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Polymorphic Generation through Solvent Selection: Ranitidine Hydrochloride

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Abstract:

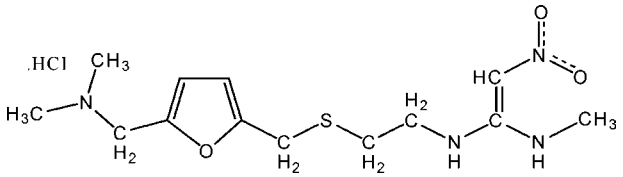
The fundamental processes of crystal nucleation and growth are strongly dependent on the solvents used in the crystallization process. Consequently, the product quality is also affected by the choice of solvent used in the process. In this study, several solvents were used, and their impact on the polymorphic generation of ranitidine hydrochloride (RAN-HCl) was studied using two different recrystallization modes. The solid-state FTIR and UV spectrophotometer were used for characterization and quantification of two polymorphic forms of RAN-HCl. It was found that methanol concentration greater than 10 wt % at nucleation onset favored formation of Form 2. The best results with respect to the solid bulk density were achieved with acetonitrile as an antisolvent.

Introduction

Ranitidine hydrochloride (RAN-HCl) is a histamine H_2-receptor blocker that is used in clinical practice for the treatment of duodenal ulcers, heartburn, acid reflux, and Zollinger−Ellison syndrome. Since gastric secretion requires stimulation of H_2 histamine receptors, by blocking these receptors, ranitidine hydrochloride indirectly inhibits stomach acid secretion, allowing healing to occur in the area of ulceration or damage by acid.[1] The chemical formula of RAN-HCl is $C_{13}H_{22}N_4O_3S{\cdot}HCl$, and the structure of one of the possible tautomers is shown in Scheme 1.[2]

Ranitidine hydrochloride (RAN-HCl) is the salt produced by the reaction between HCl and ranitidine base (RAN-B) and is found in two different polymorphic forms, designated as Form 1 and Form 2, and several solvates.[3] The enamine moiety of the RAN-HCl molecule is responsible for the existence of two different tautomeric polymorphs.[4] In one configuration the methylamine and nitro groups are in cis

Scheme 1. **Structure of one of possible tautomers of RAN-HCl**



arrangement, while in the other polymorphic configuration they are in the trans arrangement to each other, The type of solvent can influence the stability of a particular tautomer in the solution. In anhydrous, less polar or nonpolar solvents the intramolecular hydrogen bonds are expected to be strong and thereby lead to the enamine tautomer which is Form 1 in solid state. In aqueous and/or more polar solvents the intramolecular hydrogen bonds are expected to be weakened or disrupted and thereby lead to the nitronic acid tautomer which is Form 2 in the solid state.[5]

The first polymorphic form, Form 1, was discovered in 1978 by Allen and Hanbury Ltd. of the Glaxo group,[6] and it had poor filterability and drying characteristics. The second polymorphic form, Form 2, was also patented by the Glaxo group[7] in 1985. Murthy at al.[8] pointed out the importance of the presence of water for producing Form 2 and its absence for obtaining Form 1. Mirmehrabi et al. showed that significant amounts of strongly polar solvents favor the production of Form 2.[9] In another study,[10] Mirmehrabi et al. demonstrated a systematic approach for improving the filterability and solid density of Form 1 in reactive crystallization of RAN-HCl by manipulating the operating condi-

