Control of Physical Forms of Drug Particles for Pulmonary Delivery by Spray Drying and Supercritical Fluid Processing

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Abstract

Dry powder inhalation (DPI) is an important means of pulmonary drug delivery for both local and systemic actions. Since drugs of different solid-state chemistry can influence a wide range of physical, chemical and biological properties, control of the solid-state structures and associated behaviours of drug particles is critical for DPI formulation. Current production technology of fine drug particles for pulmonary delivery utilizes sequential batch crystallization and micronization. However, this two-step manufacturing approach often causes unwanted crystallographic damage to the particles and may induce undesirable polymorphic transformation in certain materials. In recent years, spray-drying and supercritical fluid crystallization have emerged as two cost-efficient processing technologies that allow more precise control of the crystal forms and physical properties of the powders produced in a single step operation. This article presents a critical review of these latest technological developments in DPI formulation with focus on the regulation of the physical forms of inhaled drug particles.

Keywords: Physical forms, During particles, Pulmonary delivery, Spray drying, Supercritical fluids

1. Introduction

Pulmonary drug delivery has been the subject of intensive investigation by formulation scientists and respiratory medicine practitioners/specialists. In addition to producing localized effects, drugs delivered into the lungs can be absorbed across the alveolar epithelium to exert systemic actions. Among the different types of therapeutic inhalation formulations available on the market, dry powder inhaler (DPI) has become increasingly popular as a pulmonary delivery system primarily for the following reasons: (a) being in a solid form, the drug is relatively stable chemically; (b) the inhaler is environment-friendly, as it is free from chlorofluorocarbon (CFC) propellants; and (c) the delivery is breath actuated, and does not require coordination between actuation and inhalation by the patient, as does its pressurized counterparts.

Apart from particle size, particle morphology and surface properties, the crystal form of inhaled particles is probably the next crucial parameter in line for consideration in DPI formulation. It has been well documented that solid-state phenomena such as polymorphism, solvate/hydrate formation, and change of crystallinity or the level of crystal imperfections, could all exert profound influence on the physical, chemical and mechanical properties, and ultimately, on the clinical performance of solid pharmaceuticals. Consequently, a good understanding of the solid-state behaviors of pharmaceutical materials as well as
the availability of an effective means to regulate their physical forms during production are crucial for the successful formulation of inhalation dosage forms.

Drug powders used in DPI are normally prepared by batch crystallization from a suitable solvent, followed by micronization to the optimal particle size range for deep lung delivery. However, this two-step manufacturing approach often results in highly cohesive, highly charged, and crystallographically defective materials, which are difficult to process downstream. Consequently, alternative strategies for producing readily processable and dispersible powders are being actively sought. In this regard, spray-drying and supercritical fluid processing technologies appear to hold promise, primarily because of their dual abilities to generate ultra-fine powders within the respirable size range and to control the formation of particular crystal form.

Presented in this article are general background information on pulmonary drug delivery and solid-state chemistry relevant to DPI formulation together with a review on the current applications of spray-drying and supercritical fluid crystallization technologies in regulating the physical forms of ingredients used in DPI formulation.

2. Pulmonary route as an important means of drug delivery

Asthma is a pulmonary disease characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to a variety of stimuli. Pulmonary delivery of drugs plays an indispensable role in the management of asthma. β-Adrenoceptor agonists and corticosteroids are two common classes of drugs administered via the lungs. Pulmonary drug delivery offers a number of advantages, including: (a) a small amount of drug will normally suffice for preventing or treating symptoms; (b) adverse reactions are usually much less than those produced by systemic administration; and (c) there is a rapid and predictable onset of action.

Since the introduction of the first inhaled medication, *Datura ferox*, a congener of atropine, in England in 1802, the inhalation route of drug delivery has captured increasing attention in the pharmaceutical industry. Inhalation therapy is not limited to asthma, but is also of benefit to other respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and bronchiectasis.

Lungs, with a large surface area, good vascularization, an immense capacity for solute exchange and an ultra-thin alveolar epithelium, have been actively explored as an effective route for systemic delivery of peptides and proteins. Of particular potential in this development is inhaled insulin, which may serve as an effective, well-tolerated, non-invasive alternative to subcutaneous regular insulin. Pulmonary route is considered an important means for both local and systemic drug delivery.

3. Dry powder inhalation formulations for pulmonary drug delivery

Typical inhalation formulations for pulmonary delivery include liquid nebulizer, metered dose inhaler (MDI) and dry powder inhaler (DPI).

