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ABSTRACT

A dispensing device comprising an electrohydrodynamic comminution site, means for supplying liquid to the comminution site and means for charging the comminution site to an electrical potential for causing comminution of the liquid, wherein the charging means is spaced from the comminution site and is arranged to charge the comminution site to the electrical potential for comminuting the liquid by inducing electrical charge at the comminution site.

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DIVISIONAL APPLICATION

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INVENTION TITLE:

Dispensing device

The following statement is a full description of this invention, including the best method of performing it known to us:

AN INHALER

The invention relates to an inhaler for dispensing comminuted liquid and the uses of such an inhaler, especially in medicine.

Dispensing devices are known which produce a finely divided spray of liquid droplets by electrostatic (more properly referred to as 'electrohydrodynamic') means. The droplet spray in such devices is generated by the application of an electric field to a liquid at a spray head or spray edge. The potential of the applied electric field is sufficiently high to provide comminution of the liquid from the spray head. The droplets produced are electrically charged and thus are prevented from coagulating by mutual repulsion.

Electrohydrodynamic sprayers have potential uses in many areas, including agriculture and the automotive industry and also for dispensing cosmetics and medicines.

United Kingdom patent number 1569707 describes such an electrohydrodynamic spray device principally for use in crop spraying.

United Kingdom patent number 2018627B discloses an electrohydrodynamic spray device wherein the charged droplet spray is fully or partially electrically discharged by means of an earthed electrode having a sharp or pointed edge and located downstream of the spray head. European Patent number 0234842 also uses this technology and relates to an inhaler in which charged droplet spray is discharged prior to inhalation by means of a sharp or pointed discharge electrode carrying an opposite charge to the droplet spray and located downstream of the spray head. The droplets are discharged to facilitate droplet deposition into the respiratory tract by preventing deposition of charged droplets onto the mouth and throat of the user.

According to one aspect of the invention, there is provided an inhaler comprising a comminution site, means for supplying liquid to the comminution site, means for charging the comminution site to an electrical potential for causing comminution of the liquid, means for partially or fully electrically discharging the comminuted matter, the electrical discharge means being operable to partially or fully discharge comminuted matter in response to inhalation by a user, and a conduit for supplying fully or partially electrically discharged comminuted matter to the user.

An inhaler embodying the invention facilitates coordination of release of the comminution and inhalation by the user.

An inhaler embodying the invention may further comprise valve means for closing the conduit, the valve means being arranged to be opened by inhalation by a user and so as to activate said electrical discharging means upon opening. The electrical discharge means for partially or fully discharging comminuted matter may comprise a discharge electrode coupled to said valve means such that, when said valve means is opened in response to inhalation by a user, the discharge electrode is exposed to partially or fully electrically discharge comminuted matter formed by the comminution site. The valve means may be a flap valve and the discharge electrode may project from the plane of the flap valve, the flap valve being pivotally mounted so as to be movable between closed and open positions in response to inhalation by a user such that, when the flap valve pivots to the open position, the discharge electrode is pivoted into the path of the comminuted matter facilitating coordination of release with inhalation. The discharge electrode may be arranged so as to move into a recess formed in said charging means when said valve means moves to its closed condition. An inhaler embodying the invention may be adapted to dispense comminuted matter for delivery of the upper respiratory tract, for example to deliver droplets having a diameter from about 10 to about 25 micrometres to the upper respiratory tract.

In an embodiment a sharp edged or pointed discharge electrode is fixed so as to extend upwards from the plane of the flap valve, the flap valve being pivotally fixed so as to open and close the conduit, such that when the flap valve pivots open the discharge electrode pivots into the flight path of the comminuted liquid.

In an embodiment there is provided an inhaler comprising an electrohydrodynamic comminution site, a means for supplying liquid to the comminution site, a means for charging the comminution site, a sharp edged or pointed electrode for partially or fully discharging the liquid comminution and a conduit through which the liquid comminution is administered, the conduit having a valve means activated by inhalation of the user, wherein the valve means comprises a flap shaped to seal the conduit, the flap being pivotally mounted so as to open and close the conduit, the sharp edged or pointed electrode extending upwards from the plane of the flap valve, such that in use the flap valve pivots open and the discharging means pivots into the flight path of the comminuted liquid upon inhalation by the user.