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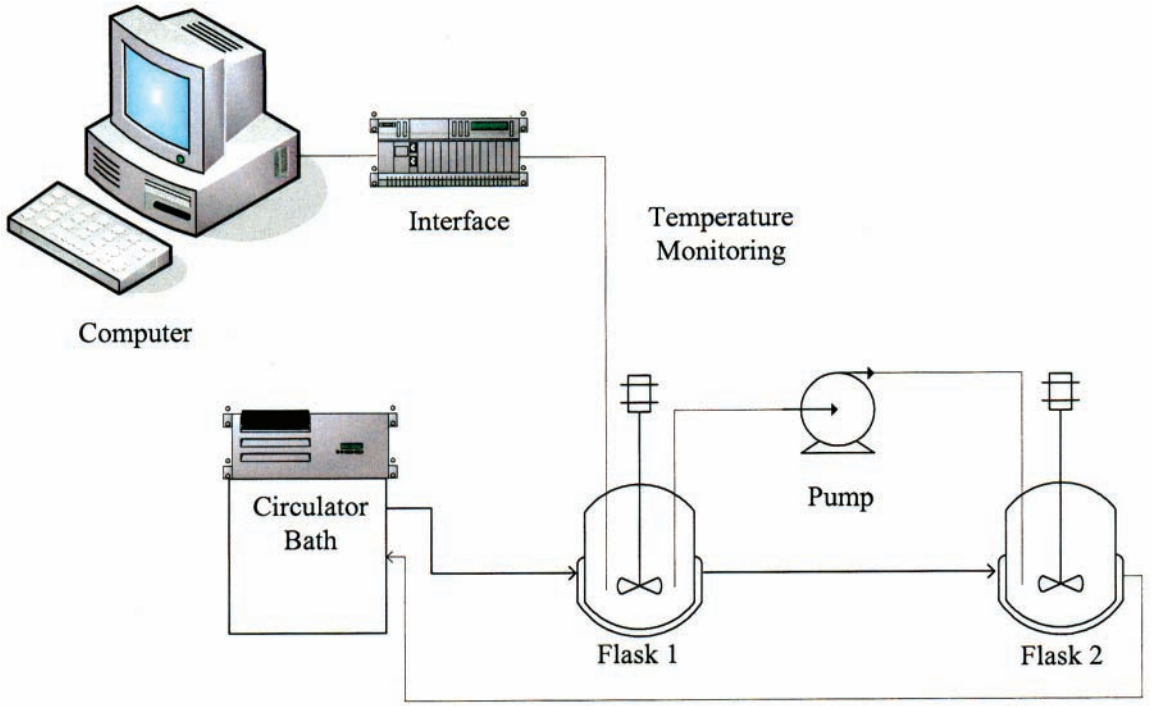

Figure 1. **Diagram of the experimental setup.**

tions such as temperature, pH, and pattern of reactant addition. This study focuses on the recrystallization of two anhydrous polymorphs of RAN-HCl and the effect of various solvent systems on the polymorphic generation. Two different regimes of antisolvent crystallization were performed: addition of antisolvent to the saturated solution and vice versa.

Materials and Methods

Materials. RAN-HCl solid forms were produced using the procedures of related patents.[6,7] HPLC-grade methanol, 2-propanol, acetonitrile, methyl ethyl ketone, and nitromethane were purchased from Sigma-Aldrich (Milwaukee, WC).

Experimental Setup. The experiments were performed in two 250-mL Bellco jacketed flasks (Vinelean, NJ). A Neslab RTE digital plus 740 bath circulator (Portmouth, NH) was used for heating and cooling. A Teflon-coated thermocouple was used for reading the temperature in the flasks. A peristaltic pump was used to pump the solution of RAN-HCl or the antisolvent. For mixing, a top-mounted, two-bladed, flat electromagnetically driven stirrer was employed. The stirrer blades were Teflon coated to reduce the corrosion and particle breakage. For monitoring the temperature and data acquisition, version 6i Labview software was employed. The logic control program for the experiments was written in Labview using the wire program language. The experimental setup is shown in Figure 1.

Analytical. The product of each experiment was dried in the oven at 50 °C under vacuum. A Bruker solid-state Fourier transformation infrared spectrometer (SS-FTIR) was used for quantitative analysis of the product with respect to the two different polymorphic structures, and the method previously developed by Mirmehrabi et al.[11] was employed. The analysis was based on monitoring the peak height at 1045 cm^{-1}, which is the characteristic peak for Form 2. Both forms contained the peak at 1075 cm^{-1}, which was used as a reference peak. The ratio of these two peaks was used for quantification of solid forms in the final product, which was a binary polymorphic mixture. The water content in the solution was determined using the Mettler-Toledo Karl-Fisher DL38 titrating device. A 50-mL Bellco jacketed flask was used for the solubility measurement. Heating was provided by an RTE-220 bath circulator (Neslab, Mississauga, ON). A thermometer with 0.1 °C resolution was used to monitor the temperature of the solution. A magnetic stirrer was employed for gentle mixing of the solution. The flask was connected to a condenser to minimize evaporation of the solvent. RAN-HCl powder was poured in excess in 25 mL of solvent, and after 2 h of mixing at a given temperature, the magnetic stirrer was stopped to let the crystals settle down. It was found experimentally that 2 h of gentle mixing was enough to reach equilibrium. A sample was taken from the supernatant with a preheated 2-mL syringe equipped with 0.45-μm filter (VWR, Canada) and transferred to a 50-mL vial, which contained preweighed water. After proper dilution of the sample with water, the concentration was measured using a UV/visible spectrophotometer. For each temperature, two samples were taken to increase the measurement confidence. A Cary Bio 100 spectrophotometer (Varian, Mississauga, ON) was used as an analytical instrument for the solubility measurement. A calibration curve was developed using solutions with known concentrations of stavudine in wt-ppm at the characteristic spectrophotometeric peak wavelength for ranitidine, 228 nm. A differential scanning

