(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2005 (19.05.2005)

PCT

(10) International Publication Number
WO 2005/044342 A1

(51) International Patent Classification[7]: A61M 5/145

(21) International Application Number:
PCT/SG2003/000257

(22) International Filing Date:
7 November 2003 (07.11.2003)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designation US*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LIQUID HOUSING CHAMBER AND LIQUID DELIVERING DEVICE CONTAINING SUCH CHAMBER

(57) Abstract: A liquid housing chamber for use in a device for administering liquid to a subject, said liquid chamber comprising a cavity defined by a base and a surrounding sidewall, said sidewall including an upper rim; a deformable membrane attached to the upper rim and covering said cavity; and an outlet located in the base; wherein said base is inclined from about said outlet to said surrounding sidewall and is formed of a substantially rigid material.

WO 2005/044342 A1

Liquid Housing Chamber and Liquid Delivering Device Containing such Chamber

Field of the Invention

The invention relates to painless injection devices.

Background of the Invention

Human skin has three layers. The outermost layer is the stratum corneum which is about 10-15 microns thick. It has very low permeability to liquid drugs. Immediately underneath the stratum corneum is a layer called the viable epidermis which is 50-100 microns thick. The viable epidermis contains living cells but few nerves and no blood vessels. The third layer is called the dermis and forms the bulk of the skin and contains living cells, blood vessels and nerves.

One of the conventional ways to deliver liquid drugs into a human body is the hypodermic injection using syringes and needles, in which the needle penetrates the skin into subcutaneous tissue and the drug is then injected using the syringe. When a subcutaneous injection is given, it passes through each of the three layers and subsequently causes pain due to stimulation pain receptors (nociceptors) in the dermis. This is a particularly significant problem in relation to children. However, even many older persons have an aversion to being injected by a hypodermic needle and, consequently, they will experience stress and anxiety at the prospect of requiring such an injection. Some such persons may even refuse treatment as a result.

In addition, the injection rate of a hypodermic syringe is controlled manually by the user (eg, a doctor, nurse or the patient). This injection rate cannot be accurately controlled or consistently maintained. Also the rate of injection may not be the desirable rate and, often if a desired rate is known, it is very difficult to control this manually.

However, when a micro needle array, with a proper length, is used, it typically penetrates only the stratum corneum and stops in the viable epidermis. The drug can then be delivered manually or automatically without causing pain.

In addition, irrespective of the mode of parenteral liquid delivery (whether by hypodermic needle, micro-array, intravenous, intramuscular or other), there is a need to be able to deliver the drug at controlled rates until substantially all of the drug has been delivered. For example, where the drug is a hormone replacement or cancer medicine, a substantially consistent rate of delivery will enable a much more stable drug

concentration curve and therefore better therapeutic effect than is achieved by periodic intermittent injections.

In addition to the desirability of administering a drug at a substantially consistent rate, there is also the need for devices that are able to release a drug (in liquid form) in small volumes and at precise or desired rates. This would be particularly beneficial to diabetics who generally need a regular supply of insulin in their blood stream to aid the absorption of glucose.

A relatively new therapy, known as "continuous drug infusion" has been suggested in which a portable delivery device is attached to, or implanted inside, the patient's body. The device would preferably be able to deliver an exact amount of a drug (e.g. insulin) at desired (preset or program set) rates into the patient's blood. In order to produce such an infusion system, a precision liquid delivery device is required.

Some of the currently available commercial devices have a number of problems. Some devices have been too large to be comfortably fitted to a patient. Others have been too expensive to allow the devices to be disposable. Some devices have difficulty in preventing the access of gas bubbles to the drug liquid, whilst their device is in operation. Injecting liquids containing gas into patients can have disastrous effects. Other devices have a two-way action which allows the drug liquid to be sucked into the device and then released from the device. This two-way action has the disadvantage of allowing contaminates and gases to mix with the drug liquid. A further disadvantage of known prototypes is that they can only be operated in a limited number of orientations, thereby restricting their effectiveness.

In addition to the above, there is a need to provide such liquid delivery devices in which the chamber which contains the drug liquid is easily refillable or disposable so that the device can be readily "recharged" for ongoing use. The present invention is directed towards ameliorating at least some of the above mentioned disadvantages of the prior art and it provides a useful alternative.

The present invention may be used for any medical (or other) applications which require the precise delivery of a drug or other liquid. Some non-limiting examples of such applications may include insulin infusion systems, cancer drug infusion systems, the on-demand delivery of hypertension drugs and hormones and the delivery of liquid drugs to prematurely born babies in intensive care situations and the like.

In this specification, where a document, act or item of knowledge is referred to or discussed, this reference or discussion is not an admission that the document, act or item of knowledge or any combination thereof was at the priority date:

(i) part of common general knowledge; or

(ii) known to be relevant to an attempt to solve any problem with which this specification is concerned.

Summary of the Invention

According to a first aspect of the invention, there is provided a liquid housing chamber for use in a device for administering liquid to a patient, said liquid chamber comprising: a cavity defined by a base and a surrounding sidewall, said sidewall including an upper rim; a deformable membrane attached to the upper rim and covering said cavity; and an outlet located in the base; wherein said base is inclined from about said outlet to said surrounding sidewall and is formed of a substantially rigid material.

The outlet may be located at any suitable position. However, preferably the outlet is located at a central portion of the base. It has been found that a contoured base is desirable and preferably, the base is bowl-shaped or cone-shaped. The degree of curvature of a bowl-shaped base of a liquid housing chamber according to the present invention is preferably conformed or determined by computation results of the membrane's deformation under pressures, using a proper mathematical model and finely modified by experiments. When an ideal hyper-elastic material is employed for the deformable membrane, the mathematical model may be the Mooney-Rivilin model. When another type of material is employed for the deformable membrane, the model may be different. The computation method can be either analytical or numerical. In the present invention, the numerical method of finite element analysis (FEA) is used. It will be appreciated that the suitable shapes and the method of obtaining the suitable shape will fall within the scope of the present invention. Alternatively, adequate (but less than optimal) results may also be able to be achieved where the cross-sectional shape of the bowl-shaped base is substantially semicircular or substantially parabolic.

The sidewall of a liquid housing chamber according to the present invention may be formed from any suitable material. However, it has been found that a material which is substantially rigid is preferable. Additionally, according to a particularly preferred embodiment, the sidewall has a curved contour which corresponds with the contour of the base so that the base and the sidewall together form a cavity having a bowl-shaped

contour. Alternatively, in one embodiment, the sidewall may have an inclined contour which corresponds with the contour of the base so that the base and the sidewall together form a cavity having a cone-shaped contour.

According to a particularly preferred embodiment of this aspect of the invention, the contour of the cavity is adapted so that, when said deformable membrane is fully expanded within said cavity, there is no substantial residual volume (the so-called dead volume) between the membrane and either the base or the side wall.

The membrane for the liquid chamber of the present invention is preferably impermeable to fluids, including liquids and gases. Preferably, the membrane is formed of materials selected from hyper-elastic materials, and materials with high elasticity and high plasticity.

According to one preferred embodiment, the liquid chamber is adapted to be connected to pressure exerting means, said pressure exerting means being adapted to exert pressure upon said deformable membrane, causing the membrane to expand into said cavity, thereby forcing the liquid to be expelled through the outlet. Preferably, the liquid chamber is removably connectable to the pressure exerting means.

A pressure exerting means for a liquid chamber according to the present invention may be of any suitable type. However, in one preferred embodiment, the pressure exerting means comprises an electrolytic chamber adapted to contain an electrolyte and, in use, to generate a gas which causes pressure to be exerted upon said deformable membrane. Preferably such an electrolytic chamber comprises at least one pair of electrodes located at least partially within said electrolytic chamber. Said electrolytic chamber is adapted to contain an electrolyte and preferably the electrolyte is in the form of an electrolytic solution.

According to another preferred embodiment, the liquid chamber and electrolytic chamber are adapted so that the liquid chamber is housed at least partially within said electrolytic chamber. Preferably, the liquid chamber is positioned in substantially co-axial alignment with the electrolytic chamber and preferably both chambers are substantially cylindrical in shape.

According to a further preferred embodiment, the electrolytic chamber is connected to, or preferably removably connected to, a control unit adapted to cause a potential difference in the electrodes, thereby causing an electric current to pass between the electrodes through said solution. Preferably, the control unit is adapted to regulate the electric current passing between the electrodes.

According to another preferred embodiment, the liquid chamber is adapted so that when the electrolytic chamber contains said electrolytic solution, the liquid chamber contains a liquid, and a current is passed through said electrolytic solution via said electrodes (a) gas is generated from the electrolytic solution thereby increasing pressure inside the electrolytic chamber; (b) that increase in pressure is transferred to said liquid chamber via deformation of said deformable membrane; and (c) a determinable amount of said liquid is released from said liquid chamber via said outlet.

