Microcrystallization for inhalation particles

Exploring precipitation techniques as an alternative to batch micronization

Darragh Murnane
King's College London

With the exception of solution formulations, the majority of pMDI formulations and all dry powder inhaler (DPI) formulations require the production of a solid particulate with an aerodynamic particle size distribution (PSD) of 1-6 μm for successful inhalation therapy. For many years, production of these particles has relied on batch crystallization followed by size reduction. Most manufacturers perform the size reduction step by air jet milling, a technology invented at the end of 19th century and developed for inhalation medicine since the 1960s.

An abundance of academic and industrial research into alternative particle production techniques has taken place over the years [1], but as yet only one product (spray-dried insulin) has reached the market. Many product developers perceive this lack of progress as a failure of alternative techniques to deliver on the large scale, but progress has also suffered as the result of an ideological rejection of production techniques alternative to micronization. However, given recent advances in our ability to produce controlled crystal forms and homogeneous particle populations, crystallization of active pharmaceutical ingredient (API) while limiting crystal growth to the respirable size range seems like the natural next step.

Challenges presented by micronization

Batch crystallization represents an integral process in the purification and isolation of APIs. The development of an API for an inhalation formulation inevitably involves an intense and increasingly automated screen to identify possible solid state forms. Thereafter, the crystallization process requires stringent control in order to optimize the properties of the resultant crystals, including size, shape and, in particular, crystal form [2]. Only the advent of process analytical technologies such as *in situ* particle sizing, imaging, and concentration measurements has enabled reproducible production of optimal crystal products.

It seems highly illogical to expend the necessary effort to produce high quality crystals only to then subject the product to a high energy size reduction process like micronization. The deleterious effects of micronization on particle crystallinity and surface energy have been well documented over the last twenty years, but the pharmaceutical industry has accepted these problems due to the perception that micronization easily and cost-effectively produces particles in a narrow PSD suitable for inhalation. However, its defenders generally forget that micronization involves a size classification technique, and the classifier usually rejects a large fraction of API particles in the process.

Focusing on the final PSD of the product ignores the fact that micronization of most APIs proves to be a rather difficult process dependant on material properties such as crystal hardness, bulk powder properties such as flow, and the mill performance. As a result, micronization is a key unit operation requiring attention to optimization, but deciding which endpoint to investigate presents challenges [3].

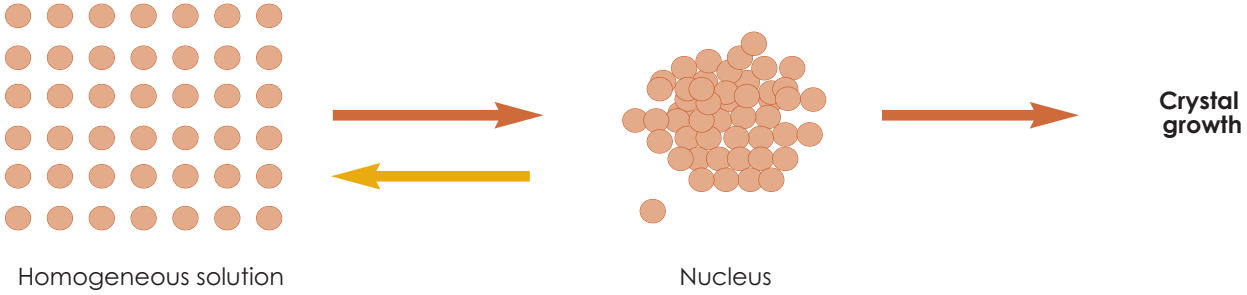
For example, investigating only particle size excludes the effects of micronization on surface energy, although altering surface energy has been demonstrated to affect the key aerosolization process of DPIs [4]. In addition, many materials, such as salmeterol xinafoate, which required the engineering of a spherical crystalline agglomerate simply to enable jet milling, prove unsuitable for inhalation. Even for those materials amenable to micronization, the crystals undergo uncontrolled and unpredictable impaction events during milling, leading to unpredictable intra-batch and inter-batch heterogeneity of particle populations, frequently rendering the results unsuitable for formulation development.

