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- My husband and parents for their support and encouragement

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Part A : Technology Description

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EXECUTIVE SUMMARY

Stability studies were undertaken at ambient (25ºC/60%RH) and accelerated conditions (40ºC/75%RH) to determine the effect of changing of hard gelatin capsule supplier on a phenytoin sodium (100 mg) capsule formulation. Three hard gelatin capsule suppliers: RP Scherer (Supplier A), Capsugel (supplier B) and Associated Caps (Supplier C) were used in the study. Capsules were analyzed just after filling of the capsules (T0), after 1 month (T1), after 2 months (T2) and after 3 months (T3) after being stored in securitainers under the above-mentioned conditions. The moisture content of the empty shells as well as the capsule contents were analysed at each time-point. The capsule disintegration time was recorded at each time point. Multi-point dissolution testing was performed at each time point to determine the release of the active substance in each case. Based on the achieved results, the best capsule shell supplier was recommended, and other suggestions were made to improve the capsule formulation.

CHAPTER 1

INTRODUCTION

1.1 ASPEN PHARMACARE

Aspen Pharmacare is the largest generics pharmaceutical manufacturer in South Africa. Aspen Pharmacare annually produces 1500 million tablets, 1.5 million litres of liquids, ointments and creams and 50 million sales packs, with a staff of more than 1000 people and a factory site of 35 000 square meters. It is also currently expanding with the addition of an Oral Solid Dosage facility next to the existing site [1].

1.2 GELATIN CAPSULE

1.2.1 History of Gelatin Capsule

The gelatin capsule was originally devised about 150 years ago as a means of masking the unpleasant taste of certain liquid medications. These capsules were crudely hand-made. In the intervening years, a sophisticated technology for the mass production of high quality capsules has become a popular alternative to tablets as a dosage form.

The word ‘capsule’ in the English language derived from the Latin word ‘capsula’, which means a small bow or container. The first recorded patent for a gelatin capsule was French Patent 5648, granted in Paris in the early 1834’s. The idea was quickly acclaimed and its use spread rapidly both inside and outside France. There are many forms of capsules and they can be divided into two main categories, which in current usage are described by the adjectives ‘hard’ and ‘soft’.

This dissertation focuses on the hard gelatin capsule. Hard capsules are used for solid medicaments. The hard gelatin capsule consists of two separate parts, each a

semi-closed cylinder in shape, one part being called a ‘cap’, having a slightly larger diameter than the other, which is called a ‘body’ and which is longer. The cap fits closely over the body to form a sealed unit. The hard gelatin capsule softens readily and dissolves after swallowing with water [2].

1.2.2 The Structure of Gelatin

Gelatin is not a naturally occurring protein, but is derived from the fibrous protein collagen, which is the principal constituent of animal skin, bone, sinew, and connective tissue. Any discussion of the structure of gelatin requires, therefore, an understanding of the nature and structure of collagen and of its conversion to gelatin. The primary structure of collagen arises from the linkage of alpha-amino and amino acids by peptide bonds to form a polymer. The collagen unit, or monomer (tropocollagen), consists of a triple helix of three polypeptide chains, each of which has a helically coiled configuration. The triple helix structure of tropocollagen can be destroyed (denaturising) by the application of heat or by the use of compounds, which destroy hydrogen bonds, with the resultant conversion to gelatin. Denaturising involves breaking only the hydrogen bonds and those hydrophobic bonds that help to stabilise the collagen helix. Boiling animal bones or skins in water results in a low yield of impure gelatin with poor physical and organoleptic properties. Commercial processes for converting collagen stock into gelatin are designed with the objective of achieving the maximum yield of gelatin consistent with commercially acceptable strength, viscosity, color, clarity and taste. Manufacture involves the removal of non-collagenous material, conversion of collagen to gelatin, purification, and then recovery of gelatin in a dry form. Some of these processes may differ for the different suppliers of empty capsule shells.

1.2.3 Gelatin: Physical and Chemical properties

Several of the amino acid residues of gelatin possess ionisable groups (carboxy, phenolic, amino, guanidine, and imidazole), which are distributed along the length of the molecule. Together with the terminal amino and carboxyl groups, the acidic and

basic side-chain groups enable gelatin to adopt a different net charge, which may be either negative or positive, depending upon the pH of the solution.
As a protein, gelatin has the unique ability to form a thermally reversible gel. The sol/gel and gel/sol transformations occur very readily when the temperature is changed over a comparatively small range. Gel strength depends upon the gelatin concentration, pH, temperature, and maturing time [3].

1.3 CAPSULE STANDARDS

The standards, which apply to capsules, can be divided into two categories. Pharmacopoeial standards control the quality of capsules in relation to their medicinal use, i.e. to ensure that they contain the correct drug in the correct dosage, and that it is available for absorption. Industrial standards control the quality of the capsule shell and its contents to ensure the efficiency of the manufacturing process and to produce a product that is acceptable to the consumer. The official pharmacopoeial standard tests are designed to ensure that capsule products comply with the minimum acceptable standard. Pharmacopoeial monographs give only brief details, if any at all, of the substances from which capsules can be made from. They make the implicit assumption that all the materials shall be of pharmacopoeial quality. Apart from gelatin, materials, which may be used, include colouring agents, plasticizers, preservatives, and surfactants.

1.3.1 Miscellaneous Pharmacopoeial Requirements

All materials to be filled into capsules must conform to certain general criteria. Additives, for example, should be innocuous, and not be responsible for reducing the stability of the active ingredient – neither should it interact with the capsule shell. The European Pharmacopoeia states that capsules should be stored in well-closed containers (until they are filled) at a temperature not exceeding 30ºC.

1.3.2 Stability function with respect to Pharmaceutical dosage forms

The stability of a pharmaceutical product refers to the actual capability of a particular formulation, in a specific container, to remain within its physical, chemical, microbiological, therapeutic and toxological specifications. Stability testing gives an assurance that the efficacy, safety and quality of the active drug substance and pharmaceutical formulation are maintained throughout the shelf-life [4].The United States Pharmacopoeia (USP) 1995 edition (pp.4064-4065) describes the term "stability" with respect to a drug dosage form, as being a reference to the "chemical and physical integrity of the dosage unit, and, when appropriate, the ability of the dosage unit to maintain protection against microbial contamination". The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, humidity) as well as the packaging components. Further, the USP 1995 edition (p. 4065) states that the "stability of manufactured dosage forms must be demonstrated by the manufacturer by the use of methods adequate for the purpose".

Stability studies (also known as shelf-life studies) of drug dosage forms, are established by means of "real time", formal, long-term tests under special temperatures and relative humidity conditions representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country, or region of the world concerned. The labelling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity (RH), air and light, on the stability of the packaged active substance or dosage form [5].

1.3.3 The Objective of Stability Testing

The International Conference on Harmonization (ICH) (1993) describes the purpose of stability testing as that of providing evidence on how the quality of a drug substance or drug product varies with time under factors such as temperature,

humidity and light and enables recommended storage conditions, re-test periods and shelf-life to be established.

Controlled room temperature delineates the allowable tolerance in storage circumstances at any location in the chain of distribution e.g. pharmacies, hospitals and warehouses.

Long-term testing, also known as real time testing can be described as the evaluation of the stability of a pharmaceutical dosage form under prescribed temperatures and humidity [4].

Accelerated testing can be described as a method of stability study designed to increase the rate of chemical and/or physical degradation or change of a pharmaceutical product by the use of exaggerated stability storage conditions as part of a formal storage program. This data, in addition to long-term stability studies may also be used to assess the longer-term chemical and/or physical effects at non-accelerated conditions [5].

The ICH has identified four climatic zones for convenience in planning for packaging and storage, and for stability studies, as described in Table 1. The values in Table 1 are based on observed temperatures and relative humidity, both outside and inside rooms, from which mean temperatures (ºC) and average relative humidity (RH) values are calculated. Derived values are based on inspection of data from individual cities and on allowances for a margin of safety in assignment of these specified conditions. This concept in dividing the world into four zones based on defining the annual climatic conditions prevalent in these zones has grouped South Africa in climatic Zone II [6]. The conditions of storage likely to be encountered in South Africa must be considered in the design of the stability trial.

CLIMATIC ZONE	ºC	RH
I. TEMPERATE e.g. United Kingdom; Northern Europe; Canada; Russia	21	45
II. MEDITERRANEAN SUBTROPICAL e.g. United States of America; South Africa; Japan; Southern Europe (Portugal - Greece)	25	60
III. HOT, DRY e.g. Middle East, North Africa	30	35
IV. HOT, HUMID e.g. Brazil, Indonesia, West Africa, Central America	30	70

Table 1: International climatic zones

Table 1 describes the internationally established practice of dividing the world into four climatic zones for convenience in planning for packaging and storage and for stability studies.

Where the dosage form is supported by long-term stability studies, the common international condition for long term studies specifies 25ºC ±2ºC at 60% RH ±5%RH. Accelerated studies are specified at 40ºC ±2ºC at 75%RH ±5%RH. The duration of the stability studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use.

1.3.4 Dissolution tests for capsules

The bioavailability of a dosage form is an expression of the proportion of the administered drug that reaches the systematic circulation within a given time and the time course of its removal. Bioavailability thus reflects a number of variables including aspects of formulation, differences in the extent of absorption and the factors governing drug distribution, metabolism and excretion. The aim is to provide a

consistent amount of the drug entering the bloodstream of an “average” patient and with an unvarying time course [1]. Bioavailability is measured by doing a bioequivalence study in human volunteers to prove that absorption of the active from a generic drug is similar to that of the original product. Dissolution testing can be used as a measure of the bioavailability of the active for quality control purposes.

This study focuses mainly on dissolution testing which is used as an indication of the bioavailability of the active. Dissolution testing measures the rate at which a drug is released into solution from a dosage form (in this case a gelatin capsule). The apparatus used for dissolution testing is based on a rotating wire mesh basket immersed in a glass vessel containing a specified dissolution medium. The capsule is placed in the basket, which is then rotated for a specified time. At the end of a specified time a sample of the dissolution medium is withdrawn and assayed for the drug content. The amount of drug released from the capsule must not be less than a specified proportion of the total after a specified time. In our case testing was done at four different sampling intervals, namely at 10, 20, 45 and 90 minutes.

1.4 PHENYTOIN

Phenytoin, being the active drug of interest for this dissertation, is the major drug for partial and generalized tonic-clonic seizures. Phenytoin is the oldest nonsedative antileptic drug, introduced in 1938 following a systematic evaluation of compounds.
There are 2 types of phenytoin sodium capsules, i.e. “prompt” and “extended” release capsules. These are differentiated by a dissolution test as per USP 26 which states that “prompt” capsules should release not less than (N.LT.) 90% of their contents within 30 minutes; whereas “extended” capsules should release not more than (N.M.T.) 50% in 30 minutes, 65% in 60 minutes, and N.L.T. 75% in 120 minutes [6].
At Aspen an in-house method for dissolution testing (N.L.T. 70% of active released within 45 minutes) is currently being used in the Quality Control laboratory. The following phenytoin dosage forms are being manufactured at the site, namely 50 mg

and 100 mg in a tablet form, as well as 100 mg in the capsule form (the focus of this study).

Phenytoin sodium is a weak acid with pKa of 8.3 (25ºC) and is soluble in water; however, the solution is partly hydrolyzed to the parent acid, which precipitates and turbidity develops [7]. It has been classified as a drug with 'high risk potential' with respect to bioavailability problems, and the formulation of phenytoin products by different manufacturers has been reported to have a pronounced influence on the rate and extend of absorption of the drug [8].

1.4.1 Mechanism of action

Phenytoin has major effects on several physiological systems. However, it is unclear which, if any, are related to its antileptic properties. Phenytoin also possesses an action on the heart through certain types of dysrhythmia [9]. Phenytoin affects ion conductances, membrane potentials, and the concentrations of amino acids and the neurotransmitters, namely nor-ephedrine, acetylcholine, and gamma-amino-butyric acid (GABA). Phenytoin blocks post-tetanic potentiation, which is thought to be the basis for its inhibition of the development and spread of epileptiform discharges, probably by raising membrane potentials and suppressing burst activity and repetitive firing.

The mechanism of phenytoin's action probably involves a combination of actions at several levels. Evidence seems to indicate that at therapeutic concentration, the major actions of phenytoin are to decrease excitatory neurotransmission and potentiate GABA-mediated inhibition. The median effective dose (ED_{50}) of phenytoin against maximal electroshock in mice is 9.9 mg/kg; Phenytoin has no activity against pentylenetetrazol seizures [9].

1.4.2 Pharmacokinetics

Absorption of phenytoin is highly dependant on the formulation of the dosage form. Particle size of the active pharmaceutical ingredient and pharmaceutical additives

affect the rate and extent of absorption. Oral absorption of phenytoin sodium is nearly complete in most patients, although the time to peak may range from 3 hours to 12 hours [10].

Phenytoin is strongly bound to plasma proteins. It appears certain that the total plasma level decreases when the percentage that is bound decreases, as in uremia or hypoalbuminemia, but correlation of free levels with clinical states remains uncertain. Phenytoin is strongly bound to brain proteins and is also reversibly stored in fat.

The pharmacokinetics of phenytoin is dose dependant. At very low blood levels, phenytoin metabolism is proportionate to the rate at which the drug is presented to the liver. However, as phenytoin blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolise phenytoin is approached. Further increase in dose, even though relatively small, may produce very large changes in phenytoin concentrations.

Katzung claims that the half-life of phenytoin varies from 12 to 36 hours, with an average of 24 hours for most patients in the low to mid therapeutic range [10]. At low blood levels, it takes 5 to 7 days to reach steady-state blood levels after every dosage change; at higher levels it may take 4 to 6 weeks before blood levels are stable**.**

1.5 BACKGROUND INFORMATION OF PHENYTOIN CAPSULES AT ASPEN PHARMACARE

Dissolution test failures (dissolution being low) of phenytoin sodium 100 mg capsules encountered lead to an investigation in order to address the problem. Different actions were taken which included the following:

- The manufacturing operations were reviewed.
- Variations in the hardness of individual slugs (the ingredients compacted to increase bulk density and then subsequently milled and blended to produce a satisfactory powder, i.e. the compressed granule prior to encapsulation) were investigated, since the slugging process is difficult to control.

- All raw material batch numbers, machinery used and in process controls were reviewed to see if there were any obvious trends. Nothing conclusive was observed.
- The dissolution results of all phenytoin batches manufactured since 1997 were tabulated – which showed there were sporadic occurrences of dissolution failures at various times.
- The storage conditions for the capsule shells were investigated to see if the manufacturer's requirements were being met.
- It was also found that capsule shells of different suppliers have an impact on the instant release dissolution profile. The original supplier of capsule shells to Aspen Pharmacare is known as RP Scherer; subsequently, the suppliers Capsugel and Associated Caps were also used.

This dissertation focuses on the three different suppliers of hard gelatin capsules to Aspen Pharmacare, and to investigate the possible effect each capsule supplier might have on the dissolution profile of the phenytoin sodium capsules.

