Experiment and Simulation of Electrospray Particle Flows for Controlled Release of Drugs

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ABSTRACT
Electro HydroDynamic Atomisation (EHDA) disperses a liquid into small, highly charged droplets. We show that this method can be used to produce particles that release a drug at a desired rate. This is done by spraying a solution of bio-degradable polymers and an enzyme, which represents the effective drug. The release rate can be varied by modification of the polymer matrix. It is further demonstrated that the enzyme fully retains its functionality in the EHDA process. Practical use of this technique for medicine production requires a scaled-up design, which must be based on an adequate model of the particle flow in the charged droplet spray plume. As a step in this direction, the most important result is a scale-up relation that allows simulations of an experimental spray with millions of particles, using only a few thousand model particles. The experimental spray is examined with a Phase Doppler Particle Analyser (PDPA) set-up, and the resulting density and velocity profiles are compared to the numerical results. There is a qualitative agreement between experiment and model.

1. Introduction

A spray of uniformly charged particles is an example of a granular system, the flow behavior of which is governed by the repulsive particle-particle interaction. This many-body problem is not easy to solve but the investigation of charged sprays is of special interest, because a spray process can be used for the production of particles for a wide variety of materials. In particular, the phenomenon of electro hydrodynamic atomization (EHDA) or electrospray allows dispersion of a liquid into equally sized droplets. Since they are highly charged, their mutual repulsion avoids aggregation, and they retain their uniform size. EHDA has the potential of producing uniformly sized particulate products from a large variety of materials [1,2]. One of the most interesting options is the production of new drugs with designed, well-defined release characteristics [3-6]. A condition for this field of applications is that the dispersion process is "soft" enough to avoid chemical modification of fragile bio-molecules [7]. The present study will prove this for a special but probably representative case. It will also be shown that EHDA enables design of particles that release the effective agent slowly and with an adjustable rate.

In developing EHDA into a production technique satisfying the quantitative needs for drug production, we meet the challenge of scaling up the present laboratory set-ups. This requires modeling of a system containing millions of particles mutually interacting via a second-order force law. The present study represents an important step in this direction, by applying a simulation technique that assumes a smaller, feasible number of particles and finding a scale-up relation that translates the result to the real world system. The numerical simulation results are compared to experimental results obtained through phase Doppler particle analysis.

2. Electro Hydro Dynamic Atomisation (EHDA)

If a fluid forms a droplet at the end of a capillary tube, the droplet deforms into a cone (Taylor cone) under the action of an electric field. Under suitable conditions, a jet is formed

at the cone tip (cone jet mode). The jet is unstable due to its high charge density and breaks into small, charged droplets. These droplets have a charge that is close to the so-called Rayleigh limit charge, i.e. the highest charge a droplet can have without exploding. In the cone jet mode the flow and field conditions can be adjusted in a way that equally sized particles are formed [8,9]. Particle sizes from nanometers till tens of micrometers can be achieved. Fig. 1 shows a magnified photo of the spray formation and a high-speed camera picture of the the break-up of the jet into droplets

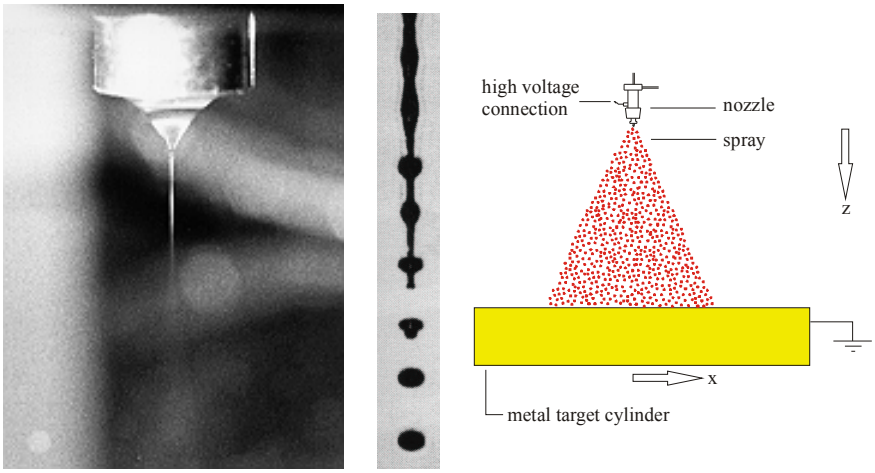


Fig. 1. Electrospraying of the liquid in the cone-jet (left) mode and the jet break-up process (center). The outer nozzle diameter is 5 mm, the inner nozzle is 1 mm. Scheme of the experimental set-up (right) with a spray below the cone. The distance from the nozzle to the target cylinder is about 20 cm.

An experimental set-up used for the present study is schematically shown in Fig. 1. (right). Droplet velocity and size measurements are done with a Phase Doppler Particle Analyser (PDPA). The PDPA equipment measures the number, the size and the velocity of the droplets at a single spot [8,9,10]. A 9:1 ethanol/triethylene glycol mixture is sprayed onto a grounded cylindrical metal target with a flow rate of 7.0 ml/h. The nozzle is set to an electric potential of 18 kV, the target is grounded. The PDPA transceiver and receiver are in front of and behind the plane shown in Fig. 1, respectively. By moving the equipment and thus the point of focus, velocity profiles can be measured. This set-up uses simple geometries and primarily serves the purpose of delivering experimental data to be compared with the model described in section 5.
The occurrence of droplet evaporation adds considerable complexity to the process, because the droplets exceed the Rayleigh limit by shrinking and thus explode to form smaller droplets. Monodispersity is then lost. In the experiment, we are reasonably sure that evaporation does not occur upstream of the measuring zone. If evaporation is too strong corona discharge can be used to reduce the charge of the droplets.

3. Proof of Enzyme Survival under EHDA

Since in EHDA high voltages are applied and high shear forces occur, we examined if easily decomposed substances, like enzymes, are not affected by electrospraying. For this purpose, a solution of the enzyme α-amylase in water was atomised by EHDA. The composition of the solution by weight was 5 % of glucose, 10 % of polyethylene glycol (PEG, 4 600 mw. Aldrich) and 0.03 % of the enzyme protein (bacterial α-Amylase (Sigma)). The enzyme content in the dry particles was thus 0.2%. To check the enzyme activity after atomization, a standard colorimetric test with the dye Amylopectin Azure (Sigma) was performed. About 80 mg of particles were collected on a glass fiber filter. Then the filter was immersed in 100 ml of a pH7 buffer solution. After 15 minutes of gentle agitation, dissolving the particles, 10 ml

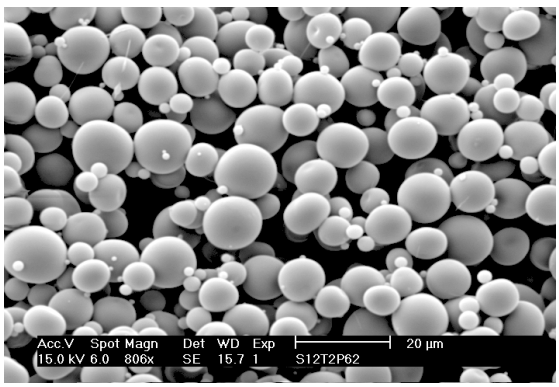
of this solution was added to 100 ml of a pH7 buffer containing 0.5 g of Amylopectin Azure. The concentration of Amylopectin Azure was checked every 5 minutes by colorimetry. The whole test was performed at 22^{O}C. The same test was done with 0.5 ml of the primary, not electrosprayed solution. The comparison showed that the enzyme activity was the same within the experimental error before and after electrospraying. Thus the EHDA process proves to be "soft" enough to retain the protein structure. We presume that this experiment is representative for all proteins used in drug formulation.

4. Production and Test of Particles for Controlled Drug Release

A solution of a drug and a biodegradable polymer is electrosprayed in a set-up with a corona discharge unit in order to neutralize the droplets. The spray is then passed through a diffusion dryer, and the resulting solid particles are deposited in a glass fibre filter. As precursors for a polymer matrix, PLGA (poly-DL-lactide-co-glycolide 50:50, Aldrich) and PEG (polyethylene glycol, 4 600 mw, Aldrich) were selected. Both polymers are biodegradable and have been approved by the American Food and Drug Administration authorities as drug components. PLGA slowly decomposes in the human body. PEG is a waxy solid. This polymer was added to the precursor solution to modify the hydrolysis rate of the PLGA particles. Hydrolysis is an important mechanism in the drug release process. As an example of a drug, we used paclitaxel (taxol), a medicine against certain types of cancer. It is extracted from yew trees. The drug content in the dry particles was one percent by weight. A mixture of dichloromethane and acetone was used as a solvent. The filters with collected particles were left in a dryer at 40^{O}C for thorough drying overnight.

Fig. 2. (left) shows a micrograph of the particles. The size distribution was fairly narrow, but there was also a fraction of much smaller particles. It is not clear if these very small particles originate from the droplet break-up process or from Rayleigh disintegration. The contribution of these particles to the volume of the system is very small. The average particle size as measured with an optical particle counter (Topas, volumetric display) was 13 µm.

The drug release characteristics of both PLGA/Paclitaxel particles and PLGA/PEG (10:1 weight ratio)/Paclitaxel particles were investigated. To simulate the release in the human body liquid environment, the particle-loaded collection filter was immersed in 200 ml of a pH7 buffer solution with a small addition of sodium azide to prevent bacteria growth. 1 ml samples were periodically taken from the solution to measure the paclitaxel release into the liquid as a function of time. They were analyzed with respect to the paclitaxel content by means of liquid chromatography. The cumulative paclitaxel release with time, measured with liquid chromatography, is shown in Fig. 2 (right).



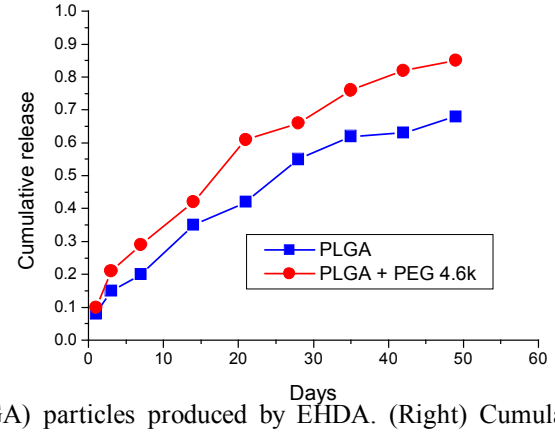


Figure 2. (Left) Paclitaxel containing polymer (PLGA) particles produced by EHDA. (Right) Cumulative release of paclitaxel from polymer (PLGA, PEG) microparticles.

The release rate is not far from constant over a time span of 30 days. The initial burst of the active substance might be associated with the very small particles and from drug on the particle surfaces which can be avoided by coating particles with a inert layer. PEG has the effect of increasing drug release. Thus the release characteristics could be tailored to the needs by adjusting the polymer mixture.

5. Particle Flow Model

While the potential of the EHDA principle for the production of slow release medicine is evident from the results above, the problem of scaling up the process to deliver sufficient quantities has not been solved yet. Since we will deal with a completely different electric field and space charge situation in any multi-nozzle system, this requires a model that adequately reflects the spray evolution between the nozzle and the target. Our approach consists in modeling the individual trajectories of the charged droplets in the spray, taking into account gravity, drag, external fields, and self-interaction due to the uni-polar charge on the droplets [8,10,11]. The experimental data that have been obtained with the PDPA measurement described in section 2 is used to test the model.

For each droplet produced, the equation of motion,

$$m_i \frac{d\vec{v}_i}{dt} = q_i \vec{E} + \vec{f}_D + \sum_{j \neq i} \frac{f_q^2 q_i q_j \vec{r}_{ji}}{4\pi\varepsilon_0 r_{ji}^3} + m_i \vec{g} \ , \qquad (1)$$

with the drag force

$$\vec{f}_D = C_D \frac{\pi}{8} \rho_{air} d_i^2 (\vec{v}_{air} - \vec{v}_i) \left| \vec{v}_{air} - \vec{v}_i \right| \ , \qquad (2)$$

is solved for each time-step *dt*, for each particle *i*. The particles are inserted with a certain rate and initial velocity at the tip of the nozzle [10]. The droplet production time (or the inverse production rate) was decreased in comparison with reality, while the Coulomb interaction charge q was systematically increased by the factor of f_q. For the numerical solution of the equations of motion for each particle, several assumptions lead to the four terms in Eq. (1):

(i) The first term corresponds to the force on the particles due to the external electric field between the charged nozzle and the target cylinder. For the computation of the electric field MATLAB/FEMLAB was used [10,11].

(ii) The second term is the drag force, where the atmosphere is here assumed to be at rest. The drag coefficient leads to Stokes drag in the laminar regime and to turbulent drag for large relative velocities, with a transient regime in between [9,10].

(iii) The third term is the particle-particle self-interaction, where the sum extends over all charged particles with charge q and charge correction factor f_q. Image charges are not taken into account here.

(iv) The fourth term is the gravitational force.

(v) All other forces and a change of droplet properties (evaporation) are neglected.

Starting the simulation with single particles being produced one by one, it takes some time until a steady state situation evolves. The spray shape is shown in Fig. 3. (left).

Besides the other forces, which are not affected by other particles, the strong, long-range Coulomb forces cause every droplet to interact with all other droplets. This leads to a many-body problem with immense computational effort for large particle numbers. The limits of our computing power (single processor) were reached with about 1000 droplets, for a steady state simulation. Our approach is therefore to reduce the droplet number (in experiment, typically 10^5 droplets are in the steady-state spray) by reducing the droplet production frequency. To compensate for the resulting reduction in space charge and Coulomb interaction, the particle charge (in the particle-particle interaction term) is increased by a

factor f_q. The problem is then reduced to finding a scaling relation between charge and concentration/production-rate and verifying its validity.

