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Homm et al.

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[54] **COMPOSITIN FOR SUSTAINED RELEASE OF A MEDICAMENT AND METHOD OF USING SAME**

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[52] **U.S. Cl.**.....**424/28**, 424/27, 128/260, 128/270, 128/271, 128/285

[51] **Int. Cl.**..... **A61l 19/00**

[58] **Field of Search** 424/27, 28; 128/260, 270, 128/271, 285

[56] **References Cited**

UNITED STATES PATENTS

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[57] **ABSTRACT**

A solid, intimately admixed compostion comprising a thermoplastic, physiologically-inert polymer soluble in body fluids, and an effective amount of a suitable medicament. The composition is suitable for introduction into a body cavity, therein to be slowly dissolved by body fluids and release thereby incremental amounts of medicament. Various areas of use include intravaginal applications for spermicidal effect, subcutaneous implantation, and the like.

14 Claims, No Drawings

COMPOSITIN FOR SUSTAINED RELEASE OF A MEDICAMENT AND METHOD OF USING SAME

BACKGROUND OF THE INVENTION

The present invention relates to an improved medicament dispensing system of special use in contraception. More particularly it relates to a composition of matter useful for delivering controlled amounts of a medicament within a body cavity at a pre-determined rate.

Delivery of medicaments to a site within a body cavity is usually accomplished either systemically by oral administration or locally by direct introduction into the cavity. The systemic method has the advantage of being convenient, but because it is systemic suffers from "side effect" problems. Direct introduction has the advantage of requiring lower doses and is faster acting, but is also usually very inconvenient and quite often unpredictable in efficacy. In this method, the concentration of medicament in the body cavity is not maintained at a constant level, but is rather at a maximum just after application and declines thereafter. Thus, in order to have an effective amount of medicament in the body cavity at all times, it is necessary when using the direct introduction method to give either a moderate excess at short intervals or a large excess at longer intervals. Neither of these alternatives is satisfactorily convenient or economical.

One of the areas of major interest as regards direct introduction of medicaments into body cavities is contraception. Several contraceptive methods are currently employed. For example, there are those which prevent ovulation, those which prevent implantation, and those which prevent sperm from coming in contact with a released ovum. The first method is typified by oral administration of various drugs, usually steroids, and has the disadvantage of being systemic rather than topical. It is advantageous, however, in that administration immediately prior to coitus is not necessary.

The second method is typified by insertion into the uterus and maintenance therein of a foreign object called an intrauterine device. This method has the advantage of the first method and is also topical, but is disadvantageous because of the undesirably high possibility of perforating the uterus. Moreover, the devices are usually painful during the insertion process and usually for long periods thereafter during residency.

A third method usually involves placing some physical or chemical barrier between the sperm and the ovum and is typified by a condom, a spermicidal foam or jelly, and the like, or a combination of two or more of these. This third type has the disadvantage of requiring application just prior to coitus, but has the advantages of being topical in application and having no extravaginal effects. This method would be very desirable indeed if application of the material were required not immediately before coitus but rather at some prior time much in advance of coitus.

The present invention provides a system and method especially suited for contraceptive use of the third type, but capable of broader applications which does not have the disadvantages traditionally associated with it. That is, the invention provides a solid drug delivery system of the type which is inserted into the vagina up to 24 hours prior to coitus and slowly releases a spermicide. The system does not require removal or storage after use since it is soluble in body fluids and is diffused by the system. The present invention, therefore, in its

broader aspects provides a solid drug delivery system comprising in intimate admixture a body fluid-soluble, thermoplastic, physiologically-inert polymer and an effective amount of a suitable medicament. The term medicament includes but is not limited to spermicides, ovacides, antimicrobials, anti-inflammatories, steroidal and non-steroidal anti-fertility agents, prostaglandins, and the like, and includes any compound, drug or medicine having a desired physiological effect.

