US 20140350482A1

(19) **United States**

(12) **Patent Application Publication**

Damaj et al.

(10) **Pub. No.: US 2014/0350482 A1**

(43) **Pub. Date: Nov. 27, 2014**

(54) **RECONSTITUTION DEVICE**

(76) Inventors: **Bassam B. Damaj**, San Diego, CA (US); **Richard Martin**, San Diego, CA (US); **Michael Mueller**, San Diego, CA (US); **Daniel W. Frank**, Broomall, PA (US)

(21) Appl. No.: **14/130,668**

(22) PCT Filed: **Jul. 6, 2012**

(86) PCT No.: **PCT/US2012/045672**

§ 371 (c)(1),
(2), (4) Date: **Aug. 6, 2014**

(30) **Foreign Application Priority Data**

Jul. 6, 2011 (CA) 2745320

Publication Classification

(51) **Int. Cl.**

A61J 1/20	(2006.01)
A61K 31/5575	(2006.01)
A61K 31/137	(2006.01)
A61M 5/315	(2006.01)

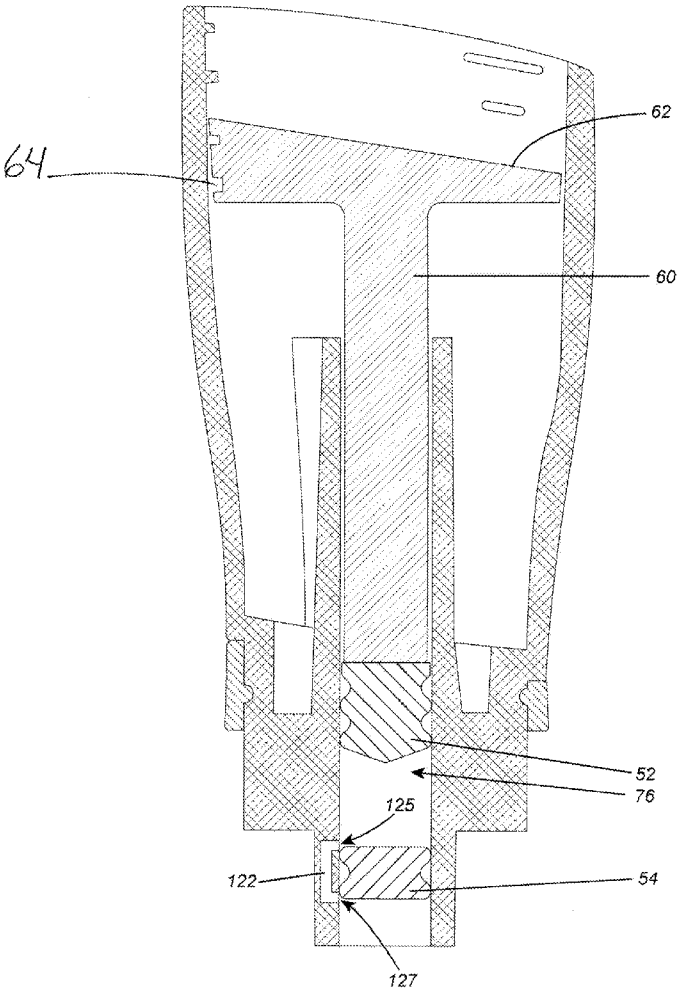
(52) **U.S. Cl.**

CPC ***A61J 1/2093*** (2013.01); ***A61K 31/5575*** (2013.01); ***A61K 31/137*** (2013.01); *A61J 2001/2031* (2013.01); *A61J 2001/2051* (2013.01)

USPC **604/218**; 514/573; 514/655; 206/570; 206/219

(57) **ABSTRACT**

The present invention relates to methods for reconstituting and relates to reconstitution devices suitable for reconstituting many different materials. Furthermore, the present invention includes methods of treatment and methods of use related to a reconstitution device or apparatus. Some embodiments are suitable for reconstituting small amounts of a pharmaceutical compositions and using the pharmaceutical composition for the treatment of sexual dysfunction.



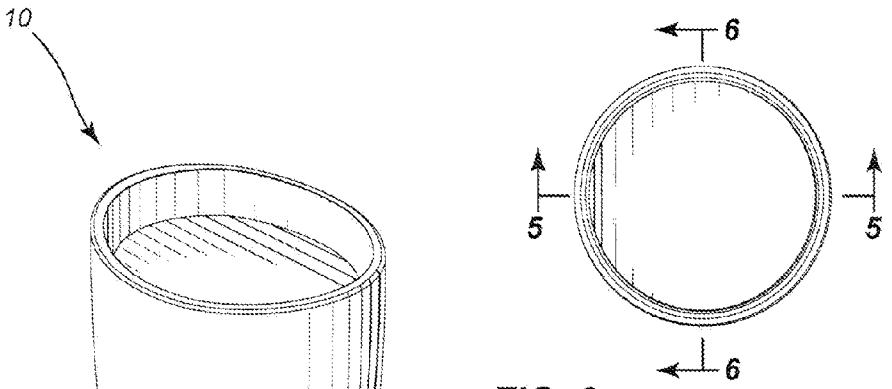


FIG. 3

FIG. 1

FIG. 2

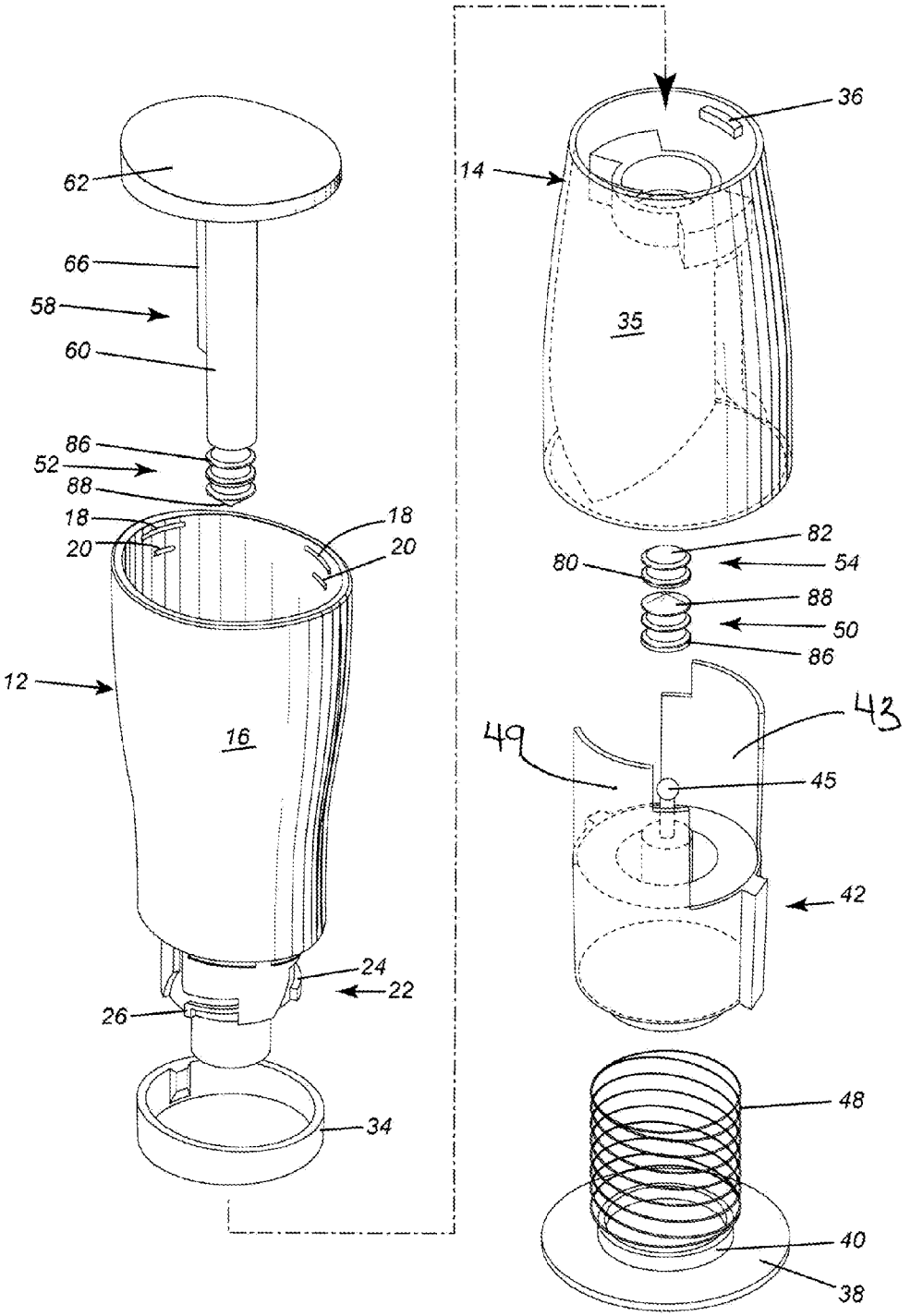

62
66
58
60
86
52
88
18
20
12
16
24
22
26
34
14
36
35
18
20
82
80
54
88
50
86
43
49
45
42
48
40
38

