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Full Papers

Control of Product Quality in Batch Crystallization of Pharmaceuticals and Fine Chemicals. Part 1: Design of the Crystallization Process and the Effect of Solvent

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Abstract:

The product quality in a crystallization process refers to the crystal size distribution (CSD), crystal morphology, polymorphic outcome and the degree of crystallinity, and purity. In addition, the product yield is also important. Properties such as the filterability and solid bulk density are directly related to the CSD. To obtain the desired product quality, attention should be paid to the various operating conditions such as the local and average levels of supersaturation, the type of the solvent, the operating temperature and pressure, the type and concentration of impurities and tailor-made additives, degree of mixedness, geometry and the mode of operation of the crystallizer, and seeding and feeding policies. In addition to these variables, the implementation of external control either in the form of a feedback controller or an optimal control policy can further improve the product quality. In Part 1 of the present communication, an attempt is made to present a systematic approach to investigate the effect of various operating conditions, i.e., the design of the crystallization processes, on the product quality. In particular the effect of the solvent in terms of the solubility and its ability to participate in forming hydrogen bonds with the solute molecules will be studied. The effect of mixing, the seeding policy, and the design of the feed system on the product quality will also be discussed. Experimental results are presented to demonstrate the effect of the operating conditions in improving the filterability and solid bulk density of ranitidine hydrochloride and another pharmaceutical compound. In Part 2, the effect of the "external control" on the product quality will be discussed.

I. Introduction

Batch crystallizers are used in the manufacture of fine chemicals, specialty chemicals, photographic materials, intermediate pharmaceuticals, and active pharmaceutical ingredients (API). The initial efforts to control the product quality in batch crystallizers were focused on the study of the various factors affecting the nucleation, growth, and aggregation mechanisms. These processes depend on the thermodynamic and kinetics factors that are governed by variables such as the local and average levels of supersaturation, the degree of intermixture, impurities, additives, the operating temperature and pressure and pH, and the type of solvent. The crystallization literature is replete with the studies on the effect of the above variables on the nucleation, growth, and aggregation mechanisms and the product quality.

The type of solvent is a major factor in polymorphic selectivity and crystal morphology of the product. This effect arises from the solvent−solute interaction at the molecular level. The solvent can facilitate favorable interactions with solute clusters or nuclei on specific growing faces, which cause reduction in interfacial tension and improve the speed of crystal growth.[1] On the other hand, if the solvent and solute molecules are strongly bonded at a special crystal surface, the rate-limiting step of growth of that face will be the removal of the solvent from that face. In this case, the bonded crystal face grows slowly or does not grow[2] at all. Davey et al.[3] demonstrated the key role of solvent in cluster formation and nucleation via hydrogen bonding.

Sato et al.[4,5] have examined the effect of supersaturation on the occurrence of polymorphic modifications of stearic

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acid in different solvents. They found that in nonpolar solvents and at temperatures less than 30 °C, which is the stable region of Form B, the A and C polymorphs form at higher supersaturations, while modification B tends to form at lower supersaturations. In polar solvents, Form B is predominant at both high and low degrees of supersaturations. These observations follow the Ostwald's rule of stages and also show the importance of solvent. The degree of supersaturation is not always the main controlling factor. For example, in cooling crystallization of L-glutamic acid and L-histidine polymorphs, which are amino acids, the degree of supersaturation is ineffective for isolating the polymorphs.[6]

Li et al.[7] showed that, in crystallization of syndiotactic polystyrene solid forms, the main controlling factor was the crystallizer temperature. They found out that, at temperatures above 230 °C, only Form β precipitated, and at temperatures below 170 °C just Form α crystallized, irrespective of other operating conditions. In the temperature range between 170 and 230 °C, both forms were produced, and the quantity of each form depended on the rate of cooling. Spruijtenburg[8] examined the polymorphs of a food colorant and also a pharmaceutical. The investigated food colorant had four polymorphs of A, B, C, and D. The selectivity of polymorphs depended on the temperature at the onset of crystallization, supersaturation, the solvent, and the water content.

The rate of generation of supersaturation plays a crucial role on the product quality of a crystallization process. For example, in a cooling crystallization, Igarashi et al.[9] showed that the less stable polymorph of glycine (α-Form) was produced at high cooling rates, and more stable polymorph (γ-Form) was produced at lower cooling rates within the same range of temperature and supersaturation. Kitamura and Sugimoto[10] studied the effect of antisolvent addition rate and the initial solute concentration on the hydrate formation and polymorphic transformation of a thiazole-derivative, 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid (BPT). This compound has three polymorphs (A, B, and C), one hydrate (BH), and one methanol solvate (D). At low initial solute concentrations, BH was produced irrespective of the water addition rate which acted as an antisolvent. At higher initial concentrations, a mixture of BH and D was formed whose composition was a function of the water addition rate. The higher the addition rate, the more BH Form (hydrate) was produced because of the local supersaturation and also accessibility of water. Later, the BH and D Forms were transformed to other polymorphs, depending on the initial solute concentration.

Impurities often suppress the growth of a crystal or act only on a special crystallographic face and thus modify the crystal habit.[11] Davey et al.[12] selected additives that inhibited the growth of a more stable polymorph of L-glutamic acid (β-form) and stabilized the metastable form (α-Form). Okamoto et al.[13] studied the effect of seven types of impurities on solution-mediated transformation of the crystal polymorphs of a drug (unstable A, metastable B, and stable C). The studied impurities were the starting materials, the reaction reagents, and the intermediates in the synthesis of the drug. They observed that just one of the impurities inhibited the transformation of B to C and the rest did not interfere with the conversion.

Other operating conditions that influence the product quality include the degree of intermixture at molecular, local, and bulk levels, seeding and the manner in which feed is introduced, and the crystallizer geometry.

Careful consideration and selection of all the above operating conditions is necessary for the control of product quality in a crystallizing system.

Another approach to improve the product quality is to implement "external control". The control studies have primarily been focused on the optimal control of the cooling rate in batch crystallizers. Few attempts have been made on the direct control of one of the process variables such as the fines suspension density, supersaturation, or the mean particle size.

The objective of this two-part communication is to discuss the main approaches that are necessary for the control of batch crystallization processes used in the pharmaceutical and fine chemical industries. Such a study, although not exhaustive, is presently lacking in the literature. This study will include consideration of the design of the crystallization process (Part 1), followed by a study of the various techniques used in the control of batch crystallizers (Part 2). In the view of the authors, careful design of the crystallization process will play a major role in improving the product quality. Further improvement in the product quality may be achieved by implementing the "external control" either in the form of "direct/inferential feedback control" or "open-loop/real time optimal control".

II. Design of the Crystallization Process

A batch crystallizer consists of a simple stirred tank reactor with internals and the feed system. The reactor vessel is often glass-lined and equipped with a mechanically driven agitator, wall baffles, a feed addition mechanism, a cooling/heating jacket, and a reflux condenser. The total volume of the crystallizer varies between several liters to several cubic meters. The following points, in the order of their significance, should be considered in the design of a crystallization process.

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II.1. Method of Generating Supersaturation. The operating costs (such as energy consumption), the product quality (such as purity, yield, size distribution, morphology, and polymorphism), and ease of operation dictate the type and the method of generating the supersaturation. The latter, however, depends on the choice of the solvent, the solubility of the solute, and its temperature sensitivity. Cooling crystallizers are always preferred due to their lower energy demand, safety, and ease of operation. However, if the solubility of the solute has a weak temperature dependence, such as sodium chloride in water, an evaporative crystallizer has to be used. In general, the use of drowning-out crystallizers should be avoided due to the introduction of another solvent and the ensuing problems with solvents separation and residual solvent in the product. There are situations, however, for which an antisolvent crystallization process must be used to increase the product yield. In reaction crystallization, the product of a homogeneous liquid-phase reaction becomes sparingly soluble and precipitates as a solid phase. Proteins and amino acids are often precipitated from an aqueous solution by changing the pH to the iso-electric point. At the iso-electric point, the solubility of proteins or amino acids that leads to the precipitation is at a minimum.

In general, cooling crystallization, if rendering the required yield, should be considered first. A combination of a cooling and an antisolvent crystallization may be used to improve the yield at the expense of adding another solvent that has to be separated in the downstream processes. This will increase the possibility of solvent entrapment in the form of residual solvent that is always undesirable. Partial solvent evaporation under vacuum, coupled with subsequent cooling crystallization, also improves the yield. It is best, however, to stick to a single method of generating supersaturation, if at all possible. This may be achieved by proper choice of the solvent as will be described in the next section.

II.2. Choice of the Solvent. Solvent has the most dramatic effect on a crystallization process. The solubility of the crystallizing species in a solvent must be in the range of 5−200 mg/mL at room temperature to make the solvent a good candidate for the crystallization process. The choice of the solvent is dictated by its solvation power, the slope of the solubility curve versus temperature, its boiling point, safety and toxicity, cost, ability to participate in forming hydrogen bonding as an acceptor or a donor, and its viscosity. Other properties of solvent that must be borne in mind include (i) the potential for the solvent to react with the compound of interest, e.g. trans-esterification processes, (ii) environmental impact, and (iii) intellectual property limitations with regard to the use of the so-called "designer solvents" such as ionic liquids. In addition high-viscosity solvents such as glycerol are not a good choice due to the inefficient filtration. Solvents that result in solubility of more than 200 mg/mL at room temperature also lead to higher viscosities. Solvents for crystallization or recrystallization should be chosen from those used in the synthesis and purification steps and with a wide boiling range.

II.2.1. Measurement of Solubility and the Metastable Limit. The first step in designing a crystallization process is to choose a solvent that has a high solvation power with a steep temperature dependency. Therefore, it is imperative to conduct preliminary solvent screening tests to identify the solubility of the crystallizing species in various solvents and their temperature dependence. This can be achieved by designing a simple experimental plan. One can also use thermodynamic relationships to predict the solubility of a compound in the various solvents and their temperature dependence. The latter technique will need at least one experimental point, as will be described later. Determination of the metastable limit and the width of the metastable zone is also important and can be achieved experimentally.

Various techniques have been used to determine the solubility of a compound in a solvent. These include gravimetric, determination of the solution density, conductivity or refractive index, measurement of solute concentration by HPLC, UV−vis, ATR-FTIR, or Raman spectroscopy. The sample used for solubility determination need not necessarily be of highest quality, but rather it could be a sample typical of that to be used in the crystallization process, complete with typical impurities and residual solvent content.

