**Abstract**

Recent advances in nanotechnology offer nano sized or nanostructured pharmaceutical particles, being as small as the size of cells such as receptors or nucleic acids, which can be engineered to provide enhanced efficacy, solubility, or biocompatibility, and to administer at much lower dosages. However, industrial production of these particles is still challenging. Among different techniques, aerosol based ones might be favorable since they are considered as contamination free processes and do not interfere with complex molecules of drugs. We, in this review, consider liquid atomization, where droplet formation is followed by conversion into solid particles. The best candidate is a method, which not only produces mono sized droplets with a diameter smaller than the inside nozzle diameter but also generates small enough start up sizes. Such a method is found in: Electro-Hydrodynamic Atomization (EHDA) or Electrospraying. Electrospraying is now a well practiced technique for producing very fine monodisperse droplets from a liquid under the influence of electrical forces. By controlling the liquid flow rate and the electrostatic potential between the liquid and the counter electrode, droplets within a narrow size range can be generated, while the mean diameter ranges from nanometers up to several micrometers. Besides generating monodisperse droplets, electrosprays are also distinguished by their self dispersing nature due to Coulomb repulsion, the possibility of trajectory control of the produced charged droplets, and the reduced risk of nozzle clogging due to the large size of the orifice compared to the size of the droplets. We will discuss different spraying modes depending on the strength of the electric stresses relative to the surface tension stress on the liquid surface and on the inertia of the liquid leaving the nozzle. However, for the production of monodisperse nanoparticles the so called cone-jet mode will be explained in depth. Scaling laws can be used to estimate the operational conditions for producing nanodroplets of a certain size. Hartman and co-workers refined the scaling laws for EHDA in the Cone-Jet mode using theoretically derived models for the cone, jet, and droplet size. By means of several examples, a generic way to produce nanoparticles, via scaling laws, from a multitude of different precursors will be discussed. Several examples of medicine particles with different properties made by EHDA will be given. Processes based on bipolar coagulation, where oppositely charged carrier particles and nano sized active agents are brought together to form composite drugs, will be discussed. Finally some attention will be given to challenges on out-scaling of EHDA methods for industrial production.

**Keywords:** EHDA, electrospray, micro droplets, nanoparticles, drug, inhalation

---

**Introduction**

During the last several decades, focus on particle technology switched from macro to micro and micro to nano scales due to significant differences in the physical (electrical, optical, magnetic, chemical and mechanical) properties realized in the nano scale.
The pharmaceutical industry as well took advantage of this shift in scale, in order to design medications or drug delivery vehicles to provide enhanced efficacy, higher stability, solubility, or biocompatibility and to administer at much lower dosages. Besides the particle size, well defined particle size distributions are useful in the production of numerous industrial products. For example, it is known that pharmaceuticals of distinct and narrow particle size distribution have robust properties with a predictive time release to the body. Micro drug particles may have additional functionalities and therapeutic effects when they are coated with nano particles or attached to various molecules such as proteins, peptides, and DNA. By organizing nano particles in a matrix, intelligent drugs can be built for sustained (controlled) delivery and enhanced efficacy. However, it still remains challenging to produce them on an industrial scale. Many of the medical formulations are prepared and converted into particles from a liquid base. Atomization, disintegration of a bulk liquid into fine droplets can be achieved by use of several forces. In this paper we will provide a brief summary of atomization techniques and concentrate only on nano or nano structured medical/pharmaceutical particles produced via electrohydrodynamic atomization (EHDA) and provide examples of potential EHDA applications in the medical industry.

**Forming particles / powders**

Particle generation can be done either via bottom up, i.e. molecular building blocks or top down, i.e. cutting up bigger structures. In the top down way, either bulk solids are broken into small pieces, as in milling, or liquids are disintegrated into fine droplets with suitable methods, as in atomization. A recent publication by Biskos et al. (2008) gives a general overview of production and measurement techniques of nano and micro aerosol particles.

Starting point for generating pharmaceutical particles of well-defined morphology and chemical composition are liquid solutions of a specified chemical composition. Disintegrating these solutions can be achieved by atomization using several techniques and these methods will be briefly discussed in the next section. Droplets formed via atomization are subsequently dried to form solid particles by crystallization. Various techniques can be used to dry pharmaceutical solutions and obtain powders with significantly different powder characteristics. The most common techniques are spray-freeze drying (sublimation), spray drying (evaporation), supercritical fluid drying (precipitation), and spray pyrolysis. Among them the spray drying is the most economical and suitable method for powder production. Spray drying involves atomization, evaporation, and collection. Depending on the primary droplet size and solute concentration of the primary droplets, solid nanoparticles of different diameters can be generated. To produce nanoparticles the initial droplet size should be already fairly small, because otherwise the begin concentration has to be unacceptably low. One should realize that the diameter of the final particle after drying equals the diameter of the initial droplet times the cube root of the volumetric concentration of the non-volatile material (van Erven et al. 2005). For example, to form a nano sized solid particle, a droplet with an initial size of less than 1 micro meter from a solution with or with less than 0.1 weight percent is needed. The choice of atomizer mainly affects the primary droplets size, and size distribution of the spray, which is very important for the uniformity and quality of the dried powder.

**Atomizers**

Atomizers suitable for aerosol based processes can be categorized depending on the forces applied to breakup the liquid into small airborne droplets (Hinds 1999); i.e. pneumatic, ultrasonic, and electrical. They produce relatively smaller primary droplets (with a size distribution between 1 and 100 μm in diameter), making them suitable for use in aerosol-based applications in nanotechnology (Biskos et al. 2008). However, the relatively low particle concentration of the produced aerosols restricts these methods for applications that require only small amounts of particles.

In pneumatic atomizers, the high forces occurring at the air-liquid interface cause the solution to break-up into small liquid droplets which become airborne and are carried away by the air flow. The particles generated by pneumatic atomization are polydisperse (with a geometric standard deviation of the size distribution, σ, of 1.4 or greater). If their size has to be controlled within a narrower range, a classifier has to be employed downstream of the particle generator. In pneumatic atomizers the droplet size not only depends on viscosity, surface tension and density, but also on atomization pressure and orifice size, thus requiring very small orifices and high pressure drops to form very small droplets (Lefebvre 1989).

In ultrasonic atomizers, a solution is broken up to
micron-sized droplets by ultrasonically vibrating its air-liquid interface, to create capillary waves. A particle-free air-stream is passed over the solution to take away the generated airborne particles. The diameter of the primary droplets produced is a function of the frequency of vibration and the physical properties of the solution, i.e., surface tension, viscosity and density. Compared to pneumatic atomizers, ultrasonic atomizers can generate relatively monodisperse particles ($\sigma$ of less than 1.2). Although the performance of ultrasonic atomizers remains inherently stable, and although they are suitable for inhalation purposes, coating and spray drying applications, their greatest drawback is low particle number concentration and increasing temperatures at prolonged operations. Ultrasonic atomizers can produce monodispersed bioactive, biocompatible, and biodegradable micro/nano particles appropriate for use in drug delivery systems, or for surface coatings in the implant and electronics industry (Felder et al. 2003, Forde et al. 2006, Freitas et al. 2004, Friend et al. 2008). Ultrasonic atomization is more suitable for low-viscosity liquids and low temperature applications. Recent reviews of ultrasonic droplet formation are provided by Biskos et al. 2008, Barreras et al. 2002, and Yule & Al-Suleimani 1997.

Electrohydrodynamic atomization (EHDA), or electrospraying, is a process where liquid can be disintegrated into uniformly sized droplets under the influence of electrical forces in a very controlled fashion. EHDA comes with plenty of unique advantages in comparison to the conventional systems, one of them being the narrow size distribution. This uniqueness makes it suitable for many industrial and academic applications. Depending on the flow rate and liquid properties, the main droplet size produced ranges from nanometers with production frequencies in the order of $10^3$ Hz to hundreds of micrometers with production frequencies of about $10^4$ Hz. Besides generating monodisperse droplets, electrospays are also distinguished by their self dispersing nature due to Coulombic repulsion, the possibility of trajectory control of the produced charged droplets, and the reduced risk of nozzle clogging due to the large size of the orifice compared to the size of the droplets. EHDA can be operated in many environmental conditions, but mainly in the ambient conditions, thus overcoming possible degradation of drugs under extreme operating conditions. Since EHDA offers many (potential) applications it will be described in more detail.

