The 22nd Polish Conference of Chemical and Process Engineering
Spała, 5-9 September, 2016

INNOVATION DAY

Thermodynamics for Pharma: Practical Application of Fundamental Knowledge

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Key words: stability, amorphous solid dispersions, pharmaceutical ingredients

Active pharmaceutical ingredients (APIs) are often complex compounds exhibiting a very low aqueous solubility. Therefore, they only slowly dissolve in the body when administered as crystalline solids, which leads to a very low bioavailability. For this reason, about 80% of the promising APIs currently under development never make it into a medicine. Several approaches to increase the bioavailability of APIs have been presented in literature.

One of them is salt formation by ionization of functional groups which can be achieved by adding an acid or a base and therewith changing the pH in the solution. The observed increase in solubility depends on the acid constant of the API as well as on the amount and nature of the acid or base added.

Another approach is the application of amorphous API forms that exhibit a higher solubility as well as a higher dissolution rates than the crystalline API forms. However, they are thermodynamically less stable and will recrystallize upon storage or after dissolution in the body. One possibility to stabilize amorphous APIs is to molecularly dissolve them in an amorphous polymer which acts as carrier matrix. However, the API loading in these so-called amorphous solid dispersions usually exceeds the API solubility in the polymer. Therefore, these formulations are again usually not thermodynamically stable, but amorphous phase separation and even recrystallization of the API might occur during storage. This depends on the thermodynamic phase behaviour and is to a great extend influenced by the kind of API and polymer, by temperature, and by relative humidity.

Due to this complexity, these API/polymer formulations are so far usually found by trial-and-error procedures. Thermodynamic understanding and modeling of the underlying phenomena, however, is a valuable tool to improve and to speed up this process.

The talk will give an overview about the thermodynamic phase behaviour of systems containing pharmaceuticals. The influence of temperature, co-solvents, additives and pH on the solubility of APIs in water as well as in organic solvents will be discussed, whereas the latter is of particular interest during API production. Particular emphasis will be placed on the phase behaviour of amorphous solid dispersions.

All phenomena will be discussed based on experimental data for various pharmaceutical systems. Finally, it will be shown that thermodynamic modelling today allows for reliable correlations and even predictions of the phase behaviour of API systems. It can thus drastically reduce the experimental effort for developing the optimal API formulation and its processing.