(12) STANDARD PATENT APPLICATION (11) Application No. **AU 2005234689 A1**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Dispensing device

(51)[7] International Patent Classification(s)
A61D 007/00 **A61M 035/00**

(21) Application No: **2005234689** (22) Date of Filing: **2005.11.18**

(43) Publication Date: **2005.12.08**
(43) Publication Journal Date: **2005.12.08**

(62) Divisional of:
2002220352

(71) Applicant(s)
Acrux DDS Pty Ltd

(72) Inventor(s)
Bayly, Mark Simon; Wong, Kon Euan

(74) Agent / Attorney
Phillips Ormonde & Fitzpatrick, Level 21 367 Collins Street, Melbourne, VIC, 3000

2005234689 18 Nov 2005

ABSTRACT

A hand-held device for dispensing a substance and applying that substance to the skin of a host, said device including a hollow body, a substance capsule mounted within said body, a container for said substance forming part of said capsule, a spray nozzle, actuator means connected to the interior of said container and being operable to cause a metered quantity of said substance to be dispensed through said nozzle in the form of a spray, said device further including an actuator mounted on said body and being operable to cause operation of said pump, and absorption means locatable in alignment with said nozzle and being operable when so located to absorb a pre-use quantity of said substance dispensed through said nozzle during at least a first of a series of operations of said actuator means, said absorption means being removable from said alignment to enable a full charge of said substance to be dispensed through said nozzle during a subsequent one of said series of operations of said actuator means.

AUSTRALIA

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Name of Applicant:

Acrux DDS Pty Ltd

Actual Inventor(s):

Kon Euan Wong, Mark Simon Bayly

Address for Service and Correspondence:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Invention Title:

DISPENSING DEVICE

Our Ref : 759651
POF Code: 463409/463409

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

DISPENSING DEVICE

The present application is a divisional application from Australian Patent Application number 2002220352 the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to a device for dispensing a substance, such as a pharmaceutical, medicinal, or therapeutic substance, and applying that substance to the skin of a host animal (eg. a human). The invention is particularly concerned with a device that is operable to dispense a metered quantity of a substance in the form of a spray or mist. More specifically, the invention is concerned with transdermal and/or percutaneous delivery of substances, and in particular liquids containing a physiologically active agent.

BACKGROUND OF THE INVENTION

Drug delivery is the process of taking a drug and incorporating it into a dosage form to enable the drug to; reach its target within the body; be delivered at effective concentrations; be absorbed in a timely manner; not produce toxic side-effects; and be in a convenient form for the patient. The transdermal route of drug delivery has been extensively explored as a means for effective drug delivery.

Traditionally, transdermal drug delivery systems have employed occlusive patch devices that are adhered to the skin for prolonged periods of time in order to deliver the drug across the skin and into the bloodstream at effective concentrations. However, transdermal patches suffer from major problems. Such problems include skin irritation at the site of application; poor cosmetic acceptability by the user; complex manufacturing processes; and limited flexibility for changing the dose applied. Adhesive transdermal matrix patches require complex and critical manufacturing steps, including: preparation of drug solution; thermal blending of adhesive; precision coating onto the release liner; controlled drying of patch (requires many in-process tests); laminating of the backing of the patch; die-cutting of different patch sizes; final packing in foil-lined blister pack. (Jenkins A.W. Developing the fematrix™ transdermal patch. Pharm. J. 1995 Vol 255 Aug 5 pp 179-181).

There have been attempts to overcome such problems by reverting to the use of traditional non-occlusive topical vehicles, such as gels, creams and lotions, however the use of these vehicles for transdermal drug delivery has

been constrained by their limited application to the full range of transdermal drug candidates due to a low transdermal flux. Gels, creams and lotions also suffer from messy application methods; poor dosage control during application; unacceptably long drying-times on the skin; and significant patient-to-partner transfer of the drug. Consequently, in US Patent No. 6,299,900 titled Dermal Penetration Enhancers and Drug Delivery System Involving Same, Reed et al., provide an improved non-occlusive, volatile:non-volatile transdermal drug delivery system that overcomes the above limitations of traditional transdermal drug delivery systems (eg., patches, gels, creams, lotions).

The foregoing problems have led to the development of devices for the controlled application of volatile:nonvolatile liquid formulations to the skin, such as that disclosed in US Patent No. 6,113,008 for example, which is a device for applying an occlusive spray-on bandage to the skin. That device suffers from the limitation of not providing means to prevent actuator nozzle blockage by the preferred film-forming aerosols during its normal use, and is also restricted by its axial nozzle orientation to practical application to the forearm only. That is unless the patient is willing to lie down during operation of the device for application to other traditional sites such as the abdomen, upper buttocks and thigh. Such an approach would then also pose the additional problem of a lack of dip-tube pick-up from the liquid reservoir, solutions to which are available, such as that described in US Patent No. 5,624,060, but which would add significant cost and complexity to the utility of the device disclosed by US Patent No. 6,113,008. That device also relies upon a vent in the dispensing shroud that is open to ambient in order to prevent any pressure build-up when using the preferred pressurized aerosols, and that leads to spray drift with consequent loss of some of the dispensed substance.

