PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 9/00, A61F 2/02	A1	WO 93/21902
		(43) International Publication Date: 11 November 1993 (11.11.93)

(21) International Application Number: PCT/US93/03850

(22) International Filing Date: 23 April 1993 (23.04.93)

(30) Priority data:
07/874,342 24 April 1992 (24.04.92) US

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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: BIOCOMPATIBLE, THERAPEUTIC, IMPLANTABLE DEVICE

(57) Abstract

This invention relates to an implantable, biocompatible device possessing at least one cavity within which live cells can be introduced and maintained such that when the device is implanted into a subject, the cells are in continuous interaction with the subject's bodily fluids to provide a therapeutic or prophylactic effect to the subject that requires a direct interactive contact with the body's fluids, wherein at least one portion of the outside thereof comprises a non-porous, semi-permeable, biocompatible film formed from a copolymer comprising about 5 to 45 wt % of at least one hard segment, and about 95 to 55 wt % of at least one soft segment, substantially impermeable to cells and particulate matter. Multiple embodiments of the device of this invention are provided.

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BIOCOMPATIBLE, THERAPEUTIC, IMPLANTABLE DEVICE

Field of the Invention

This invention relates to an implantable, biocompatible, therapeutic or prophylactic device for introducing live cells into the body of the subject in need of a therapeutic prophylactic treatment. The cells contained in the device are placed in a continuous direct interaction with the body fluids of the subject so that they can provide the therapeutic or prophylactic effect needed by the subject. The present device has at least one portion of its outside surface made from a non-porous, semi-permeable, biocompatible film having specific tensile strength, ultimate elongation, and water absorption, the film being permeable to molecules of variable molecular weights, e.g., up to about 6,000 and higher, and in some cases, up to about 600,000 molecular weight and higher, and substantially impermeable to cells and particulate matter. When the device is filled with live functional cells, the device is implanted in a specific part in a subject's body in a manner such that the cells are placed in direct interactive contact with the subject's body fluids, permitting the cells to reproduce and/or remain viable. The cells exert their therapeutic effect on the subject in response to the continuous interactive communication with the subject's body fluids.

Description of the Background

A variety of diseases result from deficient production of proteins such as hormones by the human body. Other diseases are the result of a genetic

deficiency that results in an abnormal product being released into the bloodstream. In cases such as when the deficiency is associated with the production of protein, whether one may be lacking or an abnormal protein is being produced, compensatory therapy or prophylactic treatment is, in general, precluded from being administered by the oral route. Most protein compositions are degraded in the gastrointestinal (G.I.) tract and must, therefore, be administered by injection. Although widely used, this method of administration has a plurality of detrimental effects, such as the fact that injections are painful and a potential for infection, as well as producing momentary deleteriously high levels of the product in the blood.

Four methods of immunological isolation used up to the present time are as follows:

(1). Extravascular diffusion chambers.

(2). Intravascular diffusion chambers.

(3). Intravascular ultrafiltration chambers.

(4). Microencapsulation.

All these approaches have detrimental features that are summarized below.

I. They produce host fibrotic response to the implant and are unstable, e.g., in alginate microencapsulation.

II. There are limitations to the diffusion of nutrients across semi-permeable membranes of the prior art with decreasing permeability as protein deposition, blood clotting or fibrous ingrowth block

the passage of nutrients through the pores of the membrane.

III. A lag time is observed in the permeability and diffusion of glucose and insulin across prior art semi-permeable membrane barriers, resulting in a delay of a reaction by the cells to the host's glucose levels in blood.

Membranes used in prior art implants and methods, with the possible exception of microencapsulation with friable gels, have employed microporous semi-permeable membranes. Such membranes have been fabricated from impermeable polymers with pores being introduced into the material through processing conditions and/or leachable additives. MILLIPORE® and NUCLEOPORE®, or polycarbonate microporous membranes utilized by the prior art are made from inherently impermeable polymers and do not support long-term cell viability. Other semi-permeable membranes demonstrate poor blood compatibility as well as low permeability proficiency for the transport of glucose and insulin across the membranes. It should be noted that a microporous membrane may have acceptable high permanent flux in a pressure-driven process such as ultrafiltration, but, at the same time, have very low permeability in a concentration-driven process such as the <u>in vivo</u> method of this invention. When the microporous membranes are placed in direct contact with a body fluid such as blood, they accumulate a fibrin layer which becomes a major barrier to mass transportation through the membrane.

AVCOTHANE-51® resulted from the combination of two commercially available polymers, a silicone and a polyurethane, both of which are widely used as fabric coatings. AVCOTHANE-51® is utilized in biomedical devices such as an intra-aortic balloon. The sole improvements introduced for its biomedical applications were the use of highly purified starting materials, the filtration of the product solution and clean conditions for the fabrication of blood-contacting surfaces. Another biomedical polyurethane, AVCOTHANE-610®, also called CARDIOMAT-610®, and ANGIOFLEX® are presently being used in blood pumps and trileaflet heart valves.

The thermoplastic material PELETHANE® was first applied to the manufacture of cannulae for blood vessels, and later of catheters. This material had originally been developed as an extrusion molding resin exhibiting superior hydrolytic stability over their polyester-based counterparts. Table 1 below lists some of the biomedical polyurethanes available in the U.S. market.

In general, polyetherurethane block or segmented copolymers exhibit good biocompatibility along with high strength and elastomeric properties. This unique combination of properties is due in part to the two-phase morphology of the polyurethane molecule. In a typical polyurethane, aggregated aromatic or aliphatic urethane or urea segments constitute a hard glassy or semicrystalline phase, while low glass transition temperature (Tg) oligomeric segments comprise the liquid-like, rubbery soft phase or segment. The morphology of a polyurethane depends on many factors, including hard

and soft segment chemistry, segment polarity differences, hard segment content, and hard and soft segment molecular weights.

In both polyurethaneureas and polyurethanes, the chemistry of the soft segment affects the degree of phase separation in the polymer, which in turn affects its bulk and surface properties and subsequent biocompatibility. Polyurethaneureas, similar to the ones disclosed in this patent only as to their hard segment compositions, have been shown to be resistant to degradation in several applications (Paynter, et al., "The Hydrolytic Stability of Mitrathane, a Polyurethaneurea - An X-ray Photoelectron Spectroscopy Study", J. Biomed. Mater. Res. 22:687-698 (1988); Szycher, et al. "Blood Compatible Polyurethane Elastomers", J. Biomater. Appl. 2:290-313 (1987)).

The application of natural and synthetic polymer membranes to the separation of gaseous and liquid mixtures of low molecular weight has been reported in a number of reviews. Many studies of membrane permeability to simple low molecular weight (MW) permeants have been reported in which the composition of glassy-rubbery or crystalline-rubbery copolymers are varied. A polyurethane multipolymer membrane different from the one disclosed herewith has been shown to be water and salt permeable. In thermoplastic segmented block copolymers where one block or segment is glassy or crystalline (hard segment) and another is rubbery or liquid-like (soft segment), the permeation of molecules occurs primarily through the soft segment. The relatively impermeable hard segment, provides physical integrity

to the polymer by virtue of its strong intermolecular interactions with like segments on adjacent molecules, even under conditions which may cause swelling of the soft segment.

Okkema, et al. disclose a series of polyether polyurethanes based on polyethylene oxide (PEO), polytetramethylene oxide (PTMO) and mixed PEO/PTMO soft segments suitable as blood contacting surfaces, but with a hard segment content of 55 wt%, too high to be useful in the present invention. (Okkema et al.,"Bulk, Surface, and Blood-Contacting Properties of Polyurethanes Modified with Polyethylene Oxide", J. Biomater. Sci. Polymer. Edn.1(1):43-62 (1989)).

Takahara, et al. disclose the preparation of Segmented Poly (etherurethaneureas) (SPUU) with hydrophilic and hydrophobic polyether components. (Takahara et al., "Surface Molecular Mobility and Platelet Reactivity of (SPUUS) with Hydrophilic and Hydrophobic Soft Segment Components", J. Biomater. Sci. Polymer. Edn. 1(1):17-29 (1989)). Platelet adhesion and dynamic contact angle measured after adsorption of bovine serum albumin revealed that the SPUUs with hydrophilic soft segments had a non-adhesive surface.

Chen, et al. examine the relationship between structure and properties of polyether based polyurethanes. (Chen et al.,"Synthesis, Characterization and Permeation Properties of Polyether Based Polyurethanes", J. Appl. Polym. Sci. 16: 2105-2114 (1972)). Of particular interest is the testing of the transport of water and low molecular weight salt through polymeric membranes made of

elastomers that are block copolymers consisting of hard and soft segments, with the former acting as physical crosslinks.

U.S. Patent 3,804,786 to Sekmakas discloses water-dispersible cationic resins, particularly polyurethane resins prepared by reaction of a resinous polyepoxide with a polyisocyanate to provide an hydroxy-functional polyurethane with tertiary amine functionality. These resins are useful for electrode position at the cathode.

U.S. Patent 3,826,768 to Suzuki and Osonol discloses a process for preparing polyurethane compositions by dispersion of polyurethane-containing isocyanates made from polyols and organic isocyanates in water under specified conditions.

U.S. Patent 3,852,090 to Leonard et al. discloses the utilization of a urethane film for waterproofing a breathable textile substrate.

U.S. Patent 4,124,572 to Mao relates to thermoplastic polyurethanes prepared by a specified method. The thus produced elastomers are useful for automotive products, applications such as cattle ear tags, coatings and coated fabrics.

U.S. Patent 4,183,836 to Wolfe, Jr. discloses a water-based polyurethane dispersion and its preparation by reacting an aliphatic diisocyanate with three critical active hydrogen compounds to form a pre-polymer containing carboxyl and free isocyanate groups, and then dispersing the pre-polymer in an aqueous medium with a tertiary amine and a diamine.

These dispersions are useful in coating applications such as textile materials.

U.S. Patent 4,190,566 to Noll et al. relates to non-ionic, water dispersible polyurethanes with substantially linear molecular structure and lateral polyalkylene oxide polyether chains containing ethylene oxide units of specified content.

U.S. Patent 4,202,880 to Fildes et al., discloses sustained release delivery means comprising a biologically active agent, i.e., a drug, a linear hydrophilic block polyoxyalkylene-polyurethane copolymer, and optionally a buffer. A single hydrophilic soft segment is used. Only the hard segment is hydrophobic.

U.S. Patent 4,202,957 to Bunk, et al. discloses polyurethane polyether-based elastomers which are thermoplastic and recyclable, and have increased high temperature resistance that makes them suitable for injection molding.

U.S. Patent 4,224,432 to Pechhold et al. discloses a polyurethane comprising a reaction product of a polymerizate of tetrahydrofuran and an alkylene oxide, an organic polyisocyanate and a chain extender which is an aliphatic polyol or a polyamine.

U.S. Patent 4,367,327 to Holker et al. relates to a breathable polyurethane film for coating fabrics to make them waterproof. The polyurethane film comprises in stoichiometric amounts a hard segment made of a low molecular weight diisocyanate with a difunctional compound, and a soft segment comprising

polyethylene glycol. The mechanical properties of the film are improved by crosslinking with a triisocyanate.

U.S. Patent 4,849,458 to Reed et al. discloses a hydrophilic, segmented polyether polyurethane-urea exhibiting increased tensile strength and elongation when wet with water. The polymers form clear films that are permeable to water vapor.

Many of these materials are segmented polyurethane elastomers. Some of them, moreover, have found biomedical applications virtually without being modified. However, despite their widespread use, many biomaterials were originally developed for nonmedical uses. In fact, most polyurethane materials were developed to satisfy high volume, industrial needs. A most notable example is DuPont's LYCRA® Spandex, a polyurethane utilized in the fabrication of circulatory support device components. This material was later sold under the trade name BIOMER® Segmented Polyurethane.

AVCOTHANE-51® resulted from the combination of two commercially available polymers, a silicone and a polyurethane, both of which are widely used as fabric coatings. AVCOTHANE-51® is utilized in biomedical devices such as an intra-aortic balloon. The sole improvements introduced for its biomedical applications were the use of highly purified starting materials, the filtration of the product solution and clean conditions for the fabrication of blood-contacting surfaces. Another biomedical polyurethane, AVCOTHANE-610®, also called

CARDIOMAT-610®, and ANGIOFLEX® are presently being used in blood pumps and trileaflet heart valves.

The thermoplastic material PELETHANE® was first applied to the manufacture of cannulae for blood vessels, and later of catheters. This material had originally been developed as an extrusion molding resin exhibiting superior hydrolytic stability than their polyester-based counterparts.

Although many polyurethanes and polyurethaneureas are available commercially, some of which were discussed above, none forms membranes of permeability, strength, flexibility and biocompatiblity required for growing cells by permitting the passage of nutrients, cell products and cell waste materials while preventing the passage of immunological or microbiological substances that might be detrimental to cell growth and the manufacture of cell products.

The following patents describe various devices that have been used for delivering medicaments to the body. All of these devices are constructed with copolymers that are either commercially available or are variants thereof.

U.S. Patent No. 4,631,0532 Taheri discloses an apparatus for the oxygenation of blood that comprises a hollow membrane with a central tubular portion and radially outwardly extending diffusion elements. The membrane is disposed within a sheath and both are supported by a flexible wire, one end of the membrane and the sheath being secured to the wire, and the other end of the membrane and the sheath being

secured to a separate tube through which oxygen is supplied to the hollow membrane.

U.S. Patent No. 4,710,167 to Lazorthes relates to an implantable device for chronically injecting a substance such as a therapeutant. The device is to be implanted in an accessible subcutaneous zone of the body of the patient. The device has an injection chamber bounded by an integral rigid case having a recess of rounded, concave shape. The case has a rim onto which is impermeably fixed an elastic membrane by its own rim. The elastic membrane, when at rest, is essentially planar. A catheter is connected to the injection chamber. U.S. Patent NO. 4,718,894 to Lazorthes discloses a manually actuated, implantable device to sequentially feed doses of a substance such as a therapeutant. The device comprises a reservoir consisting of a flexible pouch, a filling site located at the rim of the pouch and a manual pump. The pump has a rigid case with a recess and bearing and expulsion membrane so as to bound a volume chamber. A safety means prevents any accidental injection in the event of a spurious pressure exerted on the flexible pouch.

U.S. Patent No. 4,877,029 to Valentini et. al. relates to a medical device employing semipermeable material such as a acrylic copolymers, polyurethane isocyanate and other biocompatable semipermeable polymers, The device utilizes these materials in a tubular semipermeable conduit to receive ends of severed or damaged nerves. The conduits define lumens through which axions can regenerate to restore motor and/or sensory function.

U.S. Patent No. 4,904,260 to Ray et al relates to the implantation of two prosthetic disc capsules side-by-side into a damaged disc of the human spine that permits the maintenance of height and motion thereof.

