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(54) Title: METHODS AND SYSTEMS FOR SUPPLYING AEROSOLIZATION DEVICES WITH LIQUID MEDICAMENTS

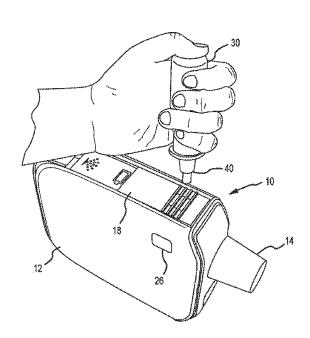
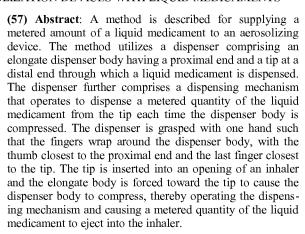


FIG.1





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METHODS AND SYSTEMS FOR SUPPLYING AEROSOLIZATION DEVICES WITH LIQUID MEDICAMENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This PCT Application claims priority to U.S. Application No. 13/830,511, filed March 14, 2013, which claims the benefit of U.S. Provisional Application No. 61/624,531, filed April 16, 2012, the complete disclosure of which is herein incorporated by reference.

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BACKGROUND OF THE INVENTION

Various types of inhalers exist for aerosolizing liquids. For example, U.S. Patent No. 5,586,550, incorporated herein by reference, describes an inhaler that comprises a dispensing apparatus in which a membrane with tapered apertures is vibrated such that liquid in contact with a rear face of the membrane is dispensed from a front face of the membrane as an aerosol. Other examples of single dose inhaler systems and medicaments that may be aerosolized are described in U.S. Patent Publication Nos. 2011/0168172 and 2001/0168170, the disclosures of which are herein incorporated by reference.

One aspect of such inhalers is the need to supply a metered amount of liquid medicament to the dispensing apparatus so that the metered amount may be aerosolized and delivered to the patient's lungs. However, delivering a known quantity of a liquid medicament (that typically must be stored in a sterile environment) has proven to be challenging, particularly when the metered quantity needs to be dispensed in a controlled and repeatable fashion. Hence, this invention relates to ways for delivering such medicaments to inhalers for subsequent aerosolizing.

BRIEF SUMMARY OF THE INVENTION

One embodiment provides a method for supplying a metered amount of a liquid medicament to an aerosolizing device in a repeatable manner. The method utilizes an aerosolization device comprising a housing having a mouthpiece, a vibratable member within the housing and disposed to eject liquid droplets through the mouthpiece, a reservoir to hold the liquid medicament until aerosolized by the vibratable member, and an opening in the housing and in

communication with the chamber. While described in connection with one specific type of inhaler, it will be appreciated that other types of aerosolization devices could be used with the methods described herein.

To supply a metered amount of liquid medicament, a dispenser is used that comprises an elongate dispenser body having a proximal end and a tip at a distal end through which a liquid medicament is dispensed. The dispenser further comprises a dispensing mechanism that operates to dispense a metered quantity of the liquid medicament from the tip each time the dispenser body is compressed.

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One critical factor of the method is the manner in which the dispenser is held and operated by a user. To facilitate dispensing, the dispenser may be grasped with one hand such that the fingers wrap around the dispenser body, with the thumb closest to the proximal end and the last or pinky finger closest to the tip. The tip of the dispenser is inserted into the opening in the housing. Then, while grasping the dispenser in the manner described, the elongate body is forced toward the tip to cause the dispenser body to compress, thereby operating the dispensing mechanism and causing a metered quantity of the liquid medicament to eject into the chamber each time the dispenser body is compressed.

Because the prescription may call for more medicament than can be supplied with a single ejection from the dispenser, the process may be repeated for as many times as is needed to supply the prescribed amount into the chamber. This may be done with a "pumping action" where the user "pumps" the dispenser (causing it to compress with each pump), until the correct number of pumps have been supplied. For example, if the prescription calls for a certain volume of the liquid medicament, the dispenser may be pumped five times, with each pump dispensing a droplet having a metered volume of one-fifth the total volume.

