

Effect of drying pressure on pore formation of drug particles produced by electrospraying

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Abstract — Electrospraying is a method of liquid atomization using electrostatic forces. In the present study, electrospraying was used in drug particle production. A poorly water soluble model drug (budesonide) was dissolved in chloroform, and the solution was atomized. Following this, the solvent was removed from the formed droplets in a drying chamber. The drying rate of the droplets can be increased by reducing the pressure in the drying chamber. The pressure reduction has a remarkable effect on pore formation and degree of crystallinity of the product. In this study, the porosity of the produced particles was studied.

I. INTRODUCTION

Most experiments on electrospraying are performed at atmospheric pressure [1]. Nevertheless, there are several studies of electrospraying into vacuum mainly, but not exclusively considering electrical colloidal thrusters [1-5]. In the present study, electrospraying was used in drug particle production, and the particles were dried both under atmospheric and reduced pressure.

Electrospraying is a method of liquid atomisation using electrostatic forces. Electrospraying of solutions or suspensions provides a method for production of fine particles, in certain conditions even down to nanometre scale [6]. In drug particle fabrication, a drug powder is dissolved in a convenient solvent. The solution is pumped through a capillary nozzle which is maintained at a high potential. A high electric field is generated at the capillary tip, which causes the meniscus to form a jet. The jet disrupts into droplets which are highly charged and relatively uniform in size. In a drying chamber, the solvent is then evaporated from the formed droplets and inside each droplet, a dense cluster of the dissolved drug remains. Hence it is possible to produce solid and dense particles uniform in size.

The size of the formed droplets and particles can easily be tailored by varying the concentration of the dissolved material, electric field strength or liquid flow rate [1,7]. Various models for estimating the size of the produced droplets in electrospraying are reviewed by Jaworek [8]. However, on top of size distribution, among the most important

properties of the particles in pharmaceutical sense are degree of crystallinity and specific surface area [9]. These properties have a remarkable influence on the functional properties of a drug. The effect of chamber pressure reduction during electro spraying on the degree of crystallinity of the product was previously studied [10].

Also the porosity of the produced particles depends mainly on the drying conditions. Quick drying tends to lead to formation of porous or hollow particles, because the drug molecules do not have time to diffuse to empty places inside the cluster [11]. In the present study, electro spraying was done both in atmospheric and reduced pressure, the latter in order to improve the drying process. The porosities of the fabricated particles were studied with SEM imaging and nitrogen adsorption, and compared.

II. MATERIALS AND METHODS

A. Materials

Budesonide is an anti-inflammatory corticosteroid. Budesonide was dissolved in chloroform at room temperature using drug material concentration of 15 g/dm^3 . Micronized budesonide was acquired from Orion Pharma (Finland).

In electro spraying, the most important properties of the solution are its conductivity, surface tension and viscosity. In such an application of processing pharmaceutical materials, the solvent should be non-toxic. Moreover, the drug material has to be soluble, but not degradable in the chosen solvent. Taking these requirements into account, chloroform was chosen as a solvent for electro spraying. It has also been found to be volatile enough in previous studies [10].

B. Particle production and drying

Budesonide solution was pumped continuously through a stainless steel capillary (manufactured by EFD, USA) with inner diameter (d_c) of 0.25 or 0.33 mm. Liquid flow was controlled using a syringe pump (NE-500, New Era Pump Systems, USA), and flow rate (Q) of 2 ml/h was used. The capillary was connected to a positive high voltage (Alpha Series II high voltage source, Brandenburg, UK). A circular metal plate (guard plate) was attached to high voltage conductor above the capillary. This was to make the electric field at the capillary tip more uniform and to prevent some external electric disturbances. The atomizing electric field formed between the capillary and a grounded circular plate electrode beneath it. The distance between these electrodes was fixed approximately at 1 cm. In the present study, atomization voltages (U) ranged between 2.6 – 3.4 kV. All samples were fabricated using stable cone-jet mode. The electro spraying equipment is presented in more detail in previous papers [10,12].

Highly charged droplets were neutralized in order to avoid adhesion to grounded surfaces. This was done using a corona neutralizer with a needle – cylinder configuration. The corona needle was connected to E.H.T. unit Type 532/D voltage source (The Isotope Developments, UK) and set to negative potential, and the cylinder electrode surrounding it was grounded. A stable corona burst was maintained at the needle tip, which causes ionization of the air. Hence the cascading droplets were neutralized.

Electrostatically atomized droplets were spray dried at room temperature in cylindrical drying chamber made of acid-proof steel, in pressures (p) of 0.7 – 1 atm. When atomiza-

tion was done in reduced pressure, the solutions were set in vacuum for 30 - 60 seconds prior to electro spraying. This was done to remove the dissolved gas from the solution in order to prevent formation of bubbles in the capillary while electro spraying. As from now on, the atomization voltage U , liquid flow rate Q , drug material concentration in the solvent c , inner diameter of the capillary d_c and the drying pressure p , are referred to as *atomization parameters*.

C. Particle characterization

Produced particles were studied using scanning electron microscope (Cambridge S200, UK). SEM samples were prepared by collecting particles on a nylon filter. The samples were coated with a 20-30 nm layer of gold to improve their conductivity. Samples were stored in room temperature in desiccator containing silica gel for two days before the imaging.

For the specific surface area measurements, the electro sprayed samples were collected from the walls (using upper limit of 30 cm from the bottom) and from the bottom of the drying chamber. Nitrogen adsorption measurements at 77 K were done with TriStar 3000 gas sorption apparatus (Micromeritics, Norcross, USA). The specific surface areas of the particles were determined from the obtained adsorption isotherm using the equation by Brunauer, Emmett and Teller (BET equation) [13]. Before the measurement, the samples were prepared by heating (65 °C) in a vacuum for 1 -2 hours. Each sample was measured four times.

III. RESULTS

A. Scanning electron microscopy

Produced budesonide particles were studied with SEM imaging. During the fabrication of the samples, the values of atomization parameters were as follows: $c = 15 \text{ g/dm}^3$, $Q = 2.0 \text{ ml/h}$, $U = 3.1 - 3.4 \text{ kV}$ and $d_c = 0.33 \text{ mm}$. SEM images of the fabricated particles are presented in Fig. 1.

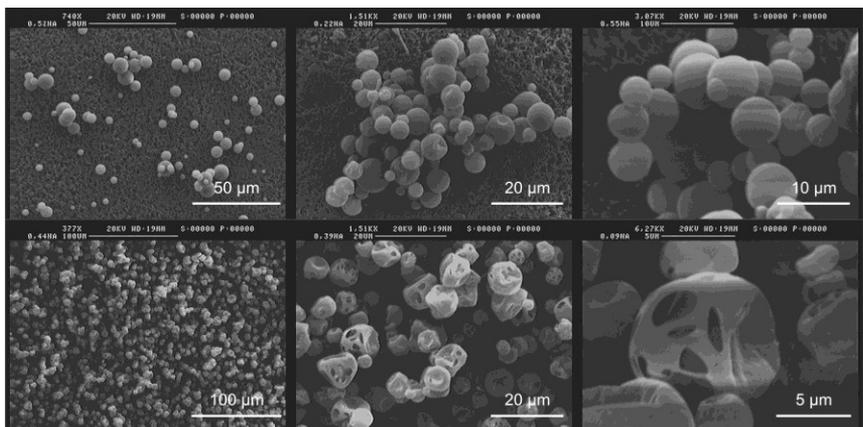


Fig. 1. Budesonide particles electro sprayed in 1.0 atm (upper row) and in 0.7 atm (lower row).

Based on the SEM images, budesonide particles fabricated under atmospheric pressure seem to have a smooth surface and very regular spherical form. Instead, the particles dried under reduced pressure seem more porous and collapsed. The size of the pores can be approximated to be around one micrometer. The pressure reduction increases the evaporation rate of the solvent from the particles, which in turn seems to increase the formation of pores. The structure on the background of the particles in Fig. 1 is the nylon filter on which the particles were collected.

Based on the SEM images, the particle size distribution was determined using Image-Pro Plus (Version 1.3) -program. More than 700 particles were analyzed. The particle size distribution was found to be quite narrow with the mean particle diameter of 4.9 μm .

B. Nitrogen adsorption

The samples for the specific surface area (A) measurements were collected during four electro spraying sessions for each pressure, using otherwise similar conditions. Values of the atomization parameters were as follows: $c = 15 \text{ g/dm}^3$, $Q = 2.0 \text{ ml/h}$, $U = 2.8 - 3.0 \text{ kV}$ and $d_c = 0.25 \text{ mm}$. The sample masses were 97 mg ($p = 1 \text{ atm}$) and 70 mg ($p = 0.7 \text{ atm}$). The obtained surface area results for atmospheric and reduced pressure are presented in Table 1.

TABLE 1: SPECIFIC SURFACE AREA (A) AND CORRESPONDING STANDARD DEVIATION (SD) FOR DIFFERENT DRYING PRESSURES

p [atm]	A [m^2/g]	sd
1	0.91	0.27
0.7	1.42	0.34

Based on the nitrogen adsorption measurements, the particles produced in pressure of 0.7 atm have notably larger specific surface area than those produced in pressure of 1 atm. It is decent to assume that the drying pressure does not affect the size of the produced particles, and the obtained specific surface areas can be compared directly. Hence it can be calculated that, the specific surface area obtained in 1 atm is 64 % of that obtained in 0.7 atm.

C. Crystallinity

The effect of pressure reduction on crystallinity of the particles produced by electro spraying was previously studied. It was discovered that, for a volatile enough solution (chloroform) electro spraying in a reduced pressure lead to formation of notably more amorphous particles than electro spraying in atmospheric pressure. This is most likely due to the fast solidification during drying: the drug molecules do not have enough time to arrange in the crystal lattice, which causes the formation of amorphous material [14]. For budesonide particles produced by electro spraying, the discovered maximum degrees of crystallinity were as follows: 21 % ($p = 1 \text{ atm}$) and 12 % ($p = 0.5 \text{ atm}$).

IV. CONCLUSIONS AND DISCUSSION

Micrometer scale drug particles were produced by electrospraying. Compared to conventional micronization processes (spray drying, milling), electrospraying has some major advantages: small particle size which can easily be tailored and very narrow size distribution.

The degree of crystallinity and porosity of drug particles affect greatly its functional properties. Knowing and controlling these properties during drug processing are of great importance. By reducing the drying pressure during electrospraying, modifying also these properties is possible. This study gives insight to the possibilities that electrospraying of pharmaceutical materials may offer.

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