Solvent Screening. To determine the solvation power of the various solvents, a series of reasonably priced nontoxic solvents with desirable physical and chemical properties from the process safety perspective are selected from the ICH (International Conference on Harmonization) Classes 3 or 2 solvents (Tables 1 and 2). It must be noted that many of the ICH solvents in Classes 2 and 3 include peroxide-forming ethers or solvents which decompose thermally, e.g. DMSO in the presence of acids, and therefore are not suitable. A small amount of the selected solvents (e.g., 5 mL) is placed in airtight vials. To each vial, a certain amount of the desired pharmaceutical solid is added, and the vials are placed in a constant-temperature bath (e.g., 30 °C) and shaken gently for a few hours. Visual inspection will reveal if there are any undissolved solids left in the vials. The solvents with limited solvation power will be discarded, an incremental weight of solid is added to the remaining vials, and the temperature is slightly increased. The procedure is repeated until a few solvents with high solvation power are selected.

Additional tests are carried out on the selected solvents to determine the temperature dependence of the solubility. A more accurate method for the determination of the solute concentration at each temperature, however, is needed in this stage.

Solubility Measurement. Many experimental procedures have been developed for accurate solubility measurement. The gravimetric method is the most basic one. In this method, a solution that contains excess solids is agitated at a constant temperature, T, for a long time followed by filtration. The filtrate is weighed and placed in an oven to evaporate the solvent. After weighing the residual solids, the solubility at the corresponding temperature, T, can be calculated. The error in weighing the solvent and solids used to be a major shortcoming of this method. However, the modern balances with ±0.01 mg precision have overcome this problem. It should also be noted that fast drying of the sample could result in some solids molecules escaping with the evaporating

Table 1. **Class 2 solvents of ICH (sorted by PI)**

name	ϵ[a]	δ[b]	υ[c]	PI[d]	μ[e]	DM[f]	bp[g]	hydrogen donor atom(s) and log(K_α)	hydrogen acceptor atom(s) and log(K_β)
n-hexane	1.88	14.99	131.31	0.35	0.30	0.00	68.7	N/A[h]	N/A
methyl cyclohexane	2.02	16.27	128.19	0.86	–	0	100.9	N/A	N/A
cyclohexane	2.00	16.70	108.86	1.02	0.90	0.61	80.7	N/A	N/A
p-xylene	2.27	17.84	123.78	1.57	0.43	0.00	138.4	N/A	N/A
m-xylene	2.30	17.84	123.78	1.61	1.15	0.30	139.1	N/A	N/A
toluene	2.33	18.35	106.56	1.87	0.62	0.36	110.6	N/A	N/A
tert-1,2-dichloroethene	2.14	18.55	77.90	1.88	0.39	0.00	47.7	N/A	N/A
o-xylene	2.55	18.45	121.14	2.05	1.99	0.62	144.4	N/A	N/A
1,4-dioxane	2.20	20.16	85.66	2.25	1.21	0.00	101.3	N/A	O 1.28[i]
tetralin	2.77	19.52	136.70	2.42	2.41	0.22	207.6	N/A	N/A
2-ethoxyethanol	2.41	21.54	97.46	2.73	1.87	2.08	135.0	O 1.39	O 1.41
1,1,2-trichloroethene	3.42	18.76	90.13	3.16	0.55	0.77	87.0	N/A	N/A
c-1,2-dichloroethene	9.20	19.48	76.64	3.92	0.45	1.90	60.5	N/A	N/A
dichloromethane	9.10	20.38	64.43	3.96	0.44	1.60	39.8	N/A	N/A
methyl butyl ketone	14.60	18.14	124.12	4.09	0.56	2.68	127.7	N/A	O 1.57
pyridine	12.50	21.80	80.83	4.12	0.90	2.19	115.3	N/A	N 2.52[i]
chloroform	4.80	19.03	80.66	4.12	0.54	1.01	61.2	N/A	N/A
chlorobenzene	5.60	19.26	102.26	4.26	0.73	1.69	131.7	N/A	N/A
1,2-dimethoxyethane	7.20	17.73	104.21	4.27	0.45	1.71	84.1	N/A	O 1.69[i]
2-methoxyethanol	16.93	23.20	79.29	4.39	1.39	2.04	124.4	O 1.48	O 1.39
N-methyl pyrrolidone	32.20	23.35	96.70	4.98	1.48	4.09	202.0	N/A	O 2.81 N 0.94
N,*N*-dimethylacetamide	37.78	22.35	93.03	5.21	0.86	3.81	166.1	N/A	O 1.79 N 1.03
N,*N*-dimethylformamide	36.71	23.97	77.37	5.34	0.84	3.82	153.0	N/A	O 1.70 N 1.59
sulfolane	43.30	26.30	95.28	5.41	–	4.69	285.0	N/A	O 1.61[i]
acetonitrile	37.50	24.09	52.68	5.77	0.35	3.92	81.6	N/A	N 1.23
ethylene glycol	37.70	34.48	55.92	5.79	17.65	2.31	197.3	O 1.37	O 1.45
nitromethane	39.40	25.76	54.09	5.84	0.62	3.46	101.2	N/A	O 1.40
methanol	32.70	29.52	40.70	5.85	0.54	1.70	64.7	O 1.48[i]	O 1.36
formamide	84.00	39.28	39.89	8.37	3.33	3.73	219.9	O 1.00	O 1.76 N 1.88

[a] ϵ is dielectric constant. [b] δ is the solubility parameter, $(J/cm^3)^{0.5}$. [c] υ is the specific volume, cm^3/mol. [d] PI is the polarity index.[42] [e] μ is the viscosity, c.p. [f] DM is molecule dipole moment. [g] bp is the normal boiling point, °C. [h] N/A: not applicable, does not contain hydrogen donor/acceptor. [i] Experimental value was available, the rest are calculated.

solvent. Therefore, a moderate temperature, depending on the physical properties of the solvent, should be adopted for sample drying. This experimental procedure is relatively time-consuming, but with enough care, it can be fairly precise. Using an on-line detector, e.g. a turbidity meter, may decrease the error. Zhang et al.[14] employed a modified gravimetric method that involves adding a preweighed amount of solvent to the solids and following a cooling and heating cycle (to crystallize and dissolve the solids). They passed a laser light through the sample and observed the transmitted light to find the end-point of thermodynamic saturation. Macedo et al.[15] also used a modified gravimetric method for solubility measurement of waxes. They employed a visual microscope to track the end-point of dissolution.

An accurate solubility measurement method can be achieved by employing a UV/vis spectrophotometer. Similar to the gravimetric method, a mixture of the solvent with excess solids is agitated for a long time. The agitation is stopped until the solids settle. A sample is then withdrawn through a filter from the supernatant. The sample is diluted and used for concentration measurement with a precalibrated UV/vis spectrophotometer. In the presence of soluble impurities, HPLC should be used to distinguish the impurities from the solute molecule.

A solubility measurement method that uses only a differential scanning calorimeter (DSC) has also been reported.[16] In this method, preweighed solute and solvent are placed in a high-pressure stainless steel DSC crucible. The sample is heated at a specific heating rate. The heat released or absorbed as the solute dissolves in the solvent is detected by the DSC. The heat flow curve flattens out after all solids are dissolved, and the solution reaches equilibrium. The saturation temperature can be obtained from the DSC heating curve. This method can be considered as a high throughput solubility measurement method.

A more modern solubility measurement method uses an online FTIR for tracking the concentration changes in the solution. In this method, a standard curve should be developed to relate the concentration, temperature, and the height of the characteristic peak of the solute (or the ratio

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Table 2. **Class 3 solvents of ICH (sorted by (PI)**

name	ϵ[a]	δ[b]	v[c]	PI[d]	μ[e]	DM[f]	bp[g]	hydrogen donor atom(s) and log(K_α)	hydrogen acceptor atom(s) and log(K_β)
n-pentane	1.80	14.4	116.1	0.17	0.25	0.00	36.1	N/A[h]	N/A
n-heptane	1.92	15.2	147.0	0.39	0.50	0.00	98.4	N/A	N/A
tert-butyl methyl ether	2.60	15.1	119.9	1.34	0.33	1.36	55.2	N/A	O 1.46[i]
cumene	2.40	17.5	139.8	1.57	5.97	0.39	152.4	N/A	N/A
ethyl ether	4.30	15.5	104.7	2.65	0.22	1.15	34.4	N/A	O 1.38
butyl acetate	5.10	17.6	132.6	3.35	0.68	1.84	126.0	N/A	O 1.43
isobutyl acetate	5.60	17.2	133.6	3.40	0.65	1.87	116.7	N/A	O 1.28
isopropyl acetate	6.30	17.1	117.2	3.73	0.53	1.75	88.5	N/A	O 1.26
tetrahydrofuran	7.58	19.1	81.9	3.80	0.47	1.63	64.9	N/A	O 1.69[i]
anisole	4.30	20.1	109.2	3.86	–	1.36	153.6	N/A	O 0.3[i]
propyl acetate	6.30	18.0	115.7	4.00	0.57	1.79	101.5	N/A	O 1.27
methyl isobutyl ketone	13.11	17.8	125.8	4.01	0.60	2.70	116.5	N/A	O 1.57
1-pentanol	13.90	22.6	108.5	4.11	3.43	1.70	137.8	O 1.10	O 1.41
ethyl acetate	6.00	18.3	98.6	4.17	0.42	1.78	77.1	N/A	O 1.43[i]
3-methyl-1-butanol	15.63	22.3	108.3	4.19	3.69	1.80	131.2	O 1.11	O 1.42
2-butanol	16.68	23.8	93.0	4.31	3.25	1.66	99.6	O 0.77	O 1.46
2-methyl-1-propanol	17.70	23.8	93.0	4.36	3.27	1.64	107.7	O 1.11[i]	O 1.40[i]
1-butanol	17.80	23.3	91.9	4.37	2.60	1.66	117.7	O 1.10[i]	O 1.40[i]
methyl ethyl ketone	18.40	18.8	90.2	4.39	0.40	2.76	79.6	N/A	O 1.58
2-propanol	19.92	23.6	76.8	4.57	1.96	1.66	82.3	O 0.91[i]	O 1.36[i]
1-propanol	20.33	24.6	74.9	4.61	1.94	1.68	97.2	O 1.11[i]	O 1.41
acetone	20.70	19.8	73.9	4.61	0.31	2.88	56.3	N/A	O 1.61[i]
acetic acid	6.20	18.4	57.6	4.82	1.13	1.74	117.9	O 2.04[i]	O 1.31
methyl acetate	6.70	19.4	79.9	4.94	0.35	1.68	56.9	N/A	O 1.26
ethyl formate	7.10	18.9	80.8	4.89	0.38	1.93	54.3	N/A	O 1.30
ethanol	24.55	26.4	58.5	5.01	1.06	1.69	78.3	O 1.21[i]	O 1.41[i]
dimethyl sulfoxide	46.68	26.3	71.3	5.83	1.97	3.96	189.0	N/A	O 3.06[i]
formic acid	58.00	21.4	37.9	7.15	1.64	1.42	100.6	O 1.83	O 1.26

[a] ϵ is dielectric constant. [b] δ is the solubility parameter, $(J/cm^3)^{0.5}$. [c] v is the specific volume, cm^3/mol. [d] PI is the polarity index.[42] [e] μ is the viscosity, c.p. [f] DM is molecule dipole moment. [g] bp is the normal boiling point, °C. [h] N/A: not applicable, does not contain hydrogen donor/acceptor. [i] Experimental value was available, the rest are calculated.

of two peaks). A solution with an excess amount of solids is agitated at a constant temperature while the FTIR probe tracks the concentration changes until saturation at a given temperature reaches the point at which there is no further concentration change. At this point, from the obtained intensity, the concentration and corresponding solubility can be calculated. The major advantage of this method is that it can be used for on-line monitoring and control applications. Examples of this method can be found in refs 17−20.

Determination of the Metastable Limit. The limit of the metastable zone can be determined by preparing a slightly undersaturated solution at a given temperature and gradually cooling it while visually observing the point at which spontaneous nucleation occurs. It is imperative, however, to ensure the absence of any dissolved or solid impurity in the solution. The method can be automated by using an IR transmission cell that accurately determines the cloud point at the onset of nucleation.[21] Figure 1 depicts the schematics of a cell equipped with a cooling jacket, a thermistor, and an IR emitter−detector assembly that continuously monitors the percent transmittance and the temperature of the solution. The temperature at which transmittance drops sharply corresponds to the onset of spontaneous nucleation and the limit of the metastable zone at the given solution temperature.

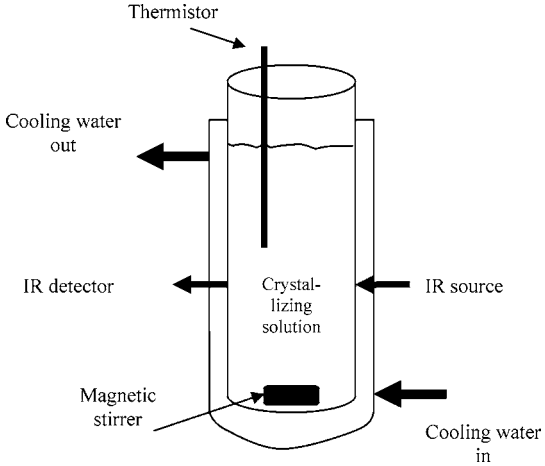


Figure 1. **Determination of the limit of the metastable zone using an IR detector.**

(17) Lewiner, F.; Klein, J. P.; Puel, F.; Fevotte, G. On-line ATR FTIR Measurement of Supersaturation during Solution Crystallization Processes. *Chem. Eng. Sci.* **2001**, *56*, 2069−2084.
(18) Fevotte, G. New Perspectives for the On-Line Monitoring of Pharmaceutical Crystallization Processes using an in Situ Infrared Spectroscopy. *Int. J. Pharm.* **2002**, *241*, 263−278.
(19) Togkalidou, T.; Tung, H.-H.; Sun, Y.; Andrews, A.; Braatz, R. D. Solution Concentration Prediction for Pharmaceutical Crystallization Processes using Robust Chemometrics and ATR FTIR spectroscopy. *Org. Process Res. Dev.* **2002**, *6*, 317−322.
(20) Fujiwara, M.; Chow, P. S.; Ma, D. L.; Braatz, R. D. Paracetamol Crystallization using Laser Backscattering and ATR FTIR Spectroscopy: Metastability, Agglomeration and Control. *Cryst. Growth Des.* **2002**, *2*, 363−370.
(21) Redman, T.; Rohani, S. On-line Determination of Supersaturation of a KCl-NaCl Aqueous Solution Based on Density Measurement. *Can. J. Chem. Eng.* **1994**, *71*, 64−71.

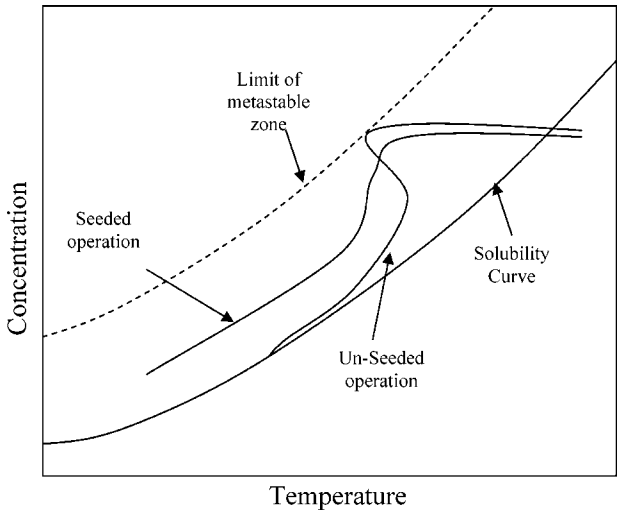


Figure 2. **Determination of the limit of the metastable zone using an on-line FTIR probe.**

The solubility and the limit of the metastable zone can also be detected for high-yield crystallization processes using an on-line FTIR probe. Figure 2 depicts, qualitatively, the nature of such a measurement. A slightly under-saturated solution is cooled. The onset of spontaneous nucleation corresponding to the limit of the metastable zone can be detected when the solute concentration drops sharply. In an unseeded crystallizer and in the absence of impurities, the solute concentration monitored by the FTIR probe drops and remains at the solubility curve as the content of the crystallizer is cooled quickly.[18]

II.2.2. Solubility Prediction. Modeling the Solubility Data in a Pure Solvent. Assuming negligible solubility of the solvent in the solid phase, for nonideal solutions we have:[22]

$$\ln\frac{f_2^L}{f_2^S} = \frac{\Delta H_{fus}}{RT_{tp}}\left(\frac{T_{tp}}{T}-1\right) - \frac{\Delta c_p}{R}\left(\frac{T_{tp}}{T}-1\right) + \frac{\Delta c_p}{R}\ln\frac{T_{tp}}{T} \quad (1)$$

where f_2^L and f_2^S are solute-pure subcooled liquid (melt) and pure solid fugacities, respectively, and T_{tp} is the triple point temperature, which can be considered as the melting point. ΔH_{fus} is the heat of fusion, and Δc_p is the difference in heat capacities of solute in liquid and solid state at absolute temperature, T. It must be noted that the first term on the right-hand side of eq 1 is the dominant one. The second and third terms are numerically much smaller compared to the first term and tend to cancel each other out.[22] Melting of many pharmaceutical compounds is accompanied by exothermic degradation so that measuring the liquid heat capacity is a formidable task. In these cases, just the first term will be used. The activity of a solute in a solvent, a_2, its solubility in mole fraction, x_2, its activity coefficient, γ_2, are related to the ratio of fugacities by:

$$a_2 = x_2\gamma_2 = \frac{f_2^S}{f_2^L} \quad (2)$$

The measured solubility is often in terms of g of solute per 100 g of solvent (shown by S). To convert the solubility in terms of mole fraction (x_2) to this unit, we have to use the following equations:

$$x = \frac{x_2}{1-x_2} \quad \text{and then} \quad S = \frac{xMM_{solute}}{MM_{solvent}} \times 100 \quad (3)$$

where MM is the molar mass, g/mol.

Having the thermal properties of a solid, the ratio of fugacities can be calculated from eq 1. Knowing γ_2, one can determine the solubility, x_2 from eq 2. For ideal systems the activity coefficient of the solute is equal to unity so that eq 1 will reduce to:

$$\ln\frac{1}{x_2^{ideal}} = \frac{\Delta H_{fus}}{RT_{tp}}\left(\frac{T_{tp}}{T}-1\right) - \frac{\Delta c_p}{R}\left(\frac{T_{tp}}{T}-1\right) + \frac{\Delta c_p}{R}\ln\frac{T_{tp}}{T} \quad (4)$$

The ideal and experimental mole fractions are related by

$$x_2 = \frac{x_2^{ideal}}{\gamma_2} \quad (5)$$

Prediction of the actual solubility requires the actual activity coefficient of the solute in the solution, γ_2, which should be calculated from the thermodynamic models.

Among the semiempirical models, the UNIQUAC model has two adjustable parameters (a_{12} and a_{21}), and the NRTL has three adjustable parameters (η_{12}, η_{21}, and α). Recently, Mirmehrabi[23] has proposed a new activity coefficient model that is much easier to use compared to the UNIQUAC and the NRTL. The new activity coefficient model has two adjustable parameters (a_1 and a_2). In what follows, a short description of each of these three models is presented. This will be followed by the application of these models in predicting the solubility of a model compound (stavudine) in pure solvents and in a mixture of solvents (see Supporting Information for tables of data).

