THE EVALUATION OF MICROWAVE DRYING ON THE POLYMORPHIC CHARACTERISTICS OF CARBAMAZEPINE GRANULES PREPARED BY THE WET GRANULATION PROCESS.

By

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in the Department of Pharmaceutics, University of the Western Cape.

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KEYWORDS

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ABSTRACT

The evaluation of microwave drying on the polymorphic characteristics of carbamazepine granules prepared by the wet granulation process.

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The drying conditions of granules for tabletting prepared by the wet granulation process traditionally involve conduction, convection and radiation heat transfer. Despite various technological advances utilizing combinations of these conditions, the drying rates for pharmaceutical granules remain relatively high. Microwave drying is an alternate source of drying for pharmaceutical granules providing a faster drying rate, cost reduction benefits as well as reduced shrinkage and structural damage to granules. Polymorphic transformation of compounds in pharmaceutical products have become an important focus area since it can have disastrous economic, therapeutic and legal implications.

The primary objective of this study was to use x-ray powder diffraction (XRPD) and fourier transform infrared (FTIR) spectral analysis to determine whether microwave drying would alter the polymorphic characteristics of carbamazepine (CBZ) contained in granules and tablets prepared by a wet granulation process, in comparison to convection tray drying. In addition, the compressed tablets from each drying method were subjected to the British Pharmacopendial [5] quality control standards to verify compliance.

Preformulation studies were conducted on CBZ and selected excipients to establish compatibility and suitability in the development of a simple fast release tablet formula. The commercial CBZ powder, termed beta (ß)-polymorph, was used to prepare an alpha (a)- and a dihydrate (DHD) polymorph. All three polymorphs were fully characterized by XRPD and FTIR spectral analysis and served as fingerprint markers for granule and tablet evaluation.

The granules were prepared in a high shear granulator using anhydrous lactose as a hydrophilic filler, sodium starch glycolate as disintegrant, silicone dioxide as glidant, magnesium strearate as

lubricant and a 5% polyvinylpolypyrrolidone in ethanol suspension, as binder. The granules were dried in equal portions in a commercial microwave oven and convection tray drying oven respectively and analyzed by XRPD and FTIR. Tablets containing 200 mg CBZ were compressed by a single-punch tablet press and subjected to a full pharmaceutical evaluation, as specified in the British Pharmacopoeia [5], as well as XRPD and FTIR analysis.

No significant differences in XRPD and FTIR spectra were recorded for granules and tablets dried by microwave and convection tray drying, respectively, to warrant confirmation that polymorphic transformation occurred.

The required drying time of seven minutes for granules in the microwave oven were ten times faster than those dried by convection oven, which required 75 minutes. No visible thermic damage or charring were detected from the differently dried granules. The average CBZ content per microwave- and convection dried tablets were 97.8 ± 4.66 % and 87.4 ± 1.34 % of the stated 200mg, respectively. These levels were well within the British Pharmacopoeia's [5] specification range of between 85 % and 115%. Both sets of tablets disintegrated completely within two minutes. The dissolution profiles for the differently dried CBZ tablets yielded a strikingly similar release pattern. The average CBZ release (n=6) for the microwave- and convection dried tablets were 83% and 85%, respectively, after forty five minutes, while the maximum drug release yielded 87% and 89% respectively after ninety minutes. Tablets from both drying methods passed the uniformity of mass, size and shape test but failed the friability test despite having adequate hardness.

It could be concluded that the results support the hypothesis that microwave drying do not alter the polymorphic characteristics of CBZ contained in granules and tablets prepared by a wet granulation process.

DECLARATION:

I declare that *The evaluation of microwave drying on the polymorphic characteristics of carbamazepine granules prepared by the wet granulation process* is my own work, that it has not been submitted for any degree or examination in any other university, and that all sources I have used or quoted have been indicated and acknowledged by complete references.

Full name..... Date .....

Signed .....

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DEDICATION

I dedicate this thesis to my best friend and wife, Carmen and my two daughters, Cameron and Nikita, who have been the pillars during the trying times under which this work was done. Without your love, support, encouragement and belief in me, this would not have been possible.

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CHAPTER 1

Introduction and Background

The drying conditions of granules for tabletting prepared by the wet granulation process traditionally involve conduction, convection and radiation heat transfer. Despite various technological advances utilizing combinations of these conditions, the drying rates for pharmaceutical granules remain relatively high [28]. Microwave drying is an alternate source of drying for pharmaceutical granules. The drying rate is faster which translate into cost reduction benefits as well as reduced shrinkage and structural damage to granules.

The application of heat to material results in temperature increases by (a) conduction - in which thermal conductivity of the material plays a large part, (b) convection - in which circulation is important, and by (c) radiation - by heat waves. Microwave heating is primarily a radiation process in which radiant heat waves cause heating through the absorption of energy quanta, while molecular collisions accompany the energy transfer in conduction and convection [8]. The energy change during microwave heating is one of loss by electromagnetic radiation of some or all its energy to the heating substance. If adequate power is available at the correct frequency, the process is further characterized by a very dramatic rate of heating throughout its volume.

Although various studies have been undertaken to evaluate the efficacy of microwave drying and its effect on physical granular characteristics [28], the economic viability of combination microwave-convection dryers [32], mapping energy distribution during microwave vacuum drying [21], very little physicochemical evaluation has been done.

The phenomenon of polymorphism of the active pharmaceutical ingredients has become an important focus area within the pharmaceutical industry. Polymorphism can be defined as the ability of a compound to exist in more than one distinct crystalline form in which the molecules have different arrangements within the crystal lattice. Polymorphs of a given substance can exhibit different physicochemical properties such as differences in crystal packing, thermodynamics,

spectroscopy and kinetics. These differences can affect both the bulk chemical properties (shelf-life, solubility, density) as well as the pharmaceutical performance of the drug substance (bioavailability, stability).

Carbamazepine is a widely used potent anticonvulsant. It has anti-epileptic and psychotropic properties, and is used to control secondarily generalized tonic-clonic seizures and partial seizures. It is also used in the treatment of trigeminal neuralgia and other neurological syndromes associated with severe pain [33].

Various reports have highlighted the polymorphic nature of this compound with reference to its different forms (monoclinic, trigonal and dihydrate) [31], transitions during grinding, compression [26], and elevated humidity levels [40], solution-mediated transformation [36] hygroscopicity and variation of its dissolution rate and bioavailability in humans [16]. Different brands of carbamazepine tablets have also had a history of bioinequivalence and clinical failure which may be due to polymorphism [34].

In the present study, the feasibility of using microwave radiation as drying source for a wet granulation process without changing the polymorphic nature of the model drug, CBZ, has been considered.

X-ray powder diffraction (XRPD) and Fourier transform infrared (FTIR) spectroscopy studies have emerged as important experimental techniques available for the characterization of polymorphic solids [6, 12, 18, 23, 26, 30, 36, 37, 38, 39, 40, 43, 44] and were the principal techniques used for monitoring CBZ following granulation and compression into tablets.

CHAPTER 2

Theory and Literature Review

2.1 Introduction

This chapter deals with the theory of wet agglomeration and drying as well as the differences between convection- and microwave drying during a wet granulation process. The phenomenon of polymorphism is discussed in detail with reference to CBZ. The theoretic background to the analytical testing methods, XRPD and FTIR, are also elaborated on.

2.2 Solid dosage form production

The majority of pharmaceutical products are produced using the wet granulation method and as the distribution is normally in the form of a tablet compressed from dry granule [18], the solvent must be removed to a level allowing compression and storage without physical or chemical breakdown.

2.2.1 Particle-Bonding Forces during Wet granulation

2.2.1.1 Attraction between solid particles

Attractive forces are short-range forces that cause solid particles to adhere to each other only if they are brought close enough together. Their effectiveness reduces drastically as the size of the particles or distance between particles increases. Therefore, in the overall mechanism of bond formation, the attractive forces initially hold and orientate the particles in a contact region long enough for stronger forces to take over. Attractive forces may be of electrostatic-, magnetic- or molecular (valence and Van der Waals) nature [14].

2.2.1.2 Interfacial forces

Agglomeration, is a process where particles are brought together into larger semi-permanent aggregates, so called granules. In wet granulation, this process is facilitated by a liquid. The liquid binds the particles by a combination of capillary and viscous forces in the wet state. At low moisture levels, called the pendular state, the particles are held together by lens-shaped rings

causing adhesion because of surface tension forces at the liquid/air interface and the hydrostatic suction pressure in the liquid bridge. A capillary state is then reached when all the air has been displaced from between the particles. The particles are held by capillary suction at the liquid/air interface which is only at the granule surface. The funicular state represents an intermediate stage between the pendular and capillary states. Although these wet bridges are only temporary structures, they are however a prerequisite for the formation of solid bridges formed by adhesives present in the liquid or granulating fluid [2].

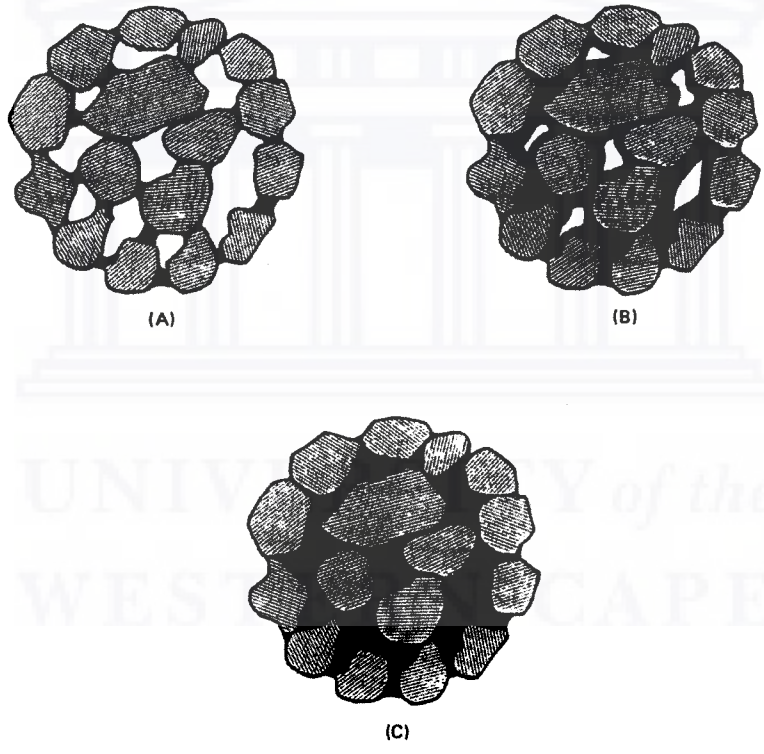

Figure 1. Spherical assembly of particles.

(A) Pendular state, (B) Funicular state and (C) Capillary state. (Adapted from reference 14)

2.2.1.3 Adhesion and cohesion forces in immobile films

Different binders provide bonds that are based on immobile liquid bridges. Highly viscous binders adhere to the surfaces of solid particles to generate strong bonds that are similar in characteristic to those that exist with solid bridges. Because the effect of the interfacial forces on the mobility of the surface liquid is significantly reduced, a constant liquid pressure cannot be formed. The binder then retains the shapes of the surfaces on which it is deposited. In addition, many viscous binders harden during the agglomeration process and form solid bridges [14]. The use of starch mucilage in pharmaceutical granulation may produce this type of film.

2.2.1.4 Solid bridges

Despite the various bonding mechanisms that contribute to the initial bonding between primary particles, it is the solid bridges that largely determine the strength of the final dried product. Solid bridges are formed by different mechanisms but only the ones common to wet granulation are discussed briefly below.

(i) Hardening binders

Adhesives such as polyvinylpyrrolidone, are commonly included in the granulating solvent which will harden or crystallize on drying. The resulting solid bridges owe their strength to the properties of the binder substance itself, the forces of adhesion between the binder and the particle and/or the physico-chemical characteristics of the particles forming the agglomerate.

(ii) Crystallization of dissolved substance

In this mechanism, the solvent used to mass the power during wet granulation may partially dissolve one of the powdered ingredients resulting in crystallization of the material once dried. The dissolved substance may then act as hardening binder and be identical to the bonded particle in nature or it may be the solid component of the binding liquid [2].

2.2.2 Granule formation

The elementary events that lead to granule formation include the following.

2.2.2.1 Nucleation

Granulation starts with particle-particle contact and adhesion due to liquid bridges. A number of

particles will join to form the pendular state and eventually densifies to form the capillary state. This three phase air-water-solid nuclei form the basis for further growth.

2.2.2.2 Transition

According to Aulton, nuclei can grow in two possible ways: either as single particles that can be added to the nuclei by pendular bridges or two or more nuclei may combine. The latter nuclei would be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. This can signal the end-point for granules to be used in tablet manufacture since the small granules will produce a uniform tablet die fill.

2.2.2.3 Ball growth

There are four possible mechanisms of ball growth as described briefly below.

(i) Coalescence

The formation of large size granules following random collision of two or more well formed granules (nuclei).

(ii). Breakage

Granules fragment and adhere to other granules forming a layer of material over the surviving granule.

(iii) Abrasion transfer

The agitation of the granule bed lead to the attrition of material from granules. Material is then transferred to other granules without any preference in either direction resulting in an increase in size.

(iv) Layering

This growth mechanism results from successive addition of material to an already formed bed of granules.

Based on these mechanisms, agglomerate growth is dependent on many interrelated phenomena and determined by the balance between coalescence and breakage [2].

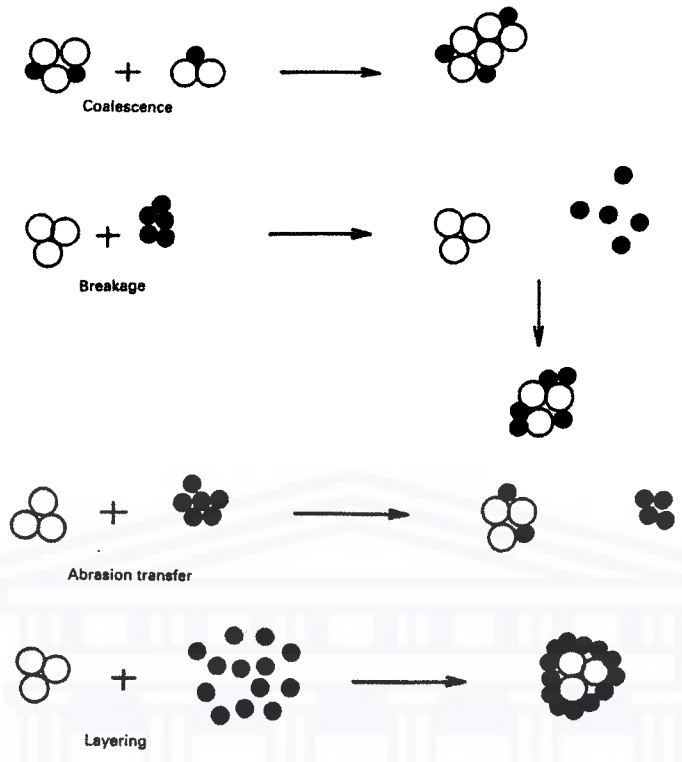

Figure 2. Mechanisms of agglomerate growth during granulation. (Adapted from reference 2)

The objective of granulation is to produce agglomerates which would contain homogeneously dispersed active ingredient(s) together with the excipients required to improve flow and prevent separation of the constituents. Wet granulation is often carried out utilizing a high-shear mixer.

The problems encountered during wet granulation can be summarily overcome by substituting the process with direct compression. However, these processes have their own problems and not all active ingredients are suitable for direct compression [2].

2.3 Types of drying methods

Pharmaceutical dryers are categorized according to the heat transfer method they employ, i.e. convection, conduction or radiant. In the current study, convection drying and microwave drying were employed in the manufacture of granules and resultant tablets.

2.3.1 Convection drying

Drying of wet solids by this method occur by circulating warm air over a wet mass resulting in the

evaporation of solvent from the drying bed until upward movement of solvent through the bed mass no longer occur and the drying at the surface will end.

In conventional or surface heating, the process time is limited by the rate of heat flow as defined by the following equation

$$\text{Rate of heat transfer, } (dH/dt) = h_c A \Delta T \qquad (1)$$

where

(dH/dt) is the rate of heat transfer (amount of heat transferred per unit time),

h_c is a heat transfer coefficient for convection heat transfer. The value of h_c is commonly a around 10-20 W m K,

A is the area in contact with the fluid,

ΔT is the temperature difference between the fluid and the surface.

The heat transfer coefficient also takes into account all the other variables in the process; such as the velocity of the fluid and its viscosity, specific heat, specific weight and thermal conductivity. These affect the turbulence generated at the solid surface and the amount of heat the fluid can carry to it. The geometry (size and shape) of the object to be heated, its orientation to the moving fluid, and the distance from adjacent objects and surfaces have a powerful effect on the value of the coefficient and, consequently, the heat transfer rate.

In convection ovens fans are used to increase the heat transfer rate. When fluids are heated, they become buoyant and tend to rise. If they cool, they tend to descend due to the gravitational pull being exerted on the gas. By increasing the velocity of the gases, they rub the product surface with greater turbulence, and that raises the convection coefficient. In addition, more energy becomes available to remove the layer of spent gases next to the surface and replacing them with a fresh consignment having a higher fluid-to-surface temperature differential.

The drying rate is also controlled by the water vapor that must pass through the boundary layers present at the surface into the turbulent air stream. The relative humidity of the air must be kept

below the saturation level and the boundary layers small in order to achieve the latter. Once it is saturated, evaporation ceases, no matter what the temperature differential [2].

Heat transfer from air is therefore relatively inefficient resulting in slow drying that can take up to 24 hours to dry wet granulations. The transfer of the heat into the body of the material from the surface also depends on its specific heat, thermal conductivity, density and viscosity. Surface heating is not only slow, but also non-uniform with the surfaces, edges and corners being much hotter than the inside of the material. Consequently, the quality of conventionally heated materials is variable and frequently inferior to the desired result.

Imperfect heating causes product rejections, wasted energy and extended process times that require large production areas devoted to ovens. Large ovens are slow to respond to needed temperature changes, take a long time to warm up and have high heat capacities and radiant losses. Their sluggish performance makes them slow to respond to changes in production requirements making their control difficult, subjective and expensive [8].

2.3.2 Microwave drying

The transmission of heat by radiation differs from heat transfer by convection and conduction in that no transfer medium needs to be present. Microwaves are produced by an electronic device known as a magnetron and operate at frequencies between 960 and 2450 MHz. Heat energy in the form of radiation can cross empty space or travel through the atmosphere virtually without loss. When microwaves fall on substances of suitable structure (small polar molecules such as water), the electrons in the molecules attempt to resonate in sympathy with the radiation and the resulting molecular friction results in heat generation [2]. The absorption of microwave energy is far greater for small polar molecules than for larger and less polar molecules. Dry solids do not resonate as well as water and therefore further heating should be avoided once the water is removed. The latter is indicated by a loss factor which is a measure of the ratio of the microwave energy absorbed by individual molecules; the higher the loss factor the greater the absorption of microwave energy [8].

With microwaves, heating the volume of a material at substantially the same rate is possible. This is known as volumetric heating. Energy is transferred through the material electro-magnetically, not as a thermal heat flux. Therefore, the rate of heating is not limited and the uniformity of heat

distribution is greatly improved. Heating times can be substantially reduced when compared to that required using convectional techniques.

Because volumetric heating is not dependent on heat transfer by conduction or convection, it is possible to use microwave heating for applications where conventional heat transfer is inadequate. Microwaves generate higher power densities, enabling increased production speeds and decreased production costs. Microwave systems are more compact, requiring a smaller equipment space. Microwave energy can also be turned on and off instantly eliminating the need for warm-up and cool-down. This increases production run times and reduces both cleaning times and chemical costs. Microwave energy is selectively absorbed by areas of greater moisture which results in more uniform temperature and moisture profiles, improved yields and enhanced product performance [8].

With the advantages offered by microwave heating borne in mind, microwave drying of pharmaceutical granules have been gaining considerable interest within latter years mainly due to the prospect of reduced drying times, shrinkage, structural damage to granules and operating costs. To this end, various types of granulators and mixers have been developed to utilize this drying technique.

Mandal [28] evaluated the morphological granule characteristics following microwave drying. His experiments were designed to compare granule characteristics following microwave drying and conventional tray drying and to study the effect of microwave radiation under different conditions such as varying the granulation fluid. Mandal concluded that microwave radiation did not modify the morphological properties of the sulfathiazole/lactose granules.

Kiekens and coworkers [22] focused on the influence of the different experimental parameters, such as chopper and mixing speeds, involved in microwave drying in combination with a high shear granulation process. That study also concluded that the major granule characteristics were not changed when different mixer and chopper speeds were used in the presence of microwave radiation.

Duschler et al. [11] evaluated a single granulating method utilizing microwave technology whereby dry mixing, granulating and drying steps were performed in a single vessel without refilling or

transportation in between and without any risk on cross contamination. An important outcome from that study was the realization that there was no adequate and reliable method of controlling the microwaves once they entered the drying cavity. To this end satisfactory mixing of batches is needed to prevent the coincidence of concentrated microwaves and immobolised granules which could result in unacceptable thermic damage.

McLoughlin et al. [31] examined the physical properties (solubility and boiling point) and dielectric properties, in terms of temperature rise, dielectric constant, and dielectric loss factor, of selected pharmaceutical actives and excipients in an attempt to better understand the factors governing the suitability of powers capable of harnessing the benefits of this technique. His findings clearly suggested that not all pharmaceutical powders (actives or excipients) are suitable for drying by this method. In general, the dielectric loss factor increases with increasing moisture content. For selected powders, the dielectric properties at the critical moisture content are significantly greater than those at higher moisture contents. In addition, McMimm et al. [32] also evaluated the effect of air conditions (velocity, temperature), and powder and solvent type on the combined microwave–convective drying kinetics of selected pharmaceutical powder systems. He concluded that microwave–convective processing typically facilitated a 50% reduction in drying time.

