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POLYSILOXANE CARRIER FOR CONTROLLED RELEASE OF
DRUGS AND OTHER AGENTS
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FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

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POLYSIOXANE CARRIER FOR CONTROLLED RELEASE OF DRUGS AND OTHER AGENTS

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The invention described herein may be manufactured and used by or for the Government of the United States of America for governmental purposes without the payment of any royalties thereon or therefor.

Our invention relates generally to a method and means for introducing a therapeutic agent into a living organism and more particularly, it relates to a polysioxane carrier that allows for controlled release of drugs and other agents within a specified region or organ of the body.

In the past, drugs or pharmaceutical preparations have been mixed with carrier agents, such as beeswax, peanut oil, starches etc., and injected intramuscularly into the body. The carrier is then slowly broken down within the body allowing a slow release of the drug. Such carriers do not give satisfactory results because they often produce undesirable effects, such as foreign body reaction and scar formation; in addition, granulomas (benign fibrous tumors) and sterile abscesses are formed at the site of the injection. In most cases the rate of release of the therapeutic agent is so rapid that frequent injections become necessary with only small amounts of active agent in each injection. Furthermore, the bulk of the carrier substance limits the amount of active agent that may be used in each injection. A further practical drawback to this form of introducing medication follows from the fact that injections are active for only a few days or a week.

Therefore, containers of many types have been designed for use within the body cavities whereby medical preparations are allowed to escape from the container through tiny openings or perforations. Experience has proven that the tiny openings and perforations are rapidly plugged with body tissues, and the dispensing action ceases in a matter of hours or a few days. More elaborate arrangements for depositing medication within the body, involved the use of a dense tablet form which is formed with a smooth, compact surface, a portion of said surface is covered with a protective, undissolvable coating, while the remaining surface of tablet is exposed to the action of the body fluids. Obviously, resorption of medication from an exposed surface in which the medicinal substance is accessible to fluids cannot be definitely controlled or predicted during dissolution of the entire tablet.

We have now discovered a method for introducing therapeutic agents into the body by means of a novel implantate that is capable of providing a uniform release of powerful drugs for long periods, as much as several years. The novel implantate can release the desired amount of active agent directly into a malfunctioning organ for immediate use and at a constant dosage rate, without interruptions or variations in the supply as is generally the case with all of the previous methods noted above. Unlike the common practices of administering medication, orally or by injections, we now provide a method in which the active agent does not encounter an uncertain course through the fluid streams in order for it to reach the area of its utility. Instead, the desired medication is made readily available in situ from an implantated carrier which releases the active agent in relatively minute amounts yet cumulatively the agent released in a sustained time interval may reach any effective dosage level. The novel carrier of our invention can also be maintained within the body as an active dispenser of medication throughout the body system and to function effectively for prolonged periods without ill effects, whereby the implanted carrier becomes virtually an artificial gland.

It is an object of the present invention to provide a method and means for implanting a drug or other agent within an organ or region of the body for relatively slow, prolonged release thereof at a constant rate.

Another object of the present invention is to provide a novel drug carrier which can be implanted into the body for long term, direct application of a drug without the disadvantages of frequent injections or by way of digestion and absorption.

Another object of the invention is to provide a chemical pacemaker for regulating the functions of the heart by means of a slow, prolonged release of a powerful drug.

A further object of the invention is to provide an implantate within the body that releases a drug at a predetermined rate based upon pharmaceutical requirements.

A still further object of the invention resides in the use of a carrier within the body for slow prolonged release of a dry, powdered drug in situ thereby preserving the drug in its more stable form until it is made available to the body.

And yet a further object of the invention is to provide a substantial increase in efficiency in the use of drugs and other agents which have a beneficial effect for a certain organ or region of the animal organism, by encapsulating said drugs to dispense them directly in the designated organ or body region at a therapeutic rate.

Still further objects and advantages of the present invention will appear from the following detailed description taken in connection with the accompanying drawings, in which:

FIG. 1 is a perspective view, partly in section, of a preferred embodiment of the present invention;

FIG. 2 is a perspective view illustrating a modification of the drug carrier shown in FIG. 1;

FIG. 3 shows a further modification of the invention in which the implantate is in the form of an artificial aortic valve;

FIG. 4 shows a cardiograph of a heart beat indicating restored heart function as a result of an implanted drug carrier, and

FIG. 5 shows a drug carrier in accordance with the invention implanted in the muscle of the heart.