U.S. Patent No. 4,850,958 to Berry et al discloses a device for in vivo extrapulmonary blood gas exchange provided with a bundle and a plurality of elongated gas permeable tubes bound at each end, the tubes being enclosed within an air tight proximal and distal chamber.

U.S. Patent No. 4,911,689 to Hatler discloses percutaneous oxygenator having a Y shaped tubular connector and a number of hollow, gas-permeable fibers provided with loops. The fiber loops can be crimped and/or twisted into a helical arrangement to enhance gas exchange.

U.S. Patent No. 4,825,940 to Meyer et al relates to a biocompatible covering surrounding the fixation helix of an implantable cardiac electrode and its lead for intravenous insertion to a selected cardiac chamber.

U.S. Patent No. 4,950,256 to Luther et al. 4,892 discloses an intravascular catheter comprising a cannula for insertion into a vascular system of a patient coated with a hydrophilic polymer containing polymyxin in the polymer to prevent the growth of microorganisms.

U.S. Patent No. 4,960,415 to Reinmuller discloses a device for inserting in wounds and wound

cavities consisting of a container with a pharmaceutical compound, the walls of the container consisting at least partly of a membrane, preferably a semi-permeable membrane, allowing the active substance to escape into the wound area. The container is preferably a dialysis tube that is conveniently connected to a drainage tube.

U.S. Patent No. 4,892,538 to Aebischer et al. discloses a device for delivering a neurotransmitter from an implanted, neurotransmitter-secreting cell culture to a target region in a subject. The cell culture is maintained within a biocompatible, semi-permeable membrane that permits the diffusion of the neurotransmitter therethrough while excluding viruses, antibodies, and other detrimental agents present in the external environment from gaining access thereto.

U.S. Patent No. 4,209,014 to Sefton relates to an implantable device for dispensing a medicament in two modes: a basal delivery rate and an augmented rate. The device includes a permeable elastic material adapted to be repeatedly compressed by a solenoid-operated piston. The device delivers a basal rate when the piston is inoperative and an augmented rate when permeable elastic material is compressed.

U.S. Patent No. 4,353,888 to Sefton discloses the encapsulation of mammalian cells in a polymeric membrane to form beads ready for introduction into a host body. The membrane allows the passage of cell substrates and secretions but prevents the passage of larger molecules such as antibodies. These are

intended to be transplanted into a host for delivery of insulin while the cells are protected against the immune reaction of the antibodies of the host. The encapsulation is done in a non-solvent such as PEG and a polymer such as acrylic/methacrylic acid ester copolymers.

U.S. Patent No. 4,883,699 to Aniuk et al. discloses an implant made from a multiple phase polymer shown in Figure 1 of the patent. The polymer may be polyurethane having characteristics different from the polymer utilized in the film or membrane of this invention.

U.S. Patent No. 4,772,267 to Brown discloses a catheter assembly shown in Figure 1 of the patent. The catheter comprises a cannula, a flashback plug, a protector, and other parts.

U.S. Patent No. 4,911,717 to Gaskill, III discloses an intravascular artificial organ having a flexible, hollow, semi-permeable catheter containing living cells or tissue. The catheter is made of a material permitting the passage of molecules of molecular weight up to 50,000 Daltons.

U.S. Patent No. 4,402,694 to Ash et al. discloses a device that can be inserted into the human body, particularly into a body cavity, for supplying a hormone to a patient. The device includes an implantable housing which is to be placed in the body and an impermeable extracoporeal segment. Pancreatic islet cells may removably be positioned in the housing to provide a hormone supply to the patient. A sensor is located within a subcutaneous

segment and connected to a dispenser releasing medication into the housing and to the patient.

Accordingly, there is still a need for an improved implantable device that is biocompatible, can permeate electrolytes and nutrients from the blood and other body fluids to permit the growth of live viable cells and therefore permitting them to live and thrive while implanted inside a human body to interact with the body fluids and provide a therapeutic or prophylactic treatment needed by a patient.

The repeated injection of a therapeutic to a patient has many disadvantages including pain and infection. Thus, the injections are usually administered as far apart as possible. This produces large increases and decreases of the therapeutant in the blood of the patient, which brings about undesirable symptoms when the level is not constant. A more effective treatment is that where the level of a compound is maintained more or less constant in accordance with the body's needs.

Diseases such as diabetes mellitus and other hormone-related diseases are characterized by either low levels or high levels of a component in blood. In the case of diabetes mellitus a low level of insulin production results in hyperglycemia, polyuria and wasting. In all of these diseases it may be desirable to maintain the hormonal levels in blood as constant as possible so that the diseases' symptoms are maintained under control at all times. This is difficult to attain by means of injections or diet. In the past, the use of a sensor to detect changes in

the blood levels of a component has been applied in association with an injection system when the levels vary from the norm. This is complex and still presents the problems of producing pain and infection as potential consequences.

Alternatively, live cells or tissue have been implanted in a patient. The transplantation of tissue has met with limited success because of immune rejection due to a poor tissue match. U.S. Patent No. 3,093,831 to Jordan encapsulated live hormone-producing cells within a membrane capsule in order to avoid this immune reaction. The membrane protects the cells but allows the free passage of hormones and nutrients. The capsules may be injected or surgically implanted. However, this method of therapy has encountered only limited application since for various reasons encapsulated cells once placed in the body only have a limited half life, usually weeks.

Other approaches involve extracorporeal devices or combinations of extracoporeal devices with portions inserted within a patients' body to have access to the blood flow. However, these devices are not readily adaptable to implantation.

All of the above-described technologies present only temporary relief since they need to be readministered or reimplanted.

SUMMARY OF THE INVENTION

This invention relates to an implantable, biocompatible device possessing at least one cavity within which live cells can be introduced and maintained such that when the device is implanted into a subject, the cells are in continuous interaction with the subject's bodily fluids to provide a therapeutic or prophylactic effect to the subject that requires a direct interactive contact with the body fluids, the improvement comprising at least one portion of the outside of the device comprises a non-porous, semi-permeable, biocompatible film formed from a copolymer comprising about 5 to 45 wt% of at least one hard segment, and about 95 to 55 wt% of at least one soft segment comprising at least one hydrophilic, hydrophobic or amphipathic oligomer selected from the group consisting of aliphatic polyols, aliphatic and aromatic polyamines and mixtures thereof; the film having a tensile strength greater than about 350 psi and up to about 10,000 psi, and ultimate elongation greater than about 300% and up to about 1,500%, and a water absorption such that the sum of the volume fraction of absorbed water and the hydrophilic volume fraction of the soft segment exceeds about 100% and is up to about 2,000% of the dry polymer volume and exceeds about 50% and is up to about 95% of the wet polymer volume and the film being permeable to molecules of up to about 6,000 to 600,000 molecular weight and substantially impermeable to cells and particulate matter; wherein when cells are introduced into the device, and the device is implanted in the subject in a manner such that the cells are placed in direct interactive contact with the subject's body fluids permitting the cells to grow, the cells exert their therapeutic effect on the subject in response to the continuous

interactive communication with the subject's body fluids. Different embodiments of the device are provided herein, including some that are made solely of a semi-permeable membrane, and others that further comprise semi-rigid parts, such as a support structure, a means for inserting and removing the device, and the like.

One particular embodiment of the present invention relates to any of the aforementioned implantable, biocompatible therapeutic or prophylactic devices wherein a hydrogel that comprises greater than about 35% water is placed within the cavity of the device to maintain an even distribution of cells within the device.

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily perceived as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a device comprising an oval, rectangular or decameric ring made of a semi-rigid polymer, two large sections of the internal cavity being enclosed by the film which is solvent sealed to the ring.

Figure 2 shows a multiple packet of film tubes which may be heat-sealed at one or both ends, or at other points.

Figure 3 shows a film insert lacking a semi-rigid structure and including various tubes placed

along side one another that are heat-sealed by themselves at both ends.

Figure 4(a) is a perspective view showing a mattress-style device made of two flat sheets of film heat-sealed around the periphery thereat and at different areas within the films to define various internal cavities with all cavities in flow communication with one another. This device has an opening that may be filled with cells and a medium, and where the opening may be heat-sealed prior to implantation. Figure 4(b) shows the top of the mattress-style device as it is filled with cells and medium.

Figure 5 shows a continuous film tube that is end-plugged with a semi-rigid disk of e.g., silicone or polyurethane. The plug may be solvent-bonded to the film.

Figure 6 shows a similar continuous tube with plugs at both ends and further having a means for maintaining the tube in an extended position. This may be a stiffener made of a semi-rigid or rigid polymer positioned within the tube.

Figure 7(a) shows a film tube that is end-sealed with an end portion that strengthens it. It also has a means for maintaining the tube in an extended position that may be made of a semi-rigid or rigid material. Figure 7(b) is a similar device comprising multiple tubes, the device having one center "stiffener" made of a semi-rigid or rigid material.

Figures 8(a), (b) and (c) are three different views of a disk comprising four film chambers in the form of a wagon wheel. In this embodiment the chambers are not connected to one another. Figure 8(d) shows a wagon wheel with seven film chambers where six film chambers surround a central film chamber, and all the outer chambers are connected to the inner or central film chamber through connecting channels within the disk.

Figure 9 shows a strip made of a semi-flexible material containing three film chambers connected to one another by channels within the structure. Cells and medium can be injected into any one of the film chambers through the structure material which then closes up again.

Figure 10(a) shows a semi-flexible polymeric structure containing two film chambers that are not connected to one another. Cells and medium may be injected through the polymeric structure. Figure 10(b) is similar to 10(a) but contains a flow channel connecting the two chambers. Figure 10(c) is still a similar structure containing six different film chambers that can be filled with cells and medium. These structures may be made as a punched pad and as in the case of Figure 10(b) the chambers may also be connected to one another.

Figure 11(a) shows a device formed by a ring and a film chamber before being filled with cells and medium. This device has a port for allowing the equalization of internal and external pressure, particularly during filling of the chamber, which is done via a syringe through the polymeric material of

the ring. The film is solvent bonded to the ring and the pressure equalization port is inserted laterally into the ring material. Figure 11(b) shows the device after being filled with cells and medium. The openings made by a syringe in the ring material close by themselves. Figure 11(c) is another embodiment of the ring-film device that contains a port for injection of the cells and the medium. This port has a non-bonded area which is heat-sealed after filling. The membrane is solvent-bonded to the disk.

Figure 12(a) shows an intradermal device similar to the one of Figure 11 except that the chamber is skewed to one side of the disk and the thicker part of the disk contains a port for injection of cells and medium. This device is inserted under the skin and the fat pad positioned thereunder. The cells and the medium are injected with a syringe through the port of injection positioned under the skin after the device has been implanted. Figure 12(b) is a perspective top view of the same device. Figure 12(c) is a perspective side view of the device showing the connector channel between the chamber and the port of injection. The latter can be made in color for best visibility and made of silicone and polyurethane semi-rigid material.

Figure 13(a) shows a device comprising a semi-flexible structure with holes that are, e.g., punched into the structure and a long film tube that is woven through the hose of the structure. Figure 13(b) shows a similar structure where the tube(s) are heat-sealed to the structure.

Figure 14(a) is a different embodiment of the device of Figure 13(a). The device of Figure 14(a) is made of two oblong disks that have holes that can accommodate the diameter of the film tube. The film tube is woven through the two oblong disks, and the disks are kept apart and the tube in an extended position by a means for holding them in that position. In this case the holes may also be punched into the disk. Figure 14(b) is a perspective side view of the device of Figure 14(a).

Figure 15(a) is a representative view of the blood flow system in an individual. The ends of the figure represent the arterial anastomosis and the venous anastomosis. It is at one of these points that the device exemplified in Figure 15(b) is inserted after being filled with cells and medium. The internal cavity is opened and in flow communication with the blood fluid which passes through it and diffuses or permeates through a film tube in accordance with the invention to reach the cells that are lodged in an open matrix, e.g., foam matrix, it having interconnected pores for strength and free cell-permeant communication. Surrounding the matrix where the cells grow is an impermeable tubular structure made of a flexible polymer that prevents the permeation of plasma under arterial pressure. On the outside of this impermeable barrier there is a microporous tissue interface providing a controlled degree of tissue ingrowth and fixation. This permits the device to stay in place and minimizes the likelihood of it sliding out of its position with time.

Figure 16 shows another circulatory device in the form of a catheter made of a semi-rigid inner conduit that is connected to a port of entry for the cells and medium and a second port to permit pressure equalization. The device in the form of a catheter comprises two concentric chambers, the inner one being the semi-rigid stiffener and fill port, and the outer one where the cells grow. The fill port runs the length of the catheter and has an opening at the opposite end from the ports of entry and pressure equalization. At the same end where the opening is positioned there is a soft radio opaque tip for insertion thereof.

Figure 17 shows another circulatory device similar to the one shown in Figure 15(b) but comprising various inner tubes for blood flow instead of one. In addition, this device has two septa and tapered ends.

Figure 18 is another embodiment of the device shown in Figure 14(a) and 14(b). This embodiment of the device has two disks with openings through which a film tube is woven between the two disks and a means for inserting the device and maintaining the tubes in an extended position.

Figure 19(a) is a variation of the device of Figure 3 where several film tubes are placed in parallel and heat-sealed to one another at the ends with a flexible structure for strength. This embodiment of the device also has an outer flexible covering with openings for passage of fluids that permit the interaction of, e.g., blood components with the cells lodged inside the film tubes. In

another embodiment the outer flexible cover is semi-permeable and may or may not have openings, but permits the passage of fluids such as those used in wound drain materials. Figure 19(b) is similar to the device of Figure 19(a) and shows the flexibility of the insert.

Figure 20(a) is a front view of another embodiment of the device. This embodiment comprises a plurality of film tubes that are heat-sealed together with a reinforcement tab at each end. Each reinforcement tab is provided with an opening that permits the insertion of means for inserting the device that may be in the form of a rod. Figure 20(b) is a side view of a similar device. Figure 21(a) shows an embodiment of the device that is similar to that of Figure 20 except for the fact that the ends of the tubes are heat-sealed at the two ends but there is no reinforcement provided those points. This figure shows the device before being inserted. Figure 21(b) shows the device in place after being implanted. The film tubes are filled with cells and engorged. The outside of the device may be a mesh implant housing or a matrix to keep the device in place.

Other objects, advantages and features of the present invention will become apparent to those skilled in the art from the following discussion.

The polymers of the present invention may be synthesized to have a specific permeability to a given permeant and/or to have a specific molecular weight cutoff, by implementing an empirical, yet systematic approach. The empirical nature of the method is mandated by the nature of the phenomenon of

permeability through dense membranes, the properties of specific permeants or non-permeants, including their solubility properties, molecular size and conformation. The inventors provide herein a systematic approach to the production of membrane polymers in accordance with the present invention, which may be used to tailor membrane properties for specific applications. This is described briefly in the following paragraphs.