Walde et al. [48] investigated the use of microwave drying on a food stabilizer, *gum karaya*, and the subsequent effect on its grinding characteristics. Results revealed that microwave drying was a good candidate for drying the gum samples and that it produced a desirable viscosity that could be used in food processing.

2.4 Polymorphism

Polymorphism can be defined as the ability of a compound to crystallize in more than one distinct crystal species. Different polymorphs of a compound exhibit differences in physicochemical properties such as dissolution rate and solubility, melting point, hardness, density, crystal shape, optical and electric properties and vapour pressure, to name a few. Many of these properties are important in pharmaceutical development and may have considerable formulation, therapeutic, legal and commercial implications within the pharmaceutical industry. One such incident of polymorphic significance was that of the antiviral compound, ritonavir. The existence of multiple crystal forms of this novel protease inhibitor had a huge impact on its commercial viability when it was marketed

in 1996 as Norvir® oral liquid and Norvir® semi-solid capsules used in the treatment of acquired immunodeficiency syndrome (AIDS) [3]. These dosage forms had to be recalled and reformulated when it was discovered that the compound had converted to a much less soluble crystal form [3].

CBZ has also had its share of polymorphic misfortunes as evidenced by the 1988 recall of CBZ tablets that reported a change in dissolution characteristics and clinical failures. It was suggested that the polymorphic transformation from the anhydrous form to the dihydrate form might have been the cause for the latter [34, 36]. Due to the polymorphic nature of this compound under various conditions [19, 26, 30, 31, 34, 36, 40], CBZ was selected as a model drug for this study to evaluate whether microwave heating of the granules would cause any polymorphic transition of the CBZ.

2.4.1 Characterization of Carbamazepine Polymorphs

There are conflicting reports as to how many polymorphs of carbamazepine exist since the generation of polymorphs differ significantly in the methodology and solvents used.

Rustichelli and coworkers [43] characterized three different polymorphic forms of CBZ. The commercial form was termed Form III. Form I was obtained by heating Form III at 170° C for 1 hour and Form II was crystallized from an ethanolic solution of Form III. Solid dispersion studies of carbamazepine polymorphs I and - II by Koester et al. [24, 25] supported the findings of Rustichelli.

Kobayashi and coworkers [23] used a similar nomenclature to Rustichelli when they characterized and evaluated the physicochemical properties of carbamazepine polymorphs (form I, form III and a dihydrate). The commercial powder served as Form I. Form II was prepared by heating Form I for 2 hours at 170° C while the dihydrate form was prepared by suspending Form I in distilled water for 24 hours at room temperature which was then dried and filtered.

Lefebvre and Guyot-Hermann [26] also characterized three polymorphic forms but his nomenclature differed. The commercial form was termed ß. The second polymorph termed a, was prepared by heating the ß-form for 2 hours at 170° C. The third polymorph was a dihydrate prepared by hydrating the a-form in water and allowing the needles to dry at room temperature.

Due to the confusion in the nomenclature and preparation of the various CBZ solid forms in the literature, the nomenclature and preparation described by Lefebvre and Guyot-Hermann [26] were used in this study. The CBZ forms relevant to this work include the commercial anhydrous monoclinic ß-form, the triclinic a-form and the dihydrate form. Tablets of CBZ were formulated with the commercial anhydrous monoclinic ß-form.

2.4.2 Stability of CBZ polymorphs

It emerged from these studies [23, 24, 25, 26, 43] that although the nomenclature and preparation of the CBZ polymorphs differed, there was consensus among the authors that the commercial form was the most stable at room temperature.

2.4.3 Dissolution behaviour of CBZ polymorphs

As stated before, the effect of polymorphism on dissolution is another important issue. In general, drugs must be absorbed into the systemic circulation to reach their site of action. If a drug exhibits dissolution rate limited absorption, different polymorphs of the drugs are very likely to exhibit different absorption profiles and bioavailabilities

Various studies of ,physicochemical properties of form I, form III and the dihydrate have been reported. The dissolution and bioavailabilities of one anhydrate and a dihydrate were investigated by Kahela and coworkers [20]. The only difference in pharmacokinetics between the two forms was a slightly higher absorption rate for the dihydrate form. The slower absorption of the thermodynamically more active anhydrous form was attributed to rapid transformation of this form to the dihydrate within an aqueous environment.

Kobayashi et al. [23] demonstrated that dissolution results decreased in order; Form III>Form I>DHD. Form III was transformed more rapidly to the DHD than Form I resulting in a decrease in dissolution rate. The solubilities of both anhydrates calculated from the initial dissolution rate of each anhydrate were 1.5-1.6 times that of the anhydrate. At the dose of 40mg/body mass there were no significant differences in the AUC between the forms suggesting that most crystalline powders of each form administered at low dose was rapidly dissolved in the gastrointestinal tract (GIT) fluid.

However, 200mg/body significantly differed in plasma-concentration-time curve of CBZ among the

polymorphic forms and the DHD. The order of the area under the curve (AUC) values was Form I>Form III>DHD. The inconsistency between the order of initial dissolution rates and that of AUC values of the high dose might have been due to rapid transformation from Form III to DHD in the GIT fluids.

Thus, different polymorphs of CBZ will result in different dissolution and bioavailability profiles due to the crystal properties during the crystallization technique. The nature and extent of these changes depend on the crystallization conditions such as presence of impurities, type of solvent and cooling rate.

2.4.4 Dissolution enhancing methods

An understanding of the polymorphism of CBZ and the influence of various excipients on the polymorphic transitions is critical to the development and performance of its solid dosage forms and ultimately its bioavailability.

By nature, CBZ is a poorly water soluble drug and many methods have been used to achieve higher dissolution rates. These included the respective uses of polyethylene glycol (PEG) and povidone dispersions [37], PEG, phospholipids, hydroxypropyl-ß-cyclodextrins (HPßCD) [12], polyvinylpyrrolidone K30 (PVP-K30) CBZ dispersions by conventional solvent evaporation and supercritical methods [44] as well as spray drying technology to enhance CBZ microparticle homogeneity [24].

Thus, although there are means to increase dissolution rates of poorly water-soluble drugs, it is crucial to be able to adequately identify and characterize drug polymorphism and crystallinity with therapeutic, formulation, legal and commercial implications in mind.

2.4.5 Techniques for analyzing solid state of drugs

In order to deal with the polymorphic nature of compounds from an early developmental stage to in-line monitoring of the solid state forms during production, it must be possible to rapidly and reliably detect and quantify the solid state properties of the drugs, both alone and in pharmaceutical dosage forms. Characterization ideally should involve investigation with several techniques, since each technique provides different information about the characteristics of the solid form.

Investigations may probe the particulate level, i.e. the properties of the crystalline structure, including X-ray diffraction (XRD), polarizing light microscopy and scanning electron microscopy, and thermal analytical techniques (thermogravimetric analysis); molecular level, i.e. the properties of the molecule itself, such as vibrational spectroscopy (Fourier Transform Infrared spectroscopy) and also the bulk level, such as solubility, micromeretics and flow properties.

2.5.1 X-Ray Powder Diffraction (XRPD)

X-rays are electromagnetic radiation lying between ultraviolet and gamma rays in the electromagnetic spectrum. Diffraction is a scattering phenomenon whereby x-rays are scattered in all directions when incident on crystalline solids. This phenomenon is described by Bragg's law which states that diffraction (constructive interference) can occur only when waves that are scattered from different regions of a crystal, in a specific direction, travel distances differing by integral numbers (n) of the wavelength (λ). Under such circumstances, the waves are in phase as described by the Bragg equation

$$\frac{n\lambda}{2 \sin \theta} = d_{hkl}, \qquad (2)$$

in which d_{hkl} represents the interplanar spacings and θ is the angle of diffraction. The spacings between and the relative intensities of the diffracted maxima can be used for qualitative and quantitative analysis of crystalline materials [45].

A solid substance can be classified as being crystalline, noncrystalline or a mixture of the two forms. In crystalline materials, the molecular or atomic species are ordered in a three dimensional array, called a lattice, within the solid particle. The latter ordering of molecular components is lacking in noncrystalline material. It is also possible for order to exist in only one or two dimensions, resulting in mesomorphic phases (liquid crystals). The relatively random arrangement

of molecules in noncrystalline substances make them poor coherent scatterers of x-rays, resulting in broad, diffuse maxima in diffraction patterns. Their crystalline counterparts yield sharply defined diffraction patterns [45].

In a fine powder, the different crystal faces are oriented randomly in all possible directions at the powder interface. This provides the basis for x-ray powder diffraction (XRPD), as the diffraction of this surface provides information on all possible atomic spacings in the crystal lattice. A single atom scatters an incident beam in all directions, and it is the structured crystal lattice that allows the diffraction only in a few directions. Therefore, if the structure lacks as in the amorphous state, scattering at all angles is detected.

X-ray powder diffractometry is widely used for the identification of solid phases. The x-ray powder pattern of every crystalline form of a compound is unique, making this technique particularly suited for the identification of different polymorphic forms of a compound [6]. To this end, XRPD spectra for CBZ and its polymorphs are well documented [12, 18, 23, 26, 30, 36, 37, 38, 39, 43, 44].

2.5.2 Fourier Transform Infrared (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) is an analytical technique used to identify organic (and in some cases inorganic) materials. This technique measures the absorption of various infrared light wavelengths by the material of interest. These infrared absorption bands identify specific molecular components and structures.

Absorption bands in the range of 4000 - 1500 wave numbers are typically due to functional groups (e.g. -OH, C=O, N-H, CH3, etc.). The region between 1500 - 400 wave numbers is referred to as the fingerprint region. Absorption bands in this region are generally due to intra-molecular phenomena, and are highly specific for each material. The specificity of these bands allows characterization of individual compounds to be performed. Various authors have used this method to generate fingerprints of the CBZ polymorphs for evaluation of the physicochemical characteristics [18, 30, 38, 43, 44].

In summary, CBZ has become a model drug to study the phenomenon of polymorphism. Various factors influence polymorph generation which translate into various physicochemical characteristics which in turn affect dissolution and bioavailability properties of the final dosage form. XRPD and

FTIR spectral analysis have emerged as powerful tools in evaluating polymorphic transitions of compounds including CBZ and form the basis of this project.

CHAPTER 3

Aims of the study

3.1 Objective of this study

The overall aim of this study was to evaluate and compare the polymorphic characteristics of carbamazepine (CBZ) following microwave drying of granules prepared by a wet granulation process and compression into tablets, to that obtained by convection drying.

3.2 Hypothesis

Microwave drying does not change the polymorphic characteristics of CBZ contained within granules and compressed tablets produced by a wet granulation process.

3.3 Study approach

The overall approach was to evaluate and compare spectroscopic data from granules and compressed tablets for the same batch dried by two different techniques (microwave –and convection oven). Both sets of data were screened against standard spectra generated for the selected polymorphs. The hypothesis would be supported if there was no or minor difference in the data obtained between the different drying techniques.

In addition, the compressed tablets from each drying method were evaluated according to the British Pharmacopendial (BP) [5] standards and the results compared to determine if any differences existed between them.

Thus, the specific objectives to be addressed included:

3.3.1. The preparation and spectroscopic characterization of three distinct CBZ polymorphs (alpha, beta, dihydrate) which served as standards.

3.3.2. Performing pre-formulation studies to determine a basic formula for tabletting.

3.3.3 Standardization of a commercial microwave oven with respect to temperatures achievable at different power settings over time.

3.3.4 The manufacture of the CBZ granules using a high shear granulator.

3.3.5 Compression of granules into tablets using a Manesty® single punch tablet press and the pharmaceutical evaluation of tablets as per BP [5] guidelines.

CHAPTER 4

Preformulation

4.1 Introduction

This chapter details the equipment, materials and methods used in the preformulation studies of CBZ and the excipients, as well as a discussion based on the results obtained.

4.2 Equipment and materials

The following equipment was used:

Light microscope (*Nikon Monocular Model Sc, Japan*); Stage micrometer (*Graticules Ltd, Tonibridge Kent, England*); Eyepiece micrometer (*Olympus, Japan*); Test sieves (*Edecott Ltd, London, England*); Test sieve shaker (*Edecott sieve shaker, E.F.L. 1MKII, London, England*); Balance (*Auhaus, Germany*); Angle or repose instrument (*UWC, South Africa)*; Bulk Density apparatus (*UWC, South Africa*); XRPD Diffractor (*D8 Advance Bruker AXS, Germany*); FTIR Spectrophotometer (*Perken-Elmer Paragon 1000, United States of America*); Moisture Balance (*Metler Toledo LJ16, Greifensee, Switzerland*); TGA analyser (*Rheometric Scientific ® STA 1500, United States of America)*; Hardness tester (*Type Ptb 301 Erweka, Pharma Test, Hainburg, West Germany*).

The following materials were used:

Carbamazepine (ß-form), Tablettose® and Explotab® were gifts provided by Aspen Pharmacare, Port Elizabeth, South Africa.

Magnesium stearate, Aerocil ®, Kollidon CL ® and ethanol (99,9%) were stock items from the University of the Western Cape (UWC), South Africa. These materials were all obtained from Protea Chemicals, Killarney Gardens, Cape Town, South Africa.

4.3 Preformulation Studies

Preformulation is a preliminary study that involves the evaluation of the physico-chemical properties of the active pharmaceutical ingredient(s) and excipients which would ultimately lead to a recipe for the manufacture of a dosage form. Since CBZ is an established drug, only certain evaluatory tests were done.

4.3.1 Identification of carbamazepine

Carbamazepine was identified by the method stipulated in the BP 1973 [4] whereby the powder (0.1 grams) was dissolved in nitric acid (2 ml) and placed in a water bath for 3 minutes.

4.3.2 Assay of carbamazepine

Carbamazepine powder was assayed according to the BP [5] specifications which specifies that CBZ powder should contain not less than 97% and not more than 103% of 5H-dibenz [b,f] azepine-5-carboxamide.

Method:

Dissolved 0.1000 grams of CBZ powder in methanol and diluted to 100 ml with the same solvent.

- Diluted 5.0 ml of this solution to 50 ml with methanol.
- Diluted 5.0 ml of the latter solution to 50 ml with methanol.
- Measured the absorbance (2.2.25) at the maxima at 285 nm.
- Calculated the content of $C_{15}H_{12}N_2O$ taking the specific absorbance to be 490.

The Beer-Lambert equation was used to determine the concentrate of the analyte in grams/100 ml using

$$C = A / A(1\%, 1cm) \qquad (3)$$

where

A = measured absorbance

A (1%, 1cm) = the absorbance of a 1% w/v (1grams /100 ml) solution in a 1 cm cell

b = pathlength in cm (usually 1 cm)

c = concentration of sample in grams/100 ml

4.3.3 Solubility

No solubility tests were performed since the data for CBZ are well documented [4, 5, 29, 45].

4.3.4 Particle size analysis

The particle size of a drug fundamentally affects dose uniformity and dissolution rate in a solid dosage formulation. Small particles are particularly important in (1) low dose, high potency candidates since large particle populations are necessary to assure adequate blend homogeneity and (2) for any drug whose aqueous solubility is poor (<1mg/ml) since the dissolution rate is directly proportional to surface area (particle size). Cohesion, adhesion and powder flow are also dependant on particle size. The particle size of CBZ was analyzed using a light microscope as well as classified by sieve analysis.

4.3.4.1 Microscopic method

Method

Added 0.1 grams of sample to 10 ml glycerol and dispersed it using a glass rod. Transferred 1 drop onto a glass slide and placed a cover slip onto the droplet to exclude air bubbles. A Nikon® monocular light microscope, fitted with an Olympus® eyepiece micrometer, was used to determine the shape and size of one hundred particles randomly selected from different areas on the slide. The microscope's ocular eye piece was calibrated with a stage micrometer, which had a linear graduated scale where one eyepiece division equaled ten micrometers. The ocular was then used to read the diameters of particles on a slide.

If the particles were spherical, then only one dimension was measured. For shapes other than spherical, the Heywood ratio for elongation (N) was used where the length (L) and breadth (B) of the particles were determined using the following equation.

$$N = L/B \qquad (4)$$

4.3.4.2 Sieve method

Standards for powders are provided in pharmacopoeiae, which indicate that the degree of coarseness or fineness of a powder is differentiated and expressed by reference to the nominal mesh size of the sieves used. Five grades of powder are specified and defined in the BP [5] as reflected in Table 1.

Table 1. Powder grades specified in British Pharmacopoeia [5].

Powder description	Requirement
Coarse powder	Not less than 95% by weight passes through a number 1400 sieve and not more than 40% by weight passed through a number 355 sieve.
Moderately fine powder	Not less than 95% by weight passes through a number 355 sieve and not more than 40% by weight passed through a number 180 sieve.
Fine powdery	Not less than 95% by weight passes through a number 180 sieve and not more than 40% by weight passed through a number 125 sieve.
Very fine powder	Not less than 95% by weight passes through a number 125 sieve and not more than 40% by weight passed through a number 90 sieve.

Sieves provide mechanical barriers allowing separation of particles on the basis of sizes down to 38um (400 mesh), subsieve material fall in the range of from 1-38um. In the present study, a nest of sieves having numbers of 500, 355, 180, 125 and 90 μm were successively mounted in descending size order on an Endecott® sieve shaker. The course 500 μm sized sieve was on top and the finer 90 μm sized sieve was at the bottom. Ten grams of CBZ powder was placed on the top sieve, closed with a sieve pan and switched on to operate shaking for 30 minutes. The amount of powder collected on each sieve was weighed and the percentage (w/w) of each powder fraction determined.

4.3.5 Powder flow

Powder flow can be evaluated by bulk density measurements and angle of repose. These measurements are useful derived parameters for assessing the impact of changes in drug bulk, as new batches become available. Changes in particle size and shape (crystal morphology) will immediately be apparent. Increase in crystal size or a more uniform shape will lead to a smaller angle and Carr's index. Milling will result in poorer flow as internal bridging occurs and the angle and Carr's index increase [49].

The angle of repose was measured whereby the powder was allowed to flow through a funnel onto a horizontal surface beneath. The angle of the conical heap yields the angle of repose as indicated by the following equation [46]:

$$\text{Tan } \theta = h/r \quad (5)$$

Where

Tan θ = tangent of the angle

h = height of the heap (cm)

r = radius of the base of the heap

Apparatus:

The apparatus used consisted of a laminated sheet of concentric graph paper which served as the base. An open-ended glass cylinder with an internal diameter of 23 mm and a height of 80 mm held the powder. A mechanical arm was used to lift the glass cylinder while a fitted cathetometer was used to measure the height of the cone of powder [46].

Figure 1. Angle of repose apparatus.

Method:

The powder was carefully poured into the glass cylinder up to a predetermined graded level. The glass cylinder was carefully lifted with the mechanical arm which allowed the powder to flow onto

base. The concentric circles were used to measure both the smallest (r1) and biggest (r2) radius of the base of the powder cone. The height (h) of the cone was measured with the cathetometer. This process was done in duplicate where after the angle of repose was calculated from equation 5. The factor "r" for this equation is given by the formula:

$$r = r1 + r2 / 2 \quad (6)$$

4.3.6 Density

Neuman (1967) and Carr (1965) [49] developed a simple test to evaluate flowability by comparing both the initial (fluff) and final (tapped) bulk volumes and the rate of packing down. Bulk density measurements are an indirect method used to characterize powder flow. The bulk density (Pb) of a powder is a characteristic of the powder, rather than the individual particles. This is given by the mass, m, of the powder occupying a known volume, v, according to the relationship:

$$Pb = M/V \text{ kg.m } (\text{ Density} = M/V) \quad (7)$$

The bulk density of a powder is differentiated from the particle density or true density of its component particles. The powder contains inter-particulate pores, while individual particles are an entire solid. Therefore a powder can have a single particle density but various bulk densities, depending on the packing of the powder bed and pack consolidation. When a reduction in bulk density occurs, the greater inter-particulate forces and arching of powders take place. Therefore, the powder is more resistant to flow [2, 9].

Fassihi, and *Kanfer* [13] evaluated the effect of compressibility and powder flow properties of various directly compressible powders as well as a three component powder mixture. While it was established that particle size has a significant effect on uniformity of flow, the data also indicated that when the compressibility index exceeded a value of about 20% a significant increase in tablet weight variation resulted irrespective of the powder flow rate.

Method

Four grams of the CBZ powder were poured into a 10 cm glass measuring cylinder. The volume of the powder was read (V loose). The motor of the tapping contraption was switched on at 100 rpm for 12,5 minutes (1250 revolutions).The volume of the powder was read afterwards (V packed).

This procedure was carried out in triplicate to determine an average tapped density. Carr's compressibility index was then determined by using the following equation:

$$\text{Compressibility (\%)} = \frac{\text{Tapped density (Pt)} - \text{Loose density (Pb)}}{\text{Tapped density (Pt)}} \times 100 \quad (8)$$

Where

$$\text{Loose density (Pb)} = \text{Weight of powder / Loose volume} \quad (9)$$

$$\text{Tapped density (Pt)} = \text{Weight of powder / Tapped volume} \quad (10)$$

In this method, the powder was tapped down in a measuring cylinder by means of a constant velocity cam. A change in packing volume occurred when the void spaces were diminished. The initial bulk volume was expressed as the loose volume which was reduced to the packed (tapped) volume. Carr's compressibility index gives a direct measure of the potential arch or bridge strength. Powders with a low bulk density tend to give relatively small tablets.