Preferably, the electrolytic chamber further comprises valve means adapted to enable release of gas from said chamber. The valve means is preferably adapted to remain closed whilst the liquid is being expelled from the liquid chamber and to remain open whilst gas is being released from said electrolytic chamber. Accordingly, following discharge of liquid from the liquid chamber, the liquid chamber can be refilled with fresh liquid whilst expelling gas from the electrolytic chamber. This can generally be done by taking advantage of the atmospheric pressure applying to the re-fill container and the lower pressure inside the liquid chamber as the cavity expands upon release of gas from the electrolytic chamber. Therefore, the electrolytic chamber (with gas removed) will be ready for re-use to again cause discharge of liquid from the re-filled liquid chamber.

Another preferred embodiment of the electrolytic chamber according to the present invention comprises a chamber membrane adapted to be positioned in face to face orientation with the deformable membrane of the liquid chamber, said chamber membrane being configured so as to correspond substantially with said deformable membrane. Preferably, there is further provided an air-release channel adapted to enable air to escape from between the deformable membrane and the chamber membrane so that said membranes can be in intimate contact. Preferably, the elasticity of the chamber membrane and the deformable membrane are substantially the same. In fact, according to a more preferred embodiment, the chamber membrane and the deformable membrane are formed of the same material and have substantially the same thickness.

The pressure exerting means according to the present invention may alternatively take the form of a hydraulic device (preferably a pneumatic device) adapted to apply a pressurised fluid (preferably a gas) to said deformable membrane. The pressurised gas may be of any suitable type. The device includes gas inlet means and gas outlet means and preferably the gas outlet means is located centrally above the deformable

membrane. It is further preferred that the gas outlet means is in substantial linear alignment with the outlet of the liquid chamber.

According to a particularly preferred form of this embodiment, the pneumatic device further includes valve means for regulating the flow of gas through the gas outlet means. In addition, preferably, there is further provided a gas buffer chamber adjacent said gas outlet means and preferably the gas buffer chamber is located immediately above said gas outlet means.

When the fluid chamber according to the present invention includes a pneumatic device, then preferably, the pneumatic device further includes a miniature pressurised gas container for supplying said gas.

In a further alternative embodiment, the pressure exerting means of the liquid chamber according to the present invention may comprise a piston device comprising a piston and piston guiding means, said piston including a piston head adapted to contact and apply pressure to the deformable membrane. The piston head may be of any suitable shape but, preferably, it is shaped so as to conform substantially to the base of the liquid chamber and, more preferably, it is shaped so as to conform substantially to the base and surrounding sidewall of the liquid chamber.

A piston device according to this embodiment most preferably includes an electric motor adapted to drive the piston up and down and it may or may not include a transmission and gear system.

Typically, the liquid in the liquid housing chamber comprises an active ingredient for administration to a patient. The active ingredient is typically a drug.

According to a second aspect of the invention, there is provided an electrolytic chamber, for use in connection with the liquid chamber of the present invention, said electrolytic chamber comprising: an electrolyte; at least one pair of electrodes at least partially immersed in said electrolyte; a valve adapted to release gas from the electrolytic chamber; and a chamber membrane adapted to be positioned in face to face orientation with the deformable membrane of the liquid chamber, said chamber membrane configured so as to correspond substantially with the deformable membrane.

Preferably, the electrolysis chamber according to this aspect of the invention comprises an electrolyte in the form of an electrolytic solution. Most preferably, the chamber is adapted to be connected to a control unit adapted to apply a potential difference to the electrodes, thereby causing an electric current to pass between the electrodes through said solution.

The valve according to this aspect of the invention is most preferably adapted to remain closed whilst electrolysis is occurring within said chamber.

According to a third aspect of the invention, there is provided a liquid delivering device for administering liquid to a patient, comprising a liquid chamber according to the present invention and administering means adapted to convey said liquid from the outlet of said liquid chamber to the patient under influence of pressure applied to said liquid chamber.

Preferably, the administering means according to this aspect of the invention includes an injection device selected from a needle and a micro-needle array and, most preferably, it is a micro-needle array. Where a micro-needle array is used, then preferably it is connectable to the liquid chamber either directly or via a flexible tube.

Preferably a device according to this aspect of the invention is adapted to release liquid at a flow rate of between 0.1 and 100 microlitres per minute.

According to a fourth aspect of this invention, there is provided a liquid delivering device for administering liquid to a patient, comprising:

(a) a sealed electrolytic chamber adapted to contain an electrolyte and having at least one pair of electrodes at least partially inside said chamber;

(b) a liquid chamber housed at least partially within said electrolytic chamber and adapted to contain a liquid, said liquid chamber comprising a base and a side wall each formed of a substantially rigid material;

(c) pressure transfer means separating said electrolytic chamber from said liquid chamber; and

(d) administering means adapted to release said liquid from said liquid chamber under influence of pressure applied to said liquid chamber,

whereby when the electrolytic chamber contains an electrolyte, the liquid chamber contains a liquid and a current is passed through said electrolyte via said electrodes:

(i) gas is generated from the electrolyte thereby increasing pressure inside the electrolytic chamber;

(ii) that increase in pressure is transferred to said liquid chamber via said pressure transfer means; and

(iii) a determinable amount of said liquid from said liquid chamber via said administering means,

wherein said sealed electrolytic chamber comprises valve means adapted to enable release of gas from said electrolytic chamber.

The valve means is preferably adapted to remain closed whilst the liquid is being expelled from the liquid chamber and to remain open whilst gas is being released from said electrolytic chamber.

According to a fifth aspect of the invention, there is provided a method of administering a liquid to a subject, said method comprising the steps of: providing a liquid delivering device according to the present invention; and administering the liquid to the subject via said liquid delivering device. Preferably the administering means is a needle and said needle is injected into the subject. More preferably, the administering means is a micro-needle array and said array is applied to the skin of the subject.

Brief description of the Drawings

Preferred embodiments of the invention will now be further explained and illustrated by reference to the accompanying drawings in which:

Figure 1A	is a schematic representation of an injection device in which a micro-needle array is connected to a syringe via a piece of flexible tubing.
Figure 1B	is a schematic representation of an injection device in which the micro-needle array is attached to the end of a syringe.
Figures 1C-E	are schematic representations of 3 alternative configurations of a micro-needle array suitable for use in the present invention.
Figures 2A-B	are schematic representations of an injection device according to a preferred embodiment of the present invention.
Figure 3A	is a schematic representation of a prior art liquid delivery device.
Figure 3B	is a graphical representation of the change of delivery weight with time using the prior art liquid delivery device illustrated in Figure 3A.
Figures 3C-F	are schematic representations of a liquid delivering device according to a preferred embodiment of the present invention.

Figure 3G is a graphical representation of the change of delivering weight with time using the liquid delivering device illustrated in Figures 3C-F.

Figure 4 is a schematic representation of a liquid delivering device according to another preferred embodiment of the present invention, which includes a valve.

Figures 5A-C and F are schematic representations of the liquid delivering device illustrated in Figure 4, at rest and in use.

Figures 5D-E are schematic representations of the liquid delivering device illustrated in Figure 4, attached to a liquid refill supply chamber following expulsion of liquid from the device.

Figures 6A-F are schematic representations of the liquid chamber and electrolysis chamber of the liquid delivering device according to another preferred embodiment of the present invention, in which electrolysis is used to expel drug from the liquid chamber.

Figures 7A-E are schematic representations of the drug chamber and electrolysis chamber of the liquid delivering device according to an alternative embodiment of the present invention, in which pneumatic means is used to expel drug from the liquid chamber.

Figures 8A-E are schematic representations of the drug chamber and electrolysis chamber of the liquid delivering device according to a further embodiment of the present invention, in which mechanical means is used to expel drug from the liquid chamber.

Detailed Description of the Preferred Embodiments

The basic structure of painless injection devices and micro-needle arrays are shown in Figure 1A. A micro needle array 1 is connected to flexible tubing 2 which is connected to syringe 3 containing the drug. The micro needle array is placed at the injection position of the skin and stuck intimately to the skin by means of adhesive plaster (tape), typically allowing the array to penetrate through the stratum corneum into the viable epidermis. The drug (in liquid form) is then injected into the human body manually. After the injection, the micro needle array and the tubing are disposed of. The syringe can be reused (or disposed of). An alternative design is to place the micro needle array at the

tip of the syringe, replacing the conventional needle (Figure 1B). The drug is injected into a human body or an animal in the same way as a conventional injection.

A micro-needle array suitable for use with the present invention may take any suitable form as can be seen by Figures 1C-E. In particular, the micro-needle array may comprise a storage area 4 to store fluid, or it may instead contain a recess 6 which engages with an actuator such as a syringe. Where the micro-needle array comprises a storage area 4, then inlet 5 may be positioned at any suitable location. For example, it may run substantially parallel to or perpendicular to the micro-needles.