1.6 PREVIOUS WORK DONE ON PHENYTOIN CAPSULES

Variations in the *in vitro* dissolution rate and bioavailability of phenytoin sodium commercial preparations have been reported and it has been suggested that these variations in different phenytoin and phenytoin sodium preparations could be attributed to formulation factors, the nature of the excipients used and to the particle size and particle shape of the active substance [12].

Lund reported that differences in the bioavailability of phenytoin formulations in which lactose and starch were used as the excipients could probably be attributed to the particle size of the active rather than the excipient used [13]. When using formulations with 50% lactose and starch, *in vitro* dissolution rates were improved [14]. Marked differences in respect of in vitro dissolution behaviour were recorded in studies done on phenytoin capsules of the same brand name produced in different countries [15].

Phenytoin release from capsules can also be influenced by pH. Complete drug release was obtained when pH-values rose from about 6 to 9.2 under experimental conditions. Drug release decreased as pH was lowered below 6. In a reported study, the bioavailability (0 to 32 hours) of a slow-release phenytoin product was 73% compared with a fast-released product [14].

Phenytoin sodium capsules will show a negative trend with respect to dissolution during shelf-life studies, especially @ 40ºC/75% RH [16]. Storage conditions of capsule shells can also influence the physical properties of shells. A short storage time of gelatin containing capsules, however, under hot humid tropical conditions appeared not to alter the dissolution properties of the shells, and changes in disintegration times and dissolution times of formulations filled in such capsules might be a reflection of changes of the powders incorporated rather than of the capsule shells [17].

1.7 MOISTURE CONTENT

The moisture contained in a material comprises all those substances which vaporise on heating and lead to weight loss of the sample. The weight lost is determined by a balance and interpreted as the moisture content. Most natural products contain moisture. The moisture content shows whether a product intended for trade or production has standard properties such as storability; agglomeration in the case of powders; microbiological stability; flow properties concentration or purity; etc.

Moisture determinations must be capable of being carried out quickly and dependably to allow possible action to be taken rapidly in the production process and avoid lengthy delays in production. Many producers today determine the moisture content of raw materials, intermediate and finished products directly at the production line, exactly as defined by quality assurance [18].

Variation in moisture content of the capsule shells due to the change of storage conditions or the moisture transfer between the capsule shell and its contents may lead to undesired physical properties, such as capsule brittleness and stickiness [19].

Structural water in and around the capsule wall also has an effect on the permeability of the capsule [20].

The moisture content of a capsule shell must be between 13 and 14% (by drying @ 105ºC) in order to prevent brittleness. Rolling a capsule between the fingers checks the brittleness – it should not shatter.

Phenytoin sodium is known to be hygroscopic. It can thus be assumed that the capsule content will remove water from the capsule shell.

1.8 DISINTEGRATION OF CAPSULES

The disintegration of a capsule is that state in which any residue of a capsule, except fragments of undissolved capsule shell, remaining on the screen of the test apparatus, is a soft mass having no palpably firm core [18].

Disintegration tests for capsules give an indication of the time taken for the gelatin shell to release its contents into the stomach.

Most pharmacopoeias attempt to simulate movement within the stomach by the use of an oscillating tube apparatus, which consists of a vertically mounted tube made of glass or Perspex, with a wire mesh base.

CHAPTER 2

EXPERIMENTAL

2.1 INGREDIENTS FOR THE MANUFACTURING OF THE PHENYTOIN SODIUM GRANULE

All materials used for the manufacturing of the phenytoin granule, together with their respective grades, are listed in Table 2.1

Ingredient	Grade	Quantity per capsule
Sodium Lauryl Sulphate	EP2002	1.5 mg
Aerosil 200	USP25	2.5 mg
Magnesium Stearate	EP2002 (Mic)	4.0 mg
Talc Purified	EP2002	20.0 mg
Sta-Rx 1500	n/a	78.0 mg
Phenytoin Sodium	EP2002	100.0mg

Table 2.1: Raw materials used for manufacturing of the Phenytoin capsule

2.1.1 Blending

The ingredients were dispensed and mixed in a stainless steel trough to obtain a homogenous mixture. These mixed powders were then passed through a comminuting mill (set at high speed impact forward fitted with a 1.6 mm screen) into a tubular bin. A uniform feed rate was maintained during milling to prevent a variable particle size distribution. After milling, the powders were blended in a tubular blender for 10 minutes at 16 rpm.

The blended powders were then compressed into slugs with a hardness specification limit between 50 to 80 Newton. The slugs were sized through a Jackson Crockett screening mill fitted with a size 16 screen into a tubular bin in which the granule was then blended again in a tubular blender for 10 minutes at 16 rpm. These blended powders were then ready for encapsulation into the three different supplier's capsules.

2.1.2 Encapsulation

Encapsulation was performed on an H&K (Hoffliger Karg Waivligen) machine with the following settings:

Dosing Disc size (mm) : 11.6 mm
Average shell mass : 206 mg

2.2 STABILITY PROCEDURES

Stability studies were undertaken at ambient (25ºC/60% Relative humidity) and accelerated (40ºC/75% Relative humidity) conditions. Gelatin capsules were stored in securitainers under ICH conditions. After filling the capsules at Aspen's factory, capsules were tested for moisture contents (empty capsules and emptied-out capsules, as well as capsule's powdered contents); disintegration of filled capsules, as well as the dissolution rate of active released within the specified time period (this is referred to as the T0 stage). The same tests were performed after one (T1), two (T2) and a three (T3) month period.

2.3 TESTING

2.3.1 Moisture determination of powdered capsule contents

Samples were prepared by emptying out 20 capsules. Approximately 0.2 g of the powdered contents (mass accurately known) was weighed on a Sartorius analytical

balance and transferred to the titration vessel of a Mettler Toledo Karl Fisher DL 38. These samples were weighed by difference by means of a weighing boat. The microprocessor of the instrument calculated the percentage water automatically from the mass of the sample weighed out.

2.3.2 Moisture determination of empty and emptied-out gelatin capsules

An aluminium dish was placed in the automatic sample chamber of a Mettler HR 73 Halogen moisture analyzer and zeroed. Approximately 1 gram of sample was spread evenly over the sample pan (sample mass was displayed on the screen of the instrument whilst it was added). The sample was dried at 105ºC and the instrument printed out the result automatically.

2.3.3 Disintegration test for capsules

A capsule was placed into each of six vertically mounted tubes, with a wire mesh base, of a Hanson Research QC-21 apparatus. A disk was placed on top of each capsule in the cylindrical tube. The tubes were raised and lowered into 900 ml of water (previously equilibrated to 37ºC±0.5ºC) at a frequency of approximately 30 strokes per minute. The time was recorded when all six capsules were completely disintegrated. i.e. when all the ingredients were released from the gelatin capsule shell.

2.3.4 Dissolution testing

Three capsules of one supplier stored at ambient and humidity temperatures and three capsules of another supplier stored under the same conditions were tested during the same run (same dissolution apparatus), using water from the same source as dissolution medium. It was required to degas the medium prior to use by means of the following method: water was heated to about 45ºC while stirring gently; it was then immediately filtered under vacuum using a filter having a porosity of 0.45 microns - a deaeration technique for removal of dissolved carbon dioxide in the water. A Distek Model Premiere 5100 was used in performing dissolution rate testing.

The system used provided for temperature control (37ºC±0. 5ºC), and is equipped with 6 glass vessels to which 900 ml of degassed dissolution medium was added.
A capsule was placed into a clean, dry basket with a wired mesh and attached to each of the six shafts of the dissolution apparatus. The shafts with the attached baskets were simultaneously immersed into the dissolution medium whilst the baskets were rotating at a constant rate of 100 rpm at time of starting the dissolution i.e. at time “0” minutes, until the end time of “90” minutes; the time being monitored by a stopwatch.
A 4 ml aliquot was withdrawn from the zone midway between the surface of the dissolution medium and the top of the rotating basket, not less than one cm from the vessel wall. This was done after 10, 20, 45 and 90 minutes and filtered through a 0.10 µm pore diameter membrane filter into a vial and analyzed by means of High Performance Liquid Chromatography (HPLC) for the active ingredient, phenytoin sodium. Results were given as dissolution profiles of percentage active released versus time. In order to fully characterize the dissolution profiles, results from the 10th, 20th, 45th and 90th minute were used.

2.3 HPLC ANALYSES

HPLC analyses were performed on the sampled dissolution aliquots using an Alliance Waters 2690 Module HPLC equipped with Millennium version 3.2 software. The mobile phase contained a mixture of 65/35 (v/v) of Methanol (Merck grade) and Milli Q water. The samples were analysed against a standard of the same concentration.

Instrumental conditions used were as follows:

A Waters 2487 Dual wavelength Absorbance detector with the wavelength set at 240 nm and sensitivity at 0.2 AUFS.
An auto-sampler set to inject 100µl.
A µBondapak C-18 (30 cm x 4 mm) column at ambient temperature.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 MOISTURE

The moisture contents of:

(i) the empty capsules prior to filling with any powder;

(ii) the emptied capsules, i.e. after it was filled with powder, stored under the relevant set of storage conditions, and emptied;

(iii) the powder contents of the emptied-out capsules was analysed for moisture content by Karl Fischer titration (par. 2.3.1); whereas the moisture content of the empty and emptied out capsules was determined by drying (par. 2.3.2). The moisture results (%) of these analyses are summarized in Table 3.1 (for ambient (25ºC/60% RH)) and Table 3.2 (for humidity storage (40ºC/75%RH)).

Supplier	Capsule	Month 0 (T0)	Month1 (T1)	Month 2 (T2)	Month 3 (T3)
RP Scherer (A)	Empty	13.5	13.5	13.5	13.6
	Emptied	12.6	12.4	12.2	12.1
	Powder	5.1	5.5	6.0	7.6
Capsugel (B)	Empty	13.1	13.2	13.2	13.2
	Emptied	13.5	13.2	12.8	11.9
	Powder	4.2	5.5	5.8	6.7
Associated (C)	Empty	13.6	13.6	13.6	13.7
	Emptied	13.2	13.0	12.9	12.8
	Powder	4.7	5.3	5.8	8.0

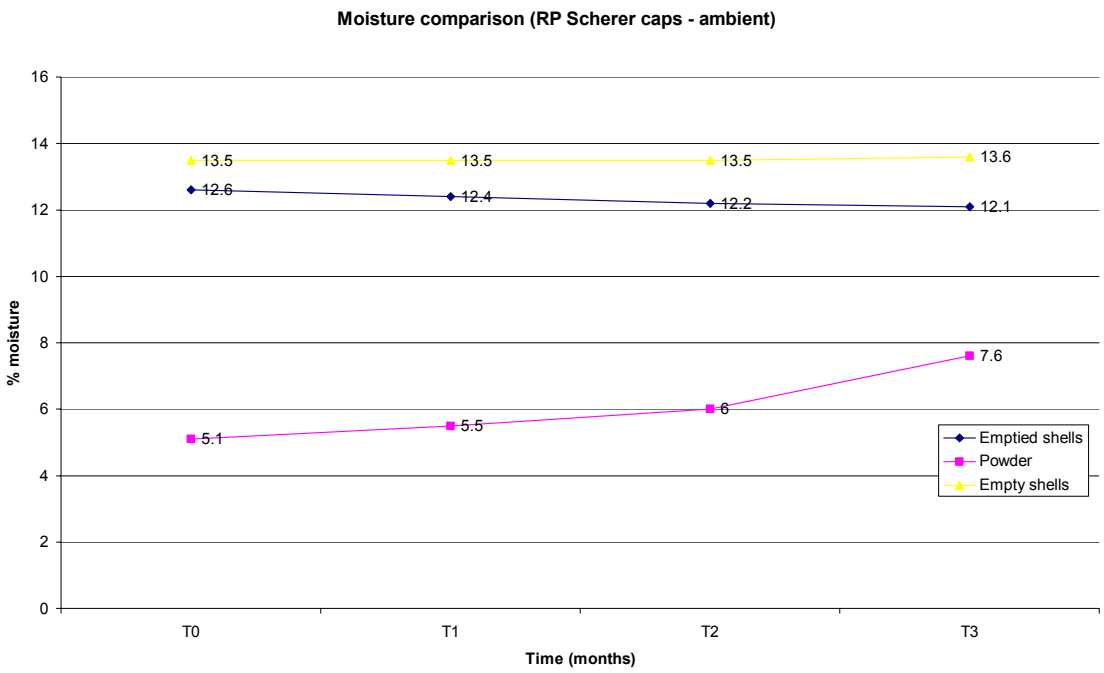
Table 3.1: Ambient storage conditions

Supplier	Capsule	Month 0 (T0)	Month1 (T1)	Month 2 (T2)	Month 3 (T3)
RP Scherer (A)	Empty	13.5	12.3	12.4	12.5
	Emptied	12.6	10.2	10.8	11.7
	Powder	5.1	8.3	9.5	12.6
Capsugel (B)	Empty	13.1	12.5	12.6	12.7
	Emptied	13.5	9.9	10.4	11.5
	Powder	4.2	7.1	8.8	11.4
Associated (C)	Empty	13.6	12.6	12.7	12.8
	Emptied	13.2	10.1	10.9	11.1
	Powder	4.7	8.1	9.7	12.5

