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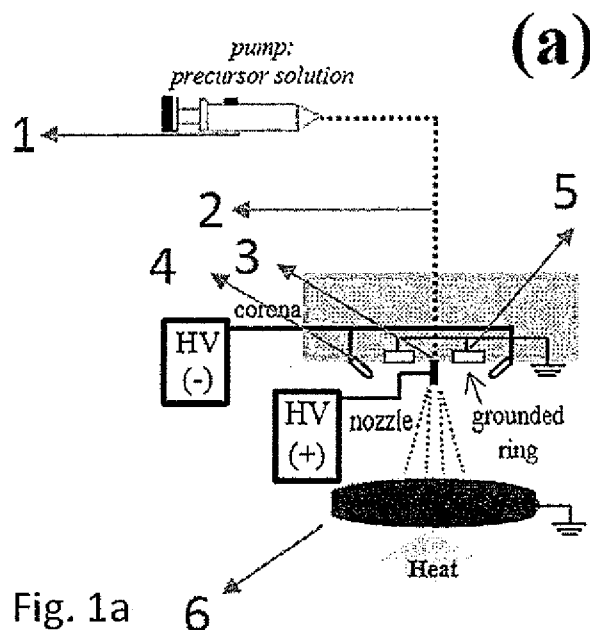
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(54) Title: TAILORED MICRO-PARTICLES



(57) Abstract: The present invention is in the field of electrospraying, and relates to a novel device and method for spraying, as well as particles obtained and use of said particles. By the present method and device characteristics of the particles can be adapted in a controlled and reliable manner and further contamination of the particles obtained is virtually absent. Precursor solution is pumped (1) to a nozzle (3). High voltage is applied to the nozzle (3) and to at least two coronas (4). The electromagnetic field may be varied. Particles are sprayed towards a grounded collector (6) which may be heated.



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TAILORED MICRO-PARTICLES

FIELD OF THE INVENTION

The present invention is in the field of electrospraying, and relates to a novel device and method for spraying, as well as particles obtained and use of said particles. By the present method and device characteristics of the particles can be adapted in a controlled and reliable manner and further contamination of the particles obtained is virtually absent.

BACKGROUND OF THE INVENTION

Electrospraying (or electro hydrodynamic atomization, EHDA) relates to a process wherein e.g. a liquid is distributed into size-distributed droplets under the influence of an electrical field. From a reservoir or the like a liquid is transported to a nozzle. The nozzle is typically coupled to a high voltage source. To apply an electrical potential and moving charged particles in an electrical field a counter electrode is provided at some distance of the nozzle electrode. By creating a high voltage between the nozzle and the counter electrode due to the electrical forces and depending on the conductivity, surface tension and viscosity of the liquid at some threshold potential, a jet forms at the tip of the nozzle that later breaks up into charged liquid droplets; therewith a spray of droplets and in a later stage particles is formed. The process is known to provide a spray of typically uniformly sized particles, which find application in aerosol delivery of e.g. a medicament.

It is considered that under evaporating condition, the initial electrosprayed droplet may go under so-called Coulomb fission if the Rayleigh limit of the charge density is reached. This is found to result in a breakdown of the initial droplet into small droplets; this increases a polydispersity of final products. Coulomb fission is found to be caused by an increase in charge density (reaching Rayleigh limit) as the volume of a droplet is decreasing due to evaporation. As an example of this effect, it is noted that thin films produced by Electrostatic Sprayed Deposition (ESD) have nanometer-size structures despite that the size of the initial sprayed droplets is typically a few tens of microns in

diameter. In physical and organic chemistry, the dispersity is a measure of the heterogeneity of sizes of molecules or particles in a mixture. A collection of objects is called monodisperse or uniform if the objects have the same size, shape, or mass. A sample of objects that have an inconsistent size, shape and mass distribution is called poly-disperse or non-uniform. The objects can be in any form of chemical dispersion, such as particles in a colloid, and polymer molecules in a solvent. Polymers can possess a distribution of molecular mass; and particles often possess a wide distribution of size, surface area and mass.

The term dispersity, represented by the symbol $\bar{D}$, can refer to either molecular mass or degree of polymerization. It can be calculated using the equation $\bar{D}M = M_w/M_n$, where M_w is the weight-average molar mass and M_n is the number-average molar mass.

The M_w is calculated as follows:

$$\bar{M}_w = \sum_i N_i M_i^2 / \sum_i N_i M_i$$

wherein N_i is the number of molecules of molecular mass M_i .

The mass average molecular mass is determined by static light scattering on a Brookhaven 90Plus.

The number average molar mass M_n is determined by measuring the molecular mass of n polymer molecules, summing the masses, and dividing by n .

$$\bar{M}_n = \sum_i N_i M_i / \sum_i N_i$$

The number average molecular mass of a polymer is determined by gel permeation chromatography, in particular by a Waters GPC using a Styragel column.

In electricity a corona discharge is an electrical discharge brought on by the ionization of a fluid surrounding a conductor that is electrically energized. The discharge will typically occur if the electric field strength around the conductor is high enough to form a conductive region, but not high enough to cause electrical breakdown or arcing to nearby objects.

