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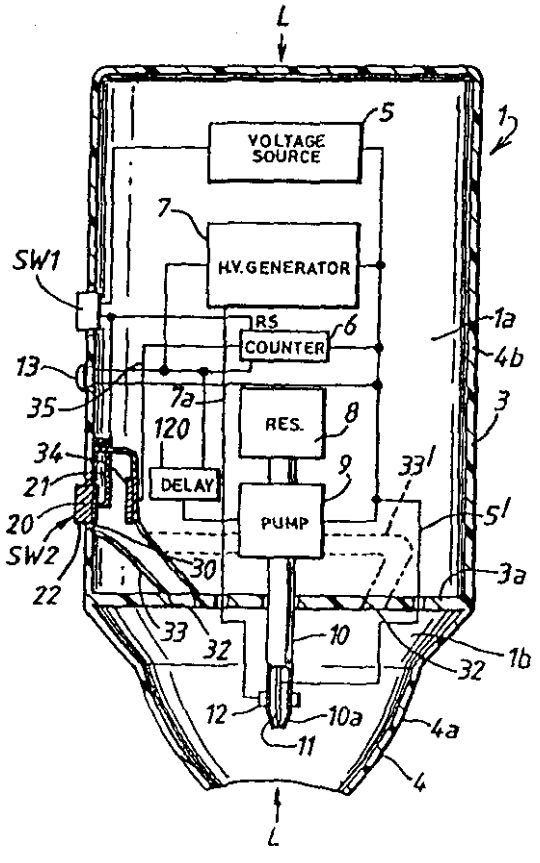
(54) Title: A NASAL INHALER

(57) Abstract

An inhaler has a housing containing a chamber (1a) providing a reservoir (8) for liquid providing an active ingredient to be supplied to a liquid outlet (10a). First and second electrodes are spaced apart (11 and 12) with the first electrode being provided at or adjacent the liquid outlet (10a). A voltage supply (5, 7) is activated in response to air flowing through an air inlet (30) of the housing to provide a potential difference between the first and second electrodes (11 and 12) to create an electric field for causing comminution of liquid issuing from the liquid supply outlet (10a) to produce a stream of electrically charged comminuted matter for supply to the nasal passages of a user via an outlet (4) of the housing.



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A NASAL INHALER

This invention relates to an inhaler for enabling delivery of an active ingredient to the nasal passages.

Conventionally, nasal inhalers are used for the supply of decongestants such as oxymetazoline and the like. The nasal passages are also a good way of supplying drugs and other medicaments into the bloodstream for treatment of ailments which are not specific to the nasal passages.

Conventional hydraulic/pump action nasal inhalers fire or eject large droplets of liquid into the nose. These droplets are polydispersed, that is they have a broad spectrum of sizes. The deposition of such droplets is primarily due to their own inertia which can lead to a very patchy distribution of the liquid. Indeed excessive deposition in one region can lead to the droplets coalescing and flowing out of a nostril or down the back of the throat which can cause an unpleasant taste or, worse, lead to detrimental side effects as a result of the drug being delivered to the digestive or pulmonary system.

It is an aim of the present invention to provide a device which enables satisfactory and efficient supply of

a substance such as a medicament or other active ingredient to the nasal mucosa avoiding deposition in non-target regions such as the lungs or the stomach.

A process for producing comminuted matter known as electrohydrodynamic comminution is described in detail in, for example, GB-A-1569707. In this process, a dispersed spray or cloud of comminuted matter such as liquid droplets which are all of substantially the same size (monodispersed) is produced by subjecting liquid emerging from an outlet to an electric field.

The device described in GB-A-1569707 is large, produces highly charged droplets and is intended primarily for spraying of crops.

Inhalers have been proposed that exploit electrohydrodynamic comminution because they have the advantage, unlike conventional inhalers, of producing a monodispersed (substantially all the same size) mist or cloud of droplets so that the droplets may be targeted more accurately. However, because the conventional wisdom is that it is difficult, if not impossible, to spray electrically charged material into a cavity, previous attempts at producing inhalers using electrohydrodynamic techniques require that the comminuted matter be electrically discharged before

inhalation. For example, EP-A-0234842 teaches that it is necessary to discharge the resulting comminution before inhalation to prevent it being deposited only on the wet conductive surfaces immediately inside the mouth or throat.

The present inventors have, surprisingly, found that, by a combination of electrohydrodynamic, discharging or partial discharging techniques and aerodynamic forces on the resultant comminution, an inhaler can be provided which generates by electrohydrodynamic means electrically charged comminuted matter which can be inhaled so as to deposit evenly onto the conductive inner surface of the nasal passages from whence an active ingredient carried by the comminution can be rapidly absorbed into the bloodstream without being inhaled into the pulmonary system.

In one aspect, the present invention provides an inhaler having electrohydrodynamic comminution means arranged to be activated by inhalation by a user, which facilitates entrainment of electrically charged comminuted matter into the air flow and thence into the nasal passages of the user.

In one aspect the present invention provides an inhaler having electrohydrodynamic comminution means with

the electrode or electrodes of the comminution means being shielded from the user so that the user cannot make direct electrical contact with the electrodes.

In one aspect the present invention provides an inhaler wherein the material to be inhaled is electrohydrodynamically produced and the electrical charge and/or size of the comminuted material, generally droplets, are/is controlled so that the material can be deposited evenly into the nasal passages but supply to the pulmonary system or the back of the throat is prevented, thereby enabling the inhaler to be used for the supply to the nasal passages of medicaments which may produce unpleasant or undesirable effects if they were supplied to the pulmonary or digestive system.

In one aspect the present invention provides an inhaler having a supply of liquid carrying an active ingredient, means for supplying the liquid to an outlet and means for subjecting liquid issuing from the outlet to an electrical field sufficient to cause comminution of the liquid to produce electrically charged comminuted matter for inhalation by the user, the liquid or liquids being selected so as to control the manner in which active ingredient in the electrically charged comminuted matter is released when the electrically charged

comminuted matter is deposited in the nasal passages. The liquid may be an oil or alcohol-based formulation allowing rapid supply of the active ingredient into the bloodstream via the surfaces of the nasal passages. As another possibility, the liquid may be such that the resulting comminuted matter has a gel-like structure enabling continued release of the active ingredient.

In one aspect the present invention provides an inhaler having means for subjecting liquid issuing from an outlet to an electric field sufficient to cause comminution of the liquid and means for causing electrically charged comminuted matter to be deposited onto the surfaces of the nasal passages. The latter means may comprise means for causing or facilitating an air flow through the inhaler which entrains the charged comminuted matter. Such an air flow may be generated by inhalation by a user, by artificial means such as a pump or a combination of both of these.

In one aspect, the present invention provides an inhaler having comminution means arranged to provide an electric field which has a strength which reduces rapidly in the direction of liquid flow from liquid supply means enabling liquid comminuted by the electric field to be easily entrained in an air flow path from the inhaler

into a nostril of a user during use.

In one aspect, the present invention provides an inhaler having means for supplying liquid to an outlet and means for subjecting liquid issuing from the outlet to an electrical field sufficient to cause comminution of liquid issuing from the outlet, and means for generating an electrical potential at the one of the first and second electrodes most remote from the liquid outlet, said means for generating the electrical potential comprising means for generating an ion current for indirectly charging said one electrode.

In this aspect, the ion current generating means may comprise a further electrode located adjacent the one electrode and means for providing a high resistance path to earth from said one electrode. The high resistance path to earth may be provided by an actual resistor in series with said one electrode or, for example, a resistive or semiconductive coating on said one electrode. Indirect charging of said one electrode reduces the possibility of deposition of comminuted matter onto said one electrode because any electrically charged comminuted matter which approaches said one electrode will be at least partially electrically discharged by the generated ions. Furthermore, a more

even deposition or greater penetration within the nasal passages should be achieved because of the at least partial discharge of some of the comminuted matter by the ion generating means.

In one aspect, the present invention provides an inhaler having means for supplying liquid to a comminution site and electrical current limiting means for limiting the supply of electrical current to the comminution site. The current-limiting means may comprise a dielectric or semi-insulating coating or sleeve or a high resistance coupled in the path from a high capacitance high voltage source to an electrode. Otherwise, a low capacitance high voltage source, such as a piezoelectric voltage source, may be used.

In one aspect, the present invention provides an inhaler capable of supplying opposite polarity comminutions to the nasal passages.

In one aspect, the present invention provides a dispensing device, which may be an inhaler, having means for supplying liquid to an outlet, means for subjecting liquid issuing from the outlet to an electrical field sufficient to cause comminution of liquid issuing from the outlet and means for controlling the size of individual elements of the comminuted matter, for example

droplets, in the resulting comminution.

Embodiments of the present invention will now be described, by way of example, with reference to the accompanying drawings, in which:

Figure 1 illustrates schematically use of an inhaler in accordance with the present invention;

Figure 2 shows a diagrammatic, part-cross-sectional view of an embodiment of an inhaler in accordance with the present invention;

Figure 3 shows a block schematic electrical diagram for the inhaler shown in Figure 2;

Figure 4 shows a part-cross-sectional view, on an enlarged scale, of part of the inhaler shown in Figure 2 to show one example of an electrohydrodynamic comminution site for the inhaler shown in Figure 2;

Figure 5 shows a part-cross-sectional view, on an enlarged scale, of part of the inhaler shown in Figure 2 to show another example of an electrohydrodynamic comminution site for the inhaler shown in Figure 2;

Figure 6 shows a part-cross-sectional view, on an enlarged scale, of part of a further embodiment of an inhaler in accordance with the present invention;

Figure 7 shows a part-cross-sectional view, on an enlarged scale, of part of another embodiment of an

inhaler in accordance with the present invention;

Figure 8 shows very schematically another example of an inhaler embodying the present invention using a compressed airflow for activation;

Figures 9a to 9d show droplet spectrums with Figure 9a showing a droplet spectrum for an inhaler embodying the invention and Figures 9b to 9d showing droplet spectrums for various forms of conventional inhaler;

Figure 10 shows a diagrammatic part cross-sectional view similar to Figure 2 of another embodiment of an inhaler in accordance with the present invention;

Figure 11 shows a diagrammatic part cross-sectional view similar to Figure 2 of another embodiment of an inhaler in accordance with the present invention;

Figure 12 shows, on an enlarged scale, part of the inhaler shown in Figure 2 to illustrate a modification thereof;

Figure 13 shows very schematically a further modification of an embodiment of an inhaler in accordance with the present invention;

Figure 14 is a diagram for illustrating the operation of an inhaler having the modification shown in Figure 13;

Figure 15 shows a part cross-sectional enlarged view

of part of another embodiment of an inhaler in accordance with the invention; and

Figure 16 shows a part cross-sectional enlarged view of part of another embodiment of an inhaler in accordance with the invention.

As illustrated schematically in Figure 1, an inhaler 1 embodying the invention is intended primarily for use as a pocket-sized, hand-held device which is actuated by a user to enable delivery of an active ingredient, drug or active ingredient into the nostril of the user. For example, the inhaler may be arranged to deliver a decongestant such as oxymetazoline to the nasal passages or to deliver drugs or other medicaments such as insulin or triptans (for example Elitriptan) into the bloodstream via the nasal mucosa. The inhaler may also be used to deliver flu vaccines such as Flumist (a product being developed by Aviron of Mountain View, California, USA) which is arranged to be effective in the relatively low temperature environment of the nasal mucosa.

The inhaler 1 comprises a housing 3. The housing may be made mainly of electrically insulative material such as a plastics material although at least a part of the housing that a user will inevitably touch in use provides an electrically conductive region that enables,

as will be described below with reference to Figures 2 and 3, an earth connection via the user. The inhaler has an outlet 4 through which liquid droplets to be inhaled are supplied to the user. The outlet 4 is sized and shaped so as to fit snugly against or slightly into the user's nostril so as to make a reasonably air-tight seal. The outlet may be detachable from the housing to allow different sized and shaped outlets to be used so as to enable a snug fit to different sizes of nostrils to enable, for example, use by both adults and children. Although a snug fit is desirable from the viewpoint of efficiency, in practice, it may be sufficient for the inhaler to be placed in close proximity to a nostril.

The inhaler 1 is rotationally symmetric about its longitudinal axis so as to be generally cylindrical. Typically, the housing will be about one inch (25.4mm) diameter and about 4 to 5 inches (102 to 127mm) in length.

Figure 2 illustrates a part sectional view through one example of an inhaler embodying the invention, while Figure 3 shows a block circuit diagram of components of the inhaler.

As shown in Figure 2, the housing 3 of the inhaler 1 has an internal wall 3a which divides the housing into

first and second chambers 1a and 1b.

In this example, the first chamber accommodates a voltage source 5 in the form of a battery. As shown most clearly in Figure 3, the positive terminal of the battery 5 is connected via a user-operable switch SW1 to a reset input of a counter 6 and to a further switch SW2. Although not shown in Figure 2, the negative terminal of the battery 5 is also connected to the electrically conductive region of the housing mentioned above so, as shown schematically in Figure 3, the user H provides a path to earth (ground). The switch SW1 is a conventional manually operable switch such as, for example, a toggle or push switch. The switch SW2 is arranged to be activated by airflow and will be described in greater detail below. A high voltage generator 7 is coupled to the battery 5 via the switches SW1 and SW2 and a counter 6 which is arranged to be reset by closure of the switch SW1 and which outputs the battery voltage to the high voltage generator positive voltage input until a predetermined count is reached when the output of the counter goes low. The high voltage generator may be a conventional electromagnetic high voltage multiplier of the type supplied by Brandenburg, Astec Europe, of High Street, Wollaston, Stourbridge, West Midlands DY8 4PG,

UK, or Start Spellman of Unit 1, Broomers Park, Broomers Hill Lane, Pulborough, West Sussex RH20 2RY, UK. As an alternative, a piezoelectric high voltage source which has a low capacitance may be used.

The first chamber 1a also contains a reservoir 8 for the liquid to be dispensed by the inhaler. The reservoir may be formed as a flexible collapsible bag or bellows - type arrangement having a chemically inert interior surface. Alternatively, a piston-like arrangement may be used so that as the liquid is used up, the piston moves with the liquid surface in the chamber so avoiding the possibility of air coming into contact with the liquid in the reservoir. A pump 9 is provided to pump liquid from the reservoir 8 to a liquid supply outlet pipe 10. The pipe is made of an insulating material which does not retain charge for any significant length of time. A suitable material is, for example, polyacetyl or Delrin (Trademark).

The liquid supply pipe 10 has an outlet nozzle 10a. A conductive core or rod 11 provided within the liquid outlet pipe terminates adjacent the nozzle outlet 10a and provides a first electrode. In this example, the first electrode 11 is coupled to the negative or earth terminal of the battery 5 via line 5'.

The outer surface of the insulative supply pipe 10 carries a second electrode 12 (see Figure 4) extending around the pipe 10. The second electrode 12 is located so as to be upstream of the tip 11a of the first electrode in the direction of the liquid flow through the liquid supply pipe 10. The first electrode 11 may, as shown, be pointed.

In this example, the second electrode 12 comprises a coated electrode having a central conductive core 12a which is coupled to a high voltage output 7a of the high voltage generator 7 and is encased in a dielectric or semi-insulating coating or sleeve 12b. Such a coated electrode is described in, for example, EP-A-0186983. The coating or sleeve may have a resistivity within the range 5×10^{11} to 5×10^{13} Ω cm and a thickness of approximately 2 mm. Suitable coatings are certain grades of sodaglass and phenolformaldehyde/paper composites. Kite brand tubes supplied by Tufnol Limited of Birmingham, England or Paxoline may be used. The core may be formed of, for example, beads of carbon tightly packed within the coating 12b. The coating should have a time constant or relaxation time over which it leaks or conducts charge of, typically, approximately 10^{-5} seconds. The second electrode 12 may, however, be uncoated.

As can be seen from Figure 2, the first and second electrodes 11 and 12 are located well within the electrically insulative housing 4 so that the portion 4a of the housing defining the chamber 1b shields the user from the electrodes so that direct contact by the user with the electrodes is avoided. The outlet 4 is sized so as to prevent a user inserting a finger into the chamber 1b. Also, although an electrical shorting is extremely unlikely, this would occur between the first and second electrodes and so would not subject the user to an electrical shock.

The pump 9 is an electrically operated pump and may be, for example, a piezoelectric pump or any other suitable form of electrically or mechanically operated pump. The pump 9 is coupled to the positive terminal of the battery 5 via the switches SW1 and SW2, and the counter 6. A delay circuit 120, for example a conventional capacitor- resistor (CR) network, may be provided between the counter 6 output and the pump so that supply of the voltage necessary to activate the pump 9 is delayed until an electric field sufficient to cause electrohydrodynamic comminution of liquid supplied to the nozzle 10a has been established between the first and second electrodes.

The output of the counter 6 is also supplied, as shown in Figure 3, to an indicator light or buzzer 13.

As shown in Figure 2, the air flow activated switch SW2 comprises a first electrical contact 20 mounted on a spring biassing arm 21 secured to the inner wall of the

housing chamber 1a. The switch SW2 has an outer insulative body 22 which is caused by the spring biassing member 21 to block an air inlet 30 provided in the housing 3. An air path from the air inlet 30 to an aperture 32 in the partition member 3a is defined by an insulative tubular body 33. An inner wall of the insulative tubular body 33 carries a further electrical contact 34 coupled via conductor 35 to the positive power supply terminal of the high voltage generator 7.

The air path tube 33 may be modified so as to provide air paths 33' coupling to two or more apertures 32 provided in the partition member 3a and evenly distributed about the longitudinal axis L as shown in dashed lines in Figure 2.

To use the inhaler 1, a person first inserts the outlet 4 into or places the outlet snugly against a nostril and then manually actuates the switch SW1 which couples the reset terminal of the counter 6 to the positive supply of the battery 5 and so resets the count of the counter. The user then inhales through their nose as they would if using a conventional inhaler. The air flow resulting from the user inhaling thus causes the contact 20 of the switch SW2 to be moved towards the contact 34 against the biassing force of the spring member 21. Once the contacts 20 and 34 of the switch SW2 make contact, power is supplied to the high voltage generator 7 which supplies the required high voltage, typically 3 to 12 kV (kilovolts) to the second electrode 12 so as to establish the necessary electric field

between the first and second electrodes 11 and 12 to provide the electrohydrodynamic comminution site. Once this electric field has been established, the delay circuit 120 provides the necessary electrical power to the pump 9 which then pumps liquid from the reservoir to the outlet nozzle 10a.

Liquid issuing from the outlet nozzle 10a is electrohydrodynamically comminuted. The separation of the first and second electrodes 11 and 12 in the radial direction (that is perpendicular to the longitudinal axis L) can be relatively small (typically about 1cm) because the coating on the second electrode enables the two electrodes to be close together whilst suppressing any electrical breakdown of the air in between. This relatively small separation results in a very high strength electric field which drops off or reduces rapidly in the longitudinal direction L. This facilitates entrainment of the resulting charged comminuted matter in the air flow through the tube 33 to the output 4 so reducing the possibility of the electrically charged matter depositing on the inner wall of the chamber 1b.

Comminuted matter then issues from the nozzle 4 and is deposited uniformly onto the conductive surface inside the nasal passages.

When a predetermined time since activation of the switch SW1 has passed, that is when the predetermined count is reached, the output from the counter 6 goes low switching off the high voltage generator 7, the pump and

the light or buzzer 13. After use, the user then can disable the device by pressing the switch SW1 again to disconnect the voltage source 5.

The counter 6 thus enables the user to be advised when the required dose of medicament has been delivered.

The coating or sleeving of the electrode 12 provides a current limiting effect to prevent excessive or dangerous currents from passing between it and the first electrode 11.

Figure 5 shows a modification in which the insulative liquid supply pipe and conductive core 10 and 11 of Figure 2 are replaced by a hollow electrically conductive capillary tube pipe 14 which provides both the first electrode and the outlet 14a. In this case, the second electrode 12 is a discrete uncoated electrode provided on the inner wall of the first chamber so as to be disposed downstream of the end of the first electrode 14 in the direction of liquid flow through the conductive pipe 14. As shown in Figure 5, the inhaler has an air supply pipe outlet 33" (which may be an extension of the pipe 33' shown in dashed lines in Figure 2) which causes, in use, an air curtain to be provided in front of the electrode to inhibit deposition of droplets on the electrode 12. This modification may also be made in the arrangement shown in Figure 2. Although shown as a discrete uncoated electrode, the second electrode 12 may in this case comprise an annular slot electrode or a number of individual electrodes distributed around the inner periphery of the wall of the second chamber 1b.

Also, the electrode 12 may be coated as described with reference to Figure 4 and may be positioned slightly upstream or adjacent the first electrode. In this case, when an electrical field sufficient to cause electrohydrodynamic comminution is established between the first and second electrodes 14a and 12, multiple jets or cones will generally be formed at the end of the conductive pipe 14.

In use, satellite droplets are sometimes produced during the electrohydrodynamic comminution. These satellite droplets will not generally present a problem and will normally deposit onto the interior surface of the inhaler or the second or counter electrode. However, if the inhalers described above are used frequently over an extended period of time, the build-up of droplets and/or residue resulting from subsequent evaporation of the droplets may adversely affect the operation of the counter electrode 12 so reducing the overall efficiency of the device. One way to avoid this problem is to design the inhaler body so that, for example, the portion 4a of the housing defining the chamber 1b can be removed (for example the housing portion 4a may be connected by screw-thread connected to the housing portion 4b) to enable a user to wipe the counter electrode to remove deposited droplets or other matter. An alternative, automatic means of maintaining the operational function of electrode 12 is described below.

Figure 6 shows a part-cross-sectional view of mainly the lower chamber 16 of another inhaler embodying the

invention. The internal construction of the upper chamber 1a is essentially the same as that described above with reference to Figure 2.

In Figure 6, the counter electrode 12' is mounted to the inner wall 1b' of the lower chamber 1b. The counter electrode 12' may be annular or may be formed by a discrete single point electrode or a number of separate electrically connected electrodes spaced apart around the wall 1b'.

The counter electrode 12' is, in this example, an uncoated electrically conductive electrode which is coupled via wire 50' and a resistor R to the conductor 5' which is coupled to the negative or earth terminal of the voltage source 5.

A further electrode 120 is mounted in a conventional manner (not shown) in the lower housing 1b so as to be considerably closer to the counter or second electrode 12 than to the first electrode 11. Typically, for the dimensions given above for the inhaler, the electrode 120 may be 2mm from the counter electrode 12' and 5mm from the first electrode 11. The counter electrode 120 is coupled via the conductor 7a to the high voltage output of the high voltage generator 7 (not shown in Figure 6).

When an inhaler having the structure shown in Figure 6 is used, the high voltage applied to the electrode 120 causes ions to be generated by corona discharge from the electrode 120. These ions migrate to the closest conductive body - in this case the counter electrode 12' - so providing an ion current to

earth via the counter electrode 12' and the resistor R which may, typically, have a value of 600 megaohms. This enables the counter electrode 12' to be indirectly charged to the required electrical potential. Any charged comminuted matter issuing from the nozzle 10a which is inadvertently attracted toward the counter electrode 12' will be at least partially electrically discharged by the ion current generated by the ion generating electrode 120 so reducing the likelihood of the charged matter depositing onto the counter electrode 12' and obviating the need for a user to wipe the counter electrode periodically.

Figure 7 illustrates a modification of the arrangement shown in Figure 6 in which the resistance provided by the coating of the counter electrode 12" is sufficient to enable the required electrical potential to be achieved at the counter electrode 12" without the need for the resistor R. In other respects, the arrangement shown in Figure 7 operates in the same manner as the arrangement shown in Figure 6.

Although Figures 6 and 7 show only one ion generating electrode 120, a plurality of ion generating electrodes 120 may be provided around the liquid supply pipe. As another possibility, the ion generating electrode may be provided by a knife edge or wire surrounding the liquid supply pipe.

It has been found that the arrangements shown in Figures 6 and 7 enable a more even distribution of comminuted matter to a greater depth within the nasal

passages; thus improving the uniformity of droplet distribution still further. This is believed to arise because electrically charged comminuted matter which comes into the vicinity of the ion injecting electrode 120 will have been at least partially electrically discharged so that some of the comminuted matter which is inhaled will be less highly charged and will therefore have a tendency to be deposited further into the nasal passages.

The air flow path in Figures 6 and 7 may be modified as described above with reference to Figure 5 to provide the second electrode with a protective air curtain.

In the arrangements described above, the airflow switch SW2 is activated by the user inhaling. It is, however, possible that the user may be so frail that they are not capable of inhaling sufficiently strongly to activate the switch SW2. In such a case, the inhaler may be provided, as shown in Figure 8, with an adaptor 100 which couples around the area of the switch SW2 and can be connected via a pipe 101 to a manually actuable device 102 such as a bladder or bellows which can be squeezed by the patient or another person such as a doctor, nurse or carer to force a flow of air to open the air inlet 30 and close the switch SW2 or to a pressurised air or gas bottle or a compressor which may be electrically operated to supply air at the desired flow rate down the pipe to the air inlet 30.

Figures 9a to 9d show experimental droplet spectra produced using a Malvern Mastersizer X manufactured by

Malvern Instruments of Malvern, UK. Figure 9a shows a typical droplet spectrum produced using a device of the type shown in Figure 1. As can be seen from Figure 9a, the medium particle or droplet diameter is around 10 μm which is at the lower end of desirable droplet diameters for nasal delivery. Figures 9b to 9d show the equivalent droplet spectra produced by three commercially available nasal inhalers with Figure 9b showing the droplet spectra produced by an "Otravine" (Registered Trade Mark) nasal inhaler which comprises a squeezable plastic bottle supplying xylometazoline hydrochloride as a nasal decongestant and is supplied by Novartis Consumer Health of Horsham RH12 4AB, UK, Figure 9c showing the droplet spectra for a "Flixonase" nasal inhaler and which uses a metering valve and a pressurised reservoir and which supplies fluticasone propionate and is supplied by Allen & Hanburys of Stockley Park, Middlesex UB11 1BT, UK and Figure 9d showing the droplet spectrum output by a "Beconase" pump action nasal inhaler which comprises beclomethasone dipropionate and is also supplied by Allen & Hanburys. As can be seen from a comparison of Figures 9b to 9d with Figure 9a, the three conventional inhalers produce a larger range of particle or droplet diameters and control over the droplet sizes is poor in comparison to that achievable with the electrohydrodynamic device shown in Figure 9a. It should also be noted that the conventional inhalers do not charge the droplets and rely on turbulence and inertia alone to deposit the droplets. Furthermore, the performance of conventional propellant

inhalers is very dependent on the air flow in the nasal passages that can be generated by the user.

The operation of the inhaler 1 shown in Figure 1 has been tested on models of the nose and it has been found that the resulting charge sprays deposit evenly over the conductive surface representing the interior of the nose. The liquid used in these experiments had an electrical resistivity of 4500Ωcm, a surface tension of 30mN/m (milli Newtons per metre) and a viscosity of 2.4cP (centipoise) and a voltage in the range of 8 to 12 kV was applied between the first and second electrodes.

The embodiments described above are intended primarily for comminuting liquids of relatively high resistivity such as oils and alcohol. Figure 10 shows a modified version of the inhaler shown in Figure 2 that is suitable for comminuting very electrically conductive liquids such as water and salt solutions.

In the inhaler 300 shown in Figure 10, the air path tube 33 shown in Figure 2 is replaced by an air path tube 330 in the form of a hollow body defining an air channel 330a which extends through an aperture 32 in the wall 3a to terminate in a ring-like nozzle outlet 331 surrounding the outlet nozzle 10a. In all other respects, the inhaler 300 shown in Figure 10 is the same as that shown in Figure 2.

The inhaler 300 operates in the same way as the inhaler 3 shown in Figure 2 apart from one significant aspect. Thus, when a user takes a sharp intake of breath through a nostril using the inhaler 300, a fast moving

stream of air is supplied via the nozzle 331 to the area in which comminution occurs. The air flow from the nozzle 331 acts to shear droplets that are electrohydrodynamically formed from liquid issuing from the outlet nozzle 10a so resulting in droplets that are smaller than they would be without the air flow. This enables the inhaler to be used for conductive liquids such as water and salt solutions which are otherwise difficult to comminute electrohydrodynamically.

Experiments have been carried out using tap water as the liquid to be comminuted with a liquid supply pipe having an outlet nozzle 10a with an internal diameter of 0.2mm and with 2.5 kilovolts applied between the first and second electrodes 11 and 12. The diameter of the tube is selected in accordance with the average expected nasal inhalation rate of a user to provide an air flow rate from the nozzle 331 sufficient to cause shearing, in this example 10m/second. Where the air flows at approximately 20 to 30 litres/minute through a tube which is coaxial with and surrounding the outlet nozzle, then generally the tube outlet should have an area of a few square millimetres so as to be comparable with the air flow impedance provided by the nasal passages.

Droplets having a diameter of approximately 20 micrometers were detected. The droplet charge to mass ratio was determined to be approximately 10^{-4} coulombs/kilogram. The droplets were thus significantly smaller than they would have been without the air flow.

