The Electrospray and Its Application to Targeted Drug Inhalation

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This review explains the fundamentals of electrostatic spray (electrospray) atomization, with emphasis on operation in the so called cone-jet mode, which produces droplets with a very narrow size distribution. Since the control of droplet size is key to maximizing distal lung deposition, the electrospray should be well-suited to targeted drug inhalation. Electrospray droplets are a few micrometers in diameter, but they originate from a much larger nozzle, which allows nebulization of suspensions without clogging. Also discussed are: the physical principles of the break-up of the liquid ligament; droplet dispersion by Coulombic forces; and the most important scaling law linking the droplet size to liquid flow rate and liquid physical properties. The effects of the most critical of those properties may result in some restrictions on drug formulation. Droplets produced by electrospray are electrically charged, so to prevent electrostatic image forces from causing upper respiratory tract deposition. The charge is neutralized by generating a corona discharge of opposite polarity. Briefly discussed are the main differences between the laboratory systems (with which the electrospray has been quantitatively characterized during research in the past 10 years) and commercial electrospray inhalers under development at BattellePharma. Some remarkable miniaturization has incorporated liquid pump, power supply, breath activation, and dose counter into a palm-size portable device. The maximum flow rates dispersed from these devices are in the range of 8–16 μL/s, which makes them suitable for practical drug inhalation therapy. Fabrication is economically competitive with inexpensive nebulizers. Dramatic improvements in respirable dose efficiency (up to 78% by comparison with commercial metered-dose inhalers and dry powder inhalers) should ensure the commercialization of this promising technology for targeted drug inhalation. Key words: targeted drug delivery, inhalation, nebulization, electrospray, electrostatic spray, aerosol. [Respir Care 2002;47(12):1419–1431]

Introduction

Deposition of inhaled aerosol occurs by 3 physical mechanisms: inertial impaction, gravitational sedimentation, and Brownian diffusion. Targeting deposition to specific areas of the respiratory tract can be achieved by controlling the size of the aerosol droplets, which in turn affects the de-

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position mechanism. The objective is to deliver the drug directly to the site of action and thereby minimize the dose required to achieve an adequate response to the inhalation therapy. This approach may be particularly advantageous when cost and/or adverse effects are of concern.

Aerosol generators for drug inhalation range from relatively simple, inexpensive types to large, expensive, and complex systems. Examples of the first category are jet nebulizers, pressurized metered-dose inhalers, and dry powder inhalers, which generate a polydisperse distribution of aerosol droplets or particles. At the other end of the spectrum are much more complex alternatives, such as the modified Sinclair-La Mer generator, capable of generating (by condensation methods) monodisperse particles to be stored in a large volume prior to inhalation. However, construction and operation of that type of generator is complex and confines its use to research applications. A few liquid nebulization technologies have recently emerged that offer control of the distribution and size of the aerosol droplets, are amenable to miniaturization, and are sufficiently inexpensive to provide appealing alternatives to traditional inhalers. The present review focuses on technologies that use one or more electrosprays to nebulize liquid formulations. The term electrostatic spray (also known as electrospray, vapor jet, or electrospray) is used in this review with reference to systems in which the dispersion of the liquid relies solely on its electric charging, so that nebulization and gas flow processes are relatively uncoupled. The potential for an electrospray-based technology for targeted inhalation was first recognized by Tang and Gomez. Recent developments at BattellePharma have generated considerable interest in this approach. Figure 1 shows the latest prototypes of inhalers developed by BattellePharma, including a portable device and a benchtop alternative. High-voltage electricity supply, pumping, droplet discharging, and breath activation have been folded into a successfully miniaturized system.

To be able to rely on the extensive characterization in the literature and to avoid being encumbered by the “bells and whirls” of commercial devices, attention here is restricted to a particular type of electrospray that captures the salient features of the BattellePharma inhalers. Such a spray can be implemented very simply by feeding a liquid

\[ S_t = \frac{\tau_D}{\tau} = \frac{\rho_D}{\sigma} \frac{D^2}{18 \mu} \times \frac{1}{\tau} \]  

be sufficiently small (< 0.1). This number is the ratio of a particle’s relaxation time, defined in terms of the particle density (\(\rho_D\)), the diameter (D), the gas dynamic viscosity (\(\mu\)), and a characteristic fluid time (\(\tau_f\)). The strong dependence of the Stokes number on size implies that targeted deposition can be achieved only through control of aerosol droplet size and size distribution, which depends on the type of aerosol generator used. For example, a nebulizer that produces an aerosol with a substantial “tail” of large droplets in the distribution would be unsuitable, since the large droplets, which contain a considerable fraction of the liquid volume aerosolized, would have relatively large Stokes numbers and would impact in the upper respiratory tract. The Stokes number relationship also implies that nebulization must be sufficiently “soft” to keep the fluid time (\(\tau_f\)) large.

