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Microencapsulation of drugs by electro-hydro-dynamic atomization

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Abstract

This paper presents practical aspects of production of polymeric particles loaded with a drug by electro-hydro-dynamic atomization (EHDA). Particles were produced from paracetamol (4-acetamidophenol), budesonide and polylactic acid containing Taxol (paclitaxel). Influence of solvent type and evaporation rate, as well as other polymers additives on particle morphology and drug release rate is demonstrated. It is shown that quickly evaporating solvents have a tendency to form hollow particles. Drug release rate from hollow particles is substantially higher than from solid ones. Addition of water-soluble polymer, polyethylene glycol, also increases drug release rate.

Keywords: Electrostatic atomization; Controlled release; Electrospray; Taxol

1. Introduction

First application of electrostatics in liquid atomization was described by William Gilbert (Gilbert, 1600). Then, the process of electrostatic atomization was described by Zeleny (Zeleny, 1914) and first mathematical description was published by Taylor (Taylor, 1964). At that moment, to distinguish atomization phenomena, when the electrostatic force is the only driving force of spraying process, the name: Electro-hydro-dynamic Atomization (EHDA) was introduced. During the last few years the number of publications describing various applications of EHDA has been growing fast. This technique is applied in analytical instrumentation—mostly in particles' production for time of flight spectrometers, coatings (Pareta and Edirisinghe, 2005), fibre production (Ciach and Gradoń, 1996) and nanoparticles formation (Ciach et al., 2002). It is also applied to the encapsulation of drugs for inhalation or injection administration, and for drug release coating (Shin et al., 2004; Xie et al., 2006; Ding et al., 2005; Reyderman and Stavchansky, 1995; Ciach, 2004; Ciach et al., 2001, 2003). Since the pieces of matter that we manipulate are getting smaller and smaller, electrostatic forces become more meaningful and handy, and that's why electrostatic technologies attract a growing interest among scientists and manufacturers.

2. Electro-hydro-dynamic atomization

The basic set-up for electrostatic atomization is equipped with a nozzle connected to the high voltage power supply and supplied with a liquid to be atomized. In the electrostatic field a droplet hanging beneath the nozzle change its shape to conical and, if the voltage is high enough, a liquid filament is ejected from a cone apex. This liquid jet, due to the Weber disturbances (Weber, 1931), breaks up to the mist of uniform droplets. Depending on the strength of the electric stresses in the liquid surface relative to the surface tension, different spraying modes will be obtained. For the production of pharmaceutical microparticles, the so called cone-jet mode seems to be the most appropriate. In this mode the process is very stable and small, monodisperse particles are formed. The schematic of atomization process is shown in Fig. 1.

In front of the nozzle a grounded conducting plate, to collect particles is usually placed. Since particles are highly charged, they are very efficiently collected by objects connected to the electrical ground or to the opposite potential. Below the nozzle a ring connected to the intermediate voltage is sometimes placed, which stabilizes a process of atomization. If solid particles should be formed by solvent evaporation, the droplets ought to be discharged beforehand to avoid disintegration (Rayleigh explosion due to mutual repulsion of electrical charges) and to help us to manipulate produced particles. To achieve that a corona needle electrode producing counter ions is placed in front of the spraying nozzle; counter ions collide with charged

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Fig. 1. Spraying process.

droplets and neutralize their high electric charge. EHDA set-up for powder production is shown in Fig. 2. This set-up is sometimes called "Delft type" since it was constructed for the first time in the Technical University of Delft, The Netherlands which once was a leading laboratory in the electrostatic atomization (Hartman, 1998).

