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(54) **Nasal spray device and method of spraying a liquid formulation**

(57) A nasal spray device comprises a non-pressurized reservoir (25) for containing a liquid formulation; a spray nozzle (50); and a manually energizable pump (10), configured to pressurize a quantity of said liquid formulation and causing the liquid formulation to move through the spray nozzle such that the liquid formulation is discharged from the spray nozzle as an aerosol spray. Said reservoir comprises a chamber that is configured to release a predetermined dose of said liquid formulation of between 25 and 150 microlitre and said pump is a manually operable positive displacement pump that forces said dose of said liquid formulation at an operating pressure of between 5 and 15 bar through said spray nozzle (50). The spray nozzle (50) comprises a membrane having a plurality of micropores of a substantially identical size below 8 micron and beyond 3 micron through which the liquid formulation passes as the liquid formulation is discharged from the device. Said membrane is configured to release said dose of said liquid formulation in a period of at least 500 milliseconds.

Nasal spray device and method of spraying a liquid formulation

The present invention relates to a nasal spray device, comprising a non-pressurized reservoir for containing a liquid formulation; a spray nozzle; and a manually energizable pump configured to pressurize a quantity of said liquid formulation and causing the liquid formulation to move through the spray nozzle such that the liquid formulation is discharged from the spray nozzle as an aerosol spray.

Current manually operable nasal spray devices deliver a nasal spray that is generated by a pressure swirl nozzle, also referred to as hollow cone nozzle. A stationary core inside such nozzle induces a rotary fluid motion which causes swirling of fluid in a swirl chamber. A liquid sheet film is discharged from the perimeter of an outlet orifice, producing a characteristic hollow cone spray pattern. Air or other surrounding gas is drawn inside the swirl chamber to form an air core within the swirling liquid. Many geometries of fluid inlets are used to produce this hollow cone pattern depending on the nozzle capacity and materials of construction. These swirl nozzles produce droplets with a size of between 20 and 200 micron within a relatively broad droplet size distribution having typically an average droplet size between 50 and 80 micron. A volume flow or discharge rate of sprays generated with swirl nozzles is relatively high and typically larger than 200 microlitre per second. This causes a considerable impact of the liquid spray in the nose. The latter is not only a drawback from a sensory point of view to the user, but also leads to a relatively short dosage time. Typically a dose of 40 microlitre is being delivered in a dosage time of less than 200 milliseconds with such a conventional nasal spray device and most of the spray happens to end no further than in the nasal vestibule.

Experimental studies have shown that many spray pump swirl nozzle devices deposit a significant amount of their drug in the anterior vestibule which is considered a less active region of the nasal cavity. This anterior vestibule deposition may be due to inertial impaction since most spray pumps are designed to release a large proportion of aerosol particles greater than 20 micron which exit the device in short time at a relatively high speed when actuated.

It is inter alia an object of the present invention to provide a nasal spray device that meets the above drawbacks without sacrificing convenience to the user substantially. In one aspect of the invention, it is an object to provide a nasal spray device that provides an improved

coverage of the nasal cavity, particularly including the olfactory region of the nasal cavity. More particularly, in a still further aspect the invention has for its object to provide a nasal spray device that is capable of aerosolizing nanoparticles, that may comprise relatively long molecules, particularly fragile biological molecules, while substantially maintaining their nanoparticle structure and molecular integrity.

In order to achieve the above object a nasal spray device of the type described in the opening paragraph, according to the invention is characterized in that said reservoir comprises a chamber that is configured to release a predetermined dose of said liquid formulation, particularly of between 25 and 150 micro litre, in that said pump is a manually operable positive displacement pump that forces said dose of said liquid formulation at an operating pressure of between 5 and 15 bar through said spray nozzle, and in that said spray nozzle comprises a membrane having micropores of a substantially identical size below 8 micron and beyond 3 micron through which the liquid formulation passes as the liquid formulation is discharged from the device.

The present invention particularly provides a nasal spray device that generates a so-called micro-jet spray. A micro-jet spray consists of a number of concurrently emitting jets, in which each jet will initially breakup into a mono-disperse primary droplet train according to a jet breakup mechanism. As a result, consecutive primary droplets have substantially identical size and propagate downstream of the nozzle in a same direction. Typically a diameter of a primary droplets is between twice and three times the diameter of the micropore that released it. This means that according the invention the primary droplets will have an identical size of between 6 and 30 micron, depending the size of the micropores by which they are generated. Eventually individual droplets may merge due to mutual coalescence which will cause a shift and certain spread in the droplet size distribution throughout the spray. The droplet size distribution remains nonetheless relatively sharp and well defined.

At this instance it is noted that the size of a micropore is being defined in the present application as representing the diameter of a circle having a same surface area as a cross sectional surface area of said micropore. Likewise the size of a droplet is being defined as the diameter of a sphere having a same volume as the volume contained by said droplet. Further

the expressions nebulizer, atomizer and spray device are used interchangeably without entailing any essential difference, unless explicitly stated otherwise.

The nasal spray device according to the invention operates on basis of a pump, particularly one that is manually energizable, to deliver an ultra-fine mist of these relatively small droplets. Due to their relatively low momentum, these droplets tend to slow down relatively rapidly as the encounter ambient air. In practice a residence time of the order of 500 milliseconds and even longer has been observed. This slow release of relatively small droplets offers a slowly moving soft mist of said liquid formulation. A patient may inhale gently via the nostril which will convey the soft mist droplets to nasal target areas further downstream the nasal cavity. A majority of the uniformly sized droplets will particularly be capable of targeting the respiratory and olfactory nasal region. This enhanced penetration is attributed to the fact that the spray device of the invention is designed to generate small, and also slowly moving particles that traverse the nasal cavity at a normal inhalation rate, thereby minimizing inertial impaction anterior to the nasal valve.

Due to the relatively sharp droplet size profile of the spray, as is associated with Rayleigh formation, only a small fraction of the soft mist spray, if any, consists of droplets of too small size, particularly smaller than 10 micron, such that they may escape further into the respiratory system of the user, particularly into the lungs. Targeting the olfactory region is especially aimed at for topical drugs that can be up taken by the brain directly, thus avoiding a blood-brain barrier. Also a clearance of nasal fluid in the olfactory region is considerably lower than in the vestibule region, allowing the formulation a longer time to be up taken by the nasal mucus tissue. These factors greatly contribute to a significantly enhanced uptake efficiency.

The pump based nasal spray device according to the invention comprises a nozzle that generates a slowly moving fine mist of the liquid formulation that may be able to reach and cover up to more than 80% of the internasal mucus layers. The invention particularly relates to a nasal spray device that may be used to aerosolize a pharmaceutical formulation for nasal administering. A specific embodiment of the nasal spray device according to the invention, to that end, is characterized in that said reservoir contains a pharmaceutically active liquid formulation, particularly one containing nanoparticles, such as formulations containing complex proteins, peptides, long chain DNA & RNA, large vesicles, liposomes and antibodies.

As an example, the pump based nasal spray device of the invention will be able to protect a user against allergic attacks or diseases caused by microorganisms or viruses, such as the SARS-Cov-2 viruses, with an appropriate anti-allergenic or prophylactic formulation. Current prophylactic formulations against SARS-Cov-2 viruses to prevent that the virus will bind to epithelial cells in the nasal cavity are, angiotensin receptor blockers, ACE inhibitors, heparin and enoxaparin derivatives. Other prophylactic medicines and vaccines include ivermectin, antibodies, glycoproteins, mRNA lipid nanoparticles, and other biologically active agents. The pump based nasal spray device of the invention may comprise a nozzle that preserves the integrity of such formulation, especially in the case of biological formulations, that are generally based on large molecules and/or nanoparticles, such as formulations containing complex proteins, peptides, long chain DNA & RNA, large vesicles, liposomes and antibodies. Current fine mist nebulizers for nasal use, on the other hand, have been found to destroy the molecular integrity of large molecules that are present in many mRNA lipid nanoparticle vaccines. This renders these conventional nebulizers unsuitable for nasal administration of many protein based or other biological drugs.