History of Electrohydrodynamic Atomization (Electrospraying)

The phenomenon of an electric effect on liquid menisci is known since the sixteenth century. William Gilbert reported in 1600 the interaction between a water droplet and a piece of amber held closely to it, leading to a conical shaped droplet. In the beginning of the 20th century Zeleny (1914, 1915, 1917) demonstrated fine droplet formation from a conical shaped meniscus, transformed from a hemispherical meniscus under an electrical stress. In the middle of the same century, theoretical and experimental works followed by Taylor (1964), Vonnegut and Neubauer (1952). It became a subject of thousands of research papers including dissertations (Meesters 1992, Geerse 2003, Hartman 1998, Wilhelm 2004), books (Bailey 1988, Michelson 1990), and special issues are dedicated to review the theory and applications of the electrospray in the Journal of Aerosol Science (issues 25 (1994) and 30 (2000)). Here we provide only highlights, and for details the reader is referred to the early reviews on particle generation via electrospray (Kozhenkov and Fuks 1976, Smith 1986, Grace and Marijnissen 1994) and more recent overviews of electrospray and its applications (Jaworek 2007, de la Mora 2007). The interest in electrospray progressively increased by the Nobel winning work of Fenn on Mass Spectroscopy for detection of macromolecules. Scaling laws for electrospraying of liquids were developed, to predict the characteristic size of the produced droplets on foreground (de la Mora and Loscertales 1994, Gañán-Calvo et al. 1997, Hartman 1999, Chen and Pui 1997). The developed scaling laws refer to the so called cone-jet mode, one of the modes that can be obtained in electrospray, and is of great interest due to its steady operation.

Electrospray modes

In EHDA, where as already mentioned a liquid jet breaks up into droplets under influence of electrical forces, different spraying modes can be obtained depending on the strength of the electric stresses relative to the surface tension stress on the liquid surface and on the kinetic energy of the liquid leaving the nozzle (Zeleny 1914, 1915, 1917, Cloupeau and Prunetloch 1994, Grace and Marijnissen 1994). For the production of monodisperse nanoparticles the so called cone-jet mode is desirable. In this mode the liquid is typically delivered through a nozzle at a flow rate of the order of $\mu$l/hr to ml/hr, and an elec-
Electric field is applied between the nozzle and a counter electrode. This electric field induces a surface charge on the growing meniscus created at the nozzle. Due to this surface charge and the electric field, an electric stress is created on the liquid-air interface. Depending on the electric field strength and the liquid flow rate, the electric stress can overcome the surface tension stress and transform the shape of the liquid surface to a cone, i.e., the Taylor cone (Taylor 1964). The tangential component of the electric field accelerates the charge carriers at the liquid surface toward the cone apex. These ions collide with liquid molecules, thereby accelerating the surrounding liquid. As a result, a thin liquid jet emerges at the cone apex (Zeleny 1914, 1915, 1917). See Fig. 1.

Besides, the aforementioned cone jet mode several other modes exist. As we will only make use of the cone jet mode for the production of nanoparticles, we will only briefly mention them. Which mode appears depends on the system parameters (flow rate, field strength, liquid properties). The earliest classification is reported by Hayati et al. 1987(a and b). The classification mostly used is made by Cloupeau and Prunet-Foch (1994) and based on the spraying geometry. However, there are also classifications based on characteristic time constants (Shiryaeva and Grigorev 1995) and its combination with a geometrical factor, (Jaworek and Krupa 1999), and also based on the emitted currents (Jurasek and Röllgen 1998). The electric field intensity near the tip of the nozzle plays a major role determining the operation mode, with the nozzle dimensions being a critical factor. Based on flow rate and applied potential, starting from zero potential, dripping, and by increasing the potential, fast dripping, intermittent cone jet (Fig. 2), cone jet (Fig. 1 and 6), and multi jet modes (Fig. 3).
can be realized (Grace and Marijnissen 1994). Microdripping, simple jet, spindle (Fig. 4) and ramified jet modes can also be seen depending on the fluid properties and flow rate. It should be noted that neither for all liquids each mode may occur nor that the modes are always realized in this systematic order. The cone-jet is as aforementioned the most interesting electrospraying mode and its stability makes it useful for various applications; production of particles, printing of bio-molecules, and precision deposition methods. The cone jet mode allows the production of aerosols within a very large range of droplet sizes for a very wide range of liquid properties in terms of conductivity, viscosity and surface tension. The size distribution of the particles produced can be monodisperse, but depending on the experimental conditions, can be bimodal or polydisperse. Due to the excess of surface charge in the liquid cone and jet, the droplets are highly charged.

Scaling of droplet size and current in the cone jet mode

In the past, several attempts have been made to model the cone-jet mode, both analytically and numerically. Various equations have been derived, to estimate the produced main droplet size, and to estimate the electric current through a liquid sprayed...
in the cone-jet mode as function of liquid properties and flow rate. Combining dimension analysis with experimental results, de la Mora and Loscertales (1994) found relationships for liquids with relatively high conductivities. Also, based on dimensional analysis and experimental results, Gañán-Calvo et al. (1997) found two different relations for the droplet size and current. Highly conductive liquids or highly viscous liquids were found to behave differently from liquids with a low conductivity and a low viscosity. In order to judge, which relation is valid, they introduced the following dimensionless number,

$$\left( \frac{\gamma^2 \varepsilon_0^2}{\mu^2 K^2 Q} \right)^{\frac{1}{2}}$$

(1)

where, \(Q\) is liquid flow rate \([m^3/s]\), \(K\) is conductivity \([S/m]\), \(\varepsilon_0\) is electric permittivity of a vacuum \([C^2/N \cdot m^2]\), \(\gamma\) is surface tension \([N \cdot m^{-1}]\), and \(\mu\) is the absolute viscosity of the liquid \([Pa \cdot s]\). This dimensionless number, viscosity number (VN) as called by Hartman (1998), is formed from multiplication of two dimensionless numbers, the ratio of flow rate to a characteristic flow rate and the viscous dimensionless parameter. The viscous dimensionless parameter is interpreted as the ratio of two characteristic velocities: the characteristic velocity in the liquid bulk and the propagation velocity of a perturbation across the jet by viscous diffusion (Gañán-Calvo et al. 1997). The viscosity number as interpreted by Hartman (1998) represents the ratio of the change in kinetic energy of the liquid jet in the axial direction over the change in viscous stress in the radial direction. If the viscosity is high or the conductivity is high, then this ratio is relatively low. The size of the jet diameter is mainly determined by the liquid flow rate, and the liquid conductivity. The higher the viscosity, and the smaller the jet radius so for higher conductivity, the smaller the difference between the axial liquid velocity in the jet center and this velocity at the jet surface becomes. The radial profile of the axial liquid velocity will then be almost flat. Gañán-Calvo (2004) investigated various scaling laws and data from them with an attempt to unify them, and found that the effect of permittivity is negligible unless polarity is important. Recent summaries of scaling laws for droplet size and current in the cone-jet mode are given by Chen & Pui (2010) and with more emphasis by de la Mora (2007). However some papers contributing to the scaling laws are overlooked in the latter.

Using his physical numerical model Hartman (1999) derived theoretically the following electric current scaling law for Newtonian liquids with a flat radial velocity profile in the jet

$$I^* = b(\gamma K Q)^{0.5}$$

(2)

\(I\) is the electric current for a jet with a flat radial profile of the axial fluid velocity. The difference with the scaling laws of de la Mora and Loscertales (1994) and of Gañán-Calvo et al. (1997) is that the liquid permittivity has completely disappeared from the scaling law. However, as mentioned Gañán-Calvo came in 2004 with comparable conclusions. By using equation (2) and experimental results of Gañán-Calvo et al. (1997) and of Hartman (1999) for “\(b\)” a value of approximately 2.17 is found. Yielding, .

$$I^* = 2.17(\gamma K Q)^{0.5}$$

For liquids where the radial velocity profile is not flat Hartman (1998) found

$$I = 0.41I^* + \frac{0.24I^*}{E_{z,max}} KQ(A_{R^0.41} + B)$$

(3)

Where \(I\) is the current for a flat radial profile of the axial velocity (equation 2) and \(E_{z,max}, R_{0.41}, A\) and \(B\) are all functions of known parameters. For the derivation of equation 3 and the computation of the different terms see the Appendix.

The value of \(I^*/I\) can be found much faster by using Fig. 5, representing, \(I^*/I\) as a function of the viscosity number. Curve fitting these data composed of experimental values with the least squares method yields \(I^*/I = 1 - 0.1 \cdot VN^{0.45}\). For a certain \(VN\), the value \(I^*/I\) can be determined graphically or by using the formula. As seen in Fig. 5, the points start to scatter around a viscosity number of 10. Fig. 5 may be safely used till a value of VN of 10.

**Scaling laws for the size**

Since the initial droplet size is one of the most decisive factors for the end product size, and EHDA quality, an empirical or semi-empirical equation for predicting the droplet size will be very useful. Works of Cloupeau and Prunet-Foch (1994), Rosell-Llompart and de la Mora (1994), Chen and Pui (1997) and Gañán-Calvo et al. (1997) provided earliest semi-empirical models for the mean droplet size. For the droplet size in the cone jet mode, Hartman (1998) also derived scaling laws. The jet break-up mechanism depends on the ratio of the electric normal stress over the surface tension stress. At low values, the jet breaks up due to varicose instabilities. At higher values, the jet starts to whip. The jet break up is now influenced by both varicose and kink instabilities.
The threshold value of the stress ratio above which the jet starts to whip is not sharply defined but it is around 0.3 (or 0.24 for whipping of the filament). Geerse (2003) also reports that for a stress ratio between 0.2 and 0.3 the jet starts to whip. A smaller stress ratio yields varicose breakup, while a higher stress ratio leads to whipping breakup. In the whipping breakup mode the size distribution of the main droplets is wider than in the varicose breakup mode.

