CHAPTER 6
PRODUCT DEVELOPMENT

6.1 Introduction

The physical and chemical characteristics of an API form the basis for the successful formulation of any dosage form. The discovery of a new active pharmaceutical ingredient (API), or the further development of an existing API, requires that the precise characteristics of the compound be determined, as part of the pre-formulation phase. Once the physico-chemical profile is established, the development of a suitable dosage form can proceed. The most manufactured and researched dosage form is the oral solid dosage form, i.e. tablets (Brittain, 2008:1; York, 2002:1).

The science of product development not only entails the design of a formulation, but also involves the assurance of excellent product quality. The main goal of formulation scientists is good patient compliance (Brittain, 2008:1; York, 2002:1).

This chapter describes the process of developing tablet formulations for the novel AZM-G being prepared during this study, as well as for the stable AZM-DH, serving as the reference. These manufactured tablets were then subjected to stability testing conditions to determine the stability of AZM-G and AZM-DH in tablet formulation. The dissolution outcomes of each of these tablet formulations in different aqueous media are also described. This product development study formed part of further research and development of the patent being described in PCT/IB2010/055842.

6.2 Solid dosage form design

The process of designing a solid dosage form (tablets or capsules) requires much research and development. The active drug compound must be characterised and fully profiled with regards to its chemical and physical properties. Another important aspect comprises choosing the best suited excipient(s) to produce an effective formulation. Excipients are also commonly referred to as the inactive ingredients in solid dosage form formulations (Alderborn, 2002:405; Brittain, 2008:347).

Apart from the excipients being used, the possibility of interactions between the active drug compound and the added excipients should also be investigated during development of the solid dosage form. Excipients should fulfil their basic functions of enabling successful tableting, whilst also facilitating the release of the active drug compound from the solid dosage form. Interactions between excipients and the active drug compound may result in the stability of the solid dosage form being altered. In some cases, excipients must deliberately interact with the active drug compound for a designed, controlled, drug release. In other instances where the active drug compound must be rapidly released, excipients must have no interactions with the active drug. Ultimately, the active drug compound should remain stable within the solid dosage form. (Brittain, 2008:347).

The two main solid dosage forms are tablets and capsules. Tablets are formulated as uncoated, coated and enteric coated. Tablets account for most of the manufactured solid dosage forms on the market. Certain active drug compounds allow for direct compaction, requiring only one or two excipients for successful tableting. Others must be granulated in order to improve their powder properties for better and more accurate tableting. Granulation of the initial active compound powder can be achieved by way of wet- or dry granulation. Before deciding whether to use the granulation or direct compaction method, the powder flow properties of the active drug compound must be evaluated (Brittain, 2008:347; Prescott & Barnum, 2000:60; Summers & Aulton, 2002: 365).

Flowability can be commonly described as the powder's ability to flow. The flow of a powder depends on its actual characteristics. Powders may flow with ease in one specific hopper, but poorly when placed in another. This means that both the material and equipment being utilised during solid dosage form development and powder flow testing are important. The flowability cannot be characterised by a single test. The behaviour of a powder in bulk volume can also be a determining factor in the development of a solid dosage form. The flow properties of a compound will furthermore ultimately affect the weight and content uniformity of a solid dosage form during manufacturing. It is thus evident that many aspects relating to the efficiency of the manufacturing process are determined by the powder flow. The flow of a powder will furthermore determine the type and extent of excipients being used during formulation and during the development of a solid dosage form (Prescott & Barnum, 2000:60; Staniforth, 2002:197).

The tableting process is coupled with the free flowing characteristics of the active drug powder and the chosen excipients. According to Staniforth (2002:197), free flowing powders are important for the following reasons:

- Uniform feed into tableting or capsule filling equipment, which allows for uniformity of tablet weight and volume-to-mass ratio.
- Reproducible filling of the capsule dosators, or the tablet dies, which allows for uniform weight and tablets with consistent physico-mechanical properties.
- Powder flow that is uneven may trap unwanted air within the particles and may ultimately encourage capping or lamination of the tablets.
- Surplus fine particles present in the powder may lead to uneven powder flow and may also result in increased contamination risks.

6.2.1 Particle size, shape and density

The flow of a powder is much influenced by the size(s) of the particles. The surface of particles is exposed to forces, i.e. cohesion and adhesion. Cohesion occurs between similar surfaces, whereas adhesion occurs between dissimilar surfaces. Free flowing powders usually consist of particles larger than 250 µm. Particles that range below 100 µm in size cause the powder to flow poorly, due to cohesive forces between the particles. In the event of the powder particle size being smaller than 10 µm, the powder flow is extremely poor (even under gravity), as a result of strong cohesive forces. The shape of the particles also affects the flow of powders. With big differences between the shapes of particles, the contact areas between particles vary, which will alter the flow properties. The density of particles also impact on the flow of powders. Particles that are densely packed display less cohesive forces than particles that are equal in shape and size, but less densely packed (Newman, 1995:275; Staniforth, 2002:201).

6.2.2 Characterisation of powder flow properties

The USP (2010) reports methods that are commonly used to determine the flow properties of powders. Among these methods are angle of repose, compressibility index (Hausner ratio and Carr index), and powder flow through a hopper (Amidon, 1995:293; Staniforth, 2002:205).

6.2.2.1 Angle of repose

The method for angle of repose is based on interparticulate cohesion, more particularly the resistance to particle movement, resulting from friction and cohesive forces. The different methods to determine the angle of repose may result in inconsistent results for the same powder and is it therefore important to be aware that the angle of repose is much dependant on the method used. It is generally described that a powder with an angle of repose in the range of 25˚ - 30˚ exhibits excellent flow properties, whereas an angle of repose higher than 66˚ would indicate extremely poor powder flow properties (Amidon, 1995:293; Staniforth, 2002:205; USP, 2010).

The method used to determine the angle of repose of azithromycin glass (AZM-G) was with the fixed height cone. The AZM-G powder was tested accordingly and it was found that the cohesive and adhesive forces were very strong, as the powder did not discharge at all. Adhesion caused the powder to form an arch on the inside surface of the hopper near the outlet, therefore restricting the outflow of the powder. The powder particles clogged together and fell through the cone onto the base below. The complete volume of powder did not discharge from the cone and therefore the powder present on the base (caused by one or two clogged powder floods) was not representative of the initial volume of powder and was it thus impossible to determine the angle of repose. However, it was evident that the powder flow properties of AZM-G were very poor.

6.2.2.2 Compressibility

Compressibility, coupled with the Hausner ratio, have been the most simple and effective methods for predicting the flow properties of powders. Both these methods rely on the volume of a powder, more specifically the bulk- and the tapped volume. The bulk volume represents a certain weight that occupies that specific volume (Prescott & Barnum, 2000:66). Accordingly, the bulk density can thus be determined with the following formula (Newman, 1995:276; Staniforth, 2002:200; USP, 2010):

$$P_B = w/v \qquad (6.1)$$

Where: P_B represents the bulk density (g/cm^3), w is the weight of the powder (g), and v is the volume of the bulk powder (cm^3). 44.158 g of AZM-G powder was transferred into a graduated cylinder. This weight of AZM-G powder occupied a volume of 80 mL. According to the formula for bulk density therefore, it was calculated that the bulk density of AZM-G should equal 0.552 g/cm^3.

The tapped density is representative of the volume that the powder occupies after it has been placed on a vibrating apparatus for a period of time. It can also be defined by the same formula being used to determine the bulk density. Hence the tapped density can be defined by:

$$P_T = w/v \qquad (6.2)$$

Where: P_T is the tapped density (g/cm^3), w is the weight of powder placed in the cylinder (g), and v is the volume occupied by the powder after vibration (cm^3) (Staniforth, 2002:200; USP, 2010). The tapped density of AZM-G powder was determined by transferring 44.158 g of AZM-G powder into a graduated cylinder. The cylinder was placed on a vibrating apparatus for 15 minutes, vibrating at an amplitude of 5. The volume of the powder was determined (60 mL) and the tapped density was calculated accordingly. The tapped density was calculated as 0.735 g/cm^3.

By using the determined bulk and tapped densities, the compressibility of AZM-G was calculated. The compressibility of a powder is defined by the following formula:

$$\% \text{ compressibility} = ((P_T-P_B)/P_T) \times 100 \qquad (6.3)$$

Where: P_T is the tapped density and P_B is the bulk density (Newman, 1995:276; Staniforth, 2002:207; USP, 2010).

The percentage compressibility was calculated as 25 %, which, according to the compressibility index (also referred to as Carr's index) of the USP (2010), meant that the flow properties of AZM-G powder was characterised as "passable" (21 - 25 %).

Compressibility can also be correlated with the Hausner ratio. This method also makes use of the bulk- and tapped density of the powder. The Hausner ratio can therefore be defined by the following formula:

$$\text{Hausner ratio} = P_T/P_B \qquad (6.4)$$

Where: P_T is the tapped density and P_B the bulk density (Staniforth, 2002:207; USP, 2010). Resulting from the two calculated densities, the Hausner ratio was calculated as 1.33, which, according to the USP (2010), characterised the flow properties of AZM-G powder as "passable". Both methods being utilised to determine compressibility hence established that the flow properties of AZM-G were passable (Staniforth, 2002:208; USP, 2010).

6.2.2.3 Flow through a hopper

This method for determining the flowability of a powder is highly regarded and is generally used for this test. The powder is allowed to flow through a hopper onto a balance that is connected to a flow-meter. As the powder flows through the hopper, the continuous weight increase is recorded and displayed on the computer. This allows for the determination of the flow rate of the powder, as well as for the quantification of the uniformity at which the flow occurs (Prescott & Barnum, 2000:66; Staniforth, 2002:208; USP, 2010).

