Crystallization by Oscillatory and Conventional Mixing at Constant Power Density

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The influence of mixing on crystallization processes has long been recognized.[1, 2] The significance of mixing in crystallization is attributed to its role in the development and distribution of supersaturation, as well as the shear forces associated with the velocity field imposed by the impeller motion. These aspects of mixing are paramount to the quality of the precipitates (particles), often characterized by their crystal size distribution (CSD), surface characteristics, chemical purity, and crystalline imperfections (defect contents).

Impeller driven stirred vessel has always been the prevalent choice in industrial crystallization for the production of pharmaceutics and specialty chemicals. However, in recent years, there has been an increasing interest in oscillatory flow mixing (OFM) as an attractive alternative mixing method, where intense eddy mixing is achieved in a baffled column by fluid oscillations. The attractiveness of this method lies in its performance enhancements over the conventional impeller-driven stirred vessel. This has been reported for processes such as heat- and mass- transfer,[3, 4] gas-liquid mixing,[5] and solid-liquid suspension.[6] However, a comparatively little attention has been paid to studies of this type of mixing on a possible improvement of the quality of precipitated particles, particularly in crystallization of low output high added-value products, such as pharmaceuticals, dyestuffs, catalysts and proteins.

This article reports, for the first time, on the feasibility of OFM to improve the quality of pharmaceutical particles. For this purpose, paracetamol (4-acetaminophenol, 99+%, Merck) was used as a model system.

Experiments were conducted in parallel using a specially designed oscillatory baffled batch crystallizer (OBBC) (Figure 1a) and classical impeller driven batch crystallizer (IDBC) (Figure 1b). The experiments were performed in both crystallizers under the same conditions of residence time (τ_r = 30 min), temperature of crystallization (T = 20 °C), initial supersaturation (20 – 50%), volume (500 mL) and power density (1.5 kW/m^3), but at distinctly different hydrodynamic environment. Paracetamol solution was prepared using the method previously described.[7] In each experiment, the solution was cooled down to a desired supersaturation before the agitation was initiated. The constant power density applied to both crystallizers was used as the reference criteria in these comparative studies. As we shall see later, this criteria is quite informative, because under the same conditions of residence time, temperature, initial supersaturation and volume of the two crystallizers, it enables us to assess the effectiveness of both mixing methods, in terms of quality of precipitated particles, for a given power input.

The power density of IDBC was estimated by the Power-Reynolds numbers correlation, which is common for most impeller driven systems;[8] while the power density of OBBC was estimated by the eddy acoustic model suitable for oscillations with frequencies and amplitudes in the range of 3-14Hz and 1-5mm, respectively.[9] A constant power density of ~ 1.5 kW/m^3 was generated in both crystallizers: in IDBC this was achieved at 800 rpm (Reynolds No, $Re \approx 2.5 \times 10^4$), whereas in OBBC this was realized at 10Hz-3mm (Oscillatory Reynolds No, $Re_o \approx 5660$). The mixing in both crystallizers under these conditions is predominantly governed by the motion of turbulent eddies.[10, 11]

At the end of each experiment particles were separated from solution by filtration. The quality of particles from each crystallizer was assessed by different physical characterization methods (Table 1) and compared one to another.

Figure 2 presents the volume-weighted median diameter of particles, D_{50}, as a function of initial supersaturation. Markedly smaller particles were precipitated in OBBC compared to those in IDBC. In addition, CSD dependence on initial supersaturation was much less sensitive in OBBC than its counterpart in IDBC. We argue that the distinctions observed is a consequence of different dynamical nucleation rates in the two

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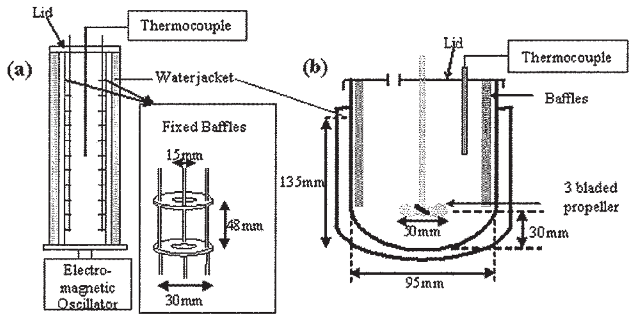

Figure 1. Setup of (a) OBBC, and (b) IDBC.