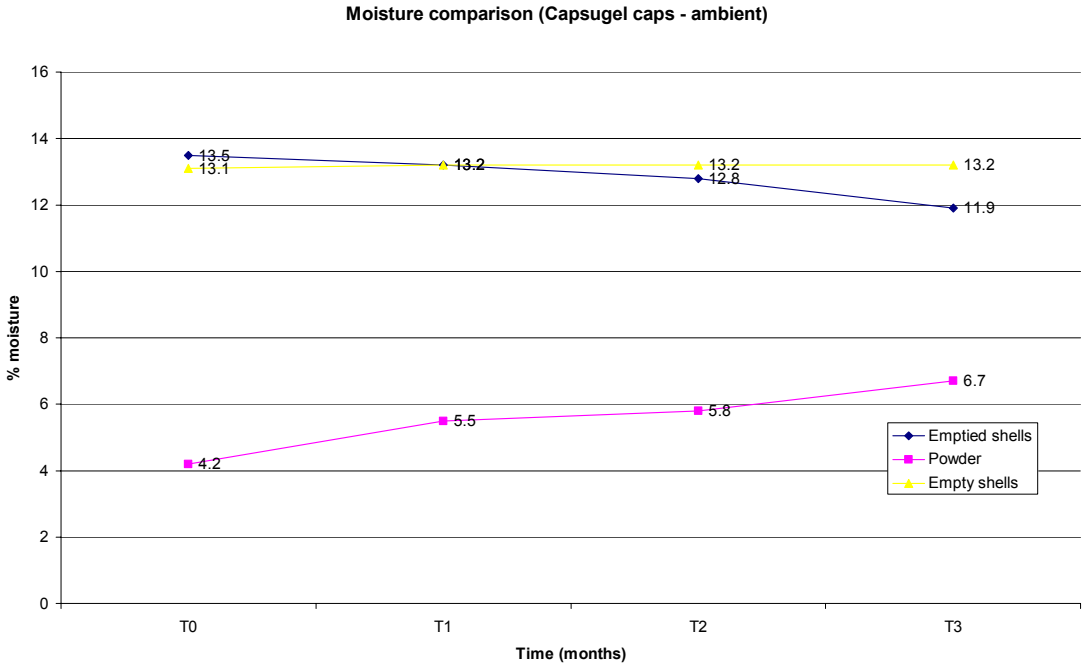
Table 3.2: Humidity storage conditions

3.2 MOISTURE COMPARISON

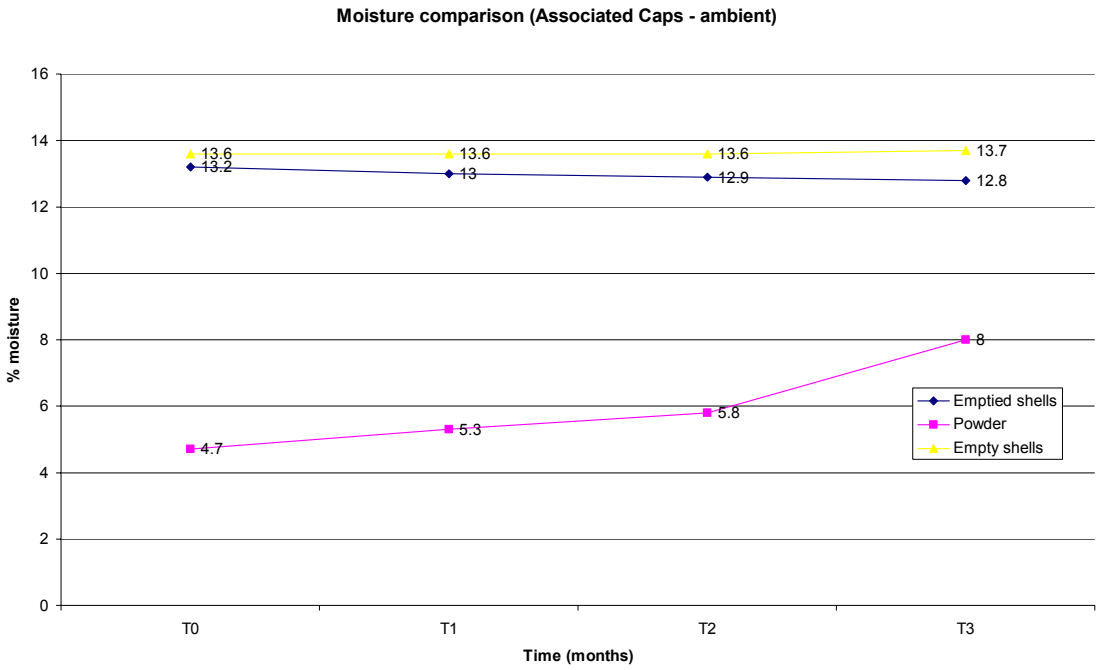
The results shown in Table 3.1 and 3.2 are summarized graphically in Graphs 3.1 to 3.6 for easier visualisation of the results obtained. These graphical representations are shown by capsule type and type of storage condition used.



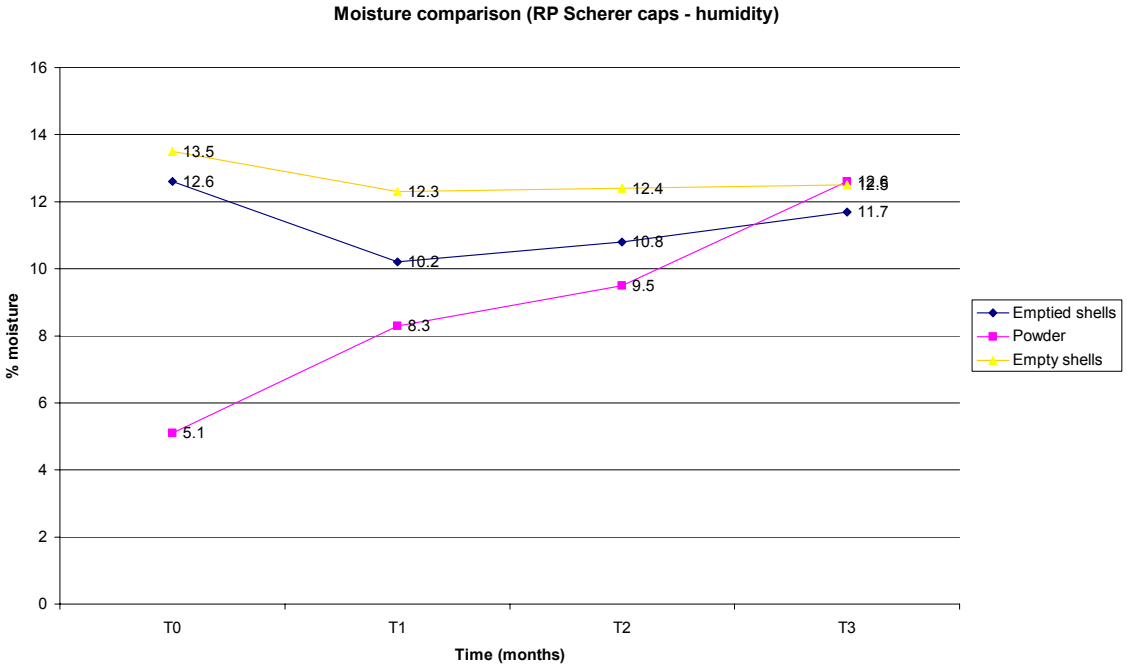
Graph 3.1



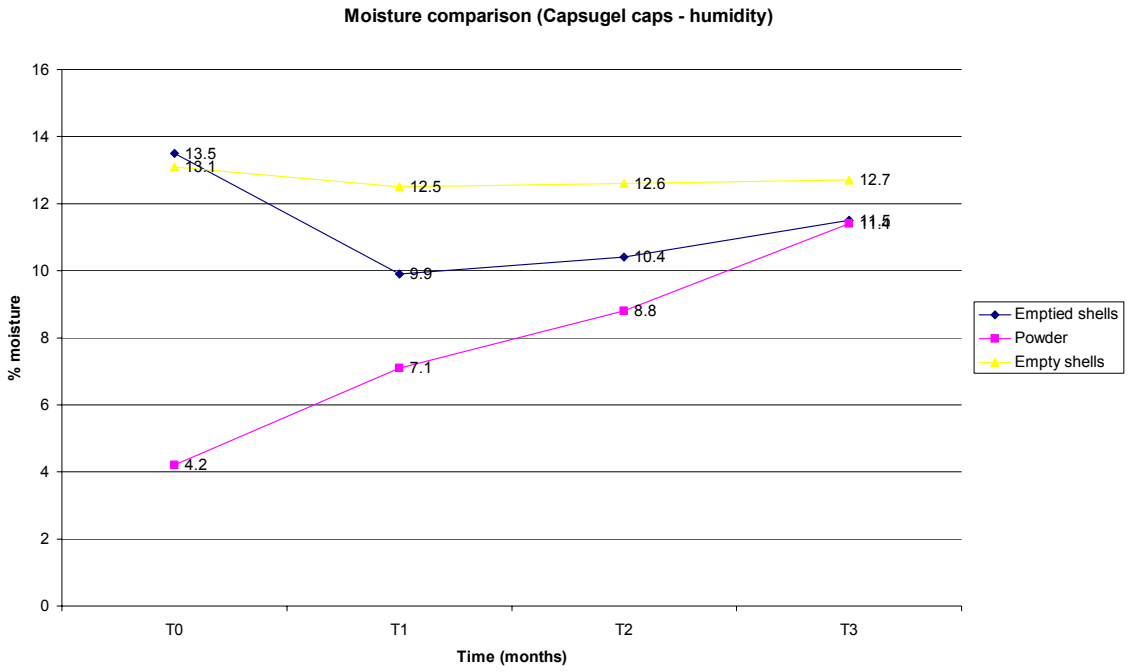
Graph 3.2



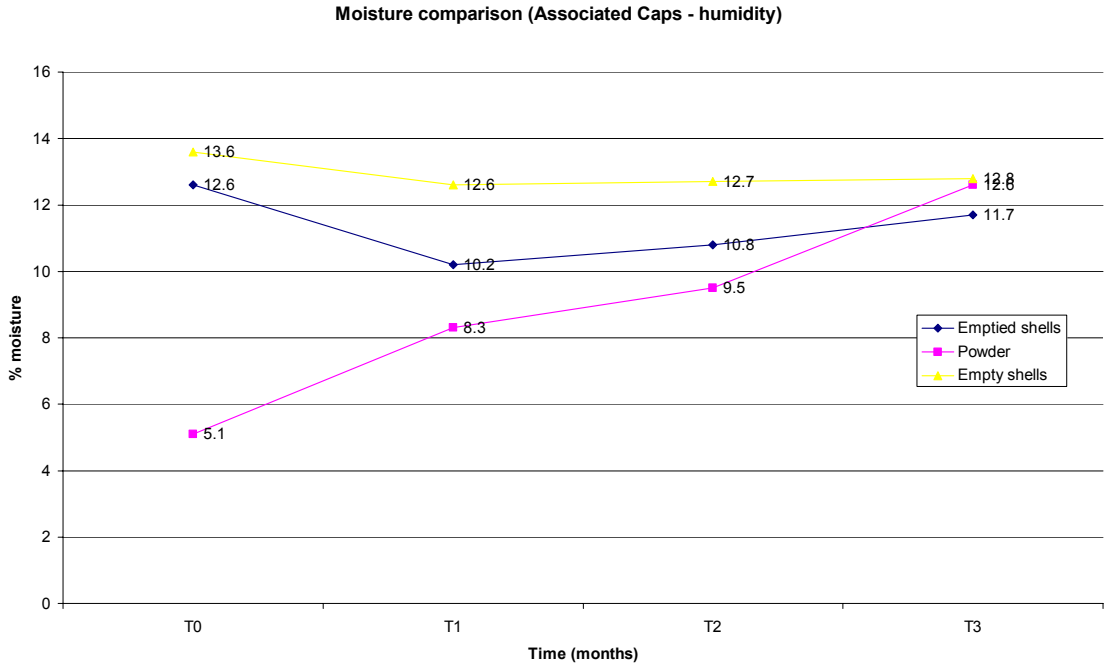
Graph 3.3



Graph 3.4



Graph 3.5



Graph 3.6

3.3 DISCUSSION

Graphs 3.1 to 3.3 show a comparison of the three types of capsules in terms of moisture uptake of the capsule shells and capsule content at ambient storage conditions at the various time points. Under ambient conditions the empty capsule shells show very little change in moisture content for all three suppliers. In all three cases, the emptied-out capsule shells shows a marked decrease in moisture content; Associated Caps showing the least change and Capsugel showing the biggest decrease in moisture content. This decrease in capsule shell moisture content correlates well with the increase in moisture contents of the emptied-out powder in all three cases, indicating the withdrawal of moisture by the hygroscopic phenytoin sodium powder from the gelatin capsule shells.

Graphs 3.4 to 3.6 show a comparison of the three capsule suppliers' capsules in terms of moisture uptake of the capsule shells and capsule contents at accelerated humidity and temperature storage conditions at the various time points. Under these conditions the empty capsule shells of all three suppliers show an interesting decrease in moisture content at T1 followed by a gradual increase in moisture content up to the T3 stage. The effect of the higher temperature (40^0C) seems to predominate up to the T1 stage, forcing moisture from the capsule shells, thereafter the higher humidity (75%) results in a steady increase in moisture content. This effect is also noticed with the emptied-out capsule shells of all three suppliers; however, in this case a much bigger drop in moisture content is evidenced at the T1 stage, showing the effect of the withdrawal of moisture by the phenytoin sodium powder in dramatic fashion. A good correlation is seen with the moisture content results of the emptied-out powders, showing a dramatic and mostly constant increase of roughly 7% over the three months in all three cases.

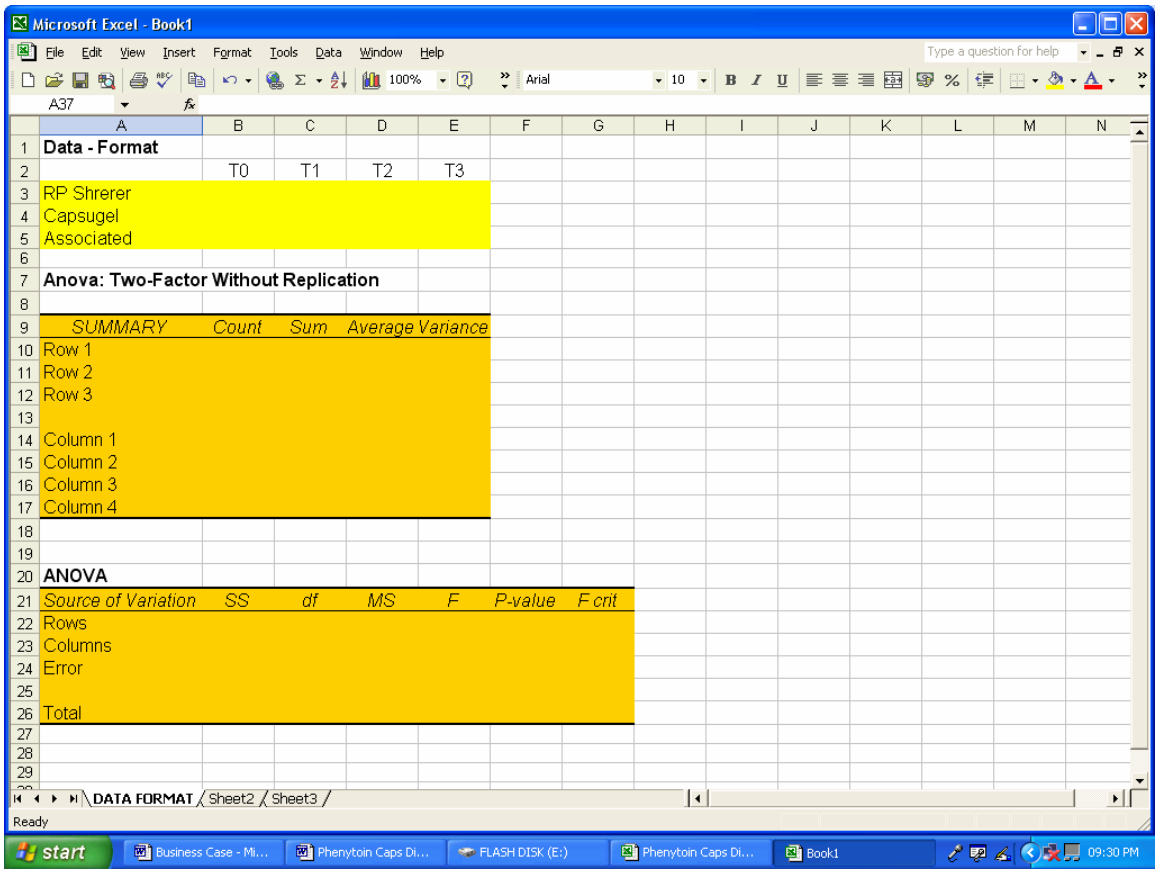
Overall, the three capsule suppliers' capsules correlate well in terms of moisture uptake from the prescribed stability conditions and storage in securitainers.