Corona discharge may be introduced to electrospray to discharge charged droplets and avoid Coulomb fission. It should however be taken into account that corona discharge is found to be capable of creating ionic wind. Application of ionic winds is considered of great interest as a tool to reg-

ulate heat in electronics instead of using bulky mechanical fans. It has been found that the efficiency not high it can still be applied in a compact area with the least energy.

Various prior art systems may be mentioned in particular, such as the ones disclosed in NL2006794C and NL2008056C, of which the disclosures are incorporated by reference.

Despite advances in the past it still is difficult to adapt characteristics of particles, and droplets with the prior art systems in a controlled manner, and some characteristics can not be adapted at all. Also the prior art systems are prone to contamination of final particles obtained. Further challenges facing application of the electrospraying technique relate to a limitation in flow rate, uncontrolled characteristics of liquids (e.g. surface tension, conductivity) and Coulomb fission due to solvent evaporation. Further, a selective deposition in e.g. semiconductors is found to cause charge accumulation on deposited film, and as a result a limitation in feasible film thickness.

Some background prior art documents recite particle production devices.

EP 1 171 243 A1 recites an electrohydrodynamic aerosol sprayer wherein a gas flow deflector is used for creating a gas flow past the spray nozzle to stabilize the Taylor cone and to transport at least a portion of the aerosol away from the region downstream of the spray nozzle. This stabilization of the cone and transport of aerosol improves the droplet size and distribution and may also reduce the deposit of droplets on the internal components of the device.

WO 2014/149695 A1 recites a method and apparatus for forming battery active material on a substrate are disclosed. In one embodiment, an apparatus for depositing a battery active material on a surface of a substrate includes a substrate conveyor system, the material electrospray dispenser assembly disposed above the substrate conveyor system, and a first heating element disposed adjacent to the material spray assembly above the substrate conveyor system.

WO 2013/100766 A1 recites a spraying device for producing a spray of particles in a carrier gas at an ambient pressure, includes a storage volume for a liquid substance;

at least one nozzle having an inlet and an outlet, the nozzle inlet being coupled to the storage volume in fluid communication; a counter electrode; an electric supply coupled between the at least one nozzle and the counter electrode for providing a first potential between the nozzle outlet and the counter electrode so as to create a first electric field between the nozzle outlet and the counter electrode. The spraying device further includes at least one discharge electrode, the at least one discharge electrode being coupled to the electric supply for providing a second potential between the discharge electrode and the counter electrode, the polarity of the second potential being opposite to the polarity of the first potential. The at least one nozzle and the at least one discharge electrode are arranged adjacent and parallel to each other and facing the counter electrode from a substantially same direction.

US 2011/041840 A recites an atomizing device, an inhaler and a method for dispensing a liquid formulation are proposed. An insert comprises a cylinder filled with the liquid, an atomizing nozzle and a piston. The piston is moved in the cylinder to pressurize the liquid and force it out of cylinder through the atomizing nozzle in order to generate a spray. The insert is received in a holder which is sealed. The insert is moved within the holder so that the sealing is ruptured before the spray is generated.

Therefore there still is a need for an improved electrospraying device, which overcomes one or more of the above disadvantages, without jeopardizing functionality and advantages.

SUMMARY OF THE INVENTION

The present invention relates in a first aspect to an electrospraying device according to claim 1, in a second aspect to a method of operating the present device according to claim 11, in a third aspect to a particle obtainable by the present device c.q. method according to claim 13, and in a fourth aspect to an inhale or particle delivery system according to claim 15. Amongst others the present invention provides improved aerosol characteristics of a spray.

The present inventors introduce an innovative idea that applies ionic winds produced by multiple coronas

along the electrospray nozzles in a turbulence-like mode. The ionic wind relates to an airflow induced by electrostatic forces linked to corona discharge arising at the tips of some sharp conductors subjected to high voltage relative to ground. The coronas are preferably from a conducting material and have sharp tips, such as needles. Preferably very thin tips are used, such as having a cross-section of less than 1 mm, preferably less than 0.5 mm, such as less than 0.2 mm. The turbulence mode may be increased by a means for varying an electro-magnetic field. For instance the potential of the coronas may be varied, such as in a repetitive manner, having a certain frequency (e.g. 50-10.000 kHz), such as in a sinusoidal mode. There may also be a phase-difference between the corona, such as a phase difference of 2π /number of coronas, or a multitude or fraction thereof. Also a feedback loop may be provided, in order to further stabilize the multi jet spinning mode. Preferably a rotating (or spinning) ionic wind is created. This has found to create particles with a unique structure and characteristics that are not accessible with traditional bulk methods, such as the above mentioned. By the introduced method and device a metastable structure, of constantly drying droplets in the electrospray, is reserved for further processing. Important elements in this approach are the electrospraying configuration of the present device and an operational mode. Therein a residence time of a droplet-particle in the gas phase increases. The residence time can be controlled by neutralizing the droplet and/or size of the droplet-particle. One can tailor a final particle size (distribution) by adjusting one or more of a liquid flow rate of the liquid, the geometry and configuration of the nozzles, to control and direct the electrical wind and its strength, providing the particles with an extended and controllable residence time in the gas phase allowing them to shape as required, the option of freezing metastable structures (of meso- and nanoscale size) of especially metal oxides, and the charge on the particle by adjusting corona discharge parameters.