The air flow rate of approximately 10m/second

mentioned above is sufficient to cause shearing and is roughly equivalent to the air flow generated by a relatively healthy person taking a sharp intake of breath.

It will be appreciated that the modification described with reference to Figure 10 may be used in combination with any appropriate ones of the modifications described with reference to any one of Figures 4 to 8 above so that, for example, the counter electrode 12 may be positioned downstream of the first electrode 11 as shown in Figure 5. It will also be appreciated that one, two or more air flow nozzles may be provided in the vicinity of the comminution area or site. All that matters is that a sufficient air flow is achieved at the comminution area or site to cause shearing without causing undue turbulence. In this regard, it will be noted that as shown in Figure 10, the outlet nozzle 331 is directed so as to provide an air flow extending obliquely of the direction in which liquid issues from the outlet nozzle 10a.

Apart from the reasons given in the introduction of this application, a person skilled in the art may have thought that it would be undesirable for the user of an inhaler to inhale charged droplets because the supply of charge to the user would, if the user was not earthed during use of the inhaler, result in a voltage rise of the user which could result in the user experiencing an unpleasant electrical shock when he subsequently was connected to earth.

The present inventors have, however, found that the rise in the voltage of an unearthed user during a single use of an inhaler embodying the invention is not sufficiently large to result in an unpleasant electrical discharge. Also, the amount of charge transferred to the user may, if desired, be controlled to a minimum. This may be achieved by, for example, formulating the liquid carrying the medicament being inhaled with a higher concentration of the active ingredient or medicament in the liquid than is normal with aqueous solutions. Thus a smaller amount of liquid need be inhaled to deliver the required dose. This reduces the overall space charge and facilitates entrainment of the comminuted matter in the air flow through the inhaler. Typically, the concentration may be increased by five fold (say from 10% to 50% by volume of the active ingredient).

If prolonged or continuous treatment is required, then the inhalers described above may be modified to periodically reverse the polarity of the voltage supplied by the high voltage generator so that the user receives droplets of one polarity charge followed by droplets of the opposite polarity charge, thereby inhibiting any significant rise in the voltage of the user. One simple way in which this may be achieved is to use as the high voltage source a piezoelectric generator which is manually activated by the user using a cam and lever arrangement because this automatically provides a polarity reversal with the voltage generated when the crystal is squeezed being of opposite polarity to the

voltage generated when the crystal is released.

In each of the examples described above, the high voltage is applied to the second or counter electrode. However, the second electrode could be omitted and the first electrode charged directly to the required high voltage, especially if a low power, low capacitance, high voltage generator, such as a piezoelectric generator, is used.

Figure 11 shows a diagrammatic part-cross-sectional view similar to Figure 2 of another embodiment of an inhaler in accordance with the present invention where the first electrode is directly charged.

The inhaler 301 shown in Figure 11 has two liquid supply pipes 10 each having an outlet nozzle 10a. The pipe 10 is coupled to a corresponding pump 9 so as to receive liquid from a corresponding reservoir 8. Although not shown explicitly in Figure 11, each pump 9 is coupled between the delay circuit 120 and the negative terminal of the voltage source 5. Each of the liquid supply pipes 10 has supported within it a first electrode 11 in the form of a conductive core. The first electrode 11 of one liquid supply pipe 10 is coupled to the high voltage output of the high voltage generator 7 (not shown in Figure 6). A further high voltage generator 7' providing a high voltage of the opposite polarity, negative in this case, has its high voltage output coupled to the first electrode 11 of the other liquid supply pipe 10. In this case, either the liquid should be sufficiently highly resistive to inhibit the direct charging of the first

electrodes 11 causing a voltage rise at the pump or the pump should be electrically isolated from the liquid.

The air flow path shown in Figure 11 is also different from that shown in Figure 2. Thus, in the inhaler 301 shown in Figure 11, the insulative tubular body 33 of Figure 2 is replaced by an insulative tubular body 333 which passes through the aperture 32 in the wall 3a so as to terminate at an air outlet nozzle 334 which, as shown in Figure 11, is coaxial with and symmetrically disposed between the two liquid outlet nozzles 10a. The inhaler 301 shown in Figure 11 operates in a similar manner to the inhaler shown in Figure 2 with the exception that two opposite polarity sprays or comminutions are produced. The air flow from the air outlet nozzle 334 is sufficient to keep the two opposite polarity comminutions apart so that two opposite polarity comminutions are supplied to the nozzle passages. This has the advantage of enabling charged, comminuted matter to be supplied to the nasal passages without altering the overall charge of the body of the user. Typically, the longitudinal axes of the two liquid supply pipes may be 12 to 15 mm apart.

It should be appreciated that the modifications described with reference to Figure 11 may be used in combination with the modifications described with reference to any one of Figures 4 to 8 above.

In each of the embodiments described above the air flow rate is controlled either by how hard the user sniffs or by, in the case of Figure 8, the operation of

the pump 102. Further control of the air flow rate in any of the above described embodiments may be provided by means of a valve in the air flow path. As an example, Figure 12 shows part of the inhaler shown in Figure 2 with a flap valve or choke 301 pivotally mounted in the air flow path 33. The flap valve may be operable by means of any conventional mechanism, for example, the flap valve may be manually rotatable by a user rotating a knob mounted to the outside of the housing or pivoting movement of the flap valve may be controlled mechanically using a camming arrangement or electromechanically using a camming arrangement and a solenoid, for example, or may be arranged to be present by a doctor, for example. Other conventional forms of valves may also be used.

As described above, the air flow from the outlet nozzle 334 serves to keep the opposite polarity sprays or comminutions apart. The amount by which the opposite polarity comminutions are kept apart, and so a degree of mixing can be controlled by controlling the air flow rate through the pipe 334 by, for example, providing a throttle or like valve in the air flow pipe 334. This air flow valve may be preset by the doctor or at factory level (for example in dependence upon the active ingredient to be delivered by the inhaler), or may be settable by the user. The zone of deposition of the comminuted matter in the nasal passages can be controlled by controlling the overall charge of the comminuted matter supplied to the nostrils of the user so enabling the area to which the active ingredient is to be

delivered to be targeted by adjusting the air flow rate with an air flow control valve.

It will be appreciated that different users or different patients may have different nasal inhalation rates which, with conventional propellant nasal inhalers, would cause the inhaled material to be deposited more deeply into the nasal passages than if the inhaler was being used by a person with a lower nasal inhalation rate. However, the nasal inhaler shown in Figure 11 has the advantage that a person with a rapid nasal inhalation rate will cause a more rapid flow of air from the air outlet nozzle 334 than will a person with a low nasal inhalation rate so that the person with the high nasal inhalation rate will receive more highly charged, less mixed, comminuted matter than the person with the low nasal inhalation rate. As more highly charged matter tends to penetrate less deeply into the nasal passages, the inhaler shown in Figure 11 provides a self-adjusting effect because the tendency of a greater inhalation rate to cause material to be deposited more deeply into the nasal passages is counteracted by the greater charge tending to cause the material to be deposited less deeply into the nasal passages.

In the arrangement shown in Figure 11, the liquid outlets 10a are parallel to one another. However, the liquid outlets may be angled towards one another, for example at 45° to the longitudinal axis L of the inhaler, which may increase the degree of mixing.

The overall charge on the comminuted matter

delivered by the inhaler and thus the depth to which that matter penetrates into the nasal passages may also be controlled by, in addition to or instead of controlling the air flow rate, controlling the relative voltages applied to the two first electrodes by adjusting the voltages supplied by the high voltage generators 7 and 7' and/or by adjusting the relative flow rates of liquid to the outlet nozzles 10a. These adjustments may be adjustments that can be made at factory level so that a single inhaler construction can be adapted within the factory for delivery of different doses (for example for children and adults) of the same active ingredient or to enable the same inhaler to be used to deliver different active ingredients which require different dosages. As another possibility, the voltages supplied by the generators and/or the flow rates may be adjustable by a doctor or nurse under clinical conditions or a pharmacist or the patient or user himself where it is acceptable for the user to control the dose supplied.

As described above, it is assumed that the same liquid is supplied to the two liquid supply pipes 10. If this is the case and relative flow rate adjustment is not required, then a single reservoir 8 and a single pump 9 may be provided. Also, instead of providing separate negative and positive polarity high voltage generators, a single generator providing a high voltage of one polarity to one of the first electrodes 11 may be provided and the other electrode may be connected to earth (ground) so that, in practice, it is charged by

induction from the directly charged first electrode. This has the advantage of requiring only a single high voltage generator so reducing the overall costs and reducing the space required within the inhaler to accommodate the high voltage generator.

Where, as shown in Figure 11, respective reservoirs and pumps 8 and 9 are provided, then the two liquid supply pipes 10 may be supplied with different liquids that, when the opposite polarity comminutions are generated, interact with one another. For example, the two liquids may contain or comprise respective reactive components that, when the two opposite polarity comminutions are produced, intermingle and react with one another so as to produce the required active ingredient. This enables, for example, short shelf life active ingredients to be formed only as and when needed. As another possibility, the two liquid supply paths may provide separate active ingredients for which reaction is not desirable but which lose their relative efficacy if they are in the presence of one another for any length of time. As another possibility, one of the liquids may contain a blowing agent which, when comminuted matter contained in the blowing agent reacts with the opposite polarity comminuted matter, causes expansion of the droplets or particles of the other comminuted matter to form low density particles, for example spheres, which can penetrate deeper into the nasal passages. As another possibility, where the liquid issuing from one of the outlets produces comminuted matter in liquid or gel-like

form, then, when the two opposite polarity comminutions mix, the liquid or gel-like comminuted matter may cover or coat particles of the other comminuted matter to form, for example, microcapsules or coated short fibres or fibrils enabling slow release of active ingredient from the cores of the coated particles. The coating material may contain a bioadhesive to prevent mucocillary clearance and to facilitate long term or sustained release of the active ingredient when used in conjunction with controlled release products.

Another advantage of having two liquid outlets is that the overall rate at which the active ingredient is delivered to the nasal passages should be higher than if only a single liquid outlet nozzle is used. It will be appreciated that more than one pair of liquid outlets may be used and that it is not necessary for there to be equal numbers of positive and negative charged first electrodes especially where, if the arrangement allows complete mixing of the comminutions, a residual charge should be ensured.

Another advantage of providing plural nozzles to achieve opposite polarity comminutions is that the comminution sprays will be more strongly attracted to one another than to the walls of the housing and so the possibility of deposition of comminuted matter onto the walls of the housing should be reduced.

Also, the arrangement shown in Figure 11 should enable larger size droplets or particles of comminuted matter to be produced carrying a given charge.

It will be appreciated that, although the counter electrodes 12 are not necessary in the arrangement shown in Figure 11, the arrangement shown in Figure 11 could be adapted to provide counter electrodes in a similar manner to that described above with reference to Figure 2 with the respective counter electrodes being coupled to the respective negative and high voltage generators 7 and 7' and the first electrodes 10 being coupled to the negative terminal of the voltage source or to the high voltage generator of opposite polarity It should also be appreciated that the counter electrodes need not be coated with a dielectric although this is often preferable. This arrangement may facilitate use of the inhaler shown in Figure 11 with more conductive liquids.

In the arrangement shown in Figure 11, the air supply outlet 334 is disposed centrally of the two liquid outlets. Although this is preferable where it is desired to keep the two opposite polarity comminutions apart, where at least some mixing is desired, then the air outlet may surround the liquid outlets and, for example, air inlet apertures may be provided in the housing wall 4a. Providing the air outlets around the liquid outlets should, in addition to facilitating desired mixing, provide an air curtain to inhibit or at least reduce further the possibility of deposition on the walls of the housing.

As discussed in WO98/03267, in electrohydrodynamic comminution, the intense electric field to which liquids issuing from the nozzle outlet 10a is subject establishes

a standing wave along the surface of the liquid producing at least one cusp or cone (depending upon the size of the outlet 10a) which emits a jet or jets of charged liquid. Small perturbations inevitably occur in the liquid jet resulting in a growth wave which causes the jet to become unstable and the net electrical charge in the liquid provides a repulsive force which counteracts the surface tension forces in the liquid to cause comminution. The growth wave will have a natural frequency and it has been found that the point at which initiation of the growth wave occurs in the jet can be controlled by superimposing upon the applied high voltage an AC signal different from the natural frequency of the growth wave enabling the size of the resulting droplets to be controlled.

The present inventors have found that, instead of a monodispersed comminution, a comminution having droplets of two or more well-defined controlled diameters can be produced by superimposing on the high voltage signal an oscillating signal comprising one or more superimposed frequencies close to natural frequency of the growth wave for the liquid being comminuted.

As shown schematically in Figure 13, a pulse or signal generator 70 is coupled to the high voltage supply line 7a of the high voltage generator by means of a high voltage capacitor C. However, it might be possible to use the natural frequency of the high voltage generator 7 and to retain some AC ripple on the H.V. output line 7a.

Any suitable form of pulse or signal generator which

may be powered by the voltage source 5 (see Figure 2 for example) of the inhaler may be used. For example, the pulse/signal generator 70 may comprise a number of voltage controlled oscillators each of which receives a respective different drive voltage derived in known manner using voltage dividing or multiplying techniques from the voltage source. As another possibility, a numerically controlled oscillator may be used. For example, the pulse/signal generator may comprise a digital memory storing at sequential addresses numerical values which are read out in sequence from the memory and supplied to a digital-to-analogue converter to reconstitute the desired wave shape. In such a case, a signal representing the superimposition of two or more frequencies may be directly generated from the numbers stored in the memory. Reference may be made to standard electronics textbooks such as 'The Art of Electronics' by Paul Horowitz and Winfield Hill for details of oscillators which may be used to provide the pulse/signal generator 70.

Figure 14 illustrates how a superimposed varying amplitude voltage can affect droplet formation with large and small amplitude impulses or "kicks" (illustrated schematically by line 71) applied to the H.V. output line giving rise to two different size droplets d and D.

When the inhaler shown in Figure 2 is modified in this manner, in use, liquid issuing from the outlet nozzle 10a is electrohydrodynamically comminuted and is deposited on the conductive surface inside the nostril as

the user inhales as described above. However, the smaller droplets which carry less charge and have lower inertia will travel further into the nasal passages than the larger droplets so enabling a more uniform deposition along the length of the nasal passages of the medicament being delivered.

It will be appreciated that superimposing three or more frequencies will allow three or more different size droplets to be produced in a controlled manner.

Instead of superimposing the different frequencies, different frequency signals may be supplied in sequence to the high voltage line 7a so that the size of the droplets produced changes in a controlled manner with time depending upon the particular drive frequency applied at the time the droplets are generated.

The arrangement discussed above with reference to Figures 13 and 14 assumes that the drive signals are sine waves. However, this need not necessarily be the case and, for example, short duration spikes having a pulse width of 1 microsecond or less may be used. Typically the drive signals provided by the pulse generator 70 will have an amplitude of about 2% of the high voltage, for example 10-100 volts and a frequency in the range of 50kHz to 10-50MHz, depending upon the desired size of the droplets.

Another possible form of oscillation device is a piezoelectric resonator with two or more resonators arranged to resonate at different frequencies being provided to achieve the required drive frequencies.

Figures 15 and 16 show schematically parts of further modified versions of the inhaler shown in Figure 2.

In the arrangement shown in Figure 15, the pump 9 is arranged to supply liquid to three liquid supply pipes 101, 102 and 103 each having a corresponding outlet 101a, 102a and 103a and each containing a conductive core or rod 111, 112 and 113. The conductive core or rod in each case is coupled to the earth terminal of the voltage generator 5 via line 5a while a second electrode 121, 122 and 123 carried by the insulative supply pipe 101, 102 and 103 is coupled to the high voltage output line 7a from the high voltage generator. Each of the supply pipes 101 to 103 has a flow regulating valve V1, V2 and V3. Each flow regulating valve V1, V2 and V3 controls the rate of flow of liquid through its associated liquid supply pipe so that the rate of flow of liquid from each of the outlets 101a, 102a and 103a is different. Any suitable form of valve, for example a simple mechanical throttle valve or an electromechanical solenoid valve, may be used. Because the flow rates to the respective outlets 101a, 102a and 103a are different, the size of the droplets produced during electrohydrodynamic comminution from the respective outlets will be different. Accordingly, the embodiment shown in Figure 15 enables three different sizes of droplets to be produced by providing respective different flow rates for the three liquid supply pipes.

It will be appreciated that two, three or more

liquid supply pipes having different liquid flow rates may be used and that the liquid flow rates may be prefixed or may be adjustable by the user. The embodiment shown in Figure 15 enables simultaneous production of different size droplets. Sequential production of different size droplets may be achieved by having a single liquid supply pipe and adjusting the flow rate with time by controlling the degree to which the liquid supply valve is open.

Figure 16 illustrates another modification. In this case, the pump 9 is provided with two or more liquid supply pipes 104 and 105 each having a central conductor or rod 114 and 115 providing a first electrode. In this case the second electrode 124 is mounted to the housing 4 wall. In this case, the liquid supply pipes 104 and 105 are of different cross-sections and therefore provide different liquid flow rates.

As another alternative, different pumps providing different flow rates may be used for the different liquid supply pipes.

The generation of comminutions at the different outlets in Figures 15 and 16 may be synchronised by superimposing upon the high voltage signal on line 7a a drive signal comparable to the natural frequency of the growth rate using the pulse generator 70.

In each of the embodiments described above, an air flow is generated within the lower portion 4a of the housing. In order to avoid air movements disrupting the Taylor cone required at the liquid outlets for

electrohydrodynamic comminution, an annular shield may be provided around the liquid pipes in the immediate vicinity of the liquid outlets 10a.

In each of the embodiments described above, the inhaler is designed to enable multiple doses to be supplied from a single reservoir or reservoirs 8. The inhaler 1 may, however, be a single dose inhaler with a reservoir containing only sufficient liquid formulation to provide a single dose. Where this is the case, then the counter 6 and LED 13 described above with reference to Figure 3 may be omitted. In the case of a single dose inhaler, the liquid supply components may be provided as a replaceable plug-in cartridge that can be replaced by the user. Where this is the case, then for ease of manufacture and because these components are relatively cheap, the liquid cartridge will generally include the first electrodes 11, and the electrodes 12 if present and if not carried by the housing portion 4a. As another possibility, the inhaler may be provided with a carousel or magazine of capsules which carousel or magazine is capable of indexed movement so that, after each use of the inhaler, a fresh capsule is moved into place for the next use. Such a magazine may be in the form of a strip carrying the capsules which is, for example, wound from one spool to another as the capsules are used up.

In the embodiments described above, the inhaler has a single outlet for a single nostril. The inhaler may be provided with twin outlets, one for each nostril.

Although particular forms of electrohydrodynamic

comminution means have been described in the examples given above, it will be appreciated that other forms of electrohydrodynamic comminution means can be used. Also, other forms of electrically operable pump may be used.

Electrically or electromechanically operated valves may be provided at appropriate points in the liquid flow path from the reservoir to the outlet 10a so as to inhibit leakage and maintain microbial integrity.

Although the above arrangements are described with reference to the supply of an active ingredient to a human being (solely by the user or with the assistance of a doctor, nurse or carer), it will, of course, be appreciated that the device may be adapted for use with other mammals with the air flow activation being controlled as described with reference to Figure 8 by a veterinarian or other person.

The active ingredient to be supplied by the inhaler may be any agent or substance to provide a desired effect in the user. For example, the active ingredient may be a medicament for use in the treatment by way of therapy, surgery or diagnosis of an animal body such as a human being or otherwise to improve quality of life. For example, the medicament may be nicotine, morphine, a vitamin, an antiseptic, an anti-inflammatory, antibiotic, anti-cancer agent or other pharmaceutical product, a vaccine, a protein, an enzyme, DNA or DNA fragments and so on because electrohydrodynamic comminution enables delivery of large molecules without denaturing them.

The liquid formulation within which the active

ingredient is supplied may be a solution, emulsion, suspension or microsuspension or any other suitable liquid form. Because viscous liquids (including oils) such as glycerine and linoleic acid can be comminuted using electrohydrodynamic comminution, the carrier liquid can be optimised for the active ingredient so that, for example, where the active ingredient is a lipophilic compound as may be the case for a drug or medicament, then the use of electrohydrodynamic comminution should simplify the preparation of the formulation for that active ingredient. Also, the use of oils and emollients has the advantages that oil-based medicaments permeate cell membranes better allowing more rapid absorption of the medicament when inhaled into the nasal passages. Also, oils and oil-based formulations should cause less irritation to the nasal passages than alcohol formulations or aqueous salts. Also oils and other low conductivity liquids produce droplets with a low charge to mass ratio so that the charge spray expands at a lower rate, reducing the likelihood of internal deposition within the device. Furthermore, such low conductivity liquids are also less likely, because they are more highly resistive, to initiate short circuits.

As is known in the art, it is extremely difficult to comminute highly electrically conductive liquids satisfactorily using electrohydrodynamic comminution without the use of surfactants which may irritate the nasal passages and so are undesirable for nasal inhalation. The use of relatively highly conductive

liquid formulations may, however, be unavoidable. For example, it may be that the amount or type of active ingredient required renders the liquid formulation highly conductive and/or the carrier liquid required, for example water or a water/ethanol mixture containing ionic components, renders the liquid highly conductive. The present inventors have, surprisingly, found that it is possible to obtain satisfactory electrohydrodynamic comminution of such relatively highly conductive liquids without the use of surfactants by incorporating an additional component into the liquid formulation in the form of a medium to high molecular weight polymer. This polymer may be a synthetic or naturally occurring polymer and the molecular weight may, typically, be in the range 40,000 to 400,000.

Experiments have been carried out using a liquid formulation consisting of 70% ethanol and 30% 0.5 mol water NaCl solution (salt water) to mimic a liquid formulation carrying an active ingredient.

A first set of experiments was carried out using PVA (polyvinyl alcohol) as the polymer. For this polymer, a molecular weight of 125,000 was chosen for the experiment. Details of these experiments are set out in table 1 below. The maximum stable flow rate was 3 microlitres/second (ml/s) per nozzle.

Table 1

Example	Formulation	Resistivity/ Ωm	Viscosity / cP
1	0.1g PVA in 10ml liquid formulation	5.54	10
2	0.2g PVA in 10ml liquid formulation	4.20	24
3	0.3g PVA in 10ml liquid formulation	4.80	72
4	0.4g PVA in 10ml liquid formulation	5.21	110
5	0.5g PVA in 10ml liquid formulation	5.10	200
6	0.6g PVA in 10ml liquid formulation	5.21	360
7	0.7g PVA in 10ml liquid formulation	5.25	700

In each of examples 1 to 7 satisfactory electrohydrodynamic comminution was achieved. Microscope photographs of the resultant comminutions were taken and it was found that, surprisingly, the geometry or structure of the comminuted matter varied with the amount of polymer added to the formulation. Thus, when the amount of polymer was 0.1g in 10ml, the resulting comminuted matter was granular in appearance consisting of spheroidal or near-spheroidal particles. When the amount of PVA was increased to 0.2g, then the comminuted matter was still granular but some of the granules had tails or were attached to fibrils. As the amount of PVA

was increased, that is going from example 2 to example 7, the amount of fibril or tail formation increased so that at example 7 the majority of the comminuted matter was formed of small fibres or fibrils.

Similar experiments were also carried out using PVP (polyvinyl pyrrolidone). Table 2 shows the results of experiments carried out using a PVP molecular weight of 360,000 and a maximum flow rate of 1.5 microlitres/second per nozzle.

Table 2

Example	Resistivity/Ωm	Viscosity / cP	Product
8	0.2g PVP in 10ml liquid formulation	4.74	10
9	0.4g PVP in 10ml liquid formulation	4.76	60
10	0.6g PVP in 10ml liquid formulation	5.36	180
11	0.8g PVP in 10ml liquid formulation	5.20	260
12	1.0g PVP in 10ml liquid formulation	5.32	480
13	1.2g PVP in 10ml liquid formulation	5.82	740

Again, in each of examples 8 to 12, satisfactory electrohydrodynamic comminution was achieved. Again, microscope photographs were taken and again the geometry

or structure of the comminuted matter was found to change with the amount of polymer added to the liquid formulation. Thus, where the amount of polymer was 0.2g in 10ml (millilitres), the comminuted matter was generally granular with few fibrils or tails, with 0.4g PVP in 10ml of the liquid formulation more fibrils or tails were seen, while with 0.6g PVP in 10ml of the formulation significant numbers of tails and fibrils were seen with few granular components. Thereafter, the number of fibrils and short fibres seen increased. As a result of further experiments carried out, a formulation with 0.5g of PVP in 10ml of the liquid formulation was found to produce granular material with a good proportion of tails or fibrils.

It can thus be seen that, surprisingly, controlling the amount of medium to high weight polymer added to the liquid formulation enables the geometry or shape of the comminuted material to be controlled so that the comminuted material can be varied from granular particles to short fibres and fibrils with, in between, the comminuted material consisting of granular matter some of which has short tails or attached fibrils. The ability to control the shape or geometry of the comminuted matter is advantageous because this means that the shape of the comminuted matter can be tailored to the desired usage. Generally, the fibrils or tails were found to be semi-solid and capable of adhering better to surfaces such as the surfaces of the nasal passages and/or to themselves, so reducing the possibility of mucocillary clearance.

Also, being able to control the size of the comminuted matter from very small granular particles having dimensions less than 1 micrometre to short fibres or fibrils enables the rate at which active ingredient is taken up by the mucous membranes to be controlled with very small particles enabling fast uptake and larger particles enabling slower, more sustained release of the active ingredient. Thus, by tailoring the geometry of the comminuted matter, the rate of delivery of the active ingredient can be controlled.

The use of electrohydrodynamic comminution as described above to enable delivery of active ingredients by inhalation through the nasal passages enables the control of the rate and location of uptake of the active ingredient so that, for example, the active ingredient can be delivered rapidly to the brain with low or little systemic uptake which is particularly important where the drug to be delivered may have deleterious systemic side effects.

The above example describes inhalers for supplying an active ingredient via the nasal passages. However, where the modification shown in Figure 8 is provided so that inhalation by the user is not required, supply of an active ingredient to other body areas, cavities or organs, or onto or into a wound is possible. Such a device may be used for supply of active ingredients to the eye because the electrodes are not exposed so inhibiting the possibility of electrical shock. Where the device is adapted for supply of an active ingredient

to the surface of the eye, then the outlet of the housing may, for example, be shaped so as to conform to the eye socket. A device having the structure of an inhaler described above with the adaptation shown in Figure 8 may be used to supply pre- or post-operative active ingredients, for example, to reduce, especially in the case of the eye, the likelihood of scar tissue forming after surgery; to supply antibiotics, antibacterials, anaesthetics and the like to the surface of the eye or into a bodily orifice; to supply comminuted matter onto an exposed interior surface of the body during surgery for example to supply an adhesive to repair an incision in an arterial wall; or to apply wound dressing or medicaments onto internal or external bodily wounds.

The final form of the comminuted matter will depend upon the liquid being comminuted. Thus, for example, if the liquid is such that it starts to solidify or gel after comminution then solid or gel-like droplets will be formed. If the liquid starts to solidify or gel just before comminution then generally small fibres or fibrils will be formed. Where the device is not being used for inhalation, then the term comminution is also intended to cover the case where the supplied liquid solidifies or gels before the applied electric field can break the liquid apart and so forms a single fibre although, strictly, in this circumstance the liquid is not comminuted because it does not necessarily break up.

Other modifications will be apparent to the person skilled in the art.

CLAIMS

1. An inhaler, comprising a housing having an outlet and an air inlet, the housing containing: liquid supply means comprising: a chamber providing a reservoir for liquid providing an active ingredient to be supplied to a user and means for supplying liquid from the reservoir to a liquid outlet; and

means for creating an electric field for causing comminution of liquid issuing from the liquid supplying means outlet in response to air flowing through the air inlet so as to produce a stream of electrically charged comminuted matter for supply to the nasal passages of the housing outlet.

2. An inhaler according to claim 1, wherein the liquid supplying means has first and second outlets; and the electric field creating means comprises a first electrohydrodynamic comminution means for subjecting liquid issuing from the first outlet to an electrical potential to cause the liquid to be comminuted to form a comminution of one polarity; and a second electrohydrodynamic comminution means for subjecting liquid issuing from the second outlet to an electrical

potential to cause the liquid to be comminuted to form a comminution of the opposite polarity, means being provided for providing an air flow to the outlet to modify any mixing of the two opposite polarity comminutions.

3. An inhaler according to claim 1, wherein the electric field creating means comprises first and second spaced apart electrodes with the first electrode being provided at or adjacent the outlet of the liquid supplying means; and voltage supplying means operable in response to air flowing through the air inlet to provide a potential difference between the first and second electrodes.

4. An inhaler according to claim 3, wherein the voltage supplying means comprises an air flow activated switch for coupling a voltage generating means across the first and second electrodes.

5. An inhaler according to claim 3, wherein the air flow activated switch comprises a closure member and spring biassing means normally biassing the closure member into a position closing off the supply of air into

the housing through the air inlet, the closure member being movable against the spring biassing to a position allowing air to flow into the housing through the air inlet in response to the air flow.

6. An inhaler according to claim 1, 2, 3, 4 or 5, wherein the housing is arranged to enable a user to create the air flow by breathing in through the housing outlet.