US Patent No. 6,261.274 discloses another dispensing device that is reliant upon a distance-gauging means to control the distance and orientation of the actuator nozzle from the skin. That device suffers from the limitation of a likelihood of variable actuator nozzle angle and/or distance relative to the skin, notwithstanding the use of a flat surface at the end of the distance-gauging means that is pressed against the skin during use. That is because in practice, the surface area of this feature needs to be restricted in order to avoid encroachment upon the dispensed substance plume during normal use of the

device. The typical length required for the distance-gauge would mean that little if any stabilizing effect is achieved during normal use, because the angle of the distance-gauge would be prone to angle changes due to normal compliance of the skin surface, a problem which is compounded by only having limited surface area of contact for the distance-gauge, as well as the leveraged effect that even a small change in the angle of the distance-gauge has on the distance and angle of the actuator nozzle relative to the skin. The device of US Patent No. 6,261,274 also suffers from the limitation that the patient needs to be able to assess the actual site at which the dispensed substance would be applied, which is a particular problem for application to the forearm, where the spacer leg could be placed on the skin but the substance then sprayed into the air, missing the skin altogether. The device therefore suffers from a high potential for variation in the surface area over which the dispensed substance is applied, and the possibility to miss the target application site.

Substance dispensing devices of the foregoing kind tend to suffer an unacceptable loss of the substance in the period between uses of the device. That loss is particularly evident in circumstances involving use of a volatile substance. Unintentional loss of the substance is wasteful, and can also interfere with the ability of the device to dispense an accurately metered quantity each time the device is operated. In that regard, accurate metering can be very important in some circumstances.

There is a need for a device having the ability to provide accurate and reproducible application of volatile:nonvolatile liquid formulations, such as those described in US Patent No. 6,299,900, at low volume levels, typically between 1 to 10 microlitre per square centimetre of application area. There is also a need for a dispensing device having means for preventing loss-of-prime (or loss-of-residual dose)

BRIEF SUMMARY OF THE INVENTION

It is an object of the present invention to provide a substance dispensing device having means for preventing, or minimising, unintentional loss of the substance. It is a further object of the invention to provide a substance dispensing device that is able to dispense an accurately metered quantity of a substance during normal use. It is yet another object of the invention to provide

a substance dispensing device having means to enable a full charge of a substance to be available for discharge preparatory to normal use of the device. Still another object of the invention is to provide a dispensing device that is particularly suitable for use in transdermal application of substances.

According to the invention there is provided a hand-held device for dispensing a substance and applying that substance to the skin of a host, said device including a hollow body, a substance capsule mounted within said body, a container for said substance forming part of said capsule, a spray nozzle, actuator means connected to the interior of said container and being operable to cause a metered quantity of said substance to be dispensed through said nozzle in the form of a spray, said device further including an actuator mounted on said body and being operable to cause operation of said pump, and absorption means locatable in alignment with said nozzle and being operable when so located to absorb a pre-use quantity of said substance dispensed through said nozzle during at least a first of a series of operations of said actuator means, said absorption means being removable from said alignment to enable a full charge of said substance to be dispensed through said nozzle during a subsequent one of said series of operations of said actuator means.

A transdermal spray applicator device according to the invention may be charged with a substance in the form of a single-phase volatile/non-volatile liquid provided within a standard plastic and/or glass container (depending on the characteristics of the active ingredient): Manufacture of the device in one of its preferred forms is relatively straight-forward, amenable to simple scale-up, and uses "off-the-shelf' componentary for the primary pharmaceutical packaging. That contrasts with the complexities involved in manufacturing occlusive patch devices as described above.

In a preferred form of the device, the nozzle outlet communicates with a space defined within a shroud of suitable configuration and size. Such a shroud is particularly useful in circumstances involving transdermal application of a substance, because it can assist in ensuring that the dispensed substance is confined to the intended target area. It is preferred that the shroud provides a complete non-vented enclosure over the target area so as to reduce the risk of spray drift and consequent loss of some of the substance being dispensed. Furthermore, the shroud can function as a distance regulating device. That is, when the open mouth of the shroud engages a surface surrounding the intended target area, the distance between the target area and the outlet of the

spray nozzle is preferably substantially equal to the ideal distance over which the substance should be sprayed on to the target area.

Reference to "non-vented" in the previous paragraph and other parts of this specification is not to be understood as demanding complete absence of exposure to the atmosphere. The preferred shroud is "non-vented" in the sense that it does not have openings deliberately formed through the side wall (e.g. as in the device of US 6,113,008), or through the outer edge intended to engage against the surface surrounding the target area.

A condition called "loss of prime" can occur in the delivery system while the device is not in use. One cause of such loss of prime is evaporation, particularly when volatile substances are being used. As a result, air occupies a space within the delivery system that was intended to be occupied by the substance. Thus, when the device is thereafter operated to discharge the substance, the quantity discharged will be less than the intended metered quantity.

A 'full charge" is to be understood as comprising a quantity of the substance substantially equal to the metered amount intended to be discharged from the device when operated in a correct manner.

A device according to the invention as described above could be disposable or rechargeable. That is, in one form, the entire device may be discarded when the contents of the capsule are exhausted, whereas in another form the capsule may be removably mounted in the hollow body of the device so as to enable removal and replacement by a fully charged capsule.

Also, in a device according to the invention, the form of the actuator means may differ according to whether the substance is dispensed by means of a manually operable pump, or by an aerosol-type process. In the former case, the pump may form part of the actuator means. In the latter case the actuator means may include a valve that is operable to connect the nozzle to the pressurized contents of the substance container.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT OF THE INVENTION

An Embodiment of the invention is described in detail in the following passages of the specification which refer to the accompanying drawings. The

drawings, however, are merely illustrative of how the invention might be put into effect, so that the specific form and arrangement of the various features as shown is not to be understood as limiting on the invention.

In the drawings:

Figure 1 is a side elevation view of one form of dispensing device.

Figure 2 is a rear elevation view of the device shown by Figure 1.

