A High-throughput Electrospray Nozzle for Nanoparticle Production

Huijing Fu, Robert A. Hoerr, and Pat J. Ryan

Nanocopoeia, Inc. 1246 University Ave West,
St Paul, MN 55104, Huijing.Fu@nanocopoeia.com

ABSTRACT

Electrospray is well-known for its capability of producing monodisperse particles with sizes ranging from a few nanometers to micrometers. Even though electrospray has been used in a wide range of research areas, its low throughput has limited widespread use of electrospray for industrial applications. In order to increase the throughput, we designed high throughput D-series nozzles which use an open-channel architecture instead of the traditional capillary structure. Compared with a single capillary nozzle, the throughput of our D-series nozzle is increased over 10 to 20 times. Our standard working platform contains 8 D-24 nozzles, with a throughput of over 0.5 grams of active pharmaceutical ingredient per hour. Monodisperse spherical particles with various sizes were generated by our D-series nozzle at different operational conditions. Particle morphology can also be controlled based on *Peclet* number.
Keywords: electrospray, nozzle, high throughput, nanoparticles

1 INTRODUCTION

Electrohydrodynamic spraying (Electrospray, ES) is a liquid atomization process which uses electric force to overcome surface tension to break up liquids. When operated at the stable cone-jet mode, monodisperse particles are generated with sizes ranging from a few nanometers to micrometers. Electrospray is a gentle process operated at ambient conditions. Chemical or biological properties of the particles are preserved without degradation due to heat or mechanical stresses. Such monodisperse particles, especially particles in the nanometer range can be beneficial in many applications[1]. At Nanocopoeia, our patented ElectroNanospray™ (ENS) process is focused on providing nano-enabled particle design, services, and equipment to the pharmaceutical industry.

Low throughput has limited widespread use of ES for industrial applications. The normal working flow rate for a single capillary electrospray system is on the order of 10 µl/min or less. The smaller the targeted particle size, the smaller the flow rate, hence, the lower the throughput.

There are two common approaches to improve the throughput. First, modify the nozzle design to allow higher flow rate while maintaining the same particle output. Second, increase the number of nozzles in one system so that the overall throughput is multiplied by the number of nozzles. In this work, we demonstrated a high-throughput nozzle design, which can increase throughput per nozzle for over 20 times. A system which integrates multiple high-throughput nozzles was also presented for its performance over time.

2 NOZZLE DESIGN AND SYSTEM INTEGRATION

2.1 Design of High-throughput Nozzle

Most electrospray processes use capillary nozzles. Depending on the targeted particle size, as well as properties of the spray solution, the operation window for flow rate is normally on the order of 10 µl/min or less. For a 1% solution, this flow rate will produce about 6 mg of particles per hour per nozzle.

In order to increase the throughput of a spray nozzle, building upon a design by D.R. Chen's group[2], we designed high throughput D-series nozzles that eliminate the capillary structure as the key functional unit; instead, an open-channel architecture is used. A sheet of fluid is delivered to the spray region which consists of a series of projections. A spray plume emits from each of the surface projections, which serve as the functional "nozzlettes". Figure 1 shows images of our D-series nozzles. The throughput can be further improved by increasing the number of nozzlettes per nozzle. For example, the throughput is doubled when using a D-24 nozzle, which has 24 nozzlettes, compared with a D-12 nozzle which has 12 nozzlettes.

Figure 1. (a) Image of 24 plumes when D-24 nozzle is spraying. (b) Pictures of first generation of D-12 (left) and D-24 nozzle (right).

2.2 Integration of High-throughput Nozzles in a Spray System

In order to characterize nozzle behavior, system performance, as well as throughput improvement capabilities, multiple spray platforms have been constructed. The main functional components of the platform are designed in modules to facilitate rapid changes. In our first system, 2 D-12 nozzles were mounted side-by-side in a manifold and operated simultaneously at high voltage (25+kV) using the same fluid feed and high voltage power supply. Further spray capacity was generated by mounting first 4 and then 8 D-24 nozzles in linear arrays, as shown in Figure 2. The unique spray pattern from each nozzle was referred as "rosette" based on their shape.