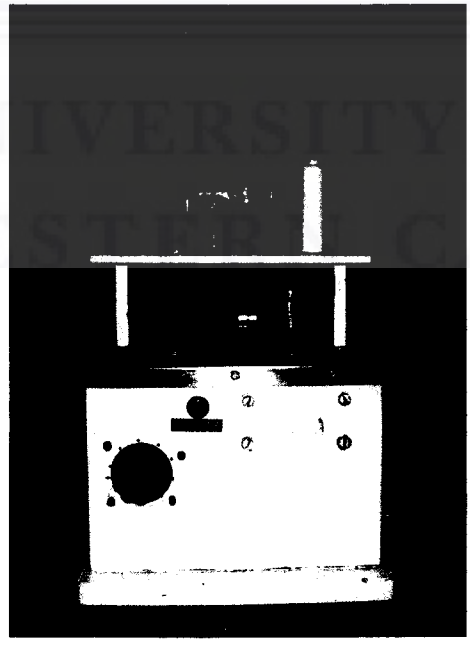

Figure 2. Bulk density apparatus.

Table 2. Carr's index (1965) as an indication of powder flow properties.

% Compressibility	Flow description
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
> 40	Extremely poor

(Table 2 adapted from reference 49)

Changes in particle size and shape will be immediately apparent. Increases in crystal size or a more uniform shape will lead to a smaller angle of repose (θ) and Carr's index. Milling will result in poorer flow as internal bridging occurs and the angle of repose (θ) and Carr's index increase.

Table 3. Relationship between angle of repose (θ) and powder flow.

Angle of repose (θ)	Flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Poor

(Table 3 adapted from reference 49)

4.3.7 Moisture content

The amount of moisture present in tablet excipients can have an influence on the compression capability of the excipients. When the amount of moisture present on the powder surface is just sufficient to fill the remaining voids in the bed, an increase in compression force will result in a decreased porosity with water being squeezed out onto the surface of the tablet. The expelled moisture can act as a lubricant at the die wall. Too much moisture may cause the material to stick to the punch surface as well as cause flow problems prior to compression. Too little moisture produce poorly formed compacts or tablets which cap easily.

4.3.7.1. Moisture Balance Method

A Mettler Toledo® moisture balance with an infrared heating unit was employed to automatically calculate the percentage moisture content

Method.

Sprinkled 1 gram of powder onto the surface of the aluminium pan of the balance and set the balance to "automatic" whereby the mass was heated at 90° C by the infrared heat source and maintained until a constant mass was reached. Took the final mass reading and determined moisture content with the following equation:

$$\% \text{ Moisture content} = \text{Moisture mass / Wet mass x } 100 \quad (11)$$

where

$$\text{Mass of moisture} = \text{Initial mass(wet) - final mass (dry) of sample} \quad (12)$$

4.3.7.2 Thermogravimetric Analysis (TGA)

Thermogravimetric analysis (TGA) is a measure of thermally induced weight loss of a material as a function of the applied temperature [12]. This method is useful in the determination of desolvation processes and compound decomposition whereby the total volatile content of a solid can be determined. When a solid is capable of decomposing by means of several discrete, sequential reactions, the magnitude of each step can be separately evaluated

The thermal behavior of the commercial CBZ sample as well as the two CBZ polymorphs was studied by means of a Rheometric Scientific ® STA 1500 analyser under dry nitrogen purge (20 ml/minute) over a temperature range of 40°-210° C at a heating rate of 40° C per minute. The instrument had a maximum heating temperature of 1500°C and was calibrated with indium (99.99%) having a melting point of 156.5° C and a heat of fusion of 28.45 $J.g^{-1}$ (at 40° C per minute). The CBZ powder sample was placed in the sample holder, inserted into the machine and switched on. The resulting thermal scan was recorded. The same procedure was followed for the two CBZ polymorphs respectively.

4.3.8 Compressibility

Compression characteristics of drugs are very useful since some drugs require inclusion of compression aids. A simple method described by Wells [49] determines whether a drug behaves plastically or elastically. In doing the latter, it would become apparent the type of vehicles to be used. Thus, if the drug has a high dose and behaves plastically, then the excipients should fragment. Examples of fragmenting excipients include lactose and dicalcium phosphate. If the drug is brittle, then the excipients should be plastic, such as microcrystalline and binders in wet granulation. Thus, although tabletted material should be plastic, capable of permanent deformation, it should also exhibit some degree of brittleness (fragmentation).

Method :

Weighed three 500 mg aliquots of drug and 5 mg (1%) magnesium stearate as lubricant and blended two samples with lubricant for 5 minutes (A and B) and the third (C) for 30 minutes by tumble mixing in a tubuhaler. Loaded sample A into the punch and die set of a Manesty® single punch tablet press on a compression setting of 35 and compressed manually, held for 1 second and released. Ejected the compact and stored in a sealed container at room temperature overnight to allow equilibration. Repeated the same procedure with sample B, but held the load for 30 seconds before releasing the pressure. Compressed sample C in precisely way as in A.

Following storage of each compact, it was crushed on a hardness tester and recorded the compact crushing strength (kg force, kP).

Table 4. Interpretation of crushing strength results.

Comparison	Plastic	Fragmenting
A and B if the strength of	A < B	A = B
A and C if the strength of	A > C	A = C
A with B with C	C < A < B	A = B = C

When materials are ductile, they deform by changing shape (plastic flow). Since there is no fracture, no new surfaces are generated during compression and a more intimate mix of magnesium stearate leads to poorer bonding as in the case of C [49]. Since these materials bond by visco-elastic

deformation and this is time-dependant, increasing the dwell time at compression B will increase bonding and strength. If a material is predominantly fragmenting, neither lubricant, mixing time(C) or dwell time (B) should affect the tablet strength.

Elastic materials do not undergo permanent change during compression (neither plastic flow nor fragmentation) and rebounds when the compressive force is released. If the bonding is weak, the compact will self-destruct and the top will detach (capping) or the whole cylinder will layer (lamination). An elastic body may under A, cap; B, probably maintain integrity but will be very weak or C, cap or laminate. Elastic material require a plastic tableting matrix or wet granulation to induce plasticity [49].

4.3.9 Selection of excipients

A simple tablet formula was to be developed with common pharmaceutical excipients which would produce tablets of suitable quality. The formula would comprise of CBZ, a diluent (lactose or dicalcium phosphate), binder solution (ethanol or water), disintegrant (sodium starch glycolate), lubricant (magnesium stearate) and glidant (silicone dioxide).The selection of excipients depended on the compression characteristic of CBZ, whether it fragmented or not.

4.3.10 Crystallization of carbamazepine polymorphs

Methodology employed by Lefebvre and Guyot-Hermann [26] was used to generate alpha- and dihydrate polymorphs.

4.3.10.1 Beta polymorph (ß-form)

The commercial CBZ was used as the beta polymorph (ß-form) and stored in an air-tight container.

4.3.10.2 Alpha polymorph (a-form)

This form was prepared by heating the ß-form for 2 hours at 170° C.

4.3.10.3 Dihydrate polymorph (DHD-form)

This form was prepared by dispensing the a-form in distilled water. The suspension was left to settle for 15 days in an oven at 43° C. The resultant needle shaped crystals were filtered and left to air dry at below 20° C in open air where after it was stored in a stoppered bottle.

4.3.11 Methodology to study polymorphism

4.3.11.1 X-Ray Powder Diffraction (XRPD)

The main characteristics and setting parameters for the D8 Advance Bruker AXS diffractor were Ni filtered CuK a radiation ($\lambda = 1.5418$ Å); power voltage of 40 kV; tube current of 40 mA; time constant of 15 seconds per position; angular speed 1° (2° Ø) per minute; using divergent and anti-scatter slits, sodium iodide scintillation counter, graphite monochromater and an angular range of $0 < 2° Ø < 40°$. The sample holder was consecutively filled with the respective powders and gently levelled before insertion into the diffractor. Measurements were automated at the parameters outlined above.

4.3.11.2 Fourier Transform Infrared (FTIR)

A Perkin-Elmer Paragon 1000 FT-IR instrument fitted with Cesium Iodide beam splitter and controlled with Spectrum® software were used in the sample analysis. Scanning parameters used a 4 cm^{-1} resolution with weak apodization. The data region was 4000-400 cm^{-1} and the number of scans per spectrum was 20. The samples were gently ground with potassium bromide (KBr), inserted into the sample holder and analyzed directly in the DRIFT mode.

4.3.12 Drying Methods

Two methods for the drying of the CBZ granules include static convection drying (convection oven) and radiation drying (microwave oven).

4.3.12.1 Convection Oven

A fifty liter forced air circulation Memert® convection oven was preheated to 60° C before any samples were dried at that temperature.

4.3.12.2 Microwave Oven & Standardization

The microwave oven was standardized whereby each of nine CSN® beakers containing 100 ml distilled water was placed on designated positions on the rotating base inside the microwave oven. The distilled water was subjected to microwave settings of one hundred percent power (HL100) for 30 seconds. The temperature of the distilled water was immediately measured with a thermometer and recorded. The same procedure was followed for the other eight samples on the different

locations on the rotating base. In this way it could be determined whether there was any variation in the electric field and hence, whether there existed a homogenous distribution of energy quanta throughout the microwave heating cavity.

In addition, the temperatures achievable at the different heat settings for different time periods were determined by the same procedure as outlined above. The power setting selected for this investigation was 100% (PL100) which yields the highest irradiation and thus allowing distinctive polymorphic determinations to be measured, if any should occur. Also, since distilled water was used as the medium to determine the temperatures achieved at varying power settings, ninety seconds at 100% power was selected as the maximum since water has a boiling point of 98°C making further irradiation pointless since the temperature would not rise above the boiling point.

4.4 Results and Discussion

4.4.1 Identification of carbamazepine

Carbamazepine is a dibenz[*b,f*] azepine-5-carboxamide, appearing as white to yellowish white crystalline powder, almost odourless with a slightly bitter taste [5].

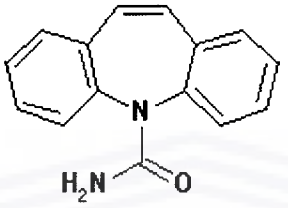

Figure 5. Chemical structure of carbamazepine.

Carbamazepine was positively identified by the characteristic orange colour that was produced.

4.4.2 Assay of carbamazpine powder

The assay for $C_{15}H_{12}N_2O$ yielded a purity of 98%.

4.4.3 Crystallization of carbamazpine polymorphs

The particle shape and melting point characteristics of the different polymorphic forms of CBZ are depicted in table 5.

Table 5. Main characteristics of the different forms of carbamazepine studied.

Property	β form	α form	Dihydrate
Behaviour when heated	Melting point between 176˚ -190˚ C	MP 190˚ C	Dehydration from 40˚ -75˚ C
Particle Shape	Ground needles	Narrow needles	Needles

4.4.4 Solubility

Carbamazepine is practically insoluble in water and ether, soluble 1in 10 of alcohol and 1 in 10 of chloroform and soluble in acetone.

4.4.5 Particle size analysis

4.4.5.1 Microscopic method

An Elongation and Haywood ratio of 1.31μm with a standard deviation (SD) of 0.37 was obtained. The length (L) and breadth (B) were 50.6μm (SD=24.89) and 39.3μm (SD=18.34) respectively. The individual results are listed in appendix 1.

4.4.5.2 Sieve method

The results of the sieve analysis for CBZ and the excipients are depicted in table 6.

Table 6. Sieve analysis of the active and other tablet excipients.

Sample	Grade
Carbamazepine (CBZ)	Moderately fine
Lactose (Tablettose ®)	Fine
Sodium starch glycolate (Explotab®)	Very fine
Polyvinylpolypyrrolidone (Kollidon CL ®)	Fine
Magnesium stearate	Very fine
Silicone dioxide (Aerocil®)	Very fine (200 μm)

4.4.6 Powder flow

The powder flow characteristics of CBZ and the other excipients are depicted in table 7 while the individual findings for the respective compounds are listed in appendices 1-7.

Table 7. Flowability (angle of repose) of CBZ and other excipients.

Sample	Ave. Height (cm) n=3	Ave. Radius (cm) n=3	Ave. Angle of repose (°) ± SD n=3
CBZ	2.03	3.15	32.90 ± 2.83
Explotab ®	1.59	3.57	24.07 ± 2.94
Tablettose ®	1.97	3.46	29.72 ± 2.41
Magnesium stearate	1.62	3.37	25.69 ± 3.42
Kollidon CL®	1.70	3.22	27.91 ± 2.60

4.4.7 Density

Carr's compressibility index for CBZ is listed in table 8.

Table 8. Density and compressibility index of CBZ.

Sample no.	Loose density (g/ml)	Packed density (g/ml)	Carr's % compressibility
1	0.42	0.45	5.61
2	0.40	0.41	3.00
3	0.40	0.42	3.80
Ave ± SD (n=3)	**0.41 ± 0.01**	**0.43 ± 0.02**	**4.14 ± 1.34**

4.4.8 Moisture content

The moisture content of CBZ and its excipients as determined with a moisture balance are shown in table 9.

4.4.8.1 Moisture Balance

Table 9. Moisture content of active and excipients.

Compound	Moisture Content Ave % ± SD (n=3)
β-CBZ	0.02 ± 0.06
α-CBZ	0.03 ± 0.05
DHD- CBZ	13.0 ± 2.02
Tablettose ®	0.5 ± 0.94
Explotab®	8.02 ± 0.95
Kollidon ®	6.02 ± 0.85
Aerosil®	2.1 ± 1.01
Magnesium stearate	3.01 ± 1.11

4.4.8.2 Thermogravimetric Analysis (TGA) of CBZ

The thermogravimetric analysis of commercial CBZ (β-form) is depicted in figure 6. This ß- form started melting at 170° C resulting in a weight loss of 0.2 grams which equated to a 0.9% moisture content. The scan also indicated that no desolvation of solvent or water occurred prior to 170° C, which was indicative of the low moisture content. Vapourisation of the compound progressed steadily beyond 220° C.

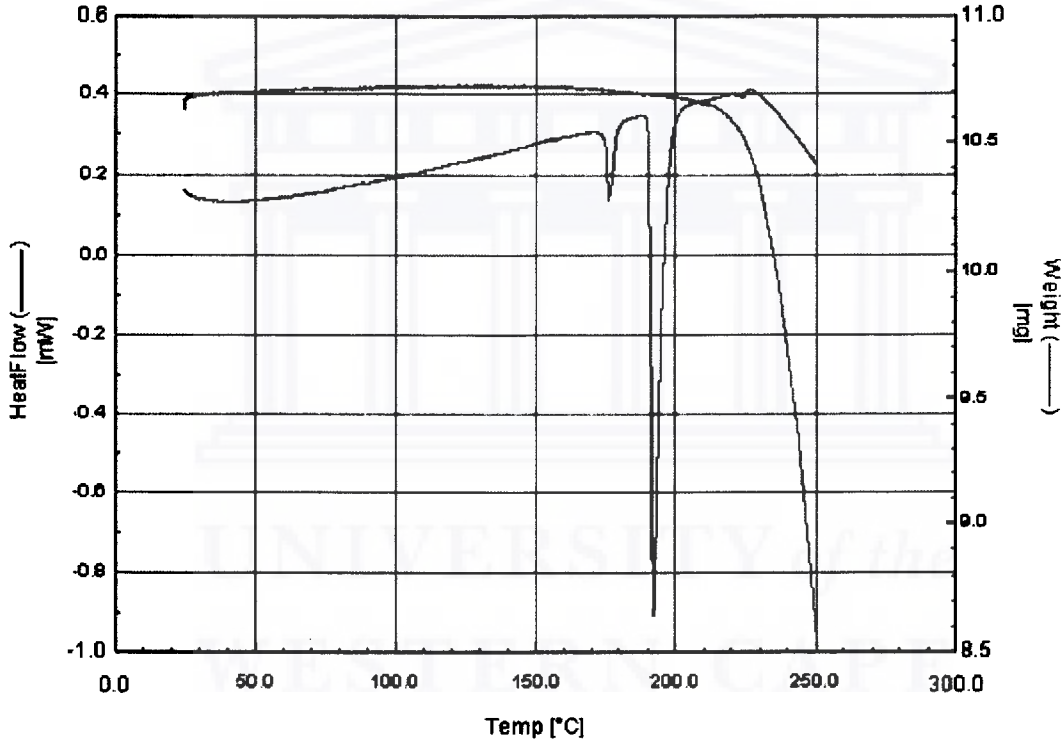

Figure 6. Thermal scan of the commercial CBZ powder (β-form).

Figure 7 shows the thermal scan of the a-CBZ polymorph that started melting at 190° C resulting in a weight loss of 0.1 grams which equated to a 0.79% moisture content. The scan also indicated that no desolvation of solvent or water occurred prior to 190° C, which was indicative of the low moisture content. Vapourisation of the compound progressed steadily beyond 200° C.

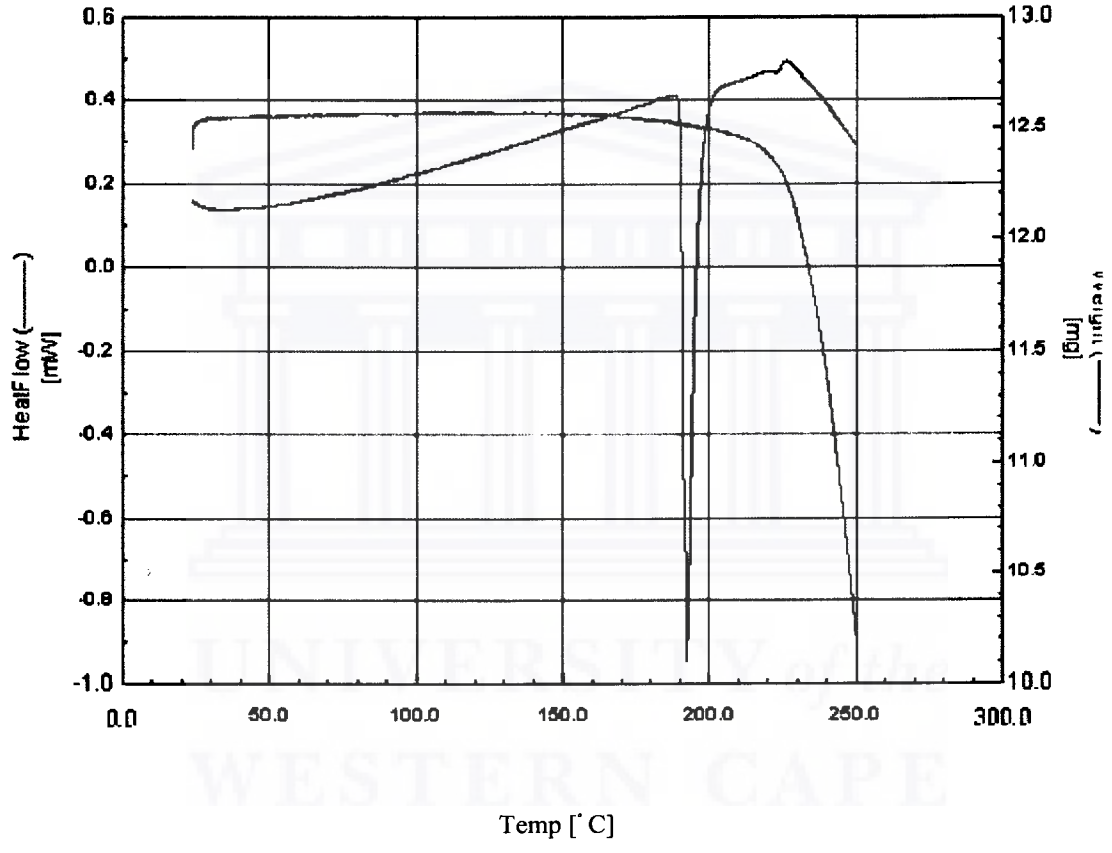

Figure 7. Thermal scan of the a-CBZ polymorph.

The thermogravimetric analysis of the dihydrate (DHD) CBZ polymorph is depicted in figure 8.

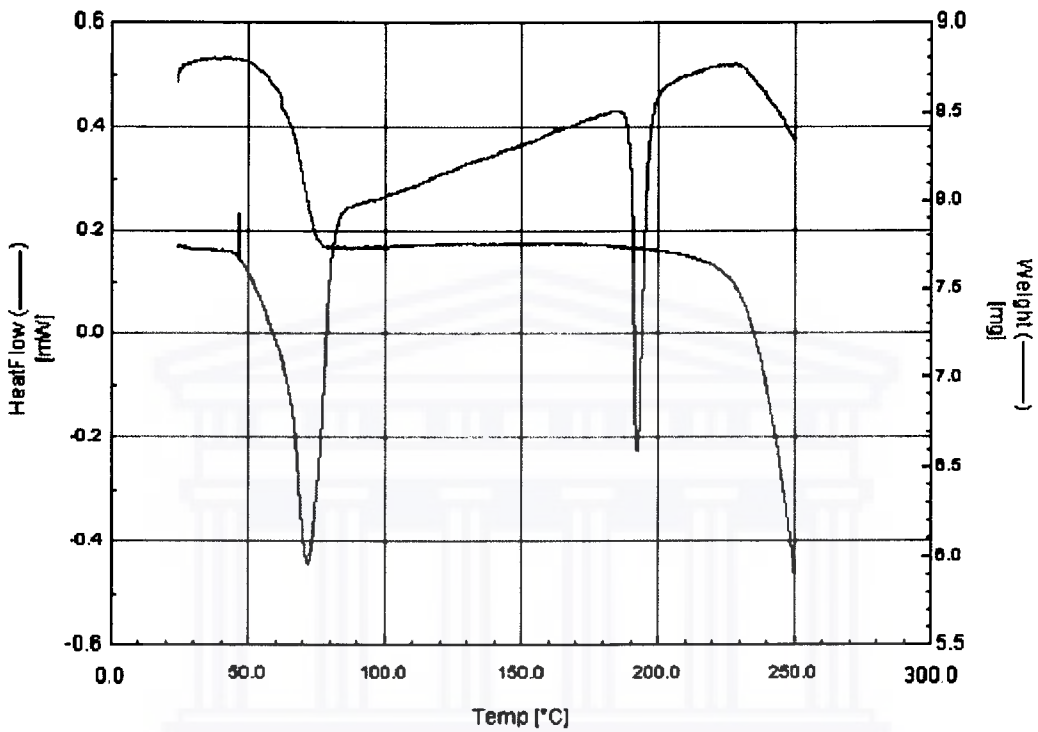

Figure 8. Thermal scan of the DHD-CBZ polymorph.