The UNIQUAC[24] and the NRTL[25] activity coefficient models are semiempirical models with adjustable parameters that require experimental data to fit these parameters. The UNIQUAC equation is

$$\ln\gamma_i = \ln\frac{\Phi_i}{X_i} + \frac{z}{2}q_i\ln\frac{\theta_i}{\Phi_i^*} + l_i - \frac{\Phi_i}{X_i}\sum_{j=1}^{m}X_j l_j - q_i'\ln\left(\sum_{j=1}^{m}\theta_j'\tau_{ji}\right) + q_i' - q_i'\sum_{j=1}^{m}\frac{\theta_j'\tau_{ji}}{\sum_{k=1}^{m}\theta_k'\tau_{kj}} \quad (6)$$

(22) Prausnitz, J. M.; Lichtenthaler, R. N.; Azevedo, E. G. *Molecular thermodynamics of fluid-phase equilibria*; Prentice-Hall: Upper Saddle River, New Jersey, 1999; pp 59−77.
(23) Mirmehrabi, M. Control of Polymorphism in Pharmaceutical Solids, Ph.D. Thesis, The University of Western Ontario, 2005.
(24) Fredenslund, A.; Jones, R. L.; Prausnitz, J. M. Group-Contribution Estimation of Activity Coefficient in Nonideal Liquid Mixtures. *AIChE J.* **1975**, *21*, 1086−1099.
(25) Yaws, C. L.; Wang, X. M.; Satyro, M. A. Solubility Parameter, Liquid Volume, and van der Waals Volume and Area. In *Chemical Properties Handbook: Physical, Thermodynamic, Environmental, Transport, Safety, and Health Related Properties for Organic and Inorganic Chemicals*; Yaws, C. L. Ed.; McGraw-Hill: New York, 1999.

where

$$\Phi_i = \frac{r_i X_i}{\sum_{j=1}^{m} r_j X_j} \quad \theta_i = \frac{q_i X_i}{\sum_{j=1}^{m} q_j X_j} \quad \theta'_i = \frac{q'_i X_i}{\sum_{j=1}^{m} q'_j X_j} \tag{7}$$

$$\tau_{ij} = \exp\left(-\frac{a_{ij}}{T}\right) \quad \tau_{ji} = \exp\left(-\frac{a_{ji}}{T}\right) l_j = \frac{z}{2}(r_j - q_j) - (r_j - 1) \tag{8}$$

a_{ij} and a_{ji} are the adjustable parameters, and the dimensionless parameters r, q, and q' are pure component constants, which depend on the van der Waals area and volume as follows:[22]

$$r_i = \frac{Q_i}{15.17} \tag{9}$$

$$q_i = \frac{R_i}{2.5 \times 10^9} \tag{10}$$

where Q_i and R_i are the van der Waals molar volume and area of the molecules. Basically, q' is equal to q, but for alcohols it differs.[22] Yaws et al.[25] have reported the van der Waals area and volume of many compounds. For cases that the van der Waals area and volume are not available, the functional group approach presented by Fredneslund et al.[24] should be used to calculate r and q. The numerical values of r and q adopting the functional group approach due to Fredneslund et al.[24] for stavudine were calculated to be equal to 9.75 and 8.01, respectively.[23]

The NRTL model is in the following form:

$$\ln \gamma_i = \frac{\sum_{j=1}^{m} \eta_{ij} G_{ji} x_j}{\sum_{l=1}^{m} G_{li} x_l} + \sum_{j=1}^{m} \frac{x_j G_{ij}}{\sum_{l=1}^{m} G_{lj} x_l} \left(\delta_{ij} - \frac{\sum_{r=1}^{m} x_r \eta_{rj} G_{rj}}{\sum_{l=1}^{m} G_{lj} x_l} \right) \tag{11}$$

$$\eta_{ji} = \frac{g_{ji} - g_{ii}}{RT} \quad G_{ji} = \exp(-\alpha_{ji}\eta_{ji}) \quad \text{and} \quad \alpha_{ij} = \alpha_{ji} \tag{12}$$

where η_{ji}, η_{ij}, and α_{ij} are the adjustable parameters. Unlike the UNIQUAC model, the NRTL does not need any molecular parameter. These two semiempirical models, the UNIQUAC and the NRTL cover a vast range of ideal and nonideal solvents such as alcohols, ketones, amines, and water.

The new model[23] can be written in a semiempirical fashion with two adjustable parameters:

$$\ln \gamma_i = \frac{a_1}{RT} (x_1^{a_2} \ldots x_n^{a_2})_{j \neq i} [a_2 x_i^{(a_2 - 1)} + (1 - n a_2) x_i^{a_2}] \tag{13}$$

where a_1 and a_2 are adjustable parameters, n is the number of components, and x is the mole fraction of various components.

To model the solubility with these activity coefficient models, the adjustable parameters should be obtained using the experimental activity coefficients and a nonlinear regression method. The optimization procedure was based on the minimization of the error between the calculated and experimental values of the activity coefficients.

$$\min_{\text{parameters}} \text{error} = \sum_{k=1}^{d} (\gamma_{2,k,\text{exp}} - \gamma_{2,k,\text{calc}})^2 \tag{14}$$

where d is the number of experimental data points, $\gamma_{2,k,\text{exp}}$ and $\gamma_{2,k,\text{calc}}$ are the experimental and calculated equilibrium activity coefficients of the solute found as follows:

1. Calculate the ideal mole fractions from eq 4 at temperatures that the solubility of solids is available.

2. Calculate the experimental activity coefficients from eq 5 using the calculated and the experimental mole fractions.

3. Write a regression program and supply the experimental mole fractions of the solvents and solute and the experimental activity coefficient of the solute. The program changes the adjustable parameters of the activity coefficient models to minimize the error in eq 14.

The solubility prediction procedure at temperature T requires the following steps:

1. Calculate the ideal mole fraction from eq 3 at temperature T.

2. Guess an initial value for the experimental solute mole fraction (solubility).

3. Calculate activity coefficient from models (the UNIQUAC, NRTL or the new model[23]) using the guessed solute mole fraction.

4. Using the calculated activity coefficient and the ideal mole fraction, calculate a new mole fraction from eq 4, and consider it as a new guess.

5. Repeat steps 3 and 4 until the mole fraction does not change by more than a set tolerance limit.

Interpolation/Extrapolation of Solubility Data in Pure Solvents. In the development stage of an active pharmaceutical ingredient (API), it often takes much effort to produce a small quantity of the API. One can use the semiempirical models presented above along with a few experimental data to interpolate/extrapolate the solubility of the API. Having the solubility data at a few temperatures, activity coefficient models can be used to predict the solubility data at other temperatures. Sometimes the solubility is available at just one temperature, e.g., 25 °C. In such cases, an acceptable assumption should be made. The temperature has a major effect on the solubility. However, the activity coefficient does not change significantly as a result of small changes in temperature. Therefore, one may assume that the activity coefficient at 1 °C above or below a given experimental temperature remains unchanged and equal to the activity coefficient at the experimental point. Using this assumption, the adjustable parameters of the UNIQUAC and also the new model[23] can be calculated. For the NRTL model with three adjustable parameters, the activity coefficient at a temperature close to the experimental point was kept equal to that of the experimental point, and the α was considered as equal to 0.3 (recommended by Prauznitz, et al.[22]).

Figure 3 illustrates the extrapolation of stavudine solubility in water using three activity coefficient models and one experimental point at 20.5 °C. The prediction results have been compared with the rest of the experimental points at

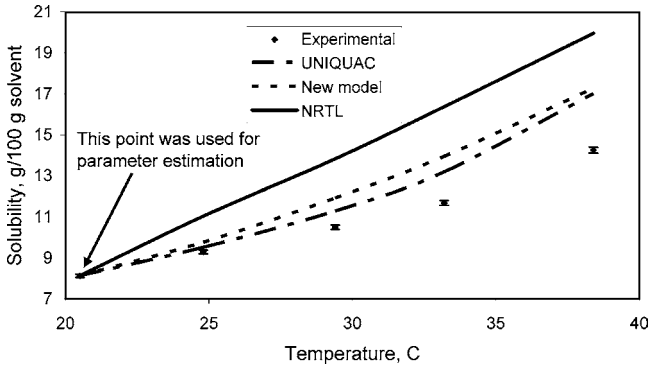


Figure 3. **Extrapolation of stavudine solubility in water using one experimental point at 20.5 °C.**

other temperatures in this figure. Prediction of solubility data with the NRTL using just one experimental point is very poor. The results of the new model[23] are comparable with the UNIQUAC equation. However, the new model[23] is much simpler compared to the UNIQUAC model.

Predicting the Solubility of Polymorphs in Pure Solvents. In polymorphic systems the solubility of different polymorphs can be used to determine the relative thermodynamic stability of the forms. The difference between the Gibbs free energy of the two forms, ΔG_{1-2}, can be calculated from the solubility data as shown below:

$$\Delta G_{1-2} \cong RT \ln\left(\frac{S_1}{S_2}\right) \tag{15}$$

where S_1 and S_2 are the solubilities of polymorphs 1 and 2 at an absolute temperature T. If $S_1 < S_2$ then ΔG_{1-2} will be negative showing that polymorph 1 is more stable than polymorph 2. The solubility data of one polymorph along with the thermal properties of both polymorphs can be used for predicting the solubility data of the second polymorph. We assumed that various polymorphs have almost the same deviation from the ideal state in the solution and the difference in solubilities is mainly due to the structural differences, which appear in thermal properties. Thus, the activity coefficients of all polymorphs in the same solvent and at the same temperature can be considered to be the same. With this assumption, we can use the adjustable parameters of the activity coefficient models that have been obtained for one of the polymorphs to predict the solubility of the other polymorphs. Figure 4 shows the prediction results for the solubility of stavudine Form 1 in methanol using the various activity coefficient models and the experimental solubility of Form 2. The adjustable parameters of the activity coefficient of Form 2 have been used for predicting the solubility of Form 1. In this case, the new model[23] predicts better than the other two models.

