United States Patent [19]

Urquhart

[11] **3,797,485**

[45] **Mar. 19, 1974**

[54] **NOVEL DRUG DELIVERY DEVICE FOR ADMINISTERING DRUG INTO BLOOD CIRCULATION IN BLOOD VESSEL**

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[22] Filed: **Mar. 26, 1971**

[21] Appl. No.: **128,303**

[52] **U.S. Cl.**..... **128/213,** 128/260, 128/268, 424/19

[51] **Int. Cl.**..... **A61m 5/00**

[58] **Field of Search**..... 128/1 R, 213, 260, 268, 128/334; 424/14, 16, 19

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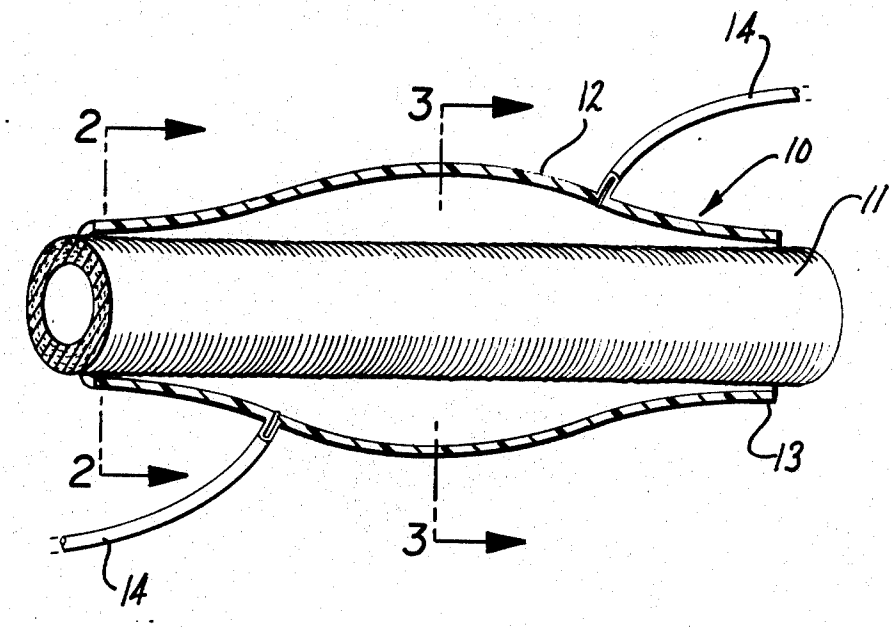
Primary Examiner—Dalton L. Truluck

[57] **ABSTRACT**

A novel drug delivery device for administering a drug into the blood circulation comprising a means for positioning a drug supply on the adventitial surface of an intact blood vessel for diffusing the drug into the blood in the blood vessel.

13 Claims, 13 Drawing Figures



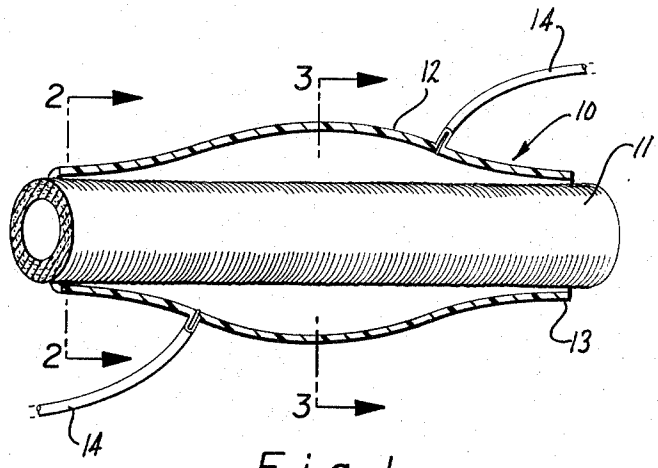


Fig. 1

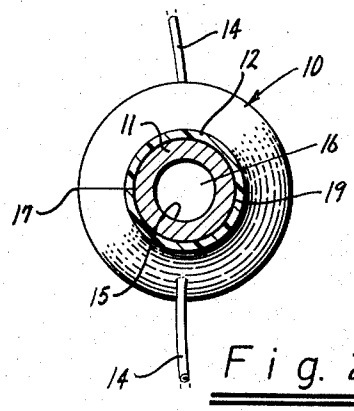


Fig. 2

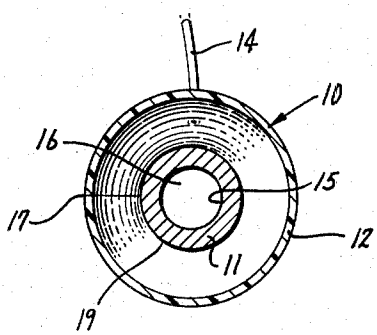


Fig. 3

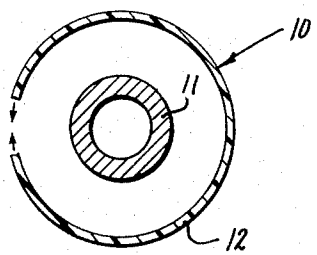


Fig. 4

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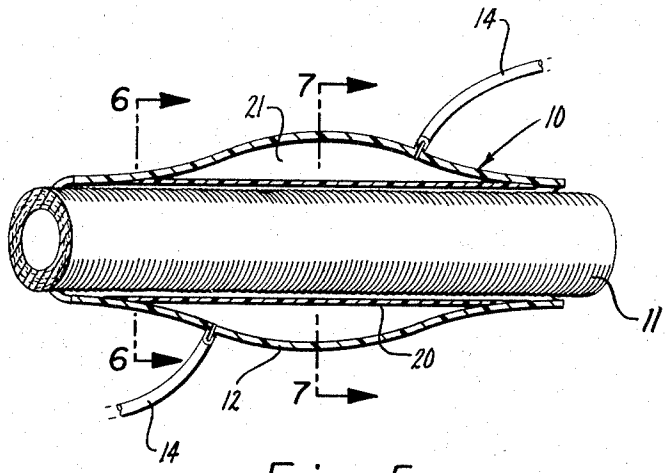

