

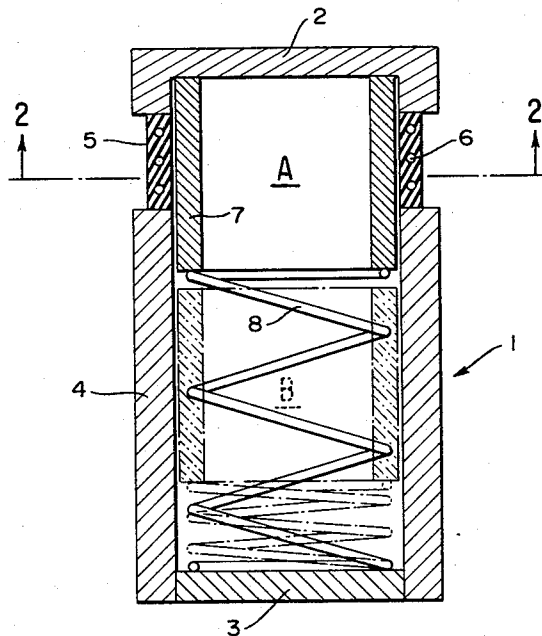


FIG. 1

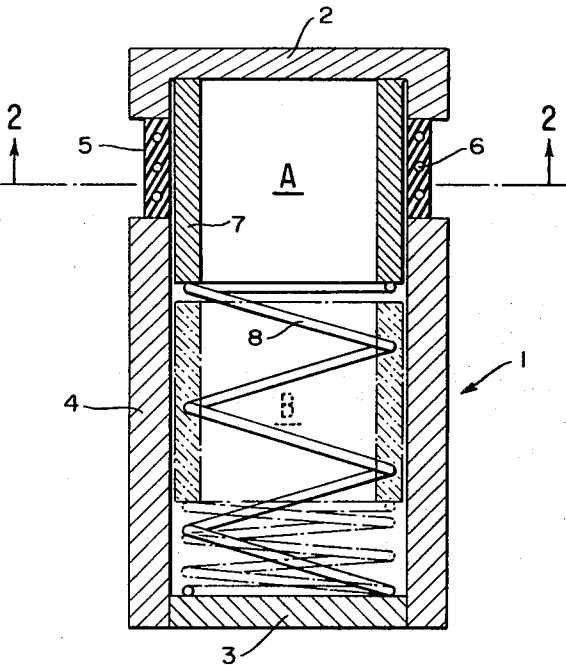
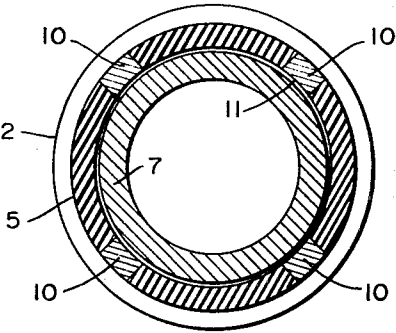


FIG. 2



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MAGNETICALLY OPERATED CAPSULE FOR ADMINISTERING DRUGS

This invention relates to a capsule activated by magnetic force to release a medicament.

Capsules implanted into the human body to administer long-acting drugs such as regulatory hormones over long periods have in general been simple passive systems. The drug diffuses from the capsule interior through the capsule walls into the body at a rate governed exclusively by the wall thickness and the concentration of the drug. No independent control is imposed either by the exterior chemical milieu of the patient or by any action on the part of the patient, to regulate the rate of drug diffusion or when administration is initiated and ceased. Since the patient either does not have a continuous need for the drug but usually has a need governed by a convenient schedule or when physiological sensation informs him of the need for the drug, it would be highly desirable to provide a drug-filled capsule implanted into the patient for the purpose of administering the drug on a non-continuous basis and/or on any convenient schedule desired by the patient through the use of means solely within his control.

The present invention provides capsules suitable for implantation into the body for administering a drug from the interior of the implanted capsule to the body by subjecting the capsule to magnetic force from a source located outside of the body. When the magnetic force is applied from one direction, a magnetic means within the capsule is caused to move thereby effecting delivery of a quantity of a drug from a storage compartment in the capsule from which it diffuses through a permeable wall portion of the capsule into living tissue.

