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Generation of Fine Pharmaceutical Particles via Controlled Secondary Nucleation under High Shear Environment during Crystallization − Process Development and Scale-up

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Abstract:

A unique semibatch crystallization process, coupling with a high-speed rotor-stator device, was developed for generation and control of fine particles. The key underlying mechanism of this process is controlled secondary nucleation under a high shear environment during crystallization, in contrast to the conventional particle breakage mechanism, i.e., milling, after the crystallization. A recycle mode operation is employed to control the residence time of the batch in the high shear domain so as to ensure the scalability of this process. In this work, the operational sensitivity to the supersaturation and particle size were first explored in the laboratory. Based on the results of the laboratory investigation, this process was successfully demonstrated in multiple 1000-L pilot scale production batches. The practical issues for the large scale operation are also illustrated.

1. Introduction

For pharmaceutical products with low aqueous solubilities, small particles with narrow particle size distribution are desirable for enhanced oral bioavailability or for inhalation therapy.[1−3] In many cases, these particle sizes can be achieved by different milling devices, for example, pin, air-attrition jet, or high shear rotor-stator, ultrasound or hydrodynamic cavitation, etc. However dry milling by pin or jet milling has drawbacks. It may result in yield loss, noise, and dusting as well as unwanted personal exposure to highly potent pharmaceutical compounds. Specifically, during the process development of a pharmaceutical compound, it is found that pin milling was unable to reduce the particle size as needed. Jet milling also suffered a significant coating issue within the mill itself.

The wet milling approach can avoid many issues that face the dry milling approach. Unfortunately, in our case, the high-speed rotor-stator device also failed to reduce the particle size effectively. Ultrasound or hydrodynamic cavitation approaches were not evaluated in our study due to the lack of availability of large scale equipment.

Since none of the milling techniques is effective, a different approach for generating fine particles is needed. It should be mentioned that due to the nature of commercial competition, we cannot release the chemical structure of this compound in this paper, except that this compound has a molecular weight of ∼ 450 which is very common among small molecule pharmaceuticals. Nevertheless, the approach presented in this report is unique, and the authors believe that its scientific value is unaffected without explicitly showing the chemical structure.

Another way to generate fine particles is through crystallization, i.e., nucleation, under high supersaturation. To accomplish it, the simplest approach is reverse addition by charging a highly concentrated feed solution directly into an anti-solvent. Very high supersaturation is generated locally, and small nuclei/crystals are rapidly formed.

In practice, however, because hydrodynamics in a stirred tank is highly variable, for example, different agitator/baffles or vessel-filled volume, etc., the introduction of feed solution to the anti-solvent in the stirred vessels undergoes variable degrees of mixing. The variable mixing creates inconsistent high supersaturation at the point of addition which leads to variable nucleation and wide particle size distribution. Consistency and robustness are major obstacles for implementing the reverse addition crystallization for large scale production batches.

The variation of mixing on local supersaturation can be reduced by lowering the addition rate of the feed stream. Nevertheless, this approach generally defeats the original purpose of reverse addition, i.e., creation of high supersaturation for formation of small particles, and larger crystals are generally formed.

One special approach to achieve rapid controlled mixing and uniform high supersaturation for the generation of small particles is the use of impinging jet mixers.[4,5] The effluent from the impinging jet mixer is often fed to an aging vessel. The residence time in the jet mixer is short and is adjustable,

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during which the solute is precipitated as either crystals or amorphous solids depending on the nature of the solute.

While an impinging jet crystallization process overcomes the local mixing and scalability issues, it does, however, require special attention to the balance of momentum of two mixing streams. If two streams are of different volumes, the mixing efficiency will be compromised. Therefore, the impinging jet approach is more suitable for mixing equal volumes of feed and anti-solvent.

In this study, the reverse addition crystallization approach is modified to overcome the uncontrolled local mixing and scalability issues encountered in the stirred tank crystallizer, as well as the momentum balance requirement of an impinging jet mixer. A semibatch crystallization process coupled with a high-speed rotor-stator device was developed for generation of small particles. The crystallizer was operated in the anti-solvent in recycle mode with the batch solution feeding to the inlet of a high-speed rotor-stator device.

