

CONVENTION

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NOTICE OF ENTITLEMENT

We, **MINNESOTA MINING AND MANUFACTURING COMPANY** of 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427, United States of America state the following in connection with Australian Patent Application 34350/93:

1. We are the nominated person.
2. The nominated person is the assignee of the actual inventors.
3. The nominated person is the applicant of the basic application listed in the declaration under Article 8 of the PCT.
4. The basic application is the application first made in a convention country in respect of the invention.

DATED: 25 October, 1995

By **PHILLIPS ORMONDE & FITZPATRICK**
Patent Attorneys for the Applicant

By:

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To: The Commissioner of Patents

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- (56) Prior Art Documents
US 4023710
US 4664107
US 3560607
- (57) Claim

1. An aerosol valve including a valve ferrule, a valve stem and at least one valve seal in which the valve seal is impregnated with a physiologically acceptable surfactant.

12. A method for imparting lubricating properties to a valve seal for an aerosol valve or to the rubber material from which the valve seal will be formed which ^{includes} ~~comprises~~ contacting the valve seal or rubber material with a solution of a physiologically acceptable surfactant for a sufficient period for the surfactant to impregnate the valve seal or rubber.

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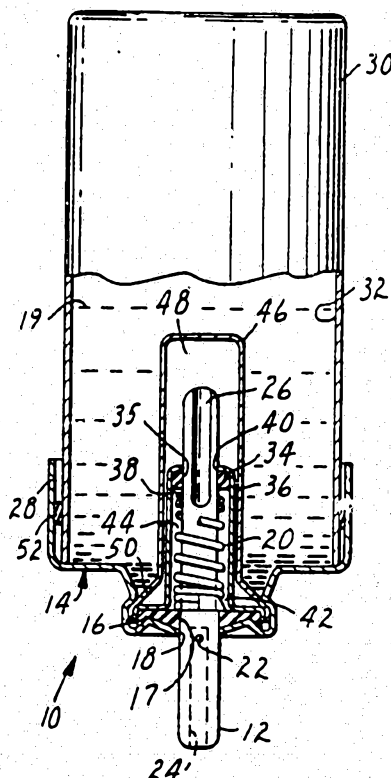
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(21) International Application Number: PCT/US93/00081 (22) International Filing Date: 6 January 1993 (06.01.93) (30) Priority data: 9200148.6 6 January 1992 (06.01.92) GB (71) Applicant (for all designated States except US): MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : GREENLEAF, David, J. [GB/GB]; 47 Outwoods Drive, Loughborough, Leicestershire LE11 3LS (GB). HOWARTH, Peter, H. [GB/GB]; 39 Waldemar Grove, Beeston, Nottinghamshire NG9 2BJ (GB). JINKS, Philip, A. [GB/GB]; 91 Rockhill Drive, Mountsorrel, Leicestershire LE12 7DS (GB).		(74) Agents: REEDICH, Douglas, E. et al.: Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US). (81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. 665233

(54) Title: AEROSOL VALVES

(57) Abstract

An aerosol valve having a valve ferrule, a valve stem (12) and at least one valve seal (16), in which the valve seal is impregnated with a physiologically acceptable surfactant. The valves of the invention exhibit improved force-to-fire and improved return force compared to valves containing untreated valve seals.



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AEROSOL VALVES

This invention relates to aerosol valves and to valve seals for use therein. The invention also
5 relates to a method of providing sustained lubrication to aerosol valves, particularly valves used for dispensing medicament to the respiratory system of a patient.

The use of aerosol devices to administer drugs or
10 other therapeutically active compounds by inhalation therapy is common. Aerosol dispensing containers are charged with a self propelling liquid composition containing the medicament dissolved or dispersed therein and provided with an aerosol valve capable of
15 discharging metered amounts of the composition. Such aerosol dispensing containers may be incorporated into a device including a breath actuated mechanism to synchronize dispensing of the medicament with inspiration by the patient. An example of such a
20 device is the AUTOHALER™ brand aerosol inhalation device (3M) disclosed, for example, in European Patent No. 147028.

