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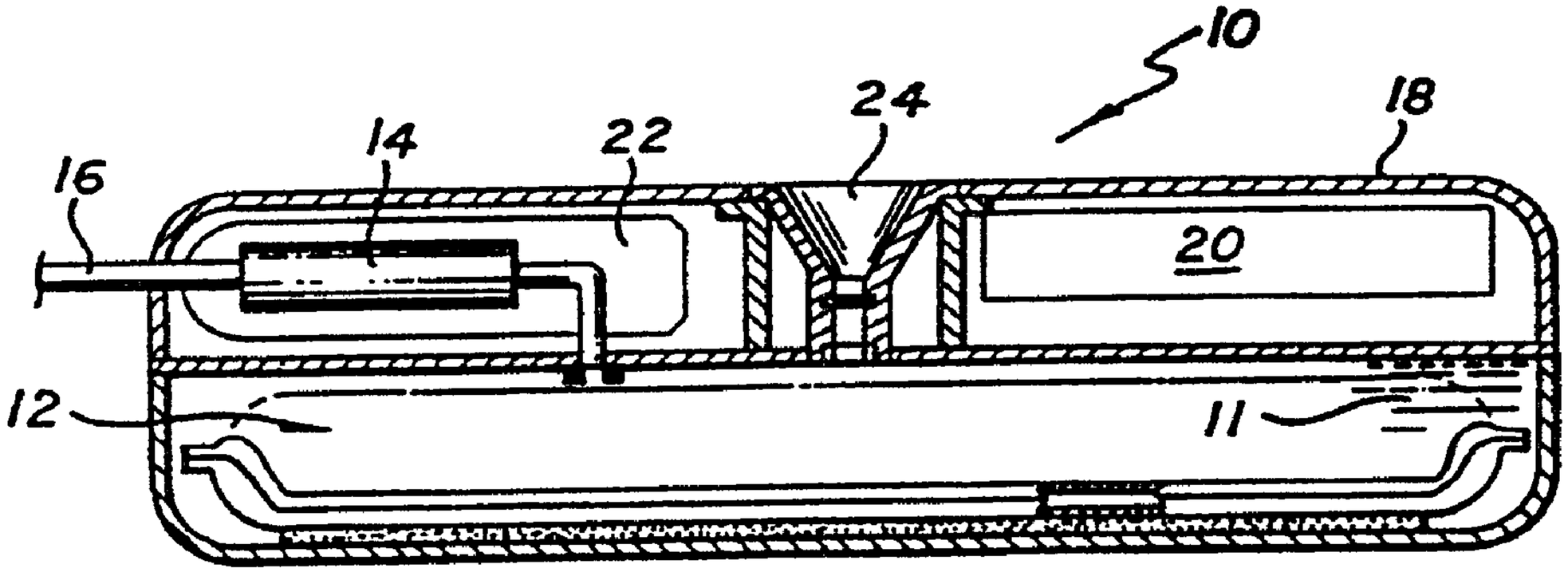
(54) Titre : POMPE SERVANT DIFFUSER UN PRODUIT MEDICAMENTEUX ET COMPORTANT UN REVETEMENT DE SURFACE CONTRE LES DEPOTS PROTEINES

(54) Title: MEDICATION INFUSION PUMP WITH PROTEIN STABILIZED SURFACE COATING



(57) Abrégé/Abstract:
A medication infusion pump is provided for use in the delivery of a selected medication to a patient, wherein the pump includes internal surface coatings defining protein stable surfaces. In accordance with the invention, hydrophilic internal surfaces and related coating methods are provided to reduce or eliminate accumulation of medication deposits which can otherwise occur when handling complex protein-based medication. Preferred hydrophilic pump surfaces include hydrophilic surfactants (PEO) or (PEG) coatings which exhibit very low protein adsorption characteristics. Several methods are disclosed for producing such coatings, including direct surface modification, covalent and noncovalent attachment of polymers, and covalent attachment through a saline primer.

