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(54) Title: MEDICATION DEVICE WITH POLYMERIC SURFACE COATING PROTECTING AGAINST PROTEIN ADHESION

(57) Abstract: A medical device includes a non-metallic surface contacted by a selected protein-based medication, said surface having a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees and exhibits a protein adsorption profile of less than about 1.0 microgram per square centimeter.

MEDICATION DEVICE WITH POLYMERIC SURFACE COATING PROTECTING AGAINST PROTEIN ADHESION

Field of the Invention

This invention relates generally to reusable and disposable medical devices that are used to store, contain or deliver protein-based medications. More particularly, this invention relates to improved medical devices that have one or more protein-contacting surfaces treated to reduce the protein adsorption and denaturation that can occur on an untreated surface.

Background of the Invention

Medication infusion pumps are generally known in the art for use in delivering a selected medication to a patient in a preprogrammed or patient-programmed manner. In recent years, infusion pumps have been developed in compact form and adapted to deliver a specific medication, such as insulin, to the patient in patient-programmed continuous doses over an extended time period. Medication infusion pumps have also been used to deliver a wide variety of other drugs to a patient. Such medications or drugs include, for example, baclofen, morphine and other pain medications, various antibiotics, and a number of chemotherapeutic agents.

As protein-based medications become more prevalent, problems arise in reliable long-term administration of these medications to a patient. More specifically, bolus drug injections are not optimal to achieve relatively constant blood concentration levels. Many of the newer protein-based medications are relatively complex, having a high molecular weight, such that bolus therapy subcutaneous drug delivery can be problematic due to relatively fast clearance by the renal and hepatic systems.

One problem encountered with medical devices is that medication contacting surfaces are typically constructed from materials, such as metals, polymers or other materials, that have low free surface energies, typically on the order of about 40 dyne/cm^2. At this low free surface energy, protein-based medications can be adsorbed quite readily and can subsequently denature on the

medication contacting surfaces. Once denaturing occurs, the protein-based substances 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 medical device having a hydrophilic internal surface coating or coatings, resulting in device surfaces that are highly stable in the presence of complex protein-based medications.

Summary of the Preferred Embodiments

In accordance with one aspect of the present invention, there is provided a medical device having a non-metallic surface contacted by a selected protein-based medication. The surface has a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees, and also exhibits a protein adsorption profile of less than about 1.0 microgram per square centimeter when measured with either albumin or insulin.

In more specific embodiments, the medical device is a medication infusion pump. The medication infusion pump can be reusable or disposable, and can be externally worn or implantable. The medical device according to the invention is not limited to a medication infusion pump, however, but can also be a device such as a prefilled medication cartridge, a syringe, a catheter, an IV bag, and the like.

Preferably, the non-metallic surface is a polymeric surface, such as a rubber, a polyurethane, a polyethylene, a polypropylene or a polyvinylchloride. In a particular preferred embodiment, the polymeric surface is comprised of a bromobutyl rubber or a chlorobutyl rubber.

Preferably, the surface treatment is a coating comprised of polymeric materials such as hydrophilic polyurethanes, polyureas, acrylics, polycarbonates or other hydrophilic materials, in particular materials such as polyethylene glycols, polyethylene/polypropylene glycol copolymers or other poloxamers which are chemically (covalently) attached to the treated surface.

In accordance with a further aspect of the present invention, there is provided a medication infusion device for contacting a selected protein-based

medication, the device having a non-metallic surface for contacting the medication. The non-metallic surface has a coating to reduce the surface contact angle and protein adsorption profile. Preferably, the non-metallic surface is a polymeric surface as set forth above, and the coating is a polymeric material as set forth above.

In accordance with still another aspect of the present invention, a component for use in a medication infusion device as described herein is provided. The component has a non-metallic surface having a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees and exhibits a protein adsorption profile of less than about 1.0 microgram per square centimeter when measured with albumin or insulin.