Only a portion of the capsule wall need be constructed of a material permeable to a drug contained in the capsule while the remainder of the capsule wall is non-permeable to the drug. A magnetically activatable means in the capsule is adapted to move within the capsule either linearly or rotationally under a magnetic force to provide or terminate contact of the drug-permeable wall portion and the drug in the capsule as desired. When the drug and permeable wall are brought into contact, the drug begins to diffuse into the permeable wall and thence, subsequently, into the body. When the drug and permeable wall are removed from contact, the permeable wall releases drugs already in it, at an ever decreasing rate, and finally is exhausted of drug. Administration of the drug can be controlled easily by the patient by positioning the source of the magnetic force outside the body to move the magnetically activatable means and provide or terminate contact of the drug and permeable wall for the period desired by the patient.

The process of this invention for administering drugs, and the capsule therefor provide substantial advantages over presently available means for administering drugs from an implanted capsule, in that administration is within the exclusive control of the patient. Furthermore, the present invention permits the administration of drugs from implanted capsules which drugs were previously administered by other means due to the need for non-continuous administration.

FIG. 1 is a sectional view of a cylindrical capsule of this invention especially suited for contraceptive drugs such as progestin, taken along the midplane coextensive with its major axis showing the magnetically operable means in two positions.

FIG. 2 is a sectional bottom view of a capsule of FIG. 1 taken along line 2—2 and provided with additional structural supports.

Referring to FIG. 1 the retaining capsule 1 having a cylindrical shape is defined by ends 2 and 3, non-permeable cylindrical wall 4 and permeable wall 5 supported on screen 6 to provide mechanical strength. The retaining capsule 1 contains a magnetic hollow piston 7, a spring 8 and either a drug solution or the drug itself. The spring 8, drug and piston 7 can be inserted into the capsule 1 by removing cap 3 and thereafter sealing the cap 3 in place. The spring 8, has a low spring constant which maintains the piston 7 against the end 2 in the rest

state. When the capsule is subjected to a magnetic force from a source outside the body, the piston 7 is moved to a position B shown by the dotted lines. The piston movement compresses the spring 8, and, because piston 7 is hollow, the contained drug, drug solution, or drug suspension moves through the piston 7 and contacts permeable wall 5. The drug diffuses through the wall 5 at a diffusion rate controlled by the thickness of wall 5 and the concentration of the drug. The rate of administration of the drug is controlled by the surface area of wall 5 and the drug diffusion rate. When it is desired to stop drug administration, as for example, to turn off a contraceptive hormone in order to permit conception, the patient reverses the process, and magnetically attracts the piston 7 to position A which movement is assisted by spring 8. When the piston is in position A, the wall 5 is effectively sealed from contact with the drug. Spring 8 maintains piston 7 in a fail-safe position; that is to say, unless a magnet force is intentionally applied to move piston 7, the neutral position of piston 7 is to seal the wall 5 from contact with the drug.

Referring to FIG. 2, the capsule of FIG. 1 is modified to include supports 10 extending between the end piece 2 and the wall 4 to provide a rigid support for membranes 5. The interior surface 11 of the supports 10 conform to that of the interior surfaces of end piece 2 and wall 4 to permit smooth and undisturbed movement of piston 7 and also to reduce the possibility of damaging wall 5. Any number of supports 10 can be used with 3, 4 or 6 being preferred.

The end pieces and rigid wall of the capsule are constructed of materials which are non-magnetic, and non-toxic, do not degrade the drug, have long durability in contact with body fluids and negligible permeability. Furthermore, any material used in the formation of the capsule must have the fundamental properties of high mechanical strength against fracture by accidental blows. Suitable materials for use in the capsule are non-magnetic metals such as tantalum, non-magnetic stainless steels, platinum, or the like or non-metals such as polycarbonates or the like. The free moving piston 7 must be of ferromagnetic materials, and in general it must be coated to prevent its corrosion in or contamination of the contained drug or drug solution. The piston can be coated with ceramic enamels by high temperature fusion, organic enamels of high strength and abrasion resistance such as phenol-formaldehyde resin, or the like.