As with the angle of repose method, the flow through a hopper resulted in the same poor flowing of AZM-G powder. The powder clogged and hence caused a blockage at the discharge opening of the hopper. Strong cohesive forces hence negatively impacted on the flow of AZM-G powder. Adhesion of the AZM-G powder to the inside surface area of the hopper also occurred. Consequently the powder flow properties of AZM-G powder could not be determined with this method.

6.2.3 Methods for improving the flow of AZM-G powder

6.2.3.1 Particle size

The flow of a powder can be positively managed by changing the size of the particles, as well by altering the size distribution of the particles. Different powders present with different optimum particle sizes that facilitate the free flow of the powders. The flow of a powder will improve with removal of the fine particles present in the batch and by replacing them with more coarse particles. This can be achieved through the granulation process. Primarily, granulation is used to improve the flow properties, as well as the ability of the powder (in a granulated state) to be compressed into a solid dosage form (tablet) (Staniforth, 2002:208).

Granulation is a process during which powder particles are aggregated to produce larger, multi-particle granules, consisting of the initial powder particles and excipients. Granules can be used as a dosage form, or it can be functionally utilised during the manufacturing of other preparations and dosage forms. The sizes of granules that are being prepared for the manufacturing of tablets differ a lot from granules that serve as a dosage form in its granulated form. The sizes of granules that are used for the production of tablets usually range between 0.2 - 0.5 mm (Summers, 2002:360). During this study particle sizes were measured with a Malvern Mastersizer 2000 (Malvern Instruments, UK). The particle size

of AZM-DH was measured and was it found that 90 % of the particles were less than 124 µm (Figure 6.1), whereas the granules of AZM-DH after wet granulation resulted in 90 % being smaller than 427.26 µm (Figure 6.2).

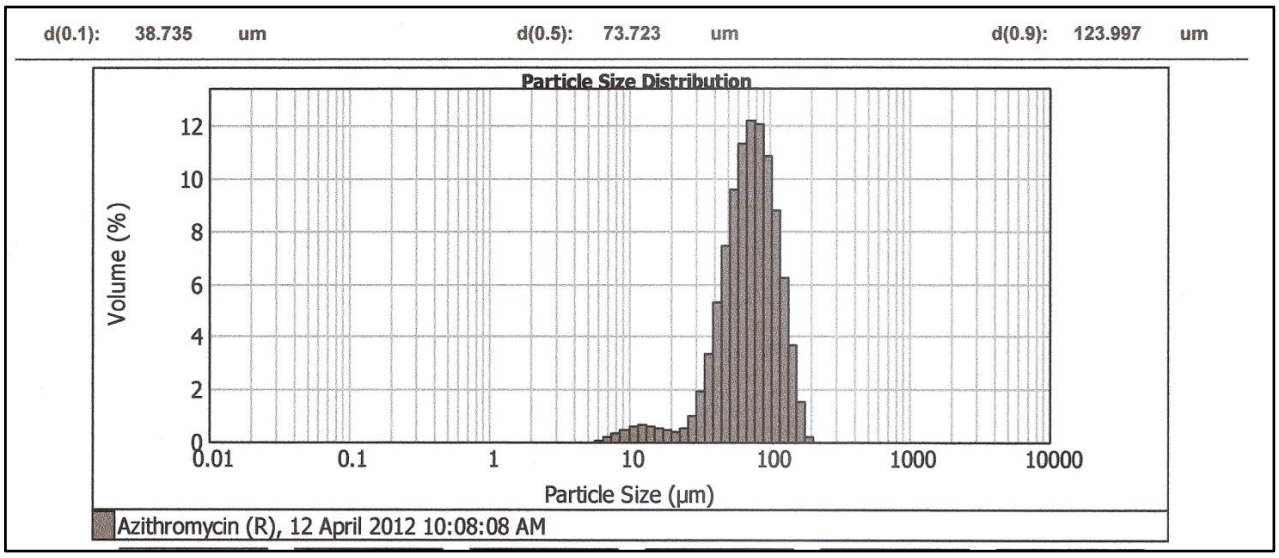

Figure 6.1 Particle size distribution of AZM-DH.

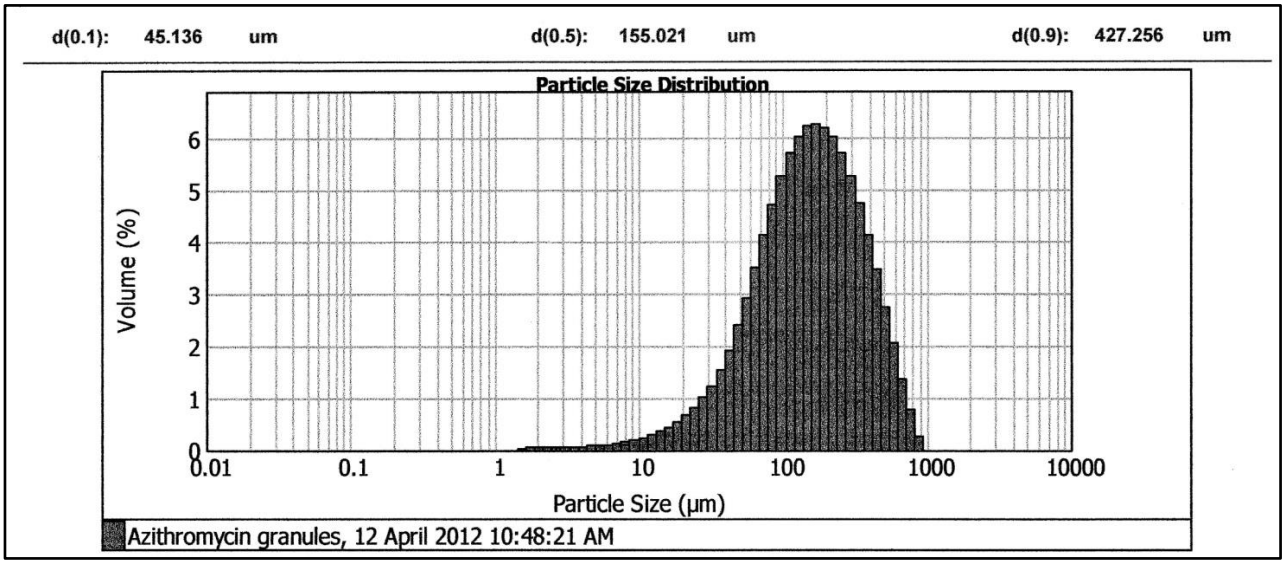

Figure 6.2 Particle size distribution of AZM-DH granules.

The particle size of AZM-G (powdered) resulted in 90 % being smaller than 117.92 µm (Figure 6.3), whilst 90 % of the granules prepared by wet granulation were smaller than 210.71 µm (Figure 6.4).

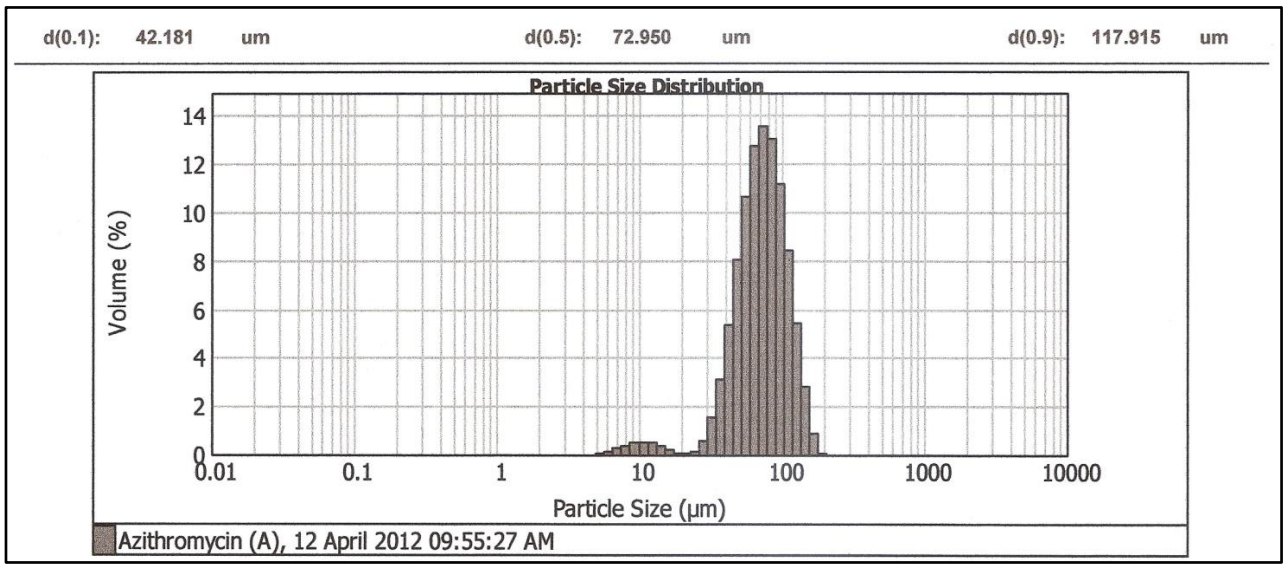

Figure 6.3 Particle size distribution of AZM-G.