In some cases, the tip may include at least one alignment feature that assists to keep the dispenser generally perpendicular to the housing while dispensing the liquid medicament. Once the metered amount has been dispensed into the chamber, the vibratable member is actuated to eject the dispensed liquid medicament as an atomized spray.

In another embodiment, the invention provides an exemplary aerosolization system. The system includes an aerosolization device comprising a housing having a mouthpiece, a vibratable

member within the housing and disposed to eject liquid droplets through the mouthpiece, a reservoir to hold the liquid medicament until aerosolized by the vibratable member, and an opening in the housing that is in fluid communication with the chamber.

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The system further includes a dispenser comprising an elongate dispenser body having a proximal end and a tip at a distal end through which a liquid medicament is dispensed. The dispenser further comprises a dispensing mechanism that operates to dispense a metered quantity of the liquid medicament from the tip each time the dispenser body is compressed. The dispenser is separate from the housing so that it may be manually interfaced with the aerosolization device.

Further, the opening defines an interface that engages with the tip such that when the tip is inserted into the opening, the interface stabilizes the dispenser in an upright orientation outside of the housing to permit the dispenser to be grasped with one hand to dispense the medicament. For example, this orientation permits a user to wrap the fingers around the dispenser body, with the thumb closest to the proximal end and the last finger closest to the tip, and while grasping the dispenser, forcing the elongate body toward the tip to cause the dispenser body to compress, thereby operating the dispensing mechanism and causing a metered quantity of the liquid medicament to eject into the chamber each time the dispenser body is compressed.

In one important aspect, the tip may include at least one alignment feature that assists to keep the dispenser generally perpendicular to the top surface of the housing while dispensing the liquid medicament. This alignment feature may comprise a circular step around the tip, a plurality of tabs protruding from the tip, and the like.

In yet another embodiment, the invention provides an exemplary method for supplying a metered amount of a liquid medicament to an aerosolizing device. The method utilizes an aerosolization device comprising a housing having a mouthpiece, a vibratable member within the housing and disposed to eject liquid droplets through the mouthpiece, and a reservoir to hold the liquid medicament until aerosolized by the vibratable member. The housing also includes a top surface and an opening in the top surface of the housing. The opening is in fluid communication with the chamber.

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The method also utilizes a dispenser that comprises an elongate dispenser body having a proximal end and a tip at a distal end through which a liquid medicament is dispensed. The dispenser further comprises a dispensing mechanism that operates to dispense a metered quantity of the liquid medicament from the tip each time the dispenser body is compressed.

With this configuration, the tip is inserted into the opening in the housing such that the dispenser body is generally perpendicular to the top surface of the housing and is seated within the opening such that the dispenser body is self-standing outside of the housing. In this orientation, the dispenser body may be compressed to operate the dispensing mechanism and cause a metered quantity of the liquid medicament to eject into the chamber each time the dispenser body is compressed.

The dispenser may be repeatedly compressed to dispense multiple metered quantities of the liquid medicament into the chamber. Further, the tip may include one or more alignment features that assist to keep the dispenser generally perpendicular to the housing while dispensing the liquid medicament so that it may be aerosolized.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates one method for grasping a dispenser in preparation for delivering a metered amount of liquid medicament to an aerosolizing apparatus.

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- Fig. 2 illustrates the dispenser of Fig. 1 when inserted into the aerosolizing apparatus and compressed in order to deliver the liquid medicament.
- Fig. 3 illustrates the dispenser of Fig. 1 when initially inserted into the aerosolizing apparatus of Fig. 1.
 - Fig. 4 illustrates the dispenser of Fig. 3 when compressed or pumped to deliver the liquid medicament.
 - Fig. 5 is a cross sectional side view of another embodiment of an aerosolizing apparatus according to the invention.
 - Fig. 6 illustrates another embodiment of a dispenser having ribs to facilitate positioning of the dispenser.

DETAILED DESCRIPTION OF THE INVENTION

Certain aspects of the invention relate to techniques for dispensing metered quantities of a liquid medicament into an aerosolizing apparatus, also referred to as an inhaler. Although useful with a wide variety of aerosolizing devices, in some cases the liquid will be dispensed into an aerosolizing apparatus comprising a housing defining a dispensing outlet or mouthpiece, a vibratable membrane or mesh having a front face exposed at the outlet and a rear face for receiving a liquid to be dispensed, and a vibrating mechanism connected to the housing and operable to vibrate the membrane to dispense aerosol of the liquid through the membrane.

