

[54] **DRUG RELEASE SYSTEM**
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3,220,960	11/1965	Wichterle	128/127 X
3,310,051	3/1967	Schulte	128/350 R X
3,313,289	4/1967	Kapral.....	128/1 R
3,527,220	9/1970	Summers	128/260
2,640,269	2/1972	Delgado.....	128/2 R
3,641,237	2/1972	Gould et al.....	128/260

[22] Filed: **May 17, 1973**

[21] Appl. No.: **361,153**

Related U.S. Application Data

[62] Division of Ser. No. 233,685, March 10, 1972, Pat. No. 3,765,414.

[52] U.S. Cl. **128/260**, 128/214 E, 128/1 R, 128/2 R

[51] Int. Cl. **A61m 31/00**

[58] Field of Search..... 128/260, 214 E, 127, 350, 128/1 R, 2 R

[56] **References Cited**

UNITED STATES PATENTS

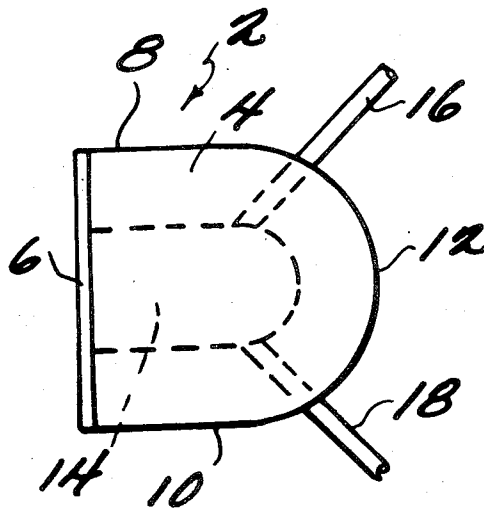
2,976,576 3/1961 Wichterle..... 128/214 R X

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Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

There is disclosed a device and method for delivery of a chemotherapeutic over a prolonged period of time to the body. In case the therapeutic has an adverse effect on the body the device can be flushed and a more suitable therapeutic substituted.

9 Claims, 5 Drawing Figures



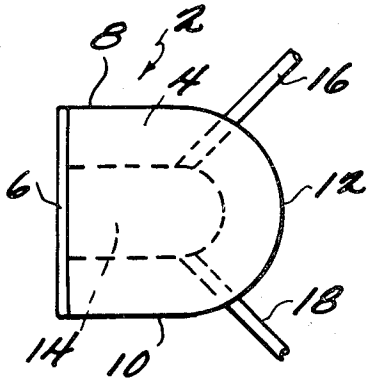


Fig. 1

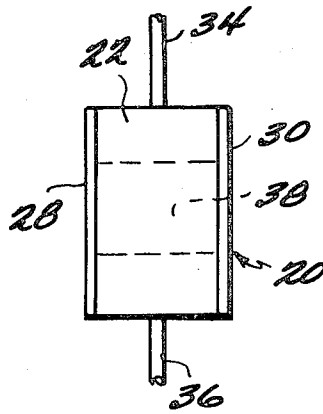


Fig. 2

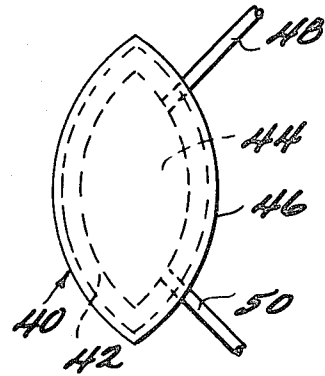


Fig. 3

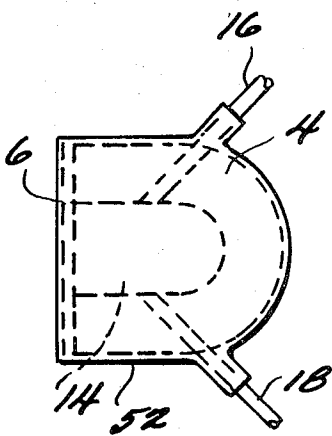


Fig. 4

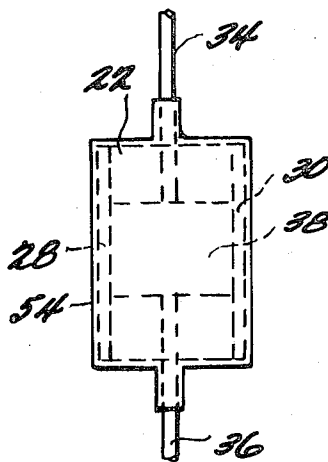


Fig. 5

DRUG RELEASE SYSTEM

This is a division, of application Ser. No. 233,685 filed Mar. 10, 1972, now U.S. Pat. No. 3,765,414.