The present inventors modulate the charge density

of the droplets by inducing an ionic wind along the spray. Using the Ionic wind assisted electrohydrodynamic atomization technique inventors explored various possibilities to reach a stable mode in terms of jet formation, spray quality and droplet-particle size and size distribution. By varying applied electrical potential and flow rate, inventors were able to electrospray different solutions. Inventors identified different regimes of jet formation and spraying modes. Inventors also explored the possibility to use multi-jet mode as a practical approach to produce particles with acceptable polydispersity. Using WO_3 as a test material, inventors demonstrated how the ionic wind assisted electrospraying deposition (ESD) technique is used to tailor morphological properties of deposited porous thin film. Advantages are amongst others a multi-jet mode as a practical way to produce particles with defined final product characteristics, tailoring mesoscopic morphology of deposited porous thin film, and overcoming the above mentioned problems.

The electrospraying configuration of the present device is considered not to relate to a classical configuration. An important difference is that the ground is positioned upwards such that the evaporating droplet experiences an airflow combined with ions of opposite charges. It has been found that as a result the droplet is neutralized, the initial size is reserved and there is no urge in reaching ground electrode or being deposited. The residence time of such neutral droplet-particle is found to increase and by applying heat along the electrospraying pathway it is found that one can also manipulate the kinetics of drying.

It is found that the required turbulence-like condition of the sprayed droplets is only possible if electrospraying in the present device takes place by a spinning mode, preferably a multi-jet mode. Spinning multi-jet mode is found to be a stable and reproducible mode that can be described as a combination of multi-jet and precession mode, which is found only accessible in presence of so-called ionic winds.

For sake of comparison it is noted that particles

with different morphology and porosity can be synthesized by prior art methods by changing a chemical composition (such as mixing ratio) and synthesizing conditions. It has been found that the collected final particles of the same chemical composition produced by the present device can have a different size and porosity, which is found to depend on e.g. the flow rate and heat applied. This present and novel approach provides one with the opportunity to collect particles having adaptable characteristics, such as a similar chemical composition, without (measurable) contamination, and with different porosity, in a one-step approach; the nature of the present device and technique has as a result that contamination is virtually absent. Moreover it has been found that the present method provides the opportunities to produce nano-meso scale crystals and particles with unique structures that are not accessible with prior art wet chemistry methods.

It has been found that the present ionic wind assisted electrospray can be used to produce individual particles with a particular morphology, porosity and even further to produce nanoscale-mesoscale crystals. This is e.g. achieved by increasing the residence time of the droplet/particles in the gas phase and at the same time providing a heat gradient. It has been found that the turbulence-like mode of spinning, which is found to be only accessible in the presence of ionic winds, as a tool to tune the droplet/particle residence time, charge density and to create particles of any desired size with tailored morphology and porosity. Increasing the residence time of constantly drying droplet in gas phase in a random flow at which the droplet is balancing the surface tension and the imposed electrical forces will results in such unique nano-micro (meso) structures that cannot be achieved in bulk methods.

The present device comprises a container for maintaining a solution. The solution may be kept at a pressure of 10 ± 1 kPa, i.e. about atmospheric. The container typically has a volume of 100 μ l-20 ml, such as 0.001-1 ml; larger and smaller sizes are in principle possible, depending on a final design of the device. The solution,

which may also be referred to as a pre-cursor solution for forming particles or the like, or likewise any fluid, suspension, solution, colloidal system, and biological system, may on application be transferred to the nozzles, typically through a tube or the like. It is noted that not only multi nozzles can be used, but also co-axial nozzles, having two liquids/fluids or more, supplied by e.g. two container or more, can be delivered and the final product will have a multi core-shell like structure. The present spraying mode is referred to as spinning multi jet because a multi jet stream mode is obtained having more than one jet streams, indicating that instead of one cone configurations that have as a result a single jet (stream) coming out of one nozzle there are more than one jet streams provided by the at least one nozzle and the induced ionic wind and possibility the ionic shielding gives a rotating effect as can be seen in figure 1-b, the last image thereof. At least two coronas are found to be required to create such an effect. It is noted that no physical component in the present device itself is rotating, The device comprises at least one nozzle, having an inside diameter and a length preferably providing capillary force, in fluid connection with the container, and wherein the at least one nozzle is preferably directed towards the collector at an angle of 90 ± 20 degrees, i.e. at a small angle deviating from perpendicular to perpendicular (with respect to a surface of the collector). The nozzle may be a coaxial nozzle. Also a potential may be applied to an inside of the nozzle, to an outside, or a combination thereof. Also a pump for pumping the solution from the container to the at least one nozzle is present. As typically amounts of fluid are very small, e.g. flow rates of 0.01 pl/s-1 ml/s, a pump may be very small as well. However there are no limitation and larger values can be adopted.

