



(51) International Patent Classification:

B05B 15/00 (2018.01) *A61M 11/06* (2006.01)
A61M 11/04 (2006.01) *A61M 16/00* (2006.01)

(21) International Application Number:

PCT/US2024/037765

(22) International Filing Date:

12 July 2024 (12.07.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/526,866 14 July 2023 (14.07.2023) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: MICRON AND SUBMICRON DIAMETER SPRAY DROPLET GENERATION

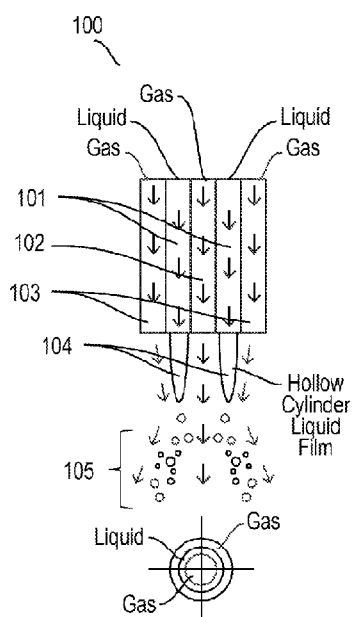


FIG. 1A

(57) Abstract: Disclosed herein are methods and devices for generating sprays with droplets of micron and submicron diameter. This is accomplished through the disintegration of a thin liquid film using an atomizing gas flow. The device comprises a nozzle device having at least three channels comprising an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel. The methods comprise use of the device for generating atomized particles.

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

MICRON AND SUBMICRON DIAMETER SPRAY DROPLET GENERATION

CROSS-REFERENCED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/526,866, filed on July 14, 2023, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] This section is intended to introduce the reader to various aspects of art, which may be related to various aspects of the present invention that are described and/or claimed below. This discussion is believed to be helpful in providing the reader with background information to facilitate a better understanding of the various aspects of the present invention. Accordingly, it should be understood that these statements are to be read in this light, and not as admissions of prior art.

[0003] Various techniques for creating spray droplets have been around for over a century. However, conventional techniques are typically incompatible with desired compounds – for example, if a DNA or RNA material is desired to be encapsulated, the product cannot be exposed to a very high shear rate, or extremes of temperature. Alternatively, if a relatively thick liquid is desired in droplet form, it can be extremely challenging for some conventional techniques to provide.

SUMMARY

[0004] In some aspects, provided herein is a nozzle device, including: at least three channels including an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel. Further provided herein is a nozzle device, wherein the inner channel and the at least one outer annular channel are in fluid communication with different gas sources. Further provided herein is a nozzle device, wherein the inner channel and the at least one outer annular channel are in fluid communication with a same gas source. Further provided herein is a nozzle device, wherein each of the at least one middle annular channel is in fluid communication with a different liquid source. Further

provided herein is a nozzle device, wherein each of the at least one middle annular channel is in fluid communication with a same liquid source. Further provided herein is a nozzle device, wherein the at least one middle annular channel includes a first middle annular channel and a second middle annular channel outside of the first middle annular channel. Further provided herein is a nozzle device, wherein the at least three channels are shaped to include a hollow straight cylinder configuration, a hollow converging cone configuration, or a diverging hollow cone configuration. Further provided herein is a nozzle device, wherein the at least three channels are shaped to include a converging-diverging configuration. Further provided herein is a nozzle device, wherein the gap width ranges from 10 to 125 micrometers. Further provided herein is a nozzle device, wherein outlets of the at least three channels are coplanar. Further provided herein is a nozzle device, wherein each of the outlets is positioned within a first plane, the first plane being perpendicular to an axis of the inner channel. Further provided herein is a nozzle device, wherein at least one outlet of the at least three channels is non-coplanar with other outlets of the at least three channels. Further provided herein is a nozzle device, wherein a ratio of a diameter of the at least one middle annular channel to a diameter of an inner channel, a diameter of at least one outer annular channel, or a combination thereof is varied.

[0005] In some aspects, provided herein is a spraying system, including: a nozzle device, the nozzle device including: at least three channels including an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel; at least one liquid source in fluid communication with the at least one middle annular channel; and at least one gas source in fluid communication with the inner channel and the at least one outer annular channel. Further provided herein is a spraying system, further including at least one gas flowing from at least one gas source through the inner channel and the at least one outer annular channel. Further provided herein is a spraying system, further including at least one liquid flowing from at least one liquid source through the at least one middle annular channel. Further provided herein is a spraying system, further including at least one control circuit configured to cause the at least one gas and the at least one liquid source to flow through the nozzle device simultaneously.

[0006] In some aspects, provided herein is a method of spraying particles, including: causing at least one liquid (*e.g.*, a solution, a suspension, an emulsion or a combination thereof) to be

dispensed in an annulus film from a nozzle; and controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles; wherein a diameter of each of the plurality of atomized particles scales with a thickness of the stretched cylindrical liquid surface. Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) is non-Newtonian. Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) is Newtonian. Further provided herein is a method, further including drying the plurality of atomized particles. Further provided herein is a method, further including coupling a liquid pump to at least one middle annular channel of the nozzle. Further provided herein is a method, further including coupling at least one gas pump to an inner channel of the nozzle and at least one outer annular channel of the nozzle. Further provided herein is a method, wherein the controlling the flow of the at least one first gas stream includes controlling a pressure of the at least one first gas stream. Further provided herein is a method, further including controlling a flow rate of the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof). Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) has an absolute viscosity greater than 100 cP. Further provided herein is a method, wherein the plurality of atomized particles are in a form of droplets. Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) includes a suspension of an organic and/or inorganic material. Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) includes a viscoelastic liquid. Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) includes at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof. Further provided herein is a method, wherein at least 50% of the at least one microorganism retains biological activity after being sprayed. Further provided herein is a method, wherein the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) includes a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof. Further provided herein is a method, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed. Further provided herein is a method, wherein the

at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) includes a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof. Further provided herein is a method, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being sprayed. Further provided herein is a method, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed. Further provided herein is a method, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 20 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 15 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 10 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 5 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with median diameter less than or equal to 1 μm . Further provided herein is a method, further including controlling a ratio of a flow rate of the at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) relative to the flow of the at least one first gas stream, the at least one second gas stream, or a combination thereof. Further provided herein is a method, wherein a ratio of a diameter of at least one middle annular channel of the nozzle to a diameter of an inner channel of the nozzle, a diameter of at least one outer annular channel of the nozzle, or a combination thereof is varied.

[0007] In some aspects, provided herein is a composition for use in a nozzle device, including: a liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) having an absolute viscosity in a range of from 1 cP to 2000 cP; wherein: the liquid upon passing through the nozzle device, causes the liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) to produce a plurality of atomized particles, and a number-weighted size distribution of the plurality of atomized particles includes more than 99% of the plurality of atomized particles being smaller than 1 micron. Further provided herein is a composition, wherein the liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) includes one or more active agents. Further provided herein is a composition, wherein the suspension includes plurality of solid particles having a size in a range of from 1 nm to 1000 nm, from 1 nm to 800 nm, from 1 nm to 500 nm, from 1 nm to 300 nm, from 1 nm to 100 nm, from 100 nm to 1000

nm, from 100 nm to 800 nm, from 100 nm to 500 nm, from 100 nm to 300 nm, from 300 nm to 1000 nm, from 300 nm to 800 nm, from 300 nm to 500 nm, from 500 nm to 1000 nm, from 500 nm to 800 nm, or from 800 nm to 1000 nm.

[0008] In some aspects, provided herein is a composition including a plurality of particles, wherein the plurality of particles are dried atomized particles, wherein the dried atomized particles are formed from a liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof), and wherein number-weighted size distribution of the plurality of particles includes more than 99% of the plurality of particles being smaller than 1 micron. Further provided herein is a composition, wherein the composition includes one or more active agents. Further provided herein is a composition, wherein the dried atomized particles retain at least 80% biological activity relative to the liquid. Further provided herein is a composition, wherein the liquid is non-Newtonian. Further provided herein is a composition, wherein the liquid is Newtonian. Further provided herein is a composition, wherein the liquid has an absolute viscosity greater than 100 cP. Further provided herein is a composition, wherein the plurality of atomized particles are in the form of droplets. Further provided herein is a composition, wherein the liquid includes a suspension of an organic and/or inorganic material. Further provided herein is a composition, wherein the liquid includes a viscoelastic liquid. Further provided herein is a composition, wherein the liquid includes at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof. Further provided herein is a composition, wherein at least 50% of the at least one microorganism retains biological activity. Further provided herein is a composition, wherein the liquid includes a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof. Further provided herein is a composition, wherein at least 50% of the plurality of therapeutic agents retain biological activity. Further provided herein is a composition, wherein the liquid includes a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof. Further provided herein is a composition, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25%. Further provided herein is a composition, wherein at least 50% of the plurality of therapeutic agents retain biological activity.

[0009] In some aspects, provided herein is a method of making a composition including: flowing a liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) from a nozzle along with a gas to form a plurality of atomized particles, wherein a number-weighted

size distribution of the plurality of particles includes more than 99% of the plurality atomized of particles being smaller than 1 micron; and exposing the plurality of atomized particles to a temperature in a range of from 3 °C to 40 °C. Further provided herein is a method, wherein the liquid is flowed from the nozzle at a pressure in a range of from 2500 bar to 500 bar. Further provided herein is a method, wherein the liquid includes one or more active agents in a range of from 0.1 µg/mL to 2000 mg/mL.

[0010] In some aspects, provided herein is a composition including: a plurality of atomized particles, wherein a diameter of each of the plurality of atomized particles scales with a thickness of a cylindrical liquid surface stretched from each of at least one annulus film of liquid by one or more gases flowing through at least a central portion of the at least one annulus film of liquid and along an outside surface of the at least one annulus film of liquid. Further provided herein is a composition, wherein each of the plurality of atomized particles includes an organic and/or inorganic material. Further provided herein is a composition, wherein each of the plurality of atomized particles includes at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof. Further provided herein is a composition, wherein at least 50% of the at least one microorganism are biologically active. Further provided herein is a composition, wherein each of the plurality of atomized particles includes a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof. Further provided herein is a composition, wherein at least 50% of the plurality of therapeutic agents are biologically active. Further provided herein is a composition, wherein each of the plurality of atomized particles includes a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof. Further provided herein is a composition, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 20 µm. Further provided herein is a composition, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 15 µm. Further provided herein is a composition, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 10 µm. Further provided herein is a composition, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 5 µm. Further provided herein is a composition, wherein size distributions of the plurality of atomized particles include median diameter less than or equal to 1 µm.

[0011] In some aspects, provided herein is a method of making a pharmaceutical composition, including: causing at least one liquid (e.g., a solution, an emulsion, a suspension, or a combination thereof) to be dispensed in an annulus film from a nozzle; and controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles; and drying the plurality of atomized particles; wherein a diameter of each of the plurality of atomized particles scales with a thickness of the stretched cylindrical liquid surface. Further provided herein is a method, wherein the at least one liquid is non-Newtonian. Further provided herein is a method, wherein the at least one liquid is Newtonian. Further provided herein is a method, wherein the at least one liquid has an absolute viscosity greater than 100 cP. Further provided herein is a method, wherein the plurality of atomized particles are in a form of droplets. Further provided herein is a method, wherein the at least one liquid includes a suspension of an organic and/or inorganic material. Further provided herein is a method, wherein the at least one liquid includes a viscoelastic liquid. Further provided herein is a method, wherein the at least one liquid includes at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof. Further provided herein is a method, wherein at least 50% of the at least one microorganism retains biological activity after being stretched from the cylindrical liquid surface. Further provided herein is a method, wherein the at least one liquid includes a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof. Further provided herein is a method, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being stretched from the cylindrical liquid surface. Further provided herein is a method, wherein the at least one liquid includes a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof. Further provided herein is a method, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being stretched from the cylindrical liquid surface. Further provided herein is a method, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being stretched from the cylindrical liquid surface. Further provided herein is a method, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 20 μm . Further provided herein is a method, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or

equal to 15 μm . Further provided herein is a method, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 10 μm . Further provided herein is a method, wherein a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 5 μm . Further provided herein is a method, wherein size distributions of the plurality of atomized particles include median diameter less than or equal to 1 μm .

[0012] In some aspects, provided herein is a system for formulating a pharmaceutical composition, including: a nozzle device adapted to receive a liquid (e.g., a solution, an emulsion, a suspension, or a combination thereof) to sufficiently stretch at least one annulus film to generate a plurality of atomized particles; and the liquid, upon passing through the nozzle device, causes the liquid to produce a plurality of atomized particles; wherein a diameter of each of the plurality of atomized particles scales with a thickness of a cylindrical liquid surface stretched from each of the at least one annulus film of liquid by one or more gases flowing along the at least one annulus film of liquid.

[0013] In some aspects, provided herein is a nozzle device for generating a plurality of atomized particles, the nozzle device including: at least one annular channel, wherein the at least one annular channel provides support to dispense an annulus film; wherein the annulus film is sufficiently stretched to generate the plurality of atomized particles. Further provided herein is a nozzle device, wherein a number-weighted size distribution of the plurality of atomized particles includes more than 99% of the plurality of atomized particles being smaller than 1 micron. Further provided herein is a nozzle device, wherein the annulus film includes a liquid having at least one active agent(s), wherein the active agent(s) in at least 50% of the plurality of atomized particles retains biological activity after being sprayed from the nozzle device.

[0014] In some aspects, provided herein is a system for generating a plurality of atomized particles, including: a nozzle device including at least one annular channel, wherein the at least one annular channel provides support to dispense an annulus film, and wherein the annulus film is sufficiently stretched to generate the plurality of atomized particles; at least one liquid source in fluid communication with the at least one annular channel; and at least one gas source in fluid communication with an inner channel and at least one outer annular channel of the nozzle device. Further provided herein is a system, further including at least one gas flowing from at least one gas source through the inner channel and the at least one outer annular channel. Further provided herein is a system, further including at least one liquid flowing from at least one liquid source through the at least one annular channel. Further provided herein is a

system, further including at least one control circuit configured to cause the at least one gas and the at least one liquid source to flow through the nozzle device simultaneously.

[0015] In some aspects, provided herein is a method for generating a plurality of atomized particles, the method including: causing at least one liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) to be dispensed in an annulus film from a nozzle device; and controlling a flow of at least one gas stream so as to sufficiently stretch the annulus film, thereby generating the plurality of atomized particles. Further provided herein is a method, wherein the at least one liquid is non-Newtonian. Further provided herein is a method, wherein the at least one liquid is Newtonian. Further provided herein is a method, further including drying the plurality of atomized particles. Further provided herein is a method, further including coupling a liquid pump to at least one middle annular channel of the nozzle. Further provided herein is a method, further including coupling at least one gas pump to an inner channel of the nozzle and at least one outer annular channel of the nozzle. Further provided herein is a method, further including controlling a flow rate of the at least one liquid. Further provided herein is a method, wherein the at least one liquid has an absolute viscosity greater than 100 cP. Further provided herein is a method, wherein the plurality of atomized particles are in a form of droplets. Further provided herein is a method, wherein the at least one liquid includes a suspension of an organic and/or inorganic material. Further provided herein is a method, wherein the at least one liquid includes a viscoelastic liquid. Further provided herein is a method, wherein the at least one liquid includes at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof. Further provided herein is a method, wherein at least 50% of the at least one microorganism retains biological activity after being sprayed. Further provided herein is a method, wherein the at least one liquid includes a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof. Further provided herein is a method, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed. Further provided herein is a method, wherein the at least one liquid includes a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof. Further provided herein is a method, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being sprayed. Further provided herein is a method, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed. Further provided herein is a method, wherein the flow

is controlled so as to obtain a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 20 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles includes a median diameter less than or equal to 15 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 10 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 5 μm . Further provided herein is a method, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with median diameter less than or equal to 1 μm . Further provided herein is a method, further including controlling a ratio of a flow rate of the at least one liquid relative to the flow of the at least one gas stream. Further provided herein is a method, wherein a ratio of a diameter of at least one middle annular channel of the nozzle to a diameter of an inner channel of the nozzle, a diameter of at least one outer annular channel of the nozzle, or a combination thereof is varied.

[0016] In some aspects, provided herein is a nozzle device for generating atomized particles from a liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof), the nozzle device including: at least one annular channel having a gap width sufficient so as to atomize the liquid upon being flowed through the at least one annular channel between one or more flowing gas(es), thereby generating a plurality of atomized particles; wherein a number-weighted size distribution of the plurality of atomized particles includes more than 99% of the plurality of atomized particles being smaller than 1 micron. Further provided herein is a nozzle device, wherein the gap width ranges from 10 to 125 micrometers.

[0017] In some aspects, provided herein is a method of encapsulating one or more active agent, wherein the method comprises flowing at least one liquid comprising one or more active agent from at least one channel of a nozzle device to form an annulus film; and flowing at least one first gas along an inner surface of the annulus film and at least one second gas along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby encapsulating one or more active agent within a plurality of atomized particles.

BRIEF DESCRIPTION OF FIGURES

[0018] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate embodiments of the present invention and, together with a general

description of the invention given above, and the detailed description of the embodiments given below, serve to explain the principles of the present invention.

[0019] **FIGS. 1A-1D** illustrate embodiments of various channel configurations of a nozzle device, including devices configured to provide liquid film shaped as a hollow cylinder sandwiched between two coaxial gas flows (**FIG. 1A**), liquid film shaped as a hollow converging cone sandwiched between two coaxial gas flows (**FIG. 1B**), liquid film shaped as a hollow diverging cone sandwiched between two coaxial gas flows (**FIG. 1C**), and liquid film shaped as a diverging cone cylinder sandwiched between two coaxial gas flows in a converging-diverging (de Laval) nozzle configuration (**FIG. 1D**).

[0020] **FIGS. 2A-2B** illustrate embodiments of a nozzle device with respect to a plane of one or more outlets.

[0021] **FIG. 3A** illustrates an embodiment of a nozzle device where the outlets of the channels share a common O-O plane.

[0022] **FIGS. 3B-3D** are illustrations of embodiments of a device where at least one outlet of a channel is not coplanar.

[0023] **FIG. 4** is an illustration of an embodiment of a nozzle device with four channels, where the two intermediate channels utilize different liquid materials.

[0024] **FIGS. 5A-5C** are photographs of spray patterns formed with different methods, including conventional pump sprays (**FIG. 5A**), aerosol sprays (**FIG. 5B**), and embodiments of the present disclosure (**FIG. 5C**).

[0025] **FIGS. 6A-6G** are graphs showing droplet size distribution measurements for three-channel nozzle assemblies with straight channels, including characteristic droplet diameters of water sprays as a function of liquid flow rate for air pressure 2 bar gauge and liquid flow gap width 25 microns (**FIG. 6A**), characteristic droplet diameters of water sprays as a function of liquid flow rate for air pressure 5 bar gauge and liquid flow gap width 25 microns (**FIG. 6B**), characteristic droplet diameters of water sprays as a function of air pressure for water flow rate of 2 ml/min and liquid flow gap width 25 microns (**FIG. 6C**), mass median droplet diameter of water sprays as a function of air pressure for various water flow rates and liquid flow gap width 25 microns (**FIG. 6D**), mass median droplet diameter of sprays for various liquids as a function of liquid flow rate at air pressure 2 bar gauge and liquid flow gap width 125 microns (**FIG. 6E**), mass median droplet diameter of water sprays as a function of air pressure for various liquid flow gaps and water flow rate of 2 ml/min (**FIG. 6F**), and mass median droplet diameter of water sprays as a function of liquid flow rate for various liquid flow gaps and air pressure 2 bar gauge (**FIG. 6G**).

[0026] **FIGS 7A-7D** are graphs showing examples of profiles of the droplet size distribution measured by laser diffraction, including volume (**FIG. 7A**) and number (**FIG. 7B**)-weighted droplet size distributions for water spray at 2 bar air pressure with liquid flow rate 2 ml/min and liquid flow gap width 25 microns, and volume (**FIG. 7C**) and number (**FIG. 7D**)-weighted droplet size distributions for ethanol spray at 2 bar air pressure with liquid flow rate 2 ml/min and liquid flow gap width 25 microns.

[0027] **FIG. 8** is a bar graph showing protein abundance for human cytomegalovirus (HCMV) particles in spray droplets analyzed by Western Blot that are generated at generated at 2000 mbar (spray 1), 1500 mbar (spray 2) and 1000 mbar (spray 3). For controls, Western Blot analysis was performed prior to atomization. The Western Blot was performed for three different proteins associated with the HCMV particles, UL99, UL26 and IE1. **FIG. 8** summarizes protein abundance determined by Western Blot for each of the three proteins, from left to right, prior to atomization at 2000 mbar (control 1), within droplets generated at 2000 mbar (spray 1), prior to atomization at 1500 mbar (control 2), within droplets generated at 1500 mbar (spray 2), prior to atomization at 1000 mbar (control 3), and within droplets generated at 1000 mbar (spray 3), respectively.

[0028] **FIG. 9** is a bar graph demonstrating retention of activity of human cytomegalovirus (HCMV) in spray droplets generated at 2000 mbar (spray 1), 1500 mbar (spray 2) and 1000 mbar (spray 3). For controls, analysis was performed with the solution prior to atomization. **FIG. 9** summarizes particles/PFU observed for HCMV particles prior to atomization (left) and after atomization (right).

[0029] **FIGS. 10A-10C** depicts a graph illustrating the preservation of the size of yeast RNA-loaded lipid nanoparticles (LNPs) after being sprayed, as determined by measuring the dynamic light scattering (DLS) intensity of the liquid samples obtained from the LNP suspension spray droplets using sodium dodecyl sulfate (SDS) surfactant of various concentrations 0.4 mM (**FIG. 10A**), 0.8 mM (**FIG. 10B**) and 1.6 mM (**FIG. 10C**).

[0030] **FIGS. 11A-11C** show results of experiments showing retention of AAV5 virus particles by atomized particles, and retention of infectious activity by the AAV5 virus particles following atomization. The atomized particles were generated at 2000 mbar (spray 1), 1500 mbar (spray 2) and 1000 mbar (spray 3). **FIG. 11A** shows results of a spectroscopic analysis for determining concentrations of virus particles prior to atomization (control), and following atomization (spray). Controls show AAV5 virus particles present in the suspension prior to atomization. **FIG. 11B** and **11C** show results of a comparative analysis of retention of

infectious activity by virus particles prior to atomization (control), and following atomization (spray). Controls show infectious activity of AAV5 virus particles prior to atomization.

[0031] FIG. 12 shows results of experiments showing retention of infectious activity by AAV2 virus particles following atomization. The atomized particles were generated at 2000 mbar (spray 1), 1500 mbar (spray 2) and 1000 mbar (spray 3). Controls show infectious activity of AAV2 virus particles prior to atomization.

[0032] It should be understood that the appended drawings are not necessarily to scale, presenting a somewhat simplified representation of various features illustrative of the basic principles of the invention. The specific design features of the sequence of operations as disclosed herein, including, for example, specific dimensions, orientations, locations, and shapes of various illustrated components, will be determined in part by the particular intended application and use environment. Certain features of the illustrated embodiments have been enlarged or distorted relative to others to facilitate visualization and clear understanding. In particular, thin features may be thickened, for example, for clarity or illustration.

DETAILED DESCRIPTION

[0033] Disclosed are methods and devices for generating sprays with droplets of micron and submicron diameter. The droplets are obtained by disintegration of one or more thin liquid film(s), generally having a shape of a hollow cylinder or hollow cone, by two streams of atomizing gas(es) flowing inside and outside of the liquid film(s) along its axis in the same direction. To organize the flow in such way, a nozzle design with at least three coaxial channels was developed along with processes for atomizing the thin liquid film(s). The atomizing gas(es) flows in inner (circular) and outer (annular) channels of the coaxial nozzle, and the liquid flows out as liquid film(s) in the middle annular channel. The contact and mixing between the two gas streams and the liquid film(s) occurs at the outlet of the nozzle. The gas flows apply shear stress and stretches tangentially the cylindrical or conical surface of the liquid film(s) along its axis from both sides of the film(s) in the same downstream direction, resulting in hydrodynamic instability disintegrating the liquid film(s) into fine droplets, forming a spray with hollow cone.

[0034] Disclosed are also methods and devices for atomization of liquids, suspensions or combinations thereof including organic and inorganic materials. As the liquids, suspensions or combinations flow through the middle annular channel(s), shear stress from inner and outer

coaxial gas streams allow for the production of particles and/or droplets, in single- or multi-layered form, that include, for example, active agents such as proteins, monoclonal antibodies, antibody fragments, nucleic acids (DNA, RNA, mRNA, siRNA), peptides, imaging agents and small molecules. Other suspended materials or droplets are described in more detail below. The methods and devices herein allow for atomization that does not substantially affect or decrease the biological activity of such agents, and can be suitable for spraying of both solutions and suspensions. The methods and devices herein also allow for high-consistency particle or droplet size distributions of a desired size and amount, and thus are highly scalable for various applications, including pharmaceutical, biomedical and environmental industries.

[0035] Disclosed are also methods and devices for atomization of liquids. The methods and devices have a wide range of utility across various industries. For example, in some embodiments, the methods and devices comprise applications including but not limited to spray drying, encapsulation, agricultural spraying, spray painting, spray coating, medical sprays and drug delivery (nasal and throat drug delivery, wound healing), 3D printing, electronics, fragrance and cosmetics, humidification and dust fighting, decontamination, fuel injection, and laser-assisted powder deposition. Furthermore, unlike conventional nozzle spraying, the methods and devices advantageously disintegrate thin liquid films for producing atomized particles. For example, **FIGs. 5A** and **5B** shows spray patterns of conventional pump and aerosol, respectively. In some embodiments, methods and devices enable formation of finer droplets and sprays with >99% of droplets smaller than 1 micron (in number-weighted droplet size distributions). **FIG. 5C** shows spray pattern generated by methods and devices described herein. In some embodiments, methods and devices atomize high viscosity liquids, suspensions of organic and inorganic materials, and viscoelastic liquids. Additionally, the methods and devices are advantageously gentle and compatible with biological materials and microorganisms. Accordingly, in some embodiments, biological materials and microorganisms retain their biological activity after atomization. Moreover, in some embodiments, methods and devices enable spraying suspensions of lipid nanoparticles encapsulating RNA/mRNA without causing aggregation of the nanoparticles in atomized droplets. In some embodiments, methods and devices allow for the creation of droplets with core and layer structures, multiple layers, and matrix-type encapsulation.

Nozzle Device and Methods of use thereof

[0036] Described herein are nozzle devices for generating atomized particles. In some embodiments, a nozzle device comprises at least three channels comprising an inner channel,

at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel. In some embodiments, the at least one middle annular channel is coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel.

[0037] FIGS. 1A-1D illustrate embodiments of various channel configurations of a nozzle device 100. The embodiments of methods and devices can include flow configurations resulting in thin liquid film flow as a hollow cylinder, as a converging hollow cone, and as a diverging hollow cone. The flow of gas can be organized in either straight cylinder, converging, diverging or converging-diverging (de Laval) shape nozzle configurations. Such embodiments are different from typical bulk liquid flow disintegration in a regular nozzle.