The dihydrate CBZ polymorph showed desolvation occurring between 40° C and 75° C resulting in a mass loss of approximately 11.3%. The latter loss in mass can mainly be attributed to the volatization of water since it was the only solvent used in the conversion of the a-CBZ polymorph to the dihydrate CBZ polymorph.

The results obtained with the thermogravimetric analysis compared well with results obtained with the moisture balance. The TGA offers some advantage over the moisture balance in that apart from yielding the loss in mass, an indication of the type of solvent being lost, is also eluded to. The latter could be identified in the difference in boiling point temperatures among the different solvents.

4.4.9 Compressibility

Compression characteristics of CBZ powder are summarized in table 10.

Table 10. Compaction characteristics of CBZ.

Sample no.	Compression force setting	Hardness (N)
A	35	13
B	35	18
C	35	8

CBZ exhibited plastic flow since the hardness of Sample A was greater than C but smaller than B. Thus, if the drug has a high dose and behaves plastically, then the excipients should fragment. Examples of fragmenting excipients include lactose and dicalcium phosphate. If the drug is brittle, then the excipients should be plastic, such as microcrystalline and binders in wet granulation. Thus although tabletted material should be plastic, capable of permanent deformation, it should also exhibit some degree of brittleness (fragmentation).

4.4.10 Formulation development

According to the BP [5], criteria for fast release CBZ tablets include a disintegration time of within 5 minutes and a 70% release of the active ingredient within 45 minutes. The United Stated Pharmacopoeia (USP) [45] also specifies a disintegration time of 5 minutes, but requires an 85% CBZ release after 40 minutes.

4.4.11 Selection of excipients

Selection of excipients was carefully considered based on the physicochemical characteristics of CBZ as well as the tablet criteria.

Since CBZ is practically insoluble in water and it has been established that the drug behaves plastically, the excipients should fragment and be soluble in water.

4.4.11.1 Diluent

There is an old pharmaceutical adage that insoluble drugs should be formulated with soluble fillers (e.g. lactose) and soluble drugs should be formulated with insoluble fillers (e.g. dicalcium phosphate). The reason for the former would seem logical from dissolution considerations, but

happens to be true in the latter case as well. If a soluble drug substance is formulated with lactose, then during the dissolution process, there is a tendency for gel formation about the drug particle and this may hinder the dissolution.

Anhydrous lactose (Tabletose®) was selected as diluent since it is soluble in water, fragments during compression, showed good stability, good flowability and low hygroscopicity. In addition it is chemically inert and compatible with CBZ [18].

4.4.11.2 Binder

A solution binder containing 5 % polyvinylpolypyrrolidone (Kollidon CL®) in ethanol (99%) was selected due its improved adhesive properties. In addition, the ethanol would dissolve some of the CBZ as well as evaporate quicker than water during drying. Ethanol (8.6) has a higher loss factor than that of water (6.1), meaning that ethanol can absorb more microwave energy than water [15]. In addition, by omitting water from the formula limits the possibility of the dihydrate polymorph from forming [36]. Thus, the loss factor is a measure of the ratio of the microwave energy absorbed by individual molecules.

4.4.11.3 Disintegrant

Sodium starch glycolate (Explotab®) was employed as the primary disintegrant. The disintegration action conferred by this compound occurs by the wetting of tablets, the penetration of dissolution liquid into the pore space, the rapid uptake of water followed by rapid and enormous swelling and hence the breakage of the tablet into granules.

Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients, such as lubricants, the disintegrant efficacy of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. The usual concentration of SSG employed in a formulation vary between 2-8 % [45]. In the present study, sodium starch glycolate was employed in a concentration of 10%.

4.4.11.4 Anti-adherent

Silicone dioxide (Aerocil®) was employed as anti-adherent at a concentration of 0.5%. It also possessed some disintegration activity.

4.4.11.5 Lubricant

Magnesium stearate was selected as lubricant owing to its superior lubrication properties and was used in concentrations between 0.5 and 1% in the formulations. The lubricant ensures that tablet formation and ejection can occur with low friction between the solid and die wall. It also provides a glossy shine to tablets which enhances its elegance.

Due to its hydrophobic nature which may retard the dissolution of a drug from a solid dosage form, reducing crushing strength as well as increase tablet friability, the lowest possible concentration was used. Therefore, blending times were carefully controlled.

4.4.12 Tablet formula.

The CBZ content was kept constant at 50% while the lactose (Tablettose®) content varied between 38.5% and 44.5%. The sodium starch glycolate (Explotab®) ranged between 4% and 10%. The remaining part of the formula consisted of PVPP (Kollidon CL®), silicone dioxide (Aerocil®) and magnesium stearate.

Table 11. Fast release CBZ tablet formulae.

Compound	Formula A	Formula B	Formula C
CBZ	50	50	50
Lactose	44.5	40.5	38.5
SSG	4	8	10
5% PVPP-EtOH susp.	qs	qs	qs
Silicone dioxide	0.5	0.5	0.5
Magnesium stearate	1	1	1

Based on the physical tablet characteristics (compression characteristics, hardness, disintegration), formula C was selected as the formula to produce the granules from. The resultant tablets from this formula would be subjected to full pharmaceutical analysis. Although, all three formulae disintegrated fast, Formula A produced tablets that capped easily while formula B was very soft and brittle.

4.4.13 Quantification methods for carbamazepine and its polymorphs

The methods used in the quantification of CBZ and its two polymorphs were X-ray powder diffraction (XRPD) and Fourier Transform Infrared spectroscopy (FTIR) respectively.

4.4.13.1 XRPD

The results of the individual scans for CBZ and its two polymorphs are depicted in figures 9, -10 and -11 and summarized in table 12.

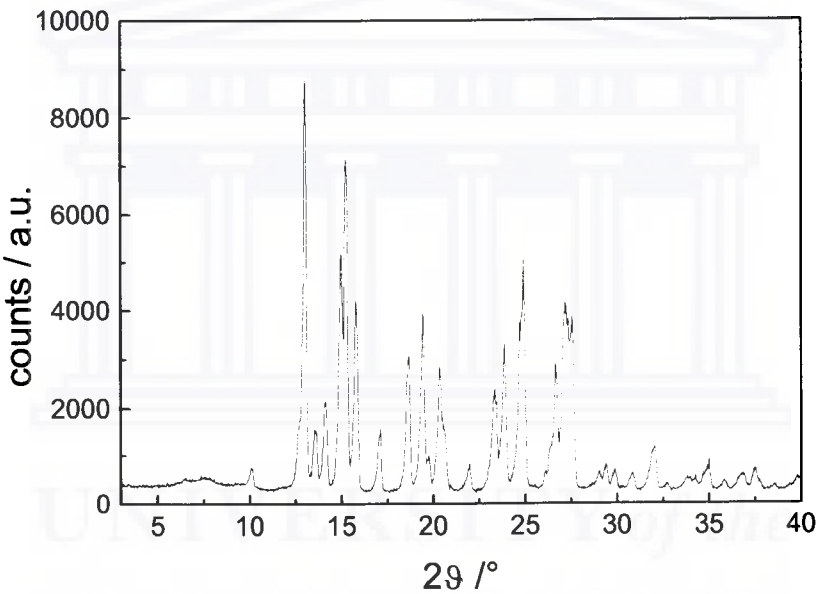

Figure 9. XRPD Scan of commercial CBZ (β form).

For the β form (Figure 9), the characteristic peaks appeared at 12.9° -, 15.4° -, 15.8° -, 18.8° -, 19.6° -, 20.4° -, 23.8° -, 24.8° - and 27.1° 2° Ø.

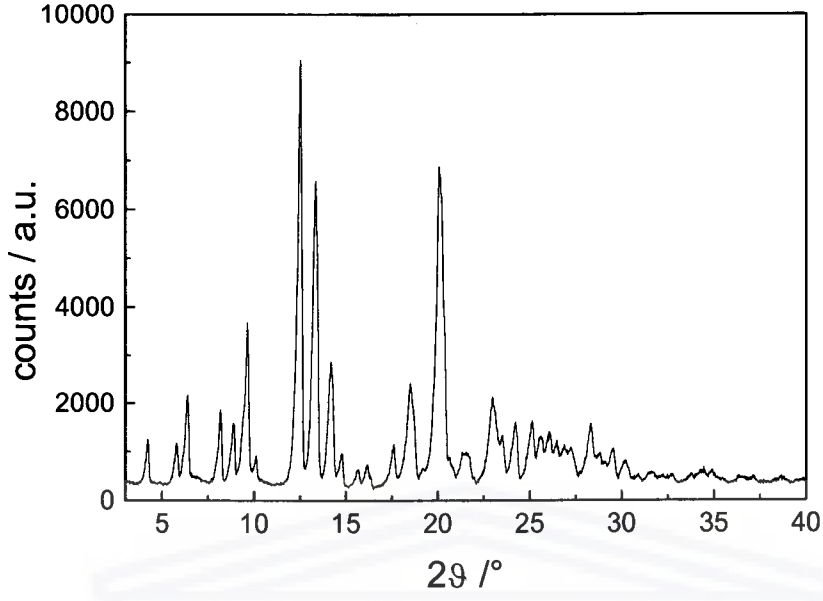

Figure 10. XRPD scan of the a-CBZ polymorph.

Figure 10 revealed that the characteristic peaks for the a-CBZ polymorph were obtained at 6.5° -, 9.6° -, 12.5° -, 13.2° -, 14.2° -, 18.6° -, 20° - and 22.7° 2° Ø respectively.

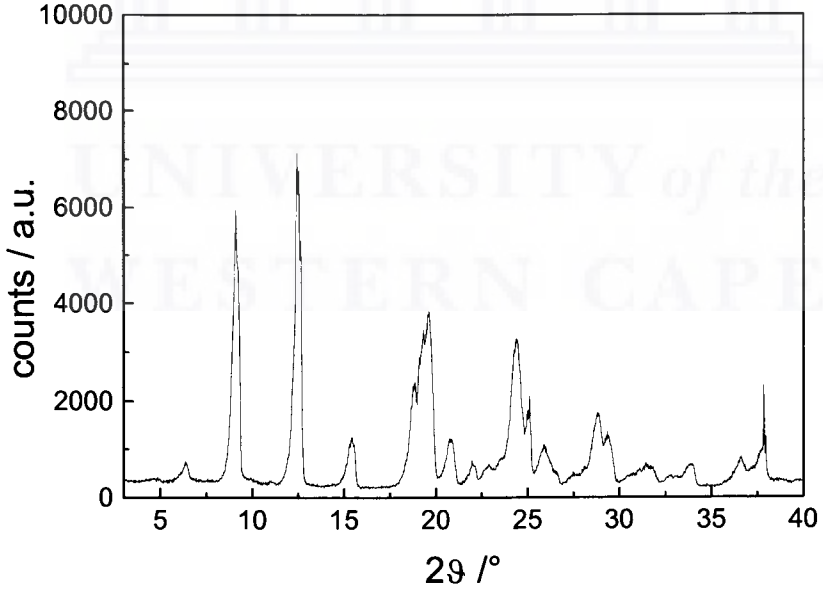

Figure 11. XRPD scan of the DHD-CBZ polymorph.

Figure 11 revealed that characteristic peaks were obtained at 9.2° -, 12.5° -, 15.4° -, 19.6° -, 24.4° -, 28.8° - and 37.9° 2° Ø respectively for the DHD-CBZ polymorph.

Table 12. XRPD peaks for commercial CBZ powder and its polymorphs at 2° Ø

ß-CBZ polymorph	a-CBZ polymorph	DHD-CBZ polymorph
12.9°	6.5°	9.2°
15.4°	9.6°	12.5°
15.8°	12.5°	15.4°
18.8°	13.2°	19.6°
19.6°	14.2°	24.4°
20.4°	18.6°	28.8°
23.8°	20°	37.9°
24.8°	22.7	
27.1°		

From the aforegoing figures and table 12 it became apparent that a clear distinction between the ß-, a- and DHD CBZ polymorphs could be made based on their peak positions.

The ß-form had its first significant peak at 12.9° 2° Ø whereas the a- and DHD-forms had peaks emerging at 6.5° 2° Ø and 9.2° 2° Ø respectively. The ß-form's peaks clustered between 12.9° and 27.1° 2° Ø with fairly significantly identifiable peaks as outlined in table12.

The a-form's peaks were slanted slightly to the left ranging from 6.5°- to 22.7° 2° Ø. The a-form displayed five significant peaks at 6.5°-, 9.6°-, 13.2° , 14.2° - and 22.7° 2° Ø respectively which were completely absent from the ß-form. In addition, the a-form lacked the significant peaks displayed by the ß-form at 15.4° -, 15.8° -, 24.8° - and 27.1° 2° Ø. An overlap of peaks between the ß-and a form were recorded at 12.5° -, 18.6° - and 20° 2° Ø.

The DHD-form was quite significant from the former two polymorphs in that its peaks were spaced fairly intermittently ranging from 9.2° to 37.9° 2° Ø. The latter peaks allow significant differentiation from the other two forms. The DHD form had similar peaks at 9.2° - and 12.5° Ø to that of the a-form but lacked the other significant peaks of this form as outlined in table 12. The DHD form also had overlapping peaks common to the ß-form at peaks 12.5° -, 15.4° -, 19.6° - and 24.4° 2° Ø. A significant identifiable peak in this form was found at 37.9° 2° Ø which was absent from both ß- and a-forms.

Thus, a generalization for distinction between the ß-form and the other two forms in this study can be based on the fact that no significant peaks emerged before 12.9° 2° Ø and none after 27° 2° Ø.

XRPD diffraction values similar to the results obtained for the ß-form in this study, were recorded by Joshi and co-workers [18] for their commercial CBZ form. The characteristic high intensity peaks were detected at 13° -, 15.2°-, 15.8°-, 19° -, 20.5°-, 24° -, 25° -and 27° 2° Ø respectively.

Rustichelli et al [43] recorded diffraction values for their CBZ polymorph I which are similar to the a-form used in this study. Their diffraction values were 6.1° -, 9.4° -, 12.25° -, 19.8° -, 19.90° - and 22.80° 2° Ø respectively.

Otsuka and co-workers [40] evaluated the effect of environmental humidity on the transformation of CBZ during grinding and recorded characteristic peaks for their dihydrate form at 12.1° -, 25.7° - and 36.5° 2° Ø respectively, which corresponded quite favourably to the DHD form of the current study.

Matsuda and co-workers [30] evaluated the photodegradation of CBZ on the surface of tablets and recorded similar XRPD peaks for their respective polymorphs termed Form I, Form II and Form III. Form I showed characteristic peaks at 12°-, 15° - and 27.2° 2° Ø respectively which correspond to the ß-form of the current study. Similarly, Form II resembled the a-form and showed characteristic peaks at 4.9°- and 13.0° 2° Ø while Form III resembled the DHD form, with characteristics peaks being recorded at 12.8°- and 19.6° 2° Ø.

4.4.13.2 FTIR

Clark [10] cited the bands 1678 cm^{-1}, 1388 cm^{-1} and 1594 cm^{-1} as characteristic principle peaks for carbamazepine when determined in potassium bromide. The individual scans for CBZ and its two polymorphs are depicted in figures 12, -13 and -14. The individual peaks for the three forms are summarized in table 13.

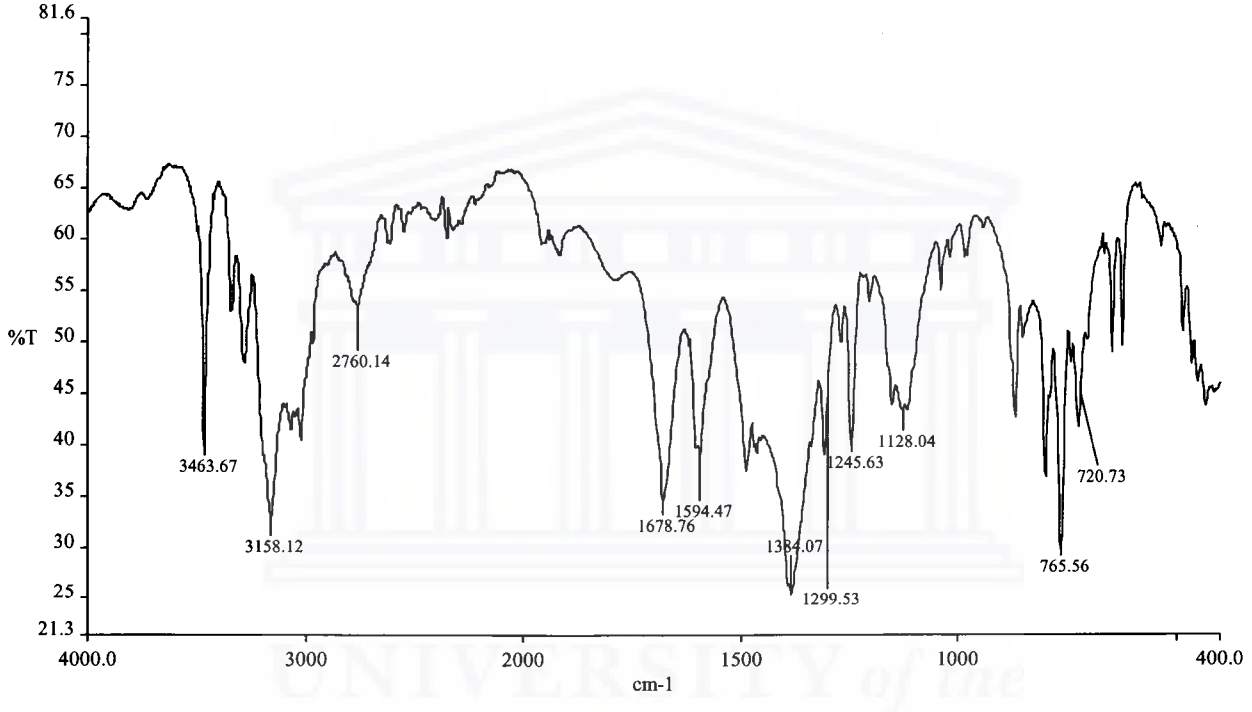

Figure 12. FTIR (DRIFT) analysis of commercial CBZ powder (β-form).

Figure 12 showed that the characteristic bands for the commercial CBZ powder (β-form) were found in the region of 3463.67 cm^{-1} (NH_2), 1678.76 cm^{-1} (C=O), 1594.47 cm^{-1} (C=C), 1384 cm^{-1} and 765.56. cm^{-1} respectively.

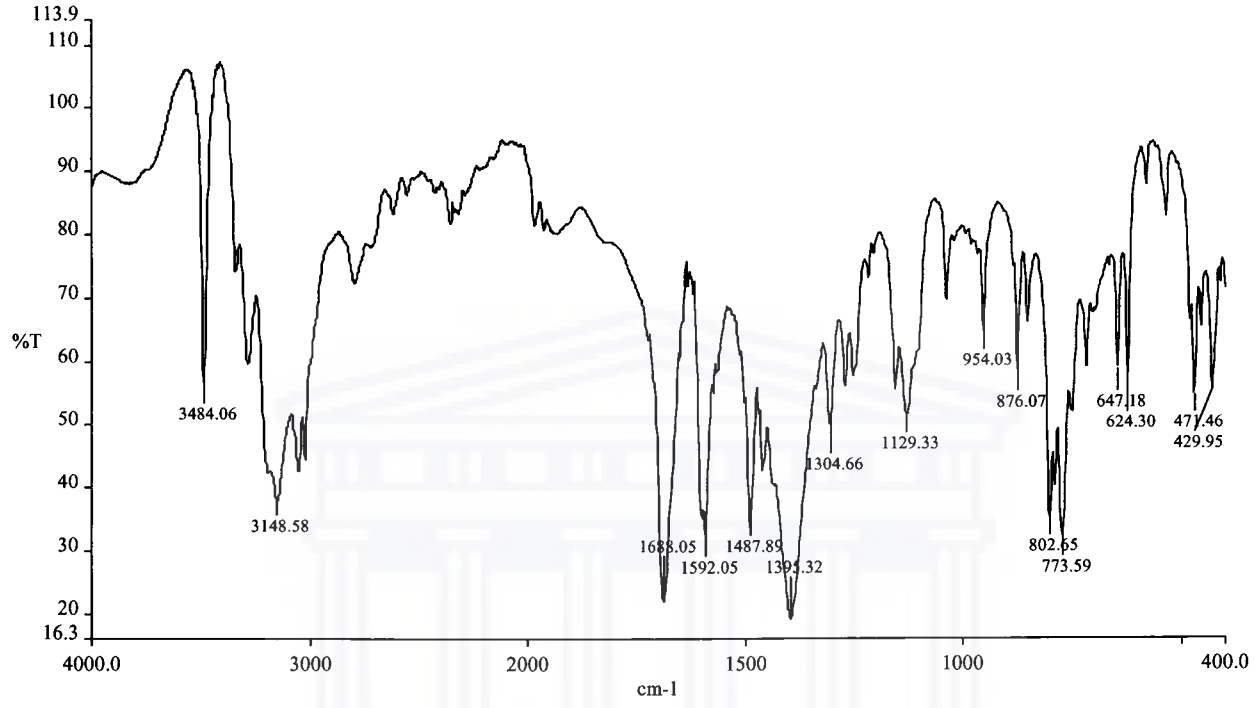

Figure 13. FTIR (DRIFT) analysis of the a-CBZ polymorph.

The characteristic bands for the a-CBZ polymorph were found in the region of 3484.06 cm^{-1}, 3148.58 cm^{-1}, 1688.05 cm^{-1}, 1592.05 cm^{-1}, 1395.32 cm^{-1} and 773.59 cm^{-1} respectively.

