

Reviews

Polymorphism in Processes of Crystallization in Solution: A Practical Review

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Abstract:

Here we review the polymorphism of organic molecules, obtained through batch crystallization in solution carried out in a stirred vessel. Preferential formation of a polymorph, crystal habit, and size depend strongly on the kinetics of the mechanisms involved. First, we recall the concepts of crystallization from solution. Second, phase transitions are introduced, discussed, and illustrated. Third, we focus on the development of batch-crystallization processes to obtain a given polymorph. Prerequisites are recalled, and experimental techniques used for the screening of polymorphs are presented. Recent developments in the determination of the kinetics of solution-mediated phase transition are reviewed, and the advantages and drawbacks of using process analytical technologies to monitor such transitions are discussed. Lastly, we present control strategies.

1. Introduction

Increasing numbers of polymorphs have been recorded over the past decades proving the growing interest in polymorphism in science and industry. The variations in the physical properties of a solid, such as crystal habit, solubility, hardness, color,¹ optical properties, melting point or chemical reactivity play an essential part in the formulation of the solid and in the application of the formulated product.² All industries producing a pure or formulated solid understand that polymorphism generates potentially very interesting applications, particularly in the pharmaceutical industry that polymorphism is most important. For example, the hardness of a crystal can favor granulation or conversion into pills.^{3,4} Conversely, the undesired crystallization of excipients into a formulation during freeze-drying can have a negative impact on the quality of the product.⁵

In terms of pharmaceutical efficacy of the drug, it is also essential to know which polymorph constitutes the crystalline phase and to identify its stability over time. The bioavailability of the active pharmaceutical ingredient (API) depends directly on its solubility, which itself depends on the type of polymorph. A drug can thus become completely ineffective if the amount of substance initially intended to enter the blood circulation system is reduced through low solubility and/or low dissolution kinetics. Moreover, if its solubility is higher than intended, the risks of side effects are increased.^{6,7} Thus, the discovery of a new polymorph of an API may delay its marketing; however, it may also extend it: for instance Zantac.²

The field of speciality chemicals offers many examples of the impact of polymorphism: organic dyes of Squarylium type present polymorphs used for optical accumulation systems, photovoltaic cells, electrophotographic processes, or the transformation of solar energy.⁸ The least stable phase of tributylvinylphosphonium bromide is employed for the polymerization of this chemical substance in solid state. The steric and collision factors that depend on the crystalline structure of the solid compound lead to a much faster reaction for the polymerization of the stable form. In the food industry, the crystal habit of solid particles influences the physical characteristics of the final product. Thus, it is usually advisable to crystallize metastable polymorphs of the fatty acids used for the production of emulsions such as creams, butter or chocolate. The solid properties of such metastable forms allow a good dispersion of the fatty acid crystals and ensure that they melt at body temperature.^{9,10}

In this paper we focus on the polymorphism of organic molecules, obtained through batch crystallization in solution carried out in a stirred vessel, excluding phase transitions in solid state, melt-mediated or interface-mediated transformations (for a general review see¹⁰). Preferential formation of a polymorph, crystal habit and size depend strongly on the kinetics of the mechanisms involved. In this review, we first recall the concepts of crystallization from solution. In the second part,

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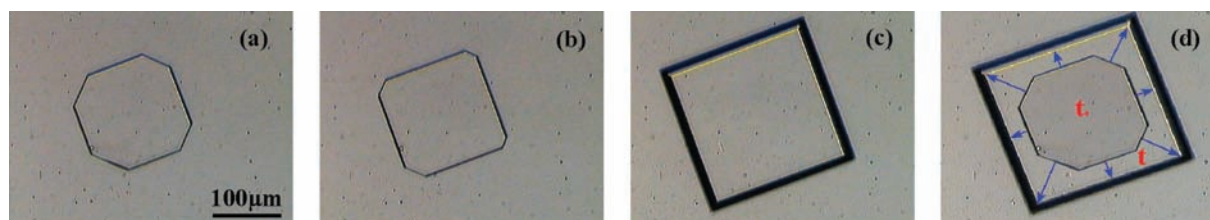


Figure 1. Growth of a BPTI crystal in 350 mM KSCN at pH = 4.9. (a–c) Frames of a time sequence obtained at different temperatures showing the evolution of the growth form as illustrated in (d), in which arrows indicate the face displacement with time (after ref 16).

phase transitions are introduced, discussed and illustrated. In the third part, we focus on the development of batch-crystallization processes to obtain a given polymorph. Prerequisites are recalled and experimental techniques used for the screening of polymorphs are presented. Recent developments in the determination of the kinetics of solution-mediated phase transition (SMPT) are reviewed. The benefits and drawbacks of using in situ video and spectroscopic probes, also denoted Process Analytical Technologies (PATs), for the monitoring of such transitions are discussed. The final section deals with control strategies.

2. Crystallization from Solution: Nucleation and Growth¹¹

2.1. Supersaturation. Supersaturation is the driving force for nucleation and growth. After dissolving the chemical species in a solvent, whether or not of a predetermined nature, the solution must be supersaturated in order to observe nucleation or growth. Supersaturation is the difference between the chemical potential of the solute molecules in the supersaturated (μ) and saturated (μ_s) states respectively. For one molecule the expression of this difference is:

$$\Delta\mu = \mu - \mu_s = kT \ln \beta \quad (1)$$

where k is the Boltzmann constant and T the temperature. To simplify, activities are considered equal to the concentrations and can be written here without specifying the units:

$$\beta = C_i/C_s \quad (2)$$

where β is the supersaturation ratio, C_i is the concentration of the solute in solution and C_s its saturated or equilibrium concentration. Obviously, this ratio is dimensionless. Moreover, if $\beta > 1$, the crystal grows; if $\beta < 1$, the crystal dissolves; and if $\beta = 1$, crystals and solution are at equilibrium.

2.2. Nucleation. When a solution is supersaturated, the solid phase forms more or less rapidly depending on the growth conditions: temperature, supersaturation, medium (chemical conditions) and hydrodynamics. Primary nucleation occurs in a solution that is clear, without crystals. It is called homogeneous nucleation if the nuclei form in the bulk of the solution. It is called heterogeneous if the nuclei preferentially form on substrates such as the wall of the crystallizer, the stirrer, or solid particles (such as dust particles). Conversely, secondary nucleation is induced by the presence of existing crystals of the same phase.

2.2.1. Nucleation Kinetics. The nucleation rate or nucleation frequency, J , is the number of crystals that form in a super-

saturated solution per unit of time and unit of volume.^{12–15} Here, we only need to recall that:

$$J = nN_0\nu \exp\left(-\frac{f\Omega^2\gamma^3}{(kT)^3 \ln^2 \beta}\right) \quad (3)$$

with f the nuclei form factor.

J is proportional to n times the solubility expressed in number of molecules per unit of volume, N_0 . ν is the frequency with which nuclei of critical size r^* become supercritical by addition of a molecule and develop into crystals. The term $nN_0\nu$ can be simply described as a pre-exponential factor K_0 .