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(54) **Title:** MEDICATION INFUSION PUMP WITH PROTEIN STABILIZED SURFACE COATING

(57) **Abstract**

A medication infusion pump is provided for use in the delivery of a selected medication to a patient, wherein the pump includes internal surface coatings defining protein stable surfaces. In accordance with the invention, hydrophilic internal surfaces and related coating methods are provided to reduce or eliminate accumulation of medication deposits which can otherwise occur when handling complex protein–based medication. Preferred hydrophilic pump surfaces include hydrophilic surfactants (PEO) or (PEG) coatings which exhibit very low protein adsorption characteristics. Several methods are disclosed for producing such coatings, including direct surface modification, covalent and noncovalent attachment of polymers, and covalent attachment through a saline primer.

MEDICATION INFUSION PUMP WITH PROTEIN STABILIZED SURFACE COATING

BACKGROUND OF THE INVENTION

This invention relates generally to medication infusion pumps, particularly of the type adapted for implantation directly into the body of a patient and for programmed operation to deliver medication to the patient. More particularly, this invention relates to an improved medication infusion pump having one or more internal hydrophilic surfaces to minimize or eliminate accumulation of medication deposits from complex protein-based medications.

Medication infusion pumps are generally known in the art for use in delivering a selected medication to a patient in a scheduled or preprogrammed manner. In recent years, infusion pumps have been developed in compact form and adapted for direct implantation into a body of a patient, to deliver a specific medication such as insulin to the patient in discrete doses over an extended time period. An implantable infusion pump of this general type includes an internal medication chamber for receiving and storing a supply of the selected medication in liquid form, in combination with a miniature pump mechanism and associated programmable control means for operating the pump mechanism to deliver discrete doses of the medication from the internal storage chamber and through a catheter to the patient. For one illustrative example of an implantable medication infusion pump of this general type see, U.S. Pat. No. 4,573,994, to Fischell et al.

The internal pump mechanism typically comprises an electromagnetically driven pulsatile pump having a solenoid operated piston mounted for reciprocation within a cylinder to draw medication from the internal storage chamber, and to deliver such medication through the catheter to the patient. The pulsatile pump operates in conjunction with an inlet check valve having a spring-loaded valve member movable between open and

closed positions with respect to an annular valve seat. The valve member and valve seat are normally constructed from biocompatable and relatively inert materials, such as a movable valve disk of a silicone elastomer material and a rigid annular valve seat defined at the end of a ferrule formed of a titanium or titanium alloy. For examples of pulsatile pump mechanisms used in implantable infusion pumps, see U.S. Pat. No. 4,568,250, to Falk et al.; U.S. Pat. No. 4,569,641 to Falk et al.; U.S. Pat. No. 4,636,150, to Falk et al.; and U.S. Pat. No. 4,714,234, to Falk et al.

Implantable medication infusion pumps of the general type described above have been used to deliver a wide variety of drugs to a patient. Such medications or drugs include, for example, insulin, baclofen, morphine, various antibiotics, and a number of chemotherapeutic agents. As protein-based medications become more prevalent, problems arise in reliable long-term administration of the medication to a patient. More specifically, regular drug injections are not optimal to achieve relatively constant blood concentration levels. Many of the newer medications comprise relatively complex protein-based substances having a high molecular weight, such that subcutaneous drug delivery can be problematic due to decreased or minimal uptake by either the capillary or omental systems. Implantable pumps for intraperitoneal or intravascular delivery resolve many of these concerns, particularly wherein the medication needs to be delivered to the patient on a regular basis for a prolonged period of time, such as one year or longer.

One problem encountered with implantable medication infusion pumps is that internal pump surfaces are typically constructed from titanium or similar metal materials. Such metallic surfaces have oxide coatings that render them hydrophobic, with typical free surface energies on the order of about 40 dyne/cm^2. At this low free surface energy, protein-based medications such as insulin can be adsorbed quite readily and can easily denature on the pump surfaces. Once denaturing occurs, the protein-based substance can aggregate to a form that is generally not bio-available to the patient and may in some cases lead to undesired immunological response.

The present invention provides an improved medication infusion pump having an internal surface coating or coatings that are hydrophilic, resulting in pumps surfaces that are highly stable in the presence of complex protein-based medications.

SUMMARY OF THE INVENTION

In accordance with the invention, a medication infusion pump is constructed with one or more internal hydrophilic surfaces for contacting complex protein based medications delivered by the pump to a patient. The use of such hydrophilic internal pump surfaces is particularly advantageous in a medication infusion pump of the type adapted for implantation into the body of a patient, and for programmable or otherwise regulated delivery of the medication to the patient over a prolonged period of time. The hydrophilic pump surfaces have been found to be particularly stable in the presence of protein based medications, thereby minimizing or eliminating undesired denaturing of the medication and/or related accumulation of aggregative deposits.

Various embodiments of this invention provide a medical device having a surface in contact with a protein based medication characterised in that said surface is treated to have a polyethylene glycol/polypropylene glycol copolymer covalently attached thereto so that the surface having the copolymer covalently attached thereto has a surface contact angle less than 45 degrees.

Other embodiments of this invention provide a method of treating a surface for use in a medical device having a surface contactable by a protein based medication, the method comprising covalently attaching to the surface a polyethylene glycol/polypropylene glycol copolymer so that the surface having the copolymer covalently attached thereto has a surface contact angle less than 45 degrees.

The surface in the above-described medical device and method may exhibit a protein adsorption profile of less than 1.0 microgram per square centimeter.

Other features and advantages of the present invention will become more apparent from the following detailed description, taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings illustrate the invention. In such drawings:

FIGURE 1 is a perspective view depicting a typical implantable medication infusion pump; and

FIGURE 2 is an enlarged and somewhat schematic vertical sectional view of the pump of FIG. 1, and illustrating an internal pump

mechanism for delivering medication from a medication storage reservoir to a patient.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As shown in the exemplary drawings, an implantable medication infusion pump referred to generally by the reference numeral 10 is provided for use in administering a selected medication to a patient in a controlled, preprogrammed manner. In accordance with the invention, the medication infusion pump 10 includes one or more internal pump surfaces bearing a hydrophilic coating or otherwise treated to exhibit hydrophilic characteristics, which have been found to substantially reduce or eliminate accumulation of undesired medication deposits particularly when the pump is used to deliver complex protein based medications such as insulin and the like. The hydrophilic internal pump surfaces have been found to significantly reduce and/or eliminate undesired adsorption of proteins on internal pump surfaces.

The medication infusion pump 10 shown in the illustrative drawings has a generally conventional overall construction and operation for delivering a selected medication 11 from an internal medication chamber or reservoir 12 (FIG. 2) through a catheter 16 to the patient. Medication delivery is accomplished by a miniature pump mechanism 14. In accordance with the present invention, surfaces of the medication chamber 12 and/or internal surfaces of the pump mechanism 14 include hydrophilic coatings to prevent adsorption of proteins and resultant accumulation of protein based medication deposits thereon.

FIGURES 1 and 2 show the medication infusion pump 10 in the form of a small substantially self-contained unit adapted for direct implantation into the body of a patient. The pump 10 comprises an hermetically sealed pump housing or case 18 formed from a biocompatable material, such as titanium or titanium alloy. The pump housing defines the internal medication reservoir 12 for receiving and storing the supply of the selected medication 11

in liquid form, such as insulin for a diabetic patient. The pump housing 18 encases the internal pump mechanism 14 in combination with electronic control circuitry 20 and a battery 22 for periodically operating the pump mechanism 14 to deliver medication doses via the catheter 16 to the patient. The control circuitry 20 is suitably preprogrammed to deliver the medication in accordance with individual patient need. An inlet or refill fitting 24 on the pump housing 18 is adapted to receive a hypodermic needle (not shown) to permit transcutaneous refilling of the medication chamber 12 without requiring surgical access to the infusion pump 10.

For a more detailed description of the overall construction and operation of implantable infusion pumps of this general type, see U.S. Patent 4,373,527 and 4,573,994.