3.4 STATISTICAL ANALYSIS OF MOISTURE RESULTS

For the purpose of this study, the Analysis of Variance (ANOVA) statistical tool was used to determine any differences between capsule suppliers for moisture content. Scientific experimentation often requires the comparison of the means of more than two samples. The comparison of the moisture content of the samples stored under different storage conditions is a typical example of such a situation. In this example, and for any one of the capsule types, there are two possible sources of variation in the results. The first source of variation that is always present is normal, random experimental error when performing a set of experiments/tests under identical conditions (e.g. weighing off a constant mass on a balance a number of times). The second source of variation is due to deliberately introducing a factor that may cause a variation in the results, for example by changing the storage conditions deliberately. In all such cases there are always confusion in the interpretation of observed results since the variation in the results may be the result of pure experimental error, or due to the deliberate variation in experimental settings, or due to both.

Analysis of Variance is an extremely powerful statistical technique which can be used to separate and estimate the magnitudes of different types of variation e.g. variation due to random experimental error and variation due to deliberately changing the experimental conditions. Generally the “null-hypothesis” is adopted that the treatment (e.g. storage conditions) means are not different, and ANOVA then determines whether the observed variances (between different treatments on one hand, and within a specific treatment – the pure, random experimental error) are the same by means of an F-test. In ANOVA, the F-test is always a one-tailed test because we are only interested in whether the variance introduced into the data results in averages that are significantly greater than would have been the case in the presence of random experimental error only [21]. The results of the ANOVA calculations, which were performed on Microsoft Excel, will be presented in the following format:

Summary:



Where:

Columns 1 to 4 represent different storage times or types of capsules.

Count The number of samples

Sum The sum of the sample results

Average The mean of the sample results

Variance The measure of deviation of the sample results (= (std. dev.) ²)

SS The sum of squares

df	The degree of freedom
MS	The mean square
F-value	The calculated F-value
F-critical	The F-value (defined by the sample size and the confidence level required for the test) is obtained from tables

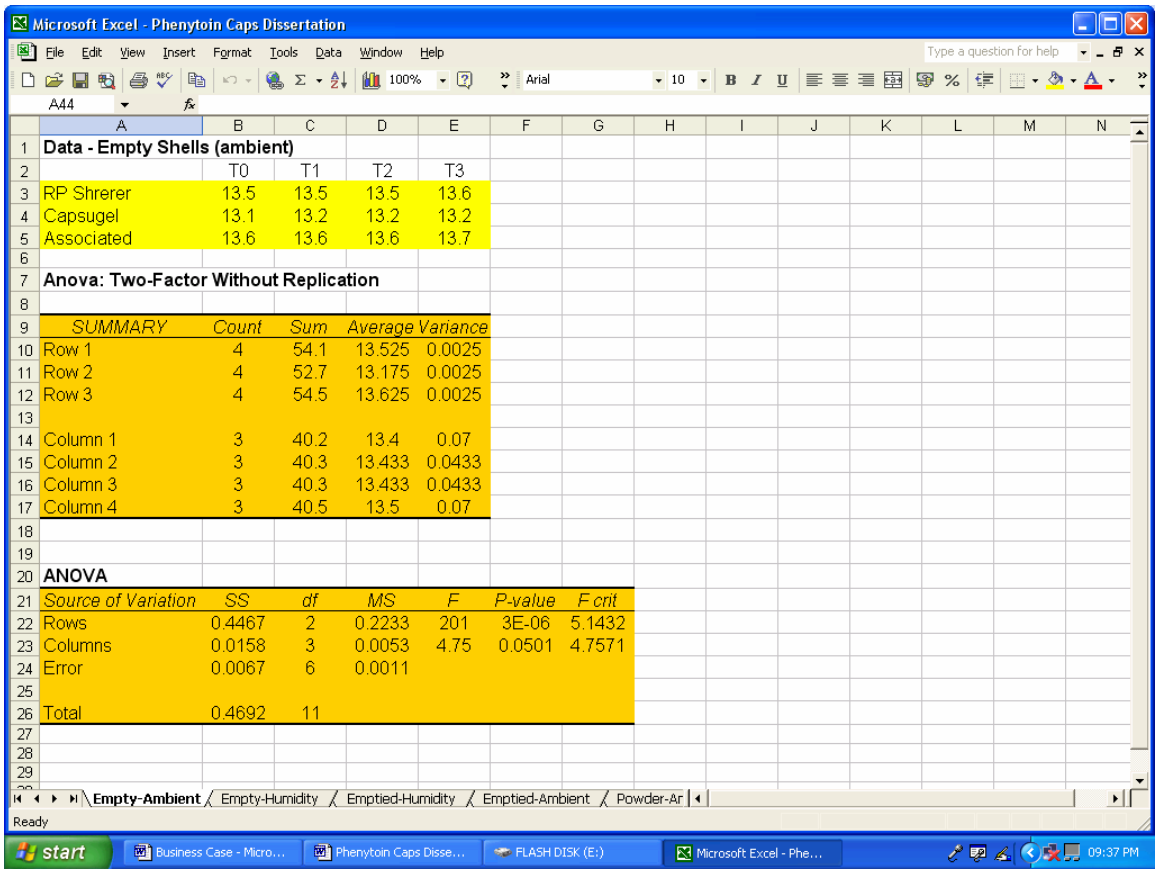
3.4.1 Two-factor ANOVA for the moisture content of empty capsule shells stored at ambient temperature

A two-factor (type of capsule, time of storage) ANOVA was performed on the data summarized in Table 3.1 for the variation in moisture content of the three types of capsules over the entire test period. The null-hypotheses adopted were:

Null-hypothesis 1: There is no difference in moisture content between capsules supplied by the three suppliers.

Null-hypothesis 2: There is no difference in the moisture contents of capsules stored for different periods of time.

The result of this analysis is shown in Table 3.3



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Data - Empty Shells (ambient)**													
2		T0	T1	T2	T3									
3	RP Shrerer	13.5	13.5	13.5	13.6									
4	Capsugel	13.1	13.2	13.2	13.2									
5	Associated	13.6	13.6	13.6	13.7									
6														
7	**Anova: Two-Factor Without Replication**													
8														
9	*SUMMARY*	*Count*	*Sum*	*Average*	*Variance*									
10	Row 1	4	54.1	13.525	0.0025									
11	Row 2	4	52.7	13.175	0.0025									
12	Row 3	4	54.5	13.625	0.0025									
13														
14	Column 1	3	40.2	13.4	0.07									
15	Column 2	3	40.3	13.433	0.0433									
16	Column 3	3	40.3	13.433	0.0433									
17	Column 4	3	40.5	13.5	0.07									
18														
19														
20	**ANOVA**													
21	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*							
22	Rows	0.4467	2	0.2233	201	3E-06	5.1432							
23	Columns	0.0158	3	0.0053	4.75	0.0501	4.7571							
24	Error	0.0067	6	0.0011										
25														
26	Total	0.4692	11											
27														
28														
29														

Table 3.3

From Table 3.3 it can be seen that the F-value for the “Rows”, i.e. different types of capsules, is greater than F-crit, meaning that there is a significant difference in the moisture content of the empty capsules of the different capsule suppliers. The null-hypothesis (No.1) is therefore rejected. For the “Columns”, i.e. for different storing times, the calculated F-value φ F-crit, hence the null-hypothesis (No.2) is retained i.e. storing the empty capsules under specified conditions for different periods of time does not influence the moisture contents.

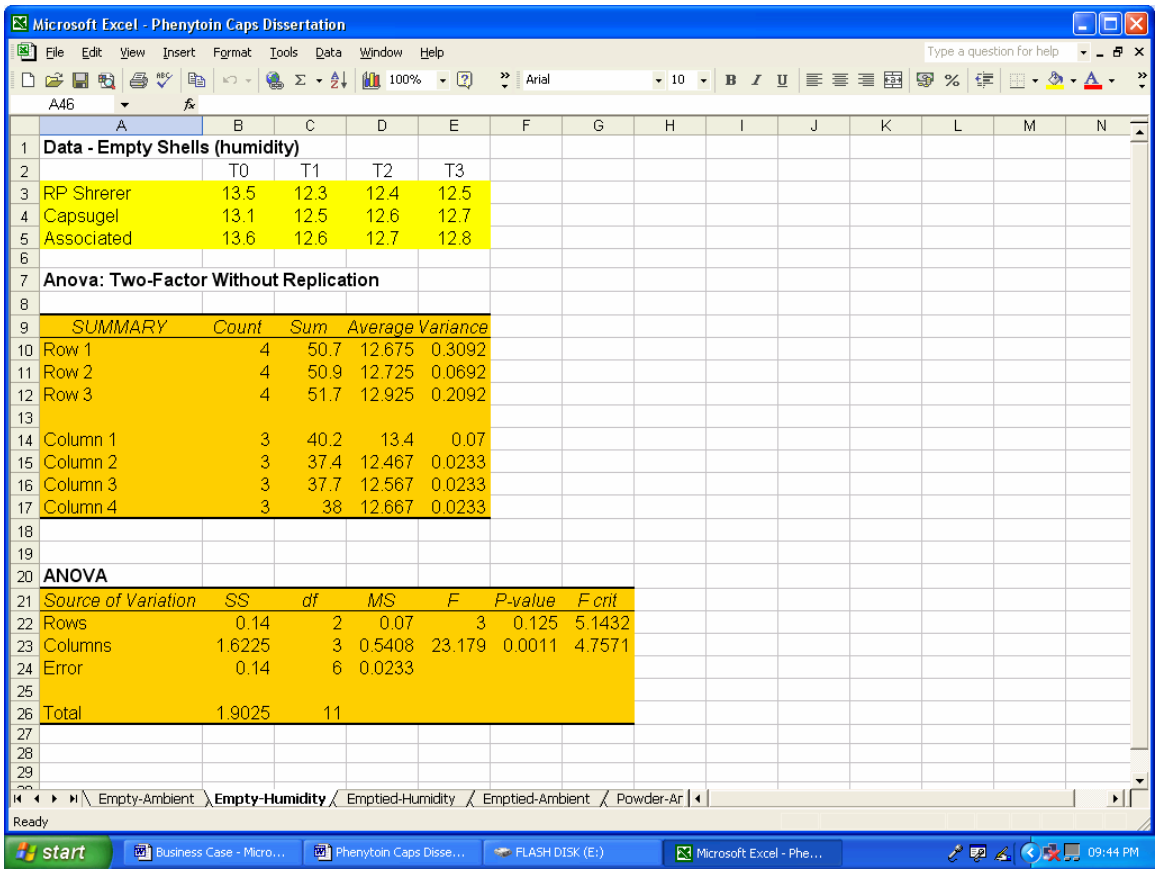
3.4.2 Two-factor ANOVA for the moisture content of empty capsule shells stored at humidity conditions

A two-factor (type of capsule, time of storage) ANOVA was performed on the data summarized in Table 3.4 for the variation in moisture content of the types of capsules over the entire test period. The null-hypotheses adopted were:

Null-hypothesis 1: There is no difference in moisture content between capsules supplied by the three suppliers.

Null-hypothesis 2: There is no difference in the moisture content of capsules stored for different periods of time.

The result of this analysis is shown in Table 3.4



	T0	T1	T2	T3
RP Shrerer	13.5	12.3	12.4	12.5
Capsugel	13.1	12.5	12.6	12.7
Associated	13.6	12.6	12.7	12.8

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
Row 1	4	50.7	12.675	0.3092
Row 2	4	50.9	12.725	0.0692
Row 3	4	51.7	12.925	0.2092
Column 1	3	40.2	13.4	0.07
Column 2	3	37.4	12.467	0.0233
Column 3	3	37.7	12.567	0.0233
Column 4	3	38	12.667	0.0233

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Rows	0.14	2	0.07	3	0.125	5.1432
Columns	1.6225	3	0.5408	23.179	0.0011	4.7571
Error	0.14	6	0.0233			
Total	1.9025	11				

Table 3.4

From Table 3.4 it can be seen that the F-value for the “Rows”, i.e. different types of capsules, is less than F-crit, meaning there is no difference in the moisture content of the empty capsules of the different capsule suppliers. The null-hypothesis (No.1) is therefore retained.

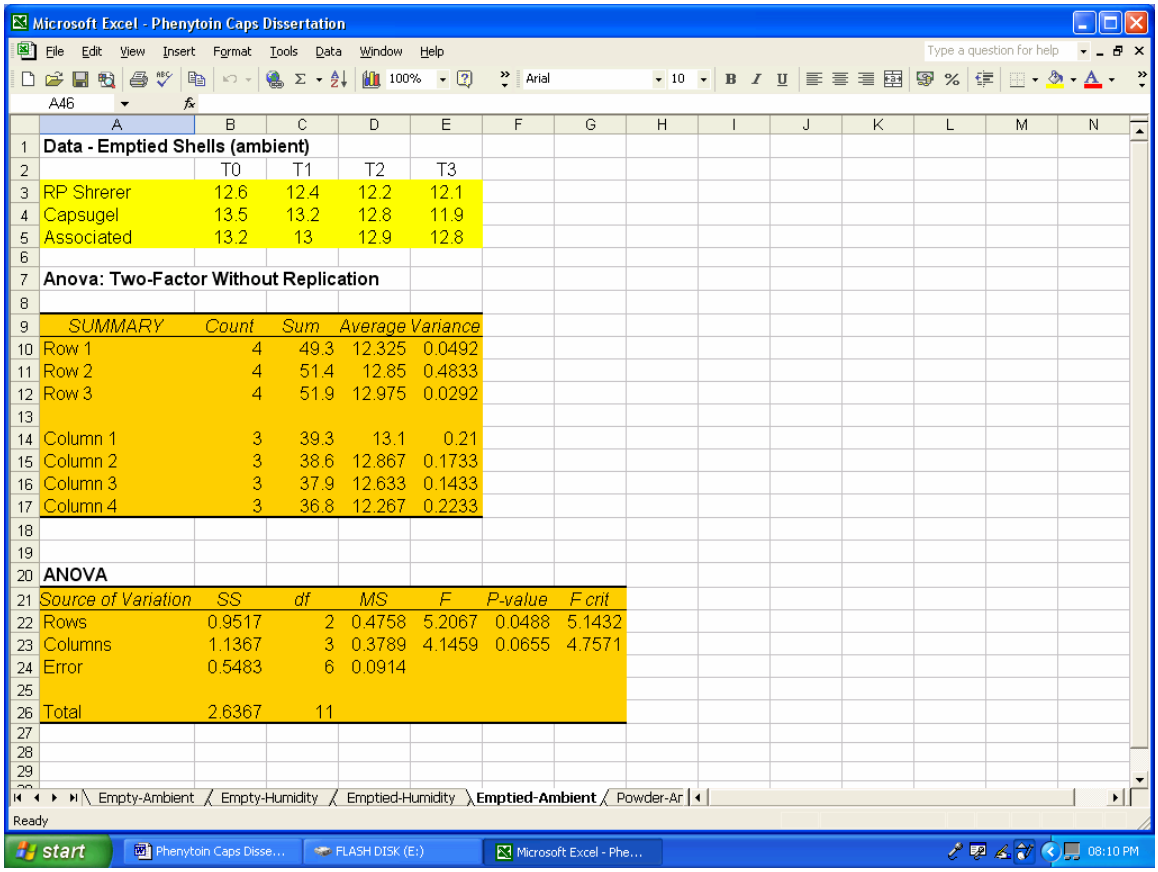
For the “Columns”, i.e. for different storage times, the calculated F-value is greater than F-crit, meaning the null-hypothesis (No.2) is rejected, i.e. storing the empty capsules under humidity conditions for different periods of time do influence the moisture content.