We have discovered in accordance with the present invention that a drug carrier may be formed in the shape of a capsule, or medicated solid which contains within an enclosed space or structure thereof a suitable drug for the purpose of implanting said carrier and drug within a living organism. Specifically, the capsule or other carrier is implanted within the tissues of an organ or in a particular region of the body for controlled release of the drug at a substantially constant level of dosage and for a long duration. The term "drug" is used in the specification and claims hereof in its broad sense as synonymous to "therapeutic agent," medicament and the like, and it is to be understood that all of such terms are intended to be inclusive of hormones, vitamins, antibiotics, anticoagulants, cancericidal agents, spermicidal
agents, vasoactive agents and other medicinals and medications effective to treat undesirable conditions existing in or on an animal body or in the body fluids.

A preferred form of our invention comprises a drug carrier formed of an organopolysiloxane rubber composition (more generally known as a silicone rubber), which is non-reactive toward the drug, non-toxic to the body, and known to be compatible with living tissue even after prolonged implantation in the living organism. The silicone can be either a conventional silicone rubber, or a composition characterized by "room temperature vulcanizing," i.e., RTV silicone rubber. Either form of silicone rubber can be fabricated into a suitable container, such as hollow, the capsule, pellet and the like, or alternatively, the silicone rubber may be formed into a prosthetic device capable of retaining within its polymer structure a suitable medication. Another embodiment of our invention is the direct injection of an RTV silicone rubber-drug fluid mixture into a body tissue, as explained in the previously discussed RTV systems. In this case, the catalyst not only brings about the vulcanization and the cross-linking of desired type, but also prevents premature curing provided the coating is applied in a suitable material such as in the previously discussed RTV systems. In this case, the catalyst not only brings about a conversion to the rubber.

The invention in its broadest aspect is directed to the phenomena of diffusion in which a powder, semi-solid or liquid migrating through a polymer wall at a relatively low rate. The mechanism by which diffusion or migrating action is achieved, may be explained on the basis of a gradient effect in which the enclosed substance relieves its internal concentration by spreading out into the adjacent medium. This action ordinarily would cease when sufficient substance has reached the outer surface or boundary of the adjacent medium. In the present case, however, the migrating molecules are advantageously being removed from the outer surface of the polymer wall by body fluids and by tissue absorption, and the migrating action continues indefinitely, or until the migrant medicinal substance has been completely consumed.

The powders, semi-solids, etc., which are capable of penetrating the polymer wall are generally those that show appreciable solubility in the polymer composition. Moreover, the ease with which these substances pass interstitially between elastomer molecules will depend to a great extent on the silicone rubber composition which is utilized in the drug carrier.

As noted above, the silicone rubber employed in this invention can be either a conventional one or an RTV type. These rubbery products are now well known in the art.

By "conventional" silicone rubber we refer to those systems which are converted to the rubbery state (i.e., they are cured) or "vulcanized" or "crosslinked" by the action of heat. The silicone polymers in such systems are predominantly linear organopolysiloxanes, having a preferred average degree of substitution of from about 1.98 to 2.02 organic groups attached directly to silicon (by carbon-silicon linkage) per silicon atom. The organic groups attached to silicon are preferably monovalent hydrocarbon radicals such as alkyl, aryl, aryalkyl, alkenyl, and aralkyl, and of these the methyl, phenyl, and vinyl radicals are most preferred. Halogenated monovalent hydrocarbon radicals may also be present as the organic groups in the silicone polymer, typical examples being chlorophenyl and 1,1,1-trifluorophenyl radicals.

Variation of the organic groups in the silicone polymer can be used to vary the solubility of the drug in the polymer, and hence can to some extent control the speed of migration of the drug through the polymer. Also, drugs which are insoluble in one type of polymer may be soluble in a different type of polymer. It is obvious that the choice of organic substitution in the polymer should take into consideration any slightly toxic or foreign body reactions brought about by the presence of that polymer in the body. Pure dimethylpolysiloxanes and dimethylpolysiloxanes which have a minor amount (for example, up to about 0.5 molar percent) of methylvinylsiloxane units present in the polymer have been studied more extensively from the toxicological standpoint than any others and have been found to be completely inert in the body, hence these are the most preferred polymers for use in our invention. There are some uses of our invention which are outside of the body, however, and in such cases any "foreign body reaction" which might be characteristic of a particular polymer would be of little or no concern.