FIG. 4

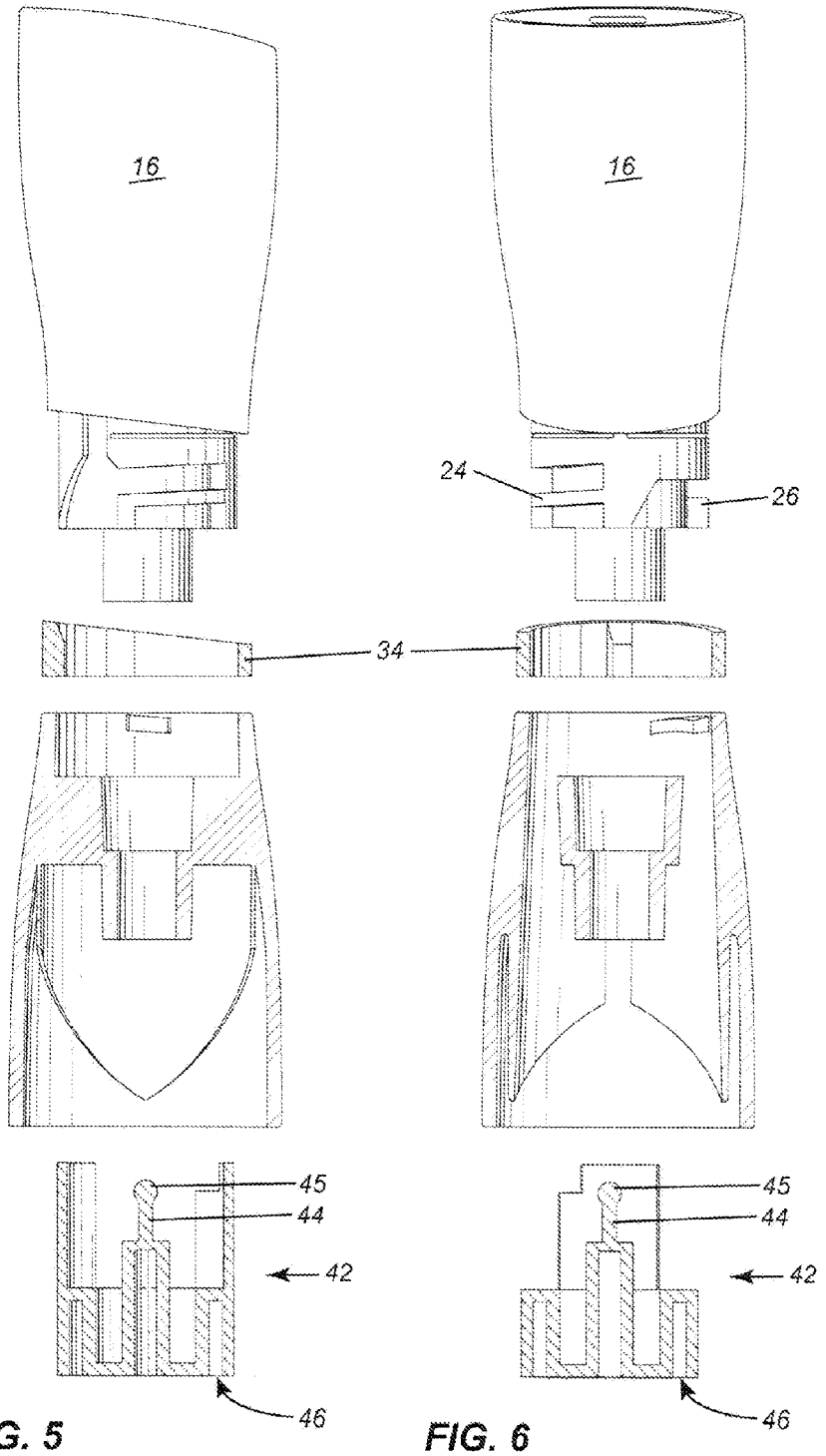


FIG. 5

FIG. 6

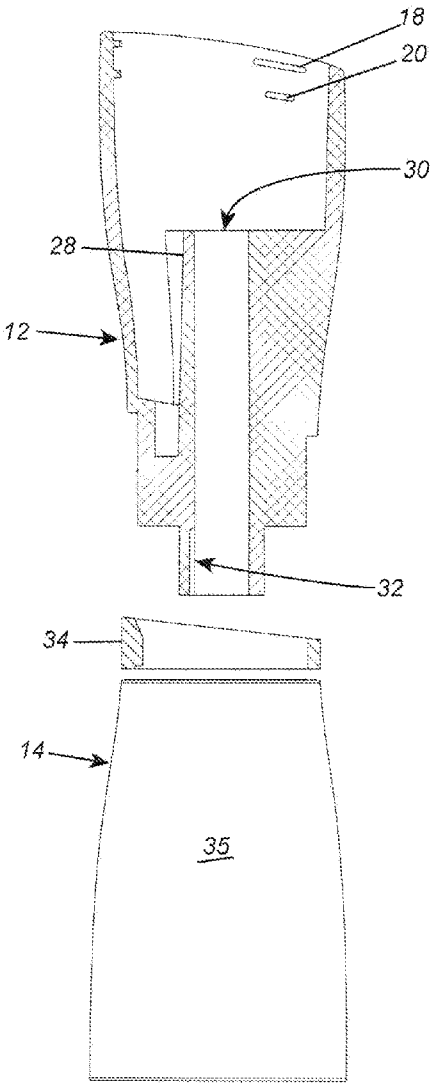


FIG. 7

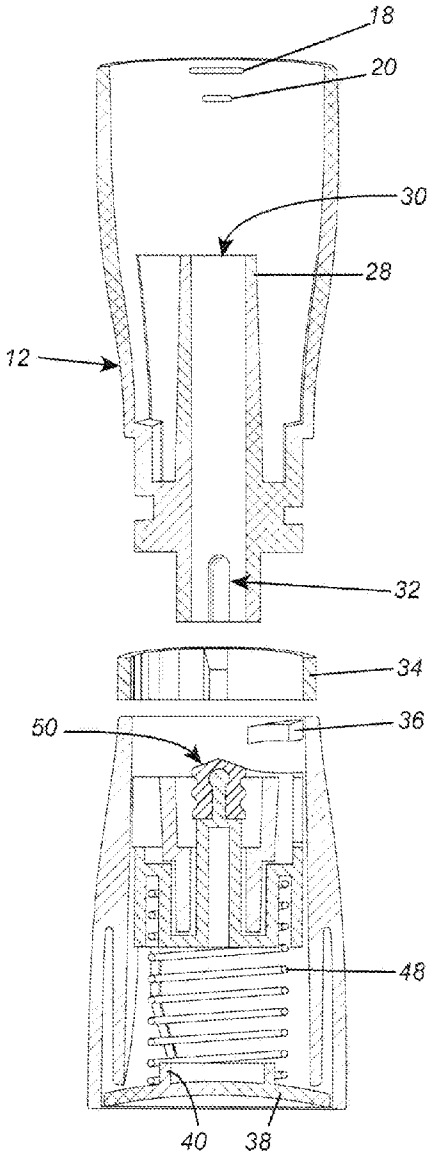


FIG. 8

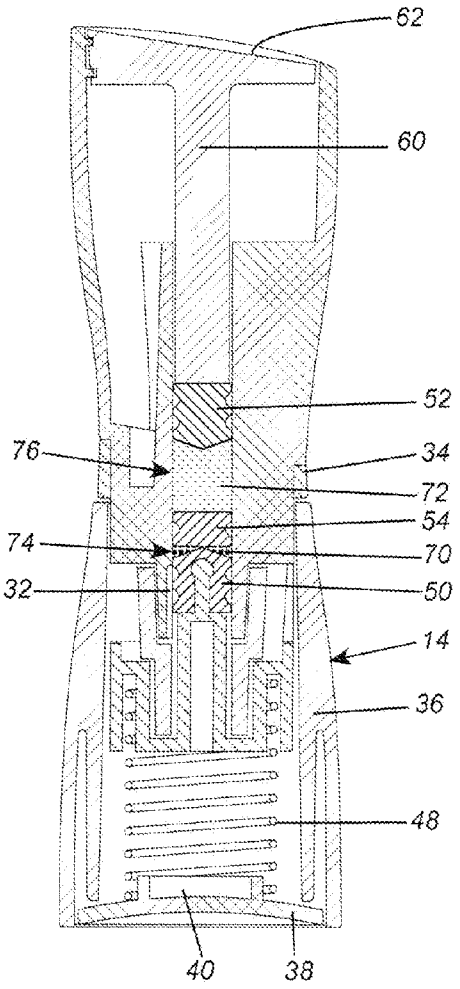

62
60
52
76
34
72
54
74
70
32
50
14
36
48
40
38

FIG. 9

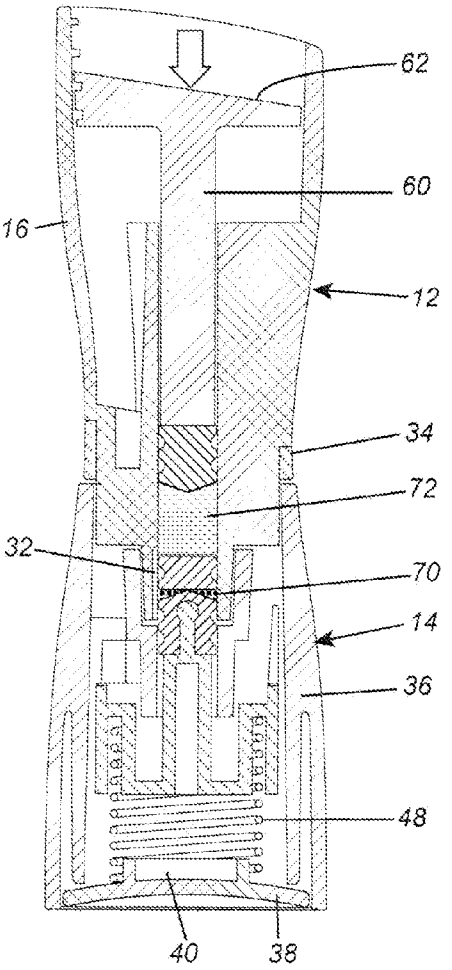

62
60
16
12
34
72
32
70
14
36
48
40
38

FIG. 10

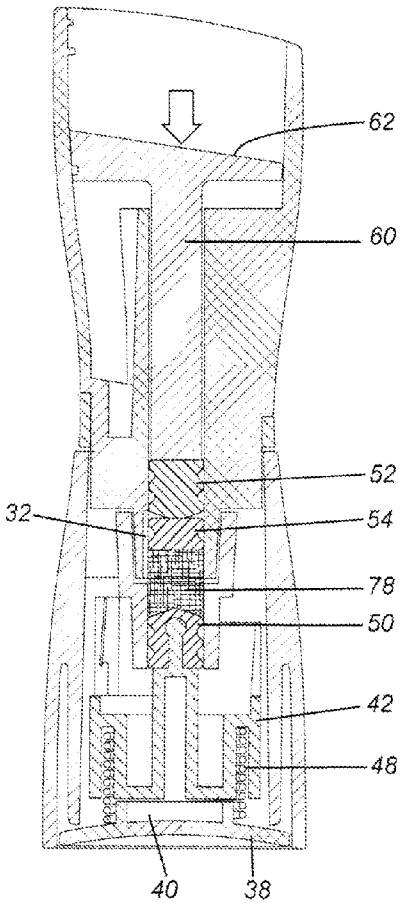


FIG. 11

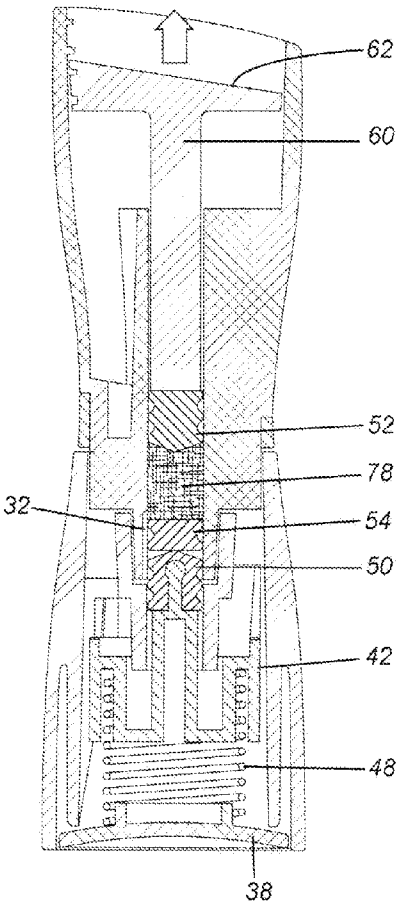


FIG. 12

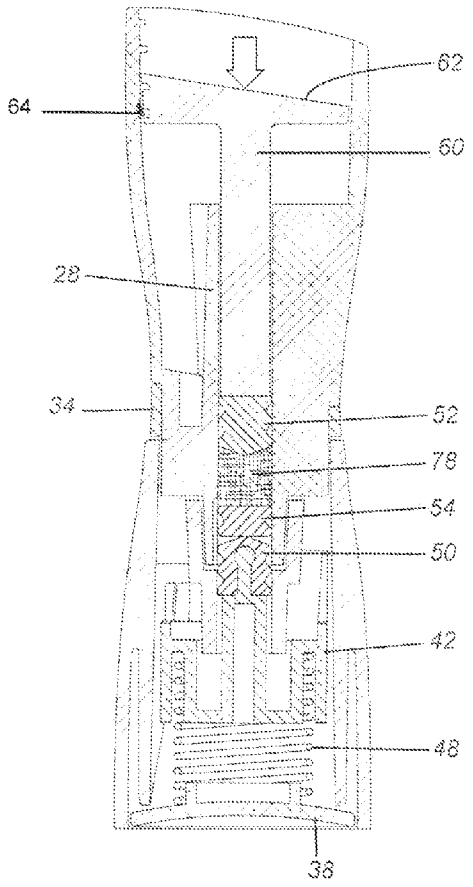


FIG. 13

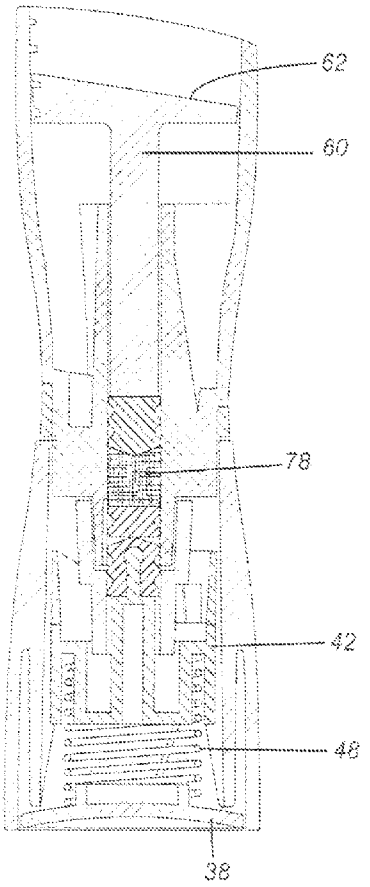


FIG. 14

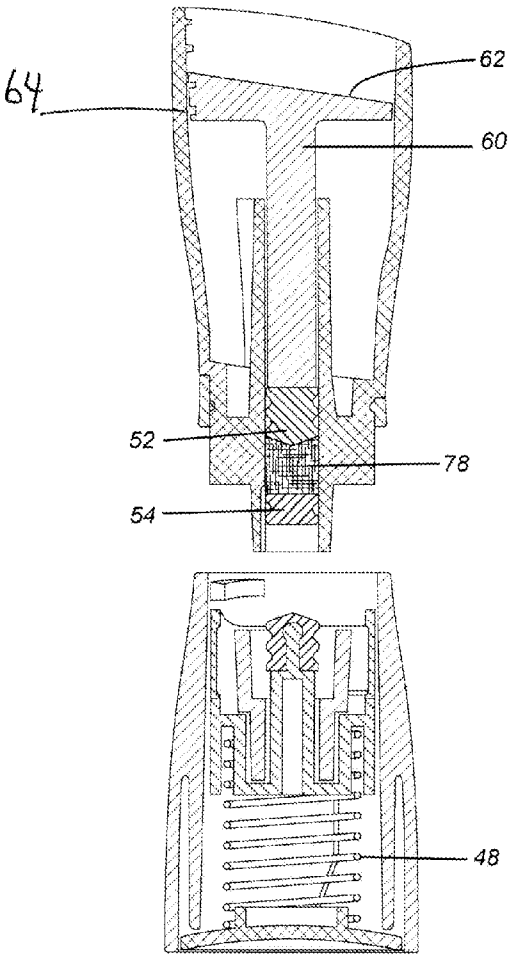


FIG. 15

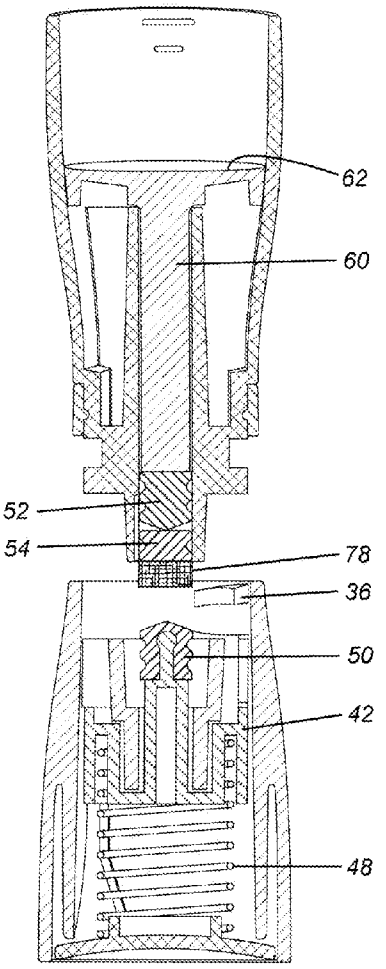


FIG. 16

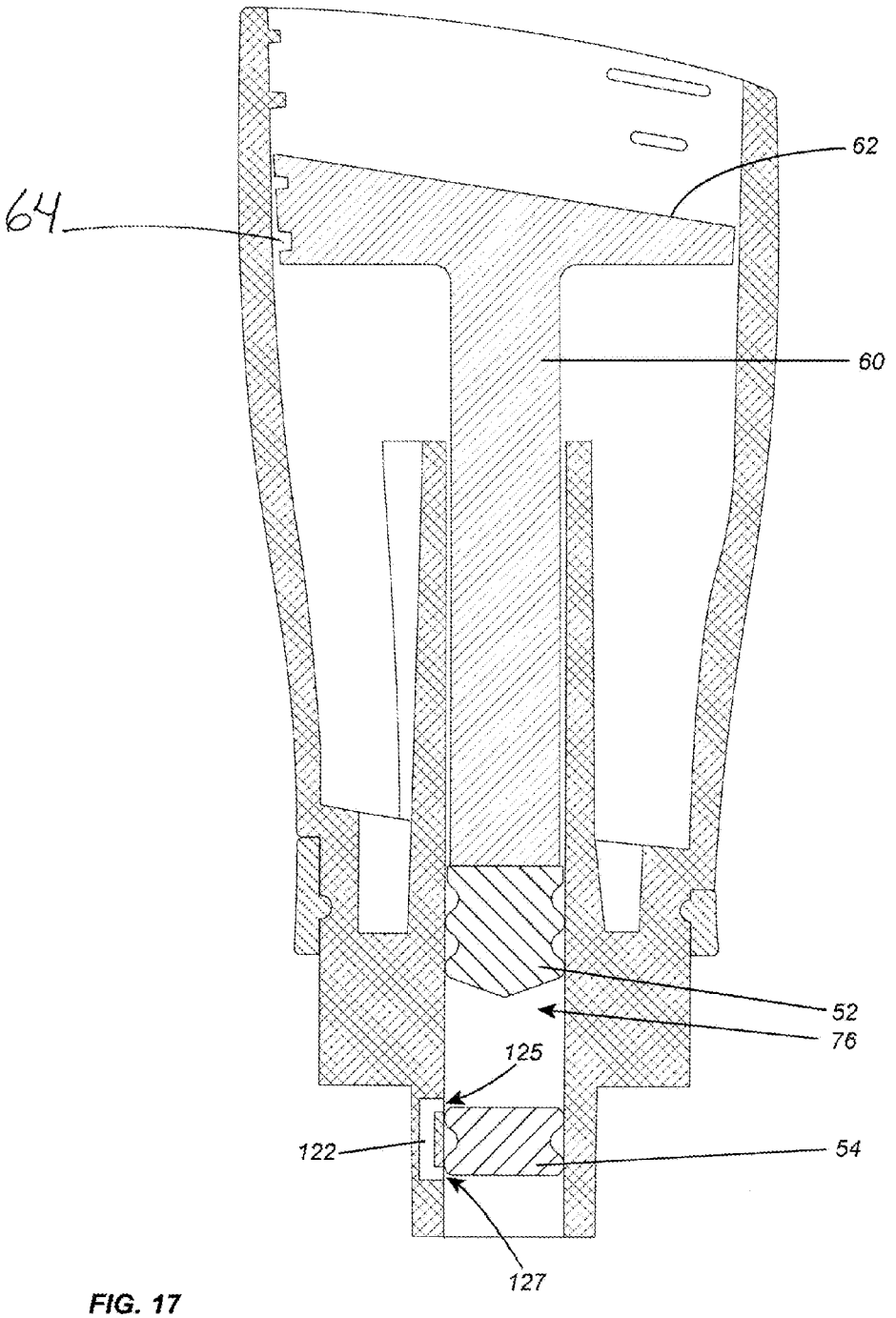


FIG. 17

RECONSTITUTION DEVICE

FIELD OF THE INVENTION

[0001] The present invention relates to methods for reconstituting and relates to reconstitution devices suitable for reconstituting many different materials. Furthermore, the present invention includes methods of treatment and methods of use related to a reconstitution device or apparatus.

BACKGROUND OF THE DISCLOSURE

[0002] In the pharmaceutical industry, the step of reconstituting a drug or other material is well known. Many pharmaceutical compositions are not capable of being stored for extended periods of time since their potency may change. In order to overcome this problem of a short shelf life, such pharmaceutical products are stored as a solid component and a liquid component. Prior to use, the two components must be mixed together.

[0003] Furthermore, while preservatives are effective in preserving some ingredients included in a pharmaceutical composition, such preservatives may cause adverse reactions with other ingredients of the pharmaceutical composition, namely the active ingredient, and result in degradation and/or spoilage. In some situations, refrigeration may be used to combat degradation or spoilage of a pharmaceutical composition. However, refrigeration is not always accessible and administration of a cooled pharmaceutical composition may reduce the effectiveness, namely solubility and penetration, of the pharmaceutical composition.

[0004] Although many reconstitution systems are directed for use with a powdered solid component and a diluent component, there are also occasions when other forms of material may be utilized. Thus, the reconstitution system may employ two liquids, or a semi liquid component such a paste along with a second component which is typically a liquid.

[0005] Several problems must be addressed in any reconstitution device such as the problem of obtaining a proper mixture. For highly soluble products such as a powder and a diluent therefore, a simple mixing of the two components is sufficient. Typically in such an arrangement, the diluent and dry components are stored in separate compartments of a device. The device will include a by-pass such that pressure on a plunger will cause the liquid to go through the by-pass to mix with the dry ingredient. Usually a simple shaking of the mixture is sufficient to assure that the mixture is properly constituted.

[0006] However, certain pharmaceutical products require a more thorough mixing and the conventional devices cannot be used. One other problem which is frequently encountered is that the components to be mixed are utilized in a small quantity and conventional mixing devices are not suitable. This is particularly the case when one of the components is in the form of a paste into which a liquid like constituent must be mixed.

[0007] Furthermore, poor application of a pharmaceutical composition can hinder the effectiveness of the pharmaceutical composition. Some advances in the ergonomics and delivery of pharmaceutical compositions have been made, see for example U.S. Pat. No. 6,224,573 (Yeager et al.). However, previous applicators that combined more than one composition together prior to administration do not have sufficient mixing mechanisms to achieve optimal composition storage, mixing, and application. Thus, there remain needs for methods of treating and devices to overcome all the issues that remain with the storage, mixing, and administration of pharmaceutical compositions.

SUMMARY OF THE INVENTION

[0008] It is an object of the present invention to provide a reconstitution system or device which is suitable for reconstituting small amounts of pharmaceutical compounds.

[0009] It is a further object of the present invention to provide methods for the reconstitution of pharmaceutical compounds and methods of treatment. Some embodiments are suitable for reconstituting small amounts of a pharmaceutical compositions and using the pharmaceutical composition for the treatment of sexual dysfunction.

[0010] According to one aspect of the present invention, there is provided a reconstitution device comprising a device suitable for mixing a first component with a second component, the device comprising first and second housings, the first and second housings being engageable together, a conduit having an internal passageway formed in the first housing, the internal passageway having a dispensing end and an inlet end, a first plunger mounted in the internal passageway proximate the dispensing end, a second plunger mounted in the internal passageway proximate the inlet end, a third plunger mounted in the internal passageway intermediate the first and second plungers, the first and third plungers defining a first compartment therebetween, the second and third plungers defining a second compartment therebetween, a plunger rod at least partially within the internal passageway at the inlet end, a moveable member located in the second housing, the moveable member engaging the first plunger, and a shearing channel formed in a side wall of the conduit to permit mixing of contents located in the first and second compartments.

[0011] According to a further aspect of the present invention, there is also provided a device for mixing a first component with a second component, the device comprising first and second housings, the first and second housing each having a partial screw thread formed on an exterior surface thereof, the first and second housings being engageable together by means of the screw threads, a conduit having an internal passageway formed in the first housing, the internal passageway having a dispensing end and an inlet end, a first plunger mounted in the internal passageway proximate the dispensing end, a second plunger mounted in the internal passageway proximate the inlet end, a third plunger mounted in the internal passageway intermediate the first and second plungers, the first and third plungers defining a first compartment therebetween, the second and third plungers defining a second compartment therebetween, a plunger rod at least partially within the internal passageway at the inlet end, a moveable member located in the second housing, the moveable member engaging the first plunger, the moveable member having at least one leg extending upwardly therefrom, the upwardly extending leg engaging the first housing such that the first and second housing cannot be disengaged from an initial first position, the arrangement being such that when the plunger rod is moved to commence transfer from the second compartment to the first compartment, the leg on the moveable member disengages from the first housing to permit rotatable movement of the first and second housings.