When compared to the ß-polymorph, the a-polymorph showed the same overall pattern except that the characteristic peaks have shifted slightly, both upward and down. The latter differences would allow distinction when CBZ is incorporated with the other excipients. The slight difference in the percentage transmission was due to varying amounts of the active ingredient being sampled and analyzed.

FTIR spectra obtained by Rustichelli et al. [43] for their polymorph I at 3484-, 1684-, 1397, 954- and 853 cm^{-1} compared favourably with the peaks obtained for the a-form in this study.

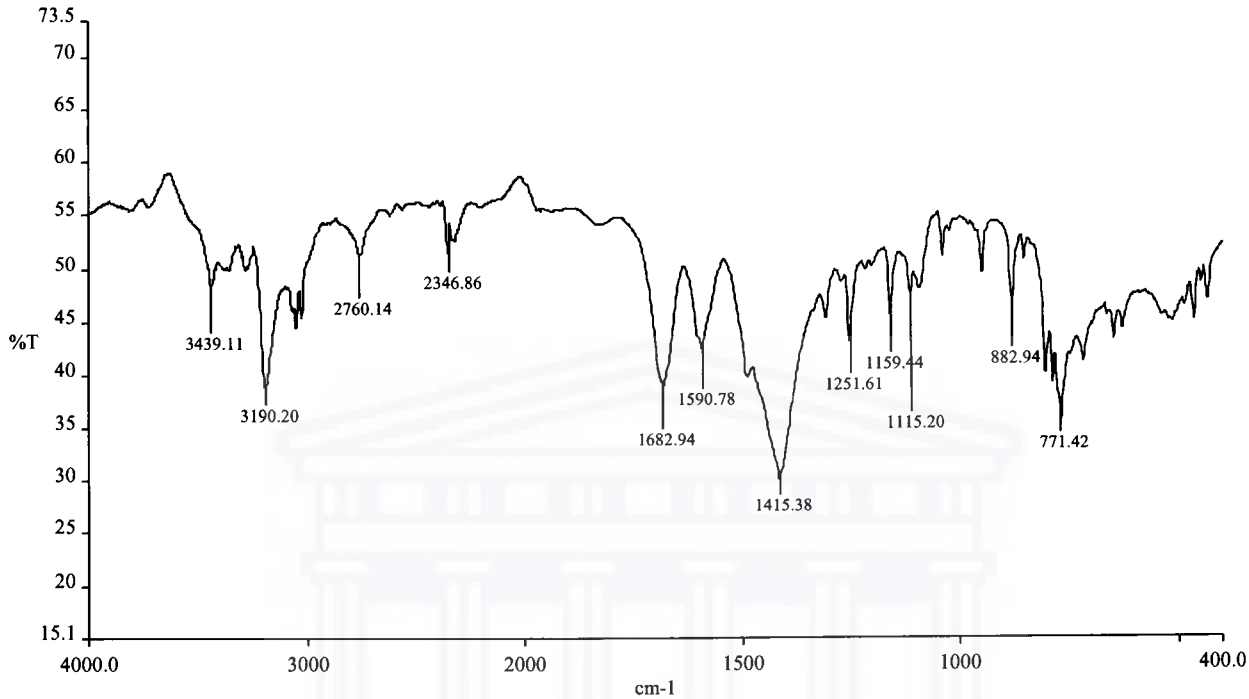

Figure 14. FTIR (DRIFT) analysis of the DHD-CBZ polymorph.

The characteristic bands for the DHD-CBZ polymorph were 3439.11 cm^{-1}, 3190.20 cm^{-1}, 1682.94 cm^{-1}, 1590.78 cm^{-1}, 1415.38 cm^{-1} and 771.42 cm^{-1} respectively.

When this form was compared to both the ß- and a-CBZ polymorphs, it became evident that the shoulder to the left of the characteristic peak 3439.11 cm^{-1} was shorter. The characteristic peaks also shifted significantly as indicated below.

Table 13. FTIR peaks for the different CBZ polymorphs.

Clarke's standard	ß-CBZ polymorph	a-CBZ polymorph	DHD-CBZ polymorph
1388 cm^{-1}	1384 cm^{-1}	1395 cm^{-1}	1415 cm^{-1}
1594 cm^{-1}	1594 cm^{-1}	1592 cm^{-1}	1590 cm^{-1}
1678 cm^{-1}	1678 cm^{-1}	1688 cm^{-1}	1682 cm^{-1}
	3158 cm^{-1}	3148 cm^{-1}	3190 cm^{-1}
	3463 cm^{-1}	3484 cm^{-1}	3439 cm^{-1}

4.4.14 Standardization of microwave oven

Table 14. Water temperature recorded (°C) at different positions within microwave cavity.

Position	1	2	3	4	5	6	7
Water	18	18	18	18	18	18	17
Temp. 1	56	56	55	54	55	53	52
Temp. 2	55	56	54	55	54	54	52
Temp. 3	56	56	55	53	54	55	51
Ave	55.5	56	54	53	54.5	54	51.5
SD	0.58	0.0	0.58	1.0	0.58	1.0	0.58

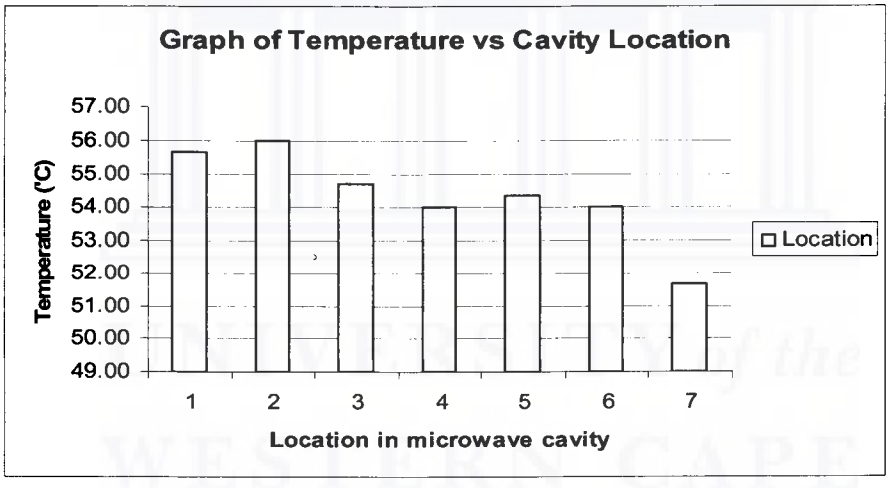

Figure 15. Temperature curves of water obtained at different locations in microwave cavity.

The average water temperature reached in the microwave heating cavity after 30 seconds at 100% power (PL100) was 54.33° C with a standard deviation of 0.62° C. The results clearly indicated that the energy transfer throughout the microwave heating cavity was not homogenous. The temperature difference within the microwave cavity between positions 1 and – 7 was 4°C. Although the rotating base somewhat compensates for the temperature difference, there would still be certain hot spot areas which could result in certain areas of the granules being heated more than others.

Table 15. Water temperature recorded (°C) for 30 seconds at different heat settings on position 1.

Power Level	1 PL100	2 PL90	3 PL80	4 PL70	5 PL60	6 PL50	7 PL40	8 PL30	9 PL20	10 PL10
Temp. 1	56	50	46	43	39	35	33	26	22	19
Temp. 2	56	52	46	43	39	37	33	28	22	19
Temp. 3	56	49	47	43	39	35	33	26	22	19
Average	**56**	**50.33**	**46.33**	**43**	**39**	**35.67**	**33**	**26.67**	**22**	**19**
SD	**0**	**1.53**	**0.58**	**0**	**0**	**1.15**	**0**	**1.15**	**0**	**0**

Table 16. Water temperature recorded (°C) for 60 seconds at different heat settings on position 1.

Power Level	1 PL100	2 PL90	3 PL80	4 PL70	5 PL60	6 PL50	7 PL40	8 PL30	9 PL20	10 PL10
Temp. 1	89	83	75	67	60	53	46	37	30	27
Temp. 2	89	83	75	67	61	53	46	37	30	27
Temp. 3	87	81	73	67	60	53	46	38	30	27
Average	**88.33**	**82.33**	**74.33**	**67**	**60.33**	**53**	**46**	**37.33**	**30**	**27**
SD	**1.15**	**1.15**	**1.15**	**0**	**0.58**	**0**	**0**	**0.58**	**0**	**0**

Table 17. Water temperature recorded (°C) for 90 seconds at different heat settings on position 1.

Power Level	1 PL100	2 PL90	3 PL80	4 PL70	5 PL60	6 PL50	7 PL40	8 PL30	9 PL20	10 PL10
Temp. 1	98	98	91	82	74	67	57	48	35	27
Temp. 2	99	96	88	81	74	66	58	48	36	27
Temp. 3	98	98	89	82	74	66	59	48	37	27
Average	**98.33**	**97.33**	**89.33**	**81.67**	**74**	**66.33**	**58**	**48**	**36**	**27**
SD	**0.58**	**1.15**	**1.53**	**0.58**	**0**	**0.58**	**1**	**0**	**1**	**0**

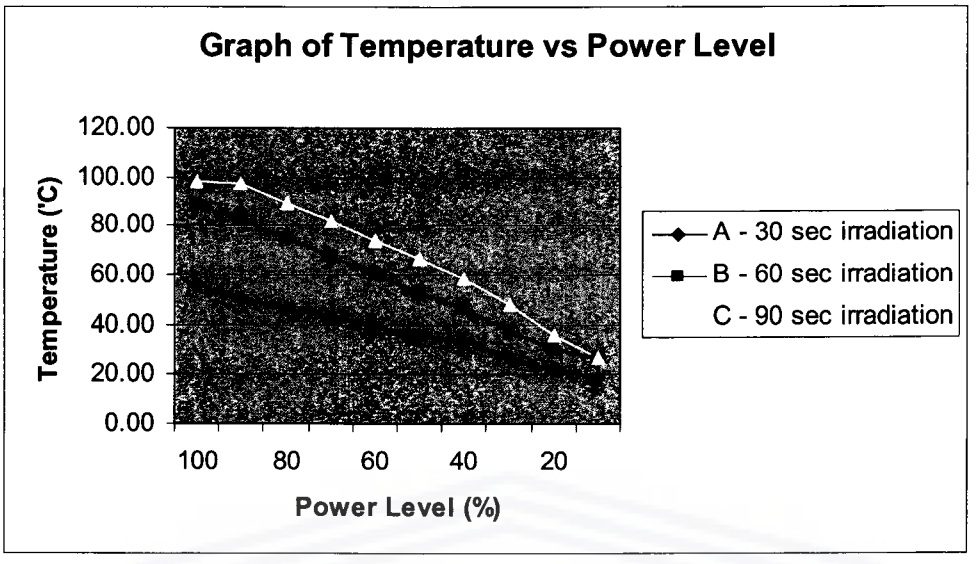

Figure 16. Temperatures curves of water samples irradiated at position 1 with different power levels and time periods.

The irradiation time at 100% power level resulted in dramatic temperature increases between the 30-, 60- and 90 second irradiation time intervals reaching averages of 56°C, 88°C and 98°C respectively. Analysis of the results revealed a huge temperature increase of 32°C between A and B (58% temperature increase) but a less significant increase of 10°C between B and C (11% temperature increase). The latter finding can be directly attributed to the thermal properties of water in that the boiling point of water had been reached. A further increase in irradiation would not result in an increase in temperature but would merely cause evaporation of the water.

Thus, the temperatures achievable within the microwave cavity as a function of the irradiation power level is dependent on the boiling point and loss factor of the solvents. As mentioned previously, the absorption of microwave energy is far greater for small polar molecules than for larger and less polar molecules. The higher the loss factor the greater the absorption of microwave energy [2].

Although excipients do not resonate as well as solvents (water, ethanol, etc.) their loss factor would contribute to the maximum irradiation temperature achieved. Further heating should be avoided once the solvent is removed. With this in mind, the only drawback to using a domestic microwave oven is the inability to accurately measure the temperature within the microwave cavity.

4.5 Conclusion

The results obtained from the experiments highlighted some useful information as outlined below.

Firstly, the physical properties of CBZ and the excipients suggested good tabletting characteristics such as compressibility, flowability, low inherent moisture content and compatibility [18]. Anhydrous lactose (Tablettose®) was selected as the hydrophilic diluent, sodium starch glycolate (Explotab®) as disintegrant, 5% PVP:Ethanol suspension as granulating fluid, silicone dioxide (Aerocil®) as glidant and magnesium stereate as lubricant.

The formulation of a carbamazepine tablet using microwave radiation as a secondary objective of this study, proved fairly successful. Although the three different formulae yielded good theoretical powder flow characteristics, no concrete indication could be obtained of the compaction characteristics of the tablets, other than the physical compression of each formula. Therefore, the ability of each formula to form compacts of suitable hardness, was used as main criteria for selection. The eventual selection of formula C as formula of choice, was subjected to a full pharmaceutical evaluation.

Secondly, two CBZ polymorphs were successfully prepared and characterized by XRPD and FTIR. The measurements from these methods would serve as standards to be used to characterize the granules and resultant tablets once manufactured. The measurements obtained using both XRPD and FTIR, were consistent with those obtained by authors elsewhere that have also studied aspects of carbamazepine's polymorphic nature [18, 30, 40, 43].

Thirdly, the energy transfer within the microwave heating cavity was not homogenous although the rotating base compensated somewhat for the temperature difference. Microwave radiation at a 100 % power level would be used for future experimentation since the maximum irradiation level would result in a faster drying time. In addition, by using the maximum power level as the drying temperature it would provide a useful guide as to whether any polymorphic transition would occur as well as any physical change to the granules. The only drawback to using a commercial microwave oven was that no absolute temperature measurements inside the heating cavity could be obtained when drying the manufactured granules. The standardization of temperatures achievable using distilled water provided an indication of the time frame in which heating to a particular point

would take. In the case of solvents, the boiling point would be the end point since no increase in temperature would be achieved beyond the boiling point.

With respect to the latter, the granule's heating profile would stem from the solvents used in the granulating fluid. Ethanol (99%) has been selected as the solvent of choice due to its superior microwave absorbing ability imparted by a higher loss factor than that of water [2]. In addition, water has been omitted since it might favour transformation of the commercial ß-form to the dihydrate form [36].

CHAPTER 5

MANUFACTURE AND EVALUATION OF CBZ TABLETS

5.1 Introduction

This chapter details the materials, equipment and methods used in the manufacture of CBZ tablets from both microwave dried- as well as convection oven dried granules and the results obtained.

5.2 Equipment and material

CBZ, lactose (Tablettose®), and sodium starch glycolate (Explotab®) were gifts provided by Aspen. Magnesium stearate, silicone dioxide (Aerocil ®) and polyvinylpolypyrrolidone (Kollidon CL®) were obtained from the University of the Western Cape (UWC) who in turn purchased them from Protea Chemicals, South Africa. Balance (Auhaus); pH meter (Sentron); Granulator; Microwave oven (Daewoo); Tablet press (Type F3, Manesty Machine Ltd, Liverpool, England) ; Hardness tester (Type Ptb 301 Erweka, Pharma Test, Hainburg, West Germany); Friabilator (Erweka Apparatebau-Gmbh, Heusentamn Kr. Offenbach, West Germany); Disintegrating Apparatus (Eweka-Apparatebau-Gmbh, Heusentamn Kr. Offenbach, West Germany), Spectrophotometer (Hitachi U-3200 spectrophotometer, Japan); Dissolution Tester (VK 700 Vankel, Optalabor, South Africa) and Millipore Filter Unit (Cameo 24 AS, DDA 02025So MSI: Micro separation Inc., USA); Tubohaler

The D8 Advance Bruker AXS diffractor was used on site at Ithemba Labs (Faure, South Africa). The Perken-Elmer Paragon 1000 FTIR instrument was used on site at the University of the Western Cape's (UWC) department of chemistry.

5.3 Granule preparation

One batch of granules was prepared and split in two for drying by microwave - and convection oven respectively.

The CBZ, lactose and SSG powders were sieved, weighed and transferred to a turbuhaler where it was blended for 5 minutes operated at 50 rpm. The powder blend was transferred to a granulator where it was further mixed. The operating speed setting on the granulator was on number 5. The 5% PVPP-ethanol suspension was added to the powder blend until caking occurred. The total granulation time ranged between 15-20 minutes. The granules were transferred to a set of Endocotte® sieves that yielded granules with 3 mm diameters. The granules were dried by the respective methods.

5.4 Drying of granules

5.4.1 Microwave oven

The granules were weighed on a top loader balance to determine its total weight and hence the theoretical moisture content to be removed (end point of drying). The granules were put onto a sheet of white paper, transferred to the microwave oven and placed on the rotating base. The granules were evenly distributed onto the paper sheet in the oven cavity. The microwave was set to 100% power (PL100) and the granules were dried for 120 second intervals until dry. The total drying time was 420 seconds. The latter process was checked by weighing the granules after every 120 second interval until a uniform weight was achieved.

5.4.2 Convection oven

The oven was preheated to 60° C. The granules were weighed, placed on a stainless steel tray and inserted into the convection oven. The granule drying process followed the same process as above whereby granule drying was determined by achieving a uniform weight. In this method, the drying interval was 15 minutes. The total drying time was 75 minutes.

5.5 Morphology of manufactured granules

The microwave dried granules were morphologically more distinct than the convection dried granules. The microwave dried granules felt harder and crisp compared to the softer feel of the

convection dried counterpart. The convection dried granules also appeared to be more dense than the microwave dried granules.

5.6 Manufacture of tablets

The dried granules were blended in a tubohaler with the appropriate amount of silicone dioxide and magnesium stearate before being transferred to a hopper that fed into the Manesty® F3 single punch tablet press having a 10 mm diameter punch and die set for the manufacture of the tablets. The fill volume of the die set was adjusted to achieve the desired tablet weight of 400mg. The compression force dial on the machine was set to 33. The latter setting was found to yield tablet hardness of between 55-65 Newton (N) which was acceptable by BP standards. The Manesty® F3 single punch tablet press did not compress at a specific force; i.e. the force applied depended on the tablet weight, its size and compressibility of the powder blend.

Figure 17. Manesty ® Type F3 single punch tablet press.

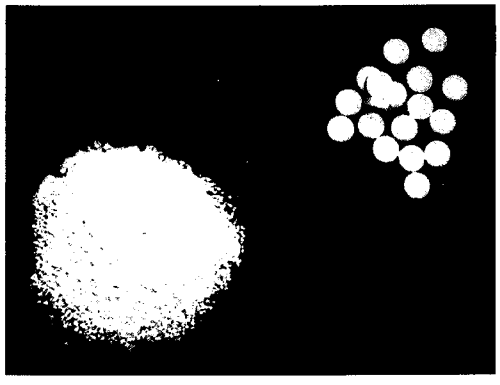

Figure 18. Granules and resultant tablets.

5.7 Polymorphic studies on granules and tablets

5.7.1 XRPD

The main characteristics and setting parameters for the D8 Advance Bruker AXS diffractor remained unchanged for the evaluation of the granules and compressed tablets to that of the evaluation of the commercial CBZ powder and its polymorphs . These were Ni filtered CuK a radiation (λ = 1.5418 Å); power voltage of 40 kV; tube current of 40 mA; time constant of 15 seconds per position; angular speed 1° (2° Ø) per minute; using divergent and anti-scatter slits, sodium iodide scintillation counter, graphite monochromater and an angular range of $3 < 2^{\circ}\ Ø < 40^{\circ}$.

5.7.2 FTIR

The instrument settings and parameters for the evaluation of the granules and compressed tablets remained unchanged to that of the evaluation of the commercial form of the CBZ powder and its polymorphs. Thus, the Perken-Elmer Paragon 1000 FTIR instrument was fitted with a Cesium Iodide beam splitter and controlled with Spectrum® software. Scanning parameters used a 4 cm^{-1} resolution with weak apodization. The data region was 4000-400 cm^{-1} and the number of scans per spectrum was 20. The samples were gently ground with potassium bromide (KBr) and analyzed directly in the DRIFT mode thus mechanically avoiding polymorphic transition possibly induced by extended grinding and during compression of the pellet.

5.8 Pharmaceutical evaluation of the trial tablet

5.8.1 Uniformity of mass

The manufactured tablets were tested for uniformity of mass as specified in the BP [5]. Twenty tablets were randomly chosen from each of the two portions of the batch since each portion was dried differently. Each tablet was individually weighed and the average weight per batch portion was calculated. The deviation in the individual tablet weights and the standard deviation were also calculated per batch portion.

5.8.2 Uniformity of size and shape

The diameter and thickness of manufactured tablets are indicators of the size and shape of the tablets. The size and shape of the tablets produced depended on the volume and weight of the fill mass, the diameter of the die and the pressure applied to the fill during compaction. According to the BP [5] specifications, twenty tablets from each portion were randomly selected and evaluated for diameter and thickness.

5.8.3 Hardness test

Tablet hardness is defined as the load required to crush or fracture a tablet. The latter is also termed crushing strength. In the current study, ten tablets from each portion were randomly selected and evaluated for their hardness using a Pharma Test Type PTB 301 hardness tester.

5.8.4 Friability test

The friability test determines the tablet's ability to retain its physical properties against friction, shock or vibration during processing. Ten tablets were randomly selected from each portion and dusted with a brush to remove any adhering powder and weighed. The tablets were placed in a Erweka friabilitator operated at 25 rpm for 4 minutes where after the tablets were removed from the apparatus, dusted and weighed to determine the percentage weight loss using the following equation:

$$\text{Percentage weight loss (\%)} = (W1 - W2) / W1 \times 100 \qquad (12)$$

The BP [5] specifies that a mass loss due to friability is satisfactory if it is less than 1%.

5.8.5 Content uniformity test

Twenty tablets were powdered and tested for a CBZ content of between 85-115% as specified in the BP [5]. Five tablets from each portion of the batch were also assayed individually for CBZ content as described below.