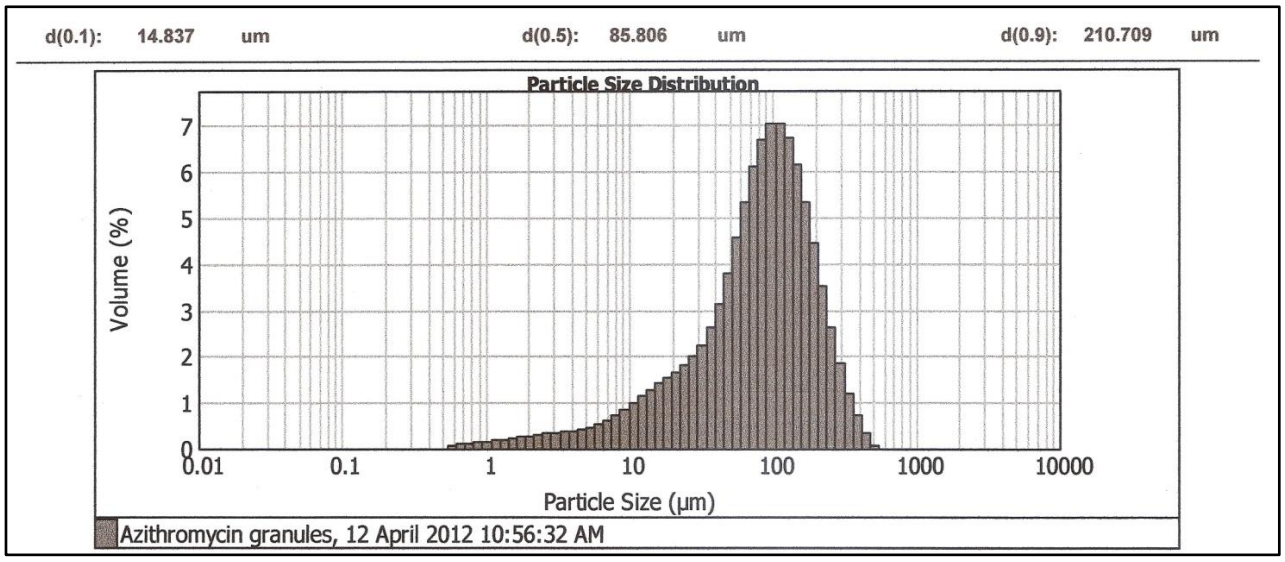

Figure 6.4 Particle size distribution of AZM-G granules.

Particle size distribution of granules is an important consideration during granulation, since a large size distribution may result in the segregation of the granules. This will cause a variation in bulk densities of the segregated granules and hence will result in large disparity in the weight and active drug compound of the manufactured products (Summers & Aulton, 2002:365).

6.2.3.2 Excipients

Inactive ingredients, or excipients, are generally utilised to improve the flow properties of powders showing poor flow capabilities. Excipients are characterised, according to their functions towards the active drug compound in a certain formula. To improve powder flow,

a group of excipients, called flow activators, or glidants, are included in the formula of the solid dosage form. This group of excipients acts on the principle of reducing the existing cohesive and adhesive forces among drug particles. As a result, the electrostatic interactions between the particles are also altered, which will ultimately improve the flow of the powder. Talc, maize starch and magnesium stearate are a few glidants that are generally used in formulations for enhancing powder flow properties (Rowe *et al*., 2009:728; Staniforth, 2002:209).

Talc is also known as hydrous magnesium silicate. It is characterised as a glidant that improves the free flowing properties of a powder. This excipient also provides additional functionalities, by acting as an anti-caking agent, a diluent for tablet and capsule formulae, and also as a lubricant for tablets and capsules. It is recommended that talc is used in concentrations of 1 - 10 % and 5 - 30 %, respectively, when added as glidant or diluent. Talc is known to absorb small amounts of water, but it is so minimal that it has little or almost no effect on a formulation. The particle sizes of talc vary between 44 µm and 74 µm (Rowe *et al*., 2009:728).

Magnesium stearate (Batch number: 21203) serves as a lubricant in both tablets and capsules. The concentration of magnesium stearate generally being used ranges between 0.25 % and 5.0 % (Rowe *et al*., 2009:404).

Copovidone (Kollidon® VA 64, Batch number: 93520356PO) is a granulation agent that facilitates the binding of granules within the tablet. It is commonly used as a binder during direct compression and wet granulation. When applied as binding agent during wet granulation and direct compression, copovidone is added in a concentration of 2.0 - 5.0 % for tablets. Copovidone also offers additional functionalities by acting as a barrier to avoid moisture uptake whilst it may further provide improved adhesion qualities, elasticity and hardness to the tablets. It is, however, reported that copovidone resulted in a weight gain of approximately 10 % after exposure to 50 % relative humidity (Rowe *et al*., 2009:196).

Croscarmellose sodium (Ac-Di-Sol®, Batch number: T017C) is an excipient that serves the function of disintegrant for tablets and capsules. It is used in formulations for direct compression and wet granulation. Croscarmellose sodium should be equally divided in the wet and dry phases during the wet granulation process. Although a concentration of 3.0 - 5.0 % is usually sufficient for performing the disintegration function during wet granulation, the proposed concentration ranges between 0.5 - 5.0 %. The particle size of Ac-Di-Sol® ranges from 45 µm to 74 µm (Rowe *et al*., 2009:206).

Microcrystalline cellulose (Avicel® PH 200, Batch number: N3937) primarily serves the function of a tablet or capsule diluent (binder) and also as a tablet disintegrant. It displays characteristics of lubrication in tablet formulae. This excipient is utilised in both wet granulation and direct compression methods. Microcrystalline cellulose is regarded as hygroscopic and may include a water content of up to 5.0 %. The particle size of Avicel® PH 200 ranges between 20 µm and 200 µm (Rowe *et al*., 2009:129).

Sodium starch glycolate (Explotab®) is primarily a disintegrant for tablets and capsules. It is readily used in tablet formulations that are prepared *via* direct compression, or wet granulation. Concentrations between 2 - 8 % are generally employed in formulations, but the optimal concentration being reported is 4 %. This excipient is very hygroscopic and has an average particle size distribution of 38 µm (Rowe *et al*., 2009:663).

6.2.4 Granulation methods

The granulation process can be performed with or without a liquid. In the event that a liquid is employed during the process, the method is referred to as wet granulation, whereas dry granulation doesn't apply any liquid. Granulation is much dependant on the use of functional excipients for developing a suitable formulation (Prescott & Barnum, 2000:74; Summers & Aulton, 2002:365).

6.2.4.1 Dry granulation

This granulation method consists of mixing the primary dry contents of the formulation, whereafter it is exposed to high pressure to ensure aggregation of the powder particles. After aggregation of the powder, one of two processes can be followed. The first process, commonly referred to as slugging, is to produce a slug (large tablet) by using a big tableting press. The other process, commonly referred to as roller compaction, forces the powder through two rollers. The rollers compact the powder to form a sheet. In both instances, the next step is to grind the intermediate product in order to generate granules that are then sieved to achieve the desired particle size distribution. The dry granulation method is often used when active drug compounds are moisture sensitive and if the compressibility of the powder is poor, due to wet granulation (Prescott & Barnum, 2000:74; Summers & Aulton, 2002:366).

6.2.4.2 Wet granulation

Wet granulation is achieved when the primary dry content of the formulation is mixed with a suitable liquid, which acts as the granulating agent. This solvent must be of such nature (preferably volatile and non-toxic) that it can be easily removed from the formulation through drying. Some of the liquids that are most often used as wet granulating agents are water, ethanol and isopropanol. These solvents possess the characteristic of inducing particle adhesion, as they bind the particles within the granules after being dried. Water is proposed to be the most used granulation solvent, but it may change the stability of the active drug compound in the formulation, when sensitive to water (hygroscopicity). After preparing the wet mass, it is placed on a sieve and carefully forced through the mesh to form wet granules. These wet granules are then exposed to dry heat in order for the granules to dry and to remove the liquid granulating agent (Prescott & Barnum, 2000:76; Summers & Aulton, 2002:366).

6.3 Direct compression of AZM-G powder

AZM-G was milled into a powder. The physico-chemical properties of this powder were then determined prior to commencing the development of a solid dosage form. The characterisation, solubility and stability of AZM-G powder were defined, as described in Chapter 5. The flow properties of AZM-G powder were also established (Section 6.2.2).

After establishing the poor flow properties of AZM-G powder, it was decided to first examine direct compression as possible method for manufacturing the tablets. Excipients were included in the formulation to attempt improving the flowability of AZM-G for effective tableting. The tablet weight of the first formulation was 700 mg, which included as much as 500 mg of AZM-G (equivalent to 500 mg AZM). The added excipients are summarised in Table 6.1. AZM-G powder was accurately weighed and transferred into a glass jar with a screw-on lid. The Kollidon® VA 64 (binding agent), Explotab® (disintegrant), and Avicel® PH 200 (diluent) were added and the lid securely affixed, before placing the jar in a Turbula (Switzerland) rotating mixer at 47 rpm for 10 minutes, to achieve equal distribution and proper mixing of the powder contents. The powder mix was then transferred into the hopper shoe of a single punch tablet press (CADMACH® SSF3, India). The punches (lower and upper) being used on the tablet press were carefully selected for tableting. The size of the two punches (12 mm diameter) was based on the approximated size and total weight of the desired tablet (700 mg).

Table 6.1 Trial formulation of a 700 mg tablet containing 500 mg of AZM-G

Ingredient	Amount
AZM-G	500 mg
Kollidon® VA 64	5 %
Explotab®	4 %
Avicel® PH 200	a.q.

Tableting of the trial formulation revealed that the flow of the powder mix was still inadequate for producing tablets with acceptable weight uniformity. The large tablet weight variation was further overshadowed by the poor compressibility of the powder mix, as the tablets were soft and brittle. A hardness test, performed on a PharmaTest PTB301 (Pharma Test, Germany), indicated the tablet hardness being only 24 N. The first formulation necessitated further investigation to improve the flow and compressibility of the azithromycin glass powder. Wet granulation was subsequently considered as a better alternative for tableting of the AZM-G powder. As discussed in Chapter 5, the stability of AZM-G was not influenced by the addition of small amounts of water, therefore granulation would be a suitable method for possibly improving the flow characteristics of AZM-G powder.