[0012] According to a still further aspect of the present invention, there is also provided a method of filling a reconstitution device comprising the steps of supplying first and second housings, the first and second housings being engage-

able together, a conduit having an internal passageway formed in the first housing, the internal passageway having a dispensing end and an inlet end, a moveable member mounted in the second housing, placing a first plunger on the moveable member, the plunger sealing the dispensing end of the internal passageway, inserting a first material in the internal passageway on the first plunger, inserting a second plunger in the internal passageway from the inlet end to seal the first material in a first compartment formed between the first and second plungers, placing a second material on top of the second plunger, inserting a third plunger to seal the second material between the second and third plungers, and placing a plunger rod adjacent the third plunger.

[0013] In one embodiment, the device, as above mentioned, includes first and second housings. The first and second housings are engageable together such that they may be retained in the assembled position for a period of time as will be discussed hereinbelow. The first and second housings are releasable.

[0014] Within one of the housings, there is provided a conduit having a hollow passageway therein. The passageway has three plungers mounted therein for containing the ingredients to be reconstituted. In one embodiment, there is provided a first plunger which is located proximate the outlet or dispensing end of the conduit as will be discussed in greater detail hereinbelow. A second plunger is mounted in the internal passageway closer to the inlet end of the conduit. However, this second plunger is not located at the very end, but rather is usually proximate the middle of the conduit.

[0015] A third plunger mounted in the passageway is intermediate of the first and second plungers. The first and third plungers define a first compartment for receiving a first ingredient while the second and third plungers define a second compartment therebetween for containing a second ingredient. Typically, the second compartment will contain the less viscous of the ingredients. A shearing channel is formed in the side wall of the conduit, again for reasons which will be discussed hereinbelow. The shearing channel is initially at least partially covered by the third plunger so as to maintain the ingredients apart.

[0016] A plunger rod is utilized to exert pressure or push on the second plunger. This results in movement of the third plunger such that access to the shearing channel is obtained. Subsequently, the ingredient in the second compartment will pass through the shearing channel to mix with the component in the first compartment.

[0017] In one embodiment, a spring member is provided which is arranged to exert pressure or bias the first plunger. Thus, after transferring the ingredient from the second compartment to the first compartment, a mixture or admixture is achieved. Subsequently, with release of the pressure on the plunger rod, the spring will cause the first plunger to move rearwardly such that the mixture or admixture is again forced to pass through the shearing channel. This can be repeated several times to ensure that the composition formed by the at least two ingredients is properly mixed. Naturally, one could use the finger of the user instead of the spring.

[0018] To assist in proper mixing, the shearing channel is sized to provide a relatively small cross-sectional area such that significant shearing is obtained. Typically, the shearing channel will have a diameter of less than 1 mm. In alternative embodiments, the diameter of the shearing channel is greater than 1 mm, less than 1 mm, 0.5 mm, or 0.3 mm. In other embodiments, the shearing channel does not have a fixed diameter; rather, the shearing channel is tapered.

[0019] As previously mentioned, the device is particularly suited for mixing of small amounts. In some instances, the total volume of the constituents would range between 0.1 and 0.2 of a cc. In alternative embodiments, the total volume is greater than 10 cc, less than 10 cc, 5 cc, 1 cc, or 0.5 cc.

[0020] The moveable member mounted in the second housing in one embodiment is connected to the first plunger. In order to do so, the moveable member has a small rod like element with an enlarged end in some embodiments. The enlarged end would enter the plunger such that the plunger will move back and forth with the moveable member.

[0021] The plunger rod is positioned to initially contact the second plunger. Thus, a portion of the plunger fits within the passageway while a further portion extends to the end of the housing which is open and thus forms a head for applying pressure to the plunger rod by the thumb or a finger of the user.

[0022] To prevent accidental movement of the plunger rod, the head is retained in position by a projection on the interior wall of the housing. The projection is sufficient to maintain the plunger rod in position until sufficient pressure is applied to the head.

[0023] Once the initial pressure is applied to the plunger rod, it will start moving the second plunger downwardly and apply pressure to the ingredient in the second compartment. This in turn will cause sufficient movement of the third plunger such that access is had to the shearing channel. The liquid will then mix with the ingredient in the first compartment. Upon releasing the plunger rod, the spring will apply sufficient pressure to the moveable member which in turn will move the first plunger rearwardly and force the mixture to again pass through the shearing channel. In some embodiments, these steps are repeated. Instead of using the spring to move the moveable member, a manual arrangement wherein a digit of the user may be employed.

[0024] In one embodiment, the initial movement of the third plunger will cause the disengagement of the first and second housings to thereby permit the housings to be disengaged when so desired. This arrangement provides the advantage that the user cannot access the ingredients without at least having gone through one mixing operation.

[0025] The present invention also includes methods of reconstitution and methods of treatment with reconstituted compositions, namely pharmaceutical compositions. Although the some embodiments have compositions for reconstitution and use for treatment are pharmaceutical compositions suitable for the treatment of sexual dysfunction, the methods disclosed herein are suitable for other compositions, such as cosmetics, foods, and vaccines.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Having thus generally described the invention, reference will be made to the accompanying drawings illustrating embodiments thereof in which.

[0027] FIG. **1** is a perspective view of a reconstitution device according to an embodiment of the present invention;

[0028] FIG. **2** is a side elevational view thereof;

[0029] FIG. **3** is a top plan view thereof;

[0030] FIG. **4** is an exploded view of the reconstitution device;

[0031] FIG. **5** is a cross sectional view of a lower portion of the reconstitution device;

[0032] FIG. **6** is a cross sectional view similar to FIG. **4** but rotated through 90 degrees;

[0033] FIG. **7** is a cross sectional view of the upper portion of the reconstitution device;

[0034] FIG. **8** is a cross sectional and exploded view of both housings forming the reconstitution device;

[0035] FIG. **9** is cross sectional view illustrating the assembled reconstitution device;

[0036] FIG. **10** is a cross sectional view similar to FIG. **8** illustrating commencement of the reconstitution constituting step;

[0037] FIGS. **11** to **14** are cross sectional views illustrating the functioning of the reconstitution device;

[0038] FIGS. **15** and **16** are cross sectional views illustrating the separating of the two housings for application of the contents; and

[0039] FIG. **17** is a cross sectional view of one of the housings showing an alternative embodiment.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Definitions.

[0040] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. As used in the specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise.

[0041] The term "administer" or "administration" means the act of giving a pharmaceutical composition to a subject.

[0042] The term "compound", "composition", "ingredient", and "component" may sometimes be used interchangeably to refer one or more chemical components.

[0043] "Disease" means any disease, condition, symptom, or indication.

[0044] The term "drug" or "pharmaceutically active agent" as used herein is intended to mean a compound or composition of matter which, when administered to an organism/subject, which is human or animal, induces a desired pharmacologic and/or physiologic effect by local and/or systemic action.

[0045] An "effective amount" means an amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease or condition. The "effective amount" will vary depending on the compound, the disease state being treated, the severity or the disease being treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner and other factors.

[0046] As used herein "excipient" means a component or an ingredient that is acceptable in the sense of being compatible with the other components of the formulation and not deleterious to a subject to which the formulation is to be administered.

[0047] The term "immediately before" or "immediately prior" generally means less than two hours before application of a composition or before the desired next step; however, this term is not limited to this timeframe because the chemical properties or desired state of a pharmaceutical composition may require a timeframe more than two hours before proceeding with the next step.

[0048] The term "immediately after" or "immediately following" generally means less than two hours after application of a composition before the desired next step; however, this term is not limited to this timeframe because the chemical properties or desired state of a pharmaceutical composition may require a timeframe more than two hours before proceeding with the next step.

[0049] "Optional" or "optionally" means that the subsequent described event or circumstance may but need not occur, and that the description includes instances where the event or circumstances occurs and instances in which it does not occur.

[0050] The term "penetration enhancer" means a chemical compound that increases the permeability of the skin to a drug.

[0051] "Pharmaceutical compositions" means a composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is actable for veterinary as well as human pharmaceutical use.

[0052] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is actable for veterinary as well as human pharmaceutical use. This language may also include pharmaceutically acceptable salts of a pharmaceutically acceptable composition.

[0053] "Subject" means mammals and non-mammals and the term does not denote a particular age or sex.

[0054] The term "pharmacological effect" as used herein encompasses effects produced in the subject that achieve the intended purpose of a therapy.

[0055] "Transdermal" application or drug delivery means delivery of a drug by passage into and though the skin and/or the underlying tissues and into the blood stream.

[0056] "Treating" or "treatment" of a disease includes preventing the disease, inhibiting the disease, and/or relieving the effects of a disease.

[0057] The methods and apparatuses disclosed herein can be used in the mixing and/or application of numerous different compositions, including vaccines, medicaments, pharmaceutical compositions, cosmetics, and food products. Although the some embodiments include applications and methods for pharmaceutical compositions, one skilled in the art will appreciate applicability of this disclosure in other areas.

[0058] Referring to the drawings in greater detail and by reference characters thereto, there is illustrated a reconstitution device which is generally designated by reference numeral **10**.

[0059] Referring to FIG. **1**, an embodiment of a reconstitution device **10** includes a first housing generally designated by reference numeral **12** and a second housing generally designated by reference numeral **14**. First housing **12** includes a wall **16**, wall **16** having first projections **18** located at a first distance from the top thereof and second projections **20** at a second distance from the top thereof. In the illustrated embodiment, there are provided two such projections **18** and **20**; it will be understood that in alternative embodiments, one or more is utilized.

[0060] At a narrower end **22** of first housing **12**, there is provided a pair of screw threads **24**, **26** for reasons which will become apparent hereinbelow. Narrower end **22** also defines first and second recesses **53**, **55** intermediate screw threads **24**, **26**.

[0061] A conduit **28** is located interiorly of first housing **12** and includes an internal passageway **30** extending therethrough. A shearing recess **32** is provided within the interior wall of conduit **28**.

[0062] A ring member generally designated by reference numeral **34** mounts over narrower end **22** of first housing **12**.

[0063] On a wall **35** of second housing **14**, there are provided a set of lugs **36** which act as threads for engaging with screw threads **24**, **26**. An end cover **38** covers the larger end of second housing **14** and is secured thereto by adhesives or welding or the like. End cover **38** includes a centering structure **40**.

[0064] Mounted interiorly of second housing **14** is a moveable member **42**. As may be seen in the drawings, moveable member **42** is provided with a center post **44** having an enlarged portion **45**. Moveable member **42** has a spring recess **46** formed therein to receive a spring **48**. At the other end, spring **48** is mounted around centering structure **40**. Moveable member **42** also has a guide rib **47**. Guide rib **47** is designed to fit within a channel **51** formed in an inner wall **57** of second housing **14**. Moveable member **42** also has first and second legs **43**, **49** extending upwardly therefrom. In an initial position, legs **43**, **49** fit within recesses **53** and **55** which will then block relative rotation of housings **12**, **14** with respect to each other. Thus, the housings cannot be easily unscrewed until moveable member **42** is moved out of position.

[0065] Reconstitution device **10** includes a first plunger **50** which is situated near the dispensing end of conduit **28**. A second plunger **52** is located rearwardly towards the inlet end of conduit **28** while a third plunger **54** is situated therebetween. It will be noted that first plunger **50** has a recess **56** to receive center post **44** of moveable member **42**.

[0066] Third plunger **54** has a side wall **80** with a concave structure. A first end wall **82** is relatively flat or planar while end wall **84** has a somewhat conical configuration. First plunger **50** has a side wall **86** with a plurality of concave recesses therein and end wall **88** (which faces third plunger **54**) has a conical configuration. Similarly, second plunger **52** also has a pair of concave recesses formed therein and an end wall **92** which is somewhat conical in configuration.

[0067] A plunger rod generally designated by reference numeral **58** is situated within conduit **28**. Plunger rod **58** includes a stem portion **60** which abuts second plunger **52** and a head **62** which fills the open end of first housing **12**. Head **62** has at least one aperture **64** which are designed to receive or engage first projections **18**. In some embodiments, the device contains two recesses or more than two recesses. Stem **60** also has a rib **66** which functions as a guide for the movement of plunger rod **58** and which engages in a slot formed in conduit **28**.

[0068] The first and third plungers define therebetween a first compartment **74** while second and third plungers define therebetween a second compartment **76**.