Assay:

- Weighed and powdered 20 tablets.
- Boiled a quantity of powder containing 60 mg CBZ with 25 ml of ethanol (96%) for a few minutes.
- Stirred the hot mixture in a closed flask for 10 minutes and filtered through sintered glass.
- Washed the flask, filtered with ethanol (96%) and added sufficient ethanol (96%) to the cooled filtrate to produce 100 ml.
- Diluted 5 ml of the filtrate to 250 ml with ethanol (96%).
- Measured the absorbance of the resulting solution at the maxima at 285 nm.
- Calculated the content of $C_{15}H_{12}N_2O$ taking 490 as the value of A (1%, 1cm) at the maximum at 285 nm.

5.8.6 Disintegration test

Complete disintegration is defined as that state in which any residue of the unit remaining on the screen of the test apparatus is a soft mass having no palpably firm core. Disintegration time is the length of time required to break up a tablet into its constituent particles.

The disintegration time of the tablets was determined as specified in the BP [5] whereby 6 tablets from each portion were subjected to the same test. The Erweka-Appratebau-Gmbh disintegration apparatus was used with the dissolution medium consisting of simulated gastric fluid maintained at 37° C ± 2° C instead of distilled water. The frequency rate was 30 cycles per minute.

5.8.7 Dissolution test

The dissolution profiles of the tablets from each portion of the batch were determined by using the rotating paddle method as described in the BP [5]. The samples were analysed by UV-visible spectroscopy using a Hitachi U-3200 spectrophotometer. A Vankel Dissolution Tester® was used to determine the dissolution profiles of the tablets. One tablet was placed into each of the six beakers containing 900 ml of freshly de-aerated simulated gastric fluid at pH 1.2 and having a

temperature of 37° ± 1° C. The rotating paddle speed was 100 rpm. Samples of 5 ml portions were withdrawn at 15 minute intervals up to 90 minutes. Each sample volume withdrawn was immediately replaced an equivalent volume of dissolution medium. The collected samples were filtered using a 0.45μm Millipore® filter and the absorbances of the filtrates determined spectrophometrically at 285 nm.

The concentration of CBZ contained in each sample was determined using a standard curve constructed by absorbances at 285nm of known concentrations i.e. 5%, 25 %, 50 %, 75 % and 100 % w/v of CBZ. The solutions were made by dissolving an appropriate amount of the CBZ powder in dissolution medium and making serial dilutions from the stock solution. After determining the concentrations of the samples from the standard curve, the percentage drug release were calculated and plotted versus time to obtain the dissolution profile. The graphic software package Graph Pad Prism (version 4) was used to obtain the dissolution curves.

According to the BP (Appendix XII D) [5], not less than 70% of the labeled amount must appear in solution within 45 minutes.

5.9 Results and Discussion

5.9.1 Drying of granules

5.9.1.1 Microwave drying

The results of the microwave drying of granules are summarized in table 18 and figure 19.

Table 18. Results of microwave drying times and resultant granule weights.

Time (sec)	0	120	240	360	420
Weight (g)	300	250.25	242.35	240.06	239.53

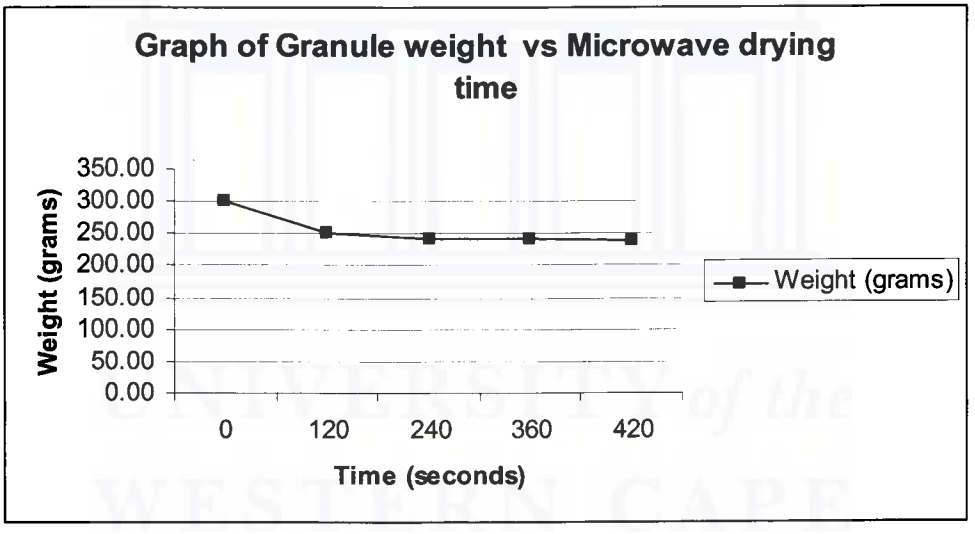

Figure19. Graph of granule weight versus microwave drying time.

5.9.1.2 Convection drying of granules

The results of the convection drying of granules are summarized in table 19 and figure 20.

Table 19. Results of convection drying times and resultant granule weights.

Time(sec)	0	900	1800	2700	3600	4500
Weight (grm)	300	277.08	257.79	244.42	239.79	237.15

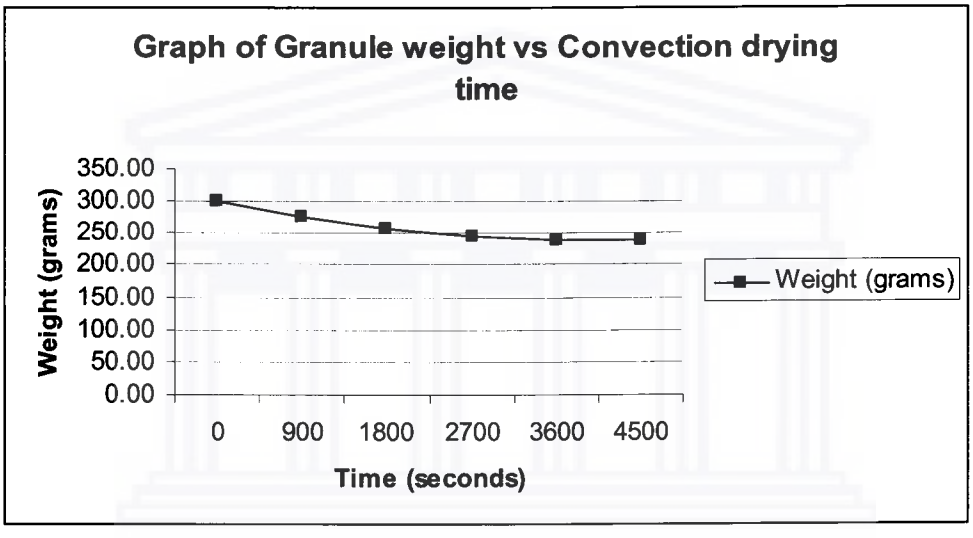

Figure 20. Graph of granule weight versus convection drying time.

The granules dried by convection oven appeared very soft and brittle with more loose powder between granules. No surface charring occurred. These granules were more dense than the granules dried my microwave irradiation.

5.9.2 Manufacture of tablets

Approximately three hundred white, flat, 9 mm diameter tablets were manufactured from the microwave dried – and convection oven dried granules.

The convection dried granules did not compress as easily as the microwave dried tablets with some capping occurring. Variation of the pressure setting below position 33 did not overcome the problem. The entire batch was compressed at setting 33 and the tablets evaluated as is.

5.9.3 Polymorphic studies on manufactured granules and tablets

Quantification of CBZ within the differently dried granules and resultant tablets were performed using XRPD and FTIR.

5.9.3.1 XRPD

The results of the XRPD scans for the differently dried granules and resultant tablets are depicted in figures 21, - 22, - 23, -24, -25 and -26.

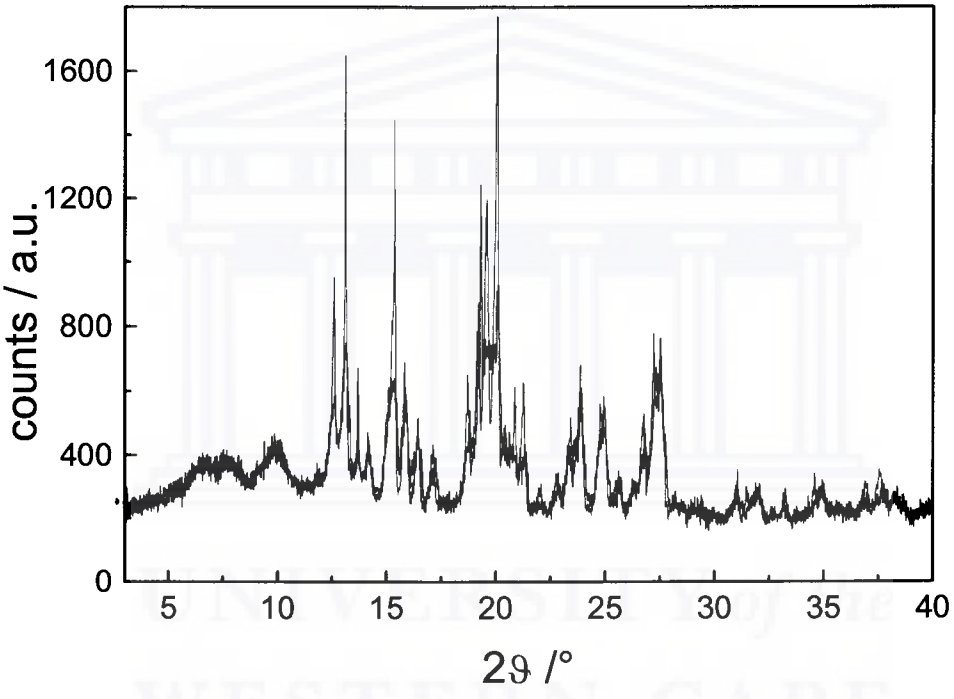

Figure 21. Superimposed XRPD scan of granules following microwave drying (•) and convection oven drying (•).

The significant peaks obtained for both microwave – and convection dried granules were produced at 12.5° -, 13° -, 15.4° -, 15.7° -, 19.3° -, 19.7° -, 20° -, 24.4° -, 24.8° and 27° 2° Ø respectively. The overall XRPD patterns for the differently dried granules are almost identical except for two peaks at 20.9° - and 21.4° 2° Ø of the convection dried granules which were more intense than the microwave dried granules. In general the convection dried granules produced peaks which were slightly more intense than those of the microwave dried granules. This fact could be explained by the fact that the convection dried granules were slightly more dense than the microwave dried granules.

Although some of the peak positions of the a-form closely overlap with those of both the ß-and dihydrate forms (12° – to 13° 2° Ø and 19.6° 2° Ø), the characteristic peaks at 6.5° - and 9.6° 2° Ø were missing. In addition, the ß-form's characteristic peaks at position 15.4° - and 15.8° 2° Ø were clearly present.

By comparing the peak positions obtained from the microwave- and convection dried granules to the fingerprints of three polymorphic forms outlined previously, it became evident that the characteristic peak produced by the dihydrate form at positions 9.2° - and 37.9° 2° Ø respectively, were absent.

An interesting observation was the emergence of three left shoulder at 6.8° -, 7.9° - and 10° 2° Ø respectively. These shoulders were relatively flat without clearly identifiable peaks that could be attributed to any particular polymorphic form. These could possibly be attributed to peaks produced by some of the tablet excipients.

It could thus be concluded that XRPD patterns of both microwave dried and convection dried granules were not significantly different to validate a polymorphic shift.

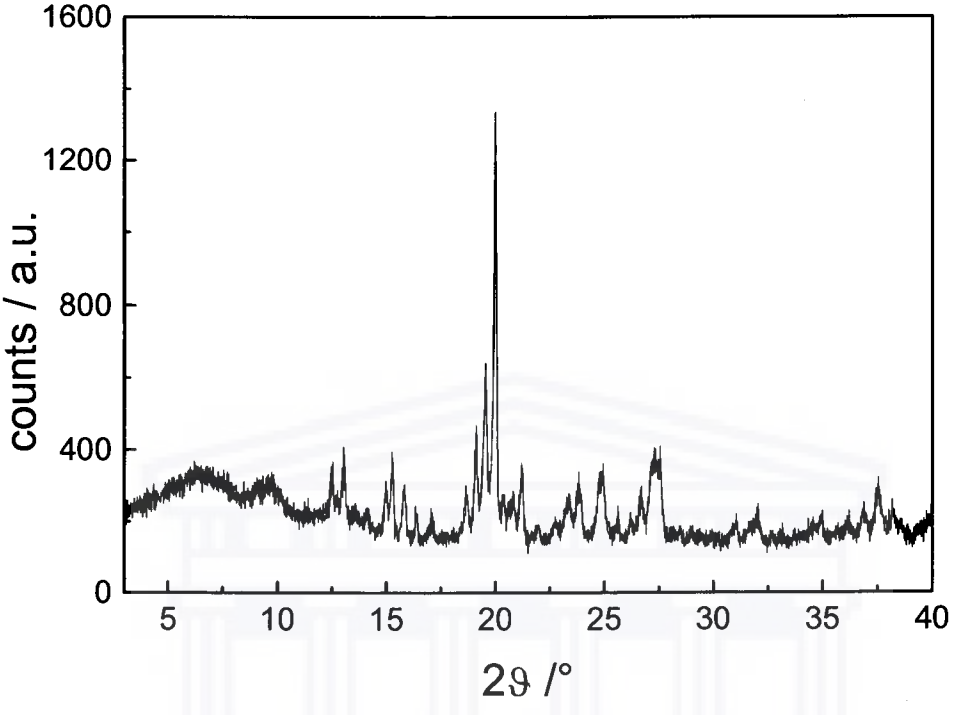

Figure 22. Superimposed XRPD scan of crushed tablet resulting from microwave drying (•) and convection oven drying (•).

Both patterns for the microwave- and convection dried tablets appeared identical with a very intense peak produced at 19.8° 2° Ø for both the microwave dried- and convection dried granules. The left shoulders at signals 6.4° - and 9.8° 2° Ø also appeared more intense. Again, appearance could be due to addition of silicone dioxide or magnesium stearate. These scans resembled the ß-form suggesting that no transformation occurred after compression.

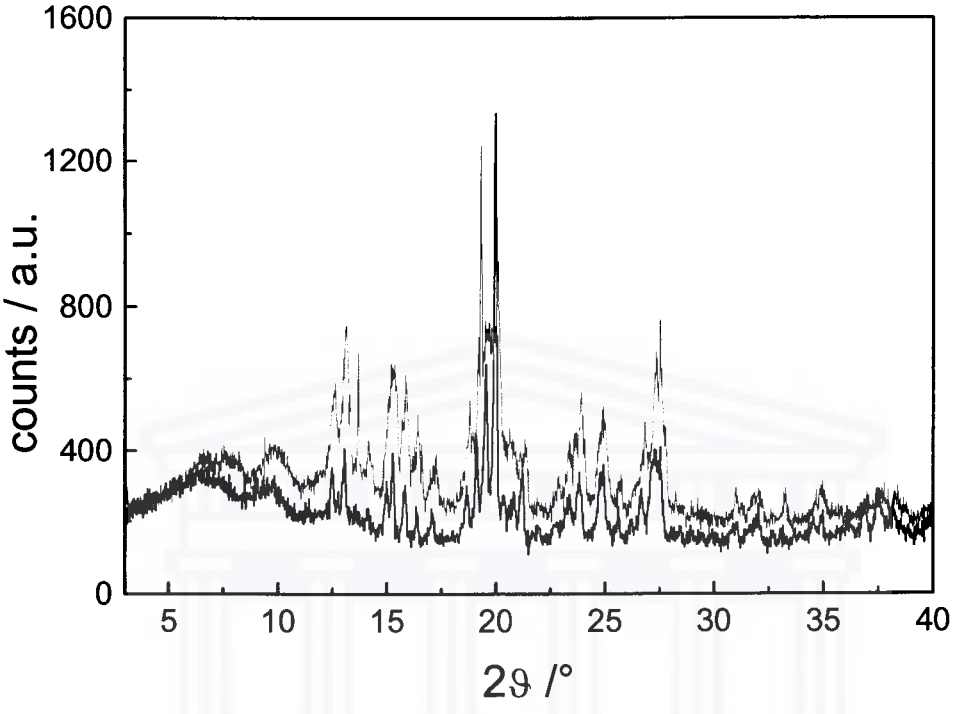

Figure 23. XRPD scan of microwave dried granules (•) and resultant tablet (•).

Both scans appeared identical in their spectral arrangement despite the granules having a slightly more intense peak at position 13.58° 2° Ø to that obtained by the compressed tablet. Since this was not a new peak it could be concluded that no transformation occurred during compression. In general, the peak intensities of the granules were more marked than those of the compressed tablet.

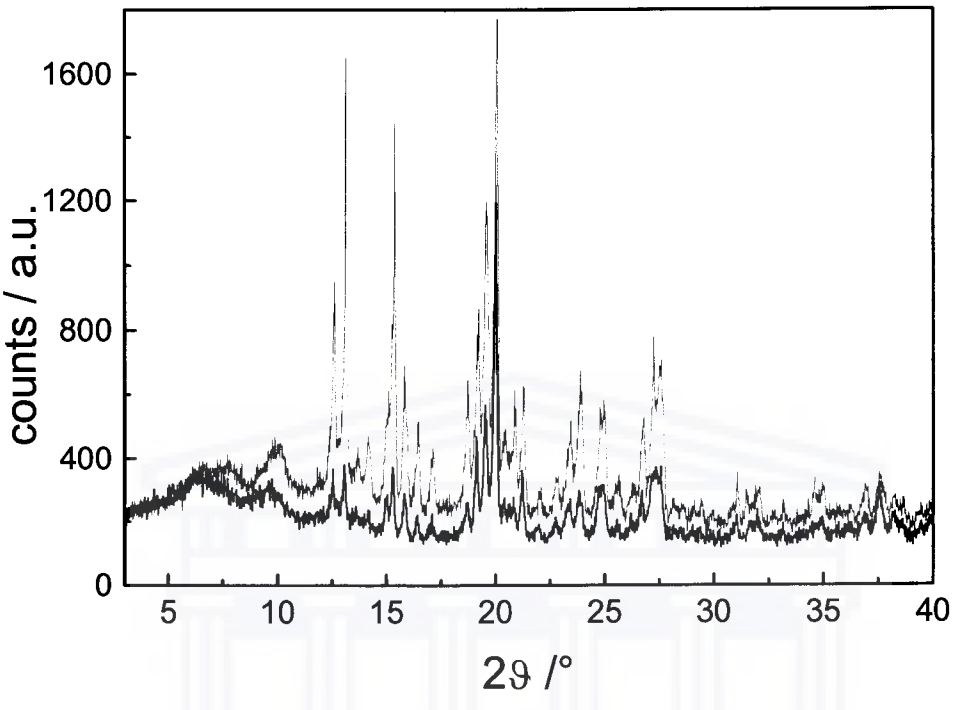

Figure 24. XRPD scan of convection dried granules(•) and resultant tablet (•).

These scans of the convection dried granules and - tablets were also identical, with the granule's peak intensities being stronger than those of the tablet. These results compared very closely with that obtained by the microwave dried granules and tablets.

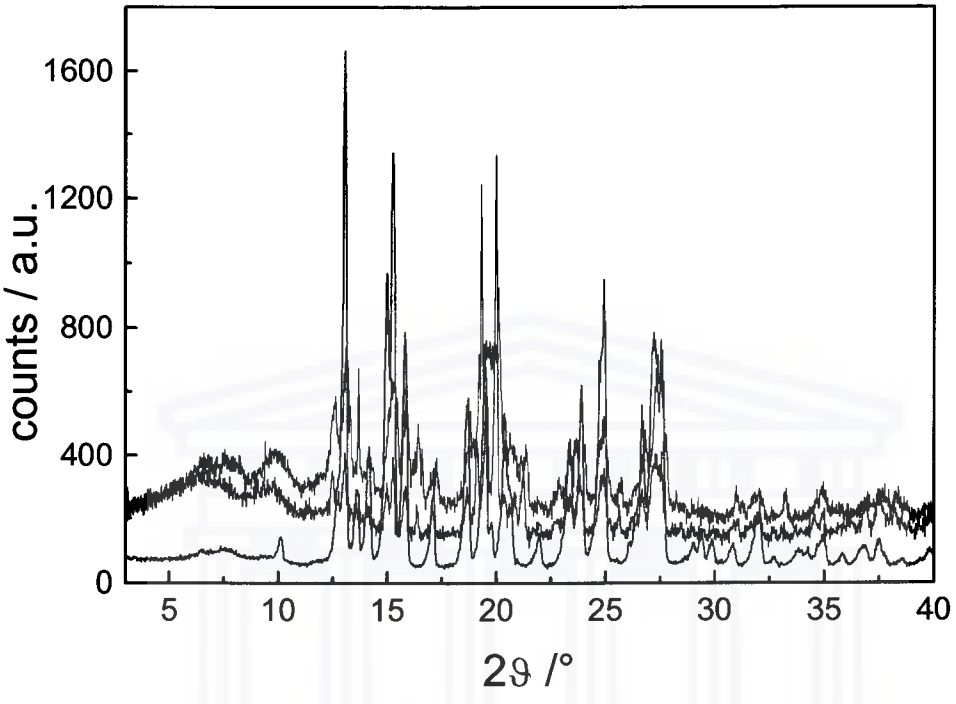

Figure 25. Superimposed comparative XRPD scans of ß-CBZ powder (•), microwave dried granules (•) and resultant tablet (•)

Evaluation of the peak intensities revealed that four new peaks emerged at positions 16.4° 2° Ø, 21.4° 2° Ø, 25.7° 2° Ø and 33.2° 2° Ø when the ß-CBZ powder was compared to the microwave dried granules and resultant tablet.