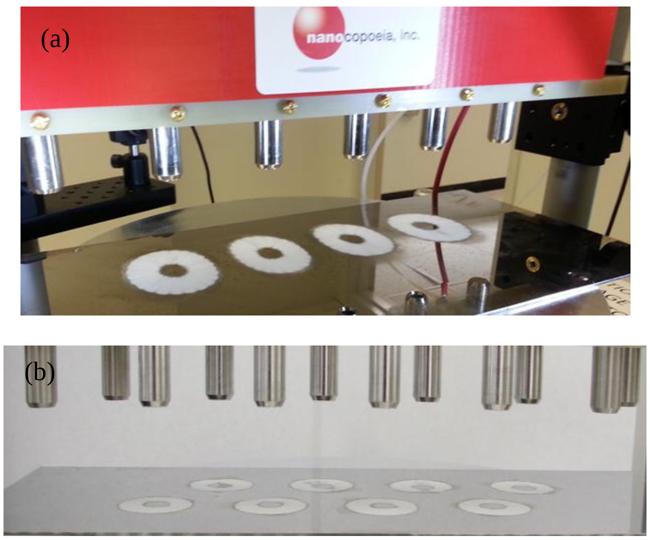


Figure 2. Nozzle array and the rosettes formed by each nozzle during spray. Note, there is one dummy nozzle on each end of the nozzle array. (a) 4-nozzle array; (b) 8-nozzle array.

Our standard working platform contains 8 D-24 nozzles, with a throughput of over 0.5 grams of active pharmaceutical ingredient (API) per hour (assuming a 1% API concentration of the spray solution). Yield from repeated spray runs with 2 D-12 nozzles over 4 months period was 10.12 ± 0.41 mg /10 min, with a COV of less than 5% (Figure 3).

3 NANOPARTICLE GENERATION AND CHARACTERIZATION

The high-throughput D-series nozzles (D-12 and D-24) were used to produce particles with a wide range of materials appropriate for use in pharmaceutical related applications.

In order to demonstrate the capability of the D-series nozzle, different drugs, polymers, and drug/polymer combinations were selected as spray candidates. Model drugs were griseofulvin (GF) and itraconazole (ITZ), both selected for their poor water solubility. Polymers included polyvinyl-pyrrolidone (PVP, Kollidon®) at different grades, and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®, SP). Different solvents, including ethanol, methanol, iso-propanol, ethanol/acetone mixture, and methanol/tetrahydrofuran (THF) mixture were used to prepare the feed solutions at solid concentrations ranging from 1% to 10% (w/v).

All spray operations were conducted at ambient conditions. Solution feed flow rates per nozzle were controlled by syringe pumps to be between 0.05 ml/min to 0.3 ml/min. An extractor plate was located at 2 mm below the nozzle. A voltage difference of around 10 kV between the nozzle and the extractor provided the required electric field to achieve electrospray. The exact voltage was adjusted for each spray condition to produce stable cone-jet operation on each nozzlette. A stainless steel plate was placed at 2" to 5" below the nozzle to collect particles. The spacing was adjusted so that only dry particles were collected for downstream analysis and characterization.

Nozzle performance has been characterized by the quality of generated particles, throughput of the nozzle, and performance over time. Timed runs and sample weights were used to determine production rate. Collected dry

