Screening for New Solid State Forms of Drug Substances and their Characterisation

E. Marti

APCh Marti Consulting, CH-4054 Basel, erwin.marti@apch.ch

The existing solid state variety of drug substances is a fact of nature which is additionally proofed by a small number of exemptions, especially also for the segment of polymorphy. The discovery of solid state forms of a given organic, inorganic and even biochemical molecule is always a procedure into a new territory. Two basic approaches are applied in their elucidation, the first a theoretical one is until now restricted to polymorphic forms and the second is based on experimental procedures. The theoretical approach is widely developed and tested, however, to gain any valuable results in future would afford additional basic research work. Computational crystallographer developped algorithms for lattice energy calculations with the attemt to predict crystal structures of a excellent physical stability [1]. As one example, results of a broad investigation applying several computer programs based on different physical theories were reported and discussed at a workshop in 1999 at the Cambridge Crystallographic Data Centre [2]. The basic difficulty is that these calculations are only performed under extremely restricted conditions, namely as an example for the temperature at 0 K however with omitting any entropic effect caused in really every polymorphic system brought from the absolute zero point to a temperature region above 0°C. The gained results proofed to be of mere academic interest. A typical example are the polymorph A and D of Cimeditine [3].

On the other hand, results are straightforward obtained if experimental data sets are integrated into these calculations. Such experimental findings are necessary, for example the X-ray powder diffraction of existing forms. Of course, the theoretical prediction with such a data set is reduced to a conformation of an already existing form.

At present, the best way for the elucidation of the variety of solid state forms for a given organic molecule are based on an experimental approach. The application of the high throughput polymorph screening yields to preliminary results for a selected organic molecule. These screening methods can be performed in quite different ways. Thermal and thermo-analytical methods combined off-line or on-line with devises based on microscopy and spectroscopicy are used and also crystallization procedures even on a level of milligrams sample weights. Additional well selected experimental procedures are necessary to crystallize such a new chemical entity in amounts allowing an extensive characterisation in respect to the physical and chemical conformation and purity as well as the physical and chemical stability [4].

Extremes are possible, so there are organic substances where only one solid state form is currently known. However, there are also organic molecules known for which 10 and even up to 100 different chemical entities exist. Such entities are co-crystals such as hydrates, solvates, salts, molecular compounds, complexes.

Additionally, all these chemical entities could be crystallised in different solid-state modifications. This further segment, the so-called polymorphy of one single chemical entity, adds another number of species: from only one, to a great many, namely in extreme cases to over 10 further crystalline forms as so-called polymorphs. The amorphous forms, also known for organic compounds and their different chemical entities, should also be mentioned within this context [5].

Examples are presented and the importance of the experimental approach for the search and characterisation of solid-state forms will be stressed. Thermoanalytical investigations and vapour-sorption measurements are extremely valuable especially in case quantitative results are anticipated [3.4.6].

References

[1] A. Gavezzotti, Crystallography Reviews, 7 (1998) 5.

[2] J.D. Dunitz, Are Crystal Structures Predictable? A Progress Report, Workbook PhandTA 5, Symp. on Pharmacy and Thermal Analysis, 19-21. Sept. 2000, Pharmacenter, University of Basel, Switzerland

[3] A. Bauer-Brandl, E. Marti, A. Geoffroy, A. Poso, J. Suurkuusk, E. Wappler and K. H. Bauer, J. Therm. Anal. Cal. 57 (1999) 7

[4] E. Marti, A. Kaisersberger, G. Kaiser, W.-Y. Ma, Thermoanalytical Characterisation of Pharmaceuticals, Netzsch-Gerätebau GmbH, 95100 Selb, (2000)

[5] J.-O. Henck, U.J. Griesser und A. Burger, Pharm.Ind. 59, 165 (1997)

[6] E. Marti, U. Griesser, M. Noisternig and J. Dillenz, Proceedings 4th Int. Symposium on Food and Rheology Structure, ETH Zürich, Switzerland (2006)