In accordance with yet another aspect of the present invention, there is provided a method of treating a non-metallic surface for use in a medical device for contacting a selected protein-based medication. The method includes the step of treating the non-metallic surface to produce a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees and exhibits a protein adsorption profile of less than about 1.0 microgram per centimeter when measured with albumin or insulin.

Preferably the non-metallic surface is a polymeric surface as set forth above, and the treating step includes the application of a coating of a polymeric material as set forth above to the polymeric surface.

In a more specific embodiment, the polymeric material is applied to the surface by dipping, spraying, pre-polymerization followed by polymeric attachment, RF-plasma attachment, grafting, or silane-based primer attachment, and subsequently cured, preferably by exposure to actinic radiation (e.g., UV radiation), free radicals, elevated temperature, RF energy, or by other chemical reactions. If needed, the application and curing steps are repeated to ensure that the entire surface is provided with the coating.

Components for medical devices treated according to the inventive method, and medical devices including such components, are also provided.

Other objects, features and advantages of the present invention will become apparent to those skilled in the art from the following detailed description. It is to be understood, however, that the detailed description and specific examples, while indicating preferred embodiments of the present invention, are given by way of illustration and not limitation. Many changes and modifications within the scope of the present invention may be made without departing from the spirit thereof, and the invention includes all such modifications.

Brief Description of the Drawings

The invention may be more readily understood by referring to the accompanying drawings in which

FIG. 1 is side sectional view depicting a typical externally mountable infusion device, and

FIG. 2 is a side sectional perspective view, partially in phantom, of a medicament reservoir used with an infusion device.

Detailed Description of the Preferred Embodiments

The present invention is related to the subject matter of U.S. Patent Application Serial No. 08/742,377, filed November 1, 1996, which pertains in part to the treatment of metallic surfaces such as titanium. The disclosure of the foregoing application is incorporated in its entirety herein by reference.

In accordance with the invention, a medication device includes one or more internal 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 medication device is used to deliver complex protein based medications such as insulin and the like. The hydrophilic internal surfaces have been found to significantly reduce and/or eliminate undesired adsorption of proteins on internal pump surfaces.

The invention can be applied to a wide range of different types of pumps, including both reusable and non-reusable pumps, as well as to both implantable

and externally worn pumps. For example, the invention is applicable to an externally worn, gas powered infusion device as described in U.S. Patent No. 5,785,688; an implantable constant-flow medication infusion pump as described in U.S. Patent Application Serial No. 08/871,830; and the pumps described in U.S. Patent Application Serial No. 09/253,382 (attorney docket no. PD-0296) and Serial No. 09/253,383 (attorney docket no. PD-0297), the disclosures of which are incorporated herein in their entireties by reference, as well as other medical devices that employ flexible displaceable membranes. These exemplary medical devices, which can be beneficially treated according to the present invention, include flexible non-metallic internal membranes which separate medicament reservoirs from propellant reservoirs. Such pumps can be driven by an elastomeric sponge surrounding the medicament reservoir (e.g., from Science Incorporated); in which a propellant reservoir is prefilled with a gas or chemical solution to generate a gas (e.g., from River Medical); or in which a gas is generated electrochemically within the propellant reservoir (e.g., from Elan Corporation or CeramTec, Inc.).

The invention can further be applied to a variety of pump surfaces including both metallic and non-metallic surfaces to reduce the surface contact angle for hydrophilic characteristics.

Furthermore, the invention is not limited to pumps, but is also suitable for application to any medical device having one or more components that are contacted by a selected protein-based medication. Such devices include, without limitation, prefilled medication cartridges having internal pistons; polymeric syringe bodies, reservoirs, plungers and plunger O-rings; polymeric catheters; IV bags; polymeric bottles and other storage containers; or the like.

Additional exemplary medical devices include replaceable or disposable syringes or reservoirs for medication infusion pumps, such as those commercially available from MiniMed Inc. and Disetronic.