7. An inhaler according to any one of the preceding claims, comprising a pump for creating the air flow.

8. An inhaler, comprising a housing having an outlet, the housing containing: a chamber providing a reservoir for liquid providing an active ingredient to be supplied to a user; means for supplying liquid from the reservoir to a liquid outlet; first and second spaced apart electrodes with the first electrode being provided at or adjacent the outlet of the liquid supplying means; and user-operable voltage supplying means for providing a potential difference between the first and second electrodes to create an electric field for causing comminution of liquid issuing from the liquid supplying

means outlet to produce a stream of electrically charged comminuted matter, the first and second electrodes being spaced from the housing outlet and being arranged so as to provide, when a potential difference is applied across them by the voltage supplying means, an electric field which reduces rapidly in the direction of liquid flow from the liquid supplying means and the housing having an air flow path to the housing outlet for causing liquid comminuted by the electric field to be entrained by the air flow for supply via the housing outlet to the nasal passages of a user.

9. An inhaler according to any one of claims 3, 5 or 8 or claims 6 and 7 when dependent on claim 3, wherein the first and second electrodes are spaced apart in a direction perpendicular to the flow of liquid from the liquid supplying means.

10. An inhaler according to any one of claims 3, 5, 8 or 9 or claims 6 and 7 when dependent on claim 3, wherein the second electrode is located downstream of the supply of liquid from the liquid outlet.

11. An inhaler, comprising a housing having an outlet,

the housing containing: a chamber providing a reservoir for liquid providing an active ingredient to be supplied to a user; means for supplying liquid from the reservoir to a liquid outlet; first and second spaced apart electrodes with the first electrode being provided at or adjacent the outlet of the liquid supplying means; and user-operable voltage supplying means for providing a potential difference between the first and second electrodes to create an electric field for causing comminution of liquid issuing from the liquid supplying means outlet to produce a stream of electrically charged comminuted matter for supply via the housing outlet to the nasal passages of a user, wherein current-limiting means are provided for limiting the supply of current by the voltage supplying means.

12. An inhaler according to any one of claims 3, 5 or 8 or claims 6 and 7 when dependent on claim 3, wherein current-limiting means is associated with one of the first and second electrodes.

13. An inhaler according to claim 11 or 12, wherein the current-limiting means comprises a dielectric or semi-insulating coating or sleeve provided on said one of the

first and second electrodes.

14. An inhaler according to claim 8, 9 or 10, wherein the voltage supplying means comprises an air flow activated switch for coupling a voltage generating means across the first and second electrodes.

15. An inhaler according to claim 14, wherein the air flow activated switch comprises a closure member and spring biassing means normally biassing the closure member into a position closing off the supply of air into the housing through the air inlet, the closure member being movable against the spring biassing to a position allowing air to flow into the housing through the air inlet in response to a user breathing in through the housing outlet or in response to an air supply to the air inlet.

16. An inhaler according to any one of claims 3, 5, 8 to 15 or 6 and 7 when dependent on claim 3, wherein the voltage supplying means comprises a further electrode positioned adjacent the second electrode and resistive means coupling the second electrode to earth, the voltage supplying means being arranged to cause the further electrode to generate an ion current for charging the second electrode to an electrical potential sufficient to

provide the electrical potential for causing comminution of liquid issuing from the outlet.

17. An inhaler, comprising a housing having an outlet and an air inlet, the housing containing: a chamber providing a reservoir for liquid providing an active ingredient to be supplied to a user; means for supplying liquid from the reservoir to a liquid outlet; means for creating an electric field for causing comminution of liquid issuing from the liquid supplying means outlet; and means for providing a flow of air towards the housing outlet so as to produce a stream of electrically charged comminuted matter for supply to the nasal passages of a user via the housing outlet.

18. An inhaler, comprising a housing having an outlet and an air inlet, the housing containing: a chamber providing a reservoir for liquid providing an active ingredient to be supplied to a user; means for supplying liquid from the reservoir to a liquid outlet; means for creating an electric field for causing comminution of liquid issuing from the liquid supplying means outlet; and means for shearing comminuted matter issuing from the liquid outlet to produce a stream of electrically charged comminuted matter of smaller size than that produced by the electric field for supply to the nasal passages of a user via the housing outlet.

19. An inhaler according to claim 18, wherein the shearing means comprises means for producing air flow in

the vicinity of liquid issuing from the liquid outlet.

20. An inhaler comprising a housing having an outlet and an air inlet, the housing containing means for supplying liquid to first and second outlets; a first electrohydrodynamic comminution means for subjecting liquid issuing from the first outlet to an electrical potential to cause the liquid to be comminuted to form a comminution of one polarity; a second electrohydrodynamic comminution means for subjecting liquid issuing from the second outlet to an electrical potential to cause the liquid to be comminuted to form a comminution of the opposite polarity; and means for providing an air flow to the outlet to modify any mixing of the two opposite polarity comminutions.

21. An inhaler according to claim 2 or 20, wherein the air flow providing means is operable to keep the two opposite polarity comminutions apart.

22. An inhaler according to claim 2, 20 or 21, further comprising means for controlling at least one of: 1) the relative flow rates of liquid to the first and second liquid outlets; 2) the relative electrical potentials to which liquid issuing from the first and second outlets is subjected; and 3) the air flow provided by the air flow providing means.

23. An inhaler according to claim 2, 20, 21 or 22, comprising a respective reservoir for each liquid outlet

the reservoirs containing different liquids.

24. An inhaler according to any one of claims 2, 20, 21, 22 or 23, wherein the first and second liquid outlets are angled towards one another.

25. An inhaler according to any one of the preceding claims, further comprising air flow control valve means for controlling air flow.

26. An inhaler comprising means for supplying liquid to a liquid outlet, voltage supply means for subjecting liquid issuing from the liquid outlet to an electric field for causing comminution of liquid issuing from the outlet, and means for controlling the size of the components, for example droplets, of the comminuted matter.

27. An inhaler comprising means for supplying liquid to a liquid outlet, voltage supplying means for subjecting liquid issuing from the liquid outlet to an electric field for causing comminution of liquid issuing from the outlet, and means for controlling the size of the comminuted matter such that the comminuted matter has at least two different controlled sizes.

28. An inhaler comprising means for supplying liquid to a liquid outlet, voltage supplying means for subjecting liquid issuing from the liquid outlet to an electric field for causing comminution of liquid issuing from the

outlet to produce a spray of droplets, and means for controlling the diameter of the droplets so that the comminuted matter consists of droplets each having one of at least two different controlled diameters.

29. An inhaler according to claim 21, 22 or 23, wherein the controlling means comprises means for superimposing on the voltage supplied by the voltage supplying means an alternating or pulsed signal.

30. An inhaler according to claim 22 or 23, wherein the controlling means comprises means for superimposing on the voltage supplied by the voltage supplying means a signal having two different frequency components for causing the comminuted matter to contain two different sizes of components.

31. An inhaler according to claim 29 or 30, wherein the superimposing means is arranged to superimpose on the voltage supplied by said voltage supplying means a signal having three or more different frequency components for causing the comminuted matter to contain three or more different sizes of components.

32. An inhaler according to claim 30 or 31, wherein said signal is arranged to consist of said frequency components superimposed simultaneously on said voltage in phase with one another.

33. A device according to claim 30 or 31, wherein said

signal is arranged such that said different frequency components are superimposed one after another on said voltage.

34. An inhaler according to any one of claims 25 to 32, wherein the means for controlling the size of the components of the comminution comprises means for regulating the liquid flow and/or the liquid composition.

35. An inhaler according to any one of claims 25 to 34, wherein the means for controlling the size of the comminution components comprises a plurality of subsidiary liquid outlets which together form the liquid outlet and respective different cross-section supply pipes for supplying liquid to each different one of the subsidiary liquid outlets.

36. An inhaler according to any one of claims 25 to 35, wherein the means for controlling the size of the comminution components comprises a plurality of subsidiary liquid outlets which together form the liquid outlet each having a respective valve means for controlling the liquid flow from the outlet.

37. An inhaler according to any one of the preceding claims, having a respective housing outlet for each nostril of a user or patient.

38. An inhaler according to any combination of the preceding claims.

39. An inhaler according to any one of the preceding claims, wherein the air flow is induced other than by inhalation.

40. An inhaler according to any one of the preceding claims, comprising a biologically acceptable carrier for the active ingredients selected from: an oil, an alcohol, a polymer or a water-based solvent.

41. An inhaler according to any one of the preceding claims, comprising a supply of liquid carrying as an active ingredient at least one of the following: a decongestant, a lipid, a vitamin, an antiseptic, an anti-inflammatory, an antibiotic, an anti-cancer agent, a vaccine, a protein, an enzyme, a bioadhesive, DNA or DNA fragments, nicotine and morphine.

42. A liquid formulation for use in an inhaler in accordance with any one of claims 1 to 38, comprising a biologically acceptable carrier liquid for an active ingredient and a polymer.

43. A liquid formulation for use in an inhaler in accordance with any one of claims 1 to 38, comprising a biologically acceptable carrier liquid for an active ingredient and a medium to high molecular weight polymer.

44. A liquid formulation for use in an inhaler in accordance with any one of claims 1 to 38, comprising a biologically acceptable carrier liquid for an active

ingredient and a medium to high molecular weight polymer such as PVA or PVP.

45. A liquid formulation for use in an inhaler in accordance with any one of claims 1 to 38, comprising a biologically acceptable carrier liquid for an active ingredient and an amount of a polymer selected from amongst the following: 0.2 to 0.7 grammes per 10 centilitres of formulation of PVA; 0.2 grammes per 10 centilitres of formulation of PVA; from 0.2 to 1.2 grammes per 10 centilitres of formulation of PVP; or 0.5 grammes per 10 centilitres of formulation of PVP.

46. A liquid formulation according to claim 42, 43, 44 or 45, further comprising as an active ingredient at least one of the following: a decongestant, a lipid, a vitamin, an antiseptic, an anti-inflammatory, an antibiotic, an anti-cancer agent, a vaccine, a protein, an enzyme, a bioadhesive, DNA or DNA fragments, nicotine and morphine.

47. A method of controlling the geometry or shape of comminuted matter produced by electrohydrodynamic comminution of at least one liquid, which method comprises controlling the geometry or shape by controlling or adjusting the amount of at least one medium to high weight polymer in the or at least one of the liquids.

48. A method of controlling the geometry or shape of

comminuted matter produced by electrohydrodynamic comminution of at least one liquid, which method comprises controlling the geometry or shape by controlling or adjusting the amount of PVA or PVP in the or at least one of the liquids.

49. A method of controlling the geometry or shape of comminuted matter produced by electrohydrodynamic comminution of at least one liquid, which method comprises controlling the geometry or shape by adding sufficient polymer to the liquid to cause at least some of the comminuted matter to have a granular form with at least some of the granules having fibrils or tails.

50. A method according to any one of claims 47 to 49, wherein the liquid comprises water and an alcohol.

51. Use of an oil-based formulation as a carrier for an active ingredient to be delivered to a user or patient as comminuted matter formed by electrohydrodynamic comminution of the formulation.

52. A dispensing device having liquid supply means for supplying liquid to a liquid outlet means and means for subjecting liquid issuing from the liquid outlet means to an electric field to cause electrohydrodynamic comminution of the liquid, wherein the liquid supply means comprises a supply of liquid in the form of an oil-based formulation carrying an active ingredient.

53. A nasal inhaler having a housing containing liquid supply means for supplying liquid to a liquid outlet means and means for subjecting liquid issuing from the liquid outlet means to an electric field to cause electrohydrodynamic comminution of the liquid to provide comminuted matter to an outlet of the housing for inhalation by a user or patient, wherein the liquid supply means comprises a supply of liquid in the form of an oil-based formulation carrying an active ingredient.

54. A delivery device having the features of the inhaler described in any one of the preceding claims but differing in that the device is arranged to supply the active ingredient to the mouth, an eye or a bodily orifice and in that air flow is induced other than by inhalation or alternatively by oral inhalation when the device is arranged to supply the active ingredient to or via the mouth.

55. A method of supplying an active ingredient to the nasal passages of a human or animal which comprises using an inhaler in accordance with any one of claims 1 to 41.

56. A method of supplying an active ingredient to an eye or bodily orifice other than the mouth or nose which comprises using a delivery device in accordance with claim 54.

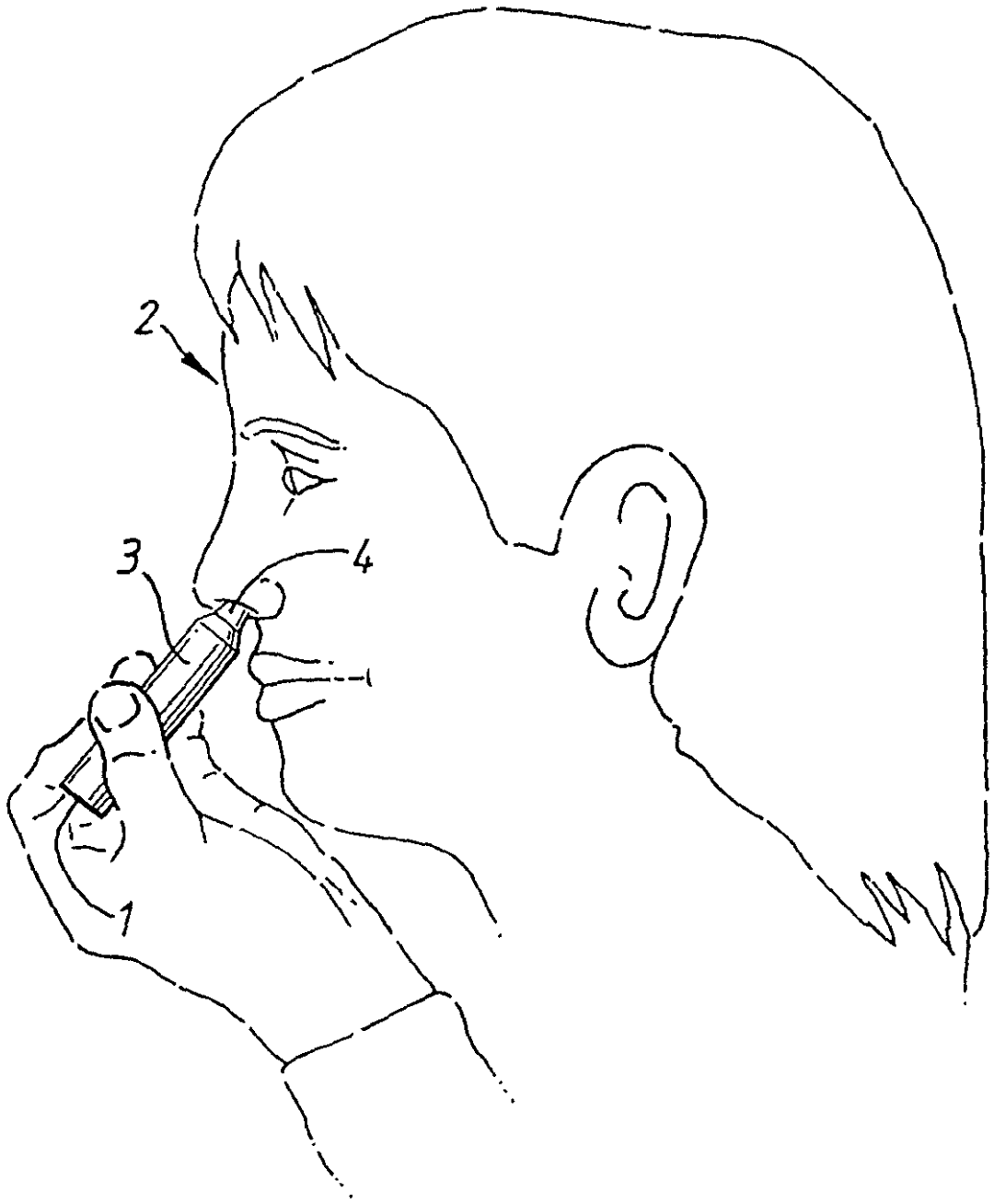


FIG. 1

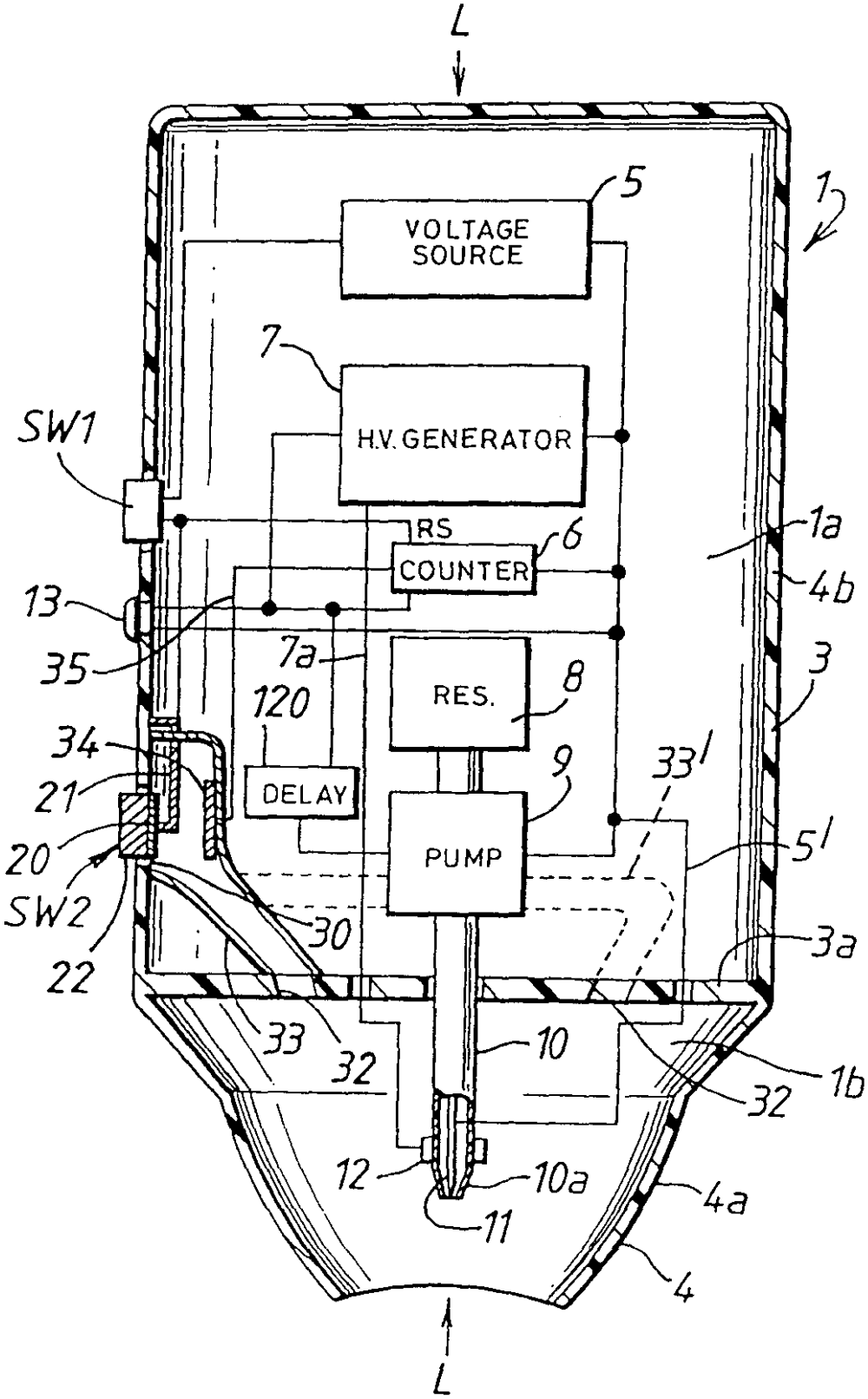
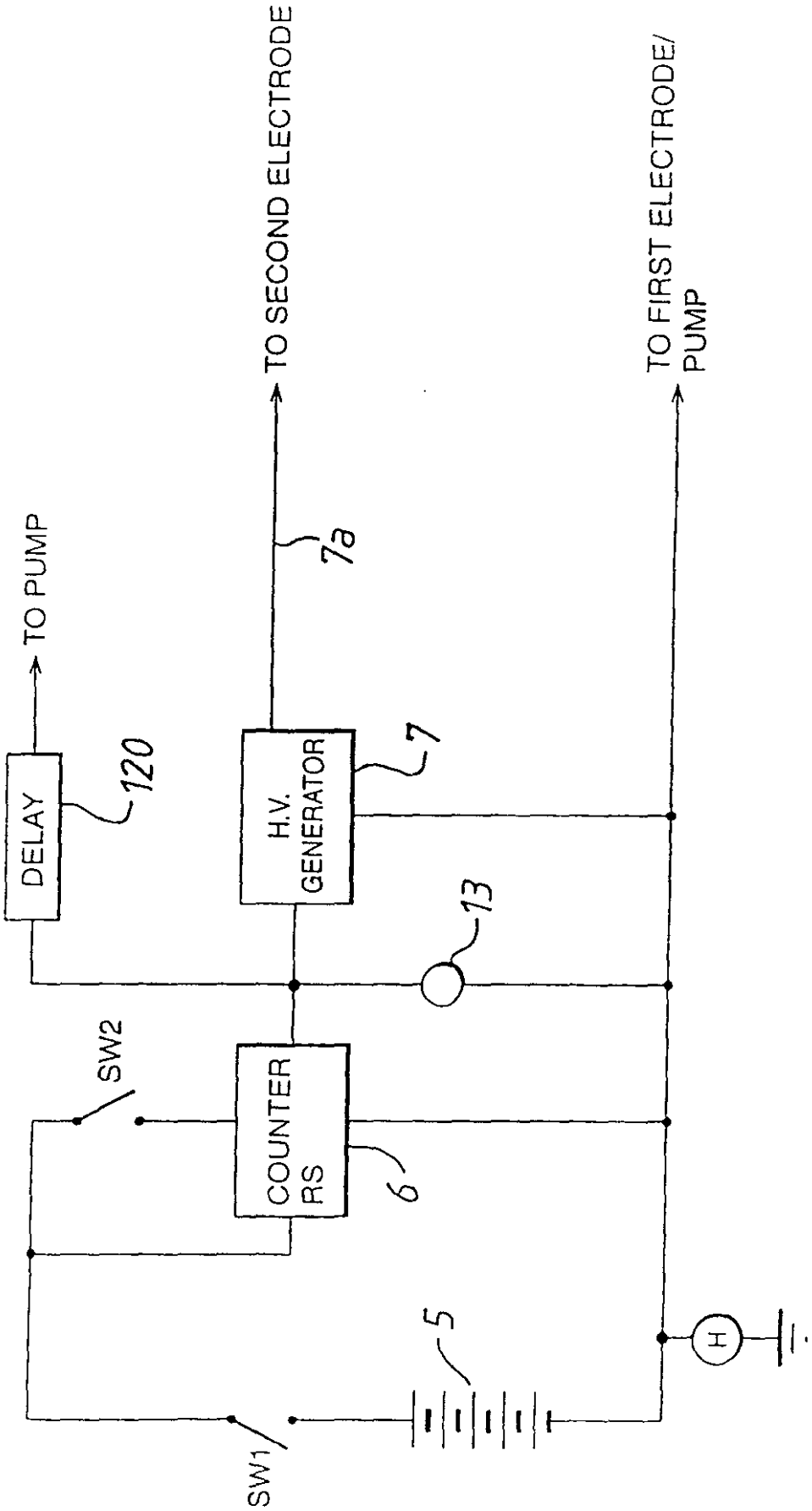

L
VOLTAGE SOURCE
5
1
7
H.V. GENERATOR
SW1
RS
6
COUNTER
1a
4b
13
35
7a
120
RES.
8
3
34
21
DELAY
9
33'
20
PUMP
5'
SW2
30
3a
22
33
32
10
1b
32
12
10a
4a
11
4
L

FIG. 2

FIG. 3


TO SECOND ELECTRODE
TO FIRST ELECTRODE/ PUMP
TO PUMP
7a
DELAY
120
H.V. GENERATOR
7
13
SW2
COUNTER RS
6
5
H
SW1

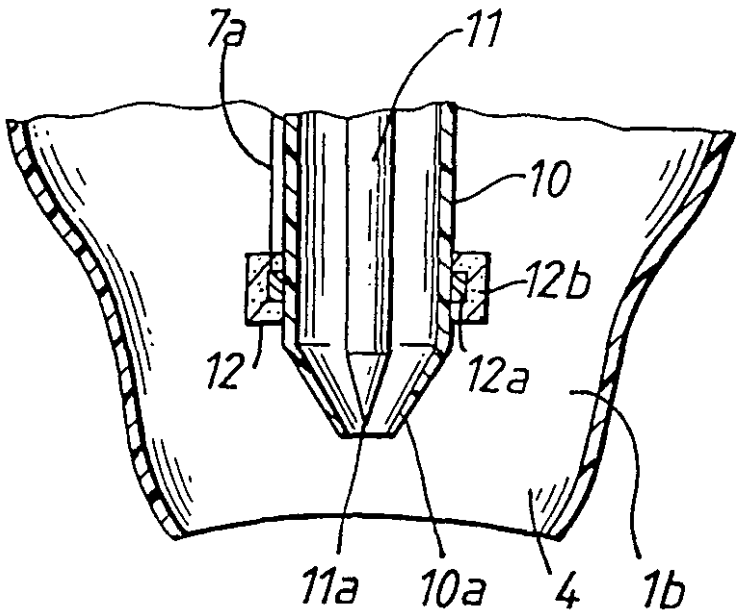


FIG. 4

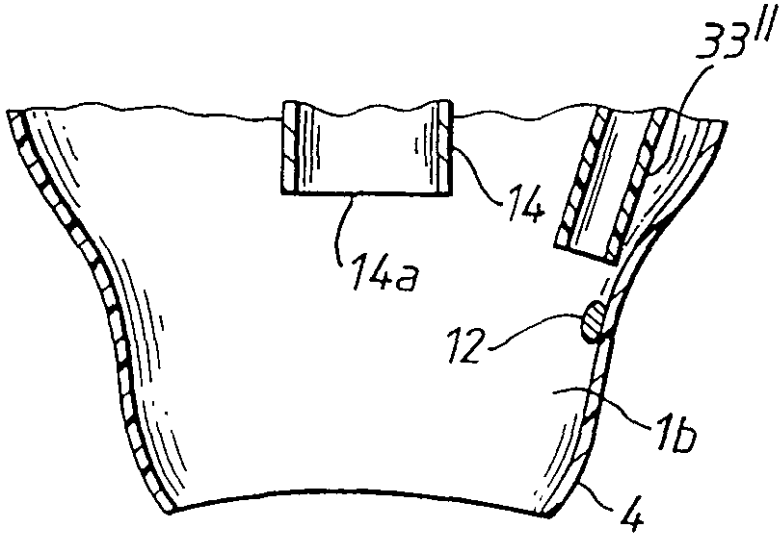


FIG. 5

FIG. 6

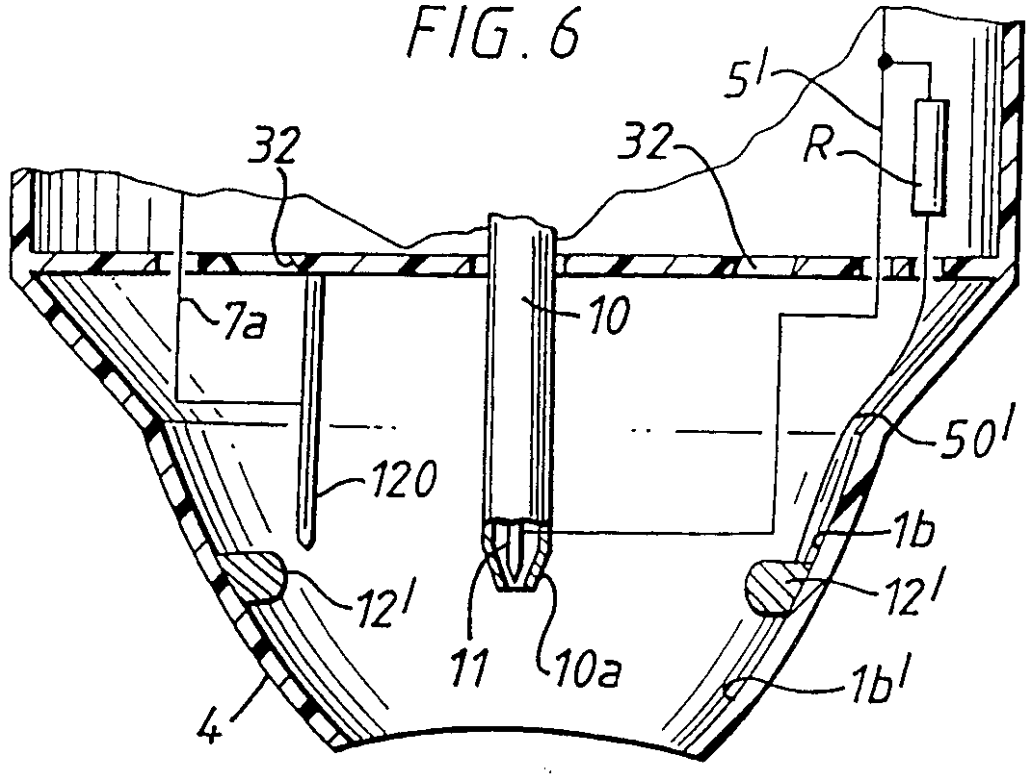
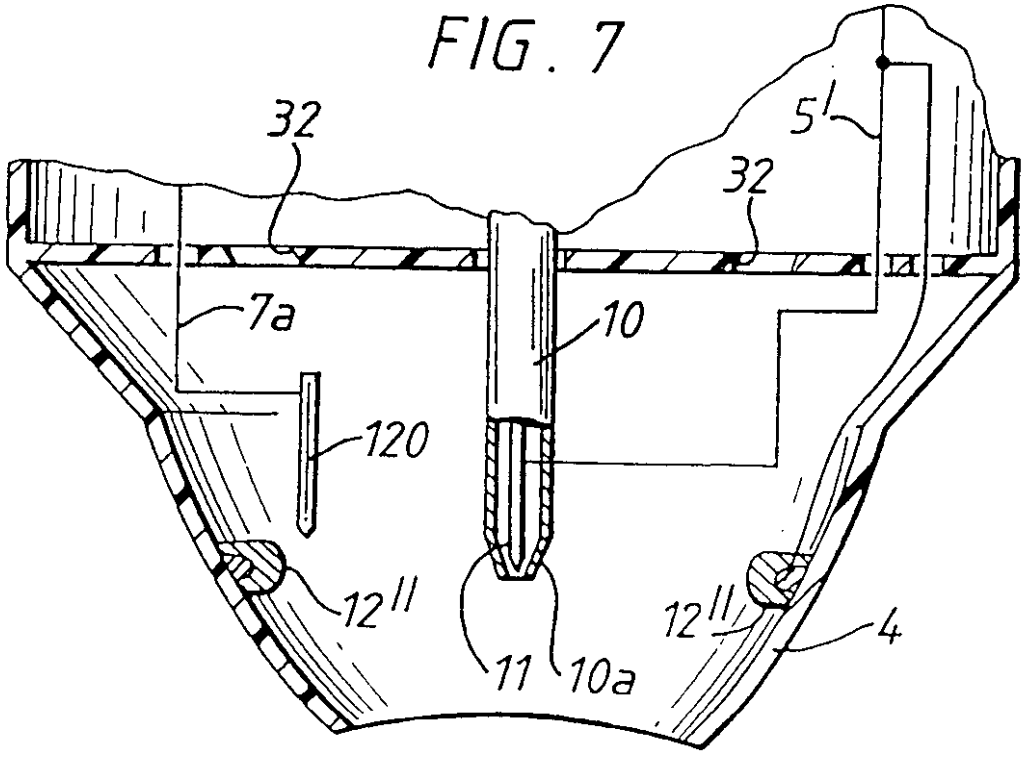