[0038] In the disclosed embodiments, a fine spray is formed by a nozzle device 100 by flowing a liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) through at least one middle annular channel 101 coaxially arranged between gas flows through an inner channel 102 and at least one outer annular channel 103 to disintegrate at least one liquid film 104. The liquid film 104 may be thin and flowing as it emerges from the at least one middle annular channel 101. In some embodiments, the liquid film 104 has the shape of a hollow cylinder or a cone. This hollow liquid cylinder or cone is sandwiched between two coaxial gas flows, which are streamed in the same direction as the liquid. In some embodiments, the two coaxial gas flows comprise a first gas flow through an inner channel 102 and a second gas flow through an outer annular channel 103. The two gas streams apply shear stress and generate hydrodynamic instability on both sides of the hollow liquid cylinder or cone. Using this “hydrodynamic stretching” by the gas flow performs thinning of the liquid film 104, breakup of the film into fine ligaments and eventually pinch off and formation of fine spray droplets 105.

[0039] FIG. 1A illustrates an embodiment of the device 100 configured to provide liquid film shaped as a hollow cylinder sandwiched between two coaxial gas flows. **FIG. 1B** illustrates an embodiment of the device 100 configured to provide liquid film shaped as a hollow converging cone sandwiched between two coaxial gas flows. **FIG. 1C** illustrates an embodiment of the device 100 configured to provide liquid film shaped as a hollow diverging cone sandwiched between two coaxial gas flows. **FIG. 1D** illustrates an embodiment of the device 100 configured to provide a liquid film shaped as a diverging cone cylinder sandwiched between two coaxial gas flows in a converging-diverging (de Laval) nozzle configuration.

[0040] In some embodiments, an initial liquid film (or annulus film) comprises a thickness in a range of from 5 microns to 200 microns, from 5 microns to 150 microns, from 5 microns to 125 microns, from 5 microns to 100 microns, from 5 microns to 50 microns, from 5 microns to 30 microns, from 20 microns to 200 microns, from 20 microns to 150 microns, from 20 microns to 125 microns, from 20 microns to 100 microns, from 20 microns to 50 microns, from 20 microns to 30 microns, from 50 microns to 200 microns, from 50 microns to 150 microns, from 50 microns to 125 microns, from 50 microns to 100 microns, from 100 microns to 200 microns, from 100 microns to 150 microns, or from 150 microns to 200 microns. In some embodiments, an initial liquid film comprises a thickness of more than 5 microns, more than 10 microns, more than 15 microns, more than 25 microns, more than 50 microns, more than 75 microns, more than 100 microns, more than 125 microns, or more than 150 microns. In some embodiments, the initial liquid film (or annulus film) has a typical thickness of 25 microns or more. In some embodiments, a resulting spray can have > 99% of droplets smaller than one micron in diameter, as can be observed from the measured number-weighted drop size distributions (see **FIGS. 6A-6G** and **7A-7D**, described in more detail below).

[0041] In some embodiments, the methods provided herein may include atomization of high viscosity liquids. In some embodiments, the liquids are Newtonian or non-Newtonian liquids. In some examples, the nozzle was tested using 85 vol% of water-glycerol solution, with viscosity 160 times more than water.

[0042] In some embodiments, the methods and systems provided herein may be capable of atomization of relatively thick liquids (*e.g.*, solutions, suspensions, emulsions, or combinations thereof) that result in droplet form. Such capabilities can be extremely challenging for some conventional techniques to provide. In particular, a thicker liquid would normally require a greater pressure to atomize the particles and/or form droplet(s) from the liquid. The methods and systems provided herein may be adapted to adjust a combination of various operating parameters so as to atomize or produce droplets from relatively thicker liquids, such as those with viscosities described in more detail below.

[0043] In some embodiments, the systems herein are configured to discharge a liquid (*e.g.*, a solution, an emulsion, a suspension or a combination thereof) from the nozzle(s) so as to form a spray film. In some embodiments, the nozzle(s) is configured to aerosolize the liquid. In some embodiments, the nozzle(s) is configured to spray the liquid, suspension or combination. In some embodiments, the nozzle(s) is configured to dispense the liquid. In some embodiments, the nozzle(s) is configured to dispense droplets of the liquid. In some embodiments, the nozzle(s) is configured to disperse droplets of the liquid. In some embodiments, the nozzle(s)

is configured to discharge droplets the liquid. In some embodiments, the nozzle(s) is configured to release droplets of the liquid. In some embodiments, the nozzle(s) comprises at least one of a spray device, an aerosol sprayer, an aerosol container, an aerosol spray pump, a device comprising a dispenser for spray delivery of the liquid, a device comprising a hose, an aerosol spray gun, an atomizer device, a manual aerosol sprayer, an automatic aerosol sprayer, or any combination thereof.

[0044] In some embodiments, the methods provided herein may include atomization of suspensions of organic and inorganic materials. In some examples, aqueous insulin suspensions and suspensions of HCMV and AAV viruses suspended in biological buffers were successfully sprayed. Accordingly, in some embodiments, methods and devices described herein are used for producing atomized particles from a suspension of virus (*e.g.*, HCMV, AAV) particles suspended in biological buffers. In some embodiments, methods and devices described herein are used for producing atomized particles from a protein suspension (*e.g.*, insulin suspension). In some embodiments, the methods provided herein may include atomization of viscoelastic liquids. In some examples, polyvinyl alcohol and PEO/PEG water solutions were successfully sprayed. Accordingly, in some embodiments, methods and devices described herein are used for producing atomized particles from polyvinyl alcohol and PEO/PEG water solutions.

[0045] In some embodiments, methods described herein are gentle and compatible with biological materials and microorganisms. Accordingly, in some embodiments, methods and devices are used for producing atomized particles comprising biological materials and/or microorganisms. For example, it was found that atomization did not decrease the biological activity of HCMV virus particles. In some embodiments, methods are suitable for spraying of both solutions and suspensions. In some examples, suspensions of biological particles (NOVOLIN insulin suspension, virus particle suspensions – HCMV, AAV) have been successfully dispensed (see **FIG. 8** and **FIG. 9**, described in more detail below). In some embodiments, suspensions may comprise lipid nanoparticles (LNPs). In some additional examples, suspensions of LNPs encapsulating RNA or mRNA were atomized into sprays, and sprayed liquids preserved the size of LNPs, so that the atomization process caused no aggregation or minimum aggregation of the LNPs compared to initial suspension (see **FIGS. 10A-10C**, described in more detail below).

[0046] In some embodiments, the methods provided herein can be used for creating droplets with a core, and a layer or multiple layers or enabling matrix-type encapsulation.

[0047] The embodiments of method and device can include flow configurations resulting in thin liquid film flow as a hollow cylinder, as a converging hollow cone, and as a diverging

hollow cone. The flow of gas can be organized in either straight cylinder, converging, diverging or converging-diverging (de Laval) shape nozzle configurations. See **FIGS. 1A-1D**. In some embodiments, the gas comprises air, O₂, CO₂, N₂, Ar, He, or any other gas or oxidizer mixture.

[0048] In some embodiments, each of the channels (i.e., inner channel 102, middle annular channel 101, outer annular channel 103) of the devices described herein comprise varying length and diameter dimensions. In some embodiments, the length of the channel is ≤ 200 cm, ≤ 150 cm, ≤ 100 cm, ≤ 50 cm, ≤ 25 cm, ≤ 10 cm, ≤ 5 cm, ≤ 3 cm, or ≤ 1 cm. In some cases, the diameter of one or more of the proximal portion, the intermediate portion, or the distal portion is less than ≤ 20 cm, ≤ 10 cm, ≤ 8 cm, ≤ 5 cm, ≤ 1 cm, ≤ 0.5 cm, or ≤ 0.1 cm.

[0049] In some embodiments, converging, diverging or converging-diverging (de Laval) shape nozzle configurations comprise varying length and diameter dimensions. In some embodiments, the length of one or more of a proximal portion, an intermediate portion, or a distal portion is ≤ 200 cm, ≤ 150 cm, ≤ 100 cm, ≤ 50 cm, ≤ 25 cm, ≤ 10 cm, ≤ 5 cm, ≤ 3 cm, or ≤ 1 cm. In some cases, the diameter of one or more of the proximal portion, the intermediate portion, or the distal portion is less than ≤ 20 cm, ≤ 10 cm, ≤ 8 cm, ≤ 5 cm, ≤ 1 cm, ≤ 0.5 cm, or ≤ 0.1 cm.

[0050] In some embodiments, nozzle devices described herein comprise length of a channel (e.g., inner channel, middle annular channel, or outer annular channel) that is at least 3 times, at least 5 times, at least 10 times, at least 20 times, at least 50 times, or more than width of the channel. In some embodiments, length of a channel (e.g., inner channel, middle annular channel, or outer annular channel) is at least 3 times width of the channel. In some embodiments, length of a channel (e.g., inner channel, middle annular channel, or outer annular channel) is at least 5 times width of the channel. In some embodiments, length of a channel (e.g., inner channel, middle annular channel, or outer annular channel) is at least 10 times width of the channel. In some embodiments, a ratio of length of a channel (e.g., inner channel, middle annular channel, or outer annular channel) and width of the channel is in a range of from 2 to 100, from 2 to 80, from 2 to 50, from 2 to 40, from 2 to 20, from 2 to 10, from 2 to 5, from 8 to 100, from 8 to 80, from 8 to 50, from 8 to 40, from 8 to 20, from 8 to 10, from 15 to 100, from 15 to 80, from 15 to 50, from 15 to 40, from 15 to 20, from 40 to 100, from 40 to 80, from 40 to 50, from 75 to 100, from 75 to 80, or from 90 to 100. In some embodiments, a ratio of length of a channel (e.g., inner channel, middle annular channel, or outer annular channel) and width of the channel is in a range of from 3 to 10.

[0051] **FIGS. 2A-2B** illustrate coaxial nozzle devices, according to exemplary embodiments of this disclosure, where outlet edges of all the channels (i.e., inner channel 102, middle annular

channel 101, outer annular channel 103) formed by the tubular members making up the nozzle can lay in the same plane perpendicular the nozzle axis, as seen at bottom of the nozzle. In some embodiments, the channels can have different lengths and/or their outlet edges can lay in different planes perpendicular to the nozzle axis. **FIG. 2A** illustrates an embodiment where gas flows through each of the inner channel 102 and the outer annular channel 103 from different inlets. **FIG. 2B** illustrates an embodiment where gas flows through each of the inner channel 102 and the outer annular channel 103 from the same inlet.

[0052] **FIGS. 3A-3D** illustrate embodiments of a nozzle device where the outlets of the channels share a common O-O plane. Depending on the channel length, the outlet edge of each channel may, independently, be coplanar with reference plane O-O shown in **FIG. 3A**, or may be located above or below the reference plane in an axial direction (see **FIGS. 3B-3D**). Thus, in terms of length or outlet positioning, there are at least 3 possible positions (outlet upstream of reference plane O-O, outlet coplanar with reference plane, or outlet downstream of reference plane). For 3 channels, a total of $3^3=27$ possible variants for each of straight cylinder, converging, diverging, or converging-diverging (de Laval) shape nozzle configurations.

[0053] In some embodiments, a triple coaxial nozzle can be used to employ a three-channel process for direct atomization of liquid into droplets by the disclosed methods.

[0054] **FIG. 4** illustrates an embodiment of a nozzle device 200 with a secondary liquid flow channel. In some embodiments, nozzle devices with multiple liquid flow channels may be used for multilayer encapsulation. Specifically, nozzle device 200 comprises a first middle annular channel 201 and a second middle annular channel 202 coaxially arranged around the first middle annular channel 201. Both the first middle annular channel 201 and the second middle annular channel 202 are coaxially arranged between gas flows through an inner channel 203 and at least one outer annular channel 204 to form a plurality of encapsulated particles 205. The adding of a channel for secondary liquid flow in between the two gas streams can allow for layering or matrix encapsulation of a main or primary liquid, resulting in spray with encapsulated particles or droplets. Such quadruple coaxial nozzle can have $3^4 = 81$ possible variants of channel arrangements for each of straight cylinder, converging, diverging, or converging-diverging (de Laval) shape nozzle configurations. In some embodiments, converging-diverging shape nozzle configuration comprises an asymmetric shape, wherein the asymmetric shape accelerates a compressible fluid to supersonic speeds in the axial direction.

[0055] In some embodiments, a fluid stream that is flowing through a channel of a nozzle device described herein is configured to flow with a swirl or vortex. In some embodiments, a flow with a swirl or vortex is such that rotation is imparted to one of the at least two fluid

streams selected from a fluid stream within an outer annular channel, a fluid stream within a middle annular channel, a fluid stream within an inner channel. In some embodiments, rotation may be imparted to the flow by a swirl chamber that generates a tangential flow by the injection of one or more fluids through any number of tangential slots. In some embodiments, an application of a swirl or vortex to a first fluid stream flowing through a channel of a nozzle device is such that the flow travels with a different angular velocity relative to a second fluid stream flowing through a different channel of the nozzle device. In some embodiments, an overall degree of swirl may be characterized through a non-dimensional swirl number, S , and estimated from laser-Doppler velocimetry measurements obtained at an exit plane of the nozzle device. In some embodiments, a range of swirl levels of a fluid stream is of $S \leq 2.5$, $S \leq 2.0$, $S \leq 1.5$, $S \leq 0.5$, $S \leq 0.1$, or $S \leq 0.05$. In some embodiments, a fluid stream leads to a faster decrease of the break-up length, and this influence may increase when such a swirl or vortex is imparted to the fluid stream, as well as for increasing swirl levels. In some embodiments, higher velocities of a fluid stream leads to a break-up length to show smaller variations. In some embodiments, the use of swirl in a fluid stream increases atomization efficacy and quality.

[0056] For multilayer encapsulation, it will be understood that more than four, multi-channel configurations can be utilized. In some embodiments, multiple channels (i.e., n -channels) for secondary liquid flows can be added in between the two gas streams. Such n -channel coaxial nozzle can have 3^n possible variants of channel length organizations for each of straight cylinder, converging, diverging, or converging-diverging (de Laval) shape nozzle configurations. In some embodiments, $n \geq 6$. In some embodiments, $3 \leq n \leq 6$. In some embodiments, $3 \leq n \leq 5$. In some embodiments, $3 \leq n \leq 4$. In some embodiments, $3 \leq n \leq 10$.

[0057] In some embodiments, to organize the disclosed atomization process in three or more channel nozzle, the supplied liquid flow rate can be controlled using, e.g., a syringe pump or a peristaltic pump. In some embodiments, the pressure of atomizing gas flow can be controlled using, e.g., a microfluidic gas pump. The regulation of liquid mass flow rate and gas pressure can be used to control the generated spray in terms of droplet size distribution and flow rate.

[0058] In some embodiments, the inner (ID) and outer (OD) diameters of each of the inner channel, the at least one middle annular channel, and the at least one outer annular channel may be defined at a desired ratio relative to one another so as to affect droplet size distributions. A gap value or gap width, as used herein, may refer to a thickness of the at least one middle annular channel. In some embodiments, a gap value may range from about 10 μm to about 125 μm . In some embodiments, a gap value may be 25 μm , 75 μm and 125 μm .

[0059] In some embodiments, a ratio between a diameter, or diameter ratio, of each of the channels (i.e., inner channel 102, middle annular channel 101, outer annular channel 103) of the nozzles may vary. In some embodiments, a diameter ratio comprises a ratio ranging from 0.05 to less than 1, from 0.1 to less than 1, from 0.5 to less than 1, from 0.8 to less than 1, from 0.05 to 0.7, from 0.1 to 0.7, from 0.5 to 0.7, from 0.05 to 0.3, from 0.1 to 0.3, or from 0.05 to 0.1. In various embodiments, the diameter ratio may have a ratio within a range bounded by any two of the following values: 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1. In some embodiments, the diameter ratio comprises a ratio between a diameter of an inner channel and at least one middle annular channel. In some embodiments, the diameter ratio comprises a ratio between a diameter of the at least one middle annular channel and a diameter of at least one outer annular channel. In some embodiments, the diameter ratio comprises a ratio between a diameter of the inner channel and a diameter of at least one outer annular channel. In some embodiments, the diameter ratio comprises a ratio between a diameter of one of the at least one outer annular channel to a diameter of another of the at least one outer annular channel.

[0060] In some embodiments, a plurality of channels (i.e., inner channel 102, middle annular channel 101, outer annular channel 103) of a nozzle device described herein comprise a bluff body. In some embodiments, a bluff body is placed at a center of any one of plurality of channels of a nozzle device in z-axis direction. In some embodiments, a bluff body is used for achieving targeted gas flow (*e.g.*, reduce/minimize gas flow) at a center of any one of a plurality of channels of a nozzle device in a z-axis direction. In some embodiments, a bluff body is configured to reduce fluid consumption in a center of any one of a plurality of channels of a nozzle device in a z-axis direction. Alternatively, in some embodiments, a bluff body minimizes a fluid flow cross sectional area of inner channel and/or helps achieve more efficient atomization process relative to a device without bluff body. In some embodiments, a gap between a bluff body and an inner wall of an inner channel is a same dimension as a gap between an outer wall of a middle annular channel and an inner wall of an outer annular channel. In some embodiments, a bluff body is a cylindrical rod introduced along z-axis of inner channel 102 of a nozzle device. In some embodiments, a bluff body is a cylindrical rod introduced along a direction of fluid flow of inner channel 102 of a nozzle device. In some embodiments, a bluff body is positioned adjacent to a first side of a channel of a nozzle device. In some embodiments, the bluff body is positioned adjacent to a second side of a channel of a nozzle device. In some embodiments, a ratio of a cross section area of a bluff body relative to a cross section area of any one of a plurality of channels of a nozzle device is in a range of from about more than 0 to about less than 1. In various embodiments, a ratio of a cross section area

of a bluff body relative to a cross section area of any one of a plurality of channels of a nozzle device is within a range bounded by any two of the following values: 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1. In some embodiments, a cross-section of a bluff body is shaped to be circular, rectangular, square, triangular or star-shaped. In some embodiments, a cross-section of the bluff body has at least one convex side or at least one concave side. In some embodiments, a bluff body is configured for cleaning a channel of a nozzle device described herein.

[0061] In some embodiments, a droplet diameter is controlled or determined based on one or more of: densities of gas and liquid, liquid surface tension, pressure of atomizing gas, cross-section areas of nozzle for liquid and gas flows (nozzle dimensions), liquid and gas viscosities, ratio between gas and liquid flow rate, or a combination thereof. As many of the other factors are fixed based on the design of the nozzle and/or the desired particles, during normal operation, it is typically the pressure of the gas that is used to control droplet diameter. In some embodiments, the flow rate of spray is controlled by, e.g., a pump supplying liquid to the nozzle.

[0062] To generate sprays of core-shell or matrix encapsulated submicron and micron-size droplets, in which the droplets consist of a core and one or multiple layers surrounding the core or one/multiple materials are dispersed as matrix, in addition to the liquid atomization theory described above, those immiscible liquid materials need to follow the phase rule and the surface tension relationship described in the article: S. Mao, M. S. Chakraverti-Wuerthwein, H. Gaudio, and A. Košmrlj, *Designing the Morphology of Separated Phases in Multicomponent Liquid Mixtures*, Phys. Rev. Lett. 125, 218003 (2020). More details are provided in PCT/US2023/024520, filed June 6, 2023.

[0063] In some embodiments, disclosed methods comprise forming atomized particles, wherein the atomized particles comprise a core, and at least one layer surrounding the core. In some embodiments, a core and at least one layer surrounding the core are immiscible. In some embodiments, a core comprises a liquid (e.g., a solution, an emulsion, a suspension, or a combination thereof).

[0064] As noted previously, the disclosed method of liquid atomization is based on the shear-induced disintegration of a liquid film of a hollow cylindrical or cone shape jammed in between two co-flowing gas streams. Hence, if the liquid film is not properly produced, the liquid is not flowing or the liquid flow rate is not sufficient, and/or the gas streams do not properly flow and/or do not provide sufficient shear, the method will not provide proper disintegration of the liquid into spray of droplets.

[0065] In some embodiments, no spray or poor spray can be the result of numerous factors, including the liquid is of high viscosity leading to insufficient liquid flow, there is a clogging of fluids in supplying channels, liquid has suspended particles that are too big, or their aggregates are bigger than the liquid channel cross section, the liquid flow is too high, or the gas supply pressure is too low. To overcome those possible problems, the flow regime needs to be reestablished as disclosed above, by altering various process parameters, and geometrical dimensions and material of the channels. The geometry dimensions of the channel cross sections can be increased or decreased, the supply pressure of liquid and/or gas flows can be increased or decreased, the material of the channels can be chosen between glass, plastic or steel to withstand the applied pressures and provide chemical and physical compatibility. In some embodiments, a material of the channels comprise one or more properties selected for an anticorrosive property and a leach resistant property. Thus, in some embodiments, a camera may be present to capture images of droplet formation, which is then analyzed and used to control the various process parameters if, for example, few or no droplets are seen.

[0066] In some embodiments, nozzle devices disclosed herein are configured to functionally attached to one or more appropriate dispensers. In some embodiments, a dispenser comprises a fluid reservoir (*e.g.*, a gas reservoir, a liquid reservoir, a suspension reservoir, an emulsion reservoir, or a combination thereof). In some embodiments, a fluid reservoir is in fluid communication with a nozzle device. For example, in some embodiments, nozzle devices are in fluid communication with two or more fluid reservoirs. In some embodiments, nozzle devices are in fluid communication with two or more fluid reservoirs, wherein at least one of the two or more fluid reservoirs is an aerosol can. In some embodiments, nozzle devices are configured to operate in batch processing devices. In some embodiments, nozzle devices are configured to operate using continuous processing devices. In some embodiments, a dispenser comprises a microchip. Accordingly, in some embodiments, a system comprising a nozzle device is made from polydimethylsiloxane (PDMS) or an equivalent or derivative thereof.

[0067] In some embodiments, nozzle devices disclosed herein are configured to dispense fragrance fluid composition. In some embodiments, nozzle devices are in fluid communication with a fragrance fluid composition. In some embodiments, a fragrance fluid composition comprises a fragrance oil. In some embodiments, a nozzle device increases a surface area of dispensed particles (*e.g.*, atomized particles) and, thereby, reduces evaporation time. For example, in some embodiments, nozzle devices are configured to dispense atomized particles comprising fragrance fluid compositions. A fragrance fluid composition generally comprises a high concentration of alcohol (*e.g.*, ethanol) for reducing evaporation time. Accordingly, in

some embodiments, nozzle devices advantageously reduce use of alcohol in fragrance fluid compositions. For example, in some embodiments, a nozzle device forms atomized particles comprising a fragrance fluid composition to increase surface area and, thereby, reduces evaporation time. In some embodiments, evaporation time of atomized particles comprising a fragrance fluid composition is in a range of from 5 milliseconds to 200 milliseconds, from 5 milliseconds to 150 milliseconds, from 5 milliseconds to 100 milliseconds, from 5 milliseconds to 50 milliseconds, from 5 milliseconds to 20 milliseconds, from 25 milliseconds to 200 milliseconds, from 25 milliseconds to 150 milliseconds, from 25 milliseconds to 100 milliseconds, from 25 milliseconds to 50 milliseconds, from 75 milliseconds to 200 milliseconds, from 75 milliseconds to 150 milliseconds, from 75 milliseconds to 100 milliseconds, from 125 milliseconds to 200 milliseconds, from 125 milliseconds to 150 milliseconds, or from 150 milliseconds to 200 milliseconds. In some embodiments, evaporation time of atomized particles comprising fragrance fluid composition is in a range of from 10 milliseconds to 100 milliseconds. In some embodiments, fragrance fluid compositions for use with nozzle devices comprises alcohol in a concentration ranging from 5% (v/v) to 65% (v/v), from 5% (v/v) to 60% (v/v), from 5% (v/v) to 50% (v/v), from 5% (v/v) to 40% (v/v), from 5% (v/v) to 30% (v/v), from 5% (v/v) to 20% (v/v), from 5% (v/v) to 10% (v/v), from 15% (v/v) to 65% (v/v), from 15% (v/v) to 60% (v/v), from 15% (v/v) to 50% (v/v), from 15% (v/v) to 40% (v/v), from 15% (v/v) to 30% (v/v), from 15% (v/v) to 20% (v/v), from 25% (v/v) to 65% (v/v), from 25% (v/v) to 60% (v/v), from 25% (v/v) to 50% (v/v), from 25% (v/v) to 40% (v/v), from 25% (v/v) to 30% (v/v), from 35% (v/v) to 65% (v/v), from 35% (v/v) to 60% (v/v), from 35% (v/v) to 50% (v/v), from 35% (v/v) to 40% (v/v), from 45% (v/v) to 65% (v/v), from 45% (v/v) to 60% (v/v), from 45% (v/v) to 50% (v/v), from 55% (v/v) to 65% (v/v), or from 55% (v/v) to 60% (v/v). In some embodiments, fragrance fluid compositions for use with nozzle devices is essentially free of alcohol. In some embodiments, essentially free of alcohol refers to a concentration of alcohol of less than 5% (v/v), less than 4% (v/v), less than 3% (v/v), less than 2% (v/v), or less than 1% (v/v). Accordingly, in some embodiments, use of nozzle devices described herein reduces chance of fire hazard for dispensers, wherein dispensers are configured to dispense fragrance fluid composition comprising higher concentration of alcohol relative to fragrance fluid composition for use with the nozzle devices.

[0068] In some embodiments, nozzle devices described herein are configured for use in agriculture. For example, in some embodiments, nozzle devices are used for dispensing atomized particles comprising one or more fertilizers, one or more pesticides, or combinations thereof. In some embodiments, atomized particles formed by nozzle devices described herein

have higher surface area and, therefore, require less time to evaporate fluid content leaving pesticides on surfaces of treated crops. Similarly, atomized particles formed by nozzle devices described herein have higher surface area and, therefore, require less time to evaporate fluid content leaving fertilizers on surfaces of treated crops and allow absorption from the surface of the treated crop. Accordingly, nozzle devices described herein advantageously reduce use of pesticides, fertilizers, or combinations thereof in agriculture relative to conventional droplet dispensers. Moreover, in some embodiments, atomized water particles are also used in crop irrigation. As described above, atomized water particles require less time for evaporation. Therefore, nozzle devices described herein advantageously increases humidity and reduce water usage in crop irrigation.

[0069] In some embodiments, nozzle devices disclosed herein are configured for use in fuel injection systems. For example, in some embodiments, nozzle devices are used for dispensing atomized particles comprising one or more fuels. In some embodiments, atomized particles comprising one or more fuels comprises a more efficient mixture of fuel and gas. Accordingly, in some embodiments, nozzle devices disclosed herein improve function of fuel injection systems relative to other conventional fuel injection systems.