Amphiphilic microcrystallization techniques

All crystallization results from a supramolecular process in which dissolved solute molecules aggregate to form regular 3-dimensional arrangements (Fig. 1). While some unusual particle conversion

Figure 1

Schematic of solution-based crystallization: nuclei form reversibly upon generation of supersaturation from a homogeneous solution. If of a critical size, nuclei undergo further growth in a regular lattice



approaches such as solvent-mediated recrystallization [5] or ultrasonic-assisted recrystallization from glasses [6] have had some success, the majority of microcrystallization approaches rely on precipitation strategies in which rapid crystallization of a substance occurs due to a dramatic change in its solubility as a result of chemical reaction such as pH-mediated precipitation or antisolvent addition.

Supersaturation, the driving force for crystallization, is defined as a concentration of substance present in solution in excess of its thermodynamically stable solubility. Rapid generation of high supersaturation, the key to precipitation-based microcrystallization, results in a high rate of nucleation. That extensive nucleation effectively depletes the supersaturation, minimizing crystal growth and producing microcrystals.

The pharmaceutical industry's fear about the use of potentially hazardous volatile organic solvents in the crystallization process has contributed to a bias against precipitation, despite the fact that the conventional crystallization used for the production of APIs typically involves the use of organic solvents. Amphiphilic crystallization, a novel, tunable aqueous crystallization system for the production of microparticles based on polymeric solvents represents an alternative.

This technique provides a safer, more consistent method of precipitation by eliminating the use of organic solvents. Amphiphilic crystallization avoids concentration changes during processing, presents no exposure of operators to volatile organic solvents, and is environmentally benign [7]. And finally, the use of mass spectrometry to confirm full solvent removal can allay any concerns about the health effects of any residual polymeric solvent.

Experimental production of microcrystals of salmeterol xinafoate (SX) and fluticasone propionate (FP) using amphiphilic crystallization has demonstrated its potential for manufacturing API within the PSD necessary for inhalation (Table 1). While the classification performed as part of the micronization process produces a narrower PSD than precipitation, where no classification is performed, the results show clearly that amphiphilic crystallization can provide a viable alternative to the use of organic solvents for the production of inhalable microcrystals.

Table 1

Particle size distributions measured by laser diffraction (mean ± SD, n = 5) of microparticles of salmeterol xinafoate (SX) and fluticasone propionate (FP)

API	D(v, 0.1) (µm)	D(v, 0.5) (µm)	D(v, 0.9) (µm)
Micronized SX	0.59 ± 0.01	1.13 ± 0.12	3.69 ± 0.23
SX-Methanol crystals	0.91 ± 0.08	4.95 ± 0.30	11.19 ± 0.35
SX-PEG 400 crystals	0.71 ± 0.02	4.50 ± 0.61	11.84 ± 1.11
SX-PEG 6000 crystals	0.55 ± 0.01	0.92 ± 0.04	10.12 ± 1.15
Micronized FP	1.01 ± 0.02	3.06 ± 0.05	7.20 ± 0.15
FP-Methanol crystals	1.90 ± 0.35	5.73 ± 0.35	20.85 ± 1.83
FP-PEG 400 crystals	0.62 ± 0.02	2.25 ± 0.09	7.59 ± 0.24

Indeed, using PEG 400 as a polymeric solvent to precipitate FP results in a smaller particle diameter following crystallization than that of micronized FP.

Achieving control of the PSD requires an understanding of the particle formation process during precipitation, which, admittedly, academic pharmacy has generally not reported. However, we can refer to chemical engineering approaches applied to a variety of other industries such as pigments and catalyst production to learn that the key to controlling PSD during precipitation is controlling the degree of nucleation and subsequent nuclei/crystal growth. Disperse supersaturation across the crystallizer, as well as cementing together of particles, results in broad PSDs, but controlling the mixing conditions in the crystallizer can adequately address both of those situations.