Fig. 5

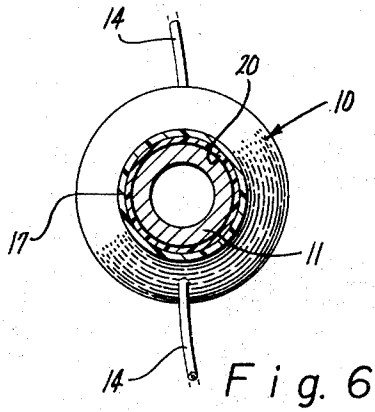

Fig. 6

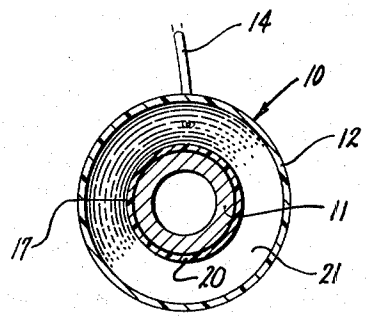

Fig. 7

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Fig. 8

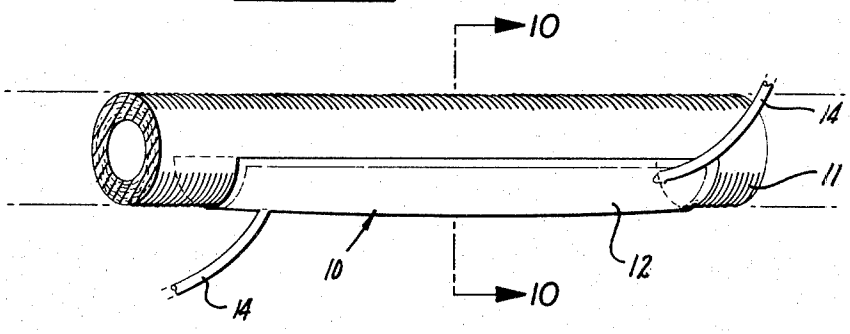

Fig. 10

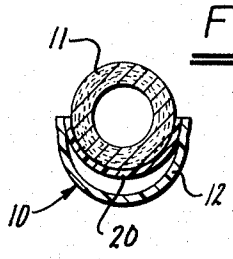

Fig. 9

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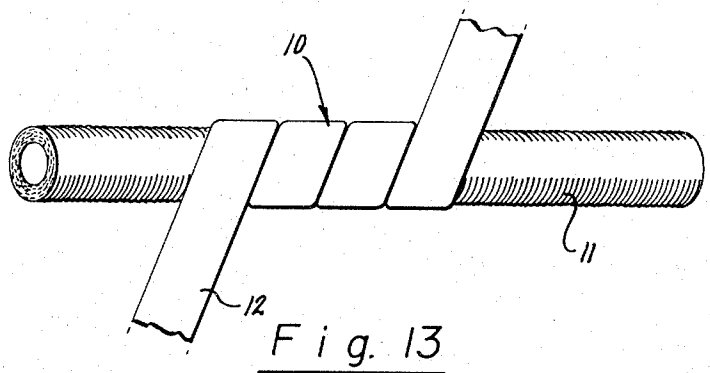

Fig. 13

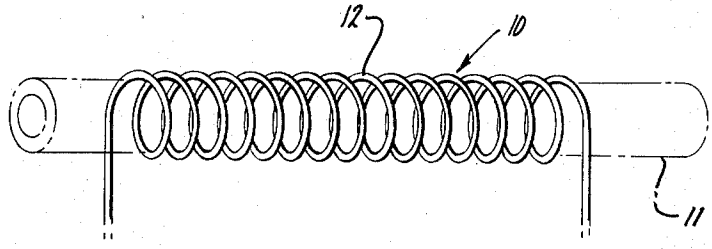

Fig. 12

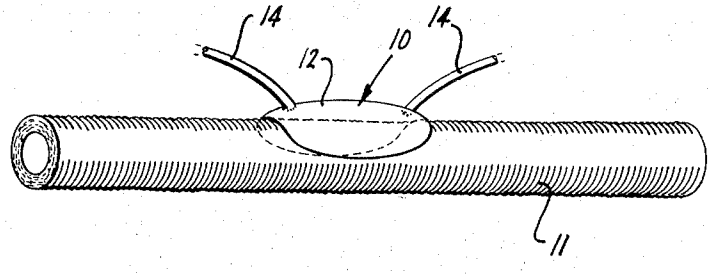

Fig. 11

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NOVEL DRUG DELIVERY DEVICE FOR ADMINISTERING DRUG INTO BLOOD CIRCULATION IN BLOOD VESSEL

BACKGROUND OF THE INVENTION

The present invention relates to a novel article of manufacture and to a method for using the article. More particularly, the invention pertains to a device for administering a drug into the blood circulation by diffusing the drug from the device on the adventitial surface of a blood vessel; and, to a method for administering a drug into the blood circulation by positioning a drug delivery device containing a drug on the adventitial surface of a blood vessel to diffuse the drug through the blood vessel wall into the circulating blood to produce either a localized or systemic pharmacological or physiological effect.

It is known to the prior art since Megendie in the early 1800's performed his experiment of exposing the jugular vein of a dog and applying a watery solution of spirituous extract of nux vomica to the exposed vein "that the walls of arteries and veins permit the passage of certain solutions inwards into the blood." Megendie's observations are recorded in *A Monograph On Veins*, by Franklin, K. J., pages 115 to 119, 1937, published by Charles C. Thomas Inc., Springfield, Illinois. Yet, even though this knowledge was known to the art since this early observation, a survey of the prior art showed that not only was there no systematic study of the permeability characteristics of the walls of arteries or veins to drugs, the prior art never conceived of any practical devices or methods for administering a drug through the walls of arteries or veins to use this route for producing a local or systemic pharmacological or physiological effect.

Prior to this invention, which makes available to the art a novel and useful device for administering a drug through the wall of an intact blood vessel, mainly arteries and veins, medical and veterinary practice used other routes of drug administration. These routes were used even though they possessed certain shortcomings that are not found when the novel device and route of this invention is used for administering a drug. For example, the oral route is the oldest and most widely used by the prior art even though many drugs administered by this route are rendered inactive by gastric acid or digestive enzymes of the gastrointestinal tract. Also, after the drug is absorbed into the blood from the gastrointestinal tract it passes through the liver where the drug is metabolized to an inactive product by that organ. These factors coupled with the uncontrolled rate of drug transit through the gastrointestinal tract makes it difficult to achieve a desired time course of concentration of the drug in the blood.

Another route occasionally used for the administration of drugs is absorption by the oral mucosa. Certain drugs are rapidly absorbed by oral mucosa and an elevated concentration of the drug in systemic blood may be achieved in this manner. However, during times when the drug is not being applied to the oral mucosa, there is an uncontrolled decline of the concentration of the drug in the blood. A graphic illustration of the drug's concentration in the blood during a dosage schedule for this route as the appearances of a series of peaks and valleys; and, often these valleys may fall below the drug concentration needed to achieve the desired effect.

The administration of drugs by injection can entail certain disadvantages. For example, very strict asepsis must be maintained to avoid infection of the blood, the vascular system, or heart. Drug administration by poor intravenous injection technique may result in perivascular injection when it is not intended; and, the typical result of injection into the blood is a sudden rise in the blood concentration followed by an uncontrolled decline.

Another method for the administration of drugs directly into the blood is the catheter technique. This technique involves the incising of a blood vessel wall and the placing of one end of a catheter through the blood vessel wall into the lumen. The other end of the catheter is connected to a pump that delivers the drug to the blood. The disadvantages associated with the catheter technique are many; for example, possible damage to the blood vessel wall, blood leaks around the catheter, the formation of thrombosis intraluminally around the foreign catheter with a risk of embolization, the blockage of the catheter lumen by thrombosis, and the risk of infection. These factors dictate that an intravascular catheter must be viewed as having a limited lifetime and usefulness.

Other known routes of drug administration are the rectal mucosa and the vaginal mucosa routes. These routes have certain known shortcomings, for example, drug absorption by these routes is often erratic or incomplete. The concentrations of drug in the blood by these routes is often variable and uncontrolled.

The prior art of drug administration by the various routes described above is largely limited to bringing about a pulsed delivery of the drug. That is, by these routes a concentrated dose of the drug is brought into contact with a drug absorbing surface over limited periods of time, often creating undesirable fluctuations in the concentration of drug in the blood and at the site of drug action. The administration of drugs by the prior art frequently failed to achieve a desired time course of drug action. In addition, the prior art never produced any kind of drug delivery device for directly introducing a drug into the blood without first penetrating by mechanical, laser, ultrasound, microwave, or surgically the wall of the blood vessels. Also, the art never conceived either of the administration of a drug into the blood for transport to an organ or receptor site or of introducing a drug into the blood for a systemic effect by administering the drug into the blood through the intact blood vessel wall.

In light of the limitations mentioned above, it should be apparent to those versed in the art that if a novel drug delivery device is made available that improves upon the prior art, such a drug delivery device would represent a useful and valuable contribution to the art. Likewise, it will be appreciated by those skilled in the art that if a novel and unobvious drug delivery device is made available to the art for the administration of drugs directly into blood in a blood vessel to produce either localized or systemic effects, without requiring any mechanical penetration of the blood vessel walls, such a system would not only represent an advancement in the art but would also have positive use in the management of health and disease in the medical and veterinary fields.

BRIEF DESCRIPTION OF OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention to provide a novel device for drug administration that essentially overcomes the problems encountered by the prior art.