[0070] In some embodiments, nozzle devices disclosed herein are configured for humidifying systems. For example, in some embodiments, nozzle devices are used for producing atomized water particles. Atomized water droplets have smaller size that results in higher surface area and lesser evaporation time relative to larger water droplets. In some embodiments, small particles refer to atomized particles having a size in a range of from 0.01 μm to 50 μm , from 0.01 μm to 20 μm , from 0.01 μm to 10 μm , from 0.01 μm to 1 μm , from 0.1 μm to 50 μm , from 0.1 μm to 20 μm , from 0.1 μm to 10 μm , from 0.1 μm to 1 μm , from 1 μm to 50 μm , from 1 μm to 20 μm , from 1 μm to 10 μm , from 10 μm to 50 μm , or from 10 μm to 20 μm . In some embodiments, small particles refer to atomized particles having a size of less than 10 μm , less than 5 μm , less than 1 μm , less than 0.1 μm , or less than 0.01 μm . Accordingly, in some embodiments, nozzle devices disclosed herein improve function of humidifying systems relative to other conventional humidifying systems.

[0071] In some embodiments, nozzle systems disclosed herein may include nozzles attached to an appropriate gas or liquid source via, *e.g.*, a pump. The nozzles may be configured to generate aerosols into a vessel, which may be a collection device. In some embodiments, a vessel may include a filter disposed in the path of the aerosol droplets. In some embodiments, a vessel may be under vacuum. In some embodiments, a system is configured to operate using

a batch process. In some embodiments, a system is configured to operate using a continuous process.

[0072] In some embodiments, one or more circuits may be present to control some or all of the process. The circuits may include one or more processors operably coupled to one or more non-transitory computer-readable storage devices. The circuits may be configured to control one or more valves. In some embodiments, a valve controls a flow of a fluid (*e.g.*, gas or liquid) through a channel of nozzle device described herein.

[0073] Extensive experimental verification of the method has been performed.

[0074] The experimental validation was performed for straight triple coaxial nozzle configuration, as shown in **FIGS. 1A** and **2A**. For this purpose, steel tubes of blunt needles with gauges 15G, 18G, 20G, 21G and 22G were used to make 3 different triple coaxial nozzle assemblies, as described previously.

[0075] The disclosed techniques can be used in a variety of industries and applications, including, *e.g.*, the chemical industry (*e.g.*, spray drying, encapsulation, spray fluidized bed coating), the pharmaceutical and biotechnological industry (*e.g.*, spray drying, encapsulation), healthcare industry and medical devices (*e.g.*, medical diagnostics and drug delivery, decontamination or humidification and dust fighting, or decontamination), fragrances and perfumes, material manufacturers (*e.g.*, 3D printing, laser assisted powder deposition), cosmetics industry, agriculture industry, food industry, laundry care and detergents, recreation industry, and automobiles, aircrafts, gas turbines, power generation (*e.g.*, fuel injection).

[0076] In some embodiments, described herein are methods of making atomized particles. In some embodiments, methods of making atomized particles comprise flowing a liquid (*e.g.*, solution, suspension, emulsion, or combinations thereof) through at least one middle annular channel of a nozzle device described herein. In some embodiments, methods comprise controlling a flow of a liquid (*e.g.*, a solution, an emulsion, a suspension, or a combination thereof) through at least one channel of a nozzle device to form an annulus film along an inner surface of the at least one middle annular channel. In some embodiments, methods comprise controlling a flow of a liquid (*e.g.*, solution, suspension, emulsion, or combinations thereof) flowing through at least one middle annular channel of a nozzle device such that Reynolds number is within a range of from 100 to 100000, from 100 to 50000, from 100 to 25000, from 100 to 10000, from 100 to 1000, from 100 to 500, from 300 to 100000, from 300 to 50000, from 300 to 25000, from 300 to 10000, from 300 to 1000, from 300 to 500, from 800 to 100000, from 800 to 50000, from 800 to 25000, from 800 to 10000, from 800 to 1000, from 5000 to 100000, from 5000 to 50000, from 5000 to 25000, from 5000 to 10000, from 15000 to 100000,

from 15000 to 50000, from 15000 to 25000, from 35000 to 100000, from 35000 to 50000, or from 75000 to 100000. In some embodiments, methods comprise controlling a flow of a liquid (*e.g.*, solution, suspension, emulsion, or combinations thereof) flowing through at least one middle annular channel of a nozzle device such that Weber number is within a range of from 10 to 5000, from 10 to 2500, from 10 to 1000, from 10 to 500, from 10 to 400, from 10 to 300, from 10 to 200, from 10 to 100, from 10 to 50, from 10 to 25, from 25 to 5000, from 25 to 2500, from 25 to 1000, 25 to 500, from 25 to 400, from 25 to 300, from 25 to 200, from 25 to 100, from 25 to 50, from 50 to 5000, from 50 to 2500, from 50 to 1000, 50 to 500, from 50 to 400, from 50 to 300, from 50 to 200, from 50 to 100, from 100 to 5000, from 100 to 2500, from 100 to 1000, 100 to 500, from 100 to 400, from 100 to 300, from 100 to 200, from 200 to 5000, from 200 to 2500, from 200 to 1000, 200 to 500, from 200 to 400, from 200 to 300, from 300 to 5000, from 300 to 2500, from 300 to 1000, from 300 to 500, from 300 to 400, from 400 to 5000, from 400 to 2500, from 400 to 1000, from 400 to 500, from 500 to 5000, from 500 to 2500, from 500 to 1000, from 1000 to 5000, from 1000 to 2500, or from 2500 to 5000. In some embodiments, methods comprise controlling a flow of a liquid (*e.g.*, solution, suspension, emulsion, or combination thereof) flowing through at least one middle annular channel of a nozzle device such that Ohnesorge number is within a range of from 0.0001 to 10, from 0.0001 to 5, from 0.0001 to 1, from 0.0001 to 0.1, from 0.0001 to 0.01, from 0.0001 to 0.001, from 0.001 to 10, from 0.001 to 5, from 0.001 to 1, from 0.001 to 0.1, from 0.001 to 0.01, from 0.01 to 10, from 0.01 to 5, from 0.01 to 1, from 0.01 to 0.1, from 0.1 to 10, from 0.1 to 5, from 0.1 to 1, from 1 to 10, from 1 to 5, or from 5 to 10.

[0077] In some embodiments, one or more gases are flown through at least one inner channel of a nozzle device described herein. In some embodiments, methods comprise controlling a flow of one or more gases flowing through at least one inner channel of a nozzle device such that Reynolds number is within a range of from 100 to 10000, from 100 to 1000, from 100 to 500, from 300 to 10000, from 300 to 1000, from 300 to 500, from 800 to 10000, from 800 to 1000, or from 5000 to 10000. In some embodiments, methods comprise controlling a flow of a gas through at least one inner channel of a nozzle device such that Weber number is within a range of from 10 to 500, from 10 to 400, from 10 to 300, from 10 to 200, from 10 to 100, from 10 to 50, from 10 to 25, 25 to 500, from 25 to 400, from 25 to 300, from 25 to 200, from 25 to 100, from 25 to 50, 50 to 500, from 50 to 400, from 50 to 300, from 50 to 200, from 50 to 100, 100 to 500, from 100 to 400, from 100 to 300, from 100 to 200, 200 to 500, from 200 to 400, from 200 to 300, from 300 to 500, from 300 to 400, or from 400 to 500. In some embodiments, methods comprise controlling a flow of a gas through at least one inner channel of a nozzle

device such that Euler number is within a range of from 1 to 100, from 1 to 80, from 1 to 50, from 1 to 20, from 1 to 10, from 10 to 100, from 10 to 80, from 10 to 50, from 10 to 20, from 30 to 100, from 30 to 80, from 30 to 50, from 60 to 100, from 60 to 80, or from 80 to 100.

[0078] In some embodiments, one or more gases are flown through at least one outer annular channel of a nozzle device described herein. In some embodiments, methods comprise controlling a flow of one or more gases flowing through at least one outer annular channel of a nozzle device such that Reynolds number is within a range of from 100 to 10000, from 100 to 1000, from 100 to 500, from 300 to 10000, from 300 to 1000, from 300 to 500, from 800 to 10000, from 800 to 1000, or from 5000 to 10000. In some embodiments, methods comprise controlling a flow of one or more gases flowing through at least one outer annular channel of a nozzle device such that Weber number is within a range of from 10 to 500, from 10 to 400, from 10 to 300, from 10 to 200, from 10 to 100, from 10 to 50, from 10 to 25, 25 to 500, from 25 to 400, from 25 to 300, from 25 to 200, from 25 to 100, from 25 to 50, 50 to 500, from 50 to 400, from 50 to 300, from 50 to 200, from 50 to 100, 100 to 500, from 100 to 400, from 100 to 300, from 100 to 200, 200 to 500, from 200 to 400, from 200 to 300, from 300 to 500, from 300 to 400, or from 400 to 500. In some embodiments, methods comprise controlling a flow of one or more gases flowing through at least one outer annular channel of a nozzle device such that Euler number is within a range of from 1 to 100, from 1 to 80, from 1 to 50, from 1 to 20, from 1 to 10, from 10 to 100, from 10 to 80, from 10 to 50, from 10 to 20, from 30 to 100, from 30 to 80, from 30 to 50, from 60 to 100, from 60 to 80, or from 80 to 100.

[0079] In some embodiments, methods comprise controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby making atomized particles. In some embodiments, stretching of a cylindrical liquid surface from out of annulus film causes hydrodynamic instability that result in disintegration of the cylindrical liquid surface into atomized particles. Accordingly, in some embodiments, methods comprise controlling a flow of at least one first gas stream flowing through at least one inner channel along an inner surface of the annulus film and at least one second gas stream flowing through at least one outer annular channel along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby making atomized particles. In some embodiments, a dimension of at least one inner channel and at least one outer annular channel affects the amount of gas used for atomization. In some embodiments, each of at least one inner channel and at least one outer annular channel independently comprises a sufficient wall thickness to ensure efficient

momentum and energy transfer between gases flowing through the at least one inner channel and at least one outer annular channel, and a liquid flowing through at least one middle annular channel of the nozzle device. If the gas channels are too wide, momentum and energy transfer aren't efficient. If the gas channels are too small, not enough momentum and energy can be supplied for atomization. In some embodiments, a flow of a liquid (*e.g.*, solution, suspension, emulsion, or combinations thereof) flowing through at least one middle annular channel, a flow of one or more gases flowing through at least one inner channel, and a flow of one or more gases flowing through at least one outer annular channel of a nozzle device is controlled to obtain a size distribution of a plurality of atomized particles comprises a median particle diameter $\leq 20\text{ }\mu\text{m}$, $\leq 15\text{ }\mu\text{m}$, $\leq 10\text{ }\mu\text{m}$, $\leq 5\text{ }\mu\text{m}$, $\leq 1\text{ }\mu\text{m}$, $\leq 0.5\text{ }\mu\text{m}$, or $\leq 0.1\text{ }\mu\text{m}$. In some embodiments, a flow of a liquid (*e.g.*, solution, suspension, emulsion, or combinations thereof) flowing through at least one middle annular channel, a flow of one or more gases flowing through at least one inner channel, and a flow of one or more gases flowing through at least one outer annular channel of a nozzle device is controlled to obtain a size distribution of a plurality of atomized particles comprises a median particle diameter in a range of from $0.05\text{ }\mu\text{m}$ to $20\text{ }\mu\text{m}$, from $0.05\text{ }\mu\text{m}$ to $15\text{ }\mu\text{m}$, from $0.05\text{ }\mu\text{m}$ to $10\text{ }\mu\text{m}$, from $0.05\text{ }\mu\text{m}$ to $5\text{ }\mu\text{m}$, from $0.05\text{ }\mu\text{m}$ to $1\text{ }\mu\text{m}$, from $0.05\text{ }\mu\text{m}$ to $0.5\text{ }\mu\text{m}$, from $0.05\text{ }\mu\text{m}$ to $0.1\text{ }\mu\text{m}$, from $0.1\text{ }\mu\text{m}$ to $20\text{ }\mu\text{m}$, from $0.1\text{ }\mu\text{m}$ to $15\text{ }\mu\text{m}$, from $0.1\text{ }\mu\text{m}$ to $10\text{ }\mu\text{m}$, from $0.1\text{ }\mu\text{m}$ to $5\text{ }\mu\text{m}$, from $0.1\text{ }\mu\text{m}$ to $1\text{ }\mu\text{m}$, from $0.1\text{ }\mu\text{m}$ to $0.5\text{ }\mu\text{m}$, from $1\text{ }\mu\text{m}$ to $20\text{ }\mu\text{m}$, from $1\text{ }\mu\text{m}$ to $15\text{ }\mu\text{m}$, from $1\text{ }\mu\text{m}$ to $10\text{ }\mu\text{m}$, from $1\text{ }\mu\text{m}$ to $5\text{ }\mu\text{m}$, from $10\text{ }\mu\text{m}$ to $20\text{ }\mu\text{m}$, or from $10\text{ }\mu\text{m}$ to $15\text{ }\mu\text{m}$.

[0080] In some embodiments, described herein are methods of encapsulating an active agent. In some embodiments, methods of encapsulating an active agent may include causing a suspension or solution of one or more active agents to be dispensed in an annulus film from a nozzle. In some embodiments, an active agent comprises an organic and/or inorganic material. The methods may further include controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles encapsulating the active agent. In some embodiments, the methods may further include a second liquid dispensed as a second annulus film from a second middle annular channel. In some embodiments, the second liquid comprises a material for layering or matrix encapsulation over particles comprising the active agent. In some embodiments, the second liquid comprises another active agent, wherein the another active agent is same or different from the active agent. In some embodiments, a first liquid and a second liquid independently flowing through a first middle annular channel and a second

middle annular channel are independently in a range of from 0.01 ml/min to 500 ml/min, from 0.01 ml/min to 300 ml/min, from 0.01 ml/min to 100 ml/min, from 0.01 ml/min to 50 ml/min, from 0.01 ml/min to 20 ml/min, from 0.01 ml/min to 10 ml/min, from 0.1 ml/min to 500 ml/min, from 0.1 ml/min to 300 ml/min, from 0.1 ml/min to 100 ml/min, from 0.1 ml/min to 50 ml/min, from 0.1 ml/min to 20 ml/min, from 0.1 ml/min to 10 ml/min, from 2 ml/min to 500 ml/min, from 2 ml/min to 300 ml/min, from 2 ml/min to 100 ml/min, from 2 ml/min to 50 ml/min, from 2 ml/min to 20 ml/min, from 2 ml/min to 10 ml/min, from 30 ml/min to 500 ml/min, from 30 ml/min to 300 ml/min, from 30 ml/min to 100 ml/min, from 30 ml/min to 50 ml/min, from 80 ml/min to 500 ml/min, from 80 ml/min to 300 ml/min, from 80 ml/min to 100 ml/min, from 200 ml/min to 500 ml/min, from 200 ml/min to 300 ml/min, or from 400 ml/min to 500 ml/min.

[0081] Further disclosed herein are methods of encapsulating one or more active agents. In some embodiments the methods comprise flowing at least one liquid comprising one or more active agents from at least one channel of a nozzle device to form an annulus film; and flowing at least one first gas along an inner surface of the annulus film and at least one second gas along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby encapsulating one or more active agents within a plurality of atomized particles. In some embodiments, the at least one liquid comprises a first liquid and a second liquid, wherein the first liquid and the second liquid are immiscible. In some embodiments, the first liquid comprising one or more active agents is encapsulated within the plurality of atomized particles by the second liquid. In some embodiments, the second liquid comprises one or more active agents. In some embodiments, the at least one liquid comprises a suspension comprising a plurality of solid particles suspended in a solution, wherein the plurality of solid particles and the solution are immiscible. In some embodiments, the plurality of solid particles comprising one or more active agents are encapsulated within the plurality of atomized particles by the solution. In some embodiments, the solution comprises one or more active agents.

[0082] In some embodiments, after being sprayed, or encapsulated, an additional coating may be applied by a fluidized bed system. This can enable a targeted release of the active ingredient. As used herein, the terms “fluid bed” or “fluidized bed” can refer to a process in which an active agent that has been spray dried and encapsulated to form atomized particles or granules, is processed through a piece of equipment (e.g., a fluidized bed reactor). The process comprises spraying a matrix material as a solution, suspension, or melt onto a fluidized powder bed. The process can produce one or more additional coatings on an atomized particle. In some

embodiments, the atomized particles can be processed through a fluidized bed and coated with an additional matrix material that can be configured to allow the atomized particles to bypass an environmental condition and release the atomized particles into a target environment. One or more additional coatings on atomized particles can be created by spraying a matrix material as a solution, suspension or melt onto a fluidized particle bed.

[0083] In some embodiments, described herein are methods of making the atomized particles comprising particles wherein at least a portion of the particles of the active agent can be made by a spray drying process. In some embodiments, the spray drying processes can comprise: causing a suspension or solution of one or more active agents to be dispensed in an annulus film from a nozzle. In some embodiments, one or more active agents comprise an organic and/or inorganic material. The methods may further include controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles encapsulating the one or more active agents. The methods may further include drying the atomized particles, recovering the particles, or any combination thereof. In some cases, the atomized particles can comprise one or more encapsulated active agents.

[0084] In some embodiments, described herein are methods of decontaminating a composition. In some embodiments, the decontaminating process can comprise: causing a suspension or solution of one or more active agents to be dispensed in an annulus film from a nozzle. In some embodiments, one or more active agents comprise decontaminating agent. The methods may further include controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles encapsulating one or more decontaminating agents, one or more dehumidifying agents, or combinations thereof.

[0085] In some embodiments, described herein are methods of humidifying or dehumidifying a surface or composition. In some embodiments, the humidifying or dehumidifying processes can comprise: causing a suspension or solution of the active agent to be dispensed in an annulus film from a nozzle. In some embodiments, one or more active agents comprise one or more humidifying agent, one or more dehumidifying agents, or combinations thereof. The methods may further include controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby

spraying a plurality of atomized particles encapsulating one or more active agents (*e.g.*, a humidifying agent, a dehumidifying agent). In some embodiments, the method further includes humidifying or dehumidifying the surface or composition until a desired relative humidity is achieved.

[0086] In some embodiments, described herein are methods of nebulizing of a liquid (*e.g.*, solution, suspension, emulsion or combinations thereof) for delivery of aerosols of submicron-size particles or droplets. Such aerosols may be used for humidification purposes or inhalation of the particles or droplets for therapeutic purposes. In some embodiments, the nebulizing can comprise: causing a suspension or solution to be dispensed in an annulus film from a nozzle. In some embodiments, the suspension or solution comprises a humidifying agent. In some embodiments, the suspension or solution comprises an active agent. The method may further include controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles encapsulating the humidifying agent or active agent.

Compositions for use in nozzle device

[0087] Disclosed herein are compositions comprising one or more active agents. In some embodiments, a composition is a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof). In some embodiments, a composition is suitable for atomization. In some embodiments, a composition upon passing through a nozzle device forms atomized particles.

[0088] In some embodiments, compositions described herein comprise a viscosity in a range of from 1 cP to 2000 cP, from 1 cP to 1500 cP, from 1 cP to 1200 cP, from 1 cP to 1000 cP, from 1 cP to 800 cP, from 1 cP to 500 cP, from 1 cP to 300 cP, from 1 cP to 100 cP, from 1 cP to 50 cP, from 100 cP to 2000 cP, from 100 cP to 1500 cP, from 100 cP to 1200 cP, from 100 cP to 1000 cP, from 100 cP to 800 cP, from 100 cP to 500 cP, from 100 cP to 300 cP, from 500 cP to 2000 cP, from 500 cP to 1500 cP, from 500 cP to 1200 cP, from 500 cP to 1000 cP, from 500 cP to 800 cP, from 1000 cP to 2000 cP, from 1000 cP to 1500 cP, from 1000 cP to 1200 cP, or from 1500 cP to 2000 cP. In some embodiments, a composition is a high viscosity liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof). In some embodiments, a high viscosity refers a viscosity is at least ten times, at least 20 times, at least 30 times, at least 40 times, at least 50 times, at least 60 times, at least 70 times, at least 80 times or more than a viscosity of water under the same condition. Alternatively, in some embodiments, a high viscosity refers to a viscosity that is greater than 10 cP, greater than 20

cP, greater than 30 cP, greater than 40 cP, greater than 50 cP, greater than 100 cP, greater than 200 cP, greater than 500 cP, or more at 20 °C. In some embodiments, a high viscosity refers to a viscosity that is greater than 10 cP, greater than 20 cP, greater than 30 cP, greater than 40 cP, greater than 50 cP, greater than 100 cP, greater than 200 cP, greater than 500 cP, greater than 1000 cP, greater than 1500 cP or more at 25 °C. Accordingly, in some embodiments, a composition comprises a viscosity of more than 100 cP at 20 °C. In some embodiments, a composition comprises a viscosity of more than 100 cP at 25 °C. In some embodiments, a composition comprises viscoelastic properties.

[0089] In some embodiments, a viscosity of a liquid (*e.g.*, solution, suspension, emulsion, or combinations thereof) is based on a total weight of the particles in a liquid (*e.g.*, solution, suspension, emulsion, or combination thereof) in an amount ranging from about 1 wt% to about 100 wt% (for example, from about 1 wt% to about 10 wt%, from about 1 wt% to about 15 wt%, from about 1 wt% to about 20 wt%, from about 1 wt% to about 25 wt%, from about 1 wt% to about 30 wt%, from about 1 wt% to about 35 wt%, from about 1 wt% to about 40 wt%, from about 1 wt% to about 45 wt%, from about 1 wt% to about 50 wt%, from about 1 wt% to about 55 wt%, from about 1 wt% to about 60 wt%, from about 1 wt% to about 65 wt%, from about 1 wt% to about 70 wt%, from about 1 wt% to about 75 wt%, from about 1 wt% to about 80 wt%, from about 1 wt% to about 85 wt%, from about 1 wt% to about 90 wt%, from about 1 wt% to about 95 wt%, or from about 1 wt% to about 100 wt%).

[0090] In some embodiments, suspensions described herein comprise plurality of solid particles having a size in a range of from 1 nm to 1000 nm, from 1 nm to 800 nm, from 1 nm to 500 nm, from 1 nm to 300 nm, from 1 nm to 100 nm, from 100 nm to 1000 nm, from 100 nm to 800 nm, from 100 nm to 500 nm, from 100 nm to 300 nm, from 300 nm to 1000 nm, from 300 nm to 800 nm, from 300 nm to 500 nm, from 500 nm to 1000 nm, from 500 nm to 800 nm, or from 800 nm to 1000 nm. In some embodiments, a suspension comprises a plurality of solid particles having a size of at least 5 times, at least 10 times, at least 20 times, at least 50 times, or at least 100 times smaller than a diameter of a channel through which the suspension is flowing through. In some embodiments, a suspension comprises a plurality of solid particles having a size of at least 10 times smaller than a diameter of a channel through which the suspension is flowing.

[0091] In some embodiments, compositions described herein comprise a pH of about 2, about 2.3, about 2.5, about 2.8, about 3, about 3.3, about 3.5, about 3.8, about 4, about 4.3, about 4.5, about 4.8, about 5, about 5.3, about 5.5, about 5.8, about 6, about 6.3, about 6.5, about 6.8, about 7, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8,

about 7.9, about 8, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, or about 9. In some embodiments, compositions comprise pH in a range of from 2 to 9, from 2 to 8, from 2 to 7, from 2 to 6, from 2 to 5, from 2 to 4, from 2 to 3, from 3 to 5, from 3 to 7, from 4 to 6, from 6 to 8, from 7 to 9, from 7 to 7.5, from 7.5 to 8, from 8 to 8.5, from 8.5 to 9, or from 7 to 8.5. In some embodiments, compositions comprise pH in a range of from 2 to 9. In some embodiments, compositions comprise pH of less than 7. In some embodiments, compositions comprise pH of greater than 7.

[0092] In some embodiments, compositions described herein comprise a physiological osmolarity. In some embodiments, a physiological osmolarity refers to an osmolarity between 280 mOsm/L to about 310 mOsm/L. In some embodiments, atomized droplets comprise an osmolarity of greater than about 250 mOsm/L, greater than about 300 mOsm/L, greater than about 350 mOsm/L, greater than about 400 mOsm/L, or greater than about 500 mOsm/L. In some embodiments, atomized droplets comprises an osmolarity in a range of from 100 mOsm/L to about 2000 mOsm/L, from 100 mOsm/L to about 1500 mOsm/L, from 100 mOsm/L to about 1000 mOsm/L, from 100 mOsm/L to about 500 mOsm/L, from 500 mOsm/L to about 2000 mOsm/L, from 500 mOsm/L to about 1500 mOsm/L, from 500 mOsm/L to about 1000 mOsm/L, or from 1000 mOsm/L to about 2000 mOsm/L.

[0093] In some embodiments, compositions described herein comprise a particle to non-particle weight ratio ranging from about 0 to about 2, such as from about 0.5 to about 1.9, or from about 1.3 to about 1.4. In various embodiments, the composition may have a particle to non-particle weight ratio within a range bounded by any two of the following values: 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.

[0094] In some embodiments, compositions described herein comprise a concentration ranging from 0.1 µg/mL to 2000 mg/mL. In some embodiments, compositions described herein comprise a particle concentration ranging from 0.1 µg/mL -1 mg/mL, 1 µg/mL -10 mg/mL, 10 µg/mL -100 mg/mL, 100 µg/mL -500 mg/mL, 500 µg/mL -1000 mg/mL, or 1000 µg/mL -2000 mg/mL.

Active Agents

[0095] In some embodiments, active agents comprise a nucleic acid. In some embodiments, a nucleic acid is a double stranded nucleic acid (*e.g.*, DNA). In some embodiments, a nucleic acid is a single stranded nucleic acid (*e.g.*, a RNA, wherein the RNA comprises a mRNA, a rRNA, a tRNA, a non-coding RNA, a long non-coding RNA, a microRNA (miRNA), a small interfering RNA (siRNA), and a single-stranded RNA (ssRNA)).

[0096] In some embodiments, a nucleic acid described herein is a vector. In some embodiments, a vector comprises a therapeutic nucleic acid. In some embodiments, a therapeutic nucleic acid encodes a protein that upon expression prevents or cures a condition. In some embodiments, a therapeutic nucleic acid comprises nucleotides in a range of from 5 to 100, 10 to 100, 20 to 100, 50 to 100, 70 to 100, or more nucleotides. In some embodiments, a therapeutic nucleic acid comprises nucleotides in a range of from 0.1 kb to 5 kb, from 0.5 kb to 5 kb, from 1 kb to 5 kb, from 2 kb to 5 kb, from 3 kb to 5 kb, or from 4 kb to 5 kb. In some embodiments, a vector is a viral vector. In some embodiments, a viral vector is derived from one or more types of viruses, including but not limited to retroviruses (e.g., lentiviruses and γ -retroviruses), adenoviruses, arenaviruses, alphaviruses, adeno-associated viruses (AAVs), baculoviruses, vaccinia viruses, herpes simplex viruses and poxviruses. In some embodiments, a viral vector is an adeno-associated viral vector. In some embodiments, a viral particle an adeno-associated viral vector is derived from an AAV1 serotype, an AAV2 serotype, AAV3 serotype, an AAV4 serotype, AAV5 serotype, an AAV6 serotype, AAV7 serotype, an AAV8 serotype, an AAV9 serotype, an AAV10 serotype, an AAV11 serotype, an AAV12 serotype, an AAV-rh10 serotype, and any combination, derivative, or variant thereof. In some embodiments, an adeno-associated viral vector is a self-complementary AAV (scAAV) vector.