Fig. 1. Prototypes of the portable inhaler (top) and of the benchtop device (bottom) developed by BattellePharma, as a result of design evolutions through the summer of 2002. (Courtesy of Donna Palmer and William Zimlich, BattellePharma, Columbus, Ohio.)
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with sufficient electrical conductivity and moderate surface tension through a capillary tube and charging it by a metal electrode in contact with the liquid and maintained at several kilovolts relative to a ground electrode a short distance away. This type of electrospray has the additional feature of a tight control of the size distribution of the aerosol, as will be shown below. The objective is to review the physical principles underlying the operation of such an electrospray and to examine the potential limitations imposed by certain requirements in the physical properties of the aerosolized liquid, which ultimately may constrain drug formulation. This review draws heavily from the work of Tang and Gomez.5,6

Experimental System and Methods

The simple schematic in Figure 2 represents most of the principal components of an electrospray system. Most of the data discussed here were collected with such an apparatus. Relevant differences with the BattellePharma system are discussed below. The system consists of a stainless steel capillary tube charged at a high electric potential, between 10 and 20 kV, and a ground electrode positioned 3 cm away, perpendicular to the tube. For simplicity the liquid is gravitationally fed from a reservoir into the tube. The flow, which is controlled by changing the height of the reservoir relative to the tube, is measured by timing the displacement of a gas bubble injected into the liquid line through a calibrated micro-syringe. More elaborate pumping and metering systems are typically used in practice. The current carried by the electrospray is monitored by an electrometer connected to the ground electrode.

The spray behavior is monitored by 2 optical diagnostic techniques: phase Doppler anemometry and flash illumination. The phase Doppler anemometry system (Dantec Electronics, Ponthius, United Kingdom) determines the size and the velocity of the droplets by light scattering. The shadowgraph flash illumination system monitors the stability of the electrospray and highlights details of the break-up process. It consists of a nanosecond flash lamp (Xenon, Woburn, Massachusetts) and a stereo zoom microscope, the latter coupled to a closed-circuit digital camera (Pulnix, Sunnyvale, California). The nanosecond flash allows us to freeze the motion of the droplets. Alternatively a 10 ns pulse laser illumination is used to photograph the electrospray scattering with a digital camera.

Liquid Break-Up, Droplet Dispersion, and Monodispersity

Figure 3 shows an ethanol drop suspended at the outlet of a metal tube. When an appropriately intense electric field is applied to the tube, by providing a voltage on the order of kilovolts, the liquid meniscus is drawn into a conical shape with a fine spray emerging from it (the electrospray), as shown in Figure 3B, which is an instantaneous picture under the illumination of a 10 ns pulse laser. Figure 4 shows a close-up view of the highlighted rectangle in Figure 3B, which reveals details of the break-up of the liquid ligament. The sequence of events leading to the formation of a spray with nearly uniform droplet sizes is observed over a broad range of operating conditions and droplet sizes and is typical of all electrosprays with narrow droplet size distributions. The images in Figure 4 pertain to a heptane electrospray that produces droplets sufficiently large to be photographed with an optical microscope.7 First (Fig. 4A) the liquid exits the cone formed at the outlet of the charged tube as a thin ligament that is stable for a short distance. This ligament then breaks up into droplets (Figs. 4B and 4C), which typically exhibit a bimodal distribution of larger primary droplets and smaller satellite droplets. Farther downstream, the droplets become nearly monodisperse as the smaller satellites, driven by the electric field, migrate rapidly away from the axis (Fig. 4C). The primary droplets left behind are quasi-monodisperse. They move downstream, are gradually displaced radially, and form a wavy signature pattern under instantaneous illumination (Fig. 4D). They eventually form a fan that coincides with the electrospray visible under appropriate illumination.7

Figure 4A shows that, before break-up occurs, axisymmetric varicose waves propagate along the ligament because of naturally occurring disturbances. Such waves lead
to a change in the pressure distribution along the liquid ligament, which is associated with the presence of surface tension. As a result, the liquid is driven away from the ligament restrictions, ultimately yielding the pinching of the continuous ligament into discrete droplets. The ratio of primary droplet to ligament diameter was measured at about 1:9, in good agreement with experimental findings of others on similar sprays.8-10 This result also confirms extensions of Rayleigh’s theory11 on the stability of uncharged capillary jets.12,13 which showed that even at relatively large charge levels the predictions of the theory are not significantly altered. Thus, electrification is responsible for extruding the liquid at the outlet of the tube into a liquid ligament through electrohydrodynamic processes in the liquid cone. The droplet size is controlled indirectly by determining the formation and diameter of the liquid ligament. Since the ligament diameter is much smaller than the tube bore, micron-size droplets can be generated from relatively large orifices without clogging, which is a unique advantage of this nebulization technique, and even liquid suspensions can be nebulized.

The sinuous pattern in the array of primary droplets in Figure 4D is not to be interpreted as indicative of a droplet trajectory. Droplets follow diverging trajectories departing from a common origin where the liquid ligament breaks up. It can be readily shown that a stream of closely spaced droplets, as in Figure 4D, is inherently unstable because of the Coulomb repulsion of droplets charged with the same polarity. If one imposes a small radial displacement on any of these droplets, a radial component of the electrostatic repulsive force in the outward direction “cascades” onto all the neighboring droplets. This effect, coupled with diverging lines of the external field between the tube and the ground electrode, ultimately leads to spray dispersion, as hinted by the wavy signature pattern of the break-up region. Thus, droplet Coulombic repulsion or, equivalently, space charge effects play a crucial role in this region: if only the external field were acting on the droplets, they would predominantly persist in their axial trajectory, without dispersing into a spray.

Satellite droplets are visible in Figure 4D. Once the satellite droplets are displaced radially by small disturbances and/or space charge effects, they can better follow the diverging lines of field because of relatively small inertia and high charge-to-mass ratio.7 They are thus removed from the core of the spray by electrostatic/inertial separation.
When evaporative effects are substantial, as is the case with relatively volatile liquids nebulized at low flow rates and producing correspondingly small droplets (e.g., diameter < 10 μm), the distinction between the core and the shroud of the aerosol is less clear. Under those conditions, the smaller droplets in the outer periphery of the spray evaporate faster than the droplets near the spray axis, because of the size-dependent rate of diameter change. Thus the droplet size distribution may broaden somewhat, as the droplets move away from the break-up region. This is typically the case for inhalation sprays.

In view of the morphology of the liquid meniscus in Figure 3, this mode of operation is called cone-jet mode. Several other types of electrostatic nebulization are also possible, as shown by Zeleny in the first systematic investigation on the subject and recently by Cloupeau and Prunet-Foch in their comprehensive study. Even though electrospray operation in a practical device may not be always in cone-jet mode, for the purpose of characterizing electrospray behavior it is best to refer to cone-jet mode, because it is well defined, the experimental conditions can be easily reproduced, and it offers optimal control of droplet size and size distribution.

Typical size distributions are measured with the phase Doppler system. Figure 5 shows sample distributions of a few water electrosprays. The mean droplet diameters are 1.4 μm (Fig. 5A), 6.1 μm (Fig. 5B), and 10 μm (Fig. 5C), which were obtained at liquid flow rates of 3.0, 19.2, and 39.4 μL/min, respectively. The first distribution was obtained from a saline solution, the others from deionized water. The liquid electric conductivity and surface tension were measured at 1.02 × 10⁻⁶ Ω⁻¹·cm⁻¹ and 73 × 10⁻³ N/m.

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respective for deionized water. The solution of water plus 0.005% of NaCl by weight had an electric conductivity of 1.2 $\times$ 10$^{-4}$ $\Omega^{-1}$ cm$^{-1}$, all other liquid properties being the same as deionized water. Notice that the droplets generated have diameter orders of magnitude smaller than the tube used in these experiments (inside diameter 0.12 mm, outside diameter 0.45 mm). The relative standard deviation (i.e., the ratio of the standard deviation to the mean diameter) is 0.14 for the smallest mean size, 0.08 for the intermediate one, and 0.06 for the largest size. The narrowness of these distributions can be contrasted with the breadth of the distribution of inexpensive commercial nebulizers routinely used for drug inhalation. Figure 5D shows one such distribution, obtained from a metered-dose inhaler. The mean diameter is about the same as that of the distribution in Figure 5B, but the relative standard deviation is now 1.12.*

To determine whether there are significant variations in droplet size across the spray and if the distributions are uniformly narrow, measurements are performed at various locations in the spray. Figure 6 shows the results of a typical radial scan at a fixed position downstream of the capillary tip. The abscissa is the radial distance from the spray axis, the left ordinate is the mean droplet size, and the right ordinate is the number density. All the size distributions are as narrow as in Figure 5A-C. In the spray core, characterized by the largest concentration of droplets, the mean diameter is approximately constant. A marked decrease in the average droplet diameter is observed only at outer radial locations, where the droplet number density begins to fall off. By ruling out a possible role of droplet evaporation at that location (in view of the short residence time), this behavior is attributable to the electrostatic/inertia separation phenomenon that confines the smaller droplets to the outer periphery of the spray. Figure 6 shows that the bulk of the flow is dispersed into droplets of rather uniform size. Consequently, measurements on the centerline, sufficiently close to the capillary tube to minimize any evaporation effect, should be representative of what is generated at the spray source.

Figure 7 shows some representative distributions obtained with the BattellePharma inhalers. They do not appear as monodisperse as the data in Figure 5. This may be the result of operation outside of the cone-jet mode or of the lack of uniformity among multiple sprays in parallel (see below). Nevertheless, the distributions appear sufficiently narrow for the goal of targeted inhalation and are significantly better than alternative nebulization techniques.

### Required Liquid Physical Properties and Scaling Laws

Correct electrospray behavior, yielding good control of size distribution, up to virtual monodispersity, depends on many variables and experimental factors, such as the geometric arrangement of the electrodes, the wettability of the electrospray source, the surrounding gas and its pressure, and the evaporation rate of the solution. Thoroughly describing its behavior in terms of all of those variables is an unrealistic task, possibly requiring an understanding of the system electrohydrodynamics that is lacking at present. On the other hand, if all the above variables are kept fixed, the system behavior can be characterized in terms of a few critical liquid physical properties, once the appropriate electric field is established to obtain the cone-jet mode. Those properties are: the electric conductivity ($k$), the dielectric constant ($\varepsilon$), the viscosity ($\mu$), and the surface tension ($\gamma$). Also critical because of its effect on droplet size is one key operating variable: the liquid flow. In the following discussion, some general scaling laws will be presented to help the user "design" the appropriate solution to obtain the optimal aerosol particle size for deposition in the respiratory tract. These scaling laws have been verified for polar fluids, such as water and alcohols, which are typical excipients. These relationships were derived from dimensional analysis and refined by Chen and Pui. The relationships were experimentally tested for a variety of liquids, including water, alcohol, benzyl alcohol, ethylene glycol, and water/alcohol mixtures, spanning a broad range of physical properties, as follows: $\gamma = 21$–80 dyn/cm, $k = 8$–700 $\mu$ $\Omega^{-1}$ cm$^{-1}$, $\varepsilon = 12$–80, $\mu = 0.89$–18 cP.
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Fig. 7. Sample distributions of 3 drugs electrosprayed by the Battelle Pharma nebulizers. A: Triamcinolone acetonide (1% dose in a polyethylene glycol and ethanol solution). Respirable fraction (RF) = 100%. Geometric standard deviation (GSD) = 1.2. B: Albuterol. In a clinical trial, 10% of a metered-dose inhaler label dose delivered via electrospray achieved the same forced expiratory volume in the first second. RF = 95%. GSD = 1.5. C: Cromolyn (perfluorocarbon emulsion). RF = 100%, GSD = 1.2. (Data from Donna Palmer and William Zimlich, Battelle Pharma, personal communication, 2002.)

From a targeted inhalation perspective, critical is the following relationship:

\[ D = f(\varepsilon)(Qe\varepsilon_0/k)^{1/3} = f(\varepsilon)(Q\tau_r)^{1/3} \]  

which shows a dependence of diameter (D) on liquid flow (Q), dielectric constant, and liquid electric conductivity. The latter 2 properties appear in the expression of the charge relaxation time (\(\tau_r\)) denoting the characteristic time with which charge in the liquid interior relaxes to the surface. There appears to be no consensus on the functional form of \(f(\varepsilon)\) appearing in Equation 1.19 This relationship is not considered in detail, since it is not critical to the intended purpose of this review. It is apparent from Equation 2 that, for a given electrosprayable solution, droplet size can be selected by varying the liquid flow issued from a single capillary. As an example, Figure 8 shows the dependence of the droplet size on liquid flow for a fixed electrode configuration for deionized water.6 For flow rates ranging from 5.8 to 42.4 \(\mu\)L/min the droplet diameter varies from 5 \(\mu\)m to about 12 \(\mu\)m. Stability problems of the spray at flow lower than 5.8 \(\mu\)L/min prevented the generation of smaller droplets.

Since saline solution is a commonly used liquid excipient in drug administration, electrosprays of water with various concentrations of NaCl were also investigated experimentally. Experiments showed that a stable spray could be established in the droplet size range relevant to targeted inhalation when the NaCl concentration was \(\leq 0.005\%\) by weight. Figure 9 shows results for the aqueous saline solution of 0.005\% NaCl by weight, for various voltages and flow rates.6 The maximum flow in the cone-jet mode was about 10 \(\mu\)L/min, and the corresponding droplet diameter was 2 \(\mu\)m. Lower concentrations of NaCl can be used to bridge the diameter gap between 2 \(\mu\)m and the smallest diameter obtained for deionized water, 5 \(\mu\)m. Compared with pure water spray, the spray of saline solution, with a measured electric conductivity of the solution 2 orders of magnitude larger than deionized water, yielded smaller droplets at constant liquid flow, which confirmed the qualitative observations of Smith.20 Thus, for aqueous solutions, control of salinity, and therefore conductivity, may offer another degree of control over droplet size.
The data in Figure 9 indicate that at a given flow and for a specific electrode configuration the electrospray can be operated only within a finite range of voltages. Below the lower voltage limit the electrospray pulsates with a discontinuous emission of mass from the liquid meniscus. Above the higher voltage limit other instabilities arise that result in either wild whipping of the jet or in the formation of several uncontrolled jets. In both cases the droplet size distribution broadens drastically. Between those two limits there is a reasonably wide range of voltages within which a stable, monodisperse spray can be established in the cone-jet mode. By searching for the voltage limits at different flow rates, one can construct a stability domain for proper operation. Figure 10 shows such a domain for the deionized water data of Figure 8.5