Another object of the invention is to provide a novel means for diffusively delivering drugs into the blood circulation in an intact blood vessel.

Still another object of the invention is to provide a novel drug delivery device.

Yet another object of the invention is to provide a device for delivering drugs directly into the blood stream by diffusion through blood vessel walls without any mechanical penetration of the like of the blood vessel wall by the drug delivery device.

Still yet another object of the invention is to provide a drug delivery device for administering drugs into the blood in a specific artery for the direct circulation of the drug to the tissues or organs supplied by that artery.

Another object of the invention is to provide a drug delivery device for administering drugs into the blood in a vein as a means of systemic administration of the drug.

A further object of the invention is to provide a drug delivery device for administering drugs into the portal vein for transport to the liver.

Still another object of the invention is to provide a drug delivery device for the administration of a physiological or pharmacological agent into the blood to produce a localized or systemic effect.

Yet still another object of the invention is to provide a drug delivery device for providing over any predetermined periods of time any predetermined concentration of drug in the blood.

Another object of the present invention is to provide a method for administering therapeutically active materials for establishing therapeutically effective concentrations of the material in the blood by applying to the adventitial surface of a blood vessel a drug delivery device for diffusively administering the material into the blood.

Further objects, features and advantages of this invention will become apparent to those skilled in the art from the following specification, drawings and annexed claims.

SUMMARY OF THE INVENTION

The invention concerns a novel and useful drug delivery device for administering a drug into the blood. The drug delivery device also serves as a reservoir for at least one drug. The device comprises a means contacting a part or the whole circumference of the adventitial surface of a blood vessel for administering a drug into the blood. The invention also concerns a method for administering a drug into the blood to produce a systemic or localized effect by positioning a drug delivery device on a part or the whole adventitial surface of a blood vessel for diffusing the drug into the blood.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing will become more apparent by reference to the attached drawings of which:

FIG. 1 is a perspective view of one embodiment of a drug delivery device of the invention;

FIG. 2 is a vertical, cross-sectional view of the drug delivery device of FIG. 1 through 1—1;

FIG. 3 is a vertical, cross-sectional view through 2—2 of the drug delivery device of FIG. 1;

FIG. 4 is a perspective view of the drug delivery device of FIG. 1 depicting a device surrounding an artery or vein prior to closure;

FIG. 5 is a perspective view of another drug delivery device of the invention illustrating a device with an interplaced rate controlling membrane for metering the drug into the artery or vein.

FIG. 6 is a schematic, cross-sectional view at 3—3 of FIG. 5 illustrating the membrane at the terminal positions of the device;

FIG. 7 is a schematic, cross-sectional view at 4—4 of FIG. 5 illustrating the membrane at the mid-section of the device;

FIG. 8 is a perspective illustration of a drug delivery device engaging and partially surrounding an artery or vein;

FIG. 9 is a vertical, cross-sectional view through 5—5 of FIG. 8 depicting the device prior to engaging the artery or vein.

FIG. 10 is a schematic illustration of the device of FIG. 8 engaging an artery or vein.

FIG. 11 is a schematic depiction of another drug device of the invention engaging a part of an artery or vein.

FIG. 12 is a perspective view of another embodiment of the invention showing a device engaging an artery or vein in spiral-like manner.

FIG. 13 is a perspective view of an embodiment of the invention showing a drug delivery device for continuously and intimately engaging a large area of an artery or vein for administering a drug into the blood stream. In the drawings in the specifications, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings are defined later in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, FIG. 1 represents one novel and useful drug delivery device for administering a medical or a veterinary drug into the blood in an artery or vein. For the purposes of this invention, the terms artery or vein are construed as the equivalent of blood vessel and this latter term is used to assist in describing the devices. In FIG. 1, there is illustrated a drug delivery device **10**, comprising a design adapted for surrounding a blood vessel **11**. The device comprises an exterior wall **12**, of low drug or fluid permeability (examples of which are presented later in the disclosure), which traverses the length of the drug delivery device **10**. The shape of the device conforms to the external shape of blood vessel **11**. The device **10**, also referrable to as a housing means, encapsulating means, means for confining a drug for delivery, or the like, tapers at its ends **13** for placing and sealing the device to blood vessel wall **11**. The tapered ends **13** are adapted to confine a drug in the device **10** and to prevent surrounding body fluids from entering the device **10**. Drug device **10** is provided with one or more pairs of inlet-outlet ports **14**, located at one or both ends of the device, or at any position on the device, for extending outwardly through the host's skin for admitting a drug into device **10**. Inlet port **14** is optionally equipped

with a bacterial filter, not shown, for preventing bacterial contamination of the device and the host during its use.

In FIG. 1, the drug device 10 is illustrated with tapered end 13; however, the device can be constructed with non-tapered ends, not shown. In this latter device, the device comprises at its outer ends a pair of terminal skirts, integrally and continuously formed for sealingly engaging the curvature of the exterior surface of an artery or vein for housing drugs in the device and for essentially preventing body fluids from entering the device. The drug device of FIG. 1 is shown as an integral unit; however, the device can be manufactured as a two part device such as two hemi-envelopes or two hemicircles, not shown, for enclosing any given length of artery or vein. The ends of a two part device can be made with integral tapered ends or the ends can be closed with plugs, not shown, suitably provided with a means for letting a blood vessel enter and exit the device. A two part device can include inlet and outlet ports for occasionally or continuously admitting a drug into the device.

FIG. 2 is a cross-sectional view through 2—2 of FIG. 1 wherein device 10 at its tapered ends 13 engages blood vessel 11. In FIG. 2, body wall 12 of device 10 surrounds the adventitial surface 19 of blood vessel 11 to form at interface 17, by sealingly closing wall 12, an integral device 10. The cross-sectional view also shows intimal surface 15 defining lumen 16 of blood vessel 11.

FIG. 3 is a cross-sectional view through 3—3 of FIG. 1 illustrating device 10 with its wall 12 surrounding blood vessel 11 to form a sealed, closed device at interface 17. Drugs, not shown, in space 18 defined by the outer surface of blood vessel 11 and the inner surface of wall 12 diffuse through the adventitial surface 19 and intimal surface 15 into blood in lumen 16 of blood vessel 11. In accompanying FIG. 4 there is illustrated another cross-sectional view of device 10 of FIG. 1 surrounding blood vessel 11 before wall 12 closes to form device 10. The wall surrounds blood vessel 11 to meet at its interface 17 as seen in FIGS. 2 and 3 to form device 10.

In FIG. 5 there is illustrated another novel drug delivery device of the invention. This device comprises a main body 10 having an exterior wall 12, an interior membrane 20 and a space 21 formed by wall 12 and membrane 20 for containing a drug or a pharmaceutical composition comprising a carrier and a drug for diffusing through membrane 20 into blood vessel 11. The device of FIG. 5 is constructed with inlet-outlet ports for admitting drug into the device or for draining drugs from the device. Inlet port 14, is optionally equipped with a bacterial filter, not shown, for preventing bacterial contamination of the device during its use. The filter is generally not needed in this device if membrane 20 is impermeable to bacteria. FIG. 6 is a cross-sectional illustration of device 10 at 6—6 of FIG. 5 at its tapered ends where the device engages blood vessel 11. Device 10 forms a closed unit where wall 12 meets at interface 17. In FIG. 6, wall 12 contacts membrane 20 as it surrounds blood vessel 11 for positioning and holding device 10 to blood vessel 11. FIG. 7 is a cross-sectional illustration at the middle section at 4—4 of FIG. 5. FIG. 7 shows wall 12 and membrane 20 joined at their interfaces 17 to form space 21. Blood vessel 11 is surrounded by membrane 20 for controlling the rate of drug delivery into blood vessel 11. The physical dimensions for the drug devices of the invention are to be construed as non-limiting, and they are generally the dimensions that correspond to the dimensions of the blood vessel and the amount of drug present in the device. A typical device constructed according to the spirit of the invention, for example, FIG. 5 comprises blood vessel 11 surrounded by space 21 of about 2 mm to 15 mm deep for carrying a drug, a pharmaceutical vehicle, penetrating agent and the like. The inner membrane, when present, is usually about 10 to 500μ thick, or thicker if desired to regulate the rate of drug diffusion, and the outer wall 12 about 0.2 mm to 5 mm thick or of like dimensions. The drug delivery device 10 generally has a longitudinal length of about 10 mm to 75 mm, and shorter or longer devices with varying circumferences can be constructed and its length and circumference will depend on the length, and circumference of the blood vessel placed within the device, the age and the size of the host, and the amount of drug to be diffused into the blood.

