Biomedical Applications of Electrosprays

Derek Dunn-Rankin
Department of Mechanical and Aerospace Engineering & Community and Environmental Medicine, UCI

Environmental Toxicology Seminar Series, University of California, Irvine, April 26, 2002
Introduction

- Work in progress
- Example of transition between mechanical engineering and biological systems
Motivation

- Breaking bulk liquids into droplets increases surface area and availability
  - evaporation
  - surface coverage
- Droplet transport
  - gravitational settling (diameter/gravity)
  - diffusion (diameter/concentration)
  - convective drag (diameter/flow)
  - electrostatic forces (charge/electric field)
- Electrosprays
  - efficiently break liquids into droplets
  - control droplet size (targeting deposit sites)
  - increase droplet dispersion
  - control droplet trajectories

Understanding physical processes opens application opportunities
Electrospray Experiment

Stainless Steel Capillary

High Voltage

Steel Mesh

Earth Ground

High Voltage Power Supply

Syringe Pump

Syringe

Ground plane/Water collector

Flow Rate Indicator

56.9 cc/hr
What is an Electrospray?

- **Process**
  - Electric field produces a cone structure in the fluid; the point of the cone is a region of high electric field
  - Fluid accelerates into the cone region, forming an unstable jet;
  - Jet breaks into charged droplets that repel each other
- **EHD** can produce a fine mist with efficient energy input
- **Low flow rate needed for small droplets**
- **Typical operating conditions**
  - capillary inner diameter, 0.594 mm
  - fluids
    - glycerin,
    - alcohol: methanol, isopropanol
    - diesel fuel,
    - water
  - voltage to 15kV
  - flow rate to 93.9 cc/hr
Taylor Cone Formation

glycerol
18 cc/hr
Taylor Cone Formation
Qualitative Results

- Required field strength for Taylor cone formation increases with capillary diameter.
- Configuration has a drastic effect on the required atomization potential.
- No external fluid breakup mechanism required for the cone jet to form.
Spray Regimes

- VOLTAGE DIFFERENCE

MULTIPLE JET

WHIPPING JET

NEAR-TAYLOR

CONE JET

PULSING CONE JET

DRIPPING

MULTIPLE JET

LOW FLOW RATE
TAYLOR CONE STABILITY

Courtesy of R. Ragucci, F. Fabiani, A. Cavaliere, P. Muscetta, C. Noviello
Alcohol Shadowgraphs

- Used 10 Hz YAG Laser
- Flow Rate: 9.49 cc/hr

7,000 Volts

5,000 Volts

4,000 Volts

2,000 Volts
Electrospray Video

dripping methanol

1 mm dia. capillary copper-vapor laser backlit ~1900 frames/second

gravity

transition to EHD spraying

multijet EHD spraying

Electrospray Video
Electrospray Analysis

\[ d_o = 3.78\pi^{-2/3} 0.6Q^{-1/2} \left( \frac{\rho\varepsilon_o}{\gamma K} \right) \]

Ganan-Calvo scaling law

\( Q \) -- fluid flow rate
\( \rho \) -- fluid density
\( \varepsilon_o \) -- permittivity of free space
\( \gamma \) -- surface tension
\( K \) -- conductivity

Droplet size does NOT depend on capillary diameter nor on electric field strength

infinite capillary perpendicular to infinite ground plane

\[ \phi_o = \frac{E_o r_c}{\sqrt{2}} \ln \left( \frac{4Z_o}{r_c} \right) \]

\( E_o \) -- electric field needed for spraying
\( Z_o \) -- distance to ground plane
\( r_c \) -- capillary radius
EHD Droplet Size vs. Flow Rate

\[ d_0 = 3.78 \pi^{-2/3} 0.6Q^{-1/2} \left( \frac{\rho \varepsilon \sigma}{\gamma K} \right) \]
Rayleigh Maximum Charge

- Based on stability analysis of charged droplet surface; charge beyond this disrupts droplet

\[ Q(r) = 8\pi \sqrt{r^3 \sigma \varepsilon_o} \]

- water surface tension
- permittivity of free space

\[ = 72.8 \times 10^{-3} \text{ N/m} \quad = 8.85 \times 10^{-5} \text{ F/m} \]