The polymer may be any of those which are soluble in body fluids such as, for example, a cellulose, a starch, an alginate, a polyvinyl alcohol, a polyvinyl pyrrolidone, a polyacrylamide, an ethyleneoxide polymer, or the like. Preferably, the solubility characteristics of the polymer are chosen so that the entire mass is totally dissolved in the body cavity fluids within a period of about 24 hours so as to give a sustained, prolonged release of medicament. Where vaginal use is contemplated, the preferred polymer is a hydroxypropyl cellulose or hydroxypropylmethyl cellulose having a molecular weight of from 60,000 to 1,000,000. Typically employable here are cellulose ethers having a high degree of ideal propyl substitution at the hydroxyl groups. From 80 to 100 percent propyl substitution is suitable. The product of the invention may be provided in the form of fibers, molded articles or extruded shapes, in which form they may then be placed in the body cavity where they will dissolve and release the medicament at a desirable rate.

The composition of the present invention will contain various amounts of polymer and medicament relative to one another depending upon many factors including the final use to which the composition will be put, the nature of the drug employed, the actual solubility characteristics of the polymer, and the like. In general, however, a composition containing up to about 30 weight percent of the medicament with the balance being essentially polymer will be suitable. Preferably, however, the amount of medicament ranges from 5 to 25 percent by weight based on the weight of the entire composition. Such a formulation is especially suitable for contraceptive use when the composition comprises a spermicide as the medicament and hydroxypropyl cellulose as the polymer.

The compositions of the present invention are prepared by intimately blending the desired polymer in any convenient form such as pellet or powder form with the appropriate amount of medicament. This intimate mixture is then spun, cast, molded, or extruded into fibers or suitable shapes, either with or without the addition of solvents or additional plasticizers.

For example, using hydroxypropyl cellulose as illustrative, a typical preparation is as follows: Hydroxypropyl cellulose powder is intimately mixed with a suitable amount of a medicament, preferably a spermicide. The resulting mixture is melt spun using standard spinning techniques into a strand and the strand chopped into pellets. These pellets are then charged into a standard melt spinning apparatus, are spun into fine fibers and the fibers chopped into lengths convenient for subsequently forming "cotton" balls from the fibers. Dry carding techniques are then employed to form cotton balls or wads. There results from this operation the preferred form of the composition of the invention when an intravaginal contraceptive system is sought. The pellets may, on the other hand, be used in the molding or

extrusion of a suitable shape, e.g., a circular film, a diaphragm, or the like.

The techniques of fiber formation may vary depending on the particular polymer being used, but these techniques are all within the skill of the art and basically form no part of the present invention. For example, when polyvinyl alcohol is used as the polymer, wet spinning techniques, using an aqueous solution of a suitable coagulating agent, e.g., Na_2SO_4, $(NH_4)_4SO_4$, $MgSO_4$, or the like may be employed. Standard wet spinning techniques are also employed when using hydroxypropylmethyl cellulose.

As stated, the preferred composition of the present invention is a mixture of hydroxypropyl cellulose with a spermicide, preferably in the form of a fibrous mass. The spermicide may be any compound known to be spermicidal and compatible with the polymeric system used. Typically acceptable are non-ionic surfactants such as ethoxylated phenoxyethanols. Such materials are well known in the art and are represented by p-diisobutylphenoxypolyethoxy ethanol, known as Triton X-100, available from Rohm & Haas, Philadelphia, Pa., nonylphenoxypoly(ethoxy)$_n$ ethanol (where n is an integer up to 21 and preferably 9), known as Tergitol TP-9 available from Union Carbide, New York, N.Y., also known as Nonoxynol, available from General Aniline & Film Corp., New York, N.Y. Other spermicides include ricinoleic acid and mercurial salts such as phenyl mercuric acetate. Among the above, the preferred spermicides are the nonylphenoxypoly(ethoxy)$_n$ ethanols with that compound wherein n is 9 being most preferred.