Modelling and Prediction of Solubility Data in a Mixture of Solvents. In some cases, such as antisolvent crystallization processes, a mixture of solvents should be used in which the solid is soluble in one solvent and sparingly soluble in the other. The solubility of a solid is not simply a linear interpolation between the solubility in two pure solvents. For instance, the solubility in a mixture of solvents can be much higher than the solubility of the same solid in each pure

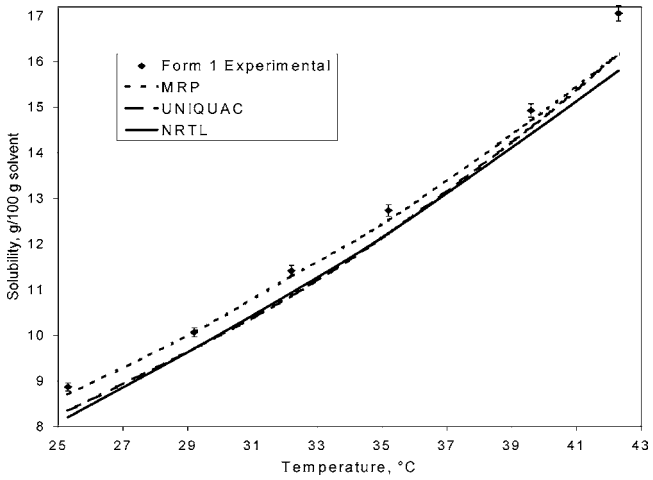


Figure 4. **Solubility prediction of stavudine Form 1 in methanol using the experimental solubility data of Form 2 (see Supporting Information).**

solvent. This usually happens when one solvent is a strong hydrogen bond donor such as water or methanol, and the other solvent is a strong hydrogen bond acceptor such as acetone or methyl ethyl ketone. Among the presented thermodynamic models, the UNIQUAC and the NRTL are able to distinguish between the adjustable parameters that correspond to solvents and solute molecules. To estimate the solubility of a compound in a mixture of two solvents, the binary adjustable parameters between each solute and each solvent in addition to the adjustable parameters between the two solvents must be obtained. The latter can be found from the liquid−liquid or vapor−liquid equilibrium data of two solvents or solubility modeling in a mixture of solvents. The solubility of stavudine in the mixture of methanol and 2-propanol and also methanol and 1,2-dimethoxyethane was studied. The interaction adjustable parameters of the UNIQUAC and the NRTL models between stavudine and each of the above pure solvents were obtained using the experimental solubility data in each pure solvent. If the interaction-adjustable parameters between the solvents are not available in the literature, then they should be calculated using the experimental data. Figure 6 illustrates the experimental solubility of stavudine Form 1 in a mixture of methanol and 1,2-dimethoxyethane along with the results of modeling. The UNIQUAC adjustable parameters (a_{23} and a_{32}) for the mixture of methanol and 2-propanol were found to be 78.927 and −53.0456 and for methanol and 1,2-dimethoxyethane were −250.8338 and 754.5349, respectively. The NRTL adjustable parameters (α_{23}, η_{23}, and η_{32}) for the mixture of methanol and 2-propanol were 0.13, −0.2338, and 6.8058 and for methanol and 1,2-dimethoxyethane were 0.049, 7.1864, and 21.9436, respectively. As it is shown in Figures 5 and 6, both the UNIQUAC and the NRTL are capable of predicting the solubility of stavudine in a mixture of solvents. This is one of the advantages of the UNIQUAC and the NRTL models. The new model,[23] in its present form, does not have such a capability and therefore is not appropriate for modeling and prediction of solids in a mixture of solvents, which establish strong interaction with each other.

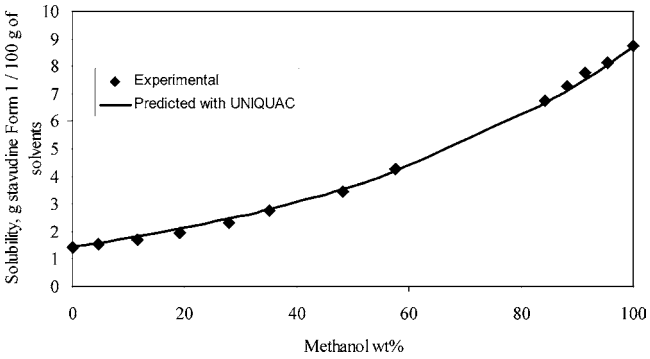


Figure 5. **Solubility prediction of stavudine Form 1 in a mixture of methanol and 2-propanol at 24.8 °C using the adjustable parameters obtained from binary systems.**

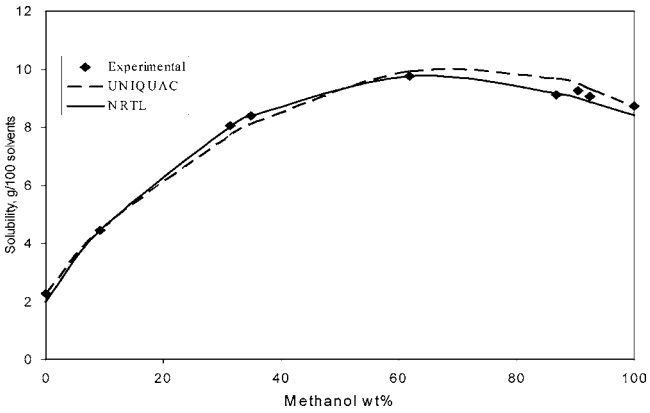


Figure 6. **Solubility modeling-prediction of stavudine Form 1 in a mixture of methanol and1,2-dimethoxyethane at 24.8 °C using the experimental solubility data (see Supporting Information).**

II.2.4. The Effect of Solvents on the Polymorphic Behavior of the Product: Intra- and Intermolecular Hydrogen Bonding. The International Conference on Harmonization has divided solvents into three main classes. Class 1 solvents (such as benzene) are carcinogenic and cause environmental hazards and, therefore, must be avoided. Class 2 solvents such as methanol are less harmful, but their use should be limited. Class 3 solvents such as 2-propanol have low toxicity (see Tables 1 and 2).

The effect of solvents on crystal polymorphism has been the subject of much debate in the literature. One common approach is to consider the polarity of the solvents. A more meaningful approach is to consider the ability of the solvent molecules to participate in hydrogen bond formation. A systematic approach for selecting the right solvent is beneficial for the control of polymorphism.

Mirmehrabi et al.[26] developed several correlations to determine the ability of the solute and solvent molecules to form intra- and intermolecular hydrogen bonds. The method is based on the calculated partial charge using the electronegativity of nitrogen and oxygen atoms. Tables 1 and 2 list the hydrogen bond-donating and -accepting ability of typical Class 2 and 3 solvents using the calculated partial charge of the nitrogen and oxygen atoms of these molecules. The correlations developed in ref 26 are used to study the solvent impact on the crystallization of ranitidine hydrochloride (RAN-HCl), as a model compound. The chemical structure of one of the tautomers of RAN-HCl is given in Scheme 1.

Scheme 1

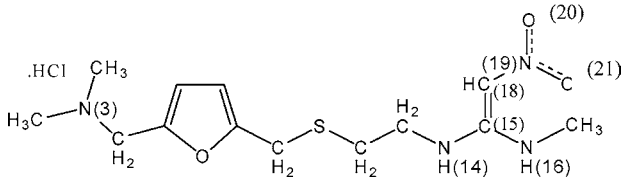
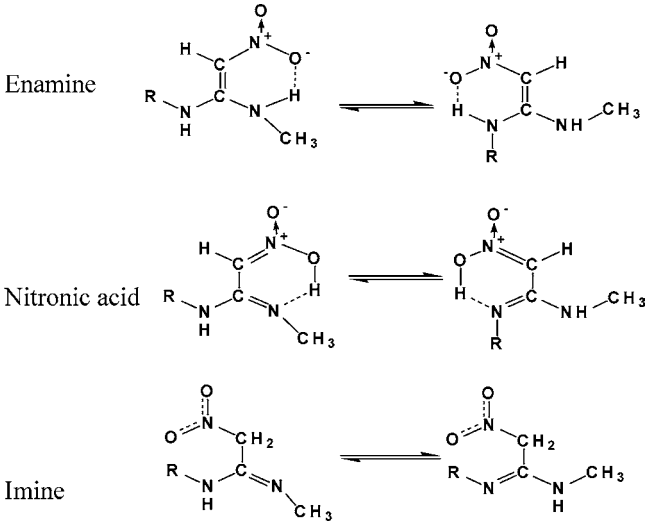


Table 3. **Partial charges of most important atoms in RAN-B and RAN-HCl molecules**

atoms of RAN-B	partial charge	atoms of RAN-HCl	partial charge
N(3)	−0.1858	*N(3)*	−0.2020
S	−0.0031	*S*	−0.0200
N(14)	−0.1604	*N(14)*	−0.1607
N(16)	−0.1537	*N(16)*	−0.1541
N(19)	−0.0209	*N(19)*	−0.0212
O(20) or O(21)	−0.1459	*O(20) or O(21)*	−0.1462

Scheme 2



The first step is to calculate the partial charges of all the atoms in the ranitidine free base (RAN-B) and RAN-HCl molecules. Table 3 presents the partial charges of the most important atoms of RAN-B and RAN-HCl molecules. The partial charge distribution given in Table 3 suggests that N(3), which is the most negative amine nitrogen in the molecule, is the best candidate to host the hydrogen of HCl. After reaction of HCl with RAN-B, the hydrogen of HCl resides on this nitrogen and makes it more negative. The chlorine will also connect to N(3) through hydrogen bonding. N(14) and N(16) also have the ability to donate/accept hydrogen bonding.

Theoretically, RAN-HCl (and RAN-B) can have three tautomers in the solution as shown in Scheme 2. Therefore, we need to examine the effect of the solvent on tautomerism of RAN-HCl. The presence of each tautomer in the solution and consequently in the solid state may depend on the type of the solvent used. Solvents that are strong hydrogen bond

(26) Mirmehrabi, M.; Rohani, S. An Approach to Solvent Screening for Crystallization of Polymorphic Pharmaceuticals and Fine Chemicals, *J. Pharm. Sci.* **2005**. In press.

donors such as methanol and water interact with the nitro group of nitroethenediamine moiety of the molecule and favor the formation of nitronic acid tautomer. For example, oxygen atom of water has a partial charge of about −0.3044 based on Pauling's electronegativity scale with $\log(K_\alpha) = 1.57$ and $\log(K_\beta) = 1.35$, representing the ability to form hydrogen bonding as a donor or an acceptor, respectively. Comparing these values with the data given in Tables 1 and 2 reveals that water is the strongest hydrogen bond donor after acetic and formic acids. However, its hydrogen bond acceptability is moderate. The hydrogen bonding between water and oxygen atoms of nitro group establishes a dipole−dipole interaction that increases the electronegativity of oxygen atoms and results in pulling an electron cloud from C(15)═C(18) to C(18)−N(19) and also in hydrogen transfer from N(14)/N(16) to O(20)/O(21). In aqueous and/or strong hydrogen bond donor solvents, the intramolecular hydrogen bonds within the solute molecules are expected to be weakened or disrupted. Therefore, the nitro group can easily rotate around C(15)−C(18) and form hydrogen bonds with other solute molecules, leading to an enhanced cluster formation and crystal growth rate. Furthermore, the amine nitrogen atoms can establish spatial hydrogen bonding with chlorine of the other molecules.