Equation 3 shows that the frequency of nucleation depends not only on the supersaturation β but also on the concentration of molecules nN_0 . All things being equal, supersaturation included, the higher the probability of intermolecular contact, the easier nucleation. Systems with high solubility meet this condition. For systems with low solubility, the solute molecules are separated by larger distances and by a greater number of solvent molecules. The probability that the molecules will come into contact and form a nucleus is thus lower.

2.3. Growth. Once the nuclei are formed and exceed the critical size, they become crystals; hereafter, we recall the basic principles of crystal growth.

2.3.1. Growth Form. A crystal is limited by its faces. The set of equivalent faces resulting from the crystal symmetry is a form. All the forms present on a crystal represent the morphology of the crystal. However, the concept of morphology alone does not fully cover the external form of the crystal, which is contained in the notion of crystal habit. The concept of habit includes the notion of face extension. However, it is important to emphasize that the growth form of the crystal only includes the faces with the slowest growth rates. This is shown by Figure 1 which represents the growth in the metastable zone of a seeded monoclinic BPTI crystal in KSCN solution.¹⁶ This experiment consists in gradually adjusting the temperature as the growth of the crystal is observed by video microscopy. From time t_0 to time t , all the faces will have migrated parallel to themselves and crossed distances proportional to their growth rates (vectors in Figure 1d). Obviously, the growth form is different at time

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t and time t_0 . The slowest faces develop at the expense of the fastest faces, which entirely disappear. Moreover, some very slow faces appear because their growth rates are slower than the others. The growth form thus depends on kinetic factors, that is to say, crystallization conditions.

2.3.2. Growth Medium and Kinetics. Growth kinetics and mechanisms depend on external factors (medium, temperature, supersaturation, and hydrodynamics) and on internal factors (structure, bonds, defects). The growth medium influences the growth kinetics of the faces in different ways. First of all, the solvent is more or less adsorbed by the faces and selectively slows down their growth rates. Solubility also plays a role: the higher the solubility, the higher the growth rate. The growth medium also influences solvation, desolvation, and complex formation.¹⁷ If not predetermined by the process, variations in temperature also produce extremely different growth rates. Lastly, hydrodynamics, or more precisely the relative velocity of the solution compared to the crystal,¹⁸ is an important parameter. When the solution is quiescent, the face grows slowly at a rate determined by the molecular diffusion of the solute towards the crystal. The growth rate of the face increases with the flow velocity of solution to the crystal. However, there is still a diffusional limitation; this growth rate tends very quickly towards a plateau and thus reaches an upper limit determined by the phenomena at the crystal surface.

3. Phase Transitions and Polymorphism: Metastable Phases

3.1. Solubility Curves. First, let us consider a dimorphic system constituted by two polymorphs I and II. At a specific temperature, polymorph II is more stable than polymorph I. The more stable polymorph has the lowest free energy G :

$$G_{II} < G_I \quad (4.a)$$

This implies that if a polymorph II is more stable than a polymorph I its chemical potential μ_{II} is lower:

$$\mu_{II,solid} < \mu_{I,solid} \quad (4.b)$$

At equilibrium, i.e. if the solid phase is in contact with its saturated solution, the chemical potentials are identical for both species in solid and liquid phases:

$$\begin{aligned} \mu_{I,solid} &= \mu_{I,solution} = \mu^0 + RT \ln a_{I,solution} \\ \mu_{II,solid} &= \mu_{II,solution} = \mu^0 + RT \ln a_{II,solution} \end{aligned} \quad (4.c)$$

Hence, eq 4.b becomes:

$$\mu^0 + RT \ln a_{II} < \mu^0 + RT \ln a_I \quad (4.d)$$

where μ^0 is the standard chemical potential (J mol^{-1}), R the gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$) and a the solution activity. From (4.d) it is deduced:

$$a_{II} < a_I \quad (4.e)$$

with $a_i = \gamma_i C_i^*$, γ_i being the activity coefficient and C_i^* the molar concentration in species i in solution in equilibrium with solid phase I. Because of the proportionality between activity and concentration, (4.e) is rewritten:

$$C_{II}^* < C_I^* \quad (4.f)$$

This important result shows that the most stable polymorph always has the lowest solubility and vice versa, whatever the solvent in contact with the solid.

A practical tip is to measure the solubility of every form in one solvent as the best way to investigate the stability relationships between polymorphs.¹⁹ If the polymorphs are stable enough in solution, this is a quick and cheap method of investigating the stability of forms and obtaining essential data such as isolation-yield or productivity for manufacturing purposes.

Figure 2 presents two possible situations for a dimorphic system:

1. The system is considered as enantiotropic if the solubility curves cross each other at a lower temperature (noted T_r , transition temperature), than the melting points of forms I and II. As presented in Figure 2a, polymorph II is less soluble under the transition temperature and therefore stable in this temperature range. Conversely, above the transition temperature polymorph I is the stable form.

2. The system is considered as monotropic if the solubility curves do not cross each other in solution. In Figure 2b, polymorph II is the stable one. The temperature range of the solubility curves is often limited in solution (for instance, by the boiling temperature of the solvent).

When solubility data are measured for a molecular species in solution, a practical tip is to use the van't Hoff plot, i.e. the Napierian logarithm of the solubility C^* (expressed in molar fraction) versus $1/T$ (K^{-1}). The solubility curve is then linearized (Figure 3). Generally, when slope modifications are detected, several solubility curves are revealed. This is a practical way to investigate the presence of several phases (polymorphs, solvates, etc.) which may have appeared during the solubility

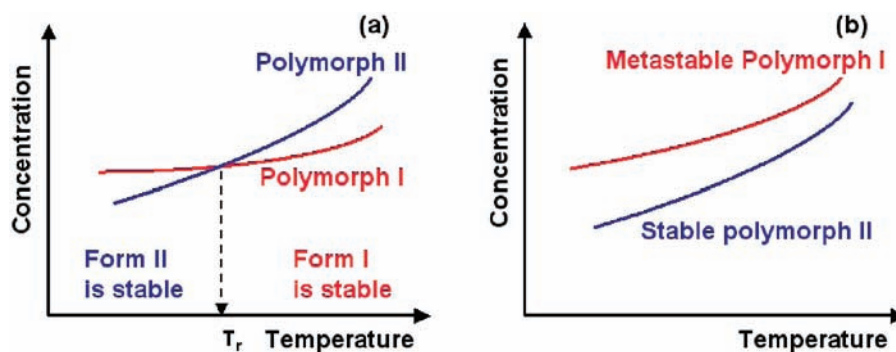


Figure 2. Solubility curves for two polymorphs I and II, related either enantiotropically (a) or monotropically (b).