[0097] In some embodiments, an active agent comprises one or more microorganisms. In some embodiments, a microorganism comprises a virus, a bacterium, or a combination thereof. In some embodiments, a microorganism is alive, dead, or attenuated. In some embodiments, a virus comprises an enveloped virus, a non-enveloped virus, or a combination thereof. In some embodiments, a nozzle device described herein is used for administering a microorganism.

[0098] In some embodiments, an active agent comprises a protein. In some embodiments, a protein comprises a polypeptide chain of greater than 10 amino acids, greater than 20 amino acids, greater than 50 amino acids, greater than 100 amino acids, greater than 500 amino acids, greater than 1000 amino acids, greater than 1500 amino acids, greater than 2000 amino acids, or more. In some embodiments, a protein comprises a polypeptide chain of at least 10 amino acids, at least 20 amino acids, at least 50 amino acids, at least 100 amino acids, at least 500 amino acids, at least 1000 amino acids, at least 1500 amino acids, at least 2000 amino acids, or more. In some embodiments, a protein comprises a polypeptide chain has a molecular weight of greater than 1 kDa, greater than 2 kDa, greater than 5 kDa, greater than 10 kDa, greater than 20 kDa, greater than 30 kDa, greater than 40 kDa, greater than 50 kDa, or more. In some embodiments, a protein comprises a polypeptide chain has a molecular weight of at least 1 kDa, at least 2 kDa, at least 5 kDa, at least 10 kDa, at least 20 kDa, at least 30 kDa,

at least 40 kDa, at least 50 kDa, at least 100 kDa, at least 150 kDa, or more. In some embodiments, a protein comprises an antibody, an antigen, an enzyme, a hormone, or a functional fragment thereof. In some embodiments, an antibody is a monoclonal antibody or antibody-drug conjugate. In some embodiments, active ingredients comprise at least one of metal-organic frameworks, stem and functional cells, functional nanoparticles, virus-like particles, viral vectors, DNAs, carbon nanotubes, liposomes, polymersomes, polyplexes, quantum dots, nanocrystals, hydrogels, and exosomes. In some embodiments, a nozzle device described herein is used for administering an antibody, an antigen, an enzyme, a hormone, or a functional fragment thereof.

[0099] In some embodiments, an active agent comprises an imaging agent. In some embodiments, an imaging agent comprises one or more contrast agents, one or more radiopharmaceutical agents, or combinations thereof. In some embodiments, a nozzle device described herein is used for administering an imaging agent.

[0100] In some embodiments, an active agent comprises a vaccine. In some embodiments, a vaccine comprises a microorganism, a nucleic acid, a protein, an antigen, or a functional fragment thereof. In some embodiments, a vaccine induces an immunological response in subject that is administered with the vaccine.

[0101] In some embodiments, active agents comprise virus particles. In some embodiments, virus particles are selected from AAV2 virus particles, AAV5 virus particles, human cytomegalovirus particles, or combinations thereof. In some embodiments, a nozzle device described herein is used for administering a composition comprising virus particles.

[0102] In some embodiments, an active agent comprises a small molecule. In some embodiments, a small molecule comprises a molecular weight of up to 1000 Da. In some embodiments, a small molecule comprises a molecular weight of less than 1000 Da, less than 900 Da, less than 800 Da, less than 700 Da, less than 600 Da, less than 500 Da, less than 400 Da, less than 300 Da, less than 200 Da, or less than 100 Da. In some embodiments, a small molecule comprises a molecular weight in a range of from 10 Da to 1000 Da, from 10 Da to 800 Da, from 10 Da to 500 Da, from 10 Da to 300 Da, from 50 Da to 1000 Da, from 50 Da to 800 Da, from 50 Da to 500 Da, from 50 Da to 300 Da, from 100 Da to 1000 Da, from 100 Da to 800 Da, from 100 Da to 500 Da, from 100 Da to 300 Da, from 300 Da to 1000 Da, from 300 Da to 800 Da, from 300 Da to 500 Da, from 500 Da to 1000 Da, from 500 Da to 800 Da, or from 800 Da to 1000 Da. In some embodiments, a nozzle device described herein is used for administering a small molecule.

Adjuvants

[0103] In some embodiments, a composition comprises one or more lipids. In some embodiments, a lipid comprises a cationic lipid, an anionic lipid, a zwitterionic lipid, or an uncharged lipid. In some embodiments, one or more lipids stabilize one or more active agents. In some embodiments, one or more lipids encapsulate one or more active agents.

[0104] In some embodiments, a composition comprises lipid nanoparticles (LNPs). In some embodiments, LNPs comprise one or more lipids, and one or more surfactants. In some embodiments, a lipid comprises a cationic lipid, an anionic lipid, a zwitterionic lipid, or an uncharged lipid. In some embodiments, a surfactant comprises a cationic surfactant, an anionic surfactant, or a zwitterionic surfactant. In some embodiments, one or more surfactants stabilize LNPs. In some embodiments, the lipids comprise modified lipids. In some embodiments, modified lipids comprise pegylated lipids. In some embodiments, surfactants comprise modified surfactants. In some embodiments, modified surfactants comprise pegylated surfactants. In some embodiments, LNPs comprise one or more ionizable lipids, phospholipids, cholesterol, and PEG lipids. In some embodiments, LNPs comprise a vector described herein.

[0105] In some embodiments, compositions comprise one or more viscosity modifier. In some embodiments, viscosity modifiers comprise viscosity lowering agents, viscosity enhancing agents, or combinations thereof. Non-limiting examples of viscosity lowering agents include ethanol, isopropyl alcohol, water, arginine, ornithine monohydrochloride, phenylalanine, thiamine phosphoric acid ester chloride dihydrate, benzenesulfonic acid and pyridoxine hydrochloride. Non-limiting examples of viscosity enhancing agents include sorbitol, maltitol, sucrose, fructose, dextrose, maltodextrin and polydextrose.

[0106] In some embodiments, compositions comprise one or more buffers. Non-limiting examples of buffer includes phosphate buffered saline (PBS); 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES); 2-(N-Morpholino)-ethanesulfonic acid (MES); piperazine-N,N'-bis(2-ethanesulfonic acid) (PIPES); N-(2-acetamido)-2-aminoethanesulfonic acid (ACES); 3-(N-morpholino)propanesulfonic acid (MOPS); 2-[[1,3-Dihydroxy-2-(hydroxymethyl)propan-2-yl]amino]ethane-1-sulfonic acid (TES); N,N-Bis(2-hydroxyethyl)glycine (Bicine); 3-[4-(2-hydroxyethyl)piperazin-1-yl]propane-1-sulfonic acid (HEPPS or EPPS); N-[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]glycine (Tricine); and 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris).

Dried atomized particles

[0107] In some embodiments, atomized particles described herein are further processed to dry and form dried atomized particles. Accordingly, in some embodiments, compositions comprise dried atomized particles. In some embodiments, dried atomized particles comprise one or more active agents described herein. In some embodiments, dried atomized particles retain an activity of at least 60%, at least 70%, at least 80%, at least 90% or at least 95% relative to activity of atomized particles before drying, wherein the activity refers to one or more of an enzymic activity, a binding activity, an immunogenic activity, or a combination thereof. Accordingly, in some embodiments, dried atomized particles comprise at least 90% immunogenic activity relative to immunogenic activity of atomized particles before drying.

Pharmaceutical Composition

[0108] In some embodiments, compositions described herein comprise pharmaceutical compositions. In some embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable salt, one or more of a vehicle, adjuvant, excipient, or carrier, such as a filler, disintegrant, a surfactant, a binder, a lubricant, or combinations thereof.

[0109] The term, “pharmaceutically acceptable excipient, carrier or diluent,” as used herein, refers to substances formulated alongside the active agent of a pharmaceutical composition that allows the active agent to retain biological activity and is non-reactive in other aspects. Such a substance can be included for purposes including, but not limited to: long-term stabilization, bulking up solid formulations that contain active agents in small amounts, or to confer a therapeutic enhancement on the active agent in the final dosage form, such as facilitating absorption, reducing viscosity, or enhancing solubility. The selection of an appropriate substance can depend upon the route of administration, the dosage form, the active agent and other factors.

[0110] Excipients may facilitate drug absorption, reduce viscosity, or enhance solubility. Excipients may also facilitate the handling of the active ingredients, improve *in vitro* stability, and/or extend pharmaceutical product shelf life. Excipient selection may vary with the route of administration for drug delivery, the unit dose, as well as the active ingredients comprising the composition.

[0111] Non-limiting examples of pharmaceutically acceptable excipients, carriers and diluents suitable for the pharmaceutical compositions disclosed herein include buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose, dextran, mannitol and the like; polypeptides or amino acids such as glycine and the like; antioxidants; chelating agents such as EDTA, glutathione and the like; adjuvants

such as aluminum hydroxide and the like; surfactants such as Polysorbate 80, Polysorbate 20, Pluronic F68 and the like; glycerol; sorbitol; mannitol; polyethyleneglycol; and preservatives. In some embodiments, an excipient may comprise: anhydrous calcium phosphate, dihydrate calcium phosphate, hydroxypropyl methylcellulose, croscarmellose sodium, GMO-free croscarmellose sodium, carbomers, magnesium aluminometasilicate, povidone (PVP), crospovidone, sorbitol, dimethicone, sodium stearyl fumarate, sodium starch glycollate, hydroxypropylcellulose, native corn starch, modified corn starch, carrageenan, alginates, silicon dioxide, microcrystalline cellulose, carboxymethylcellulose sodium, alginates, carboxymethylcellulose (CMC), sodium carboxymethylcellulose (Na CMC), carbomers, natural gums, maltitol, glucose syrup, silicones, carbomers, fatty alcohols, alcohols, carbohydrates, petrolatum derivatives, butters, waxes, DMSO, esters, fatty acids, oil-in-water (O/W) emulsifiers, water-in-oil (W/O) emulsifiers, silicas, fumed silicas, isopropyl myristate, cellulosic derivatives, xanthan gum, propylenglycol, dimethyl isosorbate, flavors, colors, functional coatings, aesthetic coatings, a pharmaceutically acceptable salt of any of these, or any combination thereof.

[0112] . In some embodiments, pharmaceutical compositions comprise one or more active agents described herein. Accordingly, in some embodiments, a pharmaceutical composition comprises a virus vector, a non-viral vector, or a combination thereof. In some embodiments, a pharmaceutical composition comprises a protein. In some embodiments, a pharmaceutical composition comprises a small molecule. In some embodiments, a pharmaceutical composition comprises an imaging agent.

Methods of making atomized particles

[0113] Disclosed herein are methods of making atomized particles described herein. In some embodiments, methods of making atomized particles comprise flowing a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) from a nozzle along with a gas to form a plurality of atomized particles. In some embodiments, a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) is flown through at least one middle annular channel of a nozzle device described herein. In some embodiments, a gas is flown through at least one inner channel and at least one outer annular channel of a nozzle device described herein.

[0114] In some embodiments, a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) is flown through a nozzle device at a flowrate in a range of from 0.1 ml/min to 50 ml/min, from 0.3 ml/min to 50 ml/min, from 0.5 ml/min to 50 ml/min, from 0.8

ml/min to 50 ml/min, from 1 ml/min to 50 ml/min, from 3 ml/min to 50 ml/min, 5 ml/min to 50 ml/min, 8 ml/min to 50 ml/min, from 0.1 ml/min to 25 ml/min, from 0.3 ml/min to 25 ml/min, from 0.5 ml/min to 25 ml/min, from 0.8 ml/min to 25 ml/min, or from 1 ml/min to 25 ml/min, from 0.1 ml/min to 10 ml/min, from 0.3 ml/min to 10 ml/min, from 0.5 ml/min to 10 ml/min, from 0.8 ml/min to 10 ml/min, or from 1 ml/min to 10 ml/min, from 0.1 ml/min to 10 ml/min, from 0.3 ml/min to 10 ml/min, from 0.5 ml/min to 10 ml/min, from 0.8 ml/min to 10 ml/min, from 1 ml/min to 10 ml/min, from 3 ml/min to 10 ml/min, 5 ml/min to 10 ml/min, 8 ml/min to 10 ml/min, from 0.1 ml/min to 5 ml/min, from 0.3 ml/min to 5 ml/min, from 0.5 ml/min to 5 ml/min, from 0.8 ml/min to 5 ml/min, or from 1 ml/min to 5 ml/min. In some embodiments, a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) is flown through a nozzle device at a pressure in a range of from 0.1 bar to 2500 bar, from 0.1 bar to 1500 bar, from 0.1 bar to 500 bar, from 0.1 bar to 100 bar, from 0.1 bar to 50 bar, from 0.1 bar to 20 bar, from 0.1 bar to 10 bar, from 0.1 bar to 5 bar, from 0.1 bar to 2 bar, from 0.1 bar to 1 bar, from 3 bar to 2500 bar, from 3 bar to 1500 bar, from 3 bar to 500 bar, from 3 bar to 100 bar, from 3 bar to 50 bar, from 3 bar to 20 bar, from 3 bar to 10 bar, from 3 bar to 5 bar, from 8 bar to 2500 bar, from 8 bar to 1500 bar, from 8 bar to 500 bar, from 8 bar to 100 bar, from 8 bar to 50 bar, from 8 bar to 20 bar, from 8 bar to 10 bar, from 30 bar to 2500 bar, from 30 bar to 1500 bar, from 30 bar to 500 bar, from 30 bar to 100 bar, from 30 bar to 50 bar, from 80 bar to 2500 bar, from 80 bar to 1500 bar, from 80 bar to 500 bar, from 80 bar to 100 bar, from 300 bar to 2500 bar, from 300 bar to 1500 bar, from 300 bar to 500 bar, from 500 bar to 2500 bar, from 500 bar to 1500 bar, or from 500 bar to 1000 bar.

[0115] In some embodiments, a gas is flown through a nozzle device at a flowrate of in a range of from 0.1 L/min to 100 L/min, from 0.5 L/min to 100 L/min, from 1 L/min to 100 L/min, from 5 L/min to 100 L/min, from 10 L/min to 100 L/min, from 20 L/min to 100 L/min, from 50 L/min to 100 L/min, from 70 L/min to 100 L/min, from 0.1 L/min to 80 L/min, from 0.5 L/min to 80 L/min, from 1 L/min to 80 L/min, from 5 L/min to 80 L/min, from 10 L/min to 80 L/min, from 20 L/min to 80 L/min, from 50 L/min to 80 L/min, from 0.1 L/min to 40 L/min, from 0.5 L/min to 40 L/min, from 1 L/min to 40 L/min, from 5 L/min to 40 L/min, from 10 L/min to 40 L/min, from 20 L/min to 40 L/min, from 0.1 L/min to 30 L/min, from 0.5 L/min to 30 L/min, from 1 L/min to 30 L/min, from 5 L/min to 30 L/min, or from 10 L/min to 30 L/min. In some embodiments, a gas is flown through a nozzle device at a pressure in a range of from 0.1 bar to 2500 bar, from 0.1 bar to 1500 bar, from 0.1 bar to 500 bar, from 0.1 bar to 100 bar, from 0.1 bar to 50 bar, from 0.1 bar to 20 bar, from 0.1 bar to 10 bar, from 0.1 bar to 5 bar, from 0.1 bar to 2 bar, from 0.1 bar to 1 bar, from 3 bar to 2500 bar, from 3 bar to 1500

bar, from 3 bar to 500 bar, from 3 bar to 100 bar, from 3 bar to 50 bar, from 3 bar to 20 bar, from 3 bar to 10 bar, from 3 bar to 5 bar, from 8 bar to 2500 bar, from 8 bar to 1500 bar, from 8 bar to 500 bar, from 8 bar to 100 bar, from 8 bar to 50 bar, from 8 bar to 20 bar, from 8 bar to 10 bar, from 30 bar to 2500 bar, from 30 bar to 1500 bar, from 30 bar to 500 bar, from 30 bar to 100 bar, from 30 bar to 50 bar, from 80 bar to 2500 bar, from 80 bar to 1500 bar, from 80 bar to 500 bar, from 80 bar to 100 bar, from 300 bar to 2500 bar, from 300 bar to 1500 bar, from 300 bar to 500 bar, from 500 bar to 2500 bar, from 500 bar to 1500 bar, or from 500 bar to 1000 bar. In some embodiments, gas flowing through at least one inner channel and at least one outer annular channel is independently in a range of from 0.1 SLPM to 500 SLPM, from 0.1 SLPM to 300 SLPM, from 0.1 SLPM to 100 SLPM, from 0.1 SLPM to 50 SLPM, from 0.1 SLPM to 10 SLPM, from 5 SLPM to 500 SLPM, from 5 SLPM to 300 SLPM, from 5 SLPM to 100 SLPM, from 5 SLPM to 50 SLPM, from 5 SLPM to 10 SLPM, from 20 SLPM to 500 SLPM, from 20 SLPM to 300 SLPM, from 20 SLPM to 100 SLPM, from 20 SLPM to 50 SLPM, from 80 SLPM to 500 SLPM, from 80 SLPM to 300 SLPM, from 80 SLPM to 100 SLPM, from 200 SLPM to 500 SLPM, from 200 SLPM to 300 SLPM, or from 400 SLPM to 500 SLPM. In some embodiments, a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) flowing through at least one middle annular channel is independently in a range of from 0.01 ml/min to 500 ml/min, from 0.01 ml/min to 300 ml/min, from 0.01 ml/min to 100 ml/min, from 0.01 ml/min to 50 ml/min, from 0.01 ml/min to 20 ml/min, from 0.01 ml/min to 10 ml/min, from 0.1 ml/min to 500 ml/min, from 0.1 ml/min to 300 ml/min, from 0.1 ml/min to 100 ml/min, from 0.1 ml/min to 50 ml/min, from 0.1 ml/min to 20 ml/min, from 0.1 ml/min to 10 ml/min, from 2 ml/min to 500 ml/min, from 2 ml/min to 300 ml/min, from 2 ml/min to 100 ml/min, from 2 ml/min to 50 ml/min, from 2 ml/min to 20 ml/min, from 2 ml/min to 10 ml/min, from 30 ml/min to 500 ml/min, from 30 ml/min to 300 ml/min, from 30 ml/min to 100 ml/min, from 30 ml/min to 50 ml/min, from 80 ml/min to 500 ml/min, from 80 ml/min to 300 ml/min, from 80 ml/min to 100 ml/min, from 200 ml/min to 500 ml/min, from 200 ml/min to 300 ml/min, or from 400 ml/min to 500 ml/min.

[0116] In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, more than 96%, more than 97%, more than 98%, or more than 99% of the plurality of atomized particles of a desired size. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality of atomized particles of a desired size. In some embodiments, a desired size refers to a size in a range of from 0.1 micron to 10 micron, from 0.1 micron to 5 micron, from 0.1 micron to 1 micron, from 0.1 micron to 0.8

micron, from 0.1 micron to 0.5 micron, from 0.4 micron to 10 micron, from 0.4 micron to 5 micron, from 0.4 micron to 1 micron, from 0.4 micron to 0.8 micron, from 0.7 micron to 10 micron, from 0.7 micron to 5 micron, or from 0.7 micron to 1 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 1 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 5 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 10 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 20 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 30 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 40 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 50 micron.

[0117] In some embodiments, a flowrate of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) thereof flowing through a nozzle device is adjusted based on a viscosity of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) for making a plurality of atomized particles of a desired size. For example, in some embodiments, a viscosity and a flowrate of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) flowing through a nozzle device are inversely proportional to each other. In some embodiments, a flowrate of a gas thereof flowing through a nozzle device is adjusted based on a viscosity of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) for making a plurality of atomized particles of a desired size. For example, in some embodiments, a viscosity of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof), and a flowrate of a gas flowing through a nozzle device are directly proportional to each other.

[0118] In some embodiments, a pressure of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) flowing through a nozzle device is adjusted based on a viscosity of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) for making a plurality of atomized particles of a desired size. For example, in some embodiments, a viscosity and a pressure of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) flowing through a nozzle device are inversely proportional to each other. In some

embodiments, a pressure of a gas thereof flowing through a nozzle device is adjusted based on a viscosity of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) for making a plurality of atomized particles of a desired size. For example, in some embodiments, a viscosity of a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof), and a pressure of a gas flowing through a nozzle device are directly proportional to each other.

[0119] In some embodiments, methods described herein form a plurality of atomized particles, wherein a number-weighted size distribution of the plurality of particles comprises more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, more than 96%, more than 97%, more than 98%, or more than 99% of the plurality atomized of particles of a desired size. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of a desired size. In some embodiments, a desired size refers to a size of smaller than 10 micron, smaller than 5 micron, smaller than 1 micron, smaller than 0.8 micron, smaller than 0.5 micron, or smaller than 0.2 micron. In some embodiments, a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles of smaller than 1 micron.

[0120] In some embodiments, a gas flown through a nozzle device comprises a relative humidity in a range of from 5% to 100%, from 5% to 70%, from 5% to 50%, from 5% to 30%, from 5% to 20%, from 5% to 10%, from 15% to 100%, from 15% to 70%, from 15% to 50%, from 15% to 30%, from 15% to 20%, from 25% to 100%, from 25% to 70%, from 25% to 50%, from 25% to 30%, from 55% to 100%, from 55% to 70%, or from 75% to 100%. In some embodiments, a gas flown through a nozzle device comprises a relative humidity of less than 5%. Relative humidity refers to a percent of saturation humidity at a particular temperature.

Methods of making dried atomized particles

[0121] Disclosed herein are methods of making dried atomized particles described herein. In some embodiments, methods of making dried atomized particles comprise: flowing a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) from a nozzle along with a gas to form a plurality of atomized particles; and exposing the plurality of atomized particles to a desired temperature for drying and, thereby, forming a plurality of dried atomized particles. In some embodiments, a plurality of atomized particles is formed by any one of the methods described herein.

[0122] In some embodiments, a desired temperature for drying is in a range of from 3 °C to 300 °C, from 3 °C to 250 °C, from 3 °C to 200 °C, from 3 °C to 150 °C, from 3 °C to 100 °C,

from 3 °C to 90 °C, from 3 °C to 80 °C, from 3 °C to 70 °C, from 3 °C to 60 °C, from 3 °C to 50 °C, from 3 °C to 40 °C, from 3 °C to 30 °C, from 3 °C to 20 °C, from 3 °C to 10 °C, from 10 °C to 70 °C, from 10 °C to 60 °C, from 10 °C to 50 °C, from 10 °C to 40 °C, from 10 °C to 30 °C, from 10 °C to 20 °C, from 20 °C to 70 °C, from 20 °C to 60 °C, from 20 °C to 50 °C, from 20 °C to 40 °C, from 20 °C to 30 °C, from 30 °C to 70 °C, from 30 °C to 60 °C, from 30 °C to 50 °C, or from 30 °C to 40 °C. In some embodiments, a plurality of atomized particles is dried by exposing the plurality of atomized particles to a temperature in a range of from 3 °C to 40 °C.

[0123] In some embodiments, a gas is flown through a nozzle device at in a temperature in a range of from 3 °C to 95 °C, from 3 °C to 90 °C, from 3 °C to 80 °C, from 3 °C to 70 °C, from 3 °C to 60 °C, from 3 °C to 50 °C, from 3 °C to 40 °C, from 3 °C to 30 °C, from 3 °C to 20 °C, from 3 °C to 10 °C, from 10 °C to 70 °C, from 10 °C to 60 °C, from 10 °C to 50 °C, from 10 °C to 40 °C, from 10 °C to 30 °C, from 10 °C to 20 °C, from 20 °C to 70 °C, from 20 °C to 60 °C, from 20 °C to 50 °C, from 20 °C to 40 °C, from 20 °C to 30 °C, from 30 °C to 70 °C, from 30 °C to 60 °C, from 30 °C to 50 °C, or from 30 °C to 40 °C. In some embodiments, a gas is flown through a nozzle device at a temperature in a range of from 3 °C to 40 °C.

[0124] In some embodiments, methods described herein form a plurality of dried atomized particles, wherein the plurality of dried atomized particles retain at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% activity relative to activity of atomized particles before drying, wherein the activity refers to one or more of an enzymic activity, a binding activity, an immunogenic activity, or a combination thereof.

Methods of coating

[0125] Described herein are methods of coating. In some embodiments, methods of coating comprise: flowing a liquid (*e.g.*, a solution, a suspension, an emulsion, or a combination thereof) from a nozzle to form a plurality of atomized particles; exposing a surface of a substrate to the plurality of atomized particles; and exposing the substrate to a desired temperature for coating the substrate with a plurality of dried atomized particles. In some embodiments, a desired temperature for drying is in a range of from 3 °C to 70 °C, from 3 °C to 60 °C, from 3 °C to 50 °C, from 3 °C to 40 °C, from 3 °C to 30 °C, from 3 °C to 20 °C, from 3 °C to 10 °C, from 10 °C to 70 °C, from 10 °C to 60 °C, from 10 °C to 50 °C, from 10 °C to 40 °C, from 10 °C to 30 °C, from 10 °C to 20 °C, from 20 °C to 70 °C, from 20 °C to 60 °C, from 20 °C to 50 °C, from 20 °C to 40 °C, from 20 °C to 30 °C, from 30 °C to 70 °C, from 30 °C to 60 °C, from 30 °C to 50 °C, or from 30 °C to 40 °C. In some embodiments, a plurality of

atomized particles is dried by exposing the plurality of atomized particles to a temperature in a range of from 3 °C to 40 °C.

[0126] In some embodiments, a substrate comprises a composition, wherein the composition comprises a tablet, a capsule, a plurality of beads, or a combination thereof. In some embodiments, a coating of a composition extends shelf life of the composition. In some embodiments, a composition comprises one or more ingredients. Accordingly, in some embodiments, a coating extends shelf life one or more ingredients of a composition. In some embodiments, coating of a composition with a plurality of dried atomized particles allows slow release of one or more ingredients of a composition in bodily fluids. In some embodiments, a coating of a composition with a plurality of dried atomized particles allow release of one or more ingredient of the composition at a desired pH. For example, in some embodiments, enteric coating of a composition with a plurality of dried atomized particles allows release of ingredients of the composition in basic pH. Accordingly, in some embodiments, enteric coating of a composition with a plurality of dried atomized particles prevents degradation of one or more ingredients of the composition in gastric acid. In some embodiments, coating of a first composition with a plurality of dried atomized particles prevents chemical and/or physical interaction of one or more ingredients of the first composition with one or more ingredients of a second composition, wherein the first composition and the second composition are mixed together. For example, in some embodiments, a composition comprises at least two sets of plurality of beads, wherein coating of at least one set of beads with dried atomized particles prevents chemical and/or physical interaction between coated beads and uncoated beads. In some embodiments, coating serves as a physical barrier between two layers of ingredients of a composition. For example, in some embodiments, coating serves as a physical barrier between two distinct layers of a tablet, wherein a first layer of the two distinct layers comprise at least ingredient that is different than a second layer of the two distinct layers.