The mixing of solution and antisolvent necessary to cause nucleation occurs in three distinct stages:

- *macromixing*, a uniform distribution of supersaturation throughout the entire crystallizer
- *mesomixing*, a turbulent breakdown of the added solution/solvent
- *micromixing*, a molecular level mixing generating supersaturation.

Rapid micromixing at the edge of mesomixing regions and a proper balance between the rates of mixing and nucleation times can achieve extensive nucleation. Optimizing the precipitation such that supersaturation is depleted rapidly by micromixing balanced with the rate of nucleation in a well macromixed environment ensures uniform crystal growth and a tight PSD.

A system with optimized mixing produced a well-controlled PSD in the manufactuing of SX and FP microcrystals using PEG 400 (Table 1). Although PEG 6000 employed with SX resulted in disperse particle growth (Table 1), further work has succeeded in optimizing the precipitation process using this solvent. The availability of techniques such as high-gravity mixing [8], porous microfiber reactors [9], and plug flow reactors [10] that improve mixing intensities suggest a bright future for microcrystallization strategies.

Controlling morphology and surface properties

The ultimate goal of particle engineering for inhalation APIs is to control the solid state of the particles, including their crystalline surface properties and morphology, which affect aerosolization. Conventional precipitation under conditions of high supersaturation often results in the production of amorphous particles instead of the desirable stable crystal forms, and studies have frequently employed amorphous polymers such as polyvinylpyrrolidone or cellulose derivatives to resist particle growth/agglomeration. Such polymers usually appear in the isolated microcrystalline particles, thus generating amorphous character, an approach that runs counter to the rationale of microcrystallization.

Supercritical antisolvent microcrystallization, on the other hand, produces particles in the stable crystal form, including several polymorphs of SX and FP, due to its ability to control temperature and pressure. Indeed, in the case of SX produced by this method, crystallinity was higher than for either material micronized in the laboratory or commercially available pre-micronized SX as measured by the resistance of the material to recrystallization upon thermal treatment (Fig. 2). Experiments also produced a highly crystalline particle of the stable polymorph of FP in spite of the massive driving force for solid formation generated by a supersaturation that exceeded the solubility by several thousand times. Further improvements in mixing modalities may extend control of polymorph production in both conventional and polymeric solvent systems.