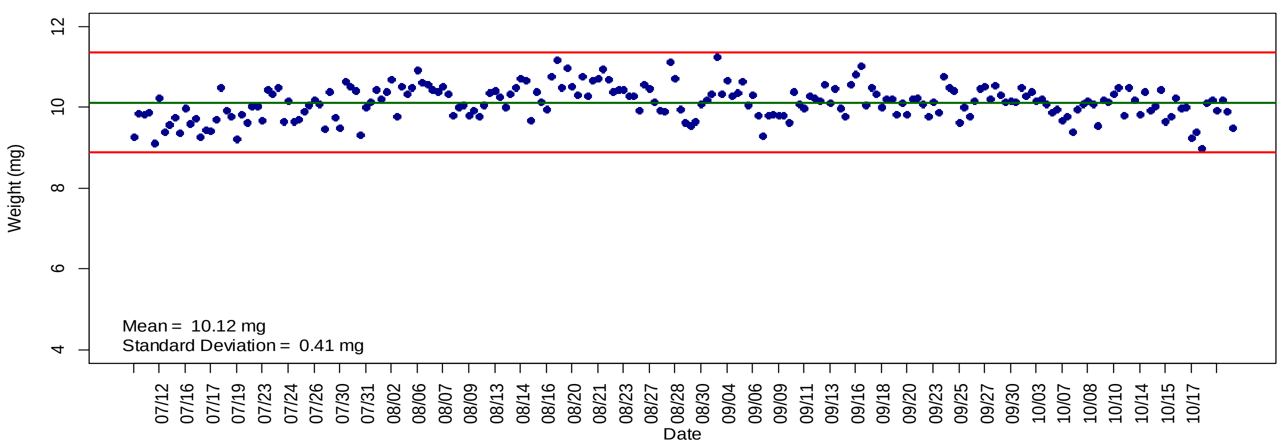


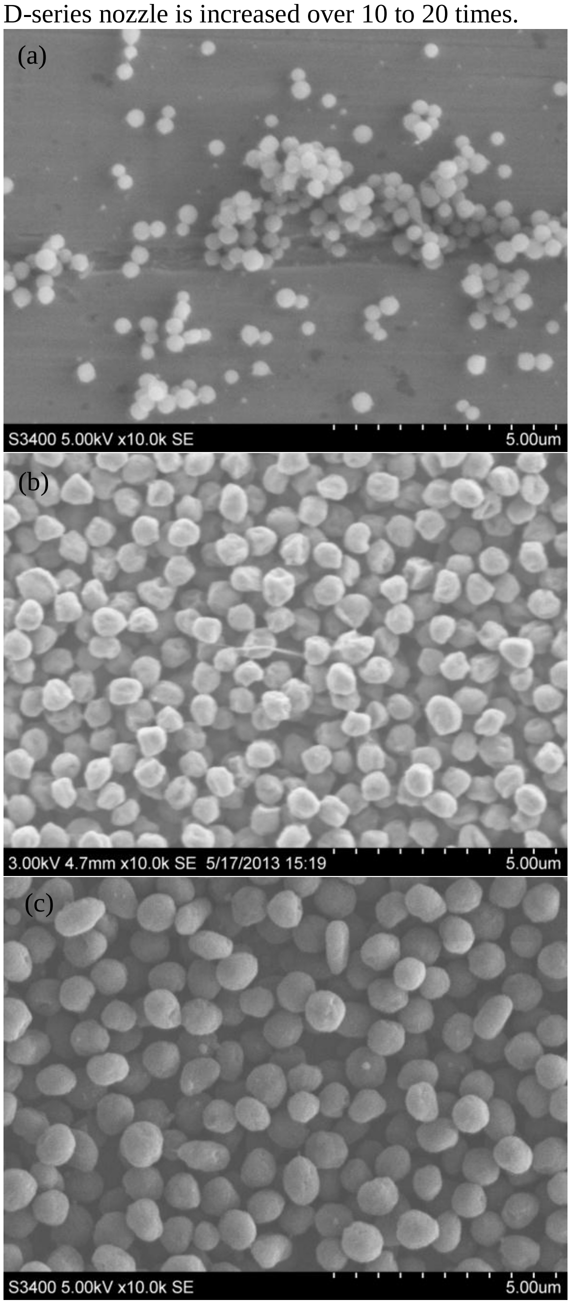
Figure 3 Control chart on yield with 2 D-12 nozzles over 4-month period

particles were characterized for size and morphology by scanning electron microscopy (SEM) imaging (S3400, Hitachi).

4 RESULTS AND DISCUSSION

4.1 Control of Particle Size

Even though our D-series nozzle forms spray from a liquid film instead of a liquid filament like most of other electrospray nozzles, the size distribution of particles produced by these two different nozzles are similar when they are operated in stable cone-jet mode. The most significant difference between the D-series nozzle and a traditional single capillary nozzle is that the throughput of the D-series nozzle is increased over 10 to 20 times.



