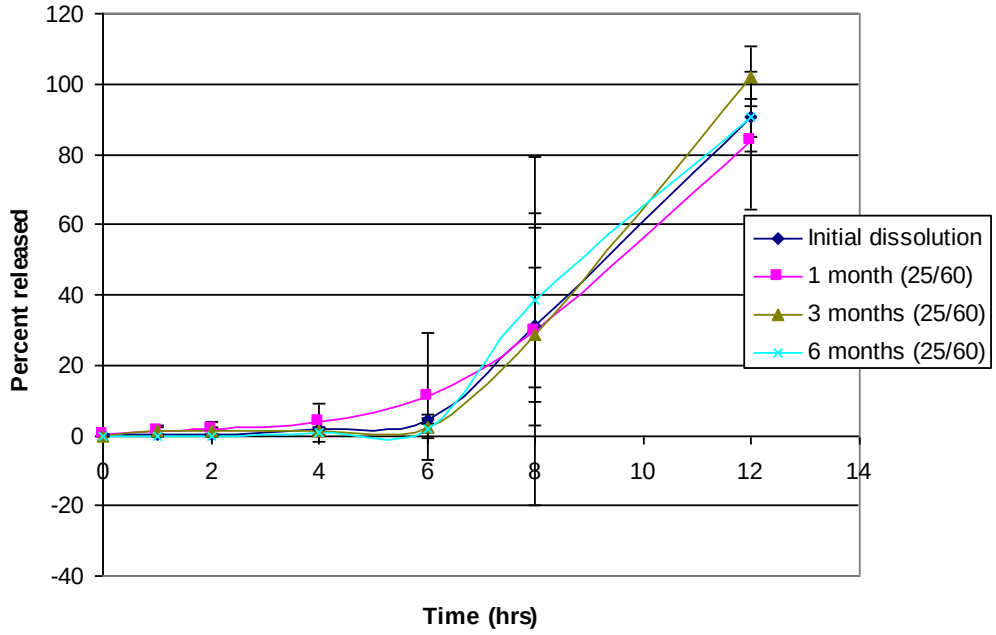
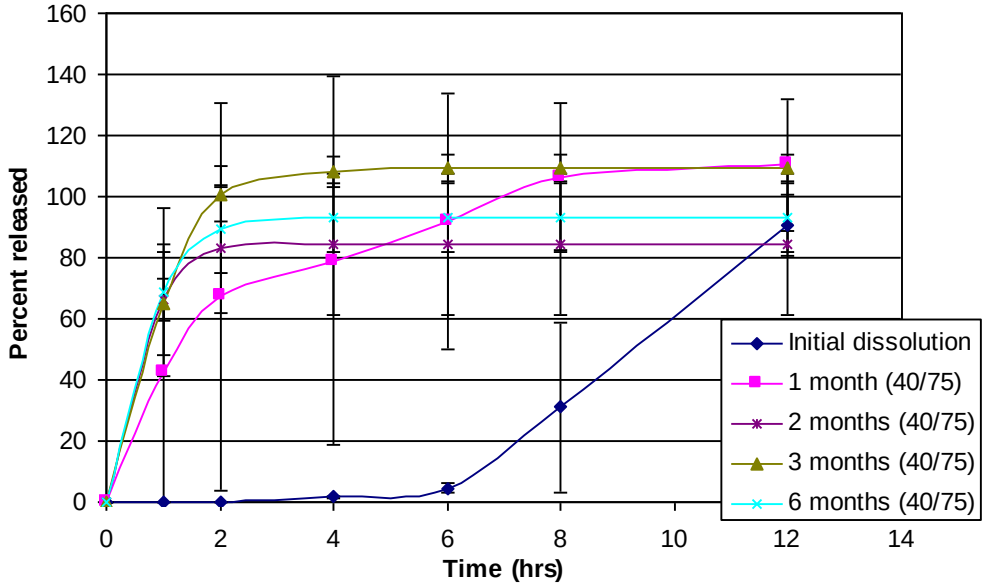


Figure 5.5 **Dissolution Profiles for Clarityne-D® Cores After Storage (Accelerated Conditions)**



5.2.2.2.2 Accelerated Conditions

Visual Appearance

Extensive discolouration and darkening of the zein coat was observed after one month's exposure, and this discolouration intensified with continued exposure. After storage for two months the cores were tacky, and adhered to the container (although they could be easily removed without breaking the coat), while after storage for three and six months the tablets were wet to the touch.

Release Profiles

Tablets stored under accelerated conditions showed a marked alteration in the shape of the release profile after one month, with 70% of the PSS released after 2 hours and 100% after 8 hours, as illustrated in Figure 5.5. Further changes in the rate and shape of the release profile were observed after exposure for 2 months, with 100% release after 2 hours. The shape of the release profile did not change markedly between 2 and 6 months of exposure. However, the observed changes following exposure for 1 and 2 months represent an unacceptable loss of release-controlling properties of the zein polymer used in this formulation.

5.2.2.2.3 Discussion and Recommendations

Zein appears to be relatively stable to moderate temperature and humidity. However, it undergoes changes on storage at elevated temperature and humidity, with a loss of rate-retarding properties, and its use as a rate-controlling membrane is therefore limited. The changes appear to occur relatively rapidly, with a substantial loss of sustained release properties after only one month of exposure. The results for the tablets exposed to accelerated conditions for one month seem to indicate that the whole tablets are affected to a greater extent than the cores, as the change in dissolution profile shape and the rate of release are greater. This apparent difference requires further investigation as it suggests a moisture-dependent effect associated with elevated temperature. The outer sugar coating present on the whole tablet appeared to retain and trap moisture. This may result in the moisture being in direct contact with the zein membrane, and any moisture-dependent

changes of the membrane would therefore be accelerated.

5.2.2.3 CLARITYNE-D®: BLISTER PACKED

5.2.2.3.1 Ambient Conditions

Visual Appearance

Tablets stored under ambient conditions showed no evidence of visual changes over the study period. However, the foil backing of the blister packaging was observed to disintegrate, change colour and flake, after 2 months of exposure.

Release Profiles

The release profiles for the tablets stored under ambient conditions exhibited no changes in either the shape of the release profile or the rate of release, as shown in Figure 5.6.

5.2.2.3.2 Accelerated Conditions

Visual Appearance

After two months of storage, one tablet had adhered to the packaging, but was easily dislodged with slight pressure. After three months, the backing of the blister pack had eroded over two of the tablets, and these two had adhered to the packaging, and were also slightly tacky. After six months, the tablets had become tacky and were slightly discoloured, with a greyish hue, similar to that observed for the exposed tablets. In addition all tablets had adhered to the packaging material.

Release Profiles

Changes in the shape of the dissolution profile and an increase in the release rate were observed after one month of exposure. However, this was not as marked as for those tablets stored in an exposed manner, and some measure of the controlled-release properties was retained. After two months the profile had altered completely and controlled release properties were no longer evident, with 100% of the PSS dose released after 4 hours. No further changes occurred during the remainder of the study period.

Figure 5.6 **Dissolution Profiles for Blister-packed Clarityne-D® After Storage (Ambient Conditions)**

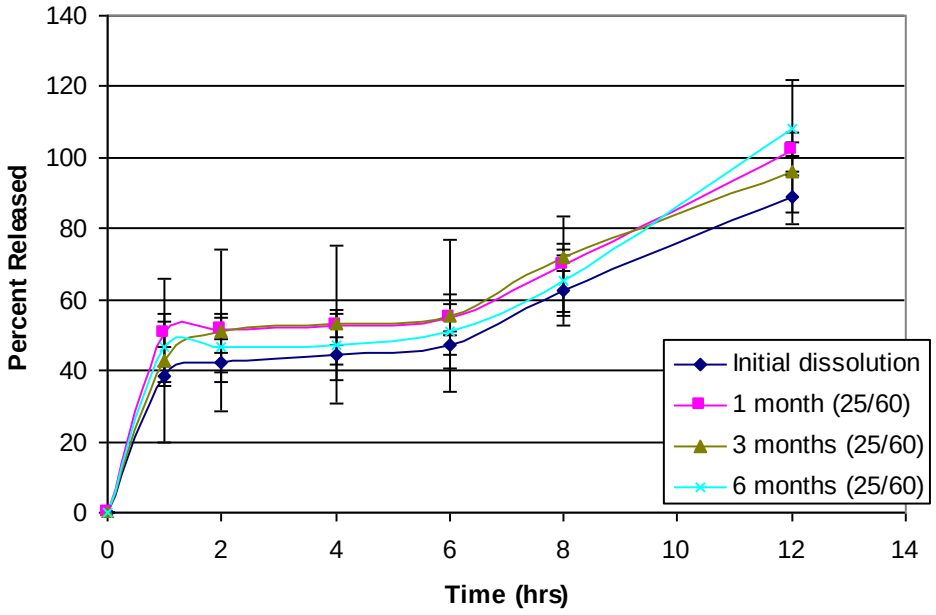
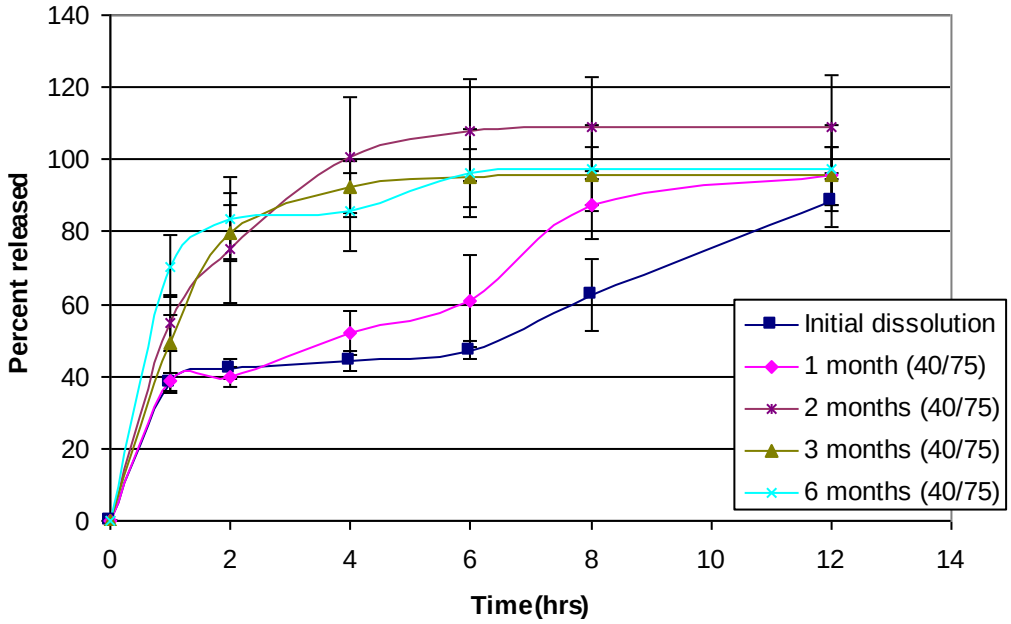


Figure 5.7 **Dissolution Profiles for Blister-packed Clarityne-D® After Storage (Accelerated Conditions)**



5.2.2.3.3 Discussion and Recommendations

The tablets stored under accelerated conditions in the blister packaging appeared to be better protected from the deleterious effects of the storage conditions as opposed to the exposed tablets, but protection was not complete, with changes to the profile evident after only one month of storage, as shown in Figure 5.7. The foil backing of the blister packaging did not maintain its integrity under either set of storage conditions, and it is therefore likely that the changes observed may be either a function of humidity, a result of an interaction with the salt-saturated atmosphere within the humidity chamber or a combination of these factors. It is possible that the metal backing reacted with the salts, causing a degradation of the foil layer, which was observed to change colour and disintegrate into small, soft flakes. The tablets were therefore no longer protected after two months. The low degree of protection afforded by the packaging is a cause for concern, particularly as this dosage form appears to be susceptible to deleterious effects when stored under the combined conditions of high humidity and temperature.

The choice of polymer used in the blister packs and the choice of backing material will determine the moisture vapour transmission rate (MVTR), and it is critical that the effectiveness of the chosen materials is evaluated [221], as some polymers, such as polyvinylidine chloride, exhibit changes in their MVTR at temperatures above 35°C, while others exhibit reduced effectiveness after storage at elevated temperature and humidity. In this instance, the material used in the packaging was not known, and therefore no specific conclusions can be drawn regarding its deterioration or the degree of protection it affords the product.

5.2.2.4 BATCH 01046002

5.2.2.4.1 Ambient Conditions

Visual Appearance

No visual changes were observed during the study period.

Release Profiles

Tablets stored under ambient conditions showed an initial decrease in release rate, which was then maintained over the subsequent assessment intervals, as depicted in Figure 5.8. This suggests the possibility of a curing process which occurs during storage. It has been reported [227,228] that ethylcellulose dispersions undergo further gradual coalescence on storage, leading to complete coalescence of the film and a consolidation of film properties. In order to assess whether this is indeed the case for this batch, three tablets were stored at 70°C for 3 hours and subsequently evaluated with respect to their dissolution profile. These tablets also exhibited a slower release profile, as illustrated in Figure 5.9, supporting the hypothesis of a curing stage. This batch contained Surelease® as the granulating fluid, and thus may undergo a curing process with consolidation of properties during the drying stage and during storage.

5.2.2.4.2 Accelerated Conditions

Visual Changes

The tablets had swollen slightly after storage for three months, and the surface was powdery. An uptake of water could be expected as the tablets contain both HPMC and MCC, which are hygroscopic and absorb water on storage [111,147,187,192]. As the sample sizes were small, no physical tests were performed, nor was water uptake assessed.

Release Profiles

The tablets stored under accelerated conditions exhibited a decrease in release rate after one month, which was subsequently maintained over the study period. The dissolution profiles are shown in Figure 5.10. These changes further support the hypothesis of a curing process. Statistical analysis of the data is discussed in §5.3.

Figure 5.8 Dissolution Profiles for Batch 01046002 After Storage (Ambient Conditions)

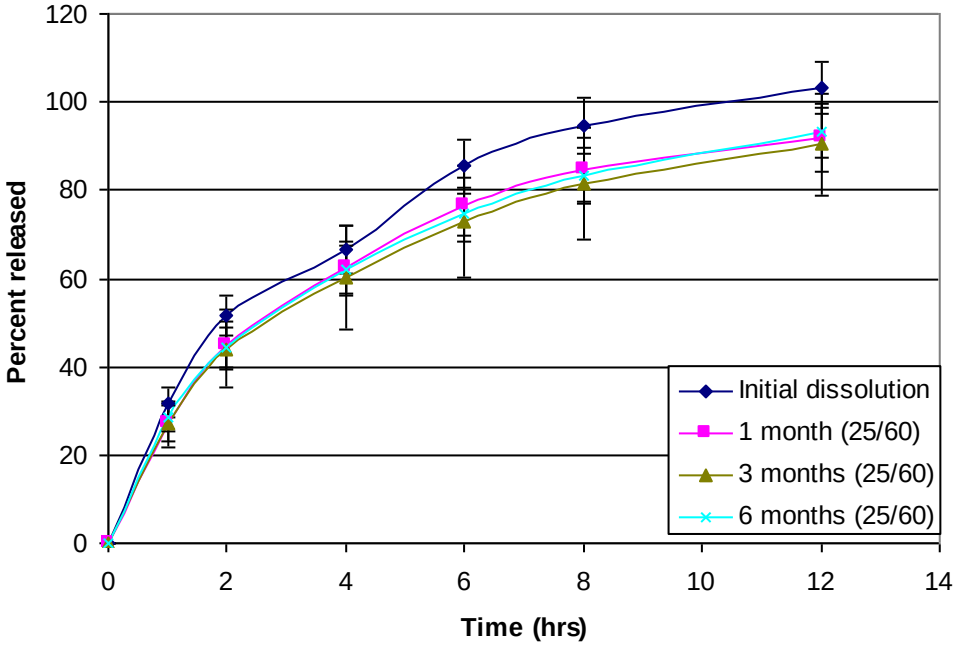


Figure 5.9 The Effect of a Curing Step on PSS Release from Batch 01046002

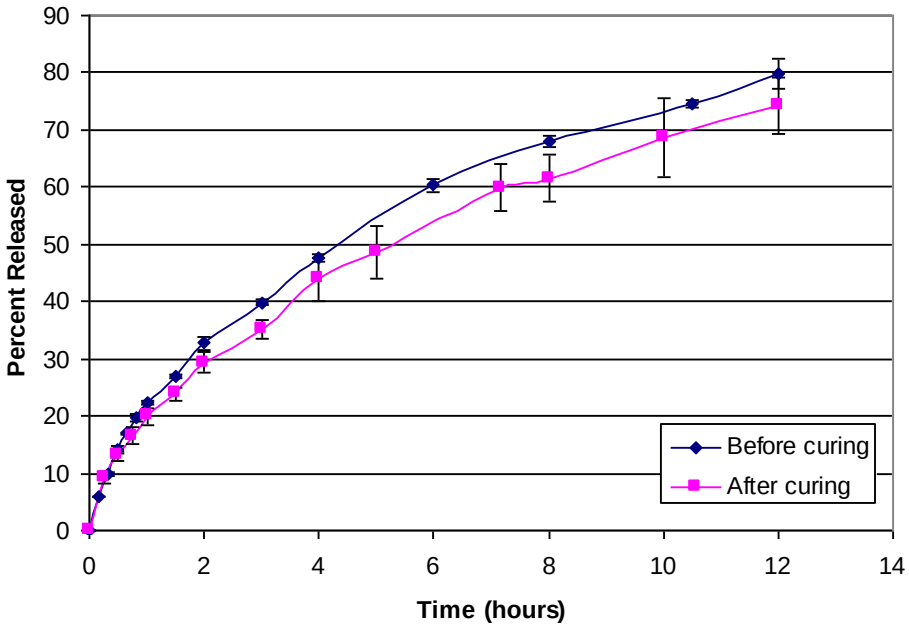
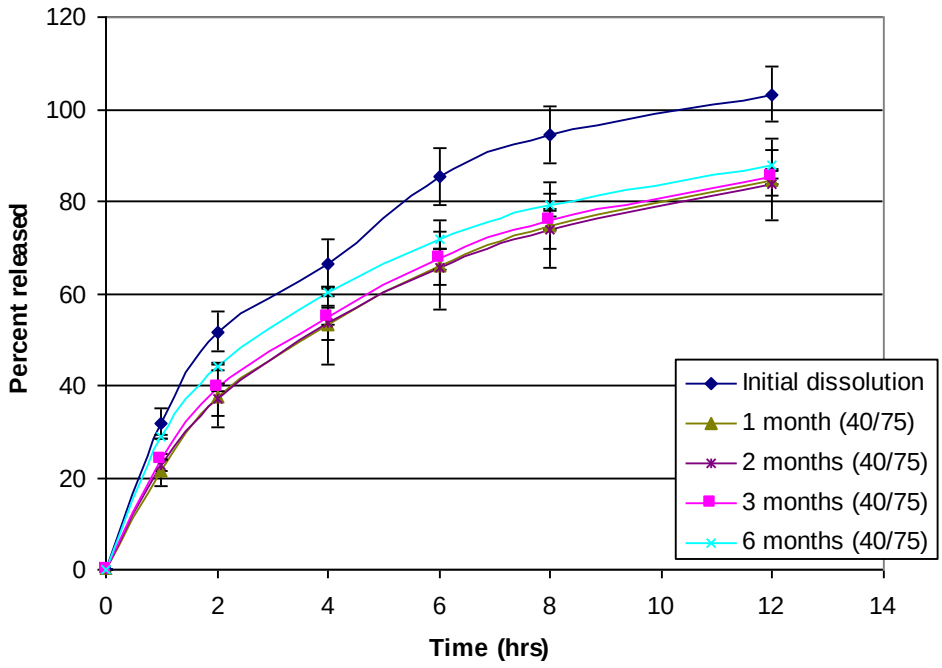


Figure 5.10 Dissolution Profiles for Batch 01046002 After Storage (Accelerated Conditions)



5.2.2.4.3 Discussion and Recommendations

The batch exhibited excellent stability under accelerated conditions over the six-month period, although the study demonstrated the need for a curing step to be built into the manufacturing process in order to eliminate any changes in the release profiles on storage and maximize the predictability of the release characteristics. This formulation showed the best resistance to elevated temperature and humidity, and was the prototype selected for further development.

5.2.2.5 BATCH 01049001

5.2.2.5.1 Ambient Conditions

Visual Appearance

No observable changes were noted for the tablets stored under ambient conditions.

Release Profiles

The tablets stored under ambient conditions showed an initial decrease in the release rate after one month of exposure, but the release rate was similar to the initial profile after three months of exposure. The release profiles are shown in Figure 5.11. After six months the release rate had decreased slightly to an intermediate value. The shape of the profile did not change substantially during this period. The fluctuations observed suggest an analytical influence rather than changes occurring within the dosage form, and do not appear to represent a relevant change as the standard deviations for all the data fall between 4.3% and 9.5% of the mean percent released.

5.2.2.5.2 Accelerated Conditions

Visual Appearance

These tablets exhibited slight swelling and softening after three months, and the surface was powdery.

Release Profiles

The release profiles from this batch are depicted in Figure 5.12. The tablets stored under accelerated conditions also showed an initial decrease after storage for one month, with a subsequent increase after two and three months of exposure, although these increases were not sufficient to return to the original rate of release, as illustrated in Figure 5.12. After six months the release profile had decreased once more, and was similar to the profile obtained after one month. As observed for the tablets stored under ambient conditions, the variation was not substantial and the shape of the profile was unchanged. The standard deviation for percent released at each time point over the study was between 4.1 and 8.8% of the mean.

Figure 5.11 Dissolution Profiles for Batch 01049001 After Storage (Ambient Conditions)

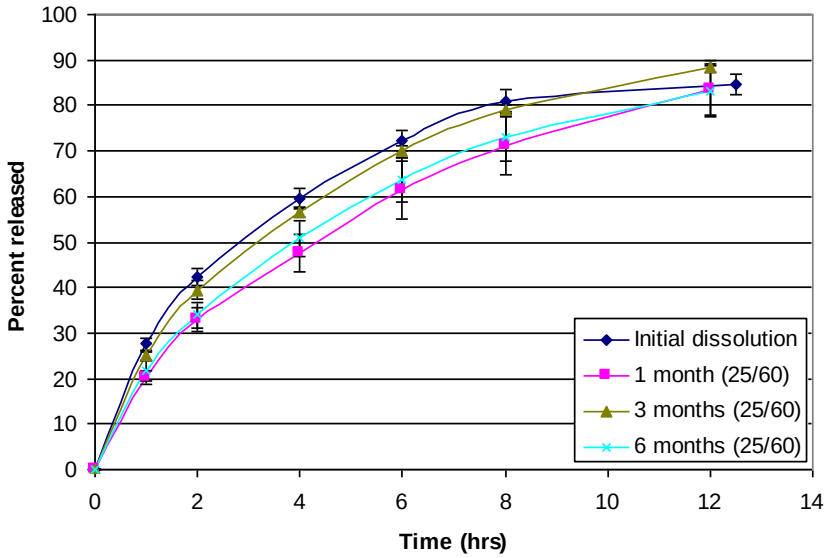
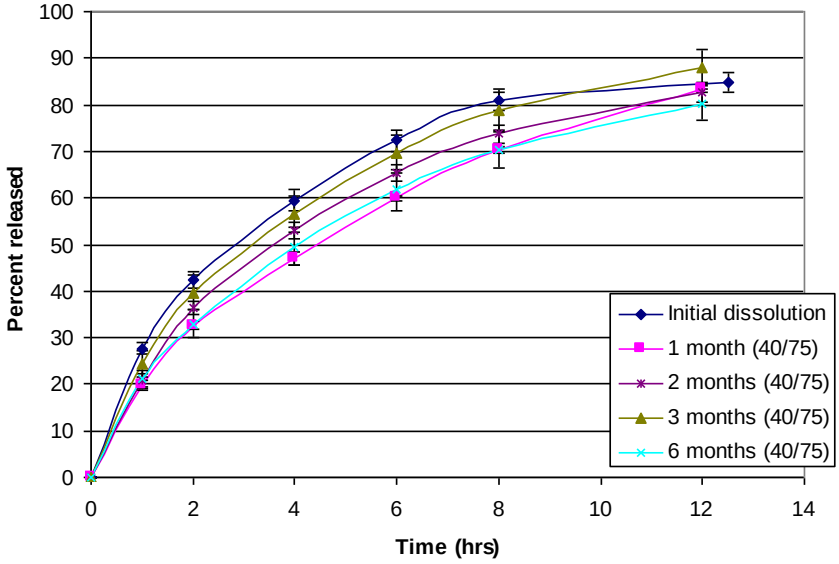


Figure 5.12 Dissolution Profiles for Batch 01049001 After Storage (Accelerated Conditions)



5.2.2.5.3 Discussion and Recommendations

The tablets stored from this batch exhibited relatively good stability, although the release profiles appear to be more variable than those obtained for Batch 01046001. There is no evidence of a curing process, and the changes observed were not found to be significant, as discussed in §5.3. The slight swelling and surface powderiness are probably a result of water absorption by MCC, colloidal silica and HPMC [111, 147]. However, any uptake of water does not appear to affect the release of PSS from this formulation.

5.2.2.6 BATCH 01049002

5.2.2.6.1 Ambient Conditions

Visual Appearance

No changes were observed.

Release profiles

The tablets stored under ambient conditions showed an initial increase in release rate after one month, which remained unaltered after three and six months, as depicted in Figure 5.13.

5.2.2.6.2 Accelerated Conditions

Visual Appearance

A slight swelling of the tablet and a powdery surface were observed.

Release Profiles

The tablets stored under accelerated conditions also showed an increase in the dissolution rate after one month's exposure, as shown in Figure 5.14. After exposure for two months the release rate had decreased to its original rate and after three months of exposure the release rate had increased to an intermediate rate. However, after six months the release rate decreased, and the resultant profile was similar to that obtained for the initial sample. As seen with the tablets stored under ambient conditions, the standard deviation bars overlap throughout the dissolution profile and the profiles are not likely to be significantly different. Statistical analysis is described in §5.3.

Figure 5.13 Dissolution Profiles for Batch 01049002 After Storage (Ambient Conditions)

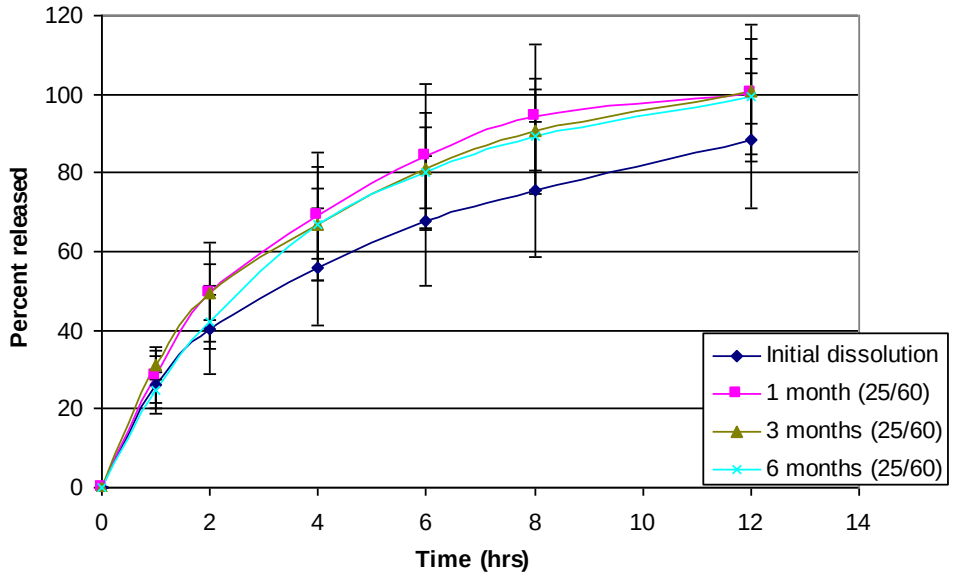
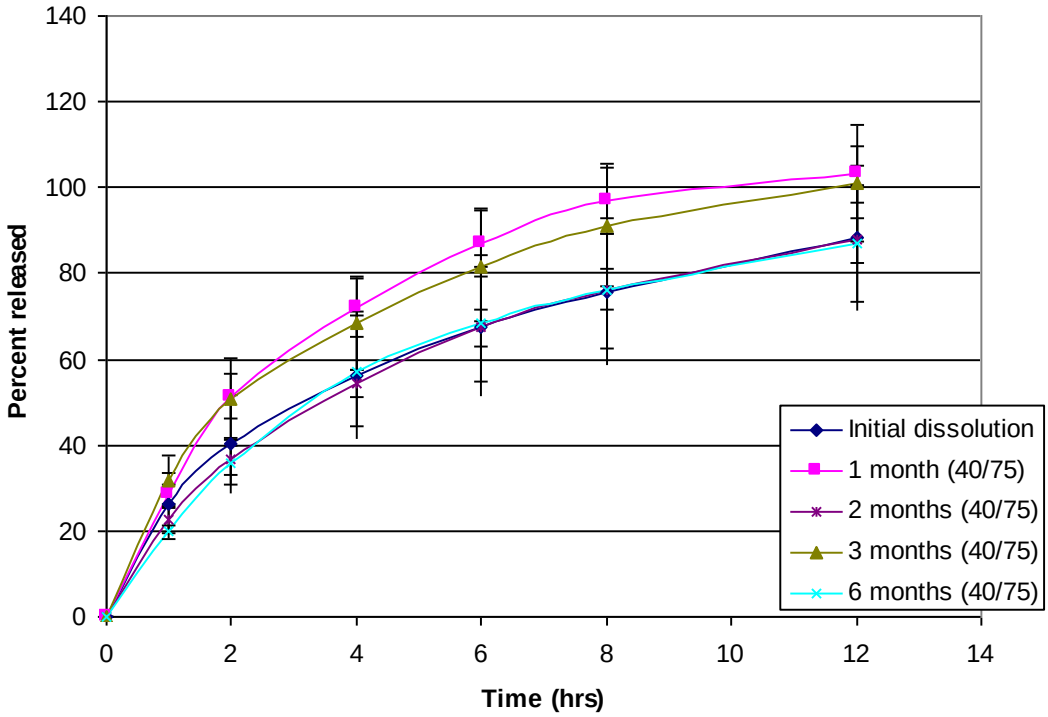


Figure 5.14 Dissolution Profiles for Batch 01049002 After Storage (Accelerated Conditions)



5.2.2.6.3 Discussion and Recommendations

This batch exhibited similar changes on storage to batch 01049001. This is expected as the two formulations both included Eudragit® NE30D as the granulation fluid. Batch 01049002 was granulated twice whereas Batch 01049001 was granulated once, as described in § 2.4.3.1.4.

5.2.2.7 BATCH 01065001

These tablets were only stored under accelerated conditions. This formulation was based on that of batch 01046002, but differed in the intra-granular proportions of PSS and MCC, and the extra-granular MCC, as described in Table 5.3.

Table 5.3 Compositions of Batches 01065001, 01068001, 01068002 and 01046002

Excipient	Quantity (% w/w)			
	01046002	**01065001**	**01068001**	**01068002**
PSS	20	15	15	14
Methocel® K4M	10	10	10	
MCC	30	35	35	36
DCP	40	40	40	50
*Surelease®	0.69	0.42.		
*Surelease® with 10% ATEC			0.41	0.34
Granules	69	67	69	78.8
Methocel® K100M	15	15	15	15
MCC	5	7	5	5
DCP	10	10	10	
Colloidal silica			0.2	0.2
Magnesium Stearate	1	1	1	1

* The amounts for the granulation fluid are expressed in g of suspension/g of powder blend

5.2.2.7.1 Accelerated Conditions

Visual Appearance

The tablets swelled slightly over time, and the surface became powdery. In addition, they were easily broken in half, whereas previously they could not be broken.

Release Profiles

This batch was expected to exhibit similar changes to Batch 01046002. However, there was no apparent pattern to the changes observed in the release profiles. The tablets exhibited an initial increase in release rate after one month of exposure, followed by a slight decrease after two months of exposure, as shown in Figure 5.15. At three months the release rate was similar to that obtained after one month, and a further slight increase was observed after six months.

5.2.2.7.2 Discussion and Recommendations

As this batch was similar to batch 01046002, similar changes were expected, but the release rate increased rather than decreased, and the changes were not as consistent as those observed with batch 01046002. The possible reason for this is that a reduced amount of ethylcellulose is present. This also supports the hypothesis that this hydrophobic polymer plays a role in the release of PSS from this formulation. The increased quantity of MCC may also have contributed to the increase in release rate, as MCC has been observed to result in increases in drug release rates relative to DCP [146]. The initial release rate of batch 01065001 was slower than that of batch 01046002, as seen in Figure 5.16. Batch 01065001 was compressed to a higher target hardness (16kp) than batch 01046002 (8kp), and this may have implications for release. The harder and more compact tablet would be expected to exhibit slower release initially, and this was observed. On storage, there is likely to be water uptake by the polymers in the two formulations, which would lead to polymer selling and an increase in porosity. Any increase in porosity would facilitate the penetration of the dissolution medium during dissolution testing, and thereby facilitate the dissolution of PSS, resulting in faster release rates. Increases in porosity are likely to lead to a greater difference in dissolution rates by this mechanism where the initial tablet is more compact, and the change in porosity represents a greater change form the initial state. The implications of the compression force used and the amount of ethylcellulose incorporated for the release rate of PSS and behaviour of these dosage forms on storage require further investigation.

Figure 5.15 **Dissolution Profiles for Batch 01065001 After Storage (Accelerated Conditions)**

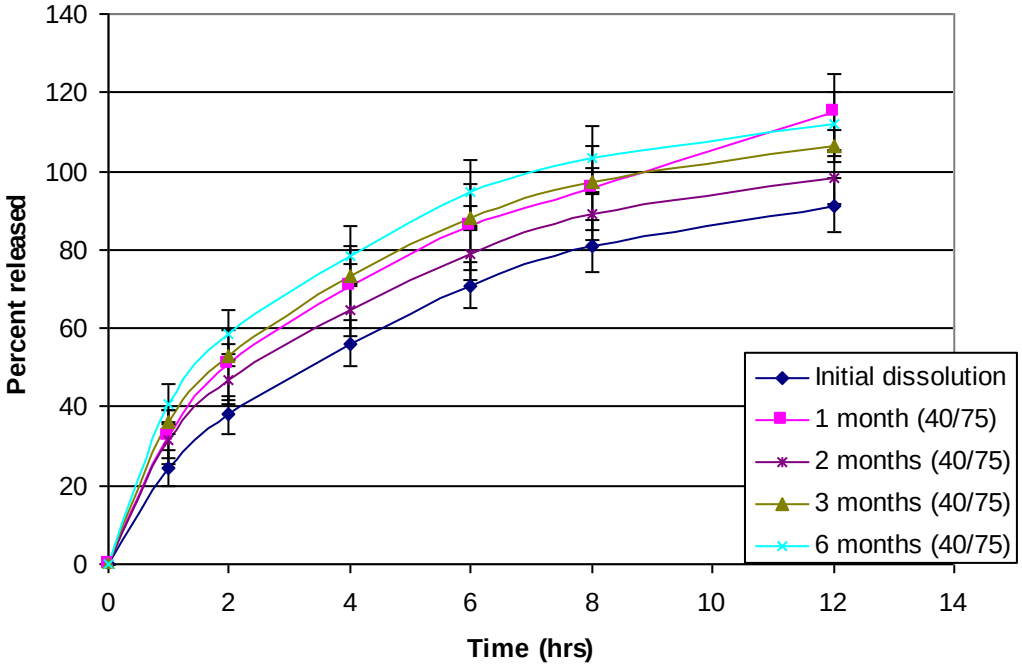
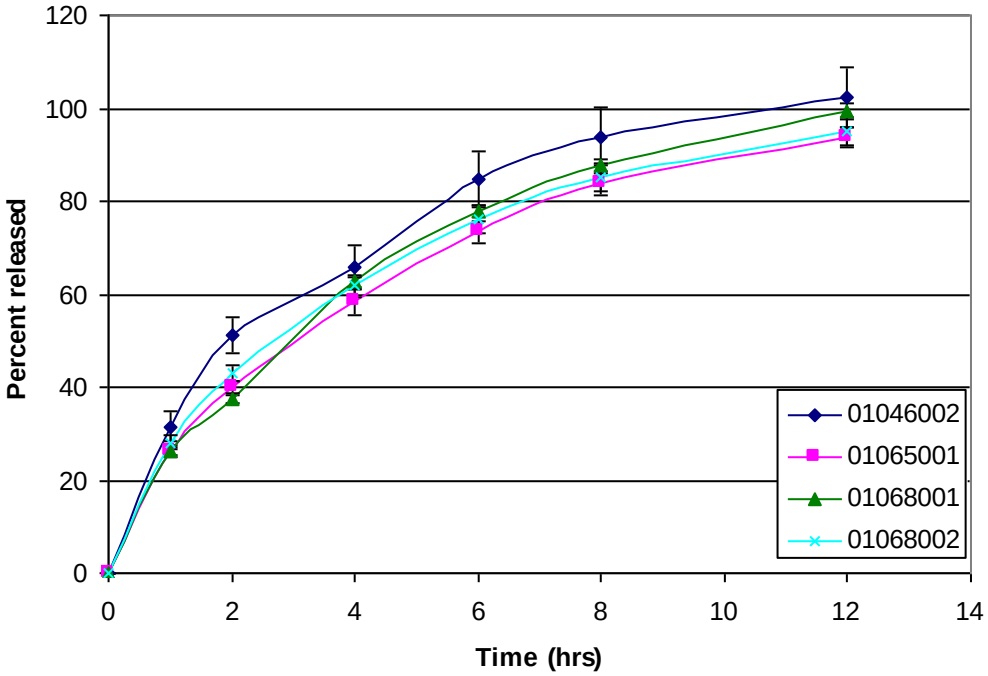


Figure 5.16 **Comparison of Batches Containing Surelease®**



5.2.2.8 BATCH 01068001

This formulation was also based on batch 01046002, with some modifications (Table 5.2), and was only stored under accelerated conditions.

5.2.2.8.1 Accelerated Conditions

Visual Appearance

The tablets were observed to swell slightly, soften and become powdery on the surface. The tablets were weighed, and a weight increase outside the relative standard deviation for weight uniformity obtained for this formulation at the initial sample time was observed after exposure for six months.

Release Profiles

A slight increase in the release rate was observed after one month, followed by a decrease after 2 months, as illustrated in Figure 5.17. After three and six months of exposure the profile followed the release pattern observed at one month, and this remained unchanged after six months.

