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Note

Aerosol flow reactor method for synthesis of drug nanoparticles

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Abstract

An aerosol flow reactor method, a one-step continuous process to produce nanometer-sized drug particles with unimodal size distribution, was developed. This method involves first dissolving the drug material in question into a suitable solvent, which is then followed by atomising the solution as fine droplets into carrier gas. A heated laminar flow reactor tube is used to evaporate the solvent, and solid drug nanoparticles are formed. In this study, the effect of drying temperature on the particle size and morphology was examined. A glucocorticosteroid used for asthma therapy, beclomethasone dipropionate, was selected as an experimental model drug. The geometric number mean particle diameter increases significantly with increasing reactor temperatures due to formation of hollow nanoparticles. Above 160 °C, however, further increase in temperature results in decreasing particle size. The produced nanoparticles are spherical and show smooth surfaces at all studied experimental conditions.

Keywords: Aerosol; Nanoparticle; Drug; Particle; Particle size

1. Introduction

Nanosized drug particles are desirable particularly to increase drug dissolution rate for poorly soluble drugs [1,2] and for drug targeting purposes [3,4]. Nanosized drug particles are also essential in various applications such as intravenous suspensions [5].

Dry and wet milling techniques have been widely used to reduce the particle size down to tens of nanometers [5]. Unfortunately, the nano-sized particles cause cake formation in the grinding materials and milling chambers, thus significantly reducing the size reduction efficiency and resulting in broad particle size distribution and non-uniformity in particle size [2,6]. Furthermore, the milling process can introduce changes in particle morphology, damage in particle crystalline structures [6], and possibly contamination, which is absolutely undesirable in pharmaceutical material handling. Methods based on high-pressure homogenisation have been shown to be effective in producing nanoparticles as aqueous suspensions [5]. However, in order to avoid particle coalescence stabilising agents must be used, which might be undesirable in some applications. Examples of other routes to drug nanoparticles include methods such as emulsification–diffusion, salting-out process, and various polymerisation methods [3]. These methods, however, generally involve several steps, need of stabilizers, or use of pharmaceutically unacceptable or environmentally hazardous solvents [7]. In some cases, the product has a low drug content, which might prevent further considerations for industrial scale.

This paper aims to demonstrate nanosized drug particle production using a novel method, aerosol route, and to study the effect of heating rate on nanoparticle size and morphology. Aerosol route is a simple and efficient one-step continuous process that can directly produce particles within a desirable particle size range with consistent and controlled properties, and avoids the use of harsh solvents or stabilizers. The method involves atomising the drug solution to create droplets, passing the droplets suspended in the carrier gas through a heated tubular laminar flow reactor and finally collecting the particles. Temperature is adjusted to evaporate the solvent and to allow particle formation to complete in the flow reactor. Because the droplets are already suspended in the carrier gas when fed into the

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reactor, the temperature history and residence time of each droplet and product particle can be properly controlled.

2. Materials and methods

2.1. Drug solution preparation

The beclomethasone dipropionate liquid feed stock was prepared by dissolving 0.25 g of beclomethasone dipropionate (Sicor S.p.A., Italy) powder in 1 l of ethanol (99.5%, Alko Oyj, Finland) at room temperature.

2.2. Experimental procedure

Experimental system set-up is presented in Fig. 1. The solution was atomised using a collision-type air jet atomiser TSI 3076 aerosol generator (TSI Inc. Particle Instruments, St. Paul, USA). The liquid solution feed rate was adjusted with a valve to approximately 0.20 ml/min. The resulting droplets were suspended into a carrier gas, nitrogen. Total carrier gas flow rate through the atomiser was 3.5 l/min, which gives the atomiser an operation pressure of 3.5 bar. Aerosol flow rate of 2.0 l/min was discarded and 1.5 l/min was passed through a heated tubular laminar flow reactor, which was used to evaporate the solvent from the droplets and to allow particle formation to complete. The reactor tube is made of stainless steel, with an inner diameter and a heated length of 30 and 800 mm, respectively. To study the effects of reactor tube temperature to particle morphology, the reactor temperature was varied between 40 and 200 °C. Beclomethasone dipropionate melts with simultaneous decomposition at 220 °C. Therefore, temperatures higher