The permeation of solutes through dense polymeric membranes is determined for the most part by the diffusivity and solubility of the permeants in the membrane polymer. If the membrane polymer absorbs a significant amount of the solvent, then the permeation of the solutes will be determined by the diffusivity and solubility of the permeants in the solvent-swollen membrane polymer.

The absorption of a solvent, e.g., water, by the membrane polymer requires that the polymer have some affinity for the solvent. In addition, by definition, the solvent must be capable of dissolving the solute/permeant. It follows, thus, that the absorption of the solvent by the membrane may increase contribution of the solubility factor to the permeability coefficient by making the environment within the membrane polymer more like the pure solvent than it was in the dry state.

In general, in addition to enhancing the solubility of the permeant in the membrane polymer, a low molecular weight solvent will often act as a plasticizer for the membrane polymer. Plasticization involves a degree of dissolution of the polymer by the plasticizer. Furthermore, as the level of plasticizer/solvent increases, the glass transition temperature of the mixture will generally decrease.

A decreased glass transition temperature suggests that the plasticizer may facilitate the relative movement of macromolecular chains by inserting themselves between adjacent chains to increase the intermolecular spacing there between. In addition to the above, plasticizer/solvents may reduce the degree of possible polymer-polymer interactions through specific interactions between the polymer and the plasticizer/solvent. A reduction in the soft segment crystallinity upon hydration, which occurs with certain membrane polymers of the present invention, is an example of the latter mechanism.

In the case of an isotropic polymer membrane, significant solvent absorption/swelling will produce a measurable increase in the physical dimensions of the membrane, e.g., along each of the x, y and z axes, by an amount approximately equal to the cube root of the volume fraction of the solvent absorbed therein. This provides direct evidence that the polymer chains have increased intermolecular distance in the swollen state since the same number of polymer molecules are now contained in a larger total volume. This increased spacing and facilitated movement of polymer chains may increase permeability by increasing the diffusivity contribution to the permeability coefficient.

Thus, the absorption of a solvent by a membrane polymer may enhance the membranes permeability by increasing both the diffusivity and the solubility of a particular permeant. One method of tailoring the membrane of the present invention to obtain a specific permeability rate and/or molecular weight cutoff, is to vary the composition and morphology of the membrane. This will effect an enhancement of the amount of solvent absorbed, and of the extent of

solubility and diffusivity that results from greater solvent absorption.

Although in some instances it may not always be possible to make exact quantitative predictions of the permeation characteristics of the resulting membrane, the inventors have found that certain qualitative and quantitative relationships exist which guide the process. The structure vs. property relationships provided in Table 1 may be used to adjust the permeability properties of the membrane through an iterative process of synthesis, membrane casting and permeability measurement, until the desired values for the intended use are attained.

In the examples provided below it is assumed that the permeant is a water-soluble macromolecule and that the solvent is water or an aqueous fluid. Those skilled in the art will know that similar approaches may be applied that are suited for other solvent/permeant systems by modifying the soft segment to facilitate the absorption of a non aqueous solvent, for example.

Table 1: Membrane Polymer Structure Versus Property Relationships

Variable	Effect
Increasing Soft Segment Molecular Weight	• Increases water absorption at constant soft segment hydrophilicity and constant soft segment content (++) • Increases permeability rate (+++) • Increases molecular weight cutoff (++) • Increases (dry) soft segment crystallinity (++) • Decreases (dry) tensile modulus unless soft segment crystallizes (-) • Increases ultimate tensile elongation unless soft segment crystallizes (+)
Increasing Soft Segment Hydrophilicity	• Increases water absorption at constant soft segment molecular weight and constant soft segment content (+++) • May increase soft segment crystallinity if hydrophilic segments crystallize (++)
Increasing Hard Segment Content	• Decreases permeability rate (- - -) • Increases tensile strength (++) • Increases tensile modulus (+++) • Increases wet strength (++)
Increased Hard Segment Domain Size	• Increases permeability rate at constant hard segment content (+)
Mixing Two or More Soft Segments	• Increases permeability rate when it decreases soft segment crystallinity (++) • Can be used to increase solubility of permeant in polymer (by adding groups which have an affinity for permeant) and therefore increase permeability (++)
Crosslinking At Low Crosslink Density	• Increases permeability if used to obtain strength by significantly reducing hard segment content. (++) • Can decrease permeability rate and molecular weight cutoff at higher crosslink density (- - -)

(+) and (-) refer to the nature of the effect and its intensity:
(+++) = Strong positive effect.
(-) = Weak negative effect, etc.

The hard segment of the copolymer of the invention may preferably have a molecular weight of about 160 to 10,000, and more preferably about 200 to 2,000. Its components also have preferred molecular weights as shown in Table 2 below.

Table 2: Preferred Molecular Weights for Hard Segment Component

Hard Segment Component	Most Preferred MW	Preferred MW
Aromatic Diisocyanates	150-270	100-500
Aliphatic Diisocyanates	150-270	100-500
Chain Extenders	60-200	18-500

Although both the hard and soft segments may be utilized in a broad range of molecular weights, Table 3 below shows typical useful molecular weight ranges and preferred molecular weight ranges for some exemplary components of the soft segment.

Table 3: Preferred Molecular Weights for Soft Segment Components

Soft Segment Component	Most Preferred MW	Preferred MW
Polyethylene oxide	1000-9,000	200-1,000,000
Polytetramethylene oxide	2000-2,900	500-50,000
Polypropylene oxide-polyethylene oxides	1000-5,000	500-50,000
Polytetramethylene oxide-polyethylene oxides	1000-2,000	500-50,000
Amine-capped polypropylene-polyethylene oxides	600-6,000	200-1,000,000
Polycarbonates	300-3,000	200-50,000
Amine-capped polytetramethylene oxides	500-2,000	200-50,000
Hydroxyl-alkyl and amine-capped silicones	200-5,000	100-20,000
Silicone-polyethylene oxides	500-5,000	200-1,000,000
Polybutadienes	500-3,000	200-50,000
Polyisobutylenes	1,000-5,000	500-10,000

The content of hard segment of the copolymer is typically about 5 to 45 wt%, the remainder of the

polymer consisting of soft segment, which may be a combination of hydrophilic, hydrophobic and amphipathic oligomers. In one preferred embodiment, the copolymer comprises about 9 to 30 wt% of the hard segment, and more preferably 10 to 28 wt% thereof. Similarly, a typical content of the soft segment is about 91 to 70 wt%, and more preferably about 90 to 72 wt%. However, other proportions of hard and soft segments are also suitable for practicing this invention.

A polymer made from this composition will have the properties described in Table 4 below.

Table 4: Characteristics of Film of the invention

Characteristics	Range
Tensile strength	about 350 and up to about 10,000 psi
Elongation at Break	about 300 % and up to about 1,500%
Water Absorption + Hydrophilic Soft Segment	about 100% and up to about 2,000% dry wt
	about 50% and up to about 95% wet wt or more preferably:
Water absorption only	about 100 % and up to about 2000% dry wt
	about 50% and up to about 95% wet wt
Thickness (when unsupported)	about 5 to 100 microns
Thickness (when supported or reinforced)	about 1 to 100 microns

This invention also provides a non-porous, semi-permeable, biocompatible film that comprises the

block copolymer of the invention. In a preferred embodiment, the film is formed from the copolymer of this invention. In another preferred embodiment the film is coated onto a support. In still another preferred embodiment, the film is an integrated part of the substrate and is made of the same or similar polymer.

In particularly preferred embodiments, the non-porous film of the invention is provided in the form of a flexible sheet and a hollow membrane or fiber. Typically, the flexible sheet may be prepared as a long rollable sheet of about 10 to 15 inches width and 1 to 6 feet length. However, other dimensions may also be selected. Of particular importance is the thickness of the sheet which may be about 5 to 100 microns, and more preferably about 19 to 25 microns when it is to be used without support or reinforcement.

The flexible sheet is prepared from the block copolymer of the invention by methods known in the art, typically, by casting, and more preferably by casting on a web or release liner. As already indicated, the composition may be coated as a film onto a substrate. Where permanently supported on a reinforcing web, e.g., a fabric, the film or membrane may be thinner, e.g., as thin as about 1 micron, whereas when used unsupported the thickness may only be as low as about 5 to 10 microns.

When membranes are fabricated from the polymer of the invention by knife-over-roll casting onto a release paper, web or liner in the form of dry films, they may have an about 1 to 100 micron nominal thicknesses on a continuous coating line. A 20-foot-long continuous web coater may be utilized having, e.g., a maximum web width of 15 inches

equipped with two forced-air ovens. In one particular embodiment, the coater may be modified for clean operation by fitting the air inlet ducts with High Efficiency Particulate Air (HEPA) filters. A nitrogen-purged coater box may be used to hold and dispense filtered polymer solutions or reactive prepolymer liquids. However, other set-ups are also suitable.

All but trace amounts of a casting solvent, e.g., dimethylformamide may be removed by coater's hot air ovens fitted with HEPA filters. After membrane casting, membrane and substrate may be further dried to reduce residual solvent content to less than about 100 ppm, as determined by liquid chromatography. The thickness of the fully-dried cast films may be measured by, e.g., using a spring micrometer sensitive to 0.0001 inch (2.5 μM) or visually by using a microscope.

The membrane of this invention may have any shape resulting from a process utilizing a liquid which is subsequently converted to a solid during or after fabrication, e.g., solutions, dispersions, 100% solids prepolymer liquids, polymer melts, etc. Converted shapes may also be further modified using methods such as die cutting, heat sealing, solvent or adhesive bonding or any of a variety of other commonly-used fabrication methods. For example, when in the form of a hollow tube, the membrane is generally prepared with a diameter of about 0.5 to 10 mm , and more preferably about 1 to 3 mm, and a thickness of about 1 to 100 microns, and more preferably about 19 to 25 microns. The hollow membrane may easily be prepared in long rollable form, and be cut to a length of about 0.75 to 31 inches, and more preferably about 0.5 to 6 inches.

In fact, any device known or to be designed that comprises at least a portion thereof made of this semi-permeable, biocompatible film or membrane of this invention is encompassed within the confines of the present invention. The film or membrane utilized in the manufacture of the present device has very specific characteristics that permit the permeation of molecules of desired molecular weights without permitting, at the same time, the passage of cells or particulate matter, or high molecular weight biological materials that would interfere with the functioning of the cells. One such example is an immunological response that may be mounted against foreign cells. This would produce a rejection of the implant with other materials where the immunological components can cross the barriers separating the cells from the blood flow. In the present device, the film or membrane of the invention does not permit the passage of molecules having molecular weights larger than a certain desired cut-off point. Thus, utilizing the polymers described herein, the films may be produced that are custom tailored for specific applications. The film utilized in the devices of this invention is non-porous and may be provided in the form of a flexible sheet, a hollow membrane or fiber. Typically, the flexible sheet may be prepared as a long rollable sheet of about ten to fifteen inches in width, and about one to six feet in length. However, other dimensions may also be selected. Of particular importance is the thickness of the sheet which may be about five to one hundred microns, and more preferably about nineteen to twenty-five microns when it is used without a support or reinforcement. The non-porous film or membrane of this invention is semi-permeable, has a tensile strength greater than

about 350 psi and up to about 10,000 psi, an ultimate elongation greater than about 300% up to about 1,500%, and a water absorption such that the sum of the volume fraction of absorbed water and the hydrophilic volume fraction of the self segment comprising the polymer exceeds about 100% and up to about 2,000% of the dry polymer volume, and exceeds about 50% and is up to about 95% of the wet polymer volume, and is permeable to molecules of up to about 6,000 to 600,000 molecular weight and substantially impermeable to cells and particulate matter.

The films or membrane of this invention may be formed from a biocompatible, hydrophilic, segmented biocompatible polyurethane copolymer that comprises about 5 to 45 wt% of at least one hard segment, and about 95 to 55 wt% of at least one soft segment comprising at least one hydrophilic, hydrophobic, or amphipathic oligomer selected from the group consisting of aliphatic polyols, aliphatic and aromatic polyamines, and mixtures thereof. Particularly preferred aliphatic polyols for the soft segment are those selected from the group consisting of linear, branched and graft polyalkylene oxides, polyalylene and polyalkenyl oxides, random and block copolymers thereof, polycarbonate polyols, hydroxyl-terminated silicones, random and block copolymers thereof, with polyalkylene oxides, linear and branched polyalkenyl, polyalkylene polyols and mixtures thereof.

Preferably, the soft segment of the polymers are selected from the group consisting of amine-terminated polyalkylene oxides and random, block and graft copolymers thereof, amine-terminated polydialkyl siloxanes, random and block copolymers thereof with polyalkylene oxides and mixtures

thereof. The end group may be selected from monofunctional aliphatic polyols, aliphatic or aromatic amines and mixtures thereof. the monofunctional aliphatic polyols of the end cap may be selected from the group consisting of monofunctional polyalkylene oxides, siloxane and mixtures thereof, and the monofunctional amines of the end group may be selected from the group consisting of dialkyl amines, amine functional siloxanes, amine terminated polyalkylene oxides, and mixtures thereof.

Typically, the soft segment is selected from the group consisting of reaction products of an organic diisocyanate with a polyamine and a polyol. The organic diisocyanate of the hard segment may be selected from the group consisting of alkyl diisocynates, arylalkyldiisocyanates, alkyl-cycloalkyl diisocynates, alkylaryl diisocyanates, cycloalkyl diisocyanates, aryl diisocyanates, and cycloalkylaryl diisocyanates, which may be further substituted with oxygen and mixtures thereof.

The polyol of the hard segment may be selected from the group consisting of alkylene cycloalkylene and arylene diols, triols, tetraalcohols, pentaalcohols and mixtures thereof.

The polyamine of the hard segment may be selected from the group consisting of alkyl, cycloalkyl and arylamines, which may be further substituted with N, O or halogen, complexes thereof with alkali metal salts and mixtures thereof.