5.2.2.8.2 Discussion and Recommendations

This batch contained ATEC as a plasticiser, an increased intra-granular content of MCC and extra-granular colloidal silica. A comparison of the initial release profiles to those of batches 01046002, 01065001 and 01068002 is shown in Figure 5.19. Less variability on storage was observed with this formulation than with batch 01065001, with the standard deviations over the study period falling between 3.5 and 5.7% of the mean percent released, although it is not as stable as batch 01046001. This batch was compressed to a target hardness (12 kp) greater than batch 01046002 (8 kp), but less than batch 01065001 (16 kp), and the reduced variability relative to batch 01065001 supports the hypothesis that the harder tablets are more affected by any absorption of water during storage than the softer tablets, particularly as the ethylcellulose content is similar. Colloidal silica is reported to absorb water [147] and can be used as a tablet disintegrant, and may also contribute to the increased release rate of PSS from this batch.

Figure 5.17 **Dissolution Profiles for Batch 01068001 After Storage (Accelerated Conditions)**

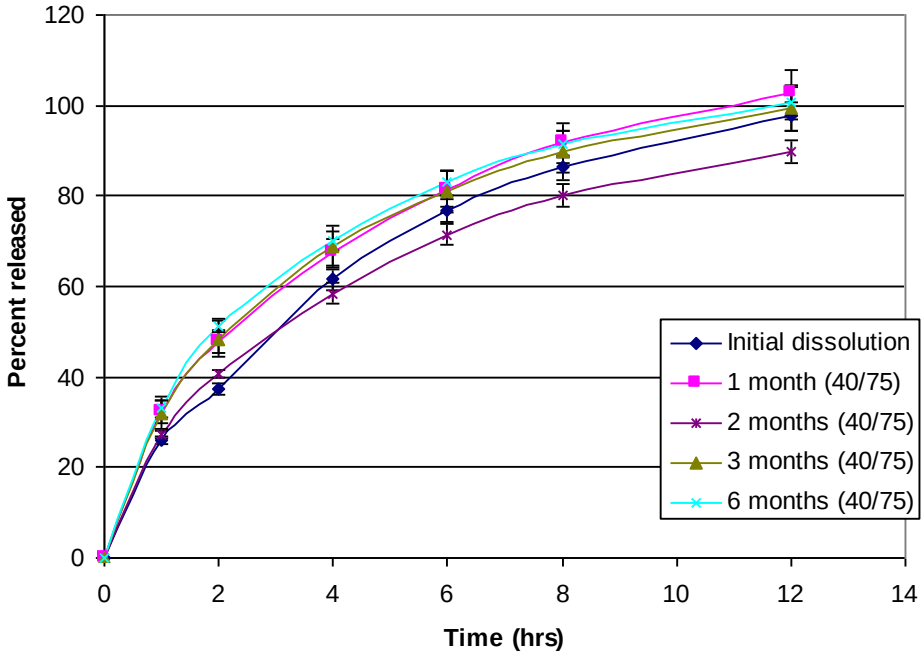
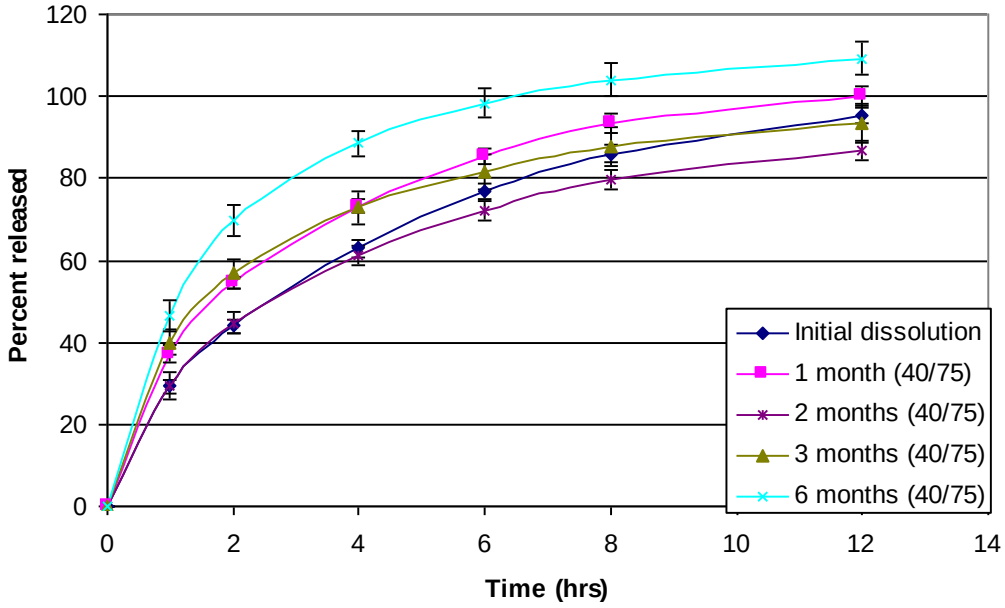


Figure 5.18 **Dissolution Profiles for Batch 01068002 After Storage (Accelerated Conditions)**



5.2.2.9 BATCH 01068002

This batch was a further modification of batch 01046001 (Table 5.2), and was only stored under accelerated conditions.

5.2.2.9.1 Accelerated Conditions

Visual Appearance

A slight softening and swelling of the tablets, and a powdery surface were observed. A weight increase outside the relative standard deviation for weight uniformity obtained initially for this formulation was observed after six months of exposure, probably as a result of water absorption by the MCC and HPMC.

Release Profiles

The tablets showed an increase in the release rate of PSS after one month followed by a decrease in release rate at two months, as depicted in Figure 5.18. After three months an increase in the release rate of PSS was observed, and a further increase occurred after exposure for six months. The shape of the release profile was not extensively altered. The standard deviation bars in this case did not overlap markedly and the overall standard deviation for each dissolution time point over the study period fell between 8.0% and 11.1%, suggesting that the changes were either a result of an analytical artefact or represented a real change in the release profile as a consequence of the storage conditions.

5.2.2.9.2 Discussion and Recommendations

A comparison of the initial profile with the other batches of similar composition is shown in Figure 5.16. This batch had an initial hardness (14 kp) comparable to that of batch 01065001 (16 kp), and showed similar changes in the release characteristics, with an increase in the release rate after six months of exposure. The inclusion of ATEC appears to make little difference in terms of the shape of the release profile. The absence of evidence of a curing process may be attributed to the presence of the plasticiser. It has

been reported that plasticisers alter further gradual coalescence of film-forming polymers [228]. The effects of altering the content of PSS, MCC and DCP appear to be small, but this requires further investigation.

5.2.2.10 BATCH 01069001

This batch was a modification of batch 01049001, in which Eudragit® RS30D was used as the granulating fluid rather than Eudragit® NE30D. In addition, it contained less intra-granular PSS and more MCC. The compositions are shown in Table 5.4. Eudragit® NE30D is a neutral copolymer of methacrylate esters. It is water-insoluble, with low water permeability, but does swell in the presence of moisture [145,147]. Eudragit® RS30D is also a copolymer of methacrylic acrid esters, but has added quaternary groups, which confer a positive charge, which increases the susceptibility of this polymer to interactions with other excipients. This polymer is water-insoluble and has low water permeability, with limited swelling behaviour [147]. A comparison of the initial release profiles is shown in Figure 5.19.

Table 5.4 Compositions of Batches 01049001, 01049002 and 01069001

Excipient	Quantity (% w/w)		
	01049001	**01049002**	**01069001**
PSS	20	20	14
MCC	30	30	36
DCP	50	50	50
*Eudragit® NE30D	0.31	0.51	
*Eudragit® RS30D			0.23
Single Granulation	**79.3**		**78.8**
Double Granulation		**78.8**	
Methocel K100M	15	15	15
MCC	5	5	5
Colloidal Silica	0.2	0.2	0.2
Magnesium stearate	0.5	1	1

* The amounts for the granulation fluid are expressed in g of suspension/g of powder blend

Figure 5.19 Comparison of Batches Containing Eudragit® NE30D and RS30D

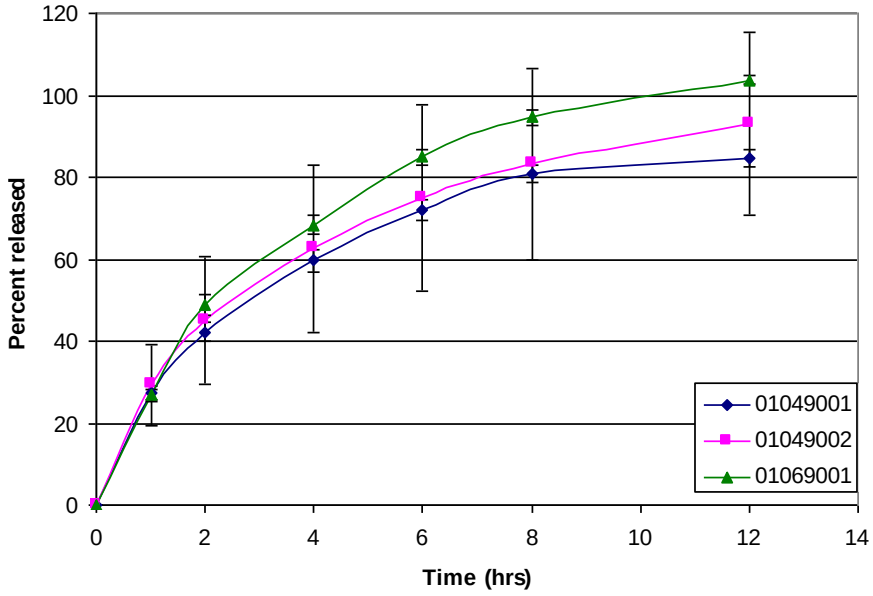
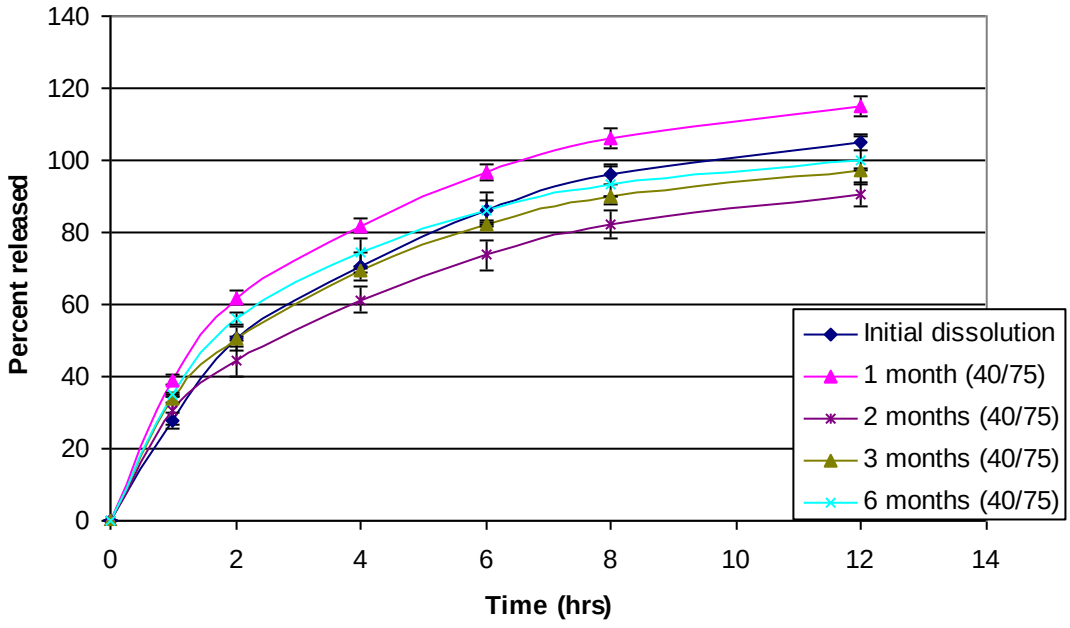


Figure 5.20 Dissolution Profiles for Batch 01069001 After Storage (Accelerated Conditions)



5.2.2.10.1 Accelerated Conditions

Visual Appearance

Slight swelling, softening and a powdery surface were noted after storage for three months. An increase in weight outside the relative standard deviation for weight uniformity initially obtained for this formulation was observed after six month's exposure.

Release Profiles

The drug release rate from these tablets increased after exposure for one month, as illustrated in Figure 5.20. After two months of exposure, however, the release rate decreased, followed by a slight increase at three months of exposure. This trend continued, with the six-month samples exhibiting a similar release profile to the initial samples. The standard deviations for percent released lay between 4.7 and 8.9% of the mean.

5.2.2.10.2 Discussion and Recommendations

Eudragit® RS30D is reported to be incompatible with magnesium stearate [147], which may account for the faster release rate as compared to batches 01049001 and 01049002. Of the Eudragits®, the NE30D polymer appears to be more suited as a rate-retarding polymer in this formulation.

5.3 STATISTICAL ANALYSIS

The statistical method described by Timm *et al* (§ 4.1.4.8) [215] was used to assess the results to determine whether the changes in the release rates from the prototype formulations constituted a relevant and significant change. As the sample sizes were too small to determine the nature of the distribution, normal distribution was assumed.

As the profile shapes were not substantially altered on storage, as seen in Figures 5.8 –

5.20, comparisons were done on the 12-hour dissolution time point. The difference in the percent released at this time point before storage was compared to the percent released after each storage interval. As it was evident that sustained release characteristics were retained in all prototype formulations, the use of the 12-hour time point was felt to provide a relevant comparison. The USP states that for controlled release dosage forms, at least 75% should be released by the specified time, which was chosen as 12 hours in this case as the desired dosage interval was 12 hours. All batches complied with this at all stability sample times with at least 75% released, indicating relatively good stability to the storage variables of temperature and humidity. A summary of the significance and relevance of any changes in the percent released by twelve hours for each prototype formulation is presented in Table 5.5, while the confidence intervals are illustrated in Figures 5.21 to 5.30.

Table 5.5 Significance and Relevance of Differences in PSS Release by 12 hours on Storage

Batch Number	Storage Condition	Exposure Time			
		1 Month	**2 Months**	**3 Months**	**6 Months**
01046002	Ambient	Decrease not significant, possibly relevant		Decrease not significant, possibly relevant	Decrease not significant, possibly relevant
01046002	Accelerated	Decrease significant, possibly relevant	Decrease significant, possibly relevant	Decrease significant, possibly relevant	Decrease significant, possibly relevant
01049001	Ambient	No significant or relevant change		Significant but not relevant increase	No significant or relevant change
01049001	Accelerated	No significant or relevant change	No significant or relevant change	No significant or relevant change	No significant or relevant change
01049002	Ambient	No significant change		No significant change	No significant change
01049002	Accelerated	No significant change	No significant change	No significant change	No significant change
01065001	Accelerated	Significant, possibly relevant increase	Possibly relevant decrease, not significant	Significant, possibly relevant increase	Significant, possibly relevant increase
01068001	Accelerated	No significant or relevant change	Possibly relevant decrease, not significant	No significant or relevant change	Significant, possibly relevant increase

01068002	Accelerated	No significant or relevant change	Significant, possibly relevant decrease	No significant or relevant change	No significant or relevant change
01069001	Accelerated	Significant, possibly relevant increase	Significant, possibly relevant decrease	Significant increase, not relevant	Possibly relevant decrease, not significant

Batch 01046002 exhibited a decrease in the release rate of PSS on storage under both ambient and accelerated conditions, but this decrease is only significant for tablets stored under accelerated conditions (Figures 5.21 and 5.22). This supports the hypothesis of a curing step for ethylcellulose which is temperature and time dependent. The relevance of the decrease in release rate is not clear, and this may become evident on repeating the study with a larger sample size. The variability in amount released for this batch is relatively large, although less than 10%, but if the assessment is confined to the amount released by batches after storage, the variability is less. These data are listed in Table 5.6. This indicates that there is good uniformity between dosage units. In addition, the results support the hypothesis of a temperature-dependent curing process, as the variability is reduced for those tablets stored under accelerated conditions, suggesting that the process is completed more rapidly under conditions of higher temperature.

Figure 5.21 90% Confidence Intervals for Batch 01046002 Stored under Ambient Conditions

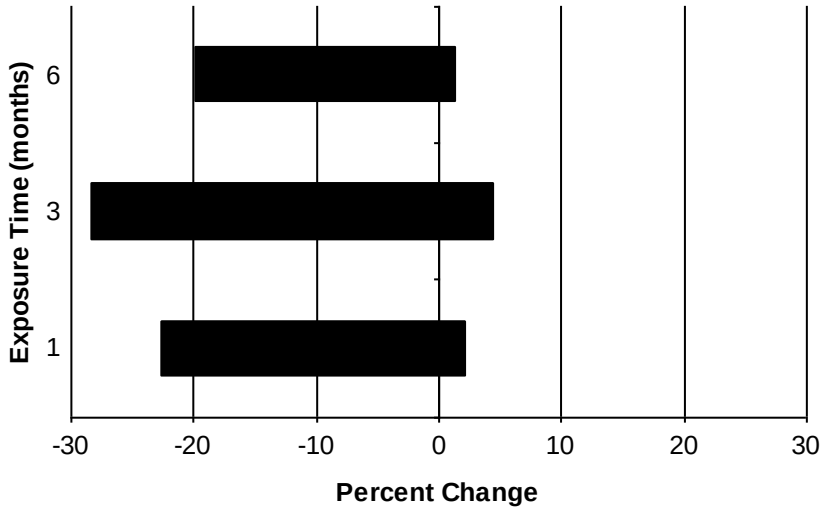


Figure 5.22 90% Confidence Intervals for Batch 01046002 Stored under Accelerated Conditions

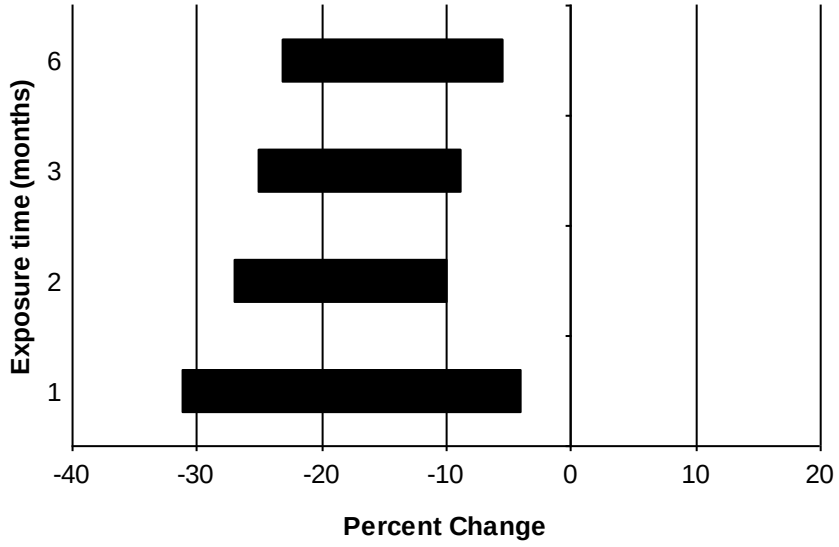


Table 5.6 Relative Standard Deviations for Amount Released at 12 hours

Batch Number	Mean ± S.D. (mg)	%RSD
01046002 Ambient	69.75 ± 6.27	9.00
*01046002 Ambient	67.81 ± 5.62	8.29
01046002 Accelerated	65.6 ± 6.21	9.46
*01046002 Accelerated	63.11 ± 3.33	5.28
01049001 Ambient	75.63 ± 3.70	4.90
01049001 Accelerated	74.55 ± 3.11	4.17
01049002 Ambient	76.09 ± 11.11	14.60
01049002 Accelerated	73.04 ± 10.42	14.26
01065001	51.06 ± 4.89	9.58
01068001	54.12 ± 3.11	5.75
01068002	54.05 ± 4.39	8.12
01069001	58.44 ± 5.12	8.76

* This data is for the amount of PSS released by 12 hours after the hypothesised curing process (in this case the data for 1- 6 months exposure)

It must be noted that not all prototype batches contained the desired PSS content of 60 mg, as these were formulated early on during the development process, and the tablet weight was not always adjusted to give the correct PSS content as the tablet weight required to give tablets of the desired hardness using the tooling available was still being assessed.

Batch 01049001 exhibited no relevant changes (Figures 5.23 and 5.24), and the only change of significance was an increase in the release rate at 3 months' exposure under ambient conditions, which was not relevant. The variability for this batch also with respect to the amount released, as described in Table 5.5, indicated good uniformity between the release profiles from the dosage units, although content uniformity was not assessed.

Figure 5.23 90% Confidence Intervals for Batch 01049001 Stored under Ambient Conditions

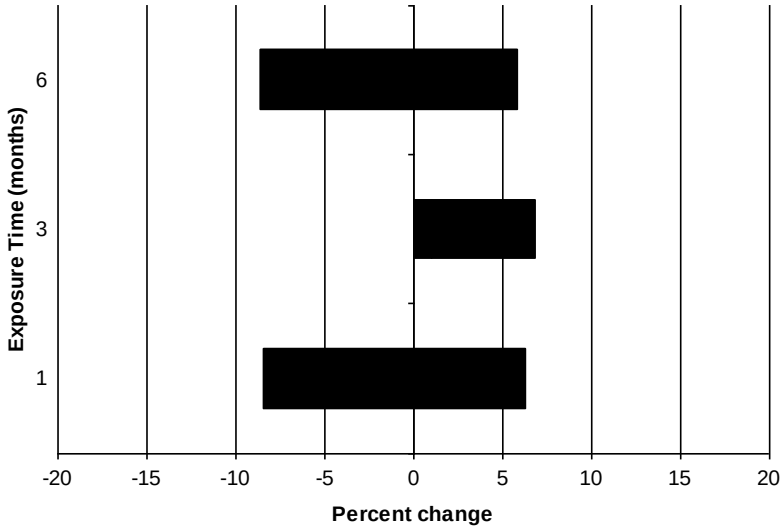
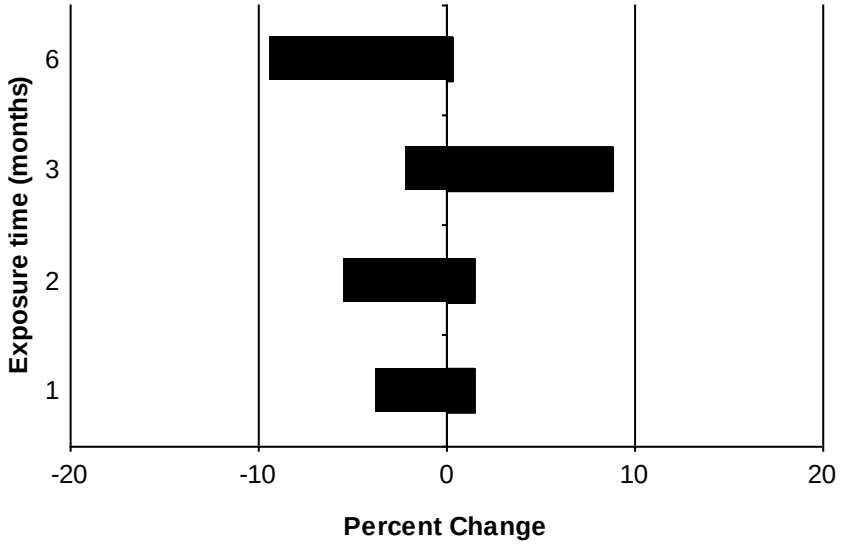


Figure 5.24 90% Confidence Intervals for Batch 01049001 Stored under Accelerated Conditions



Batch 01049002 had large confidence intervals (Figures 5.25 and 5.26) and high variability between dosage units (Table 5.5), and statistical analysis reveals that the changes were not significant. The relevance of the changes cannot be assessed as the confidence intervals suggest that there is a possible relevant increase and decrease after each period of exposure, which is meaningless. The high variability between dosage units, which is greater than 10%, suggests that this batch is not uniform, and the formulation was therefore not considered for further development. This batch was the only one placed on stability to be granulated twice, and this extra step in the manufacturing process may be the cause of the increased variability.

Figure 5.25 90% Confidence Intervals for Batch 01049002 Stored under Ambient Conditions

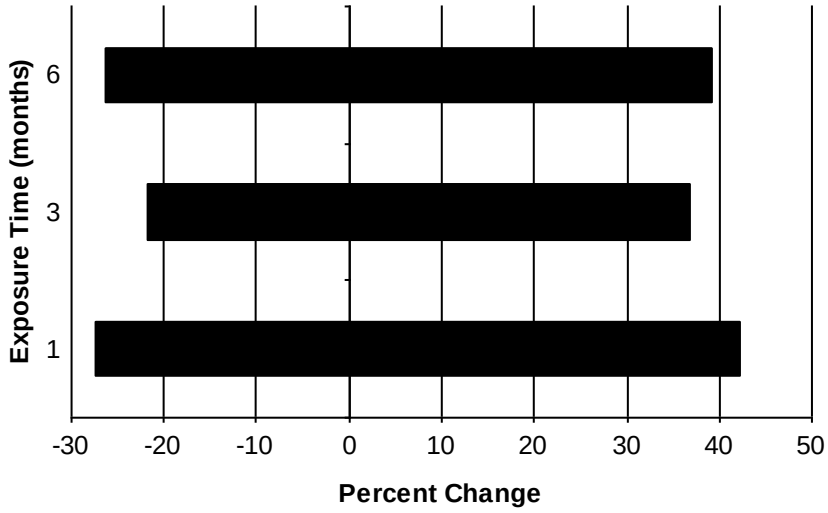
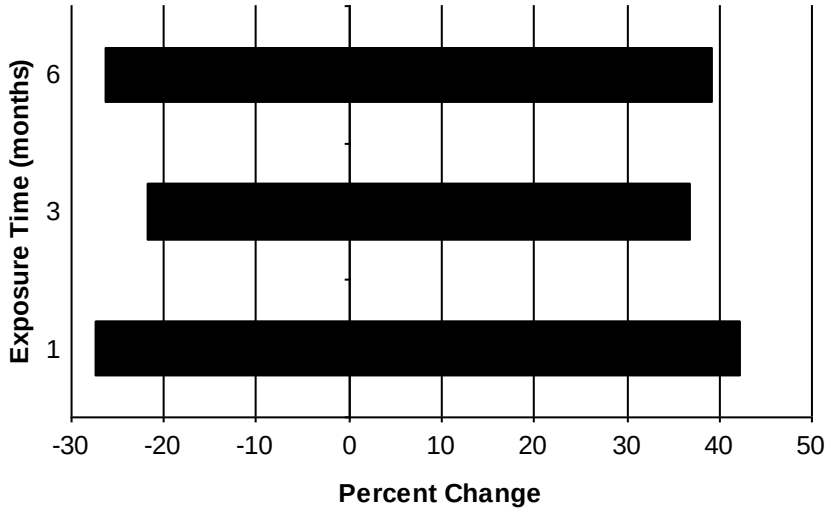


Figure 5.26 90% Confidence Intervals for Batch 01049002 Stored under Accelerated Conditions



Batch 01065001 exhibited a significant, possibly relevant increase in the release rate after exposure for 1, 3 and 6 months, and a decrease in release rate after 2 months of exposure which was not significant, but possibly (Figure 5.27). This batch was expected to undergo a curing process similar to that observed for batch 01046002, but the release rate

increased rather than decreased. The initial release rate for this batch was slower than that of batch 01046002, as illustrated in Figure 5.16, probably as a result of increased hardness. The effect of water absorption on storage is likely to increase tablet porosity and facilitate the penetration of the dissolution medium into the tablet core, increasing the release rate of PSS. This effect may counteract any curing process, particularly as the ethylcellulose content of this batch is lower than that of batch 01046002, and curing may therefore not be as predominant. The variability in the release may also be a result of a variability between dosage units, as the %RSD for the amount released from these dosage forms is relatively high, although less than 10%.

Figure 5.27 90% Confidence Intervals for Batch 01065001 Stored under Accelerated Conditions

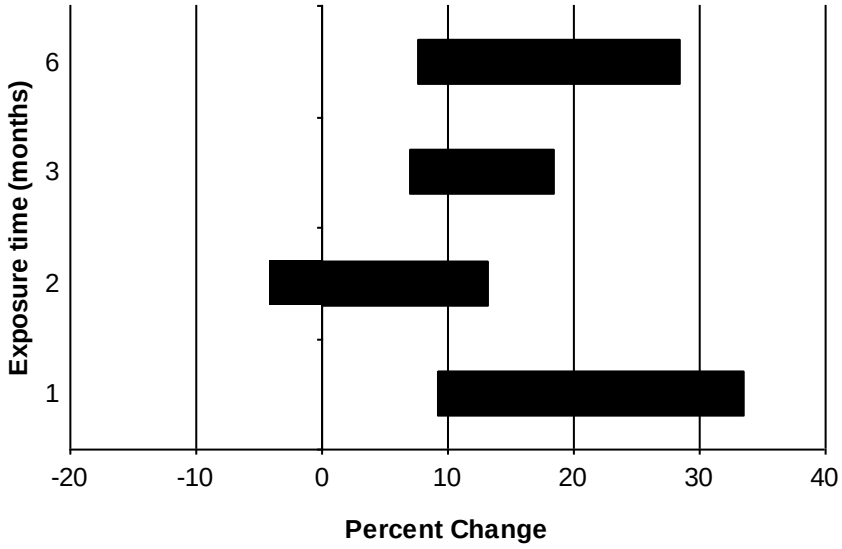
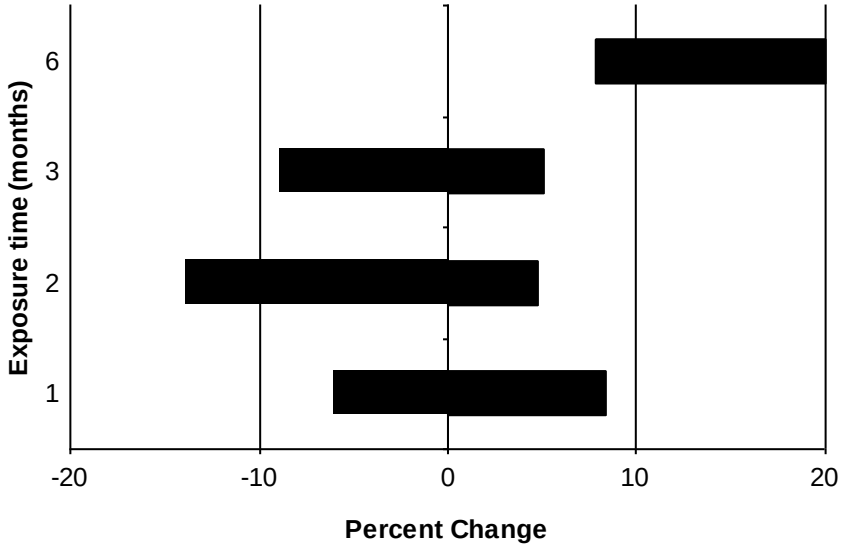


Figure 5.28 90% Confidence Intervals for Batch 01068001 Stored under Accelerated Conditions

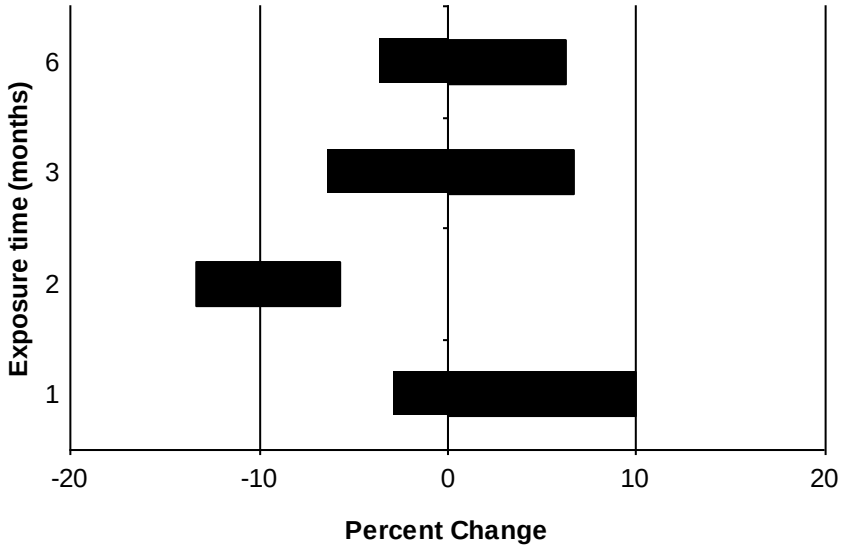


As expected, batch 01068001 behaved similarly to batch 01065001 (Figure 5.28). There were no significant changes in the release profile after 1 to 3 months of exposure, and the only change of possible relevance was a decrease in the release rate after 2 months of exposure. After storage for six months, a significant and possibly relevant increase in the release rate was observed. These changes are similar to those observed for batch 01065001, but appear to be more moderate. As this batch was of intermediate hardness (12kp) as compared with batches 01046002 (8kp) and 01065001 (16kp), this suggests that the effect of any water uptake during storage on the release profile is enhanced for tablets of higher initial hardness, as the relative change in tablet porosity would be greater. The inter-tablet variability for the amount released is relatively low, indicating good uniformity of release between dosage units.

Batch 01068002 exhibited no significant or relevant changes after 1,3 and 6 six months of exposure, but did exhibit a significant and possibly relevant decrease in the release rate after storage for two months. As expected, this is similar to the changes observed for batches 01065001 and 01068001. The changes are, however, more similar to those of

01068001. This is expected as both of these formulations contain ATEC. This batch was compressed to a similar target hardness (17 kp) to batch 01065001 (16 kp), but contains no intra-granular HPMC, present in both batches 01065001 and 01068001. In addition, the content of water-absorbing excipients is reduced. The more moderate changes support the hypothesis that water absorption during storage alters the release profile. The variability in the amount released is less than 10% (Table 5.5) and the uniformity of dosage units appears to be reasonable, with relatively small confidence intervals calculated (Figure 5.29).

Figure 5.29 90% Confidence Intervals for Batch 01068002 Stored under Accelerated Conditions

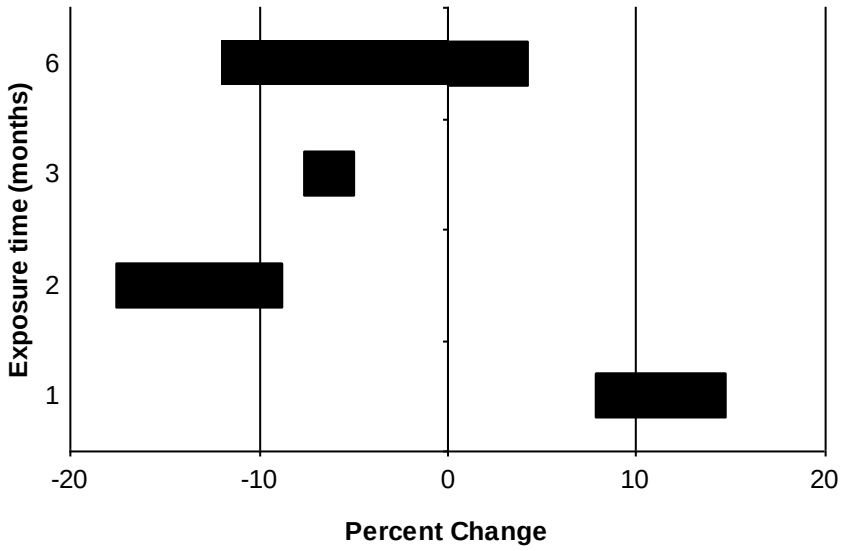


All three of these batches were expected to exhibit a curing process similar to that of 01046002, as all three contained ethylcellulose, albeit in lower quantities. It is interesting to note that while none of the three batches did exhibit a distinct curing process, all three exhibited a decrease in the release rate after two month of exposure, which was most significant for batch 01068002, the batch with the least amount of water-absorbing excipients. This trend supports the argument that the increased porosity resulting from water absorption during storage counteracts any effects of curing, particularly for tablets

of higher initial hardness. The decrease in release rate observed at two months is possibly the result of a curing process as the extent of water absorption at this time is insufficient to overcome the effect of curing, whilst after three and six months of exposure the rate-enhancing effects of water absorption are greater than the rate-retarding effects of curing. An initial rapid water uptake, followed by a second slower phase of water absorption has been observed for MCC [192] and a similar pattern may occur here. This could account for the lack of effect on the release rate observed after one month of exposure, which could be attributed to the effects of an initial rapid water absorption stage.

Batch 01069001 exhibited significant changes at one, two and three months' exposure, with possibly relevant increases at one and three months, and a possibly relevant decrease at two months. After six months of exposure a possibly relevant decrease in the release rate was observed, but this was not significant. These changes suggest that the effects of storage on this formulation are unpredictable, and that the use of Eudragit® NE30D as a rate-retarding polymer is preferable to Eudragit® RS30D for this formulation.

Figure 5.30 90% Confidence Intervals for Batch 01069001 Stored under Accelerated Conditions



5.4 DISCUSSION

As small sample sizes were used to assess drug release (n = 3), neither content uniformity assays nor physical tests were performed. However, PS is known to be stable at elevated temperature in the solid state and in solution (see §1.1.3) for periods longer than 3 months [9]. The results from these studies have limited statistical power, but enable trends to be identified, which can then be further investigated.

The use of saturated salt solutions to produce the required humidity meant that humidity could not be manipulated, and the actual humidities obtained within the chamber were higher than the theoretical values cited for the salts used and the desired levels (see §5.2.1). As 87% RH represents a large change from 75% RH, the effect of humidity may be exaggerated. However, coastal regions in South Africa have reported annual average humidities above 80% RH [224], and so the results are still applicable to the South African context. The use of saturated salt solutions also introduces the possibility of interactions between the salts and components of the tablets or packaging. This may be the cause of the degradation of the foil backing on the blister packaging, and warrants further investigation.

5.5 CONCLUSIONS

Proteinaceous zein appears to be adversely affected in conditions of elevated temperature and humidity, with changes in its release rate-retarding properties, and behaviour during dissolution testing. This raises concern about its applicability as a release-controlling polymer in controlled release formulations, and further studies are necessary to determine the exact cause of these changes. The blister packaging does appear to afford some protection to the dosage form, but this is of limited duration. The disintegration of the backing, even under ambient conditions is a cause for concern, and the stability of the

packaging materials needs to be assessed in order to determine whether this is a result of interactions with the salt-saturated atmosphere, or whether there are other contributing factors.

It has been reported that ethylcellulose dispersions undergo a curing process on storage [227,228], and this appears to occur in this study. However, curing was not observed in all formulations containing Surelease®. This may be a result of water uptake during storage, which would increase tablet porosity, with a greater change in porosity occurring for tablets of higher initial hardness. An increase in porosity would facilitate the penetration of the dissolution medium into the dosage form, resulting in more rapid release, and may counteract any curing effects. This is supported by the increased dissolution rates observed with batches 01065001 and 01068001 relative to batch 01046002, as batches 01065001 and 01068001 have an increased content of hygroscopic, swellable excipients. The reduced ethylcellulose content in the modified batches could emphasize any effect of water absorption. The use of ATEC as a plasticiser may also have altered any curing process [228]. In general, Surelease®-containing formulations exhibit relatively good stability to conditions of elevated temperature and moisture.