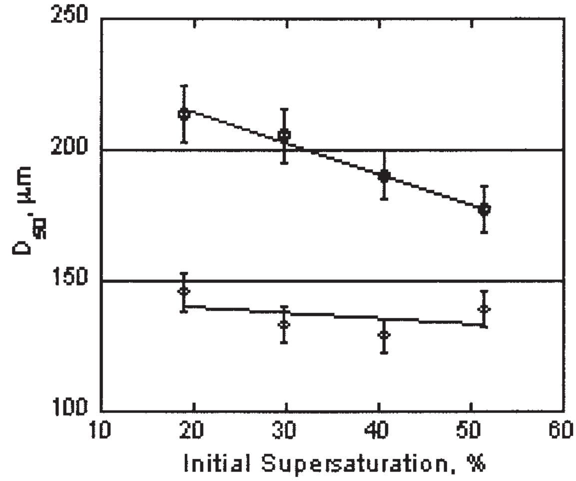

Figure 2. Final size distribution of particles precipitated in IDBC and OBBC. (○: IDBC, 800rpm (revolutions per minute); ◇: OBBC, 10Hz-3mm).

crystallizers due to expected difference in respective hydrodynamic features of the crystallizing solution. Dynamical nucleation is defined as a nucleation event that occurs due to the relative motion between different parts of the crystallization system, which includes liquid and solid in close contact.[12] The validity and further clarification of the earlier hypothesis, based on dynamic nucleation, will be considered later, by using the results of computational fluid dynamic (CFD).

Figure 3a and 3b show the SEM images of particles precipitated in IDBC and OBBC, respectively. A significant proportion of the IDBC particles have cavities near the center of the faces. On the contrary, most particles precipitated in OBBC have noticeably smoother surfaces and markedly lesser surface cavities. The cavities are caused by morphological instabilities, induced during growth by microscopic fluctuations of concentration at the crystal-solution interface.[13] At the later stage of growth, these cavities become occluded by macrosteps and, thus, form solution inclusions in particles. Such events are rather detrimental to the quality of pharmaceutical particles, especially to their chemical purity and crystalline perfections.

The presence of inclusions in a particle leads to distortion of its crystal lattice and therefore to the formation of microstrain. X-ray Powder Diffraction analysis of the precipitated particles, including Rietveld refinement, was used for line profile analysis in order to assess the microstrain.[14,15] Typical estimated microstrains in the particles precipitated in IDBC and OBBC, are presented in Figure 4. It was found that the average microstrain in OBBC particles was by a few orders of magnitude smaller than that in IDBC particles. This striking difference is consistent with the visual SEM observations (Figure 3a,b).

The evidence of the higher quality of OBBC particles advocates that the hydrodynamics in this type of crystallizer suppresses morphological instabilities. The first step in justification of this statement is underpinned by a single crystal growth study, in which it has been found that morphological interfacial instabilities could be minimized by oscillating the solution over the growing interface.[16] This minimization will be fully optimized if an additional condition is fulfilled - the relative velocity (shear rate) of the oscillatory solution with respect to the growing interface reaches the value, at which kinetic growth mode is achieved.[17] Therefore, it is reasonable to postulate that a moving particle in OBBC is much more frequently exposed to some kind of a local alternating change of solution direction than a particle in IDBC. In order to validate this proposition, CFD was used to model the hydrodynamic conditions, and evaluate the shear rate distributions in IDBC and OBBC.[18] Our modeling analysis shows the following main findings.

IDBC has markedly localized high shear rate region around the impeller blades, which decays rapidly away along the radial distance (Figure 5). The volume-averaged shear rate calculated for this system was $\sim$20 s^{-1}.

Unlike of IDBC, the modeling of the solution dynamics in OBBC shows the existence of periodic vortex shedding, which provides alternating high and low shear regions with volume-averaged shear rate of $\sim$100 s^{-1}. This shear rate, which is by one order of magnitude larger than that of IDBC accounts for: (1) an increased nucleation rate, and (2) less sensitive CSD on initial supersaturation in OBBC. The former one is in good agreement with early molecular dynamics simulation studies, which predict a substantial contribution to nucleation due to shear-induced ordering of molecules.[19, 20] The latter one is known as a consequence of higher nucleation rate.[21] In addition, much stronger presence of clock/counter-clockwise vortex pairs in oscillatory flow mixing (Figure 6), than that in IDBC (Figure 5), will result to a larger probability for interaction between boundaries of these vortices and the interfaces of growing particles in OBBC. For this reason, the overall experience of a particle in OBBC, compared to that in IDBC, is much more equivalent to the experience of a fixed single crystal growing in an oscillatory solution. It is now quite

