Microencapsulation of drugs by electrostatic atomization

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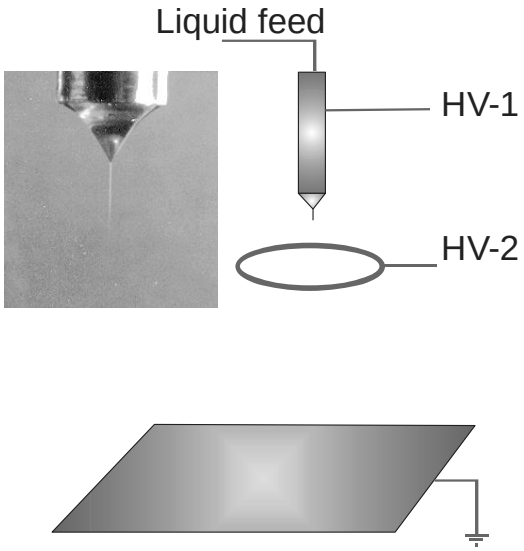
Introduction

From the moment when first primitive men saw a lighting, I am sure, we were fascinated by electrostatics. At the beginning it was mostly a fear, but slowly, interest has got superiority over the fear, and we started to investigate, explore and finally apply electrostatics. One of the applications of electrostatics is atomization of liquids. When a droplet of liquid is subjected to strong electric field, due to mutual repulsion of electrical charges inside the droplet, it change its shape to conical. If the electric field is strong enough, from the cone apex a thin liquid jet emerges, which quickly breaks up into the mist of fine droplets. The phenomenon of electrostatic spraying was probably already observed by ancient Greeks who carried out a lot of experiments with electrically charged amber, but the first known to me publication about this phenomenon appeared in 1600. It was a book by William Gilbert of Colchester titled "De Magnete", a pioneer masterpiece about electrostatics and magnetism. Since the pieces of matter we want to manipulate are nowadays smaller and smaller, electrostatic forces, which are more meaningful in this small world, are more frequently applied (Jaworek, 2008). Nowadays to avoid confusion with other spraying techniques also employing electrostatics together with other means to produce droplets, definition of Electro Hydro Dynamic Atomization (EHDA) method that employs only electrostatics, is recommended. Typical setup for EHDA and a magnified view of the working nozzle is presented in the figure 1.



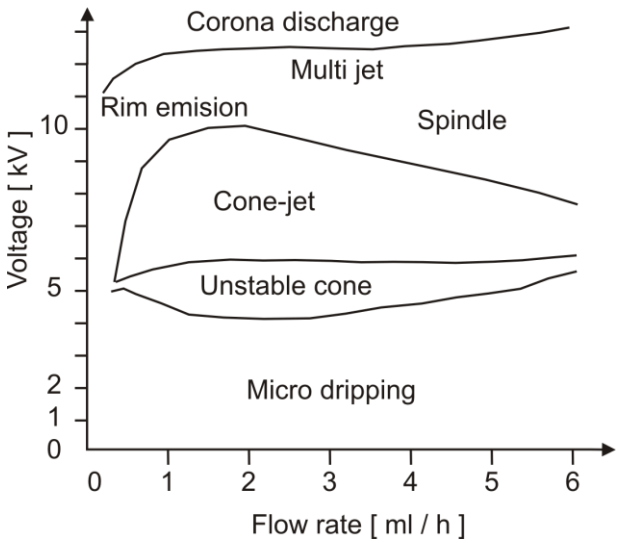


Fig. 1. EHDA setup and a spraying nozzle. **Fig. 2. Spraying modes of the EHDA.**