This approach relied heavily on the secondary nucleation phenomenon under conditions of high mixing intensity. The concept is to mix the feed stream with the recycle stream as closely as possible within the high shear (rapid energy dissipation) domain of the rotor-stator device where secondary nuclei are formed in the presence of crystalline seeds. Since the tip speed (or equivalently max shear rate or energy dissipation) of the rotor and ratio of recycle anti-solvent flow rate to feed rate can be maintained upon scale-up, this approach significantly reduces the variable degree mixing upon scaleup as encountered in the stirred tank mixing. It further eliminates the need of momentum balance between feed and anti-solvent streams as in the impinging jet crystallization. Certainly, other high-energy dissipation devices, for example, ultrasound or hydrodynamic cavitation, can be used in the recycle loop as a replacement for the rotor-stator device. However, a rotor-stator device is chosen in our work for the availability of large scale production equipment, but not the other devices.

In this work, the operational sensitivity of particle size to the supersaturation was studied in a laboratory setup to characterize the relevant process parameters. The laboratory results then were scaled to multiple 1000-L production batches to support clinical development.

1.1. Secondary Nucleation. The control of the secondary nucleation rate plays an important role in the studied process. The effect of agitation on the secondary nucleation has been reported in the literature and several references.[6] In general, the secondary nucleation rate may be represented by the semiempirical formula provided below.

$$B = k_B M_T^j \sigma^b N^s \tag{1}$$

B = nucleation rate (no. of crystal/s/m^3)
M_T = magma density (kg/m^3)
σ = supersaturation
N = rotation speed or mixing intensity (energy per unit suspension volume or impeller tip speed or stirrer speed)
j = magma density order
b = supersaturation order
s = mixing intensity order

Table 1. **Preliminary experiment (MeOH/water ratio 1:2)**

agitator	stirrer 700 rpm, 0.93 W/kg	rotor-stator 6400 rpm, 160W/kg	rotor-stator 24 000 rpm, 600 W/kg
D50(μm)	19.9	8.5	6.7

In cases where secondary nucleation is dominant, it is reported j is close to unity, b lies between 0.5 and 2.5, and S lies between 2 and 4.[6] In this process, the ratio of product solution to anti-solvent (flow ratio) increases during the course of the operation. The degree of supersaturation and the magma density depend on the solubility curve, the ratio of feed stream and recycle stream, and nucleation/crystal growth rates. The operating range of mixing intensity to obtain the desired small particle size was investigated in the laboratory experiments, and the behavior of the supersaturation and magma density were examined.

2. Process Development in the Laboratory

The direct crystallization of a pharmaceutical compound, which has a molecular weight of ca. 450, from its solution in MeOH/water was investigated. A semibatch crystallization process coupled with a high-speed rotor-stator device during the crystallization was employed. Based on eq 1, magma density, supersaturation, and mixing intensity are three key factors that control the secondary nucleation rate. In preliminary experiments, mixing intensity was studied using a high-speed rotor-stator device (Ultra-Turrax) and a regular overhead stirrer. The hot saturated solution was rapidly fed above the surface into a 100 mL crystallizer containing the anti-solvent. Nonuniform mixing is ignored in consideration of the small scale of the run.

Table 1 summarizes the off-line particle size results measured by MICROTRAC for the preliminary investigation into the effect of mixing intensity. The high-speed rotor-stator device significantly reduced the particle size while the regular overhead stirrer failed to reduce the particle size. No significant reduction in particle size was observed during 20 min of extended aging of the suspension, verifying the ineffectiveness of wet milling for reducing particles for this particular pharmaceutical compound. These experiments clearly confirmed the strong correlation between mixing intensity and secondary nucleation.

Figure 1 shows the solubility data for the compound of interest in a methanol−water system. For the semibatch operation previously described, the water fraction in the crystallizer at the beginning of operation is 1.0. The compound dissolved in methanol is then added to the system at the inlet of the rotor-stator device, decreasing the water fraction to 0.67 at the end of the addition. Assuming an instantaneous mixing of the feed stream to the recycle stream, the “local” supersaturation ratio varies from 49 to 24 (estimated by initial batch concentration and solubility data) which favors nucleation. It should be noted that neither the supersaturation ratio nor the slurry magma density is

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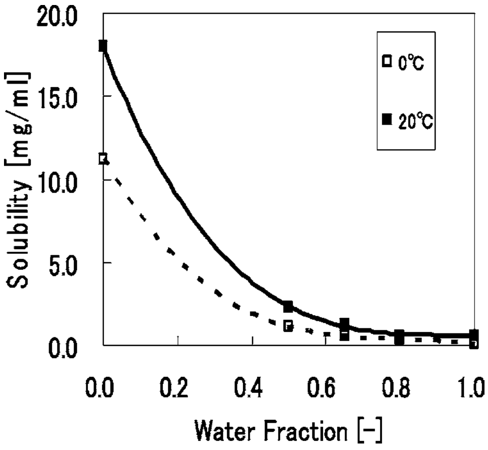