Figure 3 is a cross-sectional view taken along line III-III of Figure 2.

Figure 4 is an exploded view of the device shown by Figure 3.

Figure 5 is a view similar to Figure 3, showing a dust cap positioned over the outlet of the device,

Figure 6 is a side elevation view of the arrangement shown by Figure 5.

Figure 7 is a cross-sectional view of the dust cap shown by Figure 5.

Figure 8 is a view, on an enlarged scale of the terminal end of the dust cap stem of Figure 7, and the surface with which that end cooperates,

Figure 9 is a cross-sectional view of another form of dust cap in accordance with the invention that can be used with the device of Figures 1 to 3.

The example dispensing device I shown in the accompanying drawings includes a hollow body 2 having a chamber 3 (Figure 3) for receiving a substance capsule 4, which may be replaceable in some circumstances. The contents (the substance) of the capsule 4 will be selected to suit the intended use of the device 1. In the example shown, the capsule 4 includes a substance container 5 and a manually operable pump 6 (Figure 3) for dispensing a metered quantity of the substance. Other arrangements could be adopted, such as an aerosol-type dispenser, in which event a suitable control valve (not shown) would be provided within the upper part, or some other convenient part, of the capsule 4

In a preferred application of the device 1, the substance stored in the container 5 includes a physiologically active agent in liquid solution, and a carrier selected to promote absorption of the active agent through the skin of a host animal (eg., a human). The liquid solution preferably includes a volatile solvent, whereas the carrier is preferably non-volatile. In one application of the device the carrier may be octyl salicylate.

However the substance is driven to emerge from the device, it is preferably applied to a target area at relatively low volume levels. By way of

example, the substance may be deposited in the range of 1 to 10 microlitre per square centimetre of the target area.

It is preferred, as shown by Figure 4, that the body 2 is formed of two separable parts 2a and 2b. Those parts combine to form the chamber 3 when they are connected together as shown by Figures 1 and 6, and any suitable means may be adopted to releasably connect the two parts 2a and 2b. In the arrangement shown, pins 7 provided on the part 2a are adapted to fit within complementary holes 8 provided in the part 2b (Figure 4). The pins 7 and the holes 8 cooperate in a manner such as to resist inadvertent separation of the parts 2a and 2b,

In the particular arrangement shown, an actuator button 9 is movably mounted on the body 2 so as to be accessible at the upper end of the body 2 (Figures 1, 5 and 6). The button 9 cooperates with the pump 6 in a manner such that depression of the button 9 causes operation of the pump 6. When the pump 6 is operated, a quantity of the substance is withdrawn from the container 5 and is expelled through an outlet nozzle 10 associated with the pump 6, possibly in the form of a spray. In the arrangement shown, the button 9 locates over the outlet nozzle 10 and has an opening 11 aligned with the outlet passage **12** of the nozzle 10 so as to allow egress of the substance being dispensed. The pump 6 operates in a known manner to pressurise the contents of the substance container 5, and thereby force a metered quantity of the substance to be expelled through the nozzle 10.

A shroud 13, preferably of substantially conical form, may be connected to the side of the body 2 adjacent the nozzle 10. The shroud 13 is arranged to surround the substance spray emerging from the nozzle 10, and may serve to confine that spray so that all or most of the substance is deposited on the intended target area. In that regard, the shroud 13 is preferably non-vented as hereinbefore defined. The shroud 13 may also function as a distance regulator. That is, the distance between the nozzle 10 and the outer edge 14 of the shroud 13 may substantially correspond to the ideal distance over which the substance should be sprayed on to the target area. Such distance regulation may be particularly useful in circumstance where the device is being used for transdermal application of a substance.

As shown in Figures 5 and 6, a protective cap 15 may be removably attached to the outer end of the shroud 13 so as to close the open mouth 16

(Figure 3) of the shroud 13. The cap 15 is removed when the pump 6 is to be operated, and is replaced when the pump 6 is not in use. Any suitable means may be employed to enable releasable attachment of the cap 15. One option is to provide for snap engagement between the cap 15 and the shroud 13. By way of example, a circumferential rib 17 or lugs formed on an inner surface of a side wall 21 of the cap 15 may snap engage with an external circumferential rib 19 formed on the shroud 13 (Figure 3).

In the arrangement shown by Figures 4 to 6, the dispensing device 1 is provided with means for closing the nozzle 10 when the device is not in use. Any suitable means may be used for that purpose. In the arrangement shown by Figures 4, 5 and 6 however, the nozzle closure means includes a member 20 attached to the end wall 21 of the cap 15. Preferably, as shown, the member 20 is in the form of an elongate stem extending axially of the cap 15 in the same direction as the side wall 21. The length of the member 20 is such as to enable the outer terminal end 22 to engage around and/or within the outlet of the nozzle 10 when the cap 15 is properly in place on the shroud 13.

According to the preferred arrangement shown, the end wall 21 of the cap 15 is flexible, and the length of the member 20 is such as to cause the wall 21 to flex outwardly when the cap 15 is properly located on the shroud 13. That is, when the stem end 22 engages within or around the outlet of the nozzle 10, proper cooperative engagement between the ribs 17 and 19 cannot be achieved unless the wall 21 is caused to flex outwardly. That outward flexing is indicated, in possibly exaggerated form, by the broken line in Figure 7. As the wall 21 flexes outwards, it undergoes resilient distortion such that internal stress is developed within the wall 21. The resilience of the wall 21 is such that it tends to return to the undistorted state and thereby relieve the internal stress, but such recovery is prevented by the column strength of the member 20. The member 20 is thereby placed under compression and as a result imposes a closing force between the end 22 of the member 20 and the nozzle 10. The degree of flexing is preferably predetermined to impose a suitable closing force between the end 22 of the member 20 and the nozzle 10.

