ELSEVIER

Chemical Engineering Science 62 (2007) 2445–2453

Chemical Engineering Science

www.elsevier.com/locate/ces

Sonocrystallisation of sodium chloride particles for inhalation

Ali Abbas[a,*], Mourtada Srour[b], Patricia Tang[c], Herbert Chiou[c], Hak-Kim Chan[c], Jose A. Romagnoli[d]

[a]*Division of Engineering Science and Technology, University of New South Wales Asia, Singapore*
[b]*School of Chemical and Biomolecular Engineering, University of Sydney, Australia*
[c]*Faculty of Pharmacy, University of Sydney, Australia*
[d]*Department of Chemical Engineering, Louisiana State University, USA*

Received 26 June 2006; received in revised form 21 October 2006; accepted 14 January 2007
Available online 7 Februray 2007

Abstract

Fine sodium chloride particles are of pharmaceutical interest in aerosol delivery for diagnosis of asthma and bronchial related disorders. In this paper, stable NaCl particles with size ranging from approximately 1 μm to sub-micron range were achieved by sonocrystallisation. The effects of sonocrystallisation temperature, ultrasonic power output and salt concentration were investigated in the ranges of 5–35 °C, 22–60 W and 8–34 g/100 g water, respectively, under a fixed ultrasonic frequency of 20 kHz. Size and morphology characterisation of particles were undertaken using laser diffraction and scanning electron microscopy. Optimally prepared particles were spray dried followed by *in vitro* impaction test for inhalation efficiency determination using an Aeroliser®. Optimal conditions of temperature (< 5 °C), ultrasonic power output (~ 35 W) and salt concentration (~ 32 g/100 g water) exist that reduced the size of the crystals to the sub-micron scale. Spray drying increased the size of the prepared particles and altered the cubic shape to more rounded morphology. The fine particle fraction (based on recovery) was improved from approximately 12 to 34% when dispersion air flow rate was increased from 60 to 120 L/min. Sonocrystallisation represents an effective method for the preparation of NaCl particles suitable for pharmaceutical inhalation. The main advantage of this method is that it is rapid, simple and produces small crystal NaCl particles suitable for inhalation.

Keywords: Crystallisation; Ultrasound; Pharmaceuticals; Particle; Formulation; Dry powder inhaler

1. Introduction

Sodium chloride aerosols have been widely used as part of bronchial provocation tests to identify people with active asthma, exercised-induced asthma, and those who wish to enter particular occupations (e.g. police, army) or sports (e.g. diving). It has become practical to prepare dry NaCl powder that can be delivered using dry powder inhalers (DPIs) instead of traditional nebulisers as the former can be more efficient in challenging subjects and are also more convenient. Moreover, nebulisers, commonly used to assess the bronchial responsiveness are becoming increasingly unpopular due to: (1) varying output between nebulisers and between patients as the dose delivered differs over time; (2) aerosol exposure to the person administering the test; and (3) longer time taken to deliver the required dose (Anderson et al., 1997). When NaCl is inhaled into the airways it increases the osmolarity of the fluid lining the mucosal surfaces (Anderson et al., 1997). The bronchial muscle of an asthmatic will then contract with response to the rate of change of osmolarity. To optimise their effectiveness, the salt aerosol crystals should be formed as small as possible, hence maximising surface area.

A common way to produce NaCl powder suitable for inhalation is by micronisation (milling) for long periods of time (to increase the proportion of particles in the respirable size range $\leqslant 5$ μm) followed by vacuum oven drying (Clark et al., 1996). This procedure is energy intensive, time consuming and can introduce impurities into the product. It also has several other disadvantages including inadequate control of particle size, undesired particle shape, surface charge modifications,

* Corresponding author. Tel.: +65 6304 1426; fax: +65 6472 2849.
E-mail address: aabbas@unswasia.edu.sg (A. Abbas).

0009-2509/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ces.2007.01.052

decreased crystallinity and possible chemical degradation. Some key references are cited (Waltersson and Lundgren, 1985; Parrott, 1990; Malcolmson and Embleton, 1998; Ticehurst et al., 2000; Chan and Chew, 2003; Rasenack et al., 2004; Shoyele and Cawthorne, 2006). These disadvantages of the micronisation process ultimately jeopardise the NaCl powder performance.

Spray drying is another technique that is extensively used for the preparation of pharmaceutical inhalation particles (see for example Chawla et al., 1994; Patton et al., 1995; Stahl et al., 2002; Ameri and Maa, 2006 and the reviews by Chan and Chew, 2003; Shoyele and Cawthorne, 2006; Re, 2006). It is recognised that spray drying suffers from the limitations of low yields, thermal degradation issues, inefficiency in capturing particles less than 2 μm in size, difficulty in controlling the size distribution and fluid nozzle blockages. There are limited studies on the spray drying of NaCl for inhalation use. Chan et al. (1997) reported the cospray drying of NaCl with recombinant human Deoxyribonuclease (rhDNase) to improve the dispersion behaviour of the latter. Tang et al. (2006) observed that when spray drying alone is used to prepare NaCl particles, the product is unstable and recrystallises, forming large clumps and hence is inappropriate for inhalation.