Figure 1. **Solubility curve of Compound A.**

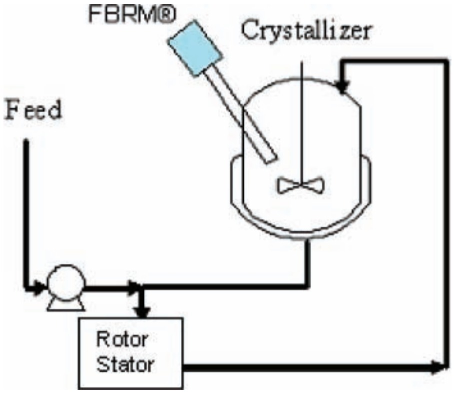

Figure 2. **Schematic diagram laboratory setup.**

Table 2. **Technical data for laboratory setup**

1. scale	600 mL (water 400 mL, MeOH 200 mL)
2. crystallizer temperature	5 °C
3. impeller speed (vessel)	300 rpm
4. feed flow rate	2−240 mL/min
5. feed temperature	60 °C
6. recycle flow rate	1800 mL/min
7. flow ratio	900−7.5
8. rotor-stator tip speed	21.4 m/s

maintained as constant due to the nature of the semibatch approach. Nevertheless, as long as the values of these parameters are reasonably maintained upon scaleup, their impact on particle size can be minimized. From the latter part of the report, the readers can find out that the change of particle size upon scale up is very small.

After the preliminary experiments, a 600 mL scale experiment including the recycle loop setup was conducted in the laboratory. A schematic diagram of the experimental setup is shown in Figure 2. The recycle loop containing the rotor-stator device was setup around a jacketed crystallizer. The linear velocity of the anti-solvent in the recycle loop was kept at 1 m/s to maintain sufficient turbulence in the loop. A hot concentrated (undersaturated) solution of the compound was fed into the suction port of rotor-stator device in the recycle loop. The linear velocity of the feed stream entering into the loop is higher than the linear velocity of the recycle stream to avoid the back-flow to the feed line. The duration of the feed was varied depending on feed flow rate. Table 2 shows the experimental conditions investigated with this setup. The main scale-up parameter was the tip speed of the rotor, as a measure of the maximum local shear rate.

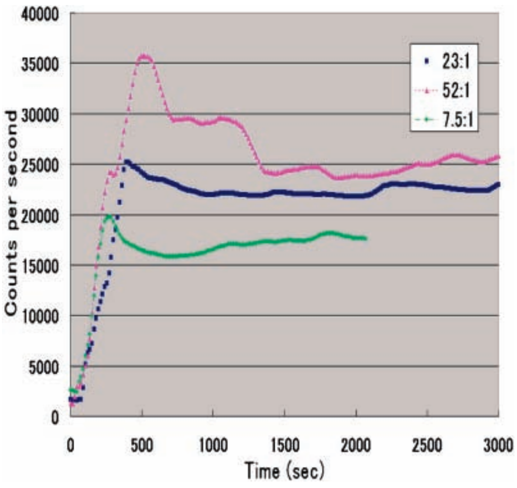

Figure 3. **Profiles of total particle counts for various flow ratios.**

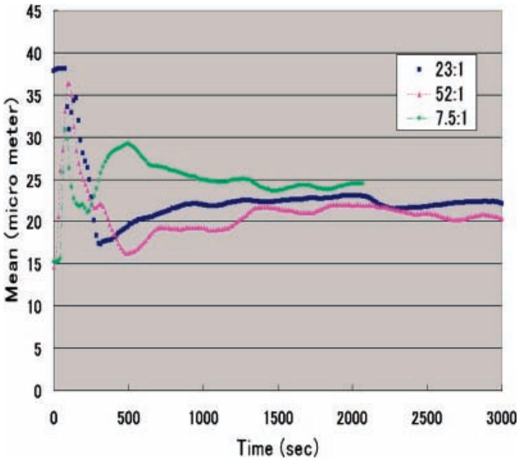

Figure 4. **Profiles of mean particle size for various flow ratios.**

The tip speed in the laboratory device was selected to match the tip speed of the production rotor stator device. The flow ratio of recycle to feed was varied to investigate its impact on particle size under the constant tip speed. This ratio also affects the operational time.

To further investigate the process dynamics, the laboratory vessel was equipped with a Lasentec focused-beam reflectance measurement (FBRM) system. Figures 3 and 4 provide temporal profiles of total particle counts per second and mean particle size, respectively.