For a detailed description of the overall construction and operation of implantable infusion pumps that are beneficially treated according to the present invention, see U.S. Patent 4,373,527 and 4,573,994, both of which are

incorporated by reference herein. For a detailed description of the construction and operation of a miniature pump mechanism, see U.S. Patents 4,568,520; 4,569,241; 4,636,150; and 4,714,234, all of which are incorporated by reference herein.

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 a medication device wherein one or more internal surfaces are coated to achieve a significant reduction in surface free energy.

Turning now to Figure 1, an externally worn medication infusion pump 10 includes propellant reservoir 12 and medicament reservoir 14 separated by flexible non-metallic (e.g, polymeric) membrane 16. Membrane 16 has a surface 18 in contact with the medicament in reservoir 14. Surface 18 is provided with a surface treatment according to the present invention. Preferably, the propellant reservoir 12 contains a gas generated electrochemically or chemically to apply pressure to the membrane 16 in order to expel the medicament from the medicament reservoir 14. The medicament is delivered to the patient via catheter 20 and an infusion set 22 having cannula 24.

In Figure 2, a prefilled medicament cartridge 30 for use with a medicament infusion pump includes a non-metallic piston 32 driven by plunger 34 into reservoir 36. Piston 32 has a surface 38 which is treated according to the invention. Reservoir 36, which can be formed from a non-metallic material such as glass, a polymer or the like, has a surface 40 which also can be treated according to the invention. As piston 32 is urged inward into reservoir 36, the medicament within reservoir 36 is supplied via orifice 42 into the medicament infusion pump (not shown) in which cartridge 30 has been inserted.

Medical devices having surfaces comprised of a non-metallic material, and components of such medical devices which are comprised of a non-metallic material or have a non-metallic surface, are beneficially prepared according to the present invention. The non-metallic surfaces can be comprised, for example, of a

polymeric material, for example a rubber such as bromobutyl rubber or chlorobutyl rubber, a polyurethane, a polyethylene, a polypropylene, a polyvinylchloride, or other similar polymeric materials. The medical device components can be made of a polymeric material, such as those listed above, or can be formed from a polymer laminate (e.g., two or more layers of different polymeric materials) or a metallized polymeric material, in which case the polymeric material has a non-metallized surface which has a surface treatment according to the invention.

The surface treatment according to the invention can be, for example, a coating formed from a polymeric material. Specific polymeric materials useful to provide a surface treatment according to the invention include, without limitation, materials such as hydrophilic polyurethanes, polyureas, acrylics, as well as other hydrophilic components. Particular materials include polyethylene glycols, polyethylene/polypropylene glycol copolymers and other poloxamers. These coatings preferably are covalently bonded to the surface which is being treated.

One particular method for forming the coating includes the steps of adsorbing the polymeric material to the surface, and then covalently attaching the polymeric material to the surface by exposure to UV radiation, RF energy, heat, X-ray radiation, gamma radiation, electron beams, or the like. If needed, the foregoing application and curing steps are carried out at least twice, more particularly at least three times, in order to avoid bubble formation and provide uniform surface coverage.

Another particular method includes the step of covalently attaching a linker molecule to the surface. Linker molecules that are useful in this embodiment of the inventive method include, without limitation, silanes of the formula SiX_3-R, wherein X is a methyl group or a halogen atom such as chlorine and R is a functional group which can be a coating material as described herein or a group which is reactive with a coating material. Particular silane-terminated compounds include vinyl silanes, silane-terminated acrylics, silane-terminated polyethylene glycols (PEGs), silane-terminated isocyanates and silane-terminated alcohols. The silanes can be reacted with the surface by various means known to

those skilled in the art. For example, dichloro methyl vinyl silane can be reacted with the surface in aqueous ethanol. The linker molecule strongly binds to the surface via -O-Si bonds or directly with the silicon atom. The vinyl group of the silane can then be reacted with polymeric materials as described herein using appropriate conventional chemistries. For example, a methacrylate-terminated PEG can be reacted with the vinyl group of the silane, resulting in a PEG that is covalently bonded to the surface of the medication device.

In accordance with a preferred surface treatment and method, a hydrophilic surfactant is applied to the selected surface of the medical device 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, 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, 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 compatible 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 surface, such as a metal or elastomeric surface of a medication device (or reservoir) by filling the medication device (or reservoir) with the Genapol solution. The Genapol surfactant which is non-ionic in nature binds to the surface, and the isopropanol solvent can be readily removed under mild conditions of heat and vacuum. After this drying step, the treated 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 surface. If required, 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. For instance, the contact angle of an untreated or uncoated polymeric surface ranges from about 88 to 125 degrees.

Protein adsorption is significantly reduced as a result of the inventive surface treatment, typically to about 1.0 microgram or less per square centimeter of the treated surface, more specifically when measured with albumin or insulin. For example, insulin adsorption after the foregoing Genapol surface treatment is less than 0.1 microgram per square cm of the surface, as compared to an adsorption of about 1.5 microgram per square cm for the uncoated surface. Similar surface treatments using other hydrophilic surfactants such as those identified above yield results of similar magnitude, although Genapol is believed to provide the best reduction in insulin adsorption.

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 tetrahydrofuran (THF) and the 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 medication device 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 deionized water with a concentration of about 2.5% which functions to cross link the protein both to the 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.

There are several ways to covalently attach a hydrophilic coating to the surface of the medication device. 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 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.

Accordingly, the present invention provides a treated surface exhibiting significant hydrophilic properties, with a reduced surface contact angle, preferably of less than about 45 degrees, and more 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 broad scope of medical devices having a surface wherein avoidance of protein-based deposits is desired.

While the description above refers to particular embodiments of the present invention, it will be understood that many modifications may be made without departing from the spirit thereof. The accompanying claims are intended to cover

such modifications as would fall within the true scope and spirit of the present invention.

The presently disclosed embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims, rather than the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A medical device having a non-metallic surface contacted by a selected protein-based medication, said surface having a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees and exhibits a protein adsorption profile of less than about 1.0 microgram per square centimeter.

2. The medical device of claim 1 wherein said surface contact angle is less than about 35 degrees.

3. The medical device of claim 1 exhibiting an insulin adsorption profile of 0.1 microgram per square centimeter.

4. The medical device of claim 1 wherein the medical device is a medication infusion pump.

5. The medical device of claim 4 wherein the medical device is reusable.

6. The medical device of claim 4 wherein the medical device is disposable.

7. The medical device of claim 4 wherein the medical device is externally worn.

8. The medical device of claim 4 wherein the medical device is implantable.

9. The medical device of claim 1 wherein the medical device is selected from the group consisting of a prefilled medication cartridge, a syringe, a catheter and an IV bag.

10. The medical device of claim 1 wherein said non-metallic surface is a polymeric surface.

11. The medical device of claim 10 wherein said polymeric surface is comprised of at least one polymeric material selected from the group consisting of a rubber, a polyurethane, a polyethylene, a polypropylene and a polyvinylchloride.

12. The medical device of claim 11 wherein said polymeric material is a bromobutyl rubber or a chlorobutyl rubber.

13. The medical device of claim 1 wherein said surface treatment is a coating comprised of a polymeric material.

14. The medical device of claim 13 wherein said coating is comprised of a material selected from the group consisting of hydrophilic polyurethanes, hydrophilic polyureas and hydrophilic acrylics.

15. A medication infusion device for contacting a selected protein-based medication, said medication infusion device having a non-metallic surface for contacting said medication, said non-metallic surface having a coating thereon to decrease the surface contact angle and protein adsorption profile thereof.