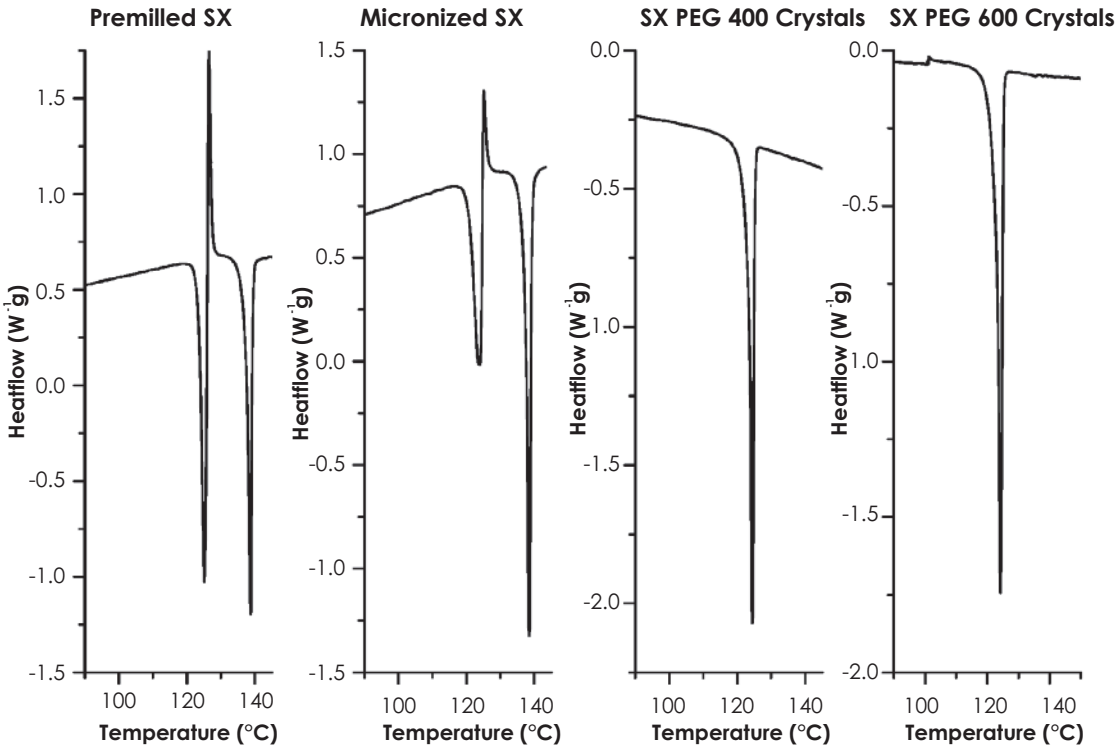
In addition to their small size, microcrystals also frequently have a needle-like shape, which, in some cases, can improve aerosolization performance. For example, in the case of FP, needle-shaped crystals displayed a higher respirable fraction (~27 %) compared to micronized material (~14 %). On the other hand, the needle shape can contribute to high back pressure in a filter and long filtration times, making isolation of the crystals difficult, but these problems can be overcome. In fact, SX crystals created using amphiphilic crystallization form large diameter flocs that break down on the filter medium under negative pressure, resulting in rapid filtration. Even in cases where filtration proves difficult, the overall process may be easier than micronization, and we can also explore other isolation operations such as hydrocyclone separation.

Understanding particle formation processes

Although pharmaceutical researchers often complain of a lack of understanding and control in regards to particle formation, our chemical engineering colleagues have provided us with some answers. In the case of amphiphilic crystallization, we have investigated thermodynamic controlling factors as well as investigating the kinetics of crystal formation [11, 12]. The coupling of *in situ* analysis techniques with supersaturation monitoring has revealed that particle formation occurs during periods of high viscosity

Figure 2

Differential scanning thermograms of salmeterol xinafoate (SX) at 2 ˚C min-1 indicating melting of the stable polymorph at 120 ˚C. Recrystallization is only observed for material where seeds of the unstable polymorph are present



that limits particle growth and agglomeration. The media used in amphiphilic crystallization also promote flocculation of microparticles, preventing further particle growth.

Advanced research in recent years has investigated the use of computational techniques to predict crystal structures and an understanding of the supersaturated state to direct crystallization. Indeed, high powered analytical techniques such as *in situ* x-ray and neutron diffraction analysis coupled with nanoscale imaging techniques have elucidated particle formation mechanisms during precipitation [13]. Employing process analytical spectroscopy such as FT-IR and FT-Raman during particle formation processes can also help us to control crystallization.

As a result of our improved understanding and control, microcrystallization techniques can now provide a suitable method for small-scale production to serve as formulation development probes during early development as well as for scaled-up production. In addition, improvements in physical stability of particles and potential improvements in aerosolization performance show microcrystallization to be a technique ripe for exploitation.

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Darragh Murnane is Lecturer in Pharmaceutics in the Department of Pharmacy, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH. Tel: +44 20 7848 4747. darragh.murnane@kcl.ac.uk. *His work was funded by MedPharm Ltd. and King's College London and performed in conjunction with Gary Martin and Christopher Marriot. This article is based on a talk that he gave at RDD Europe 2009.*