[0127] In some embodiments, a substrate comprises a metallic, wood, plastic, fabric, paper, leather, fabric, stone, cardboard, or a combination thereof. In some embodiments, coating of a surface of a substrate extends shelf life of the substrate. In some embodiments, coating is performed for enhancing aesthetics of a substrate. In some embodiments, coating is performed for affecting a color of a substrate. In some embodiments, coating is performed for enhancing an electromagnetic property of a substrate. In some embodiments, coating is performed for enhancing a conductivity of a substrate. In some embodiments, coating is performed for enhancing an insulating property of a substrate. In some embodiments, coating is performed for enhancing an optical property of a substrate. In some embodiments, coating is performed

for enhancing a mechanical property of a substrate. In some embodiments, coating is performed for enhancing a fluorescence of a substrate. In some embodiments, coating is performed for enhancing a reactivity of a substrate. In some embodiments, a surface coated with a plurality of dried atomized particles is further subjected to a downstream processing. In some embodiments, a downstream processing comprises exposing a substrate or a portion thereof to a chemical reaction, a photo reaction, a lithography reaction, an electromagnetic radiation, or combinations thereof.

Illustrative Embodiments

[0128] Embodiment 1. A nozzle device, comprising: a set of at least three coaxial tubular members that define at least three coaxial channels, each tubular member having an inlet and an outlet, the at least three coaxial tubular members including: an inner coaxial tubular member having an inner surface and an outer surface, the inner surface defining an inner coaxial channel; at least one intermediate coaxial tubular member comprising a first intermediate coaxial tubular member, each intermediate coaxial tubular member having an inner surface and an outer surface, a first intermediate coaxial channel being defined by a distance between the inner surface of the first intermediate coaxial tubular member and the outer surface of the inner coaxial tubular member; an outer coaxial tubular member having an inner surface and an outer surface, an outer coaxial channel being defined by a distance between an inner surface of the outer coaxial tubular member and an outer surface of the at least one intermediate coaxial tubular member; wherein the inlet of the inner tubular member and the inlet of the outer coaxial tubular member are configured to be operably coupled to a gas source, and the inlet of the intermediate coaxial tubular member is configured to be operably coupled to a liquid source.

[0129] Embodiment 2. The nozzle device of Embodiment 1, wherein the inner coaxial tubular member and the outer coaxial tubular member are operably coupled to different gas sources.

[0130] Embodiment 3. The nozzle device of Embodiment 1 or 2, wherein the inner coaxial tubular member and the outer coaxial tubular member are operably coupled to a same gas source.

[0131] Embodiment 4. The nozzle device of any one of Embodiments 1-3, wherein each intermediate coaxial tubular member is operably coupled to a different liquid source.

[0132] Embodiment 5. The nozzle device of any one of Embodiments 1-4, wherein at least two intermediate coaxial tubular members are operably coupled to a same liquid source.

[0133] Embodiment 6. The nozzle device of any one of Embodiments 1-5, wherein the at least one intermediate coaxial tubular member further comprises a second intermediate coaxial

tubular member having an inner surface and an outer surface, a second intermediate coaxial channel being defined by a distance from the inner surface of the second intermediate coaxial tubular member and an outer surface of the first intermediate coaxial tubular member.

[0134] Embodiment 7. The nozzle device of any one of Embodiments 1-6, wherein the set of at least three coaxial channels are configured as a hollow straight cylinder, a hollow converging cone, or a diverging hollow cone.

[0135] Embodiment 8. The nozzle device of any one of Embodiments 1-7, wherein the set of at least three coaxial channels are configured as a converging-diverging nozzle.

[0136] Embodiment 9. The nozzle device of any one of Embodiments 1-8, wherein a distance separating the inner surface of the intermediate tubular member from an outer surface of the inner tubular member is between 10 to 125 micrometers.

[0137] Embodiment 10. The nozzle device of any one of Embodiments 1-9, wherein the outlets of each tubular member of the set of at least three coaxial tubular members are coplanar.

[0138] Embodiment 11. The nozzle device of any one of Embodiments 1-10, wherein the outlet of each tubular member is positioned within a first plane, the first plane being perpendicular to an axis of the inner coaxial tubular member.

[0139] Embodiment 12. The nozzle device of any one of Embodiments 1-11, wherein the outlet of at least one tubular member of the set of at least three coaxial tubular members is non-coplanar with at least one other tubular member of the set of at least three coaxial tubular members.

[0140] Embodiment 13. A spraying system, comprising: a nozzle device of any one of Embodiments 1-12; at least one liquid pump coupled to the at least one intermediate coaxial tubular member; and at least one gas pump coupled to the inner coaxial tubular member and the outer coaxial tubular member.

[0141] Embodiment 14. The spraying system of Embodiment 13, further comprising at least one gas flowing from at least one gas source through the inner coaxial tubular member and the outer coaxial tubular member.

[0142] Embodiment 15. The spraying system of Embodiment 13 or 14, further comprising at least one liquid flowing from at least one liquid source through the at least one intermediate coaxial tubular member.

[0143] Embodiment 16. The spraying system of any one of Embodiments 1-15, further comprising at least one control circuit configured to cause the at least one gas and the at least one liquid source to flow through the nozzle device simultaneously.

[0144] Embodiment 17. A method of generating spray droplets, comprising: causing at least one liquid to be dispensed in an annulus film from a nozzle device; and controlling a flow of at least one gas stream through a central portion of the annulus film, and around an outside of the annulus film, to form a thin cylindrical liquid surface outside of the nozzle device by stretching the annulus film, to further make the cylindrical liquid surface thinner by tangential flow of gas streams inside and around the outside of the surface, and causing hydrodynamic instabilities to this cylindrical thin liquid film leading to break up into a plurality of fine droplets, where a diameter of each droplet of the plurality of fine droplets scales with a thickness of the stretched thin cylindrical liquid surface formed out of the annulus liquid film by the gas flows through a central portion of the annulus film, and around the outside of the annulus film.

[0145] Embodiment 18. The method of Embodiment 17, further comprising coupling a liquid pump to an intermediate coaxial tubular member of the nozzle device.

[0146] Embodiment 19. The method of Embodiment 17 or 18, further comprising coupling at least one gas pump to an inner coaxial tubular member and an outer coaxial tubular member of the nozzle device.

[0147] Embodiment 20. The method of any one of Embodiments 17-19, wherein controlling the flow of the at least one gas includes controlling a pressure of the at least one gas.

[0148] Embodiment 21. The method of any one of Embodiments 17-20, further comprising controlling a flow rate of the at least one liquid.

[0149] Embodiment 22. The method of any one of Embodiments 17-22, wherein the liquid has an absolute viscosity greater than 100 cP.

[0150] Embodiment 23. The method of any one of Embodiments 17-23, wherein the liquid comprises a suspension of an organic and/or inorganic material.

[0151] Embodiment 24. The method of any one of Embodiments 17-24, wherein the liquid comprises a viscoelastic liquid.

[0152] Embodiment 25. The method of any one of Embodiments 17-25, wherein the liquid comprises biological material and/or a microorganism, including but not limited to enveloped and non-enveloped viruses and bacteriophages.

[0153] Embodiment 26. The method of any one of Embodiments 17-25, wherein at least 50% of microorganisms retain biological activity after being sprayed.

[0154] Embodiment 27. The method of any one of Embodiments 17-26, wherein the liquid comprises therapeutic agents, including but not limited to proteins, monoclonal antibodies,

antibody fragments, nucleic acids (DNA, RNA, mRNA, siRNA), peptides, imaging agents and small molecules.

[0155] Embodiment 28. The method of any one of Embodiments 17-27, wherein at least 50% of therapeutic agents retain biological activity after being sprayed.

[0156] Embodiment 29. The method of any one of Embodiments 17-28, wherein the liquid comprises biological material and/or lipid nanoparticles loaded with therapeutic agents, including but not limited to nucleic acids (DNA, RNA, mRNA, siRNA), proteins, peptides, genes, imaging agents, microorganisms and small molecules.

[0157] Embodiment 30. The method of any one of embodiments 17-29, wherein a median size of lipid nanoparticles in suspension does not increase more than 25% after spraying into droplets.

[0158] Embodiment 31. The method of any one of embodiments 17-29, wherein at least 50% of therapeutic agents retain biological activity after being sprayed.

[0159] Embodiment 32. The method of any one of Embodiments 17-31, further comprising controlling parameters of flow to obtain droplet size distributions with median diameter 20 μm or smaller.

[0160] Embodiment 33. The method of any one of Embodiments 17-32, further comprising controlling parameters of flow to obtain droplet size distributions with median diameter 15 μm or smaller.

[0161] Embodiment 34. The method of any one of Embodiments 17-33, further comprising controlling parameters of flow to obtain droplet size distributions with median diameter 10 μm or smaller.

[0162] Embodiment 35. The method of any one of Embodiments 17-34, further comprising controlling parameters of flow to obtain droplet size distributions with median diameter 5 μm or smaller.

[0163] Embodiment 36. The method of any one of Embodiments 17-35, further comprising controlling parameters of flow to obtain droplet size distributions with median diameter 1 μm or smaller.

[0164] Embodiment 37. A nozzle device, comprising:

[0165] at least three channels comprising an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel

upon flow of one or more gases through at least the inner channel and the at least one outer annular channel.

[0166] Embodiment 38. The nozzle device of Embodiment 37, wherein the inner channel and the at least one outer annular channel are in fluid communication with different gas sources.

[0167] Embodiment 39. The nozzle device of Embodiment 37 or 38, wherein the inner channel and the at least one outer annular channel are in fluid communication with a same gas source.

[0168] Embodiment 40. The nozzle device of any one of Embodiments 37-39, wherein each of the at least one middle annular channel is in fluid communication with a different liquid source.

[0169] Embodiment 41. The nozzle device of any one of Embodiments 37-40, wherein each of the at least one middle annular channel is in fluid communication with a same liquid source.

[0170] Embodiment 42. The nozzle device of any one of Embodiments 37-41, wherein the at least one middle annular channel comprises a first middle annular channel and a second middle annular channel outside of the first middle annular channel.

[0171] Embodiment 43. The nozzle device of any one of Embodiments 37-42, wherein the at least three channels are shaped to comprise a hollow straight cylinder configuration, a hollow converging cone configuration, or a diverging hollow cone configuration.

[0172] Embodiment 44. The nozzle device of any one of Embodiments 37-43, wherein the at least three channels are shaped to comprise a converging-diverging configuration.

[0173] Embodiment 45. The nozzle device of any one of Embodiments 37-44, wherein the gap width ranges from 10 to 125 micrometers.

[0174] Embodiment 46. The nozzle device of any one of Embodiments 37-45, wherein outlets of the at least three channels are coplanar.

[0175] Embodiment 47. The nozzle device of any one of Embodiments 37-46, wherein each of the outlets is positioned within a first plane, the first plane being perpendicular to an axis of the inner channel.

[0176] Embodiment 48. The nozzle device of any one of Embodiments 37-47, wherein at least one outlet of the at least three channels is non-coplanar with other outlets of the at least three channels.

[0177] Embodiment 49. The nozzle device of any one of Embodiments 37-48, wherein a ratio of a diameter of the at least one middle annular channel to a diameter of an inner channel, a diameter of at least one outer annular channel, or a combination thereof is varied.

[0178] Embodiment 50. A spraying system, comprising: a nozzle device, the nozzle device comprising: at least three channels comprising an inner channel, at least one middle annular

channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel; at least one liquid source in fluid communication with the at least one middle annular channel; and at least one gas source in fluid communication with the inner channel and the at least one outer annular channel.

[0179] Embodiment 51. The spraying system of Embodiment 50, further comprising at least one gas flowing from at least one gas source through the inner channel and the at least one outer annular channel.

[0180] Embodiment 52. The spraying system of Embodiment 50 or 51, further comprising at least one liquid flowing from at least one liquid source through the at least one middle annular channel.

[0181] Embodiment 53. The spraying system of any one of Embodiments 50-52, further comprising at least one control circuit configured to cause the at least one gas and/or the at least one liquid source to flow through the nozzle device simultaneously.

[0182] Embodiment 54. A method of spraying particles, comprising: causing at least one liquid to be dispensed in an annulus film from a nozzle device; and controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles; wherein a diameter of each of the plurality of atomized particles scales with a thickness of the stretched cylindrical liquid surface.

[0183] Embodiment 55. The method of Embodiment 54, wherein the at least one liquid is non-Newtonian.

[0184] Embodiment 56. The method of Embodiment 54, wherein the at least one liquid is Newtonian.

[0185] Embodiment 57. The method of any one of Embodiments 54-56, further comprising drying the plurality of atomized particles.

[0186] Embodiment 58. The method of any one of Embodiments 54-57, further comprising coupling a liquid pump to at least one middle annular channel of the nozzle.

[0187] Embodiment 59. The method of any one of Embodiments 54-58, further comprising coupling at least one gas pump to an inner channel of the nozzle device and at least one outer annular channel of the nozzle device.

[0188] Embodiment 60. The method of any one of Embodiments 54-59, wherein the controlling the flow of the at least one first gas stream comprises controlling a pressure of the at least one first gas stream.

[0189] Embodiment 61. The method of any one of Embodiments 54-60, further comprising controlling a flow rate of the at least one liquid.

[0190] Embodiment 62. The method of any one of Embodiments 54-61, wherein the at least one liquid has an absolute viscosity greater than 100 cP.

[0191] Embodiment 63. The method of any one of Embodiments 54-62, wherein the plurality of atomized particles are in a form of droplets.

[0192] Embodiment 64. The method of any one of Embodiments 54-63, wherein the at least one liquid comprises a suspension of an organic and/or inorganic material.

[0193] Embodiment 65. The method of any one of Embodiments 54-64, wherein the at least one liquid comprises a viscoelastic liquid.

[0194] Embodiment 66. The method of any one of Embodiments 54-65, wherein the at least one liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.

[0195] Embodiment 67. The method of Embodiment 66, wherein at least 50% of the at least one microorganism retains biological activity after being sprayed.

[0196] Embodiment 68. The method of any one of Embodiments 54-65, wherein the at least one liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

[0197] Embodiment 69. The method of Embodiment 68, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

[0198] Embodiment 70. The method of any one of Embodiments 54-65, wherein the at least one liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

[0199] Embodiment 71. The method of Embodiment 70, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being sprayed.

[0200] Embodiment 72. The method of Embodiment 70 or 71, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

[0201] Embodiment 73. The method of any one of Embodiments 54-72, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

[0202] Embodiment 74. The method of any one of Embodiments 54-73, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

[0203] Embodiment 75. The method of any one of Embodiments 54-74, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 10 μm .

[0204] Embodiment 76. The method of any one of Embodiments 54-75, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 5 μm .

[0205] Embodiment 77. The method of any one of Embodiments 54-76, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with median diameter less than or equal to 1 μm .

[0206] Embodiment 78. The method of any one of Embodiments 54-77, further comprising controlling a ratio of a flow rate of the at least one liquid relative to the flow of the at least one first gas stream, the at least one second gas stream, or a combination thereof.

[0207] Embodiment 79. The method of any one of Embodiments 54-78, wherein a ratio of a diameter of at least one middle annular channel of the nozzle device to a diameter of an inner channel of the nozzle, a diameter of at least one outer annular channel of the nozzle, or a combination thereof is varied.

[0208] Embodiment 80. A composition for use in a nozzle device, comprising: a liquid having an absolute viscosity in a range of from 1 cP to 2000 cP; wherein: the liquid upon passing through the nozzle device, causes the liquid to produce a plurality of atomized particles, and a number-weighted size distribution of the plurality of atomized particles comprises more than 99% of the plurality of atomized particles being smaller than 1 micron.

[0209] Embodiment 81. The composition of Embodiment 80, wherein the liquid comprises one or more active agents.

[0210] Embodiment 82. The composition of Embodiment 80 or 81, wherein the suspension comprises plurality of solid particles having a size in a range of from 1 nm to 1000 nm, from 1 nm to 800 nm, from 1 nm to 500 nm, from 1 nm to 300 nm, from 1 nm to 100 nm, from 100

nm to 1000 nm, from 100 nm to 800 nm, from 100 nm to 500 nm, from 100 nm to 300 nm, from 300 nm to 1000 nm, from 300 nm to 800 nm, from 300 nm to 500 nm, from 500 nm to 1000 nm, from 500 nm to 800 nm, or from 800 nm to 1000 nm.

[0211] Embodiment 83. A composition comprising a plurality of particles, wherein the plurality of particles are dried atomized particles, wherein the dried atomized particles are formed from a liquid, and wherein number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality of particles being smaller than 1 micron.

[0212] Embodiment 84. The composition of Embodiment 83, wherein the composition comprises one or more active agents.

[0213] Embodiment 85. The composition of Embodiment 83 or 84, wherein the dried atomized particles retain at least 80% biological activity relative to the liquid.

[0214] Embodiment 86. The composition of any one of Embodiments 83-85, wherein the plurality of particles are plurality of atomized particles that are in the form of a plurality of droplets prior to forming the plurality of dried atomized particles.

[0215] Embodiment 86. The composition of any one of Embodiments 80-86, wherein the liquid is non-Newtonian.

[0216] Embodiment 87. The composition of any one of Embodiments 80-86, wherein the liquid is Newtonian.

[0217] Embodiment 88. The composition of any one of Embodiments 80-87, wherein the liquid has an absolute viscosity greater than 100 cP.

[0218] Embodiment 90. The composition of any one of Embodiments 80-88, wherein the liquid comprises a suspension of an organic and/or inorganic material.

[0219] Embodiment 91. The composition of any one of Embodiments 80-89, wherein the liquid comprises a viscoelastic liquid.

[0220] Embodiment 92. The composition of any one of Embodiments 80-91, wherein the liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.

[0221] Embodiment 93. The composition of Embodiment 92, wherein at least 50% of the at least one microorganism retains biological activity.

[0222] Embodiment 94. The composition of any one of Embodiments 80-91, wherein the liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

[0223] Embodiment 95. The composition of Embodiment 94, wherein at least 50% of the plurality of therapeutic agents retain biological activity.

[0224] Embodiment 96. The composition of any one of Embodiments 80-91, wherein the liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

[0225] Embodiment 97. The composition of Embodiment 96, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25%.

[0226] Embodiment 98. The composition of Embodiment 96 or 97, wherein at least 50% of the plurality of therapeutic agents retain biological activity.

[0227] Embodiment 99. A method of making a composition comprising: flowing a liquid from a nozzle device along with a gas to form a plurality of atomized particles, wherein a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles being smaller than 1 micron; and exposing the plurality of atomized particles to a temperature in a range of from 3 °C to 40 °C.

[0228] Embodiment 100. The method of Embodiment 99, wherein the liquid is flowed from the nozzle device at a pressure in a range of from 2500 bar to 500 bar.

[0229] Embodiment 101. The method of Embodiment 99 or 100, wherein the liquid comprises one or more active agents in a range of from 0.1 µg/mL to 100 µg/mL.

[0230] Embodiment 102. A composition comprising: a plurality of atomized particles, wherein a diameter of each of the plurality of atomized particles scales with a thickness of a cylindrical liquid surface stretched from each of at least one annulus film of liquid by one or more gases flowing through at least a central portion of the at least one annulus film of liquid and along an outside surface of the at least one annulus film of liquid.

[0231] Embodiment 103. The composition of Embodiment 102, wherein each of the plurality of atomized particles comprises an organic and/or inorganic material.

[0232] Embodiment 104. The composition of Embodiment 102, wherein each of the plurality of atomized particles comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.

[0233] Embodiment 105. The composition of Embodiment 104, wherein at least 50% of the at least one microorganism are biologically active.

[0234] Embodiment 106. The composition of Embodiment 102, wherein each of the plurality of atomized particles comprises a plurality of therapeutic agents selected from at least one of:

proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

[0235] Embodiment 107. The composition of Embodiment 106, wherein at least 50% of the plurality of therapeutic agents are biologically active.

[0236] Embodiment 108. The composition of Embodiment 102, wherein each of the plurality of atomized particles comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

[0237] Embodiment 109. The composition of any one of Embodiments 102-108, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

[0238] Embodiment 110. The composition of any one of Embodiments 102-109, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

[0239] Embodiment 111. The composition of any one of Embodiments 102-110, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 10 μm .

[0240] Embodiment 112. The composition of any one of Embodiments 102-111, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 5 μm .

[0241] Embodiment 113. The composition of any one of Embodiments 102-112, wherein size distributions of the plurality of atomized particles comprise median diameter less than or equal to 1 μm .

[0242] Embodiment 114. A method of making a pharmaceutical composition, comprising: causing at least one liquid to be dispensed in an annulus film from a nozzle device; and controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles; and drying the plurality of atomized particles; wherein a diameter of each of the plurality of atomized particles scales with a thickness of the stretched cylindrical liquid surface.

[0243] Embodiment 115. The method of Embodiment 114, wherein the at least one liquid is non-Newtonian.

[0244] Embodiment 116. The method of Embodiment 114, wherein the at least one liquid is Newtonian.

[0245] Embodiment 117. The method of any one of Embodiments 114-116, wherein the at least one liquid has an absolute viscosity greater than 100 cP.

[0246] Embodiment 118. The method of any one of Embodiments 114-117, wherein the plurality of atomized particles are in a form of droplets.

[0247] Embodiment 119. The method of any one of Embodiments 114-118, wherein the at least one liquid comprises a suspension of an organic and/or inorganic material.

[0248] Embodiment 120. The method of any one of Embodiments 114-119, wherein the at least one liquid comprises a viscoelastic liquid.

[0249] Embodiment 121. The method of any one of Embodiments 114-120, wherein the at least one liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.

[0250] Embodiment 122. The method of Embodiment 121, wherein at least 50% of the at least one microorganism retains biological activity after being stretched from the cylindrical liquid surface.

[0251] Embodiment 123. The method of any one of Embodiments 114-120, wherein the at least one liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

[0252] Embodiment 124. The method of Embodiment 123, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being stretched from the cylindrical liquid surface.

[0253] Embodiment 125. The method of any one of Embodiments 114-120, wherein the at least one liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

[0254] Embodiment 126. The method of Embodiment 125, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being stretched from the cylindrical liquid surface.

[0255] Embodiment 127. The method of Embodiment 125 or 126, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being stretched from the cylindrical liquid surface.

[0256] Embodiment 128. The method of any one of Embodiments 114-127, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

[0257] Embodiment 129. The method of any one of Embodiments 114-128, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

[0258] Embodiment 130. The method of any one of Embodiments 114-129, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 10 μm .

[0259] Embodiment 131. The method of any one of Embodiments 114-130, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 5 μm .

[0260] Embodiment 132. The method of any one of Embodiments 114-131, wherein size distributions of the plurality of atomized particles comprise median particle diameter less than or equal to 1 μm .

[0261] Embodiment 133. A system for formulating a pharmaceutical composition of any of the previous Embodiments comprising: a nozzle device adapted to receive the liquid to sufficiently stretch at least one annulus film to generate a plurality of atomized particles; and the liquid, upon passing through the nozzle device, causes the liquid to produce a plurality of atomized particles; wherein a diameter of each of the plurality of atomized particles scales with a thickness of a cylindrical liquid surface stretched from each of the at least one annulus film of liquid by one or more gases flowing along the at least one annulus film of liquid.

[0262] Embodiment 134. A nozzle device for generating a plurality of atomized particles, the nozzle device comprising: at least one annular channel, wherein the at least one annular channel provides support to dispense an annulus film; wherein the annulus film is sufficiently stretched to generate the plurality of atomized particles.

[0263] Embodiment 135. The nozzle device of Embodiment 134, wherein a number-weighted size distribution of the plurality of atomized particles comprises more than 99% of the plurality of atomized particles being smaller than 1 micron.

[0264] Embodiment 136. The nozzle device of Embodiment 134 or 135, wherein the annulus film comprises a liquid having at least one active agent(s), wherein the active agent(s) in at least 50% of the plurality of atomized particles retains biological activity after being sprayed from the nozzle device.

[0265] Embodiment 137. A system for generating a plurality of atomized particles, comprising: a nozzle device comprising at least one annular channel, wherein the at least one annular channel provides support to dispense an annulus film, and wherein the annulus film is sufficiently stretched to generate the plurality of atomized particles; at least one liquid source in fluid communication with the at least one annular channel; and at least one gas source in fluid communication with an inner channel and at least one outer annular channel of the nozzle device.

[0266] Embodiment 138. The system of Embodiment 137, further comprising at least one gas flowing from at least one gas source through the inner channel and the at least one outer annular channel.

[0267] Embodiment 139. The system of Embodiment 137 or 138, further comprising at least one liquid flowing from at least one liquid source through the at least one annular channel.

[0268] Embodiment 140. The system of any one of Embodiments 137-139, further comprising at least one control circuit configured to cause the at least one gas and the at least one liquid source to flow through the nozzle device simultaneously.

[0269] Embodiment 141. A method for generating a plurality of atomized particles, the method comprising: causing at least one liquid to be dispensed in an annulus film from a nozzle device; and controlling a flow of at least one gas stream so as to sufficiently stretch the annulus film, thereby generating the plurality of atomized particles.

[0270] Embodiment 142. The method of Embodiment 141, wherein the at least one liquid is non-Newtonian.

[0271] Embodiment 143. The method of Embodiment 141, wherein the at least one liquid is Newtonian.

[0272] Embodiment 144. The method of any one of Embodiments 141-143, further comprising drying the plurality of atomized particles.

[0273] Embodiment 145. The method of any one of Embodiments 141-144, further comprising coupling a liquid pump to at least one middle annular channel of the nozzle.

[0274] Embodiment 146. The method of any one of Embodiments 141-145, further comprising coupling at least one gas pump to an inner channel of the nozzle device and at least one outer annular channel of the nozzle device.

[0275] Embodiment 147. The method of any one of Embodiments 141-146, further comprising controlling a flow rate of the at least one liquid.

[0276] Embodiment 148. The method of any one of Embodiments 141-147, wherein the at least one liquid has an absolute viscosity greater than 100 cP.

[0277] Embodiment 149. The method of any one of Embodiments 141-148, wherein the plurality of atomized particles are in a form of droplets.

[0278] Embodiment 150. The method of any one of Embodiments 141-149, wherein the at least one liquid comprises a suspension of an organic and/or inorganic material.