The "conventional" silicone rubber formulation usually contains a filler to enhance the tensile strength and other physical properties of the cured rubber. Many types of such fillers are well known in the art. The so-called "reinforcing silica" fillers develop the best properties, however, and silicone rubber compositions that have been found to be inert in extensive studies involving implanting the rubber in many different body tissues. For these reasons, the silica fillers are preferred. Examples of reinforcing silica fillers include silica aerogel, fume silica, and other forms of silica having a relatively high pore volume and strict wall structure. Fillers can have organosiloxane groups attached to the surface thereof through siloxane bonding to improve the handling properties of the uncured silicone rubber formulation.

It is typical of the "conventional" silicone rubber formulations that they contain a peroxide vulcanizing agent. Again a host of suitable agents is known to the art, but when our invention is to be used by implanting the silicone rubber within the body, we prefer the use of benzoyl peroxide or dichlorobenzoyl peroxide. These agents decompose during the vulcanization and are not present in the finished rubber.

The patent literature showing the preparation of the above discussed silicone rubber is extensive. Illustrative U.S. patents include Warrick No. 2,541,137, Konkel et al. No. 2,890,188, Youngs No. 2,723,966, Tyler No. 2,863,946, and Johansson No. 3,002,551.

The RTV silicone rubbers are commercially available material and are known to the art. In general they employ the same silicone polymers as discussed above (although the polymers often contain a greater amount of silicon-bonded hydroxy groups by being deliberately end-blocked with such groups). The fillers discussed above can also be used if fillers are desired, and the cross-linking is achieved by introducing compounds such as the orthosilicates, polysilicates, and siloxanes containing silicon-bonded hydrogen atoms. This type of silicone rubber formulation will cure at room temperature when an appropriate catalyst is added, thus it is at least a two component system in which the catalyst is added just prior to use of the product. Typically the catalysts are compounds of carboxylic acids, and when the invention is to be used by implanting the silicone rubber within the body, stannous 2-ethylhexoate is the preferred species of catalyst.

It is sometimes desirable to incorporate or attach a silicone rubber "sponge" composition in the silicone rubber drug-carrier to be used as an anchoring means for the implanted unit, as described in greater detail below. The "sponged" or "foamed" type of silicone rubber is also a commercially available product, and can be obtained in an RTV form. Such systems generally employ an organosiloxane polymer containing a relatively great amount of silicon-bonded hydroxy groups, another organopolysiloxane polymer containing silicon-bonded hydrogen atoms, and fillers and metal salts can be in the previously discussed RTV systems. In this case, the catalyst not only brings about a conversion to the rub-
bery state, but also releases hydrogen gas from the hydrogen substituted polymer, this gas being the "spong-
ing" or "foaming" agent for the system.

Another commercially available RTV silicone rubber which can be used in this invention to form a "solid" (i.e., non-sponged) rubber product is a one component system in the sense that no catalyst need be added. In this system, the silicone polymer employed is one which contains two acyloxy groups (predominantly acetoxy groups) attached to terminal silicon atoms. The usual fillers can be present in this type of product. When exposed to atmo-
spheric moisture, the acyloxy groups hydrolyze to form new trifunctional siloxane units within the polymer which act as the cross-linking bridges necessary to produce the final rubbery product.

The various RTV silicone rubber products discussed above can be prepared as described in detail in, for ex-
ample, U.S. Patents No. 2,927,907 (Polmanter) and No. 3,035,016 (Brunner), and in British Patents No.
798,669 and No. 804,199.

The silicone rubber may be molded into a capsule or pellet having any convenient wall thickness and containing therein a drug or active agent—one which has been found to be capable of diffusing into and permeating the silicone rubber wall—the capsule or pellet having a surface sub-
stantially free of pores, perforations or sensibilities. The drug or active agent included therein will have a definite or characteristic rate of dif-
fusion through the container wall, which will in effect establish the dosage rate and the amount of drug which is released from a coherent surface in a given time interval. Thus, the amount of drug which is released over an ex-
tended period is based on the rate at which the drug dif-
fuses through the silicone rubber and also on the ability of the living tissues in the body to absorb the drug from the surface of the container. By limiting the transference surface of the container, as will be explained presently in greater detail, the amount of drug that reaches the surface may be effectively controlled.