16. The medication infusion device of claim 15 wherein said non-metallic surface is a polymeric surface.

17. The medication infusion device of claim 16 wherein said polymeric surface is comprised of at least one polymeric material selected from the group consisting of a rubber, a polyurethane, a polyethylene, a polypropylene and a polyvinylchloride.

18. The medication infusion device of claim 17 wherein said polymeric material is a bromobutyl rubber or a chlorobutyl rubber.

19. The medication infusion device of claim 15 wherein said coating is comprised of a polymeric material.

20. The medication infusion device of claim 19 wherein said coating is comprised of a material selected from the group consisting of hydrophilic polyurethanes, hydrophilic polyureas and hydrophilic acrylics.

21. A component for use in a medication infusion device for contacting a selected protein-based medication, said component comprising a non-metallic surface for contacting said medication, said non-metallic surface having a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees and exhibits a protein adsorption profile of less than about 1.0 microgram per square centimeter.

22. The component of claim 21 wherein said surface contact angle is less than about 35 degrees.

23. The component of claim 21 wherein said surface exhibits an insulin adsorption profile of less than about 0.1 microgram per square centimeter.

24. The component of claim 21 wherein said non-metallic surface is a polymeric surface.

25. The component of claim 24 wherein said polymeric surface is comprised of at least one polymeric material selected from the group consisting of a rubber, a polyurethane, a polyethylene, a polypropylene and a polyvinylchloride.

26. The component of claim 25 wherein said polymeric material is a bromobutyl rubber or a chlorobutyl rubber.

27. The component of claim 21 wherein the component is comprised of a polymeric material, a laminate or a metallized polymeric material.

28. The component of claim 21 wherein said surface treatment is a coating comprised of a polymeric material.

29. The component of claim 28 wherein said coating is comprised of a material selected from the group consisting of hydrophilic polyurethanes, hydrophilic polyureas and hydrophilic acrylics.

30. A method of treating a non-metallic surface for use in a medical device for contacting a selected protein-based medication, said method comprising the step of:

treating the non-metallic surface to produce a covalently attached surface treatment that defines a surface contact angle less than about 45 degrees and exhibits a protein adsorption profile of less than about 1.0 microgram per square centimeter.

31. The method of claim 30 wherein said treating step comprises treating the surface to define a contact angle less than about 35 degrees.

32. The method of claim 30 wherein said treating step comprises treating the surface to define an insulin adsorption profile less than about 0.1 microgram per square meter.

33. The method of claim 30 wherein said non-metallic surface is a polymeric surface.

34. The method of claim 33 wherein said polymeric surface is comprised of at least one polymeric material selected from the group consisting of a rubber, a polyurethane, a polyethylene, a polypropylene and a polyvinylchloride.

35. The method of claim 34 wherein said polymeric material is a bromobutyl rubber or a chlorobutyl rubber.

36. The method of claim 30 wherein said treating step comprises applying a coating comprised of a polymeric material to said surface.

37. The method of claim 36 wherein said coating is a material selected from the group consisting of hydrophilic polyurethanes, hydrophilic polyureas and hydrophilic acrylics.

38. The method of claim 37 wherein said coating material is applied to said surface by dipping, spraying, pre-polymerization followed by polymeric attachment, RF-plasma attachment, grafting or silane-based primer attachment.

39. The method of claim 38 wherein said coating material is cured after being applied to said surface.

40. The method of claim 39 wherein said coating material is cured by exposure to actinic radiation, free radicals or elevated temperature.

41. The method of claim 39 wherein said applying and curing steps are repeated at least twice.

42. The method of claim 39 wherein said applying and curing steps are repeated at least three times.

43. The method of claim 30 wherein said treating step comprises covalently attaching a linker molecule to said surface.

44. The method of claim 43 wherein said linker molecule is a silane.

45. The method of claim 44 wherein said silane is selected from the group consisting of vinyl silanes, silane-terminated acrylics, silane-terminated polyethylene glycols, silane-terminated isocyanates and silane-terminated alcohols.