Turning to FIG. 8, there is illustrated a drug delivery device fabricated according to the invention for engaging at least a part of blood vessel. The drug delivery device 10 of FIG. 8 comprises a body wall 12 which surrounds a part of the circumferential traverse surface of blood vessel 11. In FIG. 8, a part of the blood vessel is illustrated as surrounded and part not surrounded by device 10. The device is also constructed with inlet-outlet ports 14 that it may optionally house an in-line bacterial filter, not shown, and be filled and drained via transcutaneous tubes. The device may have a rate controlling membrane, not shown in FIG. 8. FIG. 9 illustrates a cross-sectional view through 10—10 of FIG. 8 depicting a part of a blood vessel 11 partially surrounded or saddled by device 10 comprised of wall 12 and an inner rate controlling membrane 20 prior to the closing of the device. The device of FIG. 9 can be closed by a membrane that joins the device to the artery or vein, or the device can be made with an inwardly curving wall and membrane to intimately contact the adventitial wall for sealing thereto. FIG. 10 illustrates the device of FIG. 8 positioned on blood vessel 11 in a closed or saddled engagement of 11. FIG. 11 is a top elevational view of another embodiment of the invention illustrating a small device 10 with a body wall 12 with inlet-outlet ports 14 staddled on a part of blood vessel 11, for diffusing a drug into a small area of 11. FIG. 12 is still another embodiment of the invention depicting a device 10 with a body wall 12 wrapped around a blood vessel 11 in spiral or helix arrangement for diffusing drugs into blood in 11. This device can be used for diffusing a drug over a small or a large area of blood vessel. FIG. 13 illustrates a device 10 having a body wall 12 surrounding blood vessel 11. This device is similar to the device of FIG. 12 and it can be used for contacting a large area of a blood vessel in a small space for diffusing a drug into the bloodstream.

DESCRIPTION OF INVENTION EMBODIMENTS

Turning now to the construction and use of the devices of the invention, wherein the devices are intended for administering a drug into blood in an artery or vein, the devices are described in the light of the drawings, example, and accompanying claims. The anatomical terms artery or vein are to be broadly construed for the purpose of this invention to include the blood vascular

system. The blood vascular system herein comprises blood and the naturally occurring conduits that circulate blood within the mammalian body that includes by way of non-limiting example the various types of blood vessels that are of general consideration of the circulation of the blood such as arteries and veins. The non-limiting examples of the system also includes blood circulation to the brain and spinal cord, coronary circulation, pulmonary circulation, gastrointestinal circulation, the hepatoportal-lienal circulation, the renal circulation, the blood vessels of the pituitary and the thyroid, placental circulation, cutaneous circulation and the like. Also, in the specification and the accompanying claims, the terms administering or administration of a drug refers generally to passage or entrance of a drug into the blood through the blood vessel wall, without any mechanical or physical instrumental penetration of the blood vessel wall. Thus, administration generally includes for the purpose of the invention the equivalent terms such as diffusion, permeation, osmosis, and the like.

In fabricating a device for surrounding at least a part or the whole surface of a blood vessel, the body wall **12** of the drug delivery device of the invention is made of natural or synthetic polymers, singly, or laminates of more than one like or unlike polymer. The polymers suitable for the purpose of the invention are those polymers that posses a low to essentially no permeability to the drugs, its carrier, or to components present in surrounding tissues or biological fluids. The phases "low permeability" and "essentially no permeability" for a drug generally are to be construed for the purpose of this invention to mean that very little or essentially none of a particular drug will pass through a given polymer as ascertained by known techniques for determining the rate of passage of drugs and the like through polymeric materials. Examples of known techniques are disclosed in *The J. Pharm. Sci., Vol* 59, No. 9, pages 1341 to 1346, and 1412 to 1419, 1970. This just described physical property of the polymer aids in substantially preventing drug diffusion from the delivery system into undesired body areas, and it also serves to prevent surrounding body fluids from entering the system.

For use with drugs of high water solubility, polymers which display low moisture permeabilities are presently preferred. Generic examples of such polymers known to the art are polyolefins such as polyethylene and polypropylene; polymers such as polytetrafluoroethylene; poly(vinylchloride); poly(vinylidene chloride); polychlorotrifluoroethylene; polyisobutylene; poly(acrylonitrile); poly(ethylene terphthalate); natural and synthetic rubber; and the like. The general characteristics of polymers possessing low moisture permeability suitable for the purpose of the invention are the polymers that have a saturated or nearly saturated carbon chain; a minimum of chain branching; a high degree of lateral symmetry, a fair degree of longitudinal symmetry and a very high proportion of relatively small, non-hydrophilic substituents. A high degree of compliance with most of these characteristics may serve to mask the lack of conformity in some one respect, such as unsaturation. Various methods and means for ascertaining and measuring moisture permeability are well known to the prior art, and they are recorded in *Industrial and Engineering Chemistry*, Vol 45, *pages* 2296 to 2306, 1953; and the references cited therein. Exemplary of specific polymeric films having low moisture permeabilities are polymeric species such as vinylidene chloride vinyl chloride copolymer with a compositional range of 92 to 8 to 50 to 50; commercially available vinylidene chloride acrylonitrile composition of 92 to 8 and 80 to 20; vinylidene chloride-acrylonitrile-vinyl chloride of 75 to 80/10/10 to 15; vinylidene chloride isobutylene of 70 to 30; butyl rubber–G–1; rubber hydrochloride and the like.

For drugs physically characterized by low water solubility, but moderate to high organic solvent solubility, the wall **12** is usually made from one or more natural or synthetic polymers that display low drug permeability and such polymers are generally those in which the specific drug has low solubility. The general characteristics known to the art for such polymers that are least permeable for organic like materials are those whose molecular structure permits close packing and usually strong intermolecular bonding. The selection of a low permeability polymer for a specific drug can usually be made by following the art known guide of like dissolves like. That is, if a particular drug is highly soluble in a particular solvent and if that solvent also swells or dissolves a particular polymer, then the solubility permeability of the drug in the polymer will be high. For example, drugs which are highly soluble in alkanols will permeate slowly through polymers which are unaffected by or insoluble in the alkanol; also, drugs which are soluble in aromatic solvents will not permeate through polymers that are unaffected by the aromatic. Examples of polymeric materials are as follows: poly(ethylene terephthalate) a condensation polymer resulting from the esterification reaction between ethylene glycol and terephthalic acid, or formed by the alcoholysis of a terephthalic acid ester with ethylene glycol; cellophane and its flexible cellulosic derivatives made from viscose; fluorocarbon polymers such as tetrafluoroethylene homopolymer; polyolefin such as polyethylene; acetal homopolymers and copolymers; modified acrylics; and the like. The polymer can be used alone or in combination with one or more polymeric materials, or it can be lined, coated, or laminated with a film or a layer of a metal or an alloy. Exemplary of metals and alloys suitable for the present purpose are tantalum, titanium, stainless steel, platinum, alloys comprising nickel, cobalt, platinum, iridium, copper, iron, manganese, tungsten and the like. Exemplary of commercially available alloys are vitallium consisting of cobalt, chromium and molybdenum; Kovar alloy consisting of about 29 percent nickel, 17 percent cobalt, 0.3 percent manganese and the balance iron; Sylvania No. 4 alloy consisting of 42 percent nickel, 5.5 percent chromium and the balance iron; and the like.

