SPECIFICATION

Improved delivery system

This invention relates to improved chemical, including drug, permeable systems and devices adapted to release a drug or other chemical at a controlled rate from a drug-containing reservoir to an aqueous liquid-containing environment, particularly to an animal, including human, body environment and to drug or chemical delivery devices including such a system. It particularly relates to such systems and devices which are comprised of a wall or walls, formed in part at least, of a porous material, including a porous fabric, pores of which contain a hydrogel, and wherein said porous material is in contact with a drug or drug-containing reservoir. More particularly, it relates to boluses comprising said systems for controlled release of drugs to ruminants and which are retained in the rumeno-reticular sac of the animals.

Drug delivery systems and devices for controlled release of drugs; i.e., controlled release and sustained or prolonged release, are well known in the art. A variety of methods have been described in the literature, including physiological modification of absorption or excretion, modification of the solvent, chemical modification of the drug, adsorption of drug on an insoluble carrier, use of suspensions and implantation pellets (Edkins, *J. Pharm. Pharmacol., 11,* 54T—66T, 1959). Other methods include mixing the drug with a carrier which is gradually disintegrated by the environment, e.g., body fluids resulting in release of the drug. Waxes, oils, fats and soluble polymers have served as carriers.

It is also known in the art to disperse the drug throughout a solid matrix material through which the drug is released by diffusion, or to enclose the drug within a capsule having a polymeric wall or walls through which the drug can pass by diffusion (U.S. 3,279,996).

U.S. 3,975,350 describes hydrogel carrier systems comprised of polyurethane polymers for use in medicinal, pesticidal, insecticidal, algaecidal, etc. applications.

U.S. 1,693,890 describes preparation of porous membranes of cellulose acetate in the form of jellies for use in dialysis. The process comprises precipitating the cellulose acetate from a solution thereof in acetic acid by addition of a non-solvent such as water. If desired, the membranes can be formed on a support. The membranes thus produced are impregnated with water but can be freed of water by washing with alcohol, acetone or any water miscible liquid.

Cellulosic polymer-liquid composite (PLC) materials in film, fiber or microspherical form, including cellulose esters such as cellulose triacetate or cellulose nitrate, or molecular mixtures thereof, as vehicles for the controlled release of various substances are described in U.S. patent 3,985,298. The substance to be released is impregnated into and within the cellulosic PLC material as a part of or as all of the liquid phase (alcohol or water or mixtures, thereof) contained within the micropores of the cellulosic PLC.

U.S. 3,846,404 describes semipermeable membranes of gelled cellulose triacetate useful as carriers for other materials such as liquids having medicinal properties. The impregnation of smooth-finish, nonwoven polyethylene fabric and plain cotton cloth with gelled cellulose triacetate to provide supported cellulose triacetate hydrogel materials is described. The use of medication-impregnated gelled cellulose triacetate products as animal implantable slow-release agents are described, as is the casting of gelled cellulose triacetate onto a woven or nonwoven supporting sheet material.

Controlled release drug delivery devices comprising a reservoir formed of a drug and a solid or liquid drug carrier and, in contact with or surrounding the reservoir, a wall formed of any of a variety of materials, including a microporous material the micropores of which contain a diffusive medium (e.g., a liquid phase comprised of a solution, a colloidal solution, a suspension, or a sol) permeable to passage of drug by diffusion, are described in one or more of the following U.S. patents: 3,993,072; 3,993,073; 3,896,819; 3,948,254; 3,948,262; 3,828,777; 3,797,494; 4,060,084 and 3,995,634.

U.S. 3,993,073 also discloses hydrophilic hydrogels of esters of acrylic acid and methacrylic acid, and cross-linked polyvinyl alcohol as suitable wall forming materials. A key feature of the devices of these patents is the use of a wall, composed in part at least, of a microporous material, pores of which contain a drug release rate controlling medium permeable to passage of drug, and a reservoir comprising drug plus a carrier which is permeable to passage of drug but at a higher rate than the permeability of the rate controlling medium housed in the pores of the microporous wall. Devices suitable for administering therapeutic or nutrient substances to ruminants and which comprise encasing the substance in a permeable, water-insoluble material having capillary or interconnecting pores extending through them and paper or cloth partially impregnated with water-insoluble polymers, e.g. cellulose acetate, are described in British Patent 1,318,259.

U.S. Patent 3,594,469 describes pellets containing magnesium and iron for administration to ruminants for supplying the ruminants with said metals over an extended period of time. In one embodiment, the pellet consists of a cylindrical tube of magnesium alloy filled with shot and some biologically active substance and plugged at both ends by porous discs.

U.S. Patent 3,938,515 makes known devices designed for continuous administration of a drug for a prolonged period comprising a reservoir containing the drug and a solid or liquid carrier permeable to the drug, and a polymeric wall surrounding the reservoir which is permeable to the drug, but at a rate

less than that of the carrier.

U.S. Patent 3,946,734 discloses a diffusion cell, designed principally for use as an implant and which is essentially a capillary, one end of which is sealed with an impervious material and the rest of the tube and the other end thereof is sealed with a porous, neutral hydrogel. The biologically active substance is placed in the capillary against the impervious material and the capillary then filled with the hydrogel (agarose, polyacrylamide) through which the biologically active medicament will diffuse.

Many of the prior art controlled release devices are described as zero order release devices. However, said devices are able to maintain zero order rates of release for relatively short fractions of their projected life span and are not practical for extended use as, for example, in ruminants. The devices of this invention, on the other hand, achieve and maintain controlled, predictable, zero order rates of release of a given drug for extended periods of time. Additionally, the prior art devices, including those comprising a drug-containing reservoir surrounding by a shaped wall formed at least in part of a microporous material, pores of which have a drug release rate controlling medium (diffusive medium) permeable to passage of drug, are subject to physical clogging or physical damage in certain use environments such as the rumeno-reticular sac of ruminants. The clogging decreases and even stops release of the drug rendering the devices inoperative for their intended purpose. The devices of this invention wherein pores of the porous material in contact with the drug-containing reservoir contain a hydrogel are essentially free of this problem and able to provide controlled and predictable release rates of drug to an aqueous liquid-containing environment for extended periods of time.

When used for controlled release of highly water-soluble drugs, prior art devices (of the type described in U.S. patents 3,993,073; 3,993,072; 3,967,618; 3,948,262; 3,948,254 and 3,896,819) prefer that the wall and/or the reservoir be formed from a material that is substantially impermeable to water in order to prevent dilution of the drug in the reservoir by absorption of body fluids into the device and decrease in drug release rate. They are, therefore, not suited for delivery of water soluble drugs, especially at relatively high rates. Further, the devices described in most of these patents require that the permeability to drug of the drug release rate controlling medium in the pores of the porous wall surrounding the reservoir be less than the permeability of the liquid carrier in the reservoir to the drug. By this means, passage of drug through the wall is the rate controlling step. The devices of the present invention are completely free from such restrictions. In fact, a significant difference of the herein-described devices over the prior art devices resides in the presence of highly water permeable hydrogel in the pores of the porous material in contact with the reservoir. Said devices depend upon diffusion of water from an aqueous-liquid environment into which the device is placed through liquid filled pores or channels in the hydrogel and into the reservoir, and the outward diffusion of drug from the reservoir to the environment. Unexpectedly, the concentration of dissolved drug in the reservoir does not diminish, resulting in a substantially constant rate of release for a prolonged time. However, the amount of drug dissolved in the reservoir varies continuously throughout the life span of the devices of this invention.

The use of a low-level of the anthelmintic agent morantel tartrate in the drinking water of calves, the calves having continuous access to the medicated water, as a means for endorparasite control is reported by Downing *et. al., Irish Vet. J.*, 221, November, 1974 and in British Patent 1,530,161. Continuous daily anthelmintic medication of calves from early April to mid-July was found to suppress worm-egg output by the calves and to prevent, or at least minimize, development of heavy larval infection on herbage.

Daily low-level feed administration of morantel tartrate to calves from turning out to mid-July was found by Jones *et. al., Brit. Vet. J.*, 134,166 (178) to successfully control parasitic gastroenteritis and lungworm infections by reducing contamination of the pasture available to the grazing calf.

The present invention provides a device for the controlled and continuous administration of a chemical to an aqueous liquid-containing environment over a prolonged period of time, said device comprising a reservoir containing said chemical, a shaped wall formed in part at least of a porous material, said porous material being in contact with at least a part of said reservoir and being insoluble in said environment while maintaining its integrity during said prolonged period of time, and a hydrogel medium means impregnating pores of said porous material, said hydrogel medium means having channels or pores which (1) permit the diffusion of aqueous liquid from said environment into said reservoir to form a solution of said chemical in said aqueous liquid and (2) permit the diffusion of said solution containing said chemical to said environment, the dissolved chemical so released being replaced by the continuous dissolving of said chemical in said reservoir and the amount of dissolved chemical in said reservoir changing continuously throughout said prolonged period of time so as to maintain the rate of chemical release to said environment substantially constant during a substantial portion of said prolonged period of time.

The improved chemical, including drug (the terms are used interchangeably herein) permeable systems and devices of this invention are of value for controlled release of drugs and other chemicals to aqueous liquid-containing environments and are of particular value for oral dosing of animals, including man, and can be used for a variety of drugs. In addition, the devices are particularly well suited for delivering highly water soluble substances at high rates, not readily achievable with prior art devices. The systems and devices of this invention provide for the controlled release of chemicals over a

prolonged period of time, are easy to produce and are reliable and easy to use. Moreover, the devices described herein maintain their physical and chemical integrity, do not clog in the environment of use and are especially valuable for oral use in a bolus-shaped form for ruminant animals. They provide, for the first time, a practical device for controlled and continuous release of chemicals, including drugs, to an aqueous liquid-containing environment and, therefore, fill a long-existing need, particularly in animal husbandry.