As shown in Figure 3, nucleation occurred rapidly at the start of the addition. The particle counts per second increased rapidly during the additional period, reached a maximum slightly after the end of the addition, and eventually decreased to a constant near the end of the run. Concurrently in Figure 4, the mean particle size decreased quickly and then reached a steady state near the end of the addition.

Figures 3 and 4 also provide some insight into the effect of flow ratio on particle size. Slower feed rate (higher flow ratios) provides higher total particle counts per second and

Table 3. **Off-line mean particle size measurements by MIRCOTRAC**

recycle/feed ratio	mean particle size (μm)
7.5:1	8
23:1	10
900:1	10

a slightly smaller mean particle size. Mean particle size was also measured off-line by MICROTRAC for selected samples with results provided in Table 3. However a slightly opposite trend with a slower feed rate between MICROTRACand FBRM is within the uncertainty of the measurement. No significant difference in final particle size was observed within the feed ratio studied which shows the robustness of the process over wide operating conditions.

The equipment available for planned production batches produced a flow ratio of approximately 50. An additional run at this flow ratio was conducted in the laboratory setup prior to the production batches. The mean particle size from this run was 10 μm by MICROTRAC. A micrograph of the crystals produced from this run is provided in Figure 5. This run further confirmed the ability to produce the desired particle size.

3. Pilot Scale Production and Results

The experimental results obtained in the 600-mL laboratory setup served as the foundation for scaleup to production batches. A comparison of the operating conditions for the production batches relative to the laboratory setup is provided in Table 4.

The key scaleup parameters were the tip speed for the rotor-stator mill and the flow ratio between the feed stream and recycle stream.

A schematic diagram of the pilot plant setup is shown in Figure 6. The compound of interest was dissolved in methanol at 60 °C in the feed tank. The crystallizer contained the anti-solvent, water, at 5 °C. The rotor-stator device was installed in the recycle loop around the crystallizer. Product solution was fed to the recycle loop at a constant feed rate into the rotor stator device. A mass flowmeter was used to control the flow ratio of the feed to the recycle stream. Three potential scaleup issues were identified based on prior experience with this type of process. The first was accumulation of solids in the rotor-stator device chamber. To mitigate this potential processing problem, an additional charge point was added to the setup to allow flushing with hot methanol. The mass flowmeter and a pressure gauge installed upstream from the rotor-stator device provided a monitoring capability for solids accumulation and obstruction of the flow path.

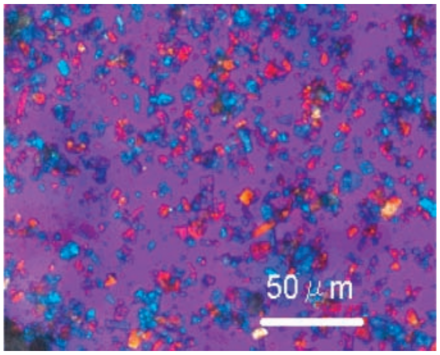

Figure 5. **Microscopic photograph of crystals from the laboratory setup at a flow ratio of 50.**

Table 4. **Operating conditions across scales**

	pilot	laboratory
1. scale (batch volume)	1000 L (660 L water, 340 L MeOH)	600 mL (400 mL water, 200 mL MeOH)
2. impeller speed (vessel)	90 rpm	300 rpm
3. temperature (crystallizer)	5 °C	5 °C
4. flow ratio (recycle/feed)	50:1	7.5:1−900:1
5. rotor-stator tip speed	21.4 m/s	21.4 m/s

Heat accumulation during the operation of the rotor-stator device and foaming in the vessel were also concerns. Equipment verification runs with only solvents were performed to investigate these potential scaleup issues. Both effects were found to be minimal in the production setup.

The production scale device used was equipped with three rotor-stator generators as shown in Figure 7. This configuration provides a high mixing intensity and a uniform supersaturation environment for the rapid generation of small