In order to form an electrospray at least one means for applying a maximum voltage of at least 1 kV to the nozzles is provided. The at least one means, or a second means, also provides a maximum voltage of at least 1 kV to the at least two coronas. The coronas may have a hydrophobic coating, leaving a tip section uncoated. Further

a collector is present for collecting or directing the spray and particles therein or formed thereof, the collector being electrically grounded and located in a spray direction and at a distance of less than 5 cm of the at least one nozzle. The distance can be 0 mm, that is the collector being at the same height as the nozzles. A material of the collector, such as a collecting plate, can be chosen from a wide variety of materials, including metals, semi-conducting materials, plastics, coated materials, etc. The collector is for collecting in principle neutralized particles. It may be of a conductive material, and it may be grounded. To illustrate the amount of freedom in selecting a suitable material it is noted that the particles can be collected even on a tissue being waved at the direction of spray at a distance that should be the end of the spraying zone, or far enough that the droplets already dried out to particles or released from the turbulence flow. How far from the nozzles the collection area is depends e.g. on the solution used and temperature applied. At least two coronas are provided being located around the nozzles, preferably at a substantial similar height as the nozzles, and the structure being electrically grounded. There may be one conducting structure per nozzle, a combined structure for all nozzles being present, or a partly combined structure and a structure for the at least one nozzle. Also at least two coronas is provided, the at least two coronas located around the at least one nozzle and around the conducting structure, preferably at a substantial similar height as the nozzles. Typically at least two coronas are provided for the combined nozzles. As with the conducting structure, also coronas may be combined.

Thereby the present invention provides a solution to one or more of the above mentioned problems.

Advantages of the present invention are detailed throughout the description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in a first aspect to a device according to claim 1.

In an exemplary embodiment the present device comprises a heat provider for heating the collector.

In an exemplary embodiment of the present device the at least one means for applying a voltage is capable of applying to the corona a voltage opposite of the voltage applied to the nozzles, e.g. the corona having a positive voltage and the nozzles having a negative voltage, or vice versa.

In an exemplary embodiment of the present device the nozzles has an inside diameter of $<500\text{ }\mu\text{m}$, preferably $1\text{--}250\text{ }\mu\text{m}$, more preferably $2\text{--}100\text{ }\mu\text{m}$, even more preferably $5\text{--}75\text{ }\mu\text{m}$, such as preferably $10\text{--}60\text{ }\mu\text{m}$, and wherein the distance is $0.1\text{mm--}10\text{ mm}$, preferably $0.2\text{mm--}5\text{mm}$, more preferably $0.3\text{mm--}2\text{mm}$, such as $0.5\text{--}1\text{ mm}$. In an example a gauge 30 needle is used.

In an exemplary embodiment of the present device the nozzles has a length of $1\text{--}10\text{ mm}$. The above dimensions provide optimal results in terms of amount of solution sprayed versus amounts of particles obtained, electrical voltage and current applied, power consumption ($\mu\text{W--mW}$), etc.

In an exemplary embodiment of the present device the nozzles has a removable or breakable sealing. Such is especially advantageous when the present device is used for spraying of constituents which are vulnerable to degradation and/or contamination, such as in the case of medicaments.

In an exemplary embodiment of the present device the collector provides a solid surface, or is partly mesh shaped.

In an exemplary embodiment of the present device the at least one means for applying a voltage provides a current of $1\text{ nA--}1\mu\text{A}$, therewith reducing power consumption, preventing risk of degradation, etc.

In an exemplary embodiment of the present device the at least one means for applying a voltage provides a high frequency pulsed electro-magnetic field, such as from $100\text{ Hz--}100\text{ kHz}$, preferably $1\text{ kHz--}10\text{kHz}$. Therewith spraying is improved, e.g. in terms of efficiency.

In an exemplary embodiment of the present device the at least one nozzle comprises an outer hydrophobic coating, which coating covers the nozzle typically par-

tially. Such is especially relevant if the fluid/solution uses water or another hydrophilic solvent, such as an alcohol. The spray-pattern and flow are further improved hereby.

5 In a second aspect the present invention relates to a method according to claim 11, comprising the steps of atomizing and charging liquid particles, spraying the particles and collecting the particles.

10 In an exemplary embodiment of the present method the collector is moved over time in a direction perpendicular to the spray direction. Therewith an even distribution of particles over a collector surface can be obtained.

15 In a third aspect the present invention relates to particles according to claim 13, obtainable by the present method and/or with the present device.

