United States Patent

[11] 3,604,417

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[54] **OSMOTIC FLUID RESERVOIR FOR OSMOTICALLY ACTIVATED LONG-TERM CONTINUOUS INJECTOR DEVICE**
2 Claims, 2 Drawing Figs.

[52] U.S. Cl. ..... 128/213, 128/225, 128/260, 128/218 R, 128/218 A, 222/389
[51] Int. Cl. A61m 05/00
[50] Field of Search ..... 128/213, 214, 215, 216, 218 R, 218 A, 218 P, 225, 260, 261, 1; 222/389, 399; 169/7, 27, 32, 33; 3/1

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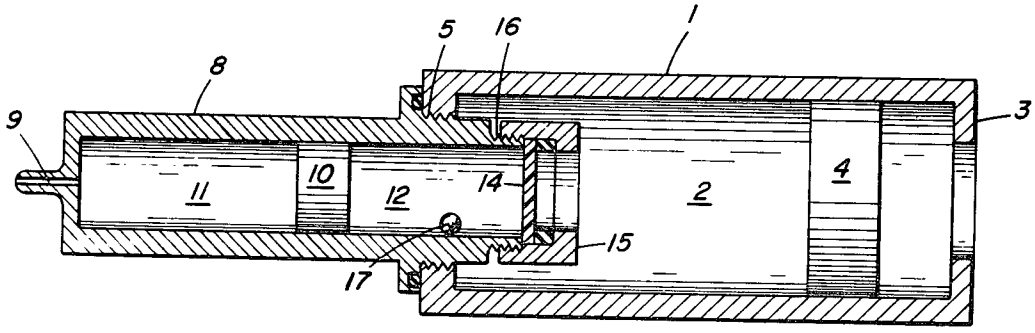
Primary Examiner—Dalton L. Truluck
Attorney—Norton S. Johnson

ABSTRACT: An improved osmotic pressure actuated injection device for long term continuous injection which has a chamber filled with the medicament to be injected and a suitable injection orifice, with a piston or similar device, the other side of he piston being a concentrated solution, such as a saturated solution, caPped with a semipermeable membrane and exposed to a second chamber having the solvent for the solution, and a freely movable piston exposed on its other side to atmospheric pressure or similar source so that the solvent moves through the semipermeable membrane increasing the osmotic pressure and so forcing the piston in the first chamber to discharge a small amount of medicament. The pressure in the solvent chamber is maIntained constant, thus preventing formation of air pockets therein.



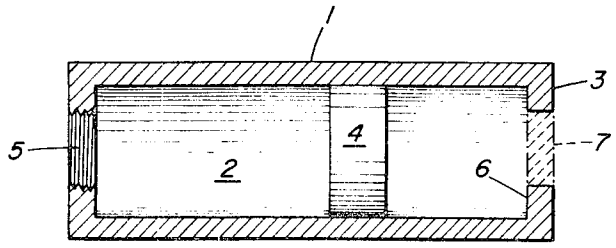


FIG. 1

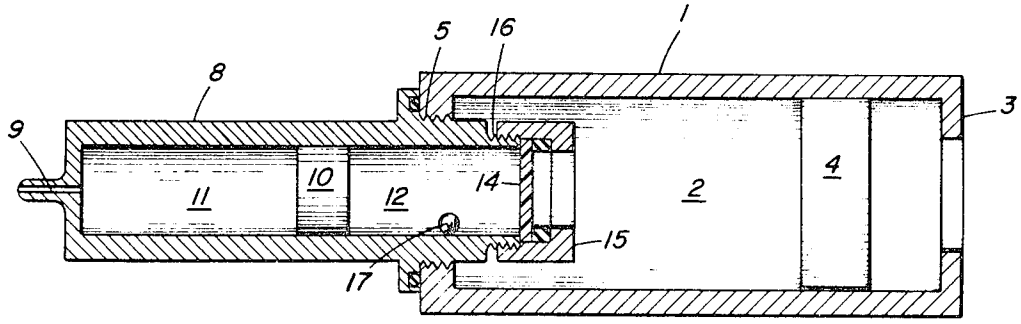


FIG. 2

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OSMOTIC FLUID RESERVOIR FOR OSMOTICALLY ACTIVATED LONG-TERM CONTINUOUS INJECTOR DEVICE

BACKGROUND OF THE INVENTION

Long-term, continuous injector devices have been developed for gradual administration of medicaments over a considerable time, such as the administration of anticancer agents, long continued administration of contraceptive drugs, and like, using gas pressure from electrolytic decomposition of water, which is not accurate, and also those that have been actuated by osmotic pressure. Normally the osmotic pressure devices have been supplied with flexible reservoirs, such as plastic bags and the like, and this has caused considerable problems, not only from the standpoint of size which makes it unsuitable for implanting in a patient and particularly in veterinary cases in an animal, but also, the tendency of air or gas bubbles to form as the solvent flows out of the reservoir into the concentrated or saturated solution has resulted in a lowering of pressure so that the final pressure on the medicament became insufficient.