Preferably, the soft segment comprises a polyethylene oxide of molecular weight greater than about 3,000 daltons, and more preferably greater than about 8,000 daltons. In another preferred embodiment, the soft segment comprises a blend of

polyols selected from the group consisting of a polyethylene oxide of molecular weight greater than about 3,000 daltons polyethylene oxide-polytetramethylene oxide and a polyethylene oxide homopolymer, a polyethylene oxide-polytetramethylene oxide copolymer and an ethylene oxide-polyethylene oxide copolymer, a polyethylene oxide polypropylene oxide copolymer and a polyethylene oxide homopolymer, a polyethylene oxide-polypropylene oxide copolymer and a polypropylene oxide homopolymer, a polyethylene oxide homopolymer and a polytetramethylene oxide homopolymer, a polyethylene oxide-containing polymer and a polycarbonate homopolymer, a polyethylene oxide-containing polymer and a polybutadiene homopolymer, and a polyethylene oxide-containing polymer and a polyisobutulene polymer, and blends thereof. Preferably the soft segment comprises a blend of a polyethylene oxide-polytetramethylene oxide copolymer and a polyethylene oxide homopolymer. Another preferred soft segment is a blend of a polyethylene oxide-polytetramethylene oxide copolymer and a polyethylene oxide-polypropylene oxide copolymer. Still another preferred soft segment is a blend of a polyethylene oxide-polytetramethylene oxide copolymer and an ethylene-oxide Polypropylene oxide polymer. Still another preferred soft segment is a blend of a polyethylene oxide-polypropylene oxide copolymer and a polyethylene oxide homopolymer. Another preferred soft segment still is a blend of a polyethylene oxide-polypropylene copolymer and a polypropylene oxide homopolymer. Also preferred is another soft segment comprising a blend of a polyethylene oxide homopolymer and a polytetramethylene oxide homopolymer providing the copolymer with a decreased tensile strength and an

elongation in the width state when compared to its dry state. Other preferred soft segments are those comprising a blend of a polyethylene oxide-containing polymer and a polycarbonate homopolymer, and blend of a polyetheylene oxide-containing polymer and a polybutadiene homopolymer, a blend of a polyethylene oxide-containing polymer and a polyisobutylene homopolymer.

A further description of the preparation of the polymer and the characteristics of the soft and hard segments and its components is provided by co-filed, co-pending, U.S. Patent application entitled COPOLYMERS AND NON-POROUS, PERMEABLE MEMBRANE THEREOF AND ITS USE FOR PERMEATING MOLECULES OF PREDETERMINED MOLECULAR WEIGHT RANGE by Robert S. Ward and Kathleen A. White, (U.S. Ser. No. 07/874,336) the text of which relating to the components, characteristics of the polymer and its mode of preparation is incorporated herein by reference. The film of the invention may be prepared by casting, and more preferably by casting on a web or release liner. However, other methods of preparation are also suitable. In addition, the composition may be coated as a film onto a substrate. Where permanently supported in a reinforcing web such as a fabric, the film or membrane may be thinner than when standing alone. Thicknesses of one micron and less are possible, whereas when used unsupported, the thickness may only be as low as about five to ten microns. Membranes or films may be made from the polymer of the invention by knife-over-roll casting onto a release paper web or liner in the form of dry films, they may have about one to one hundred micron nominal thickness on a continuous coating line. A twenty-foot long continuous web of film may be

utilized having, for example, a maximum web width of fifteen inches. The details of the preparation of the film or membrane and the hollow fibers is thoroughly described in the co-filed, co-pending application described above, the entire content of its text relating to this matter being incorporated herein by reference.

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily perceived as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying figures.

Other objects, advantages and features of the present invention will become apparent to those skilled in the art from the following discussion.

DESCRIPTION OF THE PREFERRED EMBODIMENTS AND THE BEST MODE

This invention arose from a desire by the inventors to improve on prior art technology for the in vivo treatment of patients suffering from a metabolic disease. A typical application of the present device is for the implementation of gene therapy to compensate for any deficiencies that the genetic makeup of a patient may have. In a typical example, a patient suffering from diabetes may be treated by implanting one of the present devices that is filled with cells capable of producing, i.e., insulin or another compound, when in direct contact with the patient's blood flow or other bodily fluids.

In a particularly preferred embodiment, the device serves to implant regulatable cells that are

capable of responding to changes in the levels of the compound to be regulated in blood.

Thus, for instance, cells having the capability of responding to increased glucose levels by producing increasing amounts of insulin are particularly suitable. These cells increase their production of insulin when the level of glucose in blood increases. Thus, such an implant of insulin producing cells provides a constant source of insulin in the amounts needed to regulate the blood glucose levels to a constant value.

A method for the in vivo treatment utilizing the present device is disclosed in co-pending, co-filed U.S. Application entitled "METHOD OF CULTURING VIABLE CELLS AND METHOD OF REGULATING BLOOD GLUCOSE LEVELS BY IMPLANTATION OF VIABLE CELLS IN NON-POROUS SEMI-PERMEABLE MEMBRANE", by Robert S. Ward, John Monahan and Robert Kuhn, (Attorney Docket No. SOMA 20111.USA) the portions thereof relating to the method of utilizing the present device and the related kits being incorporated herein by reference.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The different embodiments of the present devices will be described in detail with reference to the drawings.

The device (48) shown in Figure 1 is made of two polymeric film (1) sections in accordance with this invention that are solvent-sealed (3) to an oval, rectangular or decameric ring (2) made of a semi-rigid polymeric material such as polyurethane, silicone, and the like. Other materials that are not necessarily permeable to nutrients and the medium may also be utilized as long as they are biocompatible. Each portion of the film (1) is solvent-sealed (3)

all around the ring (2) and on one side thereof. This embodiment of the invention may comprise a ring (2) of different shapes and thicknesses. For instance, the ring (2) may be circular, it may be in the shape of a polygon with varying numbers of sides such as three, four, five, six, seven, eight, nine, ten, eleven, twelve sides, and the like. The ring (2) itself, may be thin or it may have some thickness in the direction determined by a plane intersecting both film (1) planes. This type of device is particularly suited for subcutaneous implantation in the peritoneal cavity. However, it may also be utilized for implantation in other areas of the body.

The embodiment shown in Figure 2 consists of a multiplicity of film tubes (12) or packets that are filled with cells and medium and then heat-sealed (5) to one another at one or both ends thereof. The device shown has three film tubes (12) or packets filled with cells that will be sealed together.

The embodiment shown in Figure 3 consists of several film tubes (12) heat-sealed to one another (7) at their ends, and may be attached (46) to a support (13) or end portion.

The device shown in Figure 4 is similar to an inflatable mattress. It consists of two films (1) that are heat-sealed (9) to one another to define cavities (47) therewithin. These cavities are filled with cells by means of a syringe (20) and a needle (50) through an opening (8) for insertion of the needle (50). Once the cells have been introduced into the device, the opening (8) may be heat-sealed (9) to obtain a totally sealed device. Figure 4(a) shows a perspective side view of the device (48) whereas Figure 4(b) shows a top view of the device (48).

The embodiment of the device (48) of this invention shown in Figure 5 consists of a continuous tube (12) having a plug (10) at one end thereof. The plug (10) is placed on the inside of the tube and it may be made of a semi-rigid material and affixed to the tube (12).

A similar embodiment of the device (48) is shown in Figure 6. In this device (48) there are two additions with respect to that of Figure 5. The first addition is a second plug (10) or reinforcement positioned inside the tube (12) at the opposite end to the first plug (10) or reinforcement. The second addition is a means (11) for maintaining a tube (12) in an extended position. The means (11) may be affixed to the terminal plugs (10) and be made of a semi-rigid or rigid material.

Another embodiment of the present device (48) is shown in Figure 7. This consists of a film tube (12) shown in Figure 7(a). The film tube (12) is maintained in its extended position by a means for doing so (11) in the form of a rod or otherwise. The means (11) for maintaining the film tube (12) in an extended position (11) is provided with an opening (14) or port for the introduction of the cells and the medium into the device (48). In addition, the ends of the film tube (12) are heat-sealed by themselves or with a reinforcement (13) or end portion to strengthen the tube (12) seal. The embodiment shown in Figure 7(b) consists of three to four film tubes (12) that are reinforced by two or three means (11) for maintaining the tubes (12) in an extended position. The ends (46) of the film tubes (12) are heat-sealed to one another and reinforced with an end portion (13) to strengthen the tube (12) seal.

Another embodiment of the device (48) of this invention is shown in Figure 8. This device (48) is in the form of a disk (15) that is provided with openings (49) that may be molded or punched out once the disk (15) is formed. Film chambers (16) are formed for lodging the cells and the medium by positioning two portions of the film (1) of the invention covering each opening (49) on both sides. The film (1) is sealed to one side of the disk (15) and the same is done on the other side. In the unfilled condition, the film chambers (16) have a small volume and in a side view they would look flat. When filled with cells and medium, the film chambers (16) have the form of an egg as is shown in Figure 8(c). Figure 8(a) is the top view of a four chamber device (48). Figure 8(b) is a perspective top side view of the same device (48) and Figure 8(d) is the top view of a seven device (48) consisting of six cell chambers (16) positioned around the border of the disk (15) and a center cell chamber (16). All the peripheral chambers (16) are in flow communication with the center chamber (16) by a means of flow communication (17) connecting each peripheral chamber (16) to the central chamber (16). Figure 9 shows another variation of the embodiment of the device (48) of Figure 8. In this device (48) a semi-rigid structure (18) has three openings (49) defining three cell chambers (16) surrounded by the film (1) of this invention. The three cell chambers (16) are in flow communication with one another by two means of flow communication (17). The cells and the medium are injected into the semi-rigid structure (18) by means of a syringe (20) and a needle (50).

Another embodiment of the device (48) of this invention is shown in Figure 10. Figure 10(a) shows

a semi-rigid structure (18) with openings (49) surrounded by the film (1) of this invention. These cavities are filled with cells and medium by injection through the semi-rigid structure (18). In this embodiment the cell chambers (16) are not in flow communication with one another. The device (48) shown in Figure 10(b) is similar to the one of Figure 10(a) except that it also contains a means for flow communication (17) between the two chambers (16) in the form of a connector between them. A device (48) with six cell chambers (16) is illustrated in Figure 10(c) above. The chambers (16) are not in flow communication with one another. The device (48) shown in Figure 11 is called an "Insulette". It has a semi-rigid ring (2) with two openings (24) each of which is covered with film (1). Each piece of film (1) is solvent-sealed (3) to the borders of the ring (2). In the top side perspective view shown in Figure 11(a), a syringe (20) with a needle (50) are shown in the process of inserting cells and medium through the ring (2). In addition, a port (19) for allowing the equalization of internal and external pressure is also shown attached to the side of the ring (2). This port (19) permits air to come out of the cell chamber (16) when material is introduced therein. Figure 11(b) shows the device (48) from a perspective top side view as in Figure 11(a) but where the chamber (16) is already filled with cells and medium. After the cells and medium are injected, the syringe (20) is removed as is the port (19) for equalizing internal and external pressure. Any openings (49) left by this removal will self seal or may otherwise be sealed with a soldering iron. Figure 11(c) shows a top view of a similar device that also contains a non-bonded fill area or port

(14) for injection of cells and medium, through which a syringe's (20) needle (50) injects the cells into the chamber (16). After the syringe is removed, the port (14) may be removed and the opening (49) leftover may be sealed by itself or be sealed with a soldering iron. Figure 12 shows an intradermal disk (15) in the form of a ring (2) a disk (15) with a large opening (49). Figure 12(a) is a side view of the ring as it is envisioned when implanted under the epidermis (21). The disk (15) or ring (2) is inserted in the fat pad (22) just below the epidermis (21). The cells and the medium are injected by means of a syringe (20) provided with a needle (50) which is inserted through the skin and into a port (14) located on the disk (15) or ring (2) for injection and withdrawal of the cells and medium. The opening (49) provided in the ring (2) or disk (15) is not centered therein. It is positioned at the opposite end from where the port (14) is located. A cell chamber (16) is defined by two portions of the film (1) of this invention that are positioned on both sides of the disk (15) or ring (2) and solvent sealed (3) or heat-sealed (51) to the disk (15) or to the ring (2). Figure 12(b) is a top view of the device (49) and Figure 12(c) is a top side view of the device (49) after the chamber (16) is filled with cells and medium. In this view a means for flow communication (17) between the port (14) for injection of cells and medium and the main chamber (16) can be seen. Another embodiment of the present device (48) is shown in Figure 13. This device (48) consists of a frame made of a semi-flexible structure (23) provided with openings (24) of a size such that they can accommodate the width or diameter of the film tube (12) when it is woven through the openings

(24) as shown in Figure 13(a). The two ends (46) of the tube are sealed after the tube (12) is filled with cells and medium. This figure shows a top view of the device (48) having a film tube (12) woven through the opening (24) of the semi-flexible structure (23). Figure 13(b) is a top view of a similar device (48), except for the fact that the tubes (12) are heat-sealed (25) to the semi-flexible structure (23). This embodiment of the device (48) is made of a multiplicity of film tubes (12) and not of one tube (12) that is interwoven through the openings (24) of the semi-flexible structure (23). A similar device (48) is shown in Figure 14. In this device (48) two disks (15) are positioned at a certain distance from one another and held at that distance by means (11) for maintaining the film tube (12) in an extended position. This may be in the form of a rod or any other means for attaining the same purpose. In this device (48) one film tube (12) is woven through the openings (24) of the two disks (15). Figure 14(b) shows a top perspective view of the same device (48).

Figure 15(a) shows a schematic representation of the blood flow (26) system in the body, having an arterial anastomosis (27) point and a venus anastomosis (52) point. Figure 15(b) shows a cross-sectional view of the device (48) of this invention where a tubular film (12) of the invention defines an internal cavity (31) for the blood to flow through. Around the film tube (12) is an open matrix (28) for lodging and growth of the cells positioned inside and impermeable flexible outer tube (29). Outside of the tube (29) is a microporous tissue interface (30) that controls the degree of tissue ingrowth and fixation of the device (48). This device (48) is inserted in

the blood vessels (26) at the arterial anastomosis (27) or venus anastomosis (52) points shown in Figure 15(a).

