Controlling Polymorphism with Membrane-Based Crystallizers: Application to Form I and II of Paracetamol

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Control of polymorphism is a key issue in several scientific, technological, and industrials fields. The various polymorphs of the same substance, having different crystalline lattices, are characterized by diverse physicochemical properties such as solubility, bioavailibility, stability, etc. This assumes special importance for organic molecules, which are more and more used in, for example, pharmaceutics, electronics, and material science applications.

As the growth of a specific polymorph arises from the crystalline nuclei overcoming their critical radius, the nucleation stage is the decisive step for the selective production of a certain polymorph. Also, polymorph transitions might occur during the growth stage because of solvent-mediated transformations. Supersaturation is the driving force for both crystal nucleation and growth. Every solution has a maximum supersaturation limit defined by the metastable zone width (MZW). The supersaturation boundary has a kinetic nature, in contrast to the saturation limit, which is thermodynamically well-defined; it depends, for example, on temperature, solution composition, cooling rate, the presence of impurities, mechanical effects, fluid dynamics, etc. MZW is very important, as its extent might have a profound effect on the yield of a crystallization process.[1]

In a previous paper,[2] we reported that the fine control of the solvent evaporation rate in membrane crystallizers[3−7] allows us to modulate the rate of achievement of supersaturation. This induced the selective crystallization of either stable or metastable polymorph of glycine, by switching between a thermodynamic and a kinetic control of the nucleation stage. Here, we studied the polymorphic yield of the membrane crystallized paracetamol.

Paracetamol (acetaminophen) is a widely used antipyretic and analgesic found in over-the-counter drugs. Three polymorphs of paracetamol are known: monoclinic[8] form I is the thermodynamically stable modification at room temperature; form II (orthorhombic)[9] is metastable at ambient conditions; form III is very unstable and was elusively obtained by crystallization from the melt.[10−12] The crystal structure of the marketed monoclinic form lacks in sliding planes; this results in poor compression properties and therefore in the requirement of binding agents for tableting, a practice which is time-consuming and adds production cost.[11−14] In this respect, much attention has been focused on the production of the more soluble form II, whose crystal structure contains slip planes that allow plastic deformation and hence characterization by higher compressibility than the monoclinic form.[12] This makes form II potentially more attractive from an industrial stand point for the direct compression in tablets.

Although form I can be easily grown from solutions in various solvents,[12] form II has been obtained, for example, from melts in a non-oxidizing atmosphere[11] and from ethanol solutions with the assistance of seed crystals (and at low temperature in order to reduce its solvent-mediated transformation to form I).[12] More recently, Mikhailenko[15] proposed a way for producing large crystals of form II from aqueous solutions by a multistep procedure that includes boiling, filtering, incubation at 40 °C for 24 h, and finally, cooling slowly to 23−18 °C for 24 h.

In the present work, commercial Paracetamol, dissolved in bidistilled water (at 12 mg/mL and 20 °C), was crystallized in static membrane crystallizers.[4] The driving force of the membrane-assisted evaporation mechanism was varied by changing the rate of solvent evaporation (J) and, hence, the rate of variation of the supersaturation, defined as $S = C/C_{equ}$ (with C being solute concentration at the nucleation point and C_{equ} the solubility).

The morphology of the paracetamol crystals obtained varied depending on the values of J: a needle morphology, typical of form II, and either an elongated prismatic morphology (Figure 1a), usual for the form I when grown at low supersaturation or a habit in which all the faces are well-developed (Figure 1b), distinctive of form I when grown at higher supersaturations.[16,17]

Crystals were analyzed by ATR-FTIR and two well-distinct types of vibrational spectra were obtained (Figure

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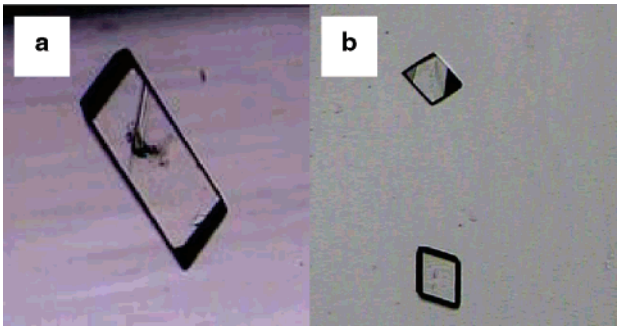

Figure 1. Optical images of the paracetamol crystals obtained for intermediate *J*: (a) $J = 4.37 \times 10^{-2}$ mL/h; (b) $J = 6.60 \times 10^{-2}$ mL/h.