The novel implantate may be varied in many ways, but it is most desirable to shape the dispensing drug carriers into tubular form of given lengths and volume capacity and having a calibrated rate of release for specified drug compositions. Hollow, tubular cartridges or capsules molded into a continuous, uniform dispensing surface and incorporating therein a preferred quantity of active agent may be made available to the medical and surgical profession as standard dispensing units. If it is desired to decrease the amount of drug which is to be released in a given period, a portion of the dispensing silicone rubber surface may be coated with a more imperious plastic substance to limit the effective transference area from which drug diffusion and absorption can occur. Al-
ternatively, a tubular container may be provided with an inner metallic or plastic casing having a number of port holes of a given dimension through which diffusion and transference action of the contained drug may be sub-
stantially regulated. Standard implantates of a specified length will provide a prescribed dosage of drug during a 24-hour interval. The implantates may also be designated in terms of desired physiological effects which they are capable of producing: A heart drug in a given tubular length may be prescribed as capable of generating on the average a given number of heart beats, for example, 70, 80, or 90 heart beats per minute.

Desirably, in carrying out the present invention, hollow, tubular containers are formed of silicone rubber having a wall thickness sufficient to provide a resilient tubular structure that is self-supporting and that does not col-
lapse or bend while implanted within the tissues of the body. While the thickness of the container determines initially the time interval which is required for the drug molecules to penetrate the polymer wall, the thickness of the silicone rubber does not affect the dispensing rate of the present carrier. After the drug has penetrated the wall, the migration of drug molecules is primarily a function of the solubility of the drug in the silicone rubber composition, and they will in effect penetrate a thin or thick wall at substantially equal rates.

It is also advantageous to provide polysiloxanes car-
riers in the form of prosthetic devices for the body into which medication is incorporated by any suitable means. For example, anti-inflammatory agents, such as heparin or Versene (ethylenediaminetetraacetic acid) may be impregnated into vascular or intravascular prostheses in order that their relatively slow rate of release from the carrier will pro-
vide sufficient protection against thrombosis. The medi-
cation may be introduced into the polysiloxane compo-
sition during the forming process of the device, or it may be diffused into the finished product. For example, the drug carrier may be formed by immersing the prosthetic device into a saturated solution of heroin, Versene, or other drug in a suitable solvent, such as alcohol, acetone, xylene or water.

Further modifications in the formation of drug carriers involves the use of relatively fluid polysiloxane of the RTV type and a medication dissolved therein. The fluid mix-
ture is injected into the tissues along with a catalyst to cause the fluid polysiloxane to polymerize in situ and
form a solid implant capable of providing a relatively slow release of medication. A mixture of 100 parts by weight of a fluid hydroxy end-blocked dimethylpolysilo-
xane (having a viscosity of about 10,000 centistokes at
25° C.) and 3 parts of ethylpolysilicate may be combined with 250 grams of penicillin and a suitable catalyst, for
example, stannous 2-ethylhexoate in an amount of about
0.5 percent based on the weight of the fluid polysiloxane. After the injected mixture has polymerized to a solid state, the penicillin is released slowly within the tissues. Fillers can be omitted from the injectable RTV material because strength of the rubber is not important. The presence of fillers, however, is not objectionable as long as an in-
jectable consistency remains in the fluid.

In connection with the embodiments of the invention illustrated in the drawing, the drug carrier of FIG. 1 is a length of silicone rubbing tubing 1, shown in cross-section as comprising a wall 2 and a confined space 3 containing therein an active agent 4, for example, dry vitamin B12 powder. The ends of the tubing are sealed with an RTV silicone rubber 5. The latter consists of methyl-
acetoxyisyl end-blocked dimethylpolysiloxane fluid, and a fume silica filler. A period of about 24 hours is neces-
sary for the seals to cure. A specific example of a carrier formed in this manner comprises about 1 cm. length of silicone rubber tubing having an inside diameter of 0.140 inch and a wall thickness of 0.030 inch. This rubber was prepared by extruding a mixture of about 75 parts poly-
mer, 24 parts fume silica and 1 part 2,4-dichlorobenzoyl peroxide. The mixture was cured 30 seconds at 730° F. and vulcanized by heating for 2 hours at 400° F. The polymer was a dimethylpolysiloxane containing about 0.14 mole percent methylvinylsiloxane units copolymerized therewith. The tubing is filled with about 20,000 micro-
grams of triiodothyronine.

