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Original Research Paper

Squeezing out ultrafine hydrophobic and poor water-soluble drug particles with water vapour

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ABSTRACT

This short communication describes a scalable new method to produce ultrafine hydrophobic or poorly soluble drug particles. Ultrafine Vitamin D3, Aspirin and Ibuprofen particles in the submicron range were produced. The method is an extension of the antisolvent vapour precipitation technique which exposes a droplet to an antisolvent vapour with reference to the dissolved materials within the droplet. In this work, the drug material was dissolved in ethanol droplets and then exposed to a convective stream of water vapour. Absorption of the water vapour into the droplet resulted in the precipitation of the particles. The precipitated submicron particles showed good dispersion behaviour in water droplets. This work will form the basis for using spray dryers as high-throughput scalable micro-precipitators.

1. Introduction

Hydrophobic or poorly water-soluble drug properties can impede the effective delivery of these drugs into humans, and affect its subsequent absorption into the site of activity. A general industrial strategy to improve the dissolution rate of these drugs, which does not required addition of excipients or carriers, is to simply reduce the size of the drug particle [1,2]. This creates a larger surface area so that the particles are more exposed to the solvent enhancing the dissolution rate of the drugs and hence the apparent solubility. For such a purpose, the drug particles are typically reduced to the nanometer scale. There are numerous potential methods to produce such fine hydrophobic particles. Drug particle milling is a commonly method used to produce to produce nano-sized drug particles in the dry form or in suspensions. Mechanical energy can be provided by air jet, rotating media or even with high pressure homogenization [3]. The starting drug materials are typically relatively large crystallized or dried drug particles. Such a straightforward method has found application in the development of many drug materials [1,4]. In all of these top-down methods, however, high-level of mechanical shearing energy is required and some materials may not be susceptible to these forms of applied energy.

One bottom up approach is to use supercritical fluid micronization [5]. In this method, the hydrophobic or poorly soluble drug material is atomized into a supercritical fluid, typically carbon dioxide, and precipitates as nano drug particles. This technique has even been successfully used to produce protein-based drug particles. While the supercritical fluid approach has an advantage of not necessitating thermal treatment, it requires relatively high pressures, in the range of 80–200 bar. Such high pressure sometimes necessitates a batch or semi-batch operation, which can be limited to relatively small scale and have substantial capital cost implications. Another common method is to precipitate the drugs as nanocrystals with microfluidic devices [6,7]. The precipitation method is capable in producing fine and relatively uniform nano drug particles. However, scaling up such microfluidic devices involves a high degree of complexity and uncertainty in control which may inhibit economical throughputs.

The team in Monash University has recently developed a new antisolvent vapour precipitation technique to produce ultrafine particles [8–11]. This technique combines the concept of spray drying and antisolvent precipitation. The premise of the technique involves exposing a droplet to vapour which is an antisolvent to the dissolved solids within the droplet. Absorption of the antisolvent vapour into the droplet leads to change in the solubility and subsequent precipitation of the dissolved solids. With the subsequent removal of the solvent and antisolvent by convective dehydration, dry ultrafine particles were obtained; magnitudes smaller

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than what would be produced if the droplets were just dried by hot air alone. Ultrafine particles in the nano- and micro-range were produced for protein and lactose, respectively.

Experiments so far on this antisolvent vapour precipitation technique were limited to the precipitation of aqueous soluble materials, exposed to ethanol vapour as the antisolvent. It was hypothesized that, this concept should also be applicable in an inversed scenario: precipitating hydrophobic or poorly soluble drugs in ethanol droplets exposed to water vapour as the antisolvent. This can be viewed as analogous to a conventional precipitation process [6,7,12]. However, this new concept involves introducing the antisolvent (water) in the form of vapour into each micro precipitating droplet and it does not require a high pressure environment. The aim of this preliminary exploratory work was to examine this hypothesis and to provide a demonstration of concept feasibility in producing ultrafine hydrophobic and poorly soluble drug particles.

2. Materials and methods

2.1. Materials

Vitamin D3 (Cholecalciferol) (Sigma) was used as a model hydrophobic drug. Aspirin (acetylsalicylic acid) was used as poorly soluble drug model. Ibuprofen was used as a model for non-soluble drug (kind donation from BASF, Germany). These drug materials were dissolved in analytical grade ethanol (Chemistry Store, Monash University) made to solutions with 3 and 5 wt% concentration for the Vitamin D3 and the other materials, respectively.