The nasal spray device according to the invention may be configured to target the deeper respiratory system, particularly the lungs, as well besides the nasal cavity. To that end a specific embodiment of the nasal device according to the invention is characterized in that said membrane of said spray nozzle comprises a second group of micropores of substantially identical size below 3 micron through which the liquid formulation passes as the liquid formulation is discharged from the device. These relatively small micropores will deliver correspondingly smaller droplets, typically smaller than 10 micron, that will be able to pass the nasal cavity to eventually target the deeper tracheal and/or even bronchial areas of the respiratory system.

In a preferred embodiment the nasal spray device according to the invention is characterized in that said pump comprises a manually actuated piston that pressurizes said dose of said liquid formulation to said operating pressure in a single stroke of said piston. A piston that pressurizes the entire dose in a single stroke provides convenience to the user, particularly if the pump mechanism is further configured to automatically fill said dose in a dedicated volume of the device prior to pressuring it. Said pump may comprises a multi shot nasal pump

that is provided with a dosing chamber for holding said dose of said liquid formulation at least temporarily and releasing said dose to said spray nozzle under said operating pressure. Alternatively said pump may be comprised by a medical syringe.

A specific embodiment of the nasal spray according to the invention is characterized in that said pump opens into a male Luer tip, in that a nostril cap is receivable onto said male Luer tip having an inlet that provides a female Luer slip connection with said male Luer tip and having an outlet to release said nasal spray, and wherein said nostril cap comprises said spray nozzle between said inlet and said outlet. This embodiment particularly allows a standard medical syringe to be used as the pump and reservoir for containing the liquid formulation. Simply mounting the nostril-cap, embodying the spray nozzle according to the invention, on top of the syringe transforms the syringe into a nasal spray device that outperforms many conventional nasal spray devices. Both the syringe and the nostril-cap may be provided as low cost disposable articles.

A further specific embodiment of the spray device according to the invention is characterized in that said nostril-cap comprises at least one inhalation channel that carries a parallel airflow of ambient air along with said spray towards the outlet, while the user inhales. Such an inhalation channel may for instance be provided in a wall of said nostril-cap, opening into environment. This induces additional airflow through the nostril-cap consisting of ambient air, while the user inhales. The spray droplets may piggyback on this additional airflow or may be carried into its slipstream to be delivered deeper into the nasal cavities. Even remotely located nasal areas inside the nasal cavity may be targeted this way. A preferred embodiment of the nasal spray device is characterized in that said nostril-cap tapers down towards said outlet to have a close nasal fit.

In a preferred embodiment said membrane comprises a ceramic layer, wherein said micropores extend over a thickness of said ceramic layer. The micropores may for instance be formed by etching and/or using micro-machining using photolithography as customary in nowadays semiconductor technology. In that respect, a specific embodiment said ceramic layer is a silicon nitride layer lying on a carrier body of a semiconductor material, particularly of silicon, wherein said carrier body is provided with at least one cavity underneath said nitride layer, wherein said at least one cavity opens downstream into at least one micropore of said

plurality of micropores, and wherein said at least one cavity is connected upstream to an outlet of said pump.

The present invention further relates to a method of spraying a liquid formulation, wherein said liquid formulation is pressurized to an operating pressure of between 5 and 15 bar using a pump to create at least a pressurized dose of said liquid formulation, wherein said pressurized dose of said liquid formulation is forced through a group of micropores in a membrane of a Raleigh type spray nozzle, said micropores having a size smaller than 8 micron, to cause said liquid formulation to breakup in at least one spray plume of liquid droplets having substantially an identical initial droplet size, and wherein said spray plume is caused to propagate with a plume propagation velocity of less than 1 m/s, particularly in a nasal cavity of a user. Such spray plume appears particularly appropriate and effective as a nasal spray for nasal administration of said liquid formulation.

The invention is thereby based on the recognition that Rayleigh breakup of the liquid formulation by means of micropores that are smaller than 8 micron will deliver spray droplets of a substantially identical initial size of typically between twice and three times the size of the micropores. These still relatively small, micron sized droplets together form an ultra-fine spray plume that will be retarded substantially instantaneously once released in and exposed to ambient air due to the relatively small kinetic energy of the individual droplets. Particularly the resulting spray plume will be slowed down to have a propagation velocity not exceeding the order of 1 m/s. It has been found that the turbulence within this spray plume together with such slow rate of movement delivers an unprecedented coverage over basically the entire nasal cavity, including the higher olfactory region.

The present invention particularly relates to a nasal spray device and method for delivering a spray from a liquid formulation comprising nano-particles that are capable of preserving the integrity of said nano-particles while said liquid formulation is converted into a spray. To that end, a special embodiment of the method of spraying a liquid formulation is characterized in that said liquid formulation contains nano-particles of a size δ and said liquid droplets contain at least one nano-particle of said nano-particles, wherein said nano-particles have a maximum size δ_{max} before rupture upon elongation; wherein said liquid formulation is subjected to a shear rate γ [per second] while passing through a micropore; and wherein said liquid

formulation is exposed within said micropore to said shear rate γ during a shear time Δt that is less than $\delta_{max}/(\delta.\gamma)$ seconds.

In a further embodiment the nasal spray device and method according to the invention are characterized in that said liquid formulation comprises nano-particles of a size δ and said liquid droplets contain said nano-particles, wherein said nano-particles have a maximum size δ_{max} before rupture upon elongation; and wherein said micropores have a length L that is smaller than the pore diameter D times δ_{max}/δ ($L<D.\delta_{max}/\delta$). In case of tapering pores the size or diameter D of the micropore is then taken as the largest diameter of the micropore. For long chain molecules, such as mRNA, etc, the length of the micropore L should be less than the total length λ of the long chain molecule ($L<\lambda$), in particular L is less than 1 micron.

The nasal spray device and method according to the invention are particularly suitable for spraying a liquid formulation that comprises nano-particles taken from a group, containing complex proteins, large biological molecules, long chain DNA & RNA, large vesicles, liposomes, bacteriophages and antibodies, while preserving the integrity of such nano-particles.

Hereinafter, the invention will be described in further detail with reference to a specific embodiment and an accompanying drawing. In the drawing:

Figure 1 shows a specific example of a nasal spray device according to the invention;

Figure 2 shows a schematic drawing of part of the device of figure 1;

Figure 3provides a comparison of a droplet size distribution between the device of figure 1 and a conventional swirl nozzle nasal spray device;

Figure 4A-D shows high-speed photography capture images of a spray generated by a nasal spray device according to the invention as compared to that of a conventional swirl nozzle nasal spray device;

figure 5A shows a high speed camera image of a nasal coverage of a liquid spray by means of said conventional swirl nozzle nasal spray device;

figure 5B shows a high speed camera image of a nasal coverage of a liquid spray by means of said nasal spray device according to the invention;

Figure 6 provides a graphical representation of the performance of a spray device according to the invention for spraying a liquid formulation containing mRNA molecules as compared to conventional spray devices; and

Figure 7 shows a schematic representation of a particular embodiment of a nasal adapter for use with nasal spray device according to the invention

It is noted that the figures are drawn purely schematically and not necessarily to a same scale. In particular, certain dimensions may have been exaggerated to a more or lesser extent to aid the clarity of any features. Similar parts are generally indicated by a same reference numeral throughout the figures.

As an example of a nasal spray device according to the invention, figure 1 shows a standard medical syringe 10 that has a movable piston 15 that is manually operable by means of a stem 20. In practice it is possible to exert an operating pressure of between 2 and 10 bar of a liquid that is contained in the reservoir 25 contained in the syringe 10 and to force said liquid at such operating pressure into the nostril-cap 40 that is mounted by means of a male-female slip connection on a tip of the syringe.