The set-up consists of a cylindrical glass tube (i.d. = 10 cm) with tapered ends. One end acts as an inlet for filtered air and the other end ducts the produced particles via a heater to the collection side. The heating, after which the produced particles are captured on a filter, is necessary to evaporate the solvent. Normally, organic solvents, such as dichloromethane or acetone evaporate very quickly especially in the form of small droplets but if the polymer is present in the solution, a jelly outer layer is formed, which slows down the evaporation drastically. The EHDA spraying nozzle of 4 mm diameter is positioned in a glass side tube (i.d. = 2.5 cm) in which also the counter electrode ring is placed close to the main glass cylinder. The distance between the nozzle-tip and the ring is 10 mm. Discharge needle is inserted in the glass cylinder opposite to the spraying nozzle. The voltage difference between the ring and the needle creates a corona discharge at the needle tip supplying negative ions for droplet

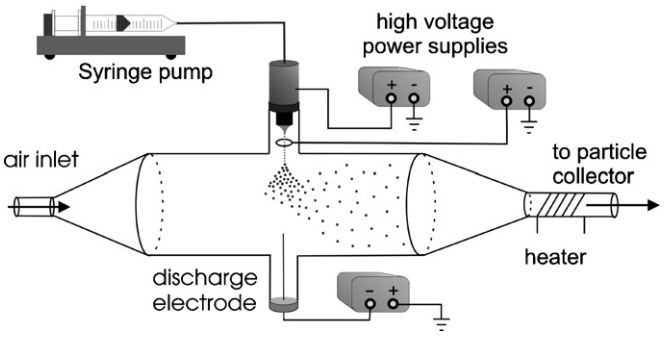

Fig. 2. Delft type EHDA particle production set-up.

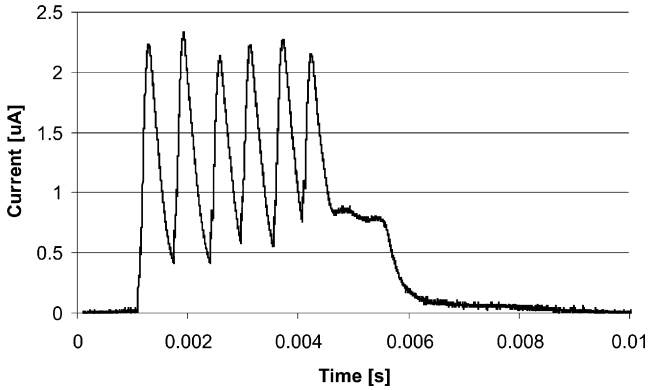

Fig. 3. Electric current flow through the cone during its unstable operation.

neutralization. The airflow through the system equals 30 L/min. Particles are collected on a membrane filter (not shown on the picture) placed downstream of the set-up. Air is drawn through the filter by a vacuum pump maintaining a small under-pressure in the spraying chamber. As a precursor for the production of drug loaded particles, a solution of drug, sometimes with addition of polymer, is supplied to the spraying nozzle. The flow rate of the solution is usually in the range of 0.5–5 mL/h. High voltage power supply set on 5–15 kV is connected to the nozzle and another HV power supply set on 3–10 kV is connected to the ring. All the presented particles were made in the set-up described above.

To obtain particles of a narrow size distribution, voltage and liquid flow rate are fixed in such way that the system operates in the cone-jet mode. For the scientist not experienced in the EHDA technique we can advice observation of the cone in the light coming from a back side, then in the cone-jet mode liquid cone became completely black. When the EHDA operates not in the cone jet mode the process itself is not stable. The whole cone or only its apex is emerging and collapsing repeatedly. During this reciprocal movements particle size distribution is very wide and sometimes large droplets are spited away. The process is very quick and cannot be noticed with a naked eye, it exhibits frequency from tens to hundreds hertz. When, in the back light, cone is perfectly black, all the light is scattered away, it means that cone is stable. When the cone is not stable, during the collapse time, part of the light is getting through and the cone is not black but sort of opaque and partially translucent. This is a practical and very reliable technique. Other method of cone stability control is monitoring of the electric current flowing through the nozzle. When EHDA operates in the cone jet mode electric current is stable, usually in the range from one to tens of microampere. Since the cone is connected to the high voltage electric current source it should be monitored via optically insulated high voltage current probe (commercially available oscilloscope equipment). When the electrostatic atomization is unstable, electric current reflects these instabilities perfectly, showing a very complex behaviour of the cone (Fig. 3) (Juraschek and Rollgen, 1998). Typical map of the stable EHDA operation for 1% paracetamol solution in isopropyl alcohol is shown in Fig. 4. It is shown as a function of nozzle voltage and liquid flow rate, all the other parameters