The Eudragits® also exhibit relatively good resistance to elevated temperature and humidity behaviour. The double granulation procedure appears to increase the variability of release while not sustaining release more effectively. Eudragit® RS30D appears to have less of a rate-retarding effect in this type of dosage form than Eudragit® NE30D.

The prototype matrix tablets exhibit improved stability of release on storage as compared to the commercial coated dosage form. Batches 01046002 and 01049001 exhibited the most stable release behaviour following storage. However, batch 01046002 was the formulation selected for further development as the observed changes were more consistent and appeared to enhance the rate-retarding properties of the formulation.

CHAPTER 6
COATING OF CORES

6.1 INTRODUCTION

The coating of tablets for either aesthetic or functional reasons is an extensively used and well-established technique. Functional coatings may be used to limit the rate of drug release or, if pH-sensitive, to delay drug release until that region of the intestine where the pH is optimal for drug delivery and absorption is reached [229]. The latter type is referred to as enteric dosage forms are not true controlled release systems and will not be discussed further. Coatings also increase the resistance of the dosage form to abrasion and its stability on storage [230].

There are a wide variety of available coatings and coating techniques that allow flexibility in regulating drug delivery [117]. In all instances, the end result is release by drug diffusion across the membrane, and this may occur in two ways:

1. The drug may diffuse through the membrane itself, in which case the partition coefficient between the membrane and the core is important: the drug should not have a very strong affinity for the membrane [97].
2. Diffusion may also take place through membrane pores formed by partial dissolution of either the membrane or a hydrophilic plasticiser, or as a result of manufacturing variables, such as membrane fracture on compression or incomplete film formation.

Semi-permeable films may also be used in osmotic dosage forms, where the drug is released through a small orifice, usually created by laser. The physico-chemical properties and morphology of the film are also important considerations and are dictated by the processing technique used [231]. Curing may be necessary to ensure that complete film

coalescence occurs [104,232]. The ultimate drug release profile is frequently a function of the aqueous solubility of the drug and the level of coating applied [233].

Drug release can be optimised by manipulating several parameters, the most obvious of which is the coating material. Usually tablet coats consist of insoluble polymers with added plasticiser, pigment and opacifier. The proportion and nature of the polymer, chemical properties [234], glass transition temperature [235], thermal gelation temperature [236], and the nature of the additives may affect the release of the active. The permeability of the polymer to the drug and to gastric fluids is also of particular importance [104,234].

It may be necessary to increase the permeability of the polymer, and this is achieved by the use of plasticisers such as polyethylene glycol. However, the plasticiser may increase the diffusivity constant of the active [234]. PEG 4000 has been found to be a suitable plasticiser for an ethylcellulose coated theophylline preparation, giving zero-order release at the 12.5 % level [104]. Microcrystalline cellulose did not give a zero-order release although it did improve the release profile in the same system [104]. Plasticisers facilitate film coalescence, which occurs more readily when there is a large degree of interaction between polymer and plasticiser, thus the choice of plasticiser is critical [237].

Pigments have been found to increase the tortuosity of pores that are formed within the membrane [234], and low pigment concentrations have been found to increase film resistance to drug diffusion, as the insoluble pigment particles act as a barrier to diffusion, increasing the tortuosity of the diffusion pathway [238].

The solubility of the drug in the polymer must also be considered, as the presence of dissolved drug within the membrane may alter the physical properties of the coat [233]. An alternative to film coating is compression coating, and in this case the porosity of the film is affected by the particle size of the polymer used [136].

The thickness of the coating layer can be manipulated in order to alter the rate of release [104,229,232,235], with thicker coats generally exhibiting slower rates of release. The coating process needs to be monitored closely, as drug migration into the coat during the coating process will influence the release profile, resulting in more rapid release or altered polymer permeability [232,239]. The application of an overcoat may decrease tackiness and slow release rates further [233,240].

Coating of tablets may be carried out in a pan or in a fluidised bed system. It has been found that the use of a Wurster column enables better film formation, with a more even distribution, a smoother appearance and good coalescence characteristics, as opposed to top-spray, tangential spray or pan techniques [231,241]. The Wurster technique is also suitable for the coating of beads and pellets. Several process variables also influence the quality of the film produced and hence the release rate of the active. Ichikana and Fukamori found that the length of the Wurster insert affected the smoothness of the coat [242], while Wan and Lai reported that an increase in the atomising air pressure resulted in inadequate film formation [243]. The temperature of the product bed during coating in fluidised-bed systems has been found to have a profound effect on film coalescence, with incomplete coalescence if it is too low or too high [228,237,244]. Amighi and Moes found that the curing time required to ensure coalescence of polymethacrylate films varied with plasticiser concentration, storage temperature and relative humidity [228]. In addition it may be necessary to cure the film to ensure complete coalescence or the release profile may change on ageing [228].

Latex-coated tablets have been shown to exhibit first-order release profiles [240] and coats applied from aqueous dispersions (latexes or pseudo-latexes) show final release characteristics that are influenced by the pH of the dispersion, as found for two different aqueous dispersions of ethylcellulose [232,237]. As hydrophobic polymers are more commonly used [238] for controlled-release coats, organic solvent systems have been

used to prepare the coating solutions. These offer greater protection against humidity, but may not form continuous films and dosage forms must be checked for organic residues [245]. In addition, organic solvents are often volatile and flammable and pose increased manufacturing risks [246]. Organic solutions generally afford greater protection against humidity, although non-continuous films may be formed as a result of more rapid drying [245]. Aqueous dispersions are preferred as this eliminates the need to test for residues, and minimizes the risk of explosions, but aqueous dispersions usually require a longer process time as water requires a higher temperature for evaporation to occur. This has implications for coalescence, which is likely to be more complete in these systems as a result of the slower evaporation rate allowing the polymer particles longer to coalesce under the capillary forces generated by the evaporating solvent. The solids content of dispersions and concentration of solutions used in the coating process may influence release, particularly for ethylcellulose, with lower solids content giving better reproducibility and uniformity [240,247], although using more dilute dispersions would require an increased application spray time to achieve the desired coating level. Aqueous dispersions enable the use of higher solids contents, from 10 -30% [248], but drying time may be substantially increased [230].

6.2 APPARATUS

Coating of tablets is usually performed in coating pans, although a fluidised bed drier can be used. Fluidised bed driers are more suited to the coating of granules than of tablets, although a fluidised bed drier with a Wurster insert can be used [248,249]. The fluidised bed system can be utilised in one of three conformations:

1. A top spray system, where the nozzle is located at the top of the chamber, and the coating is sprayed onto the product from above. Top spray systems are not the system of choice for sustained release coatings as the droplet travel distance cannot be controlled [249], but is the system of choice for granulation [248].

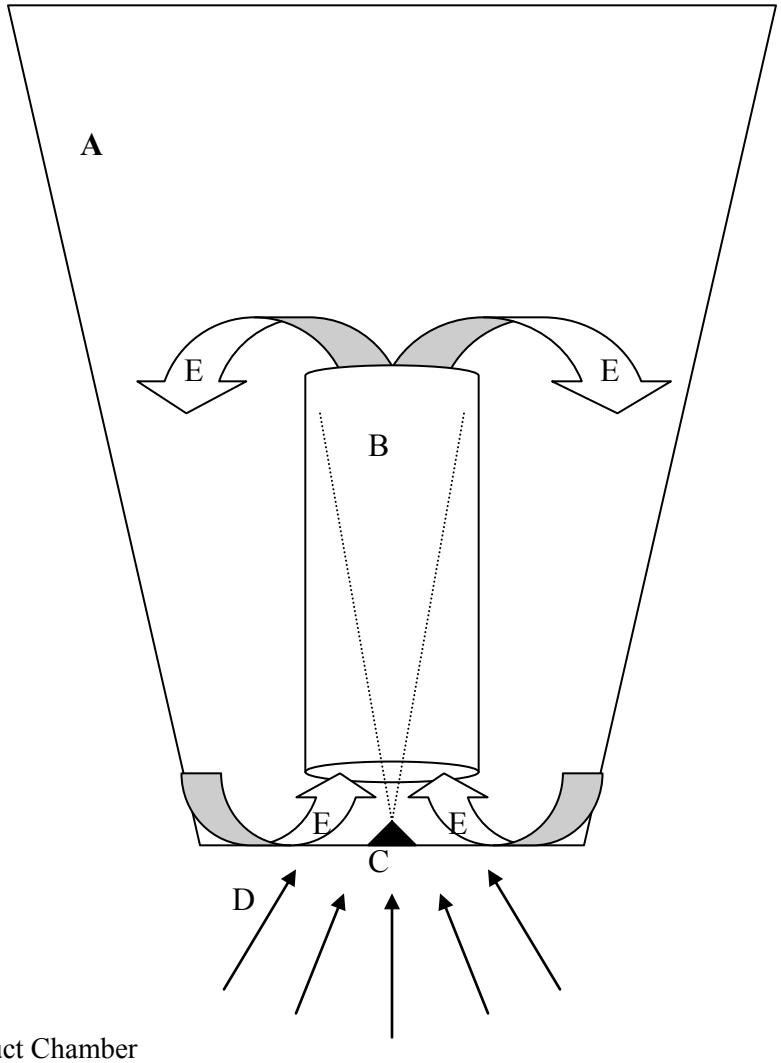
2. A tangential spray system, where the nozzle is located at the sides of the base of the product chamber and the product is sprayed tangential to its direction of motion. This system is particularly suited to the manufacture of dense pellets [248].
3. A Wurster system, where there is a central column insert, with the nozzle located at the base of this central column, and this system is most suited to coating applications [250]. In industry, precision coaters are sometimes used. These contain multiple Wurster inserts and nozzles, enabling a more rapid and efficient process.

In our laboratory, a coating pan was not available, and a fluidised bed drier with Wurster insert (Aeromatic Strea-1, AG, Switzerland) was used for the application of the coats.

6.2.1 FACTORS AFFECTING COATING

The fluidised bed drier offers good random mixing, evaporating efficiency and fast recycling [248,251], enabling the application of good quality, uniform films [252]. The film layer is built up as the substrate cycles repeatedly through the coating zone [248]. An illustration of the fluidised bed system is provided in Figure 6.1. As the substrate is fluidised, it rises upwards through the central column insert, after which it falls down on the outside of the column to the bed in a continuous cycle. The substrate is brought into contact with atomised coating solution during its passage up the column, and is dried during the downward part of the cycle by the fluidising air. The droplets of coating solution are atomised by the atomising air, after which they come into contact with the substrate. On contact they undergo spreading and coalescence as the vehicle is evaporated by the fluidising air.

Figure 6.1 Schematic Diagram of a Fluidised bed System with Wurster Insert



A - Product Chamber
B - Coating zone
C - Nozzle, with inlets for atomisation air and coating fluid
D - Fluidising air inlet
E - Path of product during coating process

There are several variables which influence the coating process within a fluidised bed system, and the final drug release profile may be influenced by one or a combination of variables [253]. These variables are discussed in the following sections.

6.2.1.1 TEMPERATURE

Temperature is an important variable, as it influences the drying capacity of the system, and consequently drying time [254]. In addition, the cooling and heating processes to which the film-forming polymer is exposed will alter the properties of the film, as it will contract or expand to varying extents. Film contraction may lead to edge splitting and peeling [255]. A high product bed temperature may prevent completion of film coalescence by increasing evaporation rates. This will lead to incomplete film coalescence and the formation of a non-continuous film, with a subsequent reduction in release rate-retarding properties [244]. Conventionally, it is the temperature of the inlet or fluidising air that can be manipulated, although the temperature of the product bed and the outlet or exhaust air should be closely monitored. A sufficiently high temperature to prevent wetting and sticking or agglomeration of the substrate is necessary [256,257], but coating efficiency is improved at lower inlet air temperatures [253] and this variable must therefore be optimised for the system. Seasonal variations in drying capacity are frequently noticed in areas of high humidity [249,254,258] and temperature may need to be altered to compensate for elevated atmospheric moisture. This is important in South Africa, where certain climatic regions experience high humidity while others experience seasonal fluctuations in humidity levels.

6.2.1.2 FLUIDISATION VARIABLES

Fluidisation of the coating substrate in the product chamber is affected by the volume of the fluidising air, the choice of air distribution plate and the height between this plate and the Wurster column (partition height) [249]. In addition, tablets have differing airflow requirements from granules and the partition height is critical parameter in ensuring smooth and rapid downbed motion [248]. The volume of fluidising air must be adjusted for the changing density in the substrate during the coating process [257] and the size of the exhaust filter must be considered as small filter sizes may become blocked and

impede fluidisation of the bed [246].

6.2.1.3 SPRAY VARIABLES

Spray rate affects coalescence, drying time, wetting and substrate agglomeration [253,257,259,260]. In turn, the choice of spray rate will be affected by the composition of the coating dispersion, the nozzle size, design and position and the atomising air pressure [247,254,257,258,261,262]. The droplet size distribution should be chosen with reference to the size of the substrate units [249], and should be as narrow as possible [261]. Increasing the atomising air pressure will usually reduce droplet size [249,263] and increase the tendency for spray-drying and inadequate film formation [243]. The nozzle height and tip size will alter the spray pattern, thus changing the effective coating zone and droplet travel distance [257]. Uncontrolled wetting and excessive agglomeration are a consequence of nozzle clogging, and should be avoided [257]. The concentration of solids in the coating solution affects the spray rate as higher concentrations are generally more viscous and consequently reduce the ability of the droplets to spread sufficiently on contact with the substrate, leading to increased spreading time [249]. High concentrations of solids allow a reduction in coating process time, as application rates are higher [247,248,249] and frequently produce slower drug release rates [253]. However, reproducibility is improved when lower polymer concentrations are used [247].

6.2.1.4 APPARATUS VARIABLES

The length of the Wurster insert can influence the surface characteristics of the applied coat [242]. The length of the product chamber for coating applications should be extended relative to the length used in granulation applications [264]. The choice of apparatus will affect the quality and functionality of the coat [254]. The substrate in a fluidised bed system is subjected a large degree of mechanical stress, and thus the integrity of the substrate surface and its resistance to abrasion are important criteria for

consideration [248,249,254,265].

6.2.1.5 OTHER CONSIDERATIONS

The structure and uniformity of the membrane will be affected by the solids content of the coating solution, the application spray rate, atomisation air pressure and drying time [254]. Film formation is achieved in two stages. There is an initial, rapid evaporation of the solvent from the substrate surface, which is followed by a slower diffusion of solvent molecules through the polymer gel with a gradual loss of macromolecule mobility [254]. Any excipients contained in the substrate may alter its ability to absorb liquid during coating, and therefore film adhesion. Any uptake of water into the substrate will increase the required drying time, and may result in stability concerns for drugs sensitive to hydrolysis. In addition, the likelihood of drug migration into the coating layer is increased, which may affect subsequent release rates from the dosage form [230,244,254]. The inclusion of pigments in the coating solution may decrease the moisture permeability of the film, which will alter final dissolution rates and possibly drying time [265,266].

6.3 SUSTAINED RELEASE COATING

6.3.1 OBJECTIVE

After the development of a suitable core tablet, it was necessary to introduce a lag phase into the release profile. This is required to prevent a burst effect with simultaneous release of PSS from the sustained release core and the immediate release portion of the formulation. The use of coatings to enable zero-order release rates and prevent burst effects has been documented previously [267,268].

6.3.2 MATERIALS AND METHODS

In order to include a lag phase, it was necessary to select a hydrophobic polymer to coat the tablet. Ethylcellulose and the polymethacrylates were considered as appropriate coating materials for this application. Ethylcellulose is the most widely used hydrophobic polymer [269] and forms tough and flexible films which are stable to heat and light, as well as being tasteless and odourless [269]. As ethylcellulose has a very low degree of water permeability [270], despite being wettable [271], the inclusion of large amounts of plasticiser may be necessary to ensure drug release [266]. The Eudragits®, or polymethacrylates, are also hydrophobic and can be selected according to defined swelling and permeability characteristics [269]. However, they form brittle films, and therefore a plasticiser is usually required [230]. Coagulation, should it occur, is irreversible [266]. In addition, the use of additives in these films may lead to film disintegration within minutes of exposure to dissolution media [230].

Ethylcellulose was selected as the film-forming polymer for the development of the selected formulation, and was used in the form of Surelease® (Colorcon, Kent, UK), which is a 25%w/v dispersion of ethylcellulose in ammoniated water with oleic acid and dibutyl sebacate, a plasticiser. The plasticisers serve to reduce internal stresses in the film, and may facilitate the coating process, increasing the mechanical stability and cohesive strength of the film [269]. However, plasticisers may also alter the release profile, particularly if they are hydrophilic, as these undergo leaching from the coat during dissolution studies, resulting in the formation of aqueous channels or pores through which the drug is then able to diffuse [269]. The use of pigments and opacifiers should be avoided in films that have been applied to modify the drug release rate, as they may alter film permeability or behaviour [269]. In this study, triethyl citrate (TEC, Morflex, North Carolina, USA) was used as a plasticiser where required.

The coating of the prototype tablets was performed using an Aeromatic Strea-1 fluidised

bed drier (Aeromatic AG, Switzerland), with a Wurster insert 182 mm in length. A peristaltic pump (Masterflex L/S, Cole-Palmer instruments, Illinois, USA) was used to deliver the coating suspension. The coating conditions are listed in Table 6.1. Surelease® was diluted from 25.4% solids to 15% solids with distilled water prior to use to facilitate spraying and increase the reproducibility obtained.

Table 6.1 Coating Conditions

Parameter	
Inlet air temperature	50 - 52°C
Outlet air temperature	46°C
Product Bed temperature	47 - 49°C
Spray rate	3.8 – 4.1 g/min
Atomising air pressure	20 psi
Drying temperature	40°C
Drying time	15 min

6.3.3 RESULTS

6.3.3.1 PRELIMINARY STUDIES

Initial coating experiments were performed on batches 01065001 and 01066001. Batch 01065001 was coated with unplasticised ethylcellulose to an actual weight gain of 10%, while 01066001 was coated to actual weight gains of 2.4, 4.3 and 7.1%. Dissolution studies were performed using USP Apparatus 3 on 6 tablets from each coating level under the conditions described in § 3.4. The release studies were conducted over a 22-hour time period, and the release profiles are illustrated in Figure 6.2. As seen in the graph, the lag phase varied according to the coating level, as expected. However, the release rate was slow, and for the 10% coating, no release was observed by 22 hours. It was interesting to observe that one tablet in the 4.3 and 7.1% batches behaved differently from the other 5, with shorter lag times. This suggests that the coating process is not ideal, and variations

in coating levels exist between tablets. This is in contrast to the literature, where Wurster systems are reported to be suitable for the coating of tablets [248,249,250]. However, the shape of the tablets used in this study may have influenced the capacity of the system to produce uniform coats, as they were extra deep convex, with a short edge. In addition, the fluidizing air flow appeared to be insufficient, requiring the use of high atomising air pressures, which would have affected the spray pattern and efficiency, as discussed below. It is possible that the use of a larger scale apparatus would overcome some of these difficulties.

As there was a pronounced effect on the release rate of PSS, and as no PSS appeared to be diffusing through the membrane for prolonged periods, TEC was included in the dispersion at a level of 10% of the solids content, in an attempt to increase the permeability of the ethylcellulose membrane. Batch 01065001 was coated with the plasticised ethylcellulose to levels of 2.4, 2.8 and 5.3%, and the release rate assessed over 22 hours. Once again, lag phases were observed, varying with the coating level, as presented in Figure 6.3, followed by zero-order release. The exception to this was the 2.4% level of coating, where no lag phase was observed, and zero-order release was observed over the 24-hour period. The release rate was more rapid in these tablets than in those not containing TEC. Once again, the coating was observed to split along the tablet edges in all tablets showing release, followed by swelling of the matrix core, predominantly in an axial direction, as shown in Figure 6.4.

Figure 6.2 Effect of an Ethylcellulose Coating on PSS Release from Hydrophilic Matrices

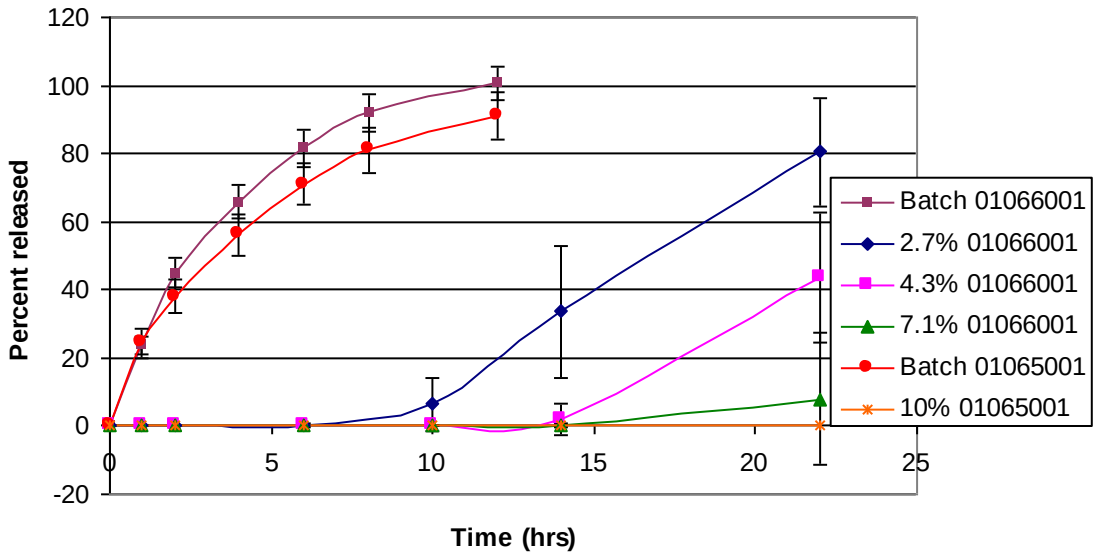


Figure 6.3 Effect of a Plasticised Ethylcellulose Coating on PSS Release from Hydrophilic Matrices

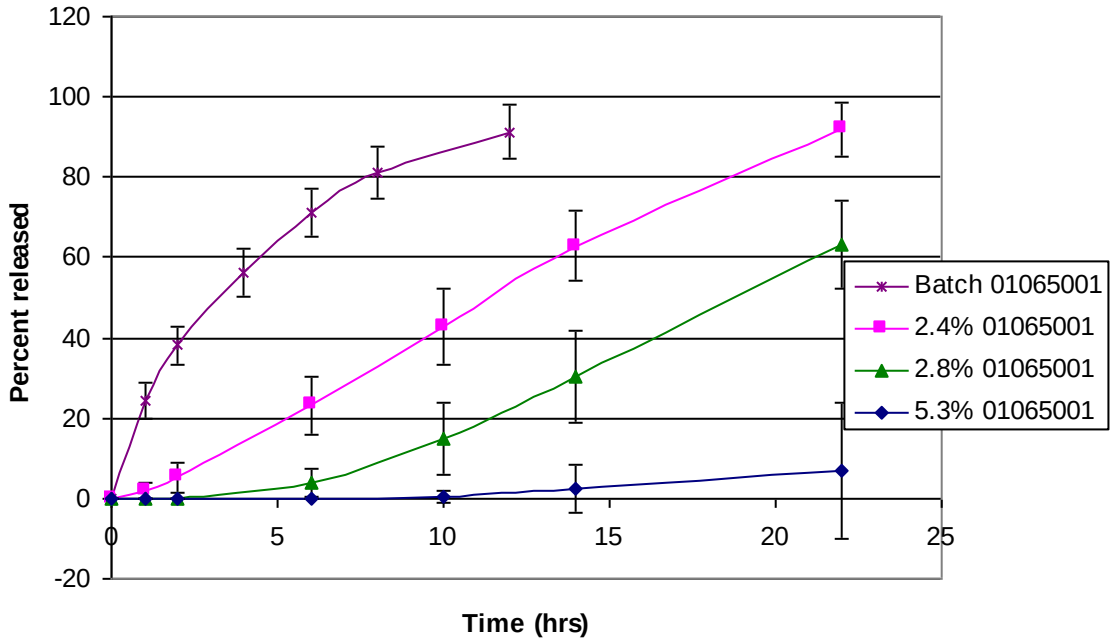
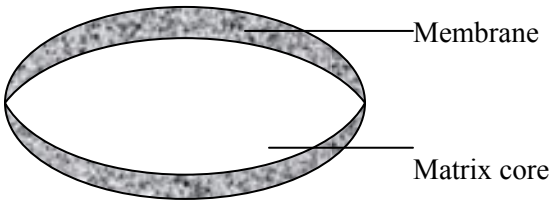
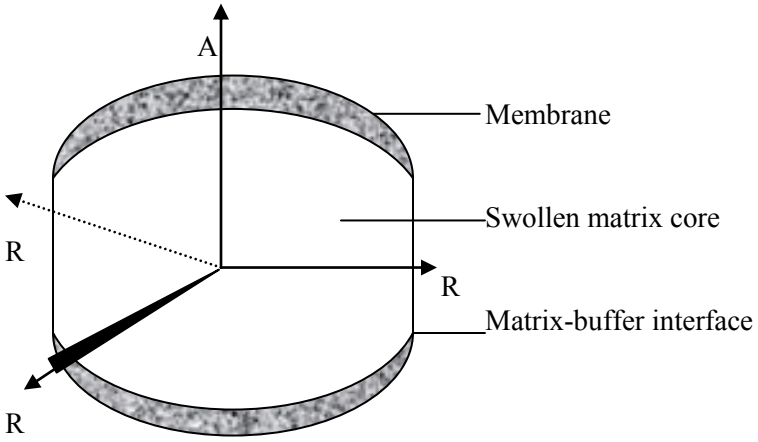


Figure 6.4 Schematic of Changes occurring on Dissolution of Coated Tablets

A. Initial Appearance



B. After Coat Splitting



A: axial
R: radial

In order for PSS to be released at the matrix-buffer interface, diffusion of PSS in the core must occur in the radial direction, as indicated by the arrows. This is opposite to the direction of swelling, which is axial. In uncoated tablets, release can occur from the any surface of the matrix, and both axial and radial diffusion will result in release. In coated tablets, release of PSS after axial diffusion is hindered by the presence of the hydrophobic coat.

The release characteristics for all these preliminary coated batches are shown in Table 6.2 and 6.3. The release of PSS from the dosage forms appeared to occur as a diffusion-controlled process, which resulted in a release profile which was linear with square-root

time for the uncoated matrix. This is expected as diffusional distance changes with time as the PSS is depleted from the outer regions of the matrix. For the coated tablets, release followed zero-order kinetics, and the profiles were linear with time.

Table 6.2 Summary of Release Characteristics

Coating	Percent	Lag (hrs)	% Released at 22 hours	Mechanism
None	0	0	100.67 ± 5.12	Diffusion
EC	2.7	6-14	80.50 ± 15.98	Zero-order
EC	4.3	14-22	43.77 ± 19.21	Zero-order
EC	7.1	14-22	7.91 ± 19.37	-
EC	10.0	>22	0	-
EC-TEC	2.4	0	91.88 ± 6.76	Zero-order
EC-TEC	2.8	6-14	63.23 ± 10.96	Zero-order
EC-TEC	5.3	10-22	6.86 ± 16.80	-

Table 6.3 Correlation Coefficients

Coating	Percent	r^2	Linearity
None	0	0.991	Square root time (1-12 hrs)
EC	2.7	0.999	Time (10-22 hrs)
EC-TEC	2.4	0.996	Time (0–22 hrs
EC-TEC	2.8	0.994	Time (6-22 hrs)

Scanning electron microscopy (SEM) was performed on some of the tablets before and after the dissolution experiments. Two representative SEM micrographs are shown in Figures 6.5 and 6.6, and it is clearly evident that the coating level is not uniform. The behaviour of the tablets suggested that the coating was weaker along the tablet edges, as the coating split along these edges in cases where release was observed, although it remained attached to the upper and lower tablet surface, which suggests that the level of coating on the edges may be lower than that on the surfaces, and that the shape of the tablet affects the ability of the system to yield uniform coats.

Figure 6.5 **Scanning Electron Micrograph of an Unplasticized Ethylcellulose Coat (4.3%)**

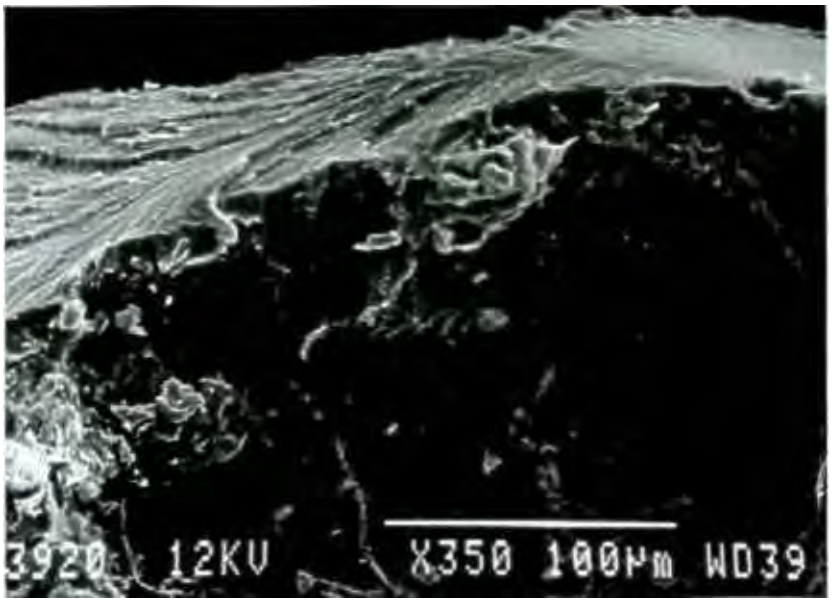
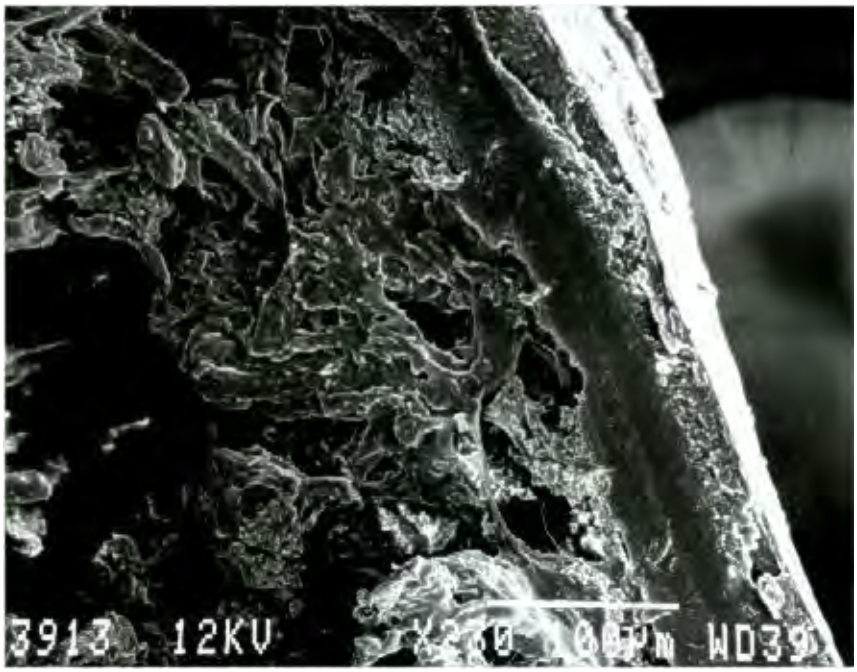


Figure 6.6 **Scanning Electron Micrograph of a Plasticized Ethylcellulose Coat (2.8%)**



These results indicate that a suitable lag phase of approximately five hours could be obtained using a plasticised ethylcellulose coat at a coating level of approximately 2.8%. The lag phase was then followed by a zero-order release profile for PSS. These data were used to define the coating parameters for the coating of the developmental batch 02008001.

The coating process in the Strea-1 requires optimisation and at present is not efficient. Actual coating levels were far lower than the theoretical levels calculated from the amount of dispersion sprayed. It was noted that a considerable portion of the ethylcellulose collected on the exhaust filter and the interior of the column. This suggested that the spray pattern was not optimised, and that the atomising air pressure was high [243]. The atomising air pressure had to be maintained at this level in order to aid the fluidisation of the tablets, as this system does not allow for the control of the volume of fluidizing air, and uses atmospheric air as the fluidizing air. This allows for efficient fluidisation of granules, but the heavier tablets required the additional air stream provided by the atomising air.

6.3.3.2 DEVELOPMENTAL BATCHES

Batches 02008001and 02010001 were coated with plasticised ethylcellulose as previously described (§ 6.3.3.1). As the coating process was not efficient, the target coating levels were not achieved, and a variety of coating levels was evaluated. As previously observed, the release profile for PSS from these tablets exhibited a lag phase followed by zero-order release. At lower coating levels, zero-order release with no preceding lag phase was observed. The release profiles for these batches are illustrated in Figure 6.7. As the release rate observed was slower than desired, the effect of an osmotic agent was evaluated. Sodium chloride was included in the granulation step of batch 02009001 and in the matrix of batch 02011001. The inclusion of sodium chloride led to a reduction in the lag phase and an increase in the release rate, although zero-order kinetics were retained, as illustrated in Figure

6.8. The correlation coefficients for the linear regression analysis of these plots are listed in Table 6.4. The effects of sodium chloride were more noticeable when it was included in the matrix than when present in the granules, probably as a result of earlier wetting and a more direct osmotic effect.

Figure 6.7 **Effect of Coating Level on PSS Release from Ethylcellulose-coated Prototype Batches**

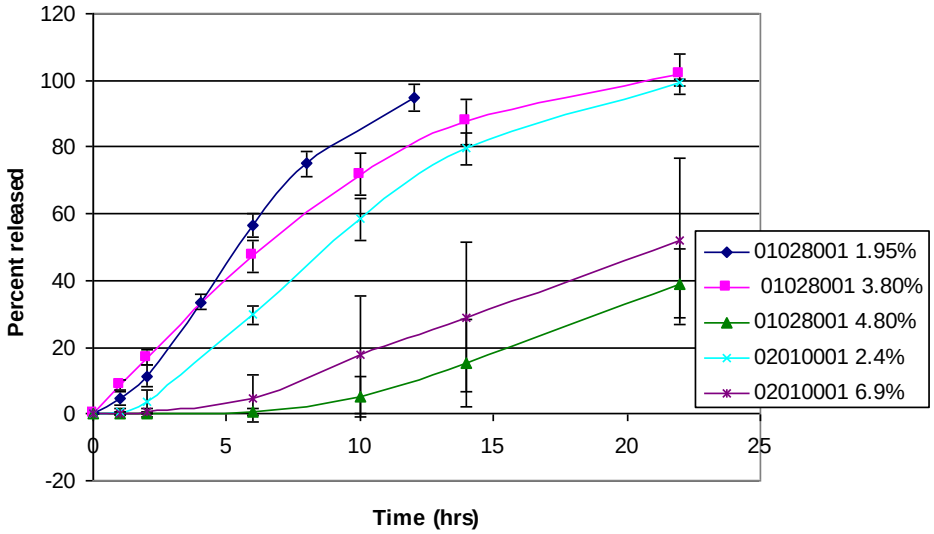


Figure 6.8 **Effect of Coating Level on PSS release from Ethylcellulose-coated Prototype Batches containing Sodium Chloride**

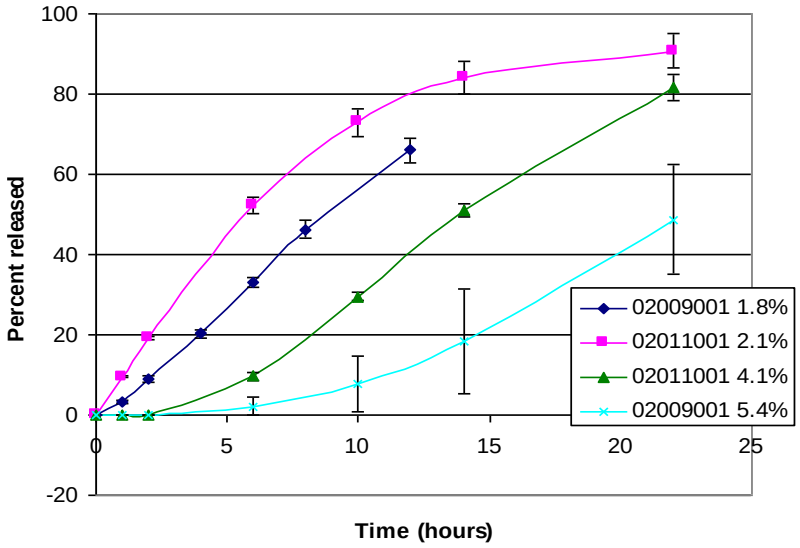


Table 6.4 Correlation Coefficients for Developmental Batches After Coating

Batch Number	Coating Level (%w/w)	r^2	Time Period (hours)	Linearity
02008001	1.95	0.998	2-14	Time
	3.80	0.986	0-14	Time
	4.80	0.998	10-22	Time
02010001	2.4	0.992	6-22	Time
	6.9	1.00	10-22	Time
02009001	1.8	0.995	0-8	Time
	5.4	0.998	10-22	Time
02011001	2.1	0.986	0-10	Time
	4.1	0.993	6-22	Time

6.3.4 DISCUSSION

A satisfactory release profile for PSS was obtained with a plasticised ethylcellulose coat, but required the inclusion of an osmotically active ingredient in the matrix to ensure that release was sufficiently rapid. The release profile obtained with batch 02010001 shows the potential for further development as a formulation of PSS with once-daily dosing.

Drug release from coated hydrophilic matrices has been observed to be dependent on the diffusion coefficient of the drug in the matrix polymer and the coating polymer [267]. If the diffusion coefficient of the drug in the coating polymer is greater than that for the matrix polymer, the matrix polymer will control release, while if the diffusion coefficient in the matrix polymer is greater than that in the coating polymer, the coating will control release. For systems where the diffusivities in the coating and core polymer are similar, both will contribute to release, with complex release mechanisms and kinetics being necessary to describe the release process. The greater the difference between the diffusivity coefficients, the greater the likelihood of zero-order release [267].