The nostril-cap is shown in more detail in figure 2 and basically comprises a plastic cone that is fitted on the tip of the syringe 10. The nostril cap 40 is received sealingly onto the male Luer tip of the syringe 10 by means of an internal female Luer slip connection at an inlet of said nostril-cap 40. The nostril-cap comprises a spray nozzle 50 proximal to an outlet 47 side that is capable of receiving said liquid at said operating pressure and converting it into a ultra-fine soft mist. To that end the nozzle 50 comprises a spray microchip of silicon that is fitted sealingly inside an internal cavity of plastic adaptor body. Said adaptor body facilitates easy handling and assembly of the nozzle device and moreover may accommodate one or more filters upstream of the spray chip.

The spray chip holds a brittle ceramic silicon nitride membrane of typical 1 micron thickness. This membrane comprises a plurality of micropores extending through said thickness. A thin silicon oxide layer may be provided between the nitride layer and the silicon body. In such case, the micropores will extend through this oxide layer as well. As a result the micropores are in open communication with one of a number of subjacent cavities that are etched through said silicon body from a backside to its front surface. These cavities convey the pressurized liquid to the micropores. The micropores were created with great precision to have a substantially identical size of 4 micron in diameter. To that end, like the other structures of the

micro-chip, the micropores are preferably created by photo lithographic aided etching and deposition techniques as customary in modern semiconductor manufacturing technology. Using these techniques at least a portion of the micropores is modified and configured to release their microjet under a diverging angle of deflection with respect to their centerline. This creates a substantially cone shaped spray pattern, said cone having an apex typically between 10 and 25 degrees.

The liquid is forced through said micropores, during operation, and breaks up into small droplets as the cohesion is no longer capable of concurring with the surface tension. This physical phenomenon is generally referred to as Rayleigh breakup and cause the liquid to breakup is essentially equal droplets of a size that is initially approximately between twice and three times the size of the releasing micropore. Eventually individual droplets may merge due to coalescence which will cause a shift and certain spread in the droplet size distribution throughout the spray. Figure 3 provides a plot in which curve A represents a typical droplet size distribution of the spray generated by this nozzle. The droplets have grown to between 20 and 40 micron. This spray nonetheless maintains a relative sharp symmetrical profile as compared to a spray that is generated by means of for instance a swirl nozzle. In order to demonstrate this, figure 3 also contains two comparison curves B, C that represent a typical profile of the droplet size distribution of a spray that was generated using conventional swirl nozzles.

To enhance the penetration into the nasal cavities by a nasal spray generated by the depicted spray device , the nostril-cap 40 comprises a number of inhalation channels 45 aside from the central cavity that carry a parallel airflow of ambient air along with said spray towards the outlet 47, while the user inhales. The spray chip of the nozzle 50 is configured to release a slowly moving liquid spray. Typically a dose of the order of between 25 and 150 micro litre is released in a period of at least 500 milliseconds by said nozzle 50.

A number of studies have proved that such a slowly moving nasal spray is an excellent method of delivering topical medication beyond the nasal valve region. This enhanced penetration is attributed to the fact that small, slow moving liquid particles are able to traverse the nasal cavity at a resting breathing rate, thereby minimizing inertial impaction anterior to the nasal valve. In addition to the delivery device, a combination of other factors can also contribute to

the efficacy of intranasal formulations. These include drug formulation characteristics, site of deposition and patient friendly use of the delivery device. These excellent deposition characteristics are achieved with a relatively simple spray pump provided by a medical syringe 10.

To explain the strong difference in droplet deposition for a soft mist nozzle of the nasal spray device according to the invention and a standard swirl nozzle, a high-speed photography capture of the initial droplet velocity and plume formation (Figure 4A-4D). These images show spray droplet trajectories for the two spray nozzles. Figure 4A shows the spray pattern of a spray generated by means of a soft mist nozzle according to the invention, while figure 4B is a magnification of the rectangular area that is marked area in figure 4A. Eddies can be observed as indicated by the arrows. Figure 4C shows the spray pattern of a spray generated by means of a standard swirl nozzle, while figure 4D is a magnification of the rectangular area that is marked area in figure 4C. Straight droplet trajectories can be observed as indicated by the arrows.

The spray plume of the swirl nozzle has an initial velocity of about 13 m/s, spraying a total volume of 100 µL in approximately 100 ms. The spray plume of the nozzle of the present invention, however, has a much lower initial velocity of less than 1 m/s, particularly about 0.7 m/s, and sprays 45 µL in 500 ms. Furthermore, the soft mist nozzle according to the invention produces much smaller droplets (Dv50 20-25 µm) than a standard nasal swirl nozzle (Dv50 60 µm) as indicated by the comparative plots of figure 3.

Essentially the standard swirl nozzle produces a short burst of relatively heavy droplets that travel all in straight trajectories in an upwards direction, as shown in figures 4C and 4D. The soft mist nozzle of the nasal spray device according to the invention, on the other hand, produces droplets in a turbulent droplet cloud travelling in all directions, as shown in figures 4A and 4B. The ballistic trajectories of the droplets of the swirl nozzles causes most droplets of the spray to be deposited only at the start of the nasal cavity. This is an inherent property of swirl nozzles, where the medium droplet size is determined by a competition between the surface tension of the liquid and inertia. In this case the medium drop size scale proportional to $v^{-2/3}$, with v the velocity. This implies that relatively small droplets as desired for nasal administration may only be obtained by increasing the velocity within a swirl nozzle.

The droplets size of the soft mist nozzle of the nasal spray device according to the invention, on the other hand, is predominantly determined by the size of the micropores, independent of the spray velocity. First of all this allows a better control of the droplet size distribution within the spray as the micropores may be created with great precision and definition. But, at least equally well important, this allows downscaling of the droplet size without increasing the droplet velocity to render an ultra fine slowly moving nasal spray that gives an unprecedented intranasal coverage in a handheld, manually energizable pump driven device.

Figures 5A and 5B show the result of an experimental setup to demonstrate the unexpected nasal coverage by the nasal spray device according to the invention. The setup uses a commercially available transparent nasal cast by Koken Co. Japan to mimic the human nasal region with an intranasal volume of 38,6 cm^3 in combination with a high speed camera. In both cases the angle of insertion is about 45 degrees at an insertion depth of 1 cm. The liquid formulation that is being used contains 1 mg/ml calcein dissolved in a 25% glycerol-water mixture to improve the optical visibility of the evolving spray. The administered dose has a volume of 100 microlitre.

Figure 5A shows the proliferation of a nasal spray within the nasal cavities using a standard conventional pump driven nasal spray device with a swirl nozzle. The figure shows large droplets and concentrations at the entrance of the nasal cavity with only a poor overall coverage of the nasal mucosa. Only 18% of cavity was covered with standard nasal spray device, resulting mainly in big droplets deposition.

Figure 5B, on the other hand, shows the proliferation and spread of the same liquid formulation over the nasal cavity using a nasal spray device according to the invention. The high speed camera image shows a slowly moving aerosol cloud that travels and deposits uniformly over the cast model. In the end ultra-fine droplets are highly distributed over substantially the entire nasal cavity, including the higher olfactory region. This soft mist nasal spray covered 58% of nasal mucosa with fine mist of small micron sized droplets.