5'
32
32
R
7a
10
120
50'
1b
12'
12'
11
10a
1b'
4

FIG. 7


32
5'
32
7a
10
120
12''
12''
11
10a
4

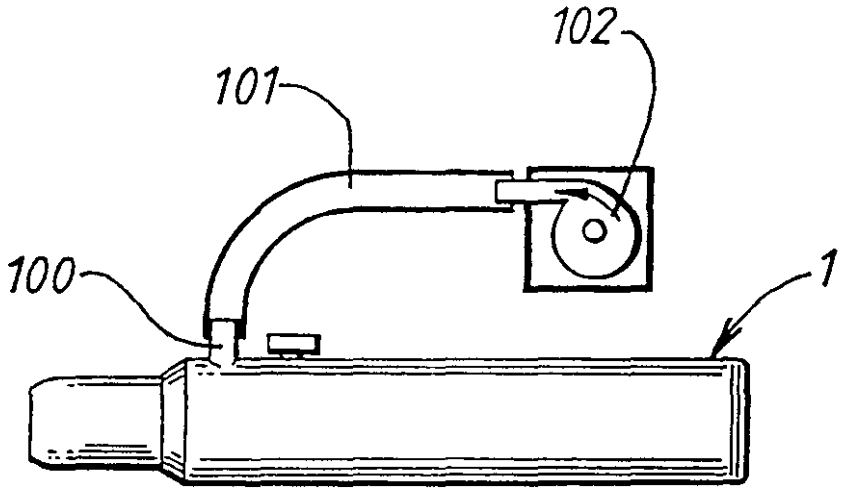


FIG. 8

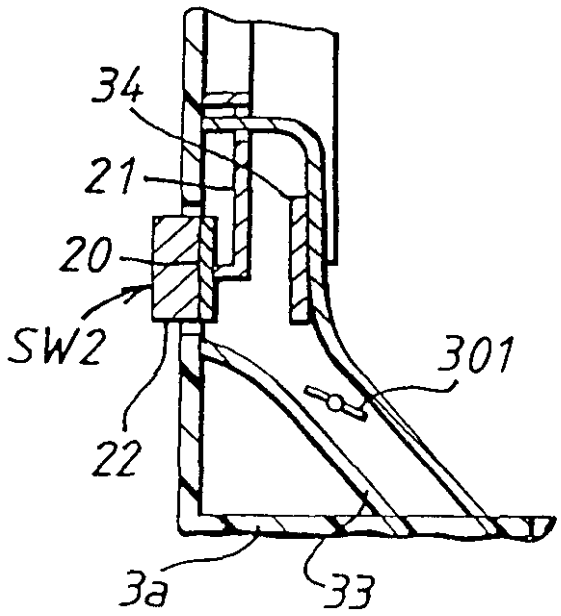


FIG. 12

FIG. 9a

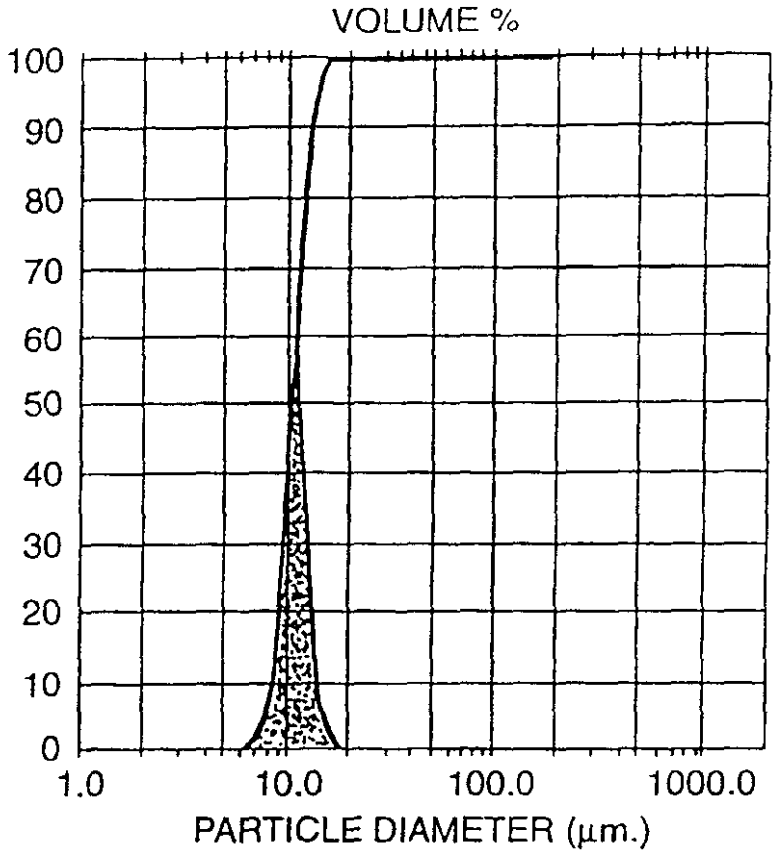

VOLUME %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
PARTICLE DIAMETER (µm.)

FIG. 9b

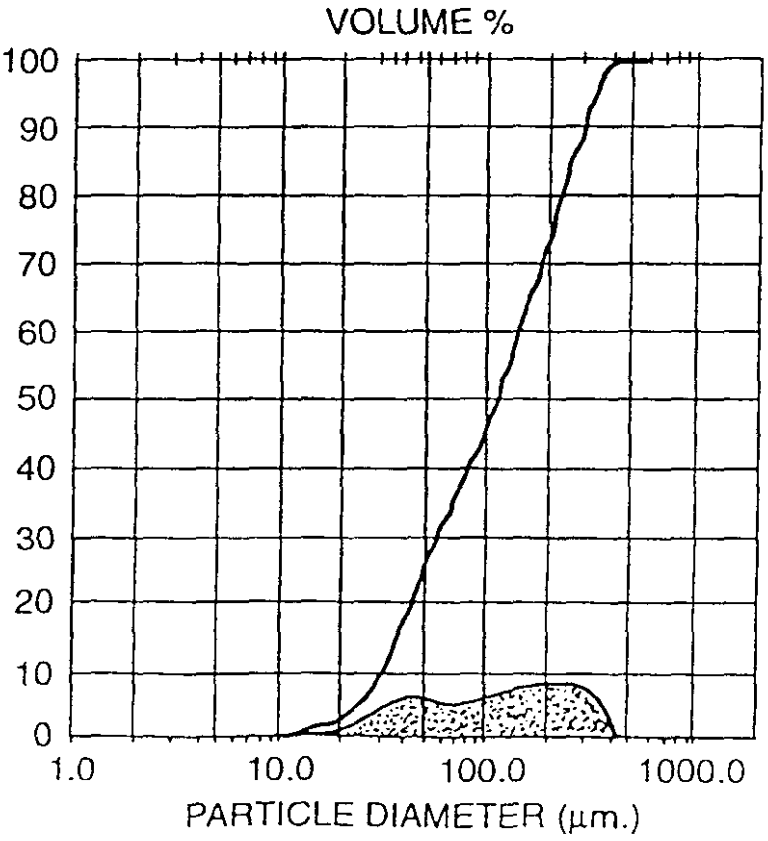

VOLUME %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
PARTICLE DIAMETER (µm.)

FIG. 9c

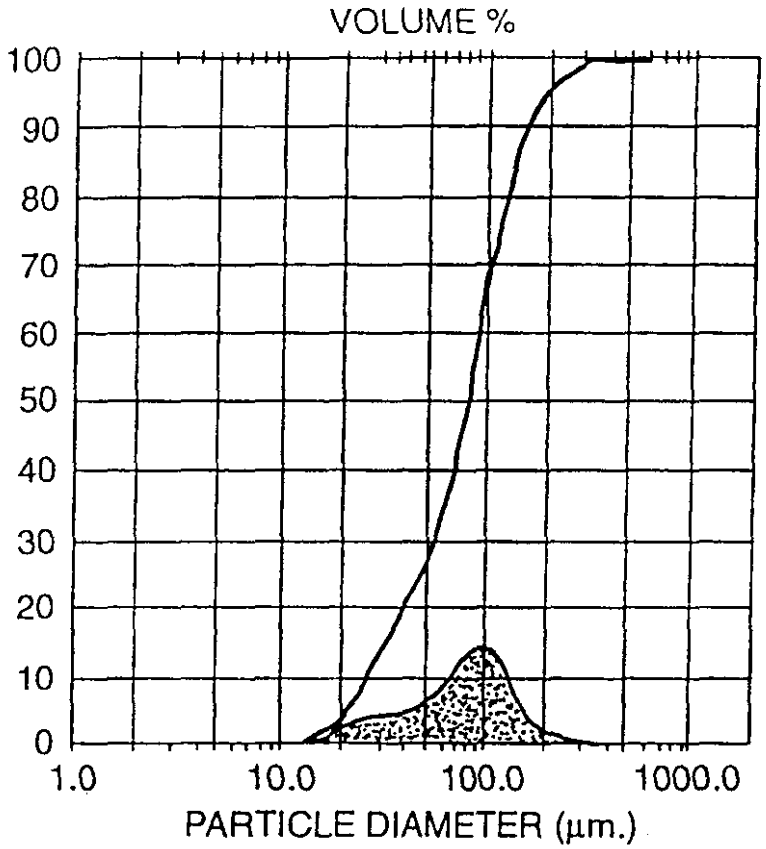
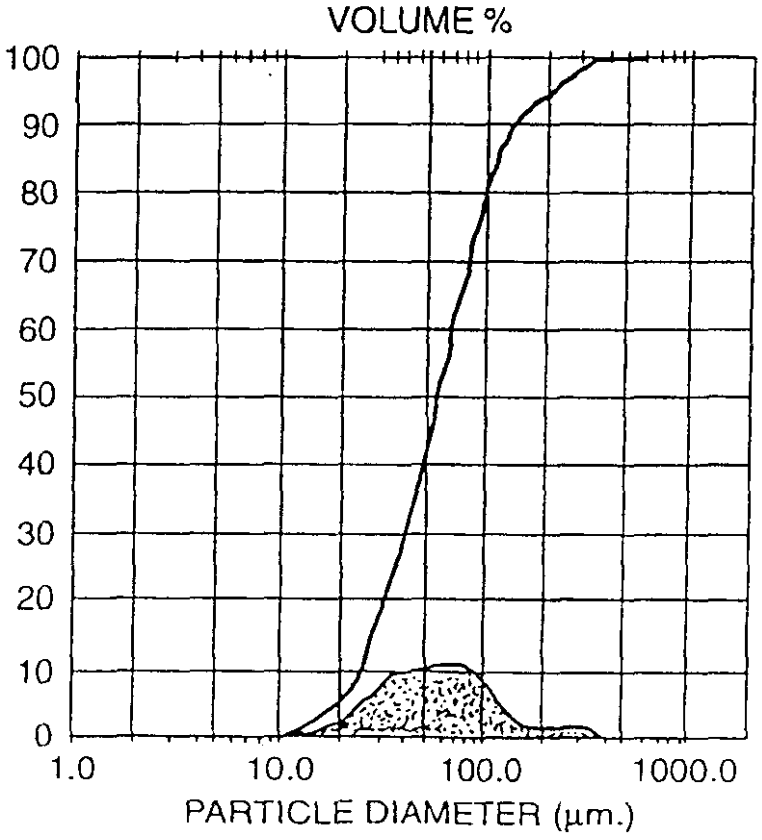

VOLUME %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
PARTICLE DIAMETER (µm.)

FIG. 9d


VOLUME %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
PARTICLE DIAMETER (µm.)

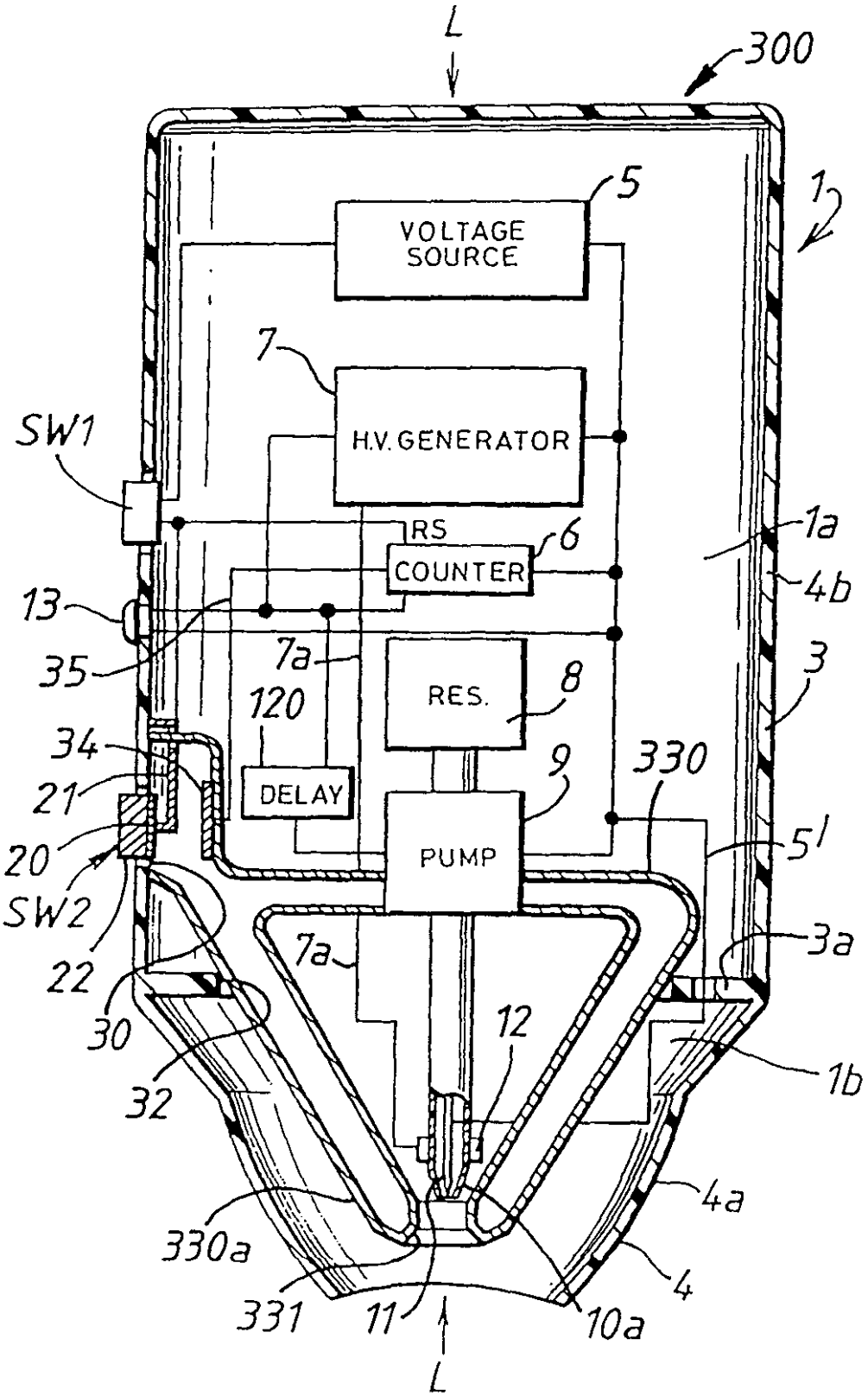

L
300
1
5
VOLTAGE SOURCE
7
H.V. GENERATOR
SW1
RS
6
COUNTER
1a
4b
13
35
7a
120
RES.
8
3
34
21
DELAY
9
330
PUMP
5
20
SW2
22
7a
3a
30
12
32
1b
4a
330a
4
331
11
10a
L

FIG. 10

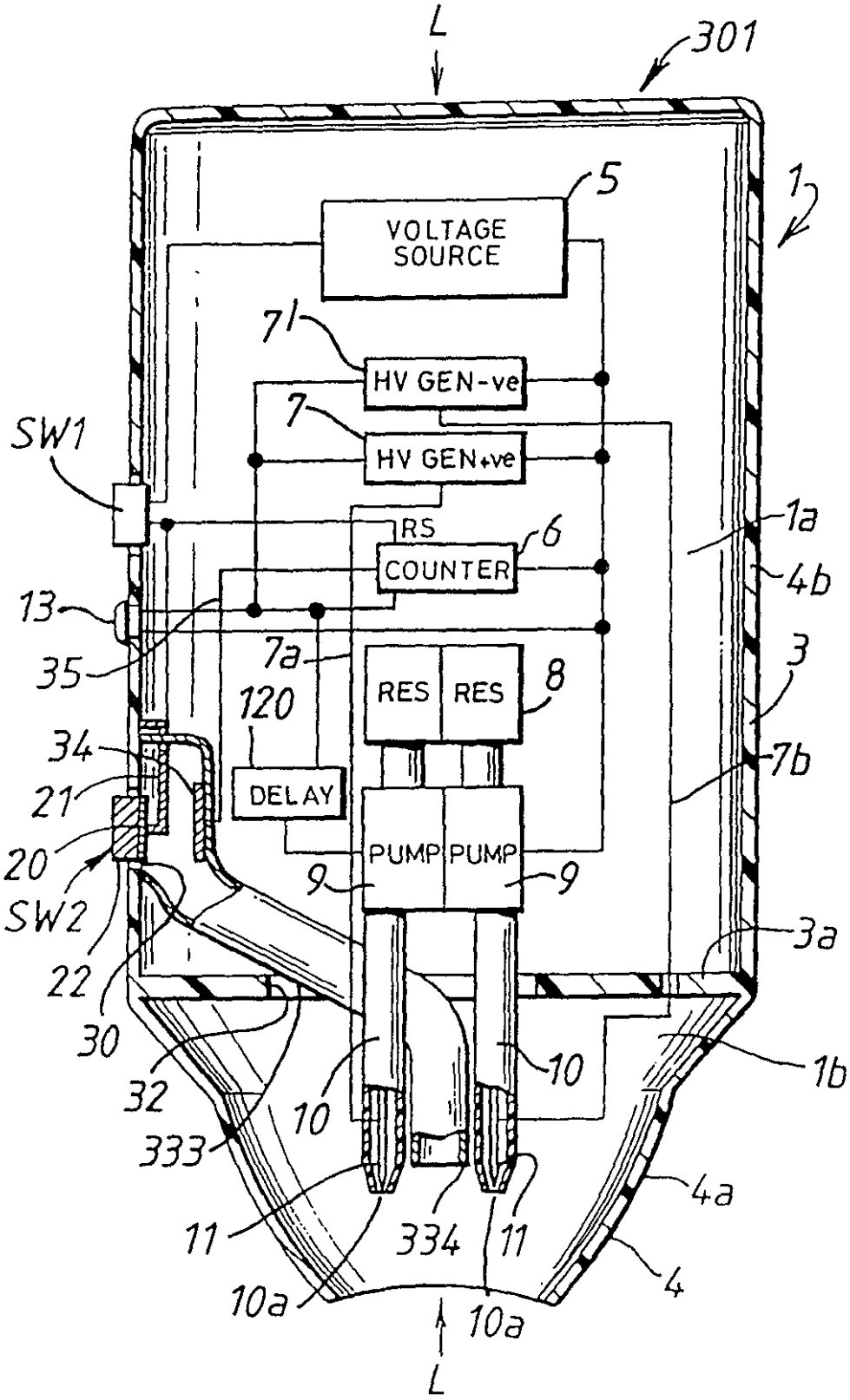
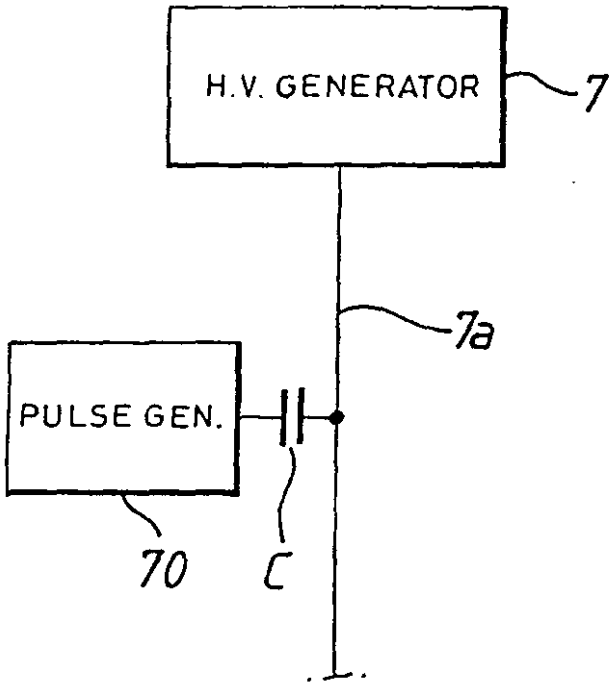

L
301
1
5
VOLTAGE SOURCE
71
HV GEN-ve
7
HV GEN+ve
SW1
RS
6
COUNTER
1a
4b
13
35
7a
RES
RES
8
3
120
34
21
DELAY
7b
20
PUMP
PUMP
9
9
SW2
3a
22
30
32
10
10
1b
333
4a
11
334
11
4
10a
10a
L

FIG. 11

FIG. 13



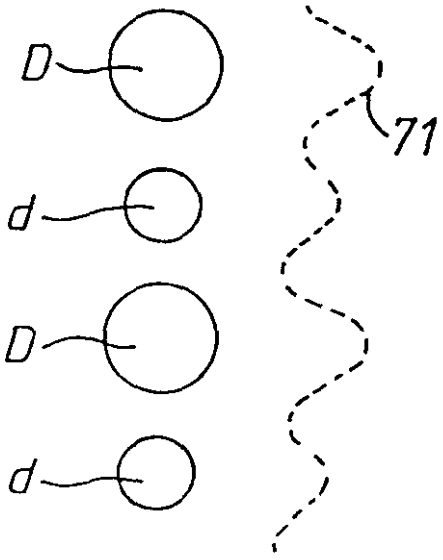


FIG. 14

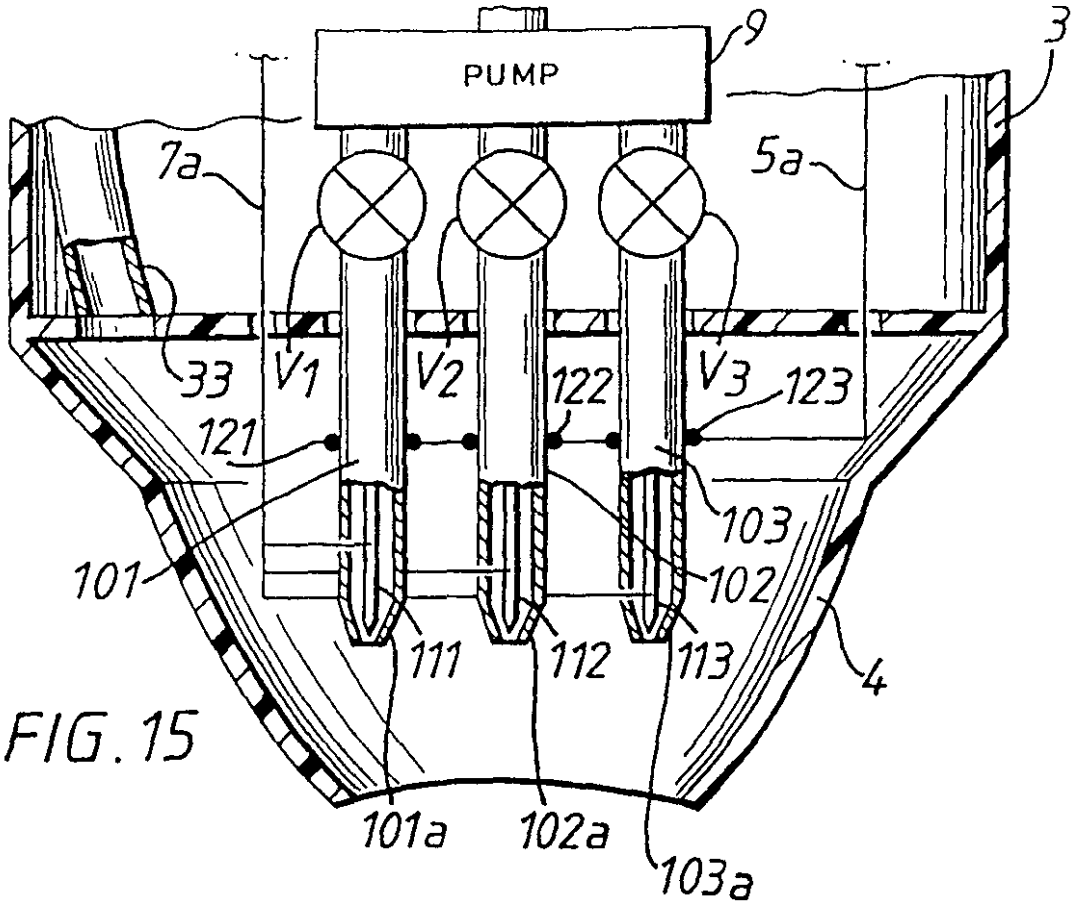

PUMP
9
3
7a
5a
33
V1
V2
V3
122
123
121
103
101
102
111
112
113
4
101a
102a
103a

FIG. 15

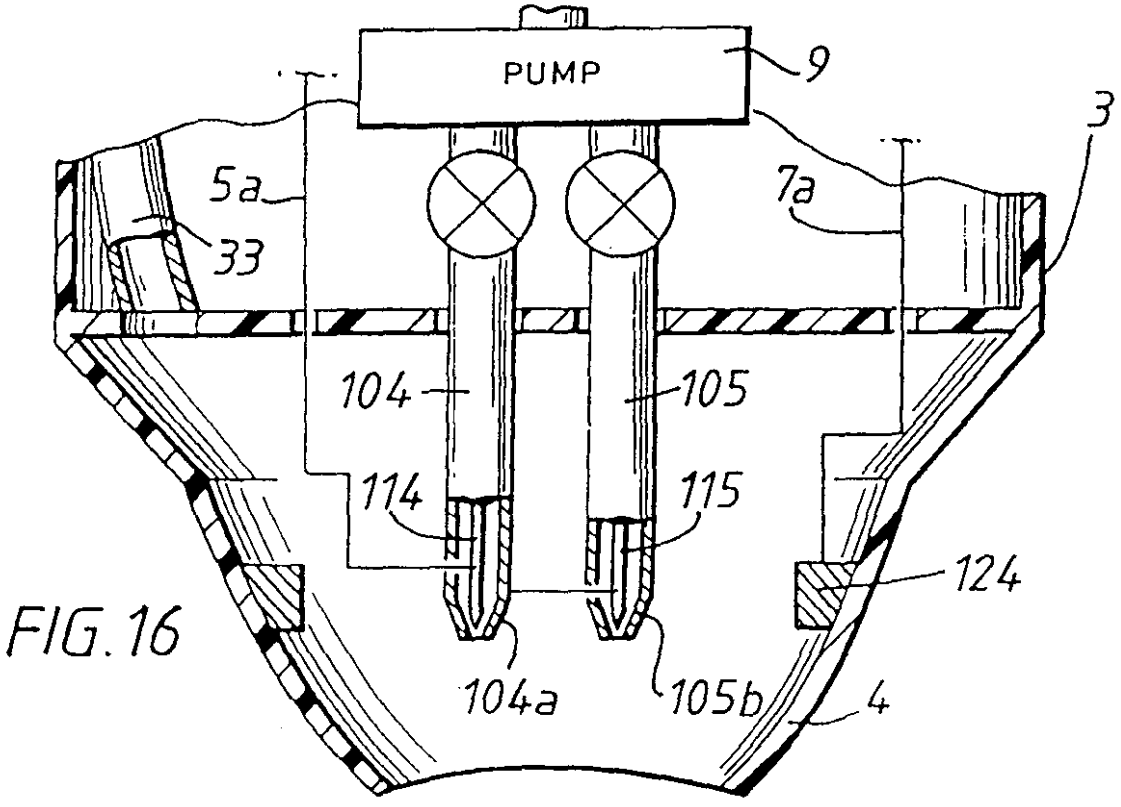

PUMP
9
3
5a
7a
33
104
105
114
115
124
104a
105b
4

FIG. 16

HK1022303.