In the absence of strong hydrogen bond donor solvents, enamine tautomer may be more stable due to the lack of extra forces to pull the electron cloud from C(15)═C(18) to C(18)−N(19). Thus, in anhydrous and/or weak hydrogen bonding donor solvents such as 2-propanol ($\log(K_\alpha) = 0.91$) or acetonitrile (dipolar and aprotic), the intramolecular hydrogen bonds are expected to be strong which stabilize the intramolecular hydrogen bonding between nitro group and the amines. This hydrogen bonding does not let the nitro group rotate around C(15)═C(18). This reduces the freedom of movement and the chances of forming hydrogen bonding with other solute molecules. Among the three tautomers, the imine structure does not seem to be particularly influenced by a specific solvent interaction.

A set of experiments conducted by Mirmehrabi et al.[27] confirms the hypothesis that strong hydrogen bond donor solvents result in the production of nitronic acid tautomer, which is the predominant tautomer in Form 2 RAN-HCl, and weak hydrogen bond donor solvents or aprotic solvents favour formation of enamine tautomer. RAN-HCl molecules can sit side by side and establish hydrogen bonds between the nitroethenediamine moieties of each other. Amine nitrogen atoms of nitronic acid and imine tautomers can establish hydrogen bonds with chlorine of the other solute molecules. But in enamine tautomer (Form 1), this hydrogen bonding is less probable. This may be the reason for the limited growth of Form 1 RAN-HCl crystals. Figure 7 illustrates the hydrogen bonding between nitroethenediamine moieties that was observed along *a* axis of Form 2 crystals and also the spatial hydrogen bonding of amine nitrogen atoms with chlorine. Indeed, this latter hydrogen bonding acts as a connector between two RAN-HCl molecules.[28] Therefore, the primary effect of solvents in the reactive crystallization of RAN-HCl is due to the formation of different tautomers that leads to two "configurational" polymorphs.

II.2.5. Other Properties of the Solvent. In addition to the solvation power and hydrogen bond formation ability, other solvent properties such as viscosity and boiling point affect the overall outcome of the crystallization process. Solution viscosity has a major effect on the level of mixing and also the diffusion of the solute molecules. In polymorphic systems, low diffusion can inhibit the solution-mediated transformation of metastable to thermodynamically more stable forms. Based on the Ostwald rule of stages, the most soluble polymorph crystallizes first and then converts to the more stable forms. High solution viscosity may retard or inhibit nucleation and growth of the more stable polymorph and allows harvesting of the metastable polymorphs.

Solution viscosity has also an effect on the filtration properties of the product. The following equation is applicable at constant pressures:[28]

$$t = \frac{\mu}{g_c(-\Delta P)}\left[\frac{c\alpha}{A}\left(\frac{V}{A}\right)^2 + R_m\frac{V}{A}\right] \tag{16}$$

and

$$\alpha = \frac{k(1 - \epsilon)}{\epsilon^3 \rho_p \phi^2} \tag{17}$$

where t is the total filtration time (s), μ is the filtrate viscosity (N·s/m), ΔP is the overall pressure difference across the filter (N/m^2), c is a constant, α is the specific cake resistance (m^{-2}), A is the cake area (m^2), V is the total volume of filtrate (m^3) collected from the start of the filtration to time t, and R_m is the filter-medium resistance (m^{-1}) that can be considered constant if the filtration medium is kept unchanged. In eq 17, k is a constant, ϵ is the cake porosity, ρ_p is the particle density (kg/m^3), and ϕ is the particle sphericity. Equation 16 illustrates that the required time for filtration is a linear function of the solution viscosity. As the viscosity of the medium increases the filtration time increases.

The boiling point of the solvent should also be considered. Although less energy-intensive, low-boiling point solvents are more dangerous to work with. The drying of the filter cake, which contains low-boiling point solvents, is safer and more practical. This is because the dryer can operate at lower temperatures and the possibility of degradation or polymorphic transformation of the product is also minimized. For high-boiling point solvents there is more flexibility in the crystallization step. However, drying will have to be at a higher temperature and will take longer. It may be advantageous to use a high-boiling solvent for the crystallization and initial cake washing and then to use a minimal amount of a lower-boiling point solvent to wash the cake free of the higher-boiling point solvent.

(27) Mirmehrabi, M.; Rohani, S.; Murthy, K. S. K.; Radatus, B. K. Optimization of Operating Conditions for Improving the Physical Properties of Form 1 Ranitidine Hydrochloride, *J. Pharm. Sci.* **2004**, *93*, 1692−1700.

(28) McCabe, W. L.; Smith, J. C. *Unit Operations of Chemical Engineering*; McGraw-Hill: New York, 1976.

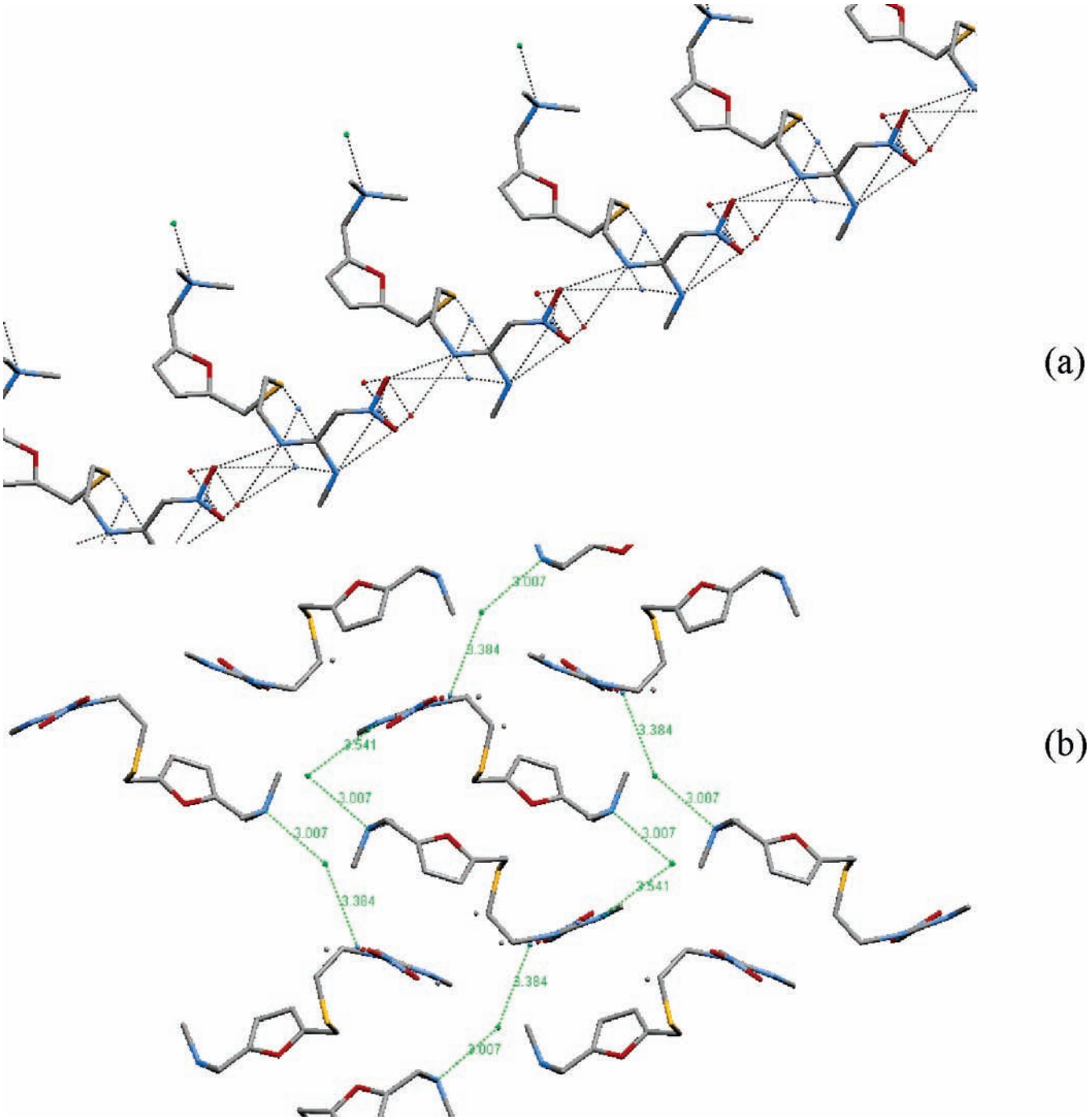


Figure 7. **Molecular packing of the two forms of ranitidine hydrochloride, (a) Form 1 and (b) Form 2.**

Another precaution in using solvents is their inflammability and hazards. The handbook of hazardous properties of solvents by Sax[3] is a good reference.

II.3. Effect of Mixing. Mixing at molecular, local, and bulk levels could have a pronounced effect on the product properties of a crystallization process. In particular, in the production of pharmaceutical solids in which reaction crystallization with fast or instantaneous reactions are involved, nucleation and growth rates and the polymorphic behavior of the product, are strongly influenced by the mixing quality in the vessel. The effect of mixing on the particle size distribution has been studied extensively[29−33] and is beyond the scope of the present discussion.

To decide whether a crystallizing system is affected by the mixing phenomenon, the various time constants associated with the micro-, meso-, and macromixing should be compared with the time constants of reaction and crystallization process (nucleation and growth). If the mixing time constants are in the same order of magnitude or larger than the crystallization and reaction time constants, the product quality will be strongly influenced by mixing, and such

(29) Pohorecki, R.; Baldyga, J. The Use of a New Model of Micromixing for Determination of Crystal Size in Precipitation. *Chem. Eng. Sci.* **1983**, *38*, 79.