The ability to produce an ultra-fine mist of relatively small droplets with an unprecedented nasal coverage renders the spray device according to the invention particularly suitable for

nasal administration of pharmaceutically active liquid formulations. This particularly relates to biological drugs, like prophylactic medicines and vaccines that may include antibodies, glyco-proteins, mRNA containing lipid nano-particles, and other biologically active agents. These generally delicate molecules or molecular nano-particle structures, however, tend to break or otherwise deteriorate when exposed to extreme shear forces that are exerted on them when using a conventional swirl nozzle or vibrating mesh. This is demonstrated in figure 6 showing a plot of the molecule size of mRNA in a liquid formulation before and after aerosolizing with different nebulizers of COVID-19 vaccine BNT162b from Pfizer/Biontech. The vaccine formulation entails lipid nano-particles with an average size δ of 300 nm, which nanoparticles further comprise mRNA chains of ca 4.000 basepairs encoding for the virus spike protein with a chain length λ of approximately 4.000x0.34 nm (= 1.36 micron). A reference curve I gives the molecule length of mRNA in the Pfizer/Biontech stock liquid, while curves II and III depict the molecule length after the same liquid formulation was sprayed using commercially available vibrating mesh nebulizers by Aeroneb and Pari eFlow respectively. Clearly the average mRNA molecule length diminished due to spraying with these current spray devices. This renders these conventional devices less suitable for spraying of relatively fragile molecular nanostructures and long molecules. The nasal spray device according to the invention, based on relatively tender Rayleigh breakup of the mRNA containing liquid formulation after having passed through relative short micropores of about 1 micron length, happens to preserve the mRNA molecule to a large extent. Also the lipid nano-particle structure with an average size of δ=300 nm is preserved using the device according to the invention, but not with the conventional vibrating mesh nebulizers. This is is attributed to the fact that vibrating mesh nebulizers cause a lot of fluid mechanical agitation in the formulation and that according to the invention the micropores have a rather short pore length L, such that the passage time t of the nanoparticles experiencing a (high) shear rate γ is still sufficient short to prevent rupture of the lipid nano-particle structure. Further experiments show that for nano-particles with an average spherical diameter δ with a maximum elongation upto δ_{max} (before rupture occurs) can be found whenever the maximum shear time Δt is less than $\delta_{max}/(\delta . \gamma)$ seconds with δ_{max}/δ is a number between 3 to 5. This implies that the length L of the micropore should not exceed the diameter D of the micropore, because the amount of shear on the nano-particle is proportional to the length L of the micropore and is inversely proportional to the diameter D of the micropore. rate in a channel with diameter D.

Another founding according to the invention is that for long chain molecules, such as mRNA with a chain length λ, the length of the micropore L according to the invention should be less than the total chain length λ of the mRNA molecule. The breakage force on the mRNA molecule due to the presence in a shear field is proportional to the chain length λ, provided that the mRNA molecule is fully stretched in the shear field. However when the mRNA molecule passes through a pore with a length L that is less than the chain length λ of the mRNA molecule, then the mRNA molecule will not be fully stretched, but will partly maintain its initial globular shape, herewith reducing the imposed breakage force on the mRNA molecule. The length of the micropore L according to the invention should therefore be less than the total chain length λ of the mRNA molecule. In particular micropores with a length L less than 1 micron have been successfully tested for this purpose. This is shown by the curve IV in figure 6 that demonstrates the mRNA molecule length λ of the liquid formulation of the same Pfizer/Biontech mRNA liquid vaccine after the formulation was sprayed using the nasal spray device according to the invention having micropores of a length L of 1 micron that is smaller than the chain length λ of the mRNA molecule. This opens an entirely new opportunity of nasal administering bio-technological pharmaceuticals that are often based on biologicals and nanoparticles, such as formulations containing complex proteins, peptides, long chain DNA & RNA, large vesicles, liposomes, antibodies. and other biological compounds as their active ingredient.

All in all the depicted nasal spray device according to the present invention provides an intranasal spray atomiser that maintains the convenience and simplicity of a swirl nozzle device, while having several benefits compared with to a traditional swirl nozzle, like:

- a low dosing volume required for nebulisation, than may be as low as 25μL while still providing an adequate therapeutic volume that is being administered;
- a droplet size that is independent of the liquid flow rate and independent of the liquid formulation; allowing a slowly moving soft mist of ultrafine droplets;
- a narrow droplet size distribution merely dependent on the diameter of the micropores that allows tailoring the deposition to specifically the nasal regions to be targeted and avoiding deep respiratory deposition;
- an optimal deposition efficacy in nasal cavity due to low plume velocity below 1.0 m/s and narrow droplet size distribution;

- an optimised plume cone angle between 10 and 25 degrees to allow wider deposition in the nasal cavity;
- limited dripping and clearance of liquid due to larger surface coverage of deposition
- low impact force due to reduced plume velocity and smaller droplet size
- Luer-lock fitting capability for easy attachment to e.g. existing medical Luer-lock syringes
- parallel inspiration flow of ambient air along the device through purposely designed air slits.

Figure 7 shows a particular embodiment of a nasal adapter 77 for use with nasal spray device according to the invention. The nasal adapter comprises the spray nozzle 70 of the nasal spray device and has moreover means for generating two additional air streams 71,73. These means enable a co-axial air pit flow 71 with a high velocity along the path of the liquid micro-jets 72 that are released by the spray nozzle 70. This co-axial pit flow will prevent coalescence of droplets within the jets that are released by the spray nozzle chip 70 . With preference the velocity of the pit air flow 71 is initially higher than the initial velocity of these microjets 72.

Additionally, said means allow a sheet flow of air 73 to be generated along the interior wall off adapter 77, indicated with the white dotted arrows, as the user inhales. This sheet flow 73 counteracts turbulence along the interior wall of airstreams containing microjet droplets that would otherwise hit the wall of the nasal adapter interface. The housing of the nasal adapter 77 has a conical shaped top that is intended to lie substantially sealingly within one of the nostrils of the user while directing the microjet droplets into the nasal cavity user. The additional air streams 71,73 may be generated passively as the user inhales through the nostril or they may be generated actively by an auxiliary supply of pressurized air, using appropriate means like a ventilator or a pressurized gas that is released once the user inhales.

While various embodiments of the invention have been described above, it should be understood that they have been presented by way of example, and not limitation. It is apparent to persons skilled in the relevant arts that various changes in form and detail can be made therein. Thus, the invention should not be limited by any of the above-described embodiments, but should be defined only in accordance with the following claims and their equivalents.

Particularly the nasal spray device may comprises a silicon chip serving as nozzle body carrying the nozzle membrane, for instance a nozzle membrane formed from a silicon nitride ceramic layer with a thickness of the order of one micron. Micropores (orifices) may be etched through such layer on a nanometre to micrometre scale using ultra high precision photo lithographic imaging, masking and etching techniques as available in modern semiconductor manufacturing technology.

The size of the micropores inside the spray chip determines predominantly the primary size of the droplets that are released in the spray. This in turn determines to a large extent the target area where the droplets will mainly land in the respiratory system. Micropores with a size between 3 micron and 8 micron will deliver droplets that are typically larger than 10 micrometer and, as a consequence, mainly target the nasal cavity, particularly the nasal turbinates, without going deeper into the respiratory system, as these droplets larger than 10 micron will generally not be able to pass the nasopharynx and will remain instead in the upper airways. Droplets of a size between 1 micron and 10 micron, on the other hand, may generally transfer through the nasopharynx to eventually deposit predominantly in the lower airways (trachea and alveoli). Droplets smaller than 1 micron will not be deposited at all, but will be exhaled substantially completely.

As shown in figure 5B the nasal spray device according to the invention enables an internasal delivery with a high coverage on the internasal tissues. For many prophylactic and other applications such internasal delivery with a high coverage will be sufficient. Some other prophylactic and other conditions, however, (also) require a deeper deposition in the lower airways. A particular embodiment of the nasal spray device according to the invention is therefore configured to deliver a liquid formulation to both upper and lower airways, in a single inhalation step when inhaled through the nose.