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A variety of containers or dispensers may be used to store the liquid medicament, then to deliver a metered quantity of the liquid into a reservoir where it will contact the rear face of the membrane. In this way, a metered quantity of liquid is dispensable at the outlet or mouthpiece by operating the vibrating mechanism for an operating period sufficient to completely aerosolize the metered quantity at the rear face. The containers or dispensers will typically have a sealed region where the liquid is stored and a mechanism for dispensing a metered amount of liquid each time the mechanism is operated. For example, the container may be compressed or pumped to eject a droplet of a known volume.

Exemplary aerosol generators that may be used in such inhalers are also described in U.S. Patent Nos. 5164740; 6629646; 6926208; 7108197; 5938117; 6540153; 6540154; 7040549; 6921020; 7083112; 7628339; 5586550; 5758637; 6085740; 6467476; 6640804; 7174888; 6014970; 6205999; 6755189; 6427682; 6814071; 7066398; 6978941; 7100600; 7032590; 7195011, and in U.S. Patent Publication Nos. 2011/0168172 and 2001/0168170, all incorporated herein by reference. These references describe exemplary aerosol generators and ways to manufacture such aerosol generators. Each are incorporated by reference for at least these features. The aerosol generators may comprise vibratable membranes having tapered aperture with a size in the range from about 3 μ m to about 8 μ m, preferably from about 3 μ m to about 6 μ m, and in some cases around 4 μ m. The membrane may be domed shaped and be vibrated by an annular piezoelectric element that circumscribes the apertures. The diameter of the membrane may be in the range from about 5 mm to about 8 mm. The membrane may also have a thickness in the range from about 50 microns to about 70 microns. Typically, the membrane will be vibrated at a frequency in the range from about 50 kHz to about 150 kHz.

A variety of liquid medicaments may be dispensed from the container. For example, the liquid medicament may comprise an insulin formulation, such as a preservative free insulation, including any of those described in U.S. Patent Publication No. 2011/0168170, previously incorporated by reference. For example, a preservative free insulin formulation that may be dispensed may be free of any preservatives, including phenol, metacresol, chloro-cresol, thymol and mixtures thereof or the like. The absence of such preservatives enable the formulations to be aerosolized as a liquid spray using a vibrating mesh or aperture plate that operates at high frequencies. The absence of such preservatives permits a dosage of the formulation to come into contact with the vibrating mesh without substantial foaming of the formulation. In turn, the formulation may be aerosolized more quickly. Further, substantially all of the liquid is able to be aerosolized. Such formulations contain water in major and human insulin in minor amount. The formulations may also include various concentrations of human insulin. For example, the concentrations may be in the range from about 100 IU insulin/ml of formulation to about 1200 IU insulin/ml of formulation, and more preferably from about 200 IU insulin/ml of formulation to about 800 IU insulin/ml of formulation. In addition to water and human insulin, the formulations may also include zinc, acetate, chloride and sodium. The zinc ion and acetate ion come from the drug substance, e.g., the insulin. The chloride ion and sodium ion are added during dissolution of the insulin and adjustment of the pH. Merely by way of example, the NaCl concentration may be about 20 mM for an 800 IU insulin/ml formulation, about 10 mM for a 400 IU insulin/ml formulation, and about 5 mM for a 200 IU insulin/ml formulation.

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Other liquid medicaments may also be dispensed. For example, such medicaments could include other protein formulations, asthma and COPD treatments, vaccines and pain relief treatments.