3.1 Nebulizer

Nebulizer is the preferred choice of many physicians for the therapy of acute asthma in an emergency care unit or for treating patients with severe asthma at home. In jet nebulizers, the aerosol is formed by a high velocity airstream from a pressurized source directed against a thin layer of liquid solution. Ultrasonic nebulizers involve the vibration of a piezoelectric crystal aerosolizing the solution. Although nebulizer can deliver more drug to the lungs than MDI or DPI, the main drawbacks of nebulizer are lack of portability, higher costs of drug delivery as a result of the greater need for assistance from healthcare professionals, and the requirement for higher drug doses to achieve a therapeutic effect.

3.2 Metered Dose Inhaler (MDI)

MDI is the most popular device for aerosolized administration of drugs. With this method, a medication is mixed in a canister with a propellant, and the preformed mixture is expelled in precise measured amounts upon actuation of the device. Proper use of MDIs requires that patients learn how to coordinate exhalation and inhalation with actuation of the device. This can be quite difficult for the juvenile and the elderly. The use of spacer device can only solve the problem partially because the bulky size of the device can be a deterrent for patients who require use of MDIs outside their homes.

In early 1990s, attempts were actively made to reformulate MDIs as a result of the mandatory ban on the use of propellant chlorofluorocarbons (CFCs), which have been implicated in the depletion of the Earth's ozone layer. Alternative propellants, such as hydrofluoroalkane 134a (HFA-134), have been extensively investigated for their potentials to replace
3.3 Dry Powder Inhaler (DPI)

Dry powder systems utilize drug alone or its blends with a suitable carrier, usually lactose, for delivery to the lungs. Drugs, carriers and devices are three important factors affecting the performance of pulmonary delivery of drugs. Unlike MDIs, delivery of medication with a DPI requires minimal patient cooperation and coordination of breathing following actuation of the device. Moreover, DPIs are small, portable devices that can be conveniently carried in a pocket or purse. Turbuhalers® and Diskhalers® are some well-known examples. There is also no need to use spacers. Furthermore, DPIs are devoid of environmentally harmful CFC propellants, as normally required in MDI formulation. Since both MDI and DPI have been shown to afford comparable efficacy in delivering the same drug and in view of the mandatory ban of CFCs use in MDIs by the United Nations, it is not surprising that DPIs have become increasingly important as a pulmonary drug delivery system over the past decade.

4. Solid state chemistry of dry powder inhalation formulations

Fine particles in DPIs may exist in different solid states, which include polymorphs, solvates (hydrates) and amorphous forms. Since pharmaceuticals in different solid states display widely different physical properties, understanding the solid state behaviours of drugs is of particular interest to formulation scientists, chemical engineers, materials scientists, physical chemists, industrial pharmacists, process chemists as well as regulatory affairs personnel involved at various stages of the drug development process. In recent years, solid state phenomena, particularly polymorphism, have attracted considerable attention in pharmaceutical industry, where regulatory control necessitates close examination of all products under development for their solid state behaviour.

4.1 Polymorphism

Many solid pharmaceuticals exist as polymorphs, or crystal forms having the same chemical composition but different internal structure in the crystal lattice, i.e., different unit cell dimensions and cell packing. Steroids, sulphonamides and barbiturates are three common classes of drugs exhibiting polymorphism. A casual online computer search in PubMed will easily reveal emerging polymorphs for new and existing compounds.

Polymorphs show a range of widely different physical and chemical properties, such as melting points, spectroscopic behaviour, solubility, density, hardness, crystal shapes, physical and chemical stability and dissolution profiles. Review on crystal polymorphism of drug substances in the European Pharmacopoeia has been prepared by the regulatory authority. Polymorphism is of vital importance in the context of patent protection, process development and product specification in pharmaceutical industry. The potential formulation problems associated with polymorphism are best exemplified by the antiviral drug, ritonavir. In the summer of 1998, Novir® (ritonavir) semi-solid capsules supplies were put on hold following the discovery of a new crystal form of ritonavir, which is much less water soluble. The existence of this new polymorph was confirmed by microscopy and powder X-ray diffraction (PXRD). The sudden emergence of this drastically less soluble polymorph has created tremendous formulation hurdles for the drug company concerned. Chloramphenicol palmitate is another well-demonstrated example of polymorphism. Maximum blood levels of the two reported polymorphic forms are 3 and 22 mg/ml respectively, which represent a seven-fold difference. If this problem is kept unchecked, significant dose-to-dose variations can occur. Despite such potential problems, one can still take advantage of the unique physical properties of a particular polymorph to improve drug formulation. For instances, the dry powder inhalation properties and in vitro respirable fraction of steroid KSR-592 were improved dramatically by changing its morphology from plates (α-form) to needles through polymorphic transformation to the β-form.

Taken pairwise, polymorphs fall into either a monotropic system or an enantiotropic system. For monotropic pairs, one polymorph is always more stable than the other. The polymorph with higher melting point has the lower Gibbs free energy at all temperatures (Fig. 1). Thus, change of low melter to high melter, being a non-spontaneous process, is not thermodynamically favourable. Transition point only exists above the melting points of the two polymorphs.