The fibrous mass suitably comprises polymer-spermicide fibers having a strand diameter of up to 50 denier (about 5.5 mils.) and preferably from 0.0004 to 0.0015 inches, and a strand length of from 0.25 to 2 inches and preferably 0.5 to 1.25 inches. Normally the mass has a bulk density of 0.1 to 0.3 and preferably 0.11 to 0.15 gms. per cc in the relaxed state. Such dimensions give a product having the appearance of cotton wadding but having sufficient resiliency and elasticity for filling the cross-section of the vaginal canal and providing occlusion of the deep inner recesses and folds, which might otherwise not receive spermicide were a foam, jelly or cream used. Typically, an effective fibrous mass weighs between 0.75 and 1.50 gms. and preferably 1.00 to 1.25 gms. It may be inserted into the vaginal canal using any of the well-known insertion techniques up to 16–24 hours before coitus. A mass of the weight and dimensions described will slowly dissolve over this period in the natural body fluids and will supply an effective dose of spermicide. It thus provides both a physical and chemical barrier to the union of sperm and ovum in a safe, reliable, topical and aesthetic fashion.

Observations of residence times of various embodiments of the present invention in several types of experimental animals (tabulated in FIG. 1) indicate that it has the desired residence time (about 16 hours) in any warm-blooded animal if used at an appropriate dose. For example, fibrous masses weighing 1.00 to 1.25 gms. will have 0.10 to 0.125 gms. of spermicide associated therewith, and this will ordinarily be suitable for virtually complete spermicidal activity over a 16-hour period. Other compositions of the invention, whether fibrous or molded or extruded shapes, behave similarly and are easily adaptable to insertion into any body cavity therein to release drug.

The following examples are given to illustrate specific embodiments of the present invention:

EXAMPLE I

Into an oscillating drum mixer are charged 15,200.0 gms. of powdered food grade hydroxypropyl cellulose (available under the tradename Klucel G (available from Hercules, Inc., Wilmington, Del., having a molecular weight of 275,000 and an idealized molar substitution of 3.0 and 1,800 gms. of diisobutylphenoxypolyethoxy ethanol, available under the name of Triton X-100, from Rohm & Haas, Philadelphia, Pa. The blend is intimately mixed and the resulting intimate mixture is charged into a 2-inch Davis-type single screw extruder equipped with a die containing six ⅛-inch circular orifices. The Extruder has three zones of melting electrically maintained at 325°F, 315°F, and 330°F, respectively. The strands are cooled as they travel down a 30-foot teflon-coated trough, at the end of which is a means for chopping the strands into ½ inch lengths. The resulting pellets are graded for size, the scraps being returned to the extruder for reuse.

The pellets are then re-extruded as above on a 1-inch Davis-type extruder equipped with a die containing a 0.018 inch circular orifice and a means for attenuating the strand as it emerges. This monofilament is collected and is chopped into lengths of between about ½ inch and about 2 inches. These lengths are then treated by standard dry-carding techniques to yield fibrous masses of the cotton wad type.

EXAMPLE II

The procedure of Example I is repeated except that 15 percent by weight of the spermicide is substituted for the 10 percent used therein.

EXAMPLE III

The procedure of Example I is repeated except that 25 percent by weight of the spermicide is substituted for the 10 percent used therein.

EXAMPLE IV

The procedure of Example I is repeated except that 5 percent by weight of nonylphenoxypoly(ethoxy)$_n$ ethanol, $n = 9$, (available from Union Carbide Corp., New York, N.Y., under the name of Tergitol TP-9) is substituted for the 10 percent by weight of Triton X-100 used therein.

EXAMPLE V

The procedure of Example IV is repeated except that 15 percent by weight of spermicide is substituted for the 10 percent used therein.

EXAMPLE VI

A wad of fibers as produced in Example II and weighing 0.300 gms. is inserted into the vagina of a female rhesus monkey and is observed periodically. Dissolution of the polymer begins immediately and continues until the wad disappears, a period of from about 17 to about 24 hours.

EXAMPLE VII

Into a tank are charged 95 parts by weight of a water-soluble copolymer of polyvinyl alcohol and allyl alco-

hol prepared in accordance with known techniques, (See Example I of U.S. Pat. No. 2,909,502), 5 parts by weight of the spermicide Triton X-100 (diisobutylphenoxypolyethoxy ethanol) and sufficient water to make a 15 percent by weight spinning solution of the spermicide mixture. After thorough mixing, filtration, and de-aeration of the spinning solution, fiber is spun from the solution by the wet method, the coagulating solution for which is a 50°C aqueous solution containing about 420g/liter of Na_2SO_4 and having a pH of about 3.9. The monofilament is collected and chopped into staples (½–1 inch lengths) suitable for formation into cotton balls by standard dry carding techniques.