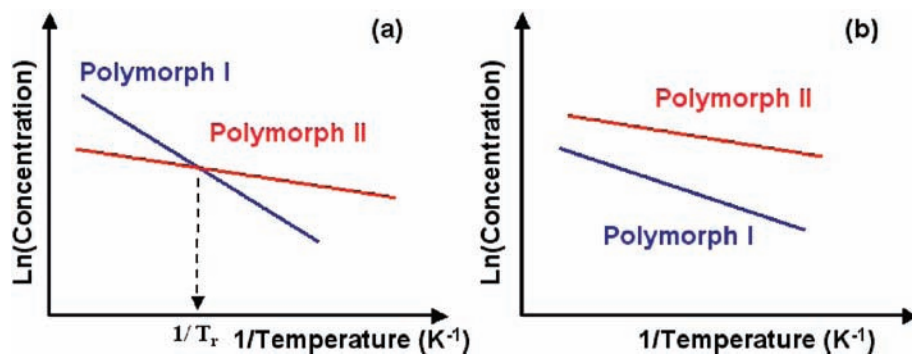


Figure 3. van't Hoff plot of solubility for a dimorphic system related either enantiotropically (a) or monotropically (b).

measurement. In this configuration, the curves plotted in Figure 2 become straight lines (Figure 3). T_r is thus given by the intersection of the straight lines. However, bear in mind that the slope discontinuity does not necessarily mean a new polymorph but could also be due to the nonideal nature of the solution, for instance the presence of a miscibility gap in the phase diagram.²⁰

The stability of the crystalline phases obtained can be assessed by DSC measurement, according to Burger–Ramburger rules.²¹ However, the phase transition which should occur with an enantiotropic system is not always detected, making discrimination between enantiotropic and monotropic systems impossible.

Indeed, using Gibbs phase rule to express the variance at the transition point for a dipolymorphic system in suspension, we obtain:

$$V = C + 1 - \Phi \quad (5)$$

with C the number of constituents ($= 2$), Φ the number of stable phases ($= 3$) and for a fixed pressure ($P = P_{\text{atm}}$). A value of $V = 0$ is calculated. There is therefore only one possible transition temperature between the two polymorphs whatever the solvent.

3.2. Metastable Phases. Another consequence of nucleation is the occurrence for kinetic reasons of unstable phases. These unstable phases may stay in a metastable state for a few seconds or several centuries. The transformation of a metastable phase into a stable phase, corresponding to the minimal free energy of the system, is called phase transition. Ostwald²² established in 1897 the rule that a chemical system does not directly tend towards equilibrium but rather towards the closest metastable state. There are many examples that support this rule, but there are also many exceptions. To illustrate the crystallization of metastable phases, let us consider the simple case of a substance with only two phases, named I and II, like the uric acids (Figure 4); their phase transition has been studied in detail.^{23,24} Usually, nucleation rate of the stable phase on the metastable phase, or

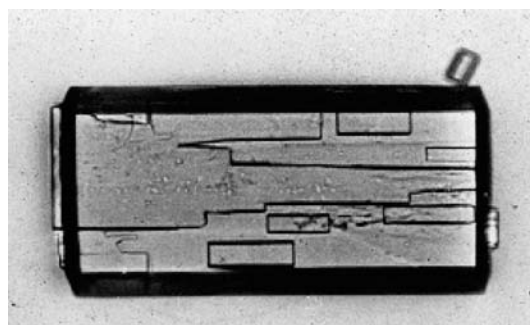


Figure 4. Uric acid phase II epitaxially grown on phase I.

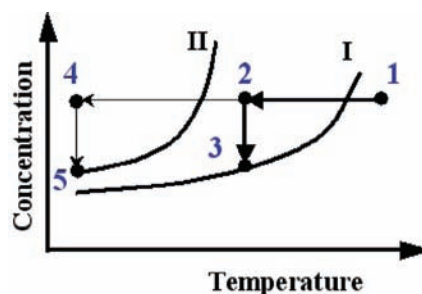


Figure 5. Schematic representation of the solubility curves of two phases, depending on temperature, in the case of a monotropic system.

the reverse, is observed.²⁵ In the particular case presented in Figure 4, the phenomenon is called heteroepitaxy.

Figure 5 is a representation of the solubility curves of two solid phases, depending on temperature where phase I is stable and phase II is metastable, according to the solubility rule. If the temperature is decreased from point 1 to point 2, the solution is supersaturated with respect only to phase I, which may nucleate at point 2 and grow from points 2 to 3. However, if the temperature is decreased directly from point 1 to point 4, then the solution is supersaturated with respect to both phases, and both have the potential to nucleate. Since $\beta_I > \beta_{II}$, it is the stable phase I that is expected to nucleate. However, if as the Ostwald rule of stages dictates, the metastable phase II nucleates prior to the stable phase, this means that the kinetic factors which impose nucleation prevail over the thermodynamic factors which impose the final equilibrium. We thus have $J_{II} > J_I$. Let us return to eq 3; as the form factor f cannot be very different between two polymorphs, the inequality $J_{II} > J_I$ can be explained only in two ways:

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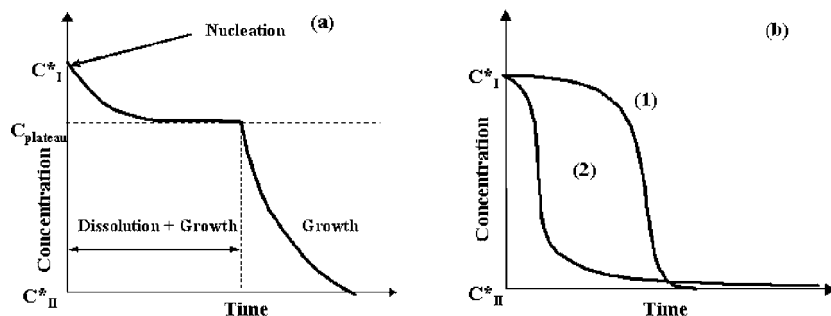


Figure 6. Concentration vs time during a polymorphic transition in solution, C^*_I and C^*_{II} are the solubilities of the two phases, (a) general profile and (b) limit profiles; curve (1) transformation is controlled by growth of the stable form (II) and curve (2) transformation is controlled by dissolution of the metastable form (I).

(1) the interfacial free energies between crystals of phases I and II and solution are as follows: $\gamma_{II} < \gamma_I$, since crystals of different phases have different surface structures (even if the crystal chemical composition is the same) and since the higher the solubility the lower the interfacial energy,^{26,27} the inequality on the interfacial energy is verified.

(2) the kinetic factor K_0 of phase II is higher than the kinetic factor of phase I, $K_{0II} > K_{0I}$, since the kinetic factor depends on the product nN_0 and is thus higher for the metastable phase.

At point 5 (Figure 5), there are 2 possibilities: either, phase I is present in the solution (appears simultaneously with phase II or by heterogeneous nucleation on phase II see Figure 4) and phase I grows at the expense of phase II, which will disappear,^{23,28–31} or else only crystals of phase II are present but are metastable.

The kinetics of transformation from phase II to I is limited either by the kinetics of dissolution of the metastable phase or by the kinetics of growth of the stable phase.³²

Finally, it is important to note that polymorphism and phase transitions comprise nucleation, growth, and dissolution processes; thus, the parameters which influence kinetics of phase transition include temperature, supersaturation, medium (chemical conditions), hydrodynamics, crystal habit, and particle size.

3.3. Kinetics of Solvent-Mediated Phase Transition (SMPT). A transformation of the solid phase can be carried out only from a less stable solid phase to a more stable one. During solid processing like crystallization in solution, the presence of a liquid phase surrounding the crystals often promotes phase transition phenomena. This modification in presence of a solvent is called SMPT.