It consists of a nozzle that conducts electricity and is connected to high voltage power supply, with a liquid supply system - usually a syringe pump. Sometimes below the nozzle a ring connected to the intermediate voltage is placed, it is used to stabilise the process but it is not necessary. Due to

mutual repulsion of electrical charges in the liquid droplet has a conical shape from which apex a liquid jet emerges. This liquid filament breaks up into droplets. Depending on voltage applied, liquid properties and liquid flow rate different modes of the atomization process can be observed. For microencapsulation of drugs two modes of EHDA operation are interested, cone-jet mode and micro-dripping mode, (Ciach 2007, Ciach 2006) . They are stable and reproducible and produce droplets of narrow size distribution. Cone-jet mode is more suitable for small droplet formation (50nm-10μm) at high frequency (1-100 MHz), and micro-dripping mode produce bigger particles at lower frequencies (0.05 – 1mm, up to 1 kHz). Second mode can also be applied in microencapsulation of leaving cells. Production and comparison of drug releasing particles obtained by EHDA operating in this two modes is presented in the following paper.

Materials and methods

Particles were made by electrostatic atomization operating in two different modes, cone-jet and micro-dripping. Because of different problems that appear in both cases they were made in two different reactors shown in the figure 3.

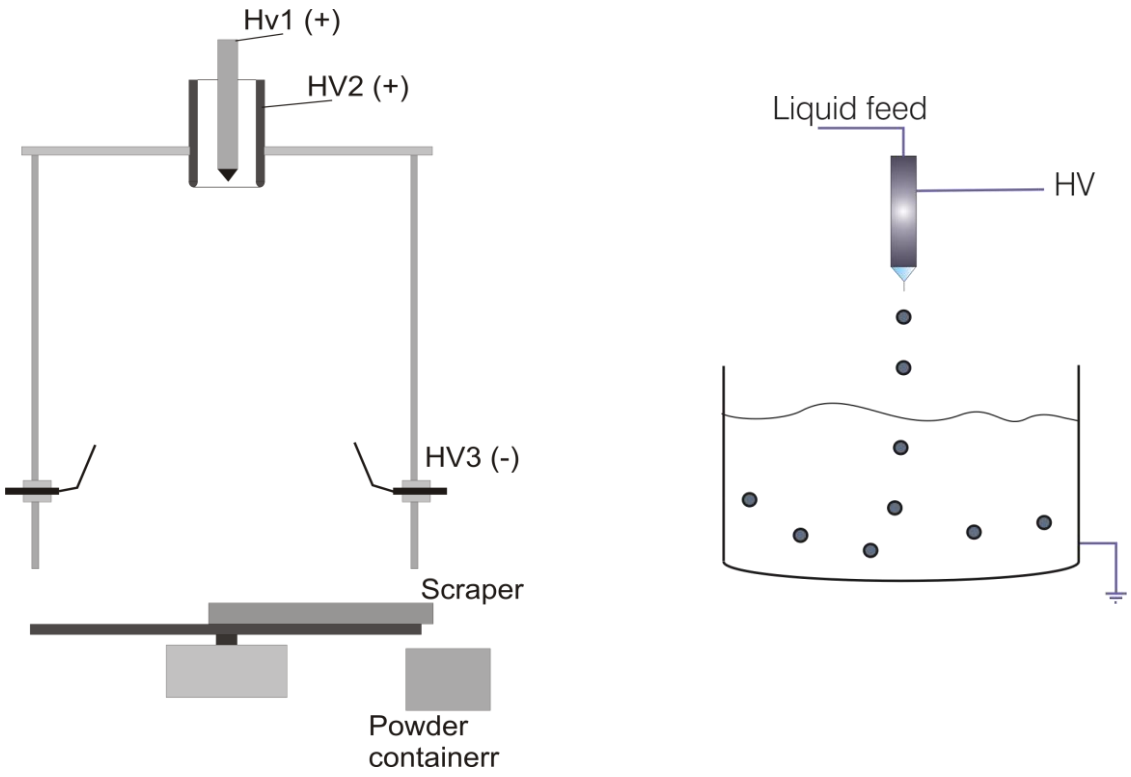


Fig. 3. Reactors for particles production, left operating in the cone-jet mode, right in the micro-dripping mode.