For enantiotropic pairs, the transition temperature exists below the melting points of both polymorphs (Fig. 2). At temperatures lower than transition temperature, the lower melter has lower Gibbs free energy.
energy, while at temperatures higher than transition temperature, the higher melter has lower Gibbs free energy. Thus, the lower melter is the more stable form below the transition temperature while the higher melter is the more stable form above the transition temperature.

4.2 Hydrates and solvates

Solvates are crystals in which solvent molecules occupy regular positions in the crystal structure. Hydrates are a subset of solvates when the solvent molecule is water. For obvious reasons, most drug crystals that fall into the category of solvates are hydrates.

Physical properties of hydrates and solvates can be quite different. Solvates must be less soluble in the same solvent than their original anhydrous counterparts, otherwise there would be no thermodynamic driving force for their crystallisation. For example, ampicillin anhydrate has a higher solubility and intrinsic dissolution rate than its trihydrate form. A significant difference in urinary excretion rates of the drug has been demonstrated in vivo. Suspensions and capsules containing the anhydrate exhibit superior bioavailabilities to analogous formulations made from the trihydrate. In the case of carbamazepine polymorphs (forms I and III) and the dihydrate, the solubilities, intrinsic dissolution rates and bioavailabilities of both anhydrous polymorphs are lower than those of the dihydrate.

In addition, hydrates are in dynamic equilibrium with the surrounding moisture, which can be described by the following relationships:

\[
K_h = \frac{a_3[A \cdot mH_2O(solid) ]}{a_1[A(solid)]a_2[H_2O]^m}
\]

where \(a_1\), \(a_2\) and \(a_3\) represent the activities of the anhydrate, water and hydrate respectively.

From the equations, it is clear that water activity and relative humidity (%RH) in a closed system are significant in influencing the hydration states of crystal forms. For example, water stoichiometry of aspartame are 0.5 below 42% and 2.5 above 58% RH. Nedocromil sodium hydrate changes from monohydrate or trihydrate to heptahemihydrate as the relative humidity increases. In addition, temperature will also influence the hydration status of pharmaceuticals. For instance, the kinetics of dehydration of aspartame hemihydrate to aspartame anhydrate has been studied with variable temperature powder X-ray diffractometry. This may adversely affect drug potency, powder flow, content uniformity, particle morphology, dissolution rate, and possibly bioavailability.

4.3 Amorphous solids

Amorphous solids are devoid of crystallinity and have no long-range order. The atoms and molecules exist in a totally disordered array. Amorphous solid can be viewed as a glass characterized by a glass transition temperature \(T_g\), defined as the temperature below which the constituent molecules are configurationally frozen in a glassy state and lack the motion typical of those in a liquid. Above the \(T_g\), the amorphous solid assumes a rubbery state exhibiting flow property and the molecules have substantial...
configurational motion.

Amorphous solids have enhanced solubility and dissolution rate in comparison to their crystalline counterparts. It has been reported that the clinical relevance of solubility enhancement associated with the amorphous form is likely to be significant, even in systems, which are only partially amorphous. However, such amorphous or glassy materials are not without problems. The Gibbs free energy of amorphous solids is higher than that of their crystalline form. There is always a tendency for the glassy materials to recrystallize into the stable crystalline form. In addition, due to their higher energy state, amorphous compounds have higher chemical reactivity.

Owing to technical difficulty in stabilizing the amorphous form, particularly for small organic molecules, only a limited number of amorphous pharmaceutical materials are available on the market. In the European Pharmacopoeia, more than 35 materials (both active ingredients and excipients) are described as being amorphous. There are five in the United States Pharmacopoeia and over 25 different dosage forms in the Physicians’ Desk Reference that contain amorphous drug substances, including antibiotics, anticoagulants, antiinflammatory agents, analgesics, hormones and preparations for both internal and external uses.

Most of the commercially available dry powder inhalation formulations employ stable crystalline polymorphs, such as salmeterol xinafoate and fluticasone, and sometimes hydrates, such as pranlukast hydrate.

Drug products (or dosage forms) may undergo changes in technological, physicochemical or biopharmaceutical properties due to polymorphic transformation which can be induced by mechanical or heat treatment or by a change in environmental conditions, e.g., relative humidity, solvents, etc. Polymorphic transformation can also occur in a number of pharmaceutical manufacturing and quality control processes, including milling, grinding, tableting, suspension preparation, granulation, dissolution, stability testing, spray drying, freeze-drying, and preparation of adsorbates or complexes. Unforeseen changes of solid state properties can pose serious problems with regard to patent protection, process development and product specification in pharmaceutical industry. Thus, a better understanding and tighter control of solid-state behavior of drugs is crucial to the development of DPI formulations.