Lubrication is an important factor in aerosol valves for use in inhalers. Lack of lubrication within
25 a valve can cause sticking and high friction between the valve seals and the valve stem. This requires high firing forces in order to actuate the valve which can cause difficulty for the patient to coordinate valve actuation and inhalation simultaneously. Lack of
30 lubrication within an aerosol valve may also result in slow return or non-return of the valve stem after actuation. Breath actuated devices require a smoothly functioning valve in order to ensure the proper function of the device.

35 The term "valve seal" used herein is used generically to refer to any of the seals employed within an aerosol valve and includes, but is not

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limited to, the diaphragm, tank seal and sealing member (parts 16, 34, and 52 of the valve shown in the accompanying drawing).

- Valve seals used in aerosol valves for inhalers
- 5 are generally subjected to a prolonged wash in a solvent, e.g., an aerosol propellant, such as Propellant 11 under reflux, in order to extract process oils and other additives which are present in the elastomer mix from which the valve rubbers are made.
- 10 The purpose of the extraction process is to remove any components from the valve seals which might be leached out by contact with the aerosol formulation in the container to which the valve is applied. The presence of such extracts in the aerosol formulation may produce
- 15 an unacceptable taste, may cause instability of the aerosol formulation or in an extreme case may be deleterious to the health of the patient.

- After the extraction process the valve seals are lubricated by a light wash in a solution of lubricant,
- 20 such as silicone, or surfactant, such as sorbitan trioleate. Such treatment has proved to be satisfactory in many cases, particularly when the valves are used with aerosol formulations containing surfactants in a sufficient amount to provide
- 25 supplementary lubrication to the valve rubbers during the life of the aerosol product. However, it has been found that such lubrication treatment is not effective for the lifetime of the aerosol product in cases where the aerosol formulations contain low levels of
- 30 surfactant or are surfactant free. The problem is particularly exacerbated when the propellant of the aerosol composition is a solvent for the lubricant or surfactant which has been applied to the valve rubber.
- Attempts to overcome this problem by washing with
- 35 concentrated solutions of lubricant or surfactant have not been successful since there appears to be no significant increase in lubrication above a certain

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concentration and higher concentrations tend to result in valve seals having sticky surfaces which can cause problems in assembly machinery used in the fabrication of the valves.

- 5 It has now been found that improved lubrication properties may be imparted to valve seals by impregnating the seals with a suitable surfactant.

Therefore according to the present invention there is provided an aerosol valve ~~comprising~~^{including} a valve
10 ferrule, a valve stem and at least one valve seal in which the valve seal is impregnated with a physiologically acceptable surfactant.

Also according to the invention there is provided a device ~~comprising~~^{including} an aerosol container containing a
15 self propelling aerosol formulation ~~comprising~~^{including} aerosol propellant and a medicament, the container being equipped with an aerosol valve.

It has surprisingly been found that by soaking valve seals for prolonged periods, e.g., at least 2
20 hours, preferably at least 4 hours, more preferably about 8 hours in a solution of surfactant the surfactant becomes absorbed or impregnates the rubber material. While not wishing to be bound by theory, it is believed the surfactant is impregnated into
25 interstices within the rubber which are formed when processing additives are extracted from the rubber and by the rubber swelling when immersed in the solvent.

Suitable surfactants include those previously employed in aerosol valves or aerosol formulations for
30 inhalation therapy. Anionic, cationic, and amphoteric surfactants are suitable. Suitable anionic surfactants include saturated and unsaturated fatty acids, preferably those containing from 10 to about 22 carbon atoms (such as oleic acid). Suitable nonionic
35 surfactants include anhydrosorbitol esters such as sorbitan trioleate. Suitable amphoteric surfactants include phosphatidyl cholines such as lecithin.



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Preferred surfactants include oleic acid and lecithin. Most preferred is sorbitan trioleate.

The solvent may be selected from those which are known to be non-toxic, a preferred solvent being

5 Propellent 11.

It has been found that the aerosol valves of the invention have improved lubrication compared with untreated valves. Accordingly the aerosol valves of the invention find particular utility when used in
10 connection with an aerosol formulation that contains less than an effective lubricating amount of surfactant. The improved lubrication properties often result in a significant reduction in the firing force compared with an untreated valve seal. Likewise a
15 significant increase in return force is often seen, which ensures the valve stem returns to the closed position without sticking. Compared to valves of the invention, valves having valve seals which are only lightly washed with a solution of surfactant lose the
20 improved properties relatively soon after the valve is put to use.