The controlled rate release systems and devices of this invention comprise a barrier or wall in contact with at least a portion of a chemical-containing reservoir and wherein the wall consists partly or entirely of a porous material, including a porous fabric material, pores of which contain a hydrogel permeable to passage of liquid from the environment through pores within the hydrogel itself and of chemical from the reservoir by diffusion. When the devices of this invention are in use, the hydrogel contains liquid from the environment, said liquid being contained within areas or channels (pores) within the hydrogel itself and which serve as pathways for diffusion of environmental liquid and transport of drug.

The systems and devices of this invention can assume a wide variety of shapes and sizes subject to the purpose for which they will be used. They can, for example, be capsule-shaped for oral use in humans and animals or cylindrical for implant or for use as a bolus in ruminants.

A favored form of device of this invention, in its broadest aspect, comprises a porous material, pores of which contain a hydrogel, especially gelled cellulose triacetate, permeable to passage of liquid from the environment and of drug by diffusion through pores within the hydrogel, said porous material in contact with at least a portion of a chemical, including drug, containing reservoir comprising chemical and, if desired, a suitable water-soluble liquid excipient, and also, if desired, a detergent, said device being made in the form of a bolus for use in the controlled release of drug to ruminant animals, especially cattle and sheep, for a prolonged time. Particular use of such boluses is for parasitological, especially helminthic, control, prophylactic and therapeutic, of gastorenteral and lungworm infections in cattle and sheep and of helminth contamination of pasture land. The term "bolus" as used herein includes devices which are generally cylindrical, spherical, spheroidal, elliptical or other form, free of sharp edges and protuberances.

The prior art devices require consideration and compromise of several factors for each use; namely, the carrier used in the reservoir; the solubility and/or permeability of the carrier to the drug contained in the reservoir; the nature of the microporous wall surrounding the reservoir; the diffusive medium contained in the pores of the microporous wall; the relative permeability rates of the diffusive medium and carrier to the drug; the relative solubilities of the drug in the diffusive medium and carrier; and the need for maintaining a substantially constant amount of dissolved drug in the reservoir.

The devices of the present invention, on the other hand, are far simpler in design and operation. For a given device, the release rate of chemical can be varied widely by the simple expedient of varying the area or thickness of porous material, including porous fabric material, pores of which are filled with hydrogel, in contact with the reservoir. Thus, manipulation of only two parameters permits control of the amount of chemical released.

FIGS. 1—5 illustrate various examples of devices according to this invention. The fact that few examples are illustrated is not to be construed as limiting the invention, many variations and equivalents of which are possible. In FIG. 1, a perspective, cross-sectional view of a device of this invention, delivery device *10* is comprised of a cylindrical wall *11* in contact with a chemical-containing reservoir *12*. Wall *11* is formed of a porous material, pores *14* of which contain a hydrogel (not indicated) through which liquid from an aqueous liquid-containing environment diffuses into reservoir *12* and chemical from the reservoir diffuses into the environment through channels or pores within the hydrogel itself. Reservoir *12* is comprised of a chemical *15* and, in a preferred embodiment of this invention, of a drug and a water-soluble excipient *16*. Ends *17* are non-permeable caps or closures.

FIG. 2, a schematic drawing of a device according to this invention, is a delivery device of the type shown in FIG. 1 but in which a perforated sleeve, e.g. stainless steel, iron, plastic, *18* is inserted as a means of controlling the surface area of the hydrogel impregnated porous wall *14* and, if metal, of increasing the weight of the device.

FIG. 3 presents an enlarged view of a porous wall *11* of a device *10* of this invention, pores *14* of which contain a hydrogel *19*, in contact with a chemical-containing reservoir *12* comprised of a chemical *15* and a water-soluble liquid excipient *16*.

FIG. 4 illustrates a delivery device shaped as a capsule and having only one closure *17*.

FIG. 5 represents a further device *10* according to this invention wherein the porous material, pores *14* of which contain a hydrogel (not illustrated), comprises the end walls of the device *10*. The cylindrical wall *18* is comprised of a non-permeable, non-porous material, in this instance, stainless steel which, in combination with the hydrogel impregnated end walls *14* enclose a reservoir *12* comprising a chemical *15* and an excipient *16*.

As illustrated above, the improved delivery devices or systems of this invention have a chemical, including drug, containing reservoir comprising a chemical and, in a preferred form, chemical and a water-soluble liquid excipient. The water-soluble liquid excipient serves several important functions, such as elimination of air from the reservoir, thus permitting greater "loading" in the manufacture of the

devices and enhancement of convective mixing within the reservoir (which assures constant rate of chemical release). Additionally, said water-soluble liquid excipient serves a still further role in that, as chemical dissolves, there is no apparent volume change as the chemical goes from the solid or crystalline state to the solution state.

Typical water-soluble liquid excipients include mono-ols and polyols, and ethers thereof, such as ethanol, ethylene glycol, propylene glycol, glycerol, polyethylene glycols, sorbitol, di- and triethylene glycol, di- and tri-propylene glycol, 1,2-dimethoxyethane, mono-C_{1-4} alkyl ethers of ethylene and propylene glycols; N,N-dimethylformamide, dimethylsulfoxide, and the like. The excipients must, of course, be compatible with the hydrogel.

Of course, when the herein-described devices are to be used for animals, including humans, or in aqueous liquid-containing environments used by animals, e.g. aquariums, fish ponds, animal and poultry water supplies, hydroponic systems, the water-soluble liquid excipient should be a physiologically acceptable substance.

The amount of water-soluble liquid escipient used per unit weight of drug depends upon the characteristics of the drug. In general, sufficient excipient is used to permit formation of the drug-excipient combination into a compact mass, and is readily determined by simple experiment.

Detergents, up to 20% by weight, based on the total weight of the reservoir (chemical, including drug, plus, if used, excipient and detergent) can be used in the reservoir to minimize possible clogging of the devices when in use. Representative detergents can be inorganic or organic in nature and include sodium and potassium hexametaphosphates and tripolyphosphates, sodium lauryl sulfate, sodium glyceryl monolauryl sulfate, dioctyl sodium sulfosuccinate, bis(1-methylamyl)sodium sulfosuccinate, polyoxyethylene sorbitan mono-oleate and other fatty acid esters, and others known to those skilled in the art. The amount of detergent when one is used is not critical and, in any instance, is kept to a minimum in order not to sacrifice loading of chemical into the reservoir. The optimal amount is determined by procedures described below.

In this specification and accompanying claims, the terms "reservoir", "chemical-containing reservoir", and "drug-containing reservoir" are used interchangeably. For convenience, since the preferred devices of this invention are those used for controlled release of drugs, the term "drug-containing reservoir" is the favored term.

The terms "porous materials", "porous membranes" or "porous walls" as used herein include porous fabric materials. Representative types of such materials are described below. The porous materials used can be isotropic, i.e., of homogeneous pore structure throughout the cross-section of the material, or can be anisotropic, i.e., of non-homogeneous pore structure. They should, of course, be insoluble and non-reactive with the environment and with the contents of the reservoir. In general, porous materials having pore sizes of from about one micron to about 100 microns can be used in the controlled release devices of this invention. Porous materials having pore structures which include continuous pores; that is, pores that effectively have an opening on both faces of the porous wall connected thereto are necessary. In order to facilitate transfer of the drug from the reservoir to the environment when the controlled release devices of this invention are used, the pores, or a portion of the pores, of the porous material are filled with a hydrogel. The net result of the combination of the porous material, pores of which are filled to a greater or lesser extent with a hydrogel, is provision of a device able to withstand clogging and physical destruction under conditions of normal use and, by maintaining its physical integrity, one which can be used in environments and situations under which previously known hydrogel devices would be destroyed and ineffective for controlled release of drugs over prolonged periods of time. The herein described devices are of particular value for use in ruminants, especially in cattle and sheep. The hydrogel-containing pores permit passage of liquid (water) through pores within the hydrogel itself by diffusion from the environment into which the controlled release device is placed when in use into the reservoir dissolving the drug. The drug then diffuses through liquid in pores of the hydrogel-containing pores of the porous material barrier at a rate dependent on the drug concentration in the solution in the reservoir, upon the resistance offered by the barrier; i.e., liquid in the pores of the hydrogel, and the effective surface area of the porous portion of the wall.

As drug leaves the device, a zone of depletion gradually forms giving rise to a moving drug/solution boundary. The diffusion of water into the device from the environment through pores within the hydrogel-containing pores of the wall into the reservoir gives rise to convective mixing of the incoming aqueous phase with the solution in the reservoir of the device. The motive force for this mixing is the difference in densities of the two solutions caused by their large concentration differences. A function of the water-soluble liquid excipient, as noted above, is to help maintain this large density difference, hence enhancing this critical mixing. The convective mixing results in a constant drug concentration within the reservoir which in turn provides controlled release of the drug over a prolonged period of time, thus insuring zero order release of drug as long as undissolved drug remains in the device. As drug is removed from the reservoir, and aqueous liquid from the environment diffuses into the reservoir, the amount of dissolved drug within the reservoir varies continuously throughout the life span of the device; that is, throughout the prolonged time period of drug release. This mechanism of drug release allows any device geometry to be adopted, the size and shape of the reservoir is not limited. This is in direct contrast to the prior art devices of U.S. 3,993,073 which depend upon, and are

so fabricated as to achieve, a substantially constant amount of dissolved drug within the reservoir, diffusion of dissolved drug within the reservoir to supply drug to the wall, and, therefore, have severe product limitations in terms of size and shape.

