

## CHAPTER 7

### CONCLUSION

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During the polymorphism studies of both didanosine and lopinavir, several non-conventional solid-state properties of each were observed. When this study was initiated (2009), no physicochemical analyses had been published on didanosine or lopinavir and, although two articles on didanosine appeared at the end of 2010, the one by Bettini *et al.* (2010:1855) featuring only a recrystallisation from DMSO with supercritical carbon dioxide as antisolvent and the one by Martins *et al.* (2010:1885), being a crystal structure elucidation of the commercial product, the field remained open for a thorough physicochemical and polymorphism study. The same is true for lopinavir, for which there is only a patent application describing several polymorphs, none of which are consistent with the recrystallisation products or glasses prepared in this study. This study therefore represents the first thorough physicochemical analysis and polymorph screening of both didanosine and lopinavir.

For didanosine, the exceptionally small size of its recrystallisation products was the main contributor to the difficulty in analysing its crystals, but it also led to some of the system's most interesting behaviour. This tendency of didanosine to form crystals too small for SXRD analysis was also encountered by Bettini *et al.* (2010:1857) and Martins *et al.* (2010:1885). The capillary network formed between the fine mesh of crystals, coupled with the thin film of solvent coating these crystals, were responsible for irreproducible drying and nullifying the contact angle during the acid lability study, but also played an important role in the stability of the system. Without the capillary and film solvent, the crystals lost their morphology and reverted back to the raw material. This metastability was observed for all of didanosine's recrystallisation products from alcohols and, coupled with the fact that they all reverted back to the raw material after about a month (even while stored in the recrystallisation medium) it is reasonable to state that the raw material is the most stable polymorph of didanosine. The fact that didanosine did not display a wide range of polymorphs can be directly attributed to its chemical structure. The structural rigidity of didanosine significantly decreases the amount of energy minima the system can adopt. Therefore, for didanosine there is only a hand few of energy optimised states, with the raw material representing the global energy minimum. The results from the solubility study showed an increase in solubility with an

increase in effective surface area, as observed from the crystal morphology. However, the clinical relevance of this increase in solubility remains debatable since the raw material is already freely soluble in water. Unfortunately, because of the film and capillary solvent, the acid lability of didanosine could not be addressed by means of morphologic differences, and the best preparation on the market for optimum bioavailability remains, in this researcher's opinion, the enteric coated capsules.

Concerning lopinavir, the chemical structure once again played a pivotal role in the polymorphic and physicochemical properties observed for this system. Lopinavir was designed to resemble a peptide, albeit a small portion of one, and the same conformational flexibility and large amounts of inter- and intramolecular interactions akin to proteins and peptides can also be observed for lopinavir. Its peptidomimetic behaviour enabled lopinavir to present in a variety of amorphous states with varying amounts of crystalline content. To investigate the physicochemical properties of each lopinavir sample, a detailed analysis of the local and global molecular relaxations, as well as the amount of amorphous content, was done. The results from the relaxation studies were in excellent coherence with the macro- and microscopic observations and several unexplained phenomena could be elucidated with these relaxation activation energies. Since lopinavir is a peptidomimetic drug, with low aqueous solubility, low permeability, extensive plasma protein binding and rapid hepatobiliary elimination, the best chance at improving its pharmacokinetic profile by means of solid-state manipulation is by preparing a polymorph or glass with better solubility than the commercial product. The glass prepared from cooling of the melt at ambient temperature displayed a 72 % increase in solubility, followed by the resin from chloroform with a 7 % increase. This seems to be at odds with the general notion that the solubility can be increased by increasing the amorphous content, since the resin from chloroform contained more crystalline material than many of the other samples analysed. An inverse correlation was found between the solubility and the activation energy required for local molecular motion ( $\Delta E_\beta$ ), suggesting that the increased local molecular motilities of the samples with low  $\Delta E_\beta$  values (with the subsequent decrease in contact angle and increase in wettability), facilitated dissolution from these regions, leading to surface roughening and an increase in effective surface area. The progression of this process, resulting from ongoing coupling of the  $\beta$ -relaxations, eventually increased the solubility of samples exhibiting the lowest  $\Delta E_\beta$  values.

The polymorphism and physicochemical data obtained from this study can enable formulators to design new dosage forms, or improve on current preparations, to address pharmaceutical and/or pharmacological issues regarding these drugs.

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