The basic phenomena involved in SMPT have already been described.³² For a dimorphic system, this transformation requires at least three mechanisms:

- primary nucleation, often heterogeneous, of the more stable solid phase (this step can be replaced by a seeding of the stable solid phase) and growth of both phases until solubility of the metastable phase is reached,
- dissolution of the metastable solid phase,
- and growth of the more stable solid by mass transfer of solute in the solution.

These three mechanisms are consecutive or concomitant. The primary nucleation of the stable polymorph, or its seeding, is thus the trigger for a polymorphic transition in a stirred crystallizer. Primary nucleation may occur on the surface of a

substrate such as, for example, a homologous impurity³³ or crystals of the metastable polymorph.³¹ Many authors have reported the heterogeneous nucleation of β L-glutamic acid (stable phase) on the faces of α L-glutamic acid (metastable phase) during the crystallization of α L-glutamic acid.^{31,34–36}

This primary nucleation stage can be the limiting stage as reported by Righini in the case of 2,6-dihydroxybenzoic acid³⁷ and by Caillet in the case of citric acid.³⁸ Once nucleation starts, the growth of the stable phase induces a decrease in concentration in solution. If this concentration becomes lower than the solubility of the metastable polymorph, the latter dissolves, thus promoting the growth of the more stable polymorph. This dissolution and growth process is often revealed through a concentration plateau positioned between the solubility of the two polymorphic forms (Figure 6a). The position of this plateau results from the competing kinetics of dissolution and growth. Two extreme cases are possible (Figure 6b). (1) The consumption of solute by growth is slower than the production of solute by dissolution, and the plateau is located in a “high” position, in the vicinity of the solubility of the metastable polymorph. Therefore, the growth mechanism of the stable polymorph limits the transition and thus is the rate-controlling step. (2) The concentration plateau is just above the solubility of the stable polymorph. The dissolution mechanism of the metastable phase limits the transition and is thus the rate-controlling step.

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In both cases, when the metastable polymorph is completely dissolved, the stable polymorph continues to grow until its solubility is reached within a certain amount of time that depends on the position of the supersaturation plateau.³⁹

Note that in industrial conditions the solid concentration is high, up to 30% weight. The presence of a larger crystalline surface and/or an increase in the interparticle collisions may favor the development of secondary nucleation mechanisms (contact or surface phenomena) of the stable phase in suspension. In the case of transition of anhydrous (metastable) to monohydrate (stable) citric acid at 15 °C, it has been demonstrated that, during their dissolution, the metastable particles are also involved in the secondary nucleation of the stable particles in development. This may be due to a contact mechanism.³⁸ Thus, when their existence is favored by operating conditions, secondary mechanisms must be taken into account in addition to primary nucleation, dissolution, and growth mechanisms. For instance, an increase in the number of stable crystals accelerates the SMPT; with a secondary nucleation involved in the transition, the concentration plateau may no longer exist.

4. Development of a Process for Obtaining a Specific Polymorph

4.1. Prerequisite. A process to produce a specific polymorph can only be developed if the thermodynamics and kinetics of the system are known. Three principal points need to be determined:

1. the number of polymorphs and/or phases
2. the relative thermodynamic stability of the polymorphs and solvates
3. the phase transition kinetics

This means that for a new API, a polymorph screening is required, since the emergence of a new polymorph can seriously compromise the process developed, as was the case for Norvir,^{40,41} where the appearance of a new and stable phase put the company into a market crisis. Dunitz and Bernstein⁴² present several well-known cases of polymorphs for which it suddenly became impossible to obtain the metastable form. The screening of all possible solid phases and determination of the most stable phase is now a prerequisite in the earlier stages of pharmaceutical process development. Moreover, it is advisable to determine the phase diagram in order to predict all possible phase transformations. Another reason for screening is to select the phase which will be developed. Thus, it is preferable *a priori* to select the most stable phase, provided it satisfies the bioavailability criteria. For API with low solubility in water, the most stable polymorph, which also has the lowest solubility, might have insufficient bioavailability. In that case, it might

become necessary to develop a metastable form which offers higher bioavailability.⁴³

Here we present the current and emerging methods for polymorph screening, and the recent work undertaken in academic or industrial laboratories on the kinetics of polymorphic transition.

4.2. Polymorph Screening. An efficient polymorph screening will advantageously combine different techniques in order to cover a large range of operating conditions.

4.2.1. Molecular Modelling. The prediction of potential polymorphs by molecular modelling is based on the energy evaluation of all possible packing arrangements in all reasonable space groups, depending on the possible molecular conformations. The resulting crystal structures of low lattice energy are potential polymorphs. This approach has been able to generate the already identified polymorphs for molecules such as primidone or progesterone.⁴⁴ However, the prediction generally gives too many crystalline structures, and many are never observed. These methods are also restricted to fairly rigid molecules, and they are based on calculations of lattice energies which are enthalpies or internal energies, while the relative thermodynamic stability of the different polymorphs depends on their Gibbs free energies.

Molecular modelling, however, remains an efficient way to confirm structures obtained by single-crystal X-ray diffraction (XRD) or to generate structures from powder XRD.⁴⁵ It is helpful to predict the crystal habit.^{46–48} It can be used to select solvents or to design tailor-made additives to obtain particular molecular arrangements in the crystal.⁴⁹ Thus, molecular modelling can be useful in discovering new polymorphs and is a good complement to experimental techniques. However, despite extensive progress, especially in the definition of new inter-/intramolecular forces, molecular modelling cannot replace experimental techniques for polymorph screening.

4.2.2. Experimental Techniques. Experimental polymorph screening largely depends on the primary nucleation kinetics of the solid phases. As presented in part 2.2, primary nucleation depends mainly on three parameters:

- chemical composition (solvent, impurity) which largely determines the value of interfacial energy γ between the nucleus and the solution
- supersaturation ratio β
- temperature T

The screening strategy consists in varying these three parameters. To cover a large range of operating parameters, crystallization experiments can be carried out in melt, in solution, or in gas phase.

4.2.2.1. Melt Crystallization. In this crystallization technique without solvent, the solid is formed by cooling the melt under controlled conditions. The interfacial energy is minimal, since

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Table 1. Classification of organic solvents for the screening of polymorphs

type of solvent	chemical species	low boiling point	high boiling point
protic - polar	alcohol/water	methanol ethanol	hexane, butane benzyl alcohol
aprotic - polar	ketone nitrogen compound amino compound ester ether chlorinated compound aromatic chlorinated compound	acetone acetonitrile ethyl acetate diethylther, methyl <i>tert</i> -butyl ether dichloromethane toluene, xylene monochlorobenzene	methyl isobutyl ketone propionitrile, dimethylformamide <i>N</i> -methyl-2 pyrrolidone isopropyl acetate, butyl acetate, ... dibutylether <i>o</i> -dichlorobenzene
aprotic - non polar	alcane aromatiques	pentane, hexane toluène, xylène	decane, ...

the wettability between the solute in solid state and in molten state is total. The activation energies of nucleation are reduced, and the nucleation of the different solid phases is facilitated. The melt is, then, *a priori* a favorable medium for the nucleation of all polymorphs and especially the most stable polymorph (at the experimental temperature), provided the mobility of the molecule in the melt is high enough and/or the impurities do not inhibit certain solid conformations. Only parameters T and β have an impact.