The scaling law for the droplet size in the varicose jet break-up (Fig. 6-a) mode as found by Hartman et al. (2000),

\[ d_{d, varicose} = c_d \left( \frac{\rho \varepsilon_o Q^4}{I^2} \right)^{1/6} \] (4)

where \( c_d \) is a constant, and \( d_{d, varicose} \) means the diameter of the droplet, of which the volume is composed.
of a primary (main) droplet and, if present, its secondary and satellite droplets. Since the volume of the main droplet is much bigger than the volume of the secondary droplets and satellites, and because the diameter scales to the volume to the power \(1/3\), \(d_{\text{varicose}}\) is close to the primary (main) droplet size. The constant \(c_s\) was found to be in the range of 1.76 to 2.05.

Assuming that the radial profile of the axial fluid velocity in the jet is flat, then the current scales according to equation (2), and relation (4) yields

\[
d_{\text{varicose}} = \frac{c_d}{b^{1/3}} \left( \frac{\rho \varepsilon_o Q^3}{\gamma K} \right)^{1/6}
\]  

(5)

Since \(b\) and \(c_s\) both have values close to 2, by approximating them by 2, giving less than 15% deviation, (5) becomes

\[
d_{\text{varicose}} = \left( \frac{16 \rho \varepsilon_o Q^3}{\gamma K} \right)^{1/6}
\]  

(6)

For the whipping jet break-up mode (Fig. 6-b) Hartman (1998) derived the following the droplet size scaling law:

\[
d_{\text{whipping}} = \left( \frac{0.8288 \varepsilon_o \gamma Q^2}{I^2} \right)^{1/3}
\]  

(7)

where, \(d_{\text{whipping}}\) is the droplet size predicted for a jet that breaks up in the whipping jet break-up mode. Again the droplet size represents a droplet with the total volume of the primary, secondary and satellite droplets. The constant 0.8 was calculated from the measured droplet sizes. However, other measurements of Gomez and Tang (1994), and Gañán-Calvo et al. (1997), indicate that this value can also be 0.49 or 0.64.

As indicated already the threshold between the varicose and whipping breakup is not sharply defined. However, which of the two droplet size scaling laws, equations (7) and (6), should be used, can easily be deduced by calculating both droplet sizes. The equation that yields the smallest droplet size is the appropriate one. This indicates whether the jet is in the varicose mode or in the whipping mode.

**Estimation of particle size from a solution**

For a spherical droplet, a simple derivation relates the diameter of the (final) solid particle \(d_p\) after drying to the primary droplet diameter (van Erven et al. 2005) by Equation 8:

\[
d_p = \sqrt[3]{\frac{\rho \varepsilon_o \gamma Q^2}{\rho_{\text{droplet}} \varepsilon_o \gamma Q^2}}
\]  

(8)

where \(f\) is the mass fraction of the material in the solution (\(\varepsilon\)), \(\rho_{\text{droplet}}\) is the density of the solution and \(\rho_{\text{particle}}\) is the density of the final (product) particle (kg/m³). This is of course only true if the particle is non porous or not hollow. By choosing the right conditions in concentration, type of solute, solvent, and drying conditions, it is possible to make hollow or porous particles. In this way also the aerodynamic diameter of the particle decreases.

**EHDA Configurations**

In the preceding sections we have shown that EHDA comes with both empirically and theoretically derived equations, which can be used as predictive tools and can thus help us to produce desired particles, or surface structures in a controlled manner. To achieve this, there exist four major EHDA configurations which have been used and reported in the literature for the production of particles.

**The first and the most commonly used basic configuration** is known as Needle - plate configuration (see Fig. 7). In some cases a ring electrode around the nozzle can be provided, as in Fig. 8, (needle - ring extractor - plate) for spray stability and to spray at lower potential differences. This configuration is ideal for direct coating medical substrates such as tablets, individual micro particles, or medical inserts. Droplets in this way can be deposited to form either discrete particles or thin films. In this and other configurations the droplets are produced from an appropriate solution. A solvent is selected to provide appropriate levels of conductivity when the solution is formed or the solution may be doped with conductivity control agents. It is essential to measure the conductivity, and surface tension of the solution. This solution containing the formulation is fed to a nozzle (B) via pumping or a pressure head delivery system (A). The flow rate of the solution is selected to produce the desired primary droplet size. It varies from \(\mu\)l/hr to ml/hr to obtain nano to micron sized droplets. In the needle to plate configuration, the required electrical field is created by applying a voltage between the capillary (B) and the counter electrode (E,F) using a high voltage power supply (C). The distance between the tip of the capillary (B) and the counter electrode (E) is selected to provide enough residence time for drying or reacting for the end product. The set up can be operated at ambient or other conditions.

The first configuration takes advantage of the charge on the particles, however in some applications the charge on the droplets is not desired, such as in using EHDA directly for inhalation purposes or...
**Fig. 7** Schematic of the capillary to plate electrospray set up, A) Syringe pump, B) Nozzle, C) High voltage supply, D) Taylor cone and droplet cloud, E) Collection substrate, F) Earthed support.

**Fig. 8** Aerosol set up to produce particles from electrospray. Droplet generation and neutralization take place inside a reactor. A drier could be included before particle collection (Adopted from Meesters et al. 1992) A) syringe pump, B) nozzle, C) high voltage supply.
sometimes for powder production. For this purpose, in the second configuration, a setup similar to the first one is enhanced by addition of a charge neutralization mechanism, such as a needle to form oppositely charged ions via corona discharge (Hartman 1998) or a radioactive source (Chen et al. 1995). An air stream carries particles to a collection point or desired location in case of inhalation. A treatment step could also be included, e.g. to induce chemical reactions (Meesters et al. 1992), see Fig. 8. In this setup a ring is used as counter electrode. The function of the ring is two fold; to stabilize the atomization at lower voltages, and shield the formation of droplets from destabilization effects of the corona discharge. The ring is connected to a high voltage power supply, but at a lower voltage than the capillary. The distance between the ring and capillary can be adjusted. The potential difference between the nozzle and the ring creates the field to produce the droplets, which will pass through the ring. In this way the droplets are not deposited as in the capillary-plate set up, but are kept airborne. However to prevent them to deposit on the reactor walls, the droplets are discharged by a corona in this case. Another reason to neutralize the droplets is the fact that during drying the volume of the droplet decreases and the surface charge density increases. Once a droplet evaporates to a critical diameter, it will reach the Rayleigh charge limit when the droplets will disintegrate into smaller ones, destroying the control on particle size (Smith et al. 2002). It should be realized that the droplets produced by EHDA carry a high electrical charge in the order of 70% of the Rayleigh limit (Hartman 1998). After the reactor the nanoparticles are collected via a grid or filter.

The third configuration involves use of oppositely charged droplets created by two oppositely charged EHDA, in the cone-jet mode, see Fig. 9. If they are directed towards each other coagulation between the droplets takes place through the electrical attraction between them (Bipolar Coagulation). In this case, droplets of different composition can be mixed and reacted to form composite or new materials (Camelot 1999). The coagulation can also be used just to neutralize the droplets. If the right conditions are chosen, it is also possible to coat one material with another.

The fourth configuration, coaxial EHDA, utilizes two coaxially aligned EHDA nozzles, as seen in Fig. 10. This could be the desired configuration to form encapsulated particles in a single step, and when right combinations are found to produce encapsulated particle in the absence of additives (Chang et al. 2009). Each nozzle is fed separately. The central one slightly protrudes to facilitate the coating by the outer liquid. In this way, controlled encapsulation can be done. The spray phenomena are mainly controlled by the properties of the outer liquid (Chen et al. 2000, Loscertales et al. 2002, Chen et al. 2005), which can be as in the case of Chen et al. (2000) very viscous and electrically conductive. However, this configuration is not limited to two coaxially aligned nozzles. Multiple layers can be produced by aligning more nozzles concentrically (Lallave et al. 2007, Kim and Kim 2010).

Medical Applications

Due to its emerging potential in biomedical and pharmaceutical applications, various aspects of EHDA on medicine are recently reviewed by Chen & Pui (2010), Marijnissen et al. (2010), Jaworek (2008), and Ciach (2007). Electrohydrodynamic atomization has been applied to produce thin films, the production of micro and nano sized particles, microencapsulation, implant coating, inhalation therapy, micro reactors via bipolar coagulation for drug powder production, making inorganic nanoparticles via electrospray pyrolysis, electrospray gene transfection and more (Chen & Pui 2010, Marijnissen et al. 2010, Jaworek 2007). The aforementioned scaling laws for the cone jet mode provide a powerful tool to the user to apply electrospray. The different medical and pharmaceutical fields in which electrospray is utilized are described in next sections.

