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Design of micron-sized salt particles by ethanol vapour drying

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ABSTRACT

Antisolvent vapour drying precipitation is a new spray drying technique in which each droplet behaves like an individual 'precipitation vessel'. As the aqueous droplet absorbs the convective ethanol vapour, the initially dissolved solutes precipitates out as ultrafine particles within the droplet. This work sought to examine the feasibility of applying the antisolvent vapour drying method to produce salt particles. Using the modified single droplet drying rig, spherical magnesium sulphate and iron sulphate particles <10 μm were produced from relative large droplets of 1–2 mm in diameter. The fine particles produced exhibited rough gravel-like surface morphology. Mixtures of iron sulphate and vitamin C at different proportions were tested and gravel-like iron sulphate particles within a bulk vitamin C matrix were produced. Rough gravel-like surface morphology was also observed for sodium chloride particles. Lactose was then incorporated into the formulation to assess if spherical ultrafine particles of a lactose-salt matrix can be produced. The precipitated particles, however, resembled the smooth ultrafine amorphous particles of lactose without distinct indication on the location of the salt material.

1. Introduction

The spray drying process converts droplets into particles by dehydration with hot air. When spraying droplets with initially fully dissolved solids, the particles produced conventionally follow the one-droplet-to-one-particle approach where one droplet will dehydrate and become one particle. This imposes constraints in producing smaller particles as smaller initial droplets are then required. Atomizing a liquid feed to such small droplets very often compromises the product throughput of the process: lower liquid feed rate is often required, coupled with very high atomization pressure or potential [1]. Alternatively, liquid feed with very low initial solute concentration can be used which effectively also reduces the powder production throughput.

For certain medical applications in which submicron particles are required, this limitation are further compounded as atomized droplet sizes in the order of less than 10 μm are required [2,3]. This can be elucidated by examining the perfect shrinkage behaviour of a droplet mathematically represented below,

$$r_{\substack{final\\particle}} = \sqrt[3]{\frac{\chi r^3_{initialdroplet}\rho_{initialdroplet}}{\rho_{finalparticle}}} \quad (1)$$

The equation above was derived considering the conservation of mass of the solute in the initial droplet throughout the drying process, where ρ is the density, χ is the initial solute concentration by mass fraction and r is the radius. Consider a possible case in point spray drying lactose as a pharmaceutical excipient: initial solute concentration of 5–15%, water density of 1.0 g cm^{-3} and lactose density of 1.5 g cm^{-3}. It can be computed that within the range of the initial lactose concentration considered, an initial droplet size of approximately 2–3 μm will be required to produce submicron particles. Although droplets in this size range can be produced via specialized atomizers such as those utilizing ultrasonic waves, these nozzles are usually associated with relatively low flow rates [4,5].

A new concept called the antisolvent vapour precipitation approach was recently introduced to overcome this limiting feature of spray drying [6]. The premise of the approach is to produce hundreds of particles within each single droplet. This approach replaces the conventional hot air with ethanol vapour. As the aqueous droplet absorbs the convective ethanol vapour, the initially dissolved solutes precipitate out as ultrafine particles within the droplet. Each droplet then behaves like an individual 'precipitation vessel'. As a result, the size of the final particles is then not directly determined by the size of the initial droplet size. This can potentially provide a possibly wider window in operating the atomization process without the need to produce fine droplets in order to produce ultrafine particles.

This new concept has been tested and is applicable for lactose, whey protein and maltodextrin in producing uniform ultrafine particles [7–10]. In particular, amorphous ultrafine lactose particles were produced in addition to ultrafine precipitated crystals. The approach has yet to be assessed for producing salt or mineral salt particles. In essence, this would present a different class of materials, as they tend to exhibit

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relatively different rates of crystallization or precipitation when compared to the lactose, whey protein or maltodextrin materials previously tested. Salts or mineral salt particles will have various important food and pharmaceutical applications. There has been on-going work to produce very fine sodium chloride (table salt) particles in order to enhance the flavouring of food but at the same time minimize the salt consumption [21]. Other examples are health supplements such as iron sulphate and calcium carbonate salts [22,23]; often produced in the tablet form. In general, smaller particle sizes will enhance the dissolution rate of the salt particles (and vice versa) and for health supplements, this will increase the bioavailability of the material. Therefore, this work aimed to assess on the applicability of the antisolvent vapour precipitation approach to produce ultrafine salt particles from relatively large droplet.

2. Materials and methods

2.1. Sample preparation

Four different salt solutions were tested in this work: iron (II) sulphate (ferrous sulphate) (Sigma), magnesium sulphate (Sigma), sodium chloride (Merck), calcium carbonate (Merck) and lactose (Sigma) solution. The solutions were prepared by dissolving the initial as purchased crystalline particles with dionized water resulting in 2–4 wt% solid solutions. All the prepared solutions used, apart from the calcium carbonate solution, was visually inspected to be clear, delineating complete dissolution of the solute, prior to the start of the experiments. For the calcium carbonate solutions, due to its low solubility in water (Table 1), the starting solution consisted of a suspension of finely nucleated solids, which gave it a slightly cloudy appearance. Therefore, the calcium carbonate solution was used to investigate how the antisolvent vapour precipitation technique affects the final particle morphology of particles formed form an initial suspension; this aspect has not been investigated before. In this work, lactose and vitamin C were further evaluated on top of the salt materials. These materials are common excipients used in the production of therapeutic products. In commercially available Iron sulphate dietary supplements, vitamin C is usually incorporated into the final product to enhance the absorption rate of iron into the body.