The present invention relates to a device and method for the delivery of chemotherapeutic agents in human or veterinary medicine, e.g. in the treatment of humans as well as domesticated animals such as dogs, cats, horses, cattle, pigs, goats, sheep, chickens, turkeys or even wild animals such as may be found in zoos, using a device having a shaped configuration, e.g. as a pouch or capsule.

The device of the present invention can be employed topically, subcutaneously or implanted at various locations in an animal or human, either above or below the integument.

The device employed in the present invention in its simplest form comprises a hollow chamber for receipt of a medicament, a tube for introducing medicament to the chamber, a tube for removing medicament from the chamber, a relatively thick body wall for such a chamber and a relatively thin membrane for controlled release of medicament to the human or veterinary host.

The process and device of the present invention permits the release of any desired medicament on a timed basis which can be as short as an hour or several hours but which can be as long as days, months or even years.

The device can also be used to permit the varying of medicine. Thus the device permits the rotation of medicaments as desired. Alternatively in the case of allergy or anaphylactic reaction, or if the patient is toxic to the medicine for example, the chamber can be flushed immediately to remove the adversely reacting material, e.g. if a patient is being given penicillin and has a reaction thereto the penicillin can be flushed out and streptomycin introduced into the chamber.

The medicament (or mixture of medicaments) can be released on a flat curve or in any way or concentration as desired.

An additional function of the device is to overcome heretofore toxic, tissue or side-effect reactions encountered using present day methods of administering medicaments such as pills, injections, etc.

The devices can be fabricated from a wide variety of polymeric materials such as natural rubber, synthetic rubbers, e.g. cis-isoprene rubber, rubbery butadiene-styrene copolymer, rubbery butadiene-acrylonitrile copolymer, polychloroprene, butyl rubber (e.g. isobutylene-butadiene copolymer 98.5 : 1.5, see also U.S. Pat. No. 2,356,128), ethylene-propylene-terpolymer rubber (e.g. ethylene-propylene-norbornadiene or ethylene-propylene-cyclooctatriene, ethylene-propylene-dodecatriene, etc. polyvinyl pyrrolidone, silicone polymers, e.g. rubbery, polydimethyl siloxane such as a medical grade silastic, polyvinyl chloride and vinyl chloride copolymers, e.g. vinyl chloride-vinyl acetate copolymer (87 : 13), N-methyl acrylamide polymers, N-butyl acrylamide polymers, diacetone acrylamide polymers, polyvinyl alcohol, polyvinyl acetate, cellulose, e.g. cellulose acetate, cellulose acetate-propionate, ethyl cellulose, methyl cellulose, carboxy-methyl cellulose and hydroxy ethyl cellulose, ethylene-vinyl acetate copolymer, polyurethanes, e.g. toluene diisocyanate reacted with polytetramethylene glycol or with ethylene glycol-propylene glycol-adipate-maleate, polyimides, e.g. from methylene dianiline or oxydianiline and pyromellitic anhydride, polyamides, e.g. nylon 6,

nylon 6,6, nylon 6,11, polyacrylonitrile, polyethers, polyesters, e.g. polyethylene terephthalate, polymerized propylene glycol adipate maleate, fluoroplastics, e.g. polytetrafluoroethylene (Teflon), tetrafluoroethylene-hexafluoropropylene copolymer, polyvinylidene fluoride, polymerized olefins, e.g. polyethylene, polypropylene, ethylene-propylene copolymer (e.g. 50:50), polyisobutylene, polybutylene, polystyrene, high impact modified polystyrene (e.g. polystyrene blended with a minor amount of rubber, polysulfones, polycarbonates such as Lexan (bisphenol A polycarbonate), polyacrylates and methacrylates, e.g. polyethyl acrylate, polymethyl methacrylate, polybutyl methacrylate, poly 2-ethylhexyl acrylate, polyalkoxyalkyl acrylates and methacrylates, e.g. polymers, methoxyethyl acrylate, ethoxyethyl acrylate, butoxyethyl acrylate, methoxypropyl acrylate, methoxyethyl methacrylate, ethoxyethyl methacrylate and methoxypropyl methacrylate, hydroxyethoxyethyl methacrylate, hydroxypropoxypropyl methacrylate, hydroxyethoxyethyl acrylate.

