Crystal Polymorphism in Pharmaceuticals: A Statistical Approach

Ulrich J. Griesser, Doris E. Braun

University of Innsbruck, Institute of Pharmacy, Innrain 52, 6020 Innsbruck, Austria

The fact that the majority of drug compounds can exist in different crystalline states (polymorphs and/or solvated forms) is particularly attested by the growing number of scientific reports and patent applications dealing with this phenomenon. Special attention has been also drawn to the prediction of polymorphism starting from the molecular structure with the result that the existing methods and computer programs are not able to successfully predict the crystal structure of even rigid organic molecules (not to mention crystalline solvates). Therefore we still rely on good experimental data in order to explore and understand the principles of such phenomena.

To get a clearer picture about the incidence of crystal forms among pharmaceuticals and to evaluate relationships between their physical and structural properties and the formation of different crystal species, we carefully collected information on the solid state properties of pharmaceutically relevant organic compounds in a database and performed investigations on many drug substances over almost two decades [1]. The special focus was directed on those drug substances, which are listed in the European Pharmacopoeia (Ph.Eur.). This historically grown, random set of the most important drug substances is particular attractive for such considerations because it stands for a representative selection of a variety of defined chemical structures that are rather well characterized. Large molecules with molecular masses above 1500 have not been considered. The present report comprises 936 compounds specified in the Ph.Eur. edition 5.5.

More than 59% of these substances are known to exist in more than one crystal form. At least 38% can form polymorphic modifications, 30% hydrates and 12% solvates with organic solvents. These numbers represent the accessible, present knowledge but considering that the solid state properties of many compounds have not been carefully examined it is certainly too low. However, neither the Cambridge Structural Database, nor the Beilstein database or the Merck Index provide comparable information. Here we roughly estimated 25%, <<1% and 10% respectively for entries with hints to polymorphism or solvate/hydrate formation.

In general, the different crystal species (polymorphs, hydrates, solvates with organic solvents) can be found in all classes of therapeutic and chemical categories but certain accumulations can be established. So, non-salts with low relative molecular masses (< 350) show the highest tendency in forming polymorphs (51%) but the lowest incidence of hydrates (21%). Salt formation doubtless favors hydrate formation but the ability of solvate formation with organic solvents is clearly lowered. Furthermore the data show clearly that the occurrence of hydrates and solvates increases with increasing molecular size of the compounds, as expected. Thus, the highest amount of solvates (> 25%) can be recognized among non-salts with molecular masses greater than 350 and salts with M_r > 350 show the highest incidence of hydrates (40%).

The analysis also reveals that particularly badly soluble compounds (~ 40% of all compounds) tend to occur in different polymorphic forms (frequency ~ 50%) or as solvates (~ 20%); whereas hydrates are dominant among freely water soluble compounds. This trend correlates also well with the lipophilicity parameters. Furthermore the occurrence of polymorphs decreased strongly with increasing number of hydrogen bond donors. Quite the opposite is true for hydrate/solvate formation. The relationship between the number of hydrogen bond acceptors and the occurrence of individual crystal species shows a similar, though weaker trend.

A simple and general picture on the relationship between the occurrence of basic types of crystalline species among drug compounds and some basic feature are summarized in the scheme below.

Polymorphs	Hydrates	Solvates (organic solvent)
• smaller molar mass • Non-salt • Low solubility and higher lipophilicity • Lower number of H-bond acceptors and - donors	• Higher mol mass • Salt • Higher solubility lower lipophilicity • higher number of H-bond acc. and -donors	• Higher mol mass • Non-Salt • lower solubility higher lipophilicity

Further intriguing insights to the solid state characteristics of active drugs are given in this presentation considering for example chirality, melting points or chemical and therapeutic classes. Finally also trends and issues related to solid state phenomena of the European pharmacopoia are discussed.

References

[1] U. J. Griesser, A. Burger, Abstract book of the XVIII Congress and General Assembly of the International Union of Crystallography, Glasgow, Scotland, 1999, p. 400.