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
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[74]专利代理机构 中国专利代理(香港)有限公司

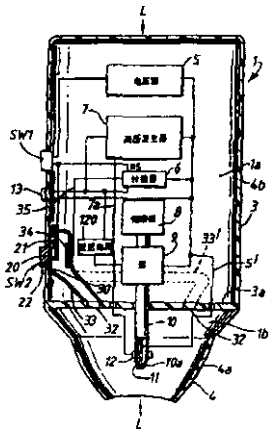
代理人 周备麟 黄力行

权利要求书7页 说明书23页 附图页数12页

[54]发明名称 鼻吸器

[57]摘要

一种具有壳体的鼻吸器,壳体内含有一个具有可将含有待输入的 活性物质的液体供入液体出口(10a)的贮液器(8)的腔室(1a)。第一和第二电极(11 和 12)互相隔开,第一电极(11)设置在液体 出口(10a)上或在其附近。随着气流流过壳体的进气口(30)而接 通电压供给装置(5,7),使第一与第二电极(11 与 12)之间形成电位差而建立一个电场,该电场使液体出口(10a)排出的液体发生雾 化,产生一股带电荷的雾化物质流,通过壳体排出管(4)供入使用 者的鼻腔内。



ISSN1008-4274

权 利 要 求 书

1. 一种具有一个带排出管和进气口的壳体的鼻吸器，所述壳体内含有一个供液装置和一个形成电场的装置，上述供液装置包含一个具有可将活性物质提供给使用者的液体的贮液器的腔室和一个可将液体从该贮液器供到液体出口的装置，

上述的形成电场的装置用于根据流过上述进气口的空气流使从供液装置出口排出的液体雾化之，以便产生一股通过上述壳体的排出管供入鼻腔内的带电荷的雾化物质流。

2. 根据权利要求 1 的鼻吸器，其特征在于，上述的供液装置具有第一和第二液体出口，而形成电场的装置具有一个使上述第一出口排出的液体承受电势而使流体雾化成一处极性雾化物质的第一电动流体雾化装置和一个使上述第二出口排出的液体承受电势而使流体雾化成相反极性的雾化物质的第二电动流体雾化装置，还设有对上述出口提供空气流以改善上述两股极性相反的雾化物质流的混合。

3. 根据权利要求 1 的鼻吸器，其特征在于，形成电场的装置具有互相隔开的第一和第二电极，其中第一电极设置在上述供液装置的出口上或其附近，和一个可随流过进气口的气流而致动以在第一与第二电极之间形成电位差的电压供给装置。

4. 根据权利要求 3 的鼻吸器，其特征在于，上述的电压供给装置具有一个用于连接跨接在第一和第二电极上的电压发生器的气流致动开关。

5. 根据权利要求 3 的鼻吸器，其特征在于，上述的气流致动开关具有一个闭合件和一个经常偏压上述闭合件使之进入切断经进气口进入壳体的气源的位置的弹簧偏压件，上述闭合件可随着气流克服弹簧偏压力而移动到允许空气流经进气口进入壳体的位置。

6. 根据权利要求 1、2、3、4 或 5 的鼻吸器，其特征在于，上述的壳体的结构可使使用者通过对壳体的排出管的吸气而形成气流。

7. 根据上述权利要求中任一项的鼻吸器，其特征在于，具有一个形成气流的泵。

8. 一种具有一个带排出管的壳体的鼻吸器，其壳体内含有：一个具有可将活性物质提供给使用者的液体的贮液器的腔室；一个从贮

液器向液体出口提供液体的装置；第一和第二隔开的电极，第一电极设置在上述供液装置的出口上或其附近；和一个由使用者操纵的电压供给装置，用于在和一与第二电极之间形成电位差以建立一个用以使供液装置出口排出的液体发生雾化而产生一股带电荷的雾化物质流的电场，上述的第一和第二电极与壳体的排出管相隔开，并设置成当上述电压供给装置在它们间施加电位差时，形成一个电场，该电场沿供液装置的液流方向急剧减弱，上述的壳体具有一个通向壳体排出管的气流道，以使电场雾化的液体由气流携带，通过壳体排出管供入使用者的鼻腔内。

9. 根据权利要求 3、5、8 或当根据权利要求 3 时的权利要求 6 和 7 的鼻吸器，其特征在于，上述的第一与第二电极沿垂直于供液装置的液流的方向互相隔开。

10. 根据权利要求 3、5、8 或 9 当根据权利要求 3 时的权利要求 6 和 7 的鼻吸器，其特征在于，上述的第二电极位于液体出口的液流的下游处。

11. 一种具有一个带排出管的壳体的鼻吸器，上述壳体内含有：一个具有可将活性物质提供给使用者的液体的贮液器的腔室；一个用于从贮液器向液体出口供液的装置；隔开的第一和第二电极，第一电极设置在供液装置的出口上或其附近；和一个由使用者操纵的电压供给装置，用于在第一与第二电极之间形成电位差而形成一个电场以使供液出口排出的液体发生雾化而产生一股带电荷的雾化物质流通过壳体排出管供入使用者鼻腔内，其特征在于，设置一个电流限制装置，用于限制由电流装置供给的电流。

12. 根据权利要求 3、5 或 8 当根据权利要求 3 时的权利要求 6 和 7 的鼻吸器，其特征在于，上述的电流限制装置与第一电极或第二电极相连接。

13. 根据权利要求 11 或 12 的鼻吸器，其特征在于，上述的电流限制装置具有一个设置在上述的第一电极或第二电极上的介电的或半绝缘的包层或者说套筒。

14. 根据权利要求 8、9 或 10 的鼻吸器，其特征在于，上述的电压供给装置具有一个用于连接一个跨接第一和第二电极上的电压发生器的气流致动开关。

15. 根据权利要求 14 的鼻吸器，其特征在于，上述的气流致动开关具有一个闭合件和一个通常偏压上述闭合件使之处在切断经进气口进入壳体的气源的位置的弹簧偏压件，上述的闭合件可随着使用者通过壳体排出管的吸气或者随着供入进气口的气流克服上述的弹簧偏压力移动到允许气流通过进气口进入壳体的位置。

16. 根据权利要求 3、5、8 或 15 或当根据权利要求 3 时的权利要求 6 和 7 的鼻吸器，其特征在于，上述电压供给装置还具有一个位于第二电极附近的附加电极和一个使第二电极接地的电阻，上述电压供给装置放置成可使上述附加电极产生一股离子流，以使第二电极充电至具有足以引起出口排出的液体雾化的电势。

17. 一种具有一个带有排出管和进气口的壳体的鼻吸器，上述壳体内含有：一个具有可将活性物质提供给使用者的液体的贮液器的腔室；一个将液体从贮液器供入液体出口的供液装置；一个用于形成电场以引起供液装置的出口排出的液体发生雾化的装置；和一个向壳体排出管提供气流以产生一股带电荷的雾化物质流经壳体排出管供入使用者鼻腔内的装置。

18. 一种具有一个带有排出管和进气口的壳体的鼻吸器，其壳体内含有：一个具有可将活性物质供给使用者的液体的贮液器的腔室；一个用于将液体从贮液器供入液体出口的供液装置；一个建立电场以使供液装置的出口排出的液体发生雾化装置；和一个用于剪切从液体出口排出的雾化物质以产生一股带电荷的雾化物质流的装置，所述的雾化物质的尺寸比由电场产生的通过壳体排出管供入使用者的鼻腔的雾化物质的尺寸小。

19. 根据权利要求 18 的鼻吸管，其特征在于，上述的剪切装置具有一个设置在液体出口排出的液体附近的产生气流的装置。

20. 一种具有一个带排出管和进气口的壳体的鼻吸器，其壳体内含有：将液体供给到第一和第二出口的装置；一种使第一出口排出的液体经受电势的作用而引起流体雾化形成一种极性的雾化物质的第一电动液压雾化装置；一种使第二出口排出的液体经受电势的作用而使液体雾化成另一种极性相反的雾化物质的第二电动流体雾化装置；和一种将气流送到出口以改善两种极性相反的雾化物质的混合的装置。

21. 根据权利要求 2 或 20 的鼻吸器，其特征在于，上述的供给气流的装置的作用是使两股极性相反的雾化物质流保持隔开状态。

22. 根据权利要求 2、20 或 21 的鼻吸器，其特征在于，还具有一个用于控制下列几项中的至少一项的装置，即（1）控制流到第一和第二液体出口的相对流速；（2）控制第一和第二出口排出的液体所受到的相对电势；和控制气流供给装置供入的气流。

23. 根据权利要求 2、20、21 或 22 的鼻吸器，其特征在于，每个液体出口具有相应的贮液器，这些贮液器装有不同的液体。

24. 根据权利要求 2、20、21、22 或 23 中任一项的鼻吸器，其特征在于，上述的第一和第二液体出口之间互相成一定角度排列。

25. 根据上述权利要求中任一项的鼻吸器，其特征在于，还具有一个用于控制气流的气流控制阀。

26. 一种鼻吸器，它具有：一个将液体供到液体出口的装置；一个用于使液体出口排出的液体经受电场作用而引起这种液体雾化的电压供给装置；和控制雾化物质成分（例如液滴）尺寸的装置。

27. 一种鼻吸器，它具有：一个将液体供到液体出口的装置；一个用于使液体出口排出的液体经受电场作用而引起这种液体雾化的电压输出装置；和一个控制雾化物质的尺寸从而使雾化物质至少是有两种不同的受控尺寸的装置。

28. 一种鼻吸器，它具有：一个将液体供到液体出口的装置；一个用于使液体出口排出的液体经受电场作用而引起这种液体雾化而形成雾滴的电压供给装置；和一个用于控制液滴的直径从而使雾化物质由分别具有至少两个不同受控直径中的一种的液滴所组成。

29. 根据权利要求 21、22 或 23 的鼻吸器，其特征在于，上述的控制装置具有一种将交变的或者说脉冲的信号叠加到由电压供给装置供给的电压上的装置。

30. 根据权利要求 22 或 23 的鼻吸器，其特征在于，上述的控制装置具有一种将含有两种不同频率分量的信号叠加在由电压供给装置供给的电压上以使雾化物质包含两种不同尺寸的成分的装置。

31. 根据权利要求 29 或 30 的鼻吸器，其特征在于，上述的叠加装置可将一种具有 3 种或更多种不同频率分量的信号叠加到上述电压供给装置供给的电压上，以使雾化物质具有 3 种或更多种不同尺寸的

成分。

32. 根据权利要求 30 或 31 的鼻吸器，其特征在于，上述的信号由上述的同时同相位地叠加在上述电压上的上述多种频率分量的组成。

33. 根据权利要求 30 或 31 的鼻吸器，其特征在于，上述的信号设置成将上述的不同频率分量一个接一个地叠加在上述电压上。

34. 根据权利要求 25～32 中任一项的鼻吸器，其特征在于，上述的控制雾化物质成分尺寸的装置具有调节液流和/或液体成分的装置。

35. 根据权利要求 25～34 中任一项的鼻吸器，其特征在于，上述的控制雾化物质成分尺寸的装置具有多个一起构成液体出口的辅助液体出口一起构成液体出口的和将液体供给到各个不同的辅助液体出口的各个截面不同的供液管。

36. 根据权利要求 25～35 中任一项的鼻吸器，其特征在于，上述的控制雾化物质成分尺寸的装置具有多个辅助液体出口，这些出口一起构成分别具有相应的用于控制通过出口的液体流量的阀的液体出口。

37. 根据上述权利要求中任一项的鼻吸器，其特征在于，为使用者或者说患者的每个鼻孔设置有相应的壳体排出管。

38. 根据上述权利要求的任何组合的鼻吸器。

39. 根据上述权利要求中任一项的鼻吸器，其特征在于，上述的气流是采用除了鼻吸之外的方法引入的。

40. 根据上述权利要求中任一项的鼻吸器，其特征在于，具有一种生物学上可用于携带活性物质的作为载体的油、酒精、聚合物或水基溶液。

41. 根据上述权利要求中任一项的鼻吸器，其特征在于，由供给液体所携带的作为活性物质的是下列物质中的至少一种：减充血剂、类脂体、维生素、抗菌剂、消炎药、抗生素、抗癌剂、疫苗、蛋白质、酶、生物粘结剂、DNA（脱氧核糖核酸）或 DNA 碎片、尼古丁和吗啡。

42. 用于根据权利要求 1～38 中任一项的鼻吸器中的液体组分，它含有一种生物学上可用于携带活性物质的液体和一种聚合物。

43. 用于根据权利要求 1～38 中任一项的鼻吸器中的液体组

分，它含有一种生物学上可用于携带活性物质的液体和一种高分子量聚合物的介质。

44. 用于根据权利要求 1～38 中任一项的鼻吸器中的液体组分，它具有一种生物学上可用于携带活性物质的液体和一种高分子量聚合物介质例如聚乙烯醇（PVA）或聚乙烯基吡咯烷酮（PVP）。

45. 用于根据权利要求 1～38 中任一项的鼻吸器中的液体组分，它具有一种生物学上可用于携带活性物质的液体，和一定量的从下列配方中选择的聚合物：每 10ml 液体组分中含 0.2～0.7g 的 PVA；每 10ml 液体组分中含 0.2g 的 PVA；每 10ml 液体组分中含 0.2-1.2g 的 PVP 或每 10ml 液体组分中含 0.5g 的 PVP。

46. 根据权利要求 42、43、44 或 45 的液体组分，其特征在于，还含有作为活性物质的下列物质中的至少一种：减充血剂、类脂体、维生素、抗菌剂、消炎药、抗生素、抗癌剂、疫苗、蛋白质、酶、生物粘结剂、脱氧核糖核酸（DNA）或 DNA 碎片、尼古丁和吗啡。

47. 一种控制由电动流体雾化法雾化至少一种液体而产生的雾化物质的几何形状或者说形状的方法，该方法包含通过控制或调节上述的液体或至少一种液体中的至少一种高分子量聚合物介质的含量来控制上述的几何形状或者说形状。

48. 一种控制通过电动流体雾化法雾化至少一种液体所产生的雾化物质的几何形状或者说形状的方法，该方法包含通过控制或调节上述的液体中或至少一种液体中的 PVA 或 PVP 的含量来控制上述的几何形状或者说形状。

49. 一种控制通过电动流体雾化法雾化至少一种液体所产生的雾化物质的几何形状或者说形状的方法，该方法包含通过向液体中流加足够的聚合物而使至少一些雾化物质具有颗粒状而至少一些颗粒具有微纤维或尾丝来控制上述的几何形状或者说形状。

50. 根据权利要求 47～49 的方法，其特征在于，上述的液体是水和酒精。

51. 在用电动流体雾化法雾化上述的组分时，用一种油基组分作为向使用者或者说患者输送活性物质的载体。

52. 一种分配装置，它具有一个将液体供给到液体出口的供液装置和一个使液体出口排出的液体经受电场作用而引起液体的电动流

体雾化的装置，其特征在于，上述的供液装置供给一种携带活性物质的油基组分形式的液体。

53. 一种带有壳体的鼻吸器，所述壳体内含有一个将液体供给到液体出口的供液装置和一个使液体出口排出的液体经受电场作用而使之发生电动流体雾化而产生向由使用者或者说患者鼻吸的壳体排出管提供的雾化物质的装置，其特征在于，上述的供液装置供给一种携带活性物质的油基组分形式的液体。

54. 一种具有上述权利要求中任一项所述鼻吸器的特征但又有差别的输送装置，其特征在于，其差别为，该装置可将活性物质供给到嘴、眼或身体上的其他孔洞中，而且当上述装置用来将活性物质供入嘴里或通过嘴供入时，气流不是通过鼻吸引入的，而是另外通过口吸引入的。

55. 一种对人或动物的鼻腔供入活性物质的方法，它包括采用根据权利要求 1～41 中任一项的鼻吸器。

56. 一种对眼睛或身体的孔洞而不是嘴或鼻供给活性物质的方法，它包括采用权利要求 54 所述的输送装置。

说　明　书

鼻吸器

本发明涉及可将活性物质输送到鼻腔内的鼻吸器.

鼻吸器通常用于输送减充血剂例如盐酸羟甲唑啉等. 鼻腔也是输送麻醉剂和其他药品到血液中用于治疗并不属于鼻腔的疾病的好途径.

普通的液压/泵作动的鼻吸器发射或者说喷出大滴的液体到鼻孔内，这些液滴是多分散的，就是说，液滴尺寸的谱线是宽谱线，这种液滴的沉积主要靠其自身的惯性，这就会使液体的分布很不均匀. 在一个部位过多地沉积液滴可导致液滴聚合并流出鼻孔或从咽喉后壁流下，使人感受到有讨厌的滋味，更坏的情况是，由于麻醉剂进入消化系统或肺的系统会产生有害的副作用.

本发明的目的是提供一种可以满意而有效地将诸如药物或其他活性物质之类的物质供入到鼻粘膜上而不会沉积到非目标部位如肺或胃中的装置.

在例如英国专利 GB-A-1569707 中详细说明过一种称之为电动流体雾化法的产生雾化物质的工艺过程. 在这种工艺中，通过使出口排出的液体经受电场的作用而产生分散的喷雾状物或雾化物质云例如尺寸全部基本相同的（单分散性的）液体微滴.

上述专利 GB-A-1569707 中所述的装置是大的装置，可产生带强电荷的液滴，并且主要用于喷洒庄稼.

业已提出多种利用电动流体雾化法的鼻吸器，它们的优点是不同于普通的鼻吸器，可以产生单分散性的（尺寸全部基本相同的）薄雾或液滴云，从而使液滴更精确地喷到目标部位上. 然而，由于按常规的知识要将带电荷 的物质喷到一种空腔内是困难的（如果不是不可能的话），所以，过去在生产利用电动流体雾化技术的鼻吸器的努力中要求雾化物质在吸入之前要先放电荷.例如欧洲专利 EP-A-0234842 提出，必需使得到的雾化物质在吸入之前放电，以防止雾化物质只沉积到嘴边或咽喉边湿的导电表面上.

本发明人意外地发现，通过电动流体力学的放电或部分放电技术与对所得雾化物质的气动力相结合可以制成通过电动流体力学装置

产生带电荷的雾化物质的鼻吸器，所述的雾化物质可被吸入而均匀沉积在鼻腔内导电的内表面上，并从这里将由雾化物质所携带的活性物质迅速吸收到血流内，而不会被吸入肺的系统中。

在一个方面，本发明提出一种具有可通过使用者鼻吸而致动的电动流体雾化装置的鼻吸器，该鼻吸器方便于将带电荷的雾化物质带入气流中并从而进入使用者的鼻腔内。

在一个方面，本发明提出一种具有电动流体雾化装置的鼻吸器，雾化装置的电极或多个电极与使用者是有屏蔽的，故使用者不会与电极有直接的电接触。

在一个方面，本发明提出一种鼻吸器，其特征在于，待吸入的物质是电动流体力学法产生的，雾化物质（通常是液滴）的电荷和/或尺寸通常是受控制的，所以雾化物质可均匀地沉积到鼻腔内，但可防止供入到肺的系统或咽喉后部，因此，本发明的鼻吸器可用于对鼻腔供给那些若送入肺的系统或消化系统会产生令人讨厌的或不希望有的作用的药物。

在一个方面，本发明提出一种鼻吸器，该鼻吸器具有：一个携带活性物质的液体的供应源；一个将上述液体供给到出口的装置；和一个使出口流出的液体经受足以引起液体雾化而产生可由使用者吸入的带电荷的雾化物质的电场的作用的装置，所选择的液体要能控制到当带电荷的雾化物质沉积在鼻腔内时便可从带电荷的雾化物质中释放出活性物质。上述的液体可以是可通过鼻腔内表面将活性物质迅速送入血流中的油或酒精基的组分，另一种可能是，上述的液体可以是那些由其得到的雾化物质具有可持续释放活性物质的胶体状结构的液体。

在一个方面，本发明提出一种鼻吸器，它具有一个可使出口排出的液体经受足以引起液体雾化的电场作用的装置和一个使带电荷的雾化物质沉积在鼻腔表面上的装置。后者可以是一种用于引起或者说有利于携带带电荷的雾化物质的空气流过鼻吸器的装置。这种气流可由使用者鼻吸或通过人造机械例如泵或上述二者相结合而产生。

在一个方面，本发明提出一种具有雾化装置的鼻吸器，所述的雾化装置可形成一个强度沿供液装置的液流方向迅速减小的电场，在使用时，由该电场雾化的液体容易夹带在气流中而从备吸器送至使用者

的鼻孔内。

在一个方面，本发明提出一种鼻吸器，它具有：一个将液体供给出口的装置；一个使出口排出的液体经受足以引起该液体雾化的电场作用的装置；和一个在第一电极与离液体出口很远的第二电极中的一个电极上产生电势的装置，这种产生电势的装置是一种产生使上述的一个电极间接带电的离子流的装置。

在这方面，上述的离子流发生装置可以具有一个设置在上述的一个电极附近的附加电极和一个形成从上述的一个电极接地的高电阻线路的装置。上述的接地的高电阻线路可具有一个与上述的一个电极串接的真实电阻器，或者例如在上述的一个电极上设置有电阻性的或半导电的包层。上述的一个电极间接带电减小了雾化物质在该一个电极上沉积的可能性，因为任何接近该一个电极的带电荷的雾化物质都会由于产生的离子而至少部分地放电。而且，由于一些雾化物质被离子发生装置至少部分地放电，故可在鼻腔内更均匀地沉积或更深地渗透。

在一个方面，本发明提出一种具有一个对雾化区供给液体的装置和一个限制供入雾化区的电流的电流限制装置的鼻吸器，该电流限制装置可以是一个介电的或半绝缘的包层或者说套筒或者是一个连接在从高电容高电压源至电极的线路上的高电阻。另外，也可以采用低电容高电压源例如压电电压源。

在一个方面，本发明提出一种可将极性相反的雾化物质供入鼻腔内的鼻吸器。

在一个方面，本发明提出一种分配器，该分配器可以是鼻吸器，它具有：一个将液体供给出口的装置；一个使出口排出的液体经受足以引起该液体雾化的电场作用的装置；和一个控制雾化物质各成分（例如所得到雾化物质中的液滴）的尺寸的装置。

下面参看附图结合实例说明本发明的实施例，附图中：

图 1 简单示出本发明鼻吸器的使用方法；

图 2 是本发明的鼻吸器的一个实施例的局部简单剖视图；

图 3 是图 2 所示鼻吸器的电路的方框示意图；

图 4 是图 2 所示鼻吸器的一部分的局部放大剖视图，示出图 2 所示鼻吸器的电动流体雾化区的一个实例；

图 5 是图 2 所示鼻吸器的一部分的局部放大剖视图，示出图 2 所示鼻吸器的电动流体雾化区的另一个实例；

图 6 是本发明的鼻吸器的另一个实施例的一部分的局部放大剖视图；

图 7 是本发明的鼻吸器的又一个实施例的一部分的局部放大剖视图；

图 8 很简单地示出用压缩气流致动实施本发明的鼻吸器的另一个实例；

图 9a～9d 是液滴线谱，其中图 9a 示出实施本发明的鼻吸器的液滴的线谱，图 9b～9d 示出各种普通鼻吸器的液滴线谱；

图 10 是本发明鼻吸器的另一个实施例的类似于图 2 是局部剖视图；

图 11 是本发明的鼻吸器的又一个实施例的类似于图 2 的局部剖视图；

图 12 是图 2 所示鼻吸器的一部分的放大图，示出它的一种改型；

图 13 很简单地示出本发明的鼻吸器的一个实施例的又一种改型；

图 14 是具有图 13 所示的改型的鼻吸器的工作情况的示意图；

图 15 是本发明的鼻吸器的又一个实施例的一部分的局部剖视放大图；和

图 16 是出本发明的鼻吸器的又一个实施例的一部分的局部剖视放大图.

如图 1 所示，实施本发明的鼻吸器 1 主要用作一种由使用者操纵将活性物质或者说药品送入患者的鼻孔内的可装入衣袋的手持式装置，例如，可用该鼻吸器将减充血剂（如：盐酸羟甲唑啉）送入鼻腔内或将麻醉剂或者其他药物例如胰岛素或 2,2,3-三甲基丁烷（例如 Elitroptan）通过鼻粘膜送入血液中. 也可用这种鼻吸器将一种在鼻粘膜的较低温度下才有效的流感疫苗例如 Flumist(美国加州 Avivon of Mountain view 公司研制的产品)送入患者鼻腔内.

鼻吸器具有一个主要由电绝缘材料例如塑料制成的壳体 3，该壳体 3 的至少在使用中不可避免地与使用者接触的部分是可通过使用者接地的导电区（这一点将在下面参看图 2 说明）. 鼻吸器 1 具有一个

供使用者吸入液滴的排出管 4，该排出管 4 的大小和形状做成能稍微滑入患者的鼻孔中并与其配合，以形成合适的气密密封．排出管 4 可以从壳体 3 拆下，而换上另一种规格的排出管 4 以便能与不同大小的鼻孔舒适地配合例如使成年人和小孩子都可用这种鼻吸器．虽然从效果的观点上看希望舒适地配合，但是，实际上，将鼻吸器 1 放置在紧靠鼻孔处就足够了．

鼻吸器 1 绕其纵轴线成旋转对称而呈大致的圆筒形，一般地说，壳体 3 的直径约为 1 英寸（25.4mm），长度约为 4～5 英寸（102～127mm）．

图 2 是本发明鼻吸器的一个实施例的局部剖视图，而图 3 示出吸入器元件的电路方框图．

如图 2 所示，鼻吸器 1 的壳体 3 具有一个内隔板 3a，该内隔板 3a 将壳体 3 分隔成第一室 1a 和第二室 1b．

在本实施例中，第一室 1a 内装有一个电池类的电压源 5，从图 3 可更清楚地看到，电池 5 的正极端通过手动开关 SW1 与计数器 6 的复位输入相连接，并与另一开关 SW2 相连接．虽然在图 2 未示出，但电池 5 的负极端也与上面提到的壳体的导电区相连接，如图 3 所示，并由使用者 H 形成其接地线路，上述的开关 SW1 是一种普通的手动开关例如拨动开关或按钮开关．开关 SW2 做成由气流致动（下面再较详细说明）．高压发生器 7 通过开关 SW1 和 SW2 以及计数器 6 与电池 5 相连接，上述的计数器 6 通过开关 SW1 的闭合而复位，当计数器的计数变低时，计数器可将电池电压输出到高压发生器的正极电压输入端，直至达到预定的计数为止．上述高压发生器可以是一种普通的电磁高压倍增器，例如由英国 Brandenbury,Astec Europe 公司（High street,Wollastow,stourbridge,West midlands Dy8 4PG UK）或英国 Start Spellman 公司（Unit1,Broomers Park,Broomers Hill Lane,Pulborough,West Sussex Rh20 2RY, UK）提供的那种倍增器．也可代之以低电容的压电高压源．

第一室 1a 内还含有一个贮存待鼻吸器分配的液体的贮液器 8，该贮液器 8 的形式可以是其内表面是化学惰性的可折叠式柔性袋或波纹管式构件．也可以采用活塞式结构，当用于输送液体时，活塞可随室内的液面移动而避免空气与贮液器 8 内的液体相接触．通过泵 9 将液

体从贮液器 8 泵送到供液管 10，该供液管 10 是用片刻不能保留电荷的绝缘材料做成的，适用的绝缘材料有例如聚醛树脂或 Delrin（商标）.