The term "hydrogel" as used herein refers to a gel having water content and is defined in Hackh's Chemical Dictionary, Fourth Edition, Grant, page 332, 1969, as "a gel produced by the coagulation of a colloid with the inclusion of water". Representative hydrogels which can be used to fill the pores of the porous material are the following: gelled cellulose triacetate, see U.S. 1,693,890 and 3,846,404; cellulose acetate hydrogels derived from cellulose acetate having an acetyl content of from 20% to 40%; polymeric hydroxyethyl methacrylate; cross-bonded polyvinyl alcohol; agarose; polyacrylamide; cross-linked partially hydrolyzed polyvinylacetate, hydroxyethyl acrylate, diethylene glycol monoacrylate, diethyleneglycol monomethacrylate, 2-hydroxypropylacrylate, 2-hydroxypropyl methacrylate, 3-hydroxypropyl acrylate, 3-hydroxypropyl methacryate, dipropylene glycol monomethacrylate, vinylpyrrolidone, acrylamide, methacrylamide, N-propylacrylamide, N-isopropylmethacrylamide, N-methylacrylamide, N-2-hydroxyethylmethacrylamide; polyurethane hydrogels comprising lightly cross-linked polymers of isocyanate terminated prepolymers which are the reaction product of a poly(alkyleneoxy)polyol with an organic diisocyanate lightly cross-linked with water or an organic polyamine, as described in U.S. 3,939,105; copolymers of ethylenically unsaturated monomers of hydroxyalkyl acrylates and methacrylates, and of alkoxy alkylene glycol acrylates and methacrylates, as described in U.S. 4,038,264; polyether polyurethane resins produced by reaction of an organic diisocyanate with a mixture of at least two diols, one of which is a water-soluble polyalkylene glycol with molecular weight of from 3,000 to 30,000 and the second of which is an oxyalkylated diphenol having from 2 to 20 oxyalkylene groups, and others as are known to those skilled in the art.

Favored hydrogels for use in this invention are polyurethanes; polymeric hydroxy lower alkyl acrylates or methacrylates, vinyl pyrrolidone, acrylamide, N-lower alkyl acrylamides and methacrylamides, especially those cross linked or copolymerized with a hydroxyalkyl acrylate or methacrylate to render the resulting coppolymer water insoluble. The preferred hydrogels are gelled cellulose triacetate, polymeric hydroxyethyl methacrylate and crossbonded polyvinyl alcohol. Especially preferred is gelled cellulose triacetate which affords smooth and efficient operation of the controlled release devices described herein.

The water present in the pores of the hydrogel can be readily replaced by water-soluble liquids such as the water-soluble liquid excipients disclosed above. Other water-soluble liquids can also be used to replace the water, including alcohols having one to four carbon atoms. As a practical matter, in order to stabilize the devices of this invention, particularly when the hydrogel is gelled cellulose triacetate, the water of the hydrogel is replaced with a suitable water-soluble liquid which has a vapor pressure lower than that of water so the devices can be stored without loss of efficiency as a result of drying out of the hydrogel. When a water-soluble liquid excipient-drug combination is used in the reservoir, it is convenient to use the same liquid to replace the water from the hydrogel.

The hydrogels themselves are porous in the sense they contain areas or regions; i.e., channels or pores, filled with water or other liquid. It is, therefore, intended throughout this specification when referred to diffusion or transport of chemicals or drugs through walls, "pores of which contain a hydrogel", or similar expression to mean that diffusion or transport, of the chemical or drug occurs via these regions rather than through the hydrogel *per se*. The hydrogel itself has liquid filled pores which serve as the diffusion pathways and, in effect, is considered as being permeable to passage of environmental liquid and of chemical from the reservoir.

The porous wall in contact with the drug-containing reservoir can be any of a variety of materials. The porous material can completely surround the reservoir or can comprise only a portion of the wall surrounding the reservoir. Suitable porous materials include porous metals, porous ceramics, sintered polyethylene, sintered poly(vinyl chloride), sintered polypropylene, sintered polystyrene and sintered poly(tetrafluoroethylene), porous polymers made from thermoplastic resins by phase separation techniques as described in *Chem. Eng. News,* December 11, 1978, p. 23, and others known to those skilled in the art.

Suitable porous fabrics are polypropylene and polyethylene, especially those fabrics of each type commonly referred to as "filter cloth", glass, poly(tetrafluoroethylene), nylon, cotton, modacrylic fibers; i.e., acrylic fibers composed of a long chain synthetic polymer containing 35—85% of acrylonitrile units; acrylic fibers; i.e. synthetic polymers having a minimum of 85% acrylonitrile by weight; polyesters; i.e., a long chain synthetic polymer composed of at least 85% by weight of an ester of a dihydric alcohol and terephthalic acid; poly(vinyl acetate), poly(vinyl chloride), poly(vinyl acetate-co-vinyl chloride), poly(vinyl alcohol), poly(vinyl alcohol-co-vinyl acetate), poly(vinyl alkyl ethers); polymers of vinylidene cyanide, vinylidene chloride, vinylidene fluoride; polyureas and others known to those skilled in the art [see *Encyclopedia of Polymer Science and Technology,* Vol. 1, 342 (1964); Vol. 8, 812 (1968); Vol. 9, 403 (1968); Vol. 10, 347, 206 (1969); Vol. 6, 275 (1967); Vol. 11, 62, 445, and 506 (1969); Vol. 14, 305, 575 (1971), Interscience Publishers, New York]. Additionally, metal screens or filter cloths including those fabricated from stainless steel, carbon steel, brass, copper, aluminum, various alloys such as nickel-copper, etc., are suitable.

The particular fabric chosen must, of course, be compatible with the hydrogel with which it is to be

impregnated and with the end use of the device. Thus, for a device to be used as a bolus for administering a drug to ruminants over a prolonged period of time, cotton would not be used as the fabric since it would undergo degradation by the ruminant. In a device to be used for controlled release of a chemical to an aqueous environment such as an aquarium or a reservoir, cotton can be used.

Nylon would not be used as the fabric when gelled cellulose triacetate is to serve as the hydrogel since it would be degraded by the formic or acetic acid used during the impregnation process.

The hydrogel impregnated porous fabric materials must, of course, be of sufficient strength, durability and inertness to drug and the use environment so that the controlled release device produced therefrom retains its physical and chemical integrity throughout its entire life.

The porous material is impregnated with an appropriate hydrogel by procedures known to those skilled in the art. A favored and relatively simple procedure for impregnating the porous material with gelled cellulose triacetate, a preferred hydrogel, comprises forcing a solution of cellulose triacetate in formic acid or acetic acid into the pores of the porous material by immersing the material in the cellulose triacetate solution contained in a vessel which can be subjected to a vacuum. Following impregnation, the cellulose triacetate "loaded" plastic is then coagulated by contact with and equilibration with a large volume of water to produce the hydrogel impregnated material. When the porous material is sintered polyethylene and the hydrogel is gelled cellulose triacetate, acetic acid is favored as solvent for the cellulose triacetate over formic acid since it wets the polyethylene better than does formic acid thus facilitating preparation of the hydrogel impregnated porous material.

When the hydrogel is derived from 2-hydroxyethyl methacrylate cross-linked with ethylene glycol dimethacrylate as described in U.S. 3,520,949, impregnation of the porous material is accomplished by filling its pores with the 2-hydroxyethyl methacryate—ethylene glycol dimethacrylate mixture and then polymerizing the mixture within the pores by addition of a free radical catalyst such as t-butyl peroctoate. In like manner, other hydrogels are impregnated into the porous wall material by such "*in situ*" procedures from appropriate reactants. When the hydrogel is cross-linked polyvinyl alcohol, the pores are filled with polyvinyl alcohol (10% aqueous solution)—resorcinol (2—3%) mixture by procedures described herein and the cross-linking is accomplished *in situ*. Other cross-linking agents can, of course, be used as is known to those skilled in the art.

For production of devices stable to storage prior to use, the hydrogel filled pores are freed of water by allowing them to equilibrate in a suitable water-soluble liquid such as, for example, the water-soluble liquid excipients enumerated above. It is, as noted, convenient to exchange the water in the hydrogel-filled pores of the porous wall material with the same water-soluble liquid used as excipient in the reservoir when the reservoir comprises a chemical-excipient combination. If chemical alone comprises the reservoir of the herein described devices, the choice of water-soluble liquid used to replace water from the hydrogel in the hydrogel-filled pores of the porous wall is determined only by the end use of the device; i.e., whether a physiologically acceptable water-soluble liquid is required. Such a liquid is conveniently placed in the hydrogel at the time of preparing the porous wall, pores of which contain a hydrogel, prior to filling the reservoir of the device as is illustrated herein.

The prior art devices most closely related to the devices of this invention; i.e. those of U.S. patents 3,993,073 and 3,993,072 depend upon different permeability rates of drug through a medium contained in the pores of the porous wall relative to that of drug in the drug-carrier phase in the reservoir. In order to achieve the zero order release rate alleged for the devices described in said patents it is essential that the medium in the walls of the devices have a lower permeability to drug than does the drug carrier within the reservoir. The medium in the wall thus becomes the drug rate of release controlling portion of the device.

Dissolved drug diffuses through the more permeable carrier to the inner wall fast enough such that the wall becomes the drug rate of release controlling portion of the device. This results in zero order release rates for some time until the receding drug boundary in the device becomes large enough to offset the difference in permeabilities between carrier and wall medium, then zero order rates are no longer achieved. Because of this, successful practical use of these devices is limited and they are not suitable for zero order delivery of large amounts of drugs in practical, useful dosage form shapes.