Mass spectrometry

The application of electrospray in the field of mass spectrometry has expanded enormously. In its simplest form, a mass spectrometer (MS) is an instrument that measures the mass-to-charge ratios m/q of ions formed when a sample is ionised by one of a number of different ionisation methods. Electrospray as a method for generating gas-phase ions was introduced in 1968 by Dole et al. His intention was to determine the mass of polystyrene macromolecules. The idea of coupling the electrospray technique to a conventional mass analyser was put forward as early as 1973 by Dole et al., and realised in 1984 by Yamashita and Fenn. Its potential for the analysis of large biomolecules was realised in 1988 by Meng et al.. Today, electrospray MS is used to analyse large biomolecules, such as proteins, nucleic acids, carbohydrates, lipids, and compounds composed of two or
Fig. 9  Schematic of the bipolar coagulation configuration and possibilities for particle production (Adopted from Camelot 1999).

Fig. 10  Dual nozzle (concentric) electrospray set up.
more of these components. Nowadays, the amount of research activities and publications in the field of electrospray MS can hardly be overlooked. Excellent reviews and books dealing with electrospray MS were written by Cole (1997), Kebarle and Tang (1993), Smith et al. (1997) and Dulcks and Jurasek (1999). The work done in Electrospray Ionization obviously proves the fact that the electrospray technique is a soft method to cause no harm to bio-molecules (e.g., DNA, peptides, and proteins), making it a distinct technique to produce pharmaceuticals based on these delicate structures.

**Carrier particle and drug particle production**

Micro and nano particles produced via the electrohydrodynamic process can be utilized for therapeutic or diagnostic purposes in medicine. Besides in the form of aerosol (inhalation particles), drugs can be delivered efficiently to certain parts of the human body as particles in emulsions or as deposited particles on engineered scaffolds (i.e. tissues, stents, bone anchors...etc.). Considering the unique advantage of the EHDA technique, one can envisage its potential future applications for advanced treating methods and also for diagnostic purposes.

Drug particles with a narrow size distribution have the unique advantage of providing more regular and predictable drug release profiles from batch to batch compared to particles with the same mean size but wider distribution. Electrospraying is an ideal route for the production of such drug particles either in pure or polymer blended form. In this case a drug or a polymer/drug combination dissolved in a suitable solvent is electrosprayed. Several authors have already reported on the production of nanoparticles with narrow size distributions using the EHDA route (de la Mora et al. 1990, Rulison and Flagan 1994, Hull et al. 1997, Gomez et al. 1998, Lenggoro et al. 2000, Ciach et al. 2002, Nakaso et al. 2003, van Erven et al. 2005, Gonzales et al. 2007, Hogan et al. 2007). A recent review on the subject is provided by Jaworek and Sobczyk (2008). If the right solution properties are achieved, EHDA can be seen as a generic way to produce well-defined nanoparticles of various compositions on demand (Marijnissen et al. 2010).

Other examples of processes that use electrospray for the production of powders and drug particles are electrostatic spray pyrolysis (ESP) and bipolar mixing. In electrostatic spray pyrolysis, electrospraying is combined with pyrolysis. The liquid that is used to spray, contains inorganic components that form the powder. Vercoulen et al. (1993) used the technique to produce a powder of SnO₂, which is used as a semi-conductor material or as an additive to alter the electric properties of powders. A precursor solution of Sn(Ac)₄ was sprayed into droplets which were dispersed into air and carried through an oven where the droplets were evaporated and the remaining particles pyrolysed. Rulison and Flagan (1994) synthesised high quality yttria powders, composed of dense submicrometer, nanocrystalline oxide particles. This method seems ideal for forming ceramic nano drug delivery vehicles.

As already mentioned, the process of bipolar coagulation (Camelot 1999), where two sprays of oppositely charged droplets are directed towards each other and the coagulation between the droplets takes place through the electrical attraction between them can also be used to produce drug particles, see Fig. 11. Bipolar mixing can also be used to coat carrier particles with drug particles, which will be treated in another section. Bipolar coagulation is such a flexible method that one of the solutions can also be selected.

![Fig. 11](image-url) Micro and nano ZrOₓ particles produced via bipolar coagulation process (Camelot et al. 1999).
invasive and historically one of the oldest methods to administer drugs and fight several lung diseases such as asthma, emphysema, bronchitis, and chronic obstructive pulmonary diseases. As new types of drugs based on proteins, peptides, and DNA are developed, inhalation routes are considered to be used for insulin delivery, cancer treatment, pain control, and nanotherapeutics (Albert et al. 2007, Kleinstreuer et al. 2008, Heijerman et al. 2009, Siekmeier R. and Scheuch 2008, Shoyle and Slowe 2006, Shoyle and Cawthorne 2006, Sung et al. 2007, Lastow 2007). What makes pulmonary administration in general an advantageous route to deliver therapeutics is the ease of administration, rapid onset because of the area available for permeation to cells and the blood stream, smaller doses administered compared to the oral administration route, and better efficacy to safety ratio compared to systematic delivery. Use of nanoparticles, in addition, could contribute by sustained release in the lung tissue (Sung et al. 2007). However, the success of administration depends greatly on the performance of the delivery device, the size distribution of the delivered particles, the lung state of the patient, and the coordination between device and patient. These aforesaid merits and needs in the pharmaceutical industry have lead into many developments in inhalation devices such as nebulizers, metered dose inhalers, and dry powder inhalers, and a quest for novel delivery devices. Advantages and disadvantages of these devices are discussed in books and reviews such as by Hickey (1996), Gradon and Marijnissen (2003), and Geller (2008). As particles flow from the nose or mouth to the deeper lung regions, they deposit due to the deposition mechanisms of impaction, sedimentation and diffusion. For a good delivery the particle size matters, so an accurate control of the size is vital, and the device should generate drug particles with a predetermined size, ideally an aerodynamic diameter of smaller than 7 micro meters (Hickey 1996, Gradon and Marijnissen 2003). Particles close to the upper limit have a higher probability to get deposited in the mouth, throat and upper airways. Smaller particles have a higher probability to reach the surface of the lower airways and alveoli. Maximum delivery efficiency to the lower airways is achieved with particles either around 20 nm or 2 μm in diameter (Hinds 1999). However, of these particles only about 30 % can efficiently reach the lower airways. The total deposition efficiency even gets lower due to a size distribution associated with the drug particles in a commercially available inhaler and due to obstructions in the patient’s lung airways. Conventional inhalers produce polydisperse drug aerosol particles with a mean particle size > 5 mm, which explains the low therapeutic efficiency of the inhaled drugs. In case of dry particle inhalers, powder dispersibility is crucial in view of the fact that such small particles tend to form agglomerates due to cohesive forces leading to variations in the particle size distribution (Weiler et al. 2010). However, a monodisperse drug aerosol with the right size reduces the dose which has to be administrated by 80%, providing the same efficacy and reducing the side effects (Zanen et al. 1998, Zanen and Lammers 1999). Besides providing polydisperse aerosols, some inhalers have other disadvantages such as the ones based on ultrasonics which may cause thermal degradation of drug particles (Hickey, 1996). The electrospray technique has the ability of producing monodisperse aerosols with a controlled and predetermined droplet size and therefore it resolves particles size distribution related issues in conventional inhalers and is a perfect technique to produce aerosols for drug inhalation (Geerse and Marijnissen 2003). Using this technique may result in a decrease of the amount of drug administered and so in a decrease of the adverse effects the inhalation drugs have on the body. The first inhaler known using the electrospray technique was patented by Noakes et al. (1989), Tang and Gomez (1994) further developed the electrospray system of Noakes et al. (1989) for the use in an inhaler. The main difference with the system of Noakes et al. (1989) is the flow of CO₂ that is used to isolate the capillary tip from the air. In this way the onset of air discharge is suppressed, which makes it possible to spray liquids with a high surface tension, like water. As mentioned, the size of the droplets may be controlled by changing the conductivity of the liquid. Gomez et al. (1999) disclosed a method to electrospray in the corona assisted cone jet mode. Noakes et al. (2000) then published a description of another EHDA device, which is more suitable for nasal delivery and upper respiratory tract treatment due to charge present on the particles. Ijspeertaert et al. (2001) described a EHDA drug atomizer where the droplets are neutralized by corona discharge. Gañán-Calvo (2003) described another device based on coaxial...
nozzles, where formulations in the form of miscible or immiscible liquids, solutions or suspensions can be delivered. His patent application focused on the production of particles but did not incorporate any means of neutralization, which may be preferred to effectively deliver therapeutics to the upper airways. The presence of a controlled charge on the particles in the case of Noakes et al. (2000) and Gañán-Calvo (2003) on the other hand ensures that they will not penetrate beyond the upper airways tract or rapidly deposit on the nasal cavity lining upon inhalation. Of course one should realize that lungs have a clearance mechanism. This should also be considered for drug particle design and administration. Since the clearance mechanisms are size dependent, it is possible to produce particles in determined sizes to avoid these mechanisms. In above mentioned inhaler devices, a patient to device coordination is still necessary. This issue is addressed by Coffee (2005). He claims that, operation with induction charging of the liquid instead of direct charging provided better control of the drop size for liquids which are difficult to EHDA. Though the number of academic efforts to design an EHDA based inhalation device is increasing and there are many patents available, there is still not a commercially viable product in the market even despite the fact that a delivery efficiency of 85% can be achieved Gomez et al. (1999). Chen and Pui (2010) note that the latest attempt was made by the Battelle Memorial Institute for a device named Mystic™, which introduction was ceased after early clinical trials.