A semi-rigid device (48) in the form of a catheter or cannula is shown in Figure 16. This device (48) is comprised of several sections. One section is surrounded by a film tube (12) in accordance with the invention, that is attached to another section made of an impermeable semi-rigid tube (29) by sutures in the form of rings (34) to the impermeable tube (29) are attached a port of entry (14) for injection of the cells and medium and a second port (19) for equalizing the pressure inside and outside of the device (48). The port of injection (14) for the cells and the medium is connected to a semi-rigid inner tube (35) positioned lengthwise inside the film tube (12). The semi-rigid inner tube (35) defines therewithin an internal cavity (16) or fill chamber. The cells grow in a cell chamber (33) surrounding the semi-rigid inner tube (35). On the outside surface of the impermeable tube (29) are positioned to means (32) for affixing the device and permitting tissue ingrowth. At the end of the internal stiffener (35) opposite the sutures (34) and the impermeable tube (29) there is a hole opening into the cell growth area (53), and at the end of the film tube (12) a soft, radiopaque tip (37) for insertion of the device (48) in a blood vessel. Still another embodiment of the device (48) of this invention is shown in Figure 17 for insertion in a blood vessel. Figure 17(a) shows a device (48) consisting of an semi-rigid outside smaller tube (35) with tapered sections (39) at both sides ending in tubular end portions (27) for insertion into the blood vessel. A cutout (38) of the semi-rigid tube

(35) shows a multiplicity of film tubes (12) alternating with an open matrix (28) for lodging and growth of the cells. This semi-rigid tube (35) is provided with a septum or port (40) at each end of its main portion. Figure 17(b) is a cross-sectional view of the device (48) and shows the multiplicity of film tubes (12) as well as the matrix (28) for lodging and growth of the cells. In addition, in this view it can be seen that on the outside of the open matrix (28) is the impermeable flexible outer tube (29). On the outside surface of the impermeable flexible outer tube (29) is positioned a microporous tissue interface (30) to facilitate the anchoring of the device (48) to the body tissue. Figure 18 shows a variation of the device of Figure 14. In the device (48) shown in Figure 18, two semi-rigid disks (15) are made of a semi-rigid material (23) and provided with openings (24) that can accommodate the diameter of a film tube (12). A multiplicity of film tubes (12) are filled with cells and medium and extended between the two disks (15) and pass through the openings (24) and heat-sealed to one another (7) or to the disk (15). The device (48) is provided with a means (41) for insertion of the device and maintenance of the tubes in the extended position that is affixed to the two disks (15). This permits the insertion of its device and its lodging in the proper place. Figure 19 shows a tampon-like device (48) made of a flexible outer structure (43) that may be made of an impermeable or a semi-permeable material such as any wound material. The flexible outer tube (43) is provided with a multiplicity of openings (36) and a multiplicity of film tubes (12) lodged inside the flexible materials (43). The tubes are heat-sealed at both ends (3) to one another as

well as to the flexible outer tube (5). The device has a means for removal (42) attached to one end thereof. Figure 19(a) shows the device (48) in its rigid position. Figure 19(b) shows the flexibility of the device (48). Still another embodiment of the device (48) of this invention is shown in Figure 20. This device (48) is referred to as a cassette and comprises of multiplicity of film tubes (12) parallel to one another that are heat-sealed to a structural polymer (25) for strength. At each end is also positioned an end portion (13) for strengthening the tube seal. Each end portion is provided with an opening (24) that accommodate a removable means for insertion of the device (44), such as a rod. This means (44) may be used for insertion and removal of the cassette. Figure 20(a) shows a front view of the device (48) whereas Figure 20(b) shows a side view of the device (48). A variation on the device of Figure 20 is that shown in Figure 21. This is a cassette consisting of a plurality of film tubes (12) heat-sealed at both ends to one another (7) at one end of the heat-sealed tubes (45) it is inserted a means for inserting and removing the device (44). Figure 21(a) shows the entire device with the removable means of insertion (44) whereas Figure 21(b) shows the device filled with cells and implanted into a matrix (28) where the film tubes (12) are engorged.

With regard to all of the above-described devices, it is preferred that the devices further comprise a hydrogel that comprises greater than about 35% water within the cavity of the device. The hydrogel serves to immobilize the cells within the device, thus insuring an even cell distribution within the device.

Suitable water-swellable gels are alginates (e.g. sodium alginate, ammonia alginates, potassium alginates, propylene glycol alginates, algins), guar gum, gum tragacanth, locust bean gum, methocel, xanthan gum, polyethylene oxide, polypropylene oxide, dextrans, acrylates, methacrylates, polyvinyl alcohol, polyvinyl pyrolidone and combinations of the above.

Those gums or resins capable of "crosslinking" may be used crosslinked or linear. For example, sodium alginate may be used "as is" or converted to its insoluble calcium form.

The preferred hydrogel is an alginate wherein the water content is greater than about 90%. The most preferred hydrogel is calcium alginate.

With regard to all of the embodiments of the present invention, it is preferred that a hydrogel, that comprises greater than about 35% water, be used to suspend the cells. The hydrogel serves to immobilize the cells within the membrane, thus insuring an even cell distribution within the membrane.

The most preferred embodiment of the instant invention comprises the implantation of a dense membrane in the form of hollow fibers where the hollow fiber is filled with calcium alginate with a water content greater than about 90%. However, it is understood that the geometry of the dense membrane can be in any form including sheets, larger diameter tubes, etc.

A further description of the preparation and use of hydrogels is provided by co-filed, co-pending U.S. Patent Application entitle METHOD OF CULTURING VIABLE CELLS AND METHOD OF REGULATING BLOOD GLUCOSE LEVELS BY IMPLANTATION OF VIABLE CELLS IN NON-POROUS, SEMI-

PERMEABLE POLYMERIC MEMBRANES by Robert S. Ward, John Monahan and Robert Kuhn (Attorney Docket No. SOMA-20111), the text of which relating to the use of hydrogels is incorporated herein by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

WHAT IS CLAIMED IS:

1. An implantable, biocompatible device possessing at least one cavity within which live cells can be introduced and maintained such that when the device is implanted into a subject, the cells are in continuous interaction with the subject's bodily fluids to provide a therapeutic or prophylactic effect to the subject, the effect requiring the direct interactive contact of the cells with the bodily fluids, wherein:

at least one outside portion of the device serves as the outside barrier of the cavity, said portion comprising a non-porous, semi-permeable, biocompatible film formed from a copolymer comprising about 5 to 45 wt% of at least one hard segment, and about 95 to 55 wt% of at least one soft segment comprising at least one hydrophilic, hydrophobic or amphipathic oligomer selected from the group consisting of aliphatic polyols, aliphatic and aromatic polyamines and mixtures thereof; the film having a tensile strength in the dry state greater than about 350 psi and up to about 10,000 psi, an ultimate elongation greater than about 300% and up to about 1,500%, and a water absorption such that the sum of the volume fraction of absorbed water and the hydrophilic volume fraction of the soft segment exceeds about 100% and up to about 2,000% of the dry polymer volume and exceeds about 50% and up to about 95% of the wet polymer volume and the film being permeable to molecules of up to about 6,000 to 600,000 molecular weight and substantially impermeable to cells and particulate matter; wherein when cells are introduced into the cavity of the device, and

the device is implanted in the subject in a manner such that the cells are placed in interactive contact with the subject's bodily fluids permitting the cells to grow, the cells exert their therapeutic effect on the subject in response to the continuous interactive communication with the subject's body fluids.

2. The implantable device of Claim 1 wherein the cavity is formed by sealing the film to at least one side of a ring.

3. An implantable device comprised of at least two devices of Claim 2 joined together at one end.

4. The implantable device of Claim 3 wherein the ends are joined together by sealing the ends to a support means.

5. An implantable device comprised of at least two devices of Claim 2 joined together at both ends.

6. The implantable device of Claim 5 wherein the ends are joined together by sealing both ends to a support means.

7. The implantable device of Claim 5 further encased in a flexible outer container possessing a multiplicity of openings.

8. The implantable device of Claim 7 wherein a means for removal of the device is attached to an end of the outer container.

9. The implantable device of Claim 1 wherein the cavity is formed by sealing the edges of the film together.

10. An implantable device comprised of at least two devices of Claim 9 joined together at one end.

11. The implantable device of Claim 10 wherein the ends are joined together by sealing the ends to a support means.

12. An implantable device comprised of at least two devices of Claim 9 joined together at both ends.

13. The implantable device of Claim 10 further possessing a means for strengthening the tube seal.

14. The implantable device of Claim 12 further possessing a means for strengthening the tube seal.

15. The implantable device of Claim 12 wherein the ends are joined together by sealing both ends to a support means.

16. The implantable device of Claim 12 further encased in a flexible outer container possessing a multiplicity of openings.

17. The implantable device of Claim 16 wherein a means for removal of the device is attached to an end of the outer container.

18. The implantable device of Claim 2 wherein two films are sealed to either side of the ring to form at least one cavity.

19. The implantable device of Claim 18 wherein the cavity formed by the ring and the film is divided into more than one cavity by sealing portions of the two films to each other.

20. The implantable device of Claim 19 wherein the device may be filled with cells by inserting the needle of a syringe through an opening, the opening being resealable.

21. The implantable device of Claim 20 wherein the cavities are in flow communication with each other.

22. The implantable device of Claim 21 wherein the device may be filled with cells by inserting the needle of a syringe through an opening, the opening being resealable.

23. The implantable device of Claim 9 wherein the cavity formed is divided into more than one cavity by sealing portions of the two films to each other.

24. The implantable device of Claim 23 wherein the device may be filled with cells by inserting the needle of a syringe through an opening, the opening being resealable.

25. The implantable device of Claim 23 wherein the cavities are in flow communication with each other.

26. The implantable device of Claim 25 wherein the device may be filled with cells by inserting the needle of a syringe through an opening, the opening being resealable.

27. The implantable device of Claim 1 wherein the cavity is a film tube and one end of the tube is sealed with a plug.

28. The implantable device of Claim 27 wherein both ends of the tube are sealed with plugs.

29. The implantable device of Claim 28 wherein a means for maintaining the tube in an extended position is inserted within the tube.

30. The implantable device of Claim 9 further possessing a means for maintaining the device in an extended position.

31. The implantable device of Claim 30 wherein the means for maintaining the device in an extended position possesses a means for introducing cells and medium into the device.

32. The implantable device of Claim 30 further possessing a means for strengthening the tube seal.

33. The implantable device of Claim 12 further possessing at least one means for maintaining the device in an extended position.

34. The implantable device of Claim 33 wherein the means for maintaining the device in an extended

position possesses a means for introducing cells and medium into the device.

35. The implantable device of Claim 33 further possessing a means for strengthening the tube seal.

36. The implantable device of Claim 33 wherein the means for maintaining the device in an extended position possesses a means for introducing cells and media into the device.

37. The implantable device of Claim 1 wherein the cavity is formed by sealing the film to both sides of an opening on a disk.

38. The implantable device of Claim 37 wherein cells may be injected into the cavity through the disk material.

39. The implantable device of Claim 38 further comprising a pressure equalization means.

40. The implantable device of Claim 37 further comprising a port for the introduction of cells and media into the cavity.

41. The implantable device of Claim 37 wherein the disk has more than one film cavity.

42. The implantable device of Claim 41 further comprising a port for the introduction of cells and media into the cavity.

43. The implantable device of Claim 41 wherein cells may be injected into the cavity through the disk material.

44. The implantable device of Claim 43 further comprising a pressure equalization means.

45. The implantable device of Claim 43 wherein the multiple film cavities are in flow communication with each other.

46. The implantable device of Claim 45 wherein cells may be injected into the cavity through the disk material.

47. The implantable device of Claim 45 further comprising a port for the introduction of cells and media into the cavity.

48. The implantable device of Claim 2 wherein cells may be injected into the cavity through the disk material.

49. The implantable device of Claim 48 further comprising a pressure equalization means.

50. The implantable device of Claim 2 further comprising a port for the introduction of cells and media.

51. The implantable device of Claim 50 further comprising a means by which the port and the cavity are in flow communication.

52. The implantable device of Claim 40 further comprising a means by which the port and the cavity are in flow communication.

53. The implantable device of Claim 9 wherein the tube of film is woven through openings in a semi-rigid frame.

54. The implantable device of Claim 53 wherein the film is sealed to itself.

55. The implantable device of Claim 54 wherein a multiplicity of film cavities are formed by sealing the film to itself.

56. The implantable device of Claim 53 wherein the film tube is sealed to the semi-rigid frame.

57. The implantable device of Claim 56 wherein a multiplicity of film tube cavities are formed by sealing the film tube to the semi-rigid frame.

58. The implantable device of Claim 9 wherein the tube of film is woven through openings in two semi-rigid disks, the disks being kept apart by a means for maintaining the tubes in an extended position.

59. The implantable device of Claim 58 wherein the film is sealed to itself.

60. The implantable device of Claim 59 wherein a multiplicity of film cavities are formed by sealing the film to itself.

61. The implantable device of Claim 58 wherein the film tube is sealed to the semi-rigid frame.

62. The implantable device of Claim 60 wherein a multiplicity of film tubes film cavities are formed by sealing the film tube to the semi-rigid frame.

63. The implantable device of Claim 53 further comprising a means for insertion of the device.

64. The implantable device of Claim 54 further comprising a means for insertion of the device.

65. The implantable device of Claim 55 further comprising a means for insertion of the device.

66. The implantable device of Claim 56 further comprising a means for insertion of the device.

67. The implantable device of Claim 57 further comprising a means for insertion of the device.

68. The implantable device of Claim 58 further comprising a means for insertion of the device.

69. The implantable device of Claim 59 further comprising a means for insertion of the device.

70. The implantable device of Claim 60 further comprising a means for insertion of the device.

71. The implantable device of Claim 61 further comprising a means for insertion of the device.

72. The implantable device of Claim 62 further comprising a means for insertion of the device.

73. The implantable device of Claim 1 wherein the cavity comprises an open matrix for the lodging and growth of cells, said matrix being surrounded by an impermeable material, said matrix having a film tube running through its length.

74. The implantable device of Claim 73 wherein the external surface of the device comprises a microporous tissue interface attached to the external surface of the impermeable material.

75. The implantable device of Claim 73 wherein the ends of the device are inserted into blood vessels so that blood flows through the film tube.

76. The implantable device of Claim 74 wherein the ends of the device are inserted into blood vessels so that blood flows through the film tube.

77. The implantable device of Claim 1 wherein the cavity comprises an open matrix for the lodging and growth of cells, said matrix being surrounded by an impermeable material and said matrix having a multiplicity of film tubes running through its length.

78. The implantable device of Claim 77 further comprising a port for the introduction of cells and media into the matrix.

79. The implantable device of Claim 77 wherein the ends of the device are inserted into blood vessels so that blood flows through the film tube.

80. The implantable device of Claim 77 wherein the external surface of the device comprises a microporous tissue interface attached to the external surface of the impermeable material.

81. The implantable device of Claim 79 wherein the ends of the device are inserted into blood vessels so that blood flows through the film tube.

82. The implantable device of Claim 77 further comprising tapered sections attached to the ends of the device wherein the tapered ends are inserted into blood vessels so that blood flows through the film tube.

83. The implantable device of Claim 82 wherein the external surface of the device comprises a microporous tissue interface attached to the external surface of the impermeable material.

84. The implantable device of Claim 82 further comprising a port for the introduction of cells and media into the matrix.

85. The implantable device of Claim 84 wherein the external surface of the device comprises a microporous tissue interface attached to the external surface of the impermeable material.

86. An implantable device comprised of three sections, the first section being comprised of the

film tube of Claim 27 with one end of the film tube comprising a radiopaque tip at the outer end of the film tube, the inner end of the film tube comprising a means for attaching the first section to a second section, said second section comprising an impermeable tube, one end of which is attached to the first section and the other end of which is attached to a third section, said third section possessing a means for introducing cells and media into the device and a means for equalizing the pressure within the device wherein the means for introducing cells and media into the device is attached to a semi-rigid inner tube that is positioned lengthwise within the device terminating at the outer end of the film tube, said semi-rigid inner tube being able to convey cells and media from the entry means to the outer end of the film tube.