For a more detailed description of the construction and operation of the miniature pump mechanism 14, see U.S. Patents 4,568,520; 4,569,241; 4,636,150; and 4,714,234.

The adsorption and subsequent denaturation of the protein-based medication on a surface does not usually depend on the exact chemical nature of the surface but instead is functionally related to its surface free energy. Accordingly, the present invention relates to an infusion pump wherein key internal surfaces are coated to achieve a significant reduction in surface contact angle. Several surface treatment methods can be used to accomplish this objective, including hydrophilic surfactants, non-covalent bonding, covalent bonding, and direct modification of the pump surface.

In accordance with a preferred surface treatment and method, a hydrophilic surfactant is applied to the selected pump surface to significantly reduce adsorption of a protein-based medication such as insulin. Several hydrophilic surfactants are available for this purpose, including but not limited to Genapol,* a block ethylene/propylene copolymer having a molecular weight of about 1800 Daltons and including a polyethylene glycol (PEG) moiety as its hydrophilic segment, available from Hoechst Celanese Co. of Somerville, New Jersey. Other hydrophilic surfactants include Tween*, a polyoxyethylene sorbitan available from Sigma Biochemicals of St. Louis, Missouri, and Brij*,

*Trade-mark

a polyoxyethylene ether also available from Sigma Biochemicals of St. Louis, Missouri. These hydrophilic surfactants include a polyethylene glycol (PEG) moiety as their hydrophilic segment and are generally biocompatable with medications such as insulin.

As one example using a hydrophilic surfactant, a 1.0% solution of Genapol*is prepared in isopropanol and then contacted with the selected titanium pump surface, such as the titanium surface of the medication reservoir 12 by filling the reservoir with the Genapol*solution. The Genapol* surfactant which is non-ionic in nature binds to the titanium surface, and the isopropanol solvent can be readily removed under mild conditions of heat and vacuum. After this drying step, the treated titanium surface is placed in a radio frequency (RF) chamber in the presence of oxygen, argon, or both, and 100-200 watts of RF power are applied to result in covalent attachment of the polymer to the titanium surface. Preferably, this process is repeated at least once. An exemplary RF chamber is available from Technics, Inc. of Newark, New Jersey. During the RF treatment step, the oxygen and/or argon plasma generates significant ultraviolet light which creates reactive polymer sites which then covalently attach to the surface. In the illustrative example, each RF step proceeded for about 10 minutes using an RF frequency of about 100 KHz.

After this surface treatment with the Genapol*surfactant and plasma, as described above, the surface contact angle is less than 10 degrees as measured by direct contact angle measurement. In this regard, the contact angle of water is a measure of its hydrophilic characteristics. A low contact angle means that the surface is wetted, whereas a high contact angle means that the surface is non-wetted or hydrophobic. The contact angle of an untreated or uncoated titanium surface is about 72 degrees.

Insulin adsorption after the Genapol*surface treatment is less than 0.1 microgram per square cm of the titanium surface, as compared to an adsorption of about 0.6 microgram per square cm for uncoated titanium. Similar surface treatments using other hydrophilic surfactants such as those

*Trade-mark

identified above yield results of similar magnitude, although Genapol* is believed to provide the best reduction in insulin adsorption.

In an alternative coating technique, the titanium pump surface is dip coated in a biopolymer material such as a polyvinyl pyrollidone available from STS Biopolymers, Rochester, New york, under the designation Slipcoat.* In this process, the surface is dip coated three times to provide a primer, base and top coating, with appropriate application of mild heat after each step to remove the solvent. After the top coat is dried, the surface contact angle is approximately 30 degrees, and the insulin adsorption profile is about 0.4 microgram per square centimeter.

A further alternative coating method in accordance with the invention utilizes a hydrophilic polyurethane, such as that marketed by Thermedics, Inc. of Woburn, Massachusetts, under the name Biomer.* In this method, Biomer is prepared in an approximate 7.0% solution with tetrahydro furan (THF) and the titanium surface to be coated is dipped therein. The dip coated surface is subsequently dried for about six hours at about 45 degrees Celsius. Subsequent hydration as by exposure to water for about one hour results in a surface contact angle and insulin adsorption profile that is too low to measure, i,e., less than about 0.04 micrograms per square centimeter.

A hydrophilic surface coating can also be prepared by the use of bovine serum albumin (BSA) dissolved in a phosphate buffered saline (PBS) solution with a concentration of about 5 milligrams per milliliter. The titanium pump surface to be coated is dipped into this solution and allowed to dry. After drying, the coated surface is dipped a second time into the BSA solution and then immediately dipped into a solution of glutaraldehyde in dionized water with a concentration of about 2.5% which functions to cross link the protein both to the titanium surface and also to itself. After drying for about two hours, at about 37 degrees Celsius, the resultant surface contact angle is about 30 degrees, and it is believed that a comparable reduction in insulin adsorption will result.

A non-covalent approach is to dip coat the selected pump

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surface with a non-reactive solution of a hydrophilic material. Such solutions might contain a hydrogel material like p-HEMA (poly hydroxy ethyl methacrylate), PVP (polyvinyl pyrollidone), or crosslinked PVA (polyvinyl alcohol) in an alcohol or ketone solution. In this case, the coating material adsorbs to the material of the pump (typically a metal like titanium or stainless steel) via hydrogen bonding or Van der Waal's forces. This physical adsorption of the polymer to the surface in many cases is strong enough to maintain structural integrity of the coating for the life of the pump. In most cases of non-covalent adsorption of a coating, surface roughness of the pump material dramatically enhances the adhesion of the coating.

Another approach to a non-covalent coating process involves a two step plasma initiated process. In the first step, a paralyne coating (plasma initiated polymerization of para-chloro xylene or other aromatic monomer) is applied to the surface of the pump. This coating by itself is very hydrophobic (surface contact angle of about 105 degrees) and not suitable for protein solutions. In a second step, CO_2 is introduced into a vacuum chamber and a plasma is initiated. The resultant process applies a coating of carboxylate functional groups to the surface of the paralyne. The resulting coating has a contact angle of about 35 degrees and is suitable for long term protein stability. Alternatively, one can use a sulfonation process (propane sultone as an example) to sulfonate the surface of the paralyne. Such a sulfonation process yields a surface that has contact angles of approximately 15 degrees with excellent protein stability.

A more robust coating can be obtained by covalant attachment of the coating material to the selected surface of the pump. There are several ways to covalently attach a hydrophilic coating to the pump surface. These include radiation, electron beam and photo induced grafting, polymerization chemical grafting and plasma deposition of polymers. In general, these methods involve an energy source and a monomer of the desired hydrophilic polymer. For example, acrylonitrile can be grafted onto a titanium surface by irradiation of acrylonitrile vapor in contact with the surface. The resulting

polymer, polyacrylonitrile (PAN) has excellent hydrophilic properties with very minimal protein interaction with the surface. A wide variety of polymers can be produced in this manner, the only requirement being that the monomer be available in reasonable purity with enough vapor pressure to be reactive in the deposition system.

In addition to the polymerization systems described above, a covalent attachment of a polymer to the surface can be accomplished via a silane (or other coupling) agent. In this case, a silane coupling is reacted with the pump surface. One typical silane for this attachment might be dichloro methyl vinyl silane which when hydrolyzed in aqueous ethanol will bond tenaciously to a metal surface through either an O-Si or metal Si bond. The vinyl group of the silane can then be reacted with a variety of either polymers or monomers. In an example, a methacrylate terminated PEG can be reacted with the terminal vinyl of the silane using conventional acrylate chemistry. The end result is a PEG that is covalently bonded to the metal surface. This reaction can be either light or peroxide initiated.

A further mechanism for creating a protein stable coating is to simply modify the surface of the pump material itself. For example, a high energy beam of either photons, electrons or other particles can be directed onto the surface of the material. In one specific example, a beam of high energy photons (short wavelength UV) irradiates a titanium surface in the presence of air and water vapor. After irradiation, the surface contains a significant fraction (greater than about 25%) of OH groups and has a contact angle of less than 20 degrees.

Accordingly, the present invention provides a treated surface exhibiting significant hydrophilic properties, with a surface contact angle of less than about 45 degrees, and preferably less than about 35 degrees. This treated surface has a low free energy and has provided demonstrated protein stability.

A variety of modifications and improvements to the present invention will be apparent to those skilled in the art. For example, it will be

apparent that the invention can be applied to a wide range of different types of pump surfaces including metallic and non-metallic surfaces to reduce the surface contact angle for hydrophillic characteristics. Moreover, it will also be apparent that the invention can be applied to a broad scope of medical devices having a surface wherein avoidance of protein-based deposits is desired. Accordingly, no limitation on the invention is intended by way of the foregoing description and accompanying drawings, except as set forth in the appended claims.

CLAIMS:

1. A medical device having a surface in contact with a protein based medication characterised in that said surface is treated to have a hydrophilic surfactant covalently attached thereto so that the surface having the hydrophilic surfactant covalently attached thereto has a surface contact angle less than 45 degrees and wherein the hydrophilic surfactant is a block ethylene/propylene copolymer which includes a polyethylene glycol moiety as a hydrophilic segment.

2. The medical device of claim 1, wherein the copolymer has a molecular weight of about 1800 Daltons.

3. The medical device of claim 1 or 2, wherein the surface contact angle is less than 35 degrees.

4. The medical device of claim 1 or 2, wherein the surface contact angle is less than 10 degrees.

5. The medical device of any one of claims 1 to 4, wherein the surface exhibits a protein adsorption profile of less than 1.0 microgram per square centimeter.

6. The medical device of any one of claims 1 to 5, wherein the protein based medication is insulin.

7. The medical device of claim 6, wherein the surface exhibits an insulin adsorption profile of less than 0.1 microgram per square centimeter.

8. The medical device of any one of claims 1 to 7, wherein said surface is formed as part of a medication infusion pump.

9. The medical device of any one of claims 1 to 8, wherein the surface is metallic.

10. The medical device of any one of claims 1 to 8, wherein the surface is titanium.

11. The medical device of any one of claims 1 to 8, wherein the surface is non-metallic.

12. A method of treating a surface for use in a medical device having a surface contactable by a protein based medication, the method comprising covalently attaching to the surface a hydrophilic surfactant so that the surface having the hydrophilic surfactant covalently attached thereto has a surface contact angle less than 45 degrees and wherein the hydrophilic surfactant is a block ethylene/propylene copolymer which includes a polyethylene glycol moiety as a hydrophilic segment.

13. The method of claim 12, wherein the copolymer has a molecular weight of 1800 Daltons.

14. The method of claim 12 or 13, wherein the surface contact angle is less than 35 degrees.

15. The method of claim 12 or 13, wherein the surface contact angle is less than 10 degrees.

16. The method of any one of claims 12 to 15, wherein the surface exhibits a protein adsorption profile of less than 1.0 microgram per square centimeter.

17. The method of any one of claims 12 to 16, wherein the protein based medication is insulin.

18. The method of claim 17, wherein the surface exhibits an insulin adsorption profile of less than 0.1 microgram per square centimeter.

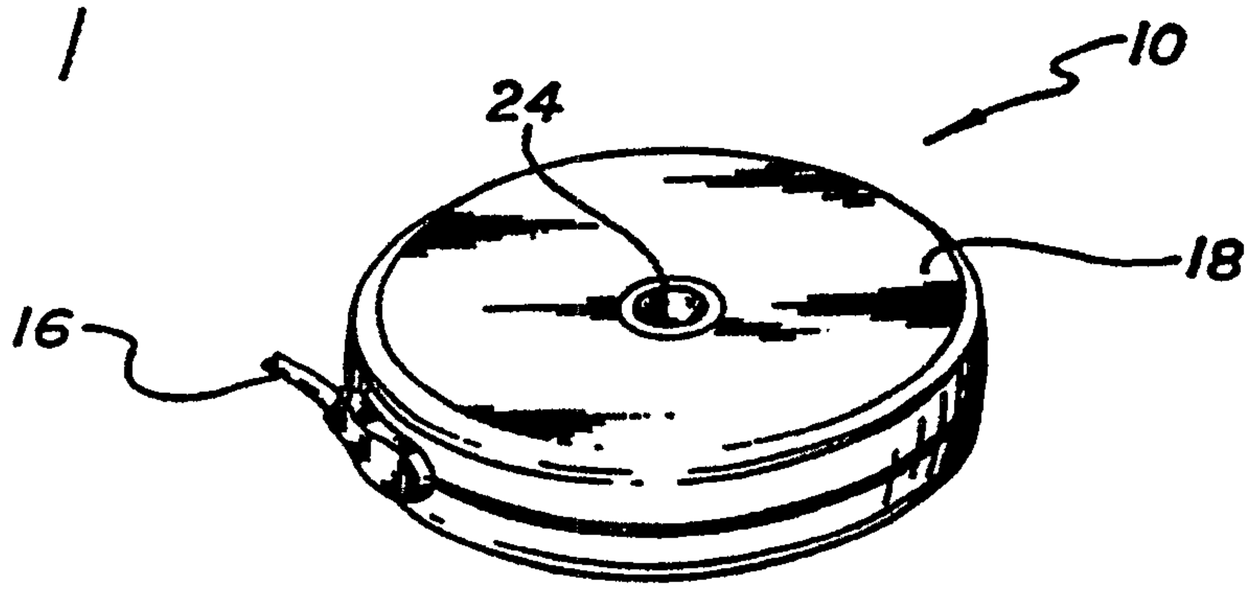
19. The method of any one of claims 12 to 18, wherein the surface is metallic.

20. The method of any one of claims 12 to 18, wherein the surface is titanium.

21. The method of any one of claims 12 to 18, wherein the surface is non-metallic.

22. The method of any one of claims 12 to 21, wherein the copolymer is covalently attached to the surface by polymeric attachment, RF-plasma attachment, grafting, or silane-based primer attachment.

