

International Union  
of Pure and Applied Chemistry (IUPAC)

Handbook of  
Pharmaceutical Salts  
Properties, Selection, and Use

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The problem is that there are practically no general definitions; each product is essentially a special case, which means that, at the beginning of development, powders with different characteristics must be prepared and formulation tests carried out so that the particle size can be chosen by *Pharmaceutical Development* scientists from among different samples provided by *Chemical Development* scientists.

Rather often, the tendency is for the *Pharmaceutical Development* scientists to request a very fine and uniform powder (typically with a median in the range 30–300  $\mu\text{m}$ ) for bioavailability requirements and for the *Chemical Development* scientists to prefer the formation of large crystals for ease of filtration and drying requirements. Compromises have to be found, and spherical agglomeration is a promising new approach.

For almost all drug substances, the final treatment is a mechanical comminution step: at least homogenizing for destroying agglomerates, and frequently milling for reducing the particle size.

## 5. Control of the Crystallization Process

### 5.1. Crystallization Steps

Generally, the final crystallization of a pharmaceutical active substance has two simultaneous objectives: to obtain the specified crystals and to purify the product so that traces of compounds resulting from the chemical synthesis are removed. This final crystallization is carried out either directly in the last synthetic step or more often on the 'crude' product. The crystallization steps are conventionally defined as follows:

- dissolution in a given solvent by raising the temperature, generally followed by filtration to eliminate foreign particles and decolorization on activated charcoal,
- nucleation after cooling, or seeding,
- crystal growth by programmed cooling,
- agglomeration of crystals (sometimes),
- attrition, due to particle collisions, which is proportional to the stirring speed.

What are the essential parameters?

To control crystallization, the following parameters must first be studied:

- supersaturation,
- seeding,
- cooling rate,
- stirring speed.

## 5.2. Supersaturation

This is the fundamental parameter, the driving force for the whole process. It is defined in different ways:

- by the difference between the concentration  $c$  of the solution and the concentration at equilibrium  $c^*$  (at the same temperature) (see Fig. 1).

$$\Delta c = c - c^* \quad (1)$$

- by the ratio of the two concentrations:

$$B = c/c^* \quad (2)$$

- or relative supersaturation

$$c_{ss} = \frac{c - c^*}{c^*} \quad (12)$$

Thermodynamically, the driving force is the difference between the chemical potentials:

$$\Delta\mu = \mu - \mu^* = k \cdot T \cdot \ln c/c^* \quad (4)$$

where  $k = 1.38 \cdot 10^{-23}$  J/K, the Boltzmann constant, and  $T$  the absolute temperature.

Industrially, supersaturation can be achieved by:

- evaporating the solvent (adiabatic crystallization),
- cooling the solution,
- adding an antisolvent to decrease solubility,
- chemical reaction: double decomposition of salts,

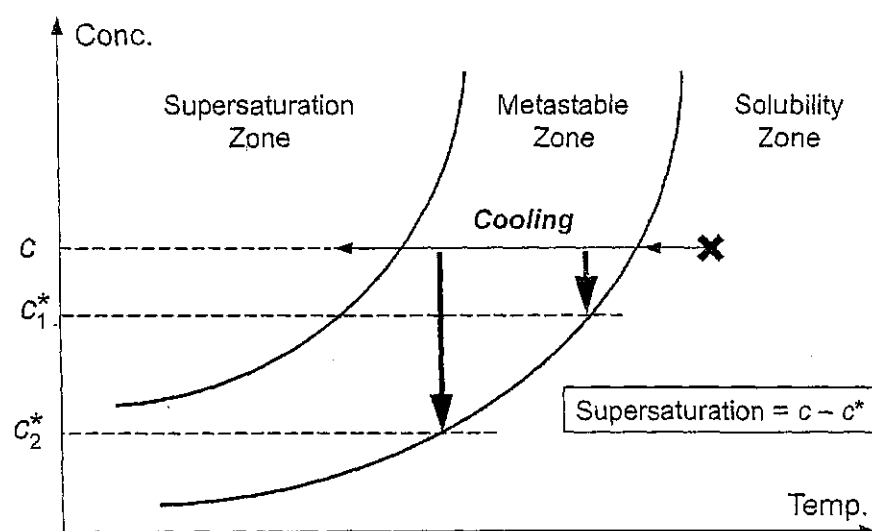


Fig. 1. Supersaturation as the driving force in the crystallization process (see text)

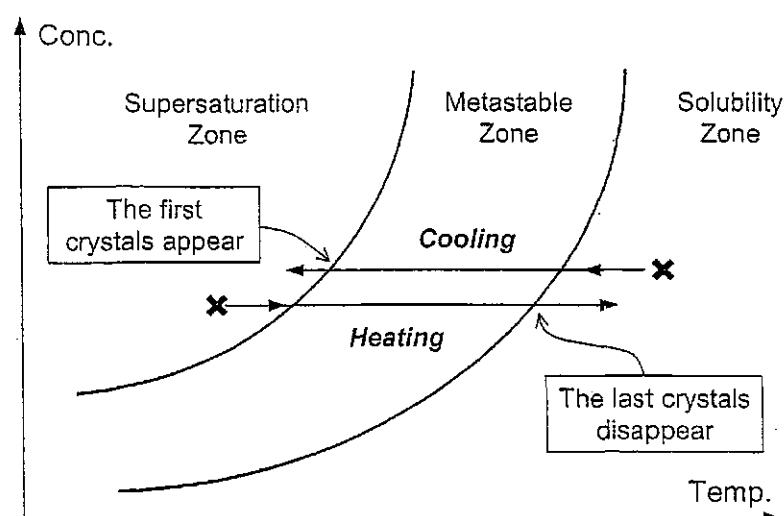


Fig. 2. Definition of the metastable zone in crystallization from solution (see text)

- changing the pH, which is a widely used process for crystallizing salts by adding acids to the active basic substance (or bases in the case of acid compounds) in solution.

When supersaturation increases, crystals spontaneously start appearing at a certain temperature, *i.e.*, primary nucleation occurs. By changing the concentration several times and repeating the operation, the supersaturation curve is obtained. By increasing the temperature, the crystals are dissolved (reverse process). This determination is repeated by varying the concentration to obtain the solubility curve. The two curves define three ranges (see Fig. 2):

- the total solubility range at high temperatures, where it is impossible to crystallize the solute,
- the metastable range between the solubility curve and the supersaturation curve, where crystallization may or may not occur, depending on the conditions,
- the supersaturation range at low temperatures, where there is necessarily excess solid.

The solubility curve is a thermodynamic limit, which depends only on the solvent/solute couple. The supersaturation curve is a kinetic limit, which essentially depends on the cooling rate but also on stirring and impurities (water content, other solvents present, particulate impurities in suspension, *etc.*).