The preferred polymers are hydrophilic polymers made from a monomer which is a hydroxy lower alkyl acrylate or methacrylate, or hydroxy lower alkoxy lower alkyl acrylate or methacrylate, e.g., 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, diethylene glycol monoacrylate, diethylene glycol monomethacrylate, 2-hydroxypropyl acrylate, 2-hydroxypropyl methacrylate, 3-hydroxypropyl acrylate, 3-hydroxypropyl methacrylate and dipropylene glycol monomethacrylate. The polymers produced from slurries of monomers are organic solvent soluble, e.g. alcohol soluble, but water insoluble. They can be prepared for example as shown in Shepherd U.S. Pat. No. 3,618,213 e.g. example 36a, or Chromacek U.S. Pat. No. 3,575,946.

The hydroxyalkyl acrylate or methacrylate less preferably can also be replaced by vinyl pyrrolidone, acrylamide, methacrylamide, N-propyl acrylamide, N-isopropyl methacrylamide, N-methylacrylamide, N-methylmethacrylamide, N-methylol acrylamide and N-methylol methacrylamide, N-2-hydroxyethyl acrylamide, N-2-hydroxyethyl methacrylamide. However, these monomers usually form water soluble homopolymers and hence they require the presence of a cross-linking agent or copolymerization with a sufficient amount of the hydroxyalkyl acrylates and methacrylates to render the copolymers water insoluble.

Other ethylenically unsaturated monomers can be used in conjunction with the above monomers or copolymers to constitute hydrophilic polymeric matrixes suitable for the entrapment of enzymes. They include neutral monomers such as acrylonitrile, methacrylonitrile, vinyl acetate, alkyl acrylates and methacrylates, alkoxyalkyl acrylates and methacrylates.

Examples of alkyl acrylates and methacrylates include methyl acrylate, ethyl acrylate, butyl acrylate, 2-ethylhexyl acrylate, methyl methacrylate and butyl methacrylates. Examples of suitable alkoxyalkyl acrylates and methacrylates are methoxyethyl acrylate, methoxyethyl methacrylate, ethoxyethyl acrylate ethoxyethyl methacrylate, propoxyethyl acrylate, butoxyethyl methacrylate, methoxypropyl acrylate, ethoxypropyl methacrylate. These comonomers when used in an amount preferably not higher than 50 percent (and usually between 0.5 and 20%) of the monomeric mixture contribute to improve the mechanical properties

of the gel. They should not be used in an amount to impair the hydrophilic nature of the polymer. Other vinyl monomers bearing ionizable functional groups can be copolymerized with the hydroxyalkyl acrylates or methacrylates to constitute ionogenic matrixes which can be useful when a basic or acidic environment is required for the stability or the optimum activity of enzymes. They include acidic type monomers such as acrylic acid, methacrylic acid, maleic acid, fumaric acid, itaconic acid, aconitic acid, cinnamic acid, crotonic acid, carboxylic acid, propiolic acid, citraconic acid, vinyl sulfonic acid, p-vinylbenzenesulfonic acid, partial esters such as mono-2-hydroxyethyl itaconate, mono-2-hydroxypropyl citraconate, mono-2-hydroxyethyl maleate, mono-2-hydroxypropyl fumarate, monomethyl itaconate, monoethyl itaconate, monomethyl cellosolve itaconate (Methyl Cellosolve is the monoethyl ether of diethylene glycol), monomethyl Cellosolve maleate, mono-2-hydroxyethyl aconitate.

They also include basic type monomers such as aminoethyl methacrylate, dimethyl aminoethyl methacrylate, monomethyl-aminoethyl methacrylate, t-butylaminoethyl methacrylate, p-amino-styrene, o-aminostyrene, 2-amino-4-vinyltoluene, diethylaminoethyl acrylate, dimethylaminoethyl acrylate, t-butylaminoethyl acrylate, piperidinoethyl acrylate, piperidinoethyl methacrylate, morpholinoethyl acrylate, morpholinoethyl methacrylate, 2-vinyl pyridine, 3-vinyl pyridine, 4-vinyl pyridine, 2-ethyl-5-vinyl pyridine, dimethylaminopropyl acrylate, dimethylamino propyl methacrylate, dipropylaminoethyl acrylate, dimethylaminoethyl vinyl ether, dimethylaminoethyl vinyl sulfide, diethylaminoethyl vinyl ether, aminoethyl vinyl ether, 2-pyrrolidinoethyl methacrylate, 3-(dimethylaminoethyl)-hydroxypropyl acrylate, 3-(dimethylaminoethyl)-2-hydroxypropyl methacrylate, 2-aminoethyl acrylate, 2-aminoethyl methacrylate. The alkylaminoethyl acrylates and methacrylates are preferred in this group. These ionogenic monomers should not be used in sufficient amounts to render the hydroxyalkyl acrylates or methacrylates water soluble. Multipolymers prepared from a mixture of 3,4 or more of the above monomers can be used. These monomers are usually used in an amount of 0.1 - 20%, preferably 1 to 15% of the total monomers.