5. Technologies for producing drug particles for dry powder inhalation formulations

Apart from solid state properties, the particle size distribution of drug powders also plays a determinant role in DPI formulations. The respirable fraction is defined by the American Conference of Governmental Industrial Hygienists (ACGIH) as the fraction of aerosolised dose in an inhalation formulation surviving the filtration and impaction mechanism of the nasopharynx. Respirable fractions of particles with different aerodynamic diameters are shown in Fig. 3.

Particles greater than about 10 μm have a respirable fraction of almost zero and deposit predominantly in the upper airways (i.e., throat and trachea) by inertial impaction. Moderate size particle can settle out from the airstream under gravitational influence. Submicron particles deposit as a result of Brownian movement mainly in the lower airways (bronchial and alveolar regions). Particles in DPI formulations should be engineered to about 5 μm or less in diameter for maximizing the deposition in the transitional and respiratory zones of the lung. Discussed below are some current powder production technologies that are potentially useful for generating drug particles within the respirable range (1-5 μm).

5.1 Micronisation

Conventionally, drug powders formulated for the inhalation route are produced by batch crystallization from a suitable solvent followed by micronization to the appropriate particle size range (1-5 μm) for deep lung delivery.

It is obvious that a substantial amount of energy is used to process the substance, which may result in either a polymorphic conversion or the generation of...
an amorphous substance. Polymorphic transformation of drugs has been widely reported, e.g., l-osetil, chloramphenicol palmitate and phenylbutazone, to name a few. Generation of amorphous domains is almost unavoidable during micronization, and the extent of amorphization is highly material dependent. As regulatory authorities worldwide impose more stringent requirements in polymorph control, micronization may not be a desirable powder production method if the solid state chemistry of drug is changed significantly during the process. Therefore, a number of single-step crystallization methods, such as spray-drying and supercritical fluid crystallization, are being investigated for their applicability in powder production for DPI formulations.

5.2 Spray-Drying

Spray drying is a one-step process that converts a liquid feed into a dried particulate form via the following stages: (a) atomization of the feed solution to form a spray; (b) spray-air contact; (c) drying of the spray; and (d) separation of the dried product from the gas stream. The heating and drying of the droplets are usually performed in a chamber to which a stream of hot dry air is admitted in a co-current (i.e., in the same direction as spray) or counter-current (i.e., in the opposite direction to spray) manner. Spray drying has been used to produce solid drug particles for inhalation. The resulting materials are usually amorphous in nature. Since the drying is normally accomplished at elevated temperatures inside the drying chamber, chemical degradation and accompanying loss of biological activity could be a problem with thermolabile compounds, for which low-temperature drying or the alternative freeze spray drying may be considered. Examples of spray-dried pharmaceutical materials are insulin, salbutamol sulphate, sodium cromoglycate, formoterol fumarate, and budesonide.

Recently, drug particles with improved pulmonary delivery have been developed using specially formulated feed solutions for the spray-drying process. Corrugated bovine serum albumin powders thus produced display better aerosol performance than spherical particles produced under similar conditions but at higher atomizing pressure. It was concluded that the surface asperities of the corrugated particles could lower the area of contact between particles, and thus reduce the particle cohesiveness. Production of large hollow porous particles with improved aerosol performance by spray drying has also been reported for albuterol, estradiol and insulin. These spray dried samples have high respirable fractions, ranging from 49% to 92%, depending on the measurement techniques.

Spray-dried hollow porous particles based on similar concept have been commercialized as PulmoSphere powder. This system has been tested with cromolyn sodium, albuterol sulfate and formoterol fumarate, and they all show improved physical stability, content uniformity and aerosolization efficiency. Clinical data also demonstrated that delivery of spray-dried budesonide PulmoSphere powder is more efficient and reproducible than that of the micronized drug from passive DPIs. Interestingly, it is suitable not only for indirect systemic delivery of drug molecules via the lungs but also for more efficient and reproducible direct delivery of the drug to the lungs from passive DPIs.

Co-spraying with additives has also been explored to improve the delivery of antiasthmatic drugs to the lung, e.g., salbutamol sulphate with L-leucine in DPI formulations.

5.2.1 Control of physical forms by spray-drying processing

The application of spray drying to generate amorphous materials is well established. The technique has been employed to produce a wide range of spray-dried materials, including enzymes (e.g., trypsin, protease, lipase), antibiotics (e.g., sulphathiazole, aureomycin, streptomycin), blood serum, plasma substitute (e.g., dextran), vitamins (e.g., brewers' yeast, vitamins A/D) and pharmaceutical gums (e.g., acacia, tragacanth, sodium alginate). Extensive research has been conducted to exploit the advantageous aspects of amorphous drug materials, e.g., salbutamol sulphate, paclitaxel, tolbutamide, clarithromycin, ursodeoxycholic acid, lactose and ketoconazole.