It was observed that no drug release occurred from tablets where the coating remained intact. If the tablet coat split, drug release appeared to follow a zero-order profile, as indicated by the correlation coefficients listed in Table 6.3 and 6.4. The absence of drug release from tablets where no splitting of the coat was observed suggests that diffusion

through the membrane is negligible, either because insufficient water is absorbed through these thicker coating layers, or because PSS has minimal diffusivity in ethylcellulose, even in the presence of a hydrophilic plasticiser. However, zero-order release profiles are observed after the coating split. As the matrix was observed to swell after the coat had ruptured, and as this swelling was in a predominantly axial direction, it is possible that the increase in exposed surface area effected by the swelling was sufficient to compensate for the increase in diffusional distance within the matrix. This could be assessed by altering the geometry of the matrix core. An alternative hypothesis is that the swelling of the matrix polymer increases the permeability of the film, as described by Morita *et al* [268] for PVA matrices coated with an ethylcellulose-HPMC-TEC coat, where the increase in film permeability compensated for the increased diffusional distance. For the tablets investigated here, release is likely to occur as a result of diffusion across the matrix-buffer interface and through the ethylcellulose film.

The inclusion of sodium chloride in the matrix enhanced the dissolution rate of PSS, both before and after coating. The contribution of this excipient and other osmotic agents requires further investigation. As sodium chloride is water-soluble, it would be expected to increase channel formation in the uncoated matrices, rendering the matrix more porous and facilitating water entry and PSS dissolution and diffusion. In the coated matrix, the osmotic pressure exerted by the sodium chloride after water entry and dissolution is expected to exert pressure on the membrane, resulting in the expulsion of dissolved PSS through pores formed on the dissolution of the TEC, and an earlier rupture of the coat. As diffusion of a drug in a polymer may be spatially- or time-dependent [272], the role of the osmotic agent is important and requires evaluation. The diffusion behaviour of PSS in both ethylcellulose and HPMC requires further characterization, in order to determine whether the diffusion is spatially-dependent, leading to different release characteristics in the axial and radial directions. The behaviour of the coated matrices dictates that radial diffusion of PSS would be required for release to occur at the matrix-buffer interface (Figure 6.4).

The extra deep convex [273] tablet geometry used here is not ideal for coating, and the effect of changes in shape should be evaluated, as the initial release may also be altered by changes in the tablet shape. This may reduce the incidence of edge splitting, leading to altered release characteristics. Unfortunately at the time at which this study was undertaken, only one set of tablet press tooling was available, and the effect of tablet geometry could therefore not be assessed.

6.3.5 CONCLUSION

Although a satisfactory release profile for PSS was obtained with the coated matrix system described, the mechanism of release from these dosage forms requires further elucidation. In particular, the contribution of various coating compositions to the mechanism of release requires assessment. It is surprising that the inclusion of TEC in this formulation did not result in a greater change in the release profile. The movement of PSS in the HPMC matrix also requires further characterization, in order to assess whether PSS exhibits spatially-dependent diffusion. The method of fronts movement analysis described by Ferrero *et al* [180] would most likely provide useful information in this regard.

These dosage forms appear to have complex release mechanisms, and a more complete understanding of the processes involved and the contribution of the various components is critical to enable further optimisation and development of the formulation. This would include studies to determine the effect of tablet geometry, other plasticisers and osmotic agents on the release profile. In addition, the role of the coat in the release mechanism requires elucidation, and the effects of using other polymers; such as the polymethacrylates as film coatings should also be assessed in order to determine whether ethylcellulose is the most appropriate of polymer for this application.

6.4 IMMEDIATE RELEASE DRUG-LOADED COATING

6.4.1 OBJECTIVE

This final phase of the development process was designed to incorporate the loratadine and an immediate release portion of PSS into the formulation. As loratadine has a long half life (§1.2.5.5) it is not necessary to sustain its release rate, and consequently it was not included in the sustained release core. In addition, it is desirable to have an immediate release portion of the pseudoephedrine dose present to achieve rapid relief from congestion, the effects of which can then be maintained by the sustained release portion.

6.4.2 MATERIALS AND METHODS

To ensure that an immediate release component could be included, it was necessary to use a hydrophilic, water-soluble coating polymer and include the drugs in the coating suspension. PSS is highly water-soluble and was therefore dissolved in the aqueous coating medium. However, loratadine is not water-soluble, and therefore had to be dispersed. HPMC is a widely used polymer for coating applications [238]. The HPMC used in the coating was of a lower viscosity than that used for the matrix core and has more rapid dissolution. As it is hydrophilic, it swells rapidly on contact with water, allowing rapid release of the active.

Opadry® II white (Batch DT 506256, Colorcon, Kent, UK), a commercial formulation of HPMC, was chosen as the coating medium. This is sold as a powder for reconstitution, and forms a white dispersion on addition to water. This product includes dispersing agents and these were likely to facilitate the dispersion of loratadine within the coating medium.

Opadry® is comprised of HPMC, a plasticiser (polyethylene glycol), a pigment and a film enhancer (lactose) [274]. The use of a pigmented film was desirable, as the rate-retarding Surelease® coat was an inelegant yellow colour. The Opadry® system also enables the use of suspensions with up to 20% w/w solids, a relatively high solids content, enabling reduced spray times, although a concentration of 15% is recommended for the Aeromatic Strea -1. In addition, Opadry® provides some protection from moisture [274], thus improving the stability of the product at elevated storage temperatures and humidities, although this was not assessed for this formulation.

The suspension was prepared as follows:
PSS was dissolved in distilled water. Loratadine was size reduced and mixed with the dry Opadry® powder in a mortar. The powder mixture was then added to the vortex of the PSS solution in small amounts while the solution was stirred with a lightning mixer (Gallenkampf). The suspension was then mixed continuously for 45 minutes prior to use. The formula for the suspension is listed in Table 6.5. Two different concentrations of suspension were used during the initial studies, a 15% w/v suspension and a 20% w/v suspension. The 15% suspension appeared to result in smoother coats, while the 20% suspension resulted in rough coats. This can be explained by a more rapid application rate with the reduced moisture content of the 20% suspension leading to reduced spreading and coalescence. In addition, drying time was reduced, and the more rapid evaporation of the water would have prevented complete droplet coalescence.

Table 6.5 Formula for the Drug-Loaded Coating Suspension

Excipient	Quantity (as a percentage of total solids content)
Pseudoephedrine sulfate	57
Loratadine	9.5
Opadry® II White Powder	33.5

The coating was carried out in an Aeromatic Strea-1 fluidised bed drier, under the conditions described in Table 6.6.

Table 6.6 Coating Conditions for Application of Immediate Release Coating

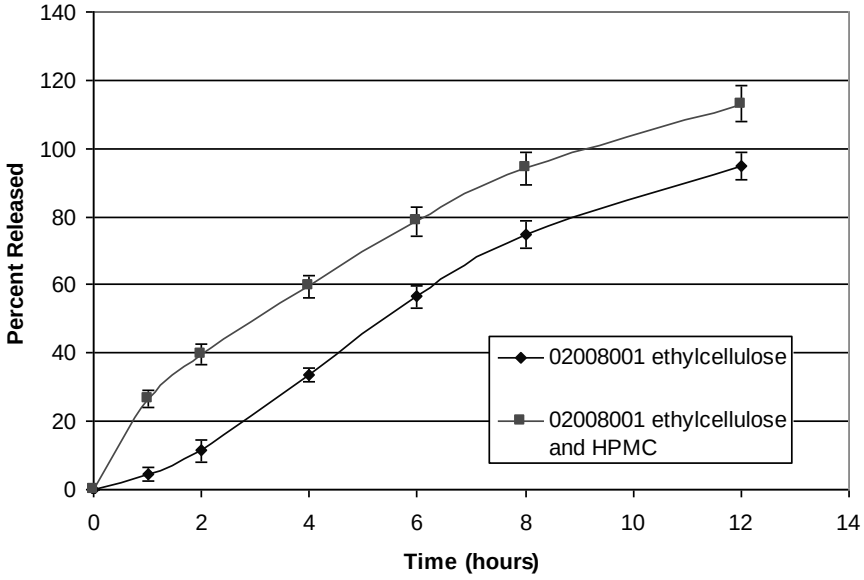
Parameter	
Inlet air temperature	54 – 60°C
Outlet air temperature	50°C
Product Bed temperature	52 – 54°C
Spray rate	3.8 – 4.1 g/min
Atomising air pressure	20 psi
Drying temperature	40°C
Drying time	15 min

6.4.3 RESULTS

The coat adhered well to the ethylcellulose surface of the coated cores. The fluid spray variables required manipulation to avoid spray drying and overwetting, and the spray pattern could not be optimised, as adequate fluidisation required the use of high atomising air pressures, as previously discussed (§ 6.3.3).

In order to ascertain the effectiveness of the coating process and characterize the release profiles from the immediate release coat, dissolution studies were carried out using USP Apparatus 3, as described in §3.1.2. This was also necessary to ensure that the release profile of the core was not altered by the presence of the outer immediate release coating. An initial coated batch coated to a lower level of PSS and loratadine was assessed, and the dissolution profile for PSS from this batch is shown in Figure 6.9. It would appear that the release rate from the core is slightly slower in the presence of the outer coat, but as expected, this change is not substantial. This is evident from the plot in Figure 6.9, which represents the difference in PSS released from the formulation before and after coating with HPMC. This plot shows that the tablets with the HPMC coat released the PSS more slowly than the tablets without the HPMC coat. In addition, the gradient of the release profile is decreased after coating with HPMC.

Figure 6.9 Release of PSS from Batch 02008001 with 3.8% Ethylcellulose and 5.5% HPMC Coat



Once again it was observed that the coating process was inefficient, and it was necessary to coat to a higher theoretical level in order to achieve the desired drug content. However, despite the inefficiency of the spray coating process, it appears to be efficient in terms of the amount of loratadine and PSS applied to each tablet, indicating high precision. The means, standard deviations and relative standard deviations of the amount of PSS and loratadine released from the immediate release portion of six tablets for both final batches are listed in Table 6.7. The small %RSD values indicate high precision in the amount of PSS and loratadine released from each tablet.

Table 6.7 Precision of Application of PSS and Loratadine by Coating

Drug Compound	Batch Number	Mean mass ± S.D. (mg)	%RSD	Target Loading	% Difference from target
PSS	02008001CC2	43.51 ± 3.18	7.31	60 mg	-27.48
	02011001CC1	59.39 ± 2.17	3.65	60 mg	-0.01
Loratadine	02008001CC2	6.76 ± 0.44	6.54	10 mg	-32.40
	02011001CC1	8.43 ± 0.42	4.98	10 mg	-15.70

Batch 02008001CC2 was coated to an actual weight gain of 19.01%, while 02011001CC1 was coated to an actual weight gain of 19.79%, and were sprayed using the same batch of coating suspension. The actual masses are lower than the target loading values of 10 mg for loratadine and 60 mg for PSS. It appears that the application of PSS is more efficient than that of loratadine, possibly as a result of the fact that the PSS was present in solution whilst loratadine was applied as a dispersion. The content of loratadine in the coating suspension should be increased in order to obtain the desired mass on the coated tablet if this processing time is to be used.

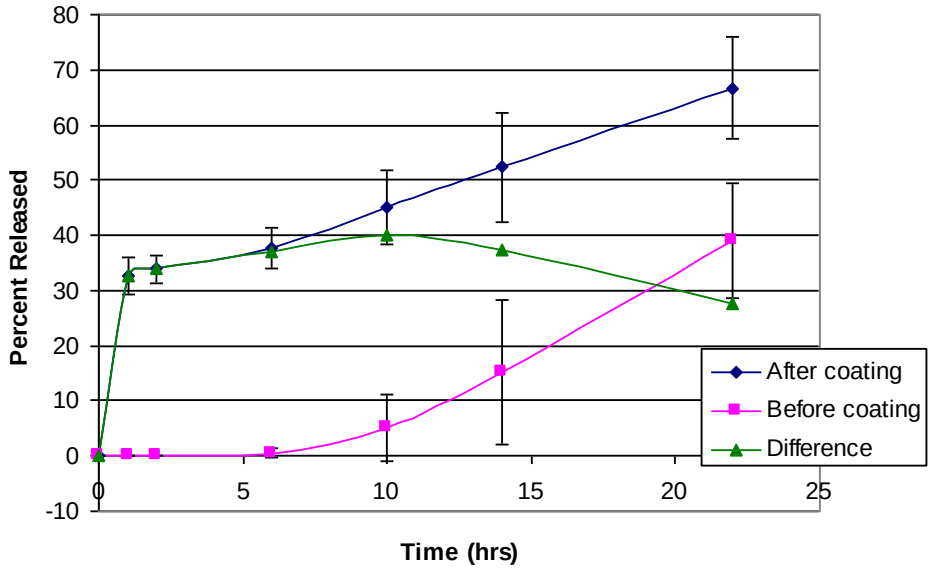
As the outer coating was intended as an immediate release coating, the rate of release was required to be rapid. This was achieved, and the outer coating was rapidly removed from the surface of the cores during dissolution, with no remaining evidence of the coat on the tablet after 15 minutes in the dissolution media. The percent released of the immediate release dose of PSS by one hour is listed in Table 6.8. All the loratadine was released within one hour from both batches of tablets assessed.

Table 6.8 Percent of Immediate-release Portion of PSS Released by 1 hour

Batch Number	Mean % released ± S.D.
02008001CC2	96.07 ± 3.65
02011001CC1	97.41 ± 0.85

The release profile for PSS for Batch 02008001CC2 before and after coating with HPMC is shown in Figure 6.10. As observed for the preliminary batch, the release from the core appears to be retarded slightly after coating with the HPMC, possibly because the hydration process is delayed slightly.

Figure 6.10 Release of PSS from Batch 02008001C Before and After Coating with HPMC



As 02011001C was the batch that gave the most promising results as a twice-daily formulation after coating with ethylcellulose, this batch was also coated with loratadine and PSS. The resulting mean dissolution profile (n = 6) was compared to that of Clarityne-D®. The release profiles for the test and reference products are illustrated in Figures 6.11 and 6.12. The two profiles were compared using the f_1 and f_2 equations, and the results of these calculations are shown in Table 6.9.

Table 6.9 Comparison of Clarityne-D® and Batch 02011001CC1 using the f_1 and f_2 equations

Time (hours)	f_1	f_2
1	20.4	55.2
2	16.2	58.6
4	15.4	59.1
6	15.9	57.8
8	12.8	59.7
12	15.4	50.0

Figure 6.11 **Comparative Release Profiles for PSS from Batch 02011001CC1 and Clarityne-D®**

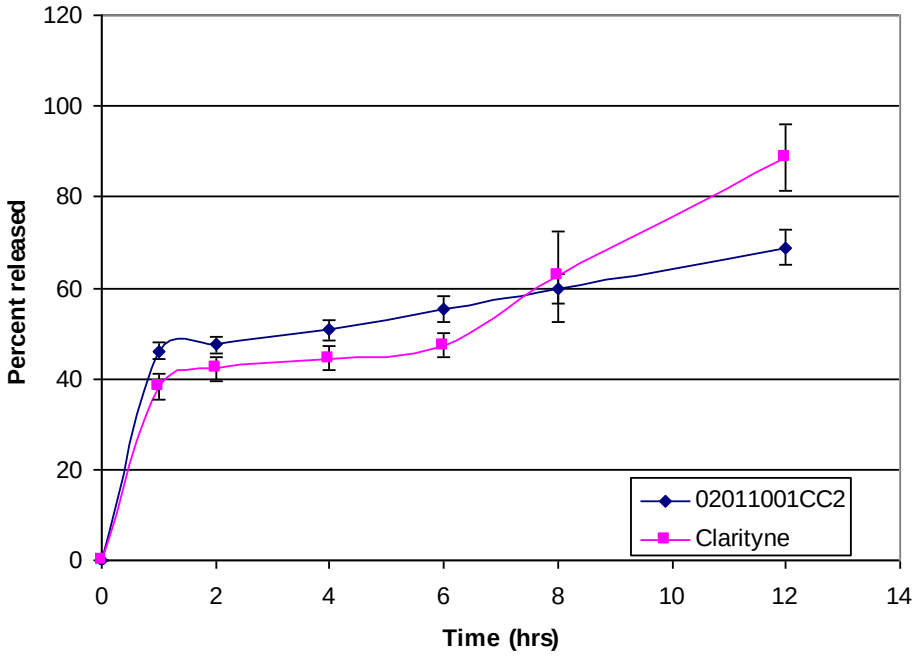
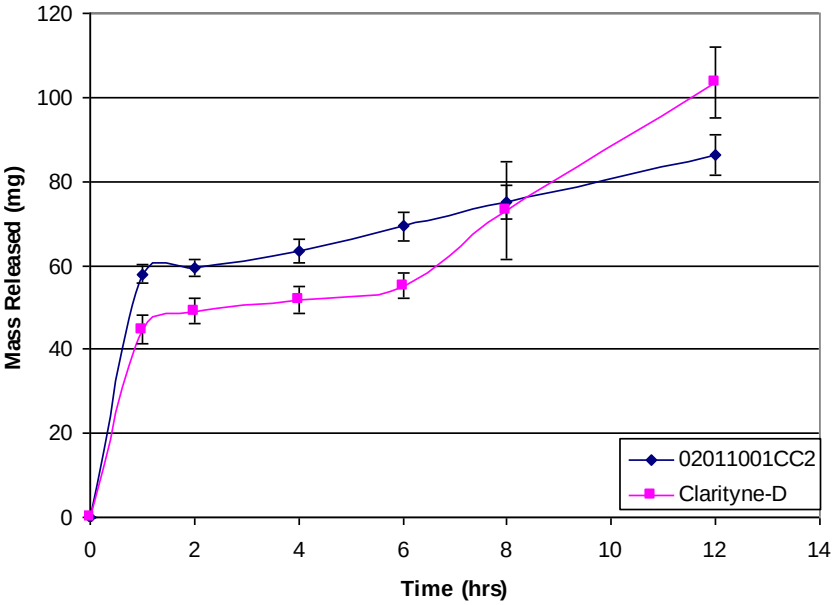


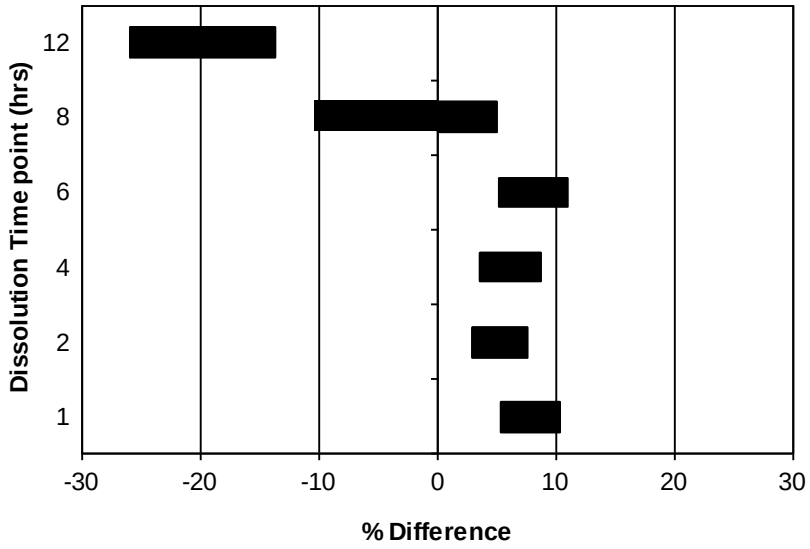
Figure 6.12 **Comparison of Mass PSS Released from Batch 02011001CC1 and Clarityne-D®**



The two dosage forms are seen as equivalent at all time points if only f_2 is considered, with values for the parameter all above 50. However, if f_1 is also taken into account, the dosage forms can only be considered equivalent at the eight-hour time point, where a value less than 15 is obtained. It is perhaps important to note that, although both equations are referred to in the FDA guidelines [149], frequently only f_2 is used or mentioned in the literature [172,173,174,275]. This may lead to an inaccurate interpretation of results, as seen with this comparison, where use of only f_2 would allow the assumption that the two formulations are similar at all time points. The consequence of this requires investigation, particularly as some authors feel that the required limit of greater than 50 for the f_2 value to indicate profile similarity is a conservative one [173].

In order to better define the degree of similarity between the profiles, the differences in the percent and mass of PSS released between the batches were also evaluated using the confidence interval analysis reported by Timm et al and described in § 4.1.4.8 [215). As the sample size was small, normal distribution was assumed. The results of this analysis indicated that the differences between the profiles were significant, but not relevant for the time period up to and including six hours. At eight hours, the differences were neither significant nor relevant, while at twelve hours, the difference was both significant and relevant, with the developmental batch showing a significantly lower release by the 12-hour time point. The calculated confidence intervals are shown in Figure 6.13.

Figure 6.13 90% Confidence Intervals for the Percent Difference in Release Between Batch 02011001CC1 and Clarityne-D®



6.4.4 DISCUSSION

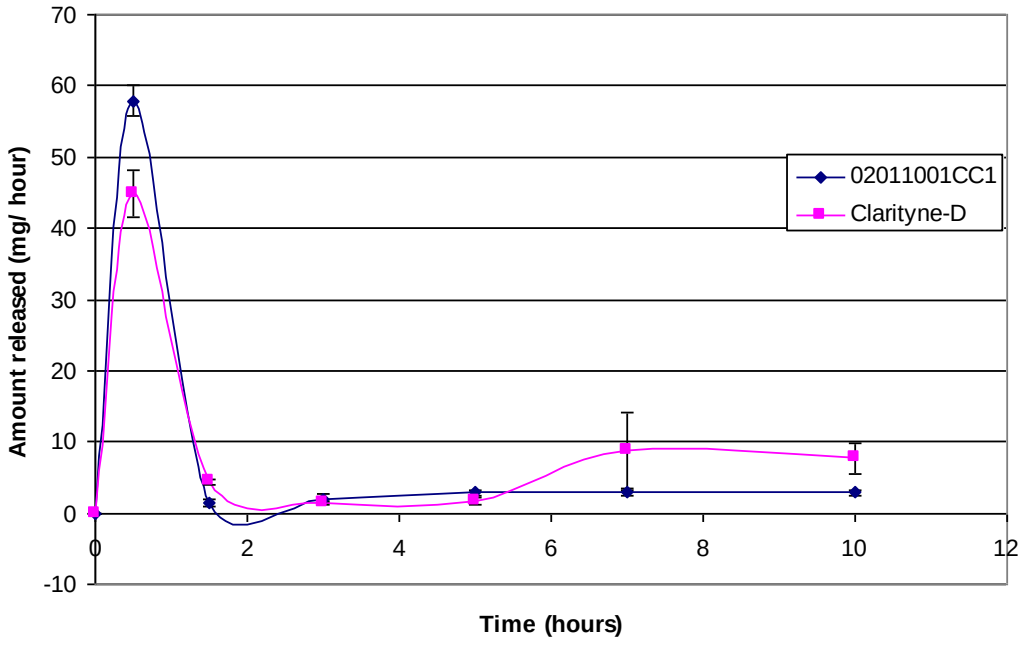
The results obtained with the developmental dosage form indicated that this dosage form has the potential for further development. The release profile obtained for Batch 02011001CC2 was similar to that of Clarityne-D®, although further optimisation is required. In particular, the Clarityne-D® exhibits a longer lag phase, followed by a more rapid zero-order release phase than that observed with this developmental formulation. The inclusion of the sodium chloride did increase the release rate in the developmental formulation, and the use of other osmotic agents warrants investigation, as a more effective agent may be found and better release profile of PSS obtained.

An *in vivo* study would be valuable as the next stage in the developmental process, in order to determine whether these differences are observed *in vivo*, as differences in release are frequently exaggerated *in vitro* [150,168]. If fewer differences were observed *in vivo* it may not be necessary to manipulate the formulation to any great extent to achieve the desired release of PSS and subsequent activity.

6.4.5 CONCLUSION

The development of this repeat action tablet resulted in a formulation with the necessary characteristics, although further development is necessary to optimise the product. This formulation showed slightly different release characteristics from Clarityne-D®, with a shorter lag phase before release from the sustained release core started, and a slower release rate from the sustained release core. Drug release from the core followed zero-order kinetics. A plot comparing the rate of release for the prototype batch and Clarityne-D® is illustrated in Figure 6.14.

Figure 6.14 Comparative Rate Plots for Batch 02011001CC1 and Clarityne-D®



The rate plots show a marked similarity, but once again the slower release by the sustained release core of the prototype tablet is evident. The release from the immediate release portion of the Clarityne-D® is lower than expected, being approximately 45 mg, as opposed to the nominal 60 mg present in the outer sugar coating. The areas under the curve (AUC) were calculated using the trapezoidal rule, and a ratio of the log AUC for the test versus reference calculated. The resultant ratio of 1.01, and the AUC values are listed in Table 6.10. This close match of *in vitro* data warrants bioequivalence studies to determine if the two formulations are bioequivalent *in vivo*. This would also allow an evaluation of whether an IVIVC for PSS can be established.

Table 6.10 Comparison of AUC for Rate Plots of Clarityne-D® and Batch 02011001CC1

Batch	AUC_0^{12}	Log AUC_0^{12}	Ratio log AUC test:reference
Clarityne-D® (reference)	758.75 mg.h	2.88	1.01
02011001CC1 (test)	810.43 mg.h	2.91	

Bioequivalence studies may also facilitate the optimisation of the prototype dosage form, as properties of the prototype tablet requiring modifications may be identified.

The effect of the two coating layers on the stability of the formulation also requires assessment, as both may undergo changes on storage, with possible curing of the ethylcellulose film and water absorption by the HPMC film. Water absorption by the HPMC coat may lead to drug leaching from the coat during storage, and this must be assessed. The outer coating layers may also alter the way in which the core tablet is affected by temperature and humidity, as the core would not be directly exposed to the environment. In addition, any water absorption by the HPMC coat may lead to some degree of water uptake by the ethylcellulose coat, which may increase the release rate of PSS by reducing the time required for wetting during dissolution. The outer HPMC coat was observed to slow the dissolution rate of the ethylcellulose-coated core. This effect may be a result of a reduced wetting rate as the HPMC swells and then dissolves, and water contact with the ethylcellulose coat would be reduced during the swelling phase of the HPMC coat. The effect of sodium chloride on the stability of the dosage form also requires assessment, as its presence may alter the water

absorbing capacity of the core tablet, which may in turn lead to increased water uptake and consequently more rapid release following storage under high humidity conditions.

The use of the fluidised bed process for tablet coating appears limited, and in this project, efficiency was poor, although the precision of the process appeared to be good. The specification in our laboratory for maximum permissible variation in sprayed drug content is 10%. All batches evaluated met this requirement. This aspect of the manufacturing process may well be improved on scale-up, and this should be evaluated.

CHAPTER 7
CONCLUSIONS

The objective of this study was to formulate a repeat-action tablet with a release profile similar to a reference product, Clarityne-D®. A different mechanism of controlling the release of the active was explored, resulting in the formulation of a coated matrix tablet, which gave a release profile similar to that of the reference product.

The inclusion of granules containing hydrophobic polymers in a hydrophilic matrix proved to be an effective means of retarding the release of PSS. This type of formulation was more effective in retarding the release rate then either matrix or granulation systems alone; and both components of the core therefore appear to contribute to the overall release profile. The addition of a hydrophobic ethylcellulose coat resulted in the introduction of a lag phase prior to PSS release. Drug release followed zero-order kinetics rather than the square-root time kinetics observed prior to coating. The release profile from this type of formulation could be manipulated by altering the characteristics and amount of coating material used, increasing flexibility and the value of the technology, as a result of a broader scope of application.

The matrix cores exhibited relatively good resistance to the effects of elevated temperature and humidity on storage as compared to the reference product. This is an important consideration for sustained release formulations in order to minimise the possibility of dose-dumping and loss of sustained-release properties, with associated risks of therapeutic inefficacy and toxicity.

The formulation developed in this study has potential for further optimisation and development. In reference to this, areas for further investigation were identified, and are explored below. In addition, the development and the assessment of this formulation enabled the identification of several key variables affecting release from this type of

formulation, and these are also discussed.

The coated granule-containing matrix formulation developed for the controlled release component represents a novel method of sustaining drug release, and is effective in retarding the release of PSS, a highly water-soluble drug. As it is difficult to sustain the release of highly water-soluble drugs, the ability of this type of dosage form to sustain the release of other drug candidates requires further investigation; particularly as the manufacturing process is relatively facile and requires no specialised equipment. The release of poorly water-soluble drugs from this formulation should also be assessed, as the release profile obtained may be suitable for sustained release preparations of compounds with these characteristics.

The use of different rate-retarding polymers for the granulation step requires further investigation, as does the effect of the amount of polymer used during granulation. In addition, other commercial ethylcellulose dispersions varying in grade or composition should be evaluated.

It was found that the release rate of PSS from the sustained release core was slower than desired after coating with ethylcellulose unless an osmotic agent, such as sodium chloride, was included. The release rate of PSS from the coated matrix core was satisfactorily increased on inclusion of this excipient. This effect could be improved, as the release rate of PSS from the prototype formulation was slower than that from Clarityne-D® cores. The effect of different osmotic agents and the effect of different concentrations of these agents should be investigated in order to optimise the composition of the formulation.

Although the release rate of the formulation without sodium chloride was too slow to provide a dosage form with 12-hourly administration, it may be possible to formulate a tablet for once-daily dosing, particularly as increasing the drug load by a factor of two

appeared to have no effect on the release rate from the matrix core (§ 3.9). As a once-daily dosage regimen is likely to improve compliance, as it is more convenient than twice daily dosing, this possibility is worth investigating.

The use of HPMC in the granules led to the formation of a malleable plastic mass on screening if the amount of granulating fluid used was not strictly controlled. This mass was difficult to screen, and decreased the granule yield substantially. The use of HPMC should therefore be investigated, as formulations without the intra-granular HPMC did not appear to be as sensitive to the amount of granulation fluid added. The use of a plasticiser of some sort would appear to be necessary, as tablets compressed with the ethylcellulose granulations in the absence of either HPMC or ATEC tended to split during dissolution testing. The effect of different plasticisers requires assessment to determine the impact of this component. In this instance, the formulation containing HPMC was selected for further development, as it appeared to undergo predictable changes on storage.

The ethylcellulose coating applied to the core to alter the release profile was effective in introducing a lag phase, but has not been optimised [276]. It appears that little or no PSS is released through the membrane, as no release was observed until the coating split, despite the presence of TEC, a water-soluble plasticiser, in the coating dispersion. The diffusion coefficient of PSS in ethylcellulose needs to be determined if the release mechanism is to be adequately characterised. The effect of increasing the amount of TEC requires investigation, as this would be expected to increase the release rate of PSS by forming aqueous pores in the membrane as it dissolves. The use of other hydrophobic polymers to provide the rate-retarding coat should also be investigated, as these may prove more effective in achieving the desired shape of release profile and rate of release.

The manufacturing process used in this study was relatively facile, and required no specialised equipment beyond that used in the manufacture of immediate release coated

tablets. This is of importance as the process has potential to be adapted to commercial applications. One limitation to the process is the number of steps required, each of which has the potential to increase variability and decrease yield and thus economic viability. However, the number of steps in the manufacturing process is similar to that required for the production of tablets by conventional wet granulation methods and coated after compression.

The manufacturing variables which may influence the behaviour of the dosage form are numerous. The considerations discussed here are those which appeared to impact on the behaviour of the dosage form produced in this study, or which may have a substantial effect on the performance of the dosage form. Importantly, the effect of scale-up requires assessment before this formulation can be said to be suitable for commercial application. It is likely that the use of more efficient blenders, particularly for the mixing of the granules with the tableting excipients would reduce the time required for the relevant steps, as well as the amounts of granulating and coating dispersions required to achieve the desired release rate of PSS, allowing optimisation of the release rate.

Four major manufacturing variables were identified with respect to the matrix core, which require further evaluation:

1. The granulation method
2. The drying time and temperature used to dry the granulations
3. The compression force used
4. The choice of tooling used during compression

It was noted that the use of a peristaltic pump appeared to enhance the efficiency of the granulation process, with less granulation fluid being required to effect particle agglomeration. This may impact on the performance of the dosage form, as the amount of rate-controlling polymer present is reduced, although it may be more efficiently distributed. The effect of high shear granulation should be assessed as this may enhance

the efficiency of the granulation process further.

The granules were also affected by drying time, with excessive drying times causing tablets produced without a matrix-forming polymer to split during dissolution testing. Excessive drying times appear to reduce the moisture content of the granules so as to decrease their ability to retain their integrity, and should be avoided. The moisture content of the granules should be monitored throughout the drying process. The stability studies indicated that ethylcellulose may undergo a curing process, and this step could possibly be built into the manufacturing process either as part of the drying process or during coating.

The results obtained indicate that the hardness of the tablets influenced the release rate, with harder tablets exhibiting slower release rates. This effect is expected, as an increased hardness is a reflection of increased compression force and these tablets are likely to be less porous, and therefore penetration of the dissolution medium into the dosage form would be hindered. As the coating process used here required that the tablets be compressed to a hardness of at least 10 kp, the effect of hardness variation on the release characteristics should be assessed. The impact of compression force on hardness could be assessed by establishing compression-hardness profiles. The effect of compression force and hardness on the release rate could then be assessed by comparing the dissolution profiles obtained from tablets manufactured at various compression forces.

The tooling used in this study was extra deep concave tooling. The geometry of matrix tablets is known to influence the release rate by altering the diffusional distances in the axial and radial planes. This factor is of critical importance for this dosage form as the shape of the dosage form used here appears to promote the edge-splitting of the film coat during dissolution. If the release mechanism postulated in § 6.3.4 is correct, release of PSS requires the splitting of the coat, with subsequent axial swelling. Alterations to the tablet geometry may alter the release rate before coating by altering the amount of

exposed surface area relative to the tablet volume. In addition, altering tablet shape may alter the tendency of the coat to split, with subsequent changes in the lag phase and release rate, and possibly in profile shape.

As noted in § 6.3.3.1, the fluid-bed process used here was not ideal as it was inefficient, and appeared to yield non-uniform coats. This would be likely to be improved in commercial applications, as the equipment used for larger batches is generally more efficient. The use of coating pans or a more efficient fluid bed drier may also increase the efficiency of the process and the quality and uniformity of the coat obtained. The effect of altering tablet geometry on the efficiency of the coating process is another factor which should be investigated.

The primary analytical and most urgent aspect requiring attention is the development of a suitable content uniformity assay. The content uniformity of these dosage forms is difficult to assess, as the HPMC used as the matrix-forming polymer forms a gel in water, and retards the release of PSS, even after the tablet has been crushed. Agitation does increase the amount of PSS in solution, but this effect is dependent on the time period for which agitation occurs, and also depends on how soon after agitation the sample is taken.

The development of a simultaneous assay for PSS and loratadine would prove useful in analysing dissolution samples from these dosage forms, and the development of a joint method is desirable, although not necessary. No joint methods have been published to date.

The release mechanism from the coated matrix core requires characterization. Front movements analysis as described by Ferrero *et al* [180] may be useful in elucidating the mechanism of release. Optimisation of the dosage form cannot be completed until the mechanism of release has been elucidated, as an understanding of the variables impacting on release is necessary before they can be manipulated to optimise the release profile.

A preliminary assessment of the stability of the formulation was performed. However, the effects of elevated temperature and humidity need to be characterised further. In particular, the effect of humidity levels between 75 and 87% should be characterised, in order to ascertain whether the effects observed here are only evident at extreme humidity levels, particularly for Clarityne-D®. The stability requires reassessment in stability chambers to preclude the possibility of interactions with salts as used in the stability assessment in this study. In general the prototype tablets appear to exhibit good resilience to the effects of elevated temperature and humidity. The effects of these variables should be re-assessed with larger sample sizes being used for dissolution testing. In addition, the extent of water uptake by the different formulations should be measured, and physical tests, particularly hardness need to be performed. The stability of the dosage form after coating with ethylcellulose and the addition of the immediate release portion also requires long-term evaluation.

The bioequivalence of the prototype formulation to Clarityne-D® requires investigation in order to ascertain if the formulations behave similarly *in vivo*. The ultimate proof of bioequivalence could only be obtained from an *in vivo* study, and the results of such a study would also enable the identification of aspects requiring modification in order to achieve a bioequivalent dosage form if necessary.

A repeat-action tablet with a proposed 12-hour dosage interval was developed, which utilised a novel sustained-release matrix formulation. The formulation has the potential to be adapted to commercial manufacture. The sustained release of PSS, a highly water-soluble drug was achieved using a matrix formulation, and this formulation may be applicable to other drug candidates. The application of an ethylcellulose coat altered the release kinetics, resulting in a lag phase followed by zero-order release. The application of an immediate release coat containing two drug compounds in an HPMC film was effective, and despite the inefficiency of the process, exhibited good precision with

respect to the amount of drug applied.