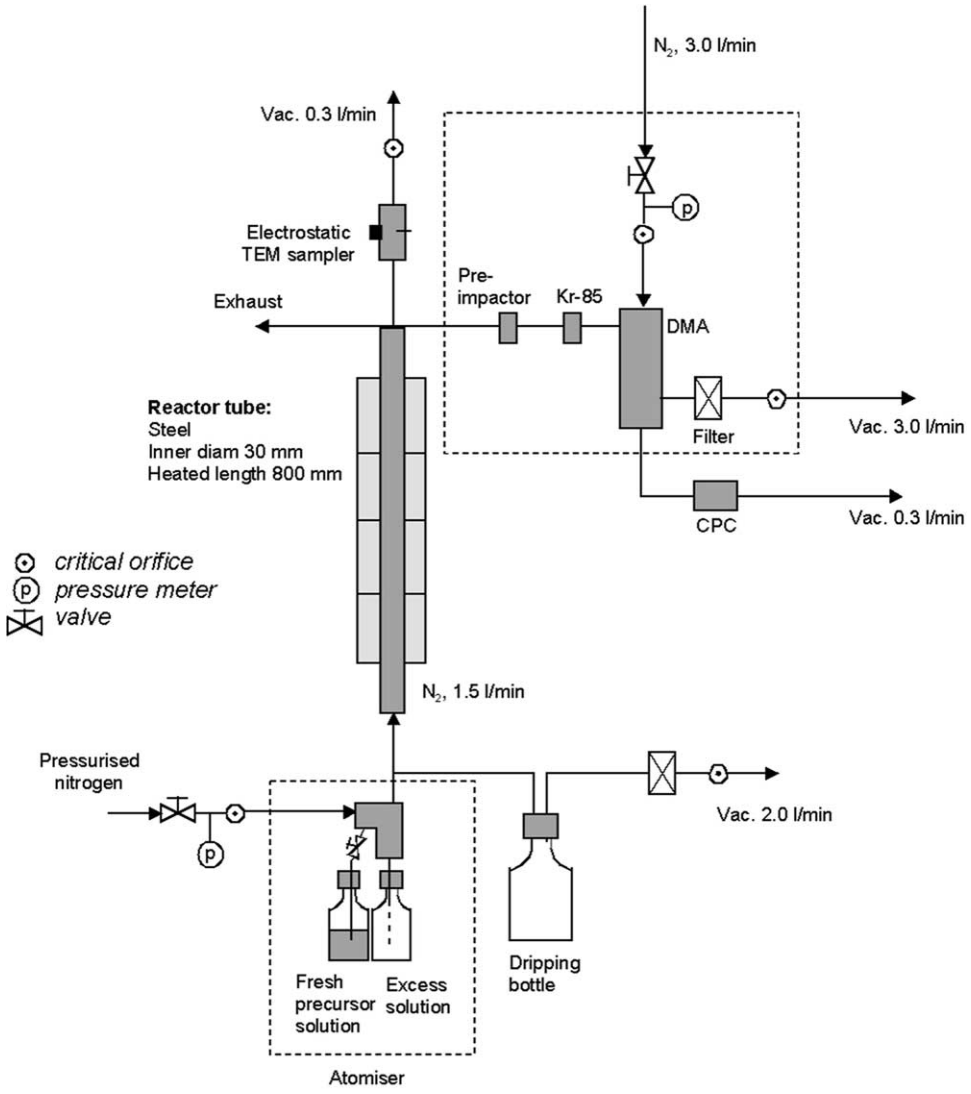

Fig. 1. Experimental set-up (N_2, clean, dry pressurised nitrogen; Vac., vacuum; l/min, standard litres per minute; Kr-85, aerosol neutraliser using ^{85}Kr β-source; DMA, differential mobility analyser; CPC, condensation particle counter).

than 200 °C were not studied. To ensure uniform temperature, the tube is heated with four separately controlled heaters, each at given temperature.