供液管 10 具有一个出口 10a，设置在供液管 10 内的导电芯件或者说导电棒 11 端接在出口 10a 附近，成为第一电极. 在本实施例中，第一电极 11 通过导线 5'与电池 5 的负极或者说接地端相连接.

绝缘供液管 10 的外表面绕有第二电极 12（见图 4）. 该第二电极 12 沿液体流过供液管 10 的方向位于第一电极尖部 11a 的上游. 上述的第一电极 11 可以是如图 4 所示的尖形的.

在本实施例中，第二电极 12 是一种包覆电极，它具有一个与高压发生器 7 的高压输出端 7a 相连接并装入一个介电的或半绝缘的包层或者说套筒 12b 内的中央导电芯件 12a. 欧洲专利 EP－A－0186983 公开过这种包覆电极. 上述的包层或者说套筒 12b 的电阻率为 $5\times10^{11}\sim5\times10^{13}\Omega$cm，其厚度约为 2mm. 合适的套筒是某些牌号的钠玻璃和酚醛树脂/纸复合材料制品. 可以采用由英格兰的伯明翰 Tufnol 公司供应的风稳片的管件或采用一种酚醛层压塑料管. 芯件 12a 可由紧密地装入套筒 12b 内的碳珠组成. 上述的套筒 12b 漏泄电荷或者说导出电荷的时间常数或者说张弛时间通常约为 10^{-6}秒. 但是，第二电极 12 也可以是不加包层的.

如图 2 所示，第一和第二电极 11 和 12 适宜地置于电绝缘的壳体 4 内，壳体 4 的形成第二室 1b 的部分 4a 将电极 12 与使用者隔开，这就避免了使用者与电极 12 直接接触. 排出管 4 出口的大小要能防止使用者的手指进入第二室 1b 内. 另外，虽然极不可能发生短路，但这种情况或许会在第一与第二电极之间发生，所以，不会使使用者遭受电击.

泵 9 是一种电动泵，例如，可以是一种压电泵，或任何其他合适的电动或机械操纵的泵. 该泵 9 通过开关 SW1 和 SW2 以及计数器 6 与电池 5 的正极端相连接. 在计数器 6 的输出端与泵 9 之间可设置延迟电路 120（例如一种普通的电容-电阻（CR）电路），因此，在第一与第二电极之间建立起足以使供入出口 10a 的液体形成电动流体雾化的电场之前，延迟供给使泵工作所需的电压.

如图 2 所示，计数器 6 的输出信号也传给指示灯或蜂鸣器 13.

从图 2 可看出，气流致动开关 SW2 具有一个安装在固定于第一室 1a 内壁上的弹簧偏压臂 21 上的第一电触片 20. 开关 SW2 具有一个来自弹簧偏压臂 21 的外绝缘体 22，用于堵住壳体 3 上形成的空气入口 30。由一个绝缘的管体 33 形成一条从气流入口 30 至隔板 3a 上的小孔 32 的气道. 绝缘管体 33 的内壁上安装又一个通过导线 35 与高压发生器 7 的正极相连接的电触片 34.

可将绝缘管体 33 改成具有可与在隔板 3a 上绕纵轴线 L 均匀分布的两个或多个小孔 32 相连接的气道 33'（如图 2 中的虚线所示）。

使用鼻吸器 1 时，先将排出管 4 插入鼻孔内或将排出管 4 安置成舒适地顶住鼻孔，然后用手压按开关 SW1 使计数器 6 的复位端与电池 5 的正极相连接，从而使计数器 6 的计数回到零位。然后，使用者像使用普通的鼻吸器那样用鼻孔吸气。由使用者吸气形成的气流引起开关 SW2 的电触片 20 克服弹簧臂 21 的偏压力而向电触片 34 移动。一旦开关 SW2 的电触片 20 与 34 互相接触，便对高压发生器 7 供电，该高压发生器 7 对第二电极 12 供给所需的高压（一般为 3～12KC（千伏）），以便在第一与第二电极 11 与 12 之间建立必需的电场，而形成电动流体雾化区. 一旦上述的电场建立起来. 延迟电路 120 便对泵 9 供入必需的电力，使泵 9 将液体从贮液器 8 泵送到出口 10a.

从出口 10a 流出的液体被电动液体力学法雾化. 第一与第二电极 11 与 12 之间沿径向（即垂直于纵轴线 L 的方向）的距离较小，因为第二电极上的包层可使两个电极紧靠在一起同时又防止它们间的空气电击穿. 由于上述的距离较小，故可形成很高强度的电场，但该电场强度沿纵向 L 急剧下降或者说减小. 这有利用空气中形成的带电荷雾化物质，从管 33 流至排出管 4，故可减少带电荷的物质沉积在第二室 1b 内壁上的可能性.

然后，雾化的物质从出口 4 排出，并均匀地沉积在鼻腔内的导电表面上.

当接通开关 SW1 经过预定的时间后，也就是达到预定的计数值后，计数器 6 的输出变低而关闭高压发生器 7、泵 9 和指示灯或蜂鸣器 13. 使用之后，使用者可按压开关 SW1 再断开电源 5 而使上述装置停止工作.

这样，计数器 6 可使使用者得知已输入所需药物剂量的时刻.

电极 12 的包层或者说套筒起到限制电流的作用，以防止的过量的或者说危险的电流在电极 12 与 11 之间流过.

图 5 示出一个改型实施例，其中，用一种即形成第一电极又形成出口 14a 的空心的导电毛细管 14 代替图 2 中的绝缘供液管 10 和导电的芯件 11. 在本实施例中，第二电极 12 是一种设置在第一室 1b 内壁上的孤立的裸电极，它位于沿液体流过导电管 14 的方向的下游处第一电极 11 的端部. 如图 5 所示，鼻吸器具有供气排出管 33"（它可以是在图 2 虚线所示的气道 33'的延伸段），这就可在使用时在电极的前面形成一种空气屏障以抑制液滴沉积在电极 12 上. 在图 2 所示的结构中，也可作上述的改型. 虽然图 5 示出孤立的裸电极 12，但是，在此情况下，第二电极 12 也可是环形的槽电极或是多个沿第二室 1b 的内壁表面分布的独立的电极. 而且，电极 12 也可以像图 4 所示那样加上包层，并可将它设置成刚好在第一电极的上游处或邻近第一电极. 在此情况下，当第一电极 11 与第二电极 12 之间建立起足以引起电动流体雾化的电场时，便将在导电管 14 的端部形成多股喷流或锥形喷流.

在使用中，有时会在电动流体雾化过程中产生伴随的液滴，这些伴随的液滴通常不会带来什么问题，它们通常会沉积在鼻吸器的内表面上或者沉积在第二电极或者说反电极上. 但是，如果长时间频繁使用上述的鼻吸器时，上述液滴的堆积和/或液滴随后蒸发所形成的残留物可能对反电极 12 的工作有不利影响而降低鼻吸器的总效率. 避免上述问题的方法之一是将鼻吸器的本体做成例如可将形成第一室 1b 的光体部分 4a 取下（例如，壳体部分 4a 可通过螺丝与壳体部分 4b 相连接），以便使使用者可擦拭反电极 12 而去除沉积的液滴或其他物质. 下面说明另一种保持反电极 12 功能的自动装置.

图 6 示出实施本发明的另一种鼻吸器的主要是下室 1b 的局部剖视图. 其上室 1a 的内部结构与上面参看图 2 所述的结构基本上是一样的.

在图 6 中，反电极 12'安装在下室 1b 的内壁 1b'上. 反电极 12'可以是环形的或者是由孤立的单点电极形成的或者是多个沿内壁 1b'隔开分布的电连接的分离电极.

在本实施例中，反电极 12'是一种导电的裸电极，它通过导线 50'

和电阻 R 与导线 5'相连接，而导线 5'则连接到电源 5 的负极端或者说接地端。

在壳体的下室 1b 内按普通方法(未示出)安装了另一个电极 120，该电极 120 离反电极或者说第二电极比离第一电极近得多。一般而言，对于上述尺寸的鼻吸器，电极 120 离反电极 12'可以是 2mm，而离第一电极 11 则为 5mm。反电极 120 通过导线 7a 与高压发生器 7 的高压输出端（图 6 中未示出）相连接。

当使用图 6 所示结构的吸入器时，加在电极 120 的高电压会使电极 120 电晕放电而产生离子，这些离子迁移至最接近的导体（在本实施例中就是反电极 12'），从而形成一种通过反电极 12'和电阻值通常为 600 兆欧姆的电阻 R 而入地的离子流，这就可使反电极 12'间接地充电到所需的电势。任何的从出口 10a 挑出的偶尔会被吸向反电极 12'的带电荷雾化物质将至少部分地被电极 120 产生的离子所形成的离子流放电之，从而减少带电荷物质沉积在反电极 12'上的可能性，并且不需要使用者定期地擦拭反电极 12'。

图 7 示出对图 6 所示结构的改型，其中，由反电极 12" 的包层形成的电阻可足以在反电极 12" 上达到所需的电势而不需要设置电阻 R。在其他方面，图 7 所示结构按图 6 所示结构相同的方式工作。

虽然图 6 和 7 只示出一个产生离子的电极 120，但是，可以围绕供液管 10 设置多个产生离子的电极 120，也可以用围绕供液管 10 设置多个刀片形的或线形的产生离子的电极。

业已发现，图 6 和 7 所示的结构可以使雾化物质更均匀地分布到鼻腔内较深处。因此更进一步改善液滴分布的均匀性。可以认为，这是由于进入离子喷射电极 120 附近区域的带电荷的雾化物质至少会部分地放电，从而使一些吸入的雾化物质带电荷很少，因此容易更好地沉积到鼻腔内。

图 6 和 7 所示的气道可以改成图 5 所示的那样，以形成具有保护性空气屏蔽的第二电极。

在上述结构中，气动开关 SW2 由使用者吸气而致动。但是，使用者可能过于虚弱以致不能足够强有力地吸气来开动开关 SW2。在这种情况下，鼻吸器 1 可以在开关 SW2 附近安装一个适配器 100(见图 8)，该适配器 100 通过导管 101 与手动装置 102（例如球胆或折箱）相连

接，该手动装置 102 可由患者或其他人如医生、护士或护工压缩，以迫使气流打开空气入口 30 并合上开关 SW2，或者将适配器 100 连接到压缩空气或气瓶或可电动的压气机，按所需流速沿管道将空气供进气口 30.

图 9a～9d 示出用英国 Malvern 仪器公司制造的 Malvern Mastersizer X 测出的试验液滴的尺寸分布谱线. 图 9a 示出用图 1 所示的装置得到的典型的液滴谱线，如图 9a 所示，介质粒子或者说液滴的直径约为 10μm，这是用于鼻吸所需的液滴直径的下限值. 图 9b～9d 示出由 3 种商用的鼻吸器产生的相当的液滴谱线，其中图 9b 是由“Otravine”（注册商标）鼻吸器产生的液滴谱线，所述的鼻吸器具有一个用于供入作为减充血剂的盐酸赛洛唑啉的可挤压塑料瓶，它是由英国 Novartis Consumer Health 公司（Horsham RH12 4AB,UK）提供的. 图 9c 示出“Flixonase”鼻吸入器产生的液滴谱线，它彩一种计量值和一种加压容器，供入丙酸氟替卡松（fluticasone propionate）它是由英国 Allen & Hanburys 公司（Stockley Park,Middlesex UB11 1BT,UK）提供的. 图 9d 示出由“Beconase”泵动鼻吸器产生的液滴谱线所述的鼻吸器含有二丙酸倍氯米松，它也是由 Allen & Hanburys 公司提供的. 从图 9b～9d 与图 9a 的比较可以看出，上述 3 种普通的鼻吸器产生的粒子或者说液滴的直径分布较宽，与图 9a 所示的电动液体雾化装置所能达到的液滴尺寸相比，它们对液滴尺寸的控制功能较差. 还应注意到，常规的鼻吸器不能使液滴带电荷，仅仅依靠扰动和惯性使液滴沉积，而且，常规的推进式鼻吸器的性能强烈地依靠使用者鼻腔内产生的气流.

已经在鼻子模型上试验过图 1 所示吸入器 1 的操作，发现，所产生的带电喷射液滴均匀地沉积在代表鼻子内腔的导电表面上. 在这些试验中所用的液体的电阻率为 4500Ω · cm，表面张力为 30mN/m（每米 30 毫牛顿），其粘度为 2.4Cp（厘泊），在第一与第二电极之间施加的电压为 8～12KV.

上述的实施例主要是针对电阻率较高的雾化液体如：油和酒精. 图 10 示出对图 2 所示吸入器的一种改型方案，该改型实施例适用于雾化导电性很好的液体如：水和盐溶液.

在图 10 所示的鼻吸器 300 中，用穿过壁 3a 上的小孔 32 并形成

气道 330a 的空心体或气道管 330 替换图 2 所示的气道管 33，该气道管的端部形成一个包围出口 10a 的环状喷出口 331，而在其他的所有方面，该鼻吸器 300 都与图 2 所示的鼻吸器相同。

鼻吸器 300 除了在一个重要的方面以外，其工作方式与图 2 所示鼻吸器 1 相同。因此，当使用者用鼻吸器 300 通过鼻孔急剧地吸气时，便通过喷出口 331 将快速移动的气流传送到会发生雾化的区域。来自喷出口 311 气流的作用是剪切从出口 10a 排出来的液体经电动流体雾化形成的液滴，从而使液滴尺寸比没有上述气流的情况下更小。这就使鼻吸器可用于导电的液体如水和盐溶液，这些液体按其他方法是难以电动流体雾化的。

用龙头自来水作为待雾化的液体进行了试验，供液管带有内径为 0.2mm 的出口 10a，在第一与第二电极 11 与 12 之间施加的电压为 2.5Kv。管子直径根据预计的使用者的平均鼻吸速度来选择，以便使喷出口 331 喷出足以引起剪切作用的气流速率（在本实施例中为 10m/s）。在流过同轴包围出口的管子的气流量为 20－30 升/分钟的情况下，管子出口面积通常应为 n 个平方毫米，以便能克服鼻腔对气流的阻抗。

测出液滴的直径约为 20μm。测出液滴的电荷与质量之比约为 10-4 库仑/公斤。因此，液滴尺寸显著小于没有气流的情况下产生的液滴。

上面提到的约为 10m/s 的气流速度足以引起剪切使用，大致相当于较健康的人急剧呼吸时所产生的气流速度。

显然，图 10 所示的上述改型可与上面图 4－8 所示的任一种改型的合适结构结合使用，例如，可将反电极 12 置于第一电极 11 之下游（见图 5）。而且，很明显，可以在雾化区或雾化部位附近设置一个、两个或多个气流出口。全部的问题就在于，要在雾化区或雾化部位获得足够的气流以便在不引起过分扰动的情况下产生剪切作用。关于这一点要注意到，如图 10 所示，喷出口 331 的方向要设置成可形成一股与出口 10a 流出的液体的方向相倾斜的气流。

除了在本申请书的前言中所述的理由之外，熟悉本技术的人们可能已经想到，使用鼻吸器的人们不希望吸入带电荷液滴，因为，若使用者在使用鼻吸器的过程中未接地的话，吸入带电荷的液滴会使使用

者电压升高，因此，在使用者随后接地时就会受到令人讨厌的电冲击.

但是，本发明人已经发现，未接地的使用者在使用一次本发明的鼻吸器时电压的升高还不足以高到会引起不愉快的放电程度. 而且，必要时还可将传至使用者的电荷量控制到最小. 为此，可以通过例如改进携带待吸入的药物的液体的配方使之具有比通常所用的水溶液更高的活性物质或者说药物的浓度. 因此，只需吸入较少量的液体便可达到所要求的剂量. 这就减少了总的空间电荷，并有利于吸入流过鼻吸器的气流中所含的雾化物质. 一般来说，上述的浓度可提高 5 倍（即活性物质的体积百分数可从 10% 提高到 50%）.

如果需要延长治疗或连续治疗，可将上述的鼻吸器加以改进，定期地转换高压发生器的供电极性. 这样，使用者在接受了带有一种极性的电荷的液滴之后，再接受具有相反极性的电荷的液滴，这就可防止使用者的电压显著升高. 为达到上述目的，可以简单地采用一种压电振荡器作为高压发生器，上述振荡器是由使用者应用凸轮连杆机构人工操纵的，这就可自动地进行极性转换，压按晶体时产生的电压将在松开晶体时变成极性相反的电压.

在上述的每个实施例中，在第二电极或者说反电极上施加高压，但是，第二电极可能被省去，故可将第一电极直接充电至所需的高压，尤其是在采用低功率、低电容的高压发生器（例如压电振荡器）时更是如此.

图 11 简单示出本发明鼻吸器的另一个实施例的类似于图 2 的局部剖视图，其中第一电极是直接充电的.

图 11 所示的鼻吸器 301 具有两个分别带有出口 10a 的供液管 10，该供液管 10 分别与对应的泵 9 相连接，故分别接收来自相应的贮液器 8 的液体. 虽然在图 11 没有明确的示出，但每个泵 9 连接在延迟电路 120 与电压源 5 的负极端之间. 每个供液管 10 内装有一个导电芯件状的第一电极 11，一个供液管 10 的第一电极 11 与高压发生器 7 的高压输出端相连接（在图 6 未示出），另一个提供相反极性（在本实施中是负极）的高压的高压发生器 7' 的高压输出端与另一个供液管 10 的第一电极相连接. 在这种情况下，或者是液体应具有足够高的抑制第一电极 11 的直接充电而引起泵的电压升高的抗力，或者是

泵应与液体电绝缘隔开.

图 11 所示的气流通过也与图 2 所示的有所不同. 在图 11 所示鼻吸器 301 中, 用一个穿过壁 3a 上的小孔 32 的绝缘管体 333 代替图 2 的绝缘管体 33, 管体 333 端部接一个空气出口 334, 如图 11 所示, 该空气出口 334 与鼻吸器同轴, 并且对称地位于两个液体出口 10a 之间. 图 11 所示鼻吸器 301 按类似于图 2 所示鼻吸器的方式工作, 只是它产生两股极性相反的喷流或者说雾化物. 空气出口 334 喷出的气流足以保持两股极性相反的雾化物质隔开, 而将两股极性相反的雾化物质送入鼻腔中. 上述结构的优点在于, 可在不改变使用者身体的总电荷的情况下将雾化物质送入鼻腔内. 一般来说, 两个供液管的纵向轴线可相隔 12~15mm.

应当明白, 图 11 所示的改型实施例可以与上述的图 4~8 所示的改型实施例结合使用.

在上述的每个实施例中, 气流速度的控制取决于使用者的吸气强度, 或者如图 8 所示取决于泵 102 的工作. 也可以借助于设置在空气流道中的阀来控制上述各实施例中的气流速度. 例如, 在图 12 示出的图 2 的鼻吸器的局部中, 在其空气流道 33 中可转动地安装了一个瓣阀或者说闸门 301. 该瓣阀 301 可以借助任何普通的机构而工作. 例如, 瓣阀 301 可以通过使用者转动一个安装在壳体外面的球形柄而手控之, 或者通过一种凸轮机构以机械方法控制瓣阀的转动, 或通过凸轮机构和电磁线圈以机电方法控制瓣阀的转动, 或者由现场医生操作. 也可采用其他的普通类型的阀.

如上所述, 从空气出口 334 喷出的气流用于使两股极性相反的喷出液流或者说雾化物质保持隔开状态. 可以通过例如在空气出口 334 内设置一个节流阀或类似的阀以控制流过出口 334 的气流速度来控制用于保持相反极性的雾化物隔开的空气量及其混合程度. 上述的气流阀可由医生或在制造厂预先调好(例如根据要由鼻吸器输送的活性物质的种类调定), 或者由使用者调节. 雾化物质在鼻腔内的沉积区可通过控制送入使用者鼻孔内的雾化物质的总电荷量来控制, 故可通过气流控制阀调节气流速度而使活性物质送到目标区域.

显然, 不同的使用者或者说不同的患者具有不同的鼻吸速度, 使用普通的推进式鼻吸器时, 鼻吸速度高的人可使被吸入的物质沉积到

比鼻吸速度较低的人使用该鼻吸器时所能达到的鼻腔内更深的部位，但是，图 11 所示的鼻吸器具有如下的优点：鼻吸速度高的人可使从空气出口 334 喷出的气流比鼻吸速度低的人更快，所以鼻吸速度高的人可接受比鼻吸能力低的人带电荷更多、混合更少的雾化物质．由于带电荷较多的物质倾向于较浅的进入鼻腔，故图 11 所示的鼻吸器是有自调节作用，因为较大的吸入速度引起的雾化物质较深地沉积到鼻腔内的倾向与较多的电荷引起的较浅地沉积到鼻腔内的倾向互相抵消了．

在图 11 所示的结构中，两个液体出口 10a 是相互平行的．但是，它们也可以相互倾斜例如与鼻吸器的纵轴线 L 成 45°，这就可提高喷出物的混合程度．

除了控制气流速度以外或者说代替控制气流速度还可以通过调节高压发生器 7 和 7' 提供的电压和/或调节流到出口 10a 的相对流速而控制加到两个第一电极 11 上的相对电压，来控制由鼻吸器传送的雾化物质的总电荷，从而控制雾化物质进入鼻腔的深度．上述的调节可以在制造厂进行，所以在工厂内可将同一结构的鼻吸器调到可用于输送不同剂量的同一活性物质（例如小孩子和成年人都可用），或者可将同一种鼻吸器调到用于输送要求不同剂量的不同活性物质．另一种可能是，在临床条件下由医生或护士，或由药剂师，或由使用者或者说患者本身调节高压发生器提供的电压和/或调节气流速度，以控制使用者所能接受的剂量．

如上所述，假定在两个供液管 10 内供入相同的液体．如果在此情况下不要求调节它们的相对流速，那么便可设置一个贮液器 8 和一个泵 9．而且，可以设置对一个第一电极 11 提供一个极性的高压的高压发生器而不是设置提供独立的正极和负极高压的高压发生器，另一个电极则可接地，所以，在实践中，由直接充电的第一电极感应充电．其好处是只需要第一的高压发生器，故可降低总的成本，并可减小在鼻吸器内装设高压发生器的空间．

在如图 11 所示的分别设置相应的贮液器 8 和泵 9 的情况下，两个供液管 10 可以供给不同的液体，如果产生极性相反的雾化物质，两股液体会相互作用．例如，两股液体可含有或者说具有相应的活性物质，如果产生极性相反的雾化物质，各组分就会相互混合和相互作

用，而形成所需的活性物质．这就可以例如只在需要时才形成短储存寿命的活性物质．另一种可能是，两个供液管 10 可提供两种不希望其发生相互反应但它们若相互出现较长时间就会损失它们的相对效力的不同的活性物质．另一种可能是，一种液体中含有发泡剂，该发泡剂在其所含的雾化物质与极性相反的雾化物质起反应时，会引起另一种雾化物质的液滴或者说颗粒膨胀而形成可以较深地进入鼻腔内的低密度的颗粒例如小球体．另一种可能是，在从一个供液管排出的液体产生液态的或凝胶状的雾化物质的情况下，如果两种极性相反的雾化物质相混合，上述的液态的成凝胶状的雾化物质可覆盖在或敷在另一种雾化物质的颗粒上而形成例如可从覆盖的颗粒芯部缓慢释放活性物质的微胶囊或带涂层的短纤维或微纤维．覆盖在外面的物质可含有一种生物粘结剂，以防止粘液纤毛的间隙，并且在要求控制产物的释放时有利于长时间地或者说持续地释放活性物质．

具有两个供液管的结构的另一个优点是，活性物质送入鼻腔内的总体速度大于只用单个供液出口时的速度．显然，也可以采用多于一对的供液管，而且对于（具体地说）在装置内可以充分混合雾化物质的情况下不需要设置等量的带正电和带负电的第一电极．保证存在残余电荷．

设置多个出口以形成极性相反的雾化物质的另一个优点是，雾化喷液相互之间比与壳体壁之间有更强的吸引力，所以，沉积到壳体内壁上的雾化物质可以减少．

另外，图 11 所示的结构应当能产生带有预定电荷的尺寸较大的雾化物质液滴或者说颗粒．

显然，在图 11 所示的实施例中虽然不需要反电极 12，但该图所示结构适合于按照图 2 所示的类似方式设置反电极 12，且各自的反电极与相应的正、负高压发生器 7 和 7' 相连接，而第一电极 11 与电源的负极端相连接，或与极性相反的高压发生器相连接．还应明白，反电极不需要加介电的包层（尽管加包层通常是有利的）．这种结构有利于使图 11 所示的鼻吸器用于导电性更好的液体．

在图 11 所示的结构中，空气出口 334 设置在两个液体出口 10a 之间的中间．虽然这对于需要使两股极性相反的雾化物保持隔开状态的情况是有利的，但是，在需要有一些混合的情况下，可以使空气出

口按包围液体出口的方式设置，例如，空气进入孔可设置在壳体壁 4a 上．围绕液体出口设置空气出口除了有利于所需的液体混合以外，还可形成一层空气屏蔽以抑制或至少是进一步减少在壳体内壁上沉积的可能性．

正如国际专利 WO 98/03267 所述，在电动流体雾化的过程中，由出口 10a 排出的液体所经受的强的电场使液体表面上形成持续的电波，从而产生至少一个发射带电荷液体喷流的尖点或锥顶（取决于出口 10a 的尺寸）．在液体喷流中不可避免地会发生小的扰动，这就会引起可使喷流变得不稳定的生长波，液体中的净电荷产生一种可抵消液体表面张力的推斥力，而引起液体的雾化．上述的生长波具有固有频率，业已发现，在喷流中发生生长波的起始点可通过将不同于生长波的固有频率的交流信号叠加在所加的高压上来控制，从而可控制所形成的液滴的尺寸．

本发明人已发现，为了产生两种或多种控制良好的直径的雾化液滴（而不是单分散的雾化），可以通过在高压信号上叠加一个含有一个或多个接近于生长波固有频率的叠加频率的振荡信号来使液体雾化．

如图 13 所示，通过高压电容器 C 将脉冲或者说信号发生器 70 与高压发生器的高压输出线 7a 相连接．但是，也可以采用高压发生器的固有频率，并在高压输出线 7a 上保持一些交流脉动．

任何可以由鼻吸器的电压源 5（例如，见图 2）供电的合适的脉冲发生器或者说信号发生器都是可以用的．例如，脉冲/信号发生器 70 可具有多个电压控制振荡器，每个振荡器接收按公知的方法用电压分比或者说倍增技术从电压源导出的相应的不同驱动电压．另一种可能是，采用多次控制振荡器，例如，脉冲/信号发生器可具有一个按顺序编址数值储存的数字存储器，上述的数值可从存储器依序读出并输入到数字/模拟转换器，以再构成所需的波形．在此情况下，代表两个或多个频率叠加的信号可从存储在存储器中的号码直接产生．若要详细了解可用作脉冲/信号发生器 70 的振荡器，可以参考标准的电子教科书例如由 Paul Horowitz 和 Winfield Hill 所著的《电子技术》．

图 14 示出振幅变化的电压的叠加如何以其加到高压输出线上的

大振幅和小振幅脉冲或者说“突跳”（图中简单地以线 71 表示）影响着液滴的形成，从而产生两种尺寸的液滴 D 和 d.

如果按上述方式改变图 2 所示的鼻吸器时，那么在使用中从出口 10a 排出的液体便被电动流体雾化之，并且如上所述在使用者鼻吸时沉积在鼻孔内部的导电表面上．但是，带有较少电荷且具有惯性较小的较小液滴将继续运动进入比大液滴更深的鼻腔内，故使输送的药物沿鼻腔长度更均匀地深积下来．

显然，叠加 3 种或更多种的频率可按可控方式产生 3 种或更多种不同尺寸的液滴．

也可以不是叠加不同的频率，而是将不同频率的信号依序加到高压输出线 7a 上，从而根据在产生液滴时所加的具体驱动频率按可控的方式随时改变所产生的液滴的尺寸．

上面结合图 13 和 14 所述的结构假设驱动信号是正弦波．但是，这不是所必需的情况，例如，可以采用脉冲宽度为 1 微秒或更短的短时尖峰脉冲．一般而言，脉冲发生器 70 产生的驱动信号的振幅约为高压的 2%（例如 10～100 伏），其频率为 50KHz～（10－50）MHz（这取决于所需的液滴尺寸）．

另一种可用类型的振荡器是压电谐振器，设置两个或多个谐振器以形成不同频率的谐振，从而达到所需的驱动频率．

图 15 和 16 简单示出图 2 所示鼻吸器的又一种改型方案的一部分．

在图 15 所示的结构中，泵 9 可对 3 个供液管 101、102、103 供液，每个供液管具有相应的出口 101a、102a、103a，并且分别含有导电芯件或者说导电棒 111、112 和 113．在所有情况下，导电芯件或者说导电棒都通过导线 5a 与电压源 5 的接地端相连接，而分别由绝缘供液管 101、102 和 103 携带的第二电极 121、122 和 123 则与来自高压发生器的高压输出线 7a 相连接．每个供液管 101、102 和 103 都具有流量控制阀 V_1、V_2 和 V_3，每个流量控制阀 V_1、V_2 和 V_3 控制流过相关供液管的液体的流速，从而使流过出口 101a、102a、103a 的液体流速互不相同．任何合适种类的阀例如简单的机械节流阀或机电的电磁阀都可以用．由于各出口 101a、102a、103a 的流速不同．故在由各出口的电动流体雾化过程中产生的液滴的尺寸也不同．因此，图 15

所示实施例可通过使3个供液管形成不同的流速而产生3种不同尺寸的液滴.