[0069] Within first compartment **74**, there is provided a first component **70**. In one embodiment, the first component **70** is in the form of a powder, paste or other fluid. Second compartment **76** contains a second component **72** which typically will be a less viscous material such a liquid. Both compartments **74** and **76** are thus sealed from any contamination.

[0070] As shown in FIG. **9**, pressure on plunger rod **58** will cause movement of second plunger **52** and third plunger **54**. Third plunger **54** will advance to a point such that shearing recess **32** is aligned with both first compartment **74** and second compartment **76** permitting a mixture **78** to be formed. The initial movement of plunger rod **58** will cause moveable member **42** to move out of its position blocking rotation of housings **12**, **14**. After removal of the pressure, as shown in FIG. **11**, spring **48** will exert pressure on moveable member **42** which in turn will drive second plunger **52** rearwardly or upwardly as shown in the drawing. The mixture **78** will then flow back into second compartment **76**. A continuing back and forth movement is exerted such that continued passage through shearing recess **32** will ensure adequate mixing of the composition **78**. The spring **48** will not cause moveable member **42** to return to its original position due to projection **20**.

[0071] After repeating the steps for the desired number of times, first housing **12** and second housing **14** are separated and mixture **78** is exposed for use.

[0072] In the embodiment of FIG. **16**, there is provided a different type of shearing channel **122**. As will be noted, shearing channel **122** is formed within the wall defining conduit **28**. Thus, third plunger **54** will abut the wall and is sized such that there is provided an inlet **125** and an outlet **127** from shearing channel **122**. When the mixing flow is reversed, the mixture enters outlet **127** and exits inlet **125**.

[0073] In addition to the embodiment described above, alternate embodiments are contemplated. For example, a plunger need not be used as a means for forcing flow or mixing of compositions held within. Therefore, as one skilled in the art would appreciate, other embodiment use other types of mechanisms to cause a composition to flow out of or into a compartment. For example, in an alternative embodiment, the walls of the conduit are compressed, causing the available volume in a compartment to decrease, and thus causing a composition contained within to flow out of the compartment. Accordingly, if the walls of the conduit are expanded outward, causing the internal volume to increase and creating a relative lower pressure, composition contained elsewhere in the device is forced to flow into the compartment. In such case, the conduct is made of a flexible and durable plastic.

[0074] Alternatively, the compartment has walls that are separate from the conduit, and in such case, the compartment is a distinct chamber. For the purposes of this disclosure, compartment and chamber may be used interchangeably to describe various embodiments.

[0075] In one embodiment, the conduit and or the chambers that form the areas for mixing is at least one removable and disposable component of the device. These components, which include chambers, plungers, shearing channels, or other components described herein, are be pre-filled with the desired compositions for mixing and administration. Therefore, in one embodiment, the device is reusable and chambers with compositions are in the form of disposable cartridges. Active ingredients and other compositions to the final pharmaceutical composition are stored in one or more pre-packaged cartridges. As noted above, such cartridges serve as chambers themselves or be inserted into chambers in certain embodiments. In such an embodiment, plungers, conduits, and other components for mixing are part of the one or more disposable cartridges.

[0076] When a composition is a chamber in subject to settling or separation, pre-mixing in a single chamber prior to combining the composition with the other chambers is desired. In such a case, as one skilled in the art would appreciate, alternative embodiments use different means of mixing, such as one of the means described herein.

[0077] Although the embodiment illustrated in the figures includes compartments shown as being separated by a

plunger, alternative embodiments use different means of separation, such as a door, wall, or permeable membrane. In the case of a wall, one embodiment includes a separation device in the shearing channel, which opens for mixing. In some embodiments, more than one conduit is used. One such embodiment uses two conduits to mix two compositions separately, which are then combined prior to or at the time of dispensing. In an alternative embodiment, the two conduits are dispensed through separate openings in the device or through the same opening but in separate steps, in which case the administration is sequential.

[0078] The coil spring, illustrated and described herein, is not the only contemplated embodiment. Other mechanical (including electronically powered) components are used to facilitate mixing in alternative embodiments. For example, one embodiment has a mechanical crank or motor. In an embodiment containing a motor, a battery is used; it should be noted, however, that a motor need not be present in the device for a battery to be included. A battery is desired for some embodiments because it allows for additional components to be included in the device.

[0079] Contemplated components include: sensors to measure the temperature, pH, viscosity, and/or other physical and chemical properties; external electronic displays; heating and/or cooling component(s); microprocessors, transmitters, and other electrical components; and/or values.

[0080] A heating or cooling component provides for two additional utilities. First, in one embodiment, the heating and/or cooling component aids in the storage of a composition in at least one chamber by providing temperature modification, notification, and/or control. Second, in another embodiment or combined with the previous embodiment, the heating and/or cooling component is used as a thermodynamic catalyst for reactions in one or more chambers. In one embodiment, the heating and/or cooling component is electrically powered or chemically facilitated. In one embodiment, one or more valves is desired or necessary to achieve a desired result because of changes in pressure before, during, or after the mixing of one or more compositions. In one embodiment, such a valve is a one way valve, capable of releasing gases resulting from mixing.

[0081] In some embodiments, compositions are stored at a pressure above or below atmospheric pressure. In one embodiment, one or more chambers fill with air. In other embodiments, one or more chambers contain a gas at above atmospheric pressure or below atmospheric pressure.

[0082] The second plunger need not be the only means of blocking passage through the shearing channel prior to activation by a user. In an alternative embodiment, the wall of the conduit has a door that is connected to the compression systems, the plungers and springs for example, that simultaneously opens the shearing channel upon initiation by a device user. In addition, in some embodiments, a third composition is stored in the shearing channel. As one skilled in the art would appreciate, one embodiment contains a shearing channel where the mixing means is one or a combination means of mixing, depending on the desired result. For example, the shearing channel may create vortex flow or utilize baffles and other protruding mixing members. In another example, the shearing channel is replaced by other mixing means. In one embodiment for example, the third plunger, which separated the two compartments in the illustrated embodiment, operates as to open a passage way for exchange of compositions stored in the two compartments; for instance, the third plunger pivots open upon activation of mixing by a user. In one embodiment, the disclosed device allows for high shear flow for efficient emulsification of components with a minimum or exact number of mixing cycles. Although high shear flow is desired in some instances, low shear flow may be desired. In such situations, another embodiment includes at least one shearing channel that is enlarged or a less shearing mixing means is used.

[0083] Depending on the compositions being mixed, the number of cycles varies in alternate embodiments. In order to ensure a proper number of cycles, in some embodiments, the device includes a cycle counter and/or a component to limit the number of cycles possible for a given administration of a dosage. In an embodiment, a cycle counter includes a mechanical wheel or crank and the counter is internal with a stopping mechanism and/or contains an external readable display for the user. A component to count and/or limit the number of cycles is mechanical in one embodiment and electrical in another.

[0084] In an alternative embodiment, the upper housing is a disposable component and the lower housing is component made for repeated use. Therefore, in one embodiment, the lower housing component is the location for features such as the cycle counter, temperature monitor, battery, and other features discussed in and foreseeable from this disclosure.

[0085] In some embodiments, after a pre-determined number of cycles, a composition in a third chamber is released into the chamber(s) where mixing is occurring. More than three chambers is used in this manner in other embodiments. Therefore, where sequential reactions of multiple components are require or desired for a final composition, the device and method can achieve the desired result. In one embodiment for example, a first composition is stored in a first chamber, a second composition is stored in a second chamber, and a third composition is then stored in a third chamber. Upon initiation of mixing the first and second compositions are combined for a desired number of mixing cycles. Next, the third composition in the third chamber is combined with the already mixed first composition and second composition. This example is useful for a reaction where initial compound in the first and second compositions cause adverse reactions with the compounds in the third composition. However, upon mixing the first and second compositions, the undesired components are chemically altered via chemical reaction and therefore, no adverse reaction occurs when the third composition is mixed with the first two. In alternative embodiments, it is desired to have the product of the reaction of the first and second compositions at equilibrium prior to mixing and reacting the product with the third composition.

[0086] Because of the area of application in some instances, one embodiment includes a throttle or regulator for limiting the rate at which the composition can be dispensed from the device. For example, one embodiment is for the treatment of male sexual dysfunction calls for application of the pharmaceutical composition in the urethra. Therefore, dispensing the pharmaceutical composition at a high rate may result in a less then desired amount of pharmaceutical composition entering and penetrating the urethra due to splatter and/or off-target application.

[0087] In an alternative embodiment, the amount in one or more chambers that is mixed and/or dispensed can be set and/or calibrated. For example, one embodiment includes 300 mcg of alprostadil in 100 mg of cream. However, in some cases, it is desirable to titrate the dosage down to 200 mcg of

alprostadil. In addition, a patient sometimes finds that the most effective and/or most tolerated dosage is somewhere between 300 mcg and 200 mcg of alprostadil. In this embodiment, the composition containing the active ingredient, alprostadil, is stored in the first chamber, a third chamber, and a fourth chamber. A different composition containing inactive ingredients is stored in the second chamber. In such an embodiment, the combined volume of all chambers is between 1 mL and 2 mL. Therefore, the first chamber contains 200 mcg of alprostadil and the third and fourth chambers each contain 50 mcg of alprostadil. In an alternative embodiment, there are only three chambers, whereby the third chamber contains 100 mcg of alprostadil. The sum of all chambers results in total of 300 mcg of alprostadil. In the device, the contents are mixed in the first chamber and second chamber. The contents of the third chamber and fourth chamber are added to the first chamber or second chamber if selected to be included in the final pharmaceutical product to be dispensed, which depends on the desired dosage.