The valve seals, or rubber from which they are made, are preferably subjected to an extraction process prior to treatment to impart improved lubrication. The
25 extraction preferably comprises a continuous wash with Propellent 11 for at least 24, normally 48 or 72 hours, the Propellent 11 being provided in a constant stream after distillation and allowed to flow back into the reservoir.

30 The treatment with solution of surfactant may be conducted on the rubber material from which the valve seals are made, or the valve seals, optionally after the seals have been assembled on the valve stem. The valve seals may be fabricated from any of the rubber
35 materials used as seals for aerosol valves, e.g., nitrile and neoprene rubbers.

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The aerosol valves of the invention are particularly useful with aerosol formulations having low levels, e.g., levels of 0.3% by weight and below of surfactant and exhibit good lubricant properties with surfactant levels of 0.1% by weight and below and with formulations which contain no surfactant. It is preferred that formulations having no, or very low levels of surfactant, are based on propellents in which the surfactant impregnating the valve seal is substantially insoluble in order to prevent leaching out of the surfactant from the valve seal on prolonged contact with the formulation. Preferred propellents are selected from Propellent 11, Propellent 12, Propellent 114, Propellent 134a, and Propellent 227.

The aerosol valves of the invention are preferably incorporated into devices for delivery of medicament to the respiratory system of a patient. Generally, although not exclusively, the medicament will be selected for treatment of the respiratory system, e.g., for asthma therapy. Suitable medicaments include salbutamol, terbutaline, rimiterol, fenoterol, pirbuterol, adrenaline, isoprenaline, ipratropium bromide, theophylline, beclomethasone, betamethasone, budesonide, formoterol, cromoglycic acid and salts and esters thereof.

Aerosol valves for use in this invention ^{may include} ~~comprise~~ a valve stem, a diaphragm having walls defining a diaphragm aperture, and a casing member having walls defining a casing aperture, wherein the valve stem passes through the diaphragm aperture and the casing aperture and is in slidable sealing engagement with the diaphragm aperture, and wherein the diaphragm is in sealing engagement with the casing member.

Metered dose aerosol devices for use in this invention ^{may include} ~~comprise~~ in addition to the above discussed valve stem, diaphragm, and casing member, a tank seal having walls defining a tank seal aperture, and a



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metering tank of a predetermined volume and having an inlet end, an inlet aperture, and an outlet end, wherein the outlet end is in sealing engagement with the diaphragm, the valve stem passes through the inlet aperture and the tank seal aperture and is in slidable engagement with the tank seal aperture, and the tank seal is in sealing engagement with the inlet end of the metering tank, and wherein the valve stem is movable between an extended closed position, in which the inlet end of the metering tank is open and the outlet end is closed, and a compressed open position in which the inlet end of the metering tank is substantially sealed and the outlet end is open to the ambient atmosphere.

Figures 1 and 2 of the accompanying drawing illustrate the construction of ^{a preferred embodiment of} an aerosol valve.

Figure 1 is a partial cross-sectional view of one embodiment of a valve wherein the valve stem is in the extended closed position,

Figure 2 is a partial cross-section view of the embodiment illustrated in Figure 1 wherein the valve stem is in the compressed open position.

Figure 1 shows device (10) comprising valve stem (12), casing member (14), and diaphragm (16). The casing member has walls defining casing aperture (18), and the diaphragm has walls defining diaphragm aperture (17). The valve stem passes through and is in slidable sealing engagement with the diaphragm aperture. The diaphragm is also in sealing engagement with casing member (14).

Valve stem (12) is in slidable engagement with aperture (18). Helical spring (20) holds the valve stem in an extended closed position as illustrated in Figure 1. Valve stem (12) has walls defining orifice (22) which communicates with exit chamber (24) in the valve stem. The valve stem also has walls defining channel (26).



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In the illustrated embodiment casing member (14) comprises mounting cup (28) and canister body (30) and defines formulation chamber (32). The illustrated embodiment further comprises tank seal (34) having 5 walls defining tank seal aperture (35), and metering tank (36) having inlet end (38), inlet aperture (40), and outlet end (42). The metering tank also has walls defining metering chamber (44) of predetermined volume, e.g., 50 μ l. Outlet end (42) of metering tank (36) is 10 in sealing engagement with diaphragm (16), and valve stem (12) passes through inlet aperture (40) and is in slidable engagement with tank seal (34).