APPENDIX I
BATCH DATA

1. DIRECT COMPRESSION MATRICES

BATCH 01026001

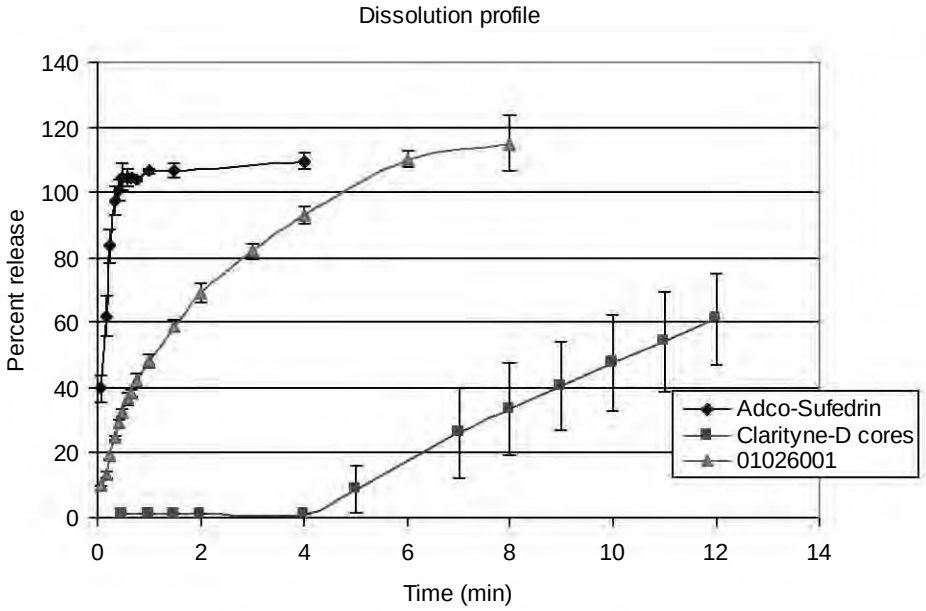
Date of Manufacture	12 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Avicel® PH102	33
Avicel® PH200	31
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	341.32 ± 3.45	1.01
Hardness (kp)	12.16 ± 0.73	5.98

Friability	passed
Weight before (20 tablets)	6.80 g
Weight after 100 drops	6.80 g
Percent lost	0.0


Dissolution profile
Percent release
Time (min)
0
20
40
60
80
100
120
140
0
2
4
6
8
10
12
14
Adco-Sufedrin
Clarityne-D cores
01026001

BATCH 01028001

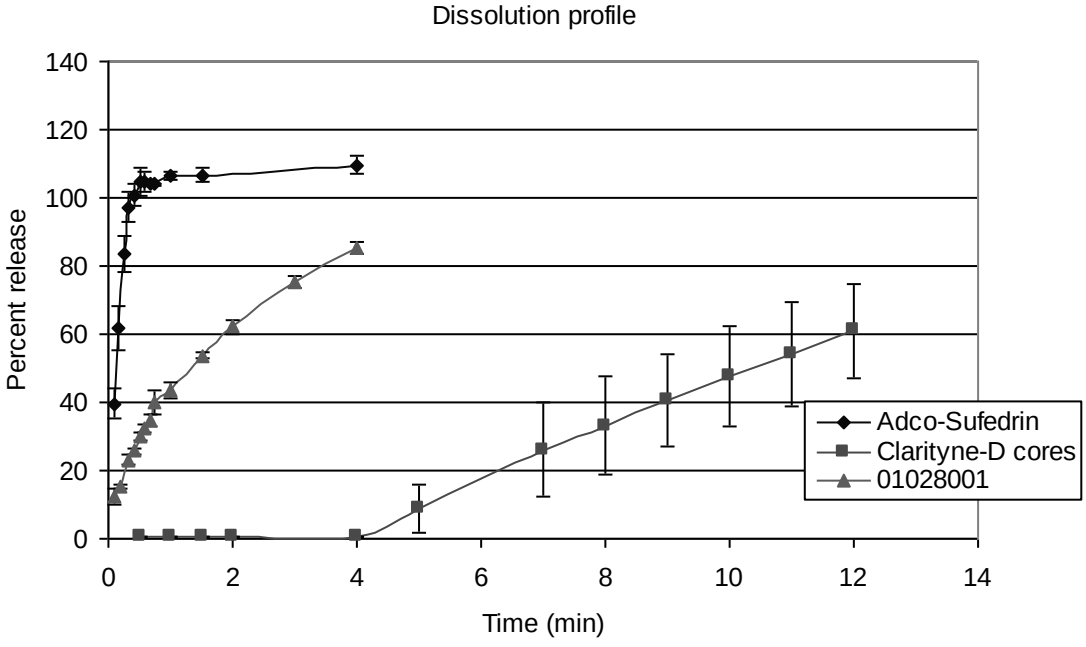
Date of Manufacture	12 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Microquick® WC595	5
Avicel® PH102	30
Avicel® PH200	30
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	335.80 ± 6.63	1.97
Hardness (kp)	10.66 ± 0.79	7.37

Friability	passed
Weight before (20 tablets)	6.62 g
Weight after 100 drops	6.62 g
Percent lost	0.0



BATCH 01030001

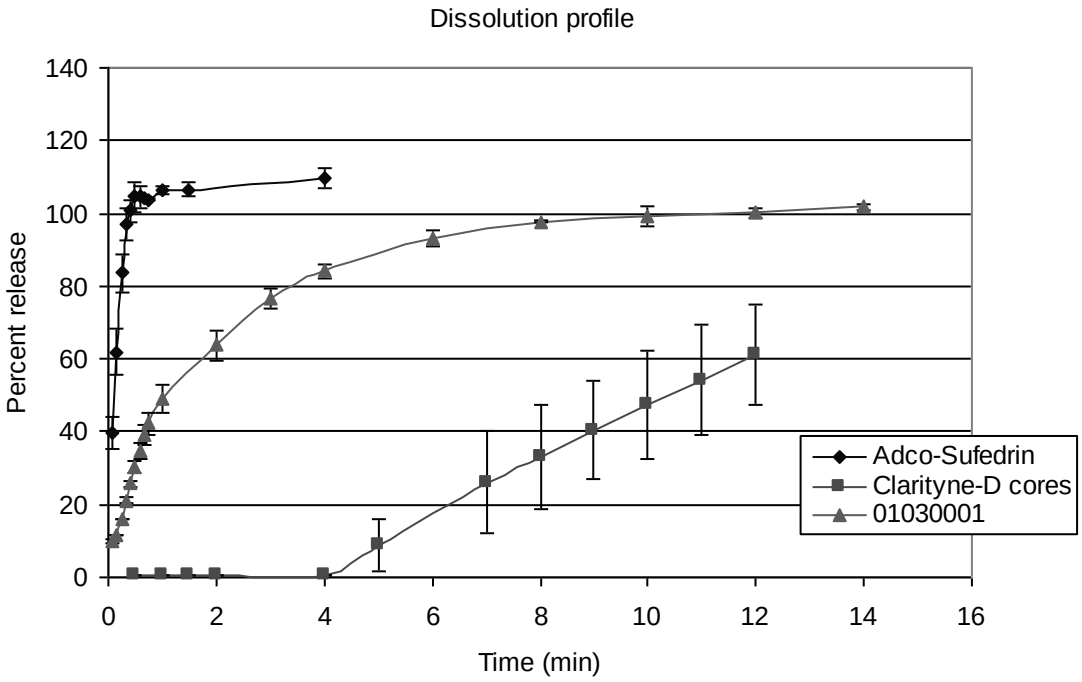
Date of Manufacture	20 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Avicel® PH102	64
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	319.72 ± 4.52	1.41
Hardness (kp)	8.77 ± 0.48	5.47

Friability	failed
Weight before (20 tablets)	6.88 g
Weight after 100 drops	6.72 g
Percent lost	2.33



BATCH 01031001

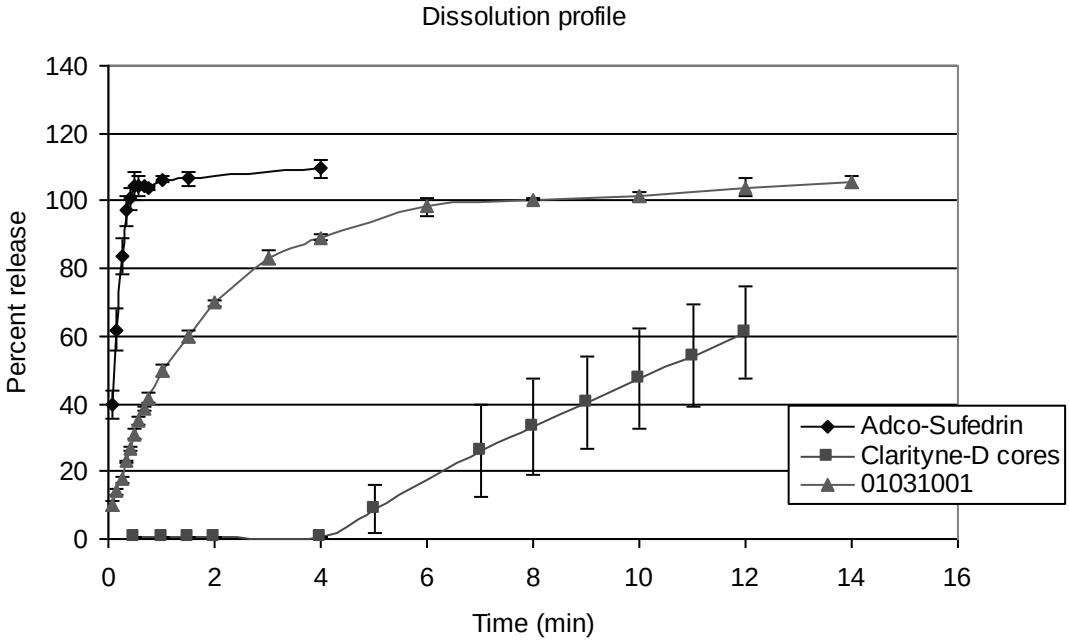
Date of Manufacture	20 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Emcocel® 90M	64
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	315.47 ± 3.47	1.10
Hardness (kp)	8.62 ± 0.68	7.93

Friability	passed
Weight before (20 tablets)	6.31 g
Weight after 100 drops	6.31 g
Percent lost	0.0



BATCH 01031002

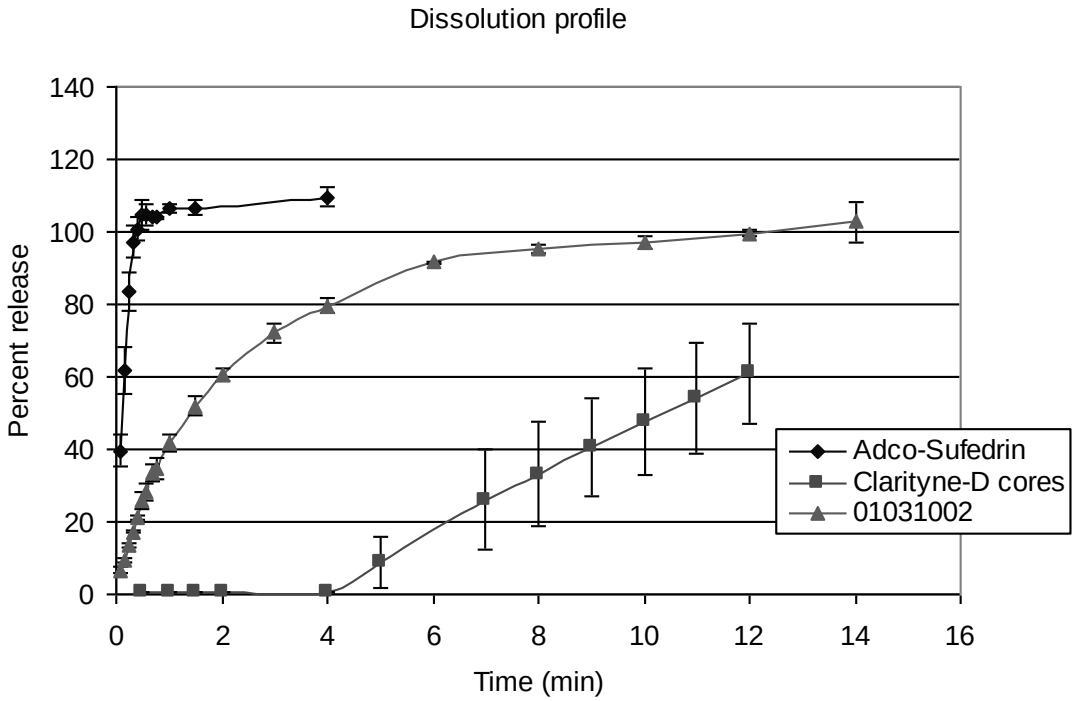
Date of Manufacture	23 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Emcocel® 90M	64
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	302.50 ± 4.29	1.42
Hardness (kp)	9.52 ± 0.56	6.07

Friability	passed
Weight before (20 tablets)	6.04 g
Weight after 100 drops	6.04 g
Percent lost	0.0



BATCH 01034001

Date of Manufacture	23 August 1999
Press	Manesty F3

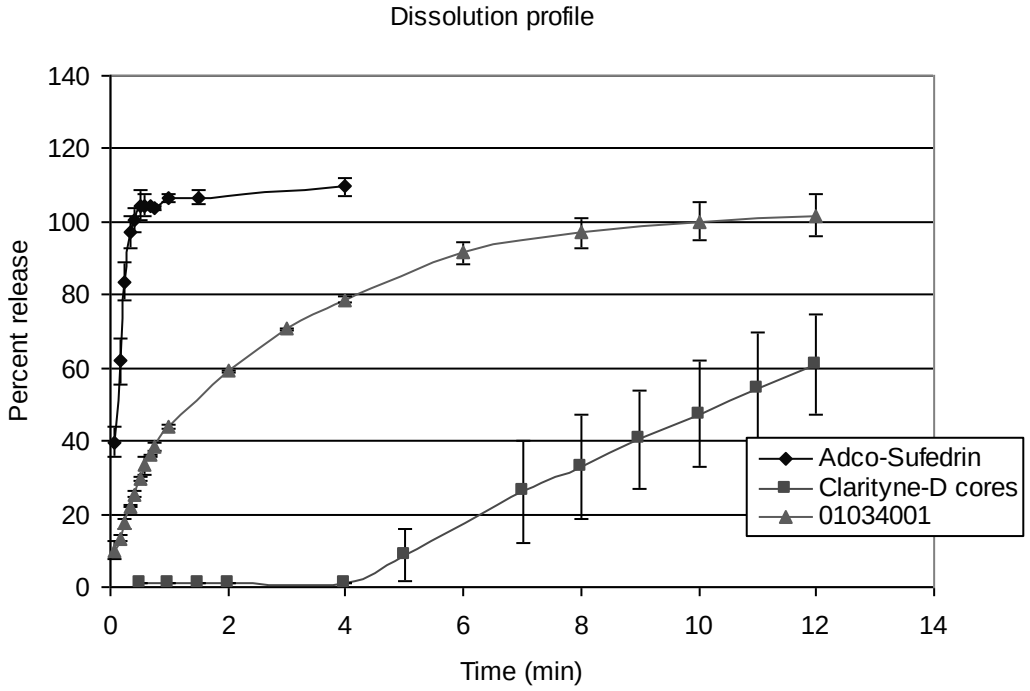
Composition (%)

Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Microquick® WC595	5
Emcocel® 90M	60
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	295.54 ± 11.16	3.78
Hardness (kp)	8.63 ± 1.25	14.54

Friability	passed
Weight before (20 tablets)	6.07 g
Weight after 100 drops	6.07 g
Percent lost	0.0



BATCH 01034002

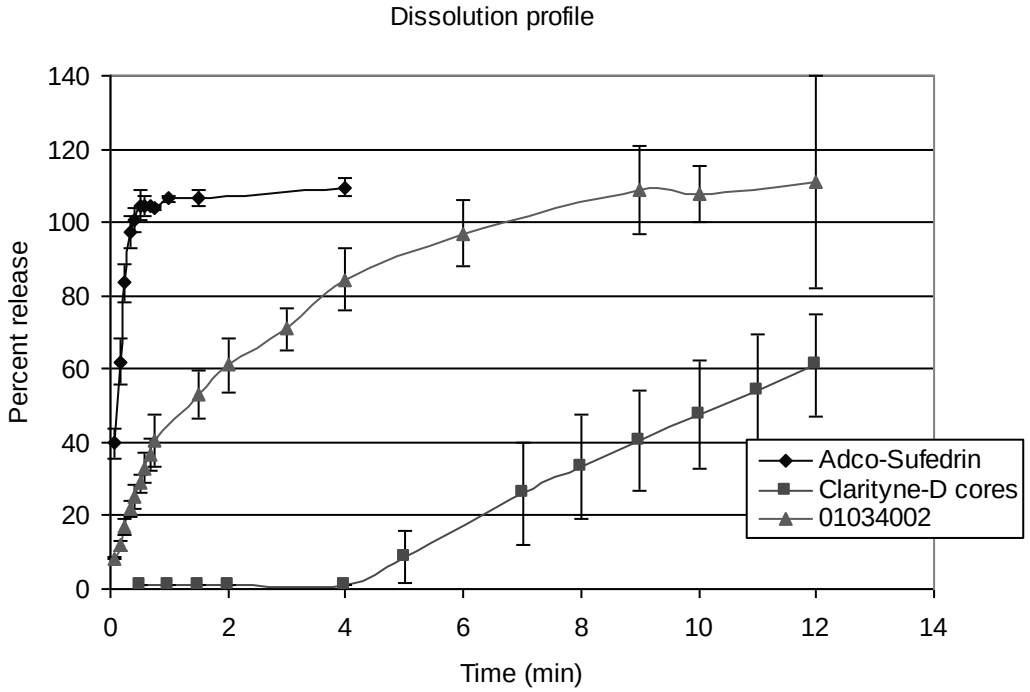
Date of Manufacture	26 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Microquick® WC595	10
Emcocel® 90M	55
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	293.69 ± 4.58	1.56
Hardness (kp)	8.34 ± 0.36	4.33

Friability	passed
Weight before (20 tablets)	5.82 g
Weight after 100 drops	5.82 g
Percent lost	0.0



BATCH 01034003

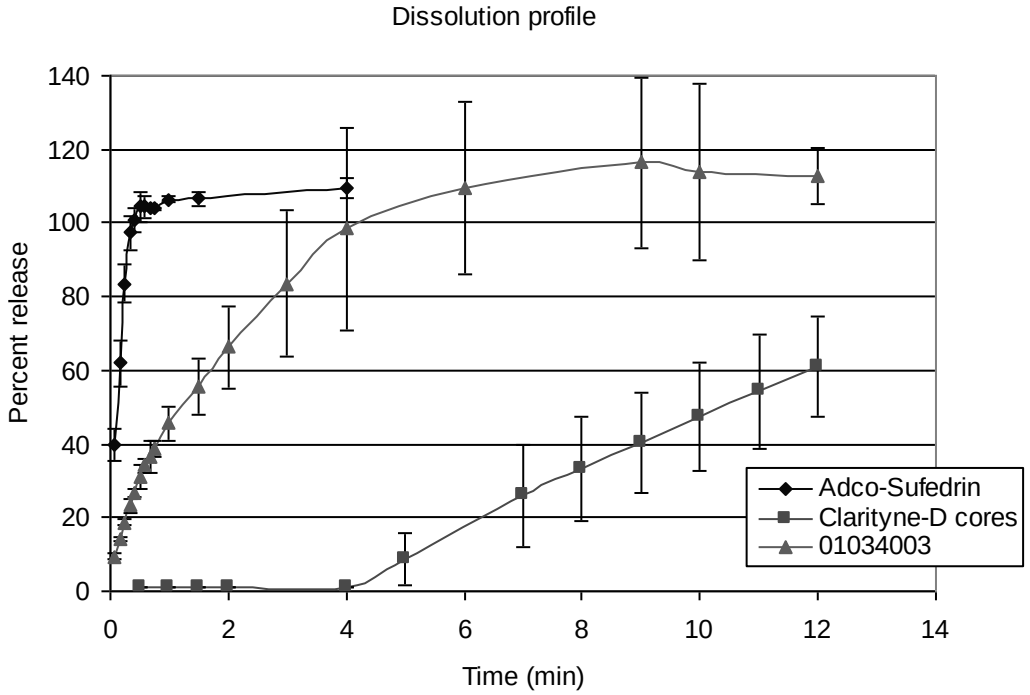
Date of Manufacture	26 August 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Microquick® WC595	15
Emcocel® 90M	50
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	294.05 ± 8.20	2.79
Hardness (kp)	7.10 ± 1.10	15.56

Friability	passed
Weight before (20 tablets)	5.82 g
Weight after 100 drops	5.82 g
Percent lost	0.0



BATCH 01038001

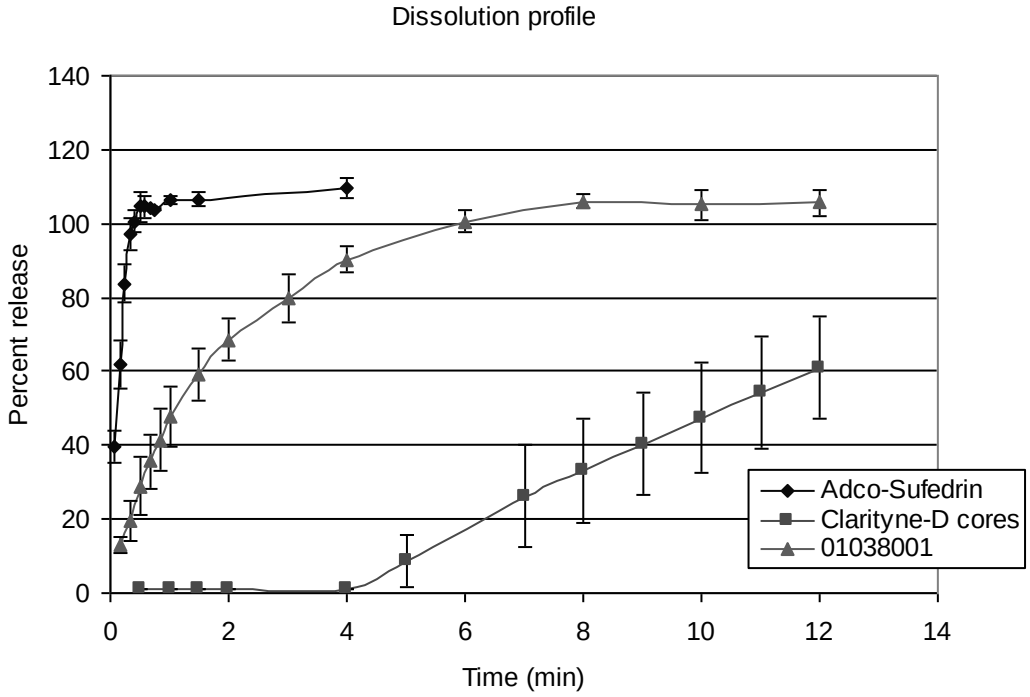
Date of Manufacture	13 September 1999
Press	Manesty F3

Composition (%)	
Pseudoephedrine Hydrochloride	20
Methocel® K4M	15
Ethylcellulose N22	7
Emcocel® 90M	57
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	296.40 ± 3.78	1.28
Hardness (kp)	6.09 ± 1.39	22.83

Friability	passed
Weight before (20 tablets)	5.87 g
Weight after 100 drops	5.86 g
Percent lost	0.17



BATCH 02002002

Date of Manufacture	19 April 2000
Press	Manesty B3B

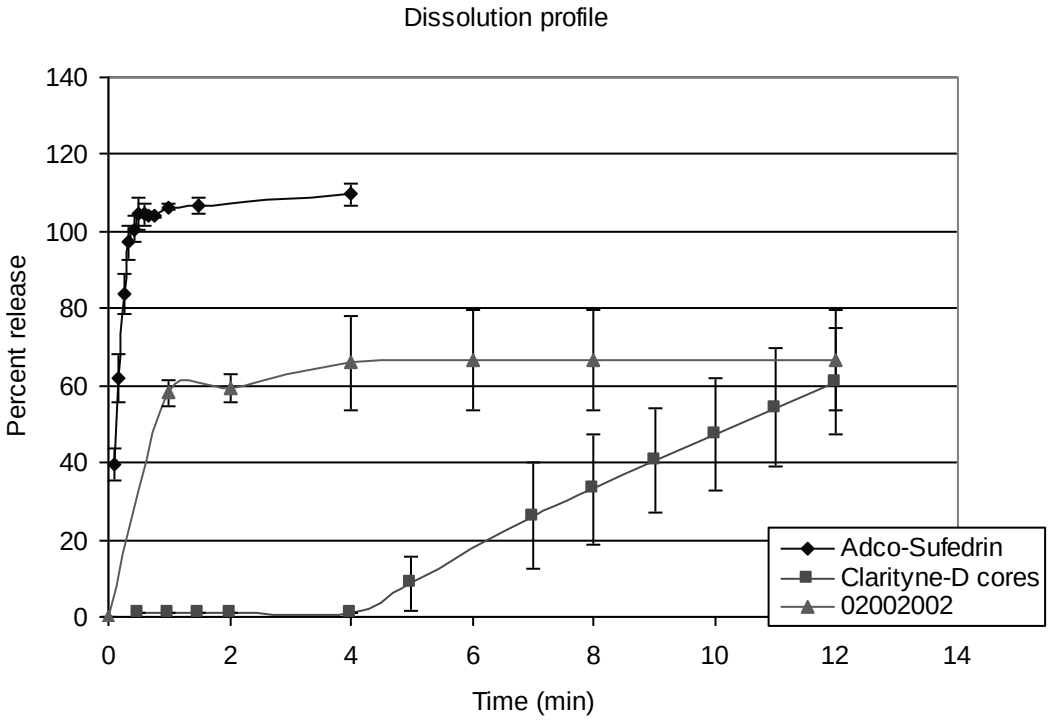
Composition (%)

Pseudoephedrine Sulfate	20
Eudragit® RSPO	15
Emcocel® 90M	64
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	462.85 ± 24.72	5.34
Hardness (kp)	7.15 ± 3.50	48.89

Friability	failed
Weight before (20 tablets)	9.16 g
Weight after 100 drops	8.81 g
Percent lost	3.82



2. GRANULATIONS

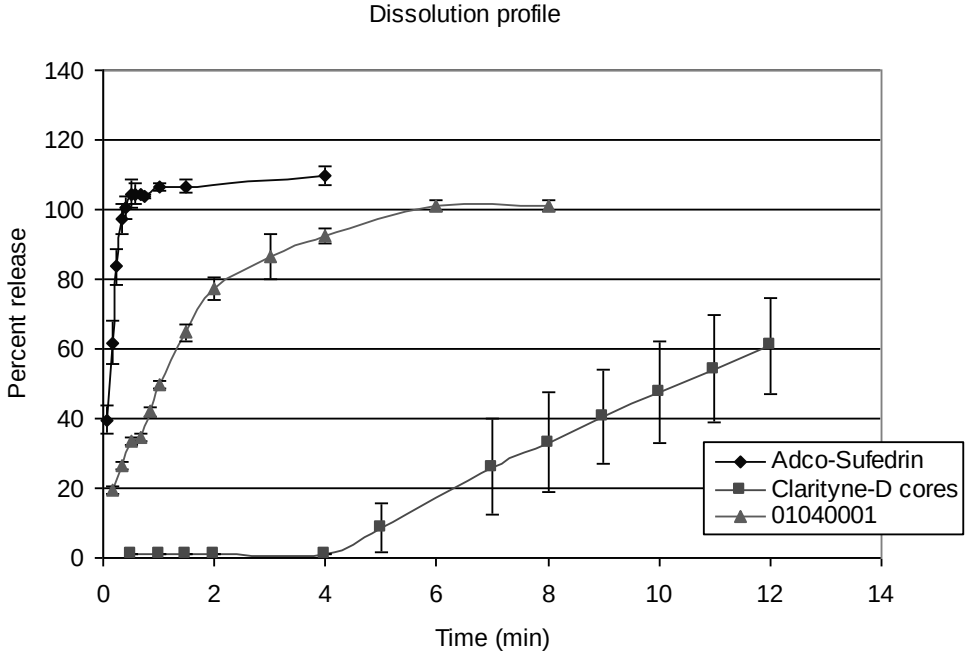
BATCH 01040001

Date of Manufacture	29 September 1999
Press	Manesty F3
Composition (%)	
Pseudoephedrine Sulfate	20
Ethylcellulose N7	20
Emcompress®	40
Emcocel® 90M	20
Ethanol	q.s.
Single granulation	99.5
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	359.27 ± 14.06	3.91
Hardness (kp)	7.97 ± 0.56	7.06

Friability	passed
Weight before (20 tablets)	7.34 g
Weight after 100 drops	7.28 g
Percent lost	0.82



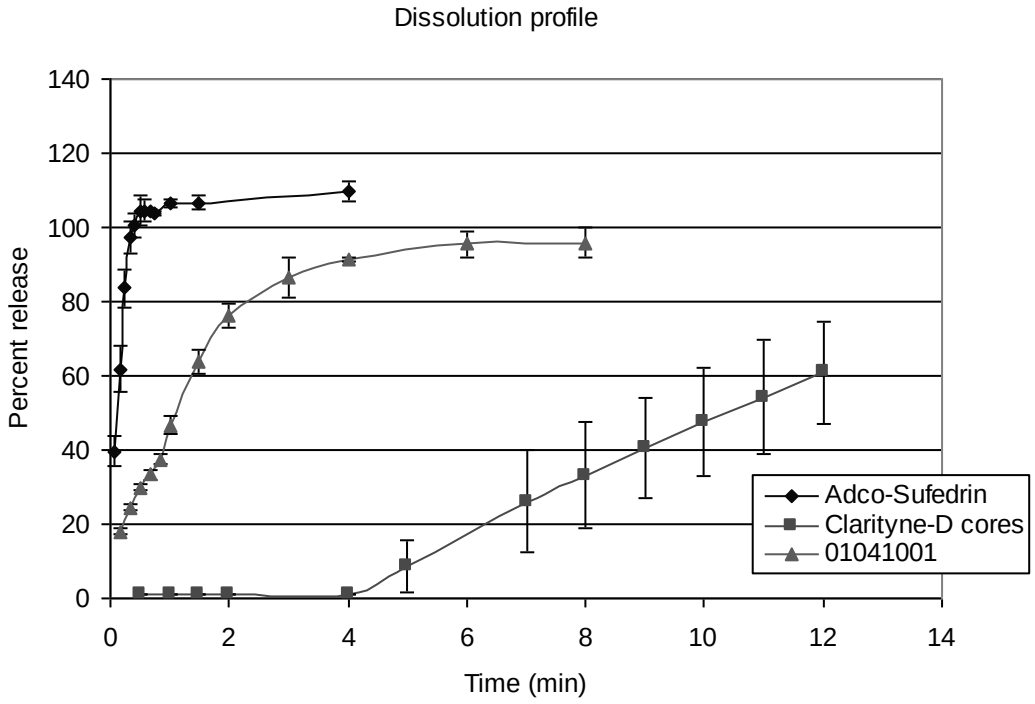
BATCH 01041001

Date of Manufacture	29 September 1999
Press	Manesty F3
Composition (%)	
Pseudoephedrine Sulfate	20
Ethylcellulose N22	20
Emcompress®	40
Emcocel® 90M	20
Isopropyl alcohol	q.s.
Single granulation	99.5
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	353.14 ± 23.53	6.66
Hardness (kp)	7.47 ± 0.98	13.06

Friability	passed
Weight before (20 tablets)	6.77 g
Weight after 100 drops	6.77 g
Percent lost	0.0



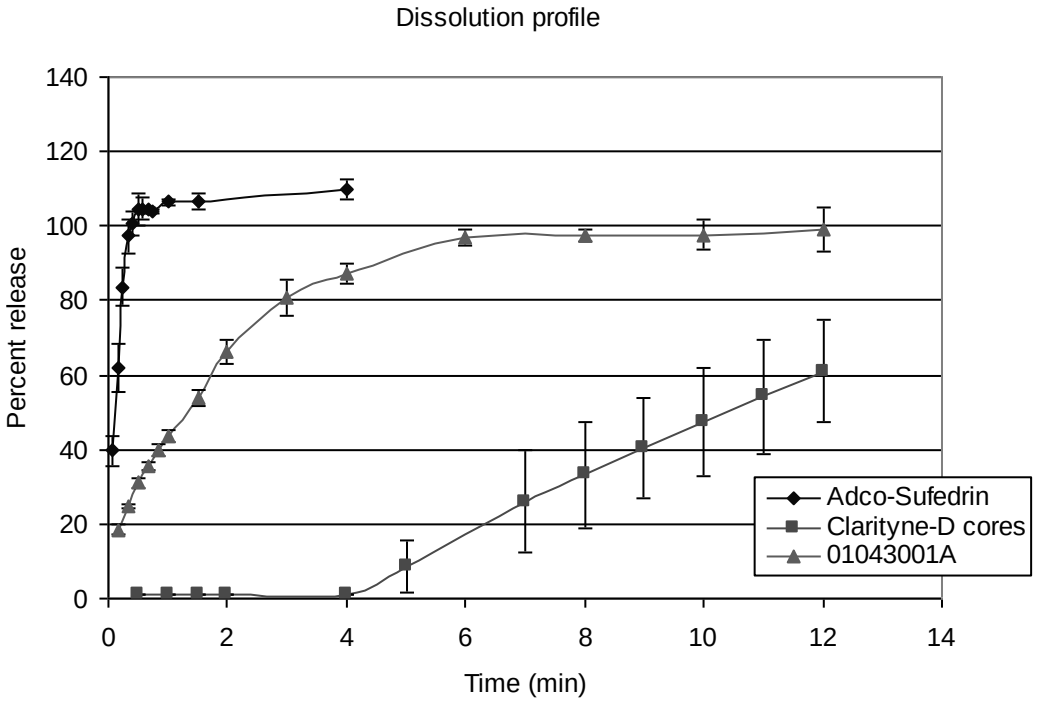
BATCH 01043001A

Date of Manufacture	19 October 1999
Press	Manesty F3
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
20% Ethylcellulose N7 in IPA	0.56g/ g powder blend
Single granulation	99.5
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	439.38 ± 10.36	2.36
Hardness (kp)	15.64 ± 1.13	7.20

Friability	passed
Weight before (20 tablets)	8.10 g
Weight after 100 drops	8.10 g
Percent lost	0.0



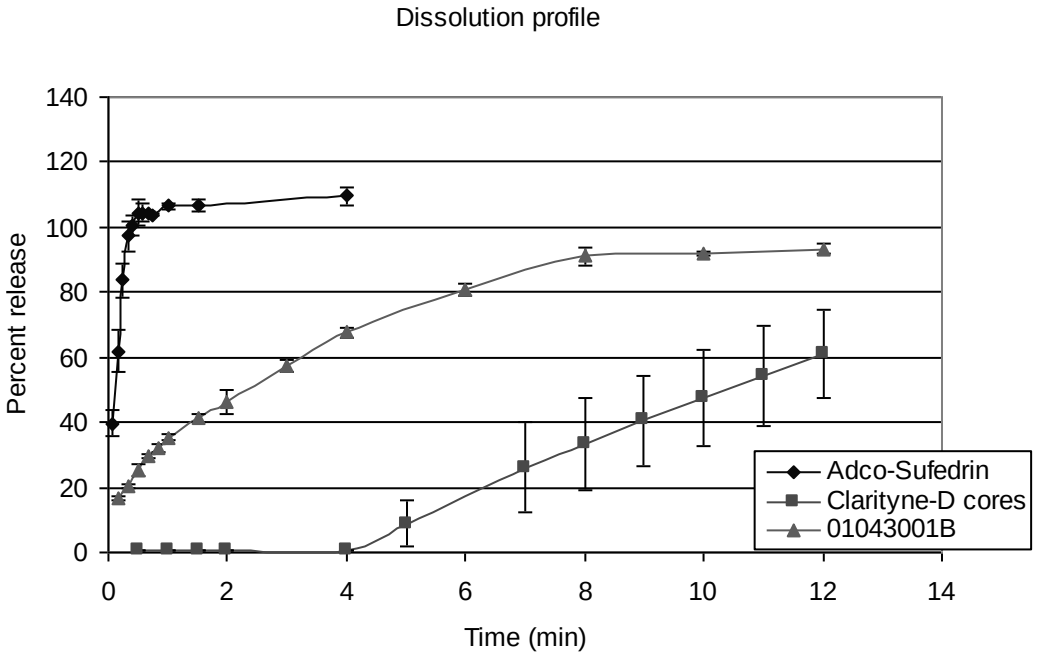
BATCH 01043001B

Date of Manufacture	19 October 1999
Press	Manesty F3
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
20% Ethylcellulose N7 in IPA	0.56 g/ g powder blend
20% Ethylcellulose N7 in IPA	0.48 g/ g granules
Double granulation	99.5
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	401.21 ± 14.89	3.71
Hardness (kp)	15.13 ± 2.32	15.34

Friability	passed
Weight before (20 tablets)	8.70 g
Weight after 100 drops	8.70 g
Percent lost	0.0



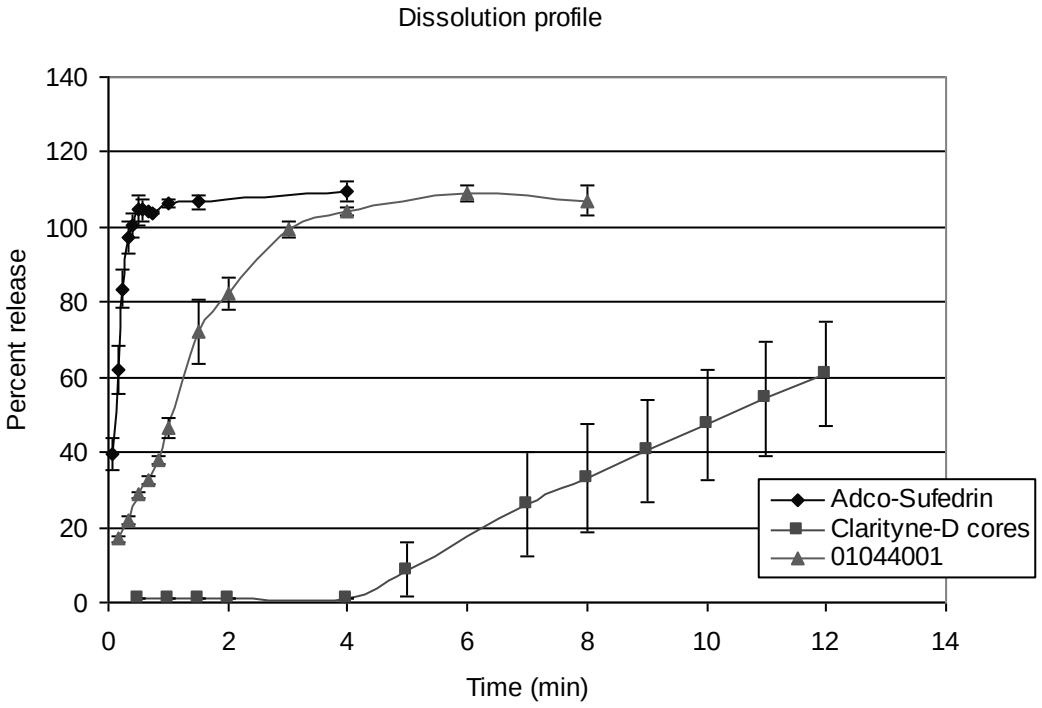
BATCH 01044001

Date of Manufacture	25 October 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
20% Ethylcellulose N7 in IPA	0.38 g/ g powder blend
20% Ethylcellulose N7 in IPA	0.30 g/ g granules
Double Granulation	99.5
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	448.16 ± 20.17	4.50
Hardness (kp)	7.31 ± 1.24	16.90

Friability	passed
Weight before (20 tablets)	8.78 g
Weight after 100 drops	8.78 g
Percent lost	0.0



