Particle design for respiratory drug delivery: Challenges and processing options

Supercritical fluid anti-solvent technologies offer a single step, efficient route for producing inhalation particles

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Particle design of drugs for lung delivery

The key to efficient lung delivery with dry powder inhalers (DPIs) and metered dose inhaler (MDI) suspension products is providing the patient with a drug powder formulation and delivery device that are capable of delivering particles to the lung in the inhalation range (1-5 μm). Ideally, for effective drug delivery to the lungs, the drug particles should have a narrow size distribution and possess low surface energetics.[1-4] Solid state properties and characteristics of an active pharmaceutical ingredient (API) affect product performance in areas such as flow properties, uniformity of dosage and bioavailability.

Limitations of micronizing drug powders for inhalation medicines

"Top down" processes, such as milling, are the current industrial standard technology used to produce particles with a suitable inhalation range (1-5 μm). However, milling provides limited control over particle shape and size as well as size distribution and morphology. In addition, milling can lead to crystal defects[5] that may affect chemical purity and lead to both physical and chemical instability and surface charging.[6,7] It is reported that small changes in primary particle characteristics may result in unacceptable variability in aerosol performance, including both inter- and intra-batch variability,[3] as well as challenges in quality by design (QbD) ambition. For example, some APIs after micronization often have high energy sites that are highly charged and have very cohesive particles, thereby resulting in downstream processing challenges and poor product performance.

Down stream material handling and product performance

To reduce cohesion between particles, improve the flowability of micronized powders and impart good secondary processing behavior, a common practice is blending the micronized API particles with larger carrier particles, typically α-lactose monohydrate in DPI formulations.[7] In dry powder blending, issues such as powder mixing efficiency (which is affected by differences in particle shape, size, density and triboelectric effects between individual components in the blend), must be considered and addressed.

During inhalation of the drug/carrier blend, the drug particles detach from the large carrier particles in the throat by transfer of the air stream's kinetic energy to the powder and drug particles are deposited in the lungs. For MDI suspension formulations, the floccula-

tion and de-aggregation behavior of the primary particles (due to surface roughness, charge and size characteristics) and their stability in the propellant require careful consideration. MDIs are reported to have major performance issues (such as poor efficiency, limitations on drug load per actuation, etc.) when highly charged drug particles are dispersed in volatile propellant liquid(s), which in turn limits their applicability to a number of potent, locally-acting drugs.[7]

Potential for drug particle design

Inhalation products are a fertile area for particle design in specialized areas such as combination therapy and low dose medicines. For example, there is now overwhelming evidence that the addition of a long-acting β2-agonist to an inhaled corticosteroid gives better control in the management of both asthma and chronic obstructive pulmonary disease in patients.[8] Combination inhalers face a challenge in that the doses of the component drugs cannot be individually titrated without changing the inhaler. Patients have a desire for products that provide the same effect, every time and are easy to administer. Therefore, having different particle characteristics in the individual components of a combination dose may lead to non-optimal dose uniformity and inter- and intra-batch consistency that will provide sub-optimal medicine for the patient. These effects are likely to be more prevalent at low dose.

Bottom up processing methods for drug particle design

Producing particles in the inhalation range can be achieved by a variety of technologies involving "bottom up" methods in contrast to "top down" milling approaches. The advantages and disadvantages of various approaches are highlighted in Table 1.

Bottom up methods offer the opportunity to design individual particle characteristics and are more aligned with QbD ambitions. However, controlled crystallization is a multistep process, difficult to control in producing micron-sized particles and is time consuming. The process can be challenging to scale, is environmentally demanding (with respect to solvent waste and energy consumption) and needs a post-processing drying stage to remove residual solvent.

Sonocrystallization, like controlled crystallization, employs multiple steps, is also challenging to scale and involves the employment of other bottom up technologies to produce a product with the desired particle characteristics. Due to a large amount of generated heat, the sonocrystallization process is likely to be damaging for heat sensitive molecules such as biomolecules. It is also environmentally unfriendly (due to solvent waste and large energy consumption).

Spray drying currently is the most commonly used bottom up method but has some limitations as scale-up laws are complex. For some heat labile and shear sensitive molecules, it cannot be used.

However, supercritical fluid (SCF) anti-solvent technologies offer a new, attractive, single step, efficient route for producing inhalation particles of pure API (small molecule or biomolecule) and API combinations (API-API, API-polymer, API-absorption enhancer) with low residual impurities, e.g. solvent. This process has been successfully scaled and operated at full cGMP compliance.