Figure 2C illustrates an electrochemical liquid delivering device 23 and a control unit 24. A micro needle array 21 is connected to the device via flexible tubing 22. In this embodiment, the control unit comprises an adjustable or programmable constant current supply and display 25 and controls 26 to adjust or make/initiate programs and display the delivery weight (or volume)/rate. Alternatively, as shown in Figure 2B, the micro needle array is directly mounted at the outlet of the liquid delivering device and the device can then be connected to the control unit.

Figure 3A illustrates a prior art liquid delivering device in which two cylindrical chambers, 31 and 32, are mounted coaxially on plate 38. Internal chamber 32 is filled with liquid (often including a drug) 35 to be delivered. An elastomeric membrane 36 seals the top opening of the internal liquid chamber and separates the two chambers. The outer chamber 31 is filled with a proper aqueous electrolytic solution 34. Two electrodes 33, are inserted in the electrolytic solution. When the electrodes are connected to a power supply, a current flows through the electrolytic solution. Electrolysis of the water of the electrolytic solution occurs, yielding gases (hydrogen and oxygen). The pressure inside the outer chamber is thus increased with time, from P1, P2... and eventually to P5. The membrane between the two chambers is deformed downwardly by the pressure, which squeezes the liquid out of the internal chamber through outlet 37.

Figure 3B is a curve showing the change of the delivered liquid weight with time. It indicates that good linearity exists between the delivered weight and the time at a constant electrolysis current before the membrane touches the bottom of the liquid chamber (when $P < P3$). After the membrane touches the chamber bottom ($P = P4$, $P5... > P3$), the delivering rate decreases and the curve is no longer linear.

However, according to the present invention, as depicted in Figures 3C to 3F, improved linearity of the delivery weight / time curve can be maintained by altering the lower

contour of the internal liquid chamber so that it substantially conforms to the shape of the membrane when it just touches the chamber bottom (ie, the shape of the membrane when P = P3). This contour can be obtained by experiments or may be calculated by algorithms such as the Mooney Rivlin model (as long as the membrane is made from a hyperelastic material).

Figures 3C to 3F show changes in the membrane shape during the injection period employed in liquid delivering device according to this embodiment of the present invention. The membrane stretches as pressure is applied to it and the liquid is expelled at a substantially constant rate in the entire delivering time period. This is illustrated by the linear curve in Figure 3G. In addition, substantially all of the liquid is expelled.

Another embodiment of the liquid delivery device is shown in Figure 4, which comprises a valve 51 at the lid of outer chamber 42. Such a valve can be controlled by controller 43.

The operating procedure of a liquid delivering device according to the embodiment of the invention comprising valve 51 is shown in Figures 5A to 5C. For simplicity, the micro-injection needle arrangement is not shown. Figure 5A depicts the device prior to electrolysis and expulsion of fluid. Figures 5B and 5C depict the device with valve 51 during electrolysis, in which valve 51 remains closed. After completion of expulsion of fluid from the device, the micro-needle array and the tubing may be removed from the actuator and disposed of.

Figures 5D and 5E depict the refilling of the liquid delivery device by refill vessel 53 through tubing 52. During this process, valve 51 is opened and gas in outer chamber 55 escapes (56). As the liquid (which contains the drug) from the refill vessel is forced into liquid chamber 54, the elastic membrane 57 resumes its original shape. This can be effected simply by enabling the gas to escape from outer chamber 55. This produces negative pressure within the liquid chamber 54. Thus atmospheric pressure in refill bottle 53 can then force the liquid from the refill bottle into the liquid chamber 54. This process continues until the drug chamber 54 is replenished and membrane 57 recovers to its original flat status (Figure 5A and 5F). Valve 51 is then closed again, ready for fresh expulsion of the liquid drug. In this embodiment, the liquid delivering device is reusable and only the micro needle array and the flexible tubing are disposable after use.

Figures 6A to 6F depict an embodiment of the invention in which the electrolysis chamber and the liquid chamber are separable. Figure 6A depicts the liquid chamber 61 and electrolysis chamber 62 in the separated state. Again, for simplicity, the tubing and micro-needle array are not depicted. The lower portion of electrolysis chamber 62 is sealed by elastic membrane 67. Electrolysis chamber 62 is mounted upon the liquid chamber 61. A control unit is connected to the electrolysis chamber. The control unit generates a proper current in order to enable electrolysis to occur. Figure 6B depicts air escape channel 63 which is provided between the two chambers to enable air to escape, when the liquid chamber 61 and the electrolysis chamber 62 are brought together, so that the two elastomeric membranes (membrane 67a at the bottom of the electrolysis chamber and membrane 67b at the top of the liquid chamber) can be in touching contact over substantially their entire area.

After the device is switched on and a constant electrolysis current is supplied to electrolysis chamber 62, the two elastomeric membranes are deformed downwardly together, squeezing the liquid out of the liquid chamber at a substantially constant rate as depicted in Figures 6B and 6C. The injection rate is dependent upon the applied current. However, due to the features of the invention, the linearity is constant for any given current that is selected.

After completion of the injection, the empty liquid chamber (together with the micro needle array and connection tubing, which are not shown in the figure) is detached and disposed of as depicted in Figures 6E and 6F. Valve 64 is opened to release the gases generated during the electrolysis until the pressure of the electrolysis chamber 62 equals the atmospheric pressure and the membrane 67a becomes flat. Then the valve is closed again. A new drug chamber with micro needle array and connection tubing is inserted and the device (ie, electrolysis chamber and control unit) can then be reused.

Figure 7A illustrates a fourth embodiment of the present invention. It employs pneumatic means to control the injection rate. Pneumatic control device 70 has control parts such as gas valve, pressure gauge, pressure regulator, display 75, and adjusting controls 74. These parts constitute a pneumatic control circuit. There is also a gas buffer chamber 76, with a gas outlet 77, at its bottom.

The control device has a gas inlet 79, connected to a pressurized gas source, such as a compressed gas supply or a compressed air cylinder. Preferably, this would be an inert gas, such as argon or nitrogen. Drug chamber 73 with a micro needle array 71, and connection tubing 72, can be mounted at the cavity of the control device, underneath

the gas buffer chamber. An airproof mechanism such as a sealing O-ring 78 makes the gas buffer chamber isolated from the outside atmosphere (Figure 7B).

The structure of liquid chamber 73 is similar to that used in the third embodiment (see Figures 5 and 6). That is, its top is covered with an elastomeric membrane 73a. The combination of array 71, tubing 72 and liquid chamber 73 may be regarded as a drug cartridge. When the gas flows into the buffer chamber 76 at a controlled rate set by control unit 70, the pressure within buffer chamber 76 increases and membrane 73a is deformed downwardly. The drug is expelled from liquid chamber 73 and is injected via tubing 72 and array 71 into the recipient as depicted in Figure 7C.

Once the preset amount of drug has been delivered, the gas flow to buffer chamber 76 ceases as depicted in Figure 7D. Then the compressed (high-pressure) air in buffer chamber 76 is allowed to flow out to the outside atmosphere through a leaking valve. When the pressure of buffer chamber 76 has returned to atmosphere pressure, the empty drug cartridge is detached and disposed of. A new drug cartridge is then mounted and a new injection can be started following the same procedure.

The outside source of pressurized gas may be replaced by a miniature-pressurized container that can be integrated into the pneumatic control device, making this embodiment portable.

Figure 8A illustrates a fifth embodiment of the injection device of the present invention when driven by electric/mechanical means. An electric motor 85, with or without a transmission gear system is installed in the device, 84. A gear, 86, mounted at the rotation shaft of the motor (or the gear system), is coupled to the thread of a moving rod, 87. The rod is moved up or down by the gear, 86. The moving direction and speed depend on the motor's rotation direction and rate (and upon the arrangement of any gear system).

Figure 8B illustrates the fifth embodiment of the invention when a drug cartridge (81, 82 and 83 in Figure 8A), which is the same as that used in the third and fourth embodiments, is inserted into the cavity of the device, 84, underneath the moving rod.

Figure 8C illustrates the fifth embodiment of the invention when the rod moves down, pushing the membrane of the drug chamber down and squeezing the drug out.

Figure 8D illustrates the fifth embodiment when the entire drug is injected out and the motor rotation direction is reversed and the moving rod retracts upwards to its original position. The empty drug cartridge is then detached and disposed of.

Figure 8E illustrates the fifth embodiment of the invention when the shape of the rod is of another design when the drug chamber has a near flat bottom contour.

When rod 87 moves downwards, it pushes membrane 83a of drug chamber 83 down and squeezes the drug out. When the entire drug has been expelled (as depicted in Figure 7D) the rotation direction of motor 85 is reversed and rod 87 retracts upwards to its original position. Empty drug cartridge 83 is then detached and disposed of. A new drug cartridge can be mounted and a new injection can be started following the same procedure as depicted in Figure 8D.