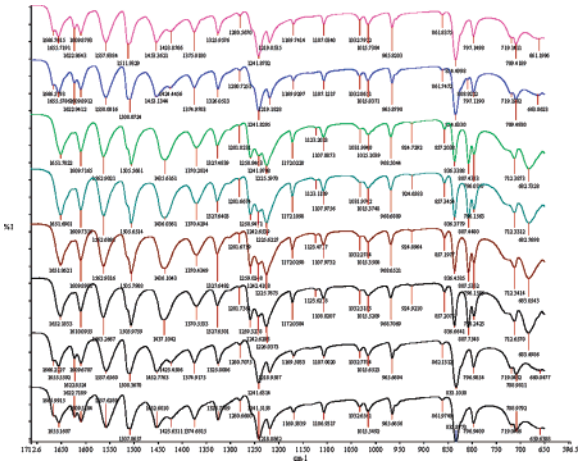

Figure 2. Total attenuated reflectance (ATR) Fourier transformed infrared (FTIR) spectra of the samples of paracetamol crystals obtained in membrane crystallization experiments at different solvent evaporation rates (from top to bottom: $J = 1.37 \times 10^{-2}$; 1.94×10^{-2}; 4.33×10^{-2}; 4.37×10^{-2}; 5.89×10^{-2}; 6.60×10^{-2}; 7.90×10^{-2}; 8.98×10^{-2} mL h^{-1}).

2). We have found the shift of some specific peaks and some absorptions patterns in the range 1700−650 cm^{-1} to be the most diagnostically useful in distinguishing between the monoclinic and orthorhombic form of paracetamol:[18−20] more specifically, in the spectra of form I, there is a peak around 1515 cm^{-1} and a strong absorption at 807 cm^{-1}, whereas in those of the form II, there are absorptions around 1666, 1622, and 1423 cm^{-1}. Mixtures of the two polymorphs have also been detected taking into account the combined presence of some of these specific signals.

In Table 1, the polymorphic yield in the crystallization of paracetamol for different *J* values, according to the infrared characterizations, is shown. The selective crystallization of one form was achieved by a careful control of the solvent evaporation rate trough the pores of the membrane. For $J \geq 7.9 \times 10^{-2}$ mL/h, the only polymorph obtained was the metastable form II, whereas for $4.33 \times 10^{-2} \leq J \leq 6.6 \times 10^{-2}$ mL/h, the thermodynamic monoclinic product appeared. In the case of $J = 1.94 \times 10^{-2}$ mL/h, a weak peak in the spectra at about 808 cm^{-1} indicates the concomitant presence in the sample of the form II, of a small amount of the modification I. This demonstrates the good accuracy of the infrared method in order to recognize the polymorphic composition of the specimens.

Table 1. Paracetamol Polymorphs Obtained at Different Conditions of Rate of Solvent Evaporation (*J*) and Corresponding Induction Time (t_{ind}) and Supersaturation at the Induction Time ($S(t_{ind})$)

J (mL/h)	t_{ind} (h)	$S(t_{ind})$[a]	polymorph
1.37×10^{-2}	64.3	1.34	II
1.94×10^{-2}	53.6	1.52	II (+I)
4.33×10^{-2}	23.5	1.91	I
4.37×10^{-2}	31.0	1.83	I
5.89×10^{-2}	24.3	1.93	I
6.60×10^{-2}	23.0	1.96	I
7.90×10^{-2}	19.5	2.00	II
8.98×10^{-2}	17.5	2.05	II

[a] Solubility data from ref 26.