(30) Kuboi, R.; Harada, M.; Winterbottom, J. M.; Anderson, A. J. S.; Nienow, A. W. Mixing Effects in Double Jet and Single-Jet Precipitation. *Proc. World Congr. III Chem. Eng.* 1986; Paper 8g, p 4.

effects should be quantified using appropriate models. Phillips et al.[33] proposed a mixing−precipitation model based on the engulfment and elongation of the eddies and applied it to a single-jet semi-batch precipitation process to describe the final particle size distribution of barium sulfate particles. Application of the model was limited to $1 \ll Sc < 4000$ and slow feed addition rates, where Sc is the Schmidt number. The characteristic time constant of macromixing was related to the circulation time and mixing on the scale of the vessel by:

$$t_c = \frac{V}{q_c} \tag{18}$$

where V is the reactor volume in m^3 and q_c is the stirrer pumping or circulation capacity in m^3/s. Mesomixing was described by coarse scale segregation of reactants with the scales of inhomogeneity larger than the Kolmogorov microscale and smaller than the integral lengths of turbulence (the inertial-convective subrange), and given by:[34]

$$t_{ms} \cong \frac{3}{2} k_{oc}^{-2/3} \epsilon^{-1/3} = \frac{3}{2} \left(\frac{5}{\pi}\right)^{2/3} N^{2/3} \epsilon^{-1/3} \tag{19}$$

where k_{oc} is the inertial-convective wavenumber in m^{-1}, ϵ is the energy dissipation rate in m^2/s^3, and N is the stirrer rate in rps. Micromixing was represented in terms of mixing in the viscous-convective and viscous-diffusive subranges of the concentration spectrum. Mixing in both subranges can be expressed by the engulfment−deformation−diffusion process. For liquids with $Sc \ll 4000$, the viscous diffuse effects are negligible, and the intensity of micromixing can be represented by the engulfment intensity parameter E in s^{-1}.

$$t_{mc} \approx \frac{1}{E} = \frac{1}{0.058} \left(\frac{\epsilon}{\nu}\right)^{1/2} \tag{20}$$

where ν is the kinematic viscosity in m^2/s.

The reaction or precipitation time constant in reactive crystallization of pharmaceuticals that involves acid−base reactions is often orders of magnitude smaller than the micromixing due to the engulfment process. The nucleation time constant is estimated by the induction time, t_{ind}, and is given by:[33]

$$t_{ind} = \frac{6 d_m^2 n^i}{D_i \ln S} \tag{21}$$

where d_m is the molecular diameter in m, D_i is the turbulent diffusivity in m^2/s, n^i is the number of ions to form a critical nucleus, and S is the supersaturation. Finally the characteristic time for the crystal growth can be written:[33−36]

$$t_G = \left(\frac{\rho G}{2M} a\right)^{-1} \bar{C}_c \tag{22}$$

where ρ is the crystal density in g/cm^3, G is the growth rate in m/s, M is the molecular mass in g/mol, a is the specific surface area of crystal in cm^2/cm^3, and $\bar{C}_c$ is the mean concentration of the precipitating agent in mol/cm^3.

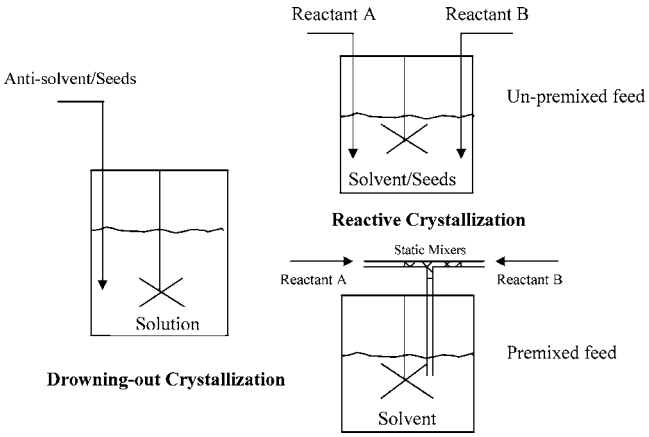


Figure 8. **The introduction of feed(s) in a drowning-out and a reactive (premixed and un-premixed reactants) crystallization process.**

II.4. The Feed System. The order and the manner of addition of reactant(s) or the antisolvent and the rate of their addition play an important role on the outcome of a crystallization process which is often overlooked.

In a drowning-out crystallization process, the antisolvent should be slowly added to the solution at high rate of mixing. If seeds are used, it is advantageous to add the seeds to the antisolvent first and then slowly introduce the suspension (antisolvent plus the seeds) to the solution. This will prevent formation of regions of high supersaturations at local and bulk levels, and therefore, excessive nucleation and deterioration of crystal habit will be avoided. In a reactive crystallization, the two reactants are brought in contact using a solvent as the medium. The operation can be carried out in a single- or a double-jet configuration, in a batch or semi-batch mode of operation, and in a premixed or an unpremixed fashion. A double-jet configuration may be used to slowly introduce the two reactant streams into the impeller region of the reactor.

Figure 8 demonstrates a few possible configurations for introducing the reactant(s) and the antisolvent in a fast crystallization process. The feed should be introduced at low flow rates and under the liquid surface in the impeller region for better mixing. The feed pipe internal diameter should be small to minimize backmixing effects.

The main objective should be to maintain a mild average (spatial, throughout the crystallizer) and uniform distribution

(31) Mercant, B.; David, R. Experimental Evidence for and Prediction of Micromixing Effects in Precipitation. *AIChE J.* **1991**, *37*, 1968.
(32) Torbacke, M.; Rasmuson, A. C. Mesomixing in semi-batch reaction crystallization and influence of reactor size. *AIChE J.* **2004**, *50*, 3107−3119.
(33) Philips, R.; Rohani, S.; Baldyga, J. Micro-Mixing in a Single-Feed Semi-Batch Precipitation Process, *AIChE J.* **1999**, *45*, 82−92.
(34) Corrsin, S. The isotropic turbulent mixer: II. Arbitrary Schmidt number. *AIChE J.* **1964**, *10*, 870.
(35) Direcksen, J. A.; Ring, T. A. Fundamentals of Crystallization: Kinetics Effects on Particle size Distributions and Morphology. *Chem. Eng. Sci.* **1991**, *46*, 2389.
(36) Baldyga, J.; Podgorska, W.; Pohorecki, R. Mixing Precipitation Model with Application to Double-Feed Semi-Batch Precipitation. *Chem. Eng. Sci.* **1995**, *50*, 1281.

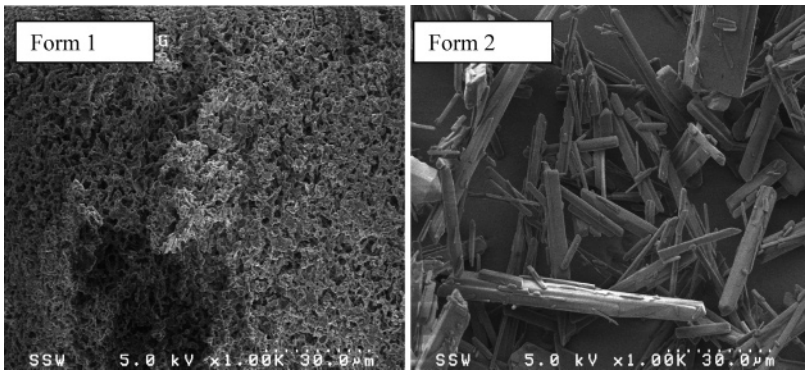


Figure 9. **The two forms of ranitidine hydrochloride.**

(at molecular, local, and bulk levels) of supersaturation and to absolutely avoid regions of high supersaturations.

II.5. The Effect of Seeding. Seeding is used to achieve many purposes in a crystallization process: reduce the induction time, suppress nucleation and enhance growth rate leading to a larger mean crystal size, and facilitate formation of a desirable polymorph in a polymorphic system. It is imperative, however, to use seeds intelligently.

It has been shown by Kubota and co-workers[37,38] and Hojjati and Roahni[39] that in a seeded cooling crystallization, a unimodal crystal size distribution can be ensured if sufficient amounts of seeds are used, irrespective of the cooling policy used. In other words, a simple approach to control a seeded cooling crystallizer and to avoid excessive nucleation is to use large amounts of seeds. A seed chart was used by Hojjati and Rohani[39] that shows the critical seed loading under various operating conditions. Beckmann[40] suggests that mass of seeds should be smaller that 10% of the mass of product. In addition, he suggests that the time of seeding, the size distribution of the seeds, and the method of addition of the seeds are important. Seeds should be introduced to a saturated solution and up to $^1/_4$ to $^1/_2$ into the metastable zone.[40] It is often advantageous to activate the seed particles (dissolve the first few layers of the atoms/molecules on the seeds) before introducing the seeds to the crystallizer. This may be achieved using seed slurries (in the saturated solvent) rather than the dry seeds.

II.6. Case Studies. To demonstrate the effect of proper design of a crystallization process on the physical properties and polymorphic structure of the product, the following two case studies related to the pharmaceutical products are briefly discussed.

Case 1: Improving the Bulk Density and Filterability of Form 1 RAN-HCl. Ranitidine hydrochloride (brand name Zantac) is one of the most frequently prescribed drugs in North America. This drug is used to block acid production in the stomach, which is implicated in indigestion, acid reflux, heartburn, ulcers, and Zollinger−Ellison syndrome. Ranitidine hydrochloride is obtained by reacting hydrogen chloride (HCl) and ranitidine free base. Ranitidine free base, a pale yellow to off-white powder, has two pK_a values of 8.20 and 2.30, which means that it can react with more than one proton. During HCl addition, the first HCl molecule reacts with the nitrogen of the dimethylamino group, and as the pH decreases, the second HCl reacts with the ethenediamine where C-protonation rather than N-protonation occurs.[27,42]

A reading of the Glaxo patent and the work of Murthy et al.[41] suggests that an important requirement for obtaining Form 2 is the presence of water and for Form 1 is the absence of water. Mirmehrabi et al.[27] also showed that significant amounts of strongly polar solvents such as methanol would favor the production of Form 2.

Figure 9 shows the crystal shapes of the two ranitidine hydrochloride polymorphs which are obtained by following the above two Glaxo procedures. Form 1 consists of very tiny crystals with a size in the range of 1−5 μm which agglomerate and form bigger particles. This polymorph is fluffy, has poor filtration characteristics and relatively low solid bulk density ranging from 0.1 to 0.15 g/mL. Form 2, on the other hand, has big individual crystals with size of 10−100 μm, good filtration properties, and relatively high solid bulk density of more than 0.3 g/mL. The objective was to improve the quality of ranitidine hydrochloride Form 1 in terms of filterability and bulk solid density. It was found that the quality of ranitidine hydrochloride Form 1 is a strong function of the operating conditions such as temperature, pH, and pattern of reactants addition.

