Characterisation of pharmaceutical materials produced by electrospraying

M Nyström*, M Murtomaa and J Salonen
Department of Physics and Astronomy, University of Turku, FI-20014 Turku, Finland

*Corresponding author. E-mail address: mhnyst@utu.fi

Abstract. Electrospraying of solutions or suspensions provides a method for production of fine particles, in certain conditions even down to nanometer size. In the present study, electrospraying was used in drug particle production. The most important properties of the produced particles in a pharmaceutical sense are size distribution, degree of crystallinity and porosity. The size of the produced particles can easily be tailored by varying the concentration of the dissolved material, electric field strength or liquid flow rate. Most experiments on electrospraying are performed at atmospheric pressure. In the present study, the produced particles were dried under atmospheric or reduced pressure, the latter in order to improve the drying process. The effect of pressure reduction on the degree of crystallinity of the produced drug particles was studied by XRD and DSC. Also the porosity of the particles depends mainly on the drying conditions. The porosity and size of the produced particles was studied by SEM imaging.

1. Introduction
In the present study, electrospraying was used in drug particle production. In this process, a drug powder is dissolved in a convenient solvent. The solution is atomised using electrostatic forces. The solvent is evaporated from the formed droplets in a drying medium, and a dense cluster of the dissolved drug remains.

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, the produced drug particles were dried both under atmospheric and reduced pressure, the latter in order to improve the drying process.

It is estimated that more than 95 % of new drug candidates suffer from limited bioavailability [6]. For poorly soluble and highly permeable drugs, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract [7]. Therefore together with the permeability, the solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. A commonly used process in modifying bioavailability of poorly soluble drugs is particle size reduction, since it increases the relative surface area of the particles. Another commonly used technique is the formation of a high-energy amorphous form. The solubility and dissolution rate can be enhanced since the physical links are weaker in the amorphous structure [8]. A porous particle has a very large surface area and small density compared to a dense particle. This has a remarkable influence on the functional properties of a drug. Hence the most important properties of the electrosprayed particles in pharmaceutical sense are size distribution, degree of crystallinity and porosity.

In the present study, budesonide was dissolved in chloroform and the solution was electrosprayed. Budesonide is known to be poorly soluble in water [8]. By electrospraying, the size of the drug
particles can be reduced down to the micrometer range. The size and the size distribution of the particles can easily be tailored by varying the concentration of the dissolved material, electric field strength or liquid flow rate. The size distribution of the produced particles was determined by SEM.

The porosity of the particles produced by electrospraying depends mainly on the drying conditions. The drying can be done quickly using heat. This tends to lead to the formation of porous or hollow particles because the drug does not have time to diffuse to empty places inside the cluster [9]. However, there are several pharmaceutical materials which are temperature sensitive or highly resistant to migration of moisture from within the solid. The structures of these materials may be damaged at increased temperature, so drying without addition of heat may be required. In the present study, the drying was done both under atmospheric and reduced pressure at room temperature. The effect of pressure reduction on the formation of pores was studied by SEM.

In addition, the pressure reduction during drying may increase the proportion of the amorphous form in the product. Due to the fast solidification, the molecules do not have enough time to arrange in the crystal lattice, which causes the formation of amorphous material. The effect of pressure reduction on the amount of amorphous content in the electrosprayed product was previously studied by DSC and XRD. The results of this research are presented in a separate paper [10]. The results obtained on budesonide are discussed briefly here.

2. Materials and methods

2.1. Materials
Budesonide is an anti-inflammatory corticosteroid. Budesonide was dissolved into chloroform at room temperature using drug material concentration of 15 g/dm³. In electrospraying the most important properties of the solution are its conductivity, surface tension and viscosity. The solvent was chosen optimising these properties and taking into account that the drug material has to be soluble, but does not degrade in the chosen solvent. Chloroform has also been found to be volatile enough in the previous studies [10]. The prepared solution was stored at room temperature and protected from light. Micronised budesonide was acquired from Orion Pharma (Finland).

2.2. Particle fabrication
In the electrospraying studies, stainless steel capillaries (manufactured by EFD, USA) with inner diameter of 0.33 mm were used. Electrostatic atomisation was carried out using Alpha Series II high voltage source (Brandenburg, UK) set to positive potential and connected to the stainless steel capillary. A grounded plate electrode with a hole in the centre was placed beneath it. The distance between these electrodes was set to approximately 1 cm. A circular metal plate was attached to HV-conductor above the capillary. This was to make the electric field near the capillary tip more uniform, and to prevent some external electric disturbances. The electrospraying equipment is presented in more detail in a previous paper [11].

In the present study, atomisation voltages ranged between 3.0 – 3.6 kV. All samples were fabricated using the stable cone-jet mode. Highly charged droplets were neutralised in order to avoid adhesion to grounded surfaces. This was done using a corona neutraliser, which was connected to E.H.T. unit Type 532/D voltage source (The Isotope Developments, UK) and set to negative potential. Liquid flow to the capillary was controlled using a syringe pump (NE-500, New Era Pump Systems, USA). Liquid flow rates ranged from 1.5 to 2.0 ml/h. Atomised droplets were spray dried at room temperature at a pressure of 0.5 – 1 atm. When atomisation was done under reduced pressure, the solution was set in a vacuum prior to electrospraying. This was done in order to prevent formation of bubbles in the capillary while electrospraying.