The injection rate is controlled by the moving speed of rod 86, which in turn is controlled by the motor/gear system. The shape of the bottom surface rod 86 can be designed in different ways. Figure 8E shows another design of the bottom surface, in which the drug chamber has a near flat bottom contour.

The word 'comprising' and forms of the word 'comprising' as used in this description and in the claims do not limit the invention claimed to exclude any variants or additions. Modifications and improvements to the invention will be readily apparent to those skilled in the art. Such modifications and improvements are intended to be within the scope of this invention.

CLAIMS

The claims defining the invention are as follows:

1. A liquid housing chamber for use in a device for administering liquid to a subject, said liquid chamber comprising:
   (a) a cavity defined by a base and a surrounding sidewall, said sidewall including an upper rim;
   (b) a deformable membrane attached to the upper rim and covering said cavity; and
   (c) an outlet located in the base;

   wherein said base is inclined from about said outlet to said surrounding sidewall and is formed of a substantially rigid material.

2. The liquid chamber of claim 1 wherein said outlet is located at a central portion of the base.

3. The liquid chamber of claim 1 or claim 2 wherein said base has a bowl-shaped contour.

4. The liquid chamber of claim 3, wherein the bowl-shaped contour is adapted to correspond with the contour of the deformable membrane in an expanded position.

5. The liquid chamber of claim 4, wherein the dimensions of the bowl-shaped contour are determined by reference to a proper mathematical model of the deformability of the deformable membrane.

6. The liquid chamber of claim 5, wherein the deformable membrane is a hyperelastic membrane and the mathematical model is the Mooney Rivilin model.

7. The liquid chamber of claim 1 or claim 2 wherein the base has a cone-shaped contour.

8. The liquid chamber of any one of claims 1 to 7 wherein the surrounding sidewall is formed of a substantially rigid material.

9. The liquid chamber of any one of claims 3 to 6 and 8 wherein the surrounding sidewall has a curved contour which corresponds with the contour of the base so

that the base and the sidewall together form a cavity having a bowl shape contour.

10. The liquid chamber of claim 7 or claim 8 wherein the surrounding sidewall has an inclined contour which corresponds with the contour of the base so that the base and the sidewall together form a cavity having a cone-shaped contour.

11. The liquid chamber of any one of claims 1 to 10 wherein the contour of the cavity is adapted so that, when said deformable membrane is fully expanded within said cavity, there is no substantial residual volume between the membrane and either the base or the side wall.

12. The liquid chamber of any one of claims 1 to 11 wherein said deformable membrane is impermeable to fluids.

13. The liquid chamber of any one of claims 1 to 12 wherein said deformable membrane is formed of materials selected from hyper-elastic materials, and materials with high elasticity and high plasticity.

14. The liquid chamber of any one of claims 1 to 13 wherein said liquid chamber is adapted to be connected to pressure exerting means, said pressure exerting means being adapted to exert pressure upon said deformable membrane, causing the membrane to expand into said cavity, thereby forcing the liquid to be expelled through the outlet.

15. The liquid chamber of claim 14 wherein said chamber is removably connectable to said pressure exerting means.

16. The liquid chamber of claim 14 or claim 15 wherein said pressure exerting means comprises an electrolytic chamber adapted to contain an electrolytic solution and, in use, to generate a gas which causes pressure to be exerted upon said deformable membrane.

17. The liquid chamber of claim 16 wherein said electrolytic chamber comprises at least one pair of electrodes located at least partially within said electrolytic chamber.

18. The liquid chamber of claim 16 or claim 17 wherein said liquid chamber and said electrolytic chamber are adapted so that the liquid chamber is housed at least partially within said electrolytic chamber.

19. The liquid chamber of claim 18 wherein said liquid chamber is positioned in substantially co-axial alignment with said electrolytic chamber.

20. The liquid chamber of claim 18 or claim 19 wherein said liquid chamber and said electrolytic chamber are substantially cylindrical in shape.

21. The liquid chamber of any one of claims 16 to 20 wherein said electrolytic chamber is connected to a control unit adapted to cause a potential difference in the electrodes, thereby causing an electric current to pass between the electrodes through said solution.

22. The liquid chamber of claim 21 wherein said control unit is adapted to regulate the electric current passing between the electrodes.

23. The liquid chamber of any one of claims 16 to 22 wherein, when the electrolytic chamber contains said electrolytic solution, the liquid chamber contains a liquid, and a current is passed through said electrolytic solution via said electrodes;

(a) gas is generated from the electrolytic solution thereby increasing pressure inside the electrolytic chamber;

(b) that increase in pressure is transferred to said liquid chamber via deformation of said deformable membrane; and

(c) a determinable amount of said liquid is released from said liquid chamber via said outlet.

24. The liquid chamber of any one of claims 21 to 23 wherein said electrolytic chamber is removably connected to said control unit.

25. The liquid chamber of any one of claims 16 to 24 wherein said electrolytic chamber further comprises valve means adapted to enable release of gas from said chamber, thereby causing said deformable membrane to retract to its original position and enabling said liquid chamber to be refilled with liquid.

26. The liquid chamber of claim 25 wherein said valve means is adapted to remain closed whilst the liquid is being expelled from the liquid chamber and to remain open whilst gas is being released from said electrolytic chamber.

27. The liquid chamber of any one of claims 16 to 26 wherein said electrolytic chamber further comprises a chamber membrane adapted to be positioned in face to face orientation with the deformable membrane of the liquid chamber, said chamber membrane being configured so as to correspond substantially with said deformable membrane.

28. The liquid chamber of claim 27 further comprising an air-release channel adapted to enable air to escape from between the deformable membrane and the chamber membrane so that said membranes can be in intimate contact.

29. The liquid chamber of claim 27 or claim 28 wherein the elasticity of the chamber membrane and the deformable membrane are substantially the same.

30. The liquid chamber of any one of claims 27 to 30 wherein the chamber membrane and the deformable membrane are formed of the same material and have substantially the same thickness.

31. The liquid chamber of any one of claims 14 to 30 wherein the pressure exerting means is a hydraulic device adapted to apply a pressurised fluid to said deformable membrane.

32. The liquid chamber of claim 31 wherein said hydraulic device is a pneumatic device which includes gas inlet means and gas outlet means.

33. The liquid chamber of claim 32 wherein said gas outlet means is located centrally above the deformable membrane.

34. The liquid chamber of claim 33 wherein said gas outlet means is in substantial linear alignment with the outlet of the liquid chamber.

35. The liquid chamber of any one of claims 32 to 34 wherein said pneumatic device further includes valve means for regulating the flow of gas through the gas outlet means.

36. The liquid chamber of any one of claims 32 to 35 further including a gas buffer chamber adjacent said gas outlet means.

37. The liquid chamber of claim 36 wherein the gas buffer chamber is located immediately above said gas outlet means.

38. The liquid chamber of any one of claims 32 to 37 wherein the pneumatic device further includes a miniature pressurised gas container for supplying said gas.

39. The liquid chamber of claim 14 or claim 15 wherein the pressure exerting means is a piston device comprising a piston and piston guiding means, said piston including a piston head adapted to contact and apply pressure to the deformable membrane.

40. The liquid chamber of claim 39 wherein the piston head is shaped so as to conform substantially with the base of the liquid chamber.

41. The liquid chamber of claim 40 wherein the piston head is shaped so as to conform substantially with the base and surrounding sidewall of the liquid chamber.

42. The liquid chamber of any one of claims 39 to 41 wherein the piston device further includes an electric motor adapted to drive the piston up and down.

43. The liquid chamber of claim 42 wherein the piston device further includes a transmission and gear system.

44. The liquid chamber of any one of claims 1 to 43 wherein the liquid comprises an active ingredient for administration to the subject.

45. The liquid chamber of claim 44 wherein the active ingredient includes a drug.

46. The liquid chamber of claim 45 wherein the active ingredient is a drug for cancer treatment.

47. An electrolysis chamber, for use in connection with the liquid chamber of any one of claims 1 to 46, comprising:

(a) an electrolytic solution;

(b) at least one pair of electrodes at least partially immersed in said electrolytic solution;

(c) a valve adapted to release gas from the electrolysis chamber; and

(d) a chamber membrane adapted to be positioned in face to face orientation with the deformable membrane of the liquid chamber, said chamber membrane configured so as to correspond substantially with the deformable membrane.

48. The electrolysis chamber of claim 47 wherein said chamber is adapted to be connected to a control unit adapted to apply a potential difference to the electrodes, thereby causing an electric current to pass between the electrodes through said solution.

49 The electrolysis chamber of claim 47 or claim 48 wherein the valve is adapted to remain closed whilst electrolysis is occurring within said chamber.

50. A liquid delivering device for administering liquid to a patient, comprising:

(a) a liquid chamber according to any one of claims 1 to 46; and

(b) administering means adapted to convey said liquid from the outlet of said liquid chamber to the subject under influence of pressure applied to said liquid chamber.

51. The device of claim 50 wherein the administering means includes an injection device selected from a needle and a micro-needle array.

52. The device of claim 51 wherein the injection device is a micro-needle array.

53. The device of claim 52 adapted so that the micro-needle array is connectable directly to the liquid chamber.

54. The device of claim 52 adapted so that the micro-needle array is connectable to the liquid chamber via a flexible tube.

55. The device of any one of claims 50 to 54 wherein said device is adapted to release said liquid at a flow rate of between 0.1 and 100 microlitres per minute.

56. A liquid delivering device for administering liquid to a patient, comprising:

(a) a sealed electrolytic chamber adapted to contain an electrolyte and having at least one pair of electrodes at least partially inside said chamber;

(b) a liquid chamber housed at least partially within said electrolytic chamber and adapted to contain a liquid, said liquid chamber comprising a base and a side wall each formed of a substantially rigid material;

(c) pressure transfer means separating said electrolytic chamber from said liquid chamber; and

(d) administering means adapted to release said liquid from said liquid chamber under influence of pressure applied to said liquid chamber,

whereby when the electrolytic chamber contains an electrolyte, the liquid chamber contains a liquid and a current is passed through said electrolyte via said electrodes:

(i) gas is generated from the electrolyte thereby increasing pressure inside the electrolytic chamber;

(ii) that increase in pressure is transferred to said liquid chamber via said pressure transfer means; and

(iii) a determinable amount of said liquid from said liquid chamber via said administering means,

wherein said sealed electrolytic chamber comprises valve means adapted to enable release of gas from said electrolytic chamber.

57. The device of claim 56 wherein said valve means is adapted to remain closed whilst the liquid is being expelled from the liquid chamber and to remain open whilst gas is being released from said electrolytic chamber.

58. A method of administering a liquid to a subject, said method comprising the steps of:

(a) providing a liquid delivering device according to any one of claims 50 to 57; and

(b) administering the liquid to the subject via said liquid delivering device.

59. The method of claim 58 wherein the administering means is a needle and said needle is injected into the subject.

60. The method of claim 58 wherein the administering means is a micro-needle array and said array is applied firmly to the skin of the subject.

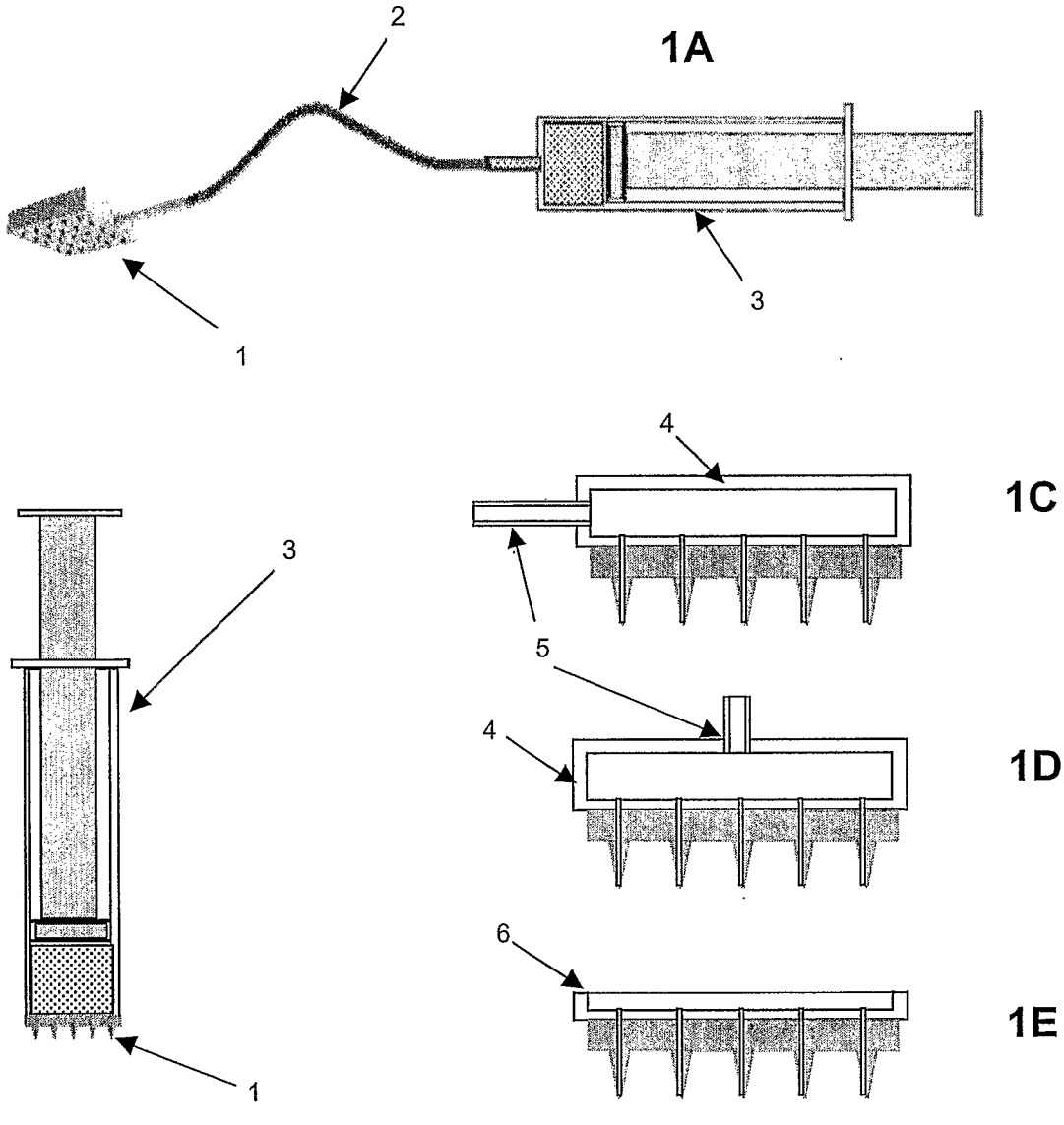
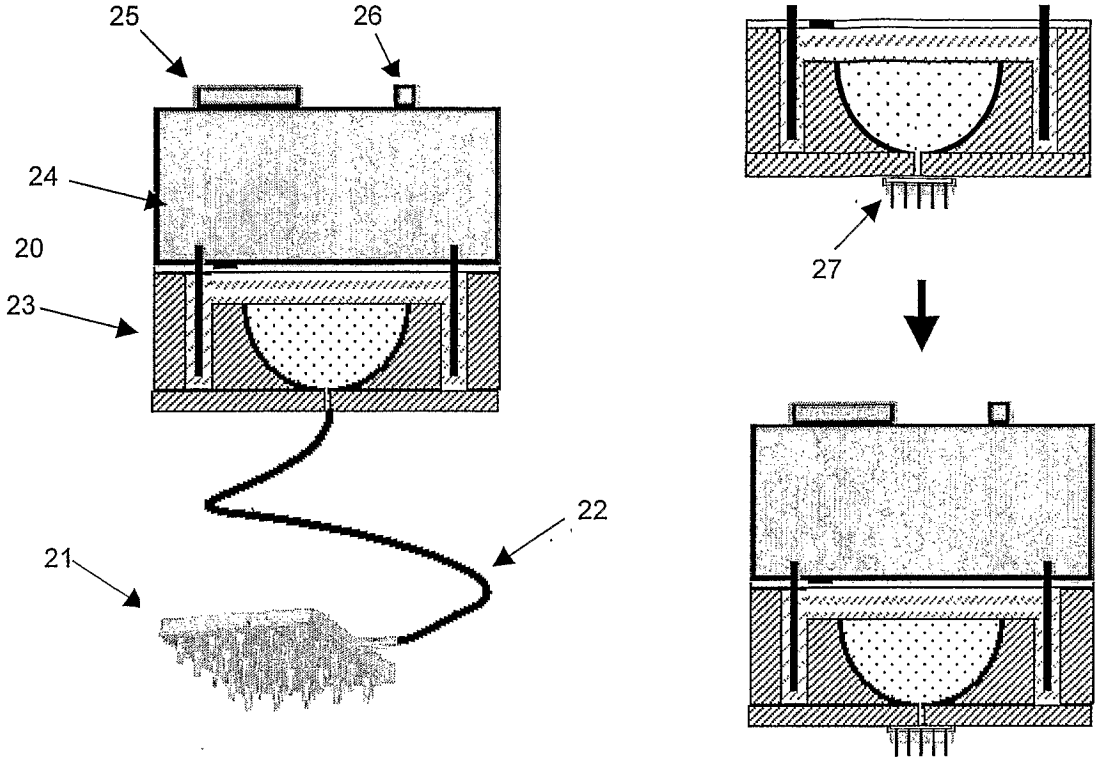
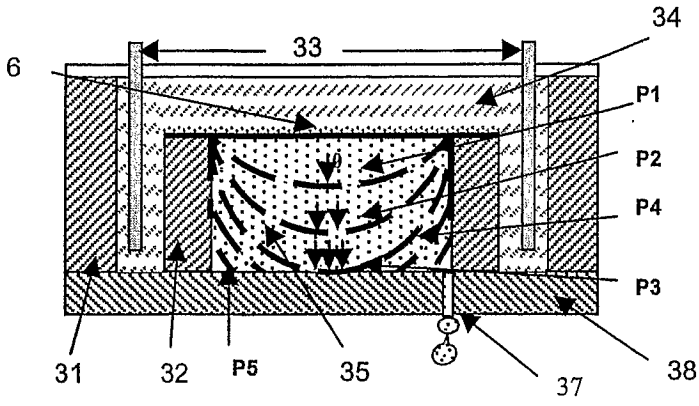