**Medical coatings and Thin film production**

Coatings for medical devices serve a numerous of useful purposes. For example, coatings can be used to change device surface properties, to incorporate drug/bioactive or antimicrobial agents for release from the surface of the device, to improve the bio compatibility and reduce the rate of rejection or to provide for cell signaling for better healing. However, in many cases vehicles used for drug administration or medical devices have a complex architecture, such as tissues or stents. In both cases, these devices require fine coatings that closely follow the micro-scale detail of the device. Coatings of this quality are not easily achievable with traditional dip or spray coating, physical or chemical vapor deposition. In addition, the coating materials can be exceedingly expensive if they contain drugs or bioactives and therefore the waste that is generated with these methods renders these processes prohibitive for use in many medical device based applications. On the contrary, electrostatic deposition processing is a highly controllable method that provides coatings that track the detail and architecture of the substrate (van Zomeren et al. 1994). Due to the targeted nature of the electrostatic deposition process, there is very little overspray or waste associated with it. Targeting is the result of the attraction between charged particles and the grounded substrate. The limitation of electrostatic deposition lies in the types of substrate that can be coated using this method. Electrostatic deposition requires that the substrate is conductive. Conductivity allows the substrate to be grounded and thereby attract coating particles. It also provides for the relaxation of the charge on the coating particle, converting it into a micro-current and thereby maintaining the particles on the surface. If the particles are still wet at the deposition then they can spread to form a thin film. In recent years the technique is extensively applied to

![Fig. 12](image-url)
deposit a wide range of ceramic thin films with nano-structures for bone material on metallic implants, and selective coating of scaffolds, see Fig. 12 (Leeuwenburgh et al. 2006a, Schacter et al. 2007, Xie et al. 2008). As can be seen from Fig. 12 micro and nano structures can be formed. Very recently Chen and Pui (2010) reported on a complex way of producing a film by EHDA to study concentration gradients in a layer with a nano scale variation, for cell growth studies.

The minute and accurate flow rate used in EHD atomization makes it usable for dispensing very precise volumes of liquid for automated high throughput chemical and biological analysis. Electric field control (Moerman et al. 2001) and pulsed high voltage (Stachewicz et al. 2009a,b, 2010a,b) are implemented to form short EHDA events and deposit near femto liter samples. Deng et al. (2010) implemented an array of micro nozzles activated by pulses to deposit active liquid suspensions. Pulsed electrosprays are also considered for manipulating single bacteria cells and forming arrays of biological reactors (Kim et al. 2010). One should consider that electrospraying viable bacteria can be used to develop devices for monitoring bioaerosols (Kim et al. 2008).

**Tailored particles**

Drug particles itself or drug loaded polymer nano and micro particles in general can be produced by a single step of electrospraying (Enayati et al. 2010). Besides the production of medical nanoparticles as such, EHDA (single nozzle or bipolar coagulation) also offers the possibility to produce more complex particles such as slow release and low density particles, which e.g. can be used in inhalation treatment. Although the low density particles suitable for inhalation have been developed for the micron size, the method can be equally used for the production of nanoparticles (Ciach et al. 2002). Low density, i.e. hollow or porous particles can be obtained with the right evaporation conditions and concentration or with coaxial electrospraying (Chang et al. 2010). In reality also other factors play an important role, such as mechanical properties and porosity of the formed solid shell as well as the surface tension of the solution and the presence of surface-active compounds. If we do not choose the composition of the droplets or the conditions of solvent evaporation properly, we can get the wrong particle structure such as small solid particles or remains of collapsed shells.

Electrospraying suspensions of nano particles in a liquid generates a spray of charged droplets that are seeded with nanoparticles, thus offering a solution for dispersing and depositing nanoparticles on a substrate. The charged nature of the nanoparticles is exploited to coat host particles. EHDA yields unipolarly charged suspensions of nanoparticles, while host particles can be charged with opposite polarity by means of tribocharging, corona or inductive charging, or they could have their charge because they are produced by electrospraying with opposite polarity. When these particles are brought into contact in an appropriate way, the mutual electrostatic attraction force between the negative and positive charge will cause a coating to be deposited on the surface. Inter-

**Fig. 13** (a) Stationary coated 165 μm alumina with 65 nm PS particles (Dabkowski et al. 2007) (b) 200 μm glass beads coated with 500 nm PS particles (Coppens 2007).
actions can be realized in three ways: nano particles can be embedded in host particles, host particles can be encapsulated with a polymer film containing nano particles, and nano particles can be discretely deposited on the surface of host particles. The coating level can be controlled by changing the interaction time, the concentration of the suspension, and controlling the charge of host particles in the spray, Fig. 13. Several possibilities to accomplish mutual interaction of oppositely charged particles in order to deposit electrospayed or electrospray formed nano particles on micro ones are studied by Dabkowski 2006, Dabkowski et al., 2007, Coppens 2007, van Ommen et al. 2008, and Ellis et al. 2010. Electrospray techniques are also tried for marking proteins with nanoparticles to fabricate biosensors (Mao et al, 2010).

However, it should be noticed that nano particles also come with a potential problem of toxicity. The dispersion of nanoparticles in gaseous phases is needed to investigate the toxicity of nanoparticles through in-vivo and in vitro routes. Electrosprays offers an optimal way of dispersion (Suh et al. 2005) of nanoparticles for toxicity studies.

Non-Spherical particles

Cell–particle interactions are complex. There is evidence that cells sense, identify and respond to particle shape, thus beside spherical particles, non spherical particles such as disk shaped, elongated or filament like morphologies could provide specific benefits (Champion et al. 2007). So for certain medical applications it might be advantageous to consider this effect and produce particles with shapes different from spheres to obtain improved biocompatibility, pharmacokinetics, targeted and sustained drug release (Simone et al. 2008, Muro et al. 2008, Mitragotri 2009 a & b, Decuzzi et al. 2010). Methods for fabricating non-spherical polymeric drug delivery particles are grouped by Champion et al. (2007) under two categories; synthesizing from scratch or modifying a spherical particle. Non spherical shapes from the EHDA process can come under the first category. Depending on the concentration, degree of entanglement, molecular weight of the polymer, solvent and other process conditions it is possible to produce fibres instead of spheres, and asymmetric or elongated particles (Hartman 1998, Almeria et al. 2010), see e.g. Fig. 14. Hong et al. 2008 reported that there is a dependence between drug to polymer ratio and particle morphology; and high drug to polymer ratio could lead to wrinkled micro particles. Production of rod or disc like micro particles is also possible using coaxial EHDA (Bhaskar et al. 2010).

Miscellaneous Applications

It is also possible to make emulsions with EHDA, by placing the spraying nozzle in a liquid medium, immiscible with the liquid to be sprayed, with the nozzle on a high potential and a submerged grounded counter electrode. In this case microemulsions, can be made. It is clear that the liquid in which is sprayed (the continuous phase of the emulsion) must have a low conductivity, Fig. 15.

Electrospray is used for dispersing hydrophobic compounds such as cholesterol, and demonstrated that when they are dispersed into aqueous solutions, they disperse faster and more efficiently in comparison to bulk mixing (Wu et al. 2009)

Most newly synthesized medicines, such as Taxol, are poorly soluble in water. Because of their poor solubility, a way to increase the solubility is to reduce the size of medicine particles and consequently increase the surface area of the particles, see Fig. 16. Chen and Pui (2010) showed that steroid particles of 13 nm diameter can be produced by EHDA.

EHDA is even considered for gene transfixation at the cellular level by Chen et al. (2000) and Wu et al. (2010). Although in this article attention is only given to production in the cone jet mode, other modes such as dripping can be used to generate relatively larger drug loaded particles (Xie and Wang 2007).

Future of EHDA - Out scaling

As shown, Electrospraying enables controlled atomization. Therapeutic aerosols with a narrow size distribution can be generated of a desired size, chemical composition, charge and morphology, hence providing a safe and controlled way of respiratory drug delivery and drug particle production. EHDA can also be used to coat particles or surfaces with medical nanoparticles in a very efficient way. This leads to cost savings in expensive pharmaceutical materials.