By utilizing the means set forth above, implantates have been employed in the body and the desired effects produced have been quantitatively correlated. A drug carrier produced in the manner described and containing 10,000 micrograms of a triiodothyronine in a silicone rubber tube having a length of 14 mm. will release approxi-
mately 10 micrograms of the drug in a 24-hour period and generally provide a heart rate increase in a dog of about 120 beats per minute.

When a drug carrier 24 mm. long is used in the same manner and containing the same drug, it will re-
lease approximately 30 micrograms in a 24-hour period, and the heart beat is stepped up to about 200 beats per minute.

An implantation involving the use of a heart drug is performed by surgery and involves the insertion of a polysiloxane capsule containing a relatively large amount
of dry powder. A capsule containing 30,000 micrograms of digitoxin may be safely utilized within the body with- out any undue or irregular release of drug. The capsule containing the drug is initially sterilized and all surface digitoxin that may have been released to the surface is carefully removed. The capsule is then implanted by sur- gery in the myocardium of the heart. The digitoxin is released at a rate of about 10 micrograms per day pro- ducting an excitable focus on the heart. This focus then drives the heart at nearly physiologic rates. There is no systemic effect from the use of the drug since it is re- leased in very low concentrations. It is axiomatic that the drug is dispersed in such low concentrations yet has been found to be effective because the entire drug re- leased in this manner is utilized directly within the heart area. Moreover, the drug need not be sterilized, since migration through the polymer wall involves molecular size whereas bacteria are many order of magnitude larger and are effectively screened out.

The embodiment of FIG. 2 illustrates the use of an open cell silicone rubber sponge layer 6 attached to the capsule surface 1 by any suitable means, as for example, by slipping a sponge sleeve 6 over the capsule surface. The sponge layer has been found to serve as an anchoring means through the cavity created in the tissue to receive the capsule; the sponge expands in the cavity and prevents movement of the capsule. More- over, it serves as a matrix for the absorption of fluid, fibrin or connective tissue in the surrounding areas after implantation. Finally, the sponge layer also acts as a wick for the transport of drug from the capsule surface to the muscle site.

As pointed out above, it is possible according to the invention to fabricate a silicone rubber prosthesis, as the aortic valve, shown in FIG. 3 in which an anti-coagulant may be impregnated into the prosthesis material to protect the valve from thrombus formation.

By utilizing a silicone rubber carrier within the myo- cardiacum of the heart, an excitable focus is produced, as shown in the cardiographic record of FIG. 4. Prior to an implant surgery on a dog with complete heart block, a fixed heart rate of approximately 55 beats per minute is indicated at A. After a sealed silicone rubber tubing (as above described and being approximately 17 mm. long) containing 20,000 micrograms of triiodothyronine powder was implanted through an incision 7 in the left ventricle of the heart, as shown in FIG. 5, a heart rate of 150 beats per minute was generated. The electrocardiograph indicates at B the impulses arising from the site of the implant, about 8 hours following the implantation.

The implantate may in some cases provide a basal level of drug, while additional dosages may be supplemented by oral medication or by injection. Thus the drug require- ments of a patient may be more effectively controlled by providing some of the drug requirement from the implantate, while the practitioner can increase or vary the medi- cation by means of supplemental doses.

Heating increases the diffusion rate so that a capsule which has been heated will start diffusion of medication more rapidly. The capsule may also include more than one drug, one drug which diffuses rapidly available to the body, while a less diffusible drug becomes available at a later time, after the first drug has served its purpose.

Whereas the novel implantate has been described above with reference to its use in dispensing drugs in the living tissues of animals, such as dogs, evidence developed in our work indicates an equally effective use of the implantate in the human body.