Figure 1

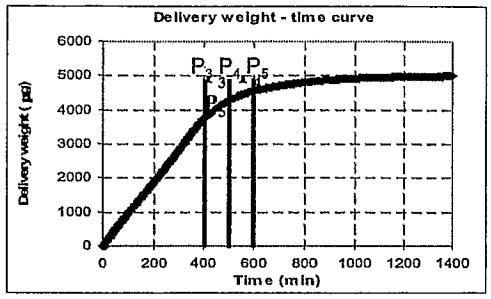


2A 2B

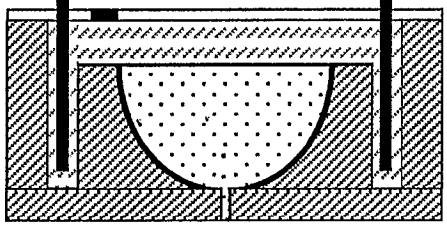
Figure 2



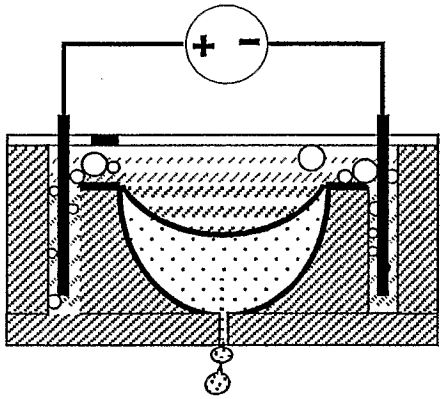
3A



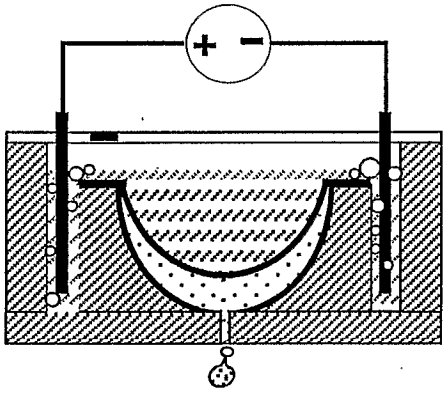
3B



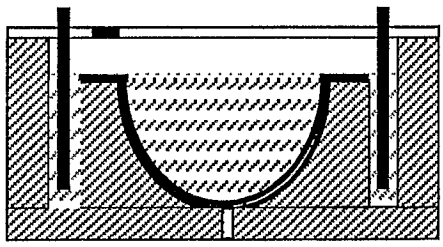
3C



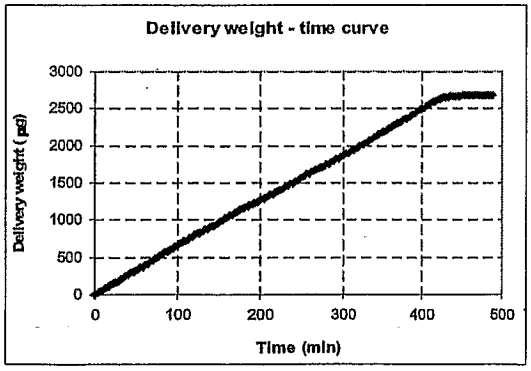
3D



3E



3F



3G

Figure 3

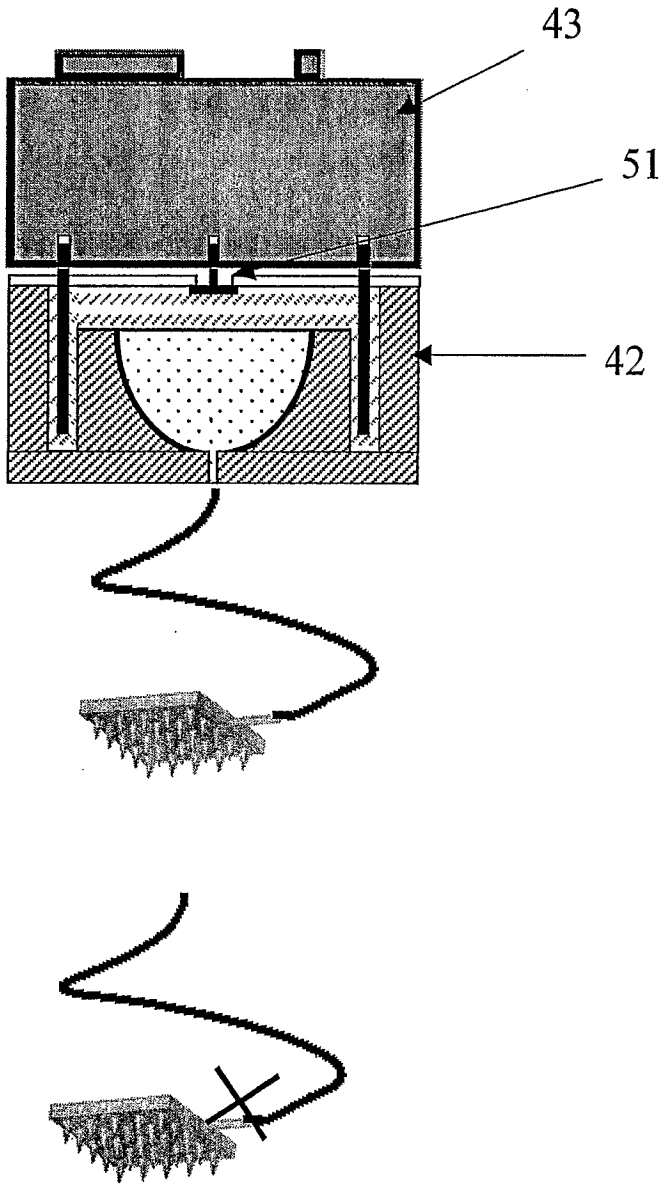


Figure 4

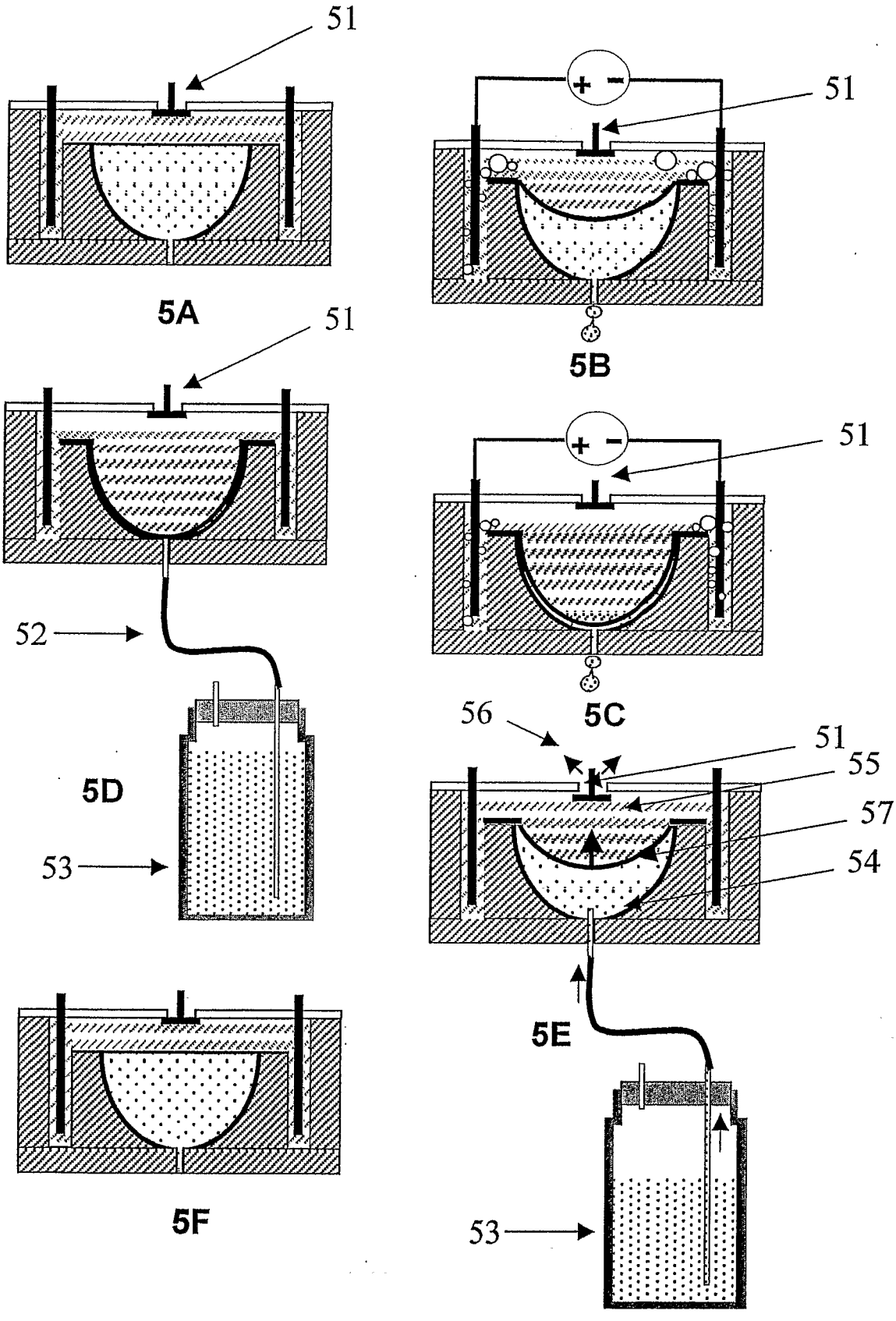


Figure 5

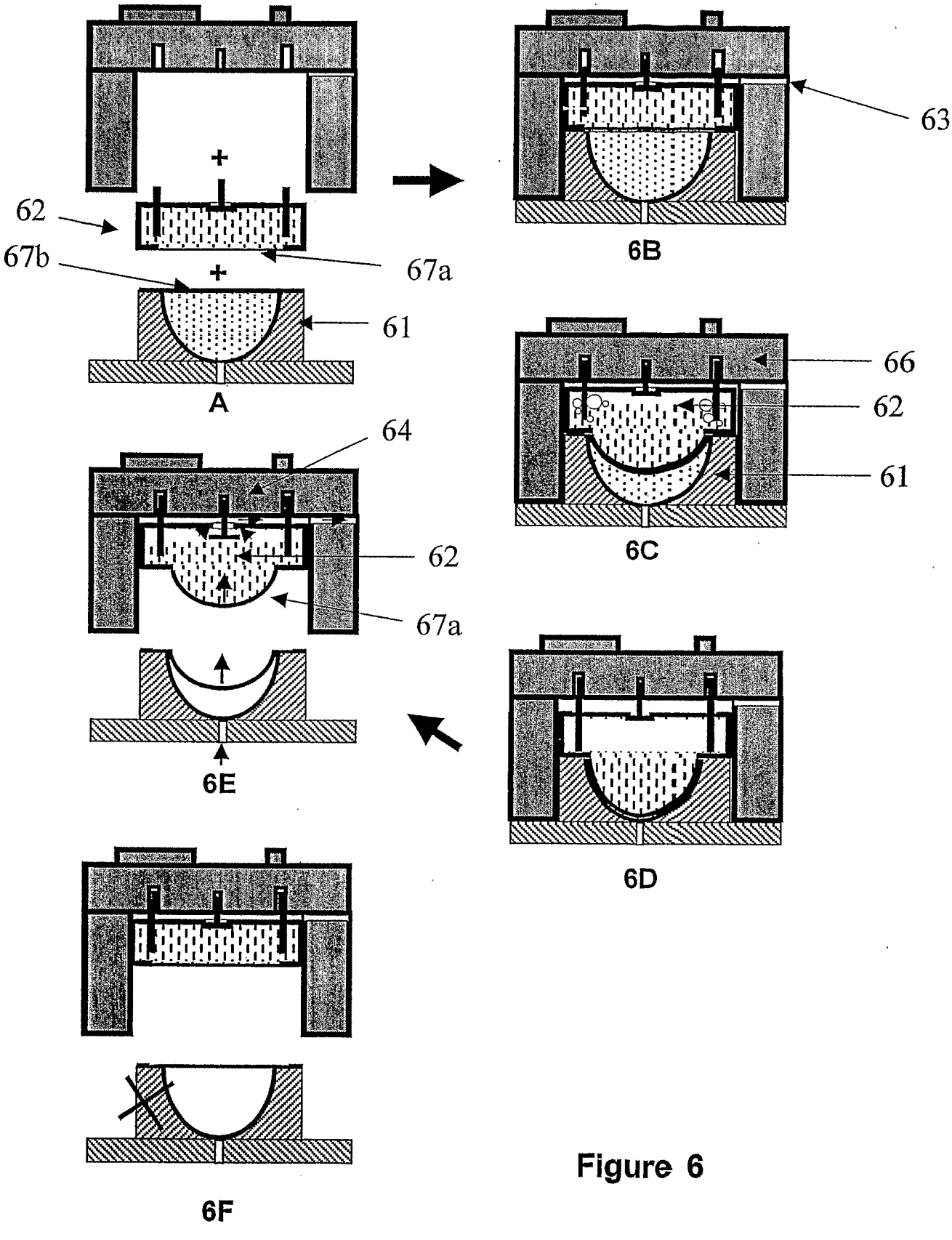


Figure 6

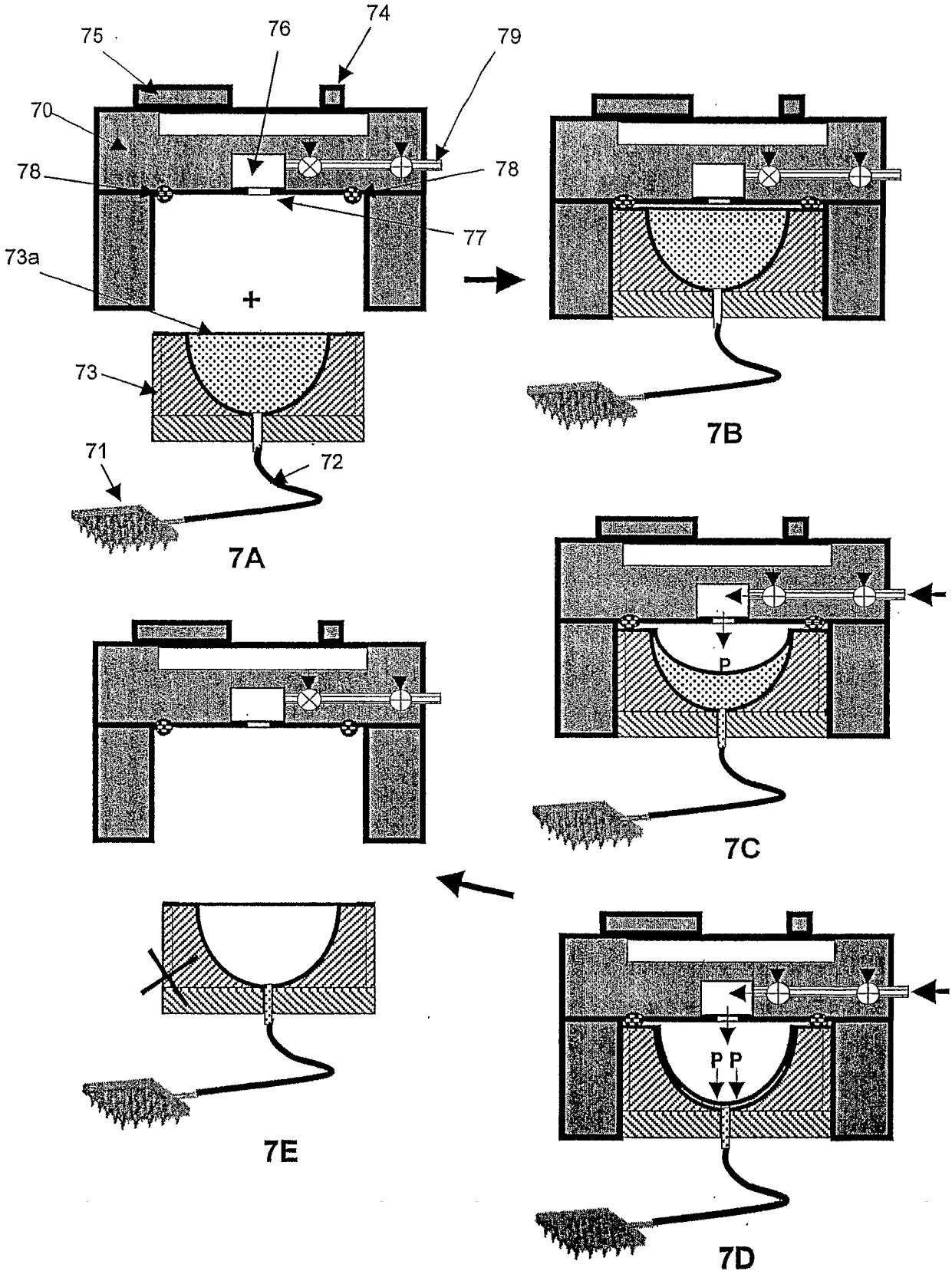


Figure 7

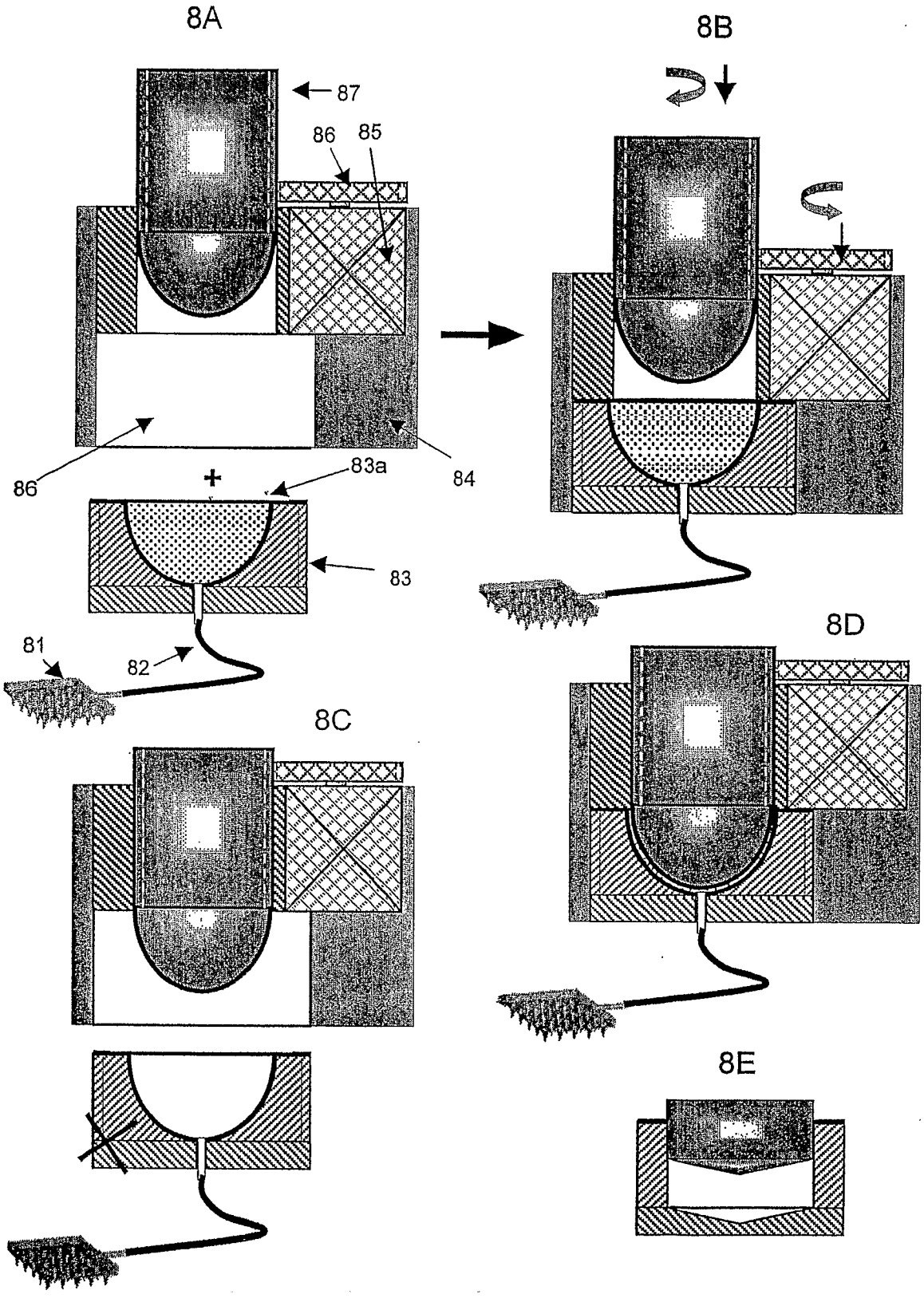


Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2003/000257

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61M 5/145

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI + keywords: membran elastic deliver inject liquid fluid cavit chamber press deform base bottom rigid firm

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2001021234 A1 (BAXTER INTERNATIONAL INC) 29 March 2001 Pages 7-18 and figures	1-3, 7, 8, 10-12, 14, 16, 17, 19-26, 44-46, 50, 51
X	US 4710167 A (LAZORTHES) 1 December 1987 Whole document	1, 3, 4, 8, 9, 11, 12, 44-46, 50, 51
X Y	WO 1995004691 A1 (RIVER MEDICAL INC) 16 February 1995 Pages 14-35 and figures 3-6 Pages 14-35	1-4, 8, 9, 11, 12, 14, 15, 50 16-24, 39

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2004	12 FEB 2004
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **Sue Thomas** Telephone No : (02) 6283 2454

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2003/000257