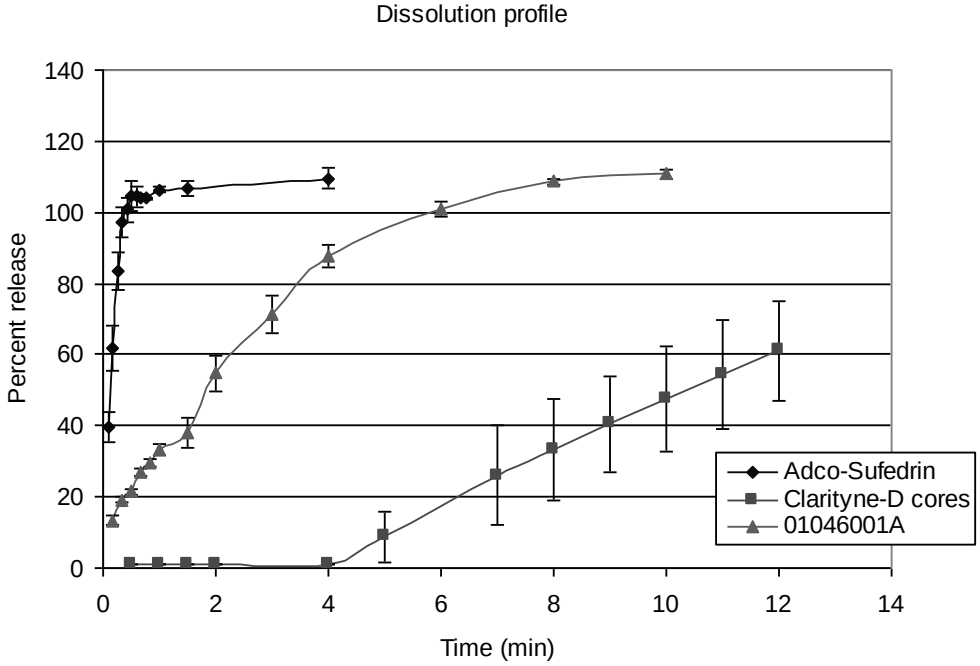
BATCH 01046001A

Date of Manufacture	4 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	40
Emcocel® 90M	40
Surelease®	0.88 g/ g powder blend
Single Granulation	90
Emcompress®	9
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	527.35 ± 17.71	3.36
Hardness (kp)	13.23 ± 2.40	18.11

Friability	passed
Weight before (20 tablets)	10.53 g
Weight after 100 drops	10.52 g
Percent lost	0.09



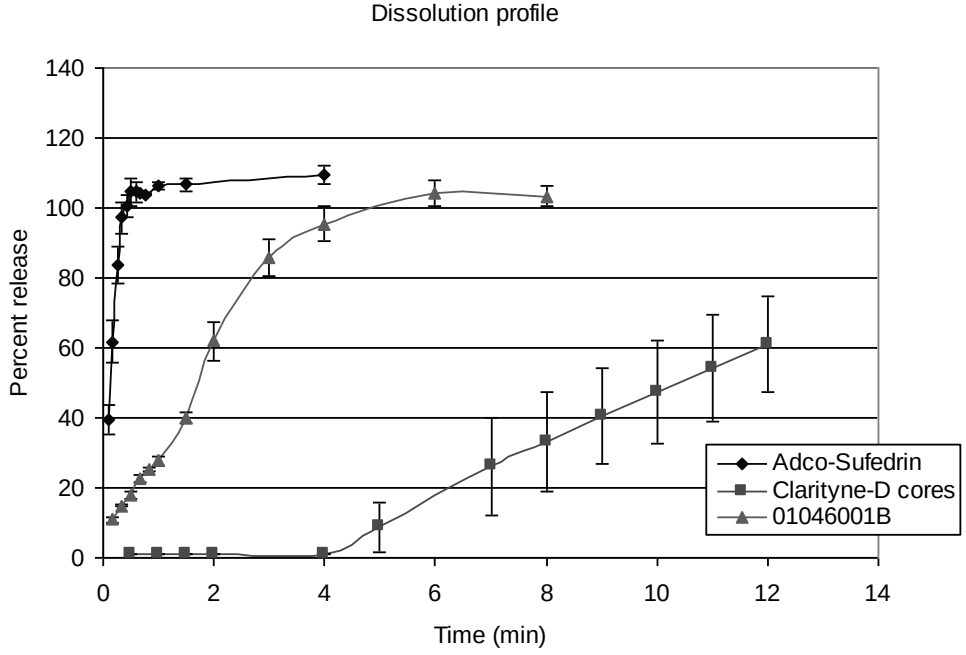
BATCH 01046001B

Date of Manufacture	4 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	40
Emcocel® 90M	40
Surelease®	0.88 g/ g powder blend
Surelease®	0.61 g/ g granules
Double Granulation	90
Emcocel® 90M	8.5
Colloidal Silica	0.5
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	524.76 ± 13.81	2.63
Hardness (kp)	9.14 ± 0.55	6.05

Friability	passed
Weight before (20 tablets)	10.33 g
Weight after 100 drops	10.28 g
Percent lost	0.48



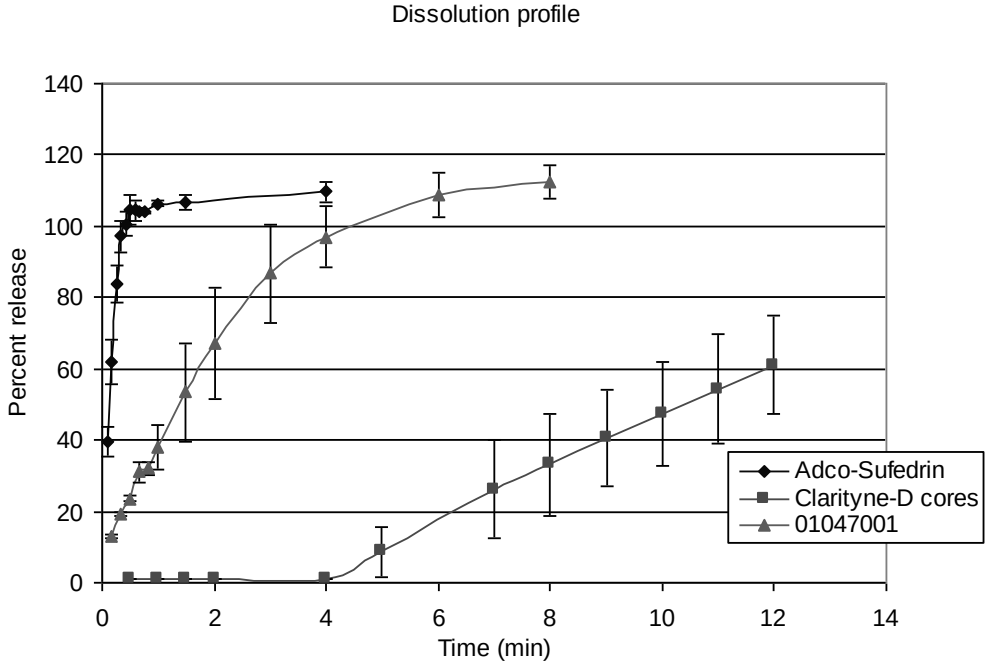
BATCH 01047001

Date of Manufacture	8 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
20% Ethylcellulose N7 in IPA	0.38 g/ g powder blend
20% Ethylcellulose N7 in IPA	0.30 g/ g granules
Double Granulation	90
Emcocel® 90M	8
Colloidal Silica	1
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	519.62 ± 17.34	3.33
Hardness (kp)	15.80 ± 2.32	14.64

Friability	passed
Weight before (20 tablets)	10.33 g
Weight after 100 drops	10.32 g
Percent lost	0.10



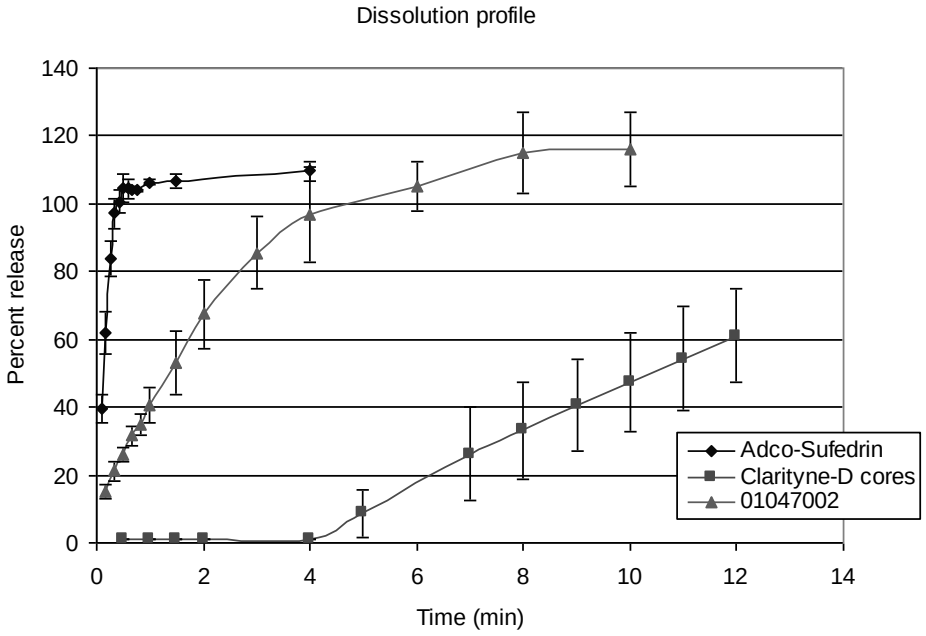
BATCH 01047002

Date of Manufacture	4 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	40
Emcocel® 90M	40
20% Ethylcellulose N7 in IPA	0.38 g/ g powder blend
20% Ethylcellulose N7 in IPA	0.30 g/ g granules
Double Granulation	75
Emcompress®	25
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	552.53 ± 26.05	4.71
Hardness (kp)	13.28 ± 1.35	10.14

Friability	passed
Weight before (20 tablets)	11.03 g
Weight after 100 drops	11.01 g
Percent lost	0.0



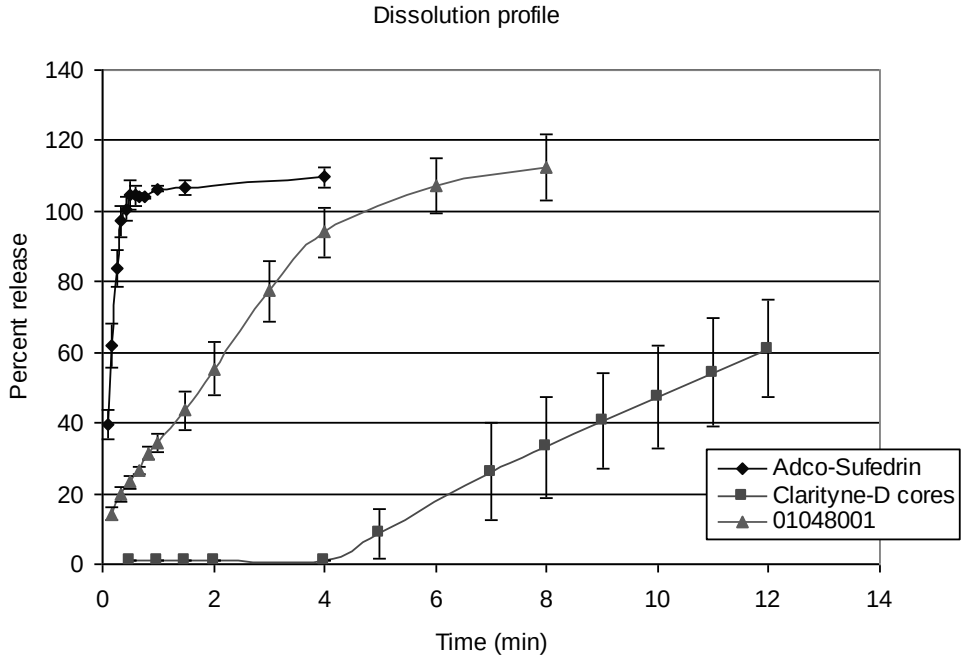
BATCH 01048001

Date of Manufacture	8 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	40
Emcocel® 90M	40
Eudragit®NE30D	0.53 g/ g powder blend
Single Granulation	90
Emcocel® 90M	8.5
Colloidal Silica	0.5
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	528.24 ± 27.96	5.29
Hardness (kp)	14.32 ± 2.60	18.19

Friability	passed
Weight before (20 tablets)	10.30 g
Weight after 100 drops	10.28 g
Percent lost	0.19



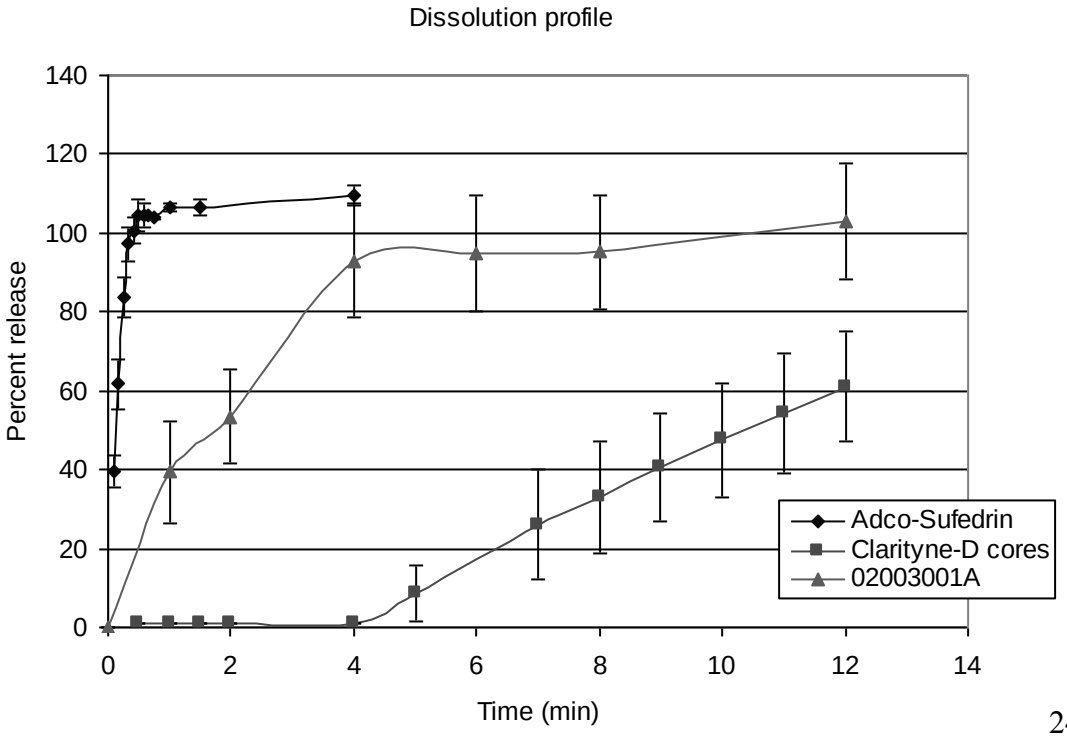
BATCH 02003001A

Date of Manufacture	17 April 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	40
Emcocel® 90M	40
Surelease®	0.49 g/ g powder blend
Surelease®	0.35 g/ g granules
Double Granulation	90
Emcocel® 90M	8.5
Colloidal Silica	0.5
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	551.79 ± 14.54	2.63
Hardness (kp)	18.20 ± 5.74	31.56

Friability	failed
Weight before (20 tablets)	9.95 g
Weight after 100 drops	9.55 g
Percent lost	4.02



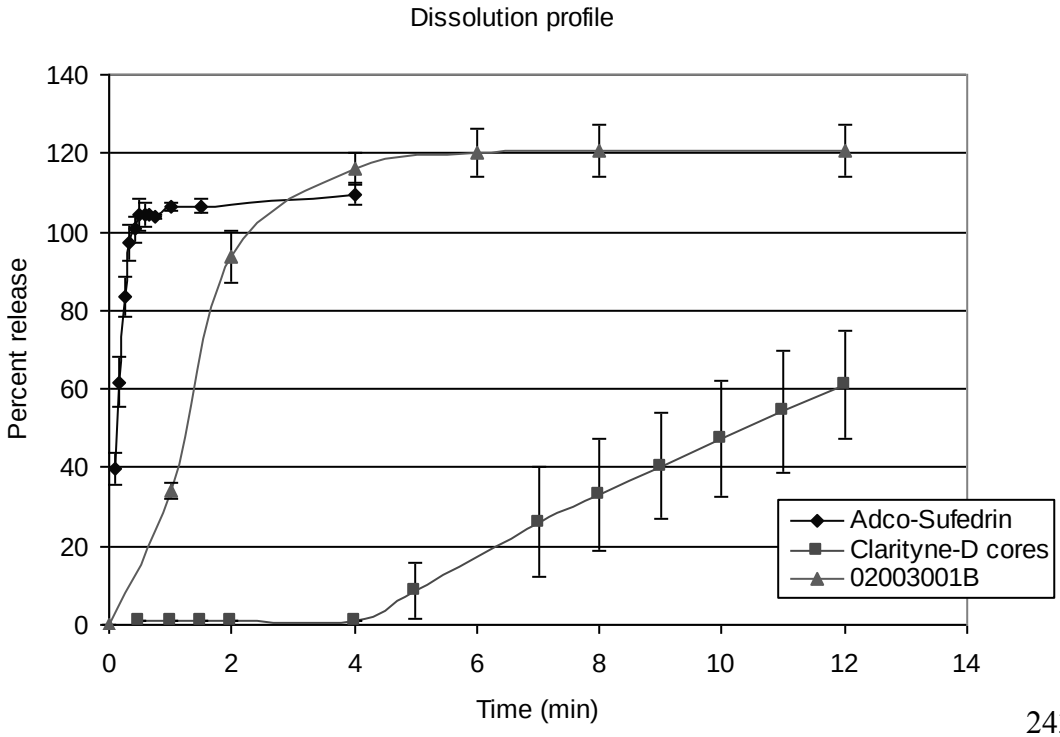
BATCH 02003001B

Date of Manufacture	17 April 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	40
Emcocel® 90M	40
Surelease®	0.49 g/ g powder blend
Surelease®	0.34 g/ g granules
Double Granulation	90
Emcocel® 90M	8.5
Colloidal Silica	0.5
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	563.66 ± 55.31	9.81
Hardness (kp)	9.72 ± 3.51	36.15

Friability	passed
Weight before (20 tablets)	10.89 g
Weight after 100 drops	10.88 g
Percent lost	0.09



3. COMPOSITE FORMULATIONS

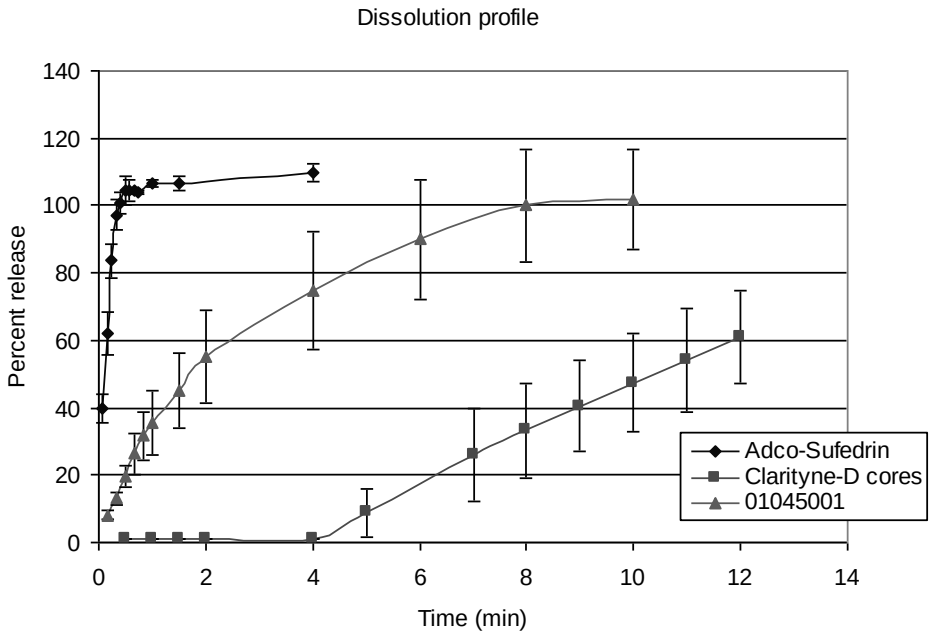
BATCH 01045001

Date of Manufacture	1 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
20% Ethylcellulose N7 in IPA	0.70g/ g powder blend
Double granulation	75
Methocel® K100M	15
Emcocel® 90M	10
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	597.12 ± 19.98	3.34
Hardness (kp)	9.69 ± 1.24	12.84

Friability	passed
Weight before (20 tablets)	11.85 g
Weight after 100 drops	11.80 g
Percent lost	0.42



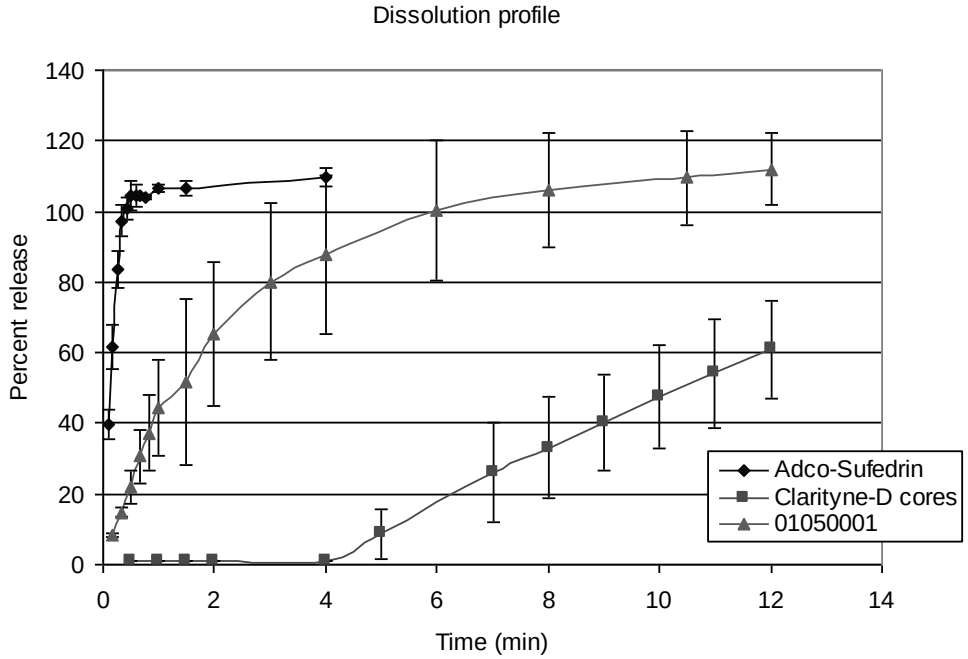
BATCH 01050001

Date of Manufacture	9 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
20% Ethylcellulose N7 in IPA	0.70g/ g powder blend
Double granulation	75
Methocel® K100M	15
Emcocel® 90M	10
Magnesium stearate	0.5

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	506.67 ± 18.44	3.64
Hardness (kp)	10.18 ± 1.92	18.82

Friability	passed
Weight before (20 tablets)	10.19 g
Weight after 100 drops	10.19 g
Percent lost	0.0



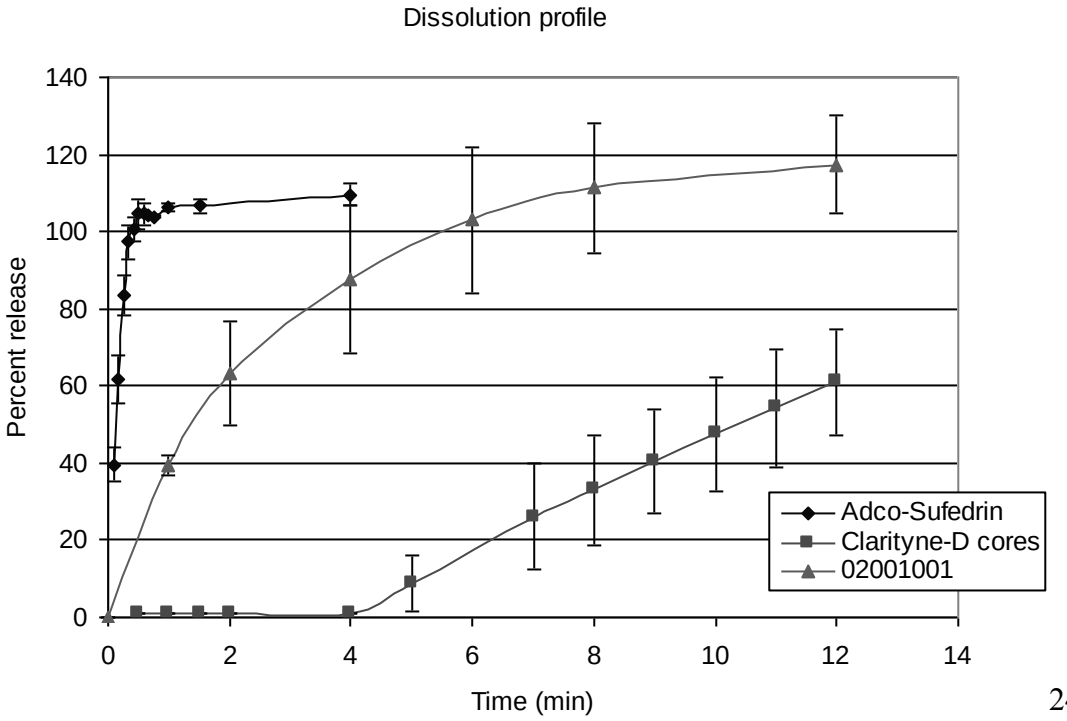
BATCH 02001001

Date of Manufacture	19 April 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	14
Emcompress®	50
Emcocel® 90M	36
Surelease®	0.71g/ g powder blend
Single granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	632.33 ± 43.28	6.84
Hardness (kp)	11.44 ± 2.82	24.71

Friability	passed
Weight before (20 tablets)	12.90 g
Weight after 100 drops	12.89 g
Percent lost	0.08



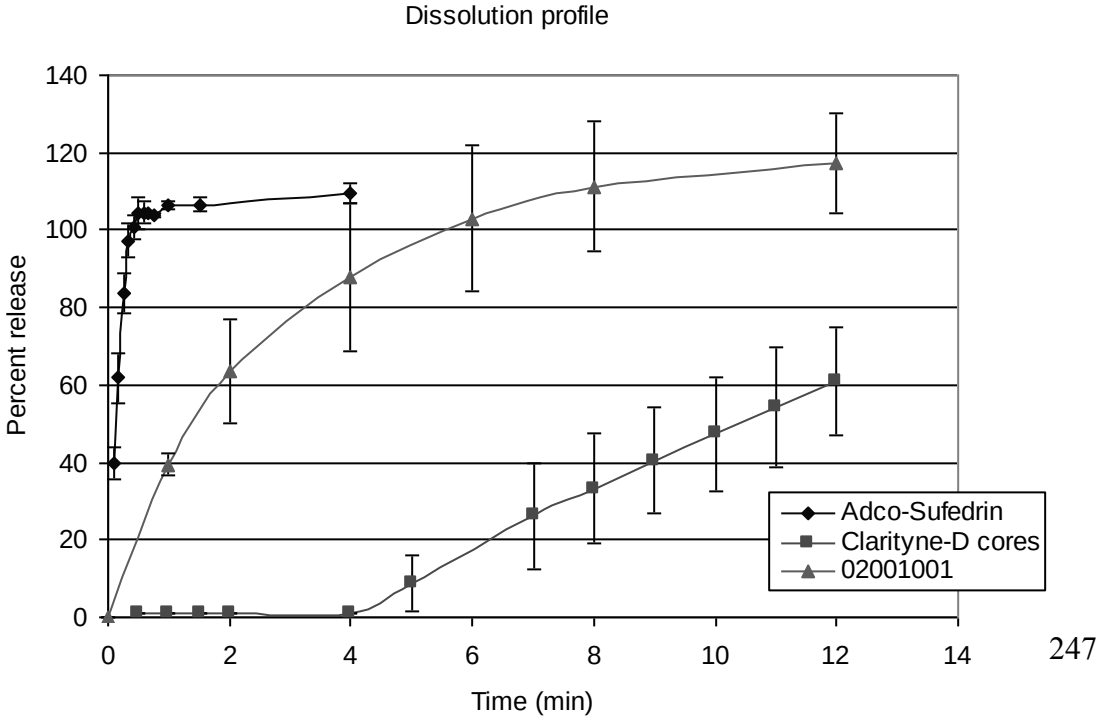
BATCH 02001002

Date of Manufacture	19 April 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	14
Emcompress®	50
Emcocel® 90M	36
Surelease®	0.71g/ g powder blend
Surelease®	0.47g/ g granules
Double granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	692.68 ± 42.40	6.12
Hardness (kp)	8.96 ± 2.95	32.88

Friability	passed
Weight before (20 tablets)	13.62 g
Weight after 100 drops	13.61 g
Percent lost	0.07



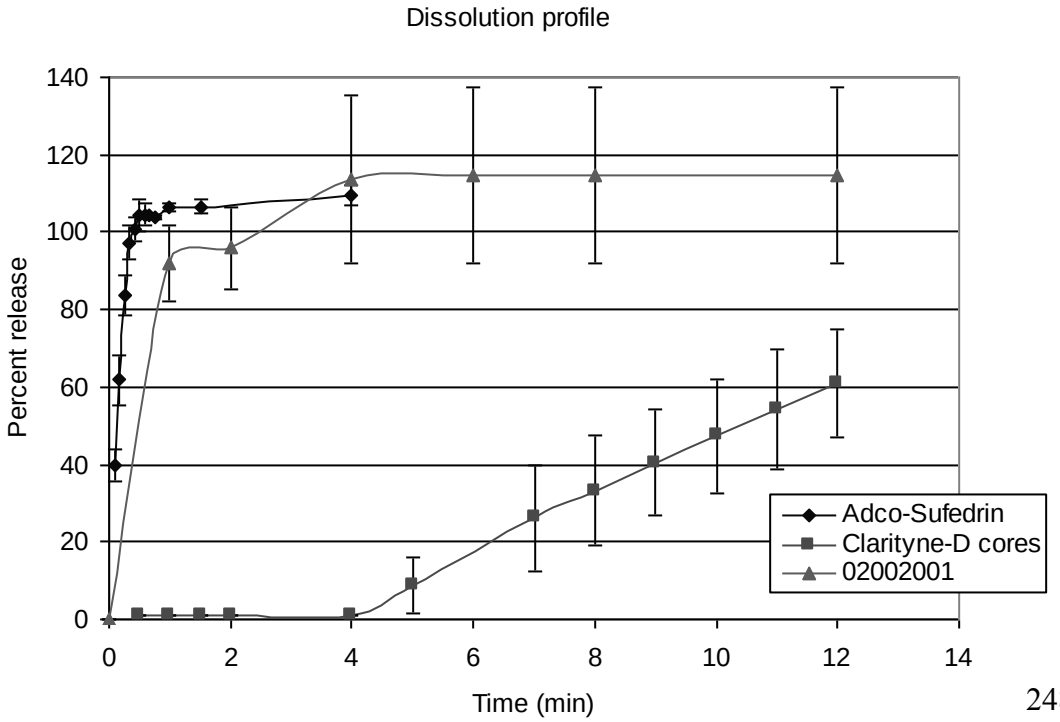
BATCH 02002001

Date of Manufacture	19 April 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	14
Emcompress®	50
Emcocel® 90M	36
20% Ethylcellulose N7 in IPA	0.71g / g powder blend
Single granulation	78.8
Eudragit® RSPO	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	650.29 ± 72.13	11.09
Hardness (kp)	8.93 ± 3.42	38.27

Friability	passed
Weight before (20 tablets)	13.85 g
Weight after 100 drops	13.84 g
Percent lost	0.07



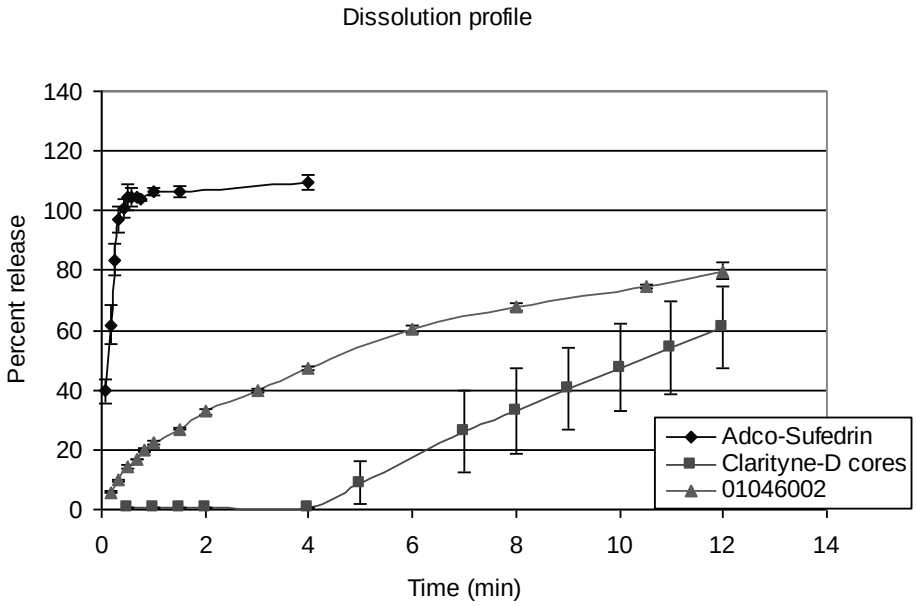
BATCH 01046002

Date of Manufacture	8 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Methocel® K4M	10
Emcompress®	40
Emcocel® 90M	30
Surelease®	0.69g/ g powder blend
Single granulation	69
Methocel® K100M	15
Emcocel® 90M	5
Emcompress®	10
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	557.08 ± 11.88	2.13
Hardness (kp)	9.53 ± 0.63	6.70

Friability	passed
Weight before (20 tablets)	11.20 g
Weight after 100 drops	11.18 g
Percent lost	0.18



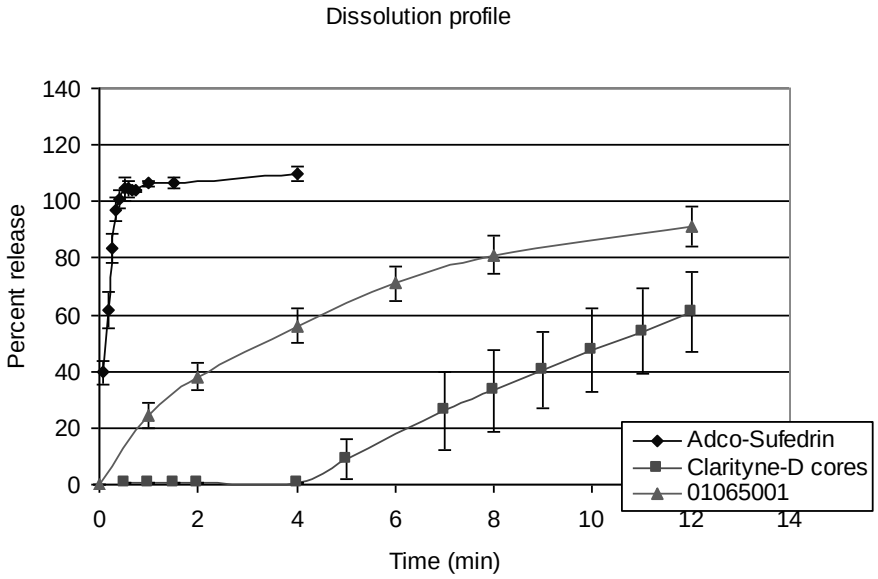
BATCH 01065001

Date of Manufacture	1 February 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	15
Methocel® K4M	10
Emcompress®	40
Emcocel® 90M	35
Surelease®	0.42g/ g powder blend
Single granulation	67
Methocel® K100M	15
Emcocel® 90M	7
Emcompress®	15
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	524.30 ± 14.69	2.80
Hardness (kp)	16.09 ± 0.77	4.78

Friability	passed
Weight before (20 tablets)	10.6354 g
Weight after 100 drops	10.6179 g
Percent lost	0.16



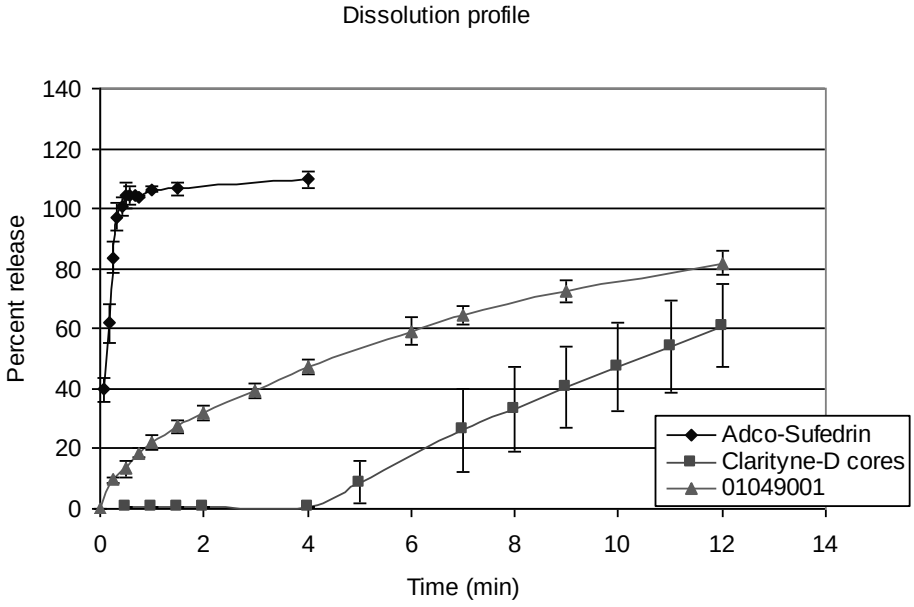
BATCH 01049001

Date of Manufacture	9 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
Eudragit® NE30D	0.31g/ g powder blend
Single granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	598.84 ± 5.47	0.91
Hardness (kp)	12.52 ± 0.84	6.71

Friability	passed
Weight before (20 tablets)	11.23 g
Weight after 100 drops	11.21 g
Percent lost	0.18