Our method of introducing drugs into the living or- ganism provides a drug carrier which is readily tolerated in living tissues and which does not deteriorate by im- plantation in the living body. Therefore, the drug car- rier may be implanted within the organ or body region to be treated to provide constant release of the drug directly within the region in which it will produce the desired beneficial effect. For example, a capsule containing dry nitrogen mustard may be implanted in (or adjacent to) a cancerous mass.

It is now feasible to utilize drugs of more suitable com- positions that are more effective within a specified body region and that eliminate extraneous injection media and oral preparations. One advantage of the method is that the active therapeutic agent in its course through the body. More effective therapeutic agents with greater physiologic activity are now contemplated as a result of this invention, whereas the previous methods of administration were not able to utilize them in their active form. For superior results can be achieved by our method since the active drug composition is not mixed with a carrier agent thus avoiding any interaction between the active drug and the carrier. In prior art methods the active agent was often combined chemically with an inactive carrier molecule which had to be separated in vivo before the active agent could be used in therapy. In accordance with the present invention, however, it is possible to utilize the most powerful drug in direct application in any desired concentration for intermediate results without the pre- carious course of the previous carriers.

Another advantage of the present invention is that the silicone rubber implantate is not dependent upon the gradual decomposition or removal of the car- rier. The container or capsule remains intact and un- changed. In the previous methods, the active molecule must initially be detached and freed from the carrier as is the case with the use of beeswax or peanut oil, in order for the drug agent to regain its therapeutic effect.

The drug employed in the present silicone rubber car- rier remains dry even with implants that have been in use in the body for many months. Thus it can be readily appreciated that this method is specifically important for compounds that are highly unstable in the wet form and which could not be utilized effectively by previous means of implantation or injection.

It is also within the purview of the present invention to employ a container made of silicone rubber composi- tion, as described herein, which incorporates within the composition a suitable anti-coagulant, such as heparin or Versene. As is now apparent from the previous discu- sion, desirable and beneficial results can be attained by means of the novel container in storing and preserv- ing whole blood. The undesirable effect of coagulation, which occurs when the blood is removed from its normal environment in the living organism, is effectively sup- pressed by placing the blood in a silicone rubber con- tainer that has been impregnated with an anti-coagulant. The minimal daily release of anti-coagulant from the con- tainer composition will prevent coagulation and thus preserve whole blood in its normal state without the usual practice of preserving the blood in ACD solution or by excessive use of anti-coagulants.

The silicone rubber container of the present invention is used to dispense minimum daily amounts of anti-co- agulant to the blood thereby obviating the need for large amounts of preservatives. The blood may now be stored for periods of up to 21 days in its normal state, and pre- ferably in accordance with the preferred practice at a temperature of about 4°C., and utilized directly in blood transusions and for other purposes which require nor- mal, whole blood, relatively free of foreign substances.

The invention may be utilized in connection with drug carriers containing any desired medical or pharmaceutical type illustrated for example by any of the anti-infectives. Such preparation include antibiotics, i.e., sulfathiazole; antibiotics, i.e., penicillin; antitubungal agents; i.e., Nystatin; antimalarial, i.e., atabrine and the antiprotozoans, i.e., halofantron, and thereby simplifies the implantation procedure. Anticoagulative plastic agents, which include, for example, nitrogen mustard, previously mentioned in the specification; cardiovascular agents, which include digitals, quinidine and nitroglycerine; con-
traceptives, for instance spermicidal agents such as hexylresorcinol, may also be utilized in accordance with the present invention. Hormonal contraceptives and the synthetic substitutes and antagonists as represented by the thyroid hormones and by insulin may be used with beneficial results. Immunological agents including for example, tetanus toxoid, renal acting agents, for example, acetazolamide, skeletal muscle relaxants and their antagonists, for example, Methycornin, central nervous system stimulants, for example, ephedrine; and central nervous system depressants, which include the barbiturates in all their various chemical modifications are also included in the invention. Anesthetics which may be used in the novel drug carrier, include procaine, an antihistamine, i.e., benadryl; a de-toxicant, dimercaprol; an enzyme, i.e., hyaluronidase and an agent affecting blood formation, i.e., liver extract. A radioactive isotope which may be included in the novel carrier is iodine 131-tagged albumin. Specific proteins find utility in accordance with the invention, as represented by gamma globulin.