Figure 7 shows the end wall 21 having an outwardly bowed configuration when in the unstressed condition. That is not essential. By way of example, the wall 21 could be flat as shown by Figure 9, when in the unstressed condition.

The effectiveness of the seal between the stem end 22 and the nozzle 10 may be enhanced by providing sealing means, such as resilient sealing means, at the end 22. Alternatively, as shown by Figures 7 and 8, the sealing means may include a relatively thin flexible circular sealing lip 23 extending generally in the axial direction of the member 20. Other types of sealing means could be adopted. Also, the sealing means may be provided on the nozzle 10 rather than the member 20, or may be provided on both the member 20 and the nozzle 10.

Figure 8 illustrates a sealing arrangement between the member 20 and the nozzle 10 that has been found satisfactory in practice. As shown, the end 22 of the member 20 is shaped to provide the sealing lip 23. The radially inner surface 24 of the lip 23 slopes inwardly and rearwardly to provide a sealing face that functions as hereinafter described. A cavity 25 is formed within the member 20 directly behind the lip 23, and that cavity functions as hereinafter described.

As also shown by Figure 8, the nozzle passage 12 emerges through a surface 26 of the nozzle 10 that is in opposed relationship with the terminal end of the member 20. The surface 26 is surrounded by a frusto-conical surface 27 that is substantially complementary to the surface 24 of the sealing lip 23. A recess 28 for receiving the sealing lip 23 is defined between the frusto-conical surface 27 and a surrounding cylindrical surface 29. The diameter of the surface 29 is preferably such that clearance exists between that surface and the stem end 22 when the stem end 22 is located within the recess 23.

Closure of the nozzle 10 occurs when the surface 24 of the sealing lip 23 is pressed against the nozzle surface 27. As previously stated, the sealing lip 23 has a degree of flexibility, and that serves to ensure that satisfactory seating engagement occurs between the surfaces 24 and 27.

The cavity 25 has been found useful because of the air space it provides beyond the nozzle surface 26. In the absence of such an air space it has been found that the stored substance tends to weep out of an exit end of the nozzle passage 12, possibly due to capillary action. It will be appreciated that other arrangements could be adopted to combat that loss of substance. Also, sealing configurations other than that particularly shown by Figure 8 could be adopted.

Guide means may be provided to guide the end 23 of the member 20 into the correct position of engagement with the nozzle 10. Such guide means can also serve to minimise damage to the sealing lip 23 when the cap 15 is being placed on the shroud 13. According to the example arrangement shown, the

guide means includes a frusto-conical guide passage 30 that extends outwards from and surrounds the outlet opening 11 of the actuator button 9 (Figures 3 and 4). As best seen in Figure 3, the passage 30 increases in cross-sectional size in a direction away from the opening 11.

Instead of using nozzle closure means as described above, the device I may be provided with means to permit the delivery system of the pump 6 to be primed in preparation for use to dispense a metered quantity of the substance. One possible form of priming means is shown by Figure 9. In that example, an absorbent pad or wad 31 is provided on the inside surface of the cap end wall 21, which need not be bowed outwards as shown by Figure 7. Priming of the pump 6 is achieved by operating the pump 6 to spray a quantity of the stored substance on to the wad 31 while the cap 15 is located over the open mouth of the shroud 13. It is usually necessary to fully depress the button 9 at least once to achieve satisfactory priming, and two or more full depressions may be required. The priming operation can be carried out while the cap 15 is secured to the shroud 13, or while it is held removed from the shroud 13. In the latter case however, the cap 15 is preferably held relatively close to the outer end of the shroud 13. The wad 31 may be removable from the cap I15 so as to enable replacement by a fresh wad, if and when necessary.

If desired, a viewing window 32 may be provided in a side of the body 2 so as to enable the user to see when the quantity of the substance in the capsule 4 is getting low (Figures 4 and 6).

It will be apparent from the foregoing description that a dispensing device according to the invention has the ability to ensure that a full metered dose of the substance is discharged each time the device is operated. The result is achieved by providing means whereby the pump can be primed preparatory to normal use.

Various alterations, modifications and/or additions may be introduced into the constructions and arrangements of parts previously described without departing from the spirit or ambit of the invention as defined by the appended claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A hand-held device for dispensing a substance and applying that substance to the skin of a host, said device including a hollow body, a substance capsule mounted with said body, a container for said substance forming part of said capsule, a spray nozzle, actuator means connected to the interior of said container and being operable to cause a metered quantity of said substance to be dispensed through said nozzle in the form of a spray, said device further including an actuator mounted on said body and being operable to cause operation of said pump, and absorption means locatable in alignment with said nozzle and being operable when so located to absorb a pre-use quantity of said substance dispensed through said nozzle during at least a first of a series of operations of said actuator means, said absorption means being removable from said alignment to enable a full charge of said substance to be dispensed through said nozzle during a subsequent one of said series of operations of said actuator means.

2. A dispensing device according to claim 1, including a cap member, said absorption means includes an absorbent pad attached to said cap member, and said cap is removably connectable to part of said device so that said pad is positioned in the path of said substance being dispensed through said nozzle.

3. A dispensing device according to claim 2, wherein said part of said device is a shroud extending around the space into which said substance is dispensed by said nozzle, said shroud has an open mouth at an outer end spaced outwardly from said nozzle, and said cap is removably connectable to said outer end.