Referring now to the Figures, one exemplary method for dispensing a metered amount of medicament into an inhaler will be described. Shown in Fig. 1 is an inhaler 10 that is constructed of a housing 12 having a mouthpiece 14. Disposed within the housing is an aerosol generator comprising a vibratable mesh similar to those described herein, as well as electronics to control operation of the aerosol generator. The mesh is positioned to eject an aerosol through mouthpiece 16 when the mesh is vibrated. Housing 12 includes a top surface 13 with a slidable cover 18 is positioned over an opening 20 (see Fig. 2). Cover 18 is slid back is to expose opening 20. Further, opening 20 leads to a reservoir 22 or funnel (see Figs. 3 and 4) that tapers toward a vibratable mesh 24 that is part of an aerosol generator that may be similar to any of

those described herein. More specifically, mesh 24 has a rear face that is exposed to reservoir 22 so that when liquid is supplied to reservoir 22 it comes into contact with the rear face of mesh 24. When mesh 24 is vibrated (by actuating an "on" button 26 that energizes the aerosol generator) the liquid is ejected from the front face of mesh 24 as an atomized spray and is available for inhalation through mouthpiece 14.

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Fig. 5 illustrates the internal components of an inhaler 100 that is similar to inhaler 10 as previously described. Inhaler 100 is constructed of a housing 112 that includes an opening 120 leads to a reservoir 122 that has an open bottom end 150 that funnels the dispensed liquid onto the rear face of a vibratable mesh (not shown) that is part of an aerosol generator 154 that has a vibratable element 155 (such as an annular piezoelectric transducer) that vibrates the mesh. Aerosol generator 154 has a circular opening 156 across which the mesh is disposed. When vibrated, the mesh ejects the liquid as an aerosolized spray into a capture chamber and to a mouthpiece. In this way, the aerosolized spray may be inhaled by inhaling from the mouthpiece.

In one embodiment, the liquid to be aerosolized is stored in a dispenser 30 that is best illustrated in Figs. 3 and 4. Dispenser 30 may conveniently be described in terms of a proximal end 32 and a distal end 34 that terminates in a tip 36. Dispenser 30 further includes a canister 38 that stores the liquid medicament in a sterile environment. Dispenser 30 includes an internal valve such that distal end 34 may be moved relative to proximal end 32, thus compressing dispenser 30. In so doing, each time dispenser 30 is compressed (or "pumped") a metered volume of liquid is ejected into reservoir 22. For example, Fig. 3 shows dispenser 30 in an uncompressed state. In Fig. 4, a force is applied to compress dispenser 30 and eject the droplet into the reservoir 22. A similar process may be used in connection with inhaler 100 where the liquid is injected into reservoir 122. This process may be repeated as many times as needed in order to dispense the proper volume of the liquid medicament into reservoir 22. After dispersing the desired amount of liquid medicament, dispenser 30 may be removed and stored for future use. Exemplary unit volumes that may be dispensed with each pump may be in the range from about 5 to about 100 microliters.

Tip 36 includes a shoulder 40 in the shape of an annular or circular step that serves as a stop to prevent further insertion of tip 36 into opening 20. Shoulder 40 is inset by a distance that is sufficient so that it not only serves as a stop by also permits tip 36 to seat within opening 20 in a

stable position that is generally vertical to the top surface 13 of housing 12. As such, once dispenser 30 is placed into opening 20, it will be self-standing in a generally vertical orientation. This position permits a user to easily grasp the disperser 30 when ready to dispense a unit volume of the liquid to the aerosol generator. Although shown with a shoulder, other seating mechanisms could be used, such as a taper that matches with the taper of opening 20, protruding tabs or wings, detents, and the like.

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One exemplary technique for operating dispenser 30 is illustrated in Figs. 1 and 2. It will be appreciated that a similar process may be used in connection with inhaler 100. In Figs. 1 and 2, dispenser 30 is grasped with one hand, such that the four fingers wrap around dispenser 30, mostly about canister 38. By using four fingers to grasp dispenser 30, a firm grip is achieved so that dispenser 30 may easily be pumped to eject the liquid. Further, the person's thumb may rest on proximal end 32 to apply a further compressive force. With the proper grip, cover 18 may be slid back and tip 34 placed into opening 20. As previously described, tip 34 includes a shoulder 40 that is wider than opening 20 so as to prevent tip 34 from coming into contact with mesh 24. Further, shoulder 40 may be designed so that tip 34 is sufficiently spaced-apart from mesh 24 so that when the full metered amount of the liquid is dispensed into reservoir 22, tip 34 does not come into contact with the dispensed liquid. In this way, when dispenser 30 is removed from the inhaler, it will not also remove some of the dispensed liquid. Typically, tip 34 will be spaced apart from mesh 24 by a distance that is in the range from about 5 mm to about 20 mm. Tip 34 may also be tapered, such as to match the taper of reservoir 22. The taper of reservoir 22 facilitates delivery of all the dispensed liquid onto the rear face of mesh 24, and the tapering of tip 34 prevents it from coming into contact with the walls of reservoir 22.

As best shown in Fig. 2, with tip 34 in place, the user presses canister 38 toward tip 34. At the same time, inhaler 10 is held in place. This causes dispenser 30 to compress. In turn, the internal valve is opened to permit a metered amount of liquid to be dispensed from tip 34 and into reservoir 22. Each time canister 38 is pressed downward, or pumped, another metered amount of liquid is ejected. This maneuver is performed as many times as is needed in order to supplied the prescribed dosage into reservoir 22.

By holding the dispenser 30 in the manner shown, this pumping action may easily occur. This is in contrast to a nasal spray dispenser, that is typically actuated in an upright manner by carefully

and simultaneously compressing the proximal end with the middle and index finger (with the tip extending between the fingers) to the distal end of the dispenser container, that is held under equal pressure by the thumb. With this type of nasal sprayer, the spray occurs when sufficient pressure is applied equally to both ends. In contrast, dispenser 30 can be easily actuated by applying pressure solely to the distal end of the dispenser when the tip is engaged with the inhaler device. The inhaler device and mating features are constructed so that a metered amount of medicament is consistently delivered from the dispenser into the device and the user may do so with unregulated pressure, provided the force is greater than or equal to that required to compress the dispenser throughout its full range. If the inhaler device is loaded while placed on a table or any other freely supported surface, the force required to compress the dispenser into the device to the point of actuation is reduced by 50% when compared to the amount of force required to disperse a volume of liquid when holding both the device and dispenser (without the aid of a support surface).

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Fig. 6 illustrates an alternative embodiment of a dispenser 80 that may be used with inhaler 10 or inhaler 100. Dispenser 80 has a tip 82 at its distal end with multiple alignment features 84 that assist to properly align and position tip 82 within opening 20 in top surface 13. Alignment features 84 may have a variety of shapes, sizes and configurations. Although shown with four equally spaced apart features 84, it will be appreciated that other numbers may be used, such as only a single alignment feature. Features 84 serve as stops to limit insertion of tip 82 into opening 20. Features 84 also provide a tactile feel to let the user know when tip 82 has been properly inserted. When all four features 84 engage the surface of inhaler 10, dispenser 80 has been properly inserted and is ready to have a metered amount dispensed into inhaler 10. Further, features 84 serve to hold dispenser 80 in a generally vertical or perpendicular orientation relative to top surface 13. In this way, dispenser 80 is self-standing when inserted into opening 20 to make it easier for a user to grasp and dispense as described in connection with Figs. 1 and 2.

The invention has now been described in detail for purposes of clarity and understanding. However, it will be appreciated that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

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1. A method for supplying a metered amount of a liquid medicament to an aerosolizing device, the method comprising:

providing an aerosolization device comprising a housing having a mouthpiece, a vibratable member within the housing and disposed to eject liquid droplets through the mouthpiece, a reservoir to hold the liquid medicament until aerosolized by the vibratable member, and an opening in the housing that is in fluid communication with the chamber;

providing a dispenser comprising an elongate dispenser body having a proximal end and a tip at a distal end through which a liquid medicament is dispensed, wherein the dispenser further comprises a dispensing mechanism that operates to dispense a metered quantity of the liquid medicament from the tip each time the dispenser body is compressed;

grasping the dispenser with one hand such that the fingers wrap around the dispenser body, with the thumb closest to the proximal end and the last finger closest to the tip; inserting the tip into the opening in the housing;

while grasping the dispenser, forcing the elongate body toward the tip to cause the dispenser body to compress, thereby operating the dispensing mechanism and causing a metered quantity of the liquid medicament to eject into the chamber each time the dispenser body is compressed.