2.3. Particle characterisation
Produced particles were studied using SEM (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 at room temperature in a desiccator containing silica gel for two days before the imaging.

Calorimetric measurements were carried out using differential scanning calorimeter (DSC, PerkinElmer Instruments, USA). The apparatus was controlled with a computer using Pyris DSC Software -program (PerkinElmer Instruments, USA). The equipment was cooled with Intracooler 2D (PerkinElmer Instruments, USA). Nitrogen was used as a scavenging gas using mass flow rate controller (B.V. 5850S, Brooks Instruments, USA), which was monitored using 0152 -control unit (Brooks Instruments, USA). Data was collected and analysed using Pyris Software Version 4.02 -software.

The crystallinity of the samples was measured using x-ray diffraction using a PW 1830 generator, PW 1820 goniometer and PW 1710 diffractometer controller (Philips Electronics, Netherlands). Data was analysed with X’Pert HighScore Version 1.0 -program. The samples were measured between 3 - 45 ° values of $2\theta$ with scanning speed of 0.02 °/s.

3. Results

3.1. Particle size

The fabricated particles appeared to be spherical and quite regularly shaped (figure 2). Based on the SEM images, particle size distribution was determined using Image-Pro Plus (Version 1.3) -program. More than 700 particles were analysed. The particle size distribution was found to be quite narrow with the mean particle diameter of 4.9 μm. The size distribution is presented in figure 1.

3.2. Porosity

The formation of pores on the produced budesonide particles was also studied with SEM. The fabrication of the samples was as described in the previous paragraph. That is, the values of the atomisation parameters were the same for the two samples, except for the drying pressure. The drying was done under atmospheric and reduced pressure, 1.0 and 0.7 atm, respectively. SEM images of the produced particles are presented in figure 2.

Based on the SEM images, budesonide particles fabricated under atmospheric pressure seem to have a smooth surface and very regular spherical form. 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 presumably 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 figure 2 is the nylon filter on which the particles were collected.

3.3. Degree of crystallinity
Another important property of a drug material on which the pressure reduction seems to have an effect is the degree of crystallinity (DOC). In previous studies it was noted that for chloroform solutions, the amount of amorphous material in the product increased when the drying pressure was decreased [10]. This was studied by DSC (differential scanning calorimeter) and XRD (x-ray diffraction). For budesonide electrosprayed at 0.5 atm, a peak most likely caused by crystallisation of the amorphous content was detected in the DSC scan. This peak did not occur on the sample dried at atmospheric pressure.

On the diffractograms of the electrosprayed budesonide samples, a clear decrease in the peak intensities was detected compared to the peaks of a crystalline reference sample. Both the samples prepared at 1.0 and 0.5 atm included a notable proportion of amorphous material, 80 and 90 %, respectively. Based on the XRD measurements on budesonide, it was also calculated that the crystallinity obtained in 0.5 atm was 56 % of the crystallinity in 1.0 atm.

4. Conclusions and Discussion
Production of microparticles of pharmaceutical materials by electrospraying was studied. The most important properties of the fabricated particles in the pharmaceutical sense are size distribution, porosity and degree of crystallinity. The bioavailability of a poorly soluble drug can be improved by modifying these properties. For particles produced by electrospraying, the particle size distribution is quite narrow and tailoring the size of the particles is relatively simple. By electrospraying into a reduced pressure, the degree of crystallinity of the product can be decreased to some extent. It also seems that porosity of the electrosprayed drug particles depends on the drying pressure. However, electrospraying into a reduced pressure is not entirely free of complications. Bubbles tend to form in the capillary when liquids with low boiling points are electrosprayed. This causes instability to the jet. Also, maintaining a stable corona discharge in the neutraliser is somewhat complex.

Nevertheless, electrospraying into reduced pressure might offer a useful method for improving the bioavailability of poorly soluble drugs by modifying the three mentioned quantities simultaneously. In the future, the porosity of the produced drug particles will be studied in more detail and the dissolution behaviour will be tested in vitro.

References
[1] Ku B K and Kim S S, J. Electrostat. 57 (2003) 109-128
[2] Bailey A G and Borzabadi E, IEEE T. Ind. Appl. 14 (1978) 162-167
[3] Kidd P W, J. Spacecraft Rockets 5 (1968) 1034
[4] Gamero-Castano M, J. Fluid. Mech. 604 (2008) 339-368
[5] Swarbrick J C, Taylor J B and O’Shea J N, Appl. Surf. Sci. 252 (2006) 5622-5626
[6] Brayden D J, Drug Discov. Today 8 (2003) 976–978
[7] Shokri J, Hanaee J, Barzegar-Jalali M, Changizi R, Rahbar M and Nokhodchi A, J. Drug. Deliv. Sci. Tec. 16 (2006) 203-209
[8] Dudognon E, Willart J F, Caron V, Capet F, Larsson T and Descamps M, Solid State Commun. 138 (2006) 68-71
[9] Ciach T, Int. J. Pharm. 324 (2006) 51-55
[10] Nyström M, Murtomaa M and Salonen J, J. Electrostat. (2011) (Submitted)
[11] Nyström M, Murtomaa M and Salonen J, J. Electrostat. 68 (2010) 42-48

Acknowledgements: Financial support from the Academy of Finland is acknowledged.