4. A dispensing device according to claim 3, wherein said shroud provides a non-vented wall around said space.

5. A dispensing device according to any preceding claim, wherein said capsule is removably mounted within said hollow body.

6. A dispensing device according to claim 5, wherein said body includes two separable parts, each of which defines a respective portion of a chamber within which said capsule is mounted.

7. A dispensing device according to any preceding claim, wherein said actuator means includes a pump connected to both said nozzle and the interior of said container so as to be operable to withdraw said substance from said container and expel the withdrawn substance through said nozzle in the form of a spray.

8. A dispensing device according to claim 7, wherein said actuator means includes a button movably mounted on said body and being operable to cause operation of said pump.

9. A dispensing device according to any one of claims 1 to 6, wherein said actuator means includes a valve, the substance within said container is pressurised, and said valve is selectively operable to connect the interior of said container to said nozzle and thereby permit dispersion of said substance in aerosol form.

10. A dispensing device according to claim 9, wherein said actuator means includes a button movably mounted on said body and being operable on a selective basis to open said valve.

11. A dispensing device according to any preceding claim, wherein said substance includes a physiologically active agent in liquid solution, and a carrier selected to promote absorption of said active agent through the skin of the host.

12. A dispensing device according to claim 11, wherein said solution includes a volatile solvent.

13. A dispensing device according to claim 11 or 12, wherein said carrier is non-volatile.

14. A dispensing device according to claim 13, wherein said carrier is octyl salicylate.

15. A dispensing device according to any preceding claim, wherein said body is arranged to be grasped by the hand of the user and has a major axis that extends transverse to the fingers of the user where so grasped, and said nozzle is arranged to dispense said substance in a lateral direction relative to said major axis.

DATED: 17 November 2005
PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
ACRUX DDS PTY LTD

David B Fitzpatrick

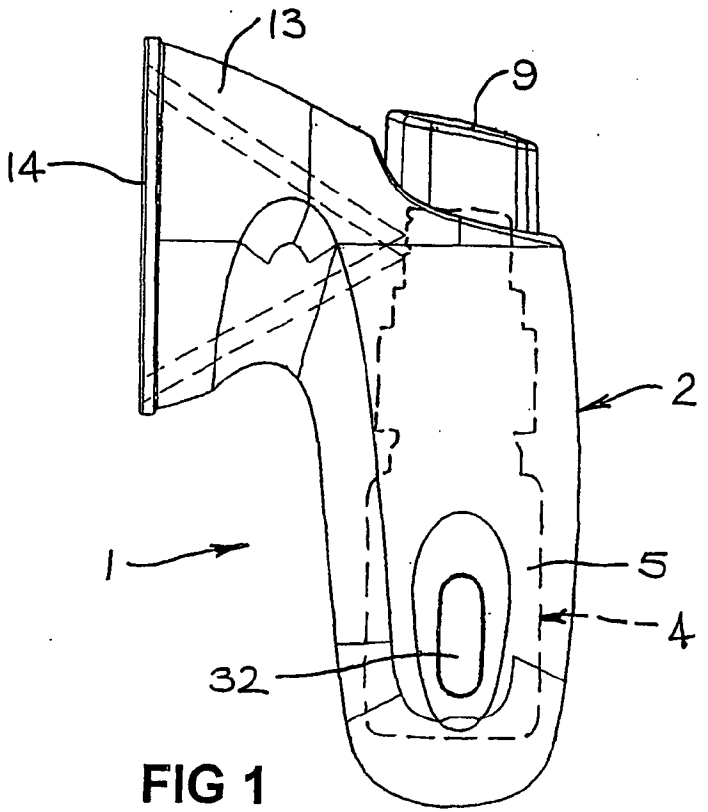

FIG 1

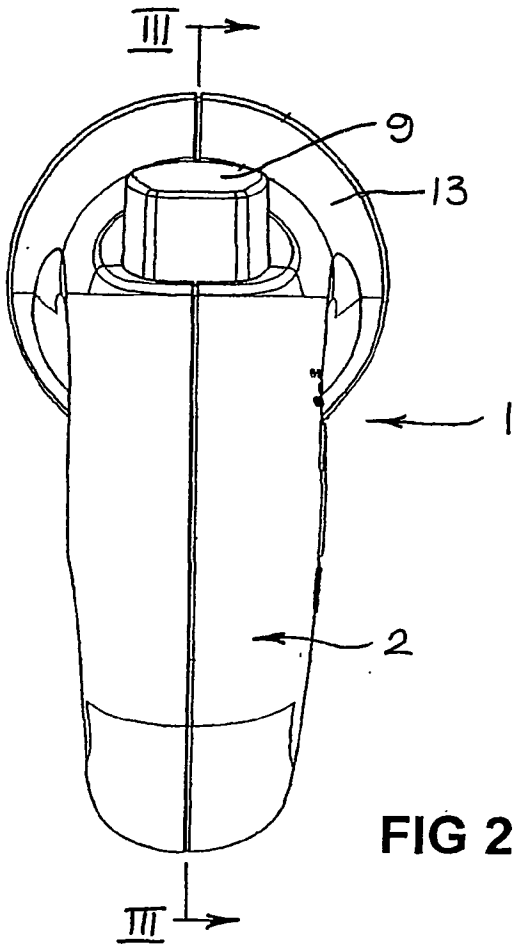

FIG 2

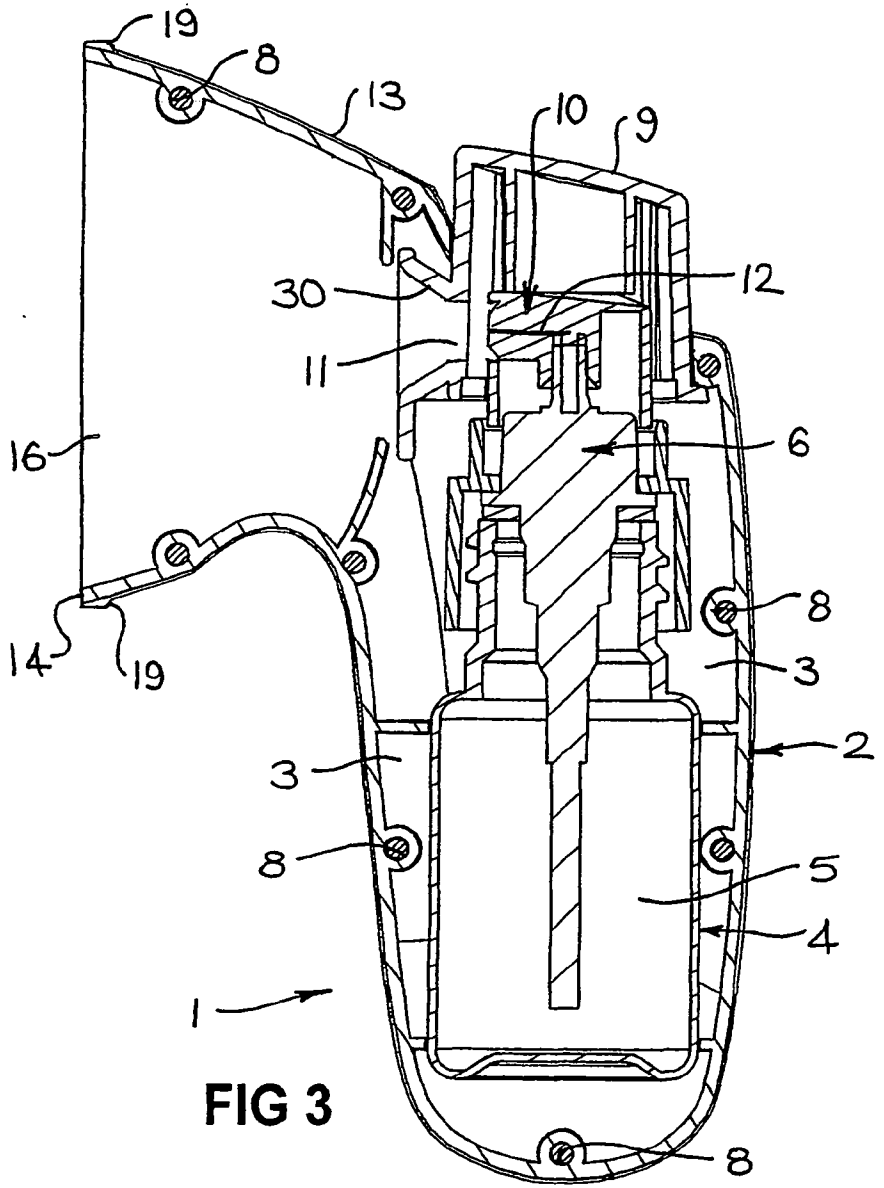
19
8
13
10
9
30
12
11
16
6
8
14
19
3
2
3
8
5
4
1
8

FIG 3

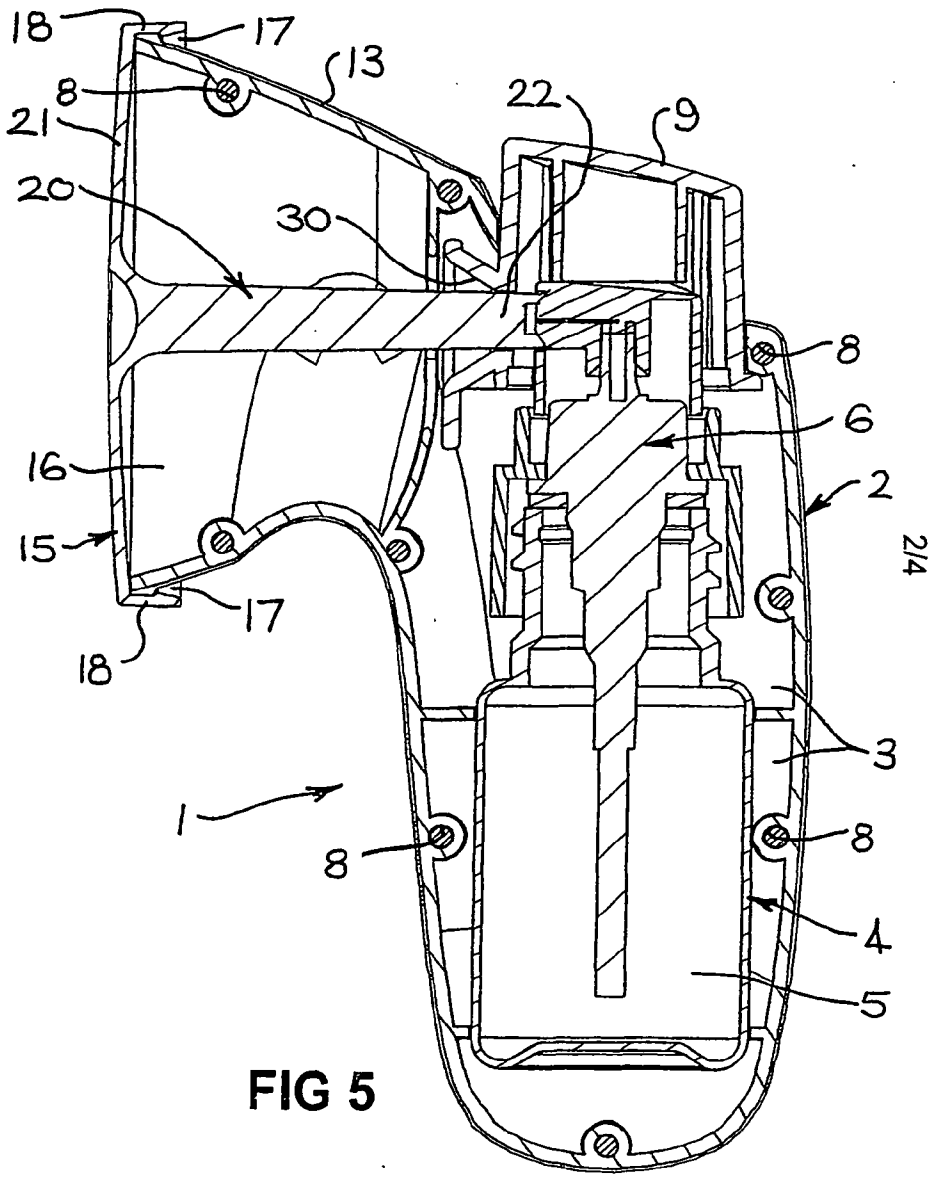
18
17
13
8
22
21
9
20
30
8
6
16
2
15
17
18
3
1
8
8
4
5