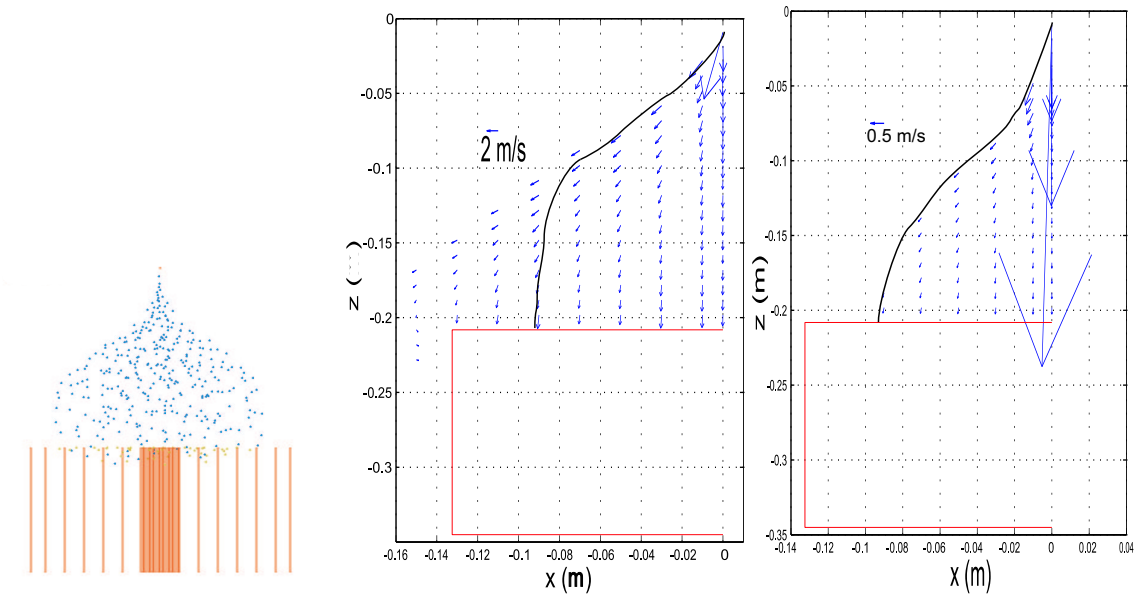


Fig. 3. (Left) Snapshot from a typical EHDA-simulation. The dots are droplets and the vertical lines are plotted around the cylinder and indicate its position with horizontal axis of symmetry. (Center) Experimental velocity profile in the left-half of the system. (Right) Corresponding velocity profile from the simulations.

In order to find the correct charge correction factor f_q, a set of simulations with various production-rates and charge correction factors was performed. The results were examined with respect to the size of the spray cloud/plume, as measured at the target, where the droplets are deposited. Two simulations were found to lead to identical deposits, if Eq. (3) describes the relation between the varied parameters:

$$\frac{f_q(1)}{f_q(2)} = \left(\frac{t_{prod}(1)}{t_{prod}(2)} \right)^{\left(\frac{0.57}{1.06}\right)} . \qquad (3)$$

Furthermore, it is possible to extrapolate from the range of simulated parameters, which charge factor has to be used for the scaled simulation (with about 1000 droplets) of an experiment (with assumed 10^5 droplets). Assuming that for the experiment, $f_q(2) = 1$ is inserted, so that one obtains $f_q(1) \approx 12$ for the ratio of production times of about 100.

The simulated and experimental velocity fields in horizontal and vertical direction are shown for a half-plane in Fig. 3, center and right, respectively. The unit of velocity is displayed as an arrow in both figures. Note that the velocity in the experiment is systematically larger than the simulation velocity. The quantitative disagreement is due to the simplifications of the model [10], the most severe of which are: (i) no image charge is used – with an image charge, particles would be accelerated more strongly towards the target, and (ii) the gas is assumed at rest – in reality the gas is accelerated by the particles and moves with them, thus reducing the drag force on the particles and allowing for larger velocities. These points are to be addressed in more detail in a future publication [12].

6. Conclusions

The present study has shown that Electro Hydrodynamic Atomization (EHDA) is a suitable tool of producing drug particles in the size range of several microns. The process is “soft”

enough to retain complicated organic molecules such as enzymes. Bio-degradable polymers added to the sprayed solution form a matrix enclosing the drug and guaranteeing slow release. In contrast to wet chemical methods, the EHDA spray drying technique exhibits great flexibility in mixing different components. It has been shown that the rate of drug release can be varied by the choice of the polymer mixture. Practical use of EHDA for medicine production depends on successful scaling up of the process. A prerequisite for designing a multinozzle system is a simulation model that adequately describes spray evolution. We have presented a simple modelling approach for the particle flow in the charged sprays. It takes into account the electric field, gravity, the drag between droplets and the gas (which is at rest), and the Coulomb interaction of the particles with each other. The model was tested, and a scale-up relation was proposed that enables simulation of realistic sprays with a much smaller number of particles as present in the experiment. Comparison with experiment showed a qualitative discrepancy between model and reality, which can be attributed to missing image charges, the static background gas or the effect of other simplifications.

7 References

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