Spray drying, an extremely rapid particle formation process, can be used to control the polymorphic forms of pharmaceuticals, provided that the operating parameters are carefully optimized. For instance, polymorphic forms (A, B and C) of abecarnil, a β-carboline derivative and a partial agonist of CNS benzodiazepine receptor, can be produced by spray drying using different solvents in the feed solutions. PXRD and DSC data showed that the resulting polymorphs are free of amorphous regions.

The pH of the feed solution has also been shown to exert a significant effect on the polymorphic forms of glycine produced by spray drying. α-Glycine was crystallized from solutions without pH adjustment.
while \( \gamma \)-glycine was the preferred polymorph formed at pH 4.0 and 8.0. The phenomenon has been attributed to the pH effect on the dimeric growth unit of \( \alpha \)-glycine\(^{45} \). Different salt forms, such as glycine HCl and diglycine HCl, can also be generated by spray drying using low pH solutions and different inlet temperatures\(^{49} \). The formation of polymorphs during spray drying has also been demonstrated for tolbutamide (polymorph IV)\(^{46} \).

5.3 Supercritical Fluid Crystallization

In recent years, supercritical fluid crystallization (SFC) technologies have gained increasing attention in the pharmaceutical industry due to their capability and versatility of producing micro-fine particles to predetermined specifications. Supercritical fluids (SFs) are those gases and liquid at temperatures and pressures above their critical points (\( T_c \) - critical temperature; \( P_c \) - critical pressure). In Fig. 4, the critical point is located at the upper end of the liquid / gas curves, and the phase area in excess of this point is the SF region. In this region, the SF exists as a single phase with several advantageous characteristics of both liquid and gas. SFs have density values that afford appreciable solvation power. In addition, the viscosity of solutes is lower in SFs than in liquids while the reverse is true for the diffusivity of solutes, which facilitates mass transfer. More importantly, SFs are highly compressible, particularly near the critical point, and thus their density and solvation power can be carefully controlled by slight adjustment of temperature or pressure.

Of all the gases available for use as SFs in industry, carbon dioxide is the most widely used one because of its low critical temperature (31.1°C), which makes it particularly suitable for heat sensitive materials, such as biologicals. In addition, it is non-flammable, non-toxic, inexpensive, recyclable and environment friendly.

The use of SFs to process pharmaceutical materials has proved to be a cost-efficient approach in generating high purity, micron-sized particles with defined morphology in a single-step operation\(^{47-49} \). SFs, by virtue of their attractive physical properties such as variable density and transport properties such as viscosity and diffusivity, and the relative ease by which these properties can be manipulated with temperature and pressure have created tremendous formulation opportunities for engineering drug particles with specific biological applications.

Extensive literature and patent surveys of various particle designs using supercritical fluids have been reported\(^{46, 50} \). A number of literature reviews are also available\(^{51-52} \). Broadly speaking, supercritical fluid crystallization technologies can be divided into two categories: 1. precipitation from supercritical solutions, e.g. Rapid Expansion of Supercritical Solution (RESS); 2. precipitation using SFs as non-solvents or antisolvents, e.g., Gas AntiSolvent (GAS), Supercritical AntiSolvent (SAS), Precipitation with Compressed Antisolvents (PCA), Aerosol Spray Extraction System (ASES), Solution Enhanced Dispersion by Supercritical fluids (SEDS\(^{75} \)).

5.3.1 Precipitation from supercritical solutions

Diagrammatic representation of Rapid Expansion of Supercritical Solution (RESS) process is shown in Fig. 5. The solute is first dissolved in SF to form a solution, which is then allowed to undergo expansion through an orifice to create extremely high supersaturation for effecting homogeneous nucleation and subsequent particle formation in the precipitation unit. It relies on the fact that solvent strength can be reduced drastically by decreasing the SF density through the rapid expansion of the fluid. Processing equipment requires a source of SF, which passes through an extractor unit to a restricted orifice positioned in a particle collection/precipitation vessel held at a lower temperature and pressure (often ambient) than the extractor unit. Primary factors influencing the particle properties include solute solubility in SF, dimensions of orifice (expansion device), expansion time scale, operating pressure/temperature in precipitator, agglomeration during SF expansion and the subsequent phase process path. Examples of materials processed by RESS include griseofulvin\(^{50} \) and salicylic acid\(^{54} \).

RESS is the technology that has been rigorously investigated. Debenedetti and his coworkers have
reported several theoretical works in relating particle properties to the RESS processing conditions\(^{55,59}\). A number of mathematical simulations and models relating to particle formation in the RESS process have also been published\(^{60,61}\).