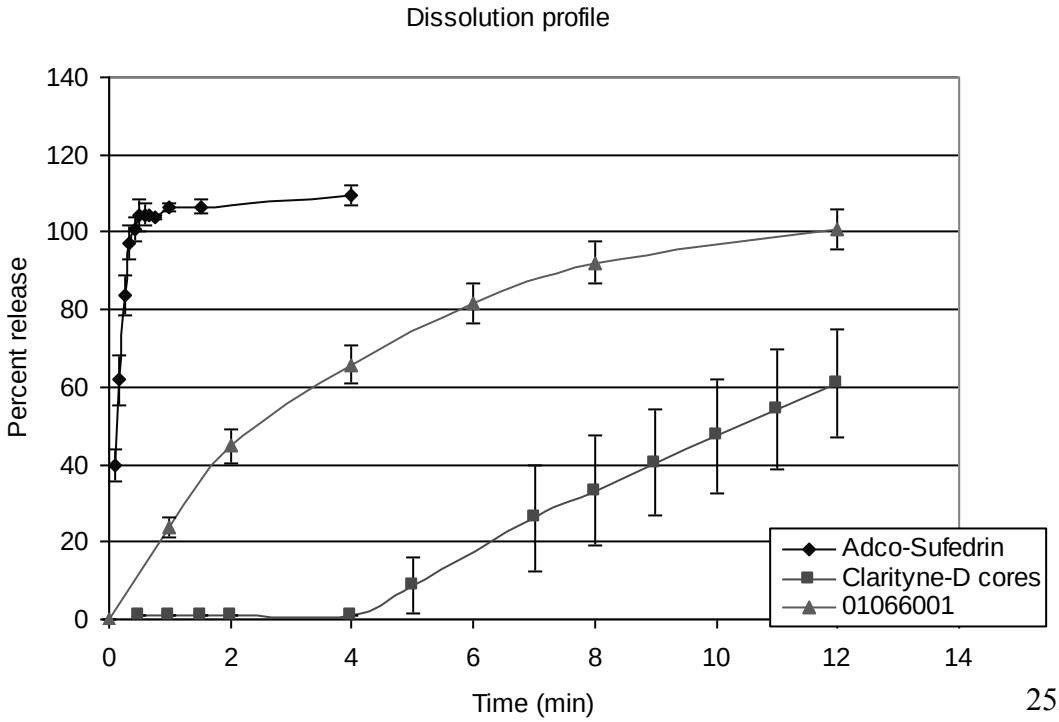
BATCH 01066001

Date of Manufacture	1 February 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	15
Emcompress®	50
Emcocel® 90M	35
Eudragit® NE30D	0.20g/ g powder blend
Single granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	553.52 ± 10.19	1.84
Hardness (kp)	17.01 ± 1.06	6.24

Friability	passed
Weight before (20 tablets)	11.1073 g
Weight after 100 drops	11.0696 g
Percent lost	0.34



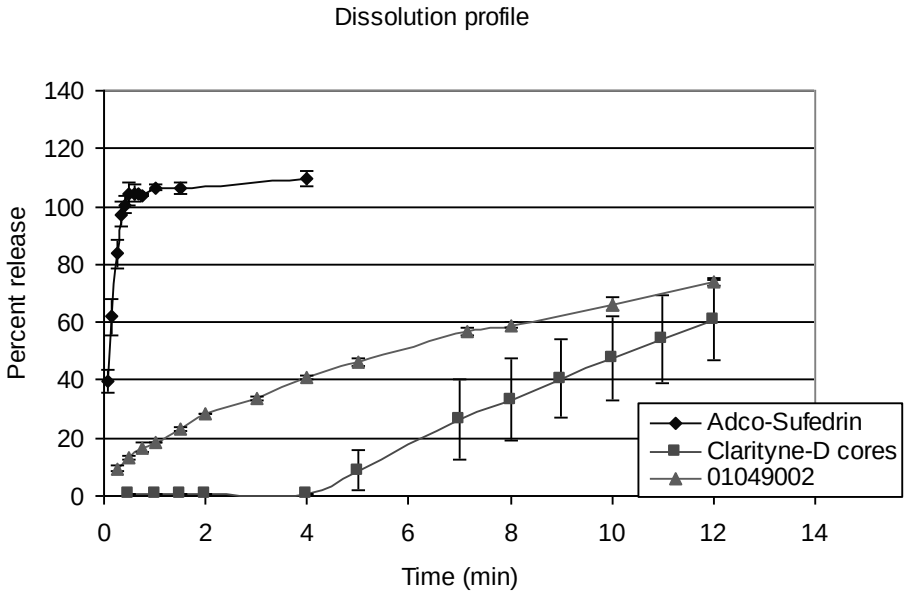
BATCH 01049002

Date of Manufacture	9 November 1999
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Emcompress®	50
Emcocel® 90M	30
Eudragit® NE30D	0.31g/ g powder blend
Eudragit® NE30D	0.18 g/ g granules
Double granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	558.08 ± 21.10	3.78
Hardness (kp)	12.10 ± 0.63	7.39

Friability	passed
Weight before (20 tablets)	11.24 g
Weight after 100 drops	11.21 g
Percent lost	0.27



BATCH 01067001

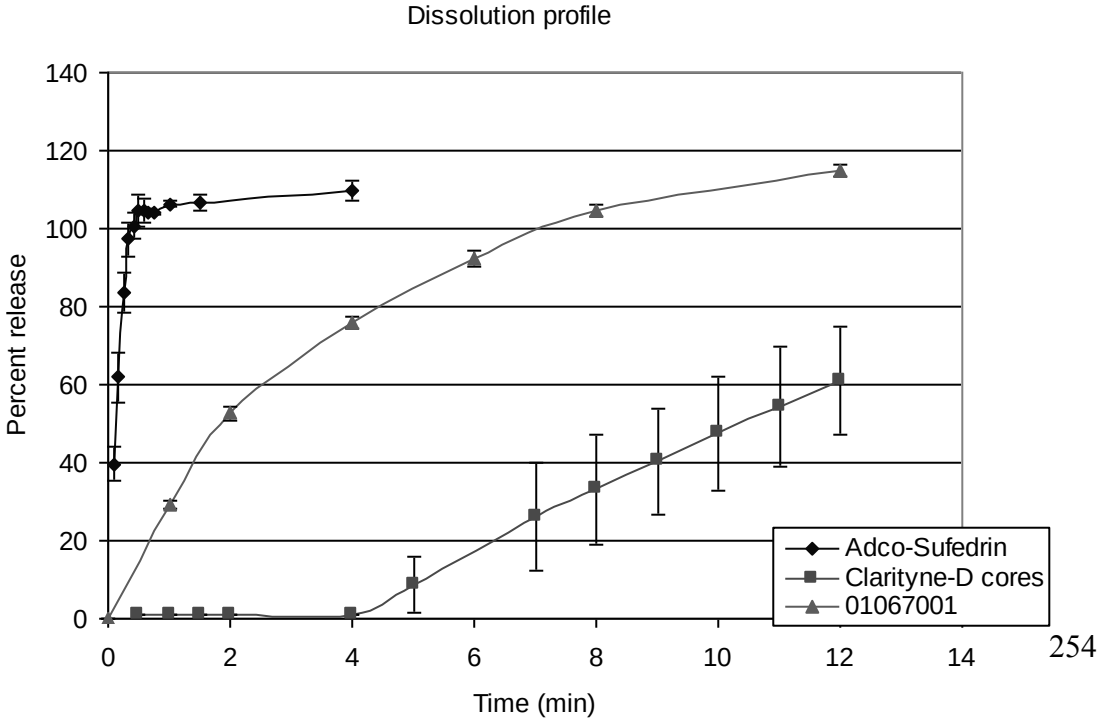
Date of Manufacture	1 February 2000
Press	Manesty B3B

Composition (%)	
Pseudoephedrine Sulfate	15
Emcompress®	50
Emcocel® 90M	35
Eudragit® NE30D	0.20g/ g powder blend
Eudragit® NE30D	0.18 g/ g granules
Double granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	570.8 ± 9.24	1.62
Hardness (kp)	14.72 ± 1.41	9.54

Friability	passed
Weight before (20 tablets)	11.4792 g
Weight after 100 drops	11.4728 g
Percent lost	0.06



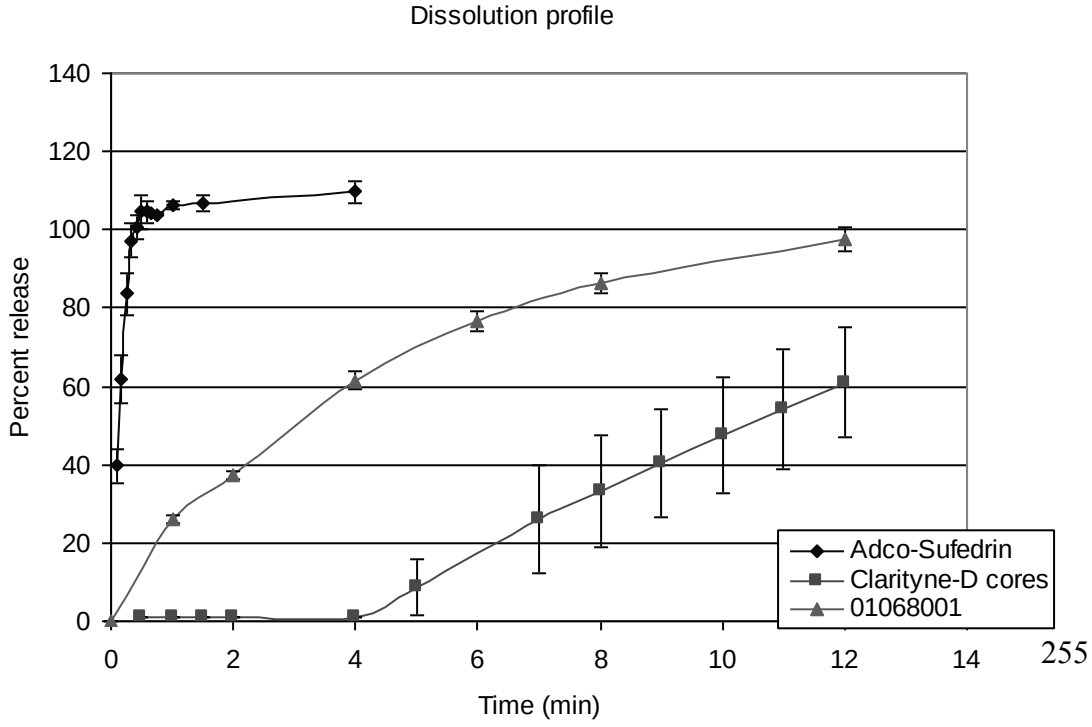
BATCH 01068001

Date of Manufacture	1 February 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	15
Methocel® K4M	10
Emcompress®	40
Emcocel® 90M	35
Surelease® with ATEC (10% w/w solids)	0.42g/ g powder blend
Single granulation	69
Methocel® K100M	15
Emcocel® 90M	5
Emcompress®	10
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	576.54 ± 7.82	1.36
Hardness (kp)	12.08 ± 0.53	4.42

Friability	passed
Weight before (20 tablets)	11.6744 g
Weight after 100 drops	11.6744 g
Percent lost	0.0



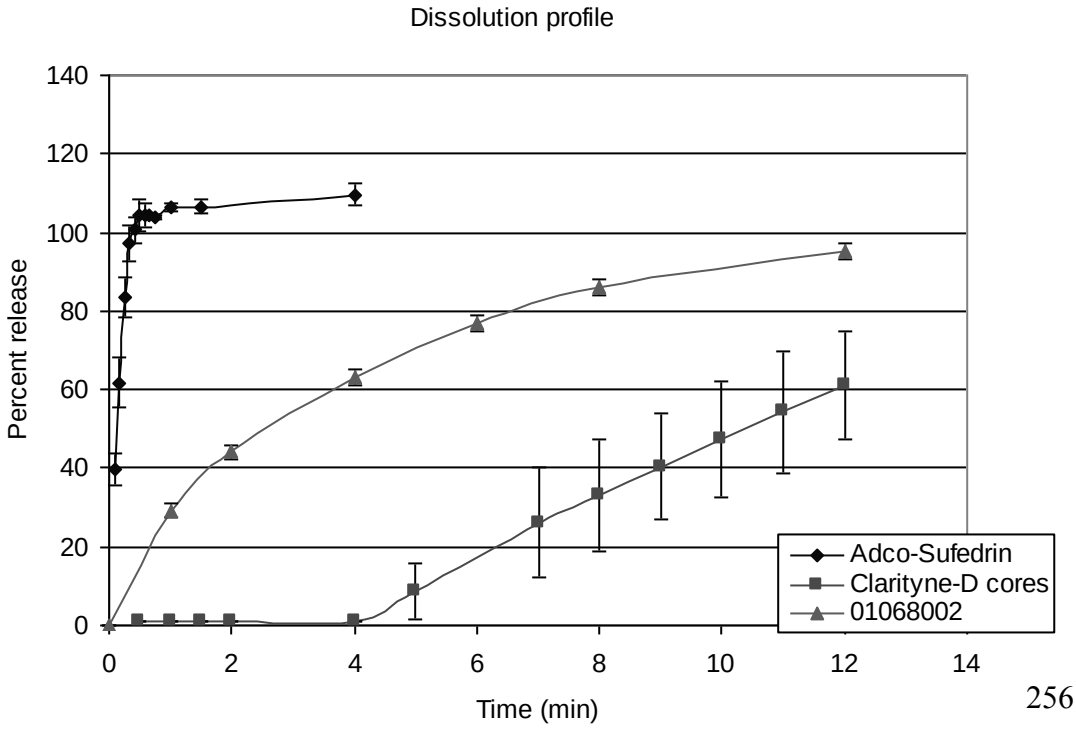
BATCH 01068002

Date of Manufacture	1 February 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	14
Emcompress®	40
Emcocel® 90M	30
Surelease® with ATEC (10% w/w solids)	0.34 g/ g powder blend
Single granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	559.43 ± 7.81	1.40
Hardness (kp)	17.81 ± 0.73	4.12

Friability	passed
Weight before (20 tablets)	11.1968 g
Weight after 100 drops	11.1107 g
Percent lost	0.77



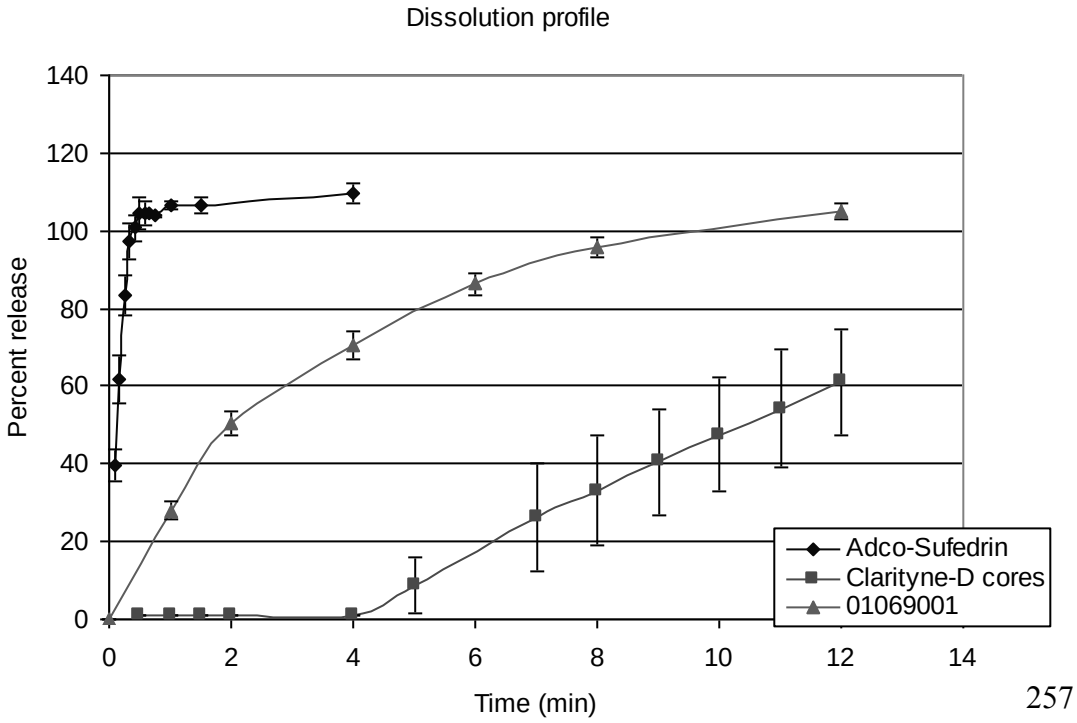
BATCH 01069001

Date of Manufacture	2 February 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	14
Emcompress®	50
Emcocel® 90M	36
Eudragit® RS30D	0.23 g/ g powder blend
Single granulation	78.8
Methocel® K100M	15
Emcocel® 90M	5
Colloidal Silica	0.2
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	562.62 ± 12.14	2.16
Hardness (kp)	14.52 ± 0.89	6.16

Friability	passed
Weight before (20 tablets)	11.2734 g
Weight after 100 drops	11.2704 g
Percent lost	0.03



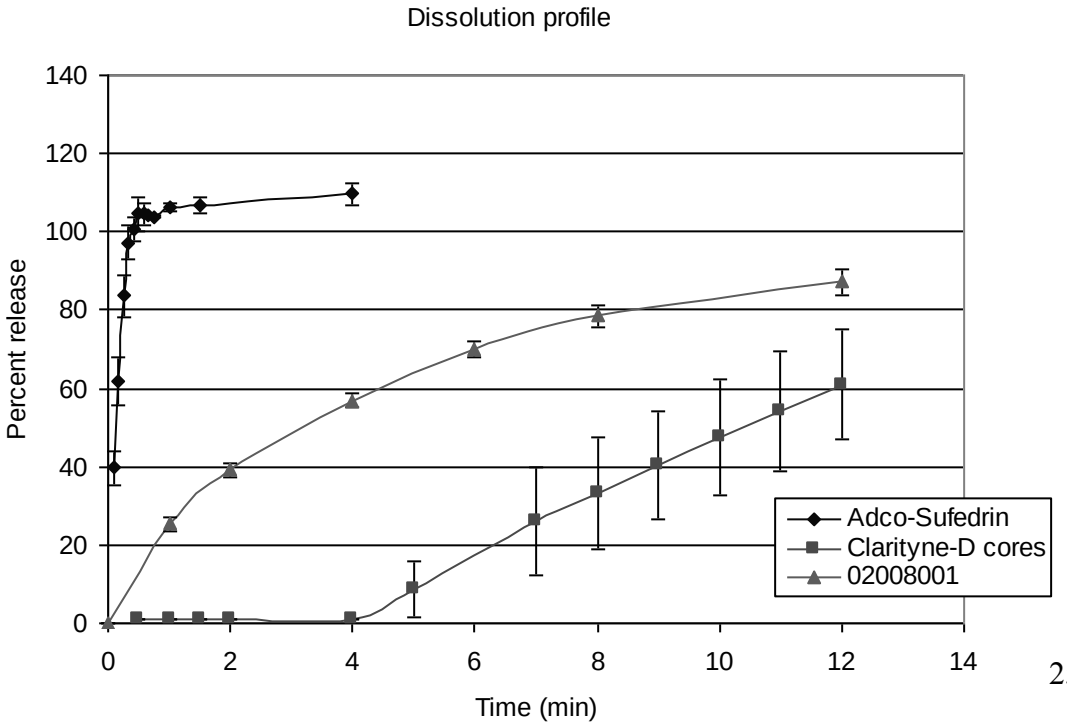
BATCH 02008001

Date of Manufacture	25 May 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Methocel® K4M	10
Emcompress®	40
Emcocel® 90M	30
Surelease®	0.21g/ g powder blend
Single granulation	69
Methocel® K100M	15
Emcocel® 90M	5
Emcompress®	10
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	527.44 ± 6.35	1.20
Hardness (kp)	13.58 ± 0.35	2.58

Friability	passed
Weight before (20 tablets)	11.41 g
Weight after 100 drops	11.41 g
Percent lost	0.0



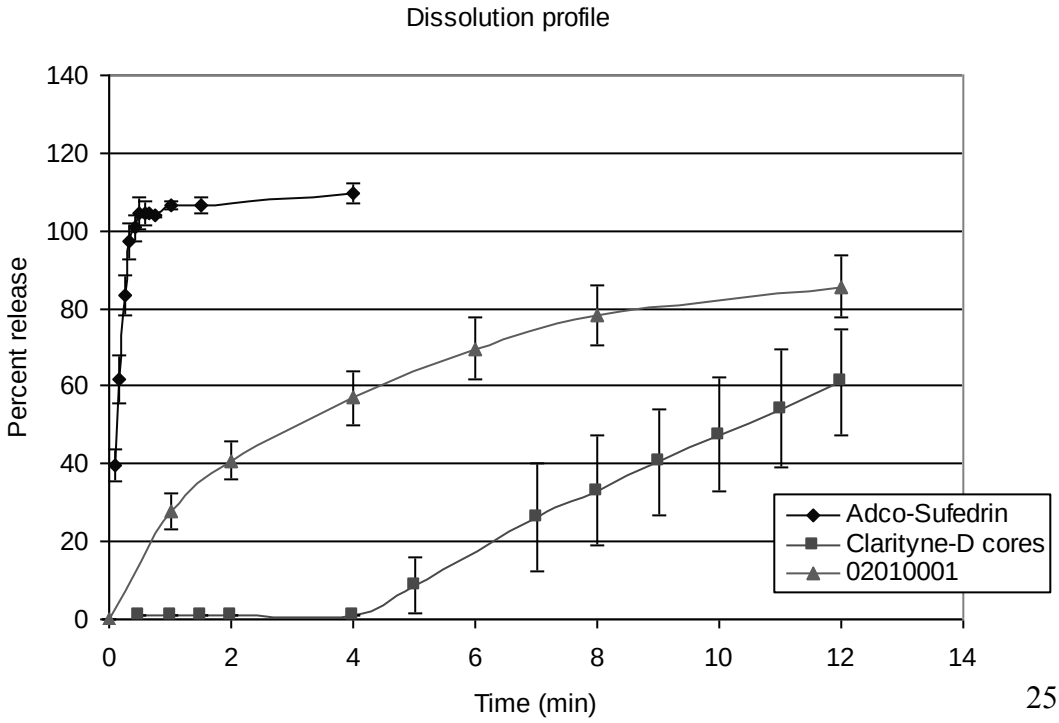
BATCH 02010001

Date of Manufacture	25 May 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	40
Methocel® K4M	10
Emcompress®	20
Emcocel® 90M	30
Surelease®	0.24g/ g powder blend
Single granulation	79
Methocel® K100M	15
Emcocel® 90M	5
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	472.39 ± 8.34	1.77
Hardness (kp)	10.11 ± 1.10	10.87

Friability	passed
Weight before (20 tablets)	9.40 g
Weight after 100 drops	9.40 g
Percent lost	0.0



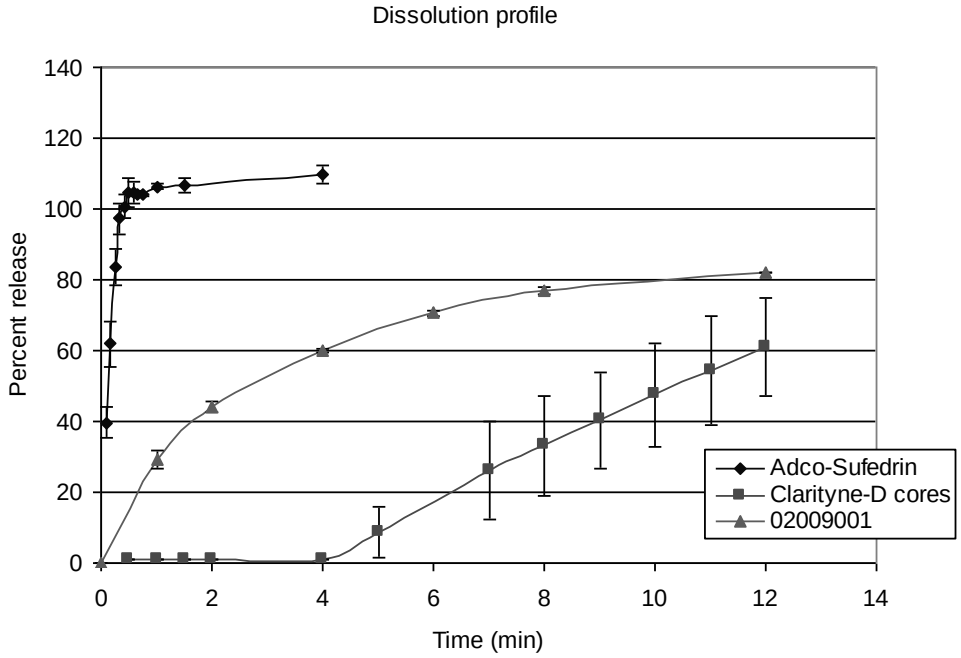
BATCH 02009001

Date of Manufacture	25 May 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Methocel® K4M	10
Emcompress®	35
Emcocel® 90M	30
Sodium Chloride	5
Surelease®	0.23g/ g powder blend
Single granulation	69
Methocel® K100M	15
Emcocel® 90M	5
Emcompress®	10
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	496.10 ± 6.64	1.34
Hardness (kp)	11.64 ± 0.52	4.43

Friability	passed
Weight before (20 tablets)	9.74 g
Weight after 100 drops	9.74 g
Percent lost	0.0



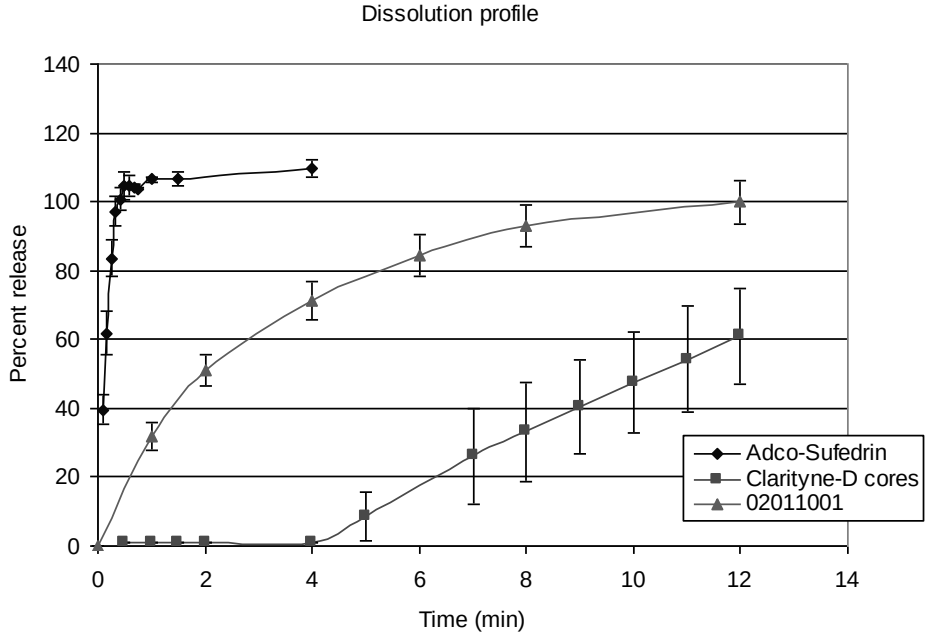
BATCH 02011001

Date of Manufacture	15 June 2000
Press	Manesty B3B
Composition (%)	
Pseudoephedrine Sulfate	20
Methocel® K4M	10
Emcompress®	40
Emcocel® 90M	30
Surelease®	0.44 g/ g powder blend
Single granulation	67
Methocel® K100M	15
Emcocel® 90M	5
Emcompress®	7
Sodium Chloride	5
Magnesium stearate	1

Physical tests

	Mean ± S.D.	**%RSD**
Weight (mg)	542.14 ± 8.50	1.57
Hardness (kp)	8.18 ± 0.62	7.56

Friability	passed
Weight before (20 tablets)	10.88 g
Weight after 100 drops	10.86 g
Percent lost	0.18



APPENDIX II

RAW MATERIALS

Raw Material	Trade Name	Supplier	Lot or batch number	Used as
Pseudoephedrine HCl		BASF-Knoll, Germany	IB5 SOJ62	Drug
Pseudoephedrine H_2SO_4		BASF-Knoll, Germany	61499	Drug
Loratadine		Reddy-Cheminor, India	NLE-8(P)E006	Drug
Ethylcellulose Dispersion	Surelease®	Colorcon, UK	IN 500111 IN 500647	Granulating fluid and coating medium
Polymethacrylate Dispersion	Eudragit® NE30D Eudragit® RS30D	Röhm, Germany	129071324 0490218032	Granulating fluid
Acetyl triethyl citrate (ATEC)		Morflex, NC, USA	N95200	Plasticizer
Triethyl citrate		Morflex, NC, USA	N95171	Plasticizer
Polymethacrylate	Eudragit® RSPO	Röhm, Germany	0490638102	Matrix forming polymer
Microcrystalline cellulose (MCC)	Avicel® PH102 Avicel® PH200 Emcocel® 90M	FMC, PA, USA FMC, PA, USA Mendell, NY, USA	7912 C M939C 2407	Granule and tablet diluent
Dibasic calcium phosphate (DCP)	Emcompress®	Mendell, NY, USA	24K	Granule and tablet diluent
Hydroxypropyl methylcellulose (HPMC)	Methocel® K4M Methocel® K15M Methocel® K100M	Colorcon, UK	NJ 23012N12 KJ 25012N02 NE 12012N01	Matrix forming polymer, granule excipient
	Microquick® WC595	FMC, PA, USA	W149	Tablet excipient
Colloidal Silica	Sipernat® 50S	Degussa, Germany	81650	Tablet excipient
Magnesium stearate		In-house		Lubricant
Sodium chloride		Saarchem, SA	8163	Osmotic tablet excipient
HPMC Dispersion	Opadry® II white	Colorcon, UK	DT 506256	Coating medium
Ethylcellulose	N22 N7	Hercules, VA, USA	43450	Matrix forming polymer, binder

APPENDIX III

BATCH PRODUCTION RECORDS

Only one coating record for the ethylcellulose coat is included for each batch. The records for the other coating levels are available on request.

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Page 1 of 5
Batch size: 750g

MANUFACTURING APPROVALS

Batch record issued by: _____ Date: 15 5 00
Master record issued by: / Date: /

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Batch size: 750g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
20	Pseudoephedrine sulfate (PSS)	RM000004	61499	150g	150.02		
10	Methocel K4M		M0539	75g	75.05		
40	Emcompress		24K	300g	300.17		
30	Emcocel 90M			225g	225.14		
q.s	Surelease	RM000010	IN500647				

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Batch size: 750g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh		
Scale	Precisa 4000		
Blender	Kenwood Major		
Pump	Masterflex		
Tubing	Masterflex LS14		
Granulator	Erweka Oscillating		
Oven			

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Page 4 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Separately screen the following materials through a 20 mesh screen.					
	Pseudoephedrine sulfate	149.73	14:12	18/5/00		
	Methocel K4M	74.91	14:21	18/5/00		
	Emcompress	300.17	14:19	18/5/00		
	Emcocel 90M	225.14	14:24	18/5/00		
2	Place the following materials in the Kenwood bowl.					
	Pseudoephedrine sulfate	149.73	14:16	18/5/00		
	Methocel K4M	74.91	14:22	18/5/00		
	Emcompress	300.17	14:20	18/5/00		
	Emcocel 90M	225.14	14:26	18/5/00		
3	Blend the materials in step 2 for 2 minutes at low speed.					
	Time started: 14:30					
	Time completed: 14:32					
	Total blending time: 2 mins					
	Speed setting: 1			18/5/00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Page 5 of 8
Batch size: 750g + 40.69 = 790.69

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done By	Checked By
4	Place the Surelease in a tared beaker and insert pump tubing.		14:31	18/5/00		
5	With the blender on low speed, add the Surelease at a pump rate of 8 – 9 for a total time of 10 minutes.					
	Time started: 14:32					
	Time completed: 14:42					
	Total time taken: 10 mins					
	Blender speed: 1					
	Pump setting: 8,-9					
	Amount of Surelease added: 160.19g (≡ 40.69 g CC)					
6	Transfer the granules to the ganulator and screen as follows, using 20 mesh screen and 100 rpm motor speed.					
	Speed: 96 - 104		14:48	18/5/00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Page 6 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
7	Place the granules on weighing paper and dry in the oven at 60 degrees for 12 hours ① Time started: 14:55 → 17:00 18.5.00 osmcs - 13hcc 19.5.00 Time completed: 01 15 Total drying time: 14 h Oven temperature: 64°C		06h20	22.5.00 22.5.00		
8	Remove the dried granules from the oven, and rescreen using the oscillating granulator (20 mesh, speed 100). Speed: 97		11hr1	22.5.00		

① Drying completed after weekend 22.5.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Page 7of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
9	Record the weight of acceptable granules obtained. Gross weight: 1460.55 Tare weight: 712.55 Net weight: 727.50	11h25	22.5.00		
10	Work out the percent yield as follows. Weight acceptable granules (AG): 727.50 Other weight accounted for (describe): test drying initial screening (mess unknown) Rescreening - 6.05g Total weight accounted for (TW): 727.50 + 6.05 = 733.55 Percent accountability = (TW/750) x 100% = NA % 92.8 % Percent yield = (AG/~~750~~ 740.65) x 100% = 97.05 %		22.5.00		
11	Transfer granules to airtight container until tableting.		N/A		

② Approved for Surelease 18.5.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02008001

Page 8 of 8
Batch size: 750g

SIGNATURE AND INITIAL REFERENCE

Full Name (print)	Signature	Initials	Date
J. VERNER	Verner	JV	18.5.00
T. ARJUN	TA	TA	22.05.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001T

Page 1 of 6
Batch size: 1040 g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
~~67~~ 69 (2)	Pseudoephedrine sulfate granules		02008001	717.6 g	717.6 g	JV	JV
15	Methocel K100M		(4) M053~~9~~968 (5)	156 g	125.56 g (5)	JV	JV
10	Emcompress		24K	104 g	104.14 g	JV	JV
~~7.5~~	Emcocel 90M			52 g	52.01 g	JV	JV
1	Magnesium stearate		(3)	10.4 g ~~10.4~~ g	10.41 g	JV	JV

(1) Typographical error JV 22.5.00
(2) Typographical error JV 22.5.00
(3) Mathematical error rectified 22.5.00
(4) Typographical error JV 22.5.00
(5) Second lot number NE12012N01 used amt = 27.49 g JV 22.5.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001T

Batch size: 1044 g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh, #44 mesh		
Scale	Precisa 4000		
Blender	Cube blender (Erweka)		
Tablet press	Manesty B3B		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001T

Batch size: 1044 g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Screen the following materials through a #20 mesh.					
	Methocel K100M	156.65	11:45	22-05-00		
	Emcompress	104.14	11:36	22-05-00		
	Emcocel 90M	52.61	11:50	22-05-00		
2	Place the following in the cube blender.					
	Pseudoephedrine sulfate granules	717.66 g	11:51	22-05-00		
	Methocel K100 M	156.65 g	11:52	22-05-00		
	Emcompress	104.14 g	11:53	22-05-00		
	Emcocel 90M	52.61 g	11:54	22-05-00		
3	Blend the materials in step 2 for 20 minutes at speed 100.					
	Time started: 11:54					
	Time completed: 12:21					
	Total blending time: 23 min					
	Speed: 113			22-05-00		

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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001T

Page 4 of 6
Batch size: 1040 g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
4	Screen the magnesium stearate using a #44 mesh.	10.4 g	12:00	22.5.00	J	
5	Add the magnesium stearate to the blender and blend for 3 minutes at 100 rpm. Time started: 12 h 26 Time completed: 12 h 29 Total blending time: 3 min Speed: 116			22.5.00	J	
6	Calculate the percent accountability and yield. Gross weight (blend): 2004.50 Tare weight: 965.54 © Net weight: ~~2004.50~~ 1038.7 g Other weight (Describe): NA Total weight accounted for (TW) = net weight + other weight = NA Percent accountability = (TW/ 1040) x 100% = NA % Percent yield = (blend/ 1040) x 100% = 99.9 %			22.5.00	J	
7	Store in airtight container until compression.			22.5.00	J	

© Entered under net weight incorrectly. 22.5.00 J.

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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001T

Page 5 of 6
Batch size: 1040 g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done by	Checked by
8	Tablet the blend on the tablet press according to the standard operating procedures. Desired Hardness: 10 - 15 kp. Desired Weight: 458 mg		22.5.2000	J	
9	© Sample 4 tablets every 15 minutes and check hardness and weight. Enter results on the in-process results sheet.		22.5.2000	J	
10	Perform physical tests of hardness, friability and weight uniformity on the final batch. Enter the results on the bulk product test reports.				
11	Store product in an airtight container.		22.5.2000	J	

© See deviation report 22.5.00 Jones

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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001T

Batch size: 1040 g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
12	Record the weight of acceptable tablets obtained. Gross weight: 936.70 g Tare weight: 60.93 g Net weight: 875.77		22-5-00	[signature]	[signature]
13	Work out the percent yield as follows. Weight acceptable tablets (AT): 875.77 g Other weight accounted for (describe): 75.49 g (vacuum cleaner) 70.191 g (Discarded end / start of run, RESI) Total weight accounted for (TW): 1021.45 g Percent accountability = (TW/ 1040) x 100% = 98.2 % Percent yield = (AG/ 1040) x 100% = 84.2 %		22-5-00	[signature]	[signature]

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 020808C01 Batch size: 1040g

IN-PROCESS TABLETING REPORT

Date	Time	Hardness	Weight
22 5 00	15 · 30	13 65	500 mg.
22 · 5 · 00	15 : 30	13 04	520 mg
	15 : 30	13 15	530 mg
	15 . 35	12 . 13	490 mg
	15 . 35	12 . 43	510 mg
	15 : 35	12 . 23	540 mg
	15 40	12 . 13	530 mg
	15 : 40	11 41	520 mg
	15 : 40	11 . 31	510 mg
	15 : 40	11 . 21	540 mg
	15 . 45	run over	run over
	15 : 45	"	"
	15 . 45	"	"
	15 . 45	"	"

RH : 57 %

T° ~~F°~~ 17.8 °C .

gross 936.70
tare : 60.93
net 875.77

Vacuum bag before : 294.27
after : 369.76
net : 75.49

Discarded tabs : 70.19 g .

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001 C3 .