3.4.3 Two-factor ANOVA for the moisture content of emptied-out capsule shells stored at ambient temperature

Null-hypothesis 1: There is no difference in moisture content between capsules supplied by the three suppliers.

Null-hypothesis 2: There is no difference in the moisture content of emptied-out capsules stored for different periods of time.

The result of this analysis is shown in Table 3.5



	A	B	C	D	E
1	**Data - Emptied Shells (ambient)**				
2		T0	T1	T2	T3
3	RP Shrerer	12.6	12.4	12.2	12.1
4	Capsugel	13.5	13.2	12.8	11.9
5	Associated	13.2	13	12.9	12.8
6					
7	**Anova: Two-Factor Without Replication**				
8					
9	*SUMMARY*	*Count*	*Sum*	*Average*	*Variance*
10	Row 1	4	49.3	12.325	0.0492
11	Row 2	4	51.4	12.85	0.4833
12	Row 3	4	51.9	12.975	0.0292
13					
14	Column 1	3	39.3	13.1	0.21
15	Column 2	3	38.6	12.867	0.1733
16	Column 3	3	37.9	12.633	0.1433
17	Column 4	3	36.8	12.267	0.2233
18					
19					
20	**ANOVA**				
21	*Source of Variation*	*SS*	*df*	*MS*	*F*
22	Rows	0.9517	2	0.4758	5.2067
23	Columns	1.1367	3	0.3789	4.1459
24	Error	0.5483	6	0.0914	
25					
26	Total	2.6367	11		

	P-value	F crit
21	*P-value*	*F crit*
22	0.0488	5.1432
23	0.0655	4.7571
24		
25		
26		

Table 3.5

From Table 3.5 it is noticed that the F-value for the “Rows”, i.e. the different types of capsules, is greater than F-crit, meaning that there is a difference in moisture content of emptied-out capsules of the three suppliers. The null-hypothesis (No.1) is therefore

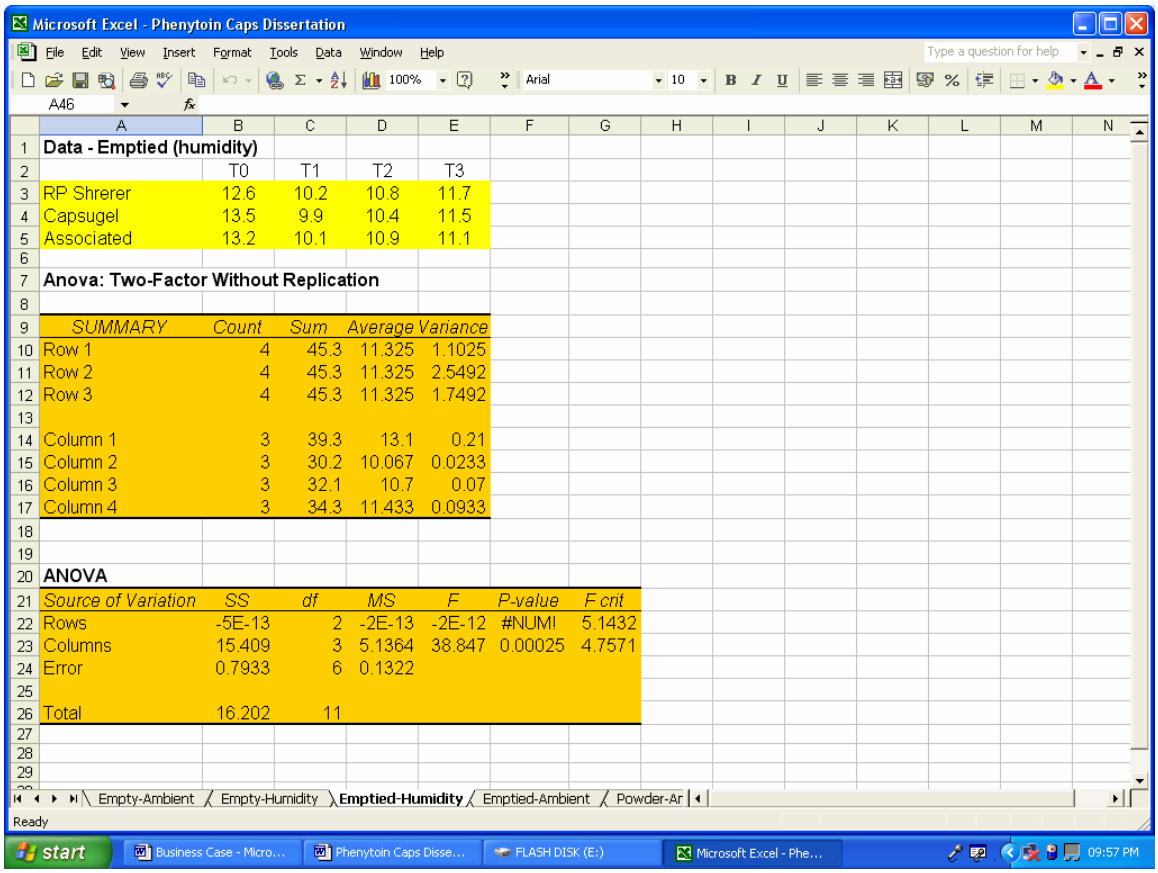
rejected. For the “Columns” i.e. different storage times, the F-value is less than F-crit, meaning there is no difference in moisture contents of emptied-out capsules stored for a period of time. The null-hypothesis (No.2) is thus retained.

3.4.4 Two-factor ANOVA for the moisture content of emptied-out capsule shells stored at humidity conditions

Null-hypothesis 1: There is no difference in moisture content between capsules being emptied out, supplied by the three suppliers.

Null-hypothesis 2: There is no difference in the moisture content of emptied-out capsules stored for different periods of time.

The result of this analysis is shown in Table 3.6



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Data - Emptied (humidity)**													
2		T0	T1	T2	T3									
3	RP Shrerer	12.6	10.2	10.8	11.7									
4	Capsugel	13.5	9.9	10.4	11.5									
5	Associated	13.2	10.1	10.9	11.1									
6														
7	**Anova: Two-Factor Without Replication**													
8														
9	*SUMMARY*	*Count*	*Sum*	*Average*	*Variance*									
10	Row 1	4	45.3	11.325	1.1025									
11	Row 2	4	45.3	11.325	2.5492									
12	Row 3	4	45.3	11.325	1.7492									
13														
14	Column 1	3	39.3	13.1	0.21									
15	Column 2	3	30.2	10.067	0.0233									
16	Column 3	3	32.1	10.7	0.07									
17	Column 4	3	34.3	11.433	0.0933									
18														
19														
20	**ANOVA**													
21	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*							
22	Rows	-5E-13	2	-2E-13	-2E-12	#NUM!	5.1432							
23	Columns	15.409	3	5.1364	38.847	0.00025	4.7571							
24	Error	0.7933	6	0.1322										
25														
26	Total	16.202	11											
27														
28														
29														

Table 3.6

From Table 3.6 it is noticed that the F-value for the “Rows”, i.e. the different types of capsules, is less than F-crit, meaning that there is no difference in moisture content of emptied out capsules of the three suppliers. The null-hypothesis (No.1) is therefore

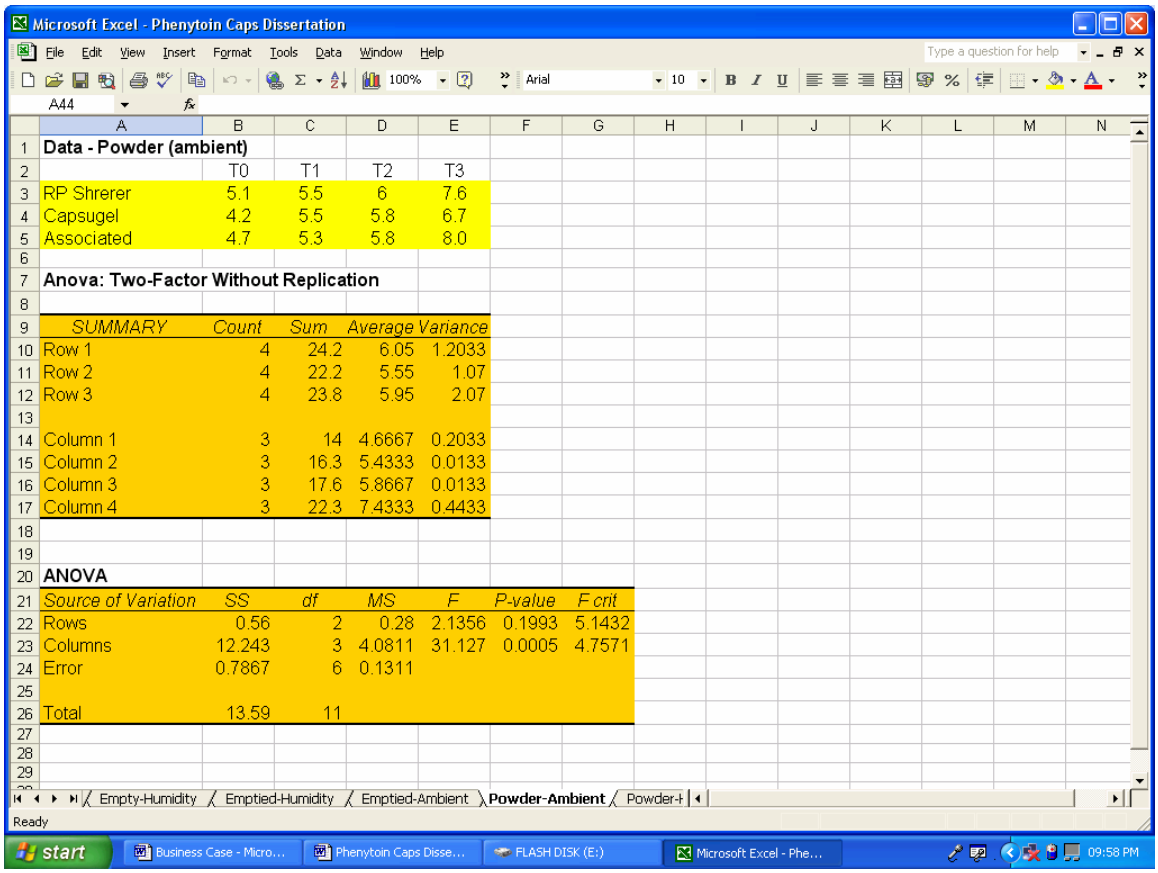
retained. For the “Columns” i.e. different storage times, the F-value is greater than F-crit, meaning there is a difference in moisture contents of emptied-out capsules stored for a period of time at humidity conditions. The null-hypothesis (No.2) is thus rejected.

3.4.5 Two-factor ANOVA for the moisture content of powdered capsule contents stored at ambient temperature

Null-hypothesis 1: There is no difference in moisture content of the powdered contents of capsules supplied by the three suppliers.

Null-hypothesis 2: There is no difference in the moisture content of the powdered contents of capsules stored for different periods of time.

The result of this analysis is shown in Table 3.7



	A	B	C	D	E	F	G
1	**Data - Powder (ambient)**						
2		T0	T1	T2	T3		
3	RP Shrerer	5.1	5.5	6	7.6		
4	Capsugel	4.2	5.5	5.8	6.7		
5	Associated	4.7	5.3	5.8	8.0		
6							
7	**Anova: Two-Factor Without Replication**						
8							
9	*SUMMARY*	*Count*	*Sum*	*Average*	*Variance*		
10	Row 1	4	24.2	6.05	1.2033		
11	Row 2	4	22.2	5.55	1.07		
12	Row 3	4	23.8	5.95	2.07		
13							
14	Column 1	3	14	4.6667	0.2033		
15	Column 2	3	16.3	5.4333	0.0133		
16	Column 3	3	17.6	5.8667	0.0133		
17	Column 4	3	22.3	7.4333	0.4433		
18							
19							
20	**ANOVA**						
21	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
22	Rows	0.56	2	0.28	2.1356	0.1993	5.1432
23	Columns	12.243	3	4.0811	31.127	0.0005	4.7571
24	Error	0.7867	6	0.1311			
25							
26	Total	13.59	11				

Table 3.7

From Table 3.7 it is noticed that the F-value for the “Rows”, i.e. the different types of capsules, is less than F-crit, meaning that there is no difference in moisture content of powdered capsule contents of the three suppliers. The null-hypothesis (No.1) is

therefore retained. For the “Columns” i.e. different storage times, the F-value is greater than F-crit, meaning there is a difference in moisture content of emptied-out capsules stored for a period of time. The null-hypothesis (No.2) is thus rejected.

3.4.6 Two-factor ANOVA for the moisture content of powdered capsule contents at humidity storage conditions

Null-hypothesis 1: There is no difference in moisture content of the powdered contents of capsules supplied by the three suppliers.

Null-hypothesis 2: There is no difference in the moisture contents of the powdered content of capsules stored for different periods of time.