### 5.3.2 Precipitation using supercritical fluids as non-solvents or antisolvents

These methods utilize a similar concept to the use of antisolvents in traditional solvent-based crystallization processes. The relatively low solubilities of drug compounds in unmodified carbon dioxide are exploited in this process wherein the solute of interest (a drug, a polymer, or both) is dissolved in a conventional solvent to form a solution\(^{51}\). The preferred ternary phase behaviour is such that the solute is virtually insoluble in dense carbon dioxide while the solvent is completely miscible with dense carbon dioxide at the recrystallization temperature and pressure\(^{51}\). The solute is recrystallized from solution in one of the three ways discussed below.

In the first method, the volume of the solution containing the solute of interest is expanded several fold by mixing with dense carbon dioxide in a vessel. Since the expanded carbon dioxide solvent has a lower solvent strength than the pure solvent, the mixture becomes supersaturated, forcing the solute to precipitate or crystallize as microparticles. This process is termed Gas AntiSolvent (GAS) recrystallization\(^{62}\). Schematic diagram of the GAS process is shown in Fig. 5. GAS was originally applied to nitroguanidine, an explosive, for which conventional comminution to reduce particle size is considered not feasible\(^{59}\). The GAS process has been applied to a number of pharmaceutical materials, including hyaluronic acid ethyl ester / protein\(^{63}\), sodium cromoglycate\(^{64}\) and lobenzarit\(^{65}\).

The second method involves spraying the solution through a nozzle as fine droplets into compressed carbon dioxide. A schematic diagram illustrating the technique is shown in Fig. 5. This process is commonly named 'Precipitation with Compressed Antisolvent' (PCA) technique and employs either organic solvent or a supercritical fluid as the antisolvent\(^{66}\). Examples of PCA processed materials are indomethacin\(^{67}\), methylprednisolone acetate and hydrocortisone acetate\(^{68}\). When a supercritical fluid is used as antisolvent, the spray process is termed 'Supercritical AntiSolvent' (SAS) process or 'Aerosol Spray Extraction System' (ASES)\(^{51}\). It has been postulated that microparticles formation results from gas phase nucleation and growth within the expanding plume, rather than nucleation within discrete liquid droplets\(^{69}\).

Examples of SAS-processed drug materials are salbutamol sulphate\(^{70}\) and griseofulvin\(^{71}\) and materials prepared by ASES process include lysozyme\(^{72}\), fluticasone\(^{73}\) and polylactide/hyoscine butylbromide\(^{74}\).

The third method, known as 'Solution Enhanced Dispersion by Supercritical Fluids’ (SEDS)\(^{75}\), utilizes a coaxial nozzle design with a mixing chamber. The arrangement provides a means whereby the drug in organic solvent solution interacts and mixes with the SF antisolvent in the mixing chamber of the nozzle prior to dispersion via a restricted orifice into a particle-formation vessel\(^{75}\). High mass transfer rates are achieved with a high ratio of SF to solvent, and high velocity of the SF facilitates break up of solution feed\(^{75}\).

In a single step operation, the SEDS\(^{75}\) technique has been demonstrated to possess the ability to produce micron-sized particles which are solvent-free, crystalline and within a narrow size range, indicat-
...that the crystal form can be controlled simply by varying the processing parameters. A wide range of pharmaceutical materials have been prepared as micron and submicron particles using the SEDS\textsuperscript{TM} process, such as lactose\textsuperscript{76}, nicotinic acid\textsuperscript{77} and paracetamol\textsuperscript{78}.

5.3.3 Control of physical forms by supercritical fluid crystallization

The potential applications of SFC technologies in the controlled production of particular physical forms of pharmaceutical materials have attracted considerable commercial and academic interests in recent years. Although existing publications in this field are relatively few and have limited scope, they can serve as a useful lead and guide to more elaborate and extensive studies in the future.

(1) Polymorphs

Fluticasone propionate exists in two polymorphic forms (I and II). Conventional crystallization and standard spray drying techniques readily yield form I. Form II, obtainable only by SFC (e.g. SEDS\textsuperscript{TM} technique), has completely different PXRD pattern from that of form I\textsuperscript{24,79}. By fine-tuning the operating variables, different proportions of forms I and II can be produced in a controlled manner. In addition, the supercritically-processed form II of fluticasone propionate has lower dynamic bulk density, higher fluidisability and better flow properties than the conventionally prepared form I sample, both before and after micronisation.

Three crystal forms (two polymorphs and one hydrate) of an oxazolidone antimicrobial, RWJ-337813, could be prepared by means of the SEDS\textsuperscript{TM} technique\textsuperscript{80}. Forms A and B are anhydrous and are monotropic to each other, with A being the stable form at ambient conditions. Form C is a hemi-hydrate. All the three crystal forms of RWJ-337813 exhibit high physical purity and high chemical integrity.

