



Unveiling the mechanism of antisolvent vapour precipitation in producing ultrafine spherical particles



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ABSTRACT

Ultrafine spherical maltodextrin and maltose particles were successfully produced with the antisolvent vapour precipitation (AVP) technique. Comparison between the two materials confirmed that a key requirement for the process is in inhibiting crystallization of the material. The precipitation process consists of: (1) an initial phase separation forming an emulsion formation, (2) phase inversion and (3) finally a water-maltodextrin shrinkage phase which forms the spherical particles driven by interfacial surface tension. Dehydrating the droplet at different stages of the process resulted in various particle morphologies; porous, smooth, microsphere network and microspheres. Higher ethanol relative humidity, higher ethanol absolute humidity and lower initial weight concentration were found to favour the formation of amorphous microspherical particles upon drying.

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1. Introduction

Spray drying has received wide attention in the food [1] and pharmaceutical industry [2] and is widely used to produce solid products from a solution or suspension commercially. The technique of spray drying takes advantage of the rapid solvent evaporation from atomized droplets. The liquid stream is atomized into fine droplets in order to increase the surface area and to accelerate the heat transfer as well as the evaporation process when it is mixed with the drying gas in the drying chamber [3]. Many literatures can be found on the technique [4], application [5] and particle formation [6,7] of spray drying. In a conventional spray dryer, a single particle typically in the range of tens or hundreds of micron is produced from each atomized droplet. The final particle size of the particle is predominantly controlled by the size of the initial atomized droplet. In commercial applications, the product fluid is normally atomized into droplets with a range of sizes. The ability to produce uniform droplets with commercial nozzle or rotating atomizers is still a challenge. This inevitably leads to dried particles of varying sizes. In similar veins, another challenge which arises is in actually producing sufficiently fine droplet sizes to produce final dried particles in the sub-micron range. Although there are commercially available 'nano-scale' spray dryers [8], these units are mainly designed for lab scale applications [9] with relatively low flow rates.

Recently, a novel antisolvent vapour precipitation has been developed for intended application in spray dryers [10]. This approach, which incorporates ethanol vapour as the convective drying medium instead of hot air allows the production of large numbers of uniform microparticles from within a single droplet at normal atmospheric conditions [11,12]. The premise of the process is in allowing the aqueous droplets to absorb ethanol vapour. This new approach was firstly explored aqueous lactose droplets in which the absorption of ethanol reduced the solubility of the lactose; precipitating the lactose. As a result, the particles produced are not directly determined by the size of the initial droplet. Furthermore, relatively smaller particles are produced without the need to generate very fine initial droplets [10].

Surprisingly, in contrary to the conventional precipitation process, amorphous lactose microspheres were obtained. Scenario based analysis showed that the conventional supersaturation based mechanism which typically describes crystallization or precipitation processes might not be adequate to describe this phenomenon. Previous work has been done to elucidate the mechanism behind this observation. Further analysis revealed that a unique 'pinched off' mechanism, in which the lactose phase separates within the droplet shrinks and eventually forming very fine spherical particles due to surface tension, could be the driving force for the process [11]. A unique observation in the previous report is that the occurrence of any crystallization within the droplet, under certain operating condition, will negate the pinch off mechanism leading to relatively large crystalline particles. It was then proposed that a prerequisite in controlling the antisolvent vapour precipitation process to generate ultrafine particles is to firstly prevent

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crystallization of the solute in the presence of progressively increasing antisolvent within the droplet.

Therefore, it was hypothesized that dissolved polymeric materials might offer a higher potential to precipitate into the ultrafine uniform particles precipitate into as it does not exhibit strong crystallization behaviour. In the past experiments, disaccharide (lactose) was mainly investigated. There is a need to examine the feasibility of the antisolvent vapour process for polymeric materials.

Polymeric materials have many applications, as a large range of pharmaceutical and food products exist in the form of synthetic or natural polymers with varying chain length. Recently, studies have been done to extend its application to control the release of inhalable powders [13]. Polymers structure, molecular weight, linearity, intra- and intermolecular interactions determine its thermal, physical and mechanical properties [14]. These are crucial in producing cellulose-based polymers, hydrocolloids and particularly polymers for drug delivery applications. In the current work, maltodextrin was used as a model polymer, as it represents a mixture of amorphous saccharides with broad molecular weight distribution (i.e. varying chain length), with a wide range of application based on its hydrolyzed polymer chain length. Maltodextrin is also widely used in the food and pharmaceutical industry for functionalities such as dispersing aid, flavour carrier, bulking agent, viscosifier and fat replacer. It is also reported to enhance the production of different powder extracts through spray drying [15,16].

The present study examined the behaviour of maltodextrin under the ethanol AVP method and the particle structures obtained at different ethanol vapour absorption rate and initial weight concentration. Further experiments with different polymeric chain lengths coupled with an in-situ observation of the precipitation process shed more light to the fundamental observation of the AVP process.