[0279] Embodiment 151. The method of any one of Embodiments 141-150, wherein the at least one liquid comprises a viscoelastic liquid.

[0280] Embodiment 152. The method of any one of Embodiments 141-151, wherein the at least one liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.

[0281] Embodiment 153. The method of Embodiment 152, wherein at least 50% of the at least one microorganism retains biological activity after being sprayed.

[0282] Embodiment 154. The method of any one of Embodiments 141-151, wherein the at least one liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

[0283] Embodiment 155. The method of Embodiment 154, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

[0284] Embodiment 156. The method of any one of Embodiments 141-151, wherein the at least one liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

[0285] Embodiment 157. The method of Embodiment 156, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being sprayed.

[0286] Embodiment 158. The method of Embodiment 156 or 157, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

[0287] Embodiment 159. The method of any one of Embodiments 141-158, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

[0288] Embodiment 160. The method of any one of Embodiments 141-159, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

[0289] Embodiment 161. The method of any one of Embodiments 141-160, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 10 μm .

[0290] Embodiment 162. The method of any one of Embodiments 141-161, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 5 μm .

[0291] Embodiment 163. The method of any one of Embodiments 141-162, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with median diameter less than or equal to 1 μm .

[0292] Embodiment 164. The method of any one of Embodiments 141-163, further comprising controlling a ratio of a flow rate of the at least one liquid relative to the flow of the at least one gas stream.

[0293] Embodiment 165. The method of any one of Embodiments 141-164, wherein a ratio of a diameter of at least one middle annular channel of the nozzle device to a diameter of an inner channel of the nozzle, a diameter of at least one outer annular channel of the nozzle, or a combination thereof is varied.

[0294] Embodiment 166. The nozzle device of any one of Embodiments 1-12 or the system of any one of Embodiments 13-16, wherein the nozzle device further comprises a bluff body that is placed at a center of any one of the at least three coaxial channels of the nozzle device in z-axis direction, and wherein the bluff body is configured achieve targeted gas flow at a center of any one of a plurality of channels of a nozzle device in a z-axis direction.

[0295] Embodiment 167. The nozzle device of any one of Embodiments 37-49 or the system of any one of Embodiments 50-53, wherein the nozzle device further comprises a bluff body that is placed at a center of any one of the at least three channels of the nozzle device in z-axis direction.

[0296] Embodiment 167. The nozzle device of any one of Embodiments 134-136 or the system of any one of Embodiments 137-140, wherein the nozzle device further comprises a bluff body that is placed at a center of the at least one annular channel of the nozzle device in z-axis direction.

[0297] Embodiment 168. A method of encapsulating one or more active agent, comprising: flowing at least one liquid comprising one or more active agent from at least one channel of a nozzle device to form an annulus film; and flowing at least one first gas along an inner surface of the annulus film and at least one second gas along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby encapsulating one or more active agent within a plurality of atomized particles.

[0298] Embodiment 169. The method of Embodiment 168, wherein the at least one liquid comprises a first liquid and a second liquid, wherein the first liquid and the second liquid are immiscible.

[0299] Embodiment 170. The method of Embodiment 169, wherein the first liquid comprising one or more active agents is encapsulated within the plurality of atomized particles by the second liquid.

[0300] Embodiment 171. The method of Embodiment 169 or 170, wherein the second liquid comprises one or more active agents.

[0301] Embodiment 172. The method of Embodiment 168, wherein the at least one liquid comprises a suspension comprising a plurality of solid particles suspended in a solution, wherein the plurality of solid particles and the solution are immiscible.

[0302] Embodiment 173. The method of Embodiment 172, wherein the plurality of solid particles comprising one or more active agents are encapsulated within the plurality of atomized particles by the solution.

[0303] Embodiment 173. The method of Embodiment 172 or 173, wherein the solution comprises one or more active agents.

EXAMPLES

[0304] The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1: Exemplary straight triple coaxial nozzle configurations

[0305] The purpose of this example is to provide exemplary straight triple coaxial nozzle configurations, such as those shown in **FIGS. 1A** and **2A**. For this purpose, steel tubes from blunt needles with gauges 15G, 18G, 20G, 21G and 22G were used to make 3 different triple coaxial nozzle assemblies, as given in **Table 1**, below. The gap values 25 μm , 75 μm and 125 μm , as given in **Table 1**, indicate the thickness of annular channel for liquid flow for each specific coaxial nozzle assembly.

[0306] **Table 1**. Configurations of constructed triple coaxial nozzles. First column provides information of three coaxial steel tubes making the nozzle as indicated by standard needle gauge, second and third column show inner (ID) and outer (OD) diameter of the tubes, and fourth column provides the width of the resulted annular channel for liquid flow.

TABLE 1. Engineering of triple coaxial nozzle

	ID (mm)	OD (mm)	Gap (μm)
15G	1.524	1.829	
18G	0.965	1.270	
20G	0.660	0.914	25
15G	1.524	1.829	
18G	0.965	1.270	
21G	0.584	0.813	75
15G	1.524	1.829	
18G	0.965	1.270	
22G	0.508	0.813	125

Example 2: Droplet size distribution measurements for three-channel nozzle assemblies with straight channels

[0307] The purpose of this example is to provide graphs of droplet size distributions resulting from three-channel nozzles with straight channel configurations. Measurements were obtained using laser diffraction from a Malvern Spraytec instrument.

[0308] **FIGS. 6A** illustrates characteristic droplet diameters of water sprays as a function of liquid flow rate for air pressure 2 bar gauge and liquid flow gap width 25 microns. **FIGS. 6B** illustrates characteristic droplet diameters of water sprays as a function of liquid flow rate for air pressure 5 bar gauge and liquid flow gap width 25 microns. **FIGS. 6C** illustrates characteristic droplet diameters of water sprays as a function of air pressure for water flow rate of 2 ml/min and liquid flow gap width 25 microns. **FIGS. 6D** illustrates mass median droplet diameter of water sprays as a function of air pressure for various water flow rates and liquid flow gap width 25 microns. **FIGS. 6E** illustrates mass median droplet diameter of sprays for various liquids as a function of liquid flow rate at air pressure 2 bar gauge and liquid flow gap width 125 microns. **FIGS. 6F** illustrates mass median droplet diameter of water sprays as a function of air pressure for various liquid flow gaps and water flow rate of 2 ml/min. **FIGS. 6G** illustrates mass median droplet diameter of water sprays as a function of liquid flow rate for various liquid flow gaps and air pressure 2 bar gauge.

[0309] Here $D[4][3]$ is mass mean diameter, $Dv50$ is mass median diameter, $D[3][2]$ is mean diameter of a droplet with the same ratio of volume to surface area as whole spray, also known as Sauter mean diameter, $D[1][0]$ is number-weighted or arithmetic mean diameter. Gly 60 and Gly 85 denote aqueous solution of glycerol with 60 wt.% and 80 wt.%, respectively.

Example 3: Profiles of the droplet size distribution

[0310] The purpose of this example is to provide graphs showing examples of profiles of the droplet size distribution measured by laser diffraction of water and ethanol sprays.

[0311] **FIGS. 7A-7B** illustrate the volume- and number-weighted droplet size distributions, respectively, for water spray at 2 bar air pressure with liquid flow rate 2 ml/min and liquid flow gap width 25 microns. **FIGS. 7C-7D** illustrate volume- and number-weighted droplet size distributions, respectively, for ethanol spray at 2 bar air pressure with liquid flow rate 2 ml/min and liquid flow gap width 25 microns.

[0312] **Tables 2** and **3** include the main parameters of the distributions of the ethanol sprays shown in **FIGS. 7C (Table 2)** and **7D (Table 3)**.

[0313] **Table 2.** Main parameters of volume-weighted size distribution for ethanol spray shown in **FIG. 7C**. (the parameters were obtained by the software of the utilized laser diffraction instrument Malvern Spraytec)

Table 2

Title	Average	σ
Trans (%)	90.8	0.07141
Dv(10) (μm)	4.165	0.01133
Dv(50) (μm)	9.17	0.01855
Dv(90) (μm)	17.42	0.04695
%V <10 μ (%)	56.32	0.148
D[4][3] (μm)	10.03	0.02434
D[3][2] (μm)	4.724	0.03495
Span	1.446	0.002483
0.5 μ < %V < 3.0 μ (%)	2.657	0.06274
%V < 1 μ (%)	4.385	0.04675

[0314] **Table 3.** Main parameters of number-weighted size distribution for ethanol spray shown in **FIG. 7D** (the parameters were obtained by the software of the utilized laser diffraction instrument Malvern Spraytec)

Table 3

Title	Average	σ
Trans (%)	90.8	0.07141
Dn(10) (μm)	0.3282	0.001725
Dn(50) (μm)	0.4263	0.003234
Dn(90) (μm)	0.5412	0.003771
%N <10 μ (%)	99.96	0.001138
D[4][3] (μm)	10.03	0.02434
D[3][2] (μm)	4.724	0.03495

Title	Average	σ
Span	0.4997	0.003425
$0.5\mu < \%N < 3.0\mu(\%)$	19.47	1.043
$\%N < 1\mu (\%)$	99.3	0.02364

Example 4: Retention of activity of human cytomegalovirus after spraying with respect to initial suspension

[0315] The purpose of this example is to illustrate the retention of human cytomegalovirus (HCMV) activity after being sprayed as atomized particles.

[0316] FIG. 8 is a graph showing protein abundance for HCMV in spray droplets analyzed by Western Blot, indicating the retention of activity of HCMV after spraying with respect to initial suspension. The initial concentration of HCMV before spraying was around 10^6 PFU/mL in buffer suspension, and the suspension was supplied at 0.5 mL/min to the triple coaxial nozzle. Nitrogen was used as atomizing gas and supplied at various pressures: spray 1 was generated by using 2000 mbar, spray 2 was generated by using 1500 mbar and spray 3 was generated by using 1000 mbar of nitrogen pressure.

[0317] FIG. 9 is a graph demonstrating retention of activity of human cytomegalovirus (HCMV) in spray droplets by comparing particle-to-PFU ratios before and after spraying. The sprays were generated by using nitrogen as atomizing gas and supplied at pressures of 2000, 1500 and 1000 mbar. The initial concentration of HCMV before spraying was around 10^6 PFU/mL in buffer suspension, and the suspension was supplied at 0.5 mL/min to the triple coaxial nozzle.

Example 5: Preservation of the size of RNA-loaded lipid nanoparticles after being sprayed

[0318] The purpose of this example is to illustrate the size preservation of yeast RNA-loaded lipid nanoparticles (LNPs) after being sprayed as atomized particles.

[0319] FIGS. 10A-10C depict graphs illustrating measurements from the dynamic light scattering (DLS) intensity of liquid samples obtained from the LNP suspension spray droplets. The suspension consisted of LNPs with concentration 50 μ g/mL dispersed in HEPES buffer with 5 wt% mannitol and small amount of sodium dodecyl sulfate (SDS) surfactant of various concentrations 0.4 mM (FIG. 10A), 0.8 mM (FIG. 10B) and 1.6 mM (FIG. 10C). One of the primary challenges with LNP suspensions lies in their stability, and the ability of LNPs to

maintain their size after spraying demonstrates the absence of LNP aggregation. This, in turn, indicates their stability and lack of degradation following exposure to the atomization process.

Example 6: Retention of activity of AAV5 after spraying with respect to initial suspension

[0320] The purpose of this example is to illustrate the retention of adenovirus (AAV5) activity after being sprayed as atomized particles. Briefly, a suspension comprising AAV5 particles was purified using successive cesium chloride gradients and diluted in 10 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA. A spectroscopic analysis was performed on a suspension comprising purified AAV5 particles, and atomized particles formed from the suspension using a nozzle device described herein. The atomized particles were formed by flowing the suspension at 0.5 mL/min through a middle annular channel of the nozzle device, and nitrogen gas through an inner channel and an outer annular channel of the nozzle device at 2000, 1500 or 1000 mbar. **FIG. 11A** shows results of spectroscopic analysis for determining concentrations of purified AAV5 particles in the suspension (control) and atomized particles (spray).

[0321] Next, retention of activity of purified AAV5 particles in atomized particles was determined by comparing plaque formation Units/mL observed for the suspension and the atomized particles. Results of the experiment are shown in **FIG. 11B**.

[0322] Additionally, retention of activity of purified AAV5 particles in atomized particles was determined by comparing a ratio of adenovirus particle to plaque formation unit (PFU) observed for the suspension and the atomized particles. Results of the experiment are shown **FIG. 11C**.

Example 7: Retention of activity of AAV1 after spraying with respect to initial suspension

[0323] The purpose of this example is to illustrate the retention of adenovirus (AAV2) activity after being sprayed as atomized particles. Briefly, AAV2 particles were produced from an AAV plasmid containing a green fluorescence protein (GFP) transgene sequence under the control of CAG promoter (CAG-GFP). AAV2 particles were then purified using an iodixanol gradient and diluted in PBS. Atomized particles were formed by flowing the suspension comprising purified AAV2 particles at 0.5 mL/min through a middle annular channel of the nozzle device, and nitrogen gas through an inner channel and an outer annular channel of the nozzle device at 2000, 1500 or 1000 mbar. Next, retention of activity of purified AAV2 particles in atomized particles was determined by comparing infectious particles/mL observed for the suspension and the atomized particles. **FIG. 12** shows results of the experiment.

What is claimed is:

1. A nozzle device, comprising:
at least three channels comprising an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel.
2. The nozzle device of claim 1, wherein the inner channel and the at least one outer annular channel are in fluid communication with different gas sources.
3. The nozzle device of claim 1, wherein the inner channel and the at least one outer annular channel are in fluid communication with a same gas source.
4. The nozzle device of any one of claims 1-3, wherein each of the at least one middle annular channel is in fluid communication with a different liquid source.
5. The nozzle device of any one of claims 1-3, wherein each of the at least one middle annular channel is in fluid communication with a same liquid source.
6. The nozzle device of any one of claims 1-5, wherein the at least one middle annular channel comprises a first middle annular channel and a second middle annular channel outside of the first middle annular channel.
7. The nozzle device of any one of claims 1-6, wherein the at least three channels are shaped to comprise a hollow straight cylinder configuration, a hollow converging cone configuration, or a diverging hollow cone configuration.
8. The nozzle device of any one of claims 1-7, wherein the at least three channels are shaped to comprise a converging-diverging configuration.
9. The nozzle device of any one of claims 1-8, wherein the gap width ranges from 10 to 125 micrometers.

10. The nozzle device of any one of claims 1-9, wherein outlets of the at least three channels are coplanar.
11. The nozzle device of claim 10, wherein each of the outlets is positioned within a first plane, the first plane being perpendicular to an axis of the inner channel.
12. The nozzle device of any one of claims 1-11, wherein at least one outlet of the at least three channels is non-coplanar with other outlets of the at least three channels.
13. The nozzle device of any one of claims 1-12, wherein a ratio of a diameter of the at least one middle annular channel to a diameter of an inner channel, a diameter of at least one outer annular channel, or a combination thereof is varied.
14. The nozzle device of any one of claims 1-13, wherein the nozzle device further comprises a bluff body that is placed at a center of any one of the at least three channels of the nozzle device in z-axis direction.
15. A spraying system, comprising:
a nozzle device, the nozzle device comprising:
at least three channels comprising an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel;
at least one liquid source in fluid communication with the at least one middle annular channel; and
at least one gas source in fluid communication with the inner channel and the at least one outer annular channel.
16. The spraying system of claim 15, further comprising at least one gas flowing from at least one gas source through the inner channel and the at least one outer annular channel.

17. The spraying system of claim 15 or 16, further comprising at least one liquid flowing from at least one liquid source through the at least one middle annular channel.
18. The spraying system of claim 16 or 17, further comprising at least one control circuit configured to cause the at least one gas and/or the at least one liquid to flow through the nozzle device simultaneously.
19. The spraying system of any one of claims 15-18, wherein the nozzle device further comprises a bluff body that is placed at a center of any one of the at least three channels of the nozzle device in z-axis direction.
20. A method of spraying particles, comprising:
 - causing at least one liquid to be dispensed in an annulus film from a nozzle; and
 - controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles;
 - wherein a diameter of each of the plurality of atomized particles scales with a thickness of the stretched cylindrical liquid surface.
21. The method of claim 20, wherein the at least one liquid is non-Newtonian.
22. The method of claim 20, wherein the at least one liquid is Newtonian.
23. The method of any one of claims 20-22, further comprising drying the plurality of atomized particles.
24. The method of any one of claims 20-23, further comprising coupling a liquid pump to at least one middle annular channel of the nozzle.
25. The method of any one of claims 20-24, further comprising coupling at least one gas pump to an inner channel of the nozzle and at least one outer annular channel of the nozzle.
26. The method of any one of claims 20-25, wherein the controlling the flow of the at least one first gas stream comprises controlling a pressure of the at least one first gas stream.

27. The method of any one of claims 20-26, further comprising controlling a flow rate of the at least one liquid.
28. The method of any one of claims 20-27, wherein the at least one liquid has an absolute viscosity greater than 100 cP.
29. The method of any one of claims 20-28, wherein the plurality of atomized particles are in a form of droplets.
30. The method of any one of claims 20-29, wherein the at least one liquid comprises a suspension of an organic and/or inorganic material.
31. The method of any one of claims 20-30, wherein the at least one liquid comprises a viscoelastic liquid.
32. The method of any one of claims 20-31, wherein the at least one liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.
33. The method of claim 32, wherein at least 50% of the at least one microorganism retains biological activity after being sprayed.
34. The method of any one of claims 20-31, wherein the at least one liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.
35. The method of claim 34, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.
36. The method of any one of claims 20-31, wherein the at least one liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

37. The method of claim 36, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being sprayed.

38. The method of claim 36 or 37, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

39. The method of any one of claims 20-38, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

40. The method of any one of claims 20-39, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

41. The method of any one of claims 20-40, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 10 μm .

42. The method of any one of claims 20-41, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 5 μm .

43. The method of any one of claims 20-42, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with median diameter less than or equal to 1 μm .

44. The method of any one of claims 20-43, further comprising controlling a ratio of a flow rate of the at least one liquid relative to the flow of the at least one first gas stream, the at least one second gas stream, or a combination thereof.

45. The method of any one of claims 20-44, wherein a ratio of a diameter of at least one middle annular channel of the nozzle to a diameter of an inner channel of the nozzle, a diameter of at least one outer annular channel of the nozzle, or a combination thereof is varied.

46. A composition for use in a nozzle device, comprising:
a liquid having an absolute viscosity in a range of from 1 cP to 2000 cP;

wherein:

the liquid upon passing through the nozzle device, causes the liquid to produce a plurality of atomized particles, and

a number-weighted size distribution of the plurality of atomized particles comprises more than 99% of the plurality of atomized particles being smaller than 1 micron.

47. The composition of claim 46, wherein the liquid comprises one or more active agents.

48. The composition of claim 46 or 47, wherein the liquid comprises plurality of solid particles having a size in a range of from 1 nm to 1000 nm, from 1 nm to 800 nm, from 1 nm to 500 nm, from 1 nm to 300 nm, from 1 nm to 100 nm, from 100 nm to 1000 nm, from 100 nm to 800 nm, from 100 nm to 500 nm, from 100 nm to 300 nm, from 300 nm to 1000 nm, from 300 nm to 800 nm, from 300 nm to 500 nm, from 500 nm to 1000 nm, from 500 nm to 800 nm, or from 800 nm to 1000 nm.

49. A composition comprising a plurality of particles, wherein the plurality of particles are dried atomized particles, wherein the dried atomized particles are formed from a liquid, and wherein number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality of particles being smaller than 1 micron.

50. The composition of claim 49, wherein the composition comprises one or more active agents.

51. The composition of claim 49 or 50, wherein the dried atomized particles retain at least 80% biological activity relative to the liquid.

52. The composition of any one of claims 49-51, wherein the liquid is non-Newtonian.

53. The composition of any one of claims 49-51, wherein the liquid is Newtonian.

54. The composition of any one of claims 49-53, wherein the liquid has an absolute viscosity greater than 100 cP.

55. The composition of any one of claims 49-54, wherein the liquid forms plurality of atomized particles prior to forming the dried atomized particles, wherein the atomized particles are in the form of droplets.
56. The composition of any one of claims 49-55, wherein the liquid comprises a suspension of an organic and/or inorganic material.
57. The composition of any one of claims 49-56, wherein the liquid comprises a viscoelastic liquid.
58. The composition of any one of claims 49-57, wherein the liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.
59. The composition of claim 58, wherein at least 50% of the at least one microorganism retains biological activity.
60. The composition of any one of claims 49-57, wherein the liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.
61. The composition of claim 60, wherein at least 50% of the plurality of therapeutic agents retain biological activity.
62. The composition of any one of claims 49-57, wherein the liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.
63. The composition of claim 62, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25%.
64. The composition of claim 62 or 63, wherein at least 50% of the plurality of therapeutic agents retain biological activity.
65. A method of making a composition comprising:

flowing a liquid from a nozzle along with a gas to form a plurality of atomized particles, wherein a number-weighted size distribution of the plurality of particles comprises more than 99% of the plurality atomized of particles being smaller than 1 micron; and

exposing the plurality of atomized particles to a temperature in a range of from 3 °C to 40 °C.

66. The method of claim 65, wherein the liquid is flowed from the nozzle at a pressure in a range of from 2500 bar to 500 bar.

67. The method of claim 65 or 66, wherein the liquid comprises one or more active agents in a range of from 0.1 µg/mL to 2000 mg/mL.

68. The method of any one of claim 65-67, wherein the composition comprises a core-shell or matrix encapsulated droplets comprising one or more active agent.

69. A composition comprising:

a plurality of atomized particles, wherein a diameter of each of the plurality of atomized particles scales with a thickness of a cylindrical liquid surface stretched from each of at least one annulus film of liquid by one or more gases flowing through at least a central portion of the at least one annulus film of liquid and along an outside surface of the at least one annulus film of liquid.

70. The composition of claim 69, wherein each of the plurality of atomized particles comprises an organic and/or inorganic material.

71. The composition of claim 69, wherein each of the plurality of atomized particles comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.

72. The composition of claim 71, wherein at least 50% of the at least one microorganism are biologically active.

73. The composition of claim 69, wherein each of the plurality of atomized particles comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

74. The composition of claim 73, wherein at least 50% of the plurality of therapeutic agents are biologically active.

75. The composition of claim 69, wherein each of the plurality of atomized particles comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

76. The composition of any one of claims 69-75, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

77. The composition of any one of claims 69-76, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

78. The composition of any one of claims 69-77, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 10 μm .

79. The composition of any one of claims 69-78, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 5 μm .

80. The composition of any one of claims 69-79, wherein size distributions of the plurality of atomized particles comprise median diameter less than or equal to 1 μm .

81. A method of making a pharmaceutical composition, comprising:
causing at least one liquid to be dispensed in an annulus film from a nozzle; and
controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles; and
drying the plurality of atomized particles;
wherein a diameter of each of the plurality of atomized particles scales with a thickness of the stretched cylindrical liquid surface.

82. The method of any one of claims 81, wherein the at least one liquid is non-Newtonian.

83. The method of any one of claims 81, wherein the at least one liquid is Newtonian.
84. The method of any one of claims 81-83, wherein the at least one liquid has an absolute viscosity greater than 100 cP.
85. The method of any one of claims 81-84, wherein the plurality of atomized particles are in a form of droplets.
86. The method of any one of claims 81-85, wherein the at least one liquid comprises a suspension of an organic and/or inorganic material.
87. The method of any one of claims 81-86, wherein the at least one liquid comprises a viscoelastic liquid.
88. The method of any one of claims 81-87, wherein the at least one liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.
89. The method of claim 88, wherein at least 50% of the at least one microorganism retains biological activity after being stretched from the cylindrical liquid surface.
90. The method of any one of claims 81-87, wherein the at least one liquid comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.
91. The method of claim 90, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being stretched from the cylindrical liquid surface.
92. The method of any one of claims 81-87, wherein the at least one liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.
93. The method of claim 92, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being stretched from the cylindrical liquid surface.

94. The method of claim 92 or 93, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being stretched from the cylindrical liquid surface.

95. The method of any one of claims 81-94, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

96. The method of any one of claims 81-95, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

97. The method of any one of claims 81-96, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 10 μm .

98. The method of any one of claims 81-97, wherein a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 5 μm .

99. The method of any one of claims 81-98, wherein size distributions of the plurality of atomized particles comprise median diameter less than or equal to 1 μm .

100. A system for formulating a pharmaceutical composition according to any one of method of claims 81-99 comprising:

a nozzle device adapted to receive the liquid to sufficiently stretch at least one annulus film to generate a plurality of atomized particles; and

the liquid, upon passing through the nozzle device, causes the liquid to produce a plurality of atomized particles;

wherein a diameter of each of the plurality of atomized particles scales with a thickness of a cylindrical liquid surface stretched from each of the at least one annulus film of liquid by one or more gases flowing along the at least one annulus film of liquid.

101. A nozzle device for generating a plurality of atomized particles, the nozzle device comprising:

at least one annular channel, wherein the at least one annular channel provides support to dispense an annulus film;

wherein the annulus film is sufficiently stretched to generate the plurality of atomized particles.

102. The nozzle device of claim 101, wherein a number-weighted size distribution of the plurality of atomized particles comprises more than 99% of the plurality of atomized particles being smaller than 1 micron.

103. The nozzle device of claim 101 or 102, wherein the annulus film comprises a liquid having at least one active agent(s), wherein the active agent(s) in at least 50% of the plurality of atomized particles retains biological activity after being sprayed from the nozzle device.

104. A system for generating a plurality of atomized particles, comprising:

a nozzle device comprising at least one annular channel, wherein the at least one annular channel provides support to dispense an annulus film, and wherein the annulus film is sufficiently stretched to generate the plurality of atomized particles;

at least one liquid source in fluid communication with the at least one annular channel;
and

at least one gas source in fluid communication with an inner channel and at least one outer annular channel of the nozzle device.

105. The system of claim 104, further comprising at least one gas flowing from at least one gas source through the inner channel and the at least one outer annular channel.

106. The system of claim 104 or 105, further comprising at least one liquid flowing from at least one liquid source through the at least one annular channel.

107. The system of any one of claims 104-106, further comprising at least one control circuit configured to cause the at least one gas and the at least one liquid source to flow through the nozzle device simultaneously.

108. A method for generating a plurality of atomized particles, the method comprising:

causing at least one liquid to be dispensed in an annulus film from a nozzle device; and
controlling a flow of at least one gas stream so as to sufficiently stretch the annulus film, thereby generating the plurality of atomized particles.