EXAMPLE VIII

The procedure of Example VII is repeated except that 15 percent by weight of spermicide is substituted for the 5 percent used therein.

EXAMPLE IX

The procedure of Example VII is repeated except that 25 percent by weight of spermicide is substituted for the 5 percent used therein.

EXAMPLE X

The procedure of Example VII is repeated except that 5 percent by weight of Tergitol TP-9 is substituted for the spermicide used therein.

EXAMPLE XI

The procedure of Example X is repeated except that 10 percent by weight of spermicide is substituted for the 5 percent used therein.

EXAMPLE XII

The procedure of Example X is repeated except that 15 percent by weight of spermicide is substituted for the 5 percent used therein.

EXAMPLE XIII

The procedure of Example VII is repeated except that an equal weight of each of ricinoleic acid, and phenyl mercuric acetate is substituted for the 5 percent by weight of Triton X-100 used therein.

EXAMPLE XIV

Several fibers as produced in Example II are dissolved in saline solution and are added to rabbit semen samples in vitro. Immobilization of the sperm is observed to occur. Similar results are obtained when the fibers of Examples I–XIV are utilized in this manner.

What is claimed is:

1. A composition of matter comprising an intimate admixture of a thermoplastic, physiologically-inert hydroxypropyl cellulose or hydroxypropylmethyl cellulose polymer soluble in vaginal fluids shaped as an intra-vaginal medicament applicator and up to 30 weight percent of a vaginal medicament, said intimate mixture having been melt spun by being melted, spun, cast, molded or extruded in the molten state into a fibrous mass of fine fibers, strands, pellets, balls or wads, the entire mass totally dissolving in said vaginal fluid within about 24 hours.

2. The composition of claim **1** wherein the polymer is hydroxypropyl cellulose.

3. The composition of claim **2** in which the medicament is a spermicide, ovacide, antimicrobial, prostaglandin, steroidal or non-steroidal antifertility agent.

4. The composition of claim **3** wherein the medicament is a spermicide.

5. The composition of claim **4** wherein the spermicide is present in an amount ranging from 5 to 25 percent by weight based on the weight of the entire composition.

6. The composition of claim **5** wherein the polymer is a hydroxypropyl cellulose.

7. The composition of claim **6** wherein the spermicide is nonylphenoxypoly(ethoxy)$_n$ ethanol wherein n is 9.

8. The composition of claim **6** wherein the spermicide is p-diisobutylphenoxypolyethoxy ethanol.

9. The composition of claim **5** wherein the polymer is a hydroxypropylmethyl cellulose.

10. The composition of claim **9** wherein the spermicide is nonylphenoxypoly(ethoxy)$_n$ ethanol or p-diisobutylphenoxypolyethoxy ethanol wherein n is a number up to 21.

11. The composition of claim **6** wherein the composition is in the form of a fibrous mass having a fiber diameter of from 0.0004 to 0.0015 inches, and a bulk density of from 0.11 to 0.15 gms. per cubic cm.

12. The composition of claim **11** wherein the spermicide is nonylphenoxypoly(ethoxy)$_n$ ethanol or p-diisobutylphenoxypolyethoxy ethanol wherein n is a number up to 21.

13. The method for delivering a vaginal medicament to a site within the vagina from a solid medicament delivery system which comprises introducing within the vagina an effective amount of the composition of claim **1**.

14. The method of claim **13** wherein the composition employed is from 5 to 25 percent by weight of a spermicide admixed in a hydroxypropyl cellulose.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,875,300 Dated April 1,1975

Inventor(s) Roger Homm and Gilbert Katz

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Page 1, in Title, "COMPOSITIN" should read --- COMPOSITION ---.

In Column 1, line 1, in Title, "COMPOSITIN" should read --- COMPOSITION ---.

In Column 2, line 7, "anti-fertility" should read --- antifertility ---.

In Column 2, line 63, The word cotton should be in quotation marks.

In Column 4,line 10, "Wilmington, Del., having" should read --- Wilmington, Del.), having ---.

Signed and Sealed this

fifth Day of *August 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks