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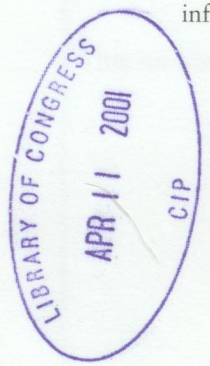

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Crystallization

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Two decades ago, crystallization was called both an art and a science. However, the field is improving quickly. The crystallization of pharmaceuticals is still sometimes regarded an art and rather a mystery. However, crystallization processes are widely used throughout the production processes of the active ingredient of a drug product, and a lot of knowledge is nowadays available.

For the crystallization of drug substances several aspects have to be considered, as the crystallization process is the last step in the chemical manufacture of pharmaceuticals. The crystallization determines a number of important properties of the drug substance, namely the purity and residual solvent content, the polymorphic form, crystal size and size distribution, and it affects downstream processes such as drying, ease of comminution and formulation of the final drug product.

The crystallization of all drug intermediates have the same goals and follows the same procedures as for other organic substances and thus will not be discussed here separately.

General Considerations for the Development of the Crystallization Process

In general, the demands on the crystallization of a drug substance differ according to the final use, e.g. if the product is used in oral dosage forms, in ointments or in liquid formulations. However, for the sake of simplicity, it is assumed here that the crystallized drug substance is to be used in an oral dosage form.

Figure 1 shows a typical crystallization process of a drug substance and the downstream processes up to the formulation of the drug product. The crystallization and the properties of the product have a great influence on all the following steps.

Impurities

Foreign and related compounds The requirements on the purity of a drug substance are strict; guidelines require a purity of typically >98%. Individual impurities with a known structure have to be below 0.5% and unidentified impurities have to be below 0.1 or 0.05%. In addition, the toxicological effect of all impurities must have been assessed in the first toxicological tests, i.e. no new impurity is allowed that has not been present in the batch used for toxicological experiments.

The purification of a drug substance via crystallization cannot be predicted easily. While foreign impurities can mostly be easily reduced, related substances like impurities stemming from side reactions in the synthesis behave in an unpredictable way. In general, the purification via crystallization will decrease with an increase in the yield, especially if the yields are >90–95%.

Residual solvent content Beside obvious solvent properties such as a certain solubility for the drug substance and an appropriate purification to yield ratio, the choice of the solvent for the crystallization of a drug substance is governed by the permissible limitations placed on the residual solvent content of the drug substance. All typical solvents have been classified according to their toxicity and tolerated daily uptakes of a solvent have been established, that are not to be exceeded by the drug product.

Three classes of solvents are distinguished: (i) those that should be avoided; (ii) those that have a limit to their daily uptake; and (iii) those for which no limits have been set up so far. Examples are benzene and dichloroethane for class 1, methanol and dichloromethane for class 2 and ethanol, ethyl acetate and acetone for class 3. In addition, good manufacturing practice (GMP) requires the manufacturer to limit the residual solvent to the lowest content possible.

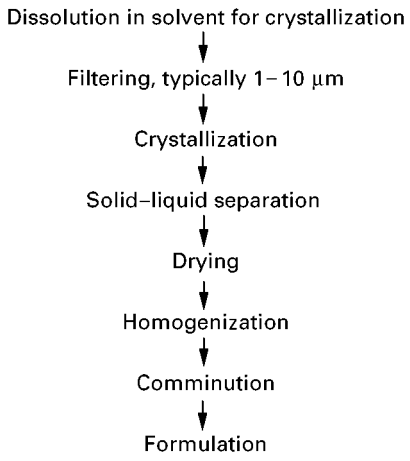

Figure 1 Typical crystallization and downstream processes up to formulation.