When the inhaler comprises a sharp edged or pointed electrode, the arrangement suitably provides that the sharp edged or pointed electrode is electrically shielded from the comminution when the valve means is closed. One particular method of achieving this is that the sharp edged or pointed electrode pivots into a recess formed in the charging means when the valve means closes.

The comminution site may be any conventional electrohydrodynamic comminution site such as a surface or edge generally provided by a thin capillary tube, a nozzle or a slot defined by two parallel plates.

Appropriate means for supplying liquid to the comminution site include mechanical or electrically powered pumps which are capable of providing the required flow rate of liquid to the comminution site such as a syringe pump or the electrically powered pump described in EP 0029301.

The comminution means of an inhaler embodying the invention can be used with a large range of flow rates, but generally operates with flow rates in the range of between 0.1 to 500μL per second, such as 0.5 to 5μL per second, especially for inhaled administration.

The charging means may be arranged to induce the electrical charge at the comminution site and may be any conventional source of electrical charge which in use is capable of inducing a charge sufficient to comminute the liquid from the comminution means, such as a high voltage generator or a piezo-electric generator. The charge required is usually of the order of 1-20 kilovolts, for example 10 kilovolts.

An inhaler embodying the invention may be adapted into any form which dispenses comminuted liquid for inhalation, for both medicinal and non-medicinal use.

An inhaler embodying the invention may be used to dispense liquids comprising components useful for human or animal health care, such as medicaments for pharmaceutical or public health care use or medically useful compounds such as anaesthetics.

Medicaments suitable for adaption for inhaled administration include those used for the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma and those used in the treatment and/or prophylaxis of disorders associated with pulmonary hypertension and of disorders associated with right heart failure by inhaled delivery.

Non-medicinal inhalation uses includes dispensing perfumes and aromas.

In an embodiment the comminution site may provide in operation droplets within the range of from about 0.1 to about 500 microns in diameter: more usually from 0.1 to 200 microns, such as 1.0 to 200 microns: examples include droplets within the range of 5.0 to 100, 0.1 to 25, 0.5 to 10 or 10 to 20 microns. A favoured range for inhaled administration is 0.1 to 25 or 0.5 to 10 microns, especially for administration to the lower respiratory tract, and 10 to 25 microns, especially for administration to the upper respiratory tract.

For a given liquid the diameter of the droplets can be controlled by varying the applied voltage and liquid flow rate using routine experimental procedures.

Liquids having viscosities within the range of from 1 to 500 centipoise and resistivities in the range of 10^2 - 10^8 ohm metres can be comminuted by the present device.

As stated above, charging the comminution site by induction has been found to provide better comminution of liquid having a lower electrical resistivity, such as is the case of aqueous solvents, including solvent mixtures, and solutions thereof and low resistivity organic solvents such as alcohols.

When used herein 'a comminution' includes a liquid droplet spray.

When used herein 'medicament' includes proprietary medicines, pharmaceutical medicines and veterinary medicines.

When used herein, unless more specifically defined herein, 'inhaled administration' includes administration to and via the upper respiratory tract, including the nasal mucosa, and the lower respiratory tract.

The description 'sharp edged or pointed' when used herein in relation to operational parts, such as a discharge electrode, also includes electrical equivalents thereof and hence includes shapes such as ridges and the like, the essential requirement being that in the embodiment the operational part has dimensions which will give rise to a sufficiently high electrical field strength so as to exceed the breakdown strength of the air. This topic is theoretically described in "Depositional Control of Macroscopic Particles by High Strength Electric Field Propulsion" by R A Coffee, in "Transactions of the Institution of Electrical and Electronic Engineers, Industry Applications, USA", Vol.

IA-10 pp 511 to 519, July/August 1974. An example is an electrical field strength of approximately 3 million volts per meter.

Liquid medicinal formulations for use in an inhaler embodying the invention may be formulated according to conventional procedures, such as those disclosed in the US Pharmacopoeia, the European Pharmacopoeia, 2nd Edition, Martindale The Extra Pharmacopoeia, 29th Edition, Pharmaceutical Press and the Veterinary Pharmacopoeia.