Notice that the value of the applied voltage is not particularly relevant. The establishment of the cone-jet mode depends on the intensity of the electric field affecting the stress applied to the fluid to overcome the surface tension and extrude the liquid ligament. Different electrode configurations require different voltages for the establishment of a given field. As a result the curves in Figure 10 can shift either up or down substantially. Typically, the operational range of the electrospray covers several hundred volts and falls in the range of 1–15 kV, depending on electrode geometry, surface smoothness, and material electric properties.

In Figure 10 notice that in principle there are 2 more bounds to the operating envelope of the electrospray: an upper liquid flow limit* and a lower one. Most of the emphasis in the scaling studies17 19 has been on the production of very small droplets. Not much was reported on the upper flow limit, except for the report by Chen and Pui,19 in which it was observed that k x Qmax is approximately constant, a result that can be explained in terms of competing characteristic lengths. Increasing the liquid conductivity thus decreases the typical flow rates that can be stably sprayed,8 which also results in smaller droplets, as the data in Figure 9 suggest.

A few relationships have also been offered for the minimum liquid flow, but they seem to be in modest agreement with experimental findings, at least for a broad range of dielectric constants.19 At least for an order-of-magnitude estimate one can use

\[ Q_{\text{min}} = (e \varepsilon_0 \gamma)/(\rho \lambda k) \]  

(3)

with the same notation of Equation 2 and with \( \rho \) denoting the liquid density, as suggested by de la Mora and Loscertales.17

Liquid viscosity intervenes by affecting the relationship of droplet size and liquid jet diameter, through the dominant instability mode that leads to break-up. However, with typical liquids of relevance to inhalation therapy, such as water and light alcohols, the role of viscosity is negligible.17

The liquid surface tension does not appear in the scaling laws above and does not affect the size of the generated droplets. However, it may affect the sprayability of solutions with high surface tension. In fact, for a fixed electrode configuration and liquid flow, the voltage necessary...
to operate a stable spray scales with the square root of the surface tension. If the surface tension is sufficiently large, as in the case of water, the necessary voltage may be higher than the electric breakdown threshold of the surrounding gas medium (usually air), and corona discharge would ensue. This phenomenon typically destabilizes the electrospray behavior and results in fairly broad size distributions unsuitable for targeted drug delivery. A natural way to tackle this problem is to use a sheath gas that has a relatively high electric breakdown threshold, to prevent or delay the onset of corona discharge. A similar approach proved effective, for example, in electrospray ionization. The water data in Figures 5, 6, and 8–11 were obtained using carbon dioxide as sheath gas. At the typical flow of inhalation studies, on the order of 10 L/min, a molar carbon dioxide concentration of < 0.5% is sufficient for the establishment of a water electrospray. Such a carbon dioxide level is sufficiently low to cause no problems, even in the treatment of asthmatic patients. Alternatively, if the addition of a sheath gas is too cumbersome, especially for portable inhalation devices, the water surface tension can be reduced by adding suitable surfactants, which is the approach pursued by BattellePharma.

Electric Charge: Consequences and the Need to Neutralize the Droplets

The dispersion of a liquid by electrostatic means offers, in addition to size control, another distinct advantage over other nebulization techniques. Because of the presence of net charge on the surface of the generated droplets, the Coulombic repulsion among droplets prevents droplet agglomeration and aids spray penetration in the host gas by causing droplet self-dispersion. For a droplet undergoing evaporation, the evaporation results solely in mass loss, while the charge remains attached to the droplet, so the charge density (charge per unit surface area) increases until a critical condition at which the droplet becomes unstable and emits “offspring.” This phenomenon occurs near the so-called Rayleigh limit, when the repulsive force of electrical charges of the same polarity overcomes the surface tension cohesive force holding the droplet together. Under evaporative conditions, which may be encountered in drug inhalation, droplet fission may be inevitable unless efforts are made to discharge the droplet. It is then relevant to examine the level of charging that the electrospray can produce and compare it to that theoretical limit.