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 199741917 A1 (CERAMATEC INC) 13 November 1997 Pages 6-16, and figures 3 and 4 Pages 6-16	1-4, 8-12, 14, 16, 17, 21-24, 44-46, 50-51 56,58,59
X	FR 2346238 A1 (RHONE-POULENC INDUSTRIES) 28 October 1977 Whole document	1-4, 8, 9, 11, 12, 14, 15, 31-34, 38, 44-46
Y	WO 2002069935 A1 (MICROLIN L C) 12 September 2002 Pages 11-20	1-3, 8, 9, 11, 12, 14, 16, 17, 19-24, 31, 39, 44-46
Y	WO 2003018089 A1 (INSTITUTE of MATERIALS RESEARCH and ENGINEERING) 6 March 2003 Pages 13-22 and abstract	18, 56
Y	EP 0209677 B1 (IVAC CORP) 25 July 1990 Whole document	25, 56
Y	WO 1995003078 A1 (ELAN MEDICAL TECHNOLOGIES LTD) 2 February 1995 Pages 6-20	56
Y	US 5135499 A (TAFANI et al) 4 August 1992 Whole document	56, 58
Y	WO 1999038553 A1 (MEDTRONIC INC) 5 August 1999 Pages 4-14 and abstract	23, 56
Y	EP 0209644 A1 (IVAC CORP) 28 January 1987 Whole document	23, 56
Y	WO 2001091846 A2 (THE PROCTER & GAMBLE CO) 6 December 2001 Abstract	51-53, 58, 60
A	US 20030105428 A1 (HOGAN et al) 5 June 2003 Whole document	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2003/000257

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

See attached sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2003/000257

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The international application does not comply with the international requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept. The International Searching Authority has found that there are different inventions as follows:

Claims 1-46 are directed to a liquid housing chamber having a first special technical feature of the base inclined from about the outlet to the surrounding sidewall .