20 In an exemplary embodiment of the present particles they are selected from a biological particle selected from the group consisting of an enzyme, a receptor and a ligand, and a medicament, a catalyst, a semiconductor material, and a sensing material. The medicament can be a for treating respiratory problems, lung diseases, such as COPD, hyper- or hypoventilation, cystic fibrosis, asthma, breakthrough cancer pain, pain in general, diabetes, wound
25 care, vaccination in general, antiviral application, antibiotic application, hormone therapy, narcotic analgesics, influenza treatment, anaphylaxis treatment, multiple sclerosis treatment, acute migraine, etc. The present system can be further adapted in such a way that it provides a
30 delivery of a low dosage (pl-pl), having advantages such as no or limited side effects, being aseptic, having a mono-disperse particle size distribution (e.g. in the μm range, e.g. 2-5 μm), acute treatment, fast effect (within 7-10 seconds), short time of application, easy to use,
35 such as a handheld design, wireless connectivity, easy to clean, durable, comprising a separate drug container. Examples of medicaments relate to corticosteroids, opiates, cannabinoids, LABA's, agonists, antagonists, hormones, such as estrogens, anticholinergics, peptides, synthetic
40 or natural analogues, Na^+ channel blockers, such as

fluticasone, salmeterol, fentanyl, Δ^9 -THC, zolmitriptan, granisetron, rimonabant, estradiol, scopolamine, teriparotide, budesonide, iloprost, lidocaine, insulin, tiotropium Br, colistin, dornase, liposomal antifungals, and tacrolimus. Molecules obtained are typically relatively small, such as less than 10 kDa, preferably < 6 kDa, such as <1kDa. The catalyst particles can be made extremely pure, which is considered a big advantage for catalyst, and also a size, porosity, morphology, and composition can be tuned precisely. Such advantages are also found in sensing materials, such as TiO_2 , and semiconductor materials.

A typical dosage (e.g. tobramycin) of 1-10 mg, in e.g. 0.01-1 ml of solvent (e.g. 70% water and 30% ethanol).

In a fourth aspect the present invention relates to an inhale or particle delivery system according to claim 15, comprising the present device.

In an exemplary embodiment the inhaler or system further comprises an inhaler mask.

The invention is further detailed by the accompanying figures and examples, which are exemplary and explanatory of nature and are not limiting the scope of the invention. To the person skilled in the art it may be clear that many variants, being obvious or not, may be conceivable falling within the scope of protection, defined by the present claims.

SUMMARY OF FIGURES

Figure 1a. Example of present device. 1b: spray patterns.

Figure 2. SEM pictures of a collector with particle. (a) prior art and (b) present invention.

Fig. 3 shows schematics of a nozzle.

Fig. 4 shows a multi-nozzle multi-corona layout.

Fig. 5 shows SEM pictures of tobramycin.

DETAILED DESCRIPTION OF FIGURES

In the figures:

1: dispensing liquid unit;

2: tubing;

3: electrospaying nozzle;

4: corona needles;

5: Grounded ring;

6: heated substrate, which can be extended to be like a tube around the whole unit.

5 Figure 1a. Example of present device. 1b: spray patterns. In the present device a container 1 with a precursor solution (solution, colloidal suspension) or fluid is provided, typically having a pump for displacing the fluid. The container is in fluid connection with the at least one nozzle
10 3 by a tubing 2 or the like. Through the nozzles the precursor solution is sprayed. Around the nozzles coronas, such as needles, wires, a tooth-like conducting object, are provided, typical two or more, such as 3-10. Typically these corona elements are evenly distributed around the nozzles, such as at
15 a relative angle (around a virtual circle) of $360/n$ degrees, n being the number of coronas. In addition a grounded element 5, such as a ring is provided. For collecting a collection substrate 6 is provided, which may be heated. The collector may be extended upwards towards the nozzles and even surround
20 the whole device.

 Figure 2. SEM pictures of a collector with particle. (a) prior art and (b) present invention. Fig. 2a shows particles that have a preferential deposition. The solvent of the solution evaporates mainly (80% or more thereof) before deposition takes place, whereas the remainder evaporates later. Particles are as a result typically stacked along rim-like structures, as is schematically indicated in the drawing at the right of fig. 2a. With the present device (see fig. 2b) evaporation of solvent takes place largely before deposition.
25 The surface roughness is different and depends on the kinetics of drying, which can be adapted via parameters such as flow rate, temperature and ionic wind. Coulomb fission is avoided and the residence time of droplets and particles in gas phase is increased, as is schematically indicated in the drawing at the right of fig. 2b. The circles show relatively
30 large and uniform particles, evenly distributed over the collecting surface, and no rims.

 Fig. 3 shows schematics of a nozzle. In fig. 3a the high voltage is applied to an internal part of the nozzle, in
40 fig. 3b to an external part. Fig. 3c shows 3 nozzles directed

in slightly different orientations.

Fig. 4 shows a cross-section of a multi-nozzle multi-corona layout. Therein 3 nozzles 3, a grounded ring 5, and six coronas 4 are shown.

Fig. 5 shows SEM pictures of tobramycin. 80 mg/ml tobramycin was applied in a 50:50 water:ethanol solution. In fig. 5a a prior art cone jet with 2.5 ml/h was used, in fig. 5b a multi jet also with 2.5 ml/h. The present system clearly performs better.

The figures are further detailed in the description of the experiments below.

EXAMPLES/EXPERIMENTS

The invention although described in detailed explanatory context may be best understood in conjunction with the accompanying examples and figures.