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Table 1. **Solubility (g of solute/100 g of solvent) of RAN-HCl Form 1 in mixture of solvents at 25 °C**

methanol + 2-propanol		methanol + acetonitrile		methanol + nitromethane	
methanol mol %	solubility	methanol mol %	solubility	methanol mol %	solubility
0	0.05	0	0.14	0	0.53
3.4	0.08	4.1	0.59	8.8	7.8
15.6	0.21	12.9	2.97	59.3	47.9
35.4	0.85	29.8	15.40	100	32.39
50.7	2.26	64.8	43.01		
70.2	6.78	71.5	47.7		
87.6	28.54	84.8	43.55		
100	32.39	100	32.39		

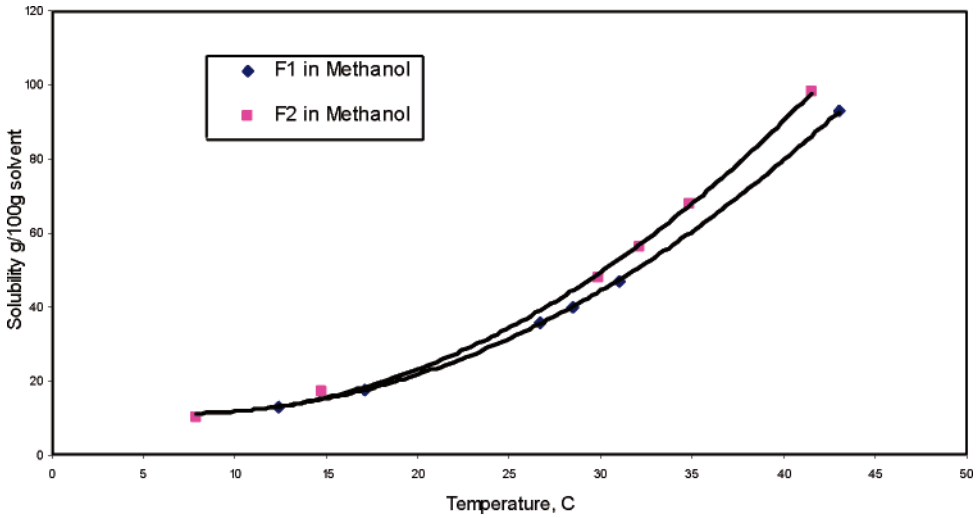

Figure 2. **Solubility of ranitidine hydrochloride polymorphs in methanol.[8]**

calorimeter (DSC, Mettler Toledo) was used for thermal analysis of the product. The crystallinity of the product was checked using Rigaku MiniFlex powder diffractometer. XRPD spectra were collected using Cu Kα (λ for K_α = 1.54059 Å) radiation obtained at 30 kV and 15 mA. The scans were run from 10° to 40° 2θ, increasing at a step size of 0.05° with a counting time of 1 s for each step. Data were processed using the MDI-Jade, version 7.5, software.

Experimental Procedure

The effect of various solvents was studied using two different crystallization methods: addition of antisolvent to a solution of RAN-HCl in methanol and addition of RAN-HCl in methanol solution to the antisolvent to study the effect of dipolar protic composition on the polymorphic generation.