However, industrial implementation still suffers from low production rates. In order to generate small sized particles, low flow rates are required. For example, a flow rate of less than 0.1 ml/h for a single nozzle is needed to obtain droplets in the micrometer diameter range. To obtain a desired size is mainly determined by flow rate and conductivity of the liquid as indicated by the scaling laws (Eq. 6). For the same droplet size it is impossible to increase the pro-
Fig. 14  Different Shapes (a to c first row and d to e second row) (a) Elongated polymer particles, (b) smooth PVP nanofibers, (c) TiO$_2$ nanofibers, (d and e) electrospun nanotubes obtained by co-spinning olive oil / PVP-TiO$_2$ precursor (Marijnissen et al. 2010).

Fig. 15  Schematic Drawing of the set up for producing Emulsions (Adapted from Meesters, 1992).

Fig. 16  
(a) Taxol; 1.0% in EtoH at 22 L/h (21 oC/ 38% RH ), 60 sec (spray time), 3 cm (spray to substrate distance), -2.1 kV (High Voltage), (b) PVP; 0.3% in EtoH at 10 L/h (22 oC/ 47% RH), 60 sec, 3 cm, -2.4 kV, (c) Taxol+PVP; 0.1% in EtoH at 20 L/h (21 oC/ 64% RH), 120 sec, 3 cm, -2.0 kV. (Marijnissen et al. 2010).
duction rate by increasing the flow rate. Thus an out-scaling rather than up-scaling is needed by means of using multiple sprays.

There are many efforts reported on out-scaling methods including the use of an array of capillaries, an array of holes in combination of non-wetting material, serrations, grooves, multi jet mode operation as summarized by Deng and Gomez (2007), and Deng et al., (2009). Increasing the number of capillary nozzles seems to be a simple and effective way of increasing the number of droplets. However, even in the simplest case of the multi jet mode operation, variation from jet to jet leads droplet size changes from one injection point to another causing a broader

Fig. 17 Schematic of multi nozzle system suggested by Hartman. (Hartman, 1998).

Fig. 18 Schematic of multi nozzle system suggested by Hartman and realized by Arnanthigo (Arnanthigo et al. 2010).
droplet size distribution. When the variation of flow rate couples with field intensity variations, operation of the out scaled system becomes unreliable. The design may also be dependent on the nature of the liquid. There is therefore a need for systematic design tools. The challenge is to have at each spraying point a uniform delivery of the liquid and equal field intensities.

Studies of Snarski and Dunn 1991, and Rulison and Flagan 1994 show that the voltage required for the steady cone-jet mode increases with a decrease in distance between the capillary nozzles. As the distance decreases in order to increase the nozzle packing density further issues will arise. Space charge, a dense charged droplet cloud, decreases the field strength at the nozzles, and so may cease the cone jet spraying of one or more nozzles. So for steady spraying a higher voltage setting is needed. So the electric field at the tip of a capillary nozzle is more often influenced by the nearby nozzles’ electric field. If the influence between the nozzles is large, also the radial component of the electric force acting on a cone is not negligible and the electric force deforms the cone at the tip of the capillary nozzle leading to no or interrupted droplet break up.

As already discussed the droplets are highly charged and to avoid Rayleigh disintegration, they have to be discharged. More jets result in a higher space charge in the gap between the cones and the counter electrodes. The higher the space charge is, the higher the required potential difference necessary for the formation of the cones. The space charge in the setup could also lead to differences in the electric field at the nozzles. The problem of the electric field can be solved by introducing a ring electrode close to the nozzle just as for a single nozzle. In that case, the electric field is determined by the field between the nozzle and the ring. Neighbouring nozzles have no longer an influence on the field at the nozzle. The problem of space charge can be solved in two ways; collecting the particles immediately after their generation on a conducting surface (counter electrode), or discharging and transporting the particles with a carrier gas flow. Fig. 17 shows a schematic representation of a multiple nozzle system as suggested by Hartman (1998), in where all the requirements have been fulfilled. Arnanthigo at al. (2010) implemented a circular design satisfying requirements suggested by Hartman (1998) but used a single pump to feed all nozzles, Fig. 18. In this configuration no neutralization is included but it can be done by corona discharge or by a radio active source.

Conclusions

Electrospraying is an important technology, and has many applications in the medical and pharmaceutical industry such as in Mass Spectroscopy, production of particles, encapsulation of particles, and thin film formation. Compared with other droplet production and film formation techniques, much smaller droplets with narrower size distribution from relatively large orifices are obtained. It is simple and can be applied in many conditions including the atmospheric ones. Electrospray produces a self dispersing cloud of droplets due to unipolar charge, thus coalescence and so variation in the particle size distribution is minimal. Charge of the droplets offers a good control on the trajectory and targeting, however for certain applications droplets have to be neutralized, which can be done by several means. As seen from the mass spectroscopy application it is even safe for large molecules, i.e. no high shear or thermal stresses are involved. The main factors determining the final product in the production of particles and films are the flow rate, electrical conductivity, surface tension, and concentration. With a right chemistry and processing conditions it is possible to tailor particles with a certain shape and surface morphology. The well established scaling laws can be used as a predictive tool. Many potential uses of electrospraying have been demonstrated in academic settings. However, developments towards higher productivity at industrially acceptable rates are needed.

Acknowledgements

The authors would like to thank L.L.F. Aghostinho and WETSUS, The Netherlands for kindly allowing us to use their high speed camera.

References

Albert H. L. Chow, Henry H. Y. Tong, Pratibhash Chattopadhyay, and Boris Y. Shekunov. (2007): Particle Engineering for Pulmonary Drug Delivery, Pharmaceutical Research, Vol. 24, No. 3, March 2007.
Almeria B., Deng W., Fahmy T.A. and Gomez A. (2010): Controlling the morphology of electrospray generated PLGA microparticles for drug delivery, Journal of Colloid and Interface Science, 343, pp.125-133.
Arnanthigo, Y., Yurteri, C., Marijnissen, J. and Schmidt-Ott, A. (2010): ‘Improved design of multi-electrospray unit with circular symmetry’, in: Meesters, G., Pfeffer, T.V., Hauser-Vollrath, C. (Eds.), Proceedings of the Sixth World Congress on Particle Technology, paper
Enayati, M., Ahmad, Z., Stride, E. and Edirisinghe, M. (2010): One-step electrohydrodynamic production of drug-loaded micro- and nanoparticles, Journal of the Royal Society Interface, 7 (45), pp.667-675.

Felder, C. B., M. J. Blanco-Prieto, et al. (2003): Ultrasonic atomization and subsequent polymer desolvation for peptide and protein microencapsulation into biodegradable polyesters, Journal of Microencapsulation 20 (5), pp.553-567.

Forde, G., J. Friend, et al. (2006): Straightforward biodegradable nanoparticle generation through megahertz-order ultrasonic atomization, Applied Physics Letters 89 (6), art.no.064105.

Freitas, S., H. P. Merkle, et al. (2004): Ultrasonic atomization into reduced pressure atmosphere - Envisaging aseptic spray-drying for microencapsulation, Journal of Controlled Release, 95 (2), pp.185-195.

Friend, J. R., L. Y. Yeo, et al. (2008): Evaporative self-assembly assisted synthesis of polymeric nanoparticles by surface acoustic wave atomization, Nanotechnology 19 (14), art.no.145301.

Gañán-Calvo, A. (2003): “Device and Method for Creating Aerosols for Drug Delivery”, US patent 695202.

Gañán-Calvo, A. M., Davila, J. and Barrero, A. (1997): Current and Droplet Size in the Electrospraying of Liquids. Scaling Laws, J. Aerosol Sci., 28 , pp.249-275.

Gañán-Calvo, A. M. (2004): On the general scaling theory for electrospraying, Journal of Fluid Mechanics, 507, pp.203-212.

Geerse, K. B. (2003): “Applications of Electrosprays From People to Plants”, PhD thesis, Delft University of Technology.

Geerse, K.B. and Marijnissen J.C.M. (2003): Electrospray as Means to Produce Monodisperse Drug Particles, pp.75-90, in Gradon, L. and Marijnissen, J. (Editors), “Optimization of Aerosol Drug Delivery”, Kluwer Academic Publishers.

Hinds, W. C. (1999): “Aerosol Technology 2nd ed.”, John Wiley & Sons, Inc., New York.

Hogan Jr. C.J., Yun K.M., Chen D.-R., Lenggoro I.W., Biswas P. and Okuyama K. (2007): Controlled size polymer particle production via electrohydrodynamic atomization, Colloids and Surfaces A: Physicochemical and Engineering Aspects, 311 (1-3), pp.67-76.

Hong, Y., Li, Y., Yin, Y., Li, D. and Zou, G. (2008): Electrohydrodynamic atomization of quasi-monodisperse drug-loaded spherical/wrinkled microparticles, Journal of Aerosol Sci., 39 (6), pp.525-536.

Hull, P., Hutchison, J., Salata, O. and Dobson, P. (1997): Synthesis of Nanometerscale Silver Crystallites via A Room-Temperature Electrostatic Spraying Process. Advanced Materials 9:5, pp.413-417.