A series of experiments using 20 g of ranitidine free base were performed. The total amount of 2-propanol (charged initially to the reactor plus the subsequent amount added with HCl) was 200 mL. The amount of HCl/IPA (18.6 wt % acid) was one equivalent to RAN-B. The RAN-B/IPA solution was filtered using Celite before each experiment. After filtrating

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(38) Kuboto, N.; Doki, N.; Yokots, M.; Jagadesh, D. Seeding Effect on Product Crystal in Batch Crystallization. *J. Chem. Eng. Jpn.* **2002**, *35*, 1063−1071.
(39) Hojjati, H.; Rohani, S. Cooling and Seeding Effect on Supersaturation and Final Crystal Size Distribution (CSD) of Ammonium Sulphate in a Batch Crystallizer. *Chem. Eng. Processing* **2004**. In press.
(40) Beckmann, W. Seeding the Desired Polymorph: Background, Possibilities, Limitations, and Case Studies, *Org. Process Res. Dev.* **2000**, *4*, 372−383.
(41) Murthy; Radatus, B. K.; Sidhu, K. P. S. Process for Production of an Improved form of Form 1 Ranitidine Hydrochloride Having Improved Filtration and Drying Characteristics. Canadian patent 2 120 874, 1995, reissued 2002.
(42) Mirmehrabi, M.; Rohani, S.; Murthy, K. S. K.; Radatus, B. Dissolution Rate and Phase Transition Studies of Ranitidine Hydrochloride Tautomeric Forms, *Int. J. Pharm.* **2004**, *282*, 73−85.
(43) Sax, N. I. *Dangerous Properties of Industrial Materials*, 8th ed; Lewis, R. J., Ed.; Van Nostrand-Rienhold: New York, 1992; 3 vols.

the crystallized mixture, the cake was washed twice with 20 mL of 2-propanol, the crystals were vacuum-dried at 45 °C, and then analyzed.

To determine the effects of temperature, solvent, manner and the rate of acid and RAN-FB addition, and pH the following experiments were performed. All the experiments were conducted in an unseeded vessel. After the completion of each experiment, the slurry was cooled from the experimental operating temperature to 25 °C in 0.5 h using a natural cooling policy. The following sets of experiments were conducted to determine the effect of reactant(s) addition rate, feed addition system (single- or double-jet configuration), pH, and the type of solvent. The objective was to determine the near optimal operating conditions in terms of improving the Form 1 RAN-HCl filterability and bulk density.

1. Rapid addition of HCl/IPA to RAN-B/IPA solution at 25 and 48 °C, maintaining the solution at 25 and 48 °C for 2 h.

2. Gradual addition (2−6 h) of HCl/IPA to RAN-B/IPA solution at 48 °C.

3. Gradual addition (2−6 h) of HCl/IPA and RAN-B/IPA concurrently to IPA at 48 °C and maintaining pH. The selected pHs were 5.0, 5.5, 6.0, 6.3, and 6.5.

4. Gradual addition (2−6 h) of HCl/IPA and RAN-B/IPA concurrently to IPA at 48 °C, maintaining the pH at 5.30 for nucleation to happen, and increasing the pH to 6.30−6.40 after nucleation.

5. Gradual addition (2.5 h) of HCl/IPA and RAN-B/*n*-propanol concurrently to *n*-propanol at 48 °C, keeping pH at 6.0.

6. Rapid addition similar to procedure 1 and also gradual addition of HCl/IPA and RAN-B/methyl isobutyl ketone (MIBK) concurrently to MIBK at 48 °C keeping the pH at 6.0.

7. Gradual addition (2.7 h) of HCl/IPA and RAN-B/IPA concurrently to 50/50 IPA/ethanol at 48 °C keeping the pH at 6.0.

Among the seven sets of experiments described above, set 4 resulted in the largest improvement in the quality of Form 1 crystalline product in terms of its filterability and bulk density. The rationale was to begin the process at low pH of 5.3 (to initiate nucleation) and then increase the pH set-point to a value between 6.3 and 6.4 to favor crystal growth. Figure 10 illustrates the pH and the infrared percent transmittance profiles during the first 100 minof this experiment recorded by the control system. As the onset of nucleation at pH 5.3, the percent transmittance decreased. Nucleation began after addition of about 10% of the stoichiometric amount (12.5 g) of HCl/IPA solution. The product obtained under these conditions had the highest solid bulk density with a maximum of 0.32 g/mL. The slurry was not sticky and was easily removed from the crystallization vessel. The cake dry substance after 15 min of filtration was consistently more than 42%. The individual crystals were rectangular, and agglomeration was not significant.

Figure 11 indicates that the solid bulk density increases with a decrease in the reactant addition rate (increase in reactant addition time) and also increases with the control

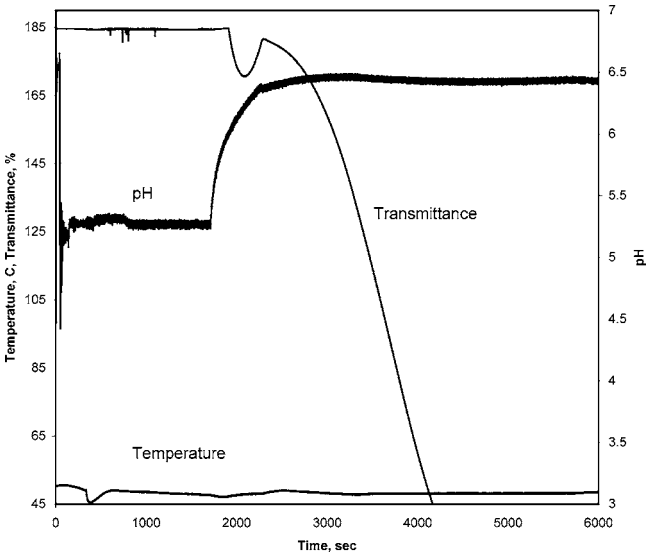

Figure 10. **Slow addition of HCl and RAN-B solutions to IPA at 48 °C, the onset of nucleation at pH = 5.3, crystal growth at pH = 6.38.**

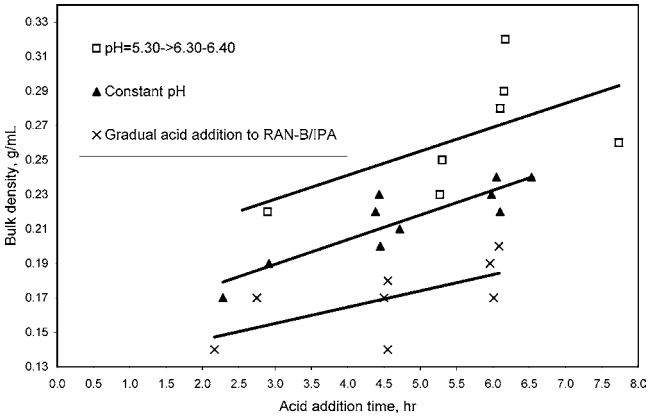

Figure 11. **Effect of reactant addition rate on the bulk density of the product in a semi-batch operation.**

of pH and proper choice of the solvent and feed system.

Case 2: Formation of a Product with a Desirable Product Polymorphic Distribution. In this case, it was desirable to form a crystalline form of a compound Y with a polymorphic distribution of approximately 40% Form A (melting point 170 ± 2 °C) and 60% Form B (melting point 163 ± 2 °C). Form A was found to be thermodynamically more stable. The crystallization was a seeded drowning-out system with water as the antisolvent. Previous attempts required the addition of mechanically prepared seeds with a composition of 40% Form A to the water and slowly adding this slurry to the solution containing compound Y. This process, however, was not reproducible. Using seeds from the previous batch often led to undesirable product in terms of its polymorphic composition.

To ensure proper polymorphic composition of the product, the seeds from a previous batch were aged to allow solution-mediated transformation of Form B to about 40% A. The suspension of the seeds in water, after being aged to the desirable polymorphic composition, was gradually added to the solution of compound Y in the solvent. Characterization of the polymorphs was done by DSC and XRPD. The

polymorphic distribution is stable on storage. We did not check polymorphic transformation during dissolution since we did not have access to an in-line instrument for this purpose. However, since one of the two forms was more stable, solution-mediated transformation did occur. It was important to maintain the supersaturation within the metastable zone to avoid spontaneous nucleation throughout the crystallization to maintain the desirable polymorphic distribution. This simple change in the design of the crystallization experiment, led to the successful and reproducible product. The product had the desirable polymorphic characteristics and was stable on storage. The product had acceptable filterability and size distribution.

III. Conclusions

A holistic approach for the control of product quality in a crystallization process was presented. The approach involves proper "design of the crystallization process" and the implementation of an "external controller". The "design of the crystallization process" was discussed in Part 1 of this communication. Discussed in general were the following: (1) the proper design of the crystallizer and its internals, (2) the rate of generating supersaturation in a cooling, an evaporative, a drowning-out, or a reactive crystallization process, (3) the choice of the solvent, involving solvent screening, (4) solubility measurement and prediction, (5) determination of the metastable zone and the role of the solvent in the formation of intra- and intermolecular hydrogen bonding between the solute molecules and between the solute and solvent molecules, (6) the effect of solvent viscosity and its boiling point, (7) the significance of the mixing at microscale, mesoscale, and macroscale (8) the design of the feed system configuration, (9) and the effect of seed loading, time of seeding and the seed size distribution. A model compound, stavudine, was considered for the solubility measurement and prediction study. Consideration of the above factors in the design of an effective crystallizing system and improving the filterability and solid density of Form 1 ranitidine hydrochloride and another pharmaceutical compound with a specific polymorphic characteristic was also discussed.

In our opinion the holistic approach for the control of the product quality in a crystallization process entails, first and foremost, a careful consideration of each factor discussed in this paper. "External control" that will be discussed in Part 2 of this series, should be implemented only after due consideration has been given to the "design of the crystallization process". External control is used as a complementary means to further improve the product quality.

Supporting Information Available

Solubility data of stavudine. This material is available free of charge via the Internet at http://pubs.acs.org.

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