6.4 Wet granulation of AZM-G powder

Various formulations (using wet granulation as preparation method, with water as granulating liquid) were examined and different mixtures used to prepare tablets. Each formulation was adapted according to the shortcomings found in prior trial formulations. Capping and lamination of tablets made formulation even more challenging. As the total weight per tablet of formulations increased, as more excipients were required to eliminate previously identified shortcomings, the flowability of the powder improved with each formulation. The tablet weight increased from the initial 700 to 950 mg (Table 6.2). All formulations contained 500 mg of AZM-G (equivalent to 500 mg AZM). The excipients being included in the different formulations are summarised in Table 6.2.

Table 6.2 Summary of excipients included in tablet formulations prepared by using wet granulation to improve powder flow properties of formulations

Formulation 1 (700 mg)	Formulation 2 (850 mg)	Formulation 3 (900 mg)	Formulation 4 (950 mg)	Formulation 5 (950 mg)
Kollidon® VA 64 (5 %)	Kollidon® VA 64 (5 %)	Kollidon® VA 64 (5 %)	Kollidon® VA 64 (5 %)	Kollidon® VA 64 (5 %)
Explotab® (4 %)	Explotab® (4 %)	Explotab® (4 %)	Explotab® (4 %)	Ac-Di-Sol® (4 %)
Avicel® PH 200 (a.q.)	Avicel® PH 200 (a.q.)	Avicel® PH 200 (a.q.)	Avicel® PH 200 (a.q.)	Avicel® PH 200 (a.q.)
	Mg stearate (0.75 %)	Mg stearate (1.25 %)	Mg stearate (1.50 %)	Mg stearate (1.50 %)
				Talc (2 %)

As seen in Table 6.2, the main differences among the formulations (Formulations 1 - 5) comprised that more filler, i.e. Avicel® PH200 was used, the concentration of magnesium stearate was increased and Explotab® (4 %) was replaced by Ac-Di-Sol® (4 %), coupled with the addition of Talc (2 %) in Formulation 5. The complete bulk manufacturing process of Formulation 5 (from the onset of wet granulation to the final tablets) is described next.

6.4.1 Bulk production of AZM-G tablets (Formulation 5)

AZM-G powder was accurately weighed to ensure an active amount equivalent to 500 mg AZM per manufactured tablet. Kollidon® VA 64 (5 %) was weighed and first added to the stainless steel mixing bowl (Figure 6.5) of a Kenwood® planetary mixer.

10 mL of the granulating solvent, water, was added to the Kollidon® VA 64 and the two ingredients mixed at a level 2 speed for approximately 5 minutes to form a uniform paste. The AZM-G powder was then slowly added to the paste, while continuing with the mixing (Figure 6.5). Ac-Di-Sol® was divided into two equal parts. The one half was added to the wet mixture, followed by the addition of Avicel® PH 200.

After preparation of the wet granulate (Figure 6.5), it was transferred onto a sieve (number 10 sieve with 2000 µm mesh size) and carefully forced through the mesh using a spatula.

The resultant granules were then placed in a conventional oven (pre-heated at 60˚C) and exposed to low, dry heat for a time of 180 minutes, long enough to remove all water from the granules. The dry granules (Figure 6.6) were removed from the oven and scooped onto a sieve having a smaller mesh size (number 20 sieve with 840 µm mesh size) and again forced through the mesh (Figure 6.6) with a spatula to produce smaller granules (Figure 6.7).

Figure 6.5 Images of the wet granulation process during which dry contents are mixed in a planetary mixer (left) to produce a wet mass of granules (right).

Figure 6.6 Images of the dried mass of granules (left) and the mesh with which the dry mass granules were sieved (right).

The granules were then weighed to determine the recovered amount of the initial mixture. The amount of each of the remaining excipients was adjusted accordingly. These excipients (Talc, magnesium stearate and the remaining half of Ac-Di-Sol®) were added to the granules in a glass jar and the lid securely closed (Figure 6.7). The jar was mounted onto the Turbula rotating mixer and allowed to thoroughly mix the contents for 10 minutes (Figure 6.7).

The mixed granulate was then poured into the hopper shoe of the CADMACH® SSF3 (India) single punch tablet press (Figure 6.8). The upper- and lower punches (14 mm diameter) were selected according to the size and weight of the desired tablets (950 mg). The first few tablets during the tableting process were disposed of as a precautionary measure, as they almost always result in tablet weight variations.

Figure 6.7 Images of the resulting dry granules after being sieved (the left) and the rotating mixer (Turbula) shaking the glass jar containing the granulated powder and excipients (right).

Figure 6.8 Images of the CADMACH® single punch tablet press (left) and the manufactured tablets (950 mg) containing 500 mg of AZM-G (right).

Scanning electron microscopy (SEM) micrographs were taken of the AZM-G powder, prior to wet granulation (Figure 6.9) and then again of the dry granules after the wet granulation process (Figures 6.9 and 6.10). The adhesive coating of the granules are clearly visible on these SEM micrographs (Figure 6.10). The tablets were visually inspected for signs of lamination or capping. No traces of either lamination or capping were observed. Eight (8) of the manufactured tablets were used to perform the tablet hardness tests, which is based on the force needed to fracture the tablet through diametral compression. The tablet hardness results were between 85 N and 98 N. Disintegration of the tablets in distilled water (37˚C) was also performed (according to USP specifications), using an Erweka ZT220 (Apollo Scientific, SA) disintegration tester. This test was repeated three times to ensure repeatability. The time it took for each tablet to completely disintegrate in water while stirring, was measured. The disintegration time was determined as being 5 minutes. The manufactured AZM-G tablets hence complied with the USP (2010) specifications, which states that a tablet should completely disintegrate within 15 minutes when placed in water (37˚C) (USP, 2010).

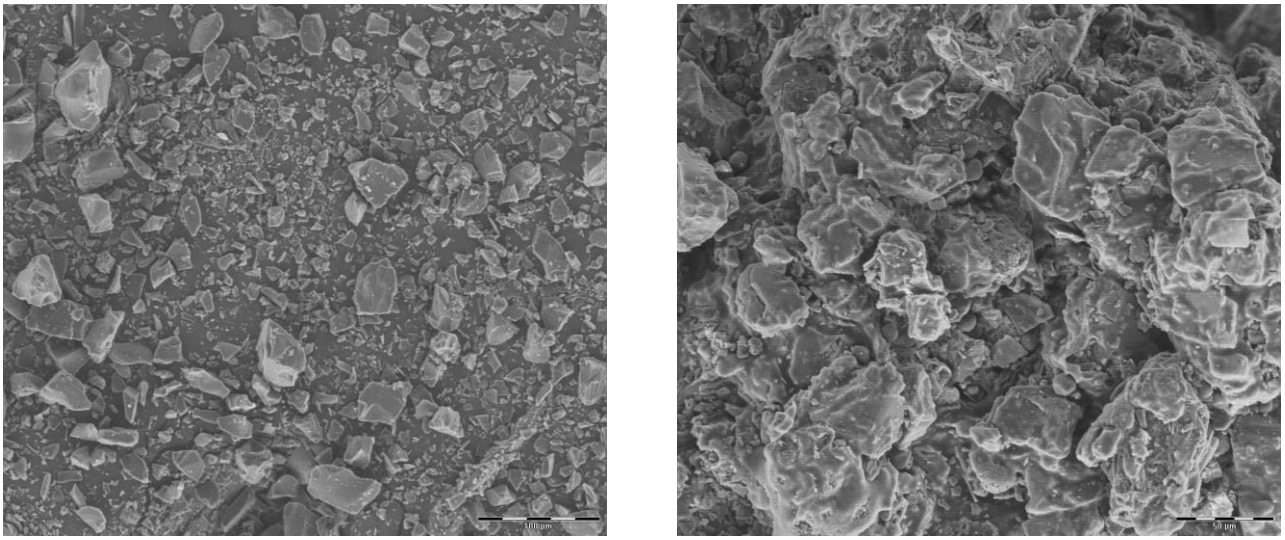

Figure 6.9 SEM micrographs of AZM-G powder (left, scale of 100 µm) and dry granules before tableting (right, scale of 50 µm).

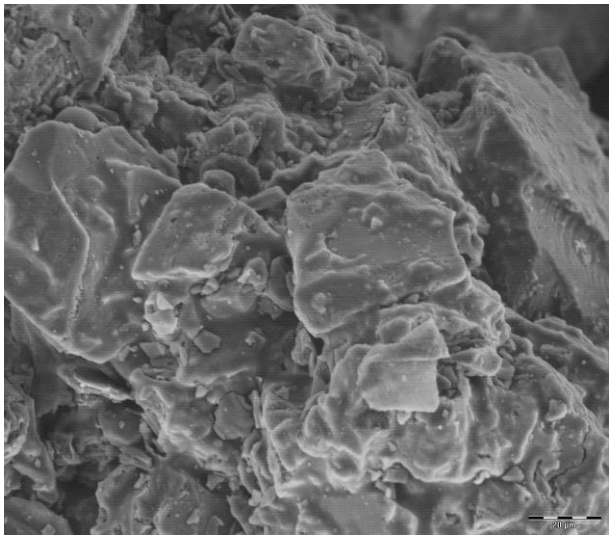

Figure 6.10 SEM micrograph of a dry granule at a higher magnification (scale: 20 µm).