As far as materials used, the spinning multi jet stream mode was observed with a range of ethanol-water mixture with weight ratio of (100:0 to 50:50). The relative distance of corona to ground ring, nozzles to ground ring and be changed in a range of dimension. For example: the coronas and grounded ring and nozzles are at the same level, the coronas are above the ring-nozzles and below the grounded ring, the coronas are above the ring-nozzles and above the grounded ring, and the coronas are below the ring-nozzles and above the grounded ring.

Using WO_3 as a test material inventors further demonstrate how the particles are produced in the present electro spraying mode. The exemplary set up consisted of a syringe pump, an electro spray nozzle (0.25 mm internal diameter (ID), 0.52 mm outer diameter (OD)) surrounded by 12 corona needles, a grounded ring and a heated collection plate. The distances between (1) the nozzles and the grounded ring, (2) the corona and the ground electrode, and (3) the nozzles and the heating plate were 6, 2 and 20 mm, respectively. A tungsten precursor solution was prepared as described by Gaury et al. [Gaury, J.; Kelder, E. M.; Bychkov, E.; Biskos, G., Characterization of Nb-doped WO_3 thin films produced by Electrostatic Spray Deposition. Thin Solid Films 2013, 534, 32-39.]: i.e., 5 ml of $\text{W}(\text{ipr})_6$ were mixed with 50 ml of 2-propanol under argon atmosphere. The as-prepared precursor solution was

then pumped through the electrospray nozzles at flow rates ranging from 0.5 to 10 ml/h. Evaporation of the droplet and oxidation of tungsten occurred during the evaporation stage (ES0, resulted in pure WO₃ nanoparticles, having a median
5 size of 8 nm.

The resulting particles were deposited on alumina (Al₂O₃) substrates placed on top of the heating plate that was maintained between 300 and 310 °C. The duration of all the depositions was 10 min. The morphological properties of the
10 resulting thin film samples were studied using a Scanning Electron Microscope (SEM; Jeol JSM-6010LA). All samples were coated by a thin layer of gold to avoid surface charge disturbances during the measurements. The figure provided as fig. 2-b is for a flow rate of 5 ml/hr.

15 In an example an antibiotic, specifically tobramycin in ethanol-water solution (10-80 mg/ml in ethanol-water with volume ration of about (80:20) to (50:50), was investigated, uniform particles as evidenced by SEM images was collected in the spinning multi jet mode. Tobramycin is of importance
20 for treating cystic fibrosis. The possibility of delivery of particles of 1-5 micrometer with a narrow size distribution in short time is found to be an effective treatment.

In a similar approach 6 mg colistin and 7.8 mg dor-nase was administered.

25 In another comparable approach for systemic therapy 5.4 mg fentanyl, and 8.9 mg cannabis were administered twice per day, and in an example as palliative care in oncological inhaler therapy.

30 It should be appreciated that for commercial application it may be preferable to use one or more variations of the present system, which would similar be to the ones disclosed in the present application and are within the spirit of the invention.

CLAIMS

1. Device (100) for electro-spraying comprising
(a) a container (1) for maintaining a solution,
(b) at least one nozzle (3), having an inside diameter and a length, in fluid connection (2) with the container,
5 (c) a pump (1) for pumping the solution from the container to the at least one nozzle,
(d) an electrically conducting structure (5), the structure being located around the nozzle preferably at a substantial similar height as the nozzle, and the structure
10 being electrically grounded,
(e) a collector (6), the collector being electrically grounded and located in a spray direction and at a distance of less than 5 cm of the at least one nozzle,
(f) at least two coronas (4), the at least two coronas located around the at least one nozzle and around the
15 conducting structure, preferably at a substantial similar height as the nozzle,
(g) at least one means for applying a maximum voltage of at least 1 kV to the nozzles and a maximum voltage of
20 at least 1 kV to the at least two coronas, and
(h) optionally a means for varying an electromagnetic field.

2. Device according to claim 1, further comprising a heat provider for heating the collector.

25 3. Device according to any of the preceding claims, wherein the at least one means for applying a maximum voltage is capable of applying to the corona a voltage opposite of the voltage applied to the nozzles.

30 4. Device according to any of the preceding claims, wherein the at least one nozzle provide capillary force, and having an inside diameter of $<500\text{ }\mu\text{m}$, and wherein the distance is 0.1mm-10 mm.

5. Device according to any of the preceding claims, wherein the nozzles have a length of 1-10 mm.

35 6. Device according to any of the preceding claims, wherein the nozzles have a removable or breakable sealing.

7. Device according to any of the preceding claims, wherein the collector provides a solid surface, or is partly

mesh shaped.

8. Device according to any of the preceding claims, wherein the at least one means for applying a voltage provides a current of 1 nA-1 μ A.

5 9. Device according to any of the preceding claims, wherein the at least one means for applying a voltage provides a high frequency pulsed electro-magnetic field.

10 10. Device according to any of the preceding claims, wherein the nozzles comprise an outer hydrophobic coating.

11. Method of operating a device according to any of the preceding claims, comprising the steps of atomizing and charging liquid particles, spraying the particles and collecting the particles.