First reactor which operates in the cone-jet mode produces small highly charged droplets. It operates at about 11kV main voltage (HV1) and 8 kV additional stabilizing voltage (HV2). Polymer – drug solution is supplied to the nozzle at the flow rate of 2 ml/h. Droplets have to be discharged to avoid Reileigh explosions and to make them manageable. To perform droplet discharge corona electrodes connected to the opposite voltage (HV3, -5kV) are employed. Discharge current should be about 2-3 times higher to assure complete droplet discharge. Dry particles are collected on the

rotating electrostatic precipitator. This modern design of EHDA powder production reactor operates stably and has a production rate of few grams per hour of almost mono-disperse particles(Ciach, 2007). In the second reactor, due to the fact that particles are much bigger and posses lower electrical charges, there are no discharge electrodes. Reactor operates at 1-5 ml/h flow rate and 2 kV potential of the nozzle. As a nozzle blunt epidemic needle of 0.5 mm i.d. has been employed. Changing solution flow rate and voltage one can manipulate particle diameter from 20μm to about 200μm. Particles are collected in the water bath with a magnetic stirrer, they have to stay there for few hours for organic solvent evaporation. In both cases particles were made of 2-5% of biodegradable polymer; poly lactic acid (Biomer 500) dissolved in dichloromethane, solution contained also 1-3% of Risperidone, drug against mental diseases like schizophrenia. Drug release rate has been tested in phosphate buffered saline (PBS) containing 1% of sodium dodecylsulphate (SDS), drug concentration was estimated by spectrophotometry in near UV region (278nm wave length).

Results

Particles produced in the presented two reactors have different sizes and different surface morphology, Fig 4.

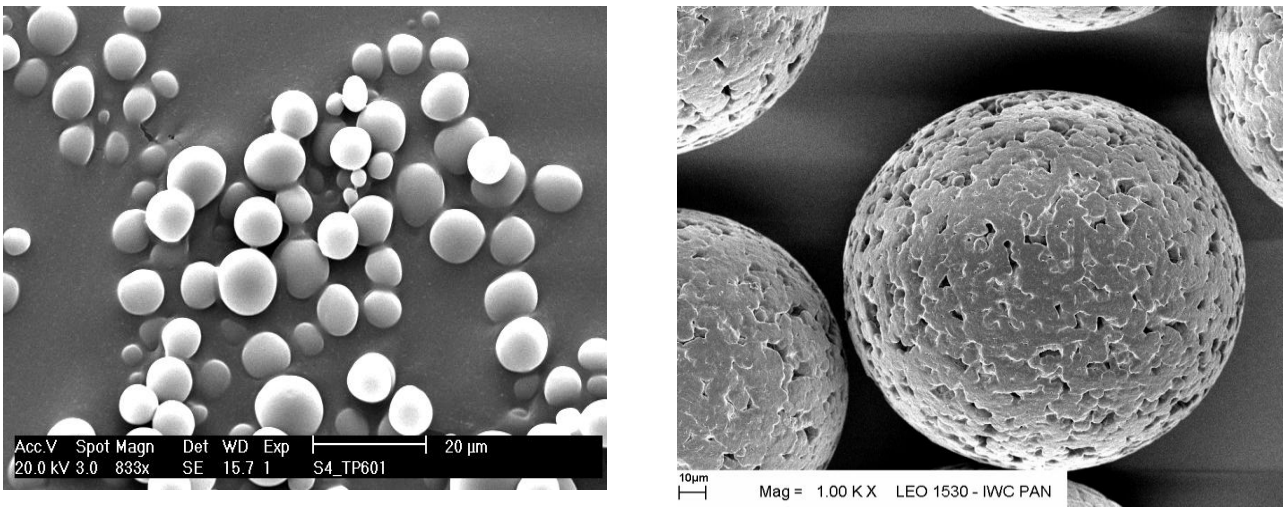


Fig. 4. Particles produced in both types of reactors, cone-jet (left) and micro-dripping (right) modes of operation.