Claims 47-49 are directed to an electrolysis chamber having a second special technical feature of a valve adapted o release gas from the chamber

Claims 50-55 are directed to a liquid delivering device having a third special technical feature of an administering means adapted to convey liquid to the subject

Claims 56-60 are directed to a liquid delivering device having all three special technical features.

Since the above groups of claims do not share any of the technical features identified, a "technical relationship" between the inventions, as defined in PCT rule 13.2 does not exist. Accordingly the international application does not relate to one invention or to as single inventive concept, *a priori*.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SG2003/000257

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	0121234	AU	67536/00	EP	1131117	US	6413238
		CN	1321096				
US	4710167	CA	1265965	DE	3670447	EP	0203633
		FR	2582221	JP	61265146	US	4710167
WO	9504691	AU	36318/95	AU	19267/95	AU	74823/94
		CN	1132481	EP	0781147	EP	0748252
		US	5588556	WO	9505211	WO	9608280
US	9741917	US	5785688				
FR	2346238	IT	1081355	JP	1442638	JP	62051630
WO	02069935	CA	2438508	US	6575961	US	2002156461
WO	03018089		NIL				
EP	0209677	DE	3672917	JP	61280869	US	4687423
WO	9503078	AU	675558	DE	69425660	EP	0708665
		JP	9505208	US	5704520	ZA	9405272
US	5135499	FR	2649617	DE	69016387	WO	9100753
WO	9938553	AU	25734/99	EP	1053036	US	6048328
EP	0209644	JP	61255668	US	4886514		
WO	0191846	AU	65056/01	CA	2376283	EP	1183064
		US	2002020688	WO	0074764	WO	0191846
US	2003105428		NIL				

END OF ANNEX