When it is necessary to render the membrane insoluble in organic solvents, this can be done by sparingly cross-linking the entrapping polymer. Preferably, the cross-linking agent is added in an amount of 1 to 10% most preferably, not over 2.0% or 2.5%, although from 0.05 to 15% or even 20%, of cross-linking agents can be used. Cross-linking renders the otherwise organic solvent soluble or watersoluble polymers insoluble, although it does not impair the hydrophilic properties.

Typical examples of cross-linking agents include ethylene glycol diacrylate, ethylene glycol dimethacrylate, 1,4-butylene dimethacrylate, diethylene glycol dimethacrylate, propylene glycol dimethacrylate, diethylene glycol dimethacrylate, dipropylene glycol dimethacrylate, diethylene glycol diacrylate, dipropylene glycol diacrylate, divinyl benzene, divinyl toluene, diallyl tartrate, allyl pyruvate, allyl malate, divinyl tartrate, triallyl melamine, N,N'-methylene bisacrylamide, diallyl maleate, divinyl ether, diallyl monoethylene glycol citrate, ethylene glycol vinyl allyl citrate, allyl vinyl maleate, diallyl itaconate, ethylene glycol diester of itaconic acid, divinyl sulfone, hexahydro-1, 3, 5-triacryltriazine,

triallyl phosphite, diallyl ester of benzene phosphonic acid, polyester of maleic anhydride with triethylene glycol, diallyl aconitate, divinyl citraconate, diallyl fumarate, ammonium dichromate.

Especially useful are water insoluble hydrophilic polymers of hydroxyalkyl acrylates and methacrylates having 2 to 4 carbon atoms in the alkyl group particularly hydroxyethyl methacrylate (HEMA), although there also can be used polymers of hydroxypropyl methacrylate, hydroxybutyl methacrylate, hydroxyethyl acrylate or hydroxy propyl acrylate. The polymers of this preferred group can be homopolymers or more preferably are copolymers containing a small amount, e.g. 0.05 to 20% preferably 0.1 to 2% of a cross-linking agent to give a sparingly cross-linked polymer. Examples of such cross-linking agents are ethylene dimethacrylate, propylene dimethacrylate, butylene dimethacrylate, ethylene diacrylate, butylene diacrylate, diethylene glycol diacrylate, diethylene glycol dimethacrylate, dipropylene glycol dimethacrylate, triethylene glycol diacrylate, triethylene glycol dimethacrylate, tartaric acid dimethacrylate, methylene bis acrylamide, triallyl cyanurate or other cross-linking agents such as disclosed in Wichterle U.S. Pat. No. 3,220,960 or Shepherd U.S. Pat. No. 3,575,123 or Shepherd U.S. Pat. No. 3,577,512 or Shepherd U.S. Pat. No. 3,618,213 can be used. The entire disclosure of the Wichterle patent and the three Shepherd patents is hereby incorporated by reference. The hydroxyalkyl acrylate (with or without the cross-linking agent can be copolymerized with a minor amount, e.g. 0.1 to 49%, usually not over 20%, of another monoethylenically unsaturated monomer, e.g. methyl methacrylate, vinyl pyrrolidone, vinyl acetate, methoxyethyl methacrylate, ethoxyethyl methacrylate, butyl acrylate, etc. The hydrophilic polymer such as a HEMA polymer can be prepared in anhydrous form, e.g. as disclosed in Shepherd U.S. Pat. No. 3,618,213 or as a hydrogel as shown in Wichterle U.S. Pat. No. 3,220,960.

The device employed in the present invention can be fabricated by utilizing conventional procedures such as injection molding, film casting, ultrasonic welding, heat sealing, cement bonding, etc. and can be prepared as a single sided membrane, a double sided membrane or a total (i.e. overall) membrane device. The devices can be rigid, semi rigid or flexible.