To this end, the average charge level has been determined experimentally by measuring the total current collected by the ground electrode. Since an electrospray operating in cone-jet mode generates a very narrow size distribution, the volume charge density of the electrospray can be well represented by a mean value calculated from the ratio between the total electric current and the total liquid flow. In Figure 11 such an average droplet charge density for deionized water sprays is plotted as a function of the average droplet diameter, the latter measured close to the spray origin to minimize possible evaporation effects. The solid line in the figure is the calculated Rayleigh limit, which is the stability limit for the charged droplet, given by:

\[ q^2 = 8 \pi^2 \varepsilon_0 \gamma D^3 \]  

in which \( q \) is droplet charge at the Rayleigh limit, \( \varepsilon_0 \) is the permittivity of the medium surrounding the droplet, \( \gamma \) is the liquid surface tension, and \( D \) is the droplet diameter. Figure 11 shows the charge density to be a decreasing function of droplet size. The large droplets with lower charge density are closer to the Rayleigh limit and thus are more likely to become unstable. As also found in other studies, the droplet charge density is not a constant fraction of the Rayleigh limit, in contrast with the predictions of models that have from time to time surfaced in the literature. Figure 11 also shows that for all the liquid flows tested, from 5.8 up to 42.4 \( \mu \)L/min, the data are well-correlated by a least squares fit curve, according to which the volume charge density varies with the inverse of the droplet diameter. This dependence suggests that these electrosprays are established at approximately constant surface charge density, and since the latter is proportional to the electric field, regardless of the particular geometry, at constant electric field.

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[Under special circumstances a weak corona has been reported to have a stabilizing effect on the spray and may enhance the flexibility of the electrospray system to generate droplets of a given size.]

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Figure 12 shows examples of droplet fission, resulting in the formation of cones that emit droplet offspring.\(^2\)(Notice that photographing the droplet fission event with an optical microscope and obtaining some spatial resolution required relatively large droplets of liquid hydrocarbons.) Typically the droplet fission phenomenon is encountered at charge levels on the order of 80% of the Rayleigh limit. Clearly this phenomenon would affect droplet size distribution and the targetable area for lung deposition.

Because the respiratory tract is virtually grounded, charged droplets would deposit predominantly in the upper respiratory tract under the action of image forces,\(^5\) even if the droplets' inertial behavior would otherwise enable deep lung penetration. Discharging the droplets is therefore necessary to prevent oropharyngeal deposition, and an electrospray aerosol delivery system must include a controlled means to discharge the droplets. Figure 13 shows the simplest discharge system.\(^5\) Discharging is performed after the droplets have dispersed, to prevent droplet coalescence near the liquid meniscus, where the droplet concentration is highest. The spray is generated between the capillary tube and a metal porous disk. The tube is shielded by a carbon dioxide sheath flow for the reasons discussed above. Both the tube and the porous metal disk are maintained at independently controlled potentials. A 2 mm hole at the center of the porous disk allows the charged droplets to pass through the disk. The inertia of the droplets traveling at high velocity near the electrospray source overcomes electrostatic attraction between the droplets and the disk and prevents their interception by the disk. Farther downstream of the porous metal disk a ground discharge needle is placed in the axis of the delivery system, at a distance of approximately 40 mm from the porous disk. The intensity of the discharge can be controlled by changing the potential difference between the porous disk and the discharge needle, while the potential difference between the tube and the porous disk is kept constant to preserve the spray stability. The discharged spray is finally delivered into a tube by a coaxial air flow.

This droplet charge neutralization scheme is similar to that implemented originally by Noakes et al\(^\text{13}\) and recently used by Meesters et al.\(^\text{21}\) In preliminary experiments a metal plate was positioned under the discharge needle and insulated from it. The plate was connected to an electrometer. By varying the voltages between the porous disk and the discharge needle, the effectiveness of the corona in discharging the spray was monitored by measuring the current on the plate with and without the electrospray. The
difference between those 2 current signals represents the net current carried by the electrospray in the presence of the discharge. Experiments showed that by adjusting the applied voltage between the porous disk and the needle, the discharge current can be controlled and therefore the electrospray can be discharged either partially or completely. The spray was observed under white light illumination. In the case of complete neutralization of the droplet charge, the droplets, instead of following well-defined trajectories partially determined by the external electric field, became tracers of the gas co-flow and followed convoluted trajectories because of the turbulence of the host co-flow. It should be mentioned that for the typical current levels of these water sprays, on the order of \( \leq 100 \) nA, the corona current generated for neutralization should yield ozone concentration small enough to pose no health hazards.\(^{12}\)

**The Need for Multiplexing**

The goal of delivering a certain liquid flow in droplets of the optimal deposition size may not be achieved with independent control of these 2 variables, because they are related to each other through some liquid physical properties, as shown in Equation 2. The implication of Equation 2 is that if drug deposition requires a particular droplet size \( (D) \) and if the liquid solution in which the drug is dissolved or suspended is fixed (i.e., for fixed \( \epsilon \) and \( k \)), the flow required by the therapeutic objective and the patient’s tolerance for the duration of aerosol inhalation may not be achievable from a single electrospray cone-jet source, so **multiplexing** is required. Indeed, the data in Figure 9 suggest that the aerosol production from a single cone-jet source is inadequate for inhalation therapy. Multiplexing is necessary in most cases, even accounting for the anticipated improvement in respirable dose efficiency and the resulting lower aerosol flow rate needed for a given therapy. Multiplexing entails replacing the single electrospray capillary tube with a matrix of closely spaced tubes, each with its own cone-jet mode spray.