2. Materials and method

2.1. Preparation of maltodextrin/maltose samples

Maltodextrins and maltose are products derived from acid and enzymatic hydrolysis of starch. The degree of hydrolysis is described in terms of their 'dextrose equivalent' (DE) value. The DE value is inversely proportional to the polymer chain length and hence, the molecular weight. Maltodextrin DE 10 (F03220, The Melbourne Food Ingredient Depot), maltodextrin DE 18 (F03380, The Melbourne Food Ingredient Depot) and maltose (M-5885, Sigma Chemical Company) solutions at concentrations of 2.5 wt.%, 5 wt.%, 10 wt.% and 15 wt.% were prepared by dissolving tapioca maltodextrin powder, maltodextrin powder and maltose hydrate grade 1 respectively in Mili-Q water.

2.2. Single droplet drying experiment

A detail explanation of the experimental set-up and working principle of the single droplet drying technique is provided by Lin and Chen [17]. This technique was further modified by Mansouri et al. to incorporate the AVP process into the single droplet drying [10]. Brief details are given here for completeness. The schematic diagram of the single droplet rig used in this experiment is shown in Fig. 1. A standard initial single droplet size of 1 μL was generated using a 5 μL gas chromatograph microsyringe (5FX, Part # 001100, SGE Analytical Science Pty Ltd, Australia) and suspended onto a glass filament positioned in the drying chamber using a separate transferring glass filament. When generating and transferring the droplet, a bypass barrier plate was used to divert the conditioned nitrogen-ethanol stream away, in order to minimize droplet evaporation before monitoring began. The bulk of the convective medium was supplied by compressed nitrogen, bubbled through two conical flasks filled with ethanol connected in series. The ethanol vapour and nitrogen convective mixture was pre-heated within a heating coil submerged in a water bath operating at 70 °C. It is important to note that the resultant ethanol vapour entering the chamber

was below 70 °C due to heat transfer limitations. Concentration of ethanol vapour was controlled by adjusting the volume (level) of ethanol in the conical flasks. Video monitoring was used to track and record the changes within the droplet with time during drying. The dried product was scraped onto a carbon stub for scanning electron microscopy (Phenom™ SEM) imaging and the sample was coated with gold/palladium (Sputter Coater Quorum SC77620).

2.3. Ethanol vapour experiment

The ethanol relative humidity (ERH) and ethanol absolute humidity (EAH) were determined by measuring the wet bulb and dry bulb temperature. Experiments were conducted over a range of 50%–100% (ERH) and 0.06–0.12 kg/kg db (EAH). These parameters were controlled by adjusting the volume of ethanol in the conical flasks. The wet bulb temperature was obtained by measuring the temperature of liquid ethanol absorbing through a wick with one end dipped into a pure liquid ethanol solution and the other end attached to the bulb of a thermometer. On the other hand, the dry bulb temperature was a measurement of the temperature of the ethanol-nitrogen gas mixture, which was done by allowing the flow of the gas mixture through a thermometer within a confined tube. Both measurements were conducted for approximately 15 min prior to the drying process in order to obtain a stable and accurate reading of the wet and dry bulb temperature. From a psychometric chart, the corresponding absolute humidity and relative humidity data were recorded.

2.4. Control experiment

The premise of the technique is in introducing ethanol into the droplet via the vapor absorption mechanism in a controlled manner. Therefore, as control experiments, it is important to gauge on the morphology of the particles attained if: (1) ethanol vapor was not used leaving only nitrogen as the convective drying medium and (2) liquid ethanol was added directly into the aqueous sample of the maltodextrin. The first control experiment was carried out by flowing nitrogen gas through empty conical flasks, directly heated by the water bath and into the drying chamber continuously for a similar drying time of 30 min. The second control experiment involved adding liquid ethanol gradually into the sample solution until precipitation occurred. The solution was sieved to obtain the precipitated products and left to dry in an oven overnight. Similarly, the products obtained were sent for SEM imaging.

3. Results

3.1. Control experiment using nitrogen gas

It is important to note that the usage of nitrogen gas as the drying medium is similar to drying with air due to the high proportion of nitrogen in air. We could observe the drying behaviour of the droplet throughout the drying process in Fig. 2(a). The size of the droplet decreased over time, the droplet turned cloudy gradually and solidification was observed. The droplet shrinkage was due to the convective drying by the flow of nitrogen gas in the chamber, which resulted in the evaporation of water from the droplet. The cloudiness of the droplet was due to the formation of solids within the droplet, as the dehydration process took place. The final particle morphology obtained under SEM was a chunk of discrete solids shown in Fig. 3(a), (i).

3.2. Control experiment using liquid ethanol

Instead of ethanol vapour, liquid ethanol was used to precipitate the sample solution. Fig. 3(a), (ii) shows the SEM image of the particles obtained, which have a smooth solid structure. This result is of great significance, as it indicates the degree of ethanol absorption into the system and the manner at which it occurred has a major influence on the

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