Ijsebaert, J.C., Geerse, K.B., Marijnissen, J.C.M., Lammers, J.-W.J. and Zanen, P. (2001): Electro-hydrodynamic atomization of drug solutions for inhalation purposes, Journal of Applied Physiology,91(6), pp.2735-2741.

Ijsebaert, J.C., Geerse, K.B., Marijnissen, J.C.M., Lammers, J.-W.J. and Zanen, P. (2001): Electro-hydrodynamic atomization of drug solutions for inhalation purposes, Journal of Applied Physiology, 91 (6), pp.2735-2741.

Jaworek A. (2008): Electrostatic micro- and nanoencapsulation and electroemulsification: A brief review Journal of Microencapsulation, 25 (7), pp.443-468.

Jaworek, A. (2007): Micro- and nanoparticle production by
Kleinstreuer, C., Zhang, Z. and Donohue, J.F. (2008): Towards new technologies in nanomaterials synthesis. In: Nanomaterials in Medicine and Environment. Inha University Press, pp. 1-15.

Kim, W. and Kim, S.S. (2010): Multishell encapsulation via electrified coaxial liquid jets. Sci. Technol. Adv. Mater., 10 (2-3), pp. 361-368.

Jaworek, A. and Krupa, A. (1999): Classification of the modes of EHD spraying. J. Aerosol Sci., 30 (7), pp. 873-893.

Jaworek, A. and Sobczyk, A.T. (2008): Electrospaying route to nanotechnology: An overview. Journal of Electrostatics, 66 (3-4), pp. 197-219.

Jurasek, R. and Röllgen, F.W. (1998): Pulsation phenomena during electrospray ionization. International Journal of Mass Spectrometry, 177 (1), pp. 1-15.

Kebarle, P and Tang L. (1993): From ions in solution to ions in the gas-phase: The mechanism of electrospray mass-spectrometry. Anal. Chem., 65, pp. 972-986.

Kim, K., Kim, W., Hwa Yun, S., Hyun Lee, J., Kim, S. and Lee, B.U. (2008): Use of an electrospray for the generation of bacterial bioaerosols. J. Aerosol Sci., 39 (4), pp. 365-372.

Kim, K., Lee, B.U., Hwang, G.B., Lee, J.H. and Kim, S. (2010): Drop-on-demand patterning of bacterial cells using pulsed jet electrospaying. Analytical Chemistry, 82 (5), pp. 2109-2112.

Kim, W. and Kim, S.S. (2010): Multishell encapsulation using a triple coaxial electrosprey system. Analytical Chemistry, 82 (11), pp. 4644–4647.

Kleinsteuere, C., Zhang, Z. and Donohue, J.F. (2008): Targeted drug-aerosol delivery in the human respiratory system. Annual Review of Biomedical Engineering, 10, pp. 195-220.

Kozhenkov, V.I. and Fuks, N.A. (1976): Electrohydrodynamic atomisation of liquids. Russian Chem. Rev., 45, pp. 1179–1184.

Lallave M., Bedia J., Ruiz-Rosas R., Rodriguez-Mirasol J., Cordero T., Otero J.C., Marquez M. and Loscortales I.G. (2007): Filled and hollow carbon nanofibers by coaxial electrospinning of Alcell lignin without binder polymers. Advanced Materials, 19 (23), pp. 4292-4296.

Lastow, O. (2007): “Numerical and Experimental Study of Electrohydrodynamic Atomisation of Aqueous Liquids”, PhD thesis, Brunel University.

Leeuwenburgh, S.C.G. (2006b): “Electrospayed calcium phosphate coatings for biomedical purposes”, PhD Thesis Radboud University Nijmegen.

Leeuwenburgh, S.C.G., Heine, M.C., Wolke, J.G.C., Pratsinis, S.E., Schoonman, J. and Jansen, J.A. (2006a): Morphology of calcium phosphate coatings for biomedical applications deposited using Electrostatic Spray Deposition Thin Solid Films, 503 (1-2), pp. 69-78.

Lefebvre, A.H. (1989): “Atomization and Sprays”, Hemisphere Publishing Company.

Lenggoro, I., Okuyama, K., de la Mora, J. and Tohge, N. (2000): Preparation of ZnS Nanoparticles by Electrospary Pyrolysis, J. Aerosol Sci., 31 (1), pp. 121-136.

Loscortales, I.G., Barrero, A., Guerrero, I., Cortijo, R., Marquez, M. and Gatián-Calvo, A.M. (2002): Micro/nano encapsulation via electrospayed coaxial liquid jets. Science, 295 (5560), pp. 1695-1698.

Mao S., Lu G., Yu K., and Chen J. (2010): Protein Viability on Au Nanoparticles during an Electrospray and Electrostatic-Force-Directed Assembly Process. Journal of Nanomaterials, vol. 2010, Article ID 196939, 6 pages, doi:10.1155/2010/196939.

Marijnissen J.C.M., Yuerte, C.U., van Erven J. and Ciach T. (2010): Medicine Nanoparticle production by EHDA in “Nanoparticles in medicine and environment Inhalation and health effects”, Marijnissen, J.C.; Gradon, Leon (Eds.), Springer.

Meesters, G., Vercoulen, P. H. W., Marijnissen, J. C. M. and Scarlett, B. (1992): Generation of Micron-Sized Droplets from the Taylor Cone. J. Aerosol Sci., 23 (1), pp. 37-49.

Meesters, G.M.H. (1992): “Mechanisms of droplet formation”, PhD thesis, Delft University of Technology.

Meng, C.K., Mann, M. and Fenn, J.B. (1988): Of protons or proteins - “A beam’s a beam for a’ that.” (O.S. Burns), Zeitschrift für Physik D Atoms, Molecules and Clusters, 10 (2-3), pp. 361-368.

Michelson, D. (1990): “Electrostatic atomization”, Bristol, England; New York, NY, USA, A. Hilger.

Mitragotri S. (2009a): In drug delivery, shape does matter, Pharmaceutical Research, 26 (1), pp. 232-234.

Mitragotri S. and Lahann J. (2009b): Physical approaches to biomaterial design, Nature Materials, 8 (1), pp. 15-23.

Moerman, R., Frank, J., Marijnissen, J.C.M., Schalkhammer, T.G.M. and Van Dedem, G.W.K. (2001): Miniaturized electrospraying as a technique for the production of microarrays of reproducible micrometer-sized protein spots, Analytical Chemistry, 73(10), pp. 2183-2189.

Muro S., Garnacho C., Champion J.A., Leferovich J., Gajewski C., Schuchman E.H., Mitragotri S. and Muzykantov V.R. (2008): Control of endothelial targeting and intracellular delivery of therapeutic enzymes by modulating the size and shape of ICAM-1-targeted carriers, Molecular Therapy, 16 (8), pp. 1450-1458.

Nakaso, K., Han, B., Alin, K.H., Choi, M. and Okuyama, K. (2003): Synthesis of non-agglomerated nanoparticles by an electrospray assisted chemical vapor deposition (ES-CVD) method. J. Aerosol Sci., 34 (7), pp. 869-881.

Noakes, T.J., Pavey, I.D., Bray, D. and Rowe, R.C. (1989): “Apparatus for producing a spray of droplets of a liquid”, U.S. patent 4829996.

Noakes, T.J., Prendergast, M.J. and Green, M.L., (2000): “Electrostatic Spraying”, US patent 6079634.

Park, C.H., Kim, K.-H., Lee, J.-C. and Lee, J. (2008): In-situ nanofabrication via electrohydrodynamic jetting of countercharged nozzles, Polymer Bulletin, 61 (4), pp. 521-528.

Rosell-Llopant, J., Fernández de la and Mora, J. (1994): Generation of monodisperse droplets 0.3 to 4 μm in diameter from electrified cone-jets of highly conducting and viscous liquids, J. Aerosol Sci., 25 (6), pp. 1093-1119.

Rulison, A. J. and Flagar, R. C. (1994): Synthesis of Yttria Powders by Electrospary Pyrolysis. J. American Ceramic Society 77, pp. 3244-3250.

Schacter, D.M., Shissias R.S., Yuerte C.U. and Escallon
Shoyele, S.A. and Cawthorne, S. (2006): Particle engineering techniques for inhaled biopharmaceuticals, Advanced Drug Delivery Reviews, 58 (9-10), pp.1009-1029.

Shoyele, S.A. and Slowey, A. (2006): Prospects of formulating proteins/peptides as aerosols for pulmonary drug delivery, International Journal of Pharmaceutics, 314 (1), pp.1-8.

Sickmeier, R. and Scheuch, G. (2008): Inhaled insulin - does it become reality? Journal of Physiology and Pharmacology, 59 (SUPPL 6), pp.81-113.

Smith, J. N., Flagan, R. C. and Beauchamp, J. L. (2002): Droplet Evaporation and Discharge Dynamics in Electrospray Ionization, Journal of Physical Chemistry, A 106:42, pp.9957-9967.