2.3. Particle characterisation

Particle size analysis was performed with TSI scanning mobility particle sizer (SMPS), equipped with long differential mobility analyser (DMA, model 3071) (TSI Inc. Particle Instruments, St. Paul, USA) and condensation particle counter (CPC, model 3027) (TSI Inc. Particle Instruments, St. Paul, USA). The particle number size distributions were measured six times at each experimental condition, and an average of the six curves was calculated and analysed. Particle morphology and structure were studied by field emission scanning electron microscope (SEM) (Leo DSM982 Gemini, LEO Electron Microscopy Inc., Oberkochen, Germany) and field emission transmission electron microscope (TEM) (Philips CM200 FEG, FEI Company, Eindhoven, The Netherlands). The samples were collected directly from the aerosol suspended in carrier gas with a point-to-plane electrostatic precipitator (InTox Products, Albuquerque, NM, USA) on holey carbon coated copper grids (Agar Scientific Ltd., Essex, England).

3. Results and discussion

To examine the effect of temperature and residence time on particle size morphology and crystallinity, reactor wall temperatures were varied from 40 to 200 °C, while carrier gas flow rate was kept constant. Fig. 2 shows examples of measured particle size distributions at various temperatures. The particle size distributions measured at temperatures below 100 °C were identical, so they are not shown for clarity. From the size distribution curves it is observed that the particle size distributions are unimodal with geometric standard deviations less than 1.7 at all studied temperatures.

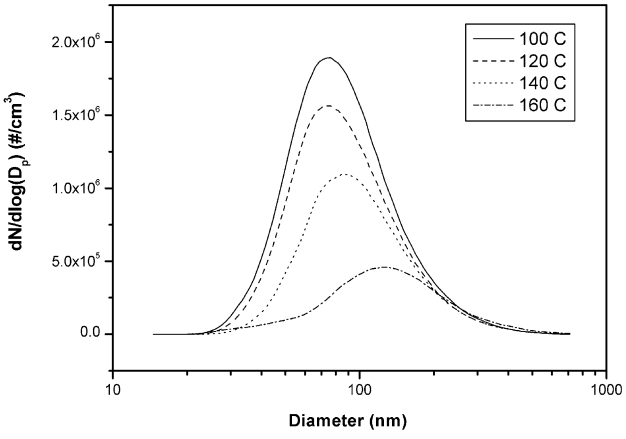

Fig. 2. Measured number particle size distribution curves at selected temperatures.

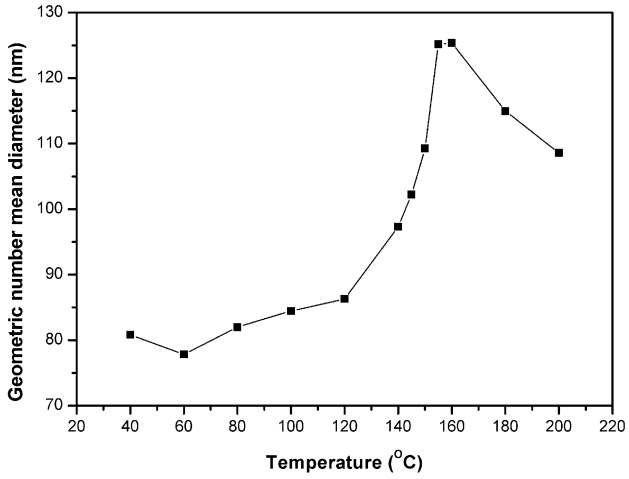

Fig. 3. Geometric number mean diameter of the synthesised particles as a function of temperature.

Fig. 3 shows number size geometric mean diameter of particles as a function of reactor temperature. It is shown that the particle mean diameter is relatively constant when the reactor temperature is varied between 40 and 120 °C. At temperatures above 120 °C the mean particle size starts to increase significantly, from 85 nm to a maximum diameter of approximately 125 nm at 160 °C. Above 160 °C, however, further increase in reactor temperatures causes the particle size to decrease again.

Based on SEM and TEM observations, the temperature does not significantly affect the particle morphology within the studied reactor temperatures. The particles are spherical and have smooth surfaces at all studied experimental conditions. Fig. 4 shows a representative SEM image of the particles produced at 100 °C. At temperatures above 120 °C, however, hollow particle formation is observed. Fig. 5 shows examples of hollow nanoparticles produced at 150 °C. This observation of hollow structures is in good agreement with the DMA results that show an increase in mean particle size at higher temperatures.