2.2. Single droplet precipitation and drying

The antisolvent vapour precipitation experiments were carried out similar to that reported by Mansouri et al. [8,9] with slight modification replacing the convective ethanol vapour with water vapour. Water vapour was generated by bubbling nitrogen from a cylinder through a head of water filled in a conical flask. The water was filled to the same level for each experimental run. In order to maintain a consistent temperature, the water vapour laden nitrogen stream was passed through a water bath maintained at 70 °C. This heated water vapour laden nitrogen stream was then passed into the drying chamber in which a single 3 μL droplet of the drug solution was suspended from a glass filament. A scheduled drying was then adopted by introducing hot air at 70 °C after a determined period of exposure to the water vapour stream. The vapour water stream was then stopped with the introduction of the hot air. Control runs were undertaken using only dry nitrogen streams without any scheduled hot air. In these control runs, the water was removed in the conical flask. The technique used in the generation and suspension of the droplet is described in detail elsewhere [13]. Such an experimental technique mimics the convective mass loss (or gained in the current case) of a droplet atomized within a spray dryer. The drying behaviour was continuously monitored using a video recorder (Sony, HDR-CX350).

2.3. Single droplet dispersion test

Dispersion of the dried particle in an aqueous medium was assessed by hanging a water droplet of 2 μm onto the dried solidified particle. The dispersion behaviour was then continuously monitored using a video recorder (Sony, HDR-CX350).

2.4. Scanning electron micrograph analysis (SEM)

The dried particle, produced in runs separate from the dispersion test, was scraped off from the glass filament and fixed onto aluminum stubs with a double sided carbon tape. The samples were coated and scanned with a bench top Phenom lab scale SEM unit.

3. Results and discussion

3.1. Drying and precipitation behaviour

The drying behaviour of the controlled experiments with Vitamin D3 and Ibuprofen is illustrated in Fig. 1. For brevity, the drying behaviour of Aspirin was not included here as it is similar to that of Ibuprofen. Compared to the drying of aqueous lactose or protein droplets [8,9], the evaporation rate of the ethanol droplets with pure nitrogen is significantly faster at 60–180 s;

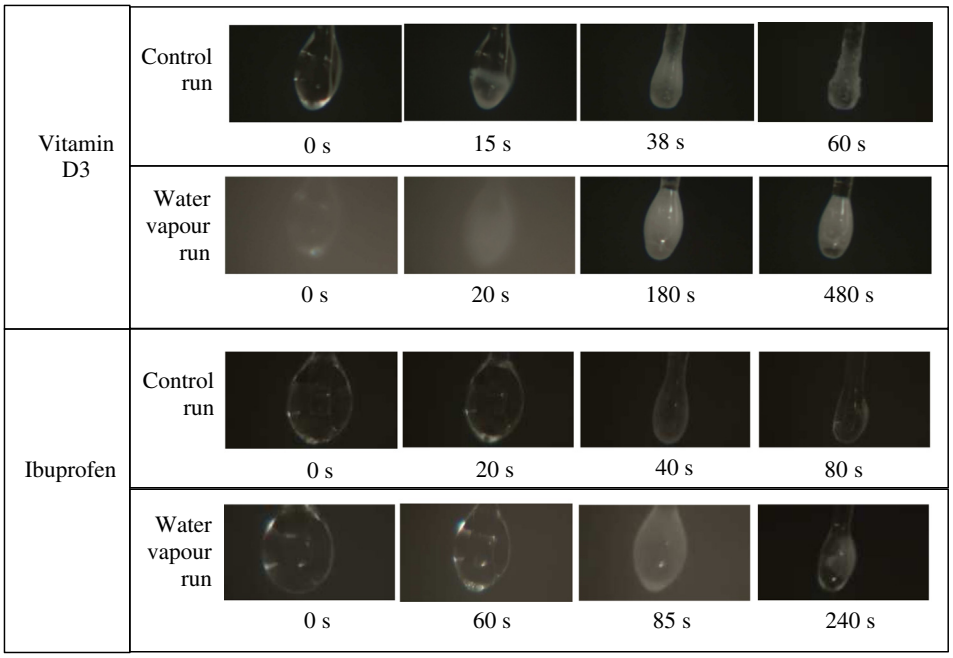

Fig. 1. Drying behaviour of the ethanol droplet containing hydrophobic or non-soluble drug material.