Body wall **12** can also be made from metals and alloys per se, for example, stainless steel, tantalum, titanium, vitallium, and the like. The use of a metal or alloy is similar to the use of any of the above mentioned polymeric materials. For example, a thin sheet of a metal or an alloy is shaped into a single part or into two parts, for example, hemi-circles for surrounding any desired length of an artery or vein. The ends of the shaped body wall is suitably sealed about an artery or vein by forming the body wall with annular skirts, closing with plugs or by using an elastomeric material that is sealed to the body wall and the artery or vein. The body wall can also have tapered ends for joining the metal or alloy to the artery or vein, usually through a thin, accordian like

piece of an elastomeric polymer sealed to the body wall and the artery or vein.

The closable surfaces of wall **12** at the interfaces **17** of the device **10**, and the fixing of the device to the blood vessel as shown in the accompanying Figure can be effected by conventional methods. For example, the sealable surface may be contacted and adhesively closed to produce a liquid tight seal between the surfaces. The adhesives suitable for performing according to the mode and manner of the invention are the medically acceptable adhesives, sealants and the like. Exemplary of adhesives are acrylic adhesives, polymers of esters of acrylic acid with alkanols, alone or copolymerized with ethylenically unsaturated monomers such as methacrylic acid, acrylamide, methacrylamide, N-alkoxymethyl acrylamides, N-alkoxymethyl methacrylamides, N-tert-butylacrylamide, itaconic acid, N-branched alkyl meleamic acid wherein the alkyl group has 10 to 24 carbon atoms, glycol diacrylates, alpha-cyanoacrylate monomers, or mixtures of these; elastomeric silicone sealants; polyurethane sealants; rubbery polymers such as polyisobutylene, polyisoprene and polybutadiene; epoxy adhesives, and modified epoxy adhesives and the like. The adhesives may be of the various kinds well known to the art such as hot melt adhesives, fast setting adhesives, cold set adhesives, single or multi-component adhesives and the like. The adhesives may be compounded with tackifiers, stabilizers, hardners and other modifiers as is well known in the art.

The closable surface **17** of the blood drug delivery device **10** can be closed by other conventional methods. For example, the system can be manufactured with an integral closable zipper, not shown; the walls may be closed by medical suturing; by plastic film tapes; by heat sealing such as impulse, radiant, infrared heat and the like; by ultrasonic sound waves in the order of 18,000 cycles and over; and by other known techniques.

The inner drug rate controlling membrane **20** that is adhesively or heat sealed to the inner surface of wall **12** is generally a naturally occurring or a synthetic material, usually a polymer, and it serves to control or regulate the rate of drug entry into an artery or vein. Membrane **20** is usually formed of a material permeable to the drug to permit the passage of the drug from the inner space or reservoir area **21** to make it available for subsequent diffusion through the wall of the artery or vein **11** and into the blood. The rate of passage of the drum from and through the membrane **20** is usually dependent on the drug, the membrane thickness and the presence and nature of the pharmaceutical vehicle and penetrating agents present for contacting the membrane. Thus, the selection of appropriate materials for fabricating the membrane will be dependent of the particular drug, and by varying the composition and thickness of the membrane, the drug release rate per area of membrane can be controlled.

The membrane can be formed by molding onto the device containing the drug, or the membrane can also be in the form of sheets of polymeric material permeable to the passage of the drug. The membrane can be placed at different positions from the inner surface of wall **12**, or it can be laminated, adhesively affixed and the like, thereto. In spiral type devices the device is composed of an outer low permeability polymer with a rate controlled membrane joined thereto. The rate controlling membrane surrounding and contacting the adventitial surface of the blood vessel.

The materials acceptable for forming the rate controlling membrane generally are materials known to the art like organopolysiloxane rubbers, commonly known as silicone rubbers, including the heat-curable silicone rubbers and the room temperature vulcanizable silicone rubbers. The silicone rubbers which are converted to the rubbery state by heat and they are predominately linear organopolysiloxanes having an average degree of substitution of about two organic groups attached to the silicon per silicon atom. The organic groups are alkyl, aryl, alkenyl, alkaryl, aralkyl and the like. One representative class of silicone polymers are the dimethylpolysiloxanes. The room temperature vulcanizable silicone rubbers are also commercially available, and, they usually employ the same silicone polymers mentioned above, although the polymer often contains a greater amount of silicon bonded hydroxy group. This type of silicone rubber will cure at room temperature in the presence of an appropriate catalyst, such as stannous 2-ethylhexoate. Exemplary patents disclosing the preparation of silicone rubbers are U.S. Pats. Nos. 2,541,137; 2,723,966; 2,863,846; 2,890,188; 2,927,907; 3,002,951; and 3,035,016.

Other polymeric materials suitable for use in forming the rate controlling membrane are the commercially available poly(hydroxyethylacrylate) and poly(hydroxyethylmethacrylate) as described in U.S. Pats. Nos. 2,976,579 and 3,220,960, and in Belgian Patent No. 701,813. Exemplary of further materials include the commercially available materials such as, vinylidene chloride vinyl chloride copolymer 40/60 and 10/90; vinylidene chloride acrylonitrile copolymer 60/40 and 12/88; vinyl chloride acrylonitrile copolymer 80/20, 75/25, 50/50 and the like; vinyl chloride diethyl fumarate; vinyl chloride butyl-α-chloracrylate; polyethylene vinyl acetate; polyvinyl acetate; polyvinyl alcohol; polyesters; plasticized polyvinyl chloride; polycarbonates; plasticized nylon; collagen; modified collagen; gelatin; and the like. Another class of materials suitable for forming the membrane are the materials known to the art as microporous, reverse osmosis and the like. Exemplary of these materials include the anisotropic permeable microporous membranes of ionically associated polyelectrolytes, the polymers formed in the coprecipitation of a polycation and a polyanion as disclosed in U.S. Pat. Nos. 3,276,589; 3,541,005; 3,541,006; 3,546,142; and the like; treated aliphatic polyamide membranes as in 2,071,253; 2,966,700; 2,999,296; 2,385,890; 3,551,331; and the like; galactose methacrylate-methyl methacrylate copolymers as in 3,542,908; and the like; cellulose ethers; and the like.

The rate of drug diffusion of any preselected drug through the membrane can be ascertained by techniques well known to the art. For example, one standard technique comprises the casting or hot pressing of a film of the material, that will eventually carry the drug, to a thicknes of about 0.5 to 100 mils, and then using the film as a barrier between a rapidly stirred saturated solution of the drug and a rapidly stirred solvent bath, both maintained at a constant temperature. Samples are periodically withdrawn from the solvent bath and analyzed for drug concentration. By plotting drug concentration in the solvent bath versus time, the per-

meability constant P of the membrane is determined by the Fick's First Law of Diffusion as follows:

Slope of plot = $(Q_1-Q_2/t_1-t_2) = P\ (AC/h)$

wherein Q_1 is the cumulative amount of drug in solvent in micrograms at t_1; Q_2 cumulative amount of drug in solvent in micrograms at t_2; t_1 is elapsed time to first sample i.e. Q_1; t_2 is elapsed time to second sample i.e. Q_2; A is the area of membranes in cm^2; C= initial concentration of drug; and h is the thickness of membrane in cm. Thus, by determining the slope of the plot, i.e. (Q_1-Q_2/t_1-t_2), and solving the equation using the known or measured values of A, C, and h, the permeability constant, P, in cm^2/time of the material or membrane for a given drug is readily determined. From this data, an appropriate polymeric membrane for any selected drug can be chosen. This polymer can be one of those mentioned above or any other polymer having the appropriate drug permeability and low toxicity when in contact with blood vessels.