It is known that fast solvent evaporation rates produce

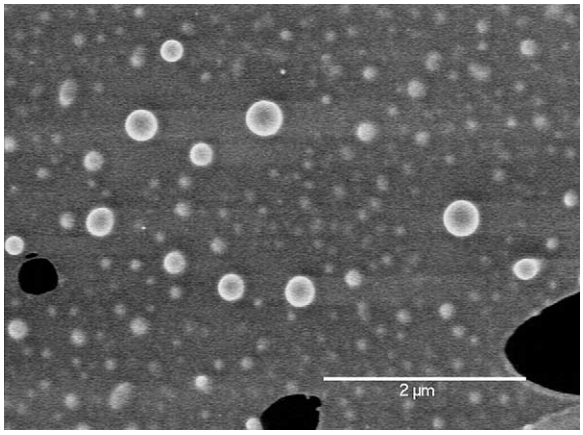

Fig. 4. SEM image of beclomethasone dipropionate nanoparticles produced at 100 °C.

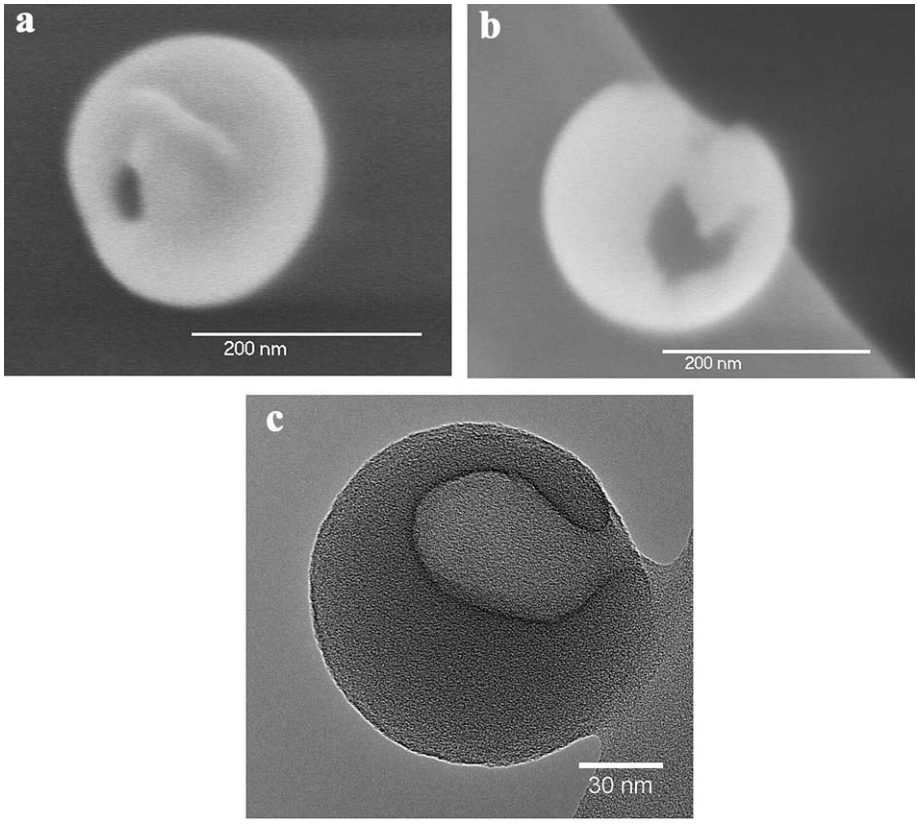

Fig. 5. (a) SEM image of a hollow particle produced at 150 °C. (b) SEM image of a hollow particle produced at 150 °C. (c) TEM image of a hollow particle produced at 150 °C.

hollow particles, whereas slower evaporation rates will create denser particles [8–10]. The droplet heating rate and solvent evaporation rate are increased as a function of increasing wall temperature. The rapid evaporation of the solvent at the particle surface at high temperatures causes the formation of a solid crust of material at the particle surface, which prevents further diffusion of solvent to the particle surface. Instead, the solvent is rapidly evaporated at the particle interior creating a cavity inside particle. Further increase in reactor temperatures to above 160 °C presumably caused a collapse of the hollow structure, which was observed as a reduction in the particle size.

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