In practice, thermal heating and cooling scans of the solid phase are performed by differential scanning calorimetry (DSC), thermogravimetry analysis (TGA), or thermomicroscopy. It is recommended that very slow heating and cooling rates be used. These studies have led to crystallization of new phases. Thus, polymorphic form III of acetaminophen was only obtained by melt crystallization.⁴³ These analyses and particularly TGA are also useful in the discrimination of solvates from polymorphs

4.2.2.2. Crystallization from Solution. Solvent-based techniques are certainly the most commonly used methods for polymorph screening. They allow the three main parameters of the nucleation, γ , β , and T to be varied. They provide interesting information for the development of the crystallization process. However, it is also important to vary operating conditions from those of the industrial process for a more exhaustive screening.

The most common approach consists in using different solvents of crystallization (or solvent mixtures). A change of solvent affects the solvent/solute interactions and, thus, the interfacial energies. The solvents are generally chosen from those authorized by the pharmacopoeia, but the choice can also be extended. Solvents covering a wide variety of polarity and proticity should be used (Table 1). If a solvent is already used in upstream stages of the process or is used for the downstream formulation stages, it can be added to the list.

To generate different supersaturation levels with a given solvent, crystallization experiments are performed using different techniques (cooling, evaporation, antisolvent, or drowning out) and varying, in each case, the operating conditions (cooling or evaporation rate, flow-rate of the added antisolvent). The evaporation of a solvent in which the API is highly soluble may give oil. This oil should be kept since crystals might appear later. Crystallization performed at high supersaturation levels (by drowning out, for instance) may give a mixture of several polymorphs. This mixture kept in suspension will eventually evolve towards the most stable polymorph. In order to detect different polymorphs, the suspension should be filtered very rapidly or *in situ* probes should be used (see section 4.4.1).

Finally, the temperature can be varied. The metastable zones are narrower at high temperature, and nucleation is, therefore, favored. If the system is enantiotropic and if the phase transition temperature is lower than the solvent boiling point, crystallization at low and high temperatures should be able to produce the two polymorphs, whether or not the Ostwald rule of stages applies.

It is essential to take into account the effect of the dissolved impurities, since impurities can inhibit or favor the nucleation and growth of specific crystalline forms. Solvent is itself an impurity for crystals. Thus, solvent–solute molecular interactions can encourage the formation of certain inter- or intramolecular assemblies, such as hydrogen bonding, and can explain the appearance of a specific polymorph in a given solvent. Tailor-made additives and solvents may even be used to control the appearance of specific polymorphs, predicted by molecular modelling for instance.⁴⁹ Similarly, a template can also control the nucleation event.⁵⁰ Several studies^{51,52} have used polymer heteronuclei to discover and selectively produce polymorphs. However, controlling polymorph production through solvent is not routinely used, and it is more common to obtain different polymorphic forms in the same solvent by acting on supersaturation.⁴³ Moreover, Boukerche et al.⁵³ used heterogeneous primary nucleation on amorphous seed to induce the appearance of the thermodynamically stable polymorph of an API. This stable phase had never been obtained before in the solvent used.

High-throughput screening (HTS), initially developed for biocrystallization,⁵⁴ is now commonly used to accelerate the identification of API phases⁵⁵ and is often outsourced. Numerous operating conditions can be applied to samples placed in small quiescent volume vials. Sometimes thousands of trials can be made automatically, and the solid phases obtained are generally analyzed by XRD or Raman spectroscopy using specially designed software. It is perhaps on this latter point that HTS is the most interesting, since numerous trials do not guarantee more efficient screening. Moreover, a limited number of

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experiments may be sufficient or may even give more exhaustive results, if the range covered by the operating conditions is wider.

4.2.2.3. Crystallization from the Gas Phase. The solid compound is sublimated at a given temperature, then condensed at a lower temperature. In fact, the solvent does not interfere, and it is possible to test the β and T parameters by varying the sublimation and condensation temperatures. Haleblian and McCrone⁵⁶ note that small temperature differences primarily tend to produce the stable polymorph, while large temperature differences produce the metastable polymorph. This is well illustrated by the study on behenic acid.⁵⁷

4.2.2.4. Crystallization in Supercritical Fluid. There are two main techniques of crystallization in supercritical fluid. First, rapid expansion of supercritical solution (RESS) is suitable for substances soluble in supercritical CO₂. In this process, supersaturation is generated by the rapid expansion of a solution of supercritical CO₂ saturated with the solute. Second, antisolvent precipitation using supercritical antisolvent solution (SAS) or solution enhanced dispersion by supercritical fluids (SEDS) techniques are suitable for substances insoluble in CO₂. In that case, the solute, dissolved in a solvent, is mixed with supercritical CO₂, which acts as antisolvent. Crystallization in supercritical fluid was mainly developed for particle design.⁵⁸ Indeed, the high levels of supersaturation reached can lead to the formation of micrometer- or submicrometer-sized particles with a narrow size distribution. Recent studies show that it is also a promising tool for polymorph screening. Two polymorphs (stable and metastable) were obtained for salmeterol xinafoate⁵⁹ by SEDS. All the known polymorphs were obtained by SEDS for sulphathiazole,⁶⁰ for carbamazepine,⁶¹ and for an API.⁶² The operating parameters are pressure, temperature, and solution and CO₂ flow rates. The authors demonstrated that supersaturation increased with pressure for constant temperature and molar composition. At high supersaturation, a mixture of the three identified polymorphs of the API was obtained from a solution prepared with ethanol or isopropanol. However, if the supersaturation is too high, amorphous particles can be produced. Lower supersaturation levels produced mainly single forms. Type of solvent was also found to be a key parameter. RESS technique has also been used to generate the four identified polymorphs of carbamazepine.⁶³ Note that crystallization in supercritical fluid for polymorph screening is also attractive due to the small amounts of raw material required.

4.2.2.5. Grinding. Powder grinding is mainly used to search for new cocrystals. Grinding can be performed with dry powder

or with powder moisturized with a few drops of solvent. This latter technique, known as solvent-drop grinding crystallization, generally enhances the transition kinetics. Thus, while searching for cocrystals by solvent-drop grinding, Rafilovich and Bernstein⁶⁴ found four polymorphs of benzidine. Moreover, grinding experiments can provide information on the behavior and the stability of powders, which can be useful in the formulation of the drug.

4.2.3. Conclusion. Despite extensive research, there is no 100% reliable methodology to reveal all the possible polymorphs of a chemical species. In particular, it is important to critically analyze both screening by molecular modelling, which may give too many solid phases, and screening by HTS methods, which may miss phases. These techniques should be viewed as complementary, and the more traditional approaches, which cannot always be automated, should not be abandoned. The total number of trials required is difficult to estimate, but performing numerous trials will not guarantee better results. Above all, it is important to combine the different techniques and to vary operating conditions (solvent properties for the crystallization from solution, low and high supersaturation, low and high temperature). All the solid samples obtained during screening should be kept, since they can be used as seed in the process development.