The drug device may be, as mentioned above, optionally equipped with an inlet-outlet port means **14** for feeding and draining active agents and the like into or from the device. The ports can be formed integral with wall **12** or they can be preformed and secured to the wall. The materials used to form the ports are those materials that are compatible with the agents and the host, and they include the materials set forth above, such as polyethylene, silicone rubber, Teflon, vitreous carbon, graphite and the like. The inlet port **14**, is optionally equipped with a bacterial filter such as the commercially available Milipore filters with pore sizes of 0.025 microns to 14 microns, Seitz filter, Amicon ultrafiltration molecular membranes, and the like.

In the specification and the accompanying claims, the term "drug" broadly includes physiologically or pharmacologically active substance for producing a localized or systemic effect or effects in mammals including humans and primates; avians; valuable domestic household, sport or farm animals, such as sheep, goats, cattle, horses etc.; or for administering to laboratory animals such as mice, rats, guinea pigs; and the like. That is, the novel drug delivery device can be used for administering drugs that are physiologically or pharmacologically active at a point in near relation to the drug delivery device, or, for administering a systemically active substance which will produce a physiological or pharmacological response at a site remote from the point of application of the drug delivery device. The active agents that may be administered include without limitation, those materials that transport across a vessel, for example, drugs acting on the central nervous system such as nitrous oxide, ethylene, cyclopropane, diethyl ether, divinyl ether, methoxyflurane and the like; hypnotics and sedatives such as pentobarbital sodium, phenobarbital, secobarbital, thiopental, etc.; heterocyclic hypnotics such as dioxopiperidines, and glutarimides; hypnotics and sedatives such as amides and ureas exemplified by diethylisovaleramide and α-bromoisovaleryl urea and the like; hypnotics and sedative alcohols such as carbomal, naphthoxyethanol, methylparafynol and the like; and hypnotic and sedative urethans, disulfanes and the like; psychic energizers such as isocarboxazid, nialamide, phenelzine, imipramine, tranylcypromine, pargylene and the like; tranquilizers such as chloropromazine, promazine, fluphenazine reserpine, deserpidine, meprobamate, benzodiazepines such as chlordiazepoxide and the like; anticonvulsants such as primidone, dipenylhydantoin, ethotoin, pheneturide, ethosuximide and the like; muscle relaxants and anti-parkinson agents such as mephenesin, methocarbomal, trihexylphenidyl, biperiden, levodopa, also known as L-dopa and L-β-3-4-dihydroxypenylalanine, and the like; analgesics such as morphone, codeine, meperidine, nalorphine and the like; antipyretics and anti-inflammatory agents such as aspirin, salicylamide, sodium salicylamide and the like; local anesthetics such as procaine, lidocaine, naepaine, piperocaine, tetracaine, dibucane and the like; antispasmodics and antiulcer agents such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine, prostaglandins such as PGE, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$ PGA and the like; anti-microbials such as penicillin, tetracycline, oxytetracycline, chlorotetracycline, chloramphenicol, sulfonamides and the like; anti-malarials such as 4-aminoquinolines, 8-aminoquinolines and pyrimethamine; hormonal agents such as prednisolone, cortisone, cortisol and triamcinolone; androgenic steroids, for example, methyltestosterone, fluoxmesterone and the like; estrogenic steroids, for example, 17β-estradiol and ethinyl estradiol; progestational steroids, for example, 17α-hydroxyprogesterone acetate, 19-nor-progesterone, norethindrone and the like; sympathomimetic drugs such as epinephrine, amphetamine, ephedrine, norepinephrine and the like; cardiovascular drugs, for example, procainamide, amyl nitrite, nitroglycerin, dipyridamole, sodium nitrate, mannitol nitrate and the like; diuretics, for example, chlorothiazide, flumethiazide and the like; antiparasitic agents such as bephenium hydroxynaphthoate and dichlorophen, dapsone and the like; neoplastic agents such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioguanine, procarbazine and the like; hypoglycemic drugs such as insulin, protamine zinc insulin suspension, globin zinc insulin, isophane insulin suspension, extended insulin zinc suspension, and other like insulins derived from animal and synthetic origin, tolbutamide, acetohexamide, tolazamide, chlorpropamide and the like; nutritional agents such as vitamins, essential amino acids, essential fats and the like; and other physiologically active agents.

The above listed and other drugs are usually admixed with a pharmaceutical carrier for feeding into the drug delivery system through the inlet conduit **14.** The pharmaceutical carriers acceptable for the purpose of this invention are the art known carriers that do not adversely affect the drug, the host or the polymers comprising the drug delivery device. Suitable pharmaceutical carriers include sterile water; saline; dextrose; dextrose in saline or in water; condensation products of castor oil and ethylene oxide combining about 30 to about 35 moles of ethylene oxide per mole of castor oil; liquid glyceryl triester of a lower molecular weight fatty acid; lower alkanols; oils such as corn oil, peanut oil, sesame oil and the like with emulsifiers such as mono- or di-glyceride of a fatty acid, or a phosphatide, e.g. lecithin, and the like; glycols; polyalkylene glycols; acetamide; N,N-dilower alkyl acetamides such as N,N-diethyl acetamide, N,N-dimethyl acetamide, N-(2-hydroxyethyl) acetamide and the like; aqueous media in the presence of a suspending agent, for example, sodium carbozy-methylcellulose, sodium alginate, polyvinylpyrrolidone and the like, alone, or with suitable dispensing agents such as lecithin, polyoxyethylene stearate and the like. The carriers may also contain ad-

juvants such as preserving, stabilizing, wetting, emulsifying agents and the like.

The drug can also be mixed with penetrating compounds that aid or assist the drug's passage through the blood vessel wall into the blood. The penetrating aid suitable for the purpose of the invention are the therapeutically acceptable penetrating aids that do not adversely affect the host, the drug or alter or adversely affect the polymers forming the drug delivery device. The penetrating aids can be used alone or they can be admixed with acceptable carriers. Exemplary of penetrating aids include, monovalent, saturated and unsaturated aliphatic, cycloaliphatic and aromatic alcohols having four to 12 carbon atoms such as hexanol, cyclohexane and the like; aliphatic, cycloaliphatic and aromatic hydocarbons having from five to 12 carbon atoms such as hexanol, cyclohexane and the like; aliphatic, cycloaliphatic and aromatic hydrocarbons having from five to 12 carbon atoms such as hexane, isopropylbenzene and the like; aliphatic, cycloaliphatic and aromatic aldehydes and ketones having from four to 10 carbon atoms such as cyclohexanone; and other penetrating agents such as aliphatic, cycloaliphatic and aromatic esters; essential oils; halogenated or nitrated aliphatic, cycloaliphatic and aromatic hydrocarbons; polyalkylene glycol salicylates; and mixtures thereof.

DESCRIPTION OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting its scope in any way, as these examples and others will become apparent to those versed in the art in the light of the present disclosure and the accompanying claims.