These peaks could be attributed to the presence of the excipients that were mixed with the CBZ to produce the granules and resultant tablets.The XRPD patterns of the microwave dried granules and resultant tablets were also identical suggesting that there was no difference between the two forms. The underlying characteristic peaks of the ß-form of CBZ were clearly identifiable suggesting that no polymorphic shift occurred.

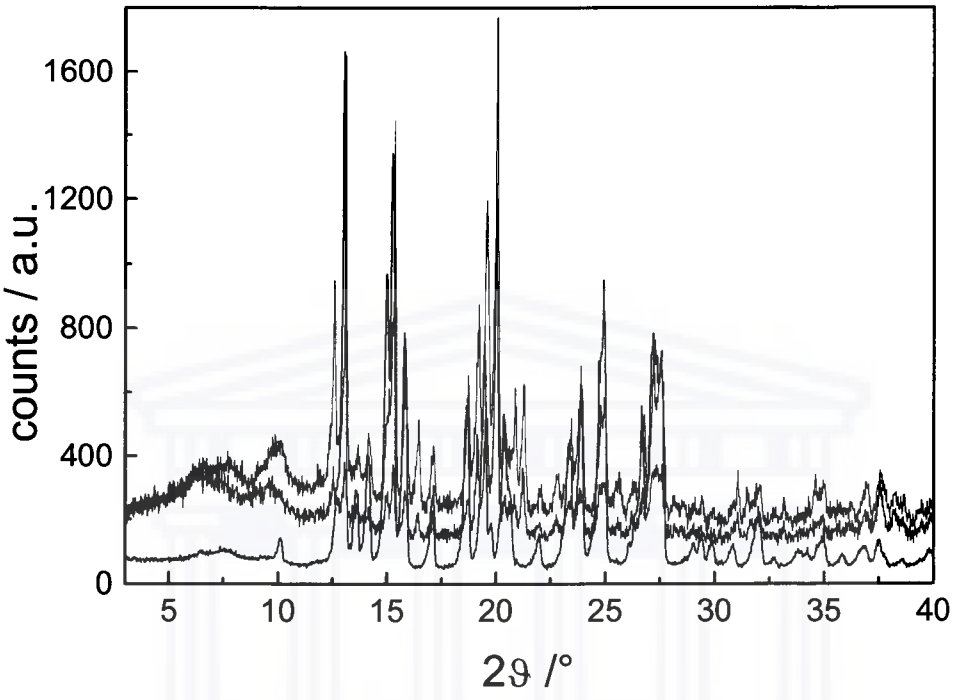

Figure 26. Superimposed comparative XRPD scans of β-CBZ powder (•), convection dried granules (•) and resultant tablet (•)

Identical peak intensities (16.4° 2° Ø, 21.4° 2° Ø, 25.7° 2° Ø and 33.2° 2° Ø) to those obtained for the microwave dried granules and - tablet (Figure 22) were recorded when the ß-CBZ powder was compared to the convection dried granules and resultant tablet.

The peak intensities of the convection dried granules and –tablets were also identical suggesting that new peaks were in fact due to the added excipients. Comparison of the characteristic peaks of the convection dried granules and - tablet clearly not only suggest close similarities to that of the ß-form but also to that of the microwave dried granules and - tablet.

Thus, these XRPD findings suggest that no significant differences existed between microwave dried granules and- tablets and those dried by convection oven. In addition, the commercial ß-form has not undergone any polymorphic transformation.

5.9.3.2 FTIR

The results of the FTIR scans for the differently dried granules and resultant tablets are depicted in figures 27, - 28, - 29, and - 30.

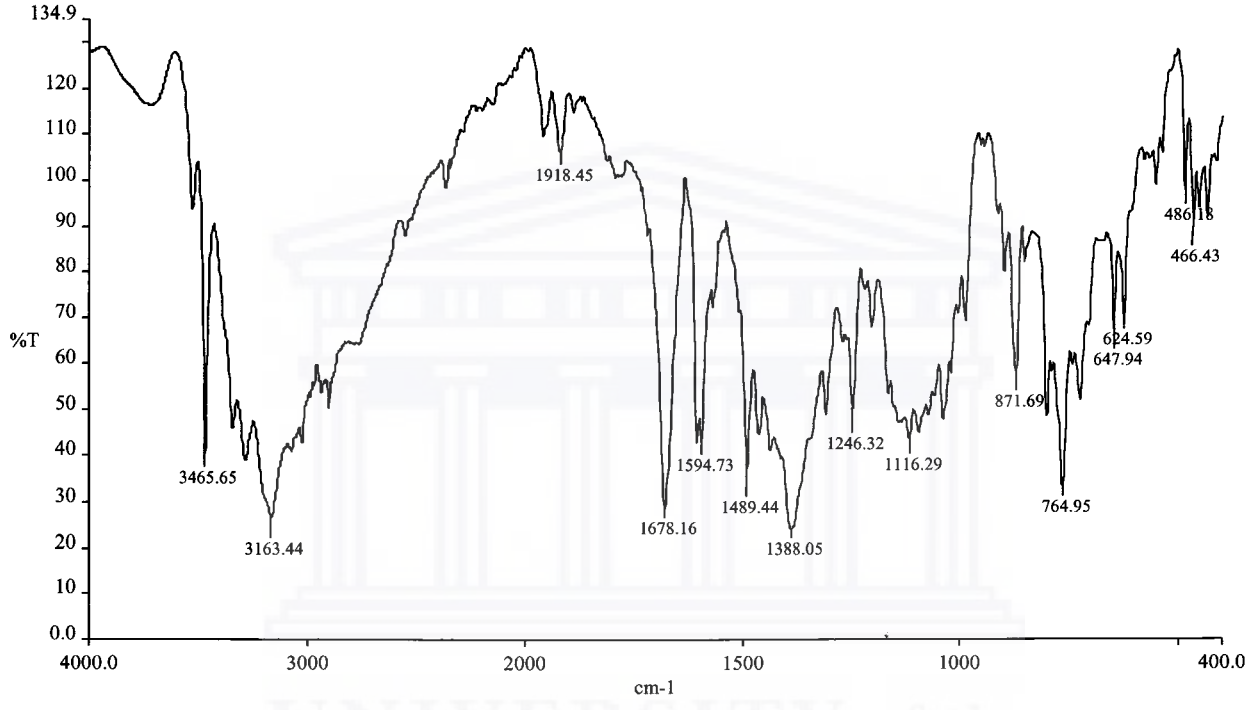

Figure 27. FTIR (DRIFT) analysis of the CBZ granules dried by microwave oven.

Figure 27 revealed that significant peaks were obtained at 3465.65 cm^{-1}, 3163.44 cm^{-1}, 1678.16 cm^{-1}, 1594.73 cm^{-1} and 1388.05 cm^{-1} respectively, for the CBZ granules dried by microwave oven.

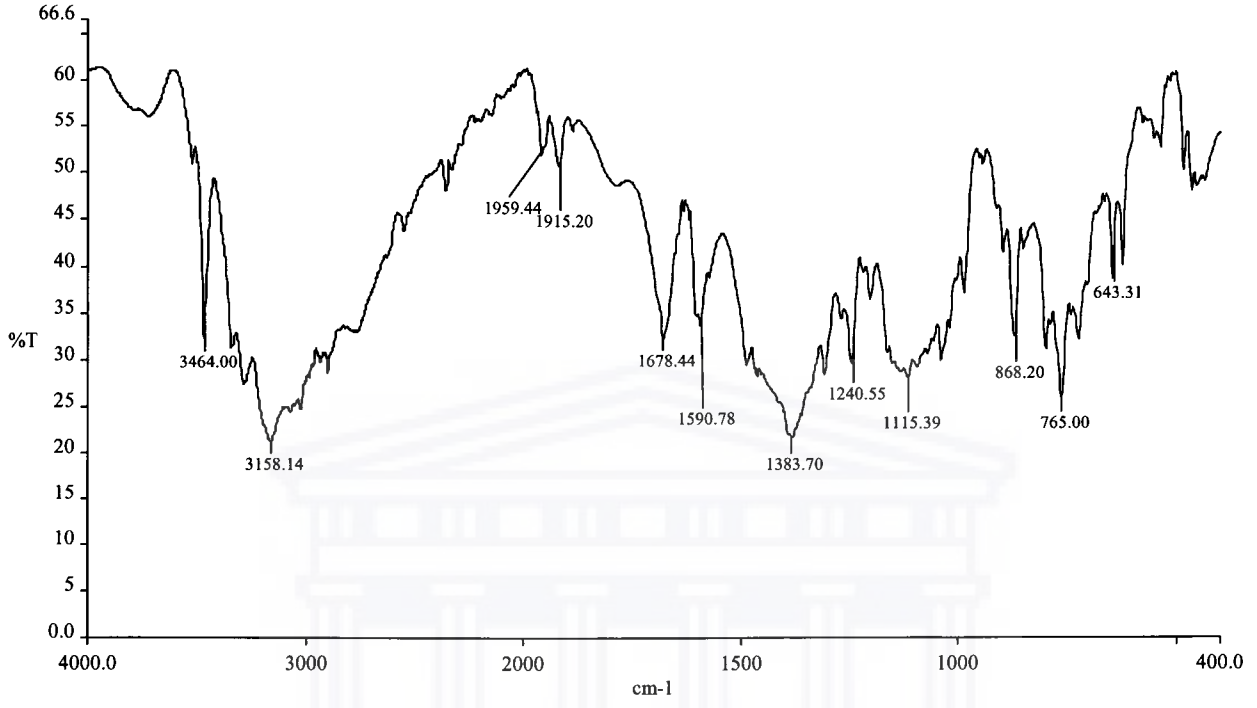

Figure 28. FTIR (DRIFT) analysis of the CBZ granules dried by convection oven.

Significant peaks were obtained at 3464 cm^{-1}, 3158.14 cm^{-1}, 1678.44 cm^{-1}, 1590.78 cm^{-1} and 1383.70 cm^{-1} respectively, for CBZ granules dried by convection oven as shown in figure 28.

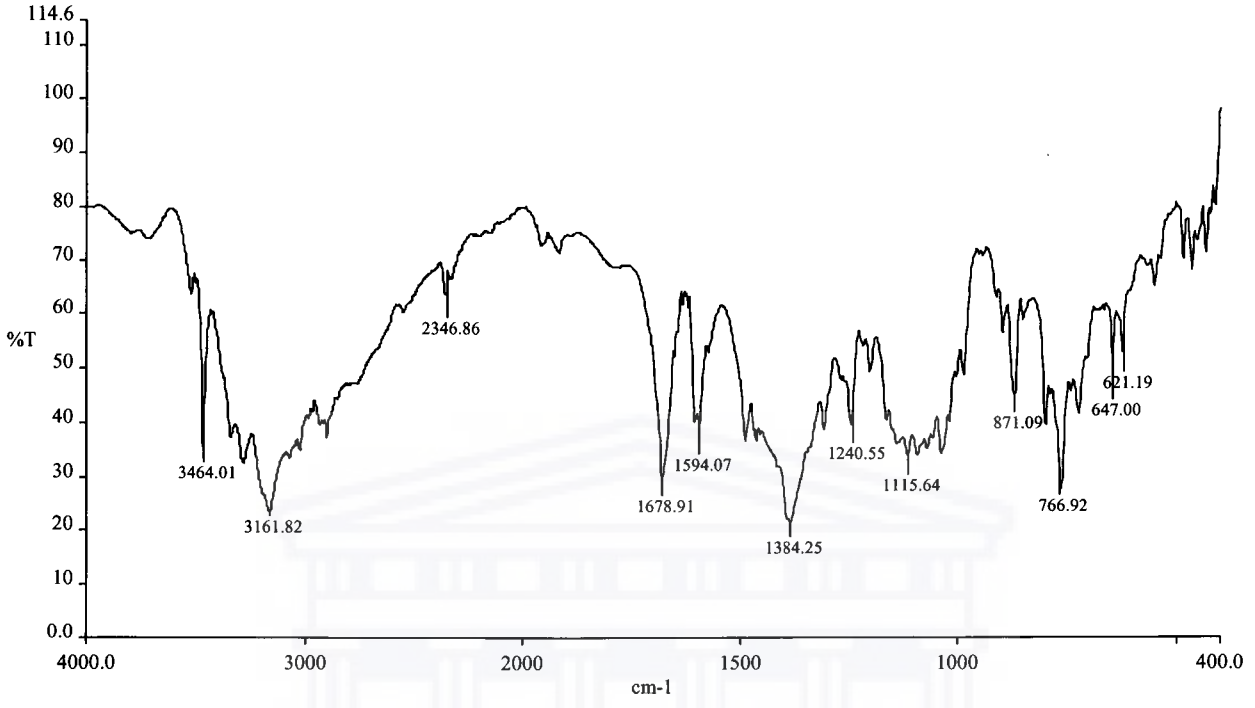

Figure 29. FTIR (DRIFT) analysis of CBZ tablets compressed from microwave dried granules.

Significant peaks were obtained at 3464.01 cm^{-1}, 3161.82 cm^{-1}, 1678.91 cm^{-1}, 1594.07 cm^{-1} and 1384.25 cm^{-1} respectively, for CBZ tablets dried by microwave oven.

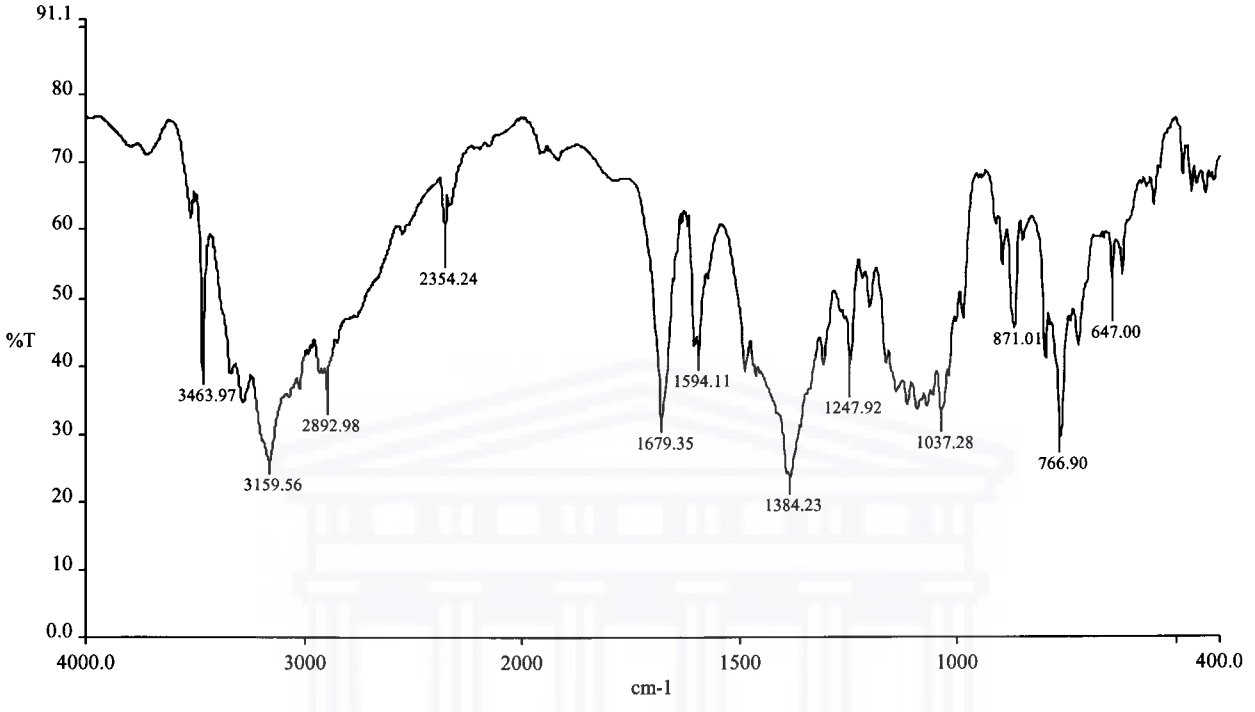

Figure 30. FTIR (DRIFT) analysis of CBZ tablets compressed from convection dried granules.

The significant bands were obtained at 3463.97 cm^{-1}, 3159.56 cm^{-1}, 1679.35 cm^{-1}, 1594.11 cm^{-1} and 1384.23 cm^{-1} respectively, for CBZ tablets dried by convection oven.

Table 20. FTIR peaks obtained for differently dried granules and resultant tablets.

Clarke's Std	ß-CBZ	M/O Granules	M/O Tablet	C/O Granules	C/O Tablet
1388 cm^{-1}	1384 cm^{-1}	1388 cm^{-1}	1384 cm^{-1}	1383 cm^{-1}	1384 cm^{-1}
1594 cm^{-1}	1594 cm^{-1}	1594 cm^{-1}	1594 cm^{-1}	1590 cm^{-1}	1594 cm^{-1}
1678 cm^{-1}	1678 cm^{-1}	1678 cm^{-1}	1678 cm^{-1}	1678 cm^{-1}	1679 cm^{-1}
	3158 cm^{-1}	3165 cm^{-1}	3161 cm^{-1}	3158 cm^{-1}	3159 cm^{-1}
	3463 cm^{-1}	3465 cm^{-1}	3464 cm^{-1}	3464 cm^{-1}	3463 cm^{-1}

Based on the results obtained from the FTIR DRIFT scans, it became clear that no major transformation occurred.

The peaks obtained at 1594 cm^{-1} for the aromatic C=C bond remained consistent for the microwave dried granules and resultant tablets. The convection oven dried granules showed a slight shift in peak at the aromatic C=C bond of 4 cm^{-1}. However, the resultant convection oven dried tablets showed no shift.

Similarly, the peaks obtained at the C=O bond remained consistent for the microwave died granules and resultant tablets at 1678 cm^{-1}. The convection oven dried granules also remained unchanged with only a minor shift of 1 cm^{-1}.

The peaks obtained at the NH_2 bond varied between 1- to 2 cm^{-1} between the microwave dried granules and -tablets; and the convection oven dried granules and -tablets respectively.

The a- and DHD polymorphs differed significantly from the β-polymorph in that the peaks at the C=O bond were respectively 10 cm^{-1} and 4 cm^{-1} apart, while the peaks at the C=C bond were respectively 2 cm^{-1} and 4 cm^{-1} apart. These peak differences served as valuable markers for detecting polymorphic shifts.

Based on the FRIR DRIFT scan results obtained, it could be concluded that no transformation of the commercial β-form occurred following microwave drying at 100% irradiation using the standard microwave oven. Similarly, no polymorphic transformation occurred when the granules were dried by convection oven at 60° C.

5.9.4 Pharmaceutical evaluation of the trial tablet

5.9.4.1 Uniformity of mass, size and shape

The results for the uniformity of mass, size and shape are given in table 21.

Table 21. Uniformity of mass, size and shape of carbamazepine tablets

	Batch 1 (Microwave dried)			Batch 2 (Convection dried)		
Serial number	**Tablet Weight (mg)**	**Diameter (mm)**	**Thickness (mm)**	**Tablet Weight (mg)**	**Diameter (mm)**	**Thickness (mm)**
1	410	10	4.2	392	10	4.0
2	405	10	4.2	399	10	4.0
3	394	10	4.2	425	10	4.4
4	393	10	4.1	398	10	4.0
5	393	10	4.1	400	10	4.4
6	398	10	4.2	399	10	4.2
7	400	10	4.2	394	10	4.1
8	396	10	4.2	388	10	4.0
9	405	10	4.3	388	10	4.0
10	395	10	4.2	385	10	4.0
11	398	10	4.2	401	10	4.4
12	401	10	4.2	399	10	4.0
13	395	10	4.2	395	10	4.0
14	399	10	4.2	389	10	4.0
15	402	10	4.2	415	10	4.3
16	397	10	4.2	405	10	4.3
17	394	10	4.2	395	10	4.0
18	398	10	4.2	392	10	4.0
19	406	10	4.3	398	10	4.0
20	404	10	4.2	402	10	4.3
Ave ± SD	**399.15 ± 4.87**	**10**	**4.2 ± 0.05**	**397.95 ± 9.33**	**10**	**4.12 ± 0.16**
Mean+5%	**419.11**			**417.85**		
Mean-5%	**379.19**			**378.05**		
SD	**28.22**			**28.14**		

The general requirement of the BP [5] is that no more than two tablets should deviate from the average weight by more than ± 5%. The deviation in mass for both the microwave- and convection dried tablets were within the limits of the BP [5]. The average diameters of both batches of tablets

were 10 mm. The standard deviation for the thickness variation among both batches of tablets were less than 5%.

5.9.4.2 Hardness test

The results of the tablet hardness for both batches (microwave dried and convection dried) are depicted in table 22.

Table 22. Tablet hardness results.

Serial no.	Hardness Batch 1 (N) (Microwave dried)	Hardness Batch 2(N) (Convection dried)
1	67	36
2	55	53
3	57	64
4	44	56
5	46	56
6	62	44
7	50	41
8	65	87
9	59	56
10	50	70
Ave ± SD	**55.5 ± 7.91**	**56.3 ± 14.90**

Tablet hardness of between 55N and 65N is regarded as conventional. The results indicated that the average tablet hardness for the microwave - and convection dried batches were 55.5N and 56.3N respectively. The hardness of both batches of tablets varied greatly as evidenced by the standard deviations. The hardness of the microwave dried tablets ranged between 44N and 67N whereas the convection dried tablets ranged between 36N and 87N. Thus, although it could be considered that the tablets from both batches were within the general range, the tablets appeared very soft.

5.9.4.3 Friability test

The results for tablet friability for both the microwave - and convection dried CBZ tablets are shown in table 23.

Table 23. Friability results for microwave - and convection dried carbamazepine tablets.