87. The implantable device of Claim 86 wherein the second section further possesses means for attaching the device within the body.

88. The implantable device of Claim 15 wherein the end portion possesses an attachment means for attaching a second, removable, insertion means for inserting the device.

89. The implantable device of 88 further possessing a means for maintaining the tubes in an extended position.

90. The implantable device of Claim 15 wherein one end of the tubes possesses an attachment means for attaching a second, removable, insertion means for inserting the device.

91. The implantable device of 90 further possessing a means for maintaining the tubes in an extended position.

92. The implantable device of 90 wherein the device is implanted into a matrix.

93. The implantable device of claim 1 wherein the cavity of the device is filled with a hydrogel, the hydrogel being comprised of greater than about 35% water.

94. The implantable device claim 93 wherein the hydrogel is an alginate.

95. The implantable device of claim 93 wherein the hydrogel is polyethylene glycol

96. The implantable device of claim 2 wherein the cavity of the device is filled with a hydrogel, the hydrogel being comprised of greater than about 35% water.

97. The implantable device claim 96 wherein the hydrogel is an alginate.

98. The implantable device of claim 96 wherein the hydrogel is polyethylene glycol.

99. The implantable device of claim 9 wherein the cavity of the device is filled with a hydrogel, the hydrogel being comprised of greater than about 35% water.

100. The implantable device claim 99 wherein the hydrogel is an alginate.

101. The implantable device of claim 99 wherein the hydrogel is polyethylene glycol.

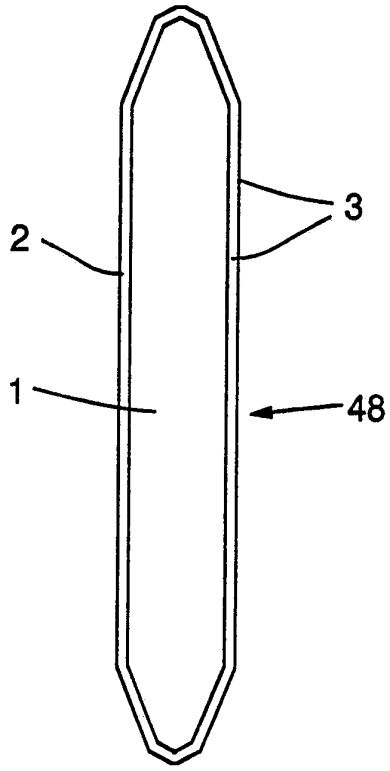

FIG. 1

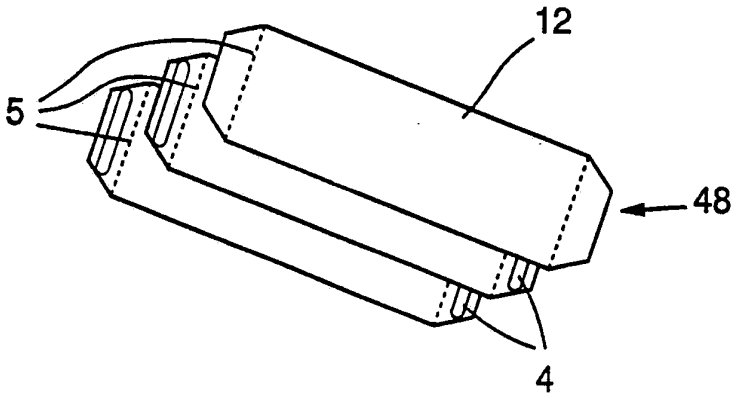

FIG. 2

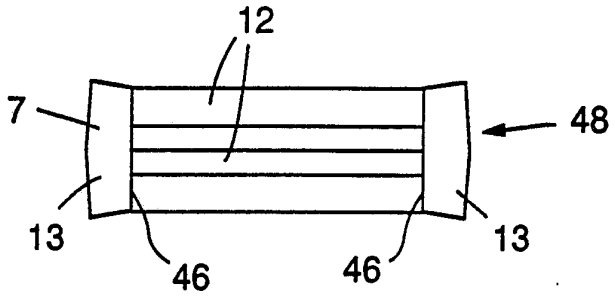

FIG. 3

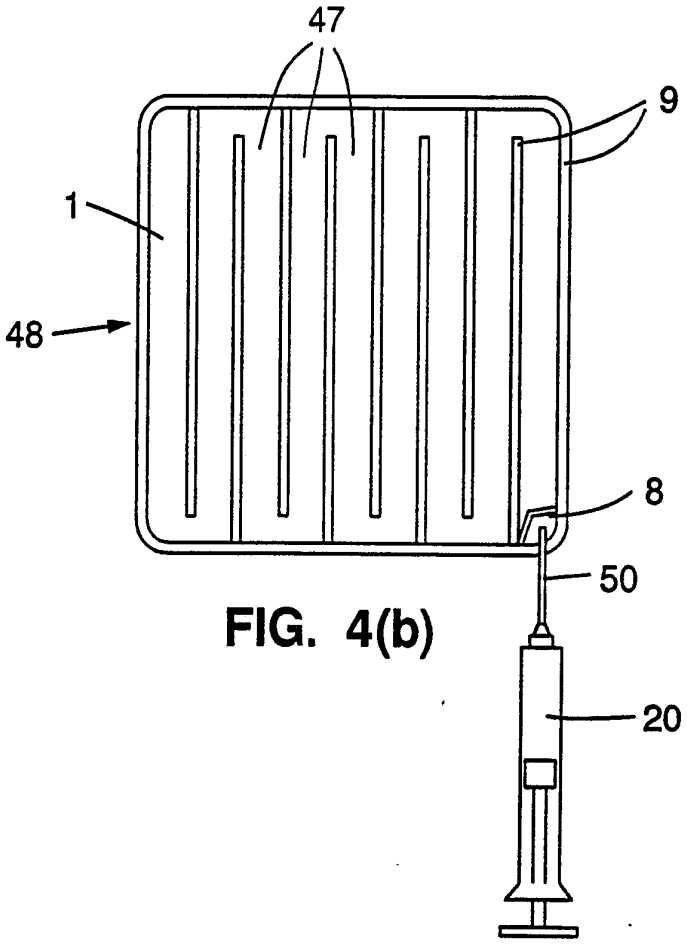

FIG. 4(b)

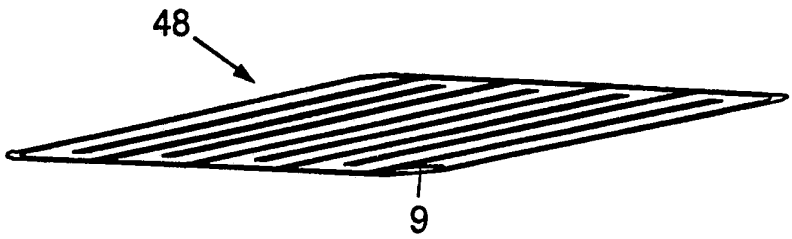

FIG. 4(a)

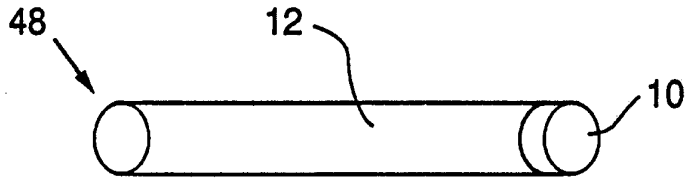

FIG. 5

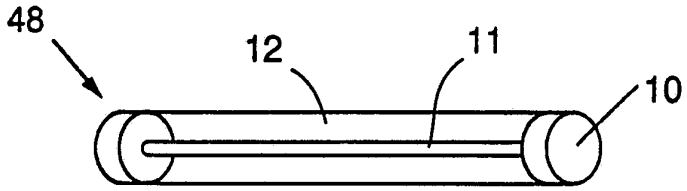

FIG. 6

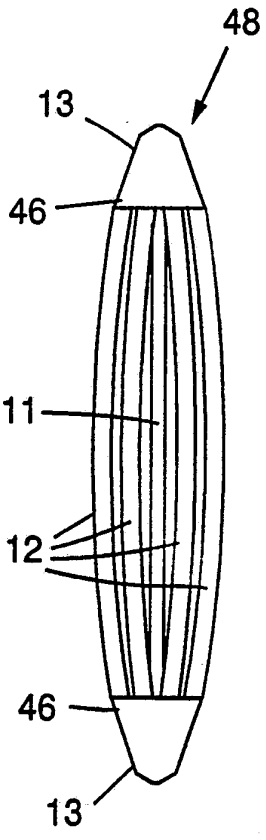

FIG. 7(b)

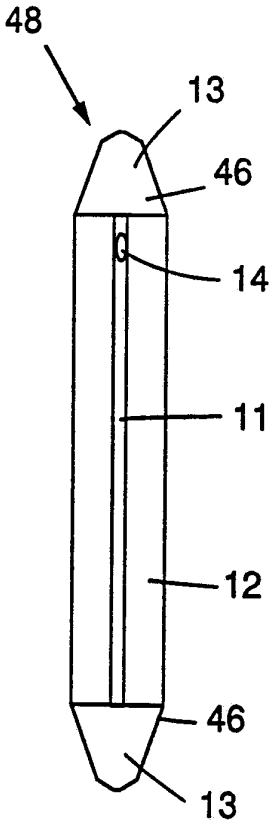

FIG. 7(a)

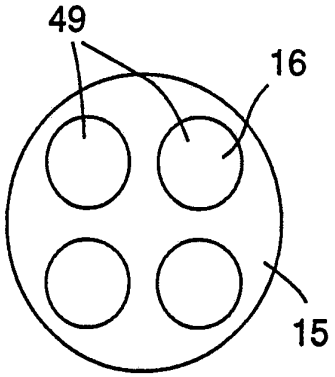

FIG. 8 (a)

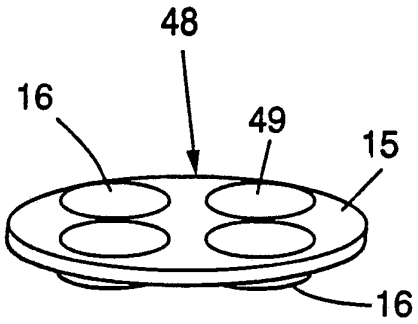

FIG. 8 (b)

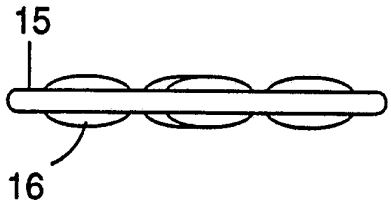

FIG. 8 (c)

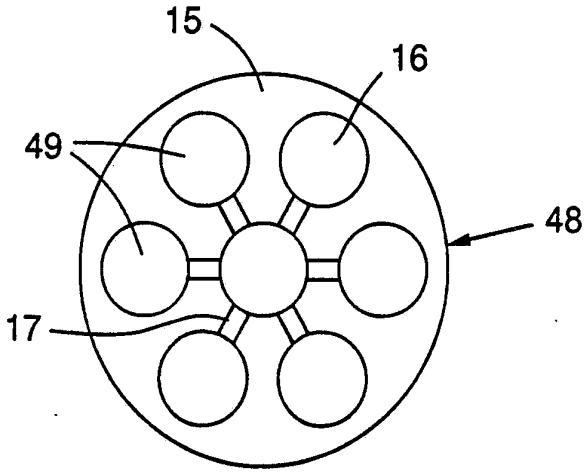

FIG. 8 (d)

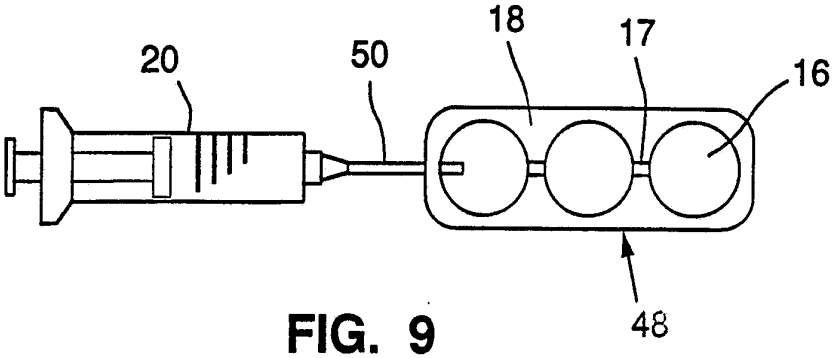

FIG. 9

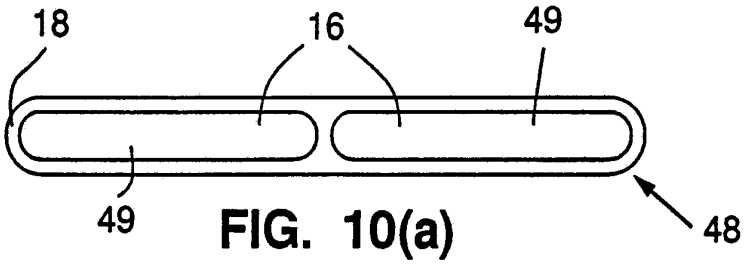

FIG. 10(a)

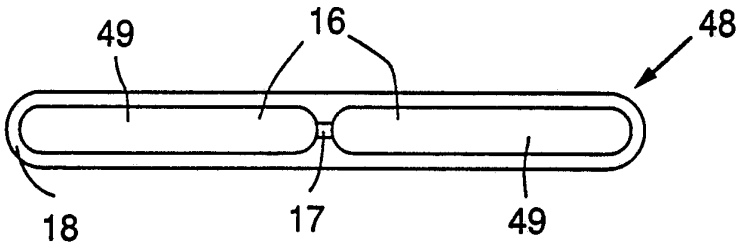

FIG. 10(b)

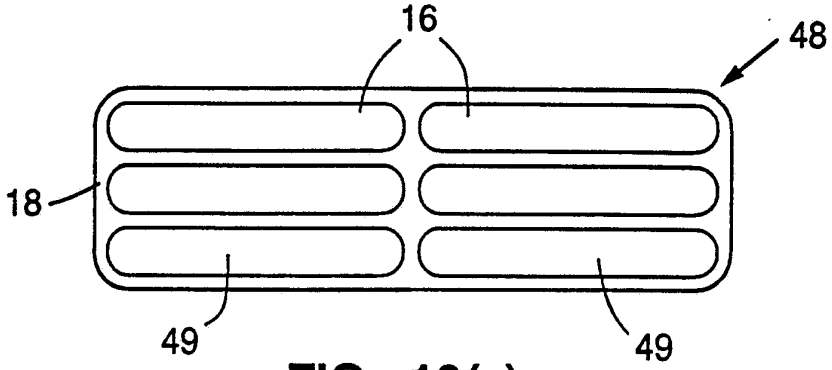

FIG. 10(c)