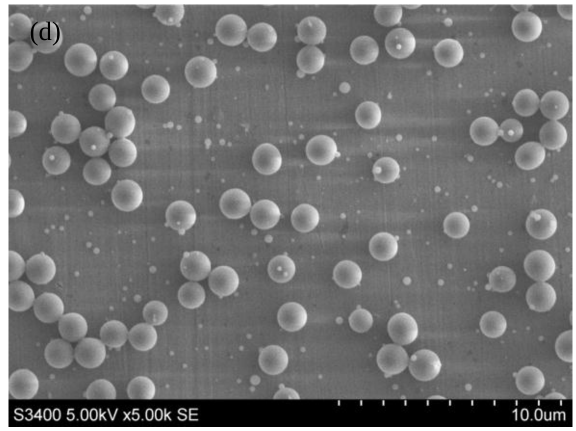


Figure 4. SEM images of particles generated by D-series nozzle at different conditions. (a) 1% Kollidon® 30 in ethanol/acetone mixture, flow rate = 0.1 ml/min, D-24 nozzle; (b) 1% GF, 1% SP in ethanol/acetone mixture, flow rate = 0.06 ml/min, D-12 nozzle; (c) 1% ITZ, 1% SP in methanol/THF mixture, flow rate = 0.12 ml/min, D-24 nozzle; (d) 2.5% Kollidon® 12 in ethanol, flow rate = 0.2 ml/min, D-24 nozzle.

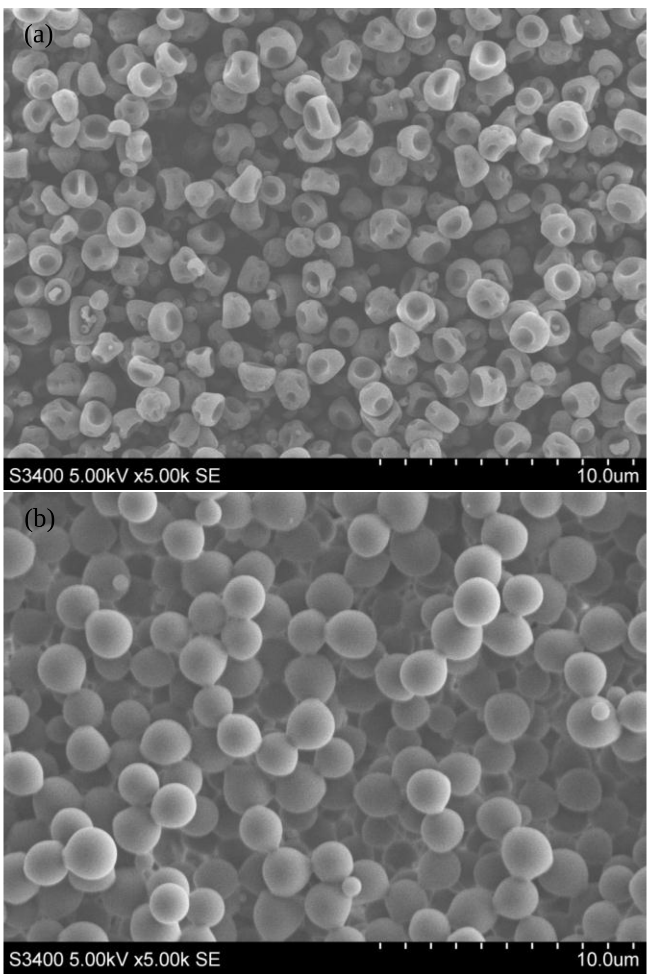
SEM images (Figure 4) show monodisperse spherical particles of various sizes, all generated by our D-series nozzle. Particles consisting of both pure polymer (two grades of Kollidon®) and drug/polymer mixture (GF/SP and ITZ/SP) are shown in Figure 4. ENS-sprayed GF/SP and ITZ/SP were mostly amorphous, compared to crystalline raw drug powder. GF/SP particles showed 15-fold solubility improvement over straight GF powder (data not shown).

The size of particles generated by an electrospray process is controlled by the properties of the spray solution and critical machine operation parameters. By varying the solid concentration, conductivity, type of solvent, and feed flow rate of a given spray solution, the resulted particle mean diameter can be adjusted over a range of hundreds of nanometer (results not shown).

4.2 Control of Particle Morphology

Electrospray initially forms droplets that have the same composition and concentration of the feed solution. As droplets travel to the collection substrate, solvent keeps evaporating from the surface of the droplet. The rate of evaporation is mainly related to droplet size, volatility of the solvent, vapor pressure of the solvent in the surrounding environment, and temperature. In the meantime, molecules of dissolved solids are always doing Brownian motion within the droplet, which helps to achieve homogeneous concentration distribution inside the droplet. Depending on the relative rate of evaporation and diffusion, which can be characterized by a dimensionless *Peclet* number, *Pe*, the morphology of dry particles can vary from solid spherical particles, wrinkled particles, dimpled particles, to even hollowed particles[3]. *Pe* less than 1 is preferred in order to get spherical particles.