Table 1. Summary of Different Methods used in the Assessment of Particle Quality

	Physical Characterization Method	Expression of Quality
Crystal Size Distribution (CSD)	Low Angle Laser Light Scattering (LALLS)	Volume weighted median diameter, D_{50}
Crystal Surface Characteristics	Scanning Electron Microscopy (SEM)	Evidence of surface cavities (morphological instabilities)
Crystalline Imperfections	X-Ray Powder Diffraction (XRPD) line broadening analysis by Rietveld Refinement	Crystalline microstrain

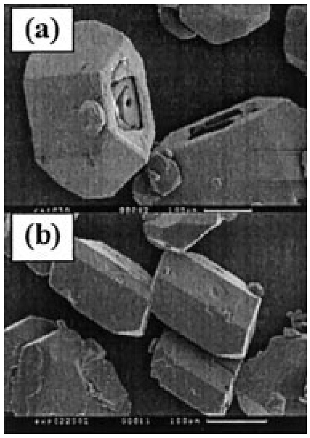

Figure 3. SEM images of Paracetamol precipitated in (a) IDBC, and (b) OBBC.

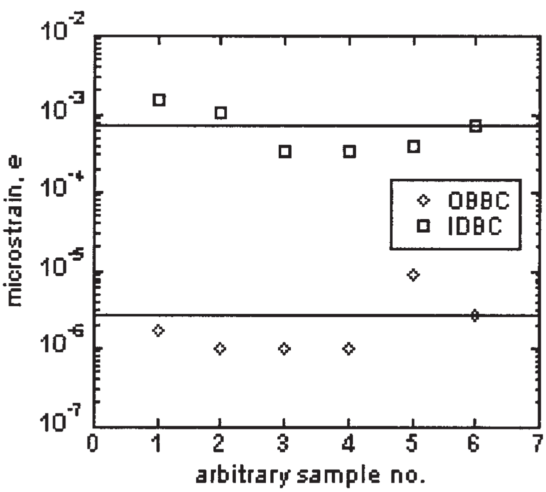

Figure 4. Microstrains of IDBC and OBBC particles.

Mean microstrain values are indicated by the horizontal lines.

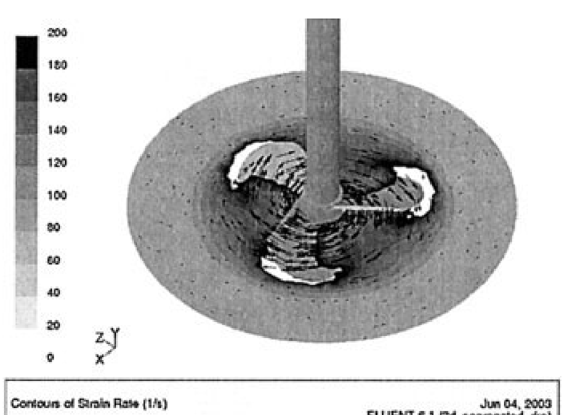

Figure 5. Shear rate contour plot showing high shear regions decay rapidly away from the impeller blades.

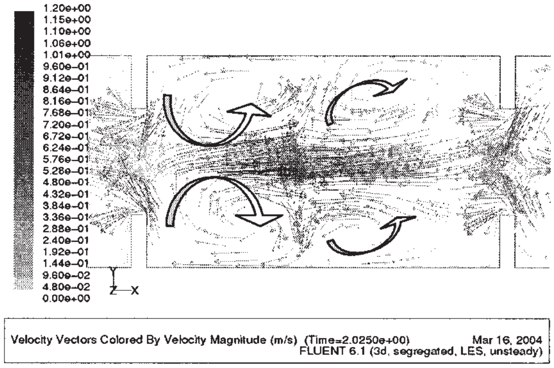

Figure 6. Velocity vector field at the center inter-baffle region during a stage of the OBBC flow cycle.

Dominant vortices and their directions are indicated by the rotation arrows.

obvious why particles nucleated and grown in oscillatory mixed crystallizer have markedly smoother surfaces and much less content of defects compared to their counterparts produced in IDBC.

In conclusion, this study has highlighted the feasibility of oscillatory flow mixing in the crystallization of high quality pharmaceutical precipitates. For a given power density, OBBC is shown to be more effective than IDBC in producing particles of smaller sizes, smoother surface, and lower microstrain (crystalline imperfections).

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