Determination of the compatibility **between polymers and low molar mass compounds**

Combining the amorphous state of an active pharmaceutical ingredient with polymers is a promising strategy to obtain long-term stable drug products with improved solubility. As part of an efficient development of amorphous solid dispersions, Solvias offers a new differential scanning calorimetry (DSC) method to determine the solubility of a given active pharmaceutical ingredient in different polymers and to select the most promising polymer for the formulation.

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DR. TIMO RAGER —
Project Leader

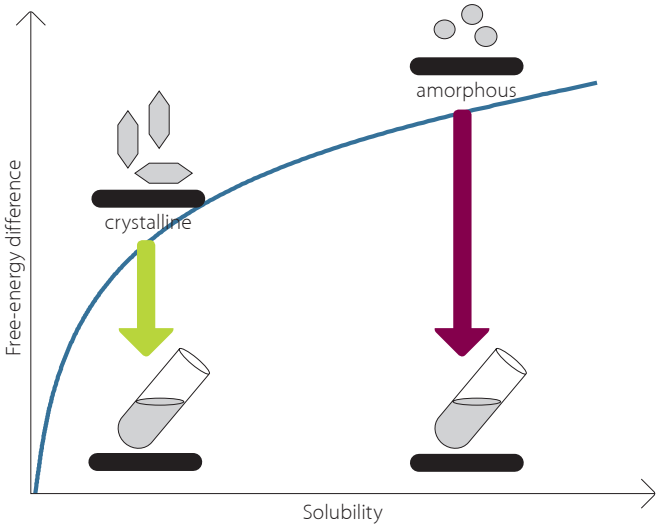
Timo Rager studied chemistry at the University of Fribourg and received his PhD from the Max Planck Institute for Polymer Research/University of Mainz in 1997. Following several postdoctoral positions, he joined Solvias in 2005 as a project leader for solid-state development. Since 2013, he has been responsible for the thermoanalytical lab.

DR. ROLF HILFIKER —
Head of Solid-State Development

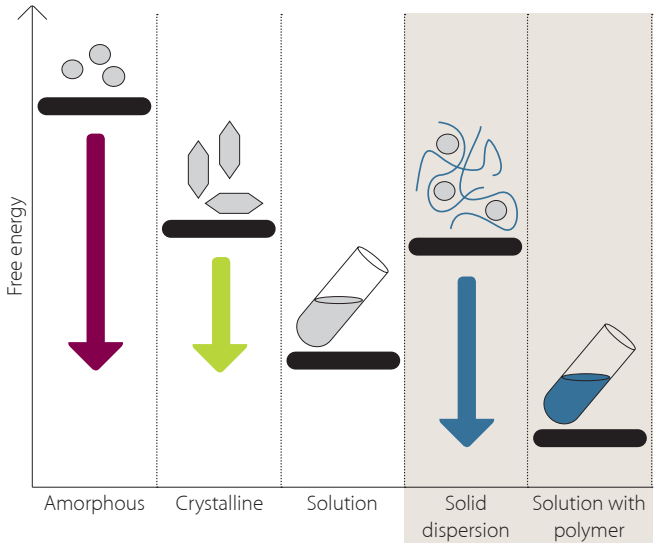
Rolf Hilfiker obtained his PhD in Physical Chemistry at the University of Basel in 1987. After a postdoc at SUNY Stony Brook (New York) and several years as a Senior Research Fellow at the University of Basel, he joined Ciba-Geigy. Since the spin-off in 1999, Rolf Hilfiker has been Head of the Department of Solid-State Development at Solvias.