4.3. Study of the Relative Stability of the Solid Phases in Solution. It is useful to study relative stability of the solid phase in solution since it can be carried out on small quantities (i.e., a few milligrams) over a long time. The process parameter investigated is temperature, since the impact of the pressure in a liquid (i.e., condensed phase) is almost negligible.

First, the different solid phases are placed in a saturated solution at controlled temperature, and their evolution is monitored. The more stable solid phase will develop at the expense of the metastable ones. For kinetic reasons, this competition may take days or weeks. The test may be run several times for different temperatures. Video monitoring can be performed in stagnant conditions in thermostatted microcells under optical microscopy.⁶⁵

Note that comparing the solubilities of different polymorphs allows their stability gap (discrepancy) to be assessed. This latter increases with difference in solubility. From one solvent to another, this stability gap can be reduced or increased, but never reversed.

4.4. Study of the Solution-Mediated Phase Transition.

4.4.1. Monitoring the SMPT with Sensing Technologies. Many analytical techniques are currently used to characterize the crystalline form.^{66,67} SMPT studies started in the 1980s by sampling solid phases during transformation. Any manipulation of withdrawn solid suspension is extremely difficult to perform appropriately since the samples are metastable or fragile. Moreover, most of these techniques are unsuitable for the in-line monitoring of industrial processes. For a decade, PATs have allowed in situ monitoring of crystallization processes (for a

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review see Barret⁶⁸). Nevertheless studies focused on SMPT are rare (see Table 2).

PATs could be classified in two parts. First, infrared spectroscopy in ATR mode^{36,69–71} and conductometric^{25,30,72–75} probes yield the time evolution of the solute concentration. With the solubility values of the different solid phases involved, the supersaturation profile can be calculated and compared with the theoretical profiles presented in the literature (Figure 6). This information helps to determine which mechanism limits the transformation. An assessment of the duration of the transition can be obtained.

The second type of probes provides direct information on the solid phases. In situ video probes are suitable when habits developed are different from one solid phase to another. This is the case for L-glutamic acid, where the α - and β -forms exhibit respectively prismatic and needlelike habits.³⁶ However, this information remains qualitative, helping to elucidate the fundamental mechanisms involved, such as the heterogeneous nucleation of a stable phase at the crystal surface of the metastable phase. A few attempts have been made to classify the polymorphs in real-time using analysis of habit transformation via in-process imaging.⁷⁶

Among the other sensing technologies, near-infrared (NIR) spectroscopy is one of the most appropriate for routine in situ used in industrial plants because the spectrophotometers traditionally used in the laboratory can be transferred to the industrial environment in a remote manner using fiber-optic waveguides and transmittance probes.⁷⁷ In the case of a Sanofi-Aventis API, it was possible to quantitatively monitor the SMPT from form I to the more stable form II.⁷⁸ It was thus possible to evaluate the effects of temperature and of the seed on SMPT. However, the disadvantage of this technique is the considerable cost of calibration since many parameters other than the solid state may disturb measurement (nature of the solvent, size of the particles, hydrodynamic conditions).

Raman spectroscopy offers the potential of much simpler calibrations. Its application to process analysis has been held back to some extent by the less mature nature of the instrumentation. This situation was changed in the early 2000s as both the instruments and the sampling equipment became more reliable. As a result, Raman spectroscopy presents a viable

alternative to NIR for SMPT monitoring,⁷⁹ and most of the studies on in situ monitoring of SMPT use such technology (Table 2). The first study showing the ability of Raman to monitor SMPT was presented by Wang⁸⁰ when the monotropic transition of progesterone from form II to form I was investigated. A calibration curve was obtained relating the shift of an appropriate peak around 1665 cm^{-1} to the weight concentration of form I. In situ monitoring elucidated the process, and the authors thus define operating parameters allowing improved crystal habit to be obtained. Similarly, Starbuck et al.⁶⁹ used Raman spectroscopy to determine the rate of polymorphic transition of complex multipolymorphic API, referred to as MK-A (polymorphs A, B, C, E, and hemihydrate, dihydrate, and NMP solvates were identified). In addition to the characterization of such complex systems, Raman spectroscopy was useful in determining improved processing conditions. Moreover, the impact of potential disturbing events was investigated: inadvertent introduction of form C in the slurry and inadvertent water leakage into the solvent. The knowledge resulting from such studies is obviously invaluable for improving the industrial production process. Ono et al.⁸¹ monitored the polymorphic composition of L-glutamic acid in suspension during SMPT (i.e., α - to β -form). In order to measure the concentration of solid phases, the calibration of the Raman spectral data was performed from measurements of dry solid mixtures of the two polymorphs. The time variations of the concentration of the metastable α -form, which nucleates at 25 °C, provided kinetic information on its transformation into the stable β -form. This Raman technology was so promising that some authors tried to measure several features of the solid state simultaneously, for example on citric acid which exhibits an SMPT at 15 °C. The anhydrous-to-monohydrate ratio and the overall solid concentration were quantitatively monitored using in situ Raman spectroscopy,⁸² while the time variation of the crystal size distribution of particles was assessed through in situ image acquisition.⁸³ The simultaneous measurement of solute concentration and polymorphic forms in flufenamic acid systems was also reported.⁸⁴ Nevertheless as far as routine exploitation of Raman technology is concerned, many problems remain unsolved. For a review of the advantages and drawbacks of such technology see ref 85.

Among particle size analyzers available, the focused beam reflectance measurement (FBRM) probe is particularly valuable, since it can be immersed in a dense suspension, thus allowing a crystalline population to be monitored during batch crystallization. Measurements provide a relative count of particles and are proportional to the particle chord length distribution. No

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Table 2. Summary of phase transition studies based on the literature available (non-exhaustive list)