Multiplexing has become easier to achieve, even at large scales, with recent progress in the field of microelectromechanical systems. Namely, by adapting the integrated circuit lithographic technology of the electronic industry to chemical and mechanical engineering applications, multiplexing can be achieved at unparalleled scales and with submicron precision. Figure 14 shows an example of the protrusions that can act as individual electrospray nozzles operated in parallel. The figure shows 3 views of a multiplexed electrospray distributor realized in silicon by deep reactive ion etching. Although the technique at this prototype stage is very expensive, it lends itself to mass production economies of scale, which has been a key factor in the extraordinary growth of the electronics industry in the last few decades.

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**Fig. 14.** Multiplexed electrospray distributor manufactured with a deep reactive ion etching microfabrication technique. (Courtesy of Xiaohui Li, James Klemic, and Mark Reed, Yale University, personal communication, 2002.)
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Electrospray entails providing a regulated voltage supply and some suitable means to pump the liquid at a controlled flow rate. In view of the small electric currents involved, an electrospray can be battery-operated, as is the case with the portable BattellePharma inhaler in Figure 1. The small current also means the device poses no health hazard, despite the high voltage, even if improperly used. Developments at BattellePharma aimed at miniaturizing the power supply and the piezoelectric pumping system have been very successful, as the scale of the device in Figure 1 suggests.

No thermal degradation of the aerosolized substance is anticipated, and the experience of the mass-spectrometry community with electrospray ionization has shown that the technique is sufficiently "soft" to cause no fragmentation, even of labile proteins and peptides. This is one of the reasons the electrospray is becoming the preferred choice to inject large, ionized macromolecules into a mass spectrometer for chemical analysis.33 In the case of insulin, which is being considered for inhalation treatment of diabetes, no loss of biological activity was found in vitro for nanopowder produced by electrospray drying.34

A potential limitation to the biomedical use of electrospray is the constraint on the conductivity of the solution to be electrosprayed, as indicated by the experiments with NaCl/water solutions. Some solutions in which pharmaceutical substances are typically dissolved and stabilized may prove too conductive for direct electrospraying in the target droplet size range. In that case, however, a variation of the sheath technique can be tried, with a sheath flow of a liquid with physical properties appropriate for good electrospray performance, as has been done in electrospray ionization for high ionic strength buffers.35

Swift emphasizes the need for a "low-volume, once-through aerosol generation," in which small volumes can be charged to the device and be completely aerosolized over a specified time interval.3 Applications in which expensive substances are used for either diagnostic or research purposes (eg, gene transfer therapy) will require more efficient systems in which very small amounts can be aerosolized with minimal losses. The electrospray is an ideal device for this purpose, since it can continuously aerosolize very small charges of liquid.36

The droplet size can be selected to promote deposition in either central or deep lungs, as required by the therapeutic goal. Since electrospray capillary tubes have large inner diameters, even suspensions can be successfully sprayed.

Although the physical principles discussed so far hold true also for the BattellePharma inhalers, the adaptation of the electrospray to the BattellePharma devices is quite different from the schematics shown in Figures 2 and 13.37 BattellePharma inhalers have 17 multiplexed electrosprays at negative potential and the corona at positive potential. The fabrication technique involves injection molding, by which the electrospray source is molded in a nonconducting material and the charge is injected into the drug solution by a metal electrode in the solution reservoir. The discharging surfaces are manufactured from stamped sheet metal. As a result of these simplifications it appears that fabrication of an electrospray-based nebulizer can be economically competitive with other types of nebulizers. The maximum flow rate of the BattellePharma device is in the range of 8–16 μL/s, which is suitable for practical inhalation therapy. The device is user-friendly, can be breath-activated, and includes a dose counter. BattellePharma experience has focused primarily on ethanol-based formulations, because they are easy to electrospray. But, as discussed above, aqueous solutions with either a carbon dioxide sheath gas or a surfactant can be successfully nebulized with this technique. A Phase I clinical trial with human volunteers and in vitro studies showed dramatically better respirable dose efficiency (by a factor of at least 2 or 3) than commercial metered-dose inhalers or dry powder inhalers (up to 78%).37

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* The result of the clinical trial is consistent with a study performed in our group in collaboration with the late David L Swift PhD of the Johns Hopkins University School of Public Health. That study tested the efficacy of the delivery system with human volunteers, using radioactively labeled aerosol. Gamma scintillation counting showed that more than 85% of the liquid reached the alveolar region.
Discussion

MacIntyre: How do you put the charge on the drug? What do you do to it so that it can pass through this system and nebulize?