To that end, the same or a further microchip within the nasal spray device may concurrently be fed with the pressurized liquid, comprising a second group of micropores having a diameter below 3 micron, for instance between 1.5 and 3 micron. The droplets emanating from these micropores tend to have a size below 10 micron that typically will not be captured in the nasal cavity but instead will pass the nose to enter the downstream respiratory tract, when inhaled.

The larger droplets from the first group of micropores, between 3 and 8 micron in diameter, are intended to be captured in the upper airways, particularly in the nasal vestibule, nasal turbinate and olfactory region. The second group of micropores with an orifice smaller than 3 micron, will create droplets that are sufficiently small to be able to target nasopharynx and lower airways (lungs) when inhaled through the nose. Due to the smaller size of these droplets and, hence, their lower mass, the smaller droplets have a lower kinetic energy and a low plume velocity. These smaller droplets follow the airstream through the upper airways into the lower airways. By varying the ratio between the number of small and large pores it is possible to tailor the ratio of prophylactic formulation deposition between the upper and lower airways.

Such nasal device according to the invention, hence, may deliver a liquid formulation containing for instance a prophylactic, pharmaceutical drug, also to both the upper and lower airways, in a single inhalation step when inhaled through the nose. The size of the micropores inside the spray nozzle predominantly determines the initial droplet size and thereby controls the target location of deposition in the upper and/or lower airways. When the micropores are combined having a pore size between 3 micron and 8 micron in one group and having a pore size smaller than 3 micron in another group, the device generate a nasal spray that will target the entire respiratory tract, when inhaled. A unique dual therapy is thus offered by a single nasal spray device for use with conditions that require coverage of both the nasal mucous membrane as well as that of the deeper respiratory region, particularly the bronchi and lungs.

Conclusies:

1. Neusspray-inrichting, omvattende een drukloos reservoir voor het bevatten van een vloeibare formulering; een sproeikop; en een handmatig activeerbare pomp die is geconfigureerd om een hoeveelheid van de vloeibare formulering onder druk te brengen en de vloeibare formulering door de sproeikop te forceren, zodanig dat de vloeibare formulering van de sproeikop ontwijkt in de vorm van een aërosol spray, met het kenmerk dat het reservoir een kamer omvat die is geconfigureerd om een vooraf bepaalde dosis van de vloeibare formulering af te geven, in het bijzonder van tussen 25 en 150 microliter, dat de pomp een handmatig bedienbare verdringerpomp is die de dosis vloeibare formulering bij een werkdruk van tussen 5 en 15 bar door de sproeikop forceert, en dat de sproeikop een membraan omvat met een hoeveelheid microporiën van een in hoofdzaak identieke grootte, kleiner dan 8 micron en groter dan 3 micron, waardoorheen de vloeibare formulering passeert wanneer de vloeibare formulering door de inrichting wordt afgegeven.

2. Neusspray-inrichting volgens conclusie 1, met het kenmerk, dat de pomp een handmatig bediende zuiger omvat die de dosis van de vloeibare formulering in een enkele slag van de zuiger tot de werkdruk onder druk brengt.

3. Neusspray-inrichting volgens conclusie 2, met het kenmerk, dat de pomp een multi-dosis nasale pomp omvat die is voorzien van een doseerkamer om de dosis van de vloeibare formulering ten minste tijdelijk vast te houden en de dosis onder genoemde werkdruk aan de sproeikop af te geven.

4. Neusspray-inrichting volgens conclusie 2, met het kenmerk, dat de pomp wordt gevormd door een medische spuit.

5. Neusspray-inrichting volgens één of meer van de voorgaande conclusies, met het kenmerk dat de pomp uitmondt in een mannelijke Luer-uiteinde, dat een neusgatadapter op het mannelijke Luer-uiteinde ontvangbaar is, met een inlaat die een vrouwelijke Luer-glijverbinding met hete mannelijke Luer-uiteinde verschaft en met een uitlaat om de neusspray af te geven, waarbij de neusgatadapter tussen de inlaat en de uitlaat de sproeikop omvat.

6. Neusspray-inrichting volgens conclusie 5, met het kenmerk, dat de neusgatadapter tenminste één inhalatiekanaal omvat dat een parallelle luchtstroom van omgevingslucht samen met de spray naar de uitlaat voert, terwijl de gebruiker inhaleert.

7. Neusspray-inrichting volgens conclusie 5 of 6, met het kenmerk, dat de neusgatadapter in de richting naar de uitlaat toe taps toeloopt om een nauwe passing in de neus te hebben.

8. Neusspray-inrichting volgens één of meer van de voorgaande conclusies, met het kenmerk, dat het membraan een keramische laag omvat, waarbij de microporiën zich uitstrekken over een dikte van de keramische laag.

9. Neusspray-inrichting volgens conclusie 6, met het kenmerk, dat de keramische laag een siliciumnitridelaag is die ligt op een dragerlichaam van een halfgeleidermateriaal, in het bijzonder van silicium, waarbij het dragerlichaam is voorzien van ten minste één holte onder de nitridelaag, waarbij de ten minste ene holte stroomafwaarts uitmondt in ten minste één microporie van de hoeveelheid microporiën, en waarbij de ten minste ene holte stroomopwaarts is verbonden met een uitlaat van de pomp.

10. Neusspray-inrichting volgens een van de voorgaande conclusies, met het kenmerk, dat de aërosol spray als Rayleigh-jets de microporiën in het membraan van de sproeikop verlaat, welke vervolgens opbreken in druppels van de aërosol spray.

11. Neusspray-inrichting volgens een van de voorgaande conclusies, met het kenmerk, dat de aërosol spray die uitgaat van de microporiën in het membraan in hoofdzaak kegelvormig is met een divergerende kegelhoek ten opzichte van een as van de sproeikop, in het bijzonder met een tophoek tussen 10 en 25 graden.

12. Neusspray-inrichting volgens een van de voorgaande conclusies, met het kenmerk dat het reservoir een farmaceutisch actieve vloeibare formulering bevat, in het bijzonder een formulering die nanodeeltjes bevat, zoals formuleringen bevattende complexe eiwitten, peptiden, lange keten DNA & RNA, grote vacuolen, liposomen en antilichamen.

13. Neusspray-inrichting volgens één of meer van de voorgaande conclusies, met het kenmerk, dat het membraan van de sproeikop een tweede groep microporiën omvat van in hoofdzaak identieke grootte, kleiner dan 3 micron, waar doorheen de vloeibare formulering passeert wanneer de vloeibare formulering door de inrichting wordt afgegeven.

14. Neusspray-inrichting volgens één of meer van de voorgaande conclusies, waarbij de vloeibare formuleringen nanodeeltjes met een grootte δ omvatten, waarbij de nanodeeltjes een maximale grootte

δ_{max} hebben voor breuk bij rek en de microporiën een lengte L hebben die kleiner is dan de poriediameter D vermenigvuldigd met δ_{max}/δ ($L<D.\delta_{max}/\delta$), in het bijzonder $L < 4D$.

15. Neusspray-inrichting volgens conclusie 14, waarbij de vloeibare formulering macromoleculen met een ketenlengte λ omvat, en dat de microporiën een lengte L hebben die kleiner is dan de ketenlengte λ van de macromoleculen, waarbij in het bijzonder L kleiner is dan 1 micron.

16. Werkwijze voor het sproeien van een vloeibare formulering, waarbij de vloeibare formulering onder druk wordt gebracht tot een werkdruk tussen 5 en 15 bar met behulp van een pomp om ten minste een onder druk staande dosis van de vloeibare formulering te creëren, waarbij de onder druk staande dosis van de vloeibare formulering wordt geforceerd door een groep microporiën in een membraan van een sproeikop van het Raleigh-type, waarbij de microporiën een grootte hebben die kleiner is dan 8 micron, om de vloeibare formulering te doen uiteenvallen in ten minste één spraypluim van vloeistofdruppels met een in hoofdzaak identieke initiële druppelgrootte, en waarbij genoemde spraypluim zich voortplant met een pluimvoortplantingssnelheid van minder dan 1 m/s.