The bioavailability of new pharmaceutical entities is increasingly limited by poor solubility. One strategy to alleviate this problem is the administration of the drug substance in its amorphous state. The amorphous state is the least stable accessible solid-state form of a substance and therefore exhibits particularly high solubility *Figure 1*. This higher solubility is always temporary, and a more stable crystalline form will separate over time from the supersaturated solution. In addition to this, an amorphous drug substance is also prone to spontaneous crystallization in the solid state. In order to prevent this crystallization, the amorphous state needs to be stabilized, preferably in a way that preserves the solubility advantage. One established technique to achieve this is the preparation of molecular dispersions of the active pharmaceutical ingredient (API) in a water-soluble polymer *Figure 2*. The interaction between API and polymer lowers the free energy of the system relative to the amorphous and crystalline reference states, while maintaining a large free-energy difference to the solution *Figure 3*.

The degree of stabilization depends strongly on the concentration of the API in the polymer. It is therefore of utmost importance to know the critical concentration for a stable formulation. Once these critical concentrations are known for combinations of a given API with different polymers, the polymer that most effectively stabilizes the amorphous form can be selected.



^ *Figure 1: The solubility of a solid correlates with the standard free-energy difference between its solid state and its solution.*



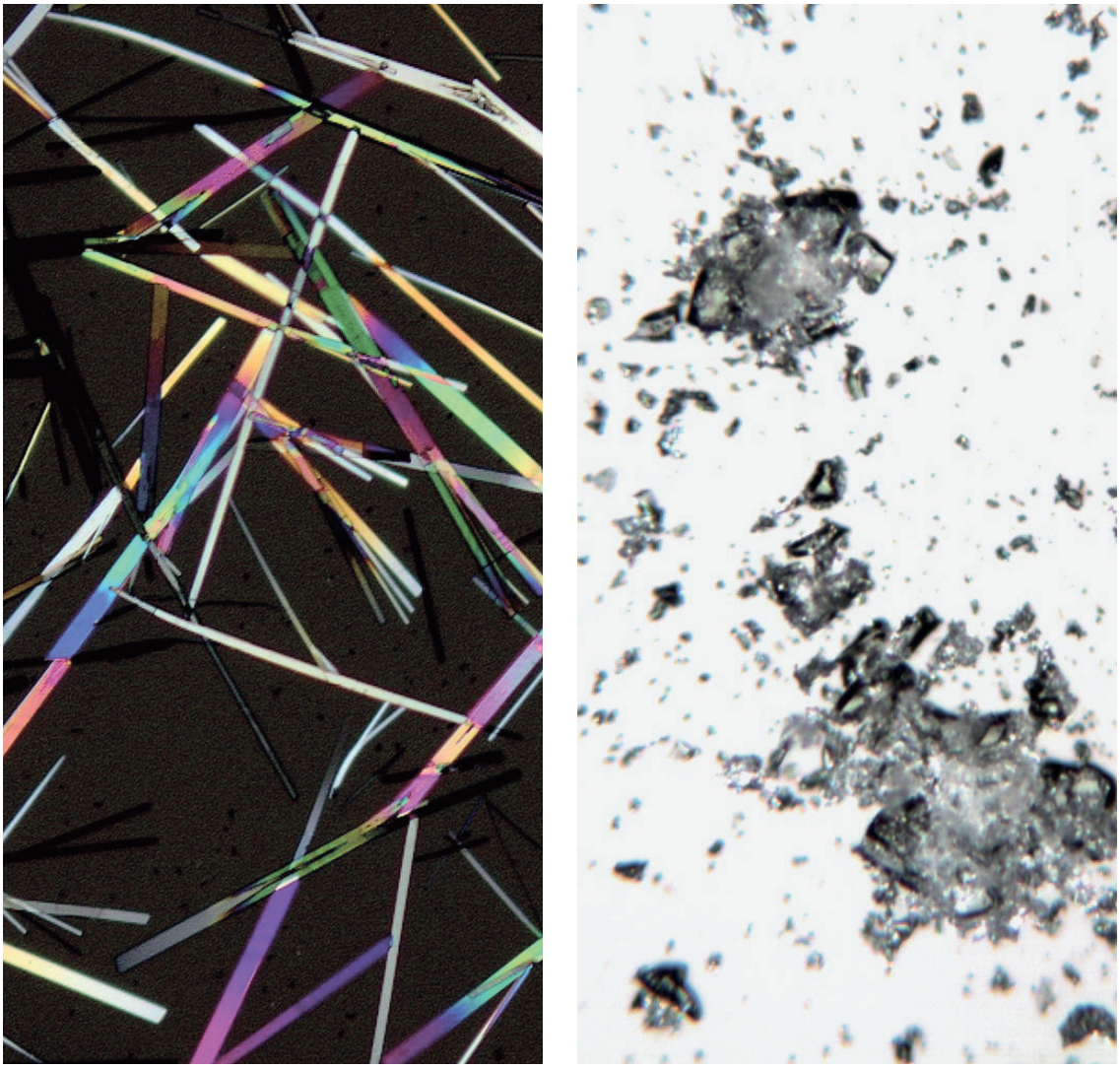
^ *Figure 3: Preparing a molecular dispersion stabilizes the amorphous state relative to the crystalline state without losing all of the solubility advantage.*