[0088] For example, prior to mixing, the subject determines whether a dose of 200 mcg, 250 mcg, or 300 mcg is desired. If the subject desires to administer a dose of 250 mcg, the contents of either the third chamber or the fourth chamber are mixed with the first chamber and the second chamber. This mixing selection is controlled by the either mechanical or electrical components on the device; for example, the user presses an external button on the device that sets the third chamber to be mixed with the first and second chambers. Then upon mixing initiation by the user, contents of the three chambers are mixed and dispensed as a dosage of 250 mcg in one of the manners described in this disclosure.

[0089] In some embodiments, the device contains one or more components for more exact mixing. For example, hand actuated plungers, such as those disclosed in U.S. Pat. No. 4,250,755 (Kenney), are used to allow for more exact dosages. Other actuating components, electronic for example, are also contemplated and desired for other embodiments. Furthermore, more precise actuating plungers are used in the dispensing of the composition other embodiments.

[0090] In one embodiment, the device is built as one assembly; therefore, the upper and lower housing element is not separated for dispensing because there is no second housing to be separated. Instead, there is an opening that can be opened at the time for dispensing. The body and components of the device are made utilizing molding or other fabrication techniques. In one embodiment, materials for such components is rigid plastic, such as polyolefin, including polyethylene, polypropylene, and the like, suitable for injection molding, and in some embodiments the plastics are clear, translucent or opaque. In the case of clear or translucent material, compositions that are subject to color change or physical property change due to spoilage is viewable by a user.

[0091] In addition to flexibility in the dimensions of the device, some embodiments of the device are designed for better application, and included additional components such as nozzles or adapters. Such nozzles or adapter are be suitable for delivery of the pharmaceutical composition onto or into the body, including the urethra, the vagina, the ear and the eye, the mouth, but delivery is not limited to those parts expressly listed here. In one such embodiment, the device includes a suitable conical nozzle for administration of a pharmaceutical composition for the treatment of male sexual dysfunction into the urethra of a subject. In another embodiment, the device includes a suitable conical nozzle for administration of a pharmaceutical composition for the treatment of female sexual dysfunction into the vagina of a subject.

[0092] In one embodiment, the device and composition are provided in a kit. In another embodiment, the kit includes additional components. For example, for the use of treating male sexual dysfunction, the kit comprises a pharmaceutical composition for treatment of erectile dysfunction, an applicator, and a contraceptive device (such as a condom). A condom is a desired kit accessory because in the case where alprostadil is used for the treatment of male sexual dysfunction, it is advisable for the male subject to use a condom when sexual intercourse is planned or takes place with a pregnant or lactating woman because the effects of alprostadil on women is not well studied.

[0093] As one skilled in the art would appreciate, the present device and components thereof can be made with nearly any dimensions, constructions, and materials suitable to practice the details of this disclosure and achieve the desired results.

Methods of Treatment.

[0094] In one embodiment, methods are used to administer a pharmaceutical composition. Where embodiments are used for the administration of a pharmaceutical application, such application includes, but is not limited to, delivery of medicament to the urethra and urethral meatus for male sexual dysfunction; direct vaginal and/or clitoral application for female sexual dysfunction; intraoral application of a vaccine or oral care product; intranasal application of a vaccine or medicament; intra-aural application; or ophthalmic application of a medicament.

[0095] In another embodiment, the methods are used to prepare and administer a pharmaceutical composition. In some embodiments, pharmaceutical compositions include an effective amount of an active ingredient and at least one other compound. However, as previously noted, the applications and methods of this disclosure not limit to pharmaceutical products. Hence, the methods herein can be used for vitamins, beauty products, foods, and the like.

[0096] Suitable formulations for mixing and administration include for example, creams, ointments, lotions, gels, semi-solids, spray-aerosols, oils, aqueous solutions, oil-in-water or water-in-oil emulsions, ointments, pastes, and solutions or suspensions. The specific compounds of a composition to be used, as will be appreciated by those skilled in the art, is one that provides for optimum drug delivery and effectiveness of the active ingredient or ingredients. For some methods, formulations for topical administration further comprise one or more of the additional ingredients as described herein. The compounds may be acid or base. Thickeners, preservatives, lubricants, penetration enhancers, excipients, suspending agents, and other non-active ingredients are included in alternative embodiments, as one skilled in the art would appreciate. In some embodiments, it is required that the compositions, components, and/or the device be sterilize.

[0097] In one embodiment, the pharmaceutical composition is stored in the device in more than one chamber. However, in some embodiments, only one chamber is used for storage. In one embodiment, one compartment contains a vasoactive agent, and an at least second compartment contains a diluent composition. When combined in the device, these at least two composition are mixed to form a pharma-

ceutical composition. The storing of the compositions in separate compartments prior to mixing increases the shelf-life of the compositions and prevents time-caused degradation of the pharmaceutical composition. Pharmaceutical compositions for alternative embodiments are disclosed in U.S. Pat. No. 7,560,489 (Frank et al.). One such composition comprises a pharmaceutically acceptable excipient and a prostaglandin, such as prostaglandin E1 (alprostadil), in the amount of 200 mcg or 300 mcg in 100 mg of cream. Other pharmaceutical compositions include, but are not limited to those compositions disclosed in U.S. Pat. No. 6,486,207 (Yeager et al.), U.S. 2002/0045665 A1 (Yeager et al.), and U.S. 2004/0241245 A1 (Lu et al.).

[0098] Routes of administration include, but are not limited to transdermal, intranasal, buccal, or rectal. In one embodiments, the route of administration is topical and transdermal. However, in some embodiment, the device is used to deliver compositions orally, as an aerosol, or liquid for example. Another example includes administration to a subject's eye, where the pharmaceutical composition is mixed immediately prior and then administered on the eye of the subject. In one embodiment, the disease for treatment is sexual dysfunction, which includes male sexual dysfunction and female sexual dysfunction.

[0099] In the treatment of female sexual dysfunction, namely female sexual arousal disorder, alprostadil acts directly on local tissues to produce increases in vaginal secretion, increases in vaginal engorgement, and acts indirectly on the central nervous system to increase sexual responsiveness and arousal.

[0100] In one embodiment for the treatment of female sexual dysfunction, at least 0.5 mg to 10 mg of the active ingredient, such as alprostadil, is topically administered. In some embodiments, compositions contain between 0.05% a 0.4% alprostadil. In such case, the pharmaceutical product is applied to the labia, clitoris and/or the vulvar region of the vagina. Optionally, the reconstitution device includes a modified applicator tip for administration in such region.

[0101] For the treatment of male sexual dysfunction, a method of treatment includes application of the pharmaceutical composition in the proximal fossa navicularis and the distal portion of the penile urethra proper. The high glycogen content and bacterial flora within the fossa navicularis provides a naturally lower pH within the space, so that lower pH compositions that provide for high solubility of alprostadil can be more easily tolerated without excess irritation of the tissues.

[0102] In the treatment of a disease, such as those mentioned above, it is sometimes necessary to pre-treat and/or post-treat an area of application, namely in transdermal administration. As mentioned above, alprostadil has a higher solubility at a lower pH. Therefore, lowering the pH of an application area with a pre-treatment and bringing the pH to a more natural level with a post-treatment is advantageous and desirable.

[0103] In one embodiment, a pre-treatment step is included, in which the area of application for the pharmaceutical composition is first contacted with a composition for pre-treating or preparation the area of application. By adding a pre-treatment step immediately before administering the pharmaceutical composition, absorption can be increased or decreased, which can allow for more control of the drug interaction and produce a more desired result. Possible pre-treatment methods include increasing or decreasing the temperature at the application area, sterilizing the application site, lowering or raising the pH, soaking the application site, which in some embodiments is a subject's tissue (Grasso & Lansdown, *Methods of measuring, and factors affecting, percutaneous absorbtion,* J. Soc. Cosmet. Chem. 23, 484-509).

[0104] In another embodiment, a post-treatment step is included. Furthermore, embodiments include one or more pre-treatment steps and one or more post-treatment steps. The post-treatment is an important step in reducing side effects, namely skin irritation in the case of topical application. Therefore, application of a post-treatment immediately after administration of a pharmaceutical composition typically decreases undesired effects.

[0105] For example, to combat side-effects of burning sensations or skin irritation, any of the following steps are taken: applying a topical vitamin E formulation (Nachbar & Korting, *The role of vitamin E in normal and damaged skin,* J. Mol. Med. 73:7-17 (1995)); rinsing the affected area with a basic soap and room temperature or cooler water to neutralize the pH, restore the area to ambient temperatures and dilute remaining drug compound (Grasso & Lansdown, *Methods of measuring, and factors affecting, percutaneous absorbtion,* J. Soc. Cosmet. Chem. 23, 484-509); application of topical immunosuppressant, such as hydrocortisone, to affected area; application of a topical analgesic, such as menthol, to the affected area (Galeotti et al, *Menthol: a natural analgesic compound,* Neuroscience Letters 322, 3:145-148 (April 2002)).

[0106] In some embodiments, the post-treatment is for sites or locations other than the pharmaceutical drug composition application site. For example, a common effect of alprostadil is irritation to skin, including hands. A subject who applies alprostadil for the treatment of sexual dysfunction must wash his or her hands after application to prevent irritation to his or her hands. Therefore, combining the pharmaceutical composition for treatment of sexual dysfunction and a post-application cleansing composition or object is desirable. In some embodiments, the post-application may be in the form of a moist tissue, which includes one or more compositions for treating irritation.

[0107] In one embodiment, the device includes a separate chamber and a separate dispenser for dispensing an anti-irritant cream. Examples of anti-irritants include but are not limited to: glycerin esters of fatty acids such as mono- or tri-glycerides of fatty acids, including their polyethylene glycol complex, polyethylene glycol or propylene glycol esters of fatty acids or vegetable oils; vegetable oils, including their hydrogenated form, such as sesame oil, soybean oil, castor oil, corn oil, palm oil, peanut oil, cacao oil, cotton seed oil, sunflower seed oil, safflower oil, almond oil or olive oil; fatty acids and fatty alcohols, and their esters, such as oleic acid, linolenic acid, linoleic acid, palmitic acid, palmitoleic acid, arachidonic acid, myristic acid, capric acid, caprylic acid, lauric acid, stearic acid, lauryl alcohol, oleyl alcohol, cetyl alcohol, stearyl alcohol, ethyl oleate, oleyl laurate, isopropyl myristate, isopropyl palmitate, 2-octyldodecyl myristate or cetyl palmitate; and a mixture thereof.

[0108] In another embodiment, for the treatment of nail fungus, the compositions to be applied include two part formulation that is sequentially applied, as described in U.S. Pat. No. 7,462,362 (Kepda et al.). In such an embodiment, the first part is a composition for quick penetration comprising an active ingredient, such as terbinafine and pharmaceutically acceptable carrier. The second part is a composition to act as

a protective barrier, comprising additional active ingredient for gradual penetration, an effective amount of film-forming polymer, and a pharmaceutically acceptable carrier.

[0109] In some embodiments, it is necessary for time passage between administration of a first product and administration of a second product.

[0110] As one skilled in the art would appreciate, the present device and components thereof can be made with nearly any dimensions, constructions, and materials suitable to practice the details of this disclosure and achieve the desired results.

EXAMPLE 1

Device and Method of Treatment of Male Sexual Dysfunction

[0111] In one embodiment for the treatment of male sexual dysfunction, two separate components of a pharmaceutically acceptable compound for the treatment of male sexual dysfunction are stored separately and mixed immediately prior to administration. In this embodiment, a reconstitution device stores, mixes, and applies the final composition. The device is constructed out of plastic and comprises an upper housing and lower housing. The conduit inside the upper housing forms two compartments. The first chamber and second chamber are designed according to the embodiment illustrated in FIG. **3**-FIG. **9**.

[0112] The first compartment includes an effective amount of the active ingredient, alprostadil in this example, and a diluent. The second compartment includes a pharmaceutically acceptable penetration enhancer, DDAIP.HCl (dodecyl-2-N,N-dimethylaminopropionate hydrochloride) in this example. The total volume of the combined compositions is approximately 1 cc.

[0113] The device is made for one time use; therefore, the compositions contained in the device are put into the respective compartments prior to a subject being giving the device.

[0114] This example contains a method of storing and mixing, whereby the two separate compositions are stored separately until mixing immediately prior to administration. Since the compositions are stable at room temperature when stored in separate compartments, there is generally no need to refrigerate the device and compositions. The compositions are then mixed immediately prior to application, which results in minimal degradation of the final pharmaceutical composition. In this example, the compositions of the two chambers are mixed thirty seconds prior to administration of the mixed composition, comprises is an effective amount of alprostadil for the treatment of sexual dysfunction. This example contains a method of treatment, where the male subject mixes the compositions immediately prior to administration and administered the composition to the urethra of the subject.

[0115] When a subject, who is typically the device user, desires to apply the pharmaceutical treatment, the subject presses down on the top of the device, where the surface of the plunger head is exposed to the external environment. Upon the user pushing down on the plunger head, the plunger is released from a locked position between two projections.

[0116] After being released from the locked position, the subject again applies downward pressure on the plunger head, which in turn engages the mixing components of the device. This pressure on the plunger rod causes movement of the second plunger and third plunger, thereby creating flow though the shearing channel and between the two chambers.

[0117] After the desired number of mixing cycles, four in this example, the upper housing and lower housing are separated and the mixture is exposed for use. The subject then dispenses the composition onto the subject's urethra.

EXAMPLE 2

Device and Method for Treatment of Nail Fungus

[0118] In one embodiment for the treatment of nail fungus, two separate pharmaceutical products are used and are administered sequentially. Furthermore, the pharmaceutical products are to be administered multiple times throughout the course of treatment.

[0119] In this embodiment, a reconstitution device stores, mixes, and applies the pharmaceutical products. The device is constructed out of plastic, has a upper housing and lower housing, two conduits, and one dispensing end.

[0120] The conduit inside the upper housing forms two compartments. The first chamber and second chamber are designed according to the embodiment illustrated in FIG. **3**-FIG. **9**.

[0121] The two compartments part of a cartridge. A first compartment includes a first composition comprising terbinafine and a pharmaceutically acceptable carrier. A second compartment includes a second composition comprising terbinafine, a film-forming polymer, and a pharmaceutically acceptable carrier.

[0122] The two compartments each contain two sub-compartments. In the first compartment, the first sub-compartment contains terbinafine in a diluent, and the second sub-compartment contains the pharmaceutically acceptable carrier. In the second compartment, the first sub-compartment contains terbinafine in a diluent, and the second sub-compartment contains the pharmaceutically acceptable carrier and a film-forming polymer.

[0123] The device and methods described herein may be combined with any suitable compositions and/or instructions for operation. It will be understood that the above described embodiment is for purposes of illustration only and that changes and modifications may be made thereto without departing from the spirit and scope of the invention.

We claim:

1. A method of mixing comprising:
filling a device with at least two compositions;
storing said at least two compositions; and
mixing said at least two compositions with said device.

2. The method of claim **1**, wherein said device comprises:
at least one housing element capable of containing at least two compositions;
and
at least one dispensing element for applying said at least two compositions.

3. The method of claim **1**, wherein said at least two compositions are mixed immediately prior to dispensing said at least two compositions.

4. The method of claim **1**, wherein said at least two compositions form a pharmaceutical composition.

5. The method of claim **1**, wherein the first composition of said at least two compositions is a pharmaceutically acceptable composition.

6. The method of claim **1**, wherein the first composition of said at least two compositions is a vasoactive agent.

7. The method of claim **1**, wherein a first composition of said at least two compositions is stored in a first compartment

and a second composition of said at least two compositions is stored in a second compartment prior to mixing.

8. The method of claim **1**, further comprising the step of administering said at least two compositions to a subject.

9. The method of claim **4**, wherein said pharmaceutical composition is administered through a route of administration selected from a group consisting of transdermal, intranasal, buccal, and rectal.

10. The method of claim **4**, wherein the temperature of said at least two compositions is changed immediately prior to administration.

11. The method of claim **4**, wherein said at least two compositions are mixed a predetermined amount.

12. The method of claim **4**, further comprising the step of administering a pre-treatment composition contained within said device to said subject immediately prior to administration of said at least two compositions.

13. The method of claim **4**, further comprising the step of administering a post-treatment composition contained within said device to said subject immediately after administration of said at least two compositions.

14. The method of claim **13**, wherein said post-treatment composition is an anti-irritant.

15. The method of claim **1**, wherein said at least two compositions comprise at least three compositions, whereby a first composition and second composition are mixed within said device, and subsequently, a third composition is mixed with said first composition and said second composition.

16. The method of claim **8**, wherein the amount of at least two compositions administered to said subject is selected from a predetermined range.

17. The method of claim **11**, wherein mixing is limited to said predetermined amount.

18. The method of claim **1**, wherein the said at least two compositions are stored in at least three compartments and an effective dosage of a pharmaceutical composition is selected by a device user who selects which said at least two compositions are mixed.

19. The method of claim **5**, wherein the effective dose is between approximately 100 mcg and 400 mcg of alprostadil.

18. The method of claim **1**, wherein an actuator is used to select the amount of a least one composition of said at least two compositions.

19. The method of claim **1**, wherein said at least two compositions are mixed with a shearing channel.

20. A method of treatment comprising:

mixing a pharmaceutical composition for the treatment of a condition in a subject immediately prior to administration; and

administering said pharmaceutical composition to a subject,

wherein said mixing occurs in a device and said device is used for said administration of said pharmaceutical composition to said subject.

21. A method of claim **20**, wherein said condition is nail fungus.

22. A method of claim **20**, wherein said condition is male sexual dysfunction.

23. A method of claim **22**, wherein said condition is erectile dysfunction.

24. A method of claim **22**, wherein said condition is premature ejaculation.

25. A method of claim **20**, further comprising a step of administering a pre-treatment composition immediately prior to administering said pharmaceutical composition.

26. A method of claim **20**, further comprising a step of administering a post-treatment composition immediately after administering said pharmaceutical composition.

27. A method of claim **20**, wherein said condition is female sexual dysfunction.

28. A method of treating sexual dysfunction comprising:

mixing a pharmaceutical composition for the treatment of sexual dysfunction in a subject immediately prior to administration; and

administering an effect amount of said pharmaceutical composition to a subject.

29. A method of claim **20**, wherein said pharmaceutical compositions is administered by a route of administration selected from a group consisting of transdermal, intranasal, buccal, and rectal.

30. A method of claim **20**, wherein said pharmaceutical compositions is administered to the urethra and urethral meatus for male sexual dysfunction; direct vaginal and/or clitoral application for female sexual dysfunction; intraoral application of a vaccine or oral care product; intranasal application of a vaccine or medicament; intra-aural application; or ophthalmic application of a medicament.

31. A method of claim **20**, where said pharmaceutical compositions is administered by injection.

32. A kit comprising:

a device for administration; and

a pharmaceutical product for the treatment of sexual dysfunction.

33. The kit of claim **32**, further comprising a contraceptive.

34. The kit of claim **33**, wherein said contraceptive is a condom.

35. The kit of claim **32**, wherein said pharmaceutical product is for the treatment of male sexual dysfunction.

36. The kit of claim **32**, wherein said pharmaceutical product is for the treatment of female sexual dysfunction.

* * * * *