The devices of the present invention, contrary to the prior art devices, when in use, have aqueous environmental medium in the wall medium as well as in the reservoir. Although permeability to the drug is the same in the liquid in the wall and reservoir, zero order release rates are attained for large fractions of the total device lifetime. In addition, maintenance of zero order release does not depend upon diffusion in the reservoir carrier, thus there are no geometirc or dose restrictions on those devices and for the first time large amounts of drugs can be delivered at zero order rates in embodiments of practical sizes and shapes.

For most efficient operation of the controlled release systems and devices of this invention, to reduce leaking and clogging, it is important that the porous material be impregnated with hydrogel as completely as possible. Devices of the same surface area can, by varying the characteristics of the membrane wall, especially its thickness, pore size, and porosity and by varying the size of the load in the reservoir, provide different dosage rates and release periods for a given drug.

As noted above, a preferred form of device of this invention is that of a bolus for use in controlled release of a drug to ruminant animals, principally to cattle and sheep, for a prolonged period. The bolus

is administered to the ruminant in such a manner, preferably by oral administration, that it remains in the rumeno-reticular sac for an extended period of time, during which period it continuously releases drug to the animal at a controlled release rate. Said devices thus permit control (prophylactic and therapeutic) of various pharmacological and physiological conditions to which the animals are subject by simple oral administration to the animals of said devices.

In order that the bolus, once introduced into the rumeno-reticular sac of cattle, remain there for an extended period, it is necessary that the bolus have a density of at least 2.0 g./ml. In practice, the density can range from as low as 2.0 to as high as 7, or even greater. Density, of course, is the most significant factor affecting retention of the bolus in the rumeno-reticular sac. Overall size of the bolus is a function of the needed dose to be given and size that can be practically administered. Based on this, once the desired size is determined, additional weight can be added to achieve desired average density. If possible, it is desirable to use maximum allowable size since larger boluses of a given density are better retained than those of lower density. However, when the average density of the bolus increases to a value greater than about 5.0, an increase in size of the bolus does not significantly improve the retention factor. The favored average density range for the bolus is from about 2.5 to about 5 g/ml.

The size of the bolus, of course, depends upon the animal to be treated therewith. For ruminants such as sheep and goats, the bolus size and weight will be less than that required for cattle. The maximum size of bolus for use in any animal is determined by the practical difficulties of administering such an object to the animal.

For administration to sheep, the minimum weight of bolus having a density of 4 which will be retained is about 1 gram. The size of a bolus will vary according to the density of the bolus. For administration to cattle, the minimum weight of bolus having an average density of 4 is about 5 grams. Again, as noted above, the upper limits of size are determined by the practical convenience of dosing the animal in question and by the minimum average density of the bolus. For example, a bolus of about 7.5 centimeters in length by 2.5 centimeters in diameter and having a density of 2.2, will have a weight on the order of about 90 grams.

The density of boluses comprising only the elements enumerated above is generally below the lower level set forth above. It, therefore, becomes necessary to increase the average density of the bolus by incorporation of a suitable high density material such as a metal (iron powder, iron shot, steel shot) or other densifiers, minerals such as $CaSO_4$, to increase the density to the desired value. Alternatively, the average density can be increased in convenient fashion by incorporating into the bolus, as an inner sleeve, a high density, perforated material, e.g. a metal (such as stainless steel, steel, especially low carbon steel, or iron) which, in turn, is surrounded by the hydrogel impregnated porous membrane. The perforations in the sleeve should be sufficiently large so as to permit free passage of drug, and liquid from the environment, through the hydrogel impregnated porous membrane. The principal functions of such a sleeve are to increase the average density of the bolus to a value such that the bolus is retained in the rumeno-reticular sac and to regulate the surface area of the hydrogel impregnated porous material in contact with the drug-containing reservoir. In addition, such a sleeve, although not necessary, also improves the physical stability of the bolus, ensuring that its physical form is substantially retained under conditions of use. A still further, and preferred, alternative comprises a bolus comprising a metal, steel or iron, cylinder, one or both ends of which are capped with a porous membrane, pores of which are impregnated with a hydrogel. Boluses of this type are preferred because of their simplicity and economy of manufacture and the ease with which their density can be adjusted. A low carbon steel in highly favored as construction material for the cylinder. Other alternatives will suggest themselves to the man skilled in the art.

The controlled release devices of this invention can be used for a variety of purposes and situations wherein controlled release of a drug or other chemical is desirable. They can be used for administering drugs and providing chemicals at sites near to or remote from the point of application of the device.They can be positioned by appropriate means in suitable locations within the animal body where they are in contact with body fluids, e.g., the stomach of farm animals, especially the rumeno-reticular sac of ruminants. Also included within the controlled release devices of this invention are those for use as depot implants for the purpose of administering a drug at a controlled rate to the host. The implants differ from devices of this invention for other purposes only in their shape which is, of course, adapted for implantation. Other uses include sublingual or buccal tablets, pessaries, suppositories, bandages and skin patches. Still other uses for the controlled release systems and devices of this invention occur in agriculture for administration of fertilizers and pesticides, in pisciculture including aquariums and fish ponds; in drainage ditches, canals and tanks as for control of algae; and in water supplies especially for animals and poultry in need of drugs for therapeutic or prophylactic treatment.

The criterion for suitable substances, drugs or chemicals, for use in the devices of this invention is that they be sufficiently soluble in water to achieve a rate of release of said drug or chemical in the use environment which will produce the desired result. For this reason, drugs and chemicals which are acids or bases, are desirably used in the form of their physiologically or pharmacologically acceptable salts. The rate of release of drug, or chemical, from the herein-described devices is dependent upon several factors such as the thickness of the wall, available surface area, effective pore diameter, porosity of the wall, the nature of the hydrogel, the concentration of the substance in the reservoir, and the solubility

thereof in the environmental liquid. The suitability of a given substance is determined as is described below.

Representative of the drugs which can be used in the devices described herein are the following: anthelmintics, including salts of morantel, pyrantel, oxantel, piperazine, diethylcarbamazine, levamisole, tetramisole, and hygromycin B; antibacterials including salts of tetracyclines, such as 5-oxytetracycline, chlorotetracycline, doxycycline and Mannich bases thereof; penicillins such as ampicillin, penicillin G; aminoglycosides such as neomycin, streptomycin, apramycin, bacitracin as its zinc or methylene disalicylic acid derivative; macrolides such as erythromycin, oleandomycin and tylosin; antibacterial growth promotants such as salts of avoparicin, polymyxin, lincomycin, banbermycin and efrotomycin; hormonal growth promotants including diethylstilbestrol, zearalanol; antiparasitic agents such as amprolium; nutritional agents such as soluble salts of magnesium, selenium, copper, and vitamins such as thiamine hydrochloride; sulfa drugs such as sulfamethazine, molluscicides such as N-tirtylmorphine; and bloat prevention agents such as alcohol ethoxylates and poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene)-polymers, e.g. poloxalene.

As noted above, the drug-containing reservoir, in a preferred form of this invention, comprises a drug and a water-soluble excipient. Devices so constructed have the advantage of offering a greater amount of drug per device and of extending the useful life of the device. However, the reservoir can contain only the chosen drug.

The devices of this invention are especially valuable as long-acting boluses for the control (therapeutic and prophylactic) of helminth infections in ruminants, cattle in particular. Protection of range animals becomes relatively convenient. In temperate climates, the low, earyl spring population of pasture larvae, the residue of the previous season's contamination, is multiplied by cycling through animals grazing thereon to produce, in the summer, a sharp increase in pasture infectivity. This condition gives rise, during the summer grazing season, to clinical parasitism and performance depression of animals grazing on said pasture.

The continuous and controlled release of anthelmintic agent; e.g., morantel in the rumeno-reticular sac of grazing animals early in the season when pasture contamination is low, suppresses helminth egg and subsequent larval output and thus breaks the above-mentioned cycle and keeps the pasture and animal worm burden at a low level. Parasitic infections of ruminants grazing on the same pasture land during the summer season is thus minimized. This method of helminth control is especially attractive and valuable for calves since they are highly susceptible to helminths when first placed on pasture. Consistent use of boluses reduces the reservoir of infective helminth forms at a given location. Utilization of anthelmintic-containing boluses of this invention in this manner prevents, or at least minimizes, the seasonal increase in pasture larvae which causes parasitic gastroenteritis and performance depression in grazing animals later in the season. In this mode of control, the period of drug release is that of the spring multiplication phase, not the period of heavy pasture contamination, larval challenge and worm infestation which produces clinical disease and performance depression. It is for this reason that this mode of usage is called "indirect control". To put it another way, the grazing of ruminants having in their rumeno-reticular sac one or more of the herein-described devices, which device permits controlled and continuous release of anthelmintic agent, e.g. morantel, to said sac, on pasture land early in the season; i.e., when larval contamination is at or near a minimum level, permits minimization of the usual seasonal increase in larval contamination of the pasture land and serves to protect animals grazing thereon throughout the entire grazing season.

For "indirect control" of helminths, the devices of this invention, preferably in the form of a bolus, are administered to ruminants at a time in the epidemiological cycle of said helminths when pasture contamination by said helminths, their eggs and/or larval stages, is at or near a minimum level. In temperate zones, this time corresponds to spring turn out; that is, the first placing (turning out) of the calves out to pasture. For maximum efficiency, the bolus is administered to the calves about two to seven days prior to turning out. In non-temperate zones of the world, e.g. semi-tropical and tropical areas, the period of lowest pasture infectivity normally occurs prior to the rainy season. Administration of the bolus to ruminants in such areas is desirably carried out within two to fourteen days before the start of the rainy season. However, because of the unpredictability as regards the rainy season, helminth control in the non-temperate zones is best achieved by the "direct control" method.

The herein-described boluses also eliminate established helminth infections from ruminants and prevent establishment of worm infections during the summer period of heavy challenge. This mode of use is called "direct control". The direct method of control protects ruminants only during the period of release of the anthelmintic agent. The indirect method of helminth control protects ruminants grazing on a given pasture for the entire season because it achieves an overall significant reduction in pasture contamination. As noted, the devices described herein provide continuous release, at a controlled rate, of drugs including anthelmintics. Particularly useful for such purposes are water-soluble salts of (E)-1,4,5,6-tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)ethenyl]pyrimidine (morantel), (E)-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)ethenyl]pyrimidine (pyrantel) and (±)-2,3,5,6-tetrahydro-6-phenyl-imidazo[2,1-b]thiazole (tetramisole) and levamisole, the *L*-(−)-form thereof. Representative of preferred water-soluble salts of pyrantel and morantel are the tartrate and citrate salts; and of tetramisole and levamisole, the hydrochloride salts.

The boluses of this invention are orally administered to animals by, for example, a balling gun. For use in calves, the desirable average release rate of morantel (calculated as base) for indirect control of helminths is on the order of 60—200 mg. (of morantel base) per day for a period of about 60 days, which covers the normal maximum survival time of the spring population of larvae. Longer release periods of from 60—120 days are desirable in the direct control mode of use since the period of exposure to heavy pasture contamination normally extents from mid-summer through autumn. Release rates of about 60—150 mg. (calculated as morantel base) per day effectively control helminth infections over such release periods. For dosing larger animals, more than one bolus can be administered. For indirect control of helminths using salts of pyrantel or levamisole, the desirable average release rates of each (calculated as free base) are on the order of 100—400 mg. and 100—500 mg. per day, respectively for about a 60 day period. For direct control, release rates of about 100—300 mg. (as free base) of pyrantel and of about 100—400 mg. (as free base) of levamisole per day effectively control helminth infections over the 60—120 day period of heaviest challenges.

Continuous, low-level administration of morantel by use of the herein described devices for helminth control gives rise to an efficacy profile surprisingly different from and advantageous to that observed on conventional therapeutic use of morantel and which could not be predicted. For example, maintenance of a protracted level of morantel tartrate or citrate (or other salt) in the gastrointestinal tract of ruminants is effective in preventing lung worm infections in said animals during the period of drug release. Further, while cattle or sheep grazing on contaminated pasture are subject to immediate reinfection by intestinal nematodes after conventional therapeutic dosing, animals receiving the bolus are essentially freed of established infection and protected from reinfection over a period of 60 days or longer.

The use of the bolus for control of pasture contamination, i.e. the indirect control method, is a unique, practical and unprecedented method of helminth control which protects ruminants, and in particular grazing ruminants, treated via this mode for the entire grazing season and affords performance benefits superior to prior art control methods. The increase in daily weight gain over untreated controls over the grazing season is substantially greater than that obtained after conventional therapy.

The rate of release of drug, or other chemical, passing from the drug-containing reservoir through the walls of controlled release devices of this invention, and the effectiveness of a given drug and/or water-soluble excipient and/or detergent combination in said devices, can readily be determined by those skilled in the art, for example, by transmission methods, or by sorption-desorption methods. A technique which can conveniently be used to select suitable porous materials and hydrogels comprises using the chosen porous material, pores of which are filled with the selected hydrogel, as a barrier between a rapidly stirred saturated solution of a drug or other chemical, the controlled release of which is desired, and a rapidly stirred solvent bath, the composition of which stimulates the aqueous liquid containing environment in which the controlled release device is to be used. The temperature of each solution is maintained at a constant value, preferably at a value approximating the average temperature of the environment in which said device will be used. Samples are withdrawn at predetermined intervals from the solvent bath and analyzed for drug concentration. Standard procedures for determining the permeability of a drug, or other chemical substance, through the porous material, pores of which are filled with hydrogel, can also be determined by standard procedures as are described in *Encyclopedia of Polymer Science and Technology,* Vols. 5 and 9, pages 65—82 and 794—807, 1968, respectively; and references cited therein; and in *Chemical Engineers Handbook,* pages 17—45, 1963, published by McGraw-Hill, Inc.

A procedure of especial value in determining the release rate for devices of this invention and the relative merits of a given excipient or detergent for use in a given device, particularly wherein the drug is morantel, in summary, is as follows. The procedure, an *in vitro* procedure, is based upon the release of a water-soluble salt of morantel, for example the tartrate, from a device made in accordance with this invention as a function of time. A morantel tartrate containing device of this invention is placed into a one-liter conical flask which is protected from light because of the photosensitivity of morantel tartrate, 500 ml. of pH 7 phosphate buffer added, and the temperature of the flask and contents adjusted to and maintained at 37°C. The flask containing the device is shaken at about 70 excursions (7.62 cm.) per minute and 5 ml. samples are withdrawn periodically. The volume of the withdrawn sample is replaced with an equivalent volume of fresh pH 7 phosphate buffer and shaking of the flask continued. The concentration of morantel in the samples is determined spectrophotometrically by measuring the absorbance of the sample at 318 nm when read against fresh pH 7 phosphate buffer. The sampling process is repeated until 5 grams of morantel tartrate have been released at which point the device is transferred to another flask containing 500 ml. of fresh pH 7 phosphate buffer and the process continued as before.

In vivo release of morantel tartrate from devices according to this invention is determined by administering the devices to, for example, normal steers or steers with rumen fistula and, after a certain period of time such as 30, 60, 90 or 120 days, removing the devices via the fistula or sacrificing the animals and recovering the devices to determine the residual morantel tartrate within the device. Tests of this sort have shown that the rate of release of morantel tartrate *in vitro* is approximately four times

that of the *in vivo* release rate.

The following examples are merely illustrative of the present invention. They are not to be construed as limiting the scope of this invention, many variations of which are possible as those skilled in the art will recognize.

EXAMPLE 1

A bolus comprising sintered poly(ethylene), pores of which are filled with gelled cellulose triacetate, and a reservoir containing morantel tartrate admixed with polyethylene glycol 400 and sodium hexametaphosphate, and having a perforated stainless steel sleeve was prepared as follows.

One end (referred to as End 1) of a sintered poly(ethylene) tube having an average pore size of 10 microns, an outside diameter of 25.4 mm. (1 inch), an inside diameter of 22.225 mm. (7/8 inch) and a length of 7.938 cm. (3 1/8 inches) was dipped into a 10% solution of cellulose acetate butyrate in methylene chloride to a depth of 4.763 mm. (3/16 inch). It was then dried in air and the other end (referred to as End 2) of the tube dipped into the cellulose acetate butyrate solution to a depth of 9.525 mm. (3/8 inch) and dried. This step was repeated. End 1 was again dipped into the cellulose acetate butyrate solution for 30 seconds, allowed to dry in air for 60 seconds, and a 22.225 mm. diameter (7/8 inch) cellulose acetate butyrate disc (3.175 mm., 1/8 inch thick) inserted into the end of the tube so as to be flush with said end. The cellulose acetate butyrate disc was floated on methylene chloride for 60 seconds prior to its insertion into End 1 of the tube. The tube was then rolled along the bench, applying finger pressure to the end thereof containing the disc, so as to insure complete binding of disc and tube. A one-hole #3 rubber stopper fitted with a glass tube of sufficient length to protrude through the one-hole rubber stopper of a vacuum flask when the tube rests upon the bottom of the flask was inserted into the tube. The protruding end of the tube was then connected to a flask containing a 6% solution of cellulose triacetate in formic acid and a vacuum of about 150 mm. of mercury applied. When the cellulose triacetate solution covered the exterior walls of the tube which had not been dipped into cellulose acetate butyrate, the tube was removed from the vacuum flask and the bulk of the cellulose triacetate wiped off. The tube was then inverted in order to drain the cellulose triacetate from the interior of the tube. The exterior and interior open ends of the tube were wiped clean with a towel. The tube was then immersed in and allowed to equilibrate in distilled water overnight. It was then removed from the water, the exterior dried with a towel and excess water shaken from the interior of the tube. The steps of impregnating the pores of the tube with cellulose triacetate and equilibrating it in distilled water were repeated. It was then equilibrated in running water for 4 hours.

The tube was tested at this point for leaks by connecting it to a nitrogen source, immersing the tube in water and applying a pressure of 0.28 kg. per square centimeter (4 psi) of nitrogen for 10 seconds. If leaks exist, the steps of impregnation and equilibration in water are repeated.

The tube was then equilibrated in polyethylene glycol 400 overnight, removed from the polyethylene glycol 400 and allowed to drain in an inverted position for 4 hours. Excess polyethylene glycol 400 was wiped from the exterior of the tube with a towel and a perforated stainless steel tube °22.225 mm (7/8 inch) outside diameter, 18.923 mm. (0.745 inch) inside diameter, 6.985 cm. (2 3/4 inches) in length and having 16 evenly spaced circular holes (7.114 mm., 9/32 inch in diameter1 inserted into the tube until it was flush against the sealed end. The cellulose triacetate shavings which resulted from insertion of the snug-fitting sleeve into the tube were removed. A cellulose acetate butyrate disc (3.175 mm.) was then inserted into the open end of the tube flush with the stainless steel sleeve and the tube trimmed so that the end of the tube was flush with the disc. The disc was removed and the tube filled with a homogeneous mixture comprising 63.31% morantel tartrate, 26.61% polyethylene glycol 400 and 10.08% sodium hexametaphosphate flush with the end of the stainless steel sleeve. The open end of the tube was filled with a 10% cellulose acetate butyrate solution which was then immediately poured off and the open end of the tube dipped into the cellulose acetate butyrate solution to a depth of 6.35 mm. (1/4 inch) and allowed to dry. A disc of cellulose acetate butyrate (floated on methylene chloride for 60 seconds immediately prior to use) was then forced into the open end of the tube, sufficient pressure being applied to force the disc against the stainless steel sleeve. The tube was then rolled along the benchtop, applying sufficient finger pressure to insure complete binding between the disc and the tube. The tube was allowed to dry for one hour after which each end of the tube was dipped into 10% cellulose acetate butyrate to a depth of 6.35 mm. (1/4 inch) and allowed to dry. The weight of the bolus was approximately 90 g., of which 24.8 g. was drug mixture. Its density was 2.2 g./ml. This device released about 250 mg. per day of morantel tartrate *in vivo* in cattle for about 60 days.

EXAMPLE 2

Three devices prepared according to Example 1 tested *in vitro* by the procedure described herein provided an approximately constant rate of release during the period of 4—17 days with a mean release rate for all three boluses of 0.927 g. of morantel tartrate per day.

Days in Vitro	Accumulated g. Morantel Tartrate Bolus 1	Bolus 2	Bolus 3
1	0.357	0.295	0.284
2	0.804	0.723	0.66
4	1.63	1.63	1.38
5	2.12	2.24	1.86
6	2.61	2.96	2.4
8	4.05	6.31	3.7
11	6.55	9.0	5.76
13	8.24	11.34	7.67
15	11.38	13.4	9.74
19	14.52	16.2	13.2
25	17.99	17.4	15.4
29	17.13	17.3	15.9

In vivo tests of 3 other boluses prepared according to Example 1 and placed in the rumeno-reticular sac of cattle showed a release rate of 0.224 g. of morantel tartrate per day when recovered at the end of 30 days. This is an *in vitro/in vivo* ratio of 4:1.

EXAMPLE 3

In vitro tests of two other boluses prepared according to Example 1 and tested as described herein provided a mean release rate over the constant rate period, 0—14 days, of 0.96 g. morantel tartrate per day.

Days In Vitro	Accumulated g. Morantel Tartrate Bolus 4	Bolus 5
1	0.51	0.59
2	1.5	2.16
3	2.4	2.2
5	4.9	5.4
6	5.1	5.9
7	6.5	6.1
10	9.7	9.7
12	11.0	11.7
14	13.5	12.6
17	14.8	13.6
19	16.4	14.6
21	17.1	14.7
24	16.8	14.7
26	16.9	14.8

In vivo tests with identical boluses placed in the rumeno-reticular sac of cattle for periods of 30—60 days provided the following results.

Bolus No.	Days In Vivo	Mean g. Morantel Tartrate Per Day
6	30	0.222
7	30	0.228
8	45	0.238
9	45	0.335
10	49	0.174
11	60	0.198
12	60	0.178

The overall mean *in vivo* rate is 0.224 g. per day and the *in vitro/in vivo* ratio is approximately 4:1.

EXAMPLE 4

Boluses were prepared from stainless steel tubes having the following dimensions: 22.225 mm. O.D. (7/8 inch), 21.336 mm. I.D. (wall thickness=0.889 mm.=0.035 inch) and 3 cm. long. The ends of the tubes were threaded (0.5 mm. at each end) to receive a collar which serves to hold a hydrogel impregnated porous fabric disc in place. The discs (22.225 mm. O.D. and 3.175 mm., 1/8 inch thick), polypropylene filter cloth having pores of 50 micron average size and impregnated with gelled cellulose triacetate, were prepared by immersing them in a 6% solution of cellulose triacetate in formic acid contained in a vessel that could be subjected to a vacuum of 25 mm. mercury or less. The flask and contents were held under vacuum for about 10 minutes, the discs removed, and wiped free of excess cellulose triacetate solution. They were then immersed in and allowed to equilibrate in distilled water overnight. The discs were then removed from the water, dried with a towel and then equilibrated with polyethylene glycol 400 overnight. The discs were removed and wiped with a towel.

Impregnated discs were mounted on one end of each of the tubes by sandwiching them between two washers, 0.254 mm. (0.01 inch) thick and of the same diameters as the steel tube. The washer adjacent to the steel tube was of cellulose acetate butyrate and the other of dental dam gum rubber. The ends were then capped with stainless steel collars having an opening 21.336 mm. in diameter. The tubes were then filled with morantel tartrate (63.3%), polyethylene glycol 400 (26.6%), sodium hexametaphosphate (10.1%) and the other end of each tube sealed as described above.

The boluses contained 21.4 g. of morantel tartrate, weighed 97 g. and had a mean density of 3.30 g./ml.

The boluses were administered to steers with rumen fistula by use of a balling gun and were removed via the fistule at intervals of 30, 45, 60, 75 and 90 days, to determine the amount of drug remaining in the bolus, from which the mean daily release rate of morantel tartrate was calculated.

Bolus	Days in Steer	Release Rate (mg./day)
1	30	67
2	30	108
3	45	82
4	45	58
5	60	136
6	60	91
7	75	71
8	75	68
9	90	67
10	90	106

The mean release rate was 85 mg./day with a standard deviation of 25 mg. In each steer significant reduction in fecal parasite egg count was observed.

EXAMPLE 5

Four boluses comprising sintered poly(ethylene), (mean pore size of 10μ) pores of which are filled with gelled cellulose triacetate, and having stainless steel sleeves within only a portion of the overall length of the boluses (so as to leave a segment of bolus free of sleeve), and reservoirs containing morantel citrate (63.3%), admixed with polyethylene glycol 400 (26.6%) and sodium hexametaphosphate (10.1%) were prepared according to the procedure of Example 1. However, in place of the perforated stainless steel sleeve used therein, unperforated sleeves of 5.08 cm., 4.445 cm., 3.175 cm. and 1.905 cm., respectively were used. The walls of the sleeves were 0.165 cm. thick. Drug mix was then loaded into each bolus so as to provide a drug-band width of 6.35, 12.70, 25.4 and 38.1 mm., respectively above the sleeves. A stainless steel plug, 12.7 mm. thick and 22.225 mm. diameter, was inserted into each of the boluses above the drug mixture. The ends of the boluses bearing the steel plug were trimmed so as to permit insertion of a cellulose acetate butyrate disc on top of the plugs and flush with the ends of the boluses. The total weight of the individual boluses was 120.0, 115.4, 106.2 and 97.0 g., respectively. The weight of drug mixture ranges from about 25.5 g. to 27.4 g. per bolus. The densities of the boluses were 3.1, 2.98, 2.75 and 2.51 g./ml., respectively.

EXAMPLE 6

In vitro tests of the release rate of morantel citrate by the boluses of Example 5 showed each of them affords constant release of drug over a period of 3—21 days. The lighter of the four boluses of Example 5 (that having the 1.905 cm. sleeve) had a mean release rate of 774.8 mg. morantel citrate per day over the 3—21 day period of constant release.

EXAMPLE 7

Fourteen boluses prepared according to Example 1 when tested *in vivo* in cattle exhibited a mean release rate of morantel tartrate of 238 mg. per day over a 60 day period. The standard deviation was 67 mg. (28%).

EXAMPLE 8

Boluses are prepared according to the procedure of Example 1 but using, in place of the drug mixture of said Example, the following chemicals in the reservoir: pyrantel tartrate (63.3%), polyethylene glycol 400 (26.6%), sodium hexametaphosphate (10.1%); morantel tartrate (100%); pyrantel hydrochloride (100%); tetramisole hydrochloride (100%); levamisole hydrochloride (85.0%), glycerol (15.0%); diethylcarbamazine citrate (100%); hydromycin B (100%); doxycycline hemihydrate hemialcoholate (100%); bacitracin methylenedisalicyclic acid (66.0%), sorbitol (22.0%), sodium lauryl sulfate (12.0%); ampicillin, sodium salt (63.5%), polyethylene glycol (26.5%), sodium hexametaphosphate (10.0%); sodium penicillin G (67.3%), N,N-dimethylformamide (22.2%), sodium glyceryl monolauryl sulfate (10.5%); neomycin complex (68.5%), dimethylsulfoxide (22.5%), sodium lauryl sulfate (10.0%); streptomycin trihydrochloride (100%); oleandomycin hydrochloride (80%), polyethylene glycol 400 (20%); tylosin hydrochloride (100%), polymyxin hydrochloride (79.5%), glycerol (15.0%), sodium lauryl sulfate (5.5%); lincomycin hydrochloride hemihydrate (100%); magnesium acetate tetrahydrate (77%), sorbitol (15%), dioctyl disodium sulfosuccinate (8%).

EXAMPLE 9

A bolus comprising sintered poly(ethylene), pores (average size 100 μ) of which are filled with a cross-linked polyvinyl alcohol hydrogel, and a reservoir containing morantel citrate (63.3%), polyethylene glycol 400 (26.6%) and sodium hexametaphosphate (10.1%), and having a perforated stainless steel sleeve is prepared according to the procedure of Example 1. In place of cellulose triacetate-formic acid solution, however, the hydrogel solution comprises an aqueous solution of 10% polyvinyl alcohol (88% hydrolyzed polyvinyl acetate) containing 3% resorcinol. The tube, following vacuum treatment to fill the pores, is wiped clean and held at 0°C. to −10°C. for 5 hours to gel the polymer. Equilibration of the tube in water is unnecessary. The tube is then tested for leaks, equilibrated in polyethylene glycol 400, filled and sealed as in Example 1.