Sodium chloride particles suitable for inhalation delivery can potentially be obtained by rapid precipitation from aqueous solutions using antisolvents. Previous studies on antisolvent NaCl crystallisation found this precipitation method to provide a limited application because it produced NaCl particles not in the respiratory range and/or particle shapes inappropriate for aerosol delivery (Zijlema et al., 1999; Doki et al., 2002; Kaneko et al., 2002; Purssell et al., 2004; Toth et al., 2005). Because of these limitations, an alternative production process will be necessary. Any new production process/procedure must satisfy aerosol particle design requirements including particle size, particle size distribution, stability, particle morphology and roughness amongst others.

Sonocrystallisation is sought here as an alternative method to affect the production of NaCl for pharmaceutical use. Apart from constituting a rapid application, sonocrystallisation also offers further advantages including smaller crystal size produced compared to conventional crystallisation, cost effectiveness of apparatus, the process can be run at ambient conditions and the reaction vessel involved is of simple geometry making the cleaning process simple for the pharmaceutical requirements. Another important advantage is that because crystal growth occurs at lower supersaturation levels where initial growth is controlled, the size distribution of the products is narrower than uncontrolled crystallisation process (Mullin and Nyvlt, 1971; Guo et al., 2006a).

The application of ultrasound to a liquid medium causes cavitation, which is a well- researched phenomenon (Margulis, 1985; Young, 1989; Suslick, 1989; Doktycz and Suslick, 1990; Flint and Suslick, 1990; Suslick, 1990; Leighton, 1994; Digby et al., 1995; Cains et al., 1998; Suslick et al., 1999; Margulis and Margulis, 2004; Flannigan and Suslick, 2005), that causes the creation of voids in the liquid due to the pressure fluctuations created by ultrasonic waves. Cavitation is the most important activity in sonocrystallisation. It assists nucleation and results in the reproducible nucleation of particles at lower supersaturation levels producing more uniform particle size and morphology (Ruecroft et al., 2005; McCausland et al., 2001). Sonocrystallisation relies on transient cavitation which forms short-lived cavities (bubbles) that end in catastrophic collapse. This occurs when the cavity is vapour filled rather than gas filled (McCausland et al., 2001) and leads to the release of large localised amounts of energy that subsequently go through a phase of extremely fast temperature reduction ultimately resulting in the generation of a significant number of nuclei. This increased nucleation results in the formation of more nuclei translating into increased crystalline surface area and consequently an increase in solute consumption by growth phenomena. Supersaturation and hence growth of crystals is distributed to the many forming nuclei leading to large numbers of smaller particles.

Recognising the benefits ultrasound can bring to crystallisation, many researchers endeavoured to study sonocrystallisation at the laboratory and industrial scales. Ratsimba et al. (1999) gave a review on sonocrystallisation. Thompson and Doraiswamy (2000) reported on the significant increase in the solubility of sparingly soluble solids subjected to ultrasound. They proposed that this could be due either to the hot spot regions produced from cavitating bubbles or due to Gibbs–Thompson effect. Lyczko et al. (2002) showed that ultrasound narrows the metastable zone width which denotes that ultrasound promotes heterogeneous nucleation. Kim et al. (2003) used ultrasound to effectively reduce the size of the crystals. They used a scaled-up process with a recirculating loop containing an in-line sonic tube. Li et al. (2003) demonstrated the suitability of high intensity ultrasound to antisolvent crystallisation. They studied the effects of varying the ultrasonic power, duration and the volume of mixture on the mean size, size distribution and shape of the crystal. They also noted the reduction in agglomeration as a consequence of the ultrasonic induction. Ruecroft et al. (2005) discussed the impact of ultrasound (intermittent or continuous insonation) on primary and secondary nucleation mechanisms. They also reviewed the developments in scale-up methods and available equipment. Virone et al. (2006) addressed the relationship between collapse pressure of the cavitating bubbles and solute nucleation rate. Guo et al. (2005) studied the effect of ultrasound on primary nucleation by measuring the induction time and metastable zone width. Their results showed that ultrasound has a significant effect on reducing the induction time and suggested that diffusion acceleration is the main reason for the reduction in the induction time. They like Li et al. (2003) also reported a reduction in agglomeration due to the application of ultrasound. Guo et al. (2005) further suggested that ultrasound can significantly enhance the homogeneous nucleation of the organic compound they studied. Miyasaka et al. (2006) studied primary nucleation induced by ultrasound and proposed that a certain ultrasonic energy (threshold) is needed to activate primary nucleation. They also discussed the control of the product crystal size via ultrasonically induced primary nucleation. Li et al. (2006) investigated the use of power ultrasound in controlling the supersaturation, nucleation and crystal