SUMMARY OF THE INVENTION

The present invention utilizes an orifice, chamber with a piston in it containing medicament, and on the other side of the piston a concentrated or saturated solution as has been used before. However, instead of a bag containing the osmotic solvent, this is contained in another chamber which screws onto the first chamber, of course being separated from the osmotic pressure solution by a conventional semipermeable osmotic membrane, and it also contains a piston which can freely slide, the other side of the piston either being connected to atmospheric pressure or to some other constant gentle pressure so that as the osmotic solvent gradually passes through the semipermeable membrane the piston slides and prevents formation of any gas voids. Atmospheric pressure is a very desirable and simple form of maintaining the piston in continuous contact with the osmotic solvent; however, other things, such as springs or other devices, may be used.

Since the two chambers are rigid, usually of a metal or strong plastic, the operation is independent of movements of a human or animal in whom it is implanted or to whom it is attached, and this is a very important characteristic, which maintains the pressure on the osmotic solution constant for long periods of time (for example as long as 1 month or more). This assures a continuous maintenance of an unbroken layer of osmotic solvent across the membrane surface regardless of the position of the subject and no gas voids can form in the reservoir, which automatically and continuously adjusts its volume by the movement of the piston to compensate for the diminishing volume of reservoir solvent during operation of the device. A long continued, gradual release of medicament, which can be at a rate as low as 0.12 ml. per day, can be maintained, and the device of the present invention therefore avoids all of the disadvantages or drawbacks of the osmotic pressure actuated injectors used hitherto.

The nature of the material of which the two chambers are formed and of the pistons is not critical. Of course the chambers must be of a material which is compatible with mammalian tissue if it is to be implanted, but otherwise any material which is sufficiently strong to maintain its shape and free-sliding fits for the two pistons may be used. For many uses, particularly where the device is attached to the patient or animal, atmospheric pressure to maintain a constant pressure on the osmotic solvent is the simplest and cheapest.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a section through a chamber containing the osmotic pressure solvent, and

FIG. 2 is a similar section showing the osmotic solvent chamber screwed onto the medicament dispensing chamber.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments will be described first generally in conjunction with the drawing followed by some specific examples giving the details of the loading and use of the instrument.

FIG. 1 shows the osmotic pressure solvent chamber at 1 with one chamber 2 filled with the osmotic pressure solvent and a sliding free piston 4 which is capable of sliding in the circular device. Lips 3 prevent the piston from leaving the chamber.

The chamber 2 has a threaded outlet 5 at one end, and in the modification shown in FIG. 1 an outlet to the atmosphere on the other end of the device, the chamber 6, which is on the other side of the piston 4. Connection to the atmosphere can be through any suitable conduit, such as a flexible elastomer if the device is embedded in the patient or animal. If it is desired to have a closed device, the end of the chamber 3 is closed, as is shown in dashed lines as an optional structure 7.

FIG. 2 shows the threaded opening 5 from the chamber 2 screwed onto external threads on a medicament dispensing vessel 8. This dispensing vessel contains a freely sliding piston 10, and a dispensing orifice 9 to which can be connected a short piece of hypodermic needle, a plastic or silastic tubing or similar device. The piston divides the device into two chambers, 11 and 12. The former is filled with the medicament which is to be gradually injected over a long period and the chamber 12 contains a concentrated solution of a suitable osmotic pressure developing solution, for example one constituting a saturated solution of the dyestuff Congo Red, (3,3'-[4,4'-biphenylenebis (azo)]bis (4-amino-1-naphthalene sulfonic acid, disodium salt). Continued saturation is provided by having some of the material present in solid form, not shown.