The result of this analysis is shown in Table 3.8

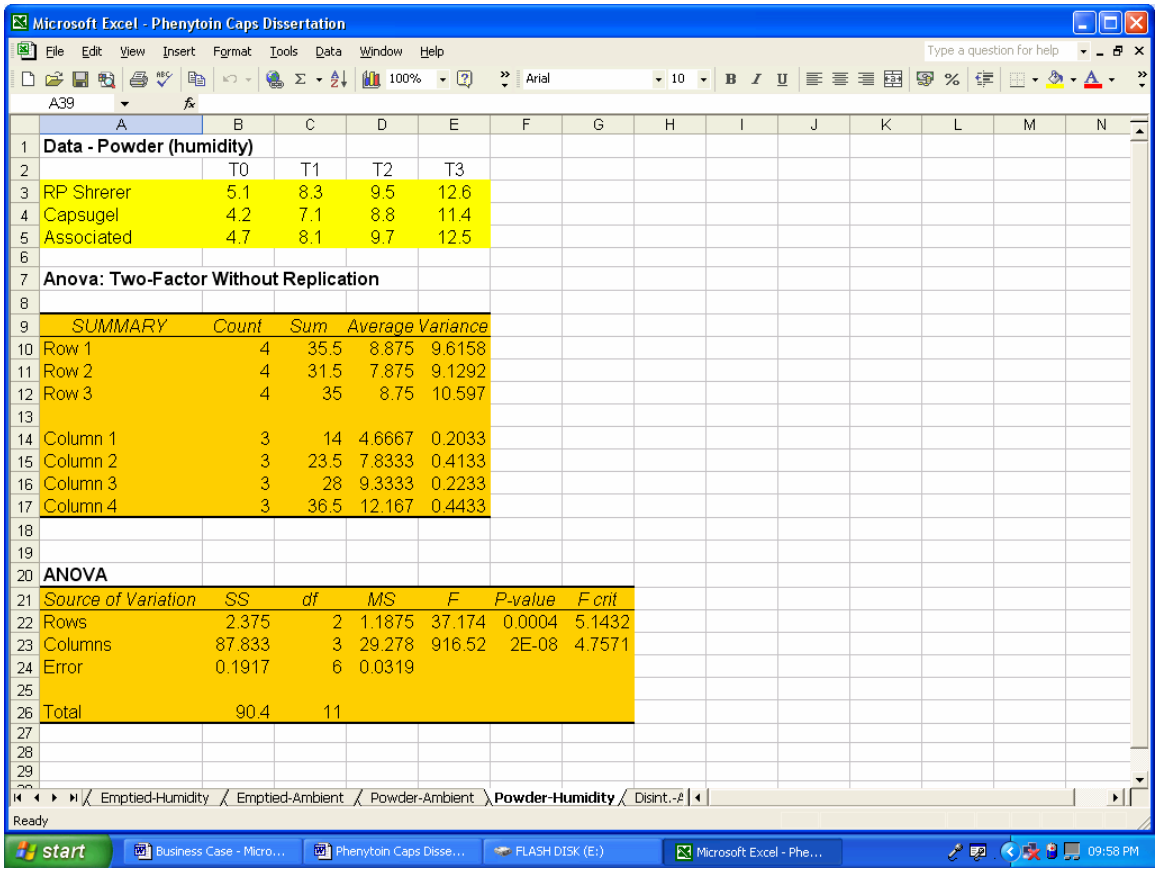


Table 3.8

From Table 3.8 it is noticed that the F-value for the “Rows”, i.e. the different types of capsules, is greater than F-crit, meaning that there is a difference in moisture content of powdered capsule contents of the three suppliers. The null-hypothesis (No.1) is

therefore rejected. For the “Columns” i.e. different storage times, the F-value is significantly greater than F-crit, meaning there is a difference in moisture content of the powdered contents of capsules stored for a period of time at humidity conditions. The null-hypothesis (No.2) is thus rejected. It is evident from the above that storage time, as well as different capsule suppliers, have got an influence on the moisture content of the filled powdered capsule contents.

3.5 DISINTEGRATION TIME (MINUTES)

Disintegration studies were performed on the filled capsules stored under ambient (25ºC/60%RH) and humidity (40ºC/45%RH) conditions as described in paragraph 2.3.3. The results of these analyses are summarized in Tables 3.9 and 3.10.

	Time			
Supplier	**T0**	**T1**	**T2**	**T3**
A	9	9	9	11
B	9	9	8	8
C	9	9	8	8

Table 3.9: Ambient

As can be observed from Table 3.9, there appears to be an increase in capsule disintegration time for supplier A over the three month ambient storage conditions, whereas the disintegration stays quite stable for supplier B and supplier C.

	Time			
Supplier	**T0**	**T1**	**T2**	**T3**
A	11	11	12	14
B	11	11	13	14
C	9	9	9	9

Table 3.10: Humidity

According to the results in Table 3.10, the capsule disintegration time for supplier C stays stable over the three-month humidity storage conditions, which is not the case for supplier A and supplier B where there is an increase in disintegration time. These

results could indicate a possible slowing of dissolution of the active from capsules from suppliers A and B.

3.6 STATISTICAL ANALYSIS OF DISINTEGRATION RESULTS

Analysis of Variance (ANOVA) was used as described previously to determine any differences between capsule suppliers for the disintegration test. The results will be presented in the same format as for moisture results.

3.6.1 Two-factor ANOVA for the disintegration time at ambient storage conditions

A two-factor (type of capsule; storage time) ANOVA was performed on the data given in Table 3.9 for the variation in disintegration time. The following null-hypotheses were adopted:

Null-hypothesis 1: There is no difference between the disintegration time of capsules stored at ambient temperature for the three capsule suppliers.

Null-hypothesis 2: There is no variation in disintegration time of any of the capsules stored over the period of storage evaluated.

The results are depicted in Table 3.11

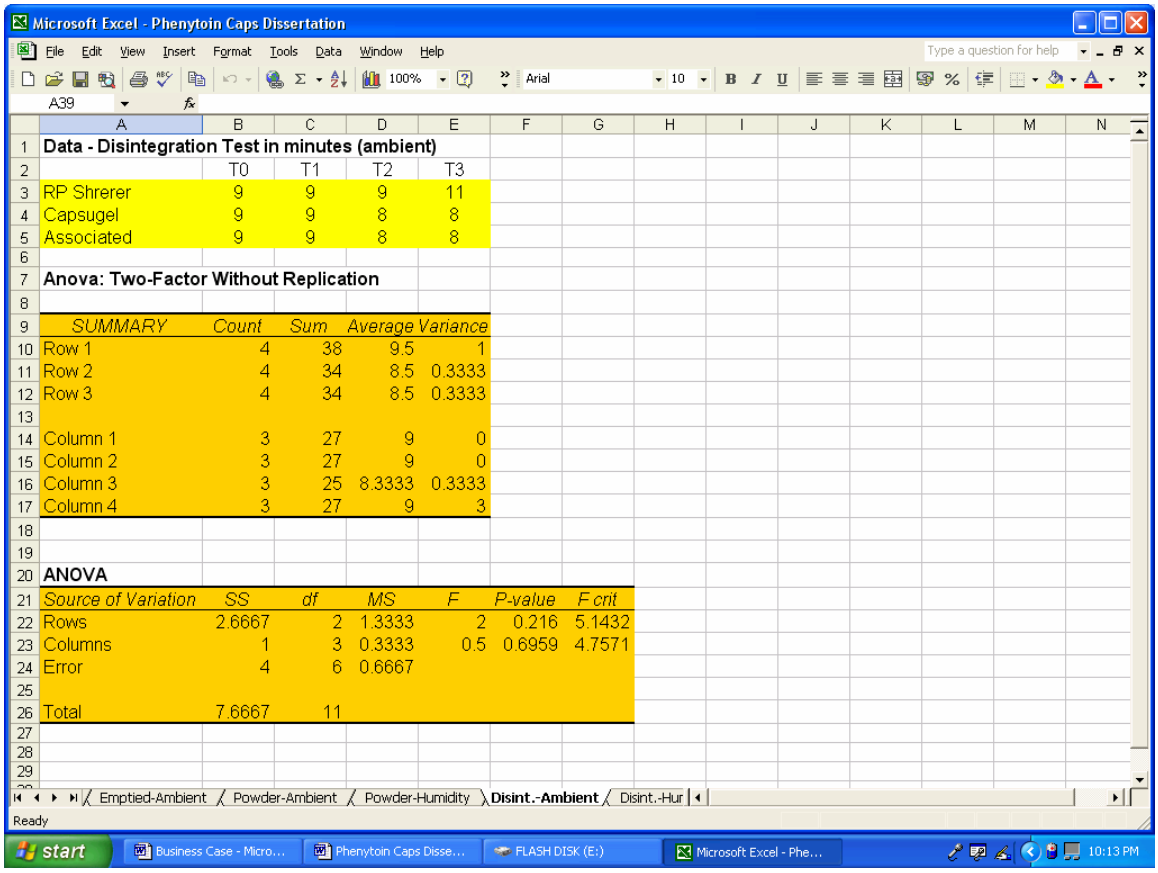


Table 3.11

As can be seen from Table 3.11 the F-values for both rows (storage time) and columns (capsule supplier) is less than F-crit, meaning that there is no variation in the disintegration time at ambient storage conditions for either storage time or capsule supplier, and both null-hypotheses are retained.

3.6.2 Two-factor ANOVA for the disintegration time at humidity storage conditions

The null-hypotheses for this ANOVA were:

Null-hypothesis 1: There is no difference in disintegration time for the capsules stored at humidity conditions for the different capsule suppliers.

Null-hypothesis 2: There is no difference in disintegration time for the capsules stored at humidity conditions over the entire storage period.

The results are shown in Table 3.12

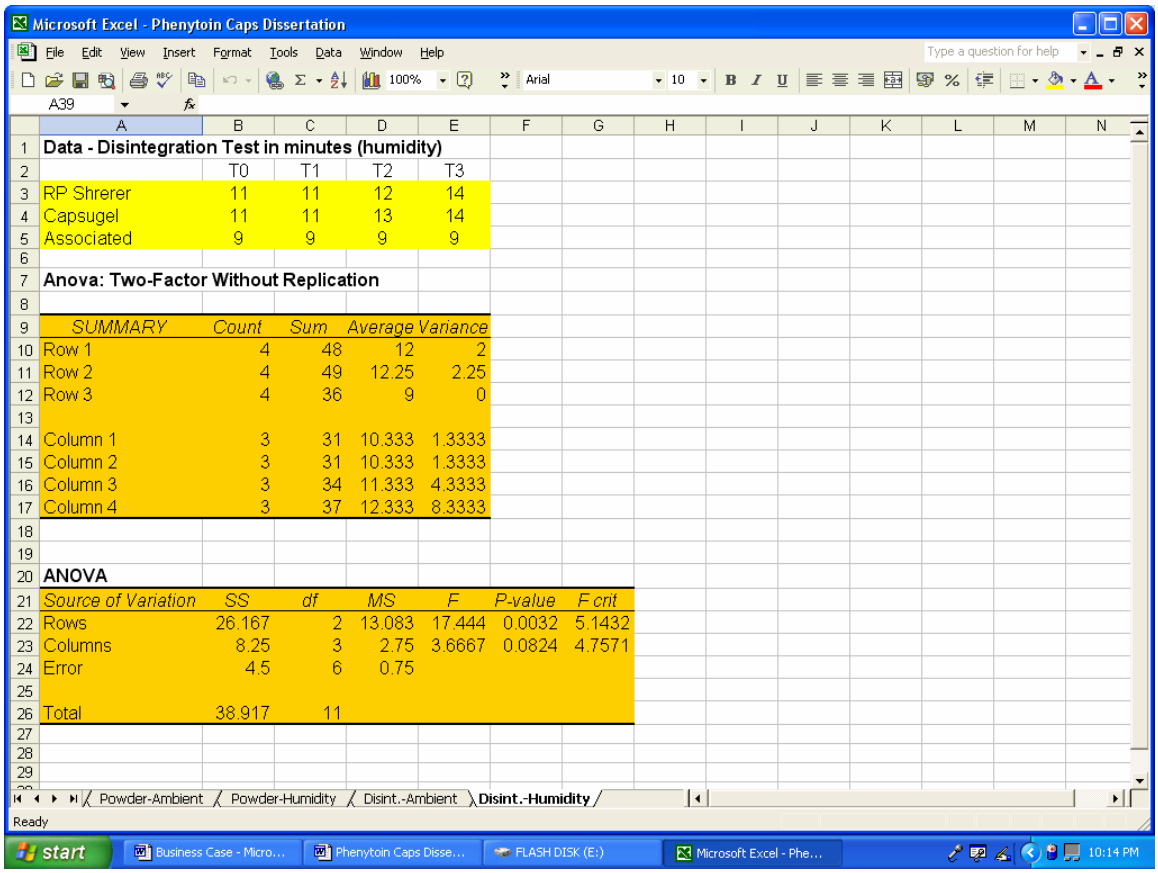


Table 3.12

From Table 3.12 it can be seen that the F-value for the “Rows”, i.e. different types of capsules, is greater than F-crit, meaning that there is a difference in the disintegration times of the capsules of the different capsule suppliers. The null-hypothesis (No.1) is therefore rejected. It is obvious from the results in Table 3.10 that capsules obtained from Associated Caps have shorter disintegration times than the capsules from the other two suppliers. For the “Columns”, i.e. for the different storing times, the calculated F-value is less than F-crit hence the null-hypothesis (No.2) is retained i.e. storing the capsules under specified conditions for different periods of time does not influence the disintegration times.

3.7 DISSOLUTION TESTING

Dissolution studies were performed on the filled capsules just after filling (T0), after being stored for three months under ambient (25ºC/60%RH) and three months under humidity (40ºC/75%RH) conditions. Three replicates were run for each type of capsule for each of the storage conditions. The results obtained are summarized in Tables 3.13 to 3.21, and shown graphically in Graphs 3.7 to 3.15.

RP Scherer (A)

	% Active Released		
Time (min)	**T0**	**T3 Ambient**	**T3 Stressed**
10	17.3	8.6	3.8
20	72	29.2	16.5
45	95	57.2	38.2
90	97.4	85	73.5

Table 3.13

Capsugel (B)

	% Active Released		
Time (min)	**T0**	**T3 Ambient**	**T3 Stressed**
10	24.2	18.5	4.4
20	88.6	55.3	16.4
45	95.6	79.9	37.9
90	95.6	97.5	79.2

Table 3.14

Associated Caps (C)

	% Active Released		
Time (min)	**T0**	**T3 Ambient**	**T3 Stressed**
10	49.9	47.4	9.9
20	100	78.2	25.6
45	101.8	94.4	56.9
90	100.3	96.7	87.5

Table 3.15

RP Scherer (A)

	% Active Released			
Time (min)	**T0**	**T1 Ambient**	**T2 Ambient**	**T3 Ambient**
10	17.3	29.2	32.3	8.6
20	72	64.4	61.4	29.2
45	95	88.3	75.2	57.2
90	97.4	97.1	88.1	85

Table 3.16

Capsugel (B)

	% Active Released			
Time (min)	**T0**	**T1 Ambient**	**T2 Ambient**	**T3 Ambient**
10	24.2	20.3	42.5	18.5
20	88.6	65.7	79.7	55.3
45	95.6	100.1	90.3	79.9
90	95.6	102.5	91.4	97.5

Table 3.17

Associated Caps (C)

	% Active Released			
Time (min)	**T0**	**T1 Ambient**	**T2 Ambient**	**T3 Ambient**
10	49.9	49.5	48.5	47.4
20	100	86.9	82.4	78.2
45	101.8	96.8	95	94.4
90	102.3	98.7	96	96.7

Table 3.18

RP Scherer (A)

	% Active Released			
Time (min)	**T0**	**T1 Stress**	**T2 Stress**	**T3 Stress**
10	17.3	6.7	8	97.4
20	72	22.3	18.6	81.5
45	95	47.1	39.9	66.8
90	97.4	81.5	38.2	73.5

Table 3.19

Capsugel (B)

	% Active Released			
Time (min)	**T0**	**T1 Stress**	**T2 Stress**	**T3 Stress**
10	24.2	5	5.6	4.4
20	88.6	21.9	17.1	16.4
45	95.6	55.3	43	37.9
90	95.6	91.6	73.2	79.2