Chlorpropamide polymorphs can also be produced by the RESS process utilizing supercritical carbon dioxide (scCO\textsubscript{2}) as the recrystallizing solvent\textsuperscript{81}. Chlorpropamide is available commercially as polymorph A (mp 129.5\degree C), and its metastable polymorph C (mp 122.5\degree C) could be prepared by recrystallization from scCO\textsubscript{2}.

(2) Hydrates

Lactose monohydrate, a carrier excipient commonly used in dry powder inhalation formulation, has been prepared by SFC. When methanol or ethanol was employed as a cosolvent, processing of lactose by the SEDS\textsuperscript{TM} technique afforded a mixture of the two anomic forms $\alpha$ and $\beta$ of lactose\textsuperscript{76}. This may be explained by the existence of an anomeric equilibrium between lactose monohydrate and anhydrous lactose resulting from partial conversion of the lactose monohydrate in solution.

(3) Amorphous forms

SAS processing of tetracycline resulted in an amorphous material\textsuperscript{82}. The observation has been attributed to an extremely rapid precipitation process, which is typical of the SAS technique. Amorphous maltose and trehalose could also be prepared by processing maltose monohydrate and $\alpha,\alpha$-trehalose dihydrate using the SEDS\textsuperscript{TM} technique\textsuperscript{83}. However, using similar technique and operating conditions, lactose and sucrose were obtained as crystalline materials. This suggests that the tendency to form amorphous materials is highly material dependent.

5.3.4 Influence of operating variables in supercritical fluid crystallization on crystal forms produced

While fundamental thermodynamic and kinetic principles constitute the basis for the efficient design and operation of any crystallization process, very few studies have specifically considered how these principles can be utilized to control or optimize material processing in supercritical fluids at elevated pressures. Most of the reported SFC studies focus on the influence of operating parameters on material properties. Though not explicitly stated, a change in any of these parameters represents a change in the crystallization conditions in a thermodynamic and/or kinetic sense. For instance, pressure and temperature are representative factors in thermodynamics while flow rate of drug solution and supercritical fluid carries an important element in kinetics. It must be noted that most of the reported SFC works are not the result of well-controlled factorial design, and they often involve concurrent changes of more than one operating variable for individual crystallization experiment. Consequently, it would not always be possible to assess and explain the contribution of each operating parameter in relation to the others based on the available literature data. Nevertheless, gross generalization can still be made with regard to the material formation under defined operating SFC conditions.