6.4.2 Bulk production of AZM-DH tablets

For the purpose of this study, AZM-DH tablets were also formulated and manufactured to serve as reference for the dissolution and stability testing studies, as described later in this chapter. In order to limit variations during this study, the same granulation method was chosen to further improve the flow of AZM-DH during preparation of the bulk powder for tableting. As with the AZM-G formulations, the granulating solvent was water. The wet granulation process was performed, as described in Section 6.4.1. The formulation used

for the production of AZM-DH tablets was similar to that of Formulation 5, according to which the bulk of AZM-G tablets were manufactured. The only difference between the final formulations was the exclusion of Talc (2 %) in the AZM-DH formulation, because the granules being prepared with AZM-DH in preliminary formulations displayed slightly better flow properties than those of AZM-G powder. The final formulation for AZM-DH tablets is provided in Table 6.3.

Table 6.3 Final formulation of AZM-DH tablets

Ingredients	Amount
AZM-DH (equivalent to 500 mg AZM)	500 mg
Kollidon® VA 64	5 %
Ac-Di-Sol®	4 %
Magnesium stearate	1.5 %
Avicel® PH 200	a.q.

A SEM micrograph of AZM-DH, prior to the wet granulation process, is shown in Figure 6.11 (left image). SEM micrographs after wet granulation of AZM-DH and its excipients (Table 6.3) clearly show the AZM-DH particles (Figure 6.11) (image on the right). Granulation of AZM-DH improved the flow properties to such an extent that reproducible tablets of 950 mg each could be manufactured in bulk. Tablets from these two batches of manufactured tablets (AZM-DH and AZM-G) were used to determine their dissolution profiles. The stability of these tablets (at 40˚C and 75 % RH) was also determined in order to establish the robustness of the two formulations, as well as to identify any possible altering effects that the excipients may have had on the stability of AZM-G in formulation.

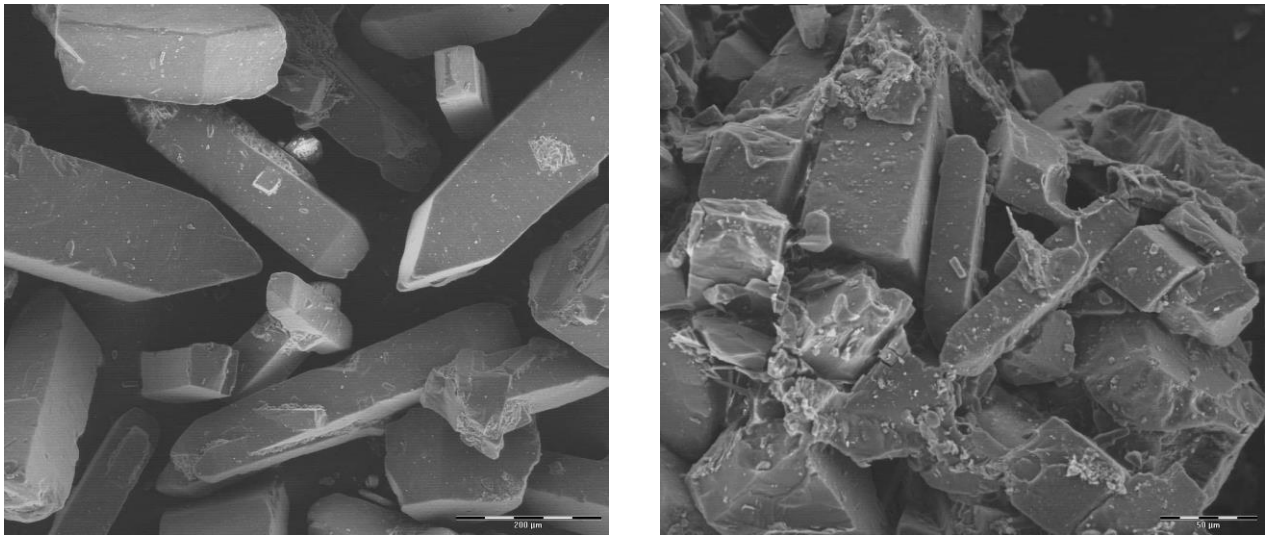

Figure 6.11 SEM micrographs of AZM-DH (left, scale: 200 µm) and dry granules before tableting (right, scale: 50 µm).

6.5 Dissolution study of AZM-DH and AZM-G in different media

The dissolution rates and dissolution profiles of AZM were determined in different aqueous media, according to the method described in Section 2.7.1. The comparative dissolution profiles obtained for AZM-DH and AZM-G are discussed next.

6.5.1 Results

6.5.1.1 Dissolution profiles in pH 4.5 acetate buffer

The fast disintegration of both the AZM-DH and AZM-G tablets in pH 4.5 acetate buffer resulted in significantly high concentrations of the active forms, even at the first sampling interval of 5 minutes (Figure 6.12). There were no significant differences in the overall profiles of the two active forms of AZM during this dissolution study, except for the initial concentrations of the released drug. The AZM-G tablets were almost completely dissolved after 5 minutes, with the AZM concentration being 95 %, where after it remained stable up until the 45 minutes sampling interval.

The AZM-DH started with an initial concentration of 91 % after 5 minutes that increased to 98 % after 10 minutes. Both tablet formulations were thus able to quickly release AZM into the medium, where after the available AZM dissolved almost completely.

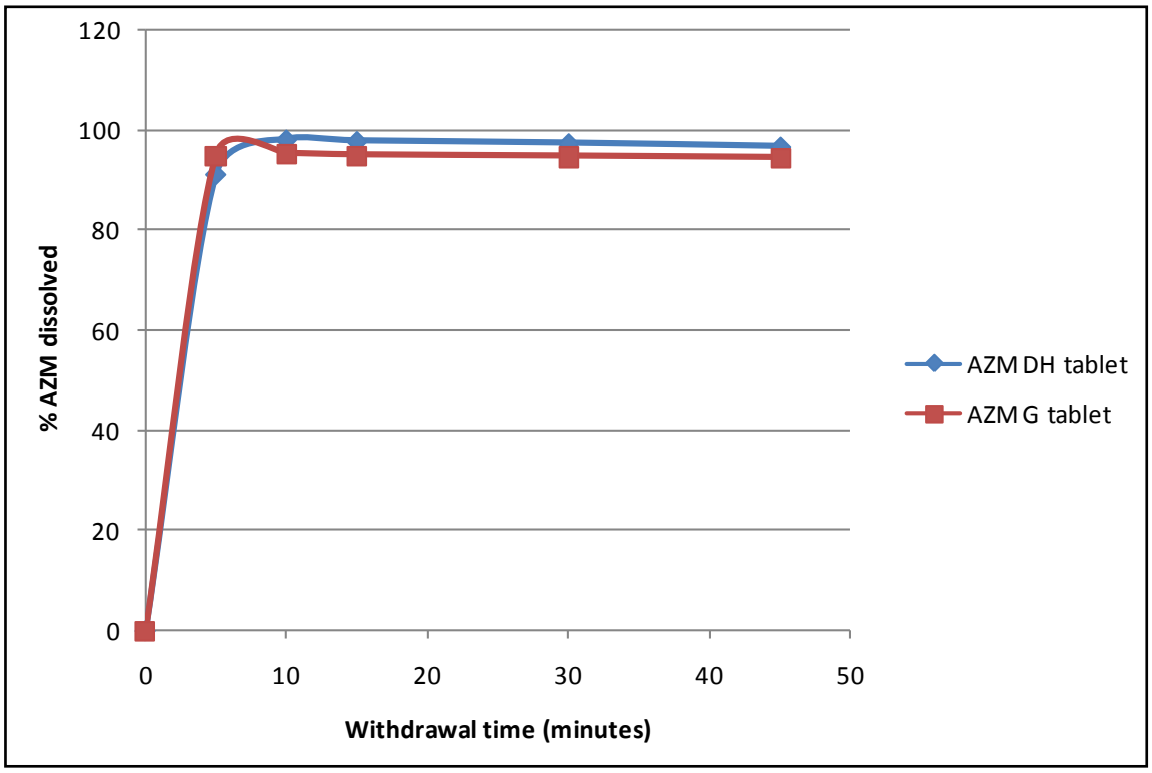

Figure 6.12 Dissolution profiles (percentage AZM dissolved as a function of time) of AZM-DH and AZM-G tablets in pH 4.5 acetate buffer.

6.5.1.2 Dissolution profiles in pH 6.8 phosphate buffer

The AZM-DH tablets disintegrated within a matter of minutes in the pH 6.8 phosphate buffer and did AZM achieve a high concentration of 78.71 % after 5 minutes (Figure 6.13).

The AZM-G tablets had dissolved at an even higher rate and were an AZM concentration of 90.84 % achieved after 5 minutes (Figure 6.13), 12.13 % more than that from the AZM-DH tablets. This faster dissolution rate could be partly attributed to the better solubility of AZM-G than AZM-DH in pH 6.8 phosphate buffer (Section 5.4). After 10 minutes, both dissolution profiles had reached a plateau (Figure 6.13), as dissolution was mostly completed.