The permeable membrane is preferably made of a cross-linked elastomer or a network polymer in a swollen solvated state which is highly permeable to the drug. Generally speaking, polymers in their glassy state are not desirable for this purpose, because of their inordinately low permeability, but cellulose acetate Loeffler type reverse osmosis membranes, suitably modified to increase pore size, may be used. The elastomeric material employed to form the permeable wall must be non-toxic, cross-linkable to the desired elastic modulus, inert to the drug and have a finite permeability to the contained drug to give accurate slow release of the drug into the body upon implantation. Non-toxic additives, usually employed in the elastomeric materials, may be employed include fillers such as silica or the like, provided only that the capsule retains its final shape after its processing and the drug can be diffused through the elastomer. For a lipid soluble medicament or drug, including steroid hormones such as the progestins, and estrogen, it is preferred to employ silicone rubbers i.e., organopolysiloxane wherein the organic groups attached is the silicon atom preferably methyl, phenyl, vinyl, or combinations thereof. This preference is because silicone rubbers have relative freedom from toxic products of vulcanization, and are inert as an implanted material.

In general, the permeable wall of the cylindrical capsule can be formed by compression molding and vulcanization, or by an equivalent procedure so that the wall material is cross-linked while being contained between mating interior and exterior molds to produce a product having a smooth continuous surface co-extensive with the interior surface of the capsule. Cross-linking can be effected in any manner well known in the

art, including ionizing radiation which is especially appropriate to silicone elastomers. After cross-linking, the permeable wall is treated to remove by-products of the cross-linking step, if any, which may be toxic or which may degrade the drug. Thus, for example, phenyl benzoate produced by thermal decomposition of benzoyl peroxide initiator can be removed by extraction. The membrane is bonded to the wall of the capsule in any convenient manner. Thus, the membrane can be molded and cross-linked while in contact with the non-permeable capsule wall to thereby provide an effective seal. The surface of the wall also can be modified or coated with a material to effect a strong seal with the membrane. Thereafter, the decomposition products from the cross-linking step can be removed from the membrane prior to filling the capsule.

Once the cylindrical capsule has been filled with the drug, the sliding piston and the retaining spring, it is convenient to seal the end plate 3 by some relatively permanent means, such as with a permanent non-toxic adhesives such as epoxy or by heat sealing the material if it be polymeric, such as a polycarbonate or the like.

It is essential that the sliding piston move freely but snugly within the capsule to provide effective sealing or contact of the permeable wall and drug. The piston material or coating used on the piston should not adhere to any of the surfaces with which it contacts and there must be geometric precision between the sliding piston and the interior surface of the capsule. The length of the sliding piston is significantly greater than the corresponding length of the permeable wall, so that when it is in the closed position leakage of the drug is minimized. Generally, the capsule is 4 to 15mm. long and 2 to 10mm. wide the piston being about 2.5mm. to 10mm. long. It is desirable to minimize the piston wall thickness to maximize the amount of drug in the capsule. While the capsule of this invention is described with reference to a magnetically operable means comprising a hollow piston, it is to be understood that the magnetically operable means can be of any geometric shape so that it moves freely but snugly within the capsule to provide effective sealing of the drug and permeable wall and permits contact of the drug and permeable wall when desired.

When the drug is a solid rather than a liquid it is desirable to form a solution thereof with a solvent or a dispersion thereof in an inert carrier liquid. The solvent employed should dissolve the drug to afford the preparation of concentrated solution, and must be inert to both the drug and the elastomeric material. A suitable carrier liquid should be inert to the drug, and capable of suspending the drug when the drug is rendered into microparticles. Thus, ideally the carrier liquid has the same density as the drug. Accordingly, the choice of solvent and elastomer is made depending upon the drug used to fill the capsule.