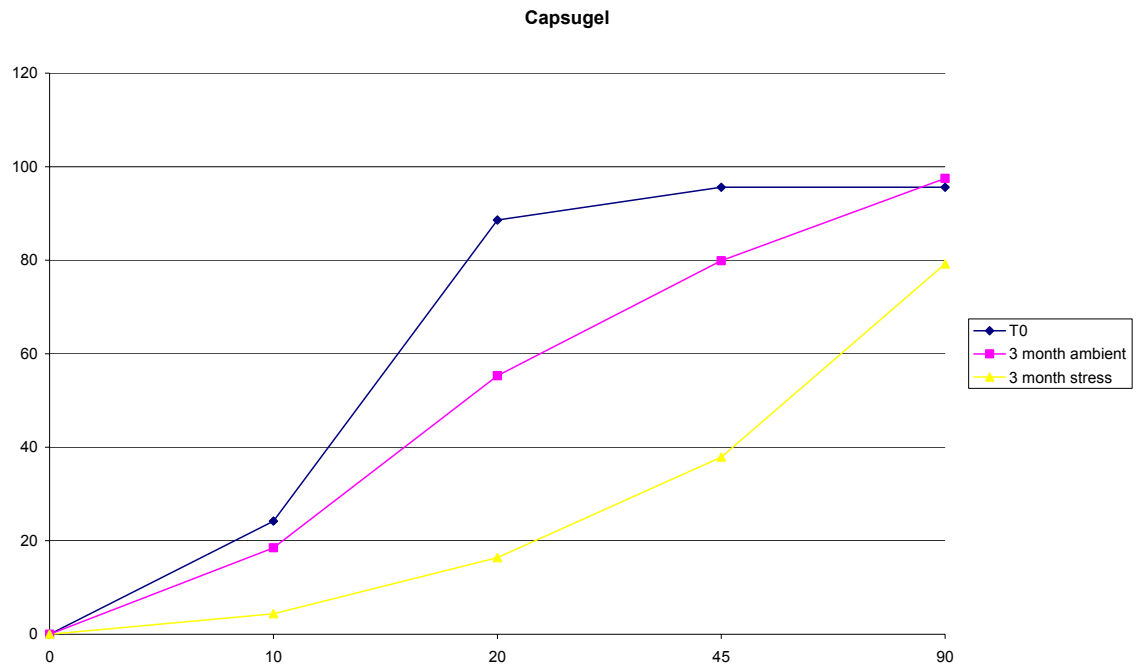
Table 3.20

Associated Caps (C)

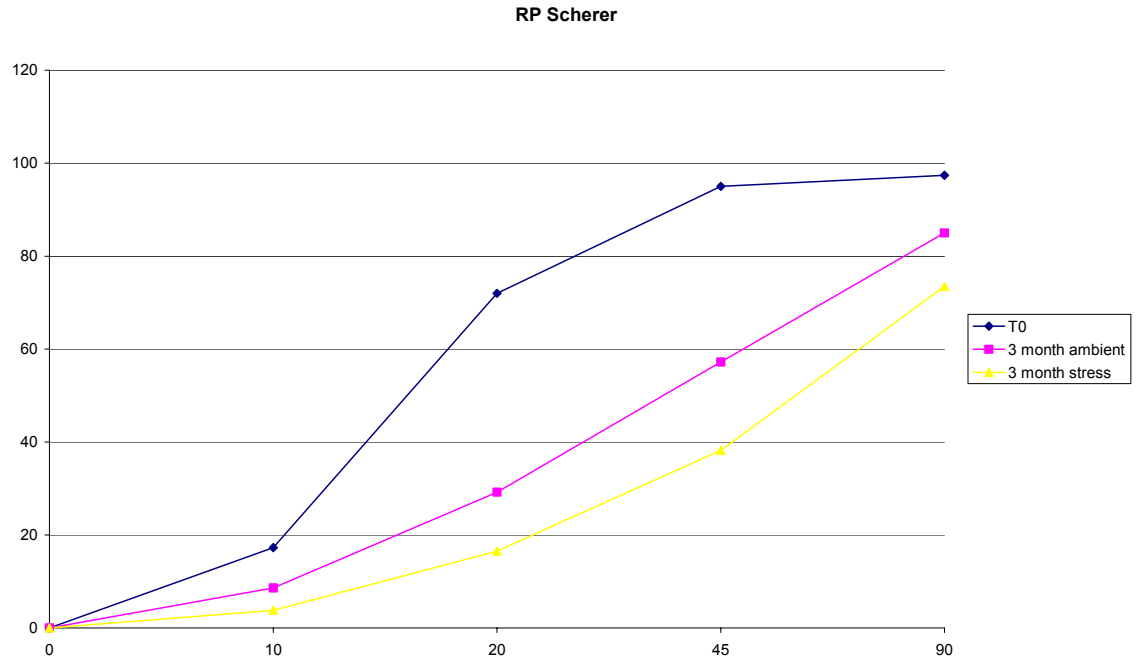
	% Active Released			
Time (min)	**T0**	**T1 Stress**	**T2 Stress**	**T3 Stress**
10	49.9	16	5.6	9.9
20	100	33.9	16.6	25.6
45	101.8	61.6	44	56.9
90	102.3	92.5	76.7	87.9