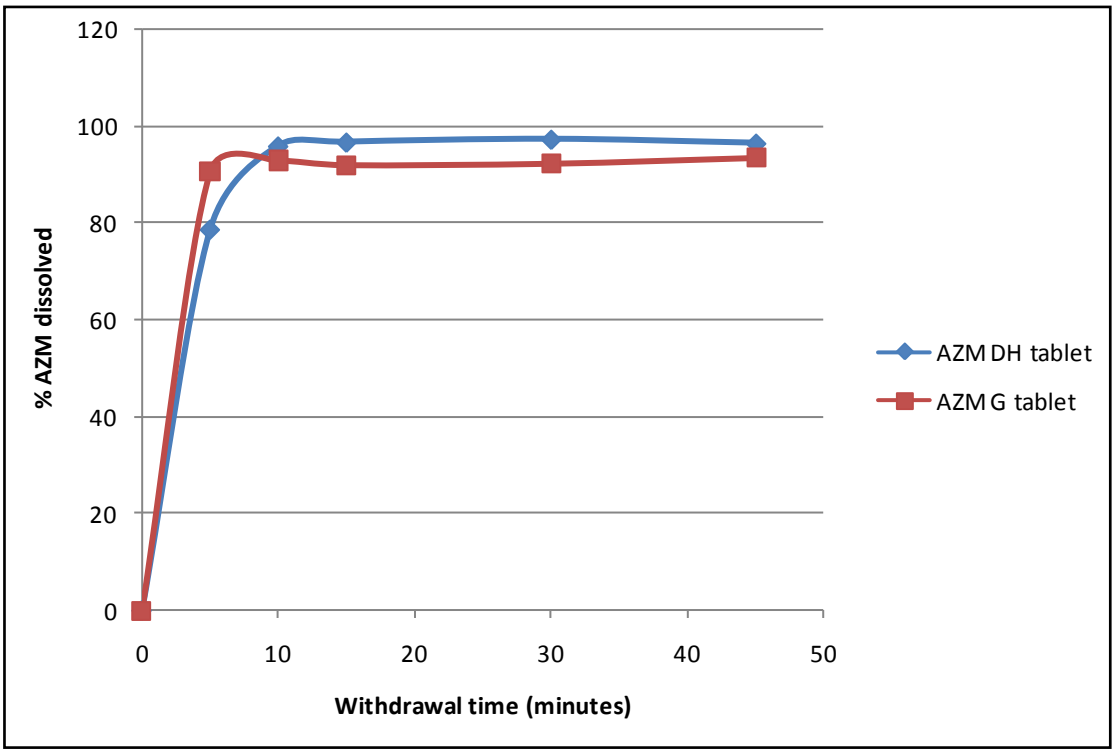

Figure 6.13 Dissolution profiles (percentage AZM dissolved as a function of time) of AZM-DH and AZM-G tablets in pH 6.8 phosphate buffer.

6.5.1.3 Dissolution profiles in water

The dissolution profiles of the two tablet formulations differed significantly in water (Figure 6.14). Disintegration of both formulations was rapid. An AZM concentration of 4.45 % was achieved from the AZM-DH tablets after 5 minutes, whereas that of the AZM-G tablets was 13.92 %. After 45 minutes, the released concentration of AZM from the AZM-DH and AZM-G tablets were 8.14 % and 17.94 %, respectively. AZM release by the AZM-G formulation was thus improved by 120 % after 45 minutes in comparison with the AZM-DH tablets. The maximum AZM percentage being dissolved from the AZM-G formulation was 19.09 % after 15 minutes. The dissolution profile of AZM-G appeared to decline after the plateau had been reached. When considering the standard deviation (0.49 - 1.33 %), the dissolution profile had indeed settled on the plateau being reached after 15 minutes. The significant differences in dissolution rates, as well as in the percentages of AZM being dissolved in water from these two formulations, were probably the result of the major improvement in the water solubility of AZM-G, compared to AZM-DH (Section 5.4).

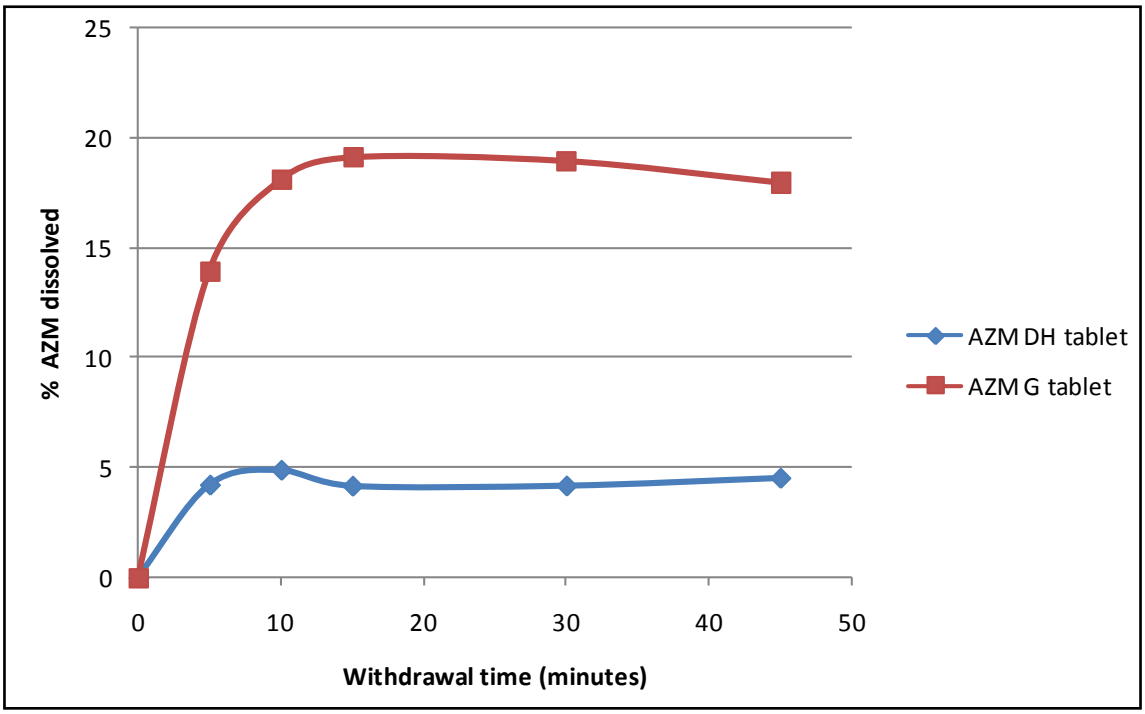

Figure 6.14 Dissolution profiles (percentage AZM dissolved as a function of time) of AZM-DH and AZM-G tablets in water.

6.5.1.4 Dissolution profiles in pH 1.2 HCl

In Section 5.4.1.1 the acid-stability of AZM was established and discussed. A dissolution study of AZM-DH and AZM-G tablets would as a result have been irrelevant, due to the degradation of AZM in 0.1 M HCl (pH 1.2). Furthermore, since the sample runtime for HPLC analysis was 15 minutes, the samples would queue up and during this time, the AZM being in solution and exposed to the acidic conditions (pH 1.2), would simply degrade.

6.5.2 Discussion

The above outcomes from the dissolution studies of AZM-DH and AZM-G tablets in different media are of high pharmacokinetic and pharmaceutical significance. The dissolution profiles of these two formulations differed most in water and to some extent in phosphate buffer (pH 6.8). The dissolution study in phosphate buffer showed a faster dissolution rate for AZM-G. It was determined that 90.84 % of the 500 mg of AZM present in the AZM-G tablets was already in solution after merely 5 minutes. This faster dissolution rate may largely have been as a result of the improved solubility (39 %) of

AZM-G over AZM-DH in phosphate buffer (pH 6.8) and the larger surface area of the active being exposed to the phosphate buffer.

The dissolution profiles of these formulations in water showed significant differences ($p < 0.05$) in the dissolution rate of AZM-DH, compared to that of AZM-G. The rate at which AZM-G was released from the tablets was much faster than that of AZM-DH. The cumulative amounts of AZM being released from the tablets and dissolved in water after 5 minutes were 4.45 % and 13.92 % for AZM-DH and AZM-G, respectively, thus already indicative of the much higher dissolution rate of AZM-G from its tablet formulation. The AZM concentrations at the end of the dissolution study were 8.14 % and 17.94 % for the AZM-DH and AZM-G formulations, respectively. The improved water solubility of AZM-G (> 300 %) and its smaller particle size (hence larger surface area being exposed to the solvent) clearly impacted on the dissolution process, as more AZM dissolved and at a faster rate when in solution, hence ultimately leading to a higher percentage of dissolved AZM.

The dissolution profiles of both AZM-DH and AZM-G in acetate buffer (pH 4.5) were similar, except for the initial values obtained after 5 minutes. These dissolution results correlated well with those solubility results previously referred to, where it was established that powdered AZM-G was 4.65 % more soluble than AZM-DH in acetate buffer at pH 4.5. The higher percentage of dissolved AZM-G after 5 minutes could be attributed to the improved solubility and the larger surface area of exposure to acetate buffer.

6.6 Stability of AZM-DH and AZM-G tablets

6.6.1 Materials and methods

This stability study was designed to subject the AZM-DH and AZM-G tablets to stability testing conditions over a period of three months. The Labcon temperature- and humidity controlled chamber was set at 40˚C and 75 % RH. The manufactured AZM-DH and AZM-G tablets were individually weighed and placed in glass petri-dishes, where after each petri-dish was wrapped in Parafilm®. Two petri-dishes were allocated for each month of stability testing, one containing the AZM-DH tablets and the other the AZM-G tablets. The tablets allocated for each month were collected at the scheduled times and were subjected to screening tests. Prior to the screening tests, the tablets were again individually weighed to compare the weight of the tablets before and during the stability

testing period. The screening tests being performed included FTIR analysis, as well as dissolution in phosphate buffer (pH 6.8) (Section 6.5.2). Dissolution in water was considered, however the phosphate buffer was chosen due to the USP suggesting dissolution tests be done in phosphate buffer (> pH 6). Analyses of the withdrawn samples during dissolution testing were performed using the validated HPLC method, as described in Section 2.3. Data processing was on an Excel® spreadsheet.

6.6.2 Results

6.6.2.1 Fourier transform infrared spectroscopy (FTIR)

The FTIR analyses outcomes of AZM-DH tablets over the duration of the stability study are illustrated in Figure 6.15. The IR spectra of the AZM-DH tablets remained similar throughout the stability testing period, as expected, because of AZM-DH being the most stable form of AZM.

