IMPROVING SOLUBILITY: STABILIZING THE AMORPHOUS STATE

Some compounds just do not have the required solubility or dissolution rate and often they are killed in the development process due to their high energy state. Amorphous materials are seen as a solution to this problem, because of their high energy state which gives rise to improved dissolution rates and apparent solubility. The big problem with amorphous materials, is that they are inherently unstable and tend to crystallize, thereby loosing these advantageous material properties. Amorphous solid dispersions are designed to overcome this problem by stabilizing the amorphous state of the active ingredient in a polymer matrix.

Crystal16 for polymer applications

The ***Crystal16*** offers an invaluable tool for automisation of amorphous solid dispersion screening, enabling the fast and effective identification of new solid dispersions of compounds. With 16 reactors at a volume of 1mL, the instrument enables scientists to determine solubility curves, assess dispersion stability and critical solution temperatures.

Increase efficiency with Crystal16

Control and reproducibility

Automating the execution of solid dispersions means more screening experiments can be carried out in the same timeframe, but also, the results are much more reproducible and controllable, which is essential for good science and answering the requirements put forward by the regulatory authorities.

Superior flexibility

In each block, experimental conditions can be varied. The screening may take into account, for instance, the effect of drug loading, type of solvent, and temperature profile on the formation of solid dispersions.

Online analysis

The ***Crystal16*** not only runs 16 experiments in parallel, it also analyzes them. In-situ turbidity measurements can provide information about the apparent solubility and the dissolution rate of the various solid dispersions obtained. The optional CrystalClear software package allows the user to graphically visualize the data and to generate reports that can be exported to Word.

Amorphous Solid Dispersions

Amorphous solid dispersions screening may be performed with the ***Crystal16*** in a automated, controlled and flexible manner. The screening may take into account, for instance, the effect of drug loading (e.g. 5, 10, 15 and 25%), type of solvent (binary or ternary systems may be also considered), and temperature profile on the formation of solid dispersions. This way, a wide set of small-scale experiments using a minimal amount of compound can be performed. For example, in one run with the 16 reactors of the ***Crystal16***, one can check the effect of two solvents, two drug loads and 4 polymers on the formation of solid dispersions for an active ingredient.

Efficient determination of solubility curves

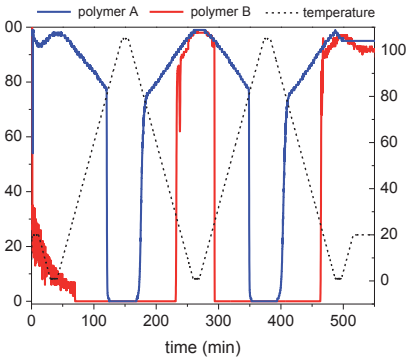
The ***Crystal16*** combines automation with integrated turbidity measurement to determine clear and cloud points resulting in solubility data at an early stage with only a minimal amount of sample. The CrystalClear software assists in identifying clear points and automatically constructs and exports solubility curves. The ***Crystal16*** can quite simply generate solubility curves for four solvents/solvent mixtures in short time with less than 100 mg of material. Based on this information, solubility curves of polymers/ excipients and solid dispersions can easily be generated.

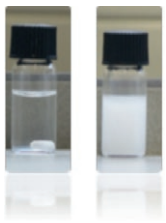
Self-assembly into micellar structures

Formation of micelles can be also followed by using the ***Crystal16***. Those type of solutions usually have a characteristic blue hue. The turbidity feature (transmission measurement) of the ***Crystal16*** can be used in such experiment to assess the formation of micelles. The formation of micelles can be also followed using the ***Crystal16***. turbidity measurements (transmission probe). Transmission profiles show undissolved scattering particles are first dispersed upon heating, and this is reflected in low transitivity. Upon further heating, the transmission increases to about 70%, where it stabilizes and giving a first indication of micelles formation.

LCST and UCST behavior

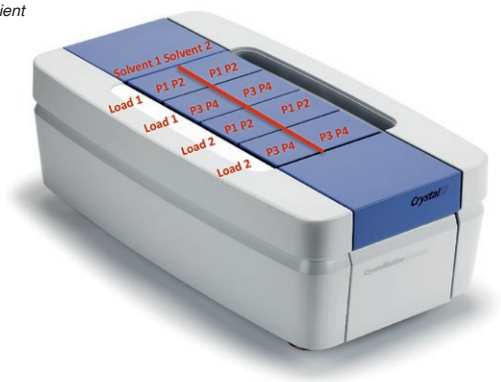
Polymer solutions sometimes show a complex thermal behavior, driven mostly by entropic forces. Some polymers show a typical thermal behaviour, dissolving at high temperatures and crashing out upon cooling. In this case the Tclear point denotes the upper critical solution temperature (UCST). In other cases however, such as those for some PEG and polyoxazoline derivates, the molecules have an inverse behavior and crash out of solution at higher temperatures. This is due to the favorable entropic effect of losing the solvation sphere of the polymer, and this temperature is called the lower critical solution temperature (LCST). This phenomenon can be used to developed controlled drug delivery systems and formulations close or at body temperature.





Figures courtesy of Prof. dr. Richard Hoogenboom (Gent University, Belgium)

Solvent: *binary and/or ternary solvent system*
Load: *drug load*
P: *Polymer/excipient*



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