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# Lactose microparticle formation from finely atomised droplets

Sean Chew [a], Shahnaz Mansouri [a], Dimas Wardhana [a], Abdurrakhman Mukhyiddin [a], Nicolas Buchmann [b], Karen Hapgood [a], Xiao Dong Chen [a,c], Meng Wai Woo [a,*]

[a] Department of Chemical Engineering, Monash University, Clayton 3800, Victoria, Australia
[b] Department of Mechanical and Aerospace Engineering, Monash University, Clayton 3800, Victoria, Australia
[c] School of Chemical and Environmental Engineering College of Chemistry, Chemical Engineering and Material Science Soochow University, Jiangsu, PR China

## HIGHLIGHTS

- Lactose microspheres produced from atomised droplets via antisolvent vapour precipitation.
- Deeper understanding into the microsphere formation mechanism based on new structures obtained.
- Microspheres produced from atomised micron-sized droplets are in the sub-micron scale.

## ARTICLE INFO

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## ABSTRACT

The antisolvent vapour precipitation method has been proven to produce uniformly sized lactose microspheres from a single droplet (~1.2 mm diameter) at atmospheric pressure. These types of particles have potential applications in the pharmaceutical industry, especially due to their high solubility and dissolution rate. This article discusses the possibility of using antisolvent vapour precipitation for finely atomised droplets. Microspheres in the sub-micron scale (~0.4 μm diameter) have been produced, much smaller than those obtained from the single droplet method (~1.0 μm diameter). These particles were not affected by ethanol exposure time (up to 60 s) or drying temperature (up to 190 °C), though the structure was related to the absolute humidity of ethanol. We hypothesise a self-emulsified, two-phase system in the droplet could be the responsible for the formation of the porous and bicontinuous structure as an increase in the absolute humidity resulted in a shrinkage phenomenon which led to the microsphere formation.



## 1. Introduction

In pharmaceutical applications, the demand for micron-sized particles used in drug delivery systems is increasing. To achieve this, several techniques can be implemented in order to reduce the particle size and distribution. For example, micro-ball or air-jet milling can be used to achieve an average particle size to approximately 5 μm (Saleem and Smyth, 2010). The size distribution of bulk particles is reduced based on the principle that collision between particles imparts stress, resulting in fracture and breakup of the bulk particles into smaller ones (Saleem and Smyth, 2010; Yokoyama and Inoue, 2007). In micro-ball milling, the bulk powder is centrifugally rotated in a chamber with small metal balls which aid in the micronisation process (Bensebaa, 2013). Air jet milling, on the other hand, uses high air velocities to induce fracture on particles when they collide (Chamayou and Dodds, 2007).

Another technique commonly implemented to produce powders with smaller size distribution is spray drying. Widely used in the industry for its large production rates, spray drying involves atomising the feed solution into minute droplets, which increases the surface area to volume ratio. Consequent contact with convective air in the system allows for rapid solvent evaporation in the drying process (Boersen, 1990). The final particle size distribution is highly dependent on feed concentration, feed rate and type of solute (Broadhead et al., 1992). The size of droplets after atomisation directly influences the size of particles produced (Li et al., 2010).

Supercritical antisolvent (SAS) precipitation is also capable of producing monodispersed nanospherical particles. Extensive pilot scale work has been conducted (Reverchon, 1999; Reverchon et al., 2008a; Reverchon et al., 2008b) which shows the reproducibility of the results. SAS precipitation involves the exposure liquid solution to supercritical fluid (usually $CO_2$) which acts as the antisolvent.

* Corresponding author. Tel.: +613 9905 9344.
*E-mail address:* meng.woo@monash.edu (M.W. Woo).

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The solute is then precipitated in the form of nano-sized particles as it mixes with the supercritical antisolvent fluid (Reverchon, 1999).

While air-jet milling is suitable for producing micron-sized particles, this process requires considerable energy input in order to accelerate the particles to a velocity suitable for fracture (Chamayou and Dodds, 2007; Saravacos and Kostaropoulos, 2002). Moreover, inefficiencies of milling on soft material were also observed; a freezing process is sometimes required in order to reduce the elasticity of the material (Saleem and Smyth, 2010). On the other hand, atomised droplets produced during spray drying have a wide variation of droplet size. Consequently, each droplet would have a different drying profile, which results in variations in particle properties in the same batch (Ilić et al., 2009; Kawakami et al., 2010). Finally, SAS precipitation involves very high operating pressures and hence high equipment cost in order to sustain the process (Reverchon, 1999).

To address these issues, a new technique has recently been developed in order to produce microparticles using antisolvent vapour to precipitate lactose from a single droplet. Using this technique, multiple smooth amorphous microspheres of uniform size ($\sim$1.0 μm in diameter) can be produced by exposing a droplet of lactose solution ($\sim$1.2 mm in diameter) to a convective mixture of ethanol vapour and nitrogen gas at atmospheric pressure (Mansouri et al., 2012). Long and short dendritic structures have also been observed using this method in addition to the smooth amorphous lactose microspheres (Mansouri et al., 2013). This technique differs from the conventional liquid antisolvent precipitation method; in liquid antisolvent precipitation, the solute (dissolved in solvent) is mixed with the liquid antisolvent in order to induce precipitation, followed by immediate spray drying to minimise the growth of particles resulting in a sub-micron particle size distribution (Hu et al., 2011).