显然，可以采用具有不同液体流速的两个、三个或更多个供液管，而且液体的流速可预先设定或可由使用者加以调节．图15所示实施例可以同时产生不同尺寸的液滴．通过控制供液阀的开启程度随时调节每个供液管中的液体流速，便可依序产生不同尺寸的液滴.

图16示出另一种改型实施例．其中，泵9带有两个或多个供液管104和105，每个供液管内具有中心导电芯件或者说导电棒114和115以构成第一电极．在此情况下，第二电极124安装在壳体4的壁上．上述的供液管104和105的横截面是不同的，因此形成不同的液体流速.

另一个方案是，不同的供液管配置可产生不同流速的不同的泵.

通过将一个类似于用脉冲发生器70时产生的生长波的固有频率的驱动信号叠加在线路7a的高压信号上，可使在图15和16中不同出口上的雾化过程同时进行.

在上述的每个实施例中，在壳体的下部4a内产生气流．为了避免空气移动破坏液体出口进行电动流体雾化所需的泰勒锥体，可在供液管周围紧靠液体出口10a设置环形屏障.

在上述的每个实施例中，鼻吸器的结构可由一个或几个贮液器8供给多种药物剂量的液体．但是，鼻吸器1可以是单一剂量鼻吸器，它的贮液器仅装有足以形成单一剂量的液体组分，在此情况下，上面结合图3所述的计数器6和蜂鸣器13可以省去．在单一剂量鼻吸器的情况下，可将供液部件设置成可由使用者更换的可更换的插入或管筒．在此情况下，为了容易制造，而且使这些部件较为便宜，上述供液管筒一般都含有第一电极11，和第二电极12（如果有第二电极且不设置在壳体下部的话）．另一种可能是，鼻吸器可具有膜片的圆盘传送带或自动储存送料装置，上述的传送带或送料装置可转位移动，所以鼻吸器每次使用后，将新鲜的膜片移至下次使用的位置．上述的自动储存送料装置可以是携带膜片的条带形，例如，当膜片用完时，上述条带便由一个卷轴绕到另一卷轴上.

在上述的实施例中，鼻吸器具有用于一个鼻孔的单一出口．鼻吸器也可具有成对的出口，即每个鼻孔用一个出口.

虽然在上述的实施例中已说明了具体形式的电动流体雾化装置，但是应当明白，其他形式的电动流体雾化装置也是可以用的，而且还可使用其他形式的电动泵.

可以在从贮液器至出口 10a 的液流通道的合适位置上设置电动的或机电操纵的阀，以防漏泄，保持微生物的整体性.

虽然上述的结构结合对人类（只由使用者操纵或借助于医生、护士或护工）供给活性物质进行了说明，但是应当明白，上述的装置当然也适用于其他的哺乳动物，由富有经验的人或其他人按结合图 8 所述方法控制气流的喷出.

鼻吸器所输送的活性物质可以是任何可为使用者产生所需效果的药剂或物质. 例如，活性物质可以是在治病时对动物身体例如人或其他动物进行治疗、手述或诊断以提供高体质的药物. 这些药物例如是：尼古丁、吗啡、维生素、抗菌剂、消炎药、抗生素抗癌剂或其他的药品、疫苗、蛋白质、酶、DNA（脱氧核糖核酸）或 DNA 碎片等，因为电动流体雾化法能够输送大分子量的药物而不会使它们变性.

输送活性物质的液体组分可以是溶液、乳胶、悬浮液或微悬浮液或任何其他合适的液体形态. 由于粘性液体（包括油类）例如甘油、亚麻酸可通过电动流体雾化法而雾化，故作为活性物质的载体是最佳的，因此，例如，在活性物质是亲脂的化合物（如：可能是麻醉剂或药物）的情况下，使用电动流体雾化法可简化活性物质组分的制备. 而且，使用油类和软化剂有如下好处：油基药物可更好地渗透细胞膜，故为吸入到鼻腔内时可更快地吸收药物. 而且油类组分和油基组分比酒精组分或盐水溶液对鼻腔的刺激性小. 另外，油类和其他导电性小的液体可产生电荷/质量比值低的液滴. 故带电荷的喷液膨胀速度较低，这就可减小在装置内部沉积的可能性. 而且上述的导电性小的液体也不大可能产生短路，因为它们电阻较大.

正如在现有技术中所知的，对于高导电性的液体来说，若不采用表面活化剂而要满意地进行电动流体雾化是十分困难的，而上述的表面活化剂对鼻腔有刺激作用，所以在鼻吸治疗中不希望采用它. 但是，使用导电性较大的液体组分又是不可避免的，例如，所需要的活性物质的数量和类型是导电性高的液体组分，和/或所需要的液体载体是例如水或含离子组分的水/乙醇混合物而使液体的导电性提高.

本发明人意外地发现，通过在高分子量聚合物介质型的液体组分中加入一种添加剂可以在不用表面活化剂的情况下对导电性较大的液体获得满意的电动流体雾化物质．上述的聚合物可以是合成的或天然的聚合物，其分子量一般为 40000～400000．

用一种由 70％酒精和 30％的 0.5 克分子 NaCl 水溶液（盐水）组成的液体组分进行了试验以模仿一种带有活性物质的液体组分．

用 PVA（聚乙烯醇）作为聚合物进行第一组试验，在本试验中，这种聚合物的分子量选为 125000．该组试验的细节列于下表 1，每个出口的最大的稳定流速为 3 毫升/秒（ml/s）．

表 1

实例	配方	电阻率/Ω·m	粘度/厘泊
1	10ml 液体组分中含 0.1gPVA	5.54	10
2	10ml 液体组分中含 0.2gPVA	4.20	24
3	10ml 液体组分中含 0.3gPVA	4.80	72
4	10ml 液体组分中含 0.4gPVA	5.21	110
5	10ml 液体组分中含 0.5gPVA	5.10	200
6	10ml 液体组分中含 0.6gPVA	5.21	360
7	10ml 液体组分中含 0.7gPVA	5.25	700

在实例 1－7 中每一个实例都获得满意的电动流体雾化物质．拍摄了所得到的雾化物质的显微照片，意外地发现，雾化物质的几何形状和结构随加入配方中的聚合物的量的变化而变化．因此，当 10ml 液体中加入 0.1g 聚合物时，得到的雾化物质在外观上是球形的或接近于球形的颗粒状．当 PVA 的量增加到 0.2g 时．雾化物质仍然是颗

粒状的，但是，有些颗粒带有尾丝或变成微纤维状．随着 PVA 的量增加．也就是从实例 2 进行到实例 7 时，微纤维或带尾丝的量增多，以致在实例 7 中大多数雾化物质成为小纤维或者说微纤维．

也用聚乙烯基吡咯烷酮（PVP）进行了类似的试验，表 2 示出其试验结果，所用的 PVP 的分子量为 360000，每个出口的最大流速为 1.5 毫升/秒．

表 2

实例	配方	电阻率/Ω·m	粘度/厘泊
8	10ml 液体组分中含 0.2gPVA	4.74	10
9	10ml 液体组分中含 0.4gPVA	4.76	60
10	10ml 液体组分中含 0.6gPVA	5.36	180
11	10ml 液体组分中含 0.8gPVA	5.20	260
12	10ml 液体组分中含 1.0gPVA	5.32	480
13	10ml 液体组分中含 1.2gPVA	5.82	740

在实例 8～13 的每个实例中也达到了满意的电动流体雾化效果．而且拍摄了显微照片，也发现雾化物质的几何形状或结构随加入到液体组分中的聚合物的量而变化．当 10ml（毫升）液体中加入 0.2g 聚合物时，雾化物质通常是带有极少微纤维或尾丝的颗粒状，在 10ml 液体组分中加入 0.4g PVP 时，可看到较多的微纤维或尾丝．

当在 10ml 液体组分中加入 0.6g 的 PVP 时，可看到大量的尾丝和微纤维，极少颗粒状，之后，微纤维和短纤维继续增多，进行进一步试验的结果发现，在 10ml 液体组分中加入 0.5g 的 PVP 时，颗粒状物质与微纤维或尾丝之间有良好比例关系．

因此，意外地看到，通过控制加入液体组分的高分子量聚合物的

介质的量可以控制雾化物质的几何形状或者说形状，使雾化物质从颗粒状变为短纤维或微纤维，其中，一部分含有颗粒的雾化物质带有短的尾丝或附加的微纤维．能够控制雾化物质的形状或者说几何形状是有利的，因为这就意味着可将雾化物质的形状改变成符合所需的用途．业已发现上述的微纤维或尾丝通常是半固体，并可以较好地粘附到诸如鼻腔内的表面上和/或它们本身互相粘附，故可减少粘液纤毛脱除的可能性．而且，由于可在直径小于 1μm 的很小颗粒至短纤维或微纤维的范围内控制雾化物质的尺寸，故可控制粘液膜吸收活性物质的速度，很小的颗粒吸收快，较大的颗粒吸收较慢，从而更持续不断地释放活性物质．因此，可以通过改变雾化物质的几何形状来控制活性物质的输送速度．

采用上述的可通过鼻腔吸入而输送活性物质的电动流体雾化法可以控制活性物质的吸入速度和部位，所以，例如，可以快速地将活性物质送到脑部，而全身极少吸收，这在输送对全身具有害副作用的麻醉剂的情况下尤其重要．

上述的实施例说明了通过鼻腔输送活性物质的鼻吸器．但是，在设置图 8 所示的改型实施例而不需要由使用者鼻吸的情况下，可以将活性物质送到其他身体部分、内腔或器官，或供到伤口内或供到伤口上．这种装置也可用于将活性物质送入眼睛，因为电极是不露出的，故可抑制电击的可能性．当这种装置用于将活性物质送到眼睛的表面时，可将壳体的排出管做成例如符合眼窝的形状．具有上述图 8 所示鼻吸器的结构的装置可用于在手术前或手术后供给活性物质，以便例如（特别是在治疗眼睛的情况下）减少手术后形成疤痕组织的可能性，也可用于供给抗生素、抗菌药、麻醉剂等到眼睛表面或供入身体的孔口内，还可在手术过程中将雾化物质供给到身体的暴露的内表面上，例如供给粘合剂修复动脉壁的切口，或者对身体的内伤口或外伤口涂敷伤口敷料或药物．

雾化物质的最终形式将取决于被雾化的液体．因此，例如若液体在雾化后开始凝固或胶凝，那么就形成固态或凝胶状微滴．如果液体刚好在雾化前开始凝固或胶凝，通常就形成小的纤维或微纤维，在上述装置不用于鼻吸的情况下，雾化一词也应包含在所加电场未将液体分裂之前供入的液体发生凝固或胶凝而形成单一纤维的情况，尽管严

格说来在此情况下液体并没有雾化，因为它不必要被破裂.

熟悉本技术的人们将会理解其他更多的改型.

说　明　书　附　图

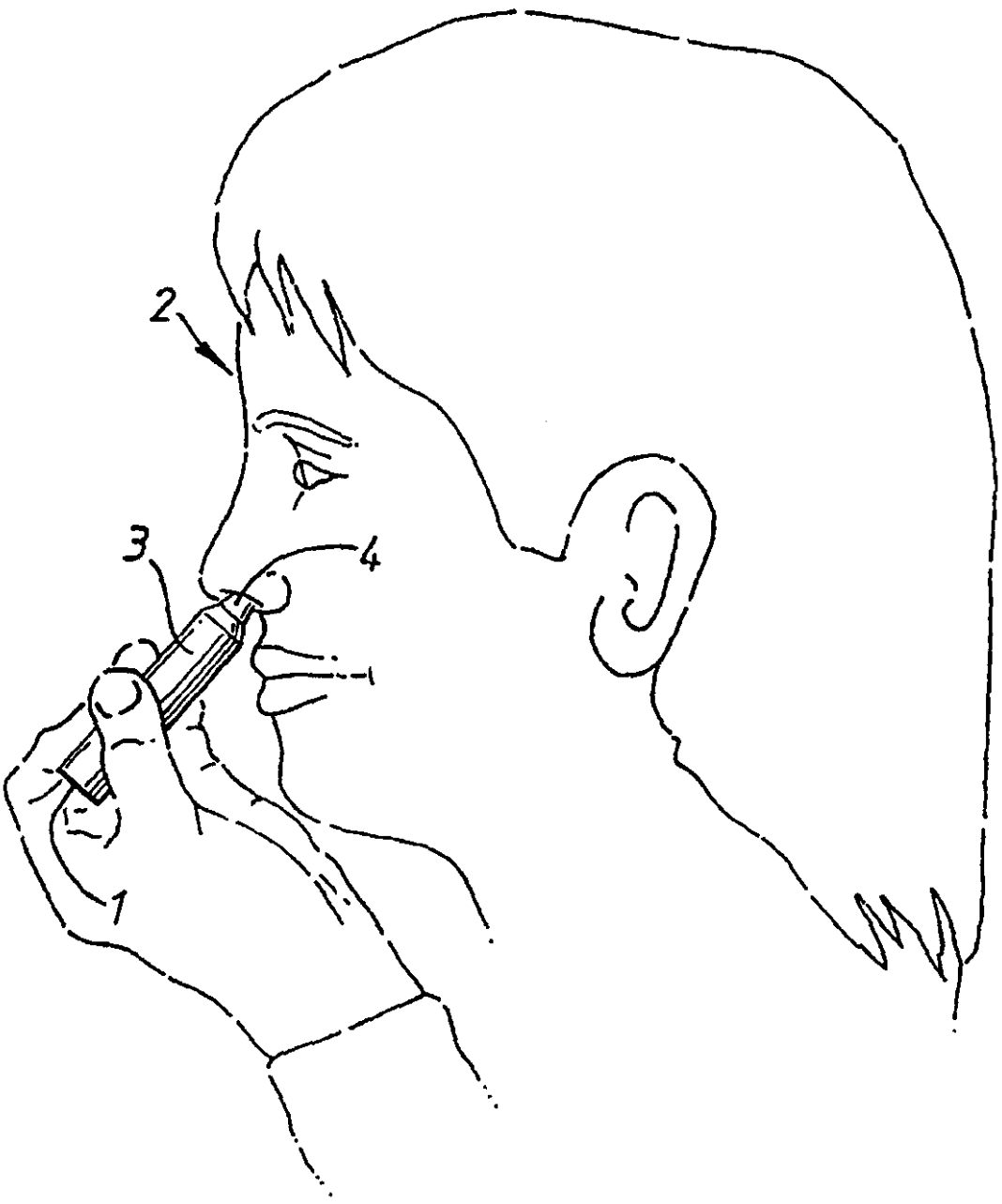


图　1

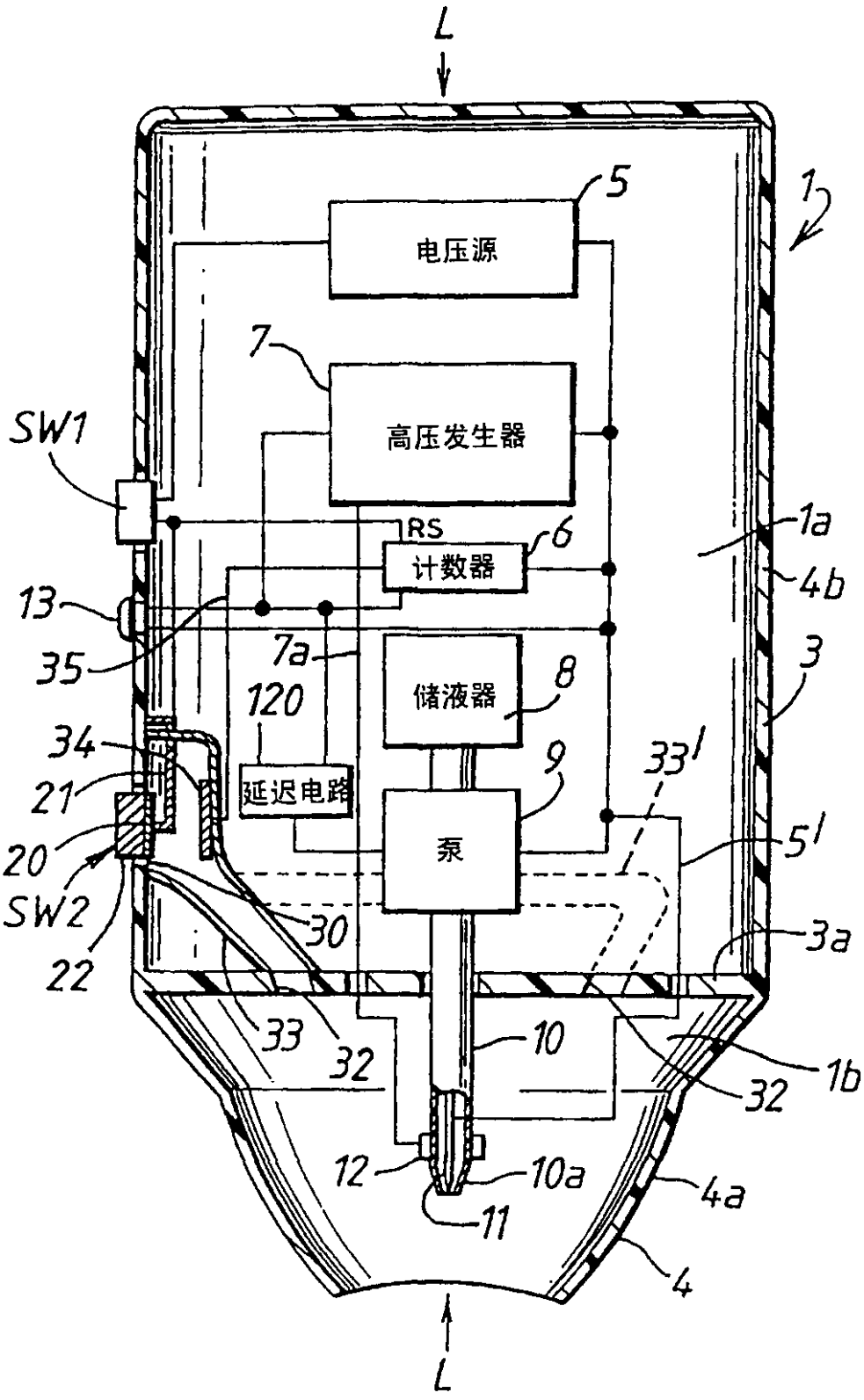

L
5
电压源
1
7
高压发生器
SW1
RS
计数器
6
1a
4b
13
35
7a
120
储液器
8
3
34
21
延迟电路
9
33'
泵
5'
20
SW2
22
30
3a
33
32
10
1b
32
12
10a
4a
11
4
L