As medicaments there can be employed compounds such as procaine penicillin, 5-fluorouracil, adrenaline (epinephrine) steroids and other hormones such as testosterone, estradiol, diethyl stilbesterol, a mixture of ethynylestradiol and mestranol, androsterone, norethandrolone (Nilevar), estrone, stilbesterol, progesterone, 11-dehydroprogesterone, desoxycorticosterone, hydrocortisone acetate, corticosterone, cortisone, 9-alpha-fluorohydrocortisone, insulin, lincomycin hydrochloride, penicillin, streptomycin, phenoxymethyl penicillin, chloramphenicol, sulfanilamide, sulfaguandine, sulfathiazole, tetracycline, clorotetracycline, hydroxytetracycline, bacitracin, neomycin, polymyxin, gramicidin, erythromycin, sulfacetamide, sulfamethizole, thyroxin sulfisoxazole, antivirals such as idoxuridine, nitrofurazone, sodium propionate, anti allergenics such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and prophenpyridamine, anti inflammatories such as dexamethasone, dexamethasone 21-phosphate, fluocinolone, prednisolone, prednisolone acetate and prednisolone 21-phosphate, decongestants

such as phenylephrine, naphazoline and tetrahydrozoline, pilocarpine, diisopropyl fluorophosphate, cyclopentolate, homatropine, hydroxyamphetamine, sedatives and hypnotics such as phenobarbital, pentobarbital sodium, butobarbital, amobarbital, secobarbital sodium, codeine, bromoisovatum, sodium and phenobarbital, pentaerythritol, tetranitrate, nitroglycerine, digi-toxin, digitalis, atabrine, heparin, hydroxystilbamide, benadryl dl-amphetamine sulfate, dextro amphetamine sulfate, vitamins, e.g. Vitamin B₁, Vitamin B₂, Vitamin E, Vitamin K, Vitamin C (ascorbic acid), tranquilizers, e.g. reserpine, chlorpromazine hydrochloride, alkaloids, e.g. belladonna, atropine sulfate, hyoscine hydro-bromide, chlorpheniramine maleate, quinidine salts, theopylline salts, ephedrine salts, pyrilamine maleate, enzymes, e.g. pepsin, trypsin, alphaamylase, phosphatases, glyoxalase, cytochrome oxidase, d-amino acid oxidase, l-amino acid oxidase, hyaluronidase.

When the polymer employed for the device to control the flow of medicament is made of a polymer which has a tissue reaction e.g. silicone, polyvinyl alcohol, Teflon and most of the other polymers which are tissue irritating, it is preferred to eliminate the tissue irritation by employing a polymer of a hydroxyalkyl acrylate or methacrylate, e.g. a HEMA polymer, as a thin biocompatible overall coating.

There are a number of different designs for the devices used in the present invention. Several of these are shown in the accompanying drawings wherein

FIG. 1 is a vertical elevation of one type of device according to the invention;

FIG. 2 is a vertical elevation of an alternative device;

FIG. 3 is a view of a bag device according to the invention having a non-toxic coating;

FIG. 4 is a vertical elevation of a device similar to that of FIG. 1 but having a biologically acceptable coating; and

FIG. 5 is a vertical elevation of a device similar to that of FIG. 2 but having a biologically acceptable coating.

Referring more specifically to FIG. 1, there is disclosed an implantable device in the shape of half of a capsule having a relatively thick body wall 4 on the body of the device, e.g. a hydrophilic hydrogel copolymer of hydroxyethyl methacrylate with 0.2% of ethylene dimethacrylate and having a relatively thin membrane end wall 6 of the same material. The wall 4 has two straight portions 8 and 10 joined by an arcuate portion 12.

The wall 4 and membrane end wall 6 enclose a hollow chamber 14 which can be filled with a drug through entry channel or tube 16. In the event it is necessary to flush out and replace the drug, this can be accomplished for example by passing a cleaning fluid or a different drug through channel or tube 16 into chamber 14 and forcing the old drug out through exit channel or tube 18. Tubes 16 and 18 can be closed off by any suitable valve outside the body. Tubes 16 and 18 can be made of the same material as the rest of the device or any other suitable material, e.g. Teflon, Silastic, polyvinyl chloride, rubber, etc. The membrane 6 can be of the same material as the wall 4 or it can be made of a different material.