Gomez: I don’t think you actually charge the drug; you charge the liquid carrier in which the drug is dissolved or suspended, in the cone on the capillary tube from which the spray issues. At the source of the electro spraying you have separation of the ions in the solution. So, for example, if you apply a positive potential, you wind up with negative ions being neutralized at the high voltage electrode, and you wind up with overall charged liquid of the same polarity. The liquid is dispersed in charged droplets, which are neutralized by the corona discharge before the solvent evaporates. So it is unlikely that there is any charge left on the drug itself, except for what may be naturally present when the drug is put in solution.

MacIntyre: So the drug starts with no charge.

Gomez: Right. No additional charge from the electrospray process.

MacIntyre: Right out of the bottle. And it’s charged inside the capillary tube and then gets sprayed.

Gomez: Right. But it’s not the drug, it’s the carrier that’s charged.

MacIntyre: I’m trying to picture if the Food and Drug Administration or somebody is going to have a problem with this. Are these drugs safe to put these charges on and to discharge? You seem to imply that it’s OK.

Gomez: I have absolutely no doubt, because what we care about is denaturation or fragmentation of the drug, and there is robust evidence from mass...
spectrometry that electrospay is a sufficiently soft ionization technique that it does not damage the drug.

Snaldone: I think ultrasonic nebulizers produce charged particles too, but by the time they get out of the device they’ve become neutral. So you could argue that the predicate devices also produce charged particles; that’s one way of addressing Food and Drug Administration concerns. Can you give us some idea of the mass of delivery? One of the advantages of nebulizers is that they can deliver milligrams of drug. How much drug can an electrospay deliver?

Gomez: I think the largest flow rate that BattellePharma has is on the order of 1 mL/min. But it’s slightly larger, Alex, do you want to comment on this?

Stenzler:* BattellePharma has pumped it up to 30 μL/s.

Gomez: Which is about 1.8 mL/min.

Snaldone: That’s comparable to a nebulizer.

Gomez: Yes. Because of the constraints that I indicated, the way they do it is with a multiplexed system of several capillary tubes.

Dolovich: You said that you’re getting rid of the smaller, satellite droplets. I wonder what size those satellite droplets are and whether they might be clinically useful?

Gomez: Actually, you don’t always get satellite droplets, because it all depends on the volatility of the liquid being nebulized. In some cases you don’t see such a distinct difference between the primary or core droplets and the satellites. It turns out that the satellites account for only 5–6% of the total. You don’t necessarily get rid of them. But because they are smaller, as small as a third of the primary droplet size, they evaporate relatively fast, so ultimately a small percentage of the stuff may go into very tiny droplets that eventually have fully evaporated. They don’t substantially affect your deposition goals. I didn’t deliberately get rid of them; it’s nature that does it for us; because the satellite droplets’ charge-per-volume is higher, they are much more “responsive,” if you will, to the electrostatic field that is imposed, as opposed to the slightly more sluggish, more inertia-driven, larger droplets.

The second factor is also inertia-related. The satellites are smaller, so they move out a little faster because of the electrostatic repulsion. So it’s a natural separation that takes place. But I wouldn’t pay too much attention to this. The example I showed was of large droplets (10–40 μm) of heptane. If you spray water in 2–3 μm droplets, you don’t see that sharp distinction between the primary and satellite droplets.

Geller: A lot of devices are “open” devices, meaning they can accommodate whatever you put into them. But it seems that if the various liquids have different electrical permittivities, conductivities, and viscosities, then each droplet might require a device made specifically for that fluid.

Gomez: I don’t think so. In principle, as you change liquid physical properties, the optimal flow rate to produce 3-μm droplets might shift, but this might only affect the level of multiplexing that you want to achieve. Since multiplexing can be done fairly easily, they would probably have different levels of multiplexing, depending on how different are the liquid properties. I’m not sure that’s the way they intend to operate, but, again, I’ve shown you only the purest form of electrostatic sprays. You can be a little more forgiving. They seem to be accepting somewhat broader sizes to be issued, and still do exceedingly well.

Fiel:* What about environmental contamination? Is release of aerosol into the ambient air decreased because of the way the particles are created by electrospay?

Gomez: The portable device I’ve seen is breath-actuated, and I presume the stationary device is also breath-actuated.

Barry: There was some work by Hashish and Bailey about 10 years ago that suggested that charging particles would improve lung deposition of nebulizer aerosol and that the charge itself had a therapeutic benefit. Do you think there’s an applicability to using the charge as a part of the therapy?

REFERENCES


Gomez: I don’t know much about the physiologic effect of charge, but for all intents and purposes, the walls of the respiratory tract are “grounded.” I would suspect that you will get very little deposition in the deep lung unless you discharge the droplets. Maybe charge has a beneficial effect, but the question is how to get the drop-

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...to deliver the droplets directly into the lung, then charge may even be useful. In that case you can have Coulombic explosion—the fission that would cause deposition onto the walls. But if you plan to inhale the aerosol through the mouth, there’s no doubt that the droplets will be intercepted in the upper respiratory tract unless they are discharged.