图 2

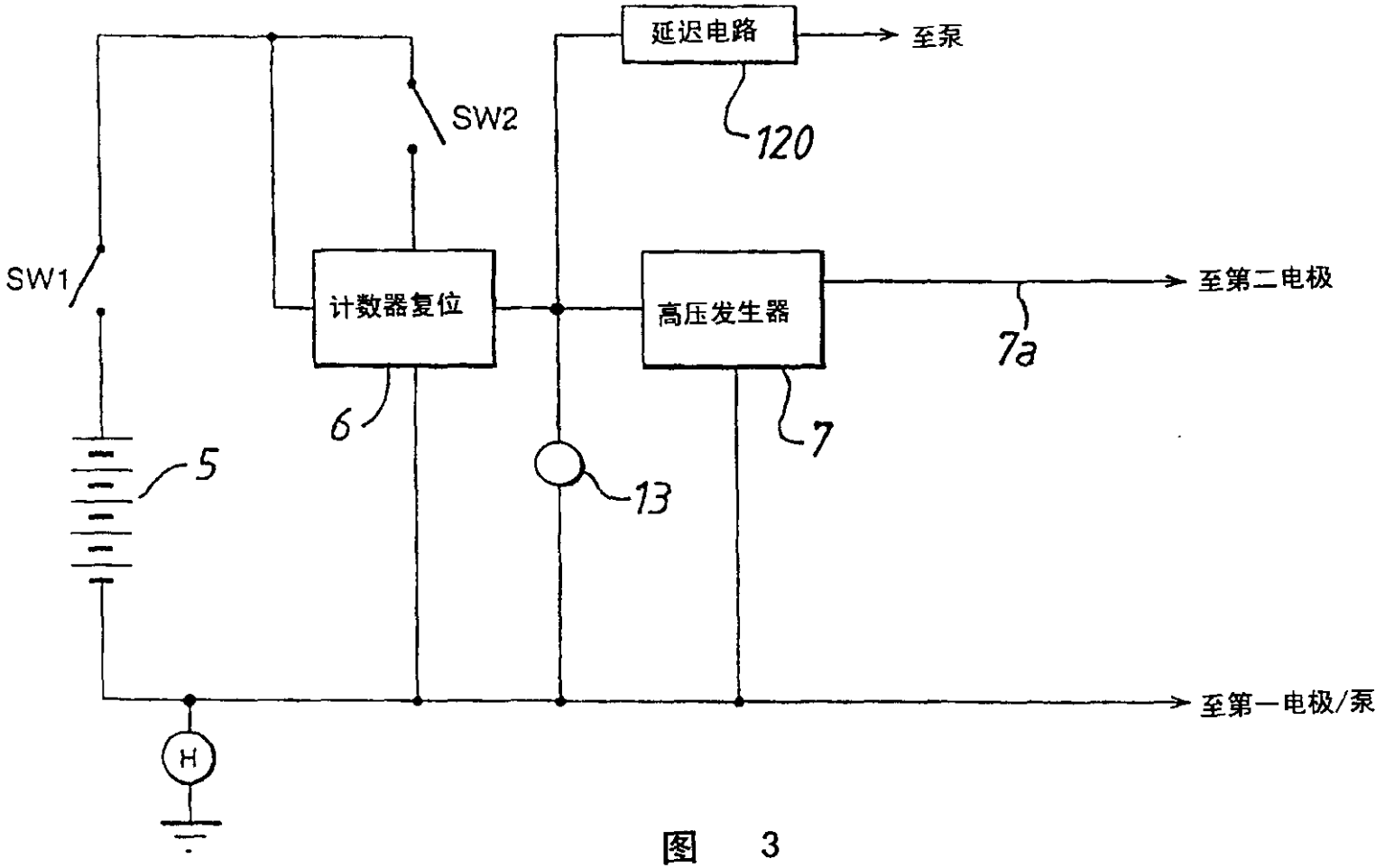


图 3

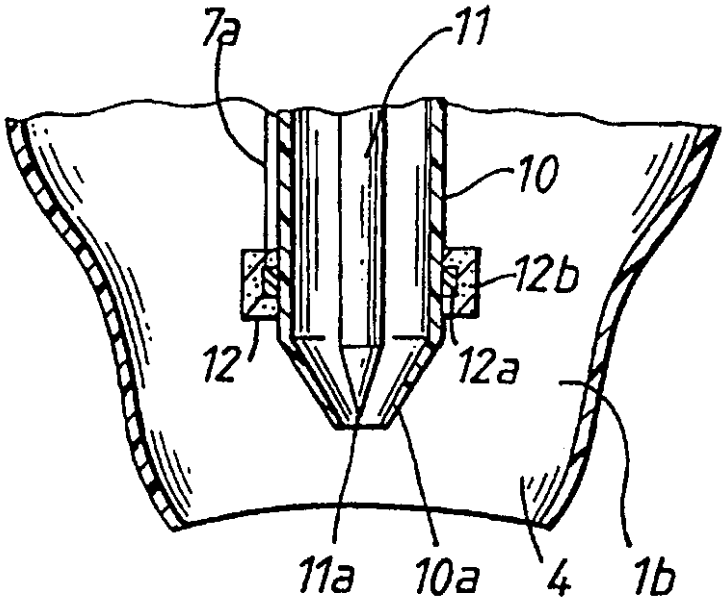


图 4

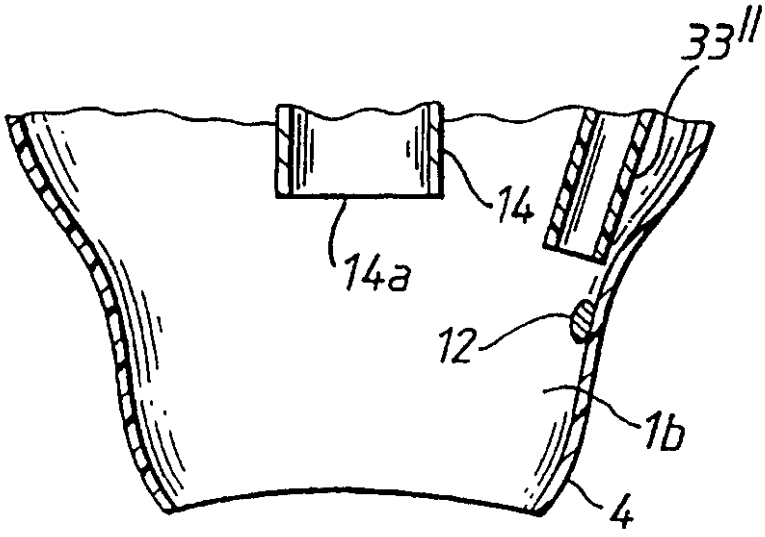


图 5

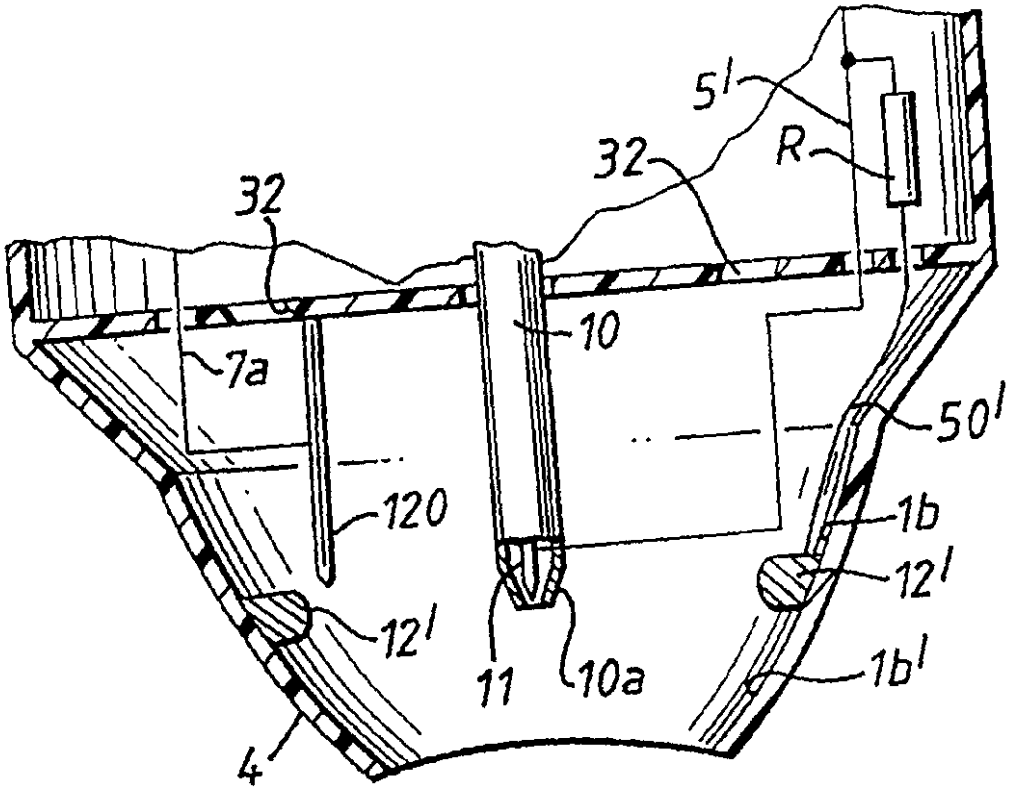

5'
R
32
32
10
7a
50'
120
1b
12'
12'
11
10a
1b'
4

图 6

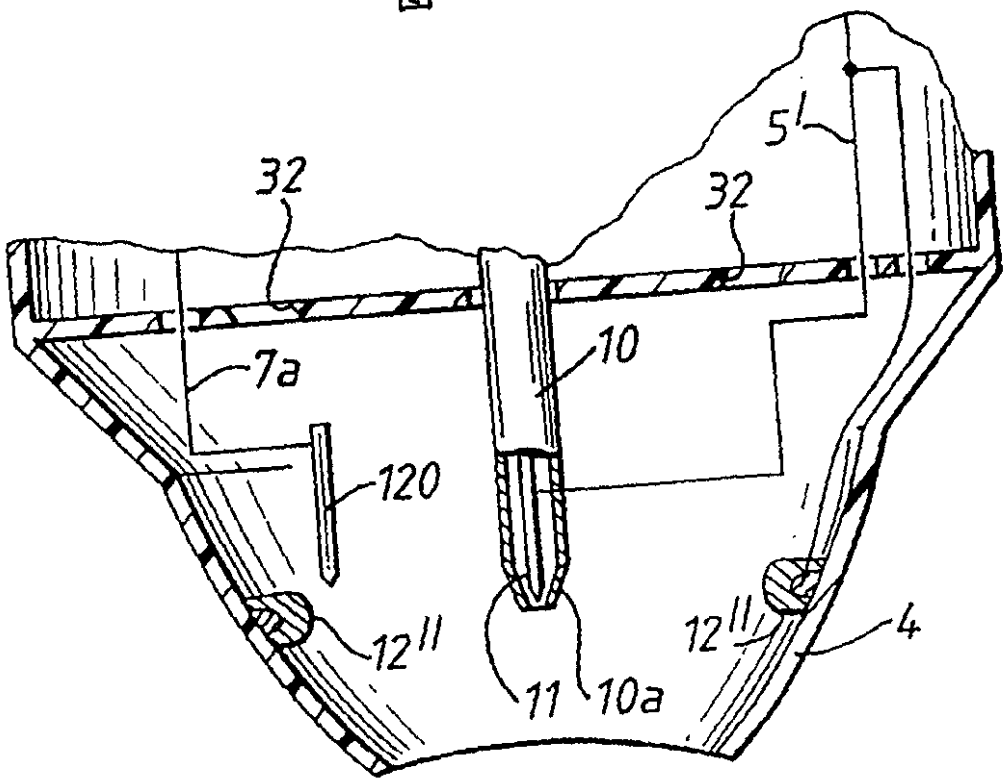

5'
32
32
10
7a
120
12''
12''
11
10a
4

图 7

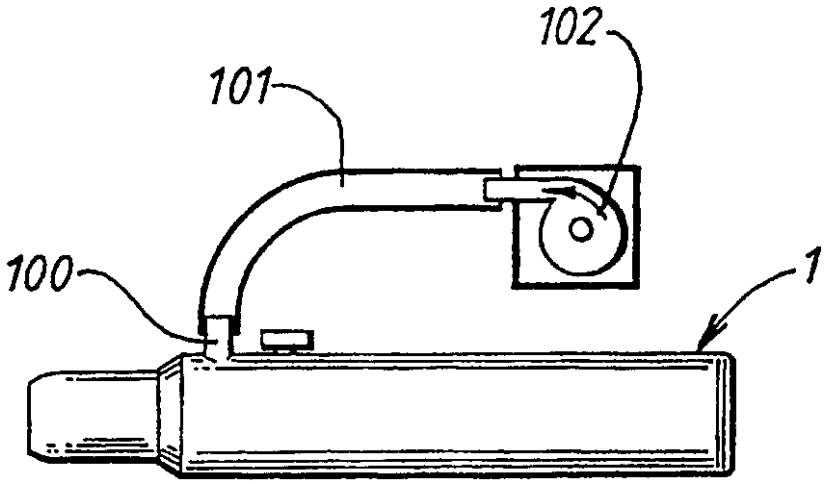


图 8

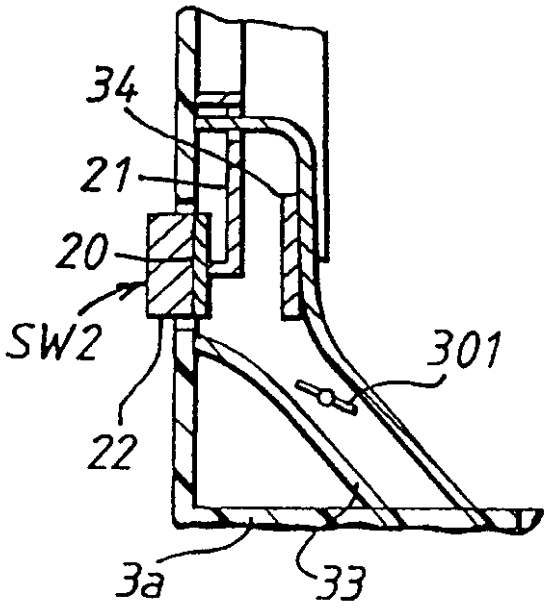


图 12

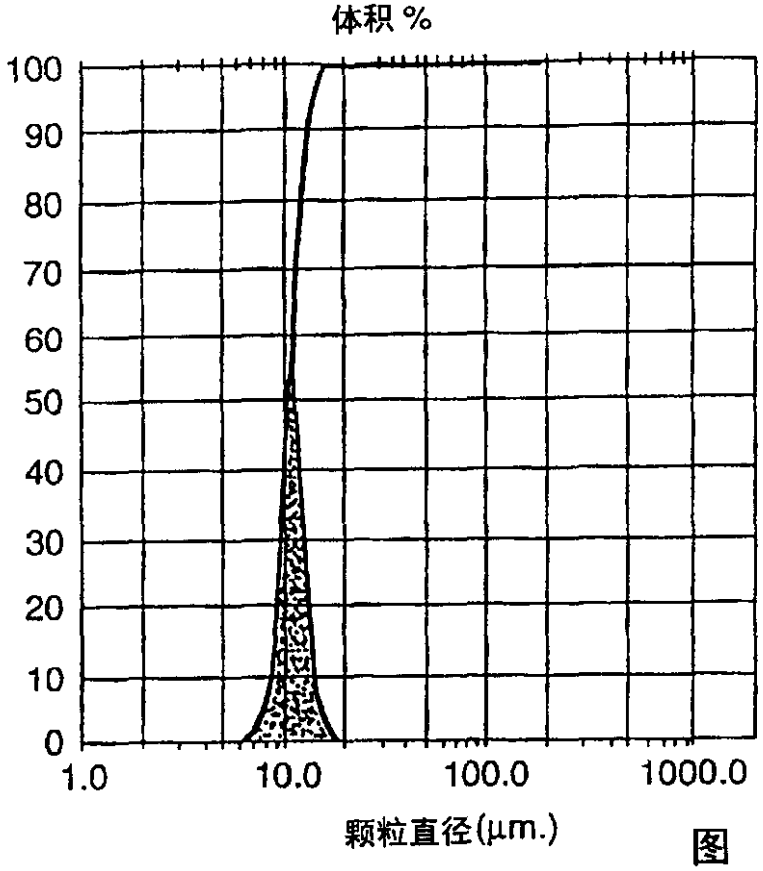

体积 %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
颗粒直径(μm.)

图 9a

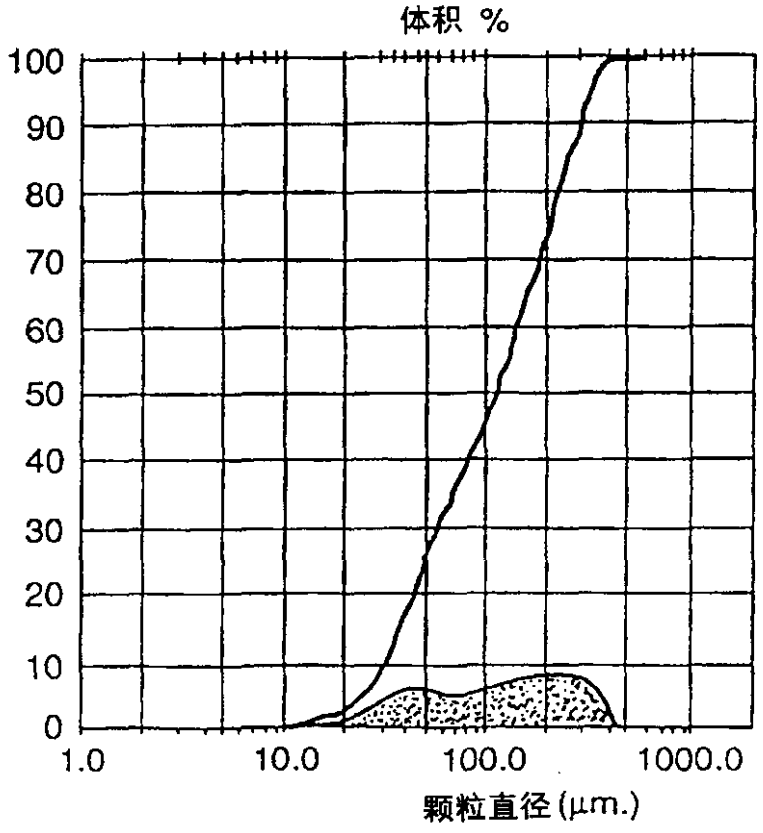

体积 %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
颗粒直径(μm.)

图 9b

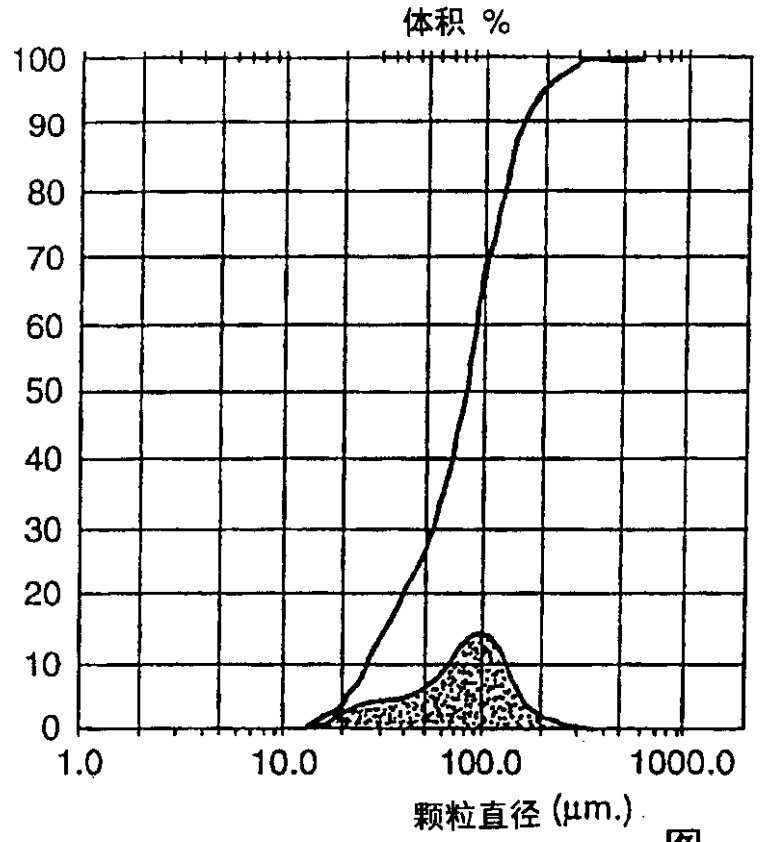

体积 %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
颗粒直径 (μm.)

图 9c

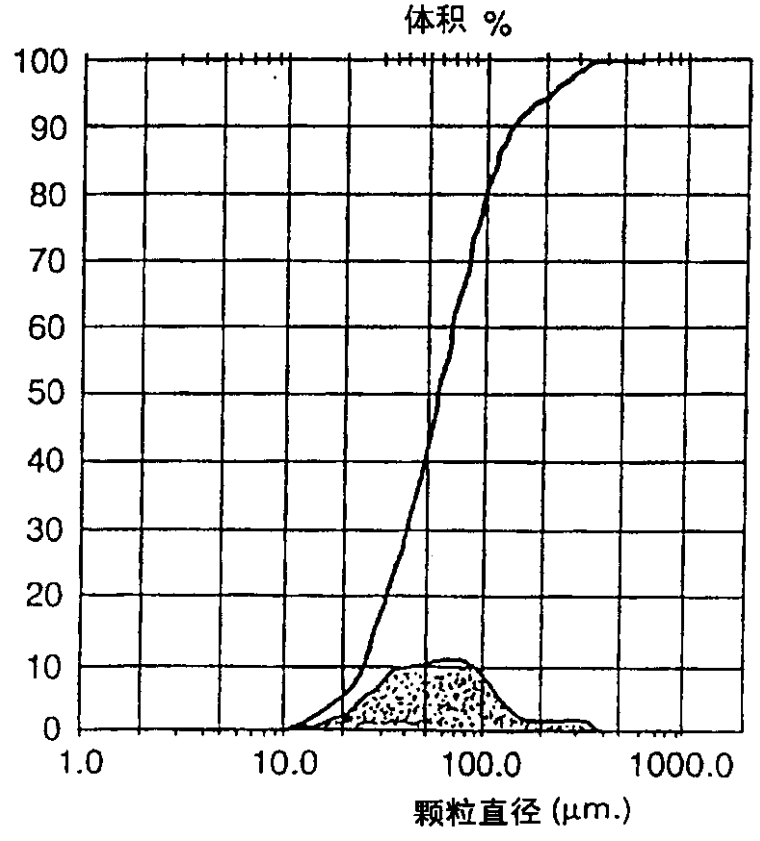

体积 %
100
90
80
70
60
50
40
30
20
10
0
1.0
10.0
100.0
1000.0
颗粒直径 (μm.)

图 9d

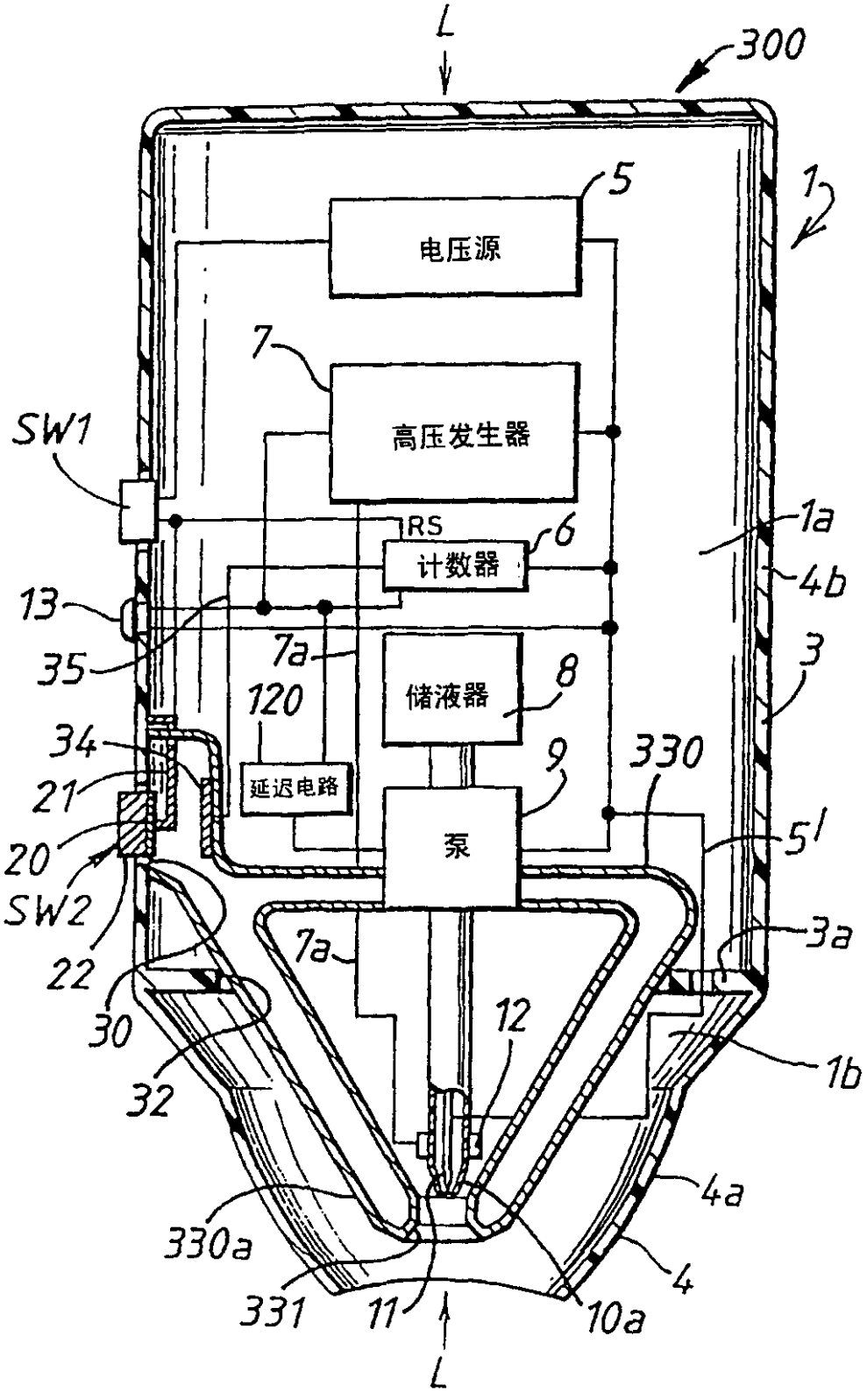

L
300
1
5
电压源
7
高压发生器
SW1
RS
6
计数器
1a
4b
13
35
7a
120
储液器
8
3
34
9
330
21
延迟电路
泵
5'
20
SW2
7a
3a
22
12
30
1b
32
4a
330a
4
331
11
10a
L

图 10

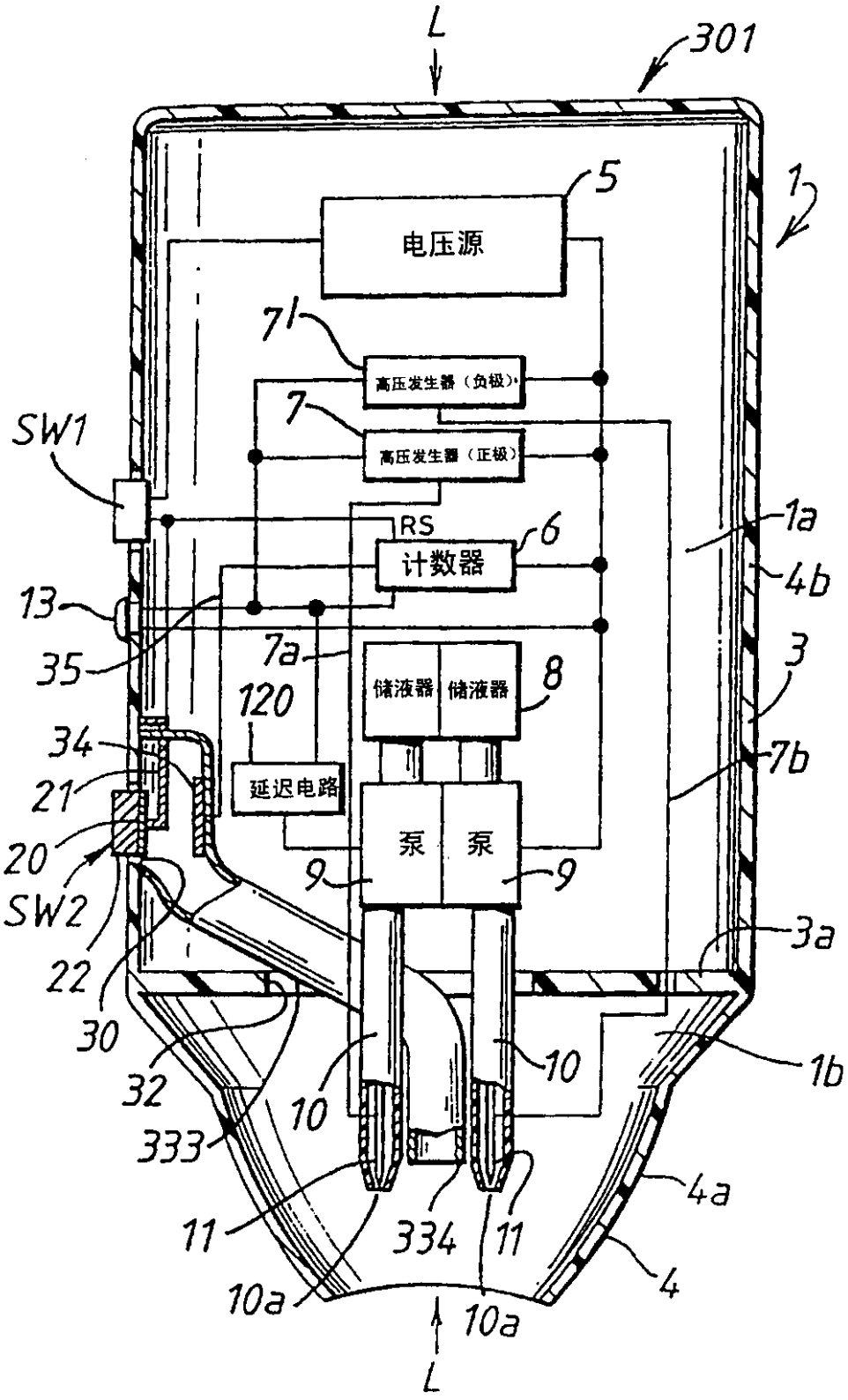

L
301
1
5
电压源
71
高压发生器（负极）
7
高压发生器（正极）
SW1
RS
6
计数器
1a
4b
13
35
7a
120
储液器
储液器
8
3
34
21
20
SW2
延迟电路
7b
泵
泵
9
9
3a
22
30
32
333
10
10
1b
4a
11
334
11
4
10a
10a
L

图 11

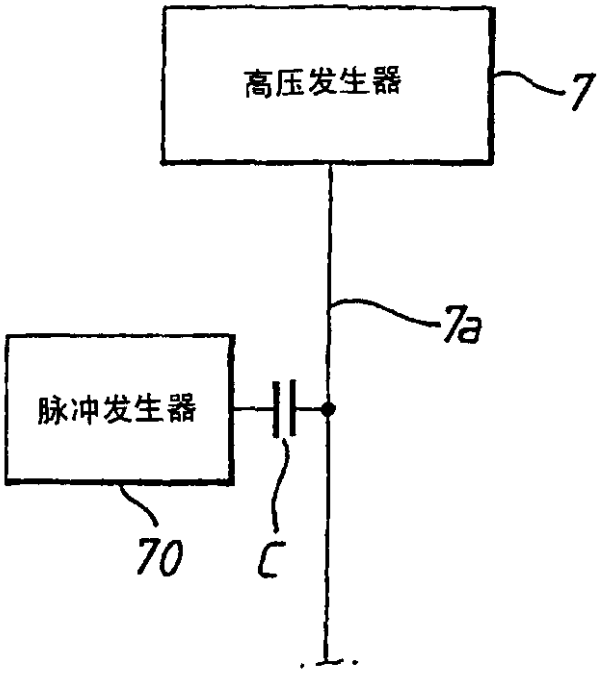


图 13

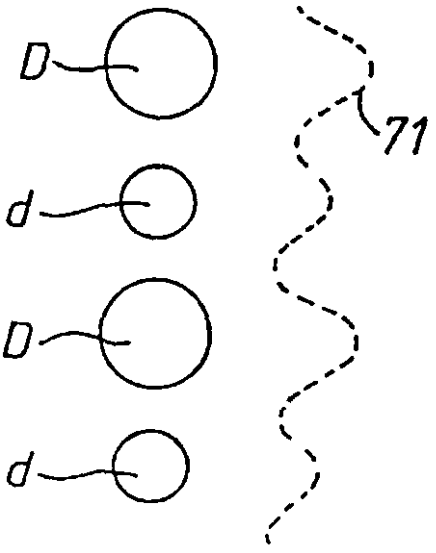


图 14

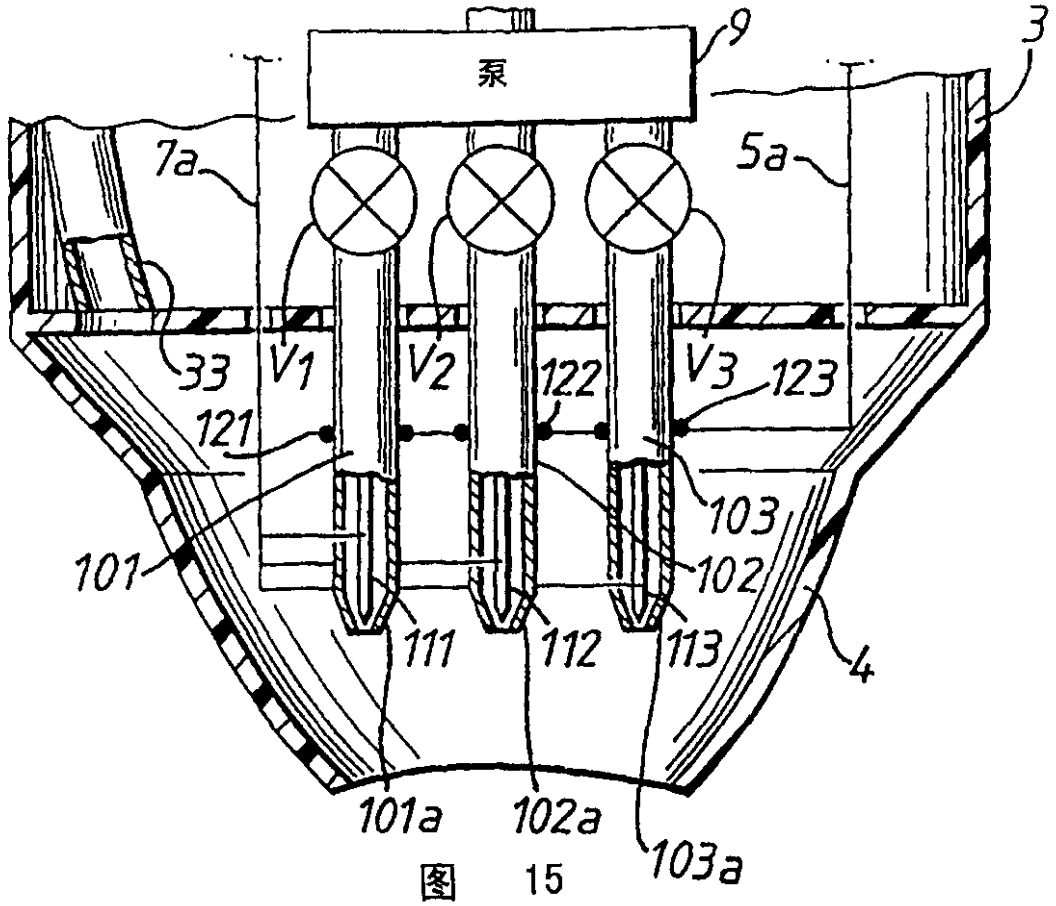


图 15

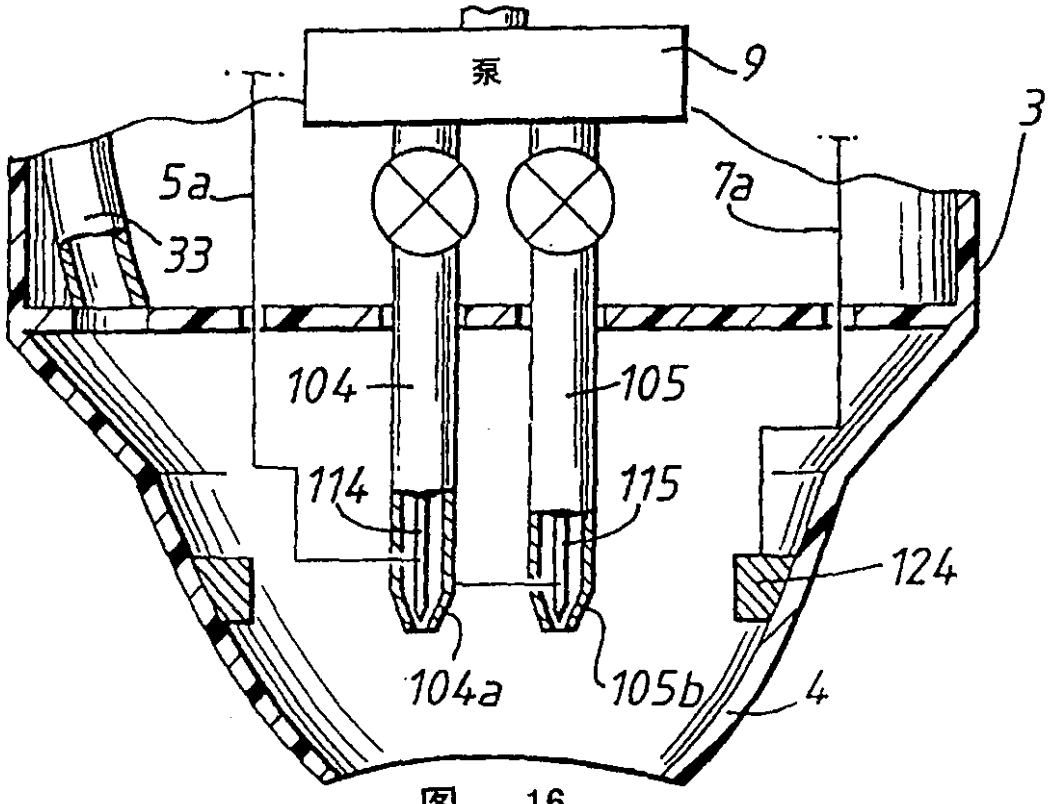


图 16