Enanatiomers and polymorphism in Venlafaxine and Odansetron

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Summary

In this thesis different aspects of polymorphism, the ability of a substance to crystallize in more than one crystal form, are studied. Because physical properties, e.g. melting enthalpy, heat capacity, and solubility, of two polymorphs can differ, the pharmaceutical industry spends a lot of money and effort in studying the phenomenon of polymorphism, because especially the solubility difference between two polymorphs can have influence on the effectivity, the bio-availability and the safety of drugs. A lot of effort is invested to find the most stable polymorph, although one is never certain that the most stable polymorph has been found. A recent example, in which the difference in bio-availability was of importance, is ritonavir. After having been on the market for almost two years, a more stable polymorph with a lower solubility and, therefore, a lower bio-availability was found. Especially the thermodynamic aspects, that play an important role concerning polymorphism of active pharmaceutical ingredients of drugs, are studied in this thesis.

After a general introduction about the phenomenon of polymorphism, the thermodynamic theory of solubility of compounds in solvents is described, with the emphasis on compounds exhibiting polymorphism. The relation between phase diagrams and solubility is treated. Starting with simple models describing the thermodynamics of solutions, assuming no mixing between the solvent and the solute in the solid state, the large variety of possible solubility curves, describing the temperature dependent solubility, are explained. In addition, pseudo polymorphs, that is solvates, are treated. The models result in a formula which makes it possible to estimate the transition temperature for an enatiotropically related system. For this only the melting temperature and the melting enthalpy of the two polymorphs are needed. Both are simply determined using Differential Scanning Calorimetry (DSC).

In the third chapter the phase behaviour of the free base of Venlafaxine, the active ingredient of a drug used to treat stress, is described. Both the polymorphic phase diagram as well as the thermodynamic relations between the three forms are studied, using DSC, X-ray Powder Diffraction (XRPD), slurry experiments and solubility measurements. The solubility of

Venlafaxine was determined in several solvents, focussing on deviations of the solubility as compared to the ideal solubility according to the van ’t Hoff equation. The nature of the deviation of the solubility was such that attributing the stability regions for polymorphs I and II, on the basis of solubility data would lead to a wrong attribution of these regions. This turned out to be the result of the concave shape of the solubility curves, a form that, from a theoretical viewpoint, is described in more detail in chapter 2. The transition temperature of polymorph I and II of Venlafaxine free base was calculated using the earlier mentioned equation to estimate the transition temperature and compared with the values extracted from the solubility data. The concave shape of the solubility curves is the result of a non neglectable temperature dependence of the melting enthalpy.

In chapter 4 the remarkable behaviour of the free base of Venlafaxine with respect to polymorphism and chiral resolution is studied. Using different complementary techniques, the three forms of Venlafaxine free base were characterized. The crystals of all the three forms are composed of almost identical enantiomerically pure layers, only the stacking of the layers is different. In case of form I alternating bi-layers of R and S layers were found, while form II consisted of alternating double bi-layers of R and S enantiomers. In case of form III, the form with the highest melting point, the enantiomer separation is complete, resulting in a racemic conglomerate. The racemic conglomerate can be obtained from solution, or via a solid-solid phase transition of the lowest melting form. Remarkably, during this phase transition the shape of the crystal is conserved. It is hypothesized that, during the phase transition occurring, the chiral separation takes place via a local melting process. Locally the melting point is lower as the result of crystal defects. Because of the local melting process, molecules are able to migrate over relatively large distances between the layers in the crystal.

The results of a morphology prediction for the three forms of the free base of Venlafaxine are presented in chapter 5. Three different methods, the Bravais-Friedel-Donnay-Harker method, the attachment-energy method and a Monte Carlo growth simulation are used for that. A comparison of the predicted and the experimentally found morphologies shows that the Monte Carlo simulation gives a semi-quantitative result for form I and II. In case of form III the correct morphology was found, but some of the predicted indices did not correspond with the experimentally found indices.

In chapter 6 the polymorphic behaviour of the free base of Ondansetron is studied. For Ondansetron, an active pharmaceutical ingredient used to treat vomiting and nausea during chemotherapy, two different crystalline forms are known: ODS-1 and ODS-2. Both forms have been grown from solution. Even using different techniques; XRPD, Nuclear Magnetic

Resonance (NMR), and DSC turned out to be not sufficient to determine if Ondansetron shows polymorphism or not. Using a combination of a badly resolved crystal structure of a vapour grown crystal, ODS-3, and molecular modelling, it was hypothesized that the crystal structure of ODS-3 best can be interpreted as a locally ordered solid solution of enantiomers. Because the similarities between the XRPD patterns of the three batches it was assumed that also ODS-1 and ODS-2 are locally ordered solid solutions of enantiomers. Different incorporations of enantiomers on a mesoscopic scale, in the solid state give rise to slightly different forms of Ondansetron. The amount of water present during the crystal growth induces subtle but important local order in the disorder. The results show in this case that although different ODS forms show different physical properties, one cannot speak of polymorphism.