46. The method of claim 43 further comprising the step of reacting said linker molecule with a polymeric material.

47. The method of claim 46 wherein said polymeric material is selected from the group consisting of hydrophilic polyurethanes, hydrophilic polyureas and hydrophilic acrylics.

48. A component for a medical device for contacting a selected protein-based medication, said component having a non-metallic surface treated according to the method of claim 30.

49. A medical device for contacting a selected protein-based medication, said medical device comprising the component of claim 48.

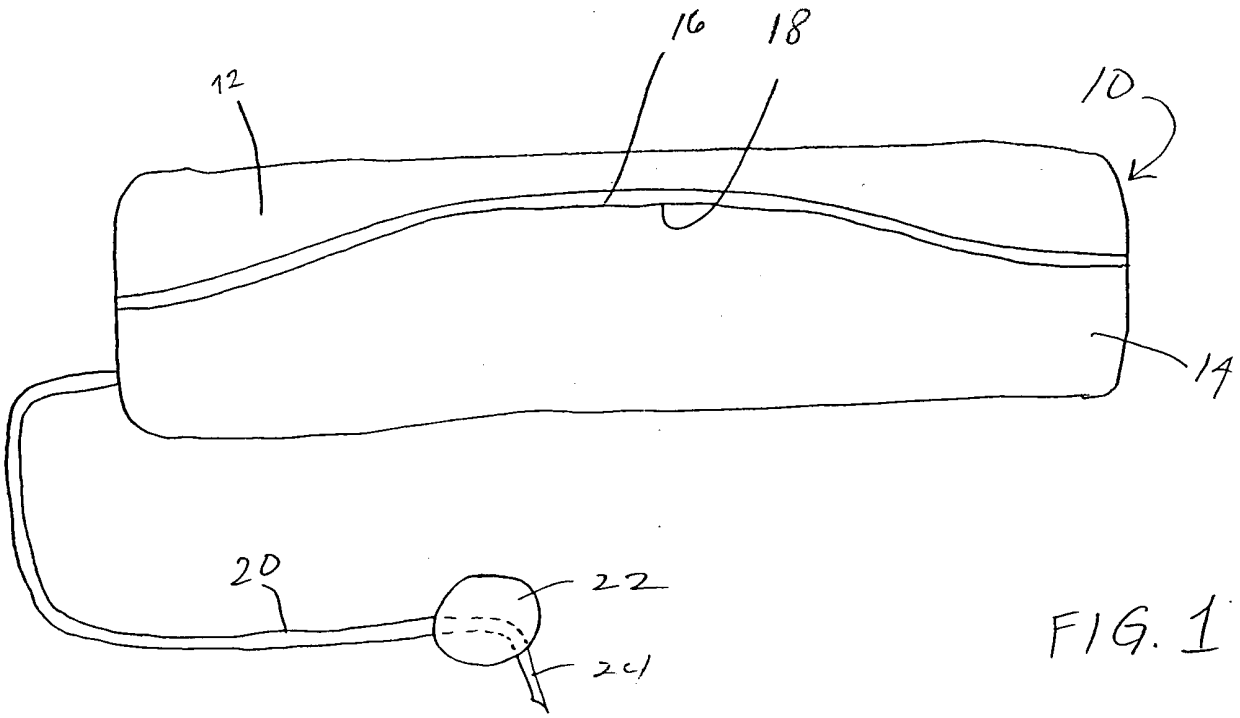

FIG. 1

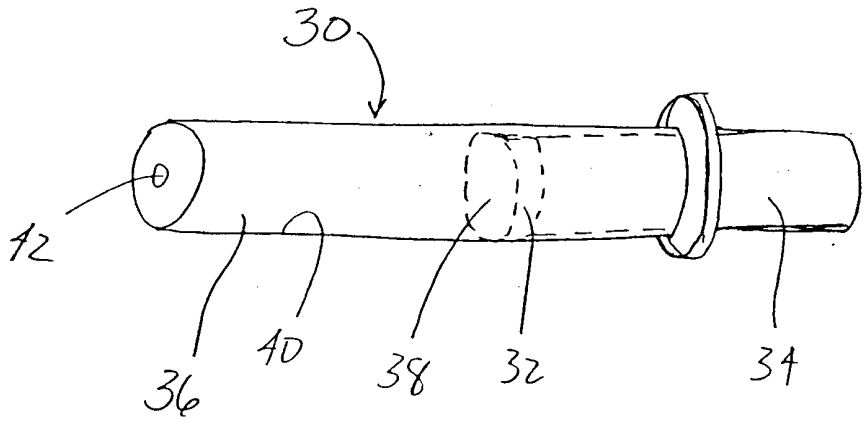

FIG. 2

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 00/14642

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L29/08 A61L31/10 A61L33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 19627 A (MINIMED INC) 14 May 1998 (1998-05-14) cited in the application abstract page 1, paragraphs 1,2 page 3, paragraph 2 page 4, paragraphs 2,3 page 6 -page 9 --- -/--	1-6, 8-11, 13-17, 19-25, 27-34, 36-49

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2000	02/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Böhm, I

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 950 256 A (LUTHER RONALD B ET AL) 21 August 1990 (1990-08-21) column 1, line 13-38 column 2, line 29-35 column 4, line 9-39 column 5, line 1-40 column 6, line 5-14 column 8, line 42-49 column 10, line 13-33	1-6, 8-11, 13-17, 19-25, 27-34, 36-49