1. Addition of Antisolvent to the Solution of RAN-HCl in Methanol. Before performing each experiment the system was purged with nitrogen to minimize the absorption of water from the air. A weighed sample of RAN-HCl was dissolved in methanol at 48 °C, and the solution was poured into the flask. The concentration of RAN-HCl was varied in each set of experiments so that the effect of the initial saturation level could be studied as well. In the other flask, 100 mL of antisolvent was poured and heated to 48 °C. After the desired temperature was reached in both flasks, the antisolvent was gradually added to the solution of RAN-HCl in methanol. The rate of the antisolvent addition was kept constant for all experiments. The main adjustable parameter was the concentration of initial RAN-HCl or, in other words, the degree of undersaturation. The time required for initializing nucleation after the addition of antisolvent was recorded for each experiment. The speed of mixing was also kept constant at 200 rpm for all experiments. After the addition of the antisolvent, the mixture of RAN-HCl in solvents was stirred for an additional 30 min at 48 °C, cooled to room temperature with 0.5 C/min cooling rate, and then filtered under vacuum and nitrogen environment to isolate the product. The product was dried overnight at 50°C under reduced pressure and then analyzed using the analytical methods mentioned above.

2. Addition of RAN-HCl in Methanol Solution to the Antisolvent. The experiment was performed in the same way as for the first method, but the only difference was the manner of addition. In these experiments, the solution of RAN-HCl in methanol was added to the antisolvent, making the antisolvent predominant throughout the experiment. The time of nucleation was recorded, and the product was analyzed in the same way as was the product of first crystallization method.

Results and Discussions

Solubility Data. The results of solubility measurements of ranitidine hydrochloride in various solvents and mixture of solvents are given in Table 1 and Figures 2 and 3. Ranitidine hydrochloride is sparingly soluble in 2-propanol, acetonitrile, and nitromethane but very soluble in methanol. The solubility of RAN-HCl Form 1 in the solvents that were