In vitro testing shows it affords controlled release of morantel citrate.

EXAMPLE 10

The procedure of Example 1 is repeated but using sintered poly(ethylene) tubes one-half as long and one-half the diameter of those used in Example 1. The resulting boluses are designed for use in sheep and afford controlled release of anthelmintic agent over an extended period of time *in vivo*.

EXAMPLE 11

The procedures of Examples 1 and 5 are repeated but using the following microporous materials in place of sintered poly(ethylene): porous ceramic, porous steel, sintered poly(propylene); sintered poly(tetrafluoroethylene); sintered poly(vinyl chloride); sintered polystyrene (average pore size of each material is 100 microns).

Each of the boluses thus produced provides controlled release of chemical over a prolonged period of time when tested *in vitro*.

EXAMPLE 12

Boluses are prepared from stainless steel tubes having the following dimensions: 22.225 mm. O.D. (7/8 inch), 21.336 mm. I.D. (wall thickness=0.889 mm.=0.035 inch) and length 7.62 cm. (3 inches). The ends of the tubes are threaded (0.5 mm. at each end) to receive a collar which serves to hold a porous, hydrogel impregnated disc in place. The discs (22.225 mm. O.D. and 3.175 mm. thick), sintered polyethylene impregnated with gelled cellulose triacetate, are prepared by immersing them in a 6% solution of cellulose triacetate in acetic acid contained in a vessel that can be subjected to a vacuum of 25 mm. mercury or less. The flask and contents are held under vacuum for about 10 minutes, the discs removed, and wiped free of excess cellulose triacetate solution. They are then immersed in and allowed to equilibrate in distilled water overnight. The discs are then removed from the water, dried with a towel and then equilibrated with polyethylene glycol 400 overnight. The discs are removed and wiped with a towel.

Impregnated discs are mounted on one end of each of the tubes by sandwiching them between two washers, 0.254 mm. (0.01 inch) thick and of the same diameters as the steel tube. The washer adjacent to the steel tube is of cellulose acetate butyrate and the other of dental dam gum rubber. The ends are then capped with stainless steel collars having an opening 21.336 mm. in diameter. The tubes are then filled with the desired chemicals and the other end of each tube sealed as described above.

Tubes (boluses) having the following chemicals in the reservoir are thus prepared: morantel citrate (63.3%), polyethylene glycol 400 (26.6%), sodium hexametaphosphate (10.1%); oxytetracycline hydrochloride (100%); pyrantel citrate (88%), glycerol (12%); pyrantel tartrate (63.3%), polyethylene

glycol 400 (26.6%), sodium lauryl sulfate (10.1%); tetramisole hydrochloride (100%); poloxalene (100%); erythromycin hydrochloride (100%); thiamine hydrochloride (100%).

EXAMPLE 13

The procedure of Example 1 was repeated with the exception that the bolus was filled with morantel tartrate rather than with the morantel tartrate-polythylene glycol 400-sodium hexametaphosphate mixture of said example. The bolus weighed 84.0 g., 18.6 g. of which was morantel tartrate.

The bolus, when tested *in vitro* according to the procedure described herein, provided a controlled and nearly constant rate of release of morantel tartrate during the test period of 8—20 days with a mean release rate of 1.36 g. per day.

Days in Vitro	Accumulated g. Morantel Tartrate
1.7	0.04
5.7	1.03
8.7	2.74
12.7	7.63
15.7	12.3
19.7	17.5
23.7	18.3
26.7	18.6

EXAMPLE 14

A low carbon steel tube having the following dimensions: Length—8.77 cm., ID—2.16 cm., O.D.—2.54 cm., and a groove 0.3 cm. deep and 0.6 cm. wide located 0.1 cm. from each end thereof to accept an aluminum crimp, and which completely encircles the tube, was sealed at one end with an ultra high molecular weight (average=2 million to 4 million, available from Glasrock, Porex Division, Fairburn, GA.) sintered polyethylene disc, average pore size 10 microns, impregnated with gelled cellulose triacetate as described in Example 15. The disc, 2.54 cm. in diameter and 0.16 cm. thick, was sealed to the tube with an aluminum crimp. The tube was then inverted and filled with a homogenous mixture comprising 54.4% morantel tartrate, 35.6% polyethylene glycol 400 and 10% sodium hexametaphosphate. The disc/crimp sealing process was repeated to provide the final bolus. The total weight of the bolus was 145.1 g., of which 41.4 g. was drug mixture. Its density was 2.8 g./ml.

The aluminum crimps at each end of the tube possessed an open center area of 3.25 $cm.^2$ resulting in a total area of 6.5 $cm.^2$ available for drug delivery. The bolus affords controlled release of morantel tartrate to cattle over a period of approximately 90 days.

EXAMPLE 15

An aluminum cylinder, 6 cm. long with an outside diameter of 2.1 cm. and a wall thickness of 0.1 cm., and grooved at the open end to accept an aluminum crimp seal was filled with a formulation comprising 70% levamisole hydrochloride, 30% polyethylene glycol 400 and sealed with a sintered, high density (0.95—0.97 g./ml.) polyethylene disc impregnated with gelled cellulose triacetate according to the process of Example 15. The bolus had a density of 2.8 g./ml. The reservoir contained 23.46 g. of the drug mixture, equivalent to 16.42 g. of levamisole hydrochloride.

The aluminum crimp used had a circular open area in its middle, said area having the diameter of 1.1 cm., affording a transport area of 0.95 $cm.^2$.

In vitro tests at 37°C. showed the bolus releases levamisole hydrochloride at a controlled rate.

Days in Vitro	Levamisol Hydrochloride Released
3	0.815
5	1.572
6	1.805
7	2.33
8	2.64
10	2.79
11	2.83
14	2.87
15	4.66
18	5.10
22	6.67

EXAMPLE 16

This example describes a field trial conducted with 40 trial calves of uniform, breed, weight (mean=150 kg.) and sex which had not previously grazed. The calves were divided into four groups of 10 each on the basis of body weight. Two of the groups were replicate medicated groups and two were replicate control groups. A worm free tracer calf was added to each of the four groups of trial calves at the start of the field trial and every four weeks thereafter. Each tracer calf was held in its paddock for two weeks, then removed and housed three weeks before slaughter for worm counts.

The trial and tracer calves were turned out on infected pasture which had been grazed the previous summer and autumn by infected cattle. The pasture was of sufficient size to hold 44 animals set-stocked for the entire grazing season and was divided into four equal and separate paddocks.

The two medicated replicate groups were orally administered a 60 day bolus prepared according to the procedure of Example 1. The boluses provided continuous release of morantel tartrate at 250 mlg./animal (equivalent to 150 mg. morantel base) per day for 60 days. The medicated groups of animals received the boluses orally two days before turning out to pasture in the spring. The presence of the bolus in each medicated animal was confirmed with a metal detector 24 hours after administration. Checks of bolus retention were conducted at two week intervals thereafter. All animals medicated, control and tracers were weighed before turning out and at 4 week intervals.

Herbage samples were collected according to the method described by Taylor (Parasitology, *31*, 473, 1939) at two week intervals beginning four weeks before start of the field trial and continued until termination of the trial.

Faecal samples for McMaster egg counts and lungworm larval counts were collected at commencement of the trial and at two week intervals thereafter. For the first eight weeks these were rectal samples (one from each animal). Thereafter, rectal samples were collected every four weeks to coincide with weighing of the animals. At intervening points samples, 10 for each group, were collected from pasture (Gibson, Veterinary Bulletin No. 7, 403—410, 1965).

Total worm counts were carried out on the abomasum, including mucosal digests, small intestine and lungs of slaughtered animals.

Group	Treatment	Paddock	No. of Animals
1	Morantel tartrate 250 mg./day	A	10 & one tracer every four weeks.
2	Morantel tartrate 250 mg./day	B	10 & one tracer every four weeks.
3	Control.	C	10 & one tracer every four weeks.
4	Control.	D	10 & one tracer every four weeks.

The data are presented graphically in Figures 6, 7 and 8. Figure 6 shows weight gains during the grazing season for both medicated and control groups. Both groups were found to gain weight at nearly the same net rate for about the first 3 months. After this time, weight gains in the control groups slowed, and even decreased for a period of time, coincident with increase in the number of pasture parasites. Medicated animals, on the other hand, continued their growth at a weight nearly equal to that observed early in the season.

Figures 7 and 8 show the parasite population throughout the grazing season for medicated and control animals. The number of eggs per gram of feces (right ordinate) and the number of larvae per kg. of dry pasture herbage (left ordinate) are plotted. The calves were turned out to pasture in mid-May; the medicated calves being orally administered the 60 day boluses two days prior to turn out which afforded them treatment to mid-July.

At the time of turning out, the number of eggs in the feces and of larvae in the pasture was low. In the control groups, Figure 7, eggs began to appear in the animals' feces in early June, reached a peak in late July and slowly decreased through August and September. These eggs lead to the increase in pasture larvae observed in late July and which reached its peak in August.

In the medicated groups, Figure 8, the production of eggs during June and July was dramatically reduced, a fact which was reflected in the significant reduction of pasture larvae during July and September.