The particular elastomer and solvent employed for a given drug are chosen in accordance with the criteria set forth above for the drug-solvent-elastomer system. Commonly employed solvents and carrier liquids useful in the present invention include glycols, such as propylene glycol; glycerol; selected animal fats; hydrogenated vegetable oils; mineral oil; silicone oils and mixtures thereof. Silicone oils include not only the common homopolymers poly [dimethyl siloxane], but also the homopolymers poly [diphenyl siloxane], poly [methyl phenyl siloxane], poly [methyl, B-carboxyethyl siloxane], and random copolymers and interpolymers based on the mer units of the above stated homopolymers. Colloidal silica may conveniently be used as a thickening agent to maintain dispersion of suspended drug, above or in combination with polymeric additives to assist in maintaining dispersion.

The following example illustrates the present invention and is not intended to limit the same.

EXAMPLE I

A cylindrical capsule of the form shown in FIG. 1 having an

internal diameter of 0.600 cm. and an internal length of 1.2 cm. is formed by injection molding from polycarbonate, with six supporting pillars, (10 in FIG. 2) equally spaced, being used as a frame on which a silicone membrane is subsequently cast. Stainless wire (20mil. diameter) is spirally wound over the six pillars so as to form a support for the silicone composition. Ends of the wire are seized by forcing them into holes drilled in the polycarbonate body above and below the membrane area, then heat sealing.

The total height of the pillars defining the membrane area is 0.40cm. A dummy plug is driven into the capsule so as to form an internal mold surface, and silicone RTV rubber of the acetox type is forced through the stainless steel wire and around the posts until it fills the space bonded by the dummy plug. A cellophane tape is applied externally by means of a dental clamp to support the liquid silicone, and air cure is allowed to occur for 24 hours, followed by immersion in 90° C., water for 1 hour to extract residual acetic acid and complete hydrolysis of the silicone rubber now solidified as a membrane around the stainless steel wire, the polycarbonate posts and the upper and lower portions of the polycarbonate body.

The dummy is removed and the capsule is filled through its open end 3 (FIG. 1) with a suspension of 25 parts estrogen hormone in 75 parts dimethyl silicone oil of viscosity 1,000 centipose, thickened by 1/4 part of Cubosil(TM) silica. A hollow cylinder formed of soft magnetic iron, machined and then coated with a ceramic to cover all areas, having a length of 0.60cm., an inside diameter of 0.35cm., and an outside diameter of 0.570cm. is inserted through the open end of the capsule and placed in the closed position but is over the membrane area. A tantalum spring exerting a force of 1.5 grams when fully collapsed, 0.6 grams when fully extended, is placed behind the hollow iron cylinder. A threaded end plate 3 is then screwed into the end of the capsule, eliminating all air from inside the capsule. Superficial heat sealing is used too at the external junction of the capsule body and the end plate to insure against leakage. The heat sealing is accomplished by a rapid use of a miniature gas oxygen torch to effect superficial fusion without heating the main body of the capsule.

The capsule is designed for implantation in the upper thigh, at a depth of 1/2cm., with the end 3 nearest the surface. A 40-gram AiNiCor rod magnet taped over the skin immediately above magnet is sufficient to keep the internal hollow iron cylinder in the open position, for release of the contraceptive estrogen. Removal of the magnet allows immediate close of the membrane area from access of the estrogen-silicone oil suspension, and within 8 hours the rate of release of estrogen falls exponentially a value approximate by 5 percent of that corresponding to full open position (magnetic retraction of the hollow iron wire).

I claim:

1. A capsule suitable for implantation in the human body which comprise
 - a wall,
 - end sections attached to said wall to define a closed hollow chamber,
 - a medicament within said chamber,
 - a portion of said wall being formed of a permeable cross-linked elastomeric composition,
 - an open hollow magnet in said chamber being movable under a magnetic force to seal or expose the permeable wall portion to the medicament,
 - and a spring means in said chamber between said magnet and one of said end sections biasing said magnet toward a position to effect sealing of said permeable wall portion from said chamber.
2. The capsule of claim 1 wherein the permeable wall is formed of a cross-linked silicone rubber.
3. The capsule of claim 1 wherein the permeable wall portion is provided with a reinforcing means.

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