In the form of the invention as shown in FIG. 2, the implant device 20 is basically in the form of an O ring having a relatively thick front wall 22 and a back wall (not shown). The side walls 28 and 30 each are of a rel-

atively thin membrane. There are also provided fluid entry channel 34 and fluid exit channel 36 into drug receiving chamber 38. The implant device, for example, can be essentially in the form of a ring similar to that in FIG. 2 of Kapral U.S. Pat. No. 3,313,289.

In the embodiment shown in FIG. 2 the two membrane sides can be of the same or different thickness. If they are of the same thickness and made of the same material, e.g. hydroxyethyl methacrylate copolymer, then the rate of diffusing materials out of the chamber will be the same. However, the rates can be varied by changing the relative thickness of the two membranes, e.g. 1.1:1, 1.5:1, 2:1, 4:1 or 10:1 so that the rates of diffusion will be different. This can be important when it is desired to introduce the same medicament simultaneously to different body organs.

The embodiment shown in FIG. 3 is in the form of a bag 40 having a single body wall 42 of polytetrafluoroethylene surrounding central drug receiving cavity 44 and a non toxic extremely thin external membrane 46 of a hydrophilic polymer of hydroxyethyl methacrylate with 0.1% ethylene dimethacrylate as a cross-linking agent. There are also provided fluid entry channel 48 and fluid exit channel 50.

The device of FIG. 4 is similar to that of FIG. 1 except that the body wall 4 and the membrane 6 are made of a biologically toxic material, e.g. Silastic (rubbery polydimethyl siloxane) and there is an overall very thin coating 52 of biocompatible material such as HEMA polymer for both the body wall and the membrane. The membrane and body wall can be of different materials, e.g. the body wall can be polytetrafluoroethylene and the membrane Silastic.

The device of FIG. 5 is similar to that of FIG. 2 except that the walls and membranes are made of a toxic material, e.g. Silastic, and the walls and membranes have an overall very thin coating 54 of biocompatible material such as a copolymer of HEMA with 0.2% of diethylene glycol dimethacrylate. Different rates of diffusion of the medicament through membranes 28 and 30 can be provided by making them of different thicknesses or by making them of different materials which can have the same or different thicknesses. Thus membrane 28 can be made of polymethyl methacrylate and membrane 30 of polyethylene.

The body wall or walls of the device are relatively thick e.g. at least 2 mm. to provide sufficient rigidity. The body wall can be as thick as 7 mm. The permeable membrane can be from 0.1 to 2 mm. thick but usually is not over 1 mm. and preferably is 0.2 to 0.5 mm. It should not be over one-half the thickness of the body wall. The body wall can be reinforced if desired, e.g. with Dacron (polyethylene terephthalate) fibers or other fibers either medially or externally.

When a coating biologically compatible material is employed over a more biologically toxic material, the outer material should be very thin, e.g. 0.01 to 0.1 micron. In the total device the inner membrane is employed to control the flow of medicament and the outer coating is solely for the purpose of preventing tissue reaction and should therefore be as thin as possible so as not to interfere with such flow.

According to the present invention there can be filled into the inner cavities in the devices of the drawings a medicament, such as for example any of those specified above, or mixture of medicaments. The medicaments can be in liquid or solid form. They also can be intro-

duced into the cavity in the form of a solution or suspension in water or other biologically acceptable liquid.

The device of the invention can be implanted subcutaneously, intramuscularly, interperitoneally or adjacent to any body organ or by any other conventional manner of implantation.

The device can be used to deliver medically active ingredients (1) to a specific area of the body, e.g. an organ such as the liver, gall bladder, stomach wall, or a lung, placed between two organs, e.g. between the pancreas and the duct leading into the intestines; (2) placed adjacent to an inoperative mass, e.g. a tumor such as a Schwannoma, (3) placed within a functioning organ system to release active ingredients to stimulate or reduce activity of the system, e.g. an implant directly into the peritoneum or into the stomach or the uterus.

As previously stated the device having a hollow, fillable chamber with ingress and egress through small hollow tubes can be formed by any conventional method. The hollow tubes at the time of implant can be brought out through the skin. The entry and exit tubes can be removed at any time if desired by gentle manipulation.

The present invention is especially effective as a method of delivery of antitumor compounds in high concentrations in the area of tumor growth. The implantable device of the invention containing the antitumor agent is placed against the tumor at the time of surgery. Because of its high degree of biologic acceptability (see Levowitz, Trans. Amer. Soc. for Artificial Internal Organs 14,82(1968) Hydron (a commercially available copolymer of 100 parts of 2-hydroxyethyl methacrylate with about 0.2 parts of ethylene glycol dimethacrylate) is particularly suitable as set forth supra for forming the walls and membranes of the devices since it evokes little or no fibroblastic reaction at implantation sites.