The chamber 12 at the end opposite the piston 10 is closed by a semipermeable membrane 14 which is clamped tightly against the end of the chamber by the clamping member 15 which shows onto a threaded shoulder 16. In the chamber 2 there is the same solvent which is used to form the solution in the chamber 12. The nature of the particular solvent is not critical as it is not contacted with the medicament or with the tissues of the patient or animal, and it may be any suitable, stable liquid. In the case of the Congo Red solution, water is a very suitable solvent. In chamber 2 water is present or, if desired, a much more dilute solution of the Congo Red. In addition to the solids mentioned above in the chamber 12, a ball of metal or noncorrodible material, such as ceramic, 17 may be provided, which will keep the saturated Congo Red solution dispersed as a result of the normal movements of the patient or animal which causes the ball to move around and to stir the solution in chamber 12 gently.

As osmotic pressure slowly and gradually builds up in chamber 12, the piston 10 moves and displaces an equal amount of medicament in chamber 11 through the orifice 9. The volume of chamber 12 of course increases as a result of the osmotic flow of solvent from chamber 2 through the semipermeable membrane 14, and a constant gentle pressure is therefore maintained on the piston 10, which results in a very slow and continuous injection of the medicament. As solvent, such as water, passes out from chamber 2 through the semipermeable membrane 14, the piston 4 moves in slightly, under atmospheric pressure in the case of this modification, or under pneumatic pressure where a closed chamber is utilized. The chamber 2, therefore, cannot develop any gas voids and there is maintained therein a gentle pressure suitable for continuous passage of solvent through the membrane. It will be noted that the piston 4 always assures that there is a constant liquid layer at the interface between the semipermeable membrane 14 and the osmotic pressure solvent in the chamber 2, and this is maintained regardless of the position of the patient or the animal in or on which the injection device is mounted.

After a long period of continuous injection, the medicament in the chamber 11 becomes exhausted and the device can then

be removed from the patient or animal and after suitable cleaning and resterilizing, refilled with medicament and osmotic pressure solvent.

Where the host is immobilized it may be desirable to actuate the magnetized balls in the Congo Red compartment **12**. To this end there may be provided a microtiming device, connected to two small magnets spaced exteriorly of the injector and at opposite ends of compartment **12**, shown in FIG. **2**. At timed intervals the balls are thus caused to roll from one end of the compartment to the other causing agitation of the Congo Red solution suspension.

EXAMPLE 1

A 2½ cc. plastic disposable syringe manufactured by Becton-Dickinson, was cut off at the 2 cc. mark. The plastic handle of the piston was removed and the remaining rubber plug was placed so that the syringe would hold a volume of 1 cc. of medicament. The remainder of the syringe contained about 0.8 gm. Congo Red and two stainless steel balls. This was covered by a sheet of semipermeable membrane obtained from a Visking dialysis sac. The membrane covered this opening tightly and the ends were folded back securely. A hollow cylinder obtained from a 5 cc. syringe of the same type, cut between the 0 and 3 cc. marks, was inserted over the ends of the semipermeable membrane. An airtight seal was made between the two plastic syringes with Dow-Corning medical grade Elastomer. The Elastomer hardened with a few minutes and supported the semipermeable membrane as well. At the other end of the cylinder the rubber plug from the 5 cc. syringe was inserted and the opening behind the plug was covered with a plastic cap with a small opening in the center. The plastic cap was sealed in place behind the 5 cc. syringe with Elastomer.

To activate the device, two hypodermic needles were inserted through the plastic walls on each side of the semipermeable membrane. These were filled with distilled water so as to exclude air bubbles on either side. The holes caused by the hypodermic needles were sealed with elastomer. The compartment designed to hold the medicament was filled with a 0.1 percent methylene blue solution by means of a thin caliber hypodermic needle inserted through the opening.

The device successfully constructed was tested in an *in vitro* system. It was warmed at 37° C. in a water bath contained in a Dubnoff shaker. The entire 1 cc. of methylene blue was expelled within 2¾ to 3 hours. When a plastic ring was glued next to the semipermeable membrane such that the diameter of the membrane exposed to fluids was about 3 mm., less than 1 cc. of the methylene blue solution was injected after a week. It was about 0.12 cc. of solution was expelled per day. The decline in volume of methylene blue could be observed from day to day.

EXAMPLE 2

It should be emphasized that a high purity Congo Red, free of contaminating ions or compounds of low molecular weight, is essential, Contaminating molecules diffuse across the semipermeable membrane and nullify or reduce the effective osmotic gradient.