EXAMPLE 1

An in vitro radioactively labeled drug experiment is performed for demonstrating the diffusion into a blood vessel as follows: first, one end of an isolated section of canine carotid artery about 4.1 cm long with an outer diameter of 1.2 cm and a thickness of 0.11 cm, is attached to a piece of poly(vinyl) chloride tubing which leads from a peristaltic pump which draws from a reservoir. The other end of the artery is cannulated with another piece of poly(vinyl) chloride tubing which leads back to the reservoir. The reservoir contains Ringer's solution. The peristaltic pump is adjusted to a rate of 80 pulses per minute to give a flow rate of the Ringer's solution of about 20 to 30 milliliters per minute, and a mean hydrostatic pressure within the artery of about 30 mm of Hg. The carotid artery is next placed into a drug delivery device made, according to the invention, of polyethylene constructed in a long, closable U-shape. The delivery system contained a mixture of 523.1 micrograms per milliliter of 1,2-H^3 hydrocortisone, commercially available from New England Nuclear Corporation, and unlabeled hydrocortisone commercially available from the Mann Laboratories Inc. The mixture is made by mixing 120 micrograms of unlabeled hydrocortisone and 60 microcuries of the isotope in 200 ml of Ringer's solution. The mixture is made to the concentration and to the specific activity for a convenient volume to perform the experiment. The temperature of the drug delivery system and the reservoir is maintained at ambient temperature, about 25°C. Next, aliquots are taken of the Ringer's solution circulating in the artery and the reservoir at various times beginning at zero time; 0.5; 1; 1.5; 2; 3; and 4 hours, and the labeled hydrocortisone in the aliquots counted with a Nuclear Chicago, Mark II liquid scintillation spectrometer. The concentrations of the hydrocortisone in the various aliquots permits computation of the quantities of hydrocortisone that diffused across the carotid arterial wall. From 0.5 to 4 hours, the quantity increased linearly with time. The data indicated that the using a novel device of the invention, the transfer rate of hydrocortisone diffusion across a 1 cm^2 section of canine carotid arterial wall is 0.4 mg/cm^2/24 hrs.

EXAMPLE 2

Following the in vitro procedure described in Example 1, an isolated section of a canine carotid artery 3.5 cm long by 1.1 cm in outside diameter and having a wall thickness of 0.093 cm is submerged in the drug delivery system containing 10 g of unlabeled α-amino acid, glycine, and 10 microcuries of 1—C^{14} glycine. All the other conditions are as described above. Next, six aliquots are taken and counted for measuring the rate into the artery from the drug delivery system. The results showed at 30 minutes, 10,940 μg of glycine had diffused across the arterial wall; at 1 hour a total of 24,610.0 μg if glycine had diffused across the arterial wall; at 1 ½ hours a total of 35,390 μg; at 2 hours a total of 47,770; at 3 hours a total of 74,000; and at 4 hours a total of 100,600 μg had diffused across the arterial wall from the drug delivery system. The average diffusion or transfer rate for glycine is 6,780 μg/cm^2/hr; or, expressed as the transfer rate of diffusion across a 1 cm^2 of canine carotid arterial wall from this drug delivery system is 170 mg/cm^2/24 hours.

EXAMPLE 3

The procedure of Example 1 is repeated in this example and all the experiment conditions are as set forth, except that the drug delivery system now contains a mixture of 1 g of unlabeled D-L-Dopa, 3-(3,4-dihydroxyphenylalamine) and 10 μc (microcuries) of 1—C^{14}-L-Dopa dissolved in 200 ml of Ringer's solution to give an initial concentration in the drug delivery system for both labeled and unlabeled Dopa of 6,840 μg/cm^3. The measured results for this experiment indicated that 550 μg/cm^2/hr of Dopa diffused into the artery. The experiment was repeated twice, with initial concentrations in the delivery system of 10,700 μg/cm^3 and 10,600 μg/cm^3. The measured diffusion rates for these experiments were 1,050 μg/cm^2/hr and 1,180.1 μg/cm^2/hr respectively. The diffusion rate across a 1 cm^2 section of canine carotid arterial wall for Dopa is 12 to 24 μg/cm^2/24 hrs.

EXAMPLE 4

The procedure of Example 1 is repeated in this example and all the conditions were as previously described, except that the drug delivery system contained 22.6 μg/cm^2 of testosterone labeled with C^{14} at position C—4. The diffusion transfer rate for testosterone is 7.07 μg/cm^2/hr.

EXAMPLE 5

An in vivo procedure that effectively demonstrates the operability of the novel drug delivery device is performed as follows: first, the left common carotid artery of an anesthestized dog is exposed by standard surgical

technique and freed from it fascia. Next, a 40 millimeter section of the exposed artery is partially surrounded within a drug delivery device that is positioned in communicating axial alignment to the artery. The drug delivery device is of an open top saddle-like configuration about 60 millimeters long, 15 millimeters wide and 15 millimeters deep, and it is made of butyl rubber. The device is fabricated with integrally formed ascending terminal skirts for retaining drugs within the device and with an inlet and outlet tubing means adhesively mounted on the side of the device thereby forming passageways. for fluid interchange with the outside environment and the interior of the drug delivery device. The inner area of the drug delivery device housing the carotid artery is filled with a saturated solution comprising 400 mg of unlabeled L-Dopa[levo-3-(3,4-dihydroxyphenyl)-alanine], and 20 μc of L-Dopa-3-C^{14} in 80 percent Ringer's solution. Blood samples at the femoral artery, and left lingual artery, a branch of the left carotid artery at about 3 cm downstream from the drug delivery device, and cerebrospinal fluid samples for radioactive counting are taken at 20 minute intervals and the measured activity expressed as μg/ml is set forth in Table 1, as follows:

TABLE 1

SOURCE

Time of Sample Minutes	Femoral Arterial Blood	Left Lingual Arterial Blood	Cerebrospinal Fluid
20	1.7	5.0	1.5
40	2.3	7.6	1.6
60	2.9	6.8	2.0
80	2.8	7.2	2.1
100	3.6	10.2	2.6
120	4.1	8.9	2.9
140	4.0	9.6	2.9

The appearance of measurable labeled samples in the femoral artery as set forth above indicates a diffusion of the drug into blood, and mixing through the general systemic circulation. The appearance of labeled material in the left lingual artery at higher concentrations than in the femoral arterial blood indicates an advantageous localization of L-Dopa in arterial blood that supplies the brain. The presence of labeled activity in the cerebrospinal fluid indicates that L-Dopa or a derivative crossed the blood brain barrier.

EXAMPLE 6

An in vivo drug delivery device for administering testosterone is performed according to the procedure as set forth in Example 5. All the conditions were as described except that the drug delivery device in this example circumferentially surrounds the artery, as in FIG. 1 and its accompanying description, and its contiguous surfaces are sealed with a commercially available cyanoacrylate adhesive to provide a closed drug delivery device. The inlet and outlet ports in this device are joined to a drug reservoir comprised of a small plastic bag, suitably mounted in the host for continually supplying drug to the device for diffusion across the arterial wall. A novel drug delivery device coupled to a drug reservoir, as described herein, can be used for supplying a drug to a needed host for extended periods for example up to 2 years.

EXAMPLE 7

The procedure described in Examples 5 and 6 is repeated in this example, and all conditions were as described with the addition of a rate controlling poly(ethylene)-vinyl acetate membrane positioned in the device. The membrane is adhesively joined to the tapered ends of the device and it contacts the advantitial surface of the blood vessel for regulating the diffusion of drugs into the bloodstream.

EXAMPLE 8

An in vivo drug delivery system for administering testosterone is performed according to the procedure as set forth in Example 5 and Example 7. All the conditions are as described except that the drug delivery device in this instance example circumferentially surrounds the artery according to FIG. 5, and its contiguous surfaces are sealed with a commercially available cyanoacrylate adhesive to provide a closed drug delivery system. The inner surface ends of the drug delivery device has attached thereto a silicone drug release membrane that is formed by mixing 70 parts by weight of polydimethylsiloxanes and 5 parts of silicone oil. The well stirred mixture of the three ingredients is first formed and then cured by adding 0.25 parts by weight of stannous octoate, then it is fixed to the device. The delivery device provides a depot of the hormone for diffusion into the blood.

EXAMPLE 9

The procedure of Example 8 is repeated in this example except that the silicone is replaced with a commercially available polyethylene-vinyl acetate copolymer, 84/16, membrane containing the hormone therethrough, and the membrane is free-floating within the system for making available the drug for diffusion across the arterial wall and into the blood.