Table 1 Productivity, yield and development prerequisites for the separation of isomers via crystallization, enzymatic resolution and chromatography

Parameter	*Crystallization*	*Enzymatic resolution*	*Chromatography*
Productivity	High	Low	Medium
Selectivity	Varies	High	Very high
Prerequisite	High	High	Low
Development time	High	High	Low to medium

Two types of limits for the residual solvent content of a drug are distinguished. Case 1 is a dosage-independent concentration limit and Case 2 is a limit for the total uptake through the drug product, that must not be exceeded by the solvent content of the drug substance and the excipients.

The mechanisms of incorporation of solvent into the crystals can be described as follows:

- The solvent is incorporated into the lattice at fixed positions during the crystallization (solvate formation). In this case, the incorporation cannot be avoided directly. In some cases, a solvent of crystallization is removed or replaced by water.
- The solvent is incorporated into the lattice as three-dimensional inclusions. The formation of inclusions is facilitated by the speed of crystallization, thus, the amount of residual solvent can be decreased by lowering the rate of crystallization. For some systems, the tendency to form three-dimensional inclusions of solvent increases with the crystal size.

If a problem with the residual solvent content of a drug arises, the clear remedy is a change of solvent.

Separation of isomers An increasing number of pharmaceutical active ingredients are either isomers or enantiomers. Typically, different isomers of a chemical compound exhibit different biological or therapeutic activities, with one of the isomers being the carrier of the activity. In some cases, the second isomer can even have an adverse biological activity. In any case, the inactive isomer constitutes an unnecessary load to the body. Thus, a separation of isomers is almost a prerequisite for the production of a drug.

Isomers can be separated by enzymatic resolution, chromatography or crystallization. **Table 1** summarizes and compares productivity, yield and development prerequisites of the three separation techniques.

The success (or possibility) of the separation of isomers via crystallization depends on the phase diagram of the two compounds.

Figure 2 shows typical phase diagrams of isomers, i.e. eutectics, solid solutions and partial solubility in the solid state. A separation of isomers in a single step is only feasible for eutectic systems. Systems forming solid solutions have to be purified in multiple steps, as for example in zone refining which is only feasible if the substance is stable in the molten state. For systems exhibiting partial miscibility in the solid state, the separation cannot be better than the partial miscibility concentrations.

In principle, isomers forming eutectics can be separated directly via crystallization. However, without using special techniques, the crystallization can only be carried out until the concentration of the mother liquor has reached the composition of the eutectic mixture. To improve the yield two ways are often pursued:

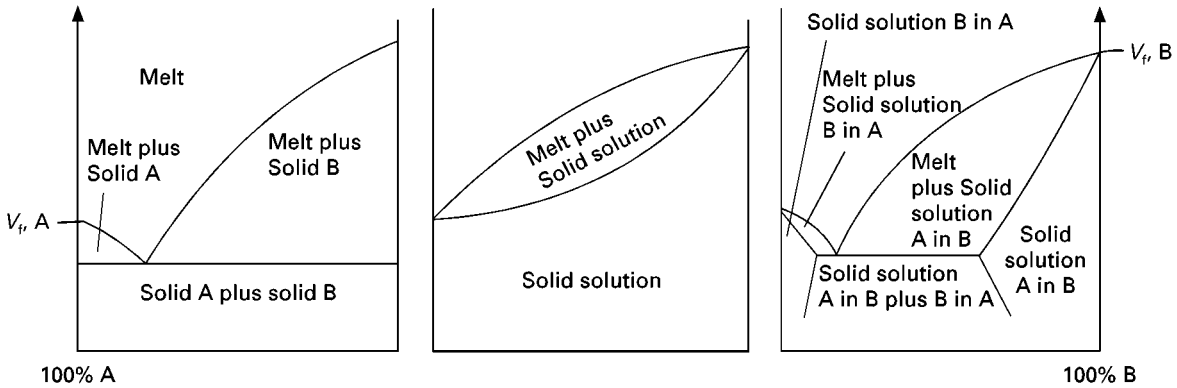

Figure 2 Typical phase diagrams for isomers: eutectics, complete miscibility in the solid state and partial miscibility in the solid

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