EXISTING METHODS FOR SOLUBILITY DETERMINATION

Predictions about long-term stability in polymeric systems are inherently difficult because of the slow equilibration in a highly viscous environment. Nonetheless, numerous methods have been proposed to determine the critical concentration. Basically, these methods can be subdivided into two approaches, a kinetic and a thermodynamic one.

An analysis of the kinetic stability of an amorphous solid dispersion is typically based on the number of glass transition steps observed in differential scanning calorimetry (DSC). When only one glass transition is detected, it is concluded that the two components are mixed intimately on a molecular level, whereas two glass transition steps indicate that phase separation has occurred. In the latter case, spontaneous crystallization of the API phase can subsequently take place.

A common technique providing information on thermodynamic stability is based on the melting point depression of the crystalline solid in the presence of increasing amounts of polymer. Ideally, these melting points describe the solubility in the binary API/polymer phase diagram as a function of temperature. The saturation limit at room temperature can then be derived from these data by extrapolation.



^ *Figure 2: Optical microscopy pictures of a crystalline drug substance (carbamazepine) and its amorphous dispersion (carbamazepine in poly[acrylic acid]).*

Information on the thermodynamic stability limit is generally more powerful than information on the kinetic stability because crystallization is inhibited permanently in thermodynamically stable formulations as long as the chemical composition is unchanged. Furthermore, considering that spontaneous crystallization requires a certain degree of supersaturation, a comparison of thermodynamic stabilities might also provide an indication of the relative kinetic stability of formulations at concentrations exceeding the critical value.

Although thermodynamic information is preferred, the method described above has the inherent disadvantage that the melting peaks broaden with increasing polymer content of the mixture. As a consequence, the correct determination of the melting temperature becomes increasingly difficult, which may induce a significant error in the extrapolated solubility value.

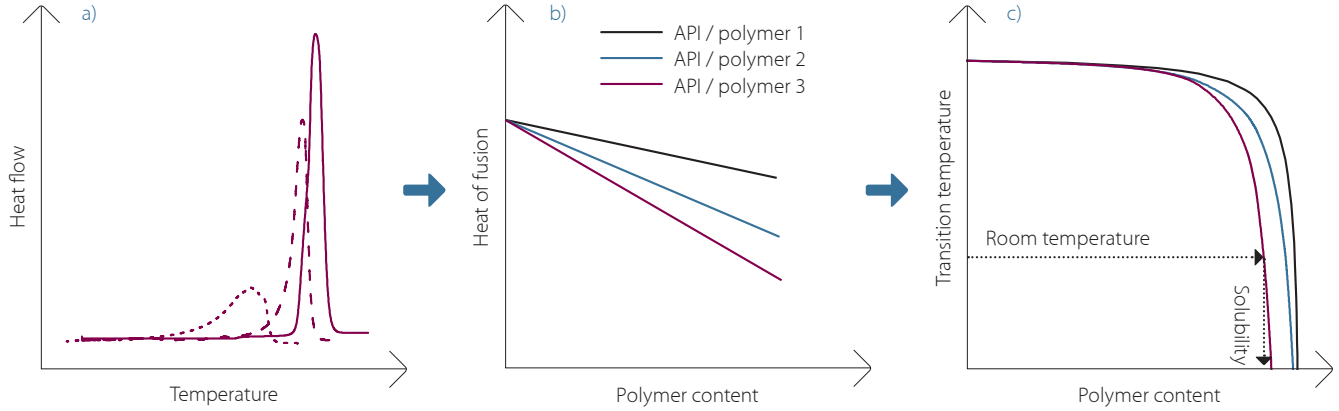
Under certain assumptions, the solubility curve for the binary API/polymer system can be calculated from the heats of fusion at different compositions.