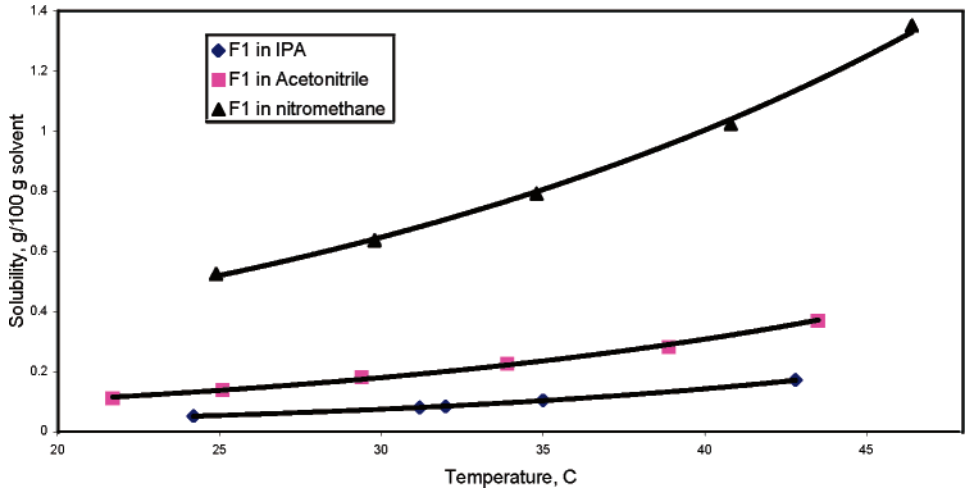

Figure 3. **Solubility of Form 1 in various solvents.**

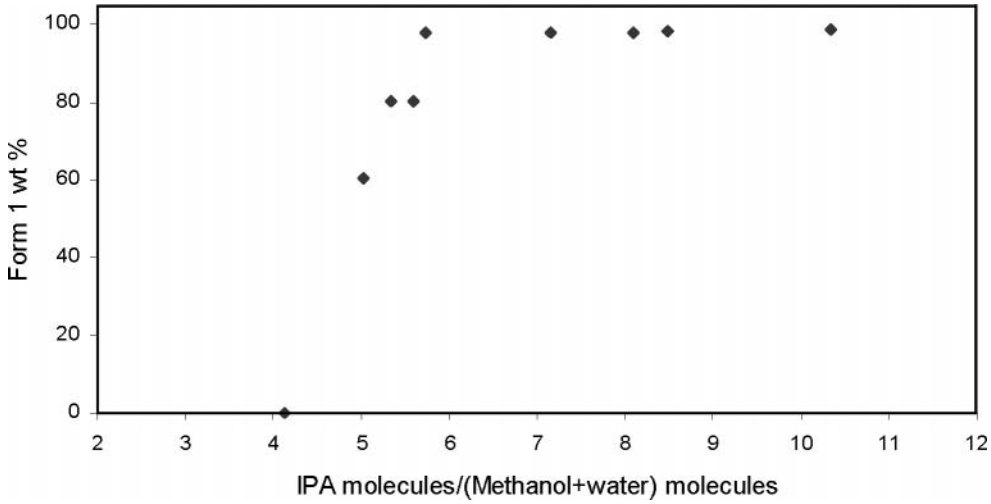

Figure 4. **Production of Form 1 vs IPA molecules/(methanol + water) molecules. The final product is a mixture of Form 1 and Form 2 or pure forms.**

used as antisolvents is shown in Figure 3. Since the crystallization had to be conducted in a mixture of solvents, the solubility in a mixture of methanol and other solvents was also obtained. The solubility in a mixture of methanol and 2-propanol is almost an exponential interpolation of the solubility of each of the pure solvents while the solubility in the mixture of methanol and acetonitrile passed through a maximum. The solubility in mixture of methanol and nitromethane was significantly higher than mixture of other solvents, making it an improper system for crystallization.

Experiments Using IPA as Antisolvent. All the experiments with direct antisolvent addition resulted in Form 2, as the concentration of methanol was always more than 10 wt % at nucleation onset and resulted in Form 2. The results of these experiments are not presented here. To keep the concentration of methanol as low as possible the reverse addition was employed in which the RAN-HCl solution was added dropwise to the antisolvent, leading to nucleation at lower methanol concentrations. For these experiments, 100 mL of IPA was used as antisolvent. The RAN-HCl solution was added to the antisolvent in 5−10 min, and in all experiments, nucleation started after the complete addition of RAN-HCl solution.

All the experiments were unseeded. It was found that at higher methanol content, the precipitation was more gradual, and it was favorable for the production of Form 2. The water content in the crystallization mixture measured with Karl Fisher ranged between 0.13 and 0.8 wt % in various experiments. The source of this water could have been absorption from air to the solvent employed or the initial RAN-HCl solid.

Figure 4 shows the composition of the final product as a function of the water and methanol molecules relative to IPA molecules at onset of nucleation. As the amount of water and methanol increases, the chance of producing Form 2 increases. There are also some ratios at which the two polymorphs exist concomitantly. The solid bulk density of the product was in the range of 0.17 to 0.20 g/mL for Form 1 and around 0.21 g/mL for Form 2. The final product of the crystallization of both forms gave a product with similar filterability and solid bulk density, with Form 2 having slightly better properties.

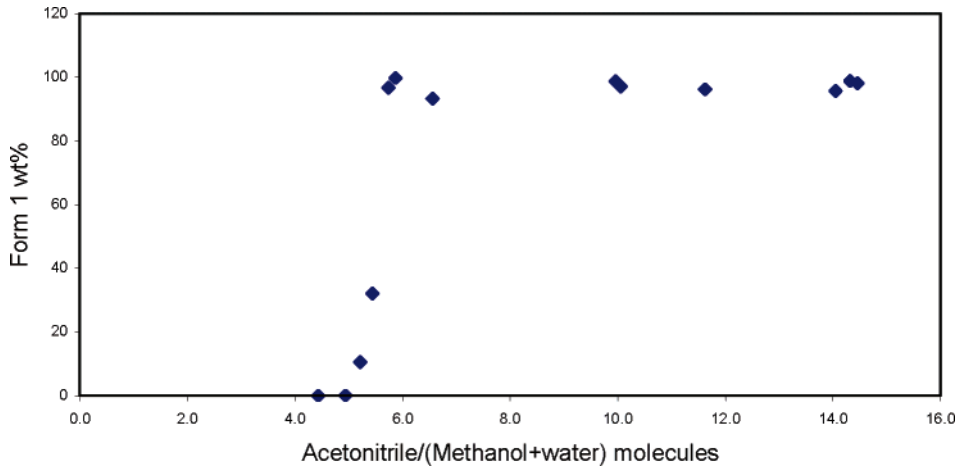

Figure 5. **Production of Form 1 vs acetonitrile molecules/(methanol + water) molecules. The final product is a mixture Form 1 and Form 2 or pure forms.**