Kollidon® was used to study the effect of molecular weight (M_w) and type of solvent on particle morphology. Two grades of Kollidon®, Kollidon® 30 and Kollidon® 12, were chosen because they are hugely different in M_w. The average M_w of Kollidon® 30 is 44-54 kDa, while that of Kollidon® 12 is 2-3 kDa. Solvents used to dissolve Kollidon® were ethanol and methanol. Ethanol has a boiling point of 78 ˚C, while methanol has a lower boiling point at 65 ˚C. Three combinations of Kollidon® and solvent were compared, including Kollidon® 30 in ethanol, Kollidon® 30 in methanol, and Kollidon® 12 in ethanol. For Kollidon® 30 in methanol, solvent evaporation rate is higher than that of Kollidon® 30 in ethanol, since methanol is more volatile than ethanol. In the meantime, the diffusion coefficient of Kollidon® 30 in methanol is also higher than in ethanol due to lower viscosity of methanol. So the overall effect on *Pe* was not clear. For Kollidon® 12 in ethanol, diffusition rate of Kollidon® 12 is higher due to its low M_w. At the same evaporation rate, *Pe* of Kollidon® 12 in ethanol should be lower than that of Kollidon® 30 in ethanol.



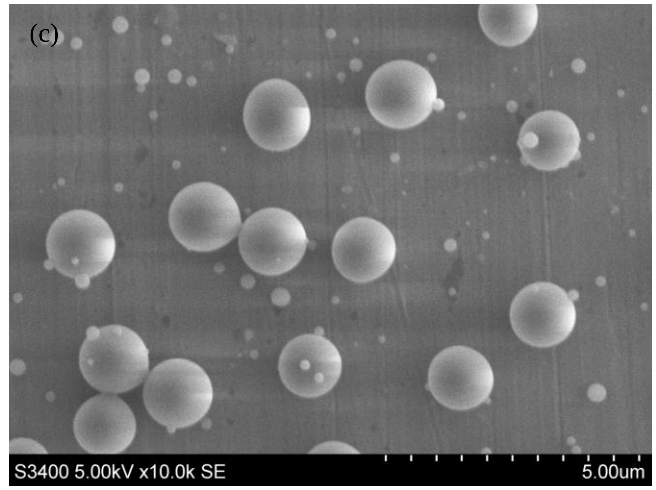


Figure 5. SEM images of Kollidon® particles generated by D-24 nozzle as a demonstration of morphology control capability. (a) 10% Kollidon® 30 in ethanol; (b) 10% Kollidon® 30 in methanol; (c) 2.5% Kollidon®12 in ethanol.

As shown in Figure 5(a), Kollidon® 30 in ethanol, which had higher M_w and higher boiling point, generated dimpled particles. By replacing ethanol with methanol (Figure 5(b)), or replacing Kollidon® 30 with Kollidon® 12 (Figure 5(b)), spherical particles were produced. There are many ways to change *Pe* number besides changing the solvent or solid. This result shows a good indication on how to achieve desired particle morphology by controlling the rate of evaporation and diffusion.

5 CONCLUSION

In summary, ElectroNanospray™ is a flexible, low-cost, single-step spray process that produces nanoparticles in a narrow, targeted-size distribution. Our revolutionary nozzle designs enable the scale-up capability of electrospray technology while leveraging all the advantages of traditional nozzles. The process is capable of controlling particle size and morphology. The modular equipment design allows for easy entry at R&D scale moving to pilot and full scale production.

REFERENCES

[1] Jaworek A. and Sobczyk A.T., Electrospraying route to nanotechnology: An overview. Journal of Electrostatics 66, 2008, 197–219.

[2] Lee, Y.H., Zhang J., & Chen, D.R. Electrohydrodynamic atomization of liquid sheet. Review of Scientific Instruments. 82, 2011, 1-3

[3] Vehring R. Pharmaceutical Particle Engineering via Spray Drying. Pharmaceutical Research. 25(5), 2008, 999-1022.