109. The method of claim 108, wherein the at least one liquid is non-Newtonian.

110. The method of claim 108, wherein the at least one liquid is Newtonian.

111. The method of any one of claims 108-110, further comprising drying the plurality of atomized particles.
112. The method of any one of claims 108-111, further comprising coupling a liquid pump to at least one middle annular channel of the nozzle.
113. The method of any one of claims 108-112, further comprising coupling at least one gas pump to an inner channel of the nozzle and at least one outer annular channel of the nozzle.
114. The method of any one of claims 108-113, further comprising controlling a flow rate of the at least one liquid.
115. The method of any one of claims 108-114, wherein the at least one liquid has an absolute viscosity greater than 100 cP.
116. The method of any one of claims 108-115, wherein the plurality of atomized particles are in a form of droplets.
117. The method of any one of claims 108-116, wherein the at least one liquid comprises a suspension of an organic and/or inorganic material.
118. The method of any one of claims 108-117, wherein the at least one liquid comprises a viscoelastic liquid.
119. The method of any one of claims 108-118, wherein the at least one liquid comprises at least one microorganism selected from at least one of: an enveloped virus, a non-enveloped virus, or a combination thereof.
120. The method of claim 119, wherein at least 50% of the at least one microorganism retains biological activity after being sprayed.
121. The method of any one of claims 108-118, wherein the at least one liquid, suspension or combination thereof comprises a plurality of therapeutic agents selected from at least one of: proteins, monoclonal antibodies, antibody fragments, nucleic acids, peptides, imaging agents, small molecules, or a combination thereof.

122. The method of claim 121, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

123. The method of any one of claims 108-118, wherein the at least one liquid comprises a plurality of lipid nanoparticles loaded with a plurality of therapeutic agents selected from at least one of: nucleic acids, proteins, peptides, genes, imaging agents, microorganisms, small molecules, or a combination thereof.

124. The method of claim 123, wherein a median size of the plurality of lipid nanoparticles does not increase more than 25% after being sprayed.

125. The method of claim 123 or 124, wherein at least 50% of the plurality of therapeutic agents retain biological activity after being sprayed.

126. The method of any one of claims 108-125, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 20 μm .

127. The method of any one of claims 108-126, wherein the flow is controlled so as to obtain a size distribution of the plurality of atomized particles comprises a median particle diameter less than or equal to 15 μm .

128. The method of any one of claims 108-127, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 10 μm .

129. The method of any one of claims 108-128, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with a median diameter less than or equal to 5 μm .

130. The method of any one of claims 108-129, wherein the flow is controlled so as to obtain size distributions of the plurality of atomized particles with median diameter less than or equal to 1 μm .

131. The method of any one of claims 108-130, further comprising controlling a ratio of a flow rate of the at least one liquid relative to the flow of the at least one gas stream.

132. The method of any one of claims 108-131, wherein a ratio of a diameter of at least one middle annular channel of the nozzle to a diameter of an inner channel of the nozzle, a diameter of at least one outer annular channel of the nozzle, or a combination thereof is varied.

133. A nozzle device for generating atomized particles from a liquid, the nozzle device comprising:

at least one annular channel having a gap width sufficient so as to atomize the liquid upon being flowed through the at least one annular channel between one or more flowing gas(es), thereby generating a plurality of atomized particles;

wherein a number-weighted size distribution of the plurality of atomized particles comprises more than 99% of the plurality of atomized particles being smaller than 1 micron.

134. The nozzle device of claim 133, wherein the gap width ranges from 10 to 125 micrometers.

135. A method of encapsulating one or more active agent, comprising:

flowing at least one liquid comprising one or more active agent from at least one channel of a nozzle device to form an annulus film; and

flowing at least one first gas along an inner surface of the annulus film and at least one second gas along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby encapsulating one or more active agent within a plurality of atomized particles.

136. The method of claim 135, wherein the at least one liquid comprises a first liquid and a second liquid, wherein the first liquid and the second liquid are immiscible.

137. The method of claim 136, wherein the first liquid comprising one or more active agents is encapsulated within the plurality of atomized particles by the second liquid.

138. The method of claim 136 or 137, wherein the second liquid comprises one or more active agents.

139. The method of claim 135, wherein the at least one liquid comprises a suspension comprising a plurality of solid particles suspended in a solution, wherein the plurality of solid particles and the solution are immiscible.

140. The method of claim 139, wherein the plurality of solid particles comprising one or more active agents are encapsulated within the plurality of atomized particles by the solution.

141. The method of claim 139 or 140, wherein the solution comprises one or more active agents.

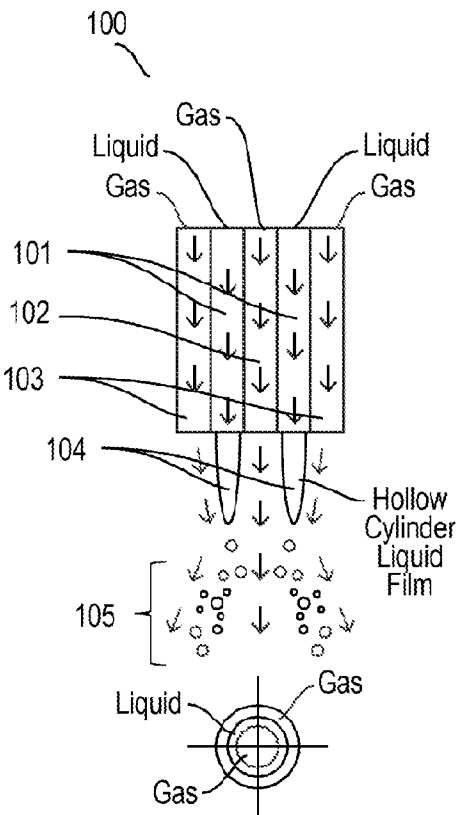


FIG. 1A

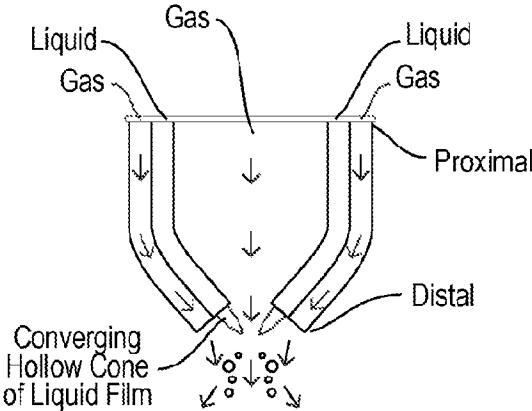
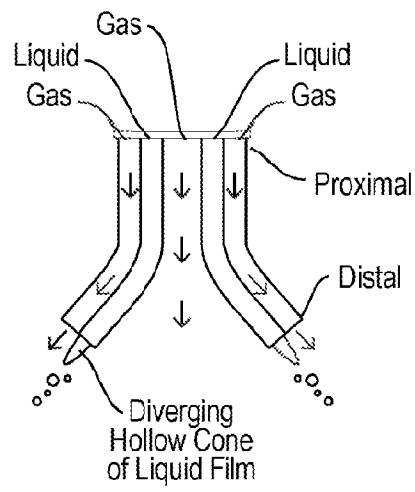
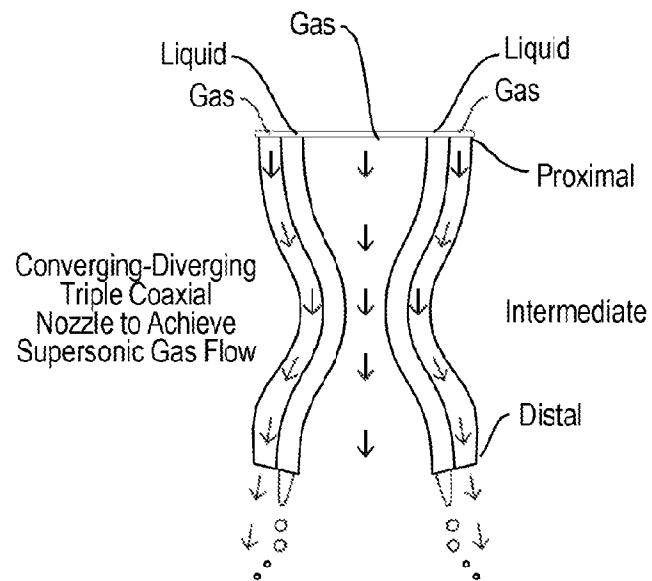


FIG. 1B

**FIG. 1C**

**FIG. 1D**

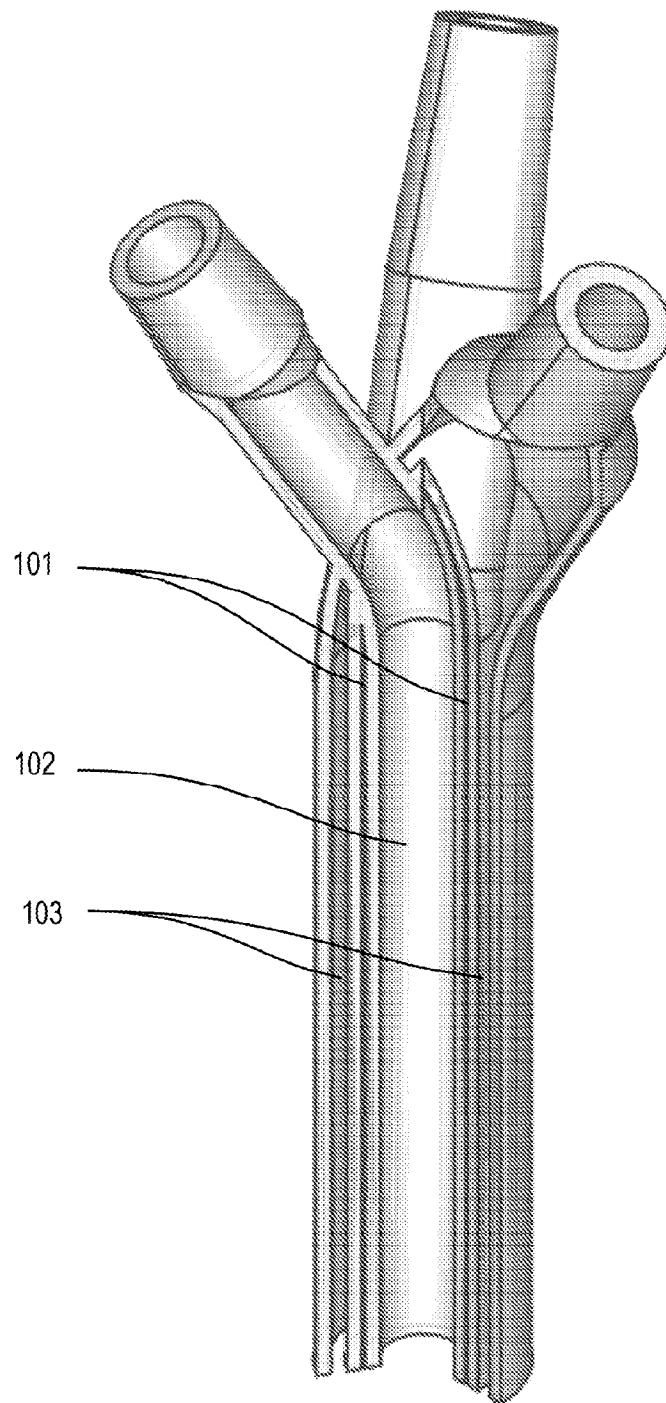
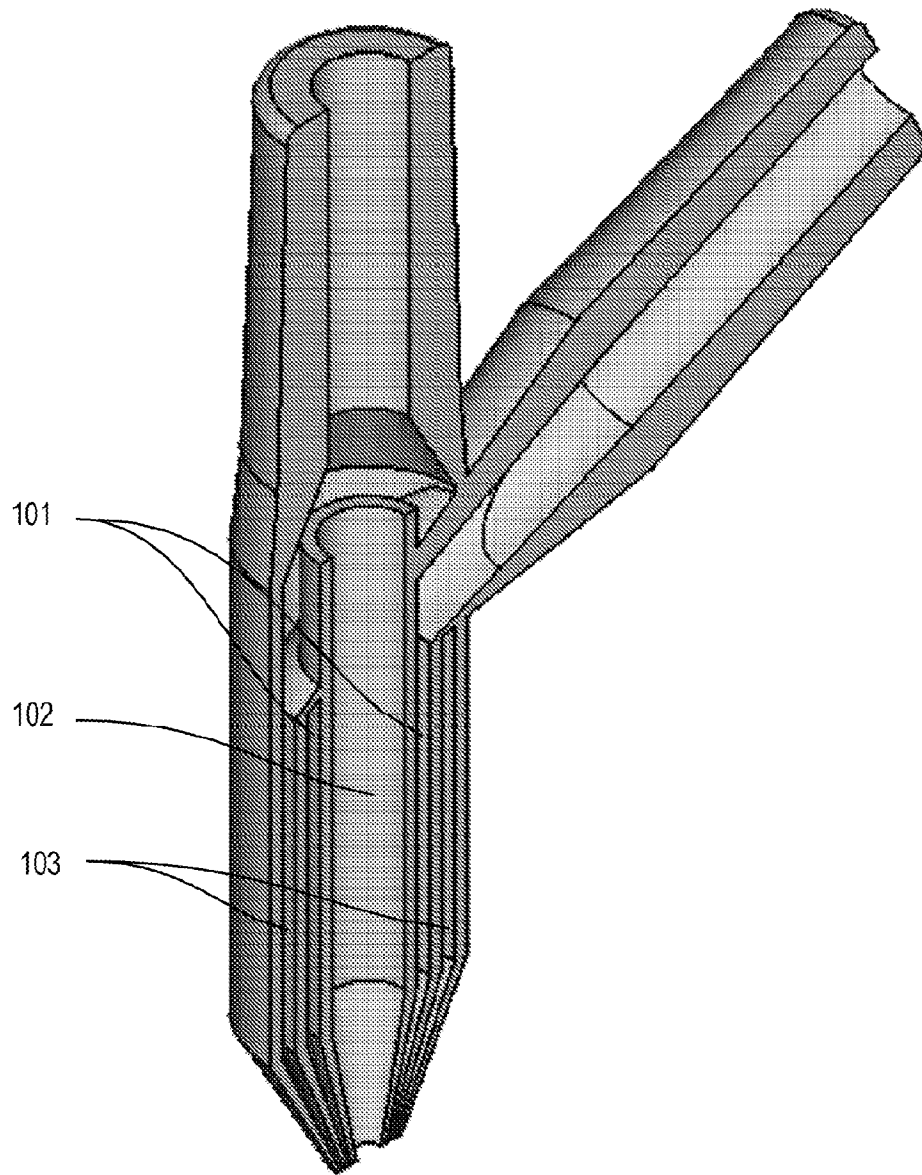


FIG. 2A

**FIG. 2B**

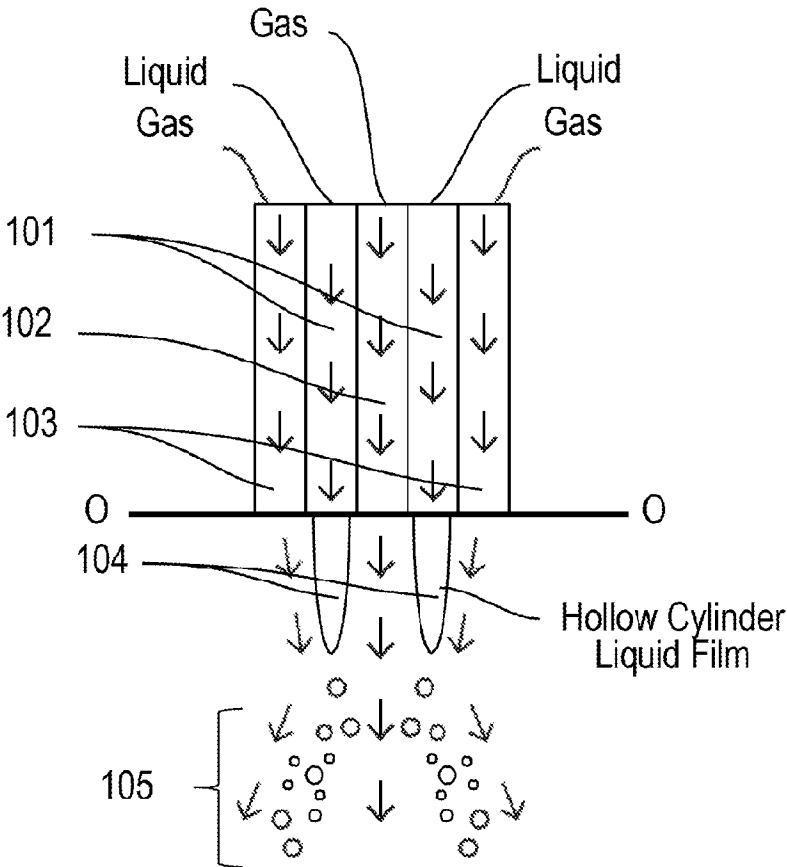
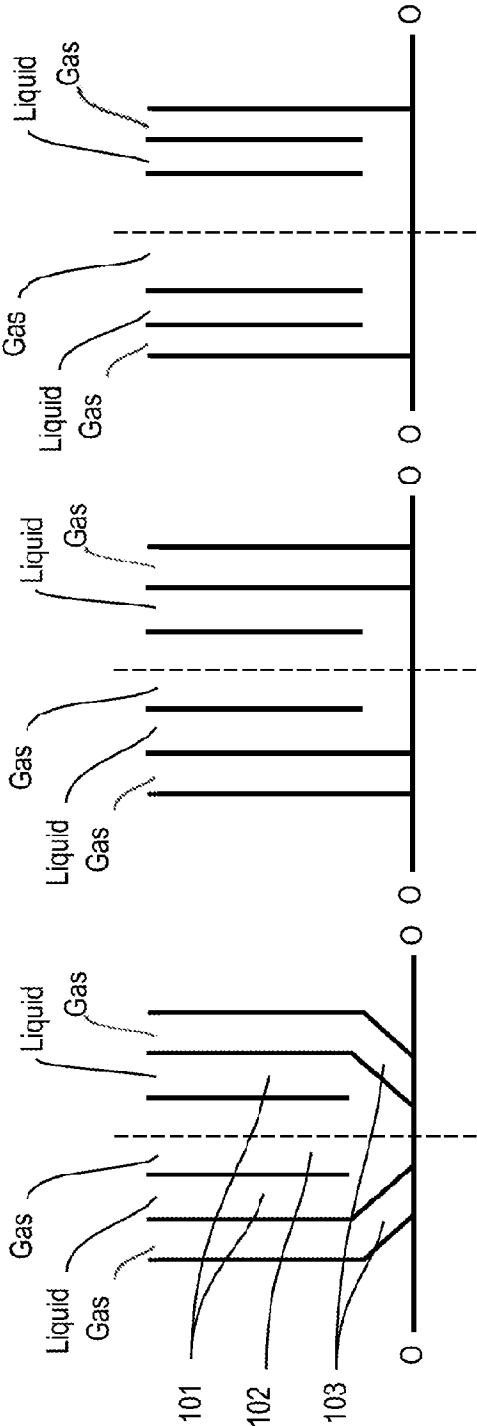