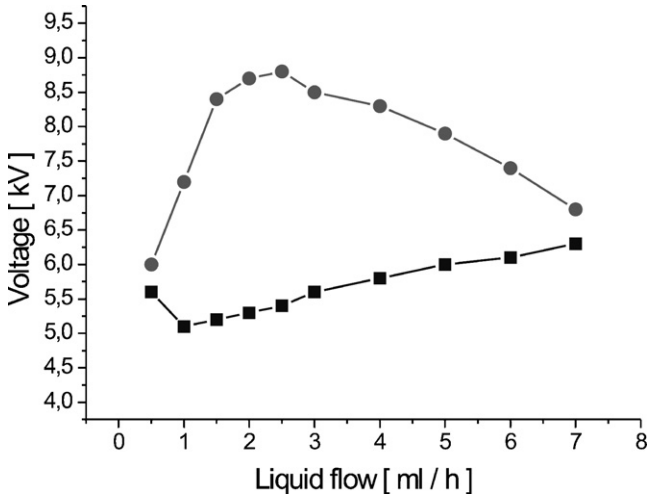

Fig. 4. Typical stability map of the EDA, cone diameter 2 mm, ring diameter 15 mm, ring voltage 3 kV, 1% paracetamol in isopropyl alcohol.

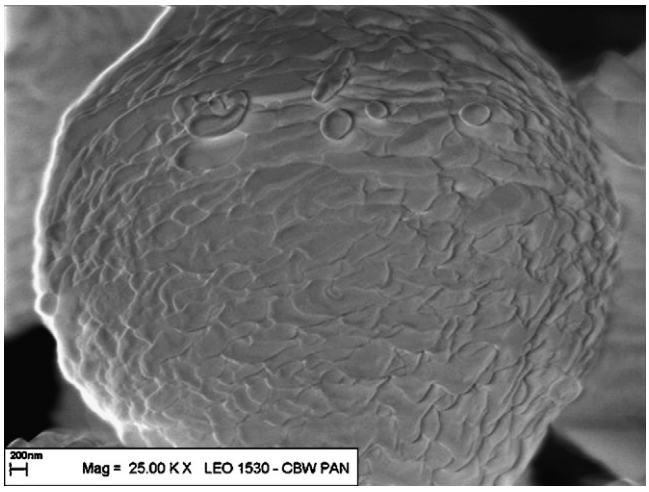

Fig. 5. Paracetamol particle obtained from the 1% isopropyl alcohol solution.

are constant, spray is stable in the area between presented two curves.

Since the EHDA process is very complex, accurate calculation of particle size beforehand is difficult, but a series of scaling laws or semi-empirical models have been developed, which help us to predict the influence of process parameters on particle size (De la Mora and Loscertales, 1994; Gañán-Calvo, 1994; Gañán-Calvo et al., 1997; Chen and Pui, 1997). For the production of certain particle sizes, a final tuning of the system by changing the liquid flow or voltage and using online particle size measurement device is necessary.

3. Drug release experiment

The experiment of in vitro Taxol release from polymer particles was done in the chemical vessel kept in the thermostat at 37 °C. To avoid rinsing particles away, about 0.5 g of powder was closed in the 2 cm long piece of hollow fibre micro filtration membrane of 10 mm external diameter and cut size 0.5 μm. This sealed membrane piece, a sort of basket, was immersed in 50 mL of water ethanol mixture 50/50 by volume. Ethanol water mixture was applied because Taxol solubility in pure water is extremely low and additionally Taxol has a tendency to adsorb on the glass walls that makes experiment result unpredictable. Solution was changed in regular time intervals and drug concentration in the solution was estimated by HPLC. It is also important to keep the sample solution warm until the measurement is done because Taxol may crystallize on the glass walls.

Described drug release experiment with water–ethanol solution does not reflect the situation in the natural fluid environment. But in the natural environment inside a human body a lot of fatty cellular walls or blood weasel walls covered by fatty structures are present, and they are good solvent for Taxol. Because a direct mimicking of that condition was difficult to achieve, we decided to use ethanol addition which substantially increases Taxol solubility.