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

Figures 1 and 2 show an embodiment of an inhaler in accordance with the invention and Figures 3 to 5 show examples of inhalers included for illustrative purposes and not falling within the scope of the invention claimed.

In Figures 1 and 2, an inhaler embodying the invention is illustrated in which a pressure reduction created by the action of breathing through a suitable ducting (1) causes a lightweight flap (2), balanced by a second member (3) pivoted at a hinge (4) and connected to a dc high voltage supply of either polarity (5) to revolve through a sufficient degree of arc to allow the second member of the flap to become exposed to the electric field and then create gaseous ions.

The flap valve thus has two actions: (a) it opens an air passage (1) to facilitate a flow of droplets; and (b) it simultaneously rotates a balancing member (3) attached to the flap (2) through a sufficient degree of arc to expose a ridge or nipple (6) having one dimension of less than about 1.0 mm radius of curvature.

The ridge, or nipple (6) may be made of any conducting or semiconducting material, such as metal or carbon-loaded plastic, and is connected to a source of high voltage (5). When not actuated by breathing, the ridge will be electrically screened by the surface of a flat electrode (7), also connected to the high voltage source (5). In this position the electrode (7) may be switched on or off by a simple switch (8).

When switched on, the electrode induces a potential of opposing polarity at the tip of a nearby nozzle (9). This induced potential causes liquid at the tip of the nozzle to emerge as a fast jet which breaks up into charged droplets. The nozzle (9) is connected to earth.

In this inhaler (a) the flat valve (2) allows droplets to be inhaled only when the valve is actuated by the act of breathing; (b) the principle of induction, rather than direct, nozzle charging improves the control of droplet size and maximum flow rate, for those liquids would otherwise be difficult to atomize electrohydrodynamically; and (c) avoids the opposite polarity droplets otherwise being so strongly attracted to the source of the induced voltage (7) that the droplets would not be available for delivery by inhalation, or other forms of deposition onto target surfaces.

Figure 3 shows an illustrative example of an inhaler in which one or more electrically floating conducting or semiconducting surfaces (10), attached to one or more capacitors (11) are used to attract and capture gaseous ions so that the electric field created by the electrode (6) acts directly upon the nozzle (8) without impingement of gas ions. Such gas ions, if allowed to reach the nozzle unimpeded, would be expected to modify the electric field surrounding the nozzle so as to prevent the emerging liquid from forming the necessary jet of liquid for atomization by the electrohydrodynamic method. The capacitor(s) is chosen to have a time constant of the same order as the time required to establish a spray cloud. This time constant will have a value, in seconds, which is the product of the capacitance, C and the resistance, R, of the capacitor. The value of CxR is thus chosen so that the capacitor will charge by bombardment of gaseous ions, until it reaches a sufficient potential to modify the electric field and to re-direct the ions toward the established spray cloud. Generally, the time constant required will be of the order of seconds or a number of milliseconds. For example, a capacitor of 0.1 microfarad with a resistance of 10 megohms will produce a time constant of one second.

Figure 3 shows one configuration that will create the required induction potential at the nozzle when the electrode (7) is energized and, after a suitable period, dependent upon the position and time constant of the capacitor(s) will then re-arrange the field to allow gaseous ions to migrate into the spray cloud so as to modify the charges on all droplets to a lower (optimal) or approximately zero value. Such droplets may then be readily inhaled.

The charged droplets are prevented from impinging upon the high voltage electrode (7) by the action of fast moving gaseous ions. These ions are created by the combination of electrode voltage, say one to ten kilovolts dc, and the radius of curvature of the small dimension of the ridge or nipple (6) on the balancing member (3) and by juxtaposition of the nozzle (9), the electrode (7) and the capacitor(s) (11) which latter may be used to increase the degree of control of the shape of the field and the timing of the essential reshaping process.

Liquid is supplied to the nozzle (9) from either a container (13) by gravity feed, or by mechanical pumping, or by an electrokinetic pumping device.

The liquid is supplied to the nozzle and the induced voltage applied by the electrode (7) before the electric field is modified to create gaseous ions by the actuation of the flap-valve (2) and/or the capacitor(s) (11).

Then, at any time after the spray cloud is developed, the breath-actuated valve and/or the capacitor(s) is actuated, whereupon the droplet trajectories are modified; moving away from their direct flight to the electrode (7), through the required angle, say to flow by viscous drag in the air movement caused by normal breathing. This action is virtually instantaneous due to the extremely low inertial forces on droplets used for inhalation therapy, which are generally less than about 10.0 μm in diameter for drug inhalation.

An alternative method of creating the required induction potential to atomize the liquid and subsequently discharge the droplets before impingement upon the induction electrode is to use an induction electrode (14) such as, for example a ring with two distinct cross-sectional radii of curvature, as shown in Figure 4. This method may be used with or without a flap valve (2), or field modifying capacitor(s) (11). The larger radius faces toward the nozzle tip, whilst the smaller radius (say less than about 1.0mm) faces away from the nozzle (9). It has be found that, by very careful design of the field pattern, charged droplets may have sufficient inertial force to pass through a gap in the electrode (14) without immediate impingement. Although these droplets are then almost immediately forced back to impinge upon the electrode, they may be prevented from doing so by the neutralizing action of the fast moving gaseous ions. It has been further discovered that production of gaseous ions by gas breakdown at the smaller radius of curvature may be delayed by maintaining the field strength at the electrode below the critical value until the charged droplets enter the field, whereupon they will increase the field strength to the critical value and immediately trigger the droplet discharge process.

The critical field strength and shape is a function of: electrode position, shape and voltage; the relative positions and potentials of the nozzle and capacitor(s) surfaces and the degree and position of space charge potential created by the charged droplets.

It has also been found that the methods of controlled field modification (with time) disclosed herein may be so set as to both discharge and, if required, to recharge the droplets to an optimal value. This could be of importance in, say, ensuring accurate deposition of droplets within a human lung, where both the droplet's mass, and its charge have controlling influence upon the zones of deposition within the system of airways through which the droplets pass during inhalation.

Figure 5 shows an illustrative example of an inhaler in which an earthed needle (15) concentrically located within a non-conducting sleeve (16) allowed liquid to flow (by gravity or other light pressure) to an outlet nozzle (17) where the liquid was exposed to a strong convergent electric field provided by a high potential supplied to the flat, smooth surface of electrode (18). This resulted in an induced electrohydrodynamic (EHD) comminution of the liquid emerging from capillary nozzle (17).

After the comminution was established (and within less than one second) a sharp element (19) of the induction electrode (18) was exposed.

The exposure of (19) above the smooth surface of (18) produced gaseous ions of the polarity of the high voltage dc generator (20). Since the EHD spray cloud was induced from a earthed electrode-nozzle (17), the gaseous ions and the spray droplets have opposing polarities. And as the gaseous ions have much greater mobility in the electric field containing both droplets and ions, the droplets were bombarded and hence electrically discharged.

In the experiment described, the distance between tip of nozzle (17) and flat electrode was 30mm. When the sharp electrode (19) was positioned to discharge the droplets, the distance between tip of nozzle (17) and needle-tip (19) was 23mm. The liquid flow-rate was 1.34 μl/sec. The high voltage source was set at a negative potential of 10.7 kilovolts.

The liquid used was 80% ethanol and 20% polyethylene glycol (200), having a viscosity of 2.2c Poise, a surface tension of 25.0m N/m, a resistivity of 1.7 x 10^3ohm.m and a density of 0.86 kg/litre.

The discharging effect was assessed to be essentially 100 per cent.

Throughout this specification and claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. An inhaler comprising a comminution site, means for supplying liquid to the comminution site, means for charging the comminution site to an electrical potential for causing comminution of the liquid, means for partially or fully electrically discharging the comminuted matter, the electrical discharge means being operable to partially or fully discharge comminuted matter in response to inhalation by a user, and a conduit for supplying fully or partially electrically discharged comminuted matter to the user.

2. An inhaler according to claim 1, further comprising valve means for closing the conduit, the valve means being arrange to be opened by inhalation by a user and so as to activate said electrical discharging means upon opening.

3. An inhaler according to claim 2, wherein said electrical discharge means for partially or fully discharging comminuted matter comprises a discharge electrode coupled to said valve means such that, when said valve means is opened in response to inhalation by a user, the discharge electrode is exposed to partially or fully electrically discharge comminuted matter formed by the comminution site.

4. An inhaler according to claim 3, wherein the valve means is a flap valve and the discharge electrode projects from the plane of the flap valve, the flap valve being pivotally mounted so as to be movable between closed and open positions in response to inhalation by a user such that, when the flap valve pivots to the open position, the discharge electrode is pivoted into the path of the comminuted matter.

5. An inhaler according to claim 3 or 4, wherein the discharge electrode is arranged so as to move into a recess formed in said charging means when said valve means moves to its closed condition.

6. An inhaler according to any one of claims 1 to 5 adapted to dispense comminuted matter for delivery to the upper respiratory tract.

7. An inhaler according to claim 6 adapted to deliver droplets having a diameter from about 10 to about 25 micrometres to the upper respiratory tract.

DATED this 23rd day of December, 1999
ELECTROSOLS LTD.
By its Patent Attorneys:
DAVIES COLLISON CAVE

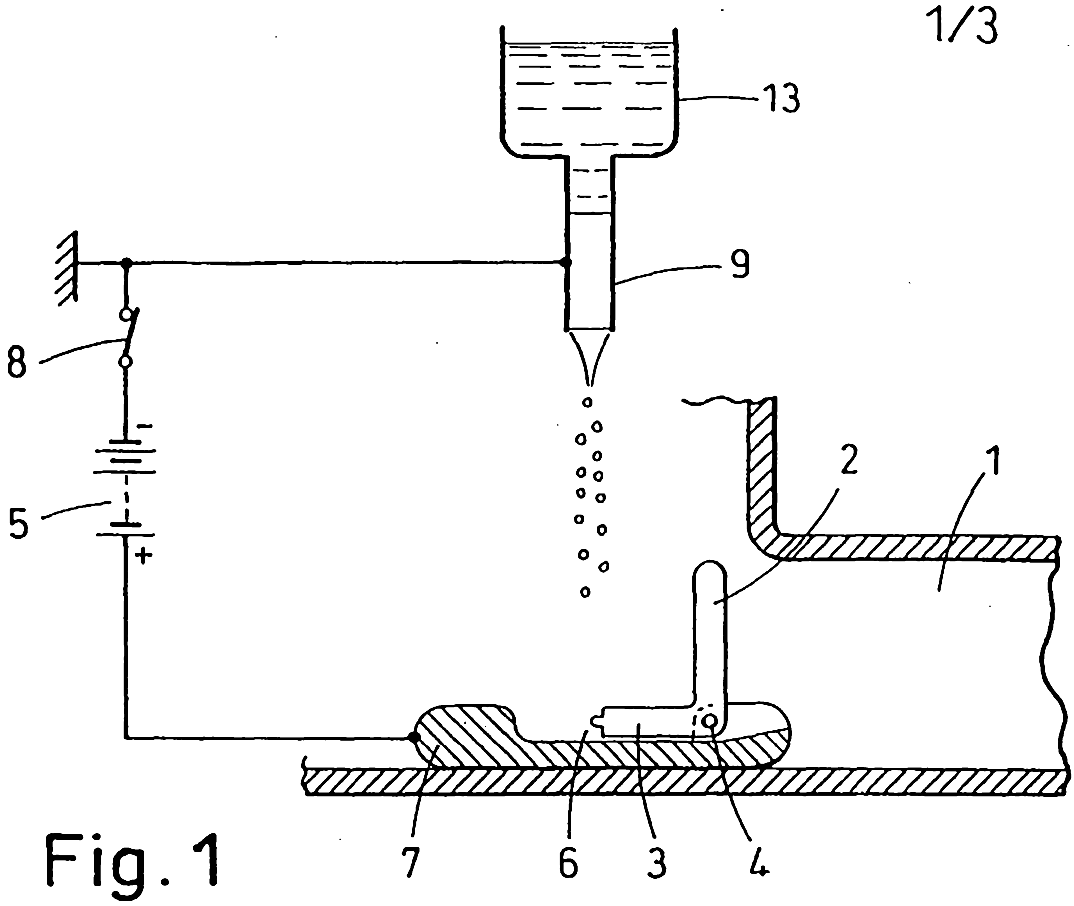

Fig. 1

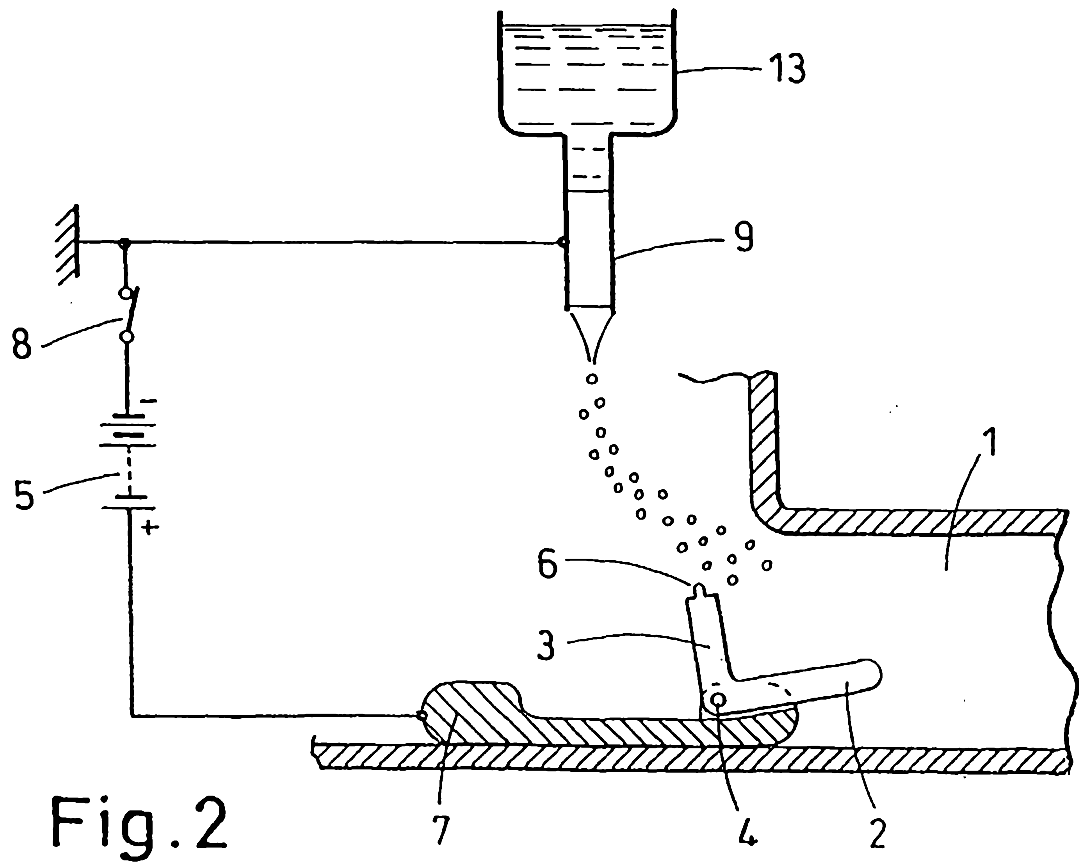

Fig. 2

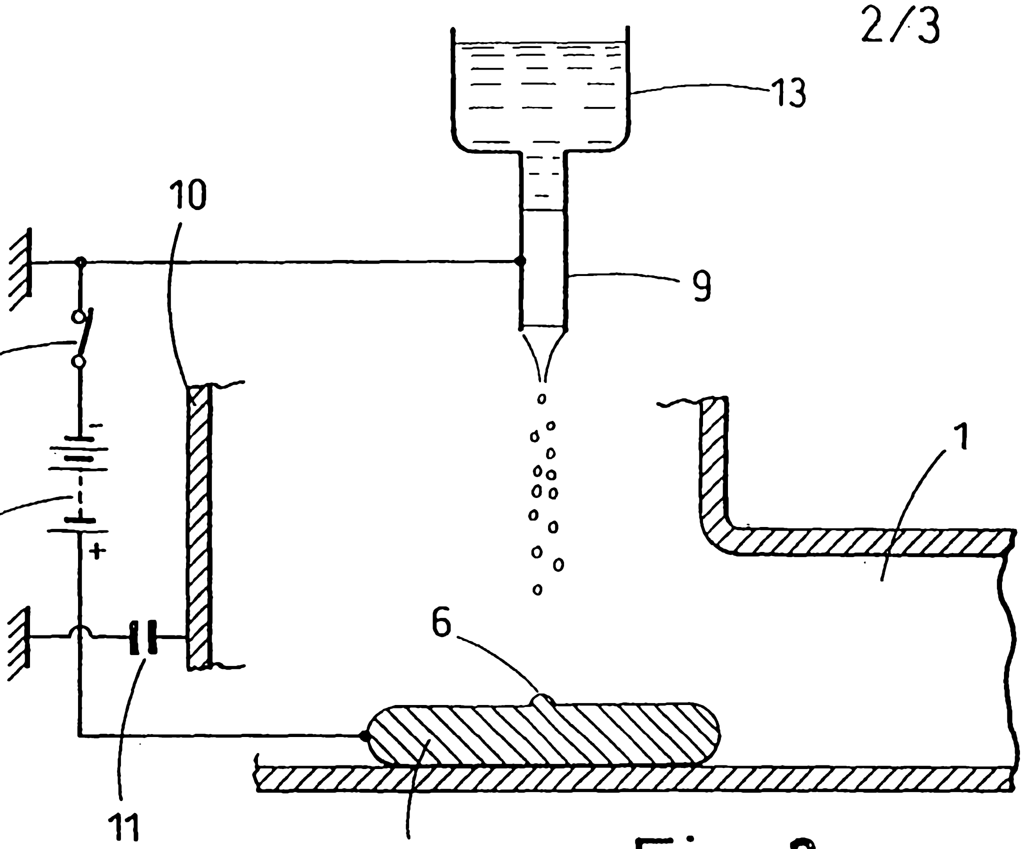

Fig. 3

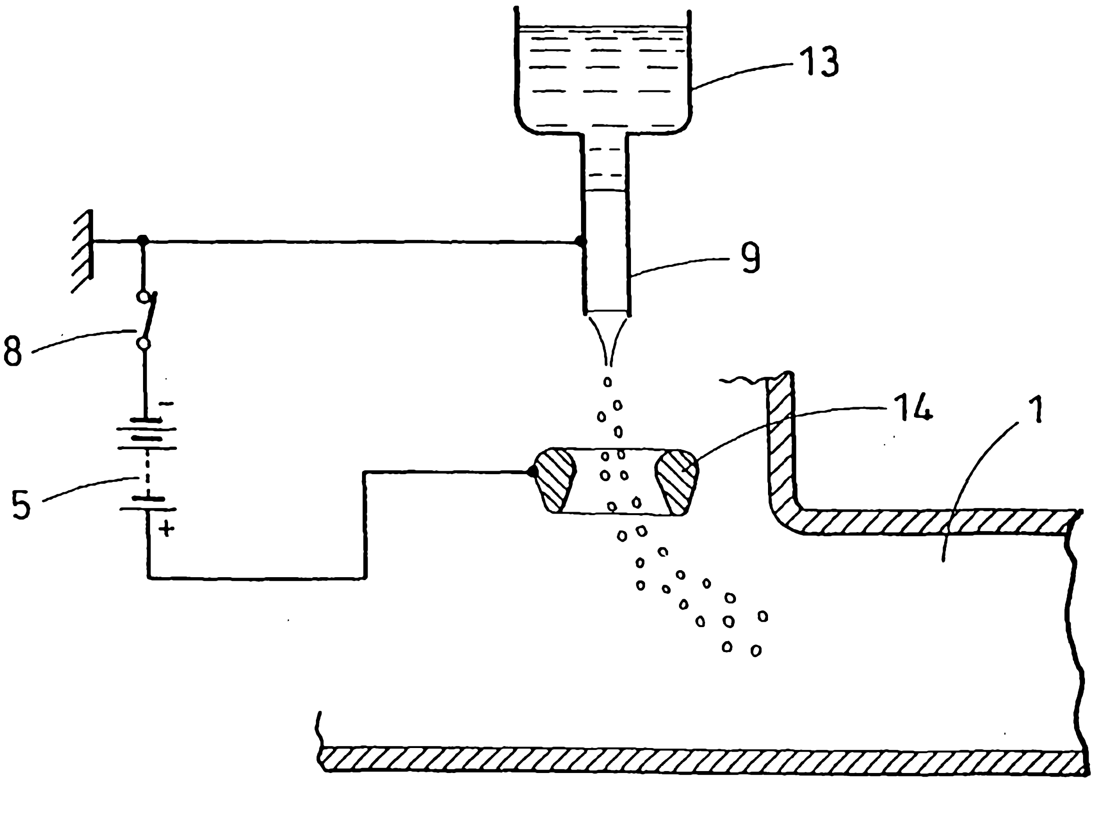

Fig. 4

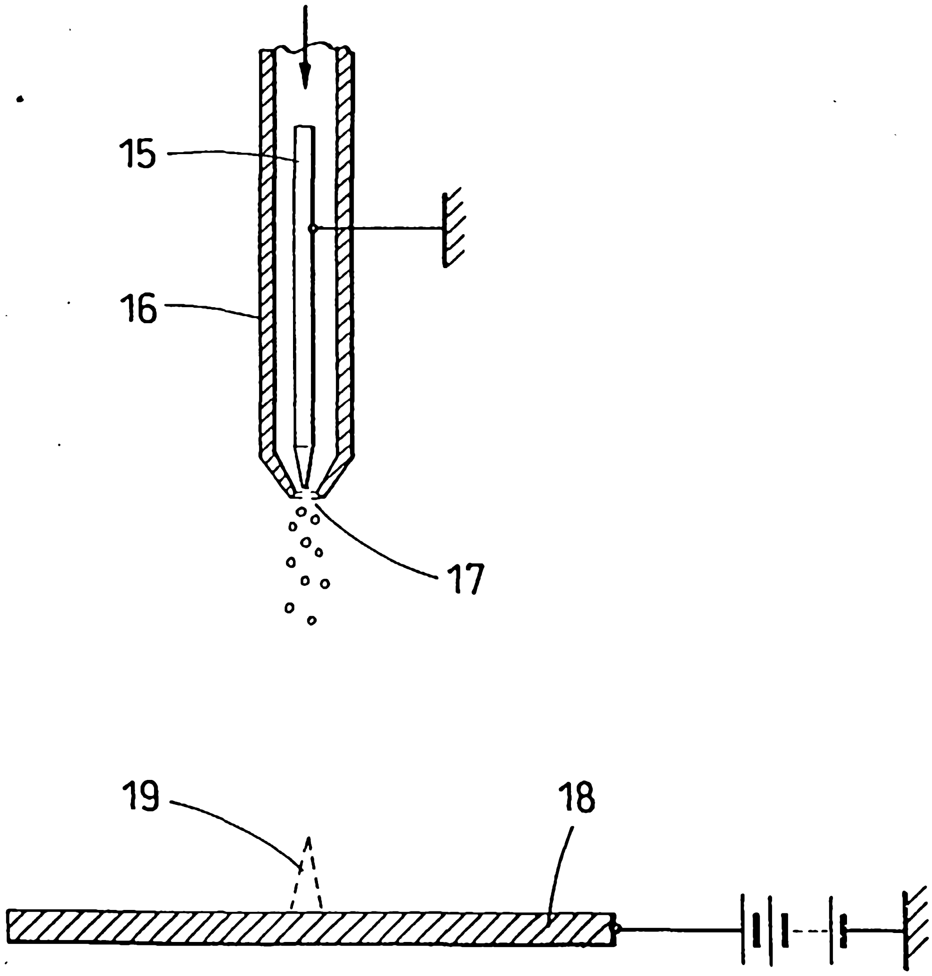

Fig. 5