FIG. 3A



200

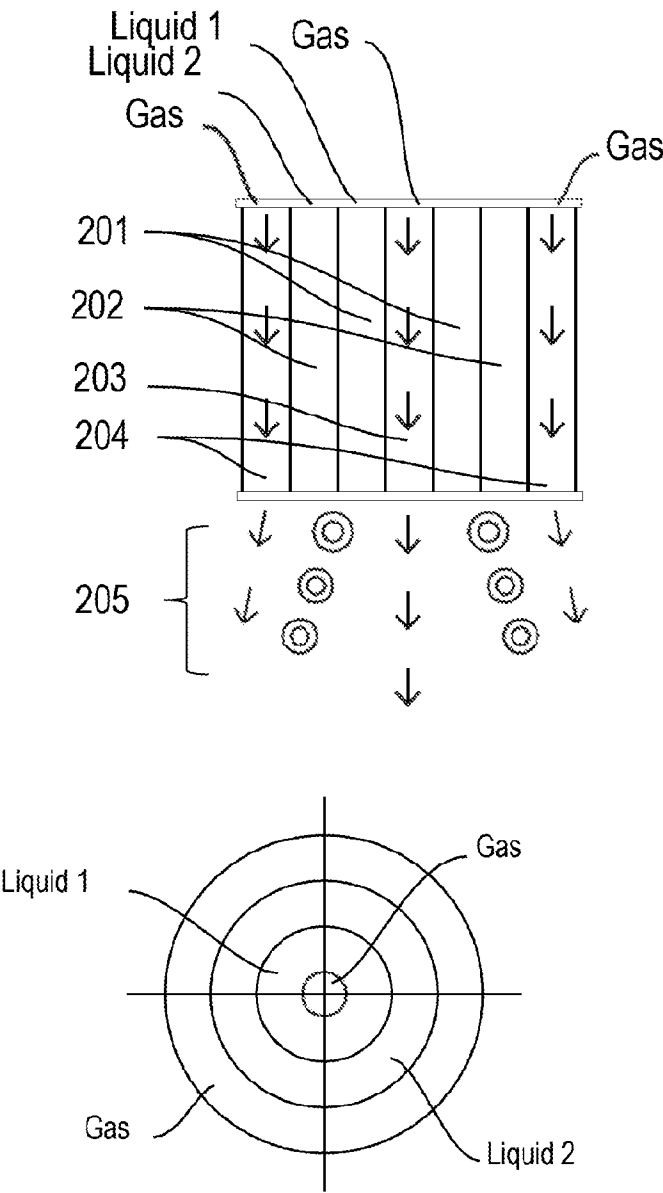


FIG. 4

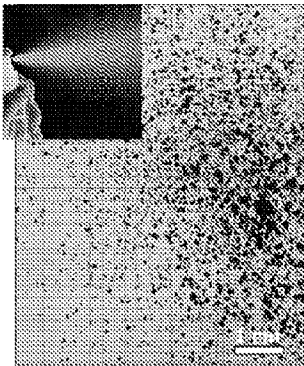


FIG. 5A

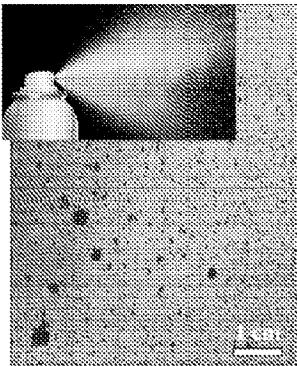


FIG. 5B

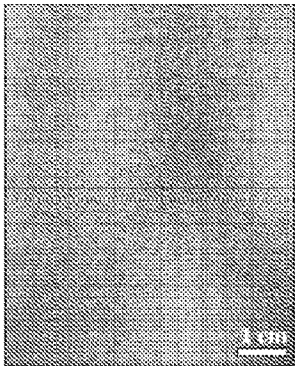


FIG. 5C

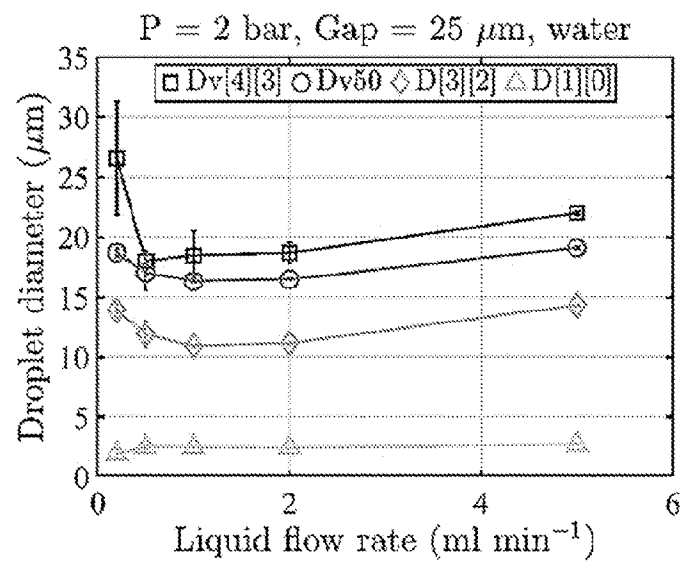


FIG. 6A

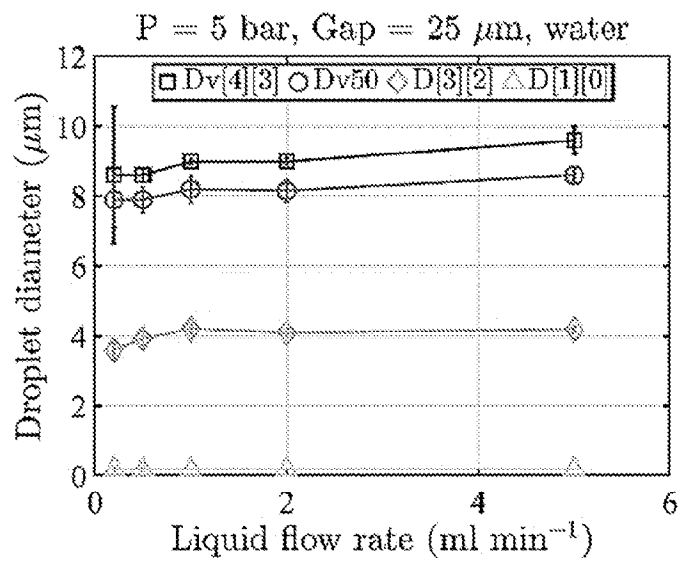


FIG. 6B

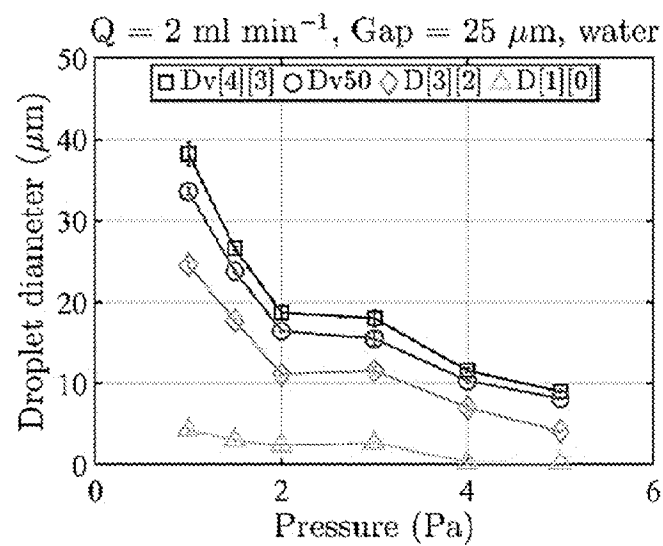


FIG. 6C

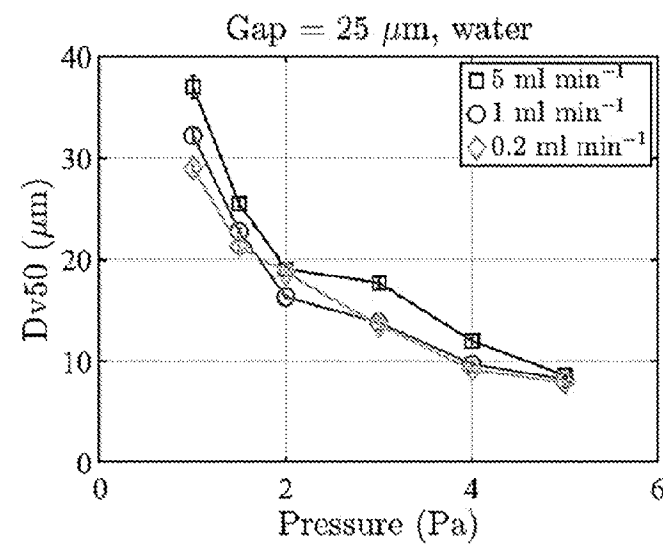


FIG. 6D

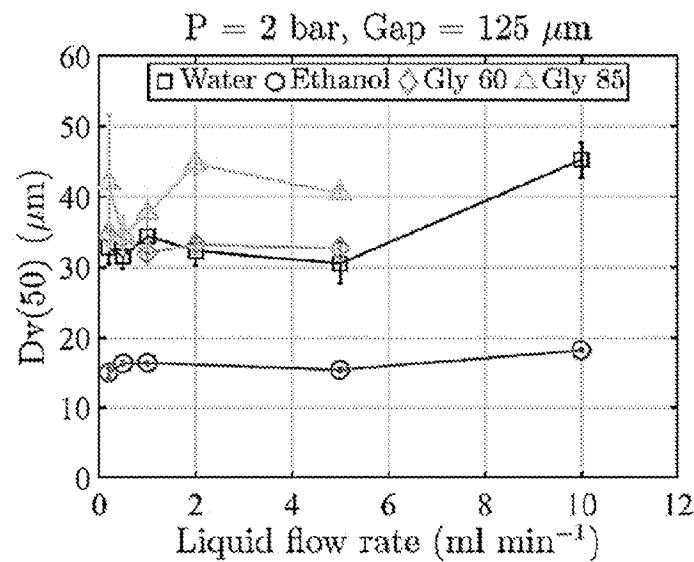


FIG. 6E

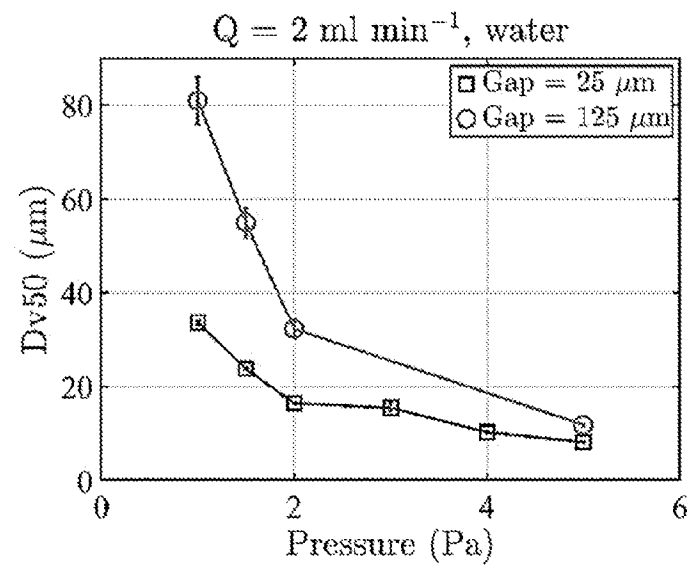
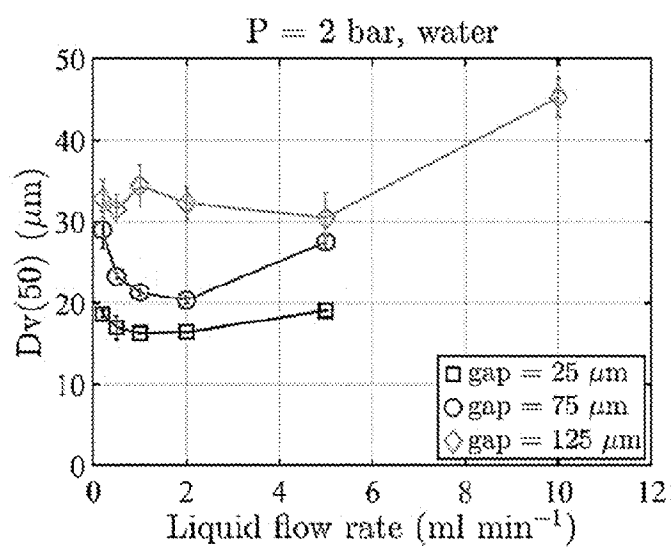
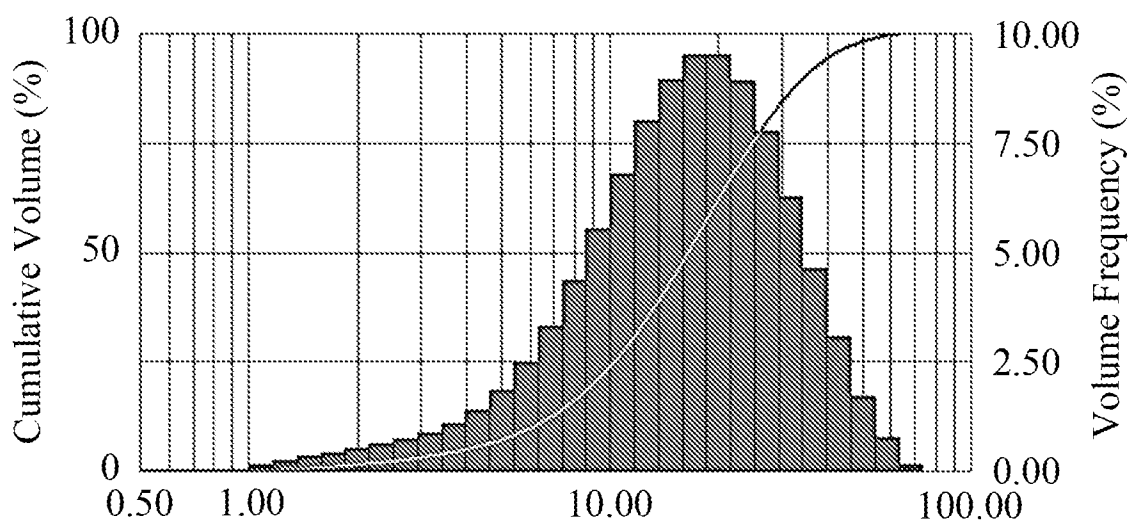
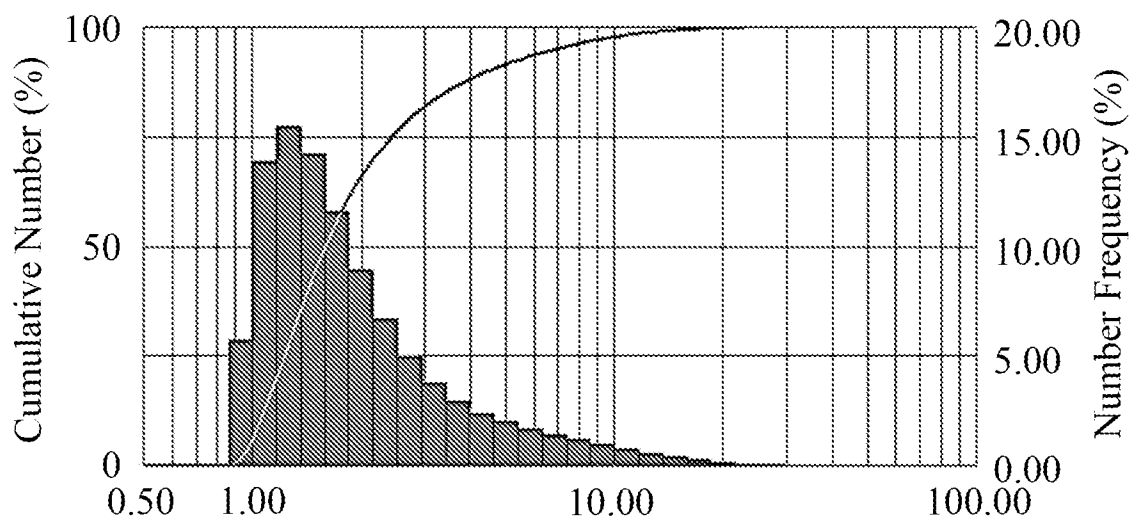
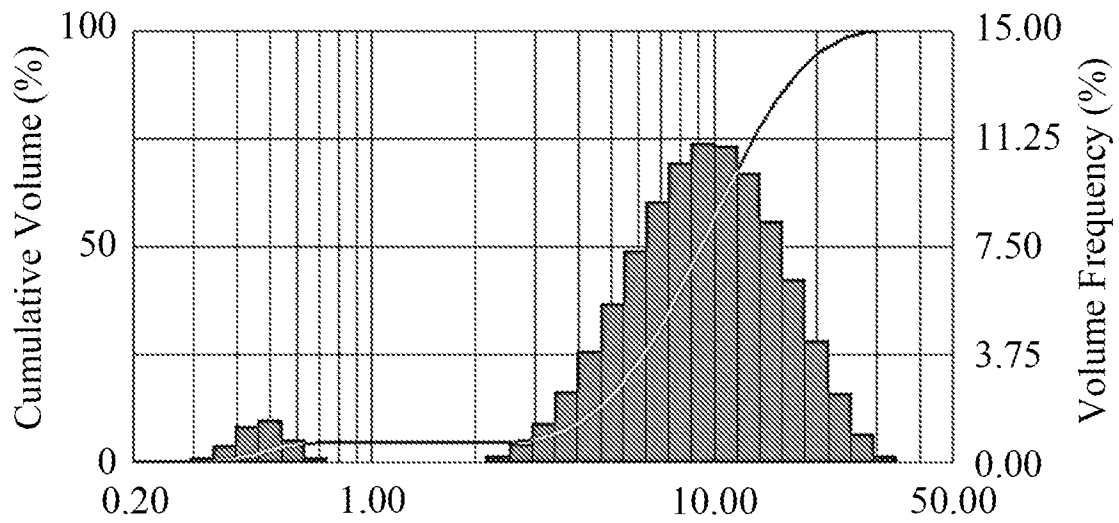
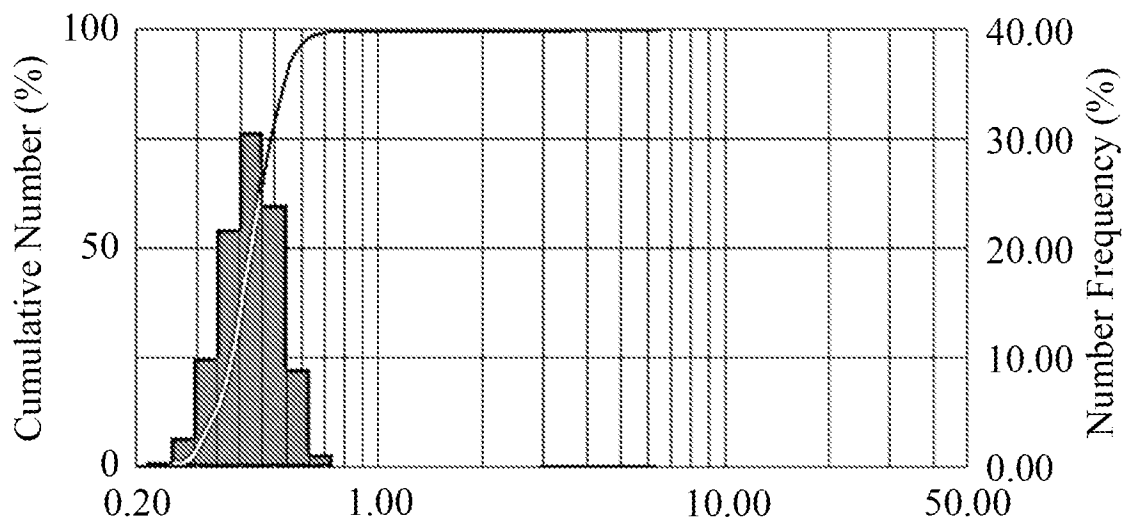
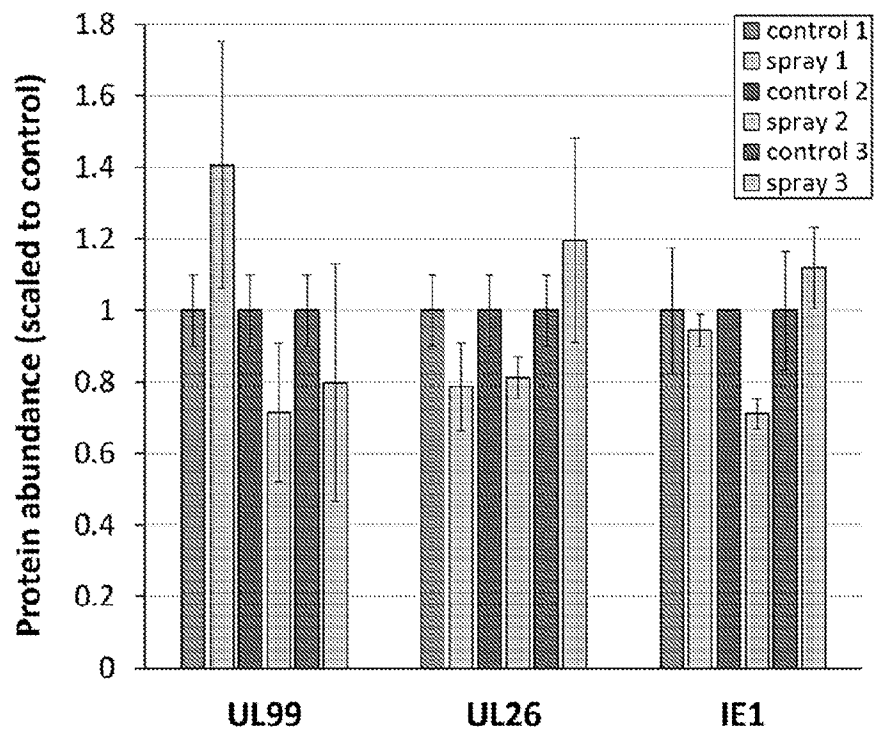


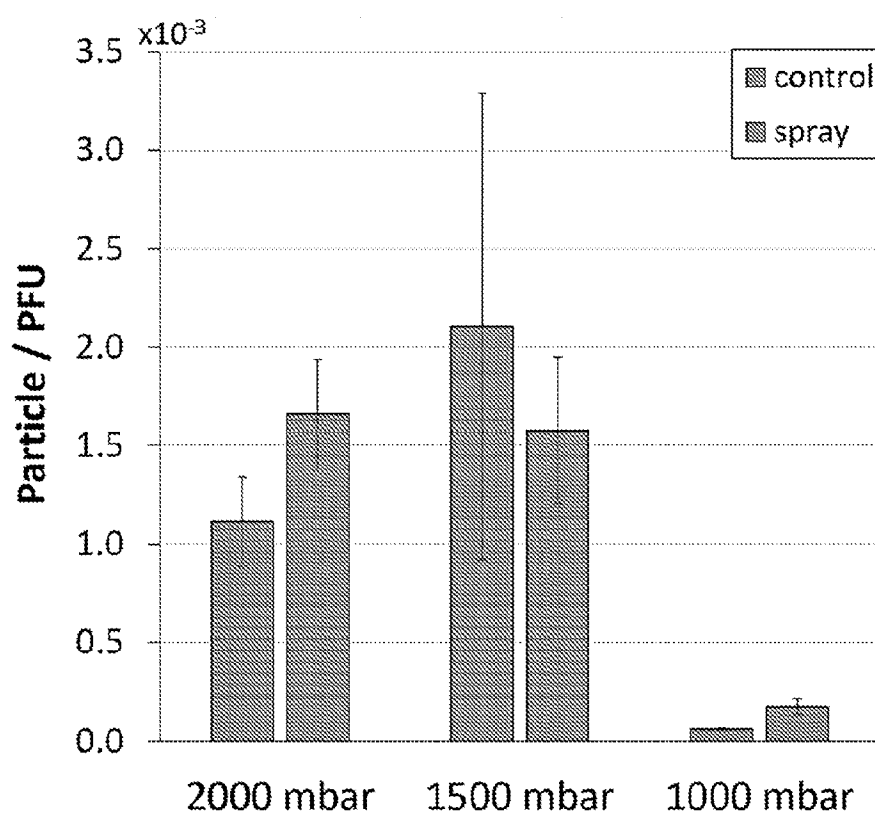
FIG. 6F

**FIG. 6G**

**FIG. 7A****FIG. 7B**

**FIG. 7C****FIG. 7D**

**FIG. 8**

**FIG. 9**

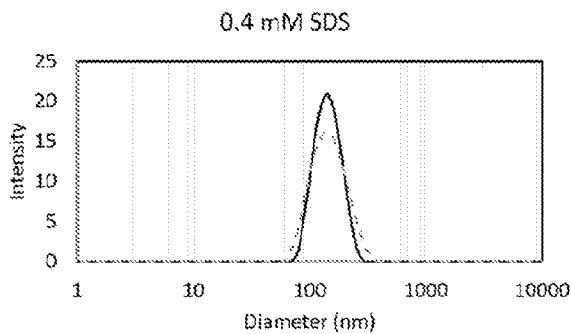


FIG. 10A

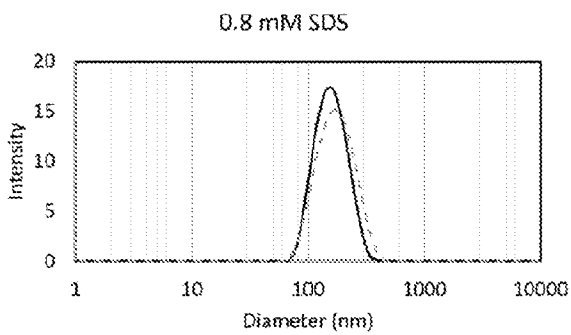


FIG. 10B

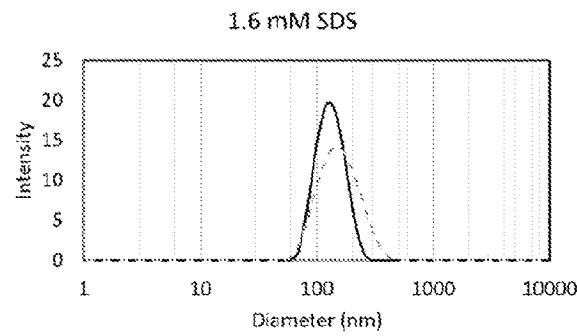


FIG. 10C

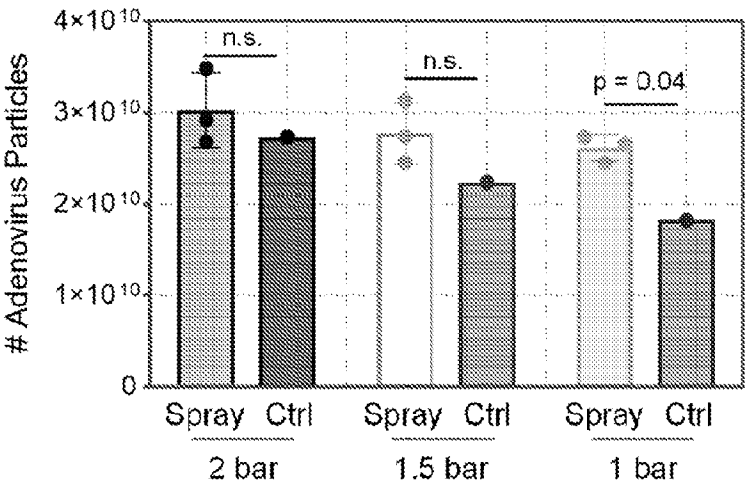


FIG. 11A

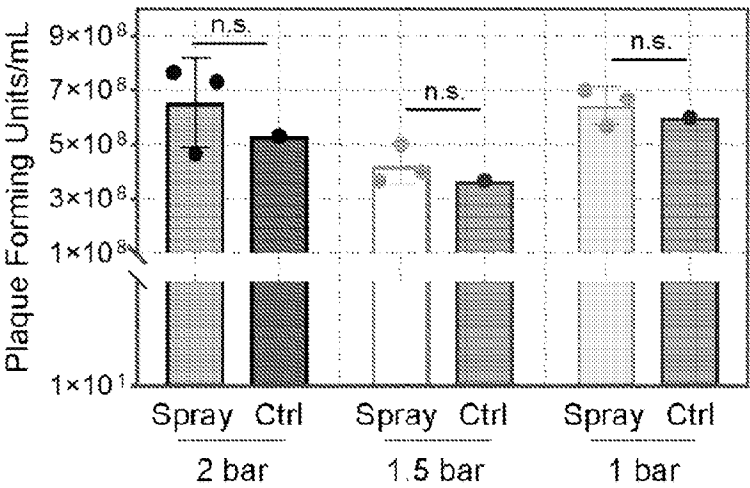
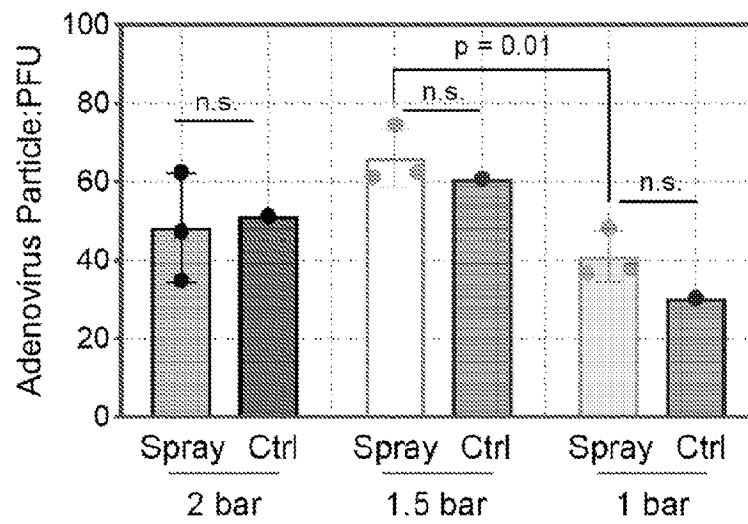


FIG. 11B

**FIG. 11C**

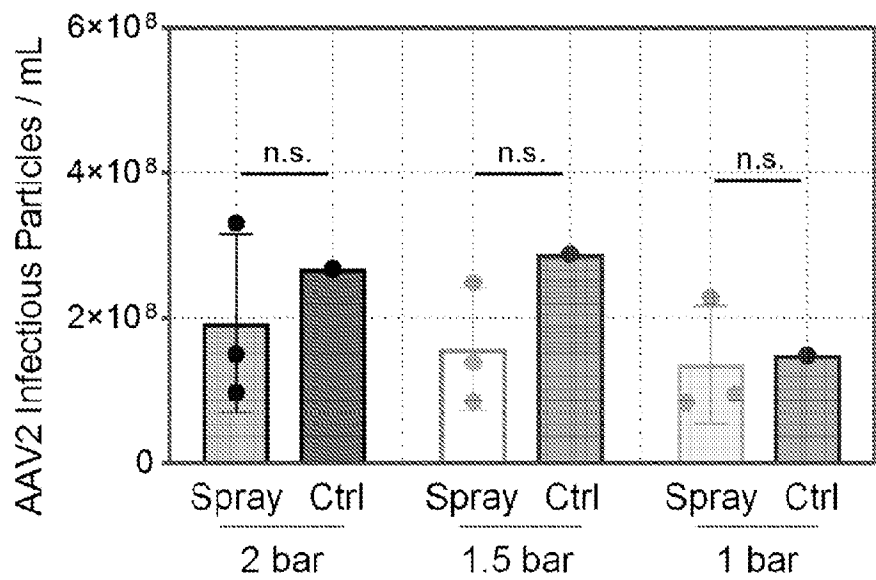


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/037765

A. CLASSIFICATION OF SUBJECT MATTERIPC: **B05B 15/00** (2024.01); **A61M 11/04** (2024.01); **A61M 11/06** (2024.01); A61M 16/00 (2024.01)CPC: **B05B15/00; A61M11/042; A61M11/06; A61M16/00; A61M2205/362**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0011899 A1 (YEATES DONOVAN B) 20 January 2011 (20.01.2011) Figs. 1 and 2B, paras. [0094, 0100, 0101, 0102]	1, 3, 4/1, 4/3, 5/1, 5/3, 15-17
Y		2, 4/2, 5/2
Y	US 7,802,569 B2 (YEATES DONOVAN B ET AL.) 28 September 2010 (28.09.2010) col. 9, lns. 47-53	2, 4/2, 5/2
A	US 2018/0099106 A1 (KAER BIOTHERAPEUTICS CORP) 12 April 2018 (12.04.2018) Entire Document	1-5, 15-17

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

05 December 2024 (05.12.2024)

Date of mailing of the international search report

16 December 2024 (16.12.2024)

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **6-14, 18-19, 24-45, 52-64, 68, 77-80, 85-100, 107, 112-132**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fee must be paid.

Group I: Claims 1-5, and 15-17 are directed toward a nozzle device.

Group II: Claims 20-23, 46-51, 65-67, 69-76, 81-84, 101-106, 108-111, and 133-141 are directed toward a method of spraying particles.

The special technical features of Group I include at least at least three channels comprising an inner channel, at least one middle annular channel, outside of the inner channel, and at least one outer annular channel outside of the at least one middle annular channel, the at least one middle annular channel being coaxially arranged between the inner channel and the at least one outer annular channel and having a gap width sufficient so as to atomize a liquid flowing through the at least one middle annular channel upon flow of one or more gases through at least the inner channel and the at least one outer annular channel.

The special technical features of Group II include at least controlling a flow of at least one first gas stream along an inner surface of the annulus film and at least one second gas stream along an outer surface of the annulus film so as to sufficiently stretch a cylindrical liquid surface from out of the annulus film, thereby spraying a plurality of atomized particles; the liquid upon passing through the nozzle device, causes the liquid to produce a plurality of atomized particle; exposing the plurality of atomized particles to a temperature in a range of from 3 °C to 40 °C.

The common technical features shared between Groups I-II are a nozzle having a channel, liquid source, gas source, atomized particles, an annulus film.

However, these common features are previously disclosed by US 2011/0011899 A1 to Yeates, D. (hereinafter "Yeates"). Yeates discloses a nozzle having a channel (nozzle having a channel; [0032]), liquid source (fluid exit port; [0032]), gas source (gas source; [0054]), atomized particles (the fluid to flow readily through the gap between the stem and annulus over the lip into the cone, both by capillary forces and by pressure differentials, and is aerosolized inside the cone closer to its apex, i.e. within the stem; [0036]), an annulus film (fluid flows over this lip 3215 to form a thin film on the inner surface of the cone 3240 within the orifice stem 3214; [0108]).

Since the common technical features are previously disclosed by the Yeates reference, these common features are not special and so Groups I-II lack unity.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/037765

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-5, 15-17**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.