4. Materials

Solvents applied in the experimental work were purchased from Polish chemical reagent distributor POCH, they were of analytical grade. Polymers: poly-lactic acid medical grade (about 100 kDa) was a gift from Purac, Budesonide was a gift from Astra Lund, Taxol was a gift from Balton, paracetamol (4-acetamidophenol) of pharmacopoeia grade was purchased from Merck, polyethylene glycol 10 000 MW was purchased from Aldrich. All the chemical substances were used without further purification or other processing.

5. Results

Morphology, as well as the internal structure of particles produced in the mentioned set-up depends strongly on the precursor type and solvent properties. To obtain solid, non-porous particles, precursor should be very well dissolvable in the solvent which was used. Exemplary system is paracetamol dissolved in isopropyl alcohol (Fig. 5).

Obtained particles are solid and consist of nanocrystals of paracetamol, as can be seen on the particle surface. Nanocrystalic structure of particles is a big advantage in the case of poorly soluble drugs; it may increase absorption speed and bioavailability. If the solubility of the precursor is low and/or solvent evaporates very quickly, shell-like particles are formed (Fig. 6). In this case precursor was Budesonide (antiastmatic drug), which maximum solubility in the solvent—isopropyl alcohol was about 2%.

Shell-like particles are formed when solvent evaporates quicker than the diffusion manages to equalize precursor concentration inside particle. Super saturation appears on the surface and precursor starts to crystallize and forms a shell. Similar influence of the evaporation rate of the solvent on the presence of cavities inside particles are also reported for particles made by other atomization techniques like spray drying or centrifugal atomization (Senuma et al., 2000). Shell particles have low density and are very useful in the pulmonary drug delivery. Similar phenomenon can be observed when particles are

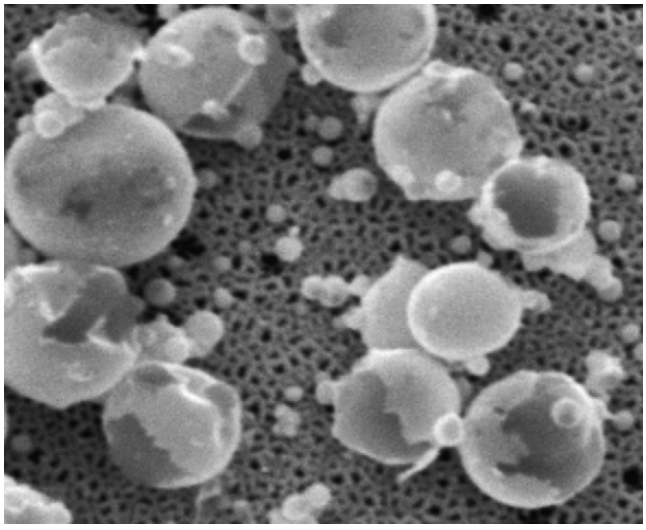

Fig. 6. Budesonide particles of about 1 μm diameter.

made of polymer solution. Depending on the solvent evaporation rate, microbaloons or solid spheres can be formed. Additionally, polymers have much bigger molecules so their diffusion coefficients are much smaller than those of simple drug molecules; in this case the tendency of hollow particle formation is even more emphasized and sometimes even unavoidable. Example of balloon-like particles is shown in Fig. 7. As can be seen in the picture, particles are hollow, they have dents and some of them are broken.

Polymers with a drug were dissolved in dichloromethane. Polymer concentration in the solution was 5%, Taxol was added as 10% of the polymer mass.

To produce solid polymer particles, evaporation rate should be kept as small as possible, thus low volatile solvents and no heating should be applied. Unfortunately, this leads to the long drying time. Example of solid drug containing polymer particles is shown in Fig. 8.

We have to admit that sometimes the presence of cavities inside particles is not easy to detect. The only on-line method is the application of the devices, which are able to estimate geometrical and aerodynamic diameters of particles simultaneously,