The use of the device of the invention permits flexibility in administering chemotherapeutic agents. Thus a drug can be discontinued at the first sign of toxicity and if the drug is ineffective, it can be readily changed.

Using 5-fluorouracil (5-FU) and the device of FIG. 2 with Hydron as the material of the body walls and membranes. The device was an O-ring with two membranes. The 5-FU was employed as a solution of 50 mg/ml. in water. It was found that within 30 minutes 20 mgs. of 5-FU were absorbed in each gram of Hydron with a gradual increase to 30 mg/gm. of Hydron in 90 minutes.

Elution of 5-FU from Hydron pledgets soaked in 0.5% 5-FU for 5 days was studied in 0.1 molar phosphate buffer and human plasma. This pattern of release was constant over the first 4 days and gradually tapered off over an interval of 120 hours.

In vivo studies in rabbits showed a similar rate of release occurred with 65% of the 5-FU entering the tissues and body fluids in the first 48 hours.

The use of individual pellets of Hydron saturated with 5-FU and implanted into the peritoneal cavity of CF₁, white mice was found to offer protection against the growth of Ehrlich's ascites tumor cells. Five days after challenging implanted mice with Ehrlich's ascites tumor cells, 21/22 mice were alive with the Hydron treatment versus 18/22 animals having Hydron with just water. On the 21st day, 17/22 animals receiving the Hydron plus chemotherapeutic agent were alive versus

4/22 having received control Hydron plus water pledgets. Thus it appeared that the Hydron plus chemotherapeutic agent offered significant protection in the mice.

However, polymer saturated with antitumor drugs cannot deliver effective serum or tissue levels. The implantable device of the invention, e.g. an O-ring of the type described using various membrane thicknesses. In vivo studies revealed fairly predictable straight line curves for release of the anti-tumor agent 5-FU with a window size of 1 cm. in diameter and 0.15 mm membrane thickness, 1 mg of 5-FU was eluted from the chamber per hour. A 1 mm. thick membrane window allowed 0.5 mg of 5-FU to be eluted per hour.

Studies employing this device implanted into the peritoneal cavity of dogs indicated that a rapid uptake of 5-FU into surrounding tissues occurred. The uptake appeared selective in that high concentrations of agents reached those tissues in contact with the reservoir and rapidly tapered off at more distant sites. Even those tissues with known predilection for the agent appeared spared.

What is claimed is:

1. A method of introducing a plurality of medicaments into an animal body which includes selecting an area of the body to be treated, implanting into the living tissues of the body a body implant device for delivery of a medicament over a long period of time comprising a chamber adapted to receive a medicament, wall means sufficiently thick to be resistant to fluid flow therethrough partially surrounding said chamber, relatively thin fluid permeable membrane means engaging said wall means and completing the surrounding of said chamber, said membrane means being adapted to permit transport of fluids between the body and said chamber, said membrane means being not over one-half the thickness of said wall means, said wall means and said membrane means being made of a water insoluble hydrophilic non-toxic polymer of a member of the group consisting of hydroxy lower alkyl acrylates, hydroxy lower alkyl methacrylates, hydroxy lower alkoxy lower alkyl acrylates, hydroxy lower alkoxy lower alkyl methacrylates, vinyl pyrrolidone, acrylamide, methacrylamide, N-lower alkyl acrylamide, N-lower alkyl methacrylamide N-hydroxy lower alkyl acrylamide and N-hydroxy lower alkyl methacrylamide first conduit means for feeding medicament to said chamber and second conduit means for rapid removal of medicament from said chamber, introducing into the chamber of the device a first medicament, allowing the device to remain within the body while permitting said first medicament to pass through said membrane means into the animal body, passing a second medicament through said first conduit means into said chamber after said device is implanted in the body, removing the first medicament through said second conduit means and permitting said second medicament to pass through said membrane means into the animal body.