Supercritical fluid processing technologies

SCF technology for drug particle formation has advanced in the past two decades, from a research tool to a product development technology. This progress has been driven by the need for high purity and chemical stability as well as the ability to design products that enable more effective, targeted delivery. Additional needs include the potential to improve dose uniformity, control particle size, achieve narrow particle size distributions and high levels of inter-and intra-batch reproducibility. Drug particles produced with SCF technology show additional, attractive, individual particle characteristics. These include smooth surface tomography and low surface energy, which deliver desirable secondary processing behavior such as good flow properties and aerosol performance.

Phase behavior in SCF processing

In SCF processing, understanding phase behavior is critical. Phase properties for pure components are easily described using a phase diagram such as that in Figure 1

Figure 1

Phase diagram of a pure substance

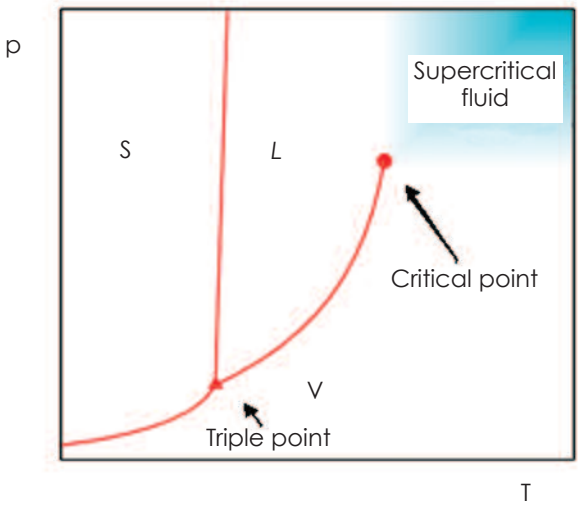


Table 1

Processes employed in production of particles suitable for inhalation

Process	Advantages	Disadvantages
Controlled crystallization	Can provide particles within inhalation range	Often multi-step, time consuming and challenging to scale
	FDA approved technology	Environmentally unfriendly as often large quantities of solvent are employed and drying stage required
		Products may exhibit high residual solvent
		Possible to produce composite particles but scale up can be challenging
Sonocrystallization	Can provide API and API composite particles within inhalation range	Employs multi-steps, time consuming and challenging to scale
		Cannot be used for heat labile molecules such as biomolecules
		Environmentally unfriendly as often requires large quantities of organic solvent and some secondary drying stage is required
Spray drying	Can provide particles within inhalation range	Scale up laws are complex
	Single step, FDA approved technology	Shear during atomization can denature macromolecules by disrupting tertiary structures or promoting aggregation
	Technology has successfully been used to process small and large molecules	Shear/compaction during powder collection can shatter particles and cause agglomeration
	Cost effective technology	Time required for collection increases exposure of the API to high gas temperature
Supercritical fluid processing (SCF) – Gas antisolvent	Can provide API and API composite particles within inhalation range	Currently available as batch process therefore limited by batch size constraints
	Single step, FDA approved technology, first inhalation product NDA filed (Levadex)	Not suitable for molecules that are soluble in the supercritical fluid
	Thermodynamic dominant process therefore scale up issues are minimized	
	Can manipulate solid state form and particle morphology	
	Particles possess low surface energetics and crystal defects, and exhibit good flow behavior	
	Cost effective, low cost of goods, typical yields > 90% after process optimization	

where the solid lines represent equilibria between two different phases. The triple point is where all three equilibrium lines meet. The vapor pressure curve ends at the critical point and thermodynamic properties such as enthalpy, entropy and internal energy of the liquid become equal to those of the gas. The region of pressures and temperatures above the critical point is called the supercritical region. The physical properties of supercritical fluids exhibit liquid-like density with gas-like viscosities, resulting in larger diffusion coefficients and mass transfer properties than liquids.