Table 3.21

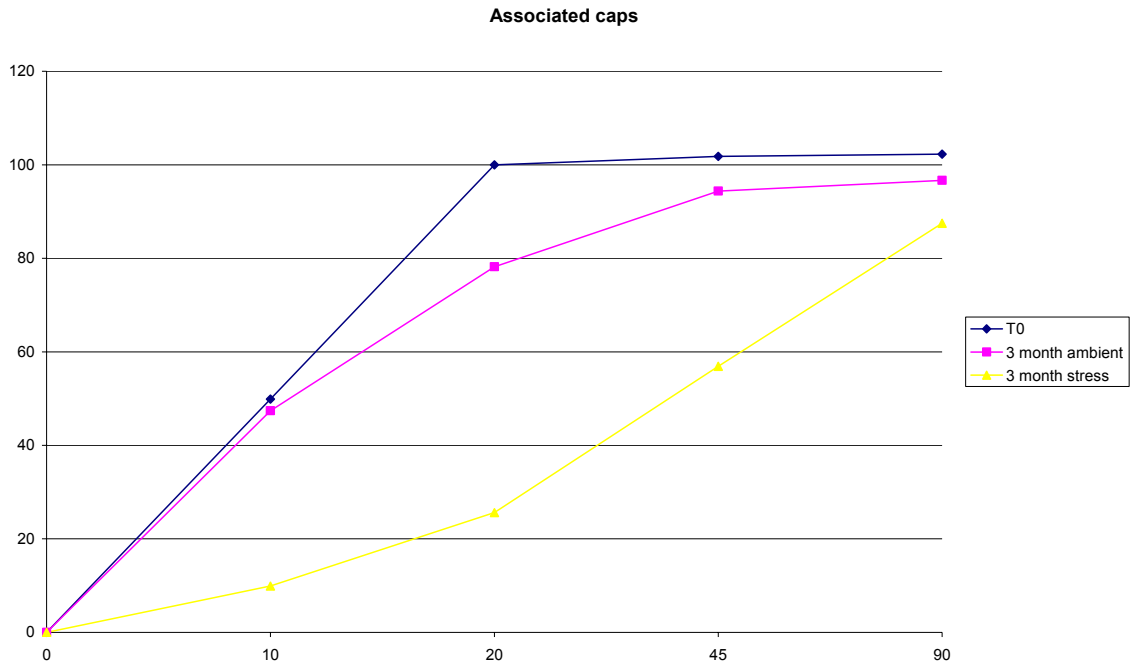
3.7.1 Dissolution profile graphs



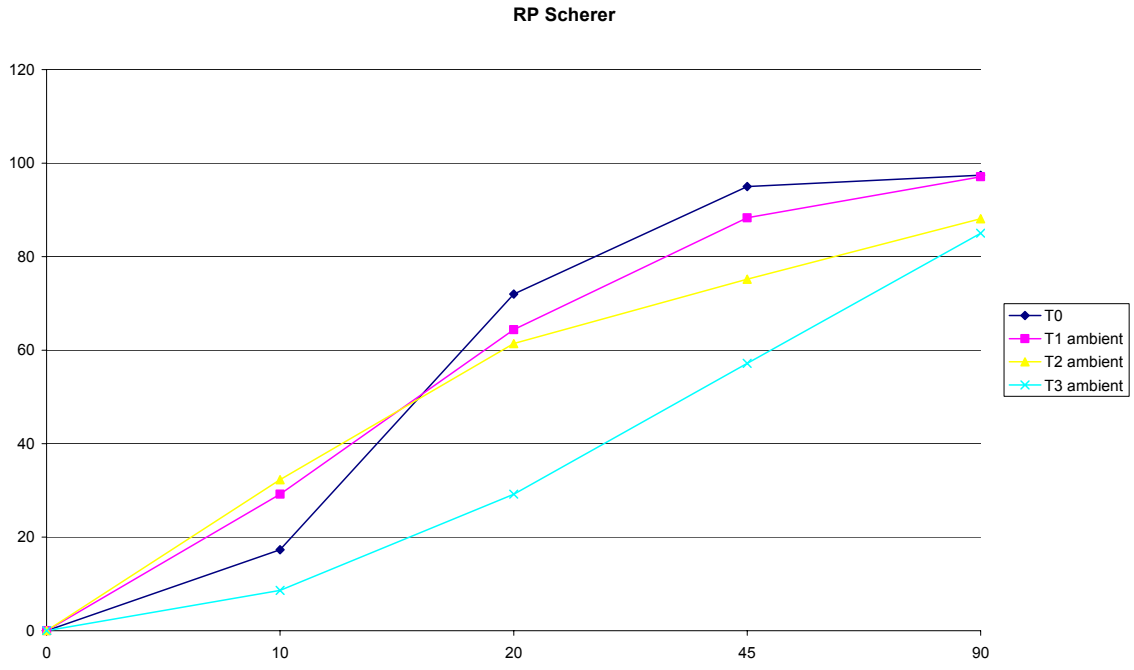
Graph 3.7



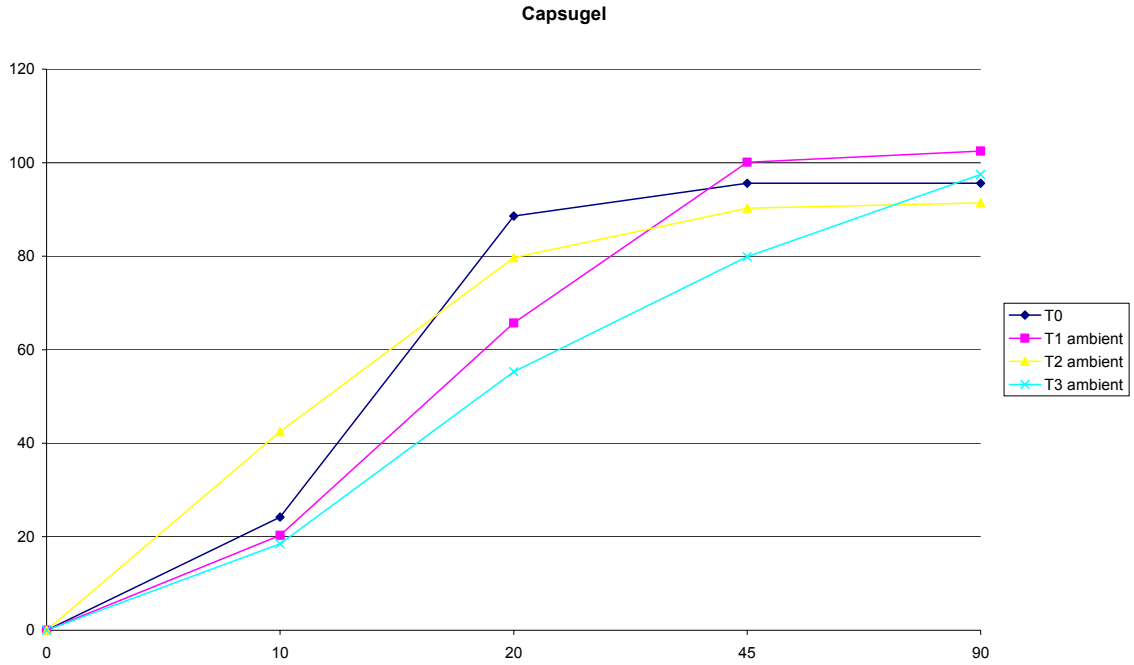
Graph 3.8



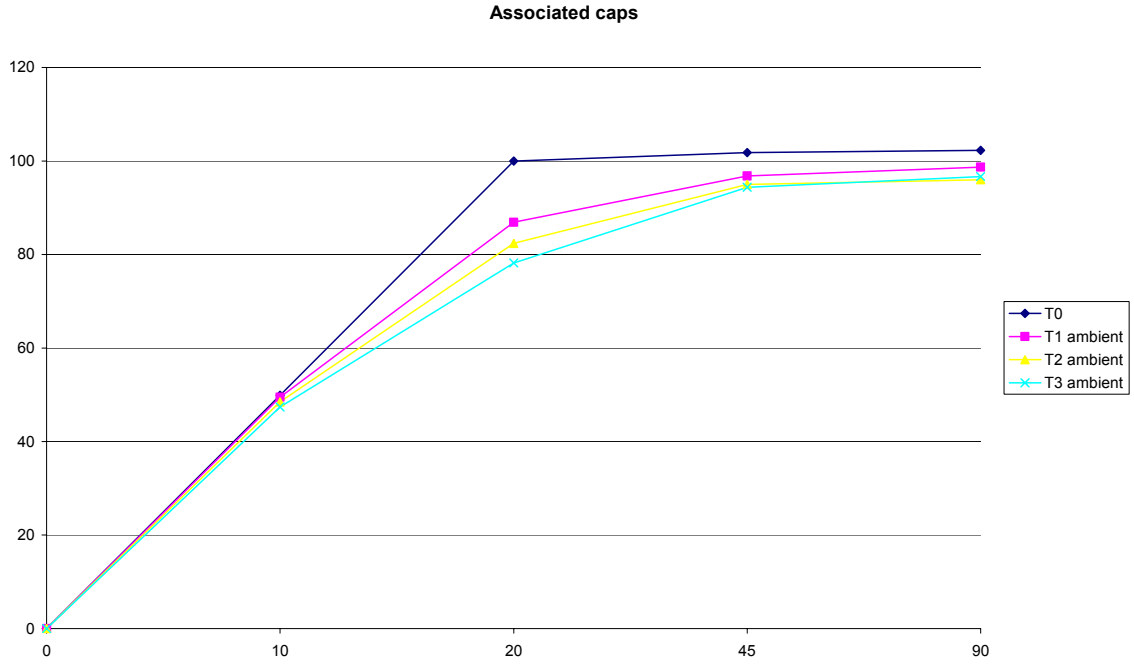
Graph 3.9



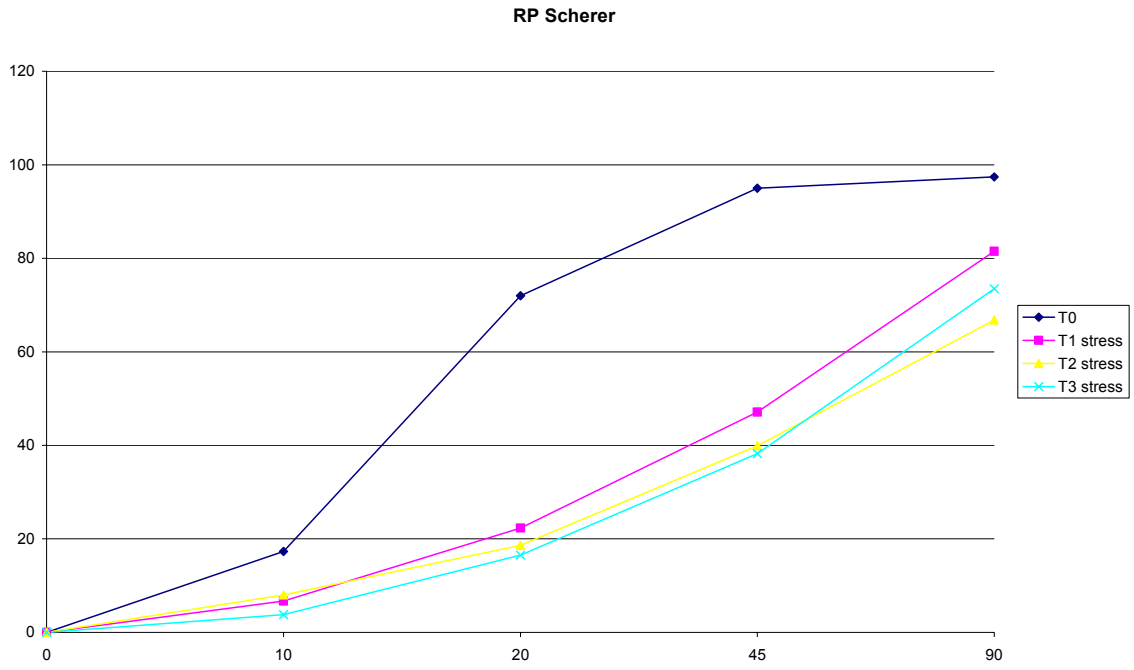
Graph 3.10



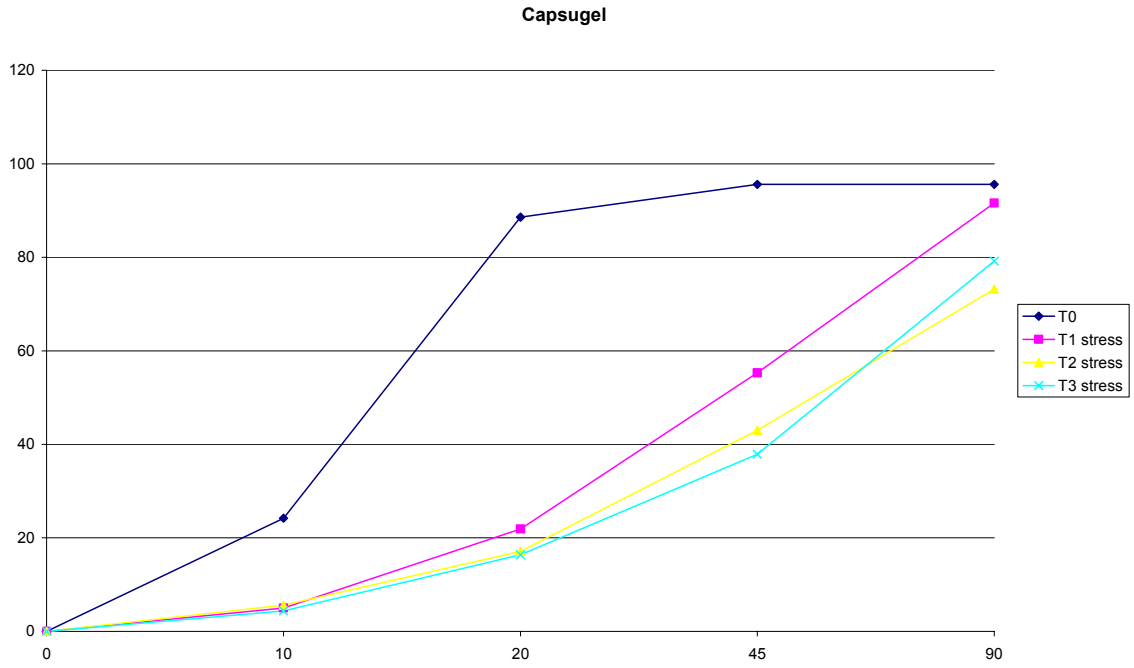
Graph 3.11



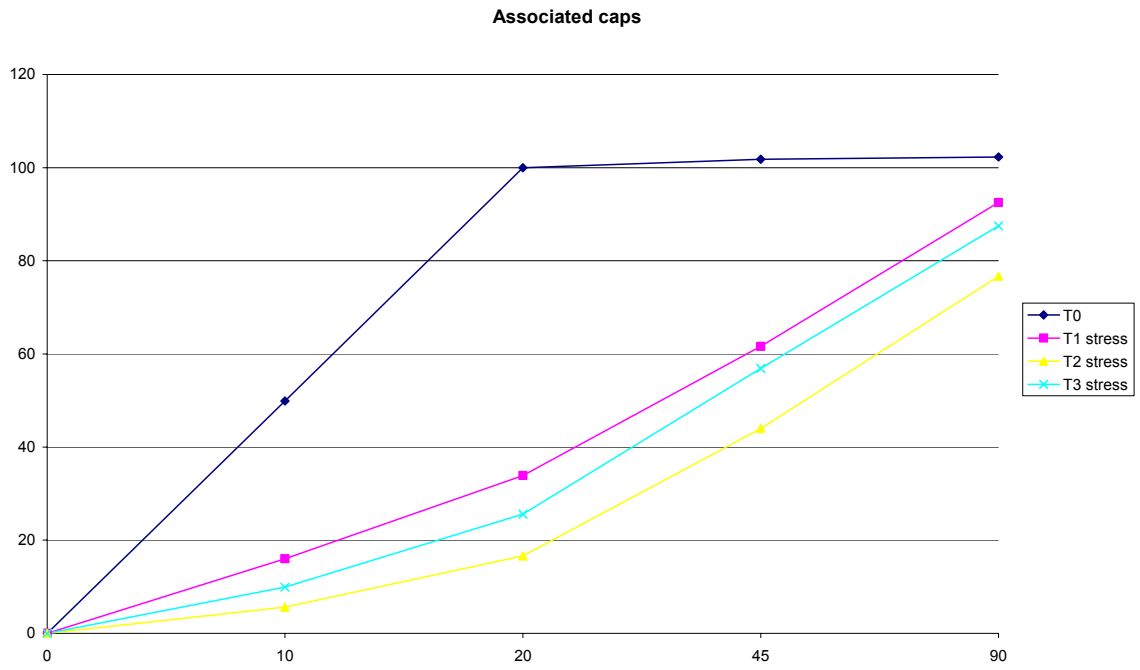
Graph 3.12



Graph 3.13



Graph 3.14



Graph 3.15

3.8 DISCUSSION OF DISSOLUTION COMPARISONS

Graphs 3.7 to 3.9 show a comparison of T0 dissolution results with T3 ambient and T3 stress conditions for all three capsule suppliers. For all three capsule suppliers dissolution passes both the USP "prompt release" criteria, not less than 90% active released in 30 minutes, as well as the in-house criteria of not less than 70% active released in 45 minutes. However, for all three capsule suppliers, ambient as well as stress conditions reduces the dissolution dramatically to fail both the USP dissolution specification as well as the in-house specification (for stress conditions) and in the case of RP Scherer both stress and ambient conditions. The Associated Caps capsules pass the in-house specification at ambient only.

Graphs 3.10 to 3.12 shows the comparison of T0 dissolution results with T1, T2 and T3 ambient condition results for all three capsule suppliers. A clear downward trend

in dissolution is evident for all three capsule suppliers. Graphs 3.13 to 3.15 shows the comparison of T0 dissolution results with T1, T2 and T3 stress condition results for all three capsule suppliers. The same downward trend (however much more dramatic) can be seen for all three capsule suppliers. All three capsule suppliers' capsules continue to release active after 45 minutes, and at 90 minutes all three pass the in-house dissolution specification of N.L.T. 70% of active released.

Overall, Associated Caps capsules shows the best dissolution results and RP Scherer seems to be the worst, based on the dissolution profiles showed in the graphs.

CHAPTER 4

CONCLUSION AND RECOMMENDATIONS

Analysis of moisture levels of emptied capsule shells showed that there was a definite trend of capsule content withdrawing moisture from the capsule shells for all three capsule suppliers. At ambient conditions the moisture content of the capsule shells stabilised whereas at stress conditions, moisture levels of both emptied capsule shells as well as capsule content continued to increase up to the T3 stage. However, it was not possible to find a significant difference between capsule suppliers in terms of moisture uptake over the storage period investigated, and this was confirmed by ANOVA analysis.

Disintegration times of capsules remained relatively constant for suppliers Capsugel and Associated Caps, whereas there was a marked increase in disintegration time of capsule supplier RP Scherer, especially at stress conditions; this was confirmed by ANOVA analysis.

The most interesting results came from the dissolution testing, where a marked decrease in dissolution was noticed for all three capsule suppliers at both ambient and stress conditions. Associated Caps gave the best dissolution results and RP Scherer the worst. Stress conditions caused a large decrease in dissolution, especially at T3, with none of the capsule suppliers' capsules passing either the in-house or USP dissolution criteria at this time-point. It should be noted that phenytoin sodium is readily converted to the insoluble acid form in the presence of water, which could account for the dramatic decrease in dissolution, especially at the higher humidity conditions. Moisture would enter the capsule from the outside, converting a layer of phenytoin sodium at the shell-content surface to the insoluble phenytoin acid, thereby further retarding dissolution of the remaining phenytoin sodium in the centre of the capsule.

It has also been shown that the excipients and/or manufacturing process exert a significantly negative effect on the dissolution release rate [16].

- The use of Associated Caps capsules is advised for phenytoin sodium capsules, as these seem to afford the best dissolution results.
- Better protective packaging should be investigated for phenytoin sodium capsules, i.e. possibly the addition of a desiccant to the securitainer or a change to a more protective blister pack.
- The capsule should be reformulated with more compatible excipients.

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PART B

BUSINESS PROPOSAL

1. SUBJECT

This business case examines the cost impact of using the chosen capsule supplier (as identified in the dissertation); in addition, the cost implications of reformulating the product will be discussed. These actions are necessary in order to improve and comply with USP dissolution criteria. These improvements are regarded as necessary, in order to protect this tender product in the market niche. This business case provides approximations of important financial consequences that should be considered in decisions involving purchasing of capsule shells and changing of a product formulation.

2. EXECUTIVE SUMMARY

Associated Capsules is the preferred supplier of phenytoin sodium gelatin capsules, as outlined in the dissertation. Improved protective packaging should also be investigated for these capsules, i.e. possibly the addition of a desiccant to the securitainer or a change to a more protective blister pack. Long-term, the product should be reformulated with more compatible excipients to guarantee a more stable product.

3. INTRODUCTION

Phenytoin sodium capsules (100 mg) is a tender product with recoveries in the order of R 3 million per annum. It is therefore important that the product should be protected in the market. Annually about 70 batches (i.e. 750 000 capsules per batch) are produced at the Aspen Pharmacare factory. The current formulation does not meet the Medicines Control Council (MCC) requirements for dissolution on stability. In order to protect the product in the market, the product needs to be reformulated to pass the USP dissolution criteria at all stability time-points. This business case provides information previously not available regarding phenytoin sodium capsules.

4. FINANCIAL METRICS

4.1 Cost price structure of phenytoin capsules

Costs	Percentage (%)
Material Costs	48.75
Operational Costs	51.25

Table 4.1

4.2 Material cost structure of phenytoin capsules

Ingredient	Percentage (%)
Active	50.86
Gelatin Capsule	40.28
Excipients	0.17

Table 4.2

4.3 Operational cost structure of phenytoin capsules

Operation	Percentage (%)
Prefitz	0.02
Slugging	51.66
Screening	1.39
Blending	0.40

Encapsulation	39.63
Analysis	6.90

Table 4.3

It can be seen from Table 4.1 that the cost to produce this product is split equally between material and operational cost. The material costing structure (Table 4.2) reveals that the active ingredient contributes 50.86% of the material cost. The empty gelatin capsules make up 40.28% of the other material costs. It is therefore very important to import capsule shells that will give the best results not only for better analytical results, but also shells that will result in the best operational outputs. It can thus be seen that if capsules are written off due to out of specification dissolution data it can be a very costly exercise. The price of capsules from the preferred supplier of capsules for phenytoin, Associated Caps is currently nearly 4 % cheaper than that of RP Scherer. This lower percentage equates to a monetary cost saving value in the order of R35 000 on annual purchasing cost of phenytoin capsule shells.

It must be considered in the long-term to look at reformulation of this product. The financial benefit will not be recouped from the material costing metrics (cost of excipients only contribute 0.17% of the total cost – refer Table 4.2) but could be recouped from the operational costs. If a formulation with a new excipient could perhaps eliminate the slugging operation the operational cost of the product could decrease by as much as 51% (Table 4.3).

Historic data on phenytoin capsules indicates that 88% of all analytical retesting in the laboratory can be contributed to dissolution problems. Reformulation of phenytoin caps will cost about R700 000 (R500 000 for a bio-study and R200 000 for reformulation costs). This amount of money will be recouped by eliminating analytical retests and repeats (currently making up about 7% of the operational cost) and reducing write-offs of batches failing dissolution.

5. PACKAGING

Phenytoin bulk capsules are currently packed into three different end items, namely Phenytoin Sodium Caps 100 mg bank bags (84’s) and Phenytoin Sodium Caps 100

mg securitainers (1000's and 100's). Currently two sachets of silica gel (2 g each) are added to the 1000's securitainer. The stability of the product could improve by using a larger quantity of silica gel per container. The stability of the 100's pack size securitainer will be improved by adding a 2 g silica gel sachet to it. The extra silica gel will result in an increase of only 0.8 % in cost for a standard batch of phenytoin capsules.

Phenytoin capsules could also be packed into Poly Vinyl Chloride (PVC) blister strips. These PVC strips create water vapour barriers which increase the stability of the capsule. Several different forms of PVC are available for pharmaceutical products. Polyvinylidene Chloride (PVDC) provides five times better barrier properties than a single layer PVC. High density fluorocarbon film (Aclar) increases the barrier ten fold compared to normal PVC. By using blister packs for phenytoin capsules it will increase the stability of the product; however, it will lead to the increase of packaging cost for this product. Currently the bank bags packaging is the most cost effective packaging method. By changing to PVC films it could increase the packaging price by more than 330%.

A more detailed cost analysis is required to work out the best cost effective packaging for phenytoin caps that will also yield acceptable stability data.

6. CONCLUSION AND RECOMMENDATIONS

- By changing capsule supplier from RP Scherer to Associated Caps a cost saving in the order of R35 000 can be achieved.
- Aspen could also reformulate the phenytoin capsule by making use of a more effective excipient that result in improved dissolution rate data; and by eliminating the slugging process. This could result in lowering the operational cost by ±50%, which in effect could decrease the total cost price of the phenytoin sodium capsule by as much as 25%.
- Aspen Pharmacare could investigate the storage of the capsules in a more protective blister pack instead of packing the capsules into the current securitainers and bank bags. Alternatively silica gel sachets could be added to

the securitainers, to protect the product better from moisture. This will however increase the cost of the final product.