Examples of additional drugs which may be included in the present drug carriers with beneficial results in accordance with this invention include adrenal corticotropic hormone; adrenal cortical hormones, such as aldosterone, desoxy corticosterone, hydrocortisone and cortisone; parathormone, pluitrin, estradiol, progesterone and testosterone.

While we have described our invention in conjunction with certain drugs and specific implantate structures, it will be realized that these materials and structures may be varied without departing from the spirit and scope of the invention, which is the method and means of introducing a drug into the body from and diffusing through the silicone implantate over a prolonged period. The drugs and silicone rubber carrier can be varied to provide various dosage rates of selected drugs that provide a large number of physiological and therapeutic requirements. Various variations which do not depart from the spirit of the invention will occur to those skilled in the art.

What is claimed is:

1. An implantate for releasing a drug in the tissues of a living organism comprising a drug enclosed in a capsule formed of silicone rubber, said capsule being made of an organopolysiloxane with a constant rate. An implantate for releasing a drug in the tissues of a living organism comprising a capsule formed of silicone rubber, said capsule consisting essentially of dimethylpolysiloxane, which contains on the average from about 1.98 to about 2.02 organic groups per silicon atom, said group being selected from the radicals consisting of monovalent hydrocarboxyl radicals and halogenated hydrocarbon radicals, and a drug enclosed in said capsule which is soluble in and capable of diffusing through said capsule at a constant rate.

7. An implantate for releasing a drug in the tissues of a living organism comprising a capsule formed of silicone rubber, said capsule consisting essentially of dimethylpolysiloxane, which contains on the average from about 1.98 to about 2.02 organic groups per silicon atom, and up to 0.5 mol percent of methylvinylpolysiloxane, and a drug enclosed in said capsule which is soluble in and capable of diffusing through said silicone rubber to the outer surface of said capsule at a constant rate.

8. A drug carrier capable of releasing a drug at a constant rate when implanted in a living organism comprising a sealed, tubular container and a drug enclosed in said container, said container being formed of a section of silicone rubber tubing and the ends of said tubing being sealed with a layer of silicone rubber, said drug being soluble in and capable of diffusing through said silicone rubber tubing to the outer surface thereof at a constant rate.

9. The method of introducing a drug into an animal body which comprises injecting within a region of said body a mixture of a drug with an organopolysiloxane fluid which undergoes vulcanization at room temperature to silicone rubber, said drug being soluble in and capable of diffusing through the silicone rubber to the outer surface thereof at a constant rate.

10. A drug carrier in accordance with claim 8 in which the silicone rubber of said end-sealing layers is formed of cured methylidiacetoxyalkyl end-blocked dimethylpolysiloxane and contains a fume silica filler.

11. An implantate in accordance with claim 5 in which the silicone rubber contains a reinforcing silica filler.

12. A drug carrier which is capable of releasing a drug at a constant rate comprising a sealed, tubular container and a drug within said container, said container being formed of a silicone rubber tubing having an inside diameter of about 0.140 inch and a wall thickness of about 0.030 inch, the ends of said tubing being sealed with a silicone rubber composition, said drug being soluble in and capable of diffusing through said silicone rubber tubing to the outer surface thereof at a constant rate.

13. A drug carrier in accordance with claim 11 in which a layer of silicone rubber sponge on the outer surface of said container, said sponge having an open cell structure to provide fluid access to said surface.

14. A method of introducing a drug into an animal body which comprises implanting within the living tissues of said body a capsule formed of silicone rubber and containing a drug which is soluble in and capable of diffusing through said silicone rubber to the outer surface thereof at a constant rate.

15. A method of preserving whole blood with a minimum amount of anti-coagulant which comprises placing said blood in a container formed of silicone rubber, which is impregnated with a solid anti-coagulant composition soluble in and capable of diffusing through said silicone rubber to the outer surface thereof at a constant rate and storing said blood in said container, said silicone rubber providing a relatively low rate of release of said composition sufficient to prevent coagulation during storage.

16. A container for storing whole blood comprising a silicone rubber vessel in which the silicone rubber is impregnated with a solid anti-coagulant composition soluble in and capable of diffusing through said silicone rubber.
to the outer surface thereof at a constant rate to provide a relatively low rate of release of said composition sufficient to prevent coagulation of said blood during storage.

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