Smith, R.D., Bruce, J.A., Wu, Q., and Lei, P. (1997): New advancement in the interaction between two sprays of electrically charged liquid drops, Experiments in Fluids, 11 (4), pp.51-59.

Shiryaeva, S.O. and Grigor’ev, A.I. (1995): The semiphenomenological classification of the modes of electrostatic dispersion of liquids, Journal of Electrostatics, 34 (1), pp.35-49.

Suh, J., Han, B., Okuyama, K. and Choi, M. (2005): Highly charging of nanoparticles through electrospray of nanoparticle suspension, Journal of Colloid and Interface Science, 287 (1), pp.135-140.

Sung, J.C., Pulliam, B.L. and Edwards, D.A. (2007): Nanoparticles for drug delivery to the lungs, Trends in Biotechnology, 25 (12), pp.563-570.

Tang, K. and Gomez, A. (1994): Generation by electrospray of monodisperse water droplets for targeted drug delivery by inhalation, J. Aerosol Sci., 25, pp.1237-1249.

Taylor, G. I. (1964): Disintegration of Water Drops in An Electric Field, Proc. R. Soc. A280, pp.383-397.

Van Erven Jan, Moerman Rob, and Marijnissen Jan C. M. (2005): Platinum nanoparticle production by EHDA, Aerosol Science and Technology, vol. 39, no 10, pp.929-934.

van Ommen J.R., Beetsra R., Nijenhuis J., Yurteri C.U. and Marijnissen J.C.M. (2008): Coating of tribocharged host particles with nanoparticles using electrospraying, Particulate Processes in the Pharmaceutical Industry II, San Juan, Puerto Rico, February 3-7.

van Zomeren A.A., Kelder E.M., Marijnissen J.C.M. and Schoonman J. (1994): The production of thin films of LiMn2O4 by electrospraying, J. Aerosol Sci., 25 (6), pp.1229-1235.

Vercoulen P.H.W., Camelot D.M.A., Marijnissen J.C.M., Pratsinis S., and Scarlett B. (1993): 'SnO2 Production by an Electrostatic Spray Pyrolysis Process. In Proc. Intern. Workshop on the Synthesis and Measurement of Ultrajine Particles, Editor Marijnissen J.C.M. and Pratsinis S. Delft University Press, Delft.

Vercoulen, P.H.W. (1995): "Electrostatic processing of particles. A tool in particle technology", PhD thesis, Delft University of Technology.

Vonnegut, B. and Neubauer, R.L. (1952): Production of monodisperse liquid particles by electrical atomization, Journal of Colloid Science, 7 (6), pp.616-622.

Weiler, C., Egen, M., Trunk, M. and Langguth, P. (2010): Force control and powder dispersibility of spray dried particles for inhalation, Journal of Pharmaceutical Sciences, 99 (1), pp.303-316.

Wilhelm, O. (2004): 'Electrohydrodynamic spraying – Transport, mass and heat transfer of charged droplets and their application to the deposition of thin functional films', PhD thesis, ETH Zurich.

Wu, Y., Chalmers, J.J. and Wyslouzil, B.E. (2009): The use of electrohydrodynamic spraying to disperse hydrophobic compounds in aqueous media, Aerosol Science and Technology, 43 (9), pp.902-910.

Wu, Y., Fei, Z., Lee, J.J. and Wyslouzil, B.E. (2010): Coaxial electrohydrodynamic spraying of plasmid DNA/poly-ethyleneimine (PEI) polyplexes for enhanced nonviral gene delivery, Biotecnomology and Bioengineering, 105 (4), pp.834-841.

Xie J., Lim L.K., Phua Y., Hua J. and Wang C.-H. (2006): Electrohydrodynamic atomization for biodegradable polymeric particle production, Journal of Colloid and Interface Science, 302 (1), pp.103-112.

Xie J. and Wang C. (2007): Electrospray in the dripping mode for cell microencapsulation, Journal of Colloid and Interface Science, 312, pp.247-255.

Xie, J., Tan, J.C. and Wang, C.-H. (2008): Biodegradable films developed by electrospray deposition for sustained drug delivery, Journal of Pharmaceutical Sci-
Zanen, P. and Lammers, J.-W.J. (1999): Reducing adverse effects of inhaled fenoterol through optimization of the aerosol formulation, Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung, 12(4), pp.241-247.

Zeleny J. (1914): The electrical discharge from liquid points and an hydrostatic method for measuring the electric intensity at their surface, Phys. Rev. 3, pp.69-91.

Zeleny J. (1915): On the condition of instability of liquid drops, with applications to the electrical discharge from liquid points, Proc. Cam. Phil. Soc., 18, pp.71-88.

Zeleny J. (1917): Instability of electrified liquid surfaces, Phys. Rev., 10, pp.1-6.

Appendix

As mentioned in the text, Hartman (1998, 1999) derived theoretically a current scaling law for Newtonian liquids with a flat radial velocity profile in the jet (Equation 2). Gañán-Calvo et al. (1997) pointed out that this radial profile is not always flat in case of a low viscous liquid, or, when the conductivity is low, and the flow rate is high. To address this issue, also theoretically, and assuming that the velocity profile in the jet can be described by a parabolic profile, Hartman derived in his dissertation (Hartman 1998) a current scaling law for Newtonian liquids, with a non-flat radial velocity profile (Equation 3). In these equations, $I^*$ is the current for a flat radial profile, $E_{z,\text{max}}$ is the maximum axial Electric field strength $[\text{V m}^{-1}]$ and can be calculated using equation (i),

$$ E_{z,\text{max}} = E_{\text{ref}} \left( \frac{Q}{Q_{\text{ref}}} \right)^{-0.44} \left( \frac{K}{K_{\text{ref}}} \right)^{-0.15} \left( \frac{\gamma}{\gamma_{\text{ref}}} \right) $$

where, $E_{\text{ref}} = 4 \times 10^6 [\text{V m}^{-1}]$, $Q_{\text{ref}} = 1.4 \times 10^{-9} [\text{m}^3 \text{s}^{-1}]$, $K_{\text{ref}} = 69 [\mu \text{S m}^{-1}]$, and $\gamma_{\text{ref}} = 0.048 [\text{N m}^{-1}]$. $r_{j0.41}$ is the radius of the jet at the position where the conduction current is equal to 41 percent of the total current $[\text{m}]$

$$ r_{j0.41} = \left( \frac{0.41I^*}{\pi E_{z,\text{max}} K} \right)^{1/2} $$

$$ A = \frac{E_{z,\text{max}} \sigma}{2 \mu' r_{j0.41}} $$

where $\sigma$ is the surface charge at $r_{j0.41}$ and defined as

$$ \sigma = \frac{0.59I^* r_{j0.41}}{2Q} $$

and, $\mu'$ is the effective viscosity.

$$ \mu' = \mu + c_\mu \rho \frac{Q}{\pi r_{j0.41}^2} \frac{dr_{j0.41}}{dz} $$

where, $c_\mu$ is a constant which equals to 0.635 and

$$ B = \frac{Q - 0.5\pi r_{j0.41}^4 A}{\pi r_{j0.41}^2} $$

For a complete derivation the reader is referred to the dissertation of R.P.A. Hartman (1998), Go to http://repository.tudelft.nl/ and search for Hartman R.P.A.
Caner U Yurteri
Caner U. Yurteri, born in 1966 in Turkey, a visiting Assistant Professor at Delft University of Technology. He received a B.S. (1987) in Mechanical Engineering from Istanbul Technical University, Turkey. He earned a M.S. (1992) and a PhD (1997) degree in Mechanical Engineering from Case Western Reserve University, U.S.A. He then joined the Chemical Engineering Department of Purdue University as a postdoctoral researcher, the Applied Science Department of the University of Arkansas at Little Rock as a research associate, Terronics Development Corporation as a research scientist, and Particle Engineering Research Center as an assistant scientist respectively. His work extensively involved Laser and Phase Doppler Anemometry and their applications to particle-laden flows. His research interests include particle technology, medical aerosols, electrostatic coating, and electrospraying.

Rob P.A. Hartman
Rob P.A. Hartman is born in 1966 in the Netherlands. He is one of the leading system designers and developers of Jewel Suite, a subsurface modeling software package for the oil industry, at JOA, the Netherlands. He holds a Masters degree in Applied Physics, a designer degree and a Ph.D degree from the Chemical Engineering Department of Delft University of Technology. The subject of his Ph.D thesis was electrohydrodynamic atomization in the cone-jet mode. He has some eighteen years experience in the field of scientific modeling software.

Jan C.M. Marijnissen
Jan C.M. Marijnissen is an Associate Professor and Head of the Aerosol Laboratory at Delft University of Technology, the Netherlands. He is a PERC Visiting Professor at the University of Florida, Gainesville, U.S.A. He holds a Masters degree from Delft University of Technology and a Ph.D. degree from the University of Minnesota, U.S.A. He has some thirty five years experience in the field of Mine Ventilation and Aerosol Technology. He has (co-)authored many articles and several books on Aerosol Technology and is a board member of different scientific associations and journals.