17. Werkwijze volgens conclusie 16, waarbij de vloeibare formulering nanodeeltjes met een grootte λ bevat en de vloeistofdruppels ten minste één nanodeeltje van de nanodeeltjes bevatten, waarbij de nanodeeltjes een maximale grootte λ_{max} hebben voordat ze breken bij rek; waarbij genoemde vloeibare formulering wordt onderworpen aan een afschuifsnelheid γ [per seconde] bij passage door een microporie; en waarbij de vloeibare formulering binnen de microporie aan de afschuifsnelheid γ wordt blootgesteld gedurende een afschuiftijd Δt die kleiner is dan $\lambda_{max}/(\lambda.\gamma)$ seconden.

18. Werkwijze volgens conclusie 16, waarbij de vloeibare formulering nanodeeltjes omvat, waarbij de nanodeeltjes een maximale grootte δ_{max} hebben voor breuk bij rek, en de microporiën een lengte L hebben die kleiner is dan de poriediameter $D.\delta_{max}/\delta$, in het bijzonder $L < 4D$.

19. Werkwijze volgens conclusie 18, waarbij de vloeibare formulering macromoleculen met een ketenlengte λ omvat, en dat de microporiën een lengte L hebben die kleiner is dan de ketenlengte λ van de macromoleculen, waarbij in het bijzonder L kleiner is dan 1 micron.

20. Werkwijze volgens een van de conclusies 16 of 19, waarbij de vloeibare formulering nano-deeltjes bevat die zijn genomen uit een groep, omvattende complexe eiwitten, grote biologische moleculen, lange keten DNA & RNA, grote vacuolen, liposomen, bacteriofagen en antilichamen.