Particles produced in the EHDA reactor working in cone-jet regime and dried in the air exhibit smooth surface while particles obtained in the second reactor showed up a porous surface. Particles obtained in the second reactor were also bigger.
The results of drug release rate from particles produced in the presented setups are depictured in the figure 5.

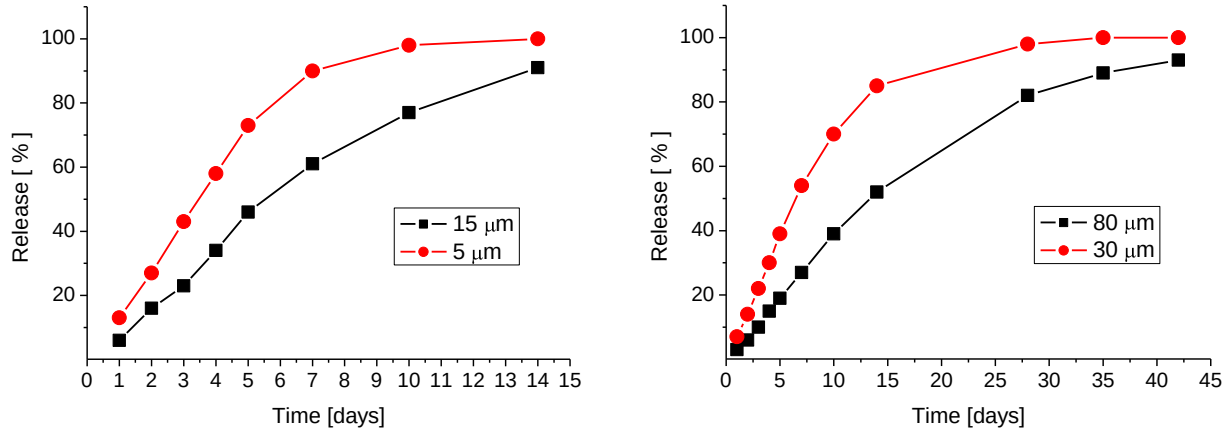


Fig. 5. Drug release rate from particles produced in the cone-jet type reactor (left) and in the micro-dripping type reactor (right).

Conclusions

Surface of the particles obtained in the cone-jet type EHDA reactor is smooth as compared to porous surface of the second type of particles. This happen probably due to the fact, that in micro-dripping type reactor wet particles are immersed in the water solution. Water diffuses into the organic solvent and working as an antisolvent precipitates polymer. Drug release characteristics of this two types of particles also exhibits different character. Cone-jet particles not only release the drug in the much shorter time, due to their size, but also shows a big initial burst of the drug. Micro-dripping particles release the drug much longer, because they are bigger. Particles produced in the cone-jet reactor are in the range of 2-20μm diameter while particles from the second type of the reactor are of 20-200 μm, in both cases particle diameter was a function of applied voltage and a liquid flow rate. Probably due to the fact that surface of the particles is depleted in the drug contents during they drying process in the water solution.
Polymer applied in particle production is fully biodegradable. Bigger particles seems to be very good for long term release of the drug after intramuscular injection, while smaller particles can be administered intra venous for shorter drug release periods.
Presented method is also useful in the encapsulation of water solution of proteins by atomization of water in organic solution of polymer, emulsion.

References

Ciach T., (2007), *Application of Electro Hydro Dynamic Atomization in Drug Delivery*, Journal of Drug Delivery Science and Technology, 17 (6), 367-375
Ciach T., (2006), *Microencapsulation of drugs by electro-hydro-dynamic atomization*, International Journal of Pharmaceutics, 324, 51–55.
Gilbert W., (1600), *De Magnete*, book.
Jaworek A. at all., (2008), *Electrospraying route to nanotechnology: An overview*, Journal of Electrostatics, 66, 199-211.