reference	studied chemical species	main results presented
[Cardew 1985] ³²	copper phthalocyanine	proposal of a SMPT model based on dissolution and growth; insights into mechanism of the SMTP are best obtained by measurement of the supersaturation profile rather than conversion data on the solid phases
[Amathieu, 1988] ²⁵	gypsum	in situ monitoring by conductimetry of the transition from hemihydrate to dihydrate of calcium sulphate heterogeneous nucleation on the surface of hemihydrate crystals quadratic dissolution rate of the hemihydrate and quadratic or linear Growth kinetic of the dihydrate
[Boistelle 1992] ¹¹⁸	pancreatic α -amylase isoenzymes	two polymorphic modifications A and B presenting an enantiotropic system with a phase transition temperature at 18 °C. Control of the stable phase with temperature
[Beckmann, 1996] ¹¹⁹	Abecarnil (API Schering)	calorimetric monitoring of the transition from polymorph B into polymorph A overall transition represented by a contact model: possible use of the Avrami-Erofeev law Evaluation of the effect of temperature via a law of Arrhenius: enthalpy of activation of 75 J/mol
[Wang 2000] ⁸⁰ [Lewiner, 2001] ⁷⁰	progesterone F (Sanofi-Aventis API)	first Raman monitoring of the SMTP from form II to form I FTIR in situ spectroscopic monitoring in ATR mode for the transition from polymorph III to IV during crystallization
[Yamanobe, 2002] ¹²⁰ [Jourani 2002] ¹²¹	D,L-methionine hydroxyapatite	Qualitative modelling of the transition from α -form to γ -form monitoring of the transformation of amorphous calcium phosphate and dihydrate dicalcique phosphate into hydroxyapatite. The overall transformation kinetics interpreted with crystal and dissolution kinetic laws
[Davey, 2002] ⁸⁸	dihydroxy-2,6 benzoic acid (model product)	monitoring of the transition between polymorphs 1 and 2 by UV spectroscopic sampling and optical microscopy overall modeling of the transition by a law integrating supersaturation, temperature; law of Arrhenius activation energy of 23 kJ/mol in toluene
[Garcia, 2002] ³⁰	Irbesartan (Sanofi-Aventis API)	in situ monitoring by conductimetry of the transition from phase A to B
[Veesler, 2003] ⁷²		dissolution controlled by the mass transfer or by the surface process depending on undersaturation selection of an additive to accelerate the dissolution of A and delay the growth of B selection of an additive to delay the dissolution of A without modifying the growth of B
[Starbuck, 2002] ⁶⁹	MK-A (API Merck)	in situ monitoring of the transition from the hemihydrate to polymorph C and from polymorph C to polymorph A by Raman spectrometry overall transition kinetics; evaluation of the effect of the temperature via a law of Arrhenius: enthalpy of activation of 61 J/g (from phase C to phase A)
[Ferrari, 2003] ³¹	glycine (model product)	off-line monitoring of the transition from polymorph β to polymorph α limiting stage is the dissolution of polymorph β effect of solubility on the kinetics
[Ferrari, 2003 and 2004] ^{31,122}	acid L-glutamic (model product)	off-line monitoring of the transition from polymorph α to polymorph β heterogeneous nucleation on the surface of polymorph β on crystals α
[Ono, 2004 ^o and 2004b] ^{35,81}	L-glutamic acid (model product)	growth of the β form is the rate limiting step nucleation of β crystals on the surface of α crystals nucleation kinetics of the stable form increases with the total area of metastable crystals, leading to higher transformation rate
[Fevotte 2004] ⁷⁸	SaC (active pharmaceutical ingredient Sanofi-Aventis)	in situ near-IR spectroscopic follow up of the SaC transition from polymorph 1 to polymorph 2
[Veesler, 2004] ⁶⁵	BPTI aprotinin, Trasylol Bayer AG	in situ monitoring of the transition of phases in quiescent thermostatted crystallizer placed under a video microscope
[Hu 2005] ⁸⁴	flufenamic acid	simultaneous monitoring of the solute concentration profile and of the solid-state composition during STMP from form III into form I

Table 2. Continued

reference	studied chemical species	main results presented
[Stoica 2005a and 2005b] ^{123,124}	steroid API	epitaxial nucleation of the stable polymorphic form on surface crystal of the metastable form when supersaturation decreases epitaxial nucleation of the metastable polymorphic form on surface crystal of the stable form when supersaturation increases
[Scholl, 2006] ³⁶	L-glutamic acid (model product)	in situ monitoring of the transformation from the α form to the β form (Raman, PVM, FTIR and FBRM probes) growth of the β form is the rate-controlling step nucleation of β crystals on the surface of α crystals nucleation kinetics of the stable form increases with the total area of metastable crystals, leading to higher transformation rate
[Qu, 2006] ¹²⁵	carbamazepine (model product)	in situ Raman monitoring of the transformation from the anhydrous state to the dihydrated state in an ethanol–water mixture growth of the dihydrated is the rate-controlling step investigation of the effects of temperature and solvent composition on the transformation rate
[Caillet 2007 and 2008] ^{82,83}	citric acid (model product)	in situ monitoring of the transition from the anhydrous form to the monohydrate form by Raman spectrometry; Simultaneous monitoring of the concentration of solid in suspension and the anhydrous /monohydrate ratio in the solid
[Barthe 2008] ⁸⁶	paracetamol	in situ monitoring of the transformation from form 2 to form 1 by FBRM probe by tracking habit modification from octahedron to needlelike shapes

calibration is necessary, and this technology can be used both in the laboratory and in the plant. FBRM measurements are highly dependent on the shape of the crystal, which means that it is reasonable to assume that a change in crystal habit can be monitored. The study performed on paracetamol, which exhibits three different polymorphic forms, illustrates that it is possible to detect the occurrence of SMPT between Form I crystals (octahedrons) and Form II crystals (needlelike) when paracetamol is crystallized in ethanol.⁸⁶ The use of a model is necessary to determine the influence of crystal shape on the chord length distribution. Considerable additional work is required to overcome the obstacle presented by a population of several solid forms exhibiting different habits and to enable, thereby, a more precise estimation of the kinetics of the transformation.⁸⁶

There is currently a trend to combine several sensing technologies. For instance, the FBRM has been used in coordination with image acquisition and Raman spectroscopy to investigate the polymorphic transformation of D-mannitol.⁸⁷ The monitoring of SMPT of L-glutamic acid has been performed simultaneously with four technologies (video, Raman, ATR-IR, and FBRM).³⁶ The sensitive information on solid phases was given by Raman spectroscopy, while the FBRM was used to monitor the evolution of the total chord counts. This study therefore necessitated quite a complex experimental protocol and the use of numerous expensive instruments. However, additional instruments are not always necessary, and the use of one, single-well-chosen technology is recommended.

4.4.2. Modeling SMPT. The dynamic data acquired through the use of sensing technologies is invaluable to analyze, understand, and design SMPT mathematical kinetic modelling.

Modeling SMPT can be carried out in two ways, either by considering a “pseudoglobal process”, or by separately distinguishing each mechanism. The former approach makes it quite easy to determine the impact of several process parameters such as temperature or supersaturation level.⁸⁸ Nevertheless, the incidence of the volume of the solution, of the specific power input from the stirring system is not taken into account. Results obtained in laboratory-scale experiment cannot be translated quantitatively to higher scales and are merely indications of trends. The second approach is a two-stage approach. First, the kinetic rate expression of each mechanism involved is obtained through specific experiments conducted with only one solid phase in suspension. For instance dissolution of the metastable phase is monitored in order to determine the values of the kinetic parameter of the dissolution law. Secondary nucleation and growth rate expressions of the stable form can be estimated through batch experiments.⁸³ Second, these dissolution and growth kinetic expressions are then combined with population balance equations in order to estimate the time evolution of the crystal size distributions corresponding to the populations of metastable and stable forms and to calculate the supersaturation profile. This approach has been found to satisfactorily describe the SMPT process,⁸⁹ revealing the intensity of each mechanism during the transformation. This allows the mechanisms which govern the transition to be determined. For instance, in the case of citric acid, the key role of the population of metastable particles in the secondary nucleation rate of the stable form has been demonstrated.⁸⁹ The model reveals the effects of the operating parameters whatever the scale considered. This approach is more valuable than the former, but requires

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Table 3. Summary of four possible situations and the strategies to be adopted for the control of the polymorphic forms

required polymorph	polymorph generated by primary heterogeneous nucleation	situations and possible strategies	examples in the literature:
stable	stable	thermodynamically and kinetically favorable situation for security reasons, seeding by the stable polymorph is recommended due to possible heterogeneous nucleation of the metastable polymorph on the surface of the particle seed	
stable	metastable	thermodynamically favorable situation seeding by the stable polymorph in order to prevent primary nucleation	API ⁷⁰
metastable	metastable	unfavorable thermodynamic situation seeding by the metastable polymorph to prevent the possible primary nucleation of stable polymorph; nevertheless, the process is in fact subject to the risk of erratic transition to the stable polymorph	Abecarnil ⁹²
metastable	stable	very unfavorable thermodynamic and kinetic situation; seeding by the metastable polymorph can be inadequate since the risk of appearance of the stable polymorph is great; the reproducibility of delivering the proper polymorph is not ensured	Norvir ⁴⁰

more complex mathematical modeling based on many more experiments.