EXAMPLE 10

A drug delivery device for diffusively administering a drug into the portal vein is manufactured as follows: first, a pair of holes in spaced apart relation are cut into a sheet of commercially available nylon for receiving a pair of nylon tubes. Then, the tubes are sealingly joined with surgically acceptable adhesive such as methyl-2-cyanoacrylate to the sheet of nylon to form an inlet and outlet port system. Next, the nylon sheet is cut and formed to a shape that corresponds to the shape of the portal vein and the ends of the sheet are inwardly tapered to define a pair of openings for the vein and for positoning and fastening the nylon to the vein. The nylon sheet, that becomes the wall of the drug delivery device, is manufactured with a drug defining space formed by the inner wall of the nylon and the advantitial wall of the vein. Next, the shaped nylon device is positioned around the vein and its contiguous surfaces formed by the longitudinal edges of the device and in axial alignment with the vein are sealingly joined with the above mentioned adhesive. The tapered ends are then sealed to the vein. The inlet-outlet ports that extend outwardly through the host's skin can be used to occasionally supply drugs to the device, or they can be joined to an internally or externally carried drug reservoir, usually a small plastic bag for continuously supplying drugs to the device.

DESCRIPTION OF INVENTIVE APPLICATION

This invention makes available to the art of novel, unobvious and useful drug delivery device for administering drugs directly into blood within a blood vessel.

The drug delivery device can serve as an in vivo reservoir of drugs and act thereby as a source of drugs for the passage or diffusion of the drug in vapor, liquid or solid form through a blood vessel wall. The drug delivery device also makes available means for regulating the rate of drug passage, that is, the device can function as a drug pace maker for metering into the blood various quantities of drugs as they are needed at various drug receptor sites, for immediate, occasional, or for continual supply.

The drug delivery device can be used by the medical and the veterinary arts in a variety of ways. For example, the delivery device can be applied to the portal vein for the direct delivery of a drug to a target organ, the liver. The delivery device can be placed on the carotid artery for administering drugs to the brain for the management of Parkinson disease. The delivery device can also be used for the delivery of any material for systemic or regional administration, for any material indicated for local administration to an organ, for the delivery of medications for local perfusion in malignancy of an extremity and the like. The drug delivery device can be used as an internal drug reservoir, and its ports can be employed for refilling the device from an external reservoir supplying predetermined quantities of a medication to an artery or vein.

The above examples and disclosure are set forth merely for illustrating the mode and the manner of the invention and various modification and embodiments can be made by those skilled in the art in the light of the invention without departing from the spirit of the invention.

We claim:

1. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a hollow, elongate, bulbous tubule member tapered at its ends and having interior and exterior wall surfaces adapted to sealingly circumferentially engage the adventitial surface of a blood vessel longitudinally extending therethrough at both the proximal and distal ends thereof to form a pair of well-defined sealed interfaces therewith, and defining reservoir means for confining a drug supply in an annular interspace between the interior wall surface of said tubule member and the exterior wall of such blood vessel, said tubule member being provided with both inlet means and outlet means for filling and emptying the interspace, and the said tubule member being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

2. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising an elongate first tubule member having interior and exterior wall surfaces adapted to circumferentially engage the adventitial surface of a blood vessel longitudinally extending therethrough at both the proximal and distal ends thereof; a second tubule member having interior and exterior wall surfaces concentrically disposed within said first tubule member, comprising drug release rate controlling membrane, and sealingly circumferentially affixed to said first tubule member at the proximal and distal ends thereof and adapted to longitudinally extend therethrough closely adjacent the adventitial surface of the blood vessel; the interior walls of said first tubule member defining a sealed, annular interspace for confining a drug supply, said first tubule member being provided with both inlet means and outlet means for filling and emptying the interspace; and the said first tubule member being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom through the membrane and to and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

3. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a hollow, elongate tubule member having interior and exterior wall surfaces and circumferentially inwardly descending skirt members integral therewith and annularly depending therefrom at both the proximal and distal ends thereof, said skirt members adapted to sealingly circumferentially engage the adventitial surface of a blood vessel longitudinally extending through the tubule member to form a pair of well-defined sealed circumferential interfaces therewith, and said tubule member and skirt members depending therefrom defining reservoir means for confining a drug supply in an annular interspace between the interior wall surface of said tubule member and the exterior wall of such blood vessel, said tubule member being provided with both inlet means and outlet means for filling and emptying the interspace, and the said tubule member and skirt members being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

4. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a hollow, elongate first tubule member having interior and exterior wall surfaces and circumferentially inwardly depending skirt members integral therewith and annularly depending therefrom at both the proximal and distal ends thereof, said skirt members adapted to sealingly circumferentially engage the adventitial surface of a blood vessel longitudinally extending through the tubule member to form a pair of well-defined sealed circumferential interfaces therewith; a second tubule member having interior and exterior wall surfaces concentrically disposed within said first tubule member, comprising drug release rate controlling membrane, and sealingly circumferentially affixed to the skirt members annularly depending from the said first tubule member and adapted to longitudinally extend therethrough closely adjacent the adventitial surface of the blood vessel; the interior walls of said first tubule member and of the skirt members depending therefrom and the exterior walls of said second tubule member defining a sealed interspace for confining a drug supply, said first tubule member being provided with both inlet means and outlet means for filling and emptying the interspace; and the said first tubule member and the skirt members depending therefrom being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom through the membrane and to and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

5. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a first saddle member having interior and exterior wall surfaces adapted to sealingly engage the adventitial surface of a blood vessel longitudinally extending thereunder completely about the periphery thereof to form a well-defined, sealed, continuous peripheral interface therewith; a second saddle member having interior and exterior wall surfaces disposed beneath said first saddle member, comprising drug release rate controlling membrane, and sealingly continuously peripherally affixed to said first saddle member and adapted to extend thereunder closely adjacent the adventitial surface of the blood vessel; the interior walls of said first saddle member and the exterior walls of said second saddle member defining a sealed interspace for confining a drug supply, said first saddle member being provided with both inlet means and outlet means for filling and emptying the interspace; and the said first saddle member being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom through the membrane and to and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

6. The drug delivery device as defined by claim 5, wherein the first saddle member is essentially uniformly semi-circular in cross-sectional configuration in the directon along the major axis thereof.

7. The drug delivery device as defined by claim 5, wherein the first saddle member is further of a configuration adapted to helically engage the adventitial surface of the blood vessel.

8. The drug delivery device as defined by claim 1, wherein the inlet means further comprises a bacterial filter.

9. In a process for administering a therapeutically effective amount of an acceptable drug into the blood within an intact blood vessel wherein the process comprises placing a drug delivery device adapted for supplying a drug on the adventitial surface of a blood vessel, the device comprised of a wall formed of a material essentially impermeable to drug within the wall forming a reservoir and adapted to embrace the adventitial surface of the blood vessel, a reservoir for supplying drug and defined by the inner surface of the wall, an inlet port and an outlet port connected to the reservoir for supplying drug to the reservoir, and wherein drug is released from the reservoir when charged with drug and in contact with the adventitial surface for diffusively administering the drug through the blood vessel and into the blood from the device.

10. In a process for administering a drug from a drug delivery device according to claim 9 wherein the drug is diffusively administered into the blood to produce a localized effect.

11. In a process for administering a drug from a drug delivery device according to claim 9 wherein in the drug is diffusively administered into the blood to produce a systemic effect.

12. In a process for administering a drug from a drug delivery device according to claim 9 wherein the device further comprises a drug release rate controlling membrane permeable to the passage of drug for controlling the rate of drug diffusion from the device to the adventitial surface of the blood vessel wall, said membrane positioned and joined to the edges of inner surface of the wall with the drug contained in the reservoir formed by the inner surface of the wall and the membrane.

13. A process for administering a drug from a drug delivery device according to claim 12 wherein the wall and membrane are adapted to form a spiral or helix shaped device.

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