2. A method of introducing a plurality of medicaments into an animal body which includes selecting an area of the body to be treated, implanting into the living tissues of the body a body implant device for delivery of a medicament over a long period of time comprising a chamber adapted to receive a medicament, wall means sufficiently thick to be resistant to fluid flow therethrough at least partially surrounding said chamber, relatively thin fluid permeable membrane means engaging said wall means and either (1) completing the

surrounding of said chamber, or (2) completely surrounding both said chamber and said wall means, said membrane means being adapted to permit transport of fluids between the body and said chamber, said membrane means being not over one-half the thickness of said wall means, said wall means and said membrane means being made of a biologically incompatible material and an extremely thin coating of a water insoluble hydrophilic non-toxic, biocompatible polymer of a member of the group consisting of hydroxy lower alkyl acrylates, hydroxy lower alkyl methacrylates, hydroxy lower alkoxy lower alkyl acrylates, hydroxy lower alkoxy lower alkyl methacrylates, vinyl pyrrolidone, acrylamide, methacrylamide, N-lower alkyl acrylamide, N-lower alkyl methacrylamide, N-hydroxy lower alkyl acrylamide and N-hydroxy lower alkyl methacrylamide surrounding all externally exposed portions of said wall means and said membrane means, said coating being sufficiently thin that it does not interfere with fluid transport through said membrane means, a first conduit means for feeding medicament to said chamber and a second conduit for rapid removal of medicament from said chamber, introducing into the chamber of the device a first medicament, allowing the device to remain within the body while permitting said first medicament to pass through said membrane means into the animal body, passing a second medicament through said first conduit means into said chamber after the device is implanted in the body, removing the first medicament through said second conduit means and permitting said second medicament to pass through said membrane means into the animal body.

3. A method according to claim 2 including the step of introducing said first medicament into said chamber after the device is implanted in the animal body.

4. A method according to claim 3 including the step of determining if said first medicament is compatible with said tissues, upon determination that a change of medicament is desirable because the animal body exhibits a toxic reaction to the first medicament promptly replacing said first medicament by a second medicament which does not have said toxic effects.

5. A method of introducing a plurality of medicaments into an animal body which includes selecting an area of the body to be treated, implanting into the living tissues of the body a body implant device for delivery of a medicament over a long period of time comprising a chamber adapted to receive a medicament, wall means sufficiently thick to be resistant to fluid flow therethrough partially surrounding said chamber, relatively thin fluid permeable membrane means engaging said wall means and completing the surrounding of said chamber, said membrane means being adapted to permit transport of fluids between the body and said chamber, said membrane means not being over one-half the thickness of said wall means, said wall means and said membrane means being made of a water insoluble hydrophilic non-toxic biocompatible polymer of a hydroxy lower alkyl acrylate or methacrylate, first conduit means for feeding medicament to said chamber and second conduit means for rapid removal of medicament from said chamber, introducing into the cham-

ber of the device a first medicament, allowing the device to remain within the body while permitting said first medicament to pass through said membrane means into the animal body, passing a second medicament through said first conduit means into said chamber after said device is implanted in the body, removing the first medicament through said second conduit means and permitting said second medicament to pass through said membrane means into the animal body.

6. A method according to claim 5 including the step of determining if said first medicament causes undesirable side effects, upon determination that the first medicament does cause undesirable side effects replacing said first medicament by a said medicament which does not have said side effects.

7. A method of introducing a plurality of medicaments into an animal body which includes selecting an area of the body to be treated, implanting into the living tissues of the body a body implant device for delivery of a medicament over a long period of time comprising a chamber adapted to receive a medicament, wall means sufficiently thick to be resistant to fluid flow therethrough at least partially surrounding said chamber, relatively thin fluid permeable membrane means engaging said wall means and at least completing the surrounding of said chamber, said membrane means being adapted to permit transport of fluids between the body and said chamber, said membrane means being not over one-half the thickness of said wall means, said wall means and said membrane means being made of a biologically incompatible material and an extremely thin coating of a water insoluble hydrophilic non-toxic, biocompatible polymer of a hydroxy lower alkyl acrylate or methacrylate surrounding all externally exposed portions of said wall means and said membrane means, said coating being sufficiently thin that it does not interfere with fluid transport through said membrane means, a first conduit means for feeding medicament to said chamber and a second conduit means for rapid removal of medicament from said chamber, introducing into the chamber of the device a first medicament, allowing the device to remain within the body while permitting said first medicament to pass through said membrane means into the animal body, passing a second medicament through said first conduit means into said chamber after the device is implanted in the body, removing the first medicament through said second conduit means and permitting said second medicament to pass through said membrane means into the animal body.

8. A method according to claim 7 including the step of introducing said first medicament into said chamber after the device is implanted in the animal body.

9. A method according to claim 8 including the step of determining if said first medicament is compatible with said tissues, upon determination that a change of medicament is desirable because the animal body exhibits a toxic reaction to the first medicament promptly replacing said first medicament by a second medicament which does not have said toxic effects.

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