Continuous research and development of active pharmaceutical ingredients are integral to the success and efficacy thereof. Solid state research includes the study of different solid forms of a single pharmaceutical compound, i.e. polymorphism and amorphism. The characterisation of polymorphs has taken its rightful place in pharmaceutical research. Part of this study hence included the screening for azithromycin (AZM) polymorphs, recrystallised from selected organic solvents. From these screening tests, it appeared that AZM had the tendency to either form a monohydrate, or the stable dihydrate. Literature describes that recrystallisation from solvents of the alcohol group mostly results in monohydrated forms.

The preparation of an anhydrous form of AZM was then attempted, using different preparation methods. An anhydrous AZM was first prepared, using the conventional dehydration process by drying AZM-DH crystals at 100°C for 60 minutes in a conventional oven. The outcomes demonstrated that complete dehydration had not occurred at these conditions and that the resulting AZM sample comprised of both the AZM monohydrate and the dihydrate.

The anhydrous form prepared through solvent evaporation, using isopropanol as solvent, proved to produce both anhydrous and amorphous AZM, with the inclusion of two isopropanol molecules for each AZM molecule. The crystals appeared amorphous at room temperature when examined with hot stage microscopy (HSM). Increased temperature had an altering effect on the stability of this amorphous AZM, as it crystallised at 62°C, after observing its glass transition at 52°C. For optimum stability, therefore, it was established that this amorphous form could not be stored at temperatures above 2°C. This amorphous form consequently shifted the focus of this study from polymorphism to amorphism.

An amorphous form (AZM-G) was subsequently prepared by way of quench cooling of the melt. AZM-G showed significantly different physico-chemical properties than would normally be expected from glasses. The unique physico-chemical properties exhibited by AZM-G included that it remained stable with exposure to high temperature and relative
humidity (40°C & 75 % RH). Constant humidity also had no plasticising effect on the structure of AZM-G. The vapour adsorption desorption isotherms being generated after exposure to increasing relative humidity of up to 95 % RH, further demonstrated the unexpected and significant stability of this amorphous form. AZM-G further showed that it only adsorbed a monolayer of moisture onto its surface, without being structurally affected by the presence thereof. The stability was furthermore proven, since an increased water content of up to 50 % had no plasticising effect on AZM-G.

AZM-G showed a significant increase (> 300 %) in aqueous solubility in comparison with the stable AZM-DH. This improved solubility resulted in the development of a solid dosage form, i.e. a tablet containing AZM-G, equivalent to 500 mg of AZM. The same formulation was used to manufacture tablets containing AZM-DH, equivalent to 500 mg of AZM. Comparative dissolution studies in different aqueous media were then performed on these two tablet formulations. The resultant dissolution profiles showed a significant improvement in the dissolution rate of AZM-G in water, due to its improved water solubility. Both tablet formulations were further exposed to accelerated temperature and relative humidity for a stability testing period of three months (40°C and 75 % RH). Due to the hygroscopicity of some of the excipients being included in these formulations, the duration of and the extreme stability conditions caused a conversion of AZM-G into the monohydrate form of AZM at month 2 and 3. This emphasised the fact that the transformation of AZM-G into the crystalline state was time dependant and not only on the presence of water/moisture.

From the outcomes of this study it also became clear that despite the improved acidic stability of AZM over other macrolides, it would still degrade when exposed to acidic conditions, therefore necessitating a film- or sugar coating to protect the AZM from the acidic conditions in the human stomach.

The improvement in solubility of AZM-G suggested that there should be an improvement in the absorption of AZM after oral administration and that the improved physico-chemical properties should positively impact on the bioavailability of AZM. The permeability of AZM-G (and AZM-DH as reference) across excised pig intestinal tissue was hence investigated in different solutions at different pH values. At higher pH values (6.8 and 7.2), transport across the membrane proved to be significantly higher, thus also demonstrating the pH dependence of AZM for its transport across intestinal tissue. The improved solubility of AZM-G had an enhancing effect on its permeability also. Consequently, it could be stated
that the solubility, together with the pH of the final solutions, directly impacted on the permeability of AZM, and could it therefore have an enhancing effect on the absorption of AZM, which in turn would positively influence its bioavailability. These research outcomes hence gave rise to the need for investigating the effect of administering lower dosages of azithromycin and to determine whether the same antimicrobial efficacy would possibly be achieved, due to maintaining the same tissue concentration levels at these lower dosages.

The success of this research project led to a PCT patent application (PCT/IB2010/055842), an accepted research article in *Pharmazie* (Odendaal et al., 2012), whilst a second article is in process for submission in due course.