4.4.3. Practical Considerations Regarding SMPT. Note that if there is a polymorphic transition, it is necessary to determine the conditions of its occurrence and its kinetics in order to determine the incidence on the industrial process. The kinetic parameters of a polymorphic transition are those which drive the kinetics of primary and secondary nucleations and dissolution and growth mechanisms, for instance nature of the solvent, temperature, solution viscosity, stirring, presence and concentration of impurities and additives, size of the crystals.⁴⁰

An important consideration is the driving force of the SMPT, i.e. the difference in solubility between solid forms. Consequently an SMPT is made easier when the difference in solubility between solid forms is large. This is supported by the literature such: the more soluble a substance in a solvent, the faster the transformation from the metastable form to the stable one.²⁶ One explanation is the larger exchange rate of molecules between forms due to higher solubilities. This has been shown for several APIs.^{90,91}

In an industrial process, an SMPT can occur as long as the solid phase is in contact with the solution, during the crystallization stage, but also during the filtration, washing, and drying stages. At an industrial scale Beckman reports that in the case of Abecarnil,⁹² mass contents varying from 5% to 10% of a solution in the downstream centrifugation and drying stages are sufficient to obtain a complete polymorphic transition. A practical means to prevent or delay an SMPT in a process is to avoid operating conditions (nature of the solvent, temperature) with high solubility levels and large differences in solubility. For instance, the solvent grade may have a tremendous impact on the SMPT kinetic rate. For an API, a salt, which is more soluble with significant water content in solution, it was clearly demonstrated that the presence of 2% of water in a technical grade acetone may strongly promote SMPT during filtration.

Rather than choosing an extra-pure solvent grade, the use of a dried technical grade was sufficient to delay the SMPT for the industrial operating time.⁷⁸

5. Achievement and Control of the Desired Polymorph

For a dimorphic system, the desired (patented) polymorph can be the stable or the metastable polymorph. Achieving it depends mainly on the prevention of primary nucleation, which is stochastic, meaning that a phase nucleated can differ from the desired phase. A seeding procedure is often used to ensure as soon as possible the presence in suspension of the desired polymorph. Table 3 summarizes the four possible situations by giving examples reported in the literature.

We add the following comments:

- When the desired polymorph is the stable polymorph, the situation is controlled by seeding the stable polymorph. Particular precautions should be taken preparing the seed: make sure that the proper polymorph is seeded, that the surface of the seed is activated so that it is completely effective, and finally that the seeds are added to a supersaturated medium, before primary nucleation.^{92–94} Seeking the stable polymorph is recommended since it is not very risky. Even if a metastable phase nucleates at the surface of the stable crystal seed, in the end the stable polymorph will grow at the expense of the metastable polymorph.

- When the desired polymorph is a metastable polymorph, there is a risk of transformation into a more stable polymorph following a heterogeneous primary nucleation. A seeding procedure of the metastable polymorph should be carried out with great care: the equipment used should be thoroughly cleaned with solvent between each operation in order to make sure that no nuclei of the stable polymorph are present in the medium, and the seeding rules presented above should be strictly applied. The trickiest point is that the seed must be free of the stable polymorph (note that less than 1% of a phase is

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undetected by X-ray diffraction or differential scanning calorimetry). The industrial process developed is potentially unreliable, which Chemburkar et al. show clearly in the case of Norvir.⁴⁰

However, other strategies can be used to avoid seeding procedures:

- When the solid generation produces a mixture of solid phases in suspension containing the desired stable polymorph, it is possible to monitor the complete transition into the stable polymorph. Seeding of the stable polymorph is no longer useful. Starbuck et al.⁶⁹ have illustrated this strategy with an API on the market. The total conversion of a mixture of polymorphs and solvates into the stable polymorph is ensured by the use of in situ Raman spectroscopy monitoring.

- The use of tailor-made additives is possible, for example to support the emergence of a metastable polymorph, which sometimes inhibits the nucleation of the stable polymorph. Several examples have already been presented in the literature.^{30,95,96} Note that this strategy is rarely applicable to the pharmaceutical industry due to the addition of chemical species, which remain soluble and do not easily satisfy legal constraints.

- Lastly, an alternative solution to enhance the nucleation of the stable polymorph at low supersaturation is to induce crystallization from metastable solutions using an external energy field (electric field,^{97–102} light,^{103–108} or ultrasound irradiation^{109–117}). In the case of polymorphism, this method can replace seeding by the desired polymorph.

6. Conclusion

Controlling polymorphism in solution is a major issue both for research and for industry, presenting substantial scientific and economic challenges.

Knowledge of the phase diagram of a solvent–solute system with polymorphs is necessary but insufficient for the development of a process enabling a specific polymorph to be obtained. While thermodynamics makes it possible to classify polymorphs according to their stability, knowledge of the kinetics of generation of polymorphs and of phase transitions makes it possible to define the crystallization process. For industrial purposes, we strongly recommend choosing the most stable polymorph when the application allows.

This review makes three key recommendations:

1. The mechanisms occurring during the generation of polymorphs and the transitions between polymorphs, namely, nucleation, growth, and dissolution, are not specific and are commonly encountered during crystallization in solution. Consequently, all process parameters such as nature of the solvent, pH, temperature, concentration, stirring, contents of additives and/or impurities, and crystal size distribution influence the control of polymorphism.

2. The use of in situ sensors is essential for rapid development of a process where a specific polymorph is required. We would add that the European and American authorities recommend the use of in situ sensors (PATs) for the control of this type of process.

3. The choice of strategy to obtain a polymorph depends on the stability of this polymorph with respect to other identified polymorphs. When the desired polymorph is the most stable identified polymorph, the seeding strategy is usually effective, and can also be replaced by a strategy of transition between polymorphs, if in situ monitoring is possible. However, when the desired polymorph is the metastable polymorph, the risk of losing it during crystallization but also during the downstream stages of concentration and formulation, is not negligible. The risk that should be taken depends on the difference in stability between the required polymorph and the most stable identified polymorph: it is reasonable if the gap in stability is small, but the risk is high if the gap of stability is large. This strategy, too, is based on seeding with the desired polymorph, but achievement of a mixture of polymorphs is possible.

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