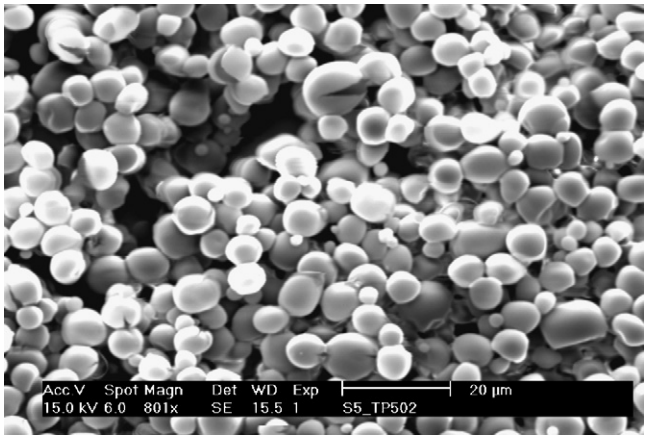

Fig. 7. Hollow particles made of poly-lactic acid and 10% Taxol (in the polymer). Obtained by EHDA of the dichloromethane solution.

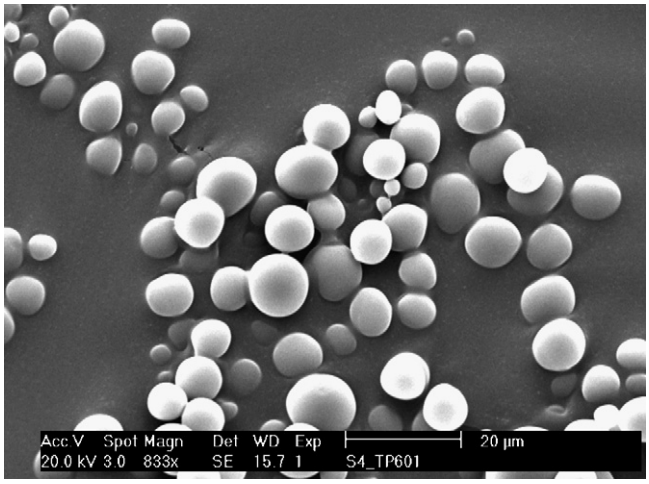

Fig. 8. Solid particles made of poly-lactic acid and 10% Taxol (in the polymer). Obtained by EHDA of dichloromethane containing 20% of cyclohexanone.

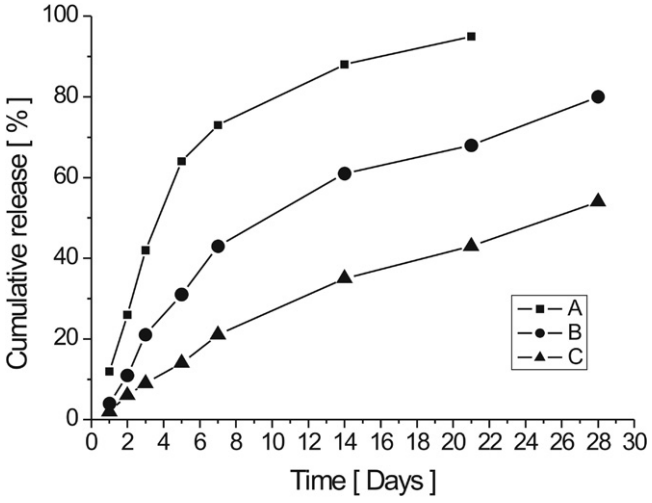

Fig. 9. Drug release from the following particles: (A) poly-lactic acid with 10% Taxol, hollow; (B) poly-lactic acid with 10% Taxol and 10% polyethylene glycol, solid; (C) poly-lactic acid with 10% Taxol, solid.

first by laser light scattering then by acceleration of particles in air flow (Aerosizer or APS). From these two diameters, particle density can be calculated. Even if the solvent evaporation rate is slow and particle drying time is long, it is difficult to achieve more than 90% of theoretical density.

The change of the solvent evaporation rate alters the internal structure of particles and also influences drug release rate. Taxol release rates from the particles shown in Figs. 7 and 8 are shown in Fig. 9.

As it can be seen in the picture, internal structure of particles influences the drug release rate. As an additional drug release modifier polyethylene glycol was used. Polyethylene glycol is dissolvable in water and accelerates the drug release rate.

6. Conclusions

Electro-hydro-dynamic atomization is a versatile technique to produce small monodisperse particles for drug delivery pur-

pose. It allows for an influence on drug release rate either by manipulation of particle internal structure or by chemical additives. Other advantage of this technique is high encapsulation efficiency in comparison to wet, emulsion based methods.

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