To some extent, these results seem to be in accordance with those previously reported by Di Profio et al.[2] and He et al.[21] for the crystallization of glycine. In those cases, the control in the solvent evaporation rate, and therefore in the rate for the achievement of supersaturation, allowed a variation in the MZW of the system, leding to the selective crystallization of one polymorph of the amino acid. Here, from Table 1, is evident that the increase in the supersaturation at the induction time of paracetamol $S(t_{ind})$ by increasing *J* indicates the increase in the MZW as *J* raises. Generally speaking, it is well-recognized that the metastable limit normally increases with the rate at which the supersaturation is generated.[22] For a given polymorphic system, the crystallization of one form is associated with the overcoming of its nucleation barrier (that is related to the MZW). During nucleation, the magnitude of the driving force for the solute molecule aggregation changes with the surface area-to-volume ratio of the embryos and gives rise to a critical radius, above which the nucleus grows and below which it redissolves into the solution. When the rate of variation of supersaturation is low, if the least stable structure or a mixture of critical nuclei form at the same time, nuclei of the more stable polymorph have time to grow at the expense of the less stable form, via solvent-mediated transfer of solute. However, for higher solvent evaporation rates, the increase in the MZW induces nucleation at higher values of supersaturation and the sudden achievement of such supersaturation leads to the nucleation and growth of the higher energetic form, which is the first to appear according to Ostwald's rule of stages.[23] Hence, in the case of high values of *J*, the rapid solvent evaporation rate resulted in the formation of the kinetically favored polymorph of paracetamol, whereas for the lower rate of solvent extraction, the formation of the more stable monoclinic form is favored. From Figure 1, it appears that for the same polymorph I, the crystal habit can be controlled by acting on the supersaturation, as the aspect ratio of crystals changes with *J*.

At glance, it is not clear why for $J < 2 \times 10^{-2}$ mL/h the form II was again obtained. This observation might induce us to consider different nucleation mechanisms in the conditions of very low *J*. In fact, the total rate of nucleation is the sum of several contributions (homogeneous, heterogeneous, surface, attrition-induced), one of which is dominant

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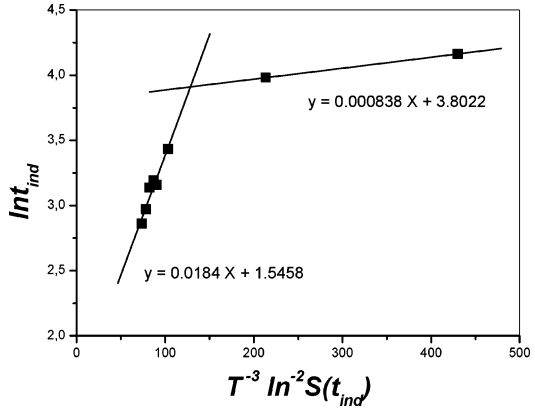

Figure 3. Behavior of the $\ln(t_{ind})$ as function of (T^{-3} $\ln^{-2}$ S). The diverse slopes of the two straight lines denoted the different nucleation mechanisms ($T = 293$ K).

in certain ranges of supersaturation. In a membrane crystallizer, the membrane matrix acts as a selective barrier for solvent evaporation, but in some cases, it is active also as support for heterogeneous nucleation.[4,6] To confirm this effect, the $\ln(t_{ind})$ as function of (T^{-3} $\ln^{-2}$ S) has been calculated from the experimental data and plotted as shown in Figure 3. The different slopes of the two straight lines fitting the experimental points identify a different nucleation mechanism in the diverse ranges of supersaturation: for high *S*, this is a prevalently homogeneous nucleation, whereas for low *S*, it is a heterogeneous nucleation pathway.[24] Therefore, the presence of the polypropylene membrane surface provides for very low values of *J* ($<2 \times 10^{-2}$ mL/h) heterogeneous nucleation sites and hence an increased chance of nucleation for the orthorhombic form of paracetamol. This is in accordance with Lang et al.,[25] who observed the selective nucleation of orthorhombic paracetamol by using isotactic polypropylene as heterogeneous support. For higher *J* values, the nucleation mechansim is predominantly homogemeous.

In conclusion, in a membrane crystallizer, depending on the operative conditions, the rate for solvent extraction and hence the rate of achievement of the supersaturation, can be finely controlled; in addition, the specific interaction between the solute molecules and the membrane surface addresses the nucleation mechanism toward the production of the high-energy form. In this way, the direct production from aqueous solutions of form II of paracetamol was selectively achieved. On the one hand, this would represent a more desirable and controllable manufacturing process of paracetamol for industrial-scale purposes. But also, more generally, the possibility of inducing polymorph selection and crystal habit modification during a crystallization process by using membrane-based techniques has been confirmed.

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