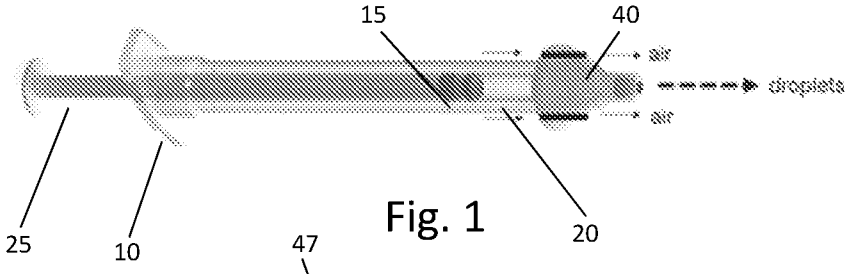

Fig. 1

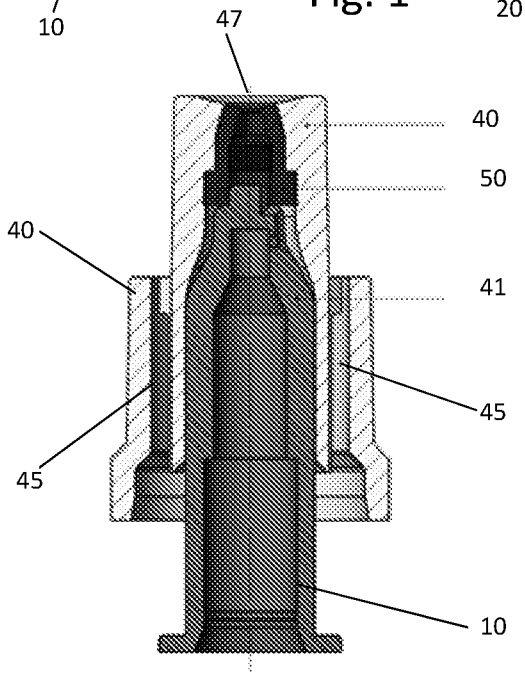

Fig. 2

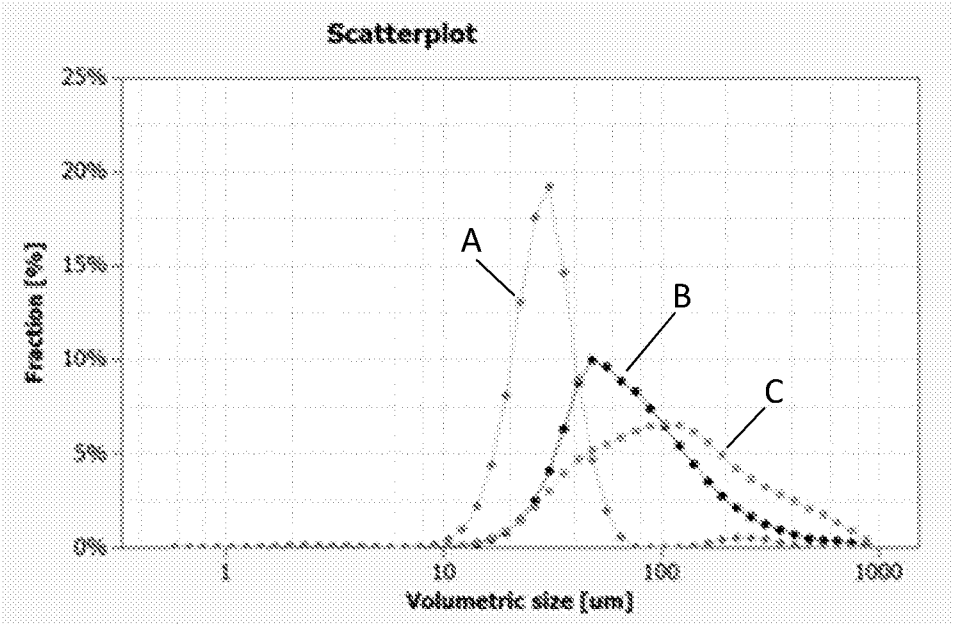

Fig. 3

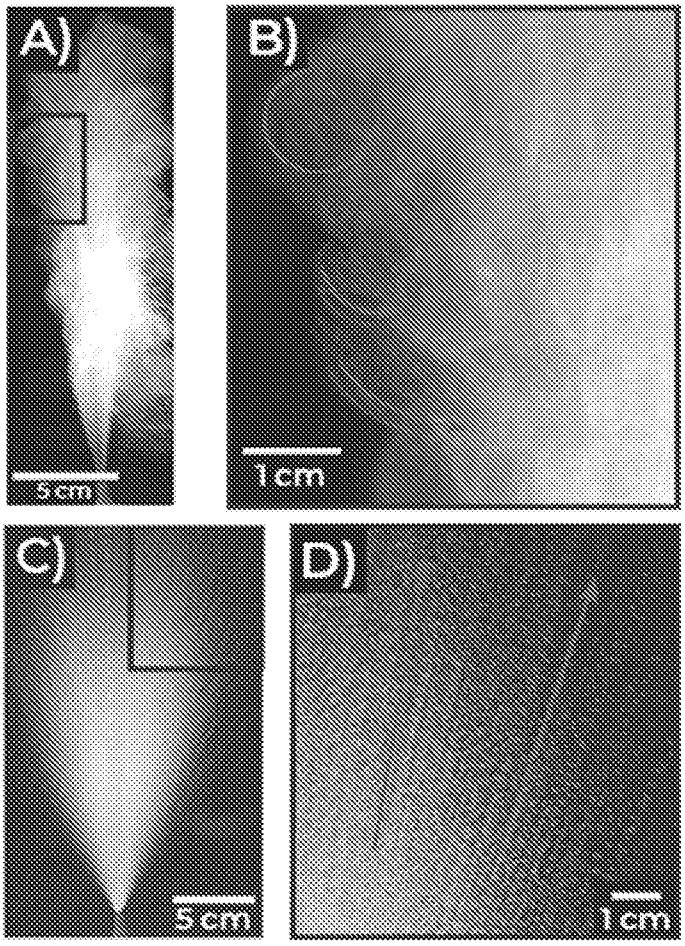

Fig. 4

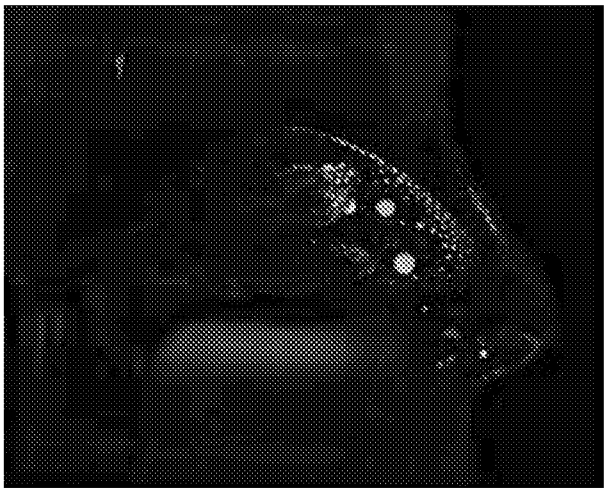

Fig. 5A

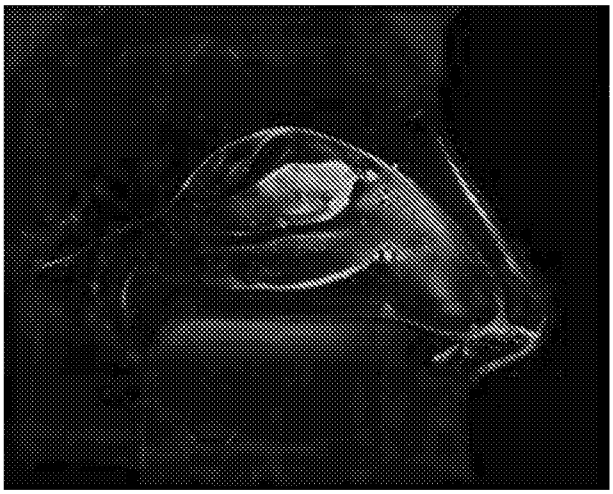

Fig. 5B

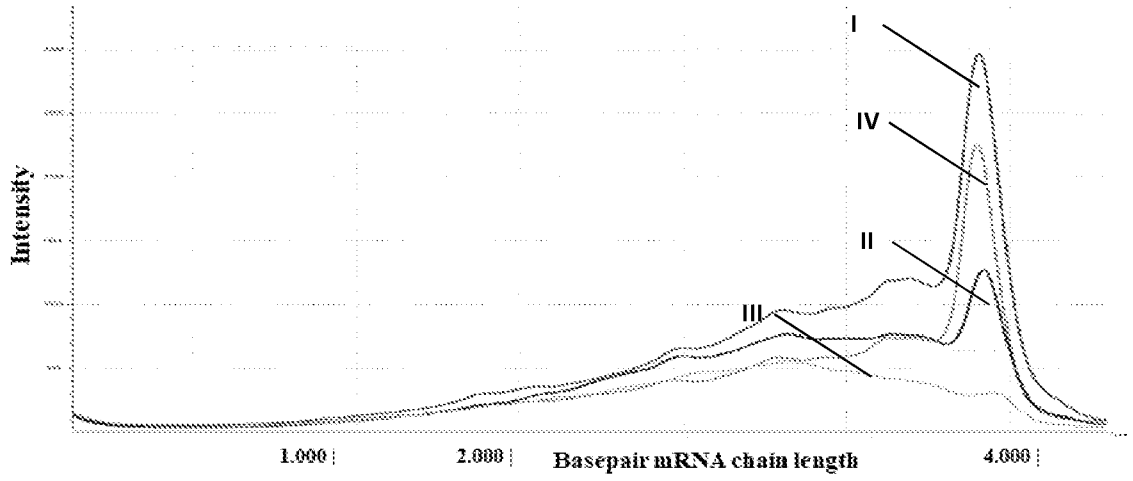

Fig. 6

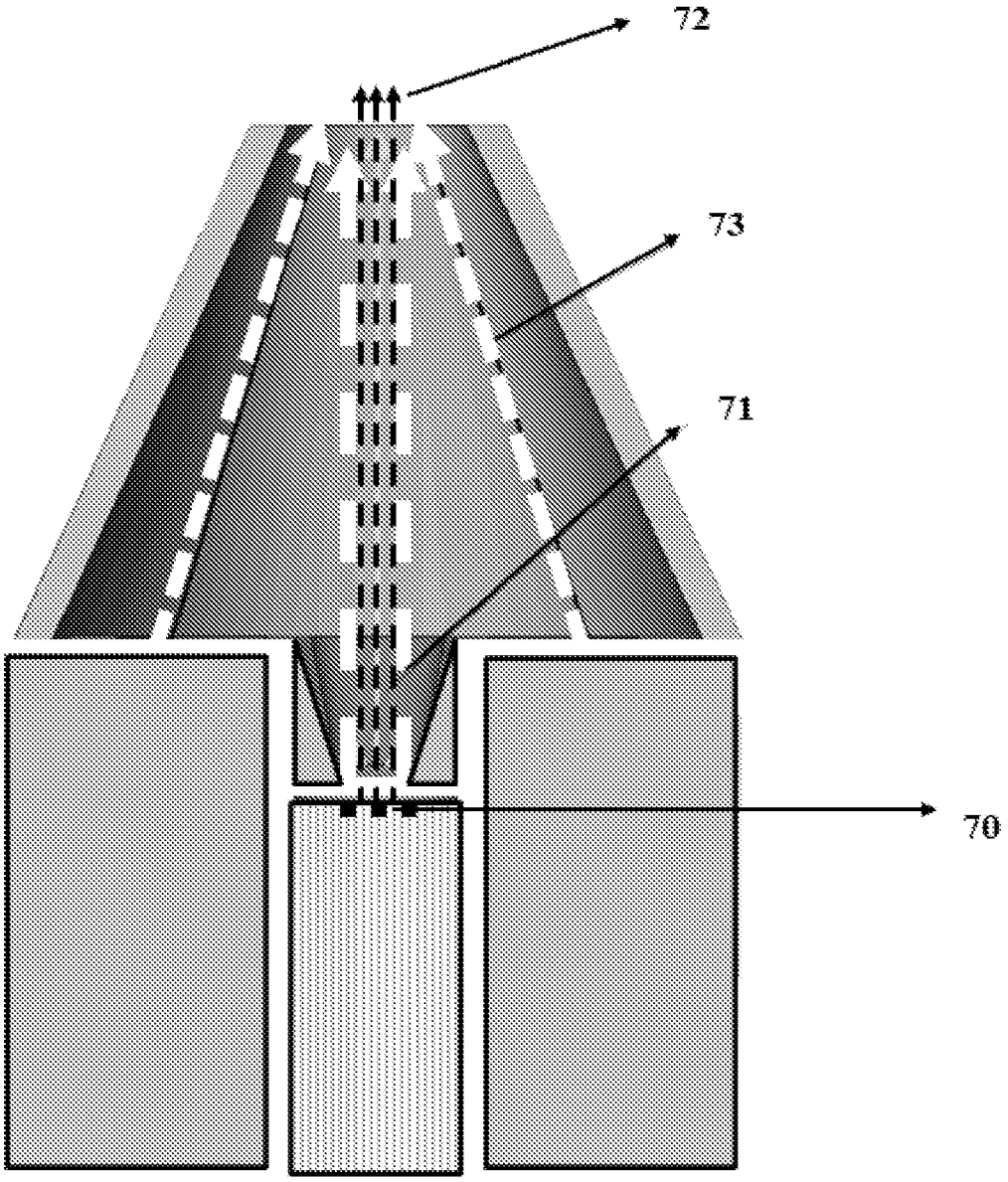

Fig. 7

SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE	KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
Nederlands aanvraag nr. **2031214**	Indieningsdatum **09-03-2022**
	Ingeroepen voorrangsdatum
Aanvrager (Naam) **Medspray B.V.**	
Datum van het verzoek voor een onderzoek van internationaal type **02-07-2022**	Door de Instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr. **SN81561**

I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven)

Volgens de internationale classificatie (IPC)

Zie onderzoeksrapport

II. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimumdocumentatie

Classificatiesysteem	Classificatiesymbolen
IPC	**Zie onderzoeksrapport**

Onderzochte andere documentatie dan de minimum documentatie, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

III.	☐	**GEEN ONDERZOEK MOGELIJK VOOR BEPAALDE CONCLUSIES**	(opmerkingen op aanvullingsblad)
IV.	☐	**GEBREK AAN EENHEID VAN UITVINDING**	(opmerkingen op aanvullingsblad)

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2031214

A. CLASSIFICATIE VAN HET ONDERWERP
INV. A61M11/00 A61M15/06
ADD.

Volgens de Internationale Classificatie van octrooien (IPC) of zowel volgens de nationale classificatie als volgens de IPC.

B. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte miminum documentatie (classificatie gevolgd door classificatiesymbolen)
A61M

Onderzochte andere documentatie dan de mimimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden)
EPO-Internal, BIOSIS, WPI Data

C. VAN BELANG GEACHTE DOCUMENTEN

Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	**WO 2019/190316 A1 (MEDSPRAY B V [NL])** **3 oktober 2019 (2019-10-03)** *** samenvatting *** *** bladzijde 1, alinea 2 *** *** bladzijde 10, alineas 2, 3 *** *** bladzijde 12, alinea 2 *** *** bladzijde 13, alinea 1; conclusies 1-27;** **figuur 1 ***	**1-20**

-/--

[X] Verdere documenten worden vermeld in het vervolg van vak C.

[X] Leden van dezelfde octrooifamilie zijn vermeld in een bijlage

° Speciale categorieën van aangehaalde documenten

"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft

"D" in de octrooiaanvrage vermeld

"E" eerdere octrooi(aanvrage), gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven

"L" om andere redenen vermelde literatuur

"O" niet-schriftelijke stand van de techniek

"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur

"T" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bezwarend is voor de octrooiaanvrage, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding

"X" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur

"Y" de conclusie wordt als niet inventief beschouwd ten opzichte van de combinatie van deze literatuur met andere geciteerde literatuur van dezelfde categorie, waarbij de combinatie voor de vakman voor de hand liggend wordt geacht

"&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie

Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid	Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type
21 oktober 2022	

Naam en adres van de instantie	De bevoegde ambtenaar
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	**Weijland, Albert**

1

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2031214

C.(Vervolg). VAN BELANG GEACHTE DOCUMENTEN

Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
A	THIAGO C. CARVALHO ET AL: "The function and performance of aqueous aerosol devices for inhalation therapy", JOURNAL OF PHARMACY AND PHARMACOLOGY : JPP, deel 68, nr. 5, 8 april 2016 (2016-04-08), bladzijden 556-578, XP55730729, GB ISSN: 0022-3573, DOI: 10.1111/jphp.12541 * het gehele document *	1-20
A	PER G DJUPESLAND ET AL: "The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview", THERAPEUTIC DELIVERY, deel 5, nr. 6, 1 juni 2014 (2014-06-01), bladzijden 709-733, XP55605330, GB ISSN: 2041-5990, DOI: 10.4155/tde.14.41 * het gehele document *	1-20

Formulier PCT/ISA/201 (vervolg tweede blad) (Januari 2004)

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Informatie over leden van dezelfde octrooifamilie

Nummer van het verzoek om een onderzoek naar de stand van de techniek

NL 2031214

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)	Datum van publicatie
WO 2019190316 A1	03-10-2019	CN 112165967 A	01-01-2021
		EP 3773832 A1	17-02-2021
		ES 2908151 T3	27-04-2022
		US 2021008577 A1	14-01-2021
		WO 2019190316 A1	03-10-2019

WRITTEN OPINION

File No.	Filing date *(day/month/year)*	Priority date *(day/month/year)*	Application No.
SN81561	09.03.2022		NL2031214

International Patent Classification (IPC)
INV. A61M11/00 A61M15/06

Applicant
Medspray B.V.

This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the application
- ☐ Box No. VIII Certain observations on the application

	Examiner
	Weijland, Albert

Application number

WRITTEN OPINION

NL2031214

Box No. I Basis of this opinion

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the application as filed.

   ☐ filed together with the application in electronic form.

   ☐ furnished subsequently for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	2, 5-7, 9, 11, 12, 14, 15, 17-20
	No:	Claims	1, 3, 4, 8, 10, 13, 16
Inventive step	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION

Box No. VII Certain defects in the application

see separate sheet

The following documents (D) are referred to in this opinion; the numbering will be adhered to the rest of the procedure:

D1: WO2019/190316

SECTION V

1. Novelty

1.1 Claims 1, 3, 4, 8, 10, 13 and 16 are anticipated by D1 and are therefore not novel.

D1 (abstract; page 1, second paragraph; page 10, second and third paragraphs; page 12, second paragraph; page 13, first paragraph; claims 1 to 27; Figure 1) describes a spray device having a spray nozzle unit and a spray nozzle body, wherein a spray nozzle boy comprises a chamber for receiving pressurized fluid ("doseerkamer", "medische spuit" according to claims 3 and 4). A micro jet spray consists of a number of concurrently emitting jets, in which each jet will break up into a mono-disperse primary droplet train according to the Raleigh breakup mechanism ("Raleigh jets" according to claims 10, 16). Said chamber is bounded by a spray wall having at least one orifice ("sproeikop" according to claim 1) that opens to an external environment, which has an identical predetermined size, within a range. The spray nozzle unit comprises a further second spray nozzle body within a further spray wall with a further spray orifice in a further predetermined range. The orifices can have a size between 0.5 and 2 micron ("kleiner dan 3 micron" according to claim 13) or on average 7.5 micron ("kleiner dan 8 micron" according to claims 1, 16) and can be flavoured for the nose ("neusspray inrichting" according to claim 1) and or mouth. Nozzle bodies can be made of glass, metals and ceramic ("keramische laag" according to claim 1). The plungers 43, 53 will advance over an axial stroke and are expelling the fluid ("vloeibare formulering" according to claim 1) out of the syringe. On a push button or other activation a number of cycles is delivered by the motor for the desired doze. The pressure is between 10 and 20 bar ("tussen 5 en 15 bar" according to claims 1, 16) in order to allow both spray nozzle units to deliver a fine mist ("aerosol spray" according to claim 1) of precisely determined droplets. A motion motor 61 is being used and a back stroke is imposed on the plungers at the end of the dosing, in order to secure a sudden drop ("drukloos" according to claim 1) or rise in pressure.

1.2 Claims 2, 5, 6, 7, 9, 11, 12, 14, 15, 17 to 20 are novel.

2. Inventive Step

Dependent claims 2, 5, 6, 7, 9, 11, 12, 14, 15, 17 to 20 do not appear to contain any additional features which, in combination with the features of claims 1 and 16 to which they refer, meet the requirements with respect to inventive step, since they can be considered as mere alternatives without resulting in any unexpected effect whatsoever.

Dependent claims 2, 5, 6, 7, 9, 11, 12, 14, 15, 17 to 20 are obvious for a person skilled in the art.

SECTION VII

3. Two part form and reference signs

3.1 Two part form

Independent claims 1 and 16 are not in the two-part form, which in the present case would be appropriate, with those features known in combination from the prior art being placed in the preamble and the remaining features being included in the characterising part.

3.2 Reference signs

The features of the preamble of the claims should also be provided with reference signs in parentheses.