Instead, antisolvent vapour precipitation involves exposing the solution to a vapour form of the antisolvent rather than mixing two liquids. Each droplet produces multiple particles due to the diffusion of antisolvent into the drop. While this single droplet drying technique mimics the convective drying process that occurs during spray drying, the drying time scale was several magnitudes larger than an actual spray dryer (approximately 30 minutes) (Mansouri et al., 2012). Relatively large droplets were used in the single droplet drying technique, at approximately 1.2 mm in diameter, which would explain the long drying time. Droplets produced by atomisers in actual spray-drying processes are usually in the range of tens or hundreds of microns and take less time to dry (Wendel and Celik, 2005).

In this article, for the first time, we will attempt to 'scale down' the antisolvent vapour precipitation approach by using atomised droplets to better mimic convective drying processes within a spray dryer. Using lactose as the solute, water as the solvent, and ethanol as the antisolvent, the effect of reducing the average droplet size by several magnitudes on the final particle size distribution will be investigated in this study. The absolute humidity of the ethanol vapour, exposure time and drying temperature, were also varied in an attempt to further understand how these variables affect the formation of the lactose microspheres.

## 2. Methodology

### 2.1. Materials

Lactose was selected as the focus material as a continuation from previous works (Mansouri et al., 2013; Mansouri et al., 2012) and for its high applicability in the pharmaceutical industry. Currently, lactose is used as a filler in dry powder inhalers and as an excipient in tablet manufacture (Kaialy and Nokhodchi, 2012; Kho and Hadinoto, 2013). The influence of particle size and morphology of lactose is highly important as the physicochemical properties of the pharmaceutical product could be affected by a slight change in these properties.

Lactose (L8783, α-lactose monohydrate) was purchased from Sigma-Aldrich, Australia. Liquid ethanol (100986, absolute) used to generate the antisolvent vapour was purchased from Merck Millipore, Australia. Water used in the experiment was distilled using Nex Power 1000 (BioEquipment Scientific).

### 2.2. Preparation of lactose microspheres

Lactose solution was prepared by dissolving 10.0 g of α-lactose in 200.0 ml of distilled water, to make a concentration of 5.0 wt% and stirred for a minimum of four hours to achieve mutarotation equilibrium of 40% α- and 60% β-lactose as determined previously (Fu et al., 2012).

Fig. 1 demonstrates the set-up of the antisolvent vapour precipitation process. Fine aqueous lactose droplets were produced using a pressure-driven atomiser operated at 300 kPa, which were collected on the surface of a petri dish (not shown). The collected lactose droplets were exposed to ethanol vapour in the precipitation chamber (A) for 20–60 seconds. The ethanol vapour was generated by bubbling air through a reservoir of liquid ethanol resulting in ethanol-laden air due to entrainment. A desiccator column (1) was used to reduce the moisture of incoming air which might induce lactose crystallisation during precipitation. The droplets were then dried with hot air at between 70 °C and 160 °C for 480 seconds, although it should be noted that the temperature on the surface of the dish was lower.

The absolute humidity of ethanol (AH) was obtained by measuring the wet bulb and dry bulb temperatures of the ethanol vapour before commencement of each run and was varied between 0.057 kg/kg air and 0.137 kg/kg air. The AH was controlled by varying the volume of ethanol in the ethanol reservoir; higher volume of liquid ethanol increased the amount of ethanol imparted to the air bubbles, thus increasing AH and vice versa. The wet bulb and dry bulb temperatures were used to calculate the AH entering the precipitation chamber. The calculations involved in determining AH are covered in the supplementary information.

### 2.3. Size analysis of atomised droplets

Size analysis of the droplets was conducted using two complementary methods. In the first method, microscope imaging was conducted by observing the collected droplets in paraffin oil under

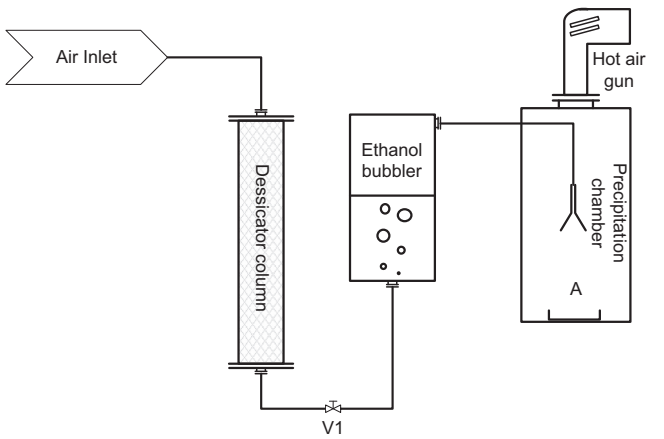


**Fig. 1.** Modified lactose microsphere set-up. V1: Flow regulator for ethanol bubbler. A: Droplet precipitation area. The droplets are collected from the atomiser using a petri dish and quickly placed into (A) where ethanol vapour is introduced followed by hot air drying.