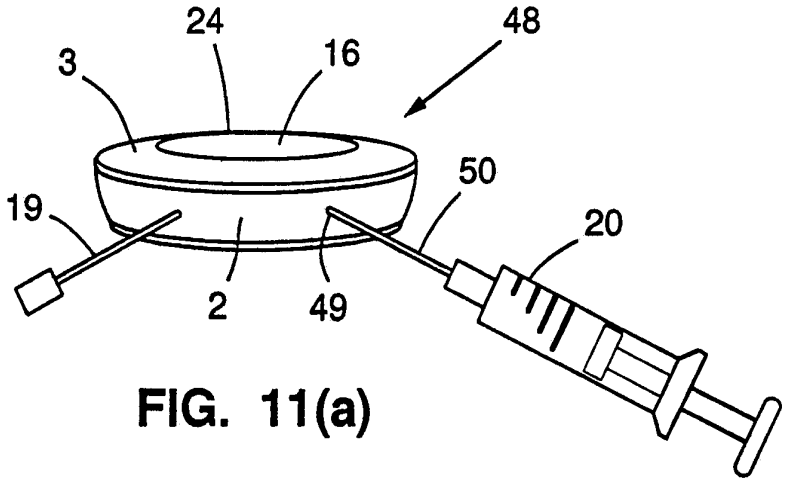

FIG. 11(a)

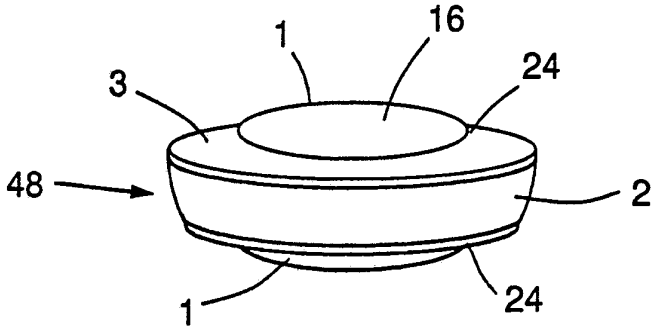

FIG. 11(b)

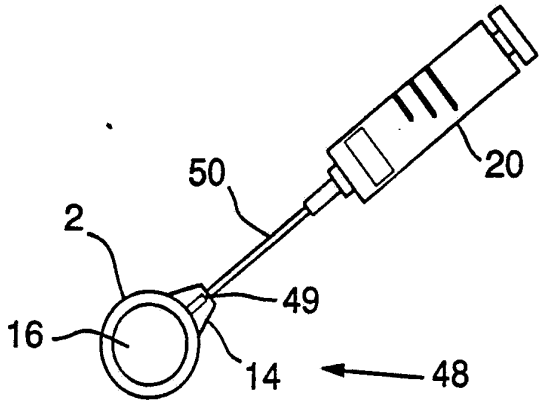

FIG. 11(c)

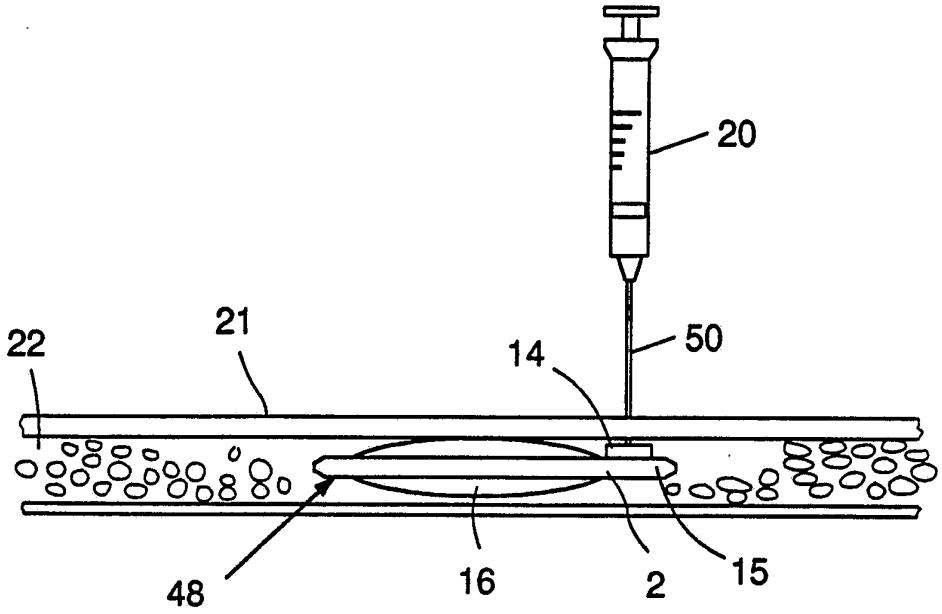

FIG. 12 (a)

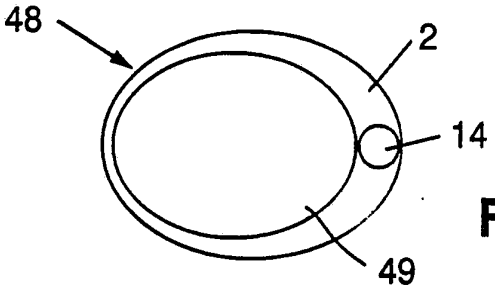

FIG. 12 (b)

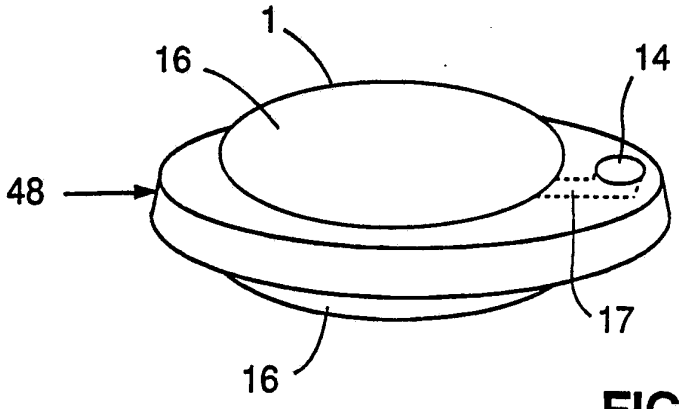

FIG. 12 (c)

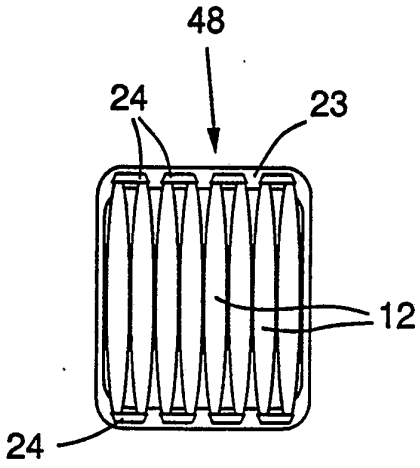

FIG. 13 (a)

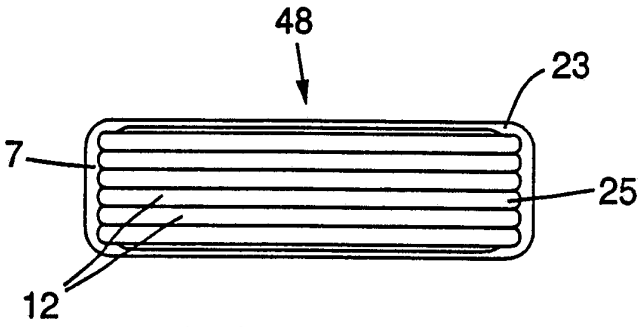

FIG. 13 (b)

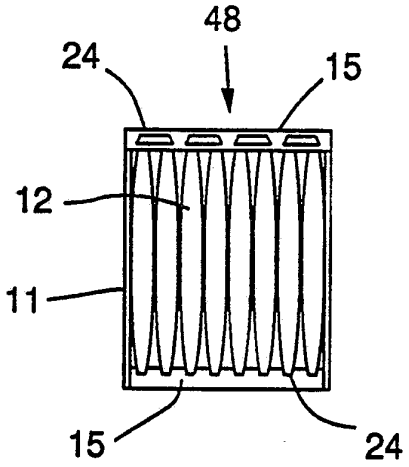

FIG. 14 (a)

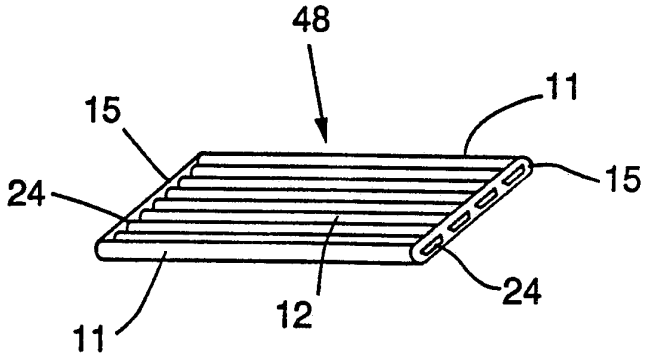

FIG. 14 (b)

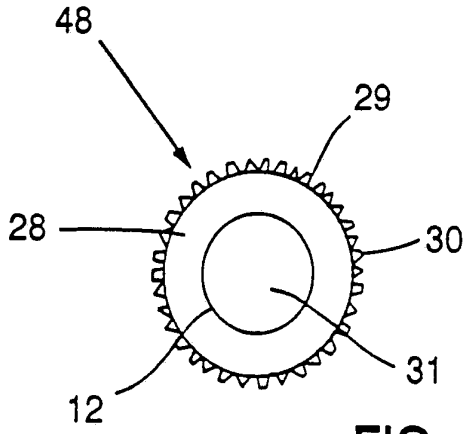

FIG. 15 (b)

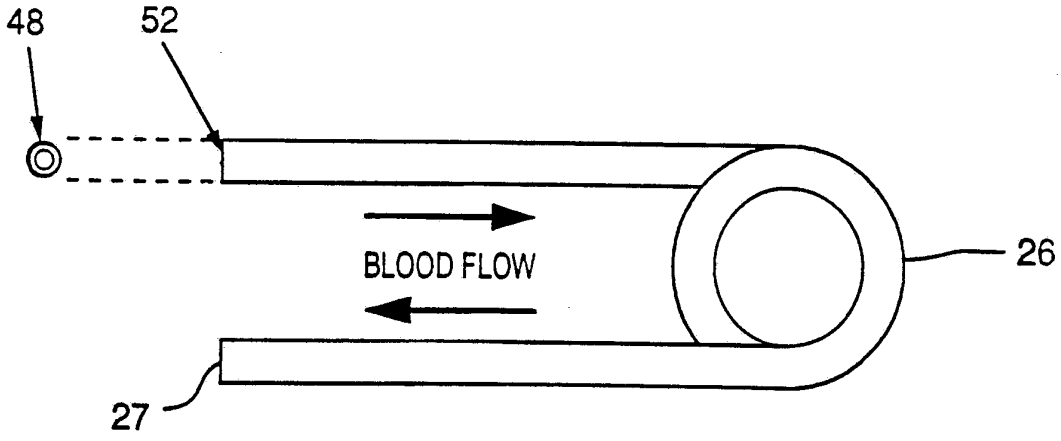

FIG. 15 (a)

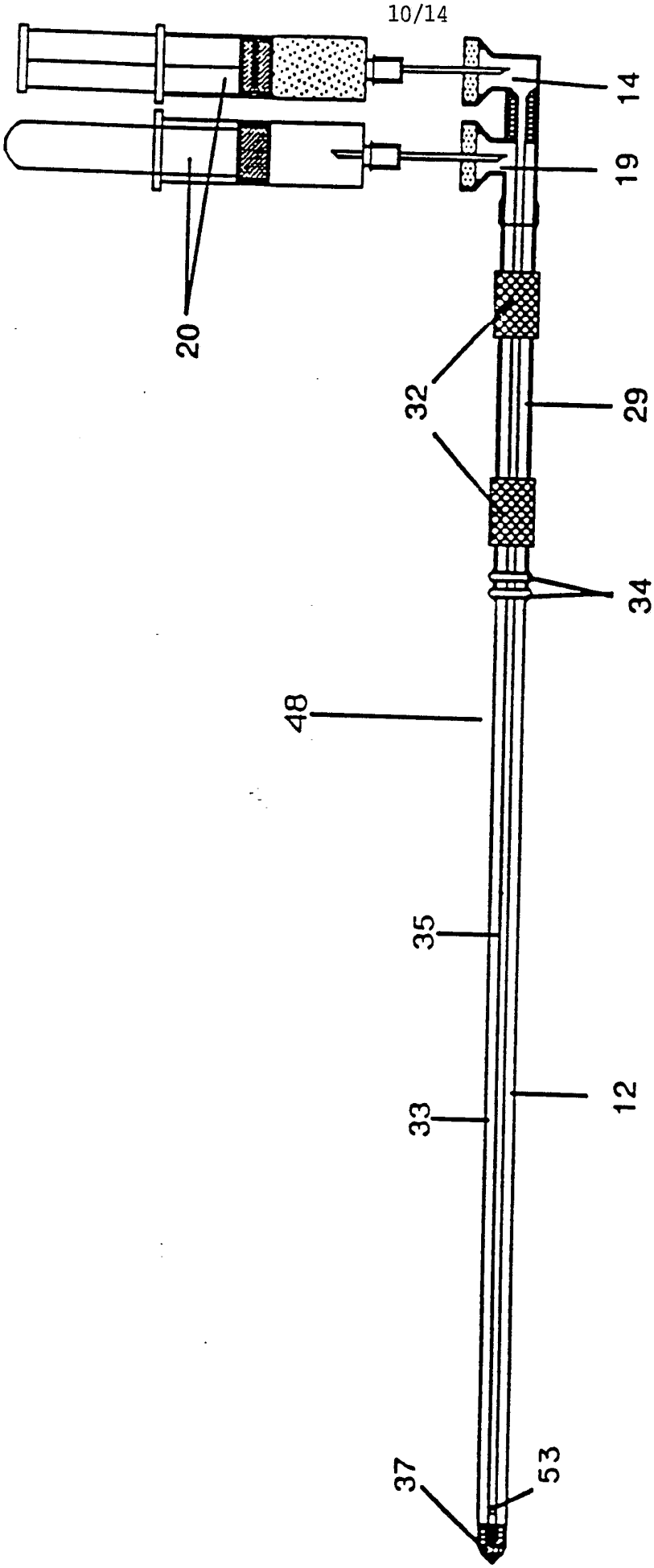

FIGURE 16

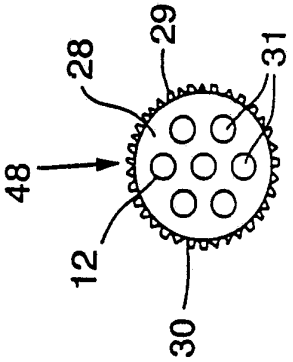

FIG. 17 (b)