Table 1 summarizes the operating parameters (temperature, pressure, solvent choice, flow rates of drug solution and supercritical fluid) used for processing specific crystal forms of various drug materials and their possible control mechanisms (i.e., thermodynamics or kinetics). The results clearly reflect...
| Compound | Operating Conditions | Operating Variables | Physical Forms | Possible control mechanism |
|----------|----------------------|---------------------|---------------|---------------------------|
| **Influence of temperature** | | | | |
| Flunisolide (84) | Flow rate of scCO₂: 9:25 ml/min | Drug solvent: Acetone | I + III | T & K |
| | Flow rate of drug solution: 0.3 ml/min | Temperature: 80°C | III | T & K |
| | Pressure: 100 bar | Temperature: 60°C | III | T & K |
| | | Temperature: 40°C | IV | T & K |
| | | Drug solvent: Methanol | | T & K |
| | | Temperature: 80°C | | T & K |
| | | Temperature: 60°C | | T & K |
| | | Temperature: 40°C | | No products |
| Salmeterol (83) | Pressure: 200 bar | Operating temperatures: 40 – 65°C | I | T |
| Xinafoate | Drug solution: 4.5% SX in methanol | 70 – 90°C | II | T |
| | Drug solution flow rate: 2.0 ml/min | | I & II | T |
| **Influence of pressure** | | | | |
| Salmeterol (83) | Pressure: 150 bar | Operating temperatures: 50 – 100°C | I | T |
| Xinafoate | Drug solution: 4.5% SX in methanol | 150 – 250°C | II | T |
| | Drug solution flow rate: 2.0 ml/min | | I & II | T |
| **Influence of solvent choice** | | | | |
| Fomoterol fumarate (86) | Flow rate of scCO₂: 18.0 ml/min | 2.0% (w/v) of drug in 99:1 methanol-water mixtures pumped at 0.3ml/min | Totally amorphous formoterol fumarate | K |
| | Temperature: 40°C | 2.0% (w/v) of drug in methanol pumped at 0.3ml/min; Totally water-saturated CO₂ flushed through the particle-forming vessel at the end of the run, followed by a rinsing period where dry CO₂ equivalent to two volumes of the vessel | Crystalline formoterol fumarate dihydrate | K |
| | Pressure: 150 bar | | | |
| Flunisolide (84) | Flow rate of CO₂: 9-25 ml/min | Drug solvent: Acetone | I + III (80°C) | T & K |
| | Flow rate of drug solution: 0.3 ml/min | Drug solvent: Methanol | III (60 and 40°C) | T & K |
| | Pressure: 100 bar | | IV (80°C) | T & K |
| | | | III + IV (60°C) | T & K |
| | | | | Unprocessed |
| Stavudine (87) | Flow rate of scCO₂: 9 ml/min | Drug solvent: Dichloromethane | I | T |
| | Flow rate of drug solution: 0.2 ml/min | Temperature: 35°C | II | T |
| | Pressure: 120 bar | 10% water in isopropanolol | I & II | K |
| | | 5% water in isopropanolol | II | K |
| Carbamazepine (88) | Flow rate of scCO₂: 0.5ml/min | Drug solvent: Methanol | I & II | T & K |
| | Flow rate of drug solution: 0.5ml/min | Temperature: 40°C | a | T & K |
| | Pressure: 150 bar | Temperature: 60°C | a and γ | T & K |
| Fluicasone propionate (79) | Drug concentration: 0.3% (w/v) | Drug solvent: Methanol | a | T & K |
| | Pressure: 100 bar | Temperature: 60°C | a and γ | T & K |
| | Solvent utilized in drug solution: | Temperature: 40°C | | |
| | Acetonitrile | Solvent: 40% | | |
| | Acetone | Solution flow rate: 2.4 ml/min | | |
| | Ethyl acetate | Solvent: Methanol / Water | | |
| | Methanol | Temperature: 45°C | | |
| | Temperature: 60°C | Temperature: 40°C | | |
| | Flow ratio of drug solution and CO₂: 0.043 | Temperature: 40°C | | |
| | Temperature: 50°C | Solution flow rate: 2.4 ml/min | | |
| | Temperature: 60°C | Solvent: Methanol / Water | | |
| | Flow rate of CO₂: 10ml/min | Solvent: Pure water | | |
| | Flow rate of drug solution: 0.2 – 25.6 ml/min | Temperature: 40°C | | |
| | CO₂ flow rate: 18.0 ml/min | Temperature: 60°C | | |
| Terbutaline sulphate (89) | Carbon dioxide: 18.0 ml/min | Solution flow rate: 2.4 ml/min | | |
| | Solvent: Acetone | Solvent: Methanol | | |
| | Temperature: 50°C; Pressure: 150 bar | Solution flow rate: 0.2 ml/min | Amorphous | T & K |
| | Solution flow rate: 2.4 ml/min; Solvent: Methanol / Water | Solvent: Pure water | Hydrate | T & K |
| | Solvent: Methanol | Temperature: 45°C; Pressure: 250 bar | A | T & K |
| **Influence of flow rate of drug solution and supercritical fluid** | | | | |
| Sulfathiazole (90) | Pressure: 200 bar | Drug solvent: Acetone | I + Amorphous, I + IV and IV produced at different temperatures and flow ratios | K |
| | Temperatures for crystallization: 0 – 120°C | Drug solution conc.: 1% w/w | | |
| | Flow rate of CO₂: 10ml/min | Drug solvent: Methanol | I, I, III, III + IV and IV resulted at different temperatures and flow ratios | K |
| | Flow rate of drug solution: 0.2 – 25.6 ml/min | Drug solution conc.: 1.5% w/w | | |

Remarks: T = Thermodynamically controlled mechanism; K = Kinetically controlled mechanism
the ability of SFC in exerting precise control over the physical forms of the materials produced.

6. Conclusion

The ability of spray drying and SFC to regulate the crystal form and associated material properties has been clearly demonstrated with a number of pharmaceutical materials. In most cases, the relative composition of the physical forms produced can be precisely controlled by varying the operating parameters. While both particle production technologies appear to be comparable in terms of their capability of generating ultrafine, free flowing, non-cohesive, dispersible particles with high respirable fraction in a single step operation, spray drying processing tends to afford amorphous materials, and is apparently less effective for controlling the crystallinity of the materials produced. Additionally, SFC offers the unique flexibility of manipulating an extra operating variable, i.e. pressure/density of the supercritical fluids, which allows a wider range of crystallization conditions to be tested for the production of specific materials or crystal forms.

Despite the aforementioned advantages of SFC techniques over spray drying processing, there has not been any SFC-based inhalation dosage forms marketed to date while a few spray-dried DPI products are already available commercially. The lack of breakthrough with DPI formulation development utilizing SFC appears to stem from an insufficient understanding of the SFC process and the material-dependent limitations of individual SFC techniques. However, as more is known about SFC and the associated techniques are further refined, and as more pharmaceutical materials are being tested for formulation potential with these technologies, it will not be long before certain SFC-based products finally make their way through the development hurdle to the market.

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