Figure 6.16 represents the results obtained for AZM-G tablets with FTIR spectroscopy. The initial spectrum (blue in Figure 6.16) of AZM-G tablets displayed the characteristic broad peak of an amorphous compound at 3500 cm^{-1}. After a month (grey) of exposure to the stability testing conditions, AZM-G still remained stable as an amorphous and anhydrous form within the tablets. The spectra of Months 2 (red) and 3 (green) resulted in a slight alteration of the characteristic broad peak (3500 cm^{-1}), as seen on Figure 6.16. This possibly represented the start of phase transformation of AZM-G into the more stable, dihydrated, crystalline form of AZM. The small peaks present at approximately 3500 cm^{-1} may have been indicative of AZM-G starting to revert into a hydrated state, although they may also have been caused by the presence of tablet excipients, due to the highly hygroscopic nature of some of the excipients used.

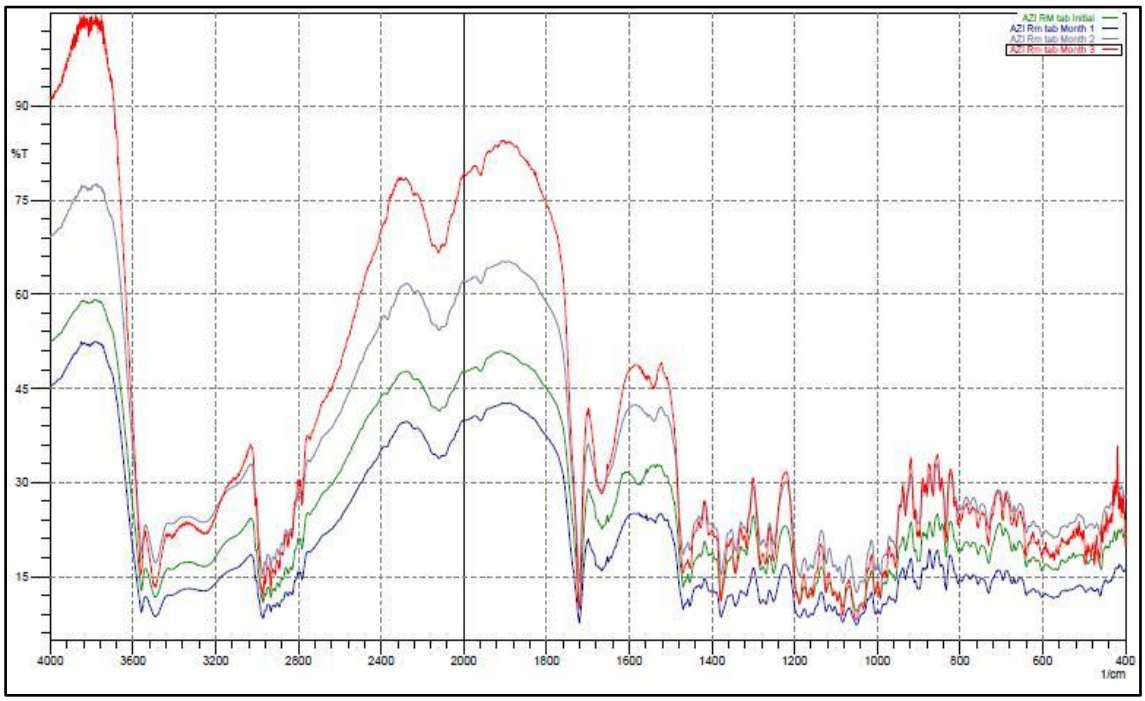

Figure 6.15 Overlay of FTIR spectra for AZM-DH tablets during the stability study. AZM-DH Initial (green), Month 1 (blue), Month 2 (grey), Month 3 (red).

All the tablets weighed approximately 20 mg more after three months, compared to their initial weights at the onset of the stability study. This probably indicated that the excipients had absorbed approximately 2 % of moisture from the accelerated humidity conditions during stability. This moisture content would have initiated and facilitated the conversion of the amorphous glass into a hydrated, more stable, crystalline state. Since the tablets were furthermore uncoated and hence without any protective outer layer, such as film- or sugar coatings, the tablets were completely exposed to the accelerated humidity and temperature conditions, which, as a result would have caused them to be much easier influenced by the storage conditions.

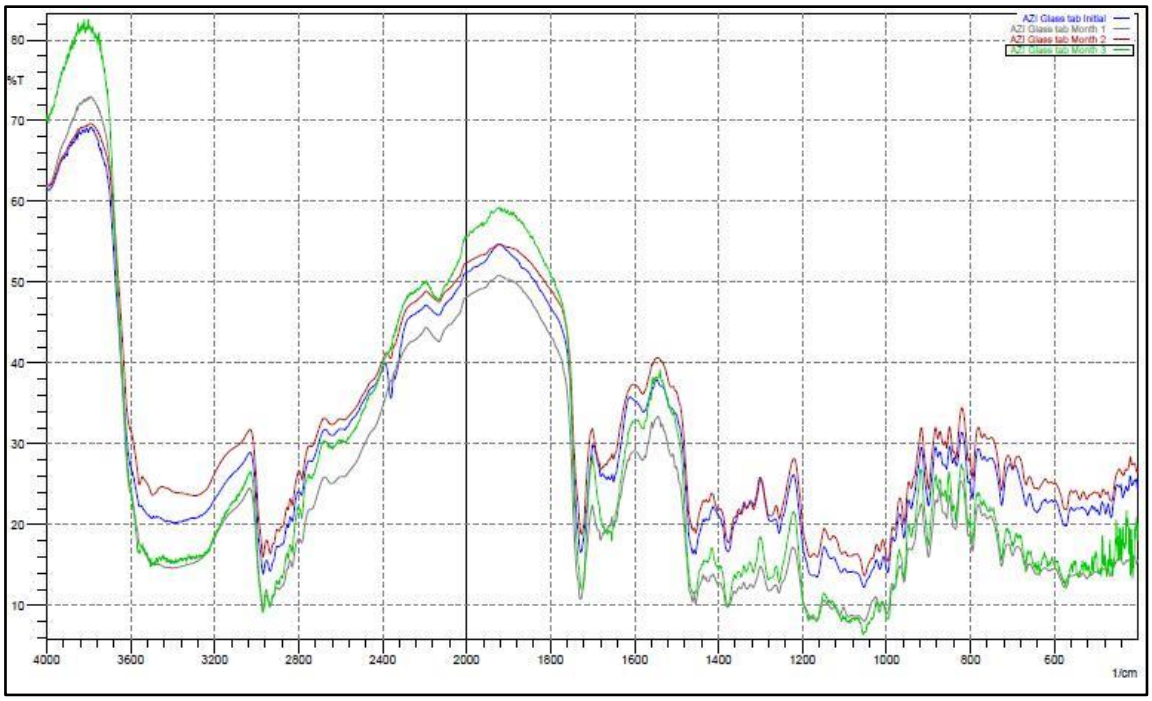

Figure 6.16 Overlay of FTIR spectra for AZM-G tablets during the stability study. AZM-G Initial (blue), Month 1 (grey), Month 2 (red), Month 3 (green).

6.6.2.2 Dissolution

Dissolution (at pH 6.8) was chosen as a screening test for the tablets during the stability trial period, in order to establish whether the conditions had had any altering effect on the dissolution profiles of the respective tablet formulations. The moisture content (humidity) or temperature may have resulted in changes in the stability of AZM-G in tablet form. These test outcomes (Figures 6.17 and 6.18) showed that the tablets, during the stability period, had similar dissolution profiles than the initial tablets in the phosphate buffer.

Despite having exposed these uncoated tablets to accelerated stability conditions over three months, the dissolution rates for both AZM-DH and AZM-G still remained unaffected in any negative way. The release of AZM from both tablet formulations remained consistent, as the content of AZM being dissolved after 45 minutes correlated well among all of the dissolution studies being performed during this stability indicating study.

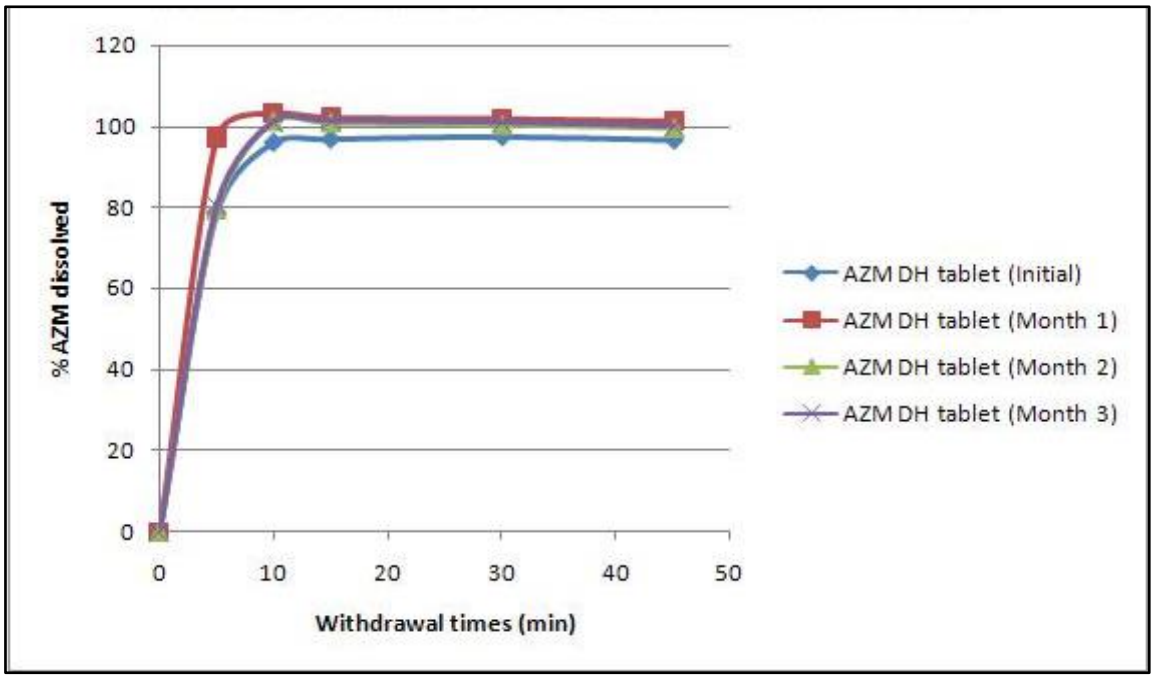

Figure 6.17 Dissolution profiles of AZM-DH tablets in pH 6.8 phosphate buffer.