The device is constructed as shown in FIG. **2** However, a 15 percent solution suspension of Congo Red is used. In our recent experiments higher concentrations tended to congeal and eventually appeared gelatinous. The Congo Red compartment was filled and five stainless steel balls of about 1.5 mm. diameter were added. The compartment was covered with a Visking semipermeable membrane with a thickness of 0.0008 inch. The water compartment obtained from a 5 cc. syringe was sealed in place as previously described, using Caulk Grip dental cement instead of Elastomer. Two drops of distilled water was added and the water compartment was covered with the rubber plunger from the 5 cc. syringe for storage before use.

To activate an injector device, the rubber plunger was removed and the water compartment filled with distilled water. A 24-gauge hypodermic needle was inserted through the plunger. The plunger was reinserted into the 5 cc. syringe, allowing the excess water to flow out through the hypodermic needle. Both the Congo Red and water compartments were free of air bubbles. The opening behind the plug was covered with a snugly fitting plastic cap with an opening in the center measuring about 3 mm. in diameter. The medicament compartment was filled with water.

Two *in vitro* experiments were carried out in a Dubnoff shaker by placing the devices in a water bath at 37° with mild but continuous agitation. The results obtained with six injector devices are listed in table **1**. Two injector devices were fastened on the backs of two sheep in an area previously shaved to remove the wool. The devices were held in place with adhesive tape and branding cement. The results are shown in table 2.

TABLE 1

Day	Time	Injector No. 1 [1]	2 [1]	3 [1]
1	0915	1.00	1.05	1.05
	1020	0.93	0.95	0.95
	1235	0.65	0.73	0.73
	1500	0.45	0.53	0.52
	1600	0.40	0.45	0.43
	1700	0.35	0.40	0.38
2	0835	0.00	0.00	0.00
		4 [1]	5 [1]	6 [1]
1	0900	1.03	1.03	1.03
	1030	0.95	0.90	0.88
	1115	0.85	0.83	0.78
	1215	0.75	0.70	0.67
	1325	0.65	0.63	0.58
	1520	0.50	0.50	0.45
	1630	0.45	0.43	0.37
2	0830	[2] 0.15	0.00	0.00

[1] Ml. solution remaining in medicament compartment.
[2] There was a large bubble in water compartment observed at this time which probably interferred with osmosis.

TABLE 2.—ACTION OF A CONTINUOUS INJECTOR CARRIED ON A SHEEP'S BACK

Day	Time	Injector No. 1 [1]	2 [1]
1	1100	1.05	1.05
	1215	0.90	0.90
	1320	0.82	0.80
	1430	0.75	0.75
	1530	0.70	0.70
	1630	0.60	0.60
2	0830	0.00	0.00

[1] Ml. solution remaining in medicament compartment.

We claim:

1. In a continuous, long-term injector device, which comprises a hollow member with injection orifice at one end adapted for connection with body tissue, a slidable piston in the member dividing it into first and second chambers and a semipermeable membrane across the end of said second chamber, the second chamber being filled with an osmotic pressure developing solution and the **69** chamber containing a medicament, the improvement which comprises,

a. a second hollow member serving as a reservoir for osmotic pressure solvent and provided with a freely sliding piston,

b. screw-threaded means securing the reservoir onto the hollow member of the injector device to maintain continuous contact of the osmotic pressure solvent with the semipermeable membrane, and

c. means for exposing the side of the sliding piston in the reservoir out of contact with solvent to a source of at least ambient pressure.

2. A injector device according to claim 1 in which the source of at least ambient pressure is the atmosphere.

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,604,417 Dated September 14, 1971

Inventor(s) Sidney Joseph Stolzenberg & Wayne Henry Linkenheimer

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Abstract of the Disclosure, line 5, "he" should read -- the --.

Abstract of the Disclosure, line 6, "caPped" should read -- capped --.

Abstract of the Disclosure, line 13, "maIntained" should read -- maintained --.

Column 1, line 12 "and like" should read -- and the like --.

Column 2, line 38 "shows" should read -- screws --.

Column 3, line 3 after "medicament" insert -- and osmotic pressure developing solution --.

Column 3, line 59 "," should read -- . -- after essential.

Column 4, line 67 "69" should read -- first --.

Signed and sealed this 18th day of April 1972.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents

FORM PO-1050 (10-69)

USCOMM-DC 60376-P69
* U.S. GOVERNMENT PRINTING OFFICE : 1969 O—366-334