EXAMPLE 17

Similar field trials were conducted according to the design of Example 16 but using only one medicated and one control group in each trial. Pertinent data are tabulated below:

Trial No.	No. of Animals Per Grp.	Mean Wt. Gain Advantage of Treated Over Control	Cumulative Egg Count Trtd	Contrl	% Reduction
1	12	17.0 kg.	0	79	100
2	13	9.0	33	146	77
3	12	32.5	67	408	84
4	11	9.5	145	436	67
5	17	18.2	135	886	85
6	18	13.4	23	62	63
7	24	17.1	34	150	77
8	31	36.5	14	28	50

EXAMPLE 18

The procedure of Example 4 is repeated but using, in place of poly(propylene) filter cloth impregnated with gelled cellulose triacetate, the following gelled cellulose triacetate porous fabrics:

Porous Fabric	Average Pore Size
poly(ethylene)	75 μ
poly(tetrafluoroethylene)	100 μ
glass	60 μ
stainless steel filter cloth	80 μ
copper screen	30 μ
modacrylic fiber[a]	10 μ
nickel-copper alloy screen[b]	50 μ

(a) copolymer of acrylonitrile (40%) and vinyl chloride (60%), sold under the trademark Dynel by Union Carbide Corp., N.Y.
(b) sold under the trademark Morel by The International Nickel Co., Inc., N.Y.

CLAIMS

1. A device for the controlled and continuous administration of a chemical to an aqueous liquid-containing environment over a prolonged period of time, said device comprising a reservoir containing said chemical, a shaped wall formed in part at least of a porous material, said porous material being in contact with at least a part of said reservoir and being insoluble in said environment while maintaining its integrity during said prolonged period of time, and a hydrogel medium means impregnating pores of said porous material, said hydrogel medium means having channels or pores which (1) permit the diffusion of aqueous liquid from said environment into said reservoir to form a solution of said chemical in said aqueous liquid and (2) permit the diffusion of said solution containign said chemical to said environment, the dissolved chemical so released being replaced by the continuous dissolving of said chemical in said reservoir and the amount of dissolved chemical in said reservoir changing continuously throughout said prolonged period of time so as to maintain the rate of chemical release to said environment substantially constant during a substantial portion of said prolonged period of time.

2. A device according to claim 1, wherein the reservoir contains the chemical in admixture with a water-soluble excipient.

3. A device according to claim 1, wherein the reservoir contains the chemical in admixture with a water-soluble liquid excipient and a detergent.

4. A device according to any one of claims 1 to 3, wherein the porous material is sintered poly(ethylene), sintered poly (propylene), sintered poly(tetrafluoroethylene), sintered poly (vinyl chloride), sintered polystyrene or a porous fabric material formed from poly(ethylene), poly(propylene), poly(tetrafluoroethylene), glass or modacrylic fibres.

5. A device according to any one of claims 1 to 4, wherein the aqueous liquid-containing environment is an animal body site.

6. A device according to claim 5, wherein the animal body site is the rumeno-reticular sac of a ruminant.

7. A device according to any one of claims 1 to 6, wherein the hydrogel medium is gelled cellulose triacetate.

8. A device according to any one of claims 1 to 7, wherein the chemical is an anthelmintic agent.

9. A device according to claim 8, wherein the chemical is a water-soluble acid addition salt of pyrantel, morantel or levamisole.

10. A device according to claim 9 wherein the water-soluble acid addition salt is selected from levamisole hydrochloride and the tartrate and citrate salts of morantel and pyrantel.

Trial No.	No. of Animals Per Grp.	Mean Wt. Gain Advantage of Treated Over Control	Cumulative Egg Count Trtd	Cumulative Egg Count Contrl	% Reduction
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EXAMPLE 18

The procedure of Example 4 is repeated but using, in place of poly(propylene) filter cloth impregnated with gelled cellulose triacetate, the following gelled cellulose triacetate porous fabrics:

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(b) sold under the trademark Morel by The International Nickel Co., Inc., N.Y.

CLAIMS

1. A device for the controlled and continuous administration of a chemical to an aqueous liquid-containing environment over a prolonged period of time, said device comprising a reservoir containing said chemical, a shaped wall formed in part at least of a porous material, said porous material being in contact with at least a part of said reservoir and being insoluble in said environment while maintaining its integrity during said prolonged period of time, and a hydrogel medium means impregnating pores of said porous material, said hydrogel medium means having channels or pores which (1) permit the diffusion of aqueous liquid from said environment into said reservoir to form a solution of said chemical in said aqueous liquid and (2) permit the diffusion of said solution containign said chemical to said environment, the dissolved chemical so released being replaced by the continuous dissolving of said chemical in said reservoir and the amount of dissolved chemical in said reservoir changing continuously throughout said prolonged period of time so as to maintain the rate of chemical release to said environment substantially constant during a substantial portion of said prolonged period of time.

2. A device according to claim 1, wherein the reservoir contains the chemical in admixture with a water-soluble excipient.

3. A device according to claim 1, wherein the reservoir contains the chemical in admixture with a water-soluble liquid excipient and a detergent.

4. A device according to any one of claims 1 to 3, wherein the porous material is sintered poly(ethylene), sintered poly (propylene), sintered poly(tetrafluoroethylene), sintered poly (vinyl chloride), sintered polystyrene or a porous fabric material formed from poly(ethylene), poly(propylene), poly(tetrafluoroethylene), glass or modacrylic fibres.

5. A device according to any one of claims 1 to 4, wherein the aqueous liquid-containing environment is an animal body site.

6. A device according to claim 5, wherein the animal body site is the rumeno-reticular sac of a ruminant.

7. A device according to any one of claims 1 to 6, wherein the hydrogel medium is gelled cellulose triacetate.

8. A device according to any one of claims 1 to 7, wherein the chemical is an anthelmintic agent.

9. A device according to claim 8, wherein the chemical is a water-soluble acid addition salt of pyrantel, morantel or levamisole.

10. A device according to claim 9 wherein the water-soluble acid addition salt is selected from levamisole hydrochloride and the tartrate and citrate salts of morantel and pyrantel.

11. A device according to claim 10, wherein the water-soluble acid addition salt is the tartrate or citrate salt of morantel.

12. A device according to claim 11, wherein the porous material is sintered poly(propylene) or sintered poly(ethylene) and the water-soluble salt is the tartrate salt of morantel.

13. A device according to any one of claims 1 to 12, wherein said device contains a high density material in such quantity that the device has a density of at least 2.0.

14. A device according to claim 13, wherein the high density material is steel and the shaped wall comprises a cylinder of said steel, the ends of which are sealed with sintered polyethylene, pores of which contain gelled cellulose triacetate.

15. A device according to claim 13, wherein the high density material is present as a perforated steel or iron sleeve within the device between the reservoir and the porous material.

16. A device according to claim 15, wherein the porous material is sintered poly(ethylene) and the hydrogel is gelled cellulose triacetate.

17. A device according to claim 15 or claim 16 wherein the aqueous liquid-containing environment is the rumeno-reticular sac of a ruminant.

18. A device according to claim 17, wherein the chemical is a water-soluble acid addition salt of morantel.

19. A device according to claim 18, wherein the water-soluble acid addition salt is the citrate salt of morantel.

20. A device according to claim 18, wherein the water-soluble acid addition salt is the tartrate salt of morantel.

21. A process for production of a device for the controlled and continuous release of a chemical to an aqueous liquid-containing environment over a prolonged period of time, which process comprises enclosing a chemical in a reservoir surrounded by a shaped wall formed in part at least of a porous material, the porous material being in contact with at least a part of the reservoir and characterized by being insoluble in the aqueous liquid and maintaining its integrity during a prolonged period of time, the pores of the porous material being impregnated with a hydrogel medium permeable to the passage of the chemical and the aqueous liquid so that the device when placed in the aqueous liquid-containing environment continuously releases the chemical from the reservoir to the aqueous liquid-containing environment at a controlled rate through the hydrogel medium, the dissolved chemical so released being replaced by the continuous dissolving of the chemical in the reservoir, the amount of dissolved chemical in the reservoir changing continuously throughout the prolonged time period, so as to maintain a substantially constant rate of chemical release to the environment during a substantial portion of the prolonged time period.

22. A process according to claim 21, wherein the reservoir contains chemical in admixture with a water-soluble excipient.

23. A process according to claim 21, wherein the reservoir contains chemical in admixture with a water-soluble liquid excipient and a detergent.

24. A process according to any one of claims 21 to 23, wherein the porous material is sintered poly(ethylene), sintered poly(propylene), sintered poly(tetrafluoroethylene), sintered (vinyl chloride), sintered polystyrene or is a porous fabric material formed from poly(ethylene), poly(propylene), poly (tetrafluoroethylene), glass or modacrylic fibres.

25. A process according to any one of claims 21 to 24, wherein the device is for location in the rumeno-reticular sac of a ruminant animal, the chemical being an anthelmintic agent.

26. A process according to claim 25, wherein the chemical is a water-soluble acid addition salt of levamisole, pyrantel or morantel.

27. A process according to claim 26, wherein the chemical is morantel tartrate.

28. A process according to any one of claims 24 to 27, wherein the porous material is sintered poly(propylene) or sintered poly(ethylene).

29. A process according to any one of claims 21 to 28, wherein the hydrogel medium is gelled cellulose triacetate.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained

(12)

PATENTS ACT 1977

SPECIFICATION NO 2020181B

Slip No 2

The following corrections were allowed under Section 76 on 26 January 1983:

Page 17, line 40, *after* chloride) *insert* or

THE PATENT OFFICE
24 June 1983

Bas 251994/2

(13)

PATENTS ACT 1977

SPECIFICATION NO 2020181B

The following corrections were allowed under Section 117 on 26 January 1983:

Page 16, line 46 *after* chloride) *insert* or

Page 17, line 40 *after* sintered (third occurrence) *insert* poly

THE PATENT OFFICE
22 February 1983

Bas 95215/2