The SCF antisolvent process

In the SCF anti-solvent processes illustrated in Figure 2, the drug or drug composite materials are dissolved in a suitable solvent/solvent system and fed with a stream of SCF, typically carbon dioxide (CO_2), through a specially designed nozzle under controlled conditions of temperature and pressure. The SCF mixes with the organic solvent phase and rapidly extracts it from solution, resulting in the rapid formation of particles that are retained in the particle formation vessel. By manipulation of the process variables of pressure, temperature, solution and SCF flow rates, solvent and solution saturation, it is possible to manipulate particle morphology, surface energetics, particle size and size distribution. The process easily can follow quality by design (QbD) philosophy and generates powders with excellent size uniformity and batch consistency, resulting in good product performance.[7]

Figure 2

A typical SCF anti-solvent process

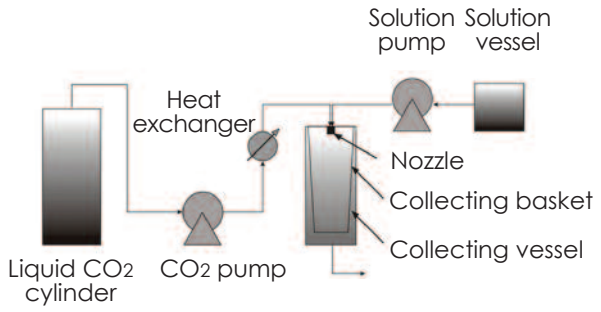
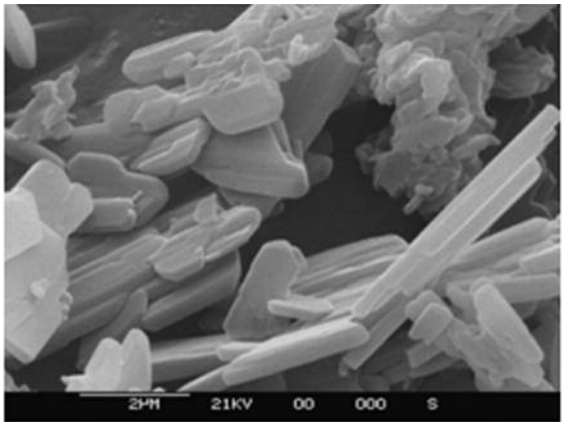
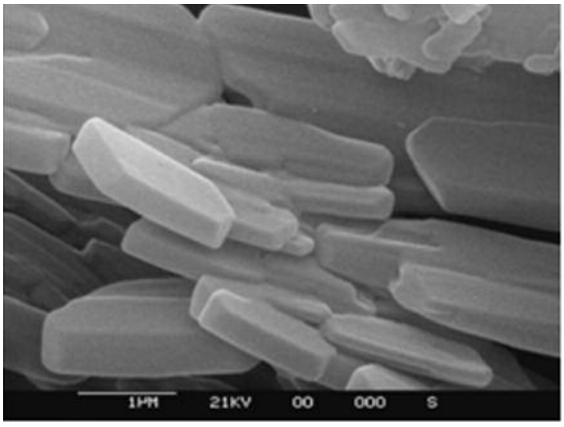


Figure 3

Comparison of micronized and SCF processed albuterol sulphate[9]



Micronized API



SCF processed API

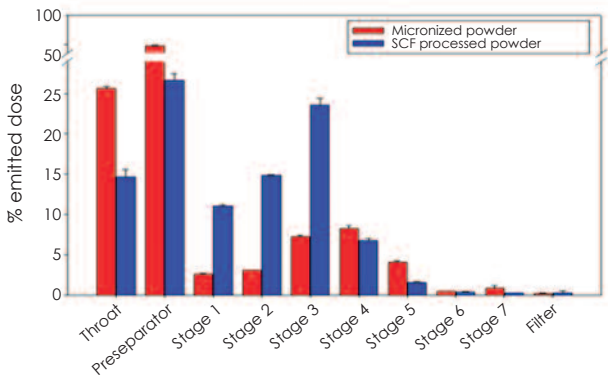
Properties and performance of SCF processed drug powders – *in vitro* and *in vivo*

Figure 3 shows scanning electron micrographs that clearly illustrate the difference in particle characteristics between micronized and SCF processed albuterol sulphate, a short-acting β2 adrenergic receptor agonist drug that is used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. In addition to providing the aerodynamic particle size and size distribution required, the SCF particles contain smoother surfaces that are less likely to localize charge and are thus less prone to aggregate than the rough-surfaced micronized powder.