When device (10) is intended for use with a suspension aerosol formulation it further comprises 15 retaining cup (46) fixed to mounting cup (28) and having walls defining retention chamber (48) and aperture (50). When intended for use with a solution aerosol formulation retaining cup (46) is optional. Also illustrated in device (10) is sealing member (52) 20 in the form of an O-ring that substantially seals formulation chamber (32) defined by mounting cup (28) and canister body (30).

Operation of device (10) is illustrated in Figures 1 and 2. In Figure 1, the device is in the extended 25 closed position. Aperture (50) allows open communication between retention chamber (48) and formulation chamber (32), thus allowing the aerosol formulation to enter the retention chamber. Channel (26) allows open communication between the retention 30 chamber and metering chamber (44) thus allowing a predetermined amount of aerosol formulation to enter the metering chamber through inlet aperture (40). Diaphragm (16) seals outlet end (42) of the metering tank.

35 Figure 2 shows device (10) in the compressed open position. As valve stem (12) is depressed channel (26) is moved relative to tank seal (34) such that inlet

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aperture (40) and tank seal aperture (35) are substantially sealed, thus isolating a metered dose of formulation within metering chamber (44). Further depression of the valve stem causes orifice (22) to
5 pass through aperture (18) and into the metering chamber, whereupon the metered dose is exposed to ambient pressure. Rapid vaporization of the propellant causes the metered dose to be forced through the orifice, and into and through exit chamber (24).
10 Device (10) is commonly used in combination with an actuator that facilitates inhalation of the resulting aerosol by a patient.

A particularly preferred device for use in the invention is a metered dose configuration substantially
15 as described above and illustrated in the drawing. Other particular configurations, metered dose or otherwise, are well known to those skilled in the art are suitable for use with the sealing members of this invention. For example the devices described in U.S.
20 Patent Nos. 4,819,834 (Thiel), 4,407,481 (Bolton), 3,052,382 (Gawthrop), 3,049,269 (Gawthrop), 2,980,301 (DeGorter), 2,968,427 (Meshberg), 2,892,576 (Ward), 2,886,217 (Thiel), and 2,721,010 (Meshberg) involve a valve stem, a diaphragm and a casing member in the
25 general relationship described herein.

The invention will now be illustrated by the following Examples.

In the following Examples the rubber components (diaphragm and metering tank seal) were treated to
30 extract processing additives by continuous washing in Propellant 11 for 48 hours at room temperature.

Example 1

This Example used a 50 μ L metered dose dispensing
35 valve commercially available from 3M Health Care under the product code A14874. The valve comprises a diaphragm (top seal) of nitrile rubber commercially

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available from Avon and a metering tank seal of nitrile rubber commercially available from Kirkhill.

Two batches of valves were built using identical manufacturer's batch number components. The valve stems were washed for 5 minutes in 1% by weight dimethicone solution in Propellent 11 and allowed to dry. The valve seals of one batch were soaked in a 2% by weight solution of sorbitan trioleate in Propellent 11 for 8 hours.

The valves were applied to aerosol containers which were filled with a medicinal formulation commercially available under the trade mark Zeisin, comprising pirbuterol acetate, 0.3% w/w sorbitan trioleate and a propellant system 70 parts Propellent 12 and 30 parts Propellent 11. The force-to-fire and return force for each valve were measured:

	<u>Untreated Valve seals</u>	<u>Treated Valve seals</u>
Force to fire (N)	27.4	22.4
Return force (N)	6.6	8.0

This reduction in firing force was achieved through minimizing valve friction; the springs being identical in both batches.

This reduction in firing force was significant enough to allow the valve to be used in the AUTOHALER™ brand aerosol inhalation device.

Tests on the same valves showed that the initial low firing forces remained constant throughout the life of the unit.

Example 2

This Example used a 50 µL metered dose dispensing valve commercially available from 3M Health Care under the product code A66122. The valve comprises diaphragm

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and tank seals of nitrile rubber commercially available from Dowty.

Two batches of valves (9 in each batch) were assembled as in Example 1, the valve stems were not
5 treated and the valve seals of one batch were treated as in Example 1.