A	US 5 328 954 A (SARANGAPANI SHANTHA) 12 July 1994 (1994-07-12) abstract column 2, line 4-9 column 3, line 10-23 column 8, line 36-45	1,4, 8-11,13, 15-17, 19-21, 24,25, 28-30, 33,34, 36,37
A	EP 0 747 069 A (COOK INC) 11 December 1996 (1996-12-11) abstract column 2, line 44-55 column 9, line 6-24 column 13, line 15-54 column 14, line 39-55 column 17, line 26-30,53-58 column 18, line 20	1,4, 8-11,13, 15-17, 19-21, 24,25, 28-30, 33,34, 36,37
A	US 4 626 244 A (REINICKE ROBERT H) 2 December 1986 (1986-12-02) the whole document column 5, line 26-33	1,4, 8-12, 15-18, 21, 24-26, 30,33-35

-/--

1

INTERNATIONAL SEARCH REPORT

Internat l Application No
PCT/US 00/14642

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 183 472 A (JAEHRLING PETER ET AL) 2 February 1993 (1993-02-02) the whole document column 3, line 59-63	1,4, 8-12, 15-18, 21, 24-26, 30,33-35

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible] Application No
PCT/US 00/14642

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819627 A	14-05-1998	CA 2241953 A	14-05-1998
		EP 0877580 A	18-11-1998
US 4950256 A	21-08-1990	AU 611030 B	30-05-1991
		AU 3549289 A	03-11-1989
		EP 0362370 A	11-04-1990
		JP 2504003 T	22-11-1990
		JP 5053146 B	09-08-1993
		WO 8909626 A	19-10-1989
US 5328954 A	12-07-1994	AU 6704494 A	08-11-1994
		WO 9424181 A	27-10-1994
EP 0747069 A	11-12-1996	US 5609629 A	11-03-1997
		AU 716005 B	17-02-2000
		AU 5588896 A	19-12-1996
		CA 2178541 A	08-12-1996
		JP 9099056 A	15-04-1997
		WO 9817331 A	30-04-1998
		US 6096070 A	01-08-2000
		US 5824049 A	20-10-1998
		US 5873904 A	23-02-1999
US 4626244 A	02-12-1986	EP 0189940 A	06-08-1986
US 5183472 A	02-02-1993	EP 0433485 A	26-06-1991
		DE 58904449 D	24-06-1993