SCF powder anti-solvent processing offers good batch consistency[9] in particle size and size distribution for steroid powders. D_{10}, D_{50} and D_{90} represent the particle sizes in a given percentage of particle population. The average particle size distribution (measured by SympaTec Helos, VMDs in three runs) for an MDI is 0.84 (SD), 1.89 (SD) and 4.37 (SD) and for a DPI is 1.23 (SD), 3.80 (SD) and 8.05 (SD) for D_{10}, D_{50}, D_{90} respectively for each device. Figure 4 shows data from an Andersen Cascade

Figure 4

Andersen cascade analysis of a micronized drug powder in comparison with an SCF produced powder[10]



Impactor test that illustrates the difference in performance between micronized and SCF processed salmeterol xinofoate.[10] The results show that more SCF particles are in the inhalable range (i.e. stages 1-5) than found with the equivalent-sized micronized powder. In Figure 5, bioavailability data is presented that demonstrate that SCF produced drug powder results in deeper and improved lung delivery in comparison with a similar sized micronized powder. The data also indicate it is possible to simplify the formulation and achieve a more targeted response.

Process scale-up and GMP processing

SCF anti-solvent technology exhibits good consistency on scale-up. Tables 2 and 3 show data that demonstrate reproducibility between a pilot plant (2 L vessel) and a manufacturing GMP plant (10 L vessel) in particle size, size distribution and residual solvent levels.

The potential value of SCF based processing for drug particle design is clearly evident. Interestingly, earlier in 2011, MAP Pharmaceuticals submitted a New Drug Application to the United States Food and Drug Administration (FDA) for Levadex, an orally inhaled migraine treatment that was developed using an SCF anti-solvent process to produce the active pharmaceutical ingredient.

In addition, recent developments in drug particle design using SCF anti-solvent processing now enable co-administration of composite particles that may either be composed of crystalline components or have a multi-component nature, e.g. drug with enhancer, wetting agent, stabilizer or polymeric material. These composites may be a particle that is either composed of a physical mixture of components that are uniformly distributed or a crystalline co-precipitate.

SCF anti-solvent processing has also been shown to be a convenient alternative process technology for particle size control of macromolecules, as it provides processing conditions of very low shear rate and low temperature, enabling particle manipulation of heat labile macromolecules without destroying the tertiary structure that is required for bio-activity.[11] It may thus provide a much needed alternative to the processes currently used (i.e., spray drying and freeze drying) for preparing dry, room temperature stable preparations of therapeutic macromolecules.

Concluding remarks

Design of drug particles for inhalation medicines is clearly an important factor in providing high quality, efficacious and safe medicines. Various approaches for generating the micron sized drug particles required have been summarized here and the key benefits of a controllable, single step, efficient process highlighted. The antisolvent supercritical fluid method is now well understood, proven at scale and operating at cGMP.

Figure 5

Drug-plasma concentration – time profiles for three suspension MDI formulations. Volunteers received a dose of 0.5 mg of micronized drug product and 0.25 mg of SCF drug powder in a single shot from an MDI device. The SCF drug product at half the dose gave either comparable or enhanced performance depending on the presence or absence of excipients.

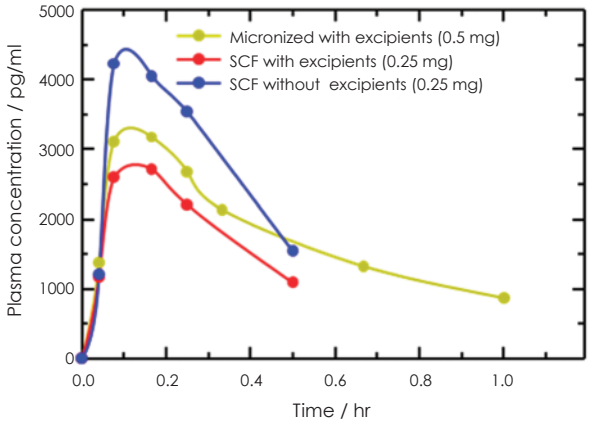


Table 2

Batch consistency on scale up from 2 liter vessel (pilot plant) to 10 liter vessel (GMP manufacturing plant) for albuterol sulphate

	Particle size		
	D_{10}	D_{50}	D_{90}
Pilot plant	0.91 microns	3.20 microns	11.96 microns
GMP plant	0.93 microns	3.17 microns	12.28 microns

	Residual solvent/ppm	
	Dichloromethane	Methanol
Pilot plant	218	Not detected
GMP plant	279	869

Table 3

Particle size analysis of two cGMP batches for an inhalation drug[10]

	Batch 1	Batch 2
D_{10}	0.89 microns	0.93 microns
D_{50}	1.62 microns	1.80 microns
D_{90}	2.75 microns	3.12 microns
VMD	1.79 ± 0.12 microns	1.94 ± 0.10 microns

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