- A method as in claim 1, further comprising repeatedly forcing the elongate
 body toward the tip to dispense multiple metered quantities of the liquid medicament into the chamber.
 - 3. A method as in claim 1, wherein the tip includes at least one alignment feature, and wherein the alignment feature assists to keep the dispenser generally perpendicular to the housing while dispensing the liquid medicament.
 - 4. A method as in claim 1, further comprising actuating the vibratable member to eject the dispensed liquid medicament as an atomized spray.
 - 5. An aerosolization system, comprising:

an aerosolization device comprising a housing having a mouthpiece, a vibratable member within the housing and disposed to eject liquid droplets through the mouthpiece, a

reservoir to hold the liquid medicament until aerosolized by the vibratable member, and an opening in the housing that is in fluid communication with the chamber;

a dispenser comprising an elongate dispenser body having a proximal end and a tip at a distal end through which a liquid medicament is dispensed, wherein the dispenser further comprises a dispensing mechanism that operates to dispense a metered quantity of the liquid medicament from the tip each time the dispenser body is compressed, wherein the dispenser is separate from the housing;

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wherein the opening defines an interface that engages with the tip such that when the tip is inserted into the opening, the interface stabilizes the dispenser in an upright orientation outside of the housing to permit the dispenser to be grasped with one hand such that the fingers wrap around the dispenser body, with the thumb closest to the proximal end and the last finger closest to the tip, and while grasping the dispenser, forcing the elongate body toward the tip to cause the dispenser body to compress, thereby operating the dispensing mechanism and causing a metered quantity of the liquid medicament to eject into the chamber each time the dispenser body is compressed.

- 6. A system as in claim 5, wherein the tip includes at least one alignment feature, and wherein the alignment feature assists to keep the dispenser generally perpendicular to the top surface of the housing while dispensing the liquid medicament.
- 7. A system as in claim 5, wherein the alignment feature comprises a circular step around the tip.
 - 8. A system as in claim 7, wherein the alignment feature comprises a plurality of tabs protruding from the tip.
 - 9. A method for supplying a metered amount of a liquid medicament to an aerosolizing device, the method comprising:

providing an aerosolization device comprising a housing having a mouthpiece, a vibratable member within the housing and disposed to eject liquid droplets through the mouthpiece, and a reservoir to hold the liquid medicament until aerosolized by the vibratable member, wherein the housing includes a top surface and an opening in the top surface of the housing, and wherein the opening is in fluid communication with the chamber;

providing a dispenser comprising an elongate dispenser body having a proximal end and a tip at a distal end through which a liquid medicament is dispensed, wherein the dispenser further comprises a dispensing mechanism that operates to dispense a metered quantity of the liquid medicament from the tip each time the dispenser body is compressed;

inserting the tip into the opening in the housing such that the dispenser body is generally perpendicular to the top surface of the housing and is seated within the opening such that the dispenser body is self-standing outside of the housing;

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compressing the dispenser body to operate the dispensing mechanism and cause a metered quantity of the liquid medicament to eject into the chamber each time the dispenser body is compressed.

- 10. A method as in claim 9, further comprising repeatedly forcing the elongate body toward the tip to dispense multiple metered quantities of the liquid medicament into the chamber.
- 11. A method as in claim 9, wherein the tip includes at least one alignment feature, and wherein the alignment feature assists to keep the dispenser generally perpendicular to the housing while dispensing the liquid medicament.
 - 12. A method as in claim 9, further comprising actuating the vibratable member to eject the dispensed liquid medicament as an atomized spray.