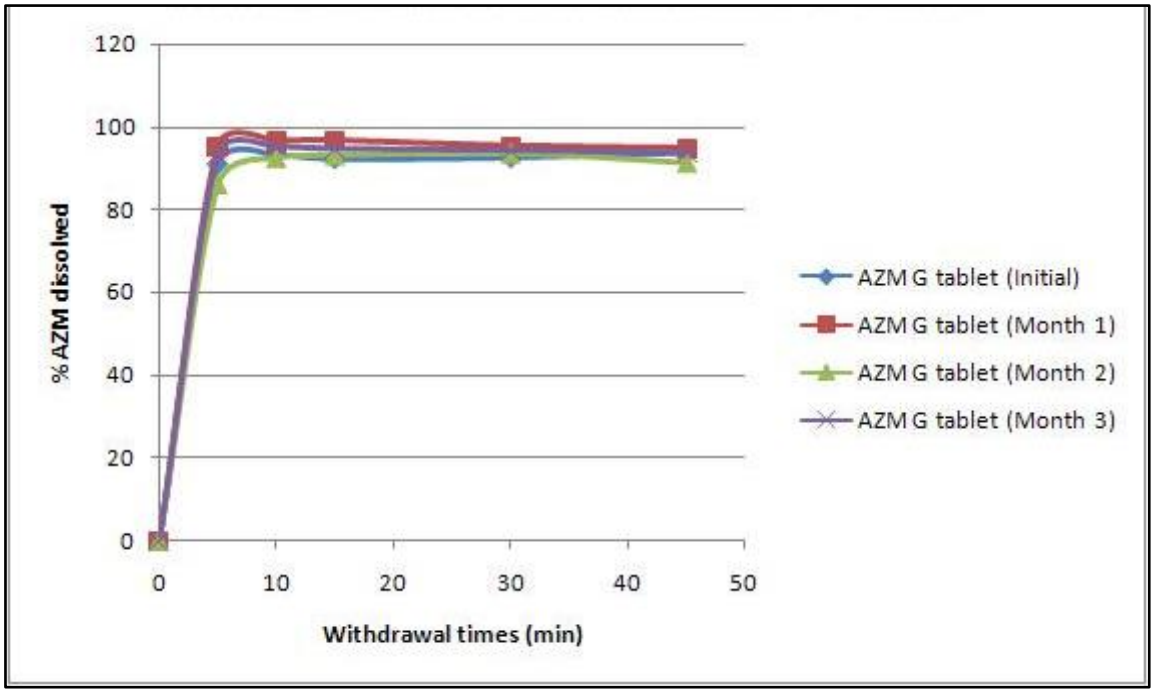

Figure 6.18 Dissolution profiles of AZM-G tablets in pH 6.8 phosphate buffer.

6.6.3 Discussion

This stability study indicated that the dissolution rate and hence the concentration of the released AZM from the tablets were not altered by the pH 6.8 buffer, with exposure to

extreme stability storage conditions (40˚C and 75 % RH). The weight of all tablets increased after three months of exposure to the accelerated temperature and humidity conditions, possibly resulting from moisture uptake by the hygroscopic excipients included in the tablet formulations. Although the tablets gained approximately 2 % in weight, the absorbed moisture did not affect the disintegration, dissolution rate, or the overall concentration of the released AZM from the tablets. These outcomes were confirmed by the consistent dissolution profiles being generated throughout the stability testing period (Figures 6.17 and 6.18).

It was, however, further established by FTIR analysis that the additional moisture content indeed affected the solid state of AZM-G within the tablet formulation. These FTIR analyses illustrated that AZM-G had started to transform into a hydrated, crystalline form after two months. This onset of transformation was evident from the small peaks appearing at 3500 cm^{-1} at months 2 and 3 (Figure 6.16). According to the IR spectra in Figure 6.16, the AZM-G within the tablet formulations had not fully transformed into the crystalline, hydrated state (i.e. monohydrate and ultimately dihydrate). The presence of crystalline excipients ruled out the possibility of characterising AZM by way of DSC, TGA and/or XRPD. It, however, became evident after two months that the accelerated stability conditions, especially humidity, started to affect the structural stability of AZM-G in the tablet formulations, due to the presence of the hygroscopic excipients. The stability of AZM-G that had been exposed to the same conditions was discussed in Chapter 5. It was evident that the AZM-G "raw material" remained stable, when tested in isolation. The excipients with their hygroscopic natures hence indeed contributed to the altering of the stability of AZM-G within the tablet formulation. This again confirmed the significance of a statement made in Section 5.5.3 that the stability of AZM-G is not only affected by moisture/water, but that its change in stability is also dependant on the time/duration of exposure to such moisture.

6.7 Conclusion

Drug and solid dosage form development has become an increasingly integral part of research in the pharmaceutical industry. Poor physico-chemical and pharmacokinetic properties make solid dosage form development very challenging. The novel form of AZM-G, being prepared during this study, has proven very stable and much more soluble in water than its stable and hydrated predecessor (i.e. AZM-DH). To determine the

dissolution rate and the effect of improved solubility on dissolution, AZM-G (as well as AZM-DH) in a solid dosage form, i.e. uncoated tablets, were formulated. The final tablet formulations each weighed 950 mg, of which 500 mg comprised the active ingredient, AZM-G or AZM-DH.

The dissolution profiles of these manufactured tablets were determined in different media at different pH values. The most promising dissolution results were obtained for AZM-G in distilled water and in phosphate buffer (pH 6.8), during which it was proven that AZM-G had faster dissolution rates from their tablet formulations, compared to AZM-DH. Improved solubility of AZM-G was evident from the final dissolution profiles obtained.

The tablets were also exposed to stability testing conditions over a period of three months. The stability study revealed that AZM-G had started to transform into a hydrated solid state after two months of exposure to 40˚C and 75 % RH. The tablets were uncoated and therefore much more susceptible to the high moisture levels in the humidity chamber. The hygroscopic excipients included in the tablet formulation may have accounted for the increase (2 %) in tablet weights after the three months. The moisture being absorbed probably also initiated the slight transformation of AZM-G into a hydrated, crystalline form, due to the plasticising effect of water. However, the stability testing conditions did not affect the release of AZM from the tablets and did the dissolution rates of AZM-DH and AZM-G remain consistent throughout the stability study.

6.8 References

ALDERBORN, G. 2002. Tablets and compaction. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 397-439.)

AMIDON, G.E. 1995. Physical and mechanical property characterization of powders. (*In* Brittain, H.G., Volume 70. Physical characterization of pharmaceutical solids, New York: Marcel Dekker, Inc. p. 281-319.)

ASHFORD, M. 2002. Bioavailability: physicochemical and dosage form factors. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 234-252.)

AULTON, M.E. 2002. Pharmaceutics: The science of dosage form design, 2nd ed. New York: Churchill Livingstone, 679 p.

AULTON, M.E. 2002. Dissolution and solubility. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 15-32.)

BRITTAIN, H.G. 2008. Introduction and overview to the preformulation development of solid dosage forms. (*In* Adeyeye, M.C. & Brittain, H.G., Volume 178. Preformulation in solid dosage form development, New York: Informa Healthcare. p. 1-16.)

BRITTAIN, H.G. 2008. Overview of the solid dosage form preformulation program. (*In* Adeyeye, M.C. & Brittain, H.G., Volume 178. Preformulation in solid dosage form development, New York: Informa Healthcare. p. 347-355.)

BRITTAIN, H.G. & GRANT, D.J.W. 1999. Effects of polymorphism and solid state solvation on solubility and dissolution rate. (*In* Brittain, H.G., Volume 95. Polymorphism in pharmaceutical solids, New York: Marcel Dekker. p. 279-330.)

NEWMAN, A.W. 1995. Micromeritics. (*In* Brittain, H.G., Volume 70. Physical characterization of pharmaceutical solids, New York: Marcel Dekker, Inc. p. 253-280.)

PRESCOTT, J.K. & BARNUM, R.A. 2000. On powder flowability. *Pharmaceutical Technology*, Oct. 2000:60-84.

ROWE, R.C., SHESKEY, P.J. & QUINN, M.E. 2009. Handbook of pharmaceutical excipients, 6th ed. Pharmaceutical Press and American Pharmacists Association,888 p.

STANIFORTH, J. 2002. Powder flow. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 197-210.)

SUMMERS, M. 2002. Powders and granules. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 360-363.)

SUMMERS, M. & AULTON, M.E. 2002. Granulation. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 364-378.)

WELLS, J. 2002. Pharmaceutical preformulation. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 113-138.)

WONG, G. & COLLINS, C.C. 2008. Dissolution testing. (*In* Adeyeye, M.C. & Brittain, H.G., Volume 178. Preformulation in solid dosage form development, New York: Informa Healthcare. p. 477-555.)

YORK, P. 2002. The design of dosage forms. (*In* Aulton, M.E., 2nd ed. The science of dosage form design. New York: Churchill Livingstone. p. 1-12.)