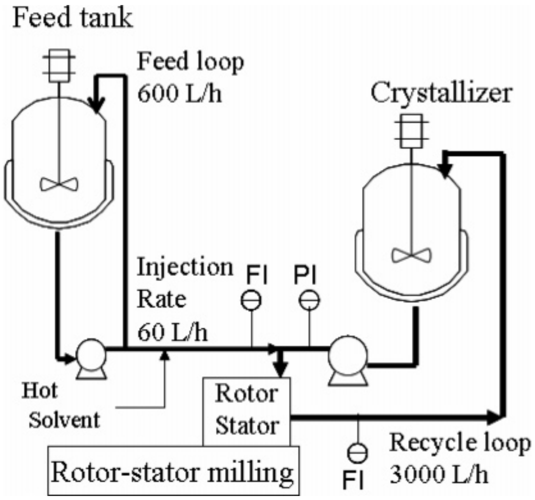

Figure 6. **Pilot scale setup.**

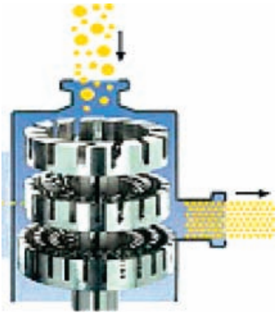

Figure 7. **Three stage rotor-stator generators.**[7]

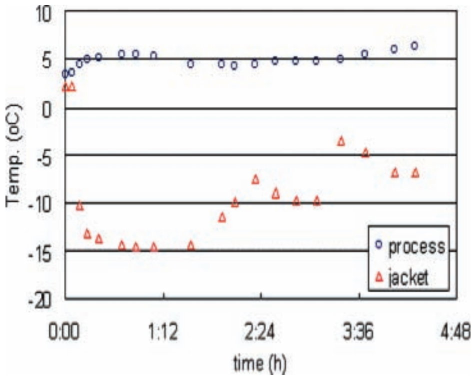

Figure 8. **Crystallizer temperature profiles during a production batch.**

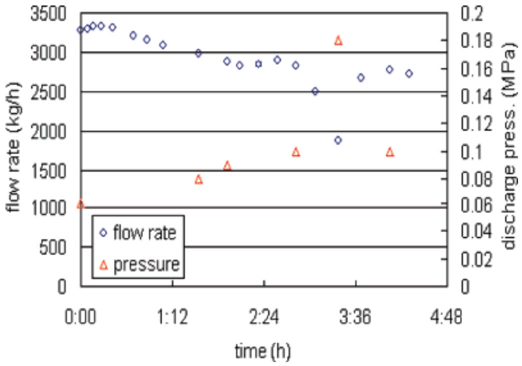

Figure 9. **Flow rate and pressure measurements for a production batch.**

Table 5. **Off-line particle size results for a production batch**

time [min]	Mv [μm]
120	9
240	10
270 (end)	9

particles by secondary nucleation. Four types of generators were available: fine, medium, coarse, and high-flow. The number of slots arrayed on the rotor varies based upon the type of generator. A combination of fine, medium, and high-flow generators was installed in this study.

The total operation time for the production batches was approximately 4.5 h. The temperature, recycle flow rate, and discharge pressure of the feed pump were monitored during the operation. Samples were taken from the process to measure the particle size off-line every 2 h. Figure 8 shows the temperature profile in the crystallizer during a particular run. At the beginning of the feed, the heat of generation was observed and the jacket temperature was manipulated to control the temperature of the crystallizer. The crystallizer temperature was held a 5 °C during most of the operations. The feed rate and discharged pressure of the pump during the operation are shown in Figure 9. The flow rate gradually decreased over the course of the addition as material accumulated in the rotor-stator device. At approximately 3 h into the operation, the pressure sharply increased, and hot methanol was injected to dissolve accumulated solids. Figure 9 clearly shows that the flowrate and the pressure returned to their former states after flushing with methanol. Off-line particle size results as measured by MICROTRAC are provided in Table 5. No variation in the mean volume was observed over the course of the operations. In addition, the results are identical to those obtained in the laboratory setup validating the scaleup of the process from the laboratory to pilot plant.

4. Conclusion

A unique semibatch crystallizer using a rotor-stator device was successfully developed for the generation of fine particles. This approach relies on the secondary nucleation phenomenon under a high shearing environment during crystallization, in contrast to the particle breakage mechanism, i.e., milling, after the crystallization. In this study, rotor-stator tip speed was kept constant for scaleup. The particle size behavior during the operation was monitored using FBRM. In the laboratory experiments, the feed to recycle flow rate ratio was varied. These experiments showed that secondary nucleation was dominant during the feeding period. After the end of the feed, the system reached steady state with no further nucleation and crystal growth. For the range of flow ratios investigated, no effect on particles was observed. For production batches, solid accumulation was monitored by an in-line pressure gauge and a flow meter. Flushing with hot methanol during operations successfully clears accumulated solids. This process was successfully demonstrated in multiple 1000-L pilot scale production batches based upon the 1-L scale laboratory results.

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