12. Method according to claim 10, wherein the collector is moved over time in a direction perpendicular to the spray direction.

13. Particles obtainable by the method according to any of claims 11-12, wherein the particles are aseptic.

14 Particles according to claim 13, having a monodisperse particle size distribution in a range of 2-5 μ m.

15 15. Particles according to any of claims 13-14, wherein the particles are selected from a biological particle selected from the group consisting of an enzyme, a receptor and a ligand, and a medicament, a catalyst, a semiconductor material, and a sensing material.

16. Inhaler or particle delivery system comprising a device according to any of claims 1-10, optionally comprising an inhaler mask.

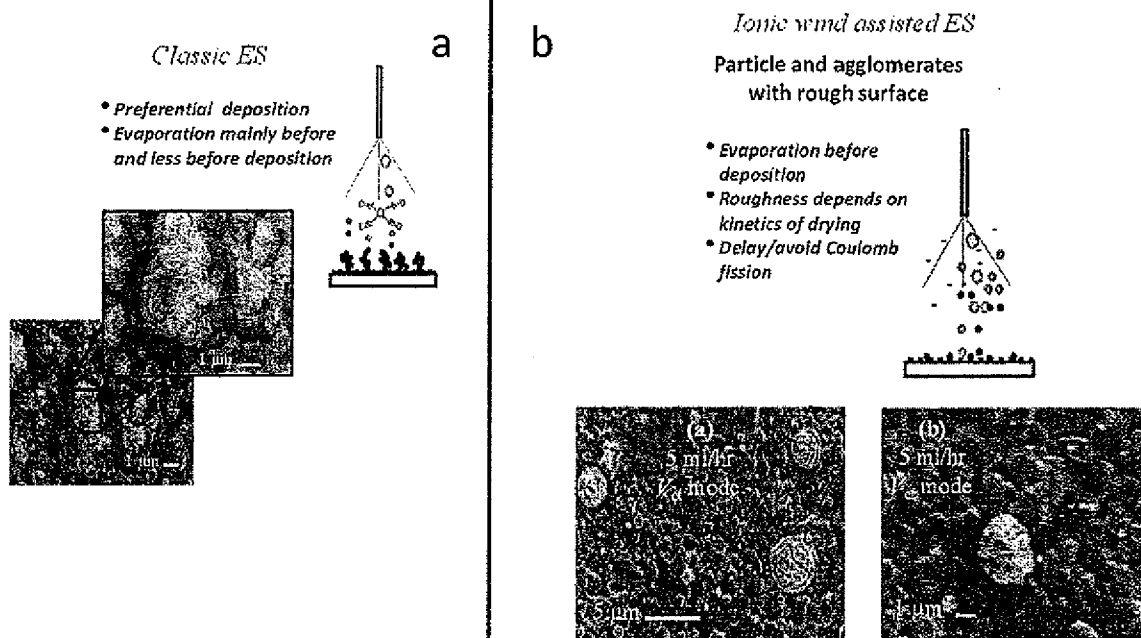
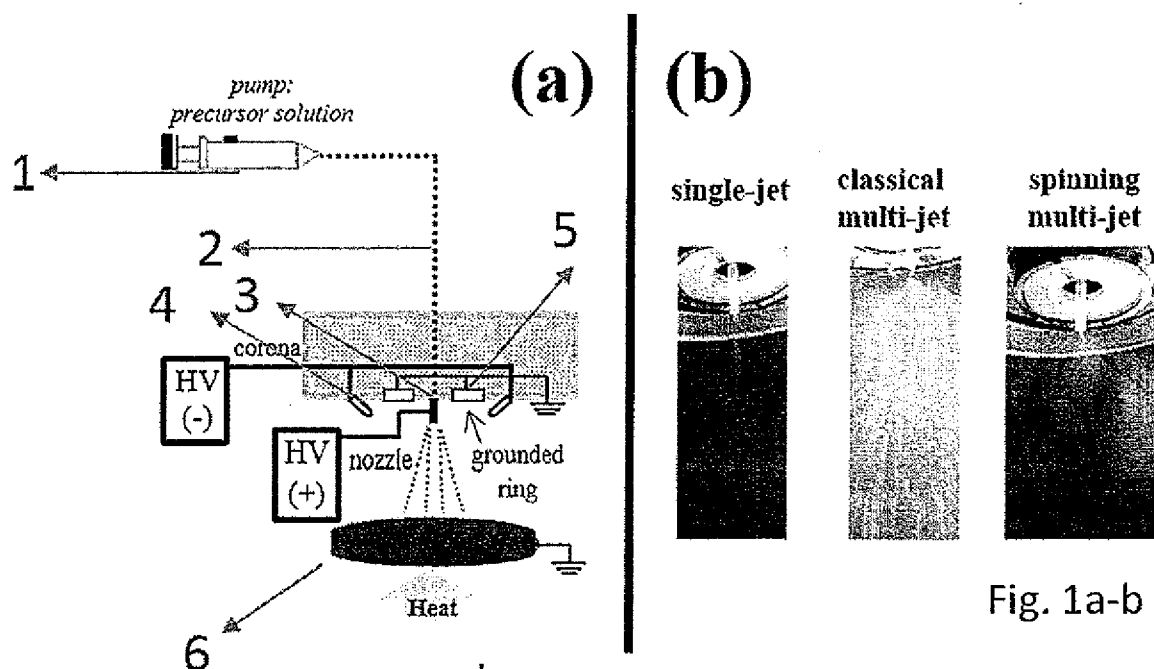
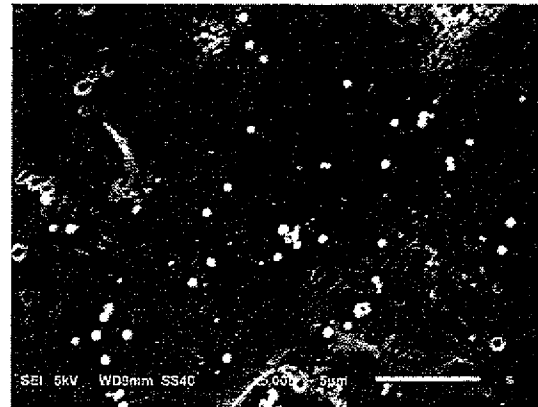
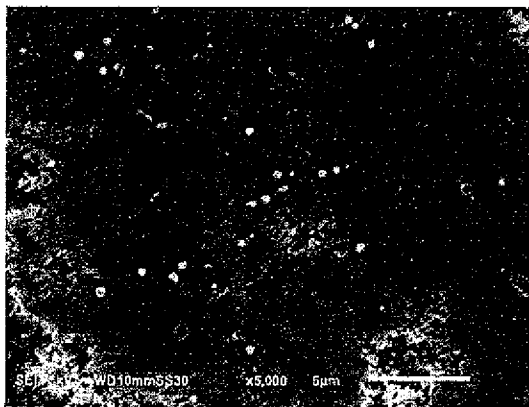
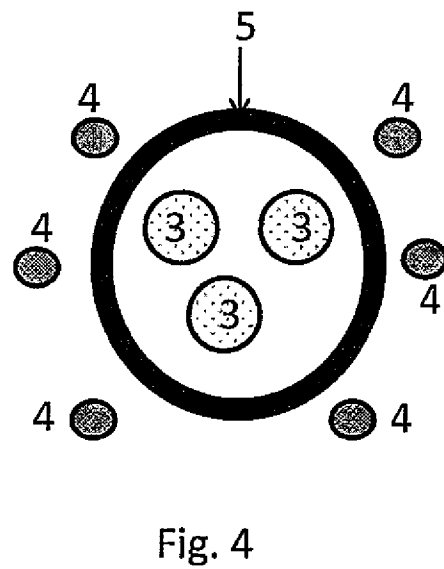
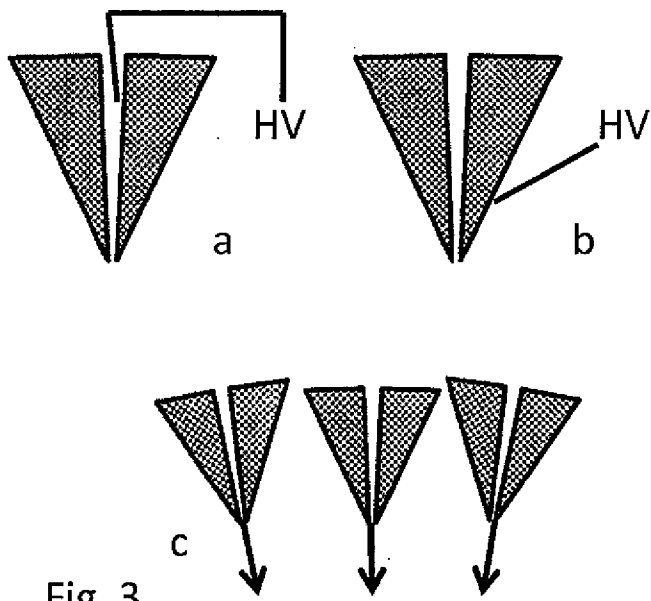


Fig. 2a-b



INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2016/050141

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61M15/00 B05B5/16 B05B5/025 B05B5/035 B05B5/053
ADD. B05B5/00

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)

A61M B05B

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 171 243 A1 (BATTELLE MEMORIAL INSTITUTE [US]) 16 January 2002 (2002-01-16)	13, 15
A	the whole document	1, 3-5, 8, 16
A	----- WO 2014/149695 A1 (APPLIED MATERIALS INC [US]) 25 September 2014 (2014-09-25) the whole document	1, 2, 7, 11, 12, 15
X	----- WO 2013/100766 A1 (GILBERT TECHNOLOGIES B V [NL]) 4 July 2013 (2013-07-04)	13, 15
A	claims 7-10, 13	1, 9, 10, 16
A	----- US 2011/041840 A1 (DUNNE STEPHEN T [GB]) 24 February 2011 (2011-02-24) figures 1-4	6
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

21 June 2016

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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International application No

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