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(54) Suppositories

(57) Hydrated bioadhesive suppository formulations for use e.g. as vaginal suppositories are formed of one or more hydrophilic polymers, such as sodium carboxymethyl cellulose, polyacrylic acids or polyacrylates, a pessary or suppository base, water in amounts in excess of 30% by weight of the formulation, and a medicament.

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BIOADHESIVE SUPPOSITORY PHARMACEUTICAL PREPARATIONS

The present invention relates to bioadhesive suppository pharmaceutical preparations which contain one or more hydrophilic polymers and relatively large amounts of water, that is, in excess of 30% by weight of the preparation, to obtain improved adherence and retention of water-soluble or water-insoluble medicament at a desired site.

It is of great advantage to both the patient and the clinician that medication be formulated so that the active drug therein be released over extended periods of time thereby resulting in reduced dosage frequency. The literature is replete with various dosage forms from which the drug may be released for an extended period of time including oral tablets, osmotic pressure devices, and dispensers utilizing semi-permeable membranes. In recent years, polymers, such as hydrophilic polymers, examples of which include hydroxypropylmethyl cellulose and other cellulose ethers, have been developed for use in sustained release compositions as disclosed

in U. S. Patents Nos. 4,389,393 to Schor et al, 4,357,469 to Schor, 3,870,790 to Lowey et al, 4,369,172 to Schor et al and 4,226,849 to Schor et al.

U. S. Patent No. 3,312,594 to Cyr et al discloses a long-lasting troche which contains a medicament and equal portions of pectin, gelatin and carboxymethylcellulose; the troche interacts with saliva to dissolve in the mouth to form an adhesive composition which secures and retains the medicament to the oral mucosa.

U. S. Patent No. 3,984,571 to Chen discloses a liquid carrier for a diagnostic or therapeutic agent which liquid carrier includes a fine particle size hydrocolloid, such as a cellulose ether, suspended in a non-aqueous water-immiscible mobile liquid. When a composition containing the diagnostic or therapeutic agent in the liquid carrier is made to contact a moist surface, the mobile liquid is drained off and the hydrocolloid (carrying the diagnostic or therapeutic agent) attaches itself to the surface.

U. S. Patent No. 4,542,020 to Jackson et al discloses antifungal suppository formulations which are substantially free of water which include an antifungal agent such as nystatin together with a hydrocolloid, such as sodium carboxymethyl cellulose or hydroxypropylmethyl cellulose and a low melting suppository base.

Noro et al, "Studies of Pharmaceutical Drug Design for Suppositories. I. Effect of Physicochemical Properties of Surfactants and Polymers on Emulsion-Type Bases", [Chem. Pharm.

Bull. 30 (8) 2900-2905 (1982)], disclose suppositories containing a suppository base such as Witepsol S55 (which contains surfactant), water, polymers such as sodium carboxymethyl cellulose or sodium polyacrylate, at least 0.5% of added surfactant, the latter two ingredients being primarily present to stabilize the emulsion formed from the water and suppository base. Noro et al form their suppositories by hydrating the polymer by mixing with water, in the presence of surfactant, and then add the suppository base.

U. S. Patent No. 4,265,875 to Byrne et al discloses controlled release suppositories which contain a polymer such as hydroxypropylmethyl cellulose (present in 30 to 65 parts by weight), water (present in 35 parts to 70 parts by weight) and a water-soluble therapeutically active ingredient. The Byrne et al suppository does not include a suppository base and consequently does not melt in vivo but retains its shape until evacuation.

In accordance with the present invention, a long-lasting bioadhesive suppository formulation is provided which has improved retention of water-soluble or water-insoluble medicament at a desired treatment site and requires reduced dosage frequency. The bioadhesive suppository formulation of the invention is formed of a water-soluble or water-insoluble therapeutically active ingredient or medicament, a water-soluble or water-insoluble hydrophilic polymer or hydrocolloid which hydrates,

becomes adhesive and increases retention time of the medicament at the treatment site, water in an amount of at least about 30% by weight of the formulation, and a low-melting suppository base composition which melts at body temperature, forms an emulsion with the water, and promotes dispersion of hydrocolloid and medicament about desired areas.

Thus, in essence, the suppository formulation of the invention is easily applied and melts at body temperature soon after insertion at the desired site to release a water-soluble hydrophilic polymer or hydrocolloid which adheres to the membranes at the desired site and retains a uniform distribution of medicament at the desired site to provide