THE SOLVIAS APPROACH

Solvias has therefore developed a slightly different approach, which is based on the evaluation of the heat of fusion of the API measured by DSC *Figure 4a*. A decrease in the heat of fusion with an increasing amount of polymer in the mixture indicates an attractive interaction between the two components in the molten state *Figure 4b*. Since an amorphous molecular dispersion is nothing else than a supercooled molten state, this approach also provides information on the stability of the dispersion. The stronger the decrease in the heat of fusion, the more attractive the interaction is, and the less polymer will be required to stabilize a certain amount of amorphous API.

In addition to this qualitative comparison of different polymers, the determination of the heats of fusion offers the possibility to calculate the solubility of the API in each polymer. The van't Hoff equation connects the heats of fusion with the phase transition temperature as a function of composition. Thus, under certain assumptions, the solubility curve for the binary API/polymer system can be calculated from the heats of fusion at different compositions *Figure 4c*, providing the limit of thermodynamic stability of the dispersions as a function of temperature.

We have recently tested this approach with several model systems, and a good correlation was found between predicted solubilities and the successful preparation of amorphous dispersions through freeze drying .[1]



^ *Figure 4: Conversion of DSC data into solubility curves.*

It should be emphasized that the applicability of this approach is linked to several preconditions, such as the melting of the API and the softening of the polymer without decomposition. Furthermore, the most stable solid-state form of the API should be known in order to investigate the relevant equilibrium by DSC. The DSC method described above has, therefore, to be seen as part of a more comprehensive study, which includes the determination of some fundamental physico-chemical and solid-state properties of the API, the selection of a polymer based on DSC data, and an in-depth characterization of amorphous dispersions with the preferred polymer *Scheme 1*.

Including the solubility determination in this stepwise approach not only provides a sound thermodynamic basis for polymer selection but also reduces the number of possible combinations at an early stage of the selection process, which implies that the necessary number of lengthy stability tests decreases. As a consequence, the selection process becomes more reliable, as well as both cost and time efficient.

1. *T. Rager, Determination of the Solubility of Crystalline Low Molar Mass Compounds in Polymers by DSC, J. Pharm. Sci. 103 (2014) 1673–1679.*

Scheme 1: Solvias program for the development of amorphous solid dispersions. >

API TO BE FORMULATED

1

CHARACTERIZATION OF THE API WITH REGARD TO ITS SOLID-STATE PROPERTIES

- Melting point and thermal stability
- Stable solid-state form at ambient temperature
- Solubility profile

DECISION ON WHETHER DSC-BASED SOLUBILITY SCREENING CAN BE PERFORMED

2

SOLUBILITY DETERMINATION IN POLYMERS BY DSC

- Preselection of polymers of interest
- DSC measurements

DECISION ON THE PREFERRED API/POLYMER COMBINATION(S)

3

PREPARATION AND CHARACTERIZATION OF AMORPHOUS SOLID DISPERSIONS FOR SELECTED API/POLYMER COMBINATION(S)

- Preparation of amorphous dispersions with variable API concentrations from the thermodynamic equilibrium value upwards
- Confirmation of amorphicity
- Behavior at variable relative humidity
- Kinetics of dissolution and recrystallization from solution
- Storage stability

DECISION ON THE MAXIMUM API CONCENTRATION