Experiments Using Acetonitrile as Antisolvent. The solubility of RAN-HCl in acetonitrile−methanol goes through a maximum. As a result of this trend, the crystallization process is more gradual and easier to control. As antisolvent is added to the RAN-HCl solution, initially the solubility increases and goes through maximum. Adding more acetonitrile decreases the solubility gradually until the solution becomes supersaturated. For each experiment, 100 mL of acetonitrile was used as antisolvent. The antisolvent was added to the RAN-HCL solution in methanol in about 50 min, and in all experiments, nucleation started after the complete addition of acetonitrile. Special care had to be taken during the experiments since acetonitrile is strongly hygroscopic, and the possibility of water absorption is high. The filtration had to be done under nitrogen atmosphere after which the product had to be immediately dried under vacuum. Conditions other than inert atmosphere resulted in a different physical appearance and chemical composition. In ambient conditions, the product changed to a yellow color and became a hard solid with higher water content. Water percent varied from 0.13 to 0.75 wt % in the crystallization mixture. The experiments were performed using the direct antisolvent addition method, and all of them were unseeded. The production of Form 1 is presented as a function of the molecular ratio of acetonitrile to water and methanol in Figure 5. The polymorphic generation in acetonitrile−methanol mixture showed the same behavior as the IPA−methanol mixture.

The highest solid bulk density for Form 1 was 0.30 g/mL, which indicated better product quality in comparison with bulk densities for the experiments conducted with IPA as the antisolvent.

On the basis of this set of experiments, it was concluded that the content of methanol and water in the crystallization mixture determined the polymorphic structure of the product. Generally, acetonitrile showed more desirable results than IPA as antisolvent in the RAN-HCl recrystallization since the nucleation was easier to control and the product was of better quality.

Experiments with Nitromethane as Antisolvent. The experiments were performed using the reverse addition antisolvent crystallization method. As the solubility of Form 1 in nitromethane (see Table 1) indicated, nitromethane was not a proper antisolvent for recrystallization of RAN-HCl. The solubility of RAN-HCl in nitromethane is relatively high, and consequently there was an inhibition for nucleation. Moreover, the solubility of RAN-HCl in mixture of methanol and nitromethane goes through a maximum, which is almost (by interpolation) at 1 g/g solvent. Even in the cases when the solution of RAN-HCl in methanol was initially supersaturated, the nucleation did not start spontaneously. After the seed addition, the nucleation would start very gradually, and the product yield was very low. The product was very fluffy and strongly hygroscopic.

Experiments with MEK as Antisolvent. The experiments were conducted using the reverse addition of the antisolvent crystallization method. The nucleation would start as soon as the first drop of RAN-HCl in methanol solution was added to the flask with 100 mL of methyl ethyl ketone (MEK), regardless of the initial saturation of the RAN-HCl solution. Throughout the experiment, very strong repulsive forces between the RAN-HCl crystals and the MEK solvents were observed. They caused all crystals to settle on the walls and the bottom of the flask, leaving the clear solution in the middle. Controlling the process was impossible, and the product was very stony (small, hard, pellet-like solid). To ensure that the product was not amorphous, the crystallinity of this product was tested using X-ray powder diffraction. After collecting the spectra, the data were processed using the MDI-Jade version 7.5 software, and the crystallintity of 92% was obtained. It can be concluded that due to the repulsive forces, crystals were agglomerated into larger solid particles, which were not easy to grind, and thus had no commercial value.

Conclusions

The solubility of RAN-HCl in the mixture of solvents can be used to design the crystallization process. The solubility that passes through a maximum indicates more gradual crystal growth and better product quality, provided that solubility is adequate to allow the concentration for initializing the nucleation to be reached. The amount of

methanol (polar protic solvent) present at the nucleation onset in the crystallization process of RAN-HCl determines the polymorphic structure of the product. Another indicator of the polymorphic structure is the ratio of molecules of less-polar to polar solvents (e.g., IPA/methanol) at the nucleation point, and it is common for different solvents. Depending on this ratio, pure polymorphs or a mixture of forms could be obtained.

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