Page 1 of 4
Batch size: 150

MASTER FORMULA AND BATCH FORMULA

Quantity	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
250g	Pseudoephedrine sulfate tablets		02008001 T	250g	150.15g		
15% soln	Surelease						
10% w/w	TEC						

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001C3

Page 2 of 4
Batch size:

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Fluid bed drier	Aeromatic Strea-1		
Scale	mettler		
Mixer	Gallenkamp		
Peristaltic pump	Masterflex, LS 13 tubing		
Digital Thermometer	Lutron		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001C 3

Batch size:

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Place the tablets in the product container	150.15	11:50	24.6.00		
2	Start the fluidising air at a rated temperature of 60 degrees and allow the tablets to circulate for 5 minutes until a product bed temperature of 45 degrees is reached. Time started: 11:51. Time completed: 11:54 Total time: 3 min					
3	Begin spraying by turning on the pump at a speed setting of 1.5 and turning on the atomising air to a pressure of 20 psi. Pump speed: 1.7 Atomising air pressure: 20 Actual spray rate: 3.55 g/min.					
4	Spray the product until a theoretical weight gain of 5%. If the product becomes tacky and no longer fluidises effectively, turn off the pump and allow the tablets to circulate freely for 2-3 minutes before recommencing spraying. Record product bed temperature, weight of surelease and time of any pauses.		11:55 – 12:07 646 601 12:09 – 12:22 601 565	24.6.00	12:25 – 12:40 565 565	

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001C 3

Batch size:

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
5	Record the following parameters at 5 minute intervals on the in process record sheet. Inlet air temperature Outlet air temperature Product temperature Atomising air pressure		24.6.00		
6	Allow the tablets to fluidise for a drying time of 20 minutes once spraying has finished.		24.6.00		
7	Record the weight of coated tablets obtained. Gross weight: 405.63 Tare weight: 248.29. Net weight: 157.34		24.6.00		
8	Work out the percent weight gain as follows. Weight coated tablets (CT): 157.34 Other weight accounted for (describe): — Total weight accounted for (TW): 157.34 Percent weight gain = (TW - 150.15 / 150.15) x 100% = 4.8 %		24.6.00		
9	Store product in an airtight container.		24.6.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 020080010C3 Batch size: 150 g

IN-PROCESS COATING REPORT

Date: 24·6·00

Time	Inlet air temperature	Outlet air temperature	Product temperature	Atomising air pressure
11:55	54	38	49	18
12:00	50	38	44	21
12:05	53	40	45	21
12:10	41	42	40	20
12:15	50	44	44	19
12:20	52	46	45	20
12:25	55	49	50	22
12:30	53	46	47	20
12:35	53	46	48	17
12:40	47	44	45	20

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001CC2

Page 1 of 4
Batch size: 125 g

MASTER FORMULA AND BATCH FORMULA

Quantity	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
~~250g~~ ① 125 g	Pseudoephedrine sulfate tablets		02008001C	~~250g~~ ① 125g	125.52g		
	Opadry Suspension with PSS / Loratadine q.s						

① correction required 27·9·00

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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02008001CC2

Page 2 of 4
Batch size: 125g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Fluid bed drier	Aeromatic Strea-1		
Scale	Mettler		
Mixer	Gallenkampf.		
Peristaltic pump	Masterflex, LS 13 tubing		
Digital Thermometer	Lutron.		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020080001CC2

Batch size: 125.5

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Place the tablets in the product container	125.52	06:45	27.9.00		
2	Start the fluidising air at a rated temperature of 60 degrees and allow the tablets to circulate for 5 minutes until a product bed temperature of 45 degrees is reached. Time started: 06:46 Time completed: 06:49 Total time: 3 mins					
3	Begin spraying by turning on the pump at a speed setting of 1.5 and turning on the atomising air to a pressure of 20 psi. Pump speed: 0.6 Atomising air pressure: 18-20 psi Actual spray rate: 3.25 g/min		06:57	27.9.00		
4	Spray the product until a theoretical weight gain of 5%. If the product becomes tacky and no longer fluidises effectively, turn off the pump and allow the tablets to circulate freely for 2-3 minutes before recommencing spraying. Record product bed temperature, weight of surelease and time of any pauses.		06:50 - 07:30 - Nozzle block 07:40 - 08:20	27.9.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020080001CC2

Batch size:

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
5	Record the following parameters at 5 minute intervals on the in process record sheet. Inlet air temperature Outlet air temperature Product temperature Atomising air pressure				
6	Allow the tablets to fluidise for a drying time of 20 minutes once spraying has finished. Dried at approx. 40°C		27.09.00		
7	Record the weight of coated tablets obtained. Gross weight: 316.75 g Tare weight: 167.31 g Net weight: 149.44 g		27.09.00		
8	Work out the percent weight gain as follows. Weight coated tablets (CT): 149.44 g Other weight accounted for (describe): – Total weight accounted for (TW): 149.44 g Percent weight gain = (TW - 125.52 / 125.52) x 100% = 19.01 %		27.09.00		
9	Store product in an airtight container.		27.09.00 27.09.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 020008001CC2 Batch size: 125·5g .

IN-PROCESS COATING REPORT

Date: 27·09·2000

Time	Inlet air temperature	Outlet air temperature	Product temperature	Atomising air pressure
06h50	58	40	46	18
06h55	58	44	48	19
07h00	58	46	50	18
07h05	58	46	50	18
07h10	58	46	53	19
07h15	58	47	53	18
07h20	56	46	51	21
07h30	56	50	55	17
07h40	54	44	50	19
07h45	58	44	54	18
07h50	56	44	53	18
07h55	58	48	55	19
08h00	56	46	54	20
08h05	58	47	53	19
08h10	57	47	54	20
08h15	56	46	53	20
08h20	54	47	52	18

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Page 1 of 8
Batch size: 750g

MANUFACTURING APPROVALS

Batch record issued by: [signature] Date: 18/5/00
Master record issued by: / Date: /

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Batch size: 750g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
40	Pseudoephedrine sulfate (PSS)	RM000004	61499	300g	300.25		
10	Methocel K4M		M0539	75g	75.01		
20	Emcompress		24K	150g	150.09		
30	Emcocel 90M			225g	225.08		
q.s	Surelease	RM000010	IN500647				

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Batch size: 750g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh		
Scale	Precisa 4000		
Blender	Kenwood Major		
Pump	Masterflex		
Tubing	Masterflex LS14		
Granulator	Erweka Oscillating		
Oven			

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Page 4 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Separately screen the following materials through a 20 mesh screen.					
	Pseudoephedrine sulfate	300.25	16:27	18·5·00		
	Methocel K4M	75.01	16:32	18·5·00		
	Emcompress	150.09	16:34	18·5·00		
	Emcocel 90M	225.08	16:30	18·5·00		
2	Place the following materials in the Kenwood bowl.					
	Pseudoephedrine sulfate	300.25	16:29	18·5·00		
	Methocel K4M	75.01	16:33	18·5·00		
	Emcompress	150.09	16:35	18·5·00		
	Emcocel 90M	225.08	16:31	18·5·00		
3	Blend the materials in step 2 for 2 minutes at low speed.					
	Time started: 16:38					
	Time completed: 16:40					
	Total blending time: 2 min					
	Speed setting: 1			18·5·00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Page 5 of 8
Batch size: 750g + 44.77 = 794.77g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done By	Checked By
4	Place the Surelease in a tared beaker and insert pump tubing.		16:39	18·5·00		
5	With the blender on low speed, add the Surelease at a pump rate of 8 – 9 for a total time of 10 minutes.					
	Time started: 16:40					
	Time completed: 16:50					
	Total time taken: 10 min					
	Blender speed: 1					
	Pump setting: 9					
	Amount of Surelease added: 176.27g (≡ 44.77g E.C)			18·5·00		
6	Transfer the granules to the ganulator and screen as follows, using 20 mesh screen and 100 rpm motor speed.					
	Speed: 105			18·5·00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Page 6 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
7	Place the granules on weighing paper and dry in the oven at 60 degrees for 12 hours ① Time started: 08h05 → 17h00 ; 08h30 Time completed: 12:04 Total drying time: 12.5 hours Oven temperature: 64°C			19.5.00 22.5.00		
8	Remove the dried granules from the oven, and rescreen using the oscillating granulator (20 mesh, speed 100). ② Speed: 97			22.5.00		

① Drying stopped over weekend - completed on Monday morning 22.5.00
② Also screened by hand. 22.5.00

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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Page 7of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
9	Record the weight of acceptable granules obtained. Gross weight: 1325.38 Tare weight: 712.78 Net weight: 612.6				
10	Work out the percent yield as follows. Weight acceptable granules (AG): 612.6 Other weight accounted for (describe): 23.5g (loss on rescreening) Initial loss on screening not known Total weight accounted for (TW): 636.1 Percent accountability = (TW/~~750~~ 794.13) x 100% = 80.0 % Percent yield = (AG/~~750~~ 794.13) x 100% = 77.05 %			22.5.00	
11	Transfer granules to airtight container until tableting.		N/A		

① Adjusted theoretical yield with surerelease®

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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02010001

Page 8 of 8
Batch size: 750g

SIGNATURE AND INITIAL REFERENCE

Full Name (print)	Signature	Initials	Date
J. VERNER	Verner	J	18·5·00
J. ARJUN		J	22·05·00

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001T

Page 1 of 6
Batch size: ~~675g~~ ③ 775g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
79	Pseudoephedrine sulfate granules		02010001	① ~~603.75~~ 612.25g	612.25	J	
15	Methocel K100M		② ~~M0539~~	116.25g	116.27	J	
5	Emcocel 90M			38.75g	38.75	J	
1	Magnesium stearate			7.75g	7.76	J	

① Incorrect calculation 22·5·00 J
② Incorrect batch # 22·5·00 J
③ Incorrect final weight 22·5·00 J

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001T

Page 2 of 6
Batch size: 795 g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh, #44 mesh		
Scale	Precisa 4000		
Blender	Cube blender (Erweka)		
Tablet press	Manesty B3B		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001T

Page 3 of 6
Batch size: 795

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Screen the following materials through a #20 mesh.					
	Methocel K100M	116.27	13:12	22-5-00		
	Emcocel 90M	38.75	13:11	22-5-00		
2	Place the following in the cube blender.					
	Pseudoephedrine sulfate granules	612.25	13:13	22-5-00		
	Methocel K100 M	116.27	13:14	22-5-00		
	Emcocel 90M	38.75	13:14	22-5-00		
3	Blend the materials in step 2 for 20 minutes at speed 100.					
	Time started: 14h12					
	Time completed: 14h32					
	Total blending time: 25 min					
	Speed: 113			22-5-00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001T

Batch size: 775g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
4	Screen the magnesium stearate using a #44 mesh.	7.35g	13:15	22-05-00		
5	Add the magnesium stearate to the blender and blend for 3 minutes at 100 rpm. Time started: 14.39 Time completed: 14.42 Total blending time: 3 min Speed: 10%			22.5.00		
6	Calculate the percent accountability and yield. Gross weight (blend): 1737.46 g Tare weight: 966.33g Net weight: 771.13 g Other weight (Describe): NA Total weight accounted for (TW) = net weight + other weight = NA Percent accountability = (TW/ NA) x 100% = NA % Percent yield = (blend/775) x 100% = 99.5 %			22.5.00		
7	Store in airtight container until compression.			22.5.00		

PHARMACEUTICS DEPARTMENT
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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001T

Batch size: 775g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done by	Checked by
8	Tablet the blend on the tablet press according to the standard operating procedures. Desired Hardness: 10-15 kp Desired Weight: 400 mg		22.5.00		
9	① Sample 4 tablets every 5 minutes and check hardness and weight. Enter results on the in-process results sheet.		22.5.00		
10	Perform physical tests of hardness, friability and weight uniformity on the final batch. Enter the results on the bulk product test reports.				
11	Store product in an airtight container.		22.5.00		

① see deviation report 22.5.00

PHARMACEUTICS DEPARTMENT
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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001T

Batch size: 775 g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
12	Record the weight of acceptable tablets obtained. Gross weight: 628.10 Tare weight: 63.23 Net weight: 564.87g		22.5.00	g	
13	Work out the percent yield as follows. Weight acceptable tablets (AT): 564.87g Other weight accounted for (describe): 188.55g 166.49g discarded tabs (end / start run, testi) 22.06g vacuum. Total weight accounted for (TW): 753.42 Percent accountability = (TW/ 775) x 100% = 97.2 % Percent yield = (AG/ 775) x 100% = 72.9 %		22.5.00	g	

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 02010001 Batch size: 775g.

IN-PROCESS TABLETING REPORT

Date	Time	Hardness	Weight
22.5.00	16h40	5.70	440
		9.07	440
		8.76	490
		9.07	480
	16h45	8.16	470
		7.84	470
		6.72	479
		9.48	460
	16h49	9.07	470
		7.13	490
		9.48	460
		8.86	450

60% RH.
17.3°C.

Bag before : 399.66g.
after : 421.72g
net . 22.06g

waste : 159.26 + 7.23 = 166.49g

Gross 628.10
Tare 63.23
net

Target : 400mg.

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001C2

Page 1 of 4
Batch size: 150 g

MASTER FORMULA AND BATCH FORMULA

Quantity	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
250g	Pseudoephedrine sulfate tablets		02010001T	250g	150.4 g		
15% soln	Surelease						
10% w/w	TEC						

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Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02010001C2

Page 2 of 4
Batch size: 150 g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Fluid bed drier	Aeromatic Strea-1		
Scale	Mettler		
Mixer	Gallenkamp F		
Peristaltic pump	Masterflex, LS 14 tubing		
Digital Thermometer	Lutron		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020100001C2

Batch size: 150g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Place the tablets in the product container	150.4 g		19.9.00		
2	Start the fluidising air at a rated temperature of 60 degrees and allow the tablets to circulate for 5 minutes until a product bed temperature of 45 degrees is reached. Time started: 12:40. Time completed: 12:41 Total time: 1 min			19.9.00		
3	Begin spraying by turning on the pump at a speed setting of 1.5 and turning on the atomising air to a pressure of 20 psi. Pump speed: 0.8 Atomising air pressure: 20 psi Actual spray rate: 4.5 g/min	start: 574.31		19.9.00		
4	Spray the product until a theoretical weight gain of 5%. If the product becomes tacky and no longer fluidises effectively, turn off the pump and allow the tablets to circulate freely for 2-3 minutes before recommencing spraying. Record product bed temperature, weight of surelease and time of any pauses.	12:42 - 13:30		19.9.00		

add: 435.5 (15%)
483 (10%).

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020100001C2

Batch size: 150g.

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
5	Record the following parameters at 5 minute intervals on the in process record sheet. Inlet air temperature Outlet air temperature Product temperature Atomising air pressure		19/9/00		
6	Allow the tablets to fluidise for a drying time of 20 minutes once spraying has finished.		19/9/00		
7	Record the weight of coated tablets obtained. Gross weight: 419.02 Tare weight: 254.96 Net weight: 164.06	wt 20 = 9.64	19/9/00		
8	Work out the percent weight gain as follows. Weight coated tablets (CT): 164.06 Other weight accounted for (describe): — Total weight accounted for (TW): 164.06 Percent weight gain = (TW - 150.4 / 150.4) x 100% = 9.1 %	after = 10.08 ∴ % coat = 6.8%	19/9/00		
9	Store product in an airtight container.		19/9/00		28

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 020100001C2 Batch size: 150g

IN-PROCESS COATING REPORT

Date: 19·9·06

Time	Inlet air temperature	Outlet air temperature	Product temperature	Atomising air pressure
12:42	54	34	42	21
12:47	55	42	43	16
12:52	60	47	50	18
12:57	54	46	47	18
13:02	51	47	47	19
13:07	49	47	43	15
13:12	50	44	45	19
13:17	56	46	46	20
13:22	50	44	43	16
13:27	51	44	43	16

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Page 1 of 8
Batch size: 750g

MANUFACTURING APPROVALS

Batch record issued by: jerner Date: 18-5-00
Master record issued by: ✓ Date: ✓

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Batch size: 750g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
20	Pseudoephedrine sulfate (PSS)	RM000004	61499	150g	150.23		
10	Methocel K4M		M0539	75g	75.01		
35	Emcompress		24K	262.5g	262.46		
30	Emcocel 90M			225g	225.03		
5	Sodium Chloride		1010200	37.5g	37.54		
q.s	Surelease	RM000010	IN500647				

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Batch size: 750g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh		
Scale	Precisa 4000		
Blender	Kenwood Major		
Pump	Masterflex		
Tubing	Masterflex LS14		
Granulator	Erweka Oscillating		
Oven			

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Page 4 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Separately screen the following materials through a 20 mesh screen.					
	Pseudoephedrine sulfate	150.23	15:24	18·5·00		
	Methocel K4M	75.01	15:30	18·5·00		
	Emcompress	262.46	15:18	18·5·00		
	Emcocel 90M	225.03	15:21	18·5·00		
	Sodium Chloride	37.54	15:32	18·5·00		
2	Place the following materials in the Kenwood bowl.					
	Pseudoephedrine sulfate	150.23	15:26	18·5·00		
	Methocel K4M	75.01	15:34	18·5·00		
	Emcompress	262.46	15:20	18·5·00		
	Emcocel 90M	225.03	15:22	18·5·00		
	Sodium Chloride	37.54	15:35	18·5·00		
3	Blend the materials in step 2 for 2 minutes at low speed.					
	Time started: 15:55					
	Time completed: 15:57					
	Total blending time: 2 min					
	Speed setting: 1			18·5·00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Page 5 of 8
Batch size: 750g + 43.75 = 793.75g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done By	Checked By
4	Place the Surelease in a tared beaker and insert pump tubing.		15:55	18·5·00		
5	With the blender on low speed, add the Surelease at a pump rate of 8 – 9 for a total time of 10 minutes.					
	Time started: 15:57					
	Time completed: 16:07					
	Total time taken: 10 mins					
	Blender speed: 1					
	Pump setting: 9					
	Amount of Surelease added: 172.26 g (≡ 43.75 g E.C.)			18·5·00		
6	Transfer the granules to the ganulator and screen as follows, using 20 mesh screen and 100 rpm motor speed.					
	Speed: 106		16:11	18·5·00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Page 6 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
7	Place the granules on weighing paper and dry in the oven at 60 degrees for 12 hours					
	① Time started: 16:23 → 17:00 18.5.00 08:05 - 17:00 19.5.00		08:30	22.5.00		
	Time completed: 12:04			22.5.00		
	Total drying time: 12.5 hours					
	Oven temperature: 64 °C					
8	Remove the dried granules from the oven, and rescreen using the oscillating granulator (20 mesh, speed 100).					
	Speed: 96			22.5.00		

① Drying completed after the weekend. 22.5.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Page 7of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
9	Record the weight of acceptable granules obtained.				
	Gross weight: 1454.24				
	Tare weight: 712.73				
	Net weight: 741.51		22.5.00		
10	Work out the percent yield as follows.				
	Weight acceptable granules (AG): 741.51g.				
	Other weight accounted for (describe): lost on screening : 2.5g initial screening unaccounted for.				
	Total weight accounted for (TW): 741.51 + 2.5 = 744.01				
	Percent accountability = (TW/750) x 100% = 93.7 %				
	① Percent yield = (AG/750) x 100% = 93.4 %		22.5.00		
11	Transfer granules to airtight container until tableting.		22.5.00		

① Adjusted weight for surelease 22.5.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02009001

Page 8 of 8
Batch size: 750g

SIGNATURE AND INITIAL REFERENCE

Full Name (print)	Signature	Initials	Date
J. VERNER			18·5·00
J. ARJUN			22·05·00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001T

Page 1 of 6
Batch size: 1050 g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
② ~~67~~ 69	Pseudoephedrine sulfate granules		02009001	724.5 g	724.50 g		
15	Methocel K100M	①	~~M0539~~	157.5 g	157.51		
10	Emcompress			105 g	105.03		
5	Emcocel 90M			52.5 g	52.51		
1	Magnesium stearate			10.5 g	10.53		

① Incorrect lot number; Batch used is NE12012N01 22·5·00
② Typographical error: 22·5·00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001T

Batch size:

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh, #44 mesh		
Scale	Precisa 4000		
Blender	Cube blender (Erweka)		
Tablet press	Manesty B3B		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001T

Batch size:

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Screen the following materials through a #20 mesh. Methocel K100M Emcompress Emcocel 90M	157.57 105.03 52.51	12h28 12h29 12h30	22-5-00 22-5-00 22-5-00		
2	Place the following in the cube blender. Pseudoephedrine sulfate granules Methocel K100 M Emcompress Emcocel 90M	724.50 157.5 105.03 52.51	12h30 12h31 12h31 12h32	22-5-00 22-5-00 22-5-00 22-5-00		
3	Blend the materials in step 2 for 20 minutes at speed 100. Time started: 12h34 Time completed: 12h56 Total blending time: 22 min Speed: 117			22-5-00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001T

Batch size: 1050

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
4	Screen the magnesium stearate using a #44 mesh.					
5	Add the magnesium stearate to the blender and blend for 3 minutes at 100 rpm. Time started: 12h57 Time completed: 13h00 Total blending time: 3 min Speed: 77			22·5·00		
6	Calculate the percent accountability and yield. Gross weight (blend): 1761.61 Tare weight: 712.75 Net weight: 1048.86 g Other weight (Describe): NA Total weight accounted for (TW) = net weight + other weight = NA Percent accountability = (TW/ 1050) x 100% = NA % Percent yield = (blend/ 1050) x 100% = 99.9 %			22·5·00		
7	Store in airtight container until compression.			22·5·00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001T

Batch size:

MANUFACTURING DIRECTIONS

Step		Procedure	Time	Date	Done by	Checked by
8		Tablet the blend on the tablet press according to the standard operating procedures. Desired Hardness: 10 - 15 Kp. Desired Weight: 460 mg		22·5·00		
9	①	Sample 5 tablets every 15 minutes and check hardness and weight. Enter results on the in-process results sheet.		22·5·00		
10		Perform physical tests of hardness, friability and weight uniformity on the final batch. Enter the results on the bulk product test reports.				
11		Store product in an airtight container.		22·5·00		

① see deviation report 22·5·00

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001T

Batch size: 1050 g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
12	Record the weight of acceptable tablets obtained. Gross weight: 1004.70 Tare weight: 63.04 Net weight: 941.66		22.5.00		
13	Work out the percent yield as follows. Weight acceptable tablets (AT): 941.66 Other weight accounted for (describe): 94.91 65.01 - End/start run + test discard tabs 29.90 - vacuum Total weight accounted for (TW): 1036.57 Percent accountability = (TW/ 1050) x 100% = 98.7 % Percent yield = (AG/ 1050) x 100% = 89.7 %		22.5.00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 02009001 Batch size: 1050g

IN-PROCESS TABLETING REPORT

Date	Time	Hardness	Weight
22-5-00	16h05	10.60	470
	16h05	11.62	500
	16h05	9.88	490
	16h05	11.31	500
	16h10	11.72	480
	16h10	9.58	510
	16h10	10.80	500
	16h10	10.90	490
	16h15	11.62	500
	16h15	10.70	500
	16h15	9.17	500
	16h15	10.09	450
	16h20	9.68	490
	16h20	4.99	440
	16h20	7.95	470
	16h20	11.57	510

RH : 60%
T° : 17.6°C

Gross 1004.70
Tare 0.3 CL
Net

Bag before : 369.76g
after : 399.66g
net : 29.90

Waste . 65.01

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020090001C 2

Page 1 of 4
Batch size:

MASTER FORMULA AND BATCH FORMULA

Quantity	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
250g	Pseudoephedrine sulfate tablets		01C091001 T	250g	200g		
15% soln	Surelease						
10% w/w	TEC						

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020090001C 2

Page 2 of 4
Batch size:

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Fluid bed drier	Aeromatic Strea-1		
Scale	Mettler		
Mixer	Gallenkampf		
Peristaltic pump	Masterflex, LS 13 tubing 14		
Digital Thermometer	Lutron		

@ LS14 tubing substituted. 19.09.00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001C2 .

Batch size: 200g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Place the tablets in the product container	200.2g	10:52	19/9/00		
2	Start the fluidising air at a rated temperature of 60 degrees and allow the tablets to circulate for 5 minutes until a product bed temperature of 45 degrees is reached. Time started: 10.52 . Time completed: 10.55 Total time: 3 min					
3	Begin spraying by turning on the pump at a speed setting of 1.5 and turning on the atomising air to a pressure of 20 psi. Pump speed: 20 0.5 Atomising air pressure: 20psi Actual spray rate: 3.2 g/min - 4.5 g/min	start weight: 350.7g 10:56		19/9/00		
4	Spray the product until a theoretical weight gain of 5%. If the product becomes tacky and no longer fluidises effectively, turn off the pump and allow the tablets to circulate freely for 2-3 minutes before recommencing spraying. Record product bed temperature , weight of surelease and time of any pauses.	10:56 - 10:59 - filling change		19/9/00	11:05 -	

To end: 575 g .

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02009001C2

Batch size: 200g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
5	Record the following parameters at 5 minute intervals on the in process record sheet. Inlet air temperature Outlet air temperature Product temperature Atomising air pressure		19/9/00	—	
6	Allow the tablets to fluidise for a drying time of 20 minutes once spraying has finished.		19/9/00		
7	Record the weight of coated tablets obtained. Gross weight: 468.50 Tare weight: 254.91 Net weight: 213.59		19/9/00		
8	Work out the percent weight gain as follows. Weight coated tablets (CT): 213.59 Other weight accounted for (describe): 0.52 (disc. tab) Total weight accounted for (TW): 214.11 Percent weight gain = (TW - 200.2 / 200.2) x 100% = 6.9 %	20 tabs uncoated: 10.27g. after: 10.98 ∴ % coat: 5.4%	19/9/00		
9	Store product in an airtight container.		19/9/00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 02009001C2 Batch size: 200g.

IN-PROCESS COATING REPORT

Date: 19/9/00.

Time	Inlet air temperature	Outlet air temperature	Product temperature	Atomising air pressure
10:56	56	26	47	20 psi
11:03	50	41	47	20
11:07.	49	40	41	21
11:12.	51	41	42	20
11:17.	52	44	44	20
11:22.	49	43	43	22
11:27.	46	44	42	20
11:32.	48	40	42	22
11:37.	50	40	39	20
11:42.	50	42	40	21
11:47.	50	40	41	20
12:05	50	42	39	20

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Batch size: 750g

MANUFACTURING APPROVALS

Batch record issued by: _____ Date: 22.5.00
Master record issued by: _____ Date: _____

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 2 of 6
Batch size: 750g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
20	Pseudoephedrine sulfate (PSS)	RM000004	61499	150g	150.13		
10	Methocel K4M		M0539	75g	75.09g		
40	Emcompress	RM000059	AC6A.	300g	300.04g		
30	Emcocel 90M		2018	225g	225.13g		
q.s	Surelease	RM000010	IN500647				

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 3 of 8
Batch size: 750g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh		
Scale	Precisa 4000		
Blender	Kenwood Major		
Pump	Masterflex		
Tubing	Masterflex LS14		
Granulator	Erweka Oscillating		
Oven			

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 4 of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Separately screen the following materials through a 20 mesh screen.					
	Pseudoephedrine sulfate	150.13	11:52	13·6·00		
	Methocel K4M	75.09	11:57	13·6·00		
	Emcompress	300.09	11:50	13·6·00		
	Emcocel 90M	225.13	11:54	13·6·00		
2	Place the following materials in the Kenwood bowl.					
	Pseudoephedrine sulfate	150.13	11:55	13·6·00		
	Methocel K4M	75.09	11:56	13·6·00		
	Emcompress	300.09	11:57	13·6·00		
	Emcocel 90M	225.13	11:58	13·6·00		
3	Blend the materials in step 2 for 2 minutes at low speed. Time started: 11:59 Time completed: 12:01 Total blending time: 2 min Speed setting: 0.5			13.6.00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 5 of 8
Batch size: 750g + 83.94

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done By	Checked By
4	Place the Surelease in a tared beaker and insert pump tubing.	641.76	12:01	13:06:00		
5	With the blender on low speed, add the Surelease at a pump rate of 8 – 9 for a total time of 10 minutes. Time started: 12:02 Time completed: Total time taken: Blender speed: 1-2 Pump setting: 4 Amount of Surelease added: 641.76 – 311.67 = 330.49g (83.94)			13·6·00		
6	Transfer the granules to the ganulator and screen as follows, using 20 mesh screen and 100 rpm motor speed. Speed: 126			13·6·00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 6 of 9
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
7	Place the granules on weighing paper and dry in the oven at 60 degrees for 12 hours Time started: 12h29 (13·6·00) – 16h30 (13·6·00), 10h00 (Time completed: 17h10 Total drying time: 11h10 Oven temperature: 60°C			14·6·00 14·6·00		
8	Remove the dried granules from the oven, and rescreen using the oscillating granulator (20 mesh, speed 100). Speed: – ①					
① screened by hand because granulator mesh torn				15·6·00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 7of 8
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
9	Record the weight of acceptable granules obtained. Gross weight: 798.42 Tare weight: 292.24 g Net weight: 504.18 g		15·6·00		
10	Work out the percent yield as follows. Weight acceptable granules (AG): Other weight accounted for (describe): 21g (wet screen loss) 277g unacceptable ∴ screen heat on WG Total weight accounted for (TW): 298 g Percent accountability = (TW/ 833.94) x 100% = 96 % Percent yield = (AG/833.94) x 100% = 60.5 %		15·6·00		
11	Transfer granules to airtight container until tableting.		15·6·00		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate granules
Batch #: 02011001

Page 8 of 6
Batch size: 750g

SIGNATURE AND INITIAL REFERENCE

Full Name (print)	Signature	Initials	Date
J. VERNER			15·6·00
J. ARJUN			15·6·00

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001T

Page 1 of 6
Batch size: 750g

MASTER FORMULA AND BATCH FORMULA

Quantity (w/w)	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
67	Pseudoephedrine sulfate granules		02011001	504.18 g	504.18 g		
15	Methocel K100M	RM0000062	M0539	112.8 g	112.82 g		
5	Emcompress	RM0000579	A06A	37.6 g	37.61 g		
5	Sodium Chloride		10102000	37.6 g	37.69 g		
7	Emcocel 90M			52.7 g	52.72 g		
1	Magnesium stearate			7.5 g	7.56 g		

PHARMACEUTICS DEPARTMENT
Faculty of Pharmacy, Rhodes University
Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001T

Batch size: 752.5

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Sieves	#20 mesh, #44 mesh		
Scale	Precisa 4000		
Blender	Cube blender (Erweka)		
Tablet press	Manesty B3B		

PHARMACEUTICS DEPARTMENT
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Grahamstown, 6140

BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001T

Batch size: 752.5g

MANUFACTURING DIRECTIONS

Step	Procedure		Weight	Time	Date	Done by	Checked by
1	Screen the following materials through a #20 mesh.						
	Methocel K100M		112.82g	10h15	15·6·00		
	Emcompress		37.61	10h16	15·6·00		
	Sodium Chloride		37.69	10h17	15·6·00		
	Emcocel 90M		52.32	10h18	15·6·00		
2	Place the following in the cube blender.						
	Pseudoephedrine sulfate granules	504.18	~~112.82~~ ①	10h19	15·6·00		
	Methocel K100 M		112.82	10h17	15·6·00		
	Emcompress		37.61	10h20	15·6·00		
	Sodium Chloride		37.69	10h21	15·6·00		
	Emcocel 90M		52.32	10h22	15·6·00		
3	Blend the materials in step 2 for 20 minutes at speed 100.						
	Time started: 10h23						
	Time completed: 10h43						
	Total blending time: 20 min						
	Speed: 96				15·6·00		

① Entered incorrectly 15·6·00

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001T

Page 4 of 6
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
4	Screen the magnesium stearate using a #44 mesh.	7.56 g	10h36	15.6.00		
5	Add the magnesium stearate to the blender and blend for 3 minutes at 100 rpm. Time started: 10h43 Time completed: 10h46 Total blending time: 3mm Speed: 98			15.6.00		
6	Calculate the percent accountability and yield. Gross weight (blend): 1282.07 Tare weight: 1054.18 Net weight: 757.89 Other weight (Describe): - Total weight accounted for (TW) = net weight + other weight = 757.89 Percent accountability = (TW/ 752.5) x 100% = 100.7 % Percent yield = (blend/752.5) x 100% = 100.7 %					
7	Store in airtight container until compression.	compressed immediately		15.6.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001T

Page 5 of 6
Batch size: 750g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done by	Checked by
8	Tablet the blend on the tablet press according to the standard operating procedures. Desired Hardness: ~~497g~~ ① 10-15 kp Desired Weight: 497g		15.6.00		
9	Sample 4 tablets every 5 minutes and check hardness and weight. Enter results on the in-process results sheet.		15.6.00		
10	Perform physical tests of hardness, friability and weight uniformity on the final batch. Enter the results on the bulk product test reports.				
11	Store product in an airtight container.		15.6.00		

① Incorrectly entered under hardness 15.6.00

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001T

Batch size: 752.5

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
12	Record the weight of acceptable tablets obtained. Gross weight: 802.57 Tare weight: 248.86 Net weight: 553.71		15.6.00		
13	Work out the percent yield as follows. Weight acceptable tablets (AT): 553.71 Other weight accounted for (describe): 125.23 : start/end + inprocess testing 71.7 : powder on press / tabs lost Total weight accounted for (TW): 196.93 + 553.71 = 750.64 Percent accountability = (TW/ 752.5) x 100% = 99.8 % Percent yield = (AG/ 752.5) x 100% = 73.6 %		15.6.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 02011001T Batch size: 750 g

IN-PROCESS TABLETING REPORT

Date	Time	Hardness (KP)	Weight (g)
15·6·2000	12:21	7.54	0.59 g
15·6·2000	12:21	8.15	0.58 g
15·6·2000	12:21	7.64	0.56
15·6·2000	12:21	7·44	0.59
15·6·2000	12:26	7.03	0.55
15·6·2000	12:26	7·74	0.54
15·6·2000	12:26	8.05	0.55
15·6·2000	12:26	7·13	0.55
15·6·2000	12:31	7·13	0.55
15·6·2000	12:31	7·23	0.55
15·6·2000	12:31	7·33	0.55
15·6·2000	12:31	7·23	0.54

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001 C 2

Page 1 of 4
Batch size: 150g

MASTER FORMULA AND BATCH FORMULA

Quantity	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
250g	Pseudoephedrine sulfate tablets		T	250g	150.96		
15% soln	Surelease						
10% w/w	TEC						

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001 C 2

Page 2 of 4
Batch size: 150

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Fluid bed drier	Aeromatic Strea-1		
Scale	Mettler PG4600		
Mixer	Gallenkamp		
Peristaltic pump	Masterflex, LS 13 tubing		
Digital Thermometer	Lutron		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001 C 2

Batch size: 150 g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Place the tablets in the product container	150.76	13h38	24.6.00		
2	Start the fluidising air at a rated temperature of 60 degrees and allow the tablets to circulate for 5 minutes until a product bed temperature of 45 degrees is reached. Time started: 13h41 Time completed: 13h43 Total time: 2 min			24.6.00		
3	Begin spraying by turning on the pump at a speed setting of 1.5 and turning on the atomising air to a pressure of 20 psi. Pump speed: 1.8 Atomising air pressure: 20 Actual spray rate: 4.15 g/min			24.6.00		
4	Spray the product until a theoretical weight gain of 5%. If the product becomes tacky and no longer fluidises effectively, turn off the pump and allow the tablets to circulate freely for 2-3 minutes before recommencing spraying. Record product bed temperature , weight of surelease and time of any pauses.			13h43 – 14h21 511 396.3 24.6.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 02011001 C 2

Batch size: 150

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
5	Record the following parameters at 5 minute intervals on the in process record sheet. Inlet air temperature Outlet air temperature Product temperature Atomising air pressure		24.6.00		
6	Allow the tablets to fluidise for a drying time of 20 minutes once spraying has finished.		24.6.00		
7	Record the weight of coated tablets obtained. Gross weight: 403.97 Tare weight: 248.91 Net weight: 155.81		24.6.00		
8	Work out the percent weight gain as follows. Weight coated tablets (CT): 155.81 Other weight accounted for (describe): 1.13 (dust. loss) Total weight accounted for (TW): 156.94 Percent weight gain = (TW - 150.76 / 150.76) x 100% = 4.1 %		24.6.00		
9	Store product in an airtight container.		24.6.00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 020110010C2 Batch size:

IN-PROCESS COATING REPORT

Date: 24·6·00

Time	Inlet air temperature	Outlet air temperature	Product temperature	Atomising air pressure
13h45	59	44	49	19
13h50	55	45	45	22
13h55	47	44	45	20
14h00	50	42	44	20
14h05	49	44	44	20
14h10	50	44	45	23
14h15	50	44	45	22
14h20	49	44	44	20

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020110001CC1

Page 1 of 4
Batch size: 125g

MASTER FORMULA AND BATCH FORMULA

Quantity	Component Name	RM #	Lot #	Amount/ Batch	Amount Dispensed	Dispensed By	Checked by
250g	Pseudoephedrine sulfate tablets		020110001C2	250g	125.6g		
	opadry suspension with PSS + Loratadine				q.s.		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020110001CC1

Page 2 of 4
Batch size: 125.6g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed by
Fluid bed drier	Aeromatic Strea-1		
Scale	Mettler		
Mixer	Gallenkampf		
Peristaltic pump	Masterflex, LS 13 tubing		
Digital Thermometer	Lutron		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020110001CC1

Page 3 of 4
Batch size: 125.6g

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Date	Done by	Checked by
1	Place the tablets in the product container	125.58	08h39	27/09/00		
2	Start the fluidising air at a rated temperature of 60 degrees and allow the tablets to circulate for 5 minutes until a product bed temperature of 45 degrees is reached. Time started: 08h40 Time completed: 08h42 Total time: 2 mins			27/09/00		
3	Begin spraying by turning on the pump at a speed setting of 1.5 and turning on the atomising air to a pressure of 20 psi. Pump speed: 0.9 Atomising air pressure: ~20 psi Actual spray rate: 4.8g/min			27/09/00		
4	Spray the product until a theoretical weight gain of 5%. If the product becomes tacky and no longer fluidises effectively, turn off the pump and allow the tablets to circulate freely for 2-3 minutes before recommencing spraying. Record product bed temperature, weight of surelease and time of any pauses.		08h45 - 09h23 Nozzle block 09h25 -	27/09/00		

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets
Batch #: 020110001CC1

Page 4 of 4
Batch size: 125.6g

MANUFACTURING DIRECTIONS

Step	Procedure	Time	Date	Done By	Checked By
5	Record the following parameters at 5 minute intervals on the in process record sheet. Inlet air temperature Outlet air temperature Product temperature Atomising air pressure		27.09.00		
6	Allow the tablets to fluidise for a drying time of 20 minutes once spraying has finished. Dried at ~ 40°C.		27.09.00		
7	Record the weight of coated tablets obtained. Gross weight: 438.57 Tare weight: 288.16 Net weight: 150.43		27.9.00		
8	Work out the percent weight gain as follows. Weight coated tablets (CT): 150.43 Other weight accounted for (describe): — Total weight accounted for (TW): 150.43 Percent weight gain = (TW - 125.58) / 125.58 x 100% = 19.79 %		27/09/00		
9	Store product in an airtight container.		27/09/00		31

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BATCH PRODUCTION RECORD

Product name: Pseudoephedrine sulfate tablets

Batch #: 020110001CC1 Batch size: 125g

IN-PROCESS COATING REPORT

Date: 27.09.00

Time	Inlet air temperature	Outlet air temperature	Product temperature	Atomising air pressure
08h45	57	46	53	17
08h50	58	46	53	17
08h55	58	47	54	21
① 09h00	57	47	52	20
09h05	57	48	53	18
09h10	58	47	54	17
09h15	57	47	53	20
09h20	58	50	56	19
09h25	62	49	57	18
09h30	58	48	52	20
09h35	58	48	51	20
09h40	56	48	51	16
09h45	60	50	54	20
09h50	58	46	51	19
09h55	57	47	52	21
10h00	57	48	51	20

① error inscribing « Jerne 27-9-00

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