2.2. Antisolvent vapour single droplet drying

The same rig used by Mansouri et al. [7,9] was employed in this work. Procedures in using the single droplet glass filament drying technique is described elsewhere [15]. In brief, a single droplet (initial volume of 1 μL) was suspended by a glass-filament in a static manner within a drying chamber. Single droplets were generated using a 5 μL gas chromatograph micro syringe (*Part# 001, 100, SGE Analytical Science Pty Ltd., Australia*). Continuous stream of nitrogen gas laden with ethanol vapour was then allowed to convectively contact the droplet. This simultaneously removes water from the droplet and allowed ethanol to be absorbed into the droplet. After the initial ethanol absorption phase, the droplet will then experience simultaneous evaporation of the water and ethanol absorbed by the droplet leading to the formation of a solid particle. For this work, for each run ethanol relative humidity in the nitrogen stream was fixed at approximately 95%. Each experimental took about 30 min to allow sufficient dehydration of the particles. Nitrogen gas used as the drying carrier gas for the ethanol vapour, which was set at 0.3 $m^3\ hr.^{-1}$ and was bubbled through conical flasks partially filled with ethanol. Pure ethanol was used in the bubbling process to generate the ethanol humidity (Chemistry Store, Monash University).

The ethanol humidity in the resultant nitrogen flow was determined by dry and wet bulb measurements with thermometers (one of them wetted with ethanol with a wick). The ethanol laden nitrogen stream is then passed through a water bath set at 70 °C resulting in the nitrogen entering the drying chamber at approximately 35 °C. In experimental runs without ethanol vapour (nitrogen only), the flasks were then left empty. A video camera fitted with magnification lenses were used to provide continuous monitoring of the drying behaviour of the droplet. Dried samples were collected at the end of each experimental runs by scraping the materials off from the glass knob.

The experimental work can be distinguished into two main parts; first there was drying of the salt solutions with only nitrogen. This was aimed as control runs to illustrate the morphology formed under the conventional drying process. The second part involved incorporating antisolvent vapour in the drying process by using the nitrogen laden with ethanol vapour to produce ultrafine particles making comparison with the conventional nitrogen only drying.

Table 1
Solubility of salts in water at 25 °C (gram/100 g).

Salt	Solubility (g/100 g water)	Source
Magnesium sulphate, 7H2O	39	Sigma-Aldrich
Iron (II) sulphate, 7H2O	29.51	Seidell [18]
Sodium chloride	36	Burgess [16]
Calcium carbonate	0.0013	Rohleder &Kroker [17]

2.3. Particles morphology and size

Scanning electron microscopy of the dried samples was undertaken using the Phenom Benchtop SEM unit (FEI Company). Particle size analysis was undertaken by measuring the diameter of the precipitated microspheres (100 particles for each particles size distribution) from the SEM pictures using the ImageJ® freeware and also by manual distribution.

3. Results and discussions

3.1. Precipitation behaviour in droplets with single solute component

Control nitrogen only experiments with sodium chloride and iron sulphate produced solid morphologies typical of spray drying (Fig. 1b and c). When the particles were crushed and viewed under SEM, chunky morphology was observed. The calcium carbonate solution, however, resulted in an agglomerate of cubic like crystals (Fig. 1a). Observations with the optical microscope (40× magnification) revealed that the agglomerate consisted of cubic like crystals in the size range of 20–150 μm (Fig. 3e). This was expected, as the solution was initially a suspension of nucleated fine solid particles. During the dehydration process, any initially soluble calcium carbonate would have a higher tendency to contribute towards the growth of the suspended 'seeds' in contrast to forming a continuous solid like those observed for the sodium chloride and iron sulphate.

When ethanol vapour was introduced into the convective medium to dehydrate the pure iron sulphate droplet, instead of a chunky morphology, individual gravel-like particles were produced. It is noteworthy that the particles shown in Fig. 2b were produced from one single droplet of approximately 1000 μm in diameter. From Eq. (1), if the droplet dehydrated into one particle, one would expect the final particle size to be in the order of 150 μm in diameter (taking an approximation of the upper limit density to be 3.0 g cm^{-3}). The distribution of the particles produced, however, is in the range of 0.4 to 2.0 μm (Fig. 3b). Very interesting is the gravel-like morphology of the particles, which could be an indication of the agglomeration of individually precipitated iron sulphate nucleus or particles.

With the positive outcome in producing discrete gravel-like spherical iron sulphate particles, further test was undertaken for magnesium sulphate particles. Magnesium sulphate is typically used in emergency asthmatic patients with severe bronchial constriction. Intravenous delivery of magnesium sulphate to the patient will act as a targeted muscle relaxant to dilate the bronchial tract [11]. It is still debatable if

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