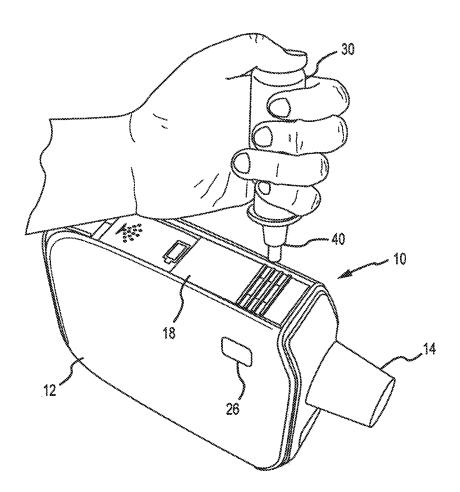


FIG.1

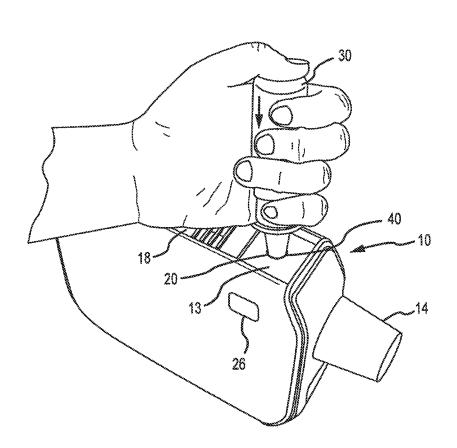
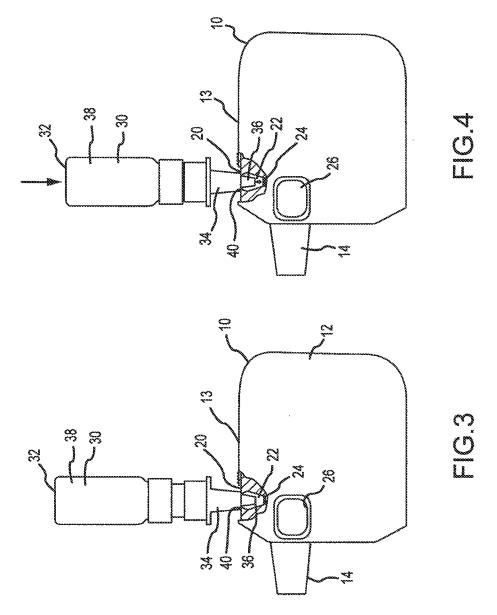


FIG.2



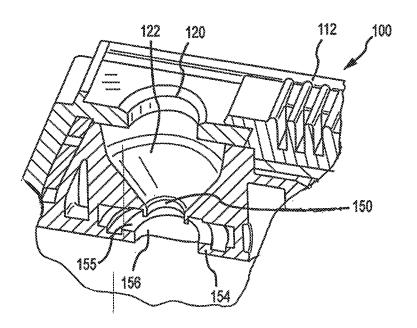


FIG.5

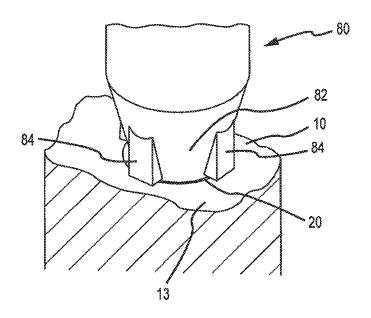


FIG.6

INTERNATIONAL SEARCH REPORT

International application No. PCT/US2013/034359

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61M 11/00 (2013.01) USPC - 128/200.14 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) IPC(8) - A61M 11/00, 11/08, 16/10, 16/18; B05B 17/00, 17/04; B65D 5/72, 5/76, 83/14, 83/16, 83/20, 83/22 (2013.01) USPC - 128/200.14, 200.18, 200.23; 222/491, 492, 493, 494			
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC - A61M 11/00, 11/02, 11/08; B05B 17/00, 17/04, 17/0615, 17/0646; B65D 83/14, 83/205, 83/206, 83/207 (2013.01)			
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Patents			
C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Category*	Citation of document, with indication, where ap	propriate, of the relevant passages	Relevant to claim No.
Y US 2	2011/0168172 A1 (PATTON et al) 14 July 2011 (14	1-12	
Y US 2	2010/0075001 A1 (SUCCAR et al) 25 March 2010	1-8	
Y wo	WO 98/22290 A1 (PAYNE) 28 May 1998 (28.05.1998) entire document		1-12
Further docu	uments are listed in the continuation of Box C.		
* Special categories of cited documents: "T" later document published after the international filing date or priority			
"A" document defining the general state of the art which is not considered to be of particular relevance "Be the document published after the international fining date of priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention			
filing date		"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	
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