Typically, droplet charge is 50-70% of Rayleigh maximum during electrospraying
Surface Tension & Conductivity

Isopropyl Alcohol: 4600 Volts

Distilled Water: 7,000 Volts

- Expected Taylor Cone Regime
- Volumetric Flow Rate: 56.9 cc/hr
- Capillary ID ~ 0.7 mm
- Distance to Ground Plane = 16 mm
Effect of Surface Tension

$E_0$ depends on surface tension

Therapeutics can act as surfactants
Applications of Electrosprays

• Commercial -- in mass spectrometry
• Concepts -- engineering
  – coatings (paint, agricultural sprays)
  – spray cooling
  – spray combustion
  – material processing
  – fire extinguishment in space
• Concepts -- biological systems
  – cryo spray cooling during laser treatment
  – pharmaceutical production
  – topical thin film application
Materials Processing

High temperature reaction of liquid feedstock to produce particles
Extinguishment by Electrosprayed Water

(a) Extinguishment by Electrosprayed Water

- From syringe driver
- Hypodermic needle
- Ring
- Spray
- EHT
- Earth

(b) Test Burners

- Cellulose plug
- 20 cm/s (cold) suction
- Metal matrix
- 10 cm/s H₂
- Flame
- Earth
- Hypodermic needle
- Ring
- Spray
- EHT
- Earth

N₂ supply
Fire Extinguishment by Electrosprayed Water

Reduced rate of smoldering propagation occasionally leading to extinction

- 0.02 ml/s (a case)
- 0.2 ml/s; 10 ml/s air assisted EHD (b case)
- Charge on droplets -- $5.7 \times 10^{-3}$ mC/ml
- ~1/2 Rayleigh maximum charge
- Extinguishment with 30 micron water film
- 63% improvement in extinguishment performance with -10kV potential on burner
Producing Inhalable Therapeutics

- The FDA lists 301 active clinical trials using protein formulations; only a handful have chosen inhalation as the delivery route, highlighting the difficulties with producing a suitable pulmonary product.

- Bioavailability of inhaled macromolecular therapeutics (proteins and plasmid DNA) is governed by the 3-dimensional structure of the molecule after aerosolization (maintain structure).

- Particle size (through transport mechanisms) affects targeting to a specific deposition site and delivered dose (control size).

Will electrosprays work?
Battelle/Pfizer Study

- Reproducible size distribution 1-6 microns, with GSD = 1.6
- High delivery efficiency in vitro: 94%
- 78% drug was deposited in respiratory tract; 4 times greater than dry powder inhaler
- Oropharyngeal deposition 6 times less than with dry powder inhaler
- Viability effects not examined

Lengsfeld et al.

- Electrospray macromolecular therapeutics
- Maintain molecular stability over a range of protein and plasmid DNA
- Effects of PH, surfactant, buffer

0.1 mg/ml DNA (10 kb) solutions containing 200 µM DTPA and 10 mM Tris-HCL at a pH=8.5 were flowed at 0.2 ml/min through a 0.56 I.D., 1.07 mm O.D. stainless steel capillary.

- Supercoiled
- Open Circle
- Linear

Conformal changes beyond 9 kV
Electrosprayed Proteins

- UV circular dichroism measure of structure
- Results relatively insensitive to spraying voltage
- Variation from lot-to-lot
- Further work is needed
Electrosprayed Protein

Circular dichroism
Lot-lot Variation: thawing procedure

![Graph showing Lot-lot Variation](image)

- Control
- O V
- 2kV
- 4kV
- 6kV
- 8kV
- 9kV

**Circular dichroism**
Conclusions

• Electrosprays produce small charged droplets
• Applications of electrosprays are wide-ranging
• Remaining challenges:
  – flow rate
  – sensitivity to fluid and device conditions
  – effects on therapeutic molecules
  – charge management
Acknowledgments

- Prof. Corinne Lengsfeld -- Denver University; pharmaceutical data supported by Valentis Inc.
- NASA microgravity program (NAG3-2226); electrospray studies
- NSF equipment grant; copper vapor laser
- Matt Rickard, Mike Papac, Jonathan Regele; electrospray photos