	Batch 1 (Microwave dried)	Batch 2 (Convection dried)
Initial Weight (g)	4.081	4.028
End Weight (g)	3.915	2.368
Difference in weight (g)	0.166	1.66
% Difference	4	41
Result	Fail	Fail

The general specification for a loss in mass due to friability is considered satisfactory if it is less than 1% [5]. As evident from the results depicted in table 24, both batches of tablets failed the friability test indicating that the tablets from both batches would not be able to withstand the physical rigors of handling and transportation. It would be highly likely that the tablets would break, chip or crack at some stage of the handling process.

Full elucidation of the reasons responsible for the high friability values obtained were not pursued.

5.9.4.4. Content uniformity test

The content uniformity test results as specified by the BP [5] for the twenty tablets yielded a CBZ content of 87% and 89% for the microwave - and convection dried batches respectively. Table 24 summarizes the CBZ content for five tablets per batch assayed individually.

Table 24. Content uniformity results for CBZ in microwave - and convection dried tablets.

Tablet	1	2	3	4	5	Ave ± SD (n=5)
M/O	106	97	95	95	96	**97.8 ± 4.66**
C/O	86	86	88	88	89	**87.4 ± 1.34**

Both batches of CBZ tablets passed the test since it contained more than the minimum requirement of 85 % of the stated quantity.

Although both batches of tablets and individual tablets from each batch complied with the specification of the minimum required 85% of the stated quantity, this assay was very subjective in that the quantity sampled might have contained more of the excipients than the active ingredient. The latter would then result in a false fail result. It was for the latter reason that each of five tablets from each batch was assayed individually. The average carbamazepine content per microwave dried tablet was 97.8 % compared to 87.4% for the convection dried tablet.

Although it became evident that the granule- and tablet characteristics of convection dried- and microwave dried processes varied, no further investigation was done.

5.9.4.5 Disintegration test

All six tablets from batches one and – two disintegrated within two minutes, well below the stipulated five minute disintegration time of the BP [5]. Both batches thus passed the disintegration test.

5.9.4.6 Dissolution test

Details of the standard curve used to quantitate the CBZ content during dissolution are given in figure 31.

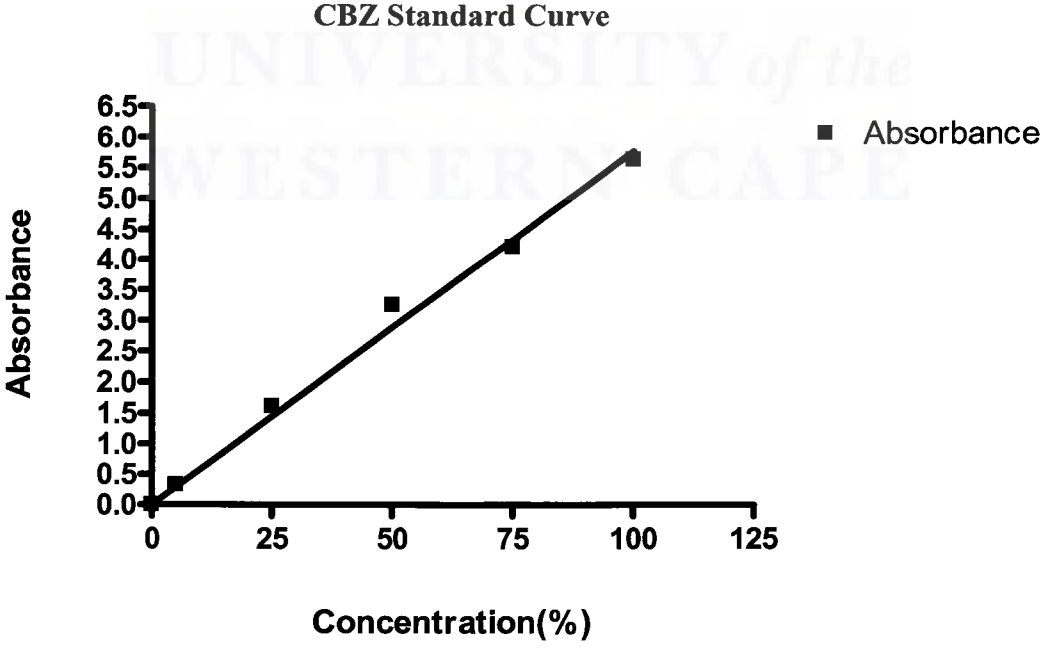

Figure 31. Standard curve for CBZ measured at 285nm

Best-fit values $y = 0.056 x + 0.124$

Slope: 0.056 ± 0.002

Y-intercept when X=0.0: 0.124 ± 0.124

X-intercept when Y=0.0: -2.208

1/slope: 17.84

95% Confidence Intervals

Slope: 0.049 to 0.062

Y-intercept when X=0.0: -0.22 to 0.469

X-intercept when Y=0.0: -9.152 to 3.643

Goodness of Fit: The standard curve was linear over a concentration range of 0.5-2mg/ml with $r^2 = 0.994$

Sy.x 0.1978, P value < 0.0001

The dissolution results for both microwave- and convection dried CBZ tablets are summarized in tables 25, -26 and figure32.

Table 25. Dissolution results of CBZ released from microwave dried tablets (n=6) into simulated gastric fluid.

	Amount (%) of Carbamazepine released into the dissolution medium at various times for batch one (microwave dried tablets).							
Time (min)	**Tablet 1 (%)**	**Tablet 2 (%)**	**Tablet 3 (%)**	**Tablet 4 (%)**	**Tablet 5 (%)**	**Tablet 6 (%)**	**Corrected Ave (%)**	**SD**
5	71.49	73.40	72.75	73.96	74.69	71.60	72.98	1.28
10	73.24	74.74	74.30	74.92	77.30	73.78	75.12	1.42
15	75.46	77.02	76.19	77.41	78.35	75.87	77.54	1.09
30	78.05	78.05	77.95	79.68	81.08	77.78	80.02	1.35
45	81.40	81.29	81.38	81.60	82.48	79.94	83.03	0.84
60	83.14	83.36	83.13	83.32	83.65	82.46	85.32	0.41
90	84.75	84.88	84.87	85.67	86.23	84.22	87.70	0.74

Table 26: Dissolution results of CBZ released from convection oven dried tablets (n=6) into simulated gastric fluid.

	Amount (%) of Carbamazepine released into the dissolution medium at various times for batch two (convection oven dried tablets).							
Time (min)	Tablet 1 (%)	Tablet 2 (%)	Tablet 3 (%)	Tablet 4 (%)	Tablet 5 (%)	Tablet 6 (%)	Corrected Ave (%)	SD
5	77.28	76.73	76.70	75.52	76.67	76.18	76.51	0.60
10	78.99	79.09	79.44	77.18	78.60	77.05	78.82	1.06
15	81.35	79.40	80.89	79.52	80.84	78.82	80.99	1.03
30	83.78	82.02	83.07	80.98	82.01	81.34	83.51	1.07
45	84.10	83.89	83.96	82.61	83.58	82.97	85.28	0.61
60	85.30	83.92	84.81	83.15	84.51	83.87	86.49	0.79
90	86.91	87.11	90.02	86.53	87.25	86.02	89.00	1.43

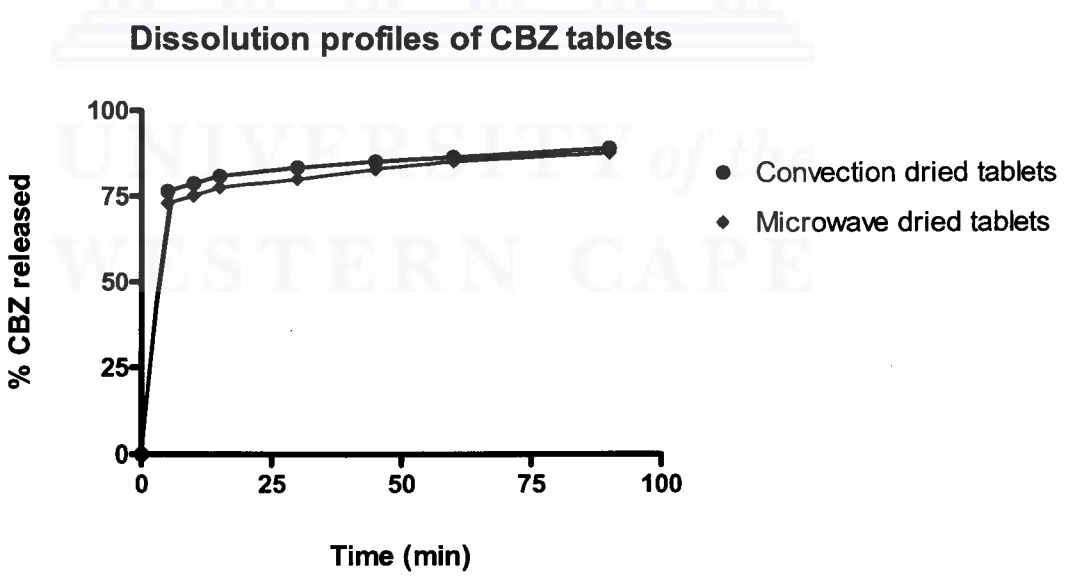

Figure 32. Dissolution profiles for microwave-and convection dried CBZ tablets.

The dissolution profiles for the differently dried CBZ tablets yielded a strikingly similar release pattern. High percentage CBZ releases of 72% and 76% were recorded for the microwave dried- and convection dried tablets respectively after five minutes. Both tablet batches yielded a CBZ release of 83% and 85% for the microwave dried –and convection dried tablets after forty five minutes respectively, which met the BP [5] requirement of a 70% drug release within that time frame. A maximum drug release of 87% and 89% were recorded for the two batches respectively after ninety minutes.

The initial high drug release could be attributed to various factors. The first was the inclusion of ethanol as solvent and secondly, PVP as binder in the granulating fluid. The ethanol contributed to some of the CBZ being dissolved during granulation. The PVP absorbed onto CBZ particles that would undoubtedly increase its wettability resulting in enhanced dissolution. Nokhodchi and co-workers [38] studied the dissolution behaviour of CBZ recrystallized from alcohol and found that additives such as PVP increased the dissolution rate and thus drug release.

Thirdly, the use of simulated gastric fluid as the dissolution media in an attempt to mimic the gastrointestinal environment, also contributed to the high drug release as opposed to using distilled water as the dissolution medium. A much lower dissolution rate would have been anticipated with the use of the latter since CBZ is practically insoluble in water [5, 29, 45]. A study conducted by Jung and co-workers [19] evaluating the dissolution profiles of different brands of CBZ tablets using different dissolution media, revealed that the latter yielded different drug release profiles. In that study, sodium lauryl sulphate (1%) yielded the highest drug release patterns whereas a hydrochloric acid solution (0.1N) yielded the lowest drug release pattern.

It can be concluded that since the dissolution profiles of the two batches were very similar, it was highly unlikely that the differently dried tablets contained different CBZ polymorphs. Nair and co-workers [37] found that the dissolution profiles for their polyethylene glycol (PEG) solid dispersions yielded a characteristic decrease in the amount of CBZ released after 30 minutes. The latter decline in drug release observed were due to the polymorphic transformation of the anhydrous CBZ to the more stable dihydrate form in water. Similar dissolution results have been observed by Murphy and co-workers [36] when they evaluated the kinetic data for the anhydrous to dihydrate transformation of CBZ in water.

5.10 Conclusion

Microwave drying of a 300 grams granule batch was 10 times faster than the equivalent dried in a convection oven. The morphology of the microwave dried granules was more compact and crisp than the convection oven dried counterparts.

Analysis of XRPD and FTIR spectra for the differently dried granules yielded no significant peak differences. All granule spectra revealed strikingly similar patterns to that of the commercial CBZ form indicating no polymorphic shift.

The compressed tablets passed all the British Pharmacopoeia [5] quality control specifications for conventional uncoated tablets (uniformity of mass, size and shape, hardness, content uniformity, disintegration and dissolution) except friability, despite having acceptable hardness ranges. The results obtained for microwave - and convection dried tablets were very similar.

The XRPD and FTIR findings suggested that no significant differences existed between microwave dried granules and – tablets and those dried by convection oven. In addition, the commercial ß-form has not undergone any polymorphic transformation.

CHAPTER 6

CONCLUSION

The overall objective of the present study was to evaluate whether microwave drying altered the polymorphic characteristics of CBZ contained in granules and tablets during a wet granulation process, in comparison to convection drying.

The hypothesis was that microwave drying do not alter the polymorphic nature of CBZ contained within granules and resultant tablets.

From the results obtained, the following conclusions could be drawn from this study

1. Distinct XRPD and FTIR spectra obtained for the commercial CBZ (ß) powder as well as the a- and DHD-CBZ polymorphs could serve as valuable markers for future study or quality control testing within the pharmaceutical industry.

2. Preformulation studies revealed complete compatibility between CBZ and the excipients anhydrous lactose, sodium starch glycloate, polyvinylpolypyrrolidone, silicon dioxide and magnesium stearate.

3. The energy transfer within the microwave heating cavity was not homogenous although the rotating base compensated somewhat for the temperature difference. No definitive temperature measurements could be obtained inside the heating cavity of the commercial microwave oven used when the granules were dried. The standardization of temperatures achievable using distilled water provided an indication of the time frame in which heating to a particular point would take. In the case of solvents, the boiling point would be the end point since no increase in temperature would be achieved beyond the boiling point.

4. The manufacture of the granules using the high shear granulator proved fairly successful and could prove economically viable when done on a larger production scale. All the tablet constituents proved microwave compatible in that none charred. Microwave drying of a 300 grams granule batch was 10 times faster than the equivalent dried in a convection oven. The

morphology of the microwave dried granules were more compact and crisp than the convection oven dried counterparts.

Analysis of XRPD and FTIR spectra for the differently dried granules yielded no significant peak differences. All granule spectra revealed strikingly similar patterns to that of the commercial CBZ form indicating no polymorphic shift.

5. The compressed tablets passed all the British Pharmacopoeia [5] quality control specifications for conventional uncoated tablets (uniformity of mass, size and shape, hardness, content uniformity, disintegration and dissolution) except friability, despite having acceptable hardness ranges. This aspect could be improved upon for commercialization. The results obtained for microwave - and convection dried tablets were very similar.

Collectively, the XRPD and FTIR findings suggested that no significant differences existed between microwave dried granules and - tablets and those dried by convection oven. In addition, the commercial ß-form has not undergone any polymorphic transformation.

Arising from this study, the following aspect could be investigated:

1. The fast release formula could be optimized for commercialization using design of experiment (DOE) and statistical analysis which have been proven to be efficient and effective in formulation and process development. The major advantage of using DOE to develop formulations would be that it provides an effective methodology to evaluate all potential factors simultaneously and in a timely manner. The effect of each factor on the final dosage form response and its significance, can be evaluated.

In summary, it could be concluded that the XRPD and FTIR results of this study confirmed that microwave radiation did not alter the polymorphic characteristics of CBZ contained within the granules and compressed tablets during a wet granulation process. However, microwave drying is not generally recommended for all active pharmaceutical substances or excipients since the thermal and dielectric properties of some substances might enhance unacceptable thermic damage. Nevertheless, the hypothesis that microwave drying do not alter the polymorphic nature of CBZ contained within granules and resultant tablets was confirmed.

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Appendix 1. Elongation and Haywood's ratios (N=L/B) for CBZ powder.

No	L (μm)	B (μm)	N	No	L (μm)	B (μm)	N	No	L (μm)	B (μm)	N	No	L (μm)	B (μm)	N
1	90	60	1.5	**26**	90	50	1.8	**51**	30	30	1.0	**76**	80	70	1.14
2	60	40	1.5	**27**	70	40	1.75	**52**	30	10	3.0	**77**	60	60	1.0
3	40	40	1.0	**28**	50	50	1.0	**53**	80	60	1.33	**78**	50	30	1.67
4	90	90	1.0	**29**	30	30	1.0	**54**	60	50	1.20	**79**	50	20	2.5
5	80	40	2.0	**30**	30	30	1.0	**55**	20	20	1.0	**80**	90	70	1.29
6	50	40	1.25	**31**	50	50	1.0	**56**	30	20	1.5	**81**	40	40	1.0
7	40	40	1.0	**32**	70	50	1.40	**57**	50	50	1.0	**82**	40	30	1.33
8	60	40	1.5	**33**	50	40	1.25	**58**	20	20	1.0	**83**	20	20	1.0
9	90	40	2.25	**34**	80	60	1.33	**59**	20	20	1.0	**84**	20	20	1.0
10	100	60	1.67	**35**	90	80	1.13	**60**	60	40	1.5	**85**	100	80	1.25
11	110	100	1.10	**36**	60	40	1.50	**61**	90	80	1.13	**86**	40	40	1.0
12	20	20	1.0	**37**	20	20	1.0	**62**	30	30	1.0	**87**	70	40	1.75
13	60	40	1.5	**38**	30	20	1.5	**63**	20	20	1.0	**88**	60	50	1.2
14	50	40	1.25	**39**	50	40	1.25	**64**	50	50	1.0	**89**	50	40	1.25
15	100	70	1.43	**40**	50	40	1.25	**65**	60	50	1.2	**90**	40	30	1.33
16	40	40	1.0	**41**	50	50	1.0	**66**	30	20	1.5	**91**	40	30	1.33
17	80	50	1.6	**42**	10	10	1.0	**67**	20	20	1.0	**92**	40	30	1.33
18	90	50	1.8	**43**	20	20	1.0	**68**	60	30	2.0	**93**	40	30	1.33
19	50	40	1.25	**44**	30	20	1.5	**69**	80	60	1.33	**94**	20	10	2.0
20	60	30	2.0	**45**	40	40	1.0	**70**	30	30	1.0	**95**	10	10	1.0
21	20	20	1.0	**46**	30	30	1.0	**71**	50	40	1.25	**96**	20	20	1.0
22	50	40	1.25	**47**	20	10	2.0	**72**	80	80	1.0	**97**	40	30	1.33
23	60	40	1.5	**48**	30	30	1.0	**73**	40	30	1.33	**98**	20	20	1.0
24	100	60	1.67	**49**	60	50	1.20	**74**	20	20	1.0	**99**	100	50	2.0
25	50	50	1.0	**50**	40	40	1.0	**75**	30	20	1.5	**100**	40	40	1.0

Ave L = 50.6 μm SD L = 24.89

B = 39.3 μm SD B = 18.34

N = 1.31 μm SD N = 0.37

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Appendix 2. Simulated gastric acid fluid composition (USP 1985)

Compound	NaCl	Pepsin	HCl	Distilled Water
Quantity	2 g	32.2 g	7.0 ml	ad 1000 ml

The sodium chloride and pepsin were dissolved in the hydrochloric acid. Sufficient distilled water was added to make up 1000 ml. The solution was stirred until all particles were dissolved. The resultant pH was 1.2 as measured by a Sentron® pH meter. The dissolution medium was de-aerated with nitrogen.

Appendix 3. Flowability (Angle of repose) of CBZ

Sample no.	Height (cm)	Radius (cm)	Angel of repose (°)
1	1.86	3.10	30.96
2	2.00	3.41	30.54
3	2.09	3.15	33.42
4	2.00	3.00	33.82
5	2.40	3.25	36.50
6	2.15	2.75	37.95
7	1.92	3.15	31.38
8	2.14	3.15	34.22
9	1.98	3.25	31.38
10	1.8	3.30	28.81
Ave	**2.03**	**3.15**	**32.90**
SD	**± 0.17**	**± 0.18**	**± 2.83**

Appendix 4. Flowability (Angle of repose) of sodium starch glycolate (Emcompress®)

(Sample no.	Height (cm)	Radius (cm)	Angel of repose (°)
1	1.59	3.4	25.17
2	1.80	3.45	27.47
3	1.63	3.55	24.70
4	1.63	3.75	23.27
5	1.31	3.9	18.79
6	1.73	3.4	27.02
7	1.36	3.7	20.30
8	1.40	3.5	21.80
9	1.66	3.4	26.10
10	1.80	3.65	26.10
Ave	**1.59**	**3.57**	**24.07**
SD	**± 0.18**	**± 0.17**	**± 2.94**

Appendix 5. Flowability (Angle of repose) of anhydrous lactose (Tabletose®)

Sample no.	Height (cm)	Radius (cm)	Angel of repose (°)
1	1.98	3.50	29.68
2	2.15	3.50	31.38
3	1.85	3.50	27.92
4	2.09	3.45	31.38
5	2.14	3.45	31.80
6	2.21	3.30	33.82
7	1.93	3.30	30.11
8	1.82	3.50	27.47
9	1.76	3.55	26.57
10	1.80	3.50	27.02
Ave	**1.97**	**3.46**	**29.72**
SD	**± 0.16**	**± 0.09**	**± 2.41**

Appendix 6. Flowability (Angle of repose) of magnesium stearate

Sample no.	Height (cm)	Radius (cm)	Angel of repose (˚)
1	1.70	3.25	27.47
2	1.52	3.25	25.17
3	1.91	3.15	31.38
4	1.90	3.25	30.11
5	1.52	3.40	24.22
6	1.69	3.20	27.92
7	1.49	3.40	23.75
8	1.41	3.70	20.81
9	1.47	3.55	22.29
10	1.57	3.55	23.75
Ave	**1.62**	**3.37**	**25.69**
SD	**± 0.18**	**± 0.18**	**± 3.42**

Appendix 7. Flowability (Angle of repose) of polyvinylpolypyrrolidone (Kollidon CL®)

Sample no.	Height (cm)	Radius (cm)	Angel of repose (˚)
1	1.90	3.00	32.21
2	1.70	3.25	27.47
3	1.78	3.15	29.68
4	1.70	3.20	27.92
5	1.73	3.25	27.92
6	1.56	3.45	24.23
7	1.61	3.25	26.57
8	1.78	3.15	29.68
9	1.76	3.10	29.68
10	1.50	3.40	23.75
Ave	**1.70**	**3.22**	**27.91**
SD	**± 0.12**	**± 0.13**	**± 2.60**