FIG 5

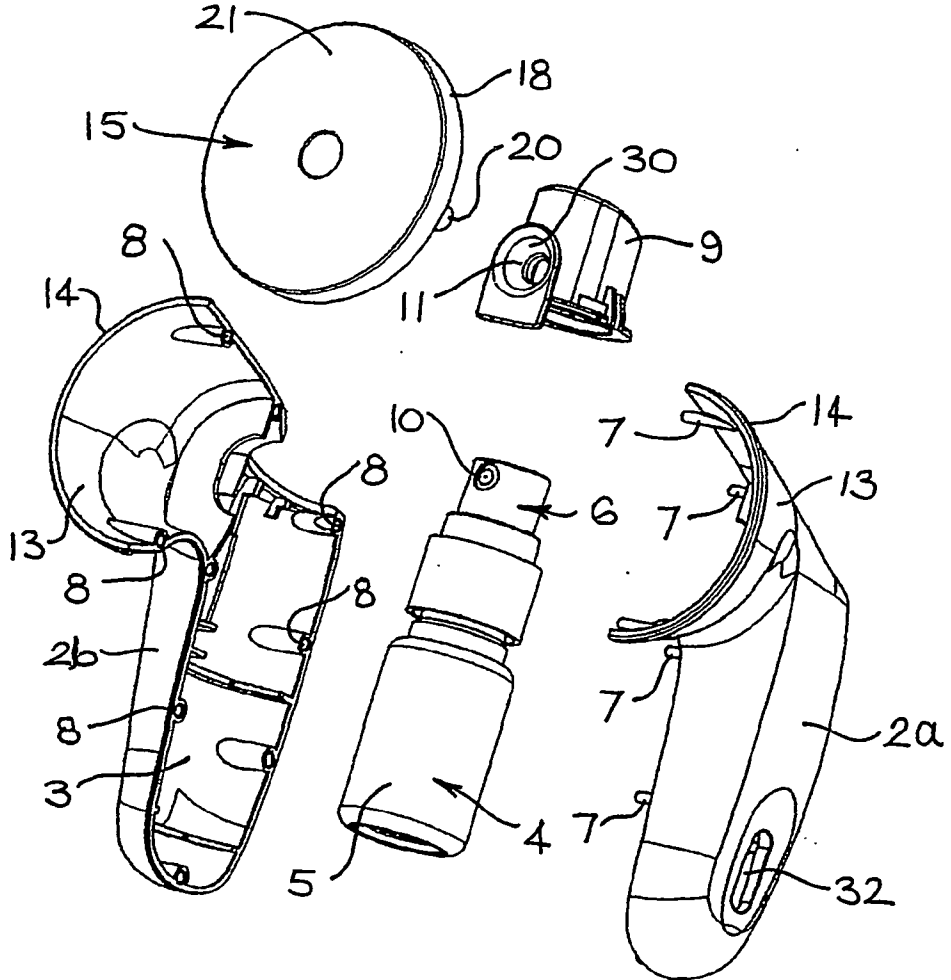
21
18
15
20
30
9
8
11
14
10
7
14
8
6
7
13
13
8
8
2b
7
8
2a
3
4
7
5
32