FIG. 1



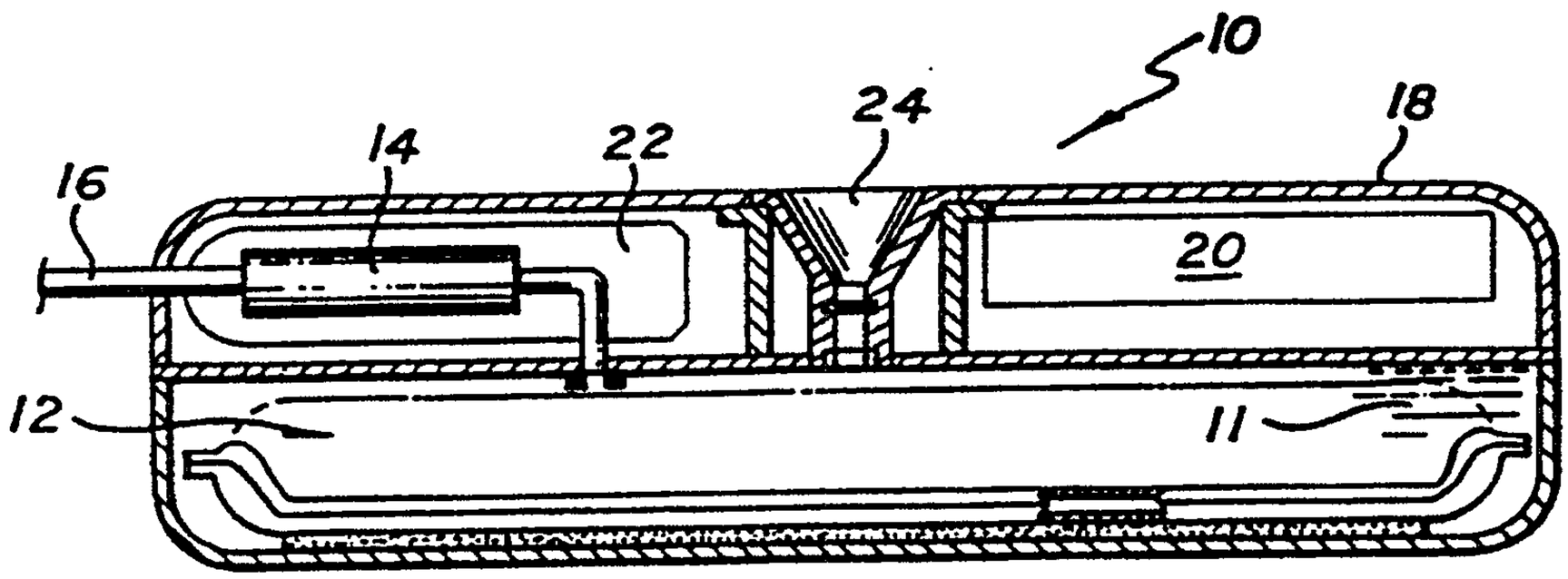
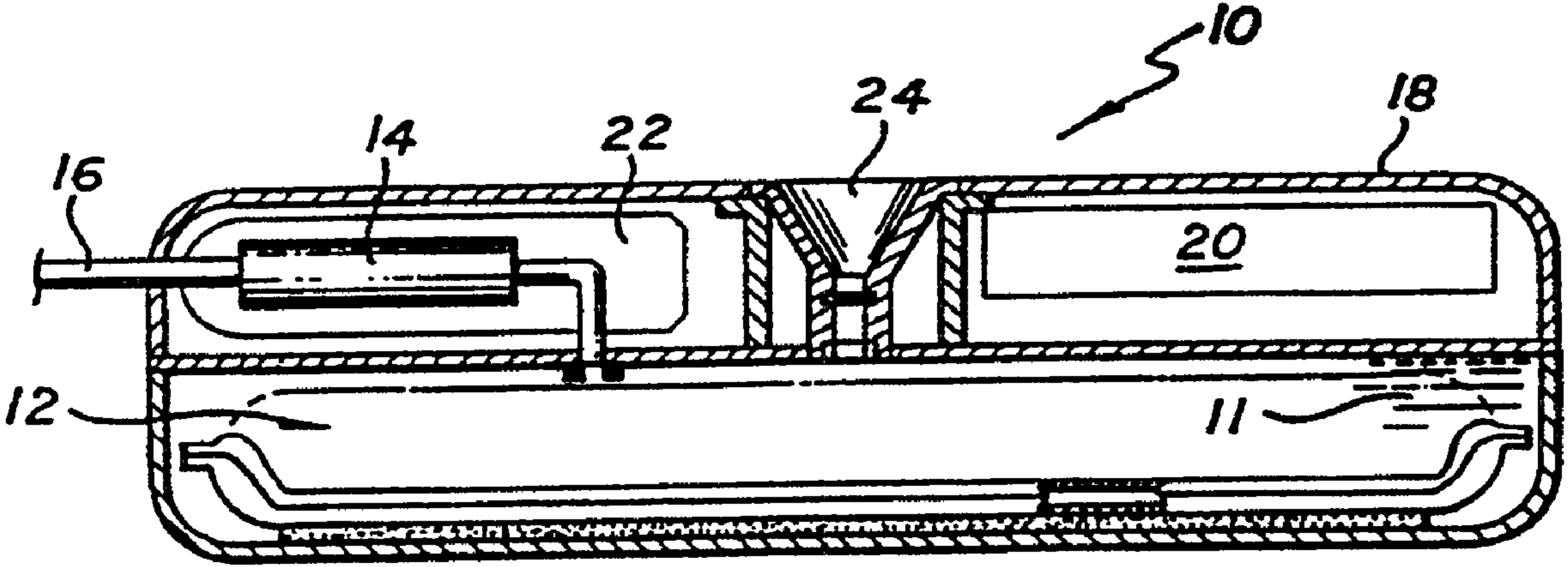


FIG. 2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