The valves were applied to aerosol containers which were filled with a medicinal formulation consisting of drug (0.24 mg/ml) and Propellant 134a.
10 The valves were tested immediately after preparation of the units and after 1 week:

	<u>Untreated</u> <u>Valve seals</u>		<u>Treated</u> <u>Valve seals</u>	
	<u>Force to</u> <u>Fire (N)</u>	<u>Return</u> <u>Force (N)</u>	<u>Force to</u> <u>Fire (N)</u>	<u>Return</u> <u>Force (N)</u>
15 Initial	27.8	2.1	22.5	5.7
20 1 week	26.6	did not return	22.3	4.6

25 It is noted that, in this case, a significant reduction in firing force and a large increase in return force was seen in the valves of the invention.

30 Example 3

The valves used were the same type as in Example 1. Two batches of valves were prepared in a similar manner to Example 1. One batch of valve seals (comparative) were washed in 1% by weight dimethicone
35 solution in Propellant 11 for 2 minutes and allowed to dry, the other batch (treated in accordance with the invention) was soaked in sorbitan trioleate as in Example 1.

The valves were applied to aerosol containers
40 which were filled with a medicinal formulation comprising beclomethasone dipropionate (100 µg/dose),

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0.5 mg/ml sorbitan trioleate and a propellant system consisting of 5% Propellant 11 and 95% of a 15:85 mixture of Propellant 114 and Propellant 12.

5	<u>Comparative Valve seals</u>	<u>Treated Valve seals</u>
Force to fire (N)	29.9	26.3
10 Return force (N)	6.4	6.8

Treatment is seen to decrease the force-to-fire
15 and increase the return force, both desirable attributes resulting from lower friction. In addition, the tendency for decreasing the return force during the life of the inhaler was less for the treated valve seals.

20

Example 4

Valves of the type used in Example 1 were used. The valve stems were washed and dried according to the general method of Example 1. The valve seals were
25 treated by soaking for 24 hours in a P11 solution containing 2 percent by weight of a surfactant listed in the table below.

The valves were crimped on to aerosol canisters containing HFC-134a or HFC-227 (as indicated) and
30 allowed to stand for three days before testing. In the table below, "Untreated" represents a control group wherein the valve seals were not treated. "P11" represents a control group wherein the valve seals were soaked for 24 hours in P11 alone. The other column
35 headings refer to the respective surfactants used to treat the valve seals. Each group contained 20 vials. "FTF" indicates force to fire the valve. "RF" indicates return force for the valve. Initial results and results after 25 doses are given in Newtons with
40 standard deviation in parentheses.

TABLE 1

Pro- pellant		Untreated		P11		Soya Lecithin		Span 85		Oleic Acid	
		FTF	RF	FTF	RF	FTF	RF	FTF	RF	FTF	RF
134a	Initial	28.05 (1.02)	6.62 (0.72)	33.59 (1.56)	543 (0.78)	27.95 (1.56)	5.13 (0.60)	25.82 (1.20)	7.83 (0.49)	25.87 (1.25)	7.72 (0.55)
	25 doses	27.87 (1.14)	6.80 (0.83)	33.36 (1.51)	5.36 (0.49)	28.80 (0.91)	5.37 (0.70)	24.92 (1.06)	8.24 (0.46)	25.77 (0.85)	7.84 (0.47)
227	Initial	27.95 (1.56)	5.32 (0.40)	32.68 (1.84)	2.69 (0.94)	24.58 (0.89)	5.73 (0.57)	24.22 (0.72)	7.22 (0.56)	25.19 (0.80)	5.87 (0.51)
	25 doses	28.67 (1.42)	4.67 (0.68)	32.58 (2.99)	1.48 (0.73)	24.77 (1.07)	5.67 (0.55)	23.48 (0.73)	7.26 (0.47)	25.47 (0.86)	5.31 (0.50)

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The table above shows that valve seals treated according to the invention with Span 85 or oleic acid show decreased force to fire and increased return force when used in connection with HFC-134a or HFC-227,

5 compared to the untreated control group. The valve seals treated according to the invention with lecithin showed decreased force to fire and increased return force compared to the untreated control group when used in connection with HFC-227 but not with HFC-134a. The

10 P11 group showed increased force to fire and decreased return force compared to control.

The claims defining the invention are as follows:

1. An aerosol valve including a valve ferrule, a valve stem and at least one valve seal in which the valve seal is impregnated with a physiologically acceptable surfactant.
5
2. An aerosol valve as claimed in Claim 1 in which the valve seal includes nitrile or neoprene rubber.
3. An aerosol valve according to Claim 1 wherein the surfactant is a C_{10} - C_{22} fatty acid, an anhydrosorbitol ester, or a phosphatidyl choline.
10
4. An aerosol valve as claimed in Claim 1 wherein the surfactant in the valve seal is sorbitan trioleate.
5. An aerosol valve according to Claim 1 wherein the surfactant is oleic acid or lecithin.
- 15 6. A device including an aerosol container containing a self propelling aerosol formulation including aerosol propellant having dissolved or dispersed therein a medicament, the container being equipped with an aerosol valve as claimed in Claim 1.
- 20 7. A device as claimed in Claim 6 in which the aerosol formulation contains less than an effective lubricating amount for an aerosol valve of a surfactant.
8. A device as claimed in Claim 6 in which the aerosol formulation includes less than 0.1% by weight of
25 surfactant.

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9. A device as claimed in Claim 6 in which the aerosol formulation is free of surfactant.

10. A device as claimed in Claim 6 in which the
5 surfactant impregnating the valve seal is substantially insoluble in the aerosol propellant.

11. A device as claimed in Claim 6 in which the propellant is selected from Propellant 11, Propellant
10 12, Propellant 114, Propellant 134a, Propellant 227, and mixtures thereof.

12. A method for imparting lubricating properties to a valve seal for an aerosol valve or to the rubber
15 material from which the valve seal will be formed which ^{includes} ~~comprises~~ contacting the valve seal or rubber material with a solution of a physiologically acceptable surfactant for a sufficient period for the surfactant to impregnate the valve seal or rubber.

20

13. A method as claimed in Claim 12 in which the solution is of a surfactant dissolved in Propellant 11.

14. A method as claimed in Claim 12 in which the
25 surfactant is a C₁₀-C₂₂ fatty acid, an anhydrosorbitol ester, or a phosphatidyl choline.

15. A method according to Claim 12 wherein the surfactant is oleic acid or lecithin.

30

16. A method according to Claim 12 wherein the surfactant is sorbitan trioleate.

17. A method as claimed in Claim 16 in which
35 sorbitan trioleate is present in a concentration of 2% by weight.

18. A method as claimed in claim 12 including the additional step of washing the valve seal or rubber material with a solvent prior to contacting with said solution.

5 19. An aerosol valve substantially as hereinbefore described with reference to the embodiment illustrated in the accompanying drawings.

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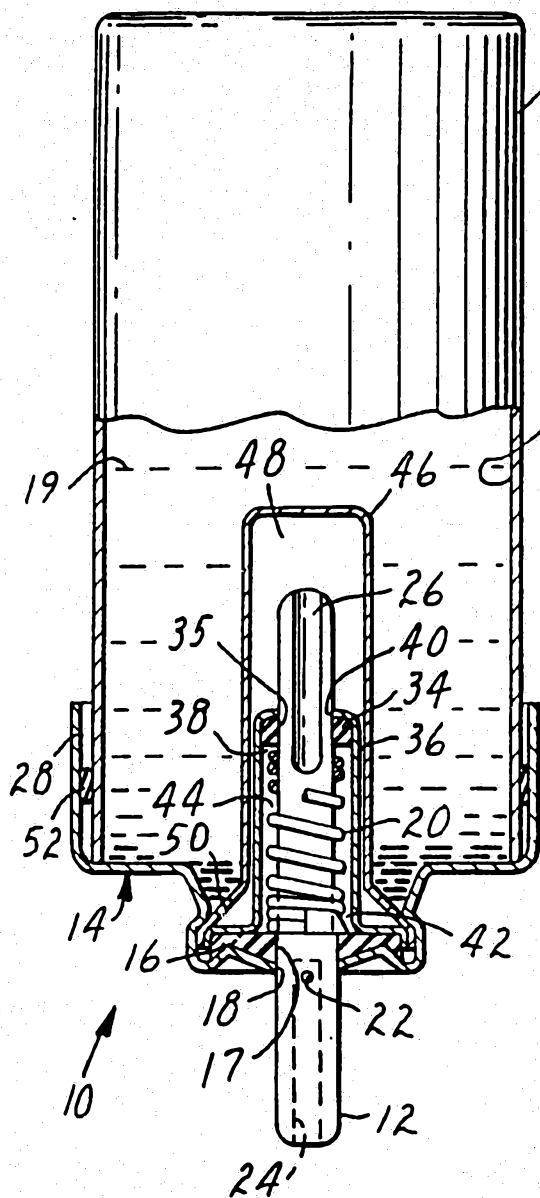