FIG 4

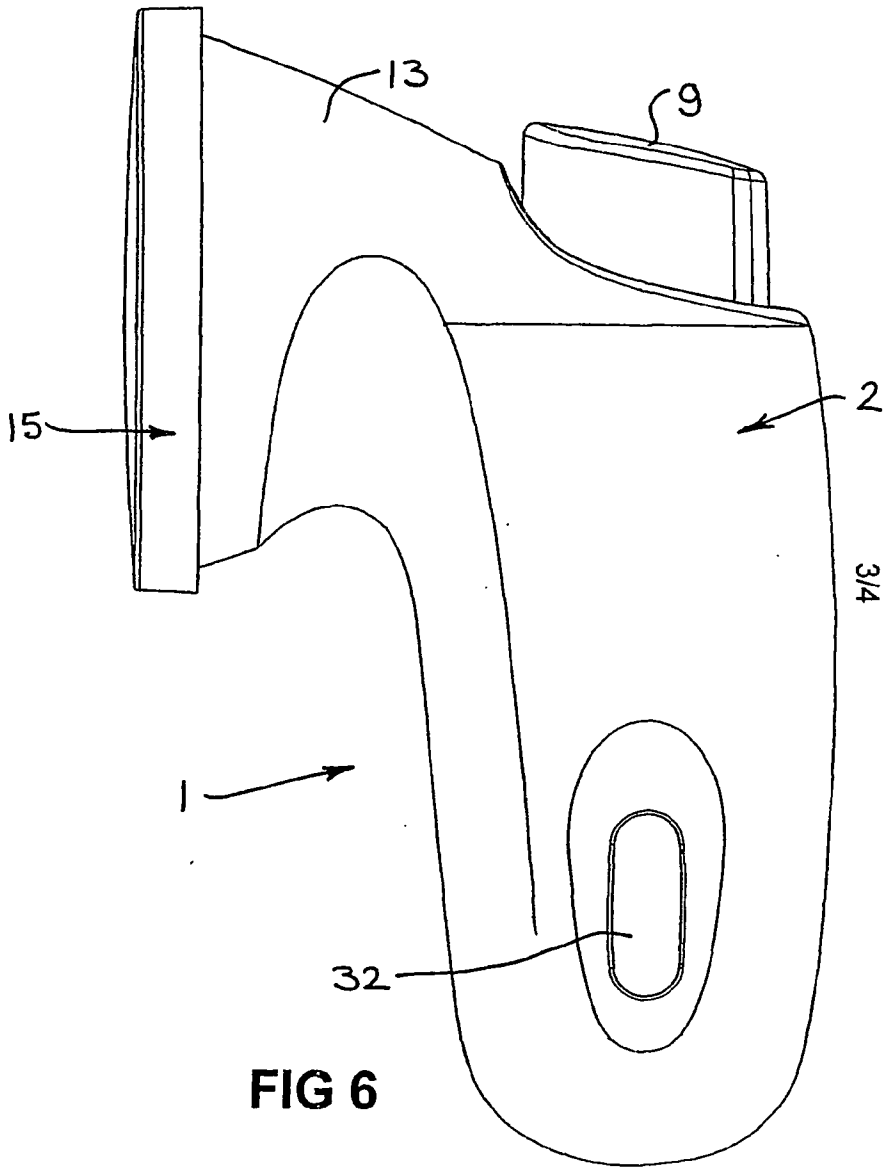
13
9
15
2
1
32

FIG 6

2005234689 18 Nov 2005

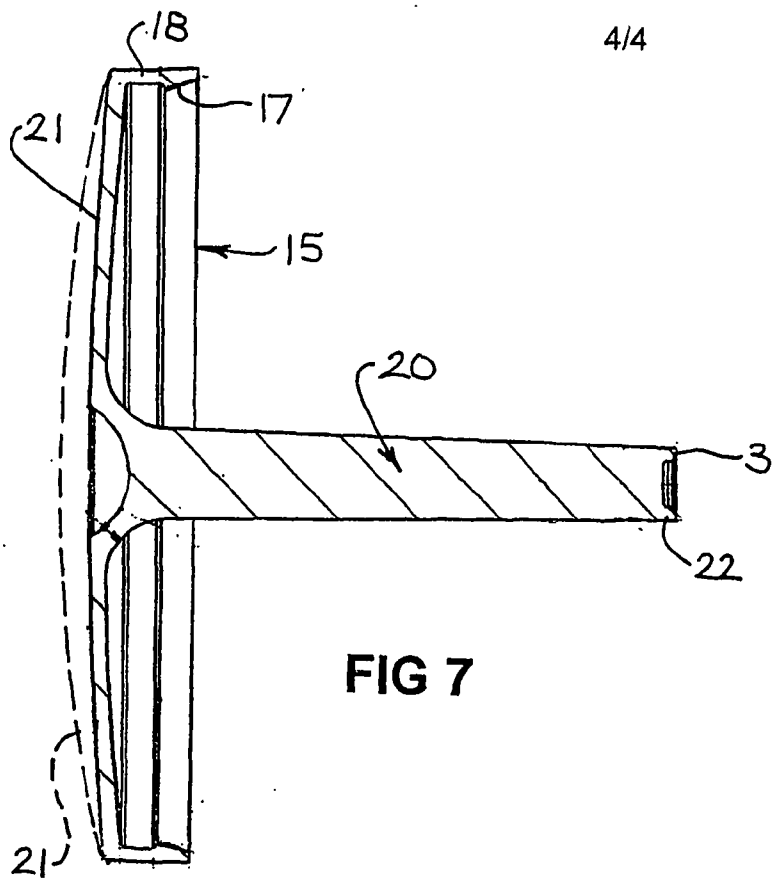

FIG 7

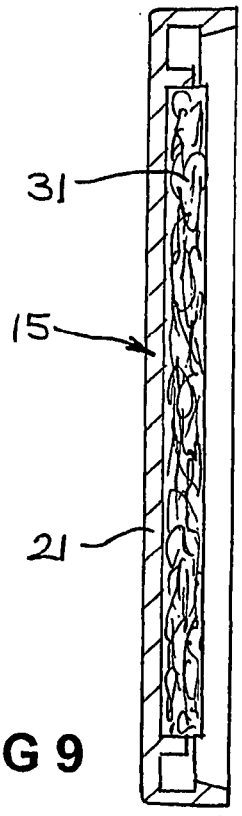

FIG 9

FIG 8