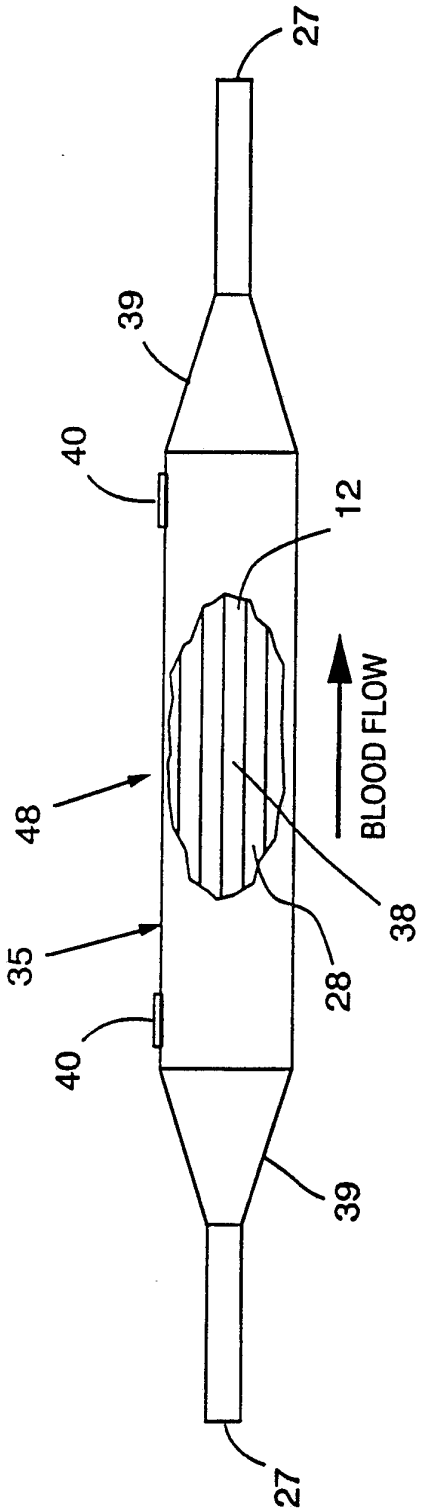

FIG. 17 (a)

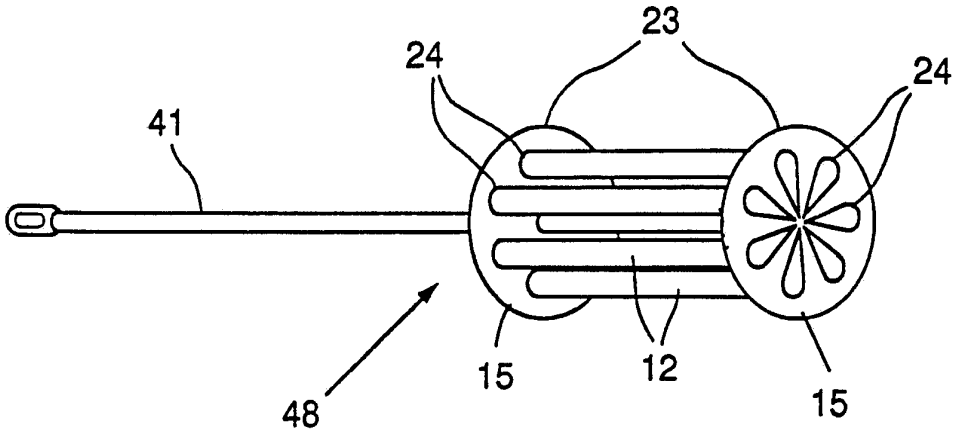

FIG. 18

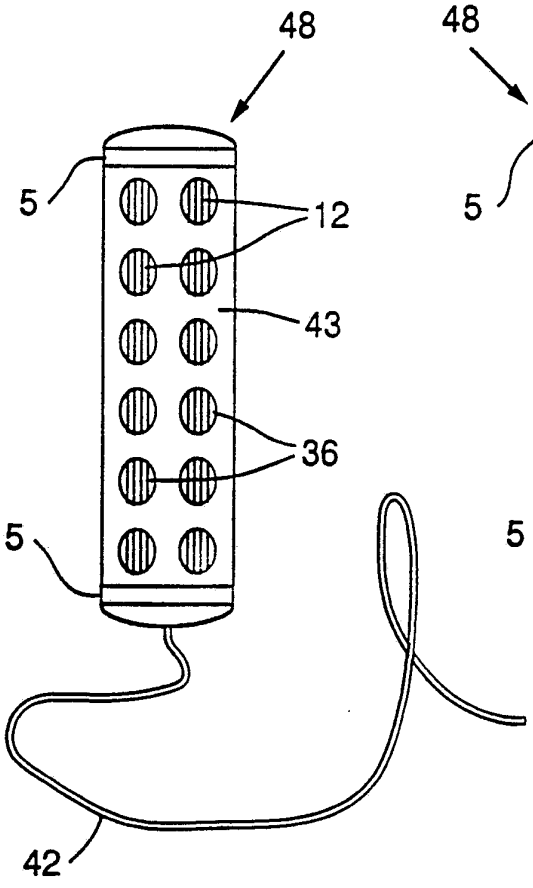

FIG. 19 (a)

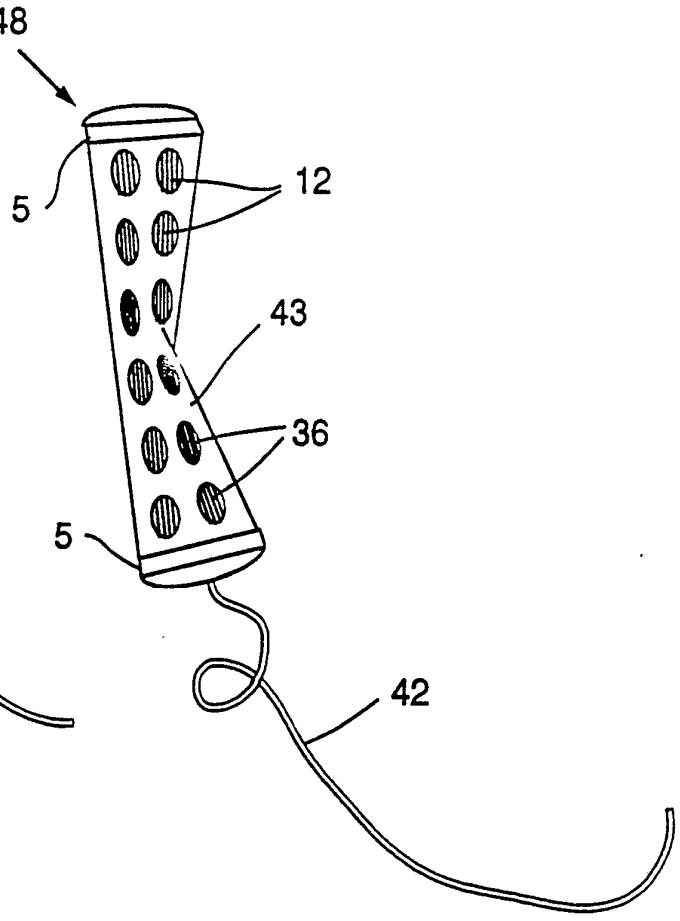

FIG. 19 (b)

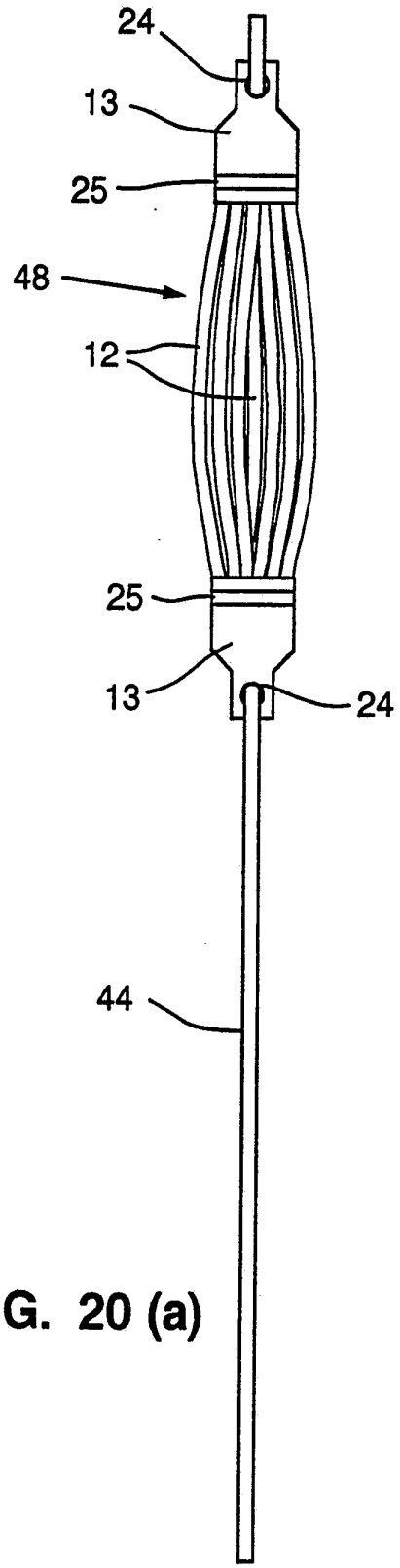

FIG. 20 (a)

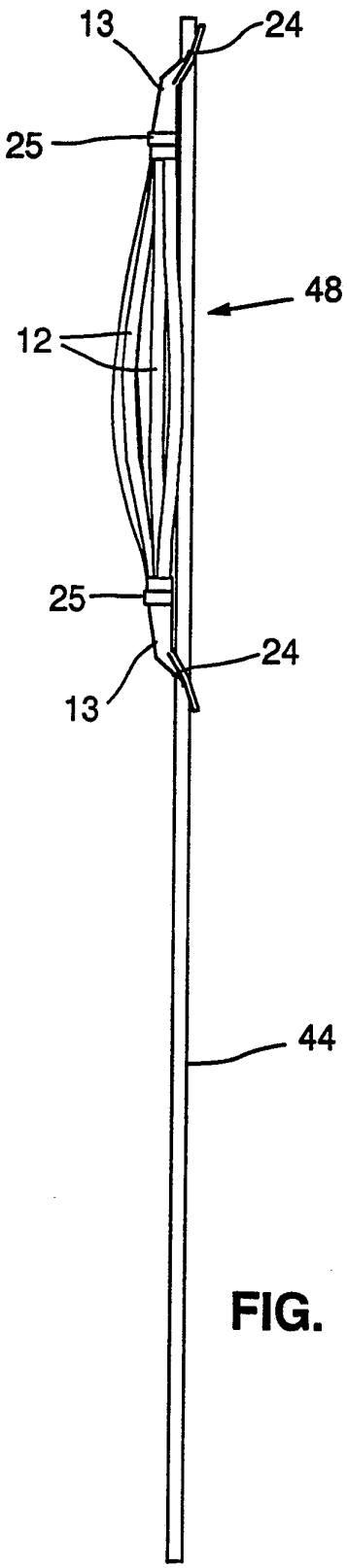

FIG. 20 (b)

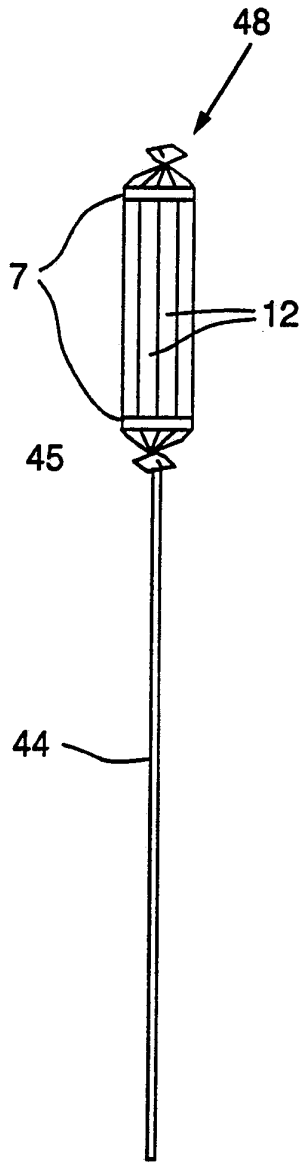

FIG. 21 (a)

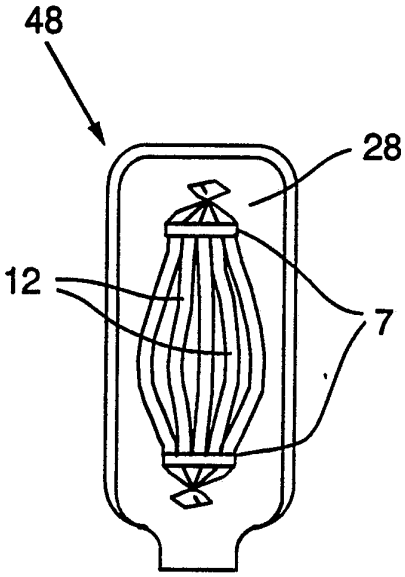

FIG. 21 (b)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/03850

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 A61K9/00; A61F2/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K ; A61F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,5 035 891 (RUNKEL ET AL.) 30 July 1991 see the whole document ---	1-101
A	BIOMATERIALS vol. 13, no. 3, March 1992, GUILDFORD (GB) pages 136 - 144 , XP258851 G.J. ZONDERVAN ET AL. 'design of a polyurethane membrane for the encapsulation of islets of langerhans' see the whole document ---	1-101
A	WO,A,9 119 783 (E.I. DU PONT DE NEMOURS AND COMPANY) 26 December 1991 see the whole document ---	1-101

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° Special categories of cited documents :[10]

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"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

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"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.

"&" 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
20 AUGUST 1993	06. 09. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BENZ K.F.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	WO,A,9 100 119 (BAXTER INTERNATIONAL INC. ET AL.) 10 January 1991 see the whole document ---	1-101
A	US,A,5 026 365 (ROSSINI ET AL.) 25 June 1991 see the whole document ---	1-101
A	US,A,4 298 002 (RONEL ET AL.) 3 November 1981 see the whole document -----	1-101

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

US 9303850
SA 73819

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
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 20/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5035891	30-07-91	None	
WO-A-9119783	26-12-91	EP-A- 0535026	07-04-93
WO-A-9100119	10-01-91	None	
US-A-5026365	25-06-91	None	
US-A-4298002	03-11-81	None	