FIG. 1

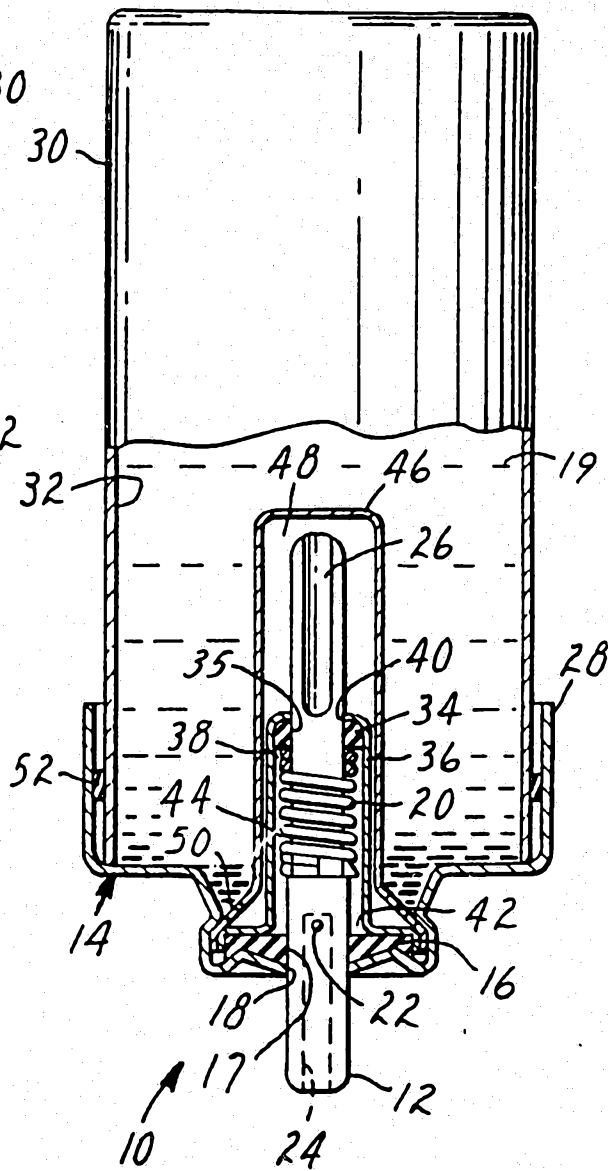


FIG. 2

INTERNATIONAL SEARCH REPORT

PCT/US 93/00081

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 B65D83/14		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	B65D ; A61M	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US,A,4 023 710 (ALEXANDER) 17 May 1977 see column 4, line 24 - column 5, line 10; figure 1 ---	1,2,6,12
A	EP,A,0 147 028 (RIKER LABORATORIES) 3 July 1985 cited in the application see page 4, line 14 - line 30; figure 1 ---	1,6,12
A	FR,A,2 528 060 (KENKYUYO) 9 December 1983 ---	
A	BE,A,654 599 (FISONS PHARMACEUTICAL LTD) 20 April 1965 -----	
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
07 APRIL 1993		
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		MARTENS L.G.R.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9300081
SA 68916

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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07/04/93

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		FR-A- 2155428	18-05-73
		NL-A- 7213272	02-04-73
		SE-B- 381190	01-12-75
EP-A-0147028	03-07-85	AU-B- 578915	10-11-88
		AU-A- 3558384	22-05-85
		CA-A- 1236359	10-05-88
		DE-A- 3470844	09-06-88
		JP-T- 61500254	20-02-86
		WO-A- 8501880	09-05-85
		US-A- 4664107	12-05-87
FR-A-2528060	09-12-83	None	
BE-A-654599	20-04-65	DE-B- 1208036	
		FR-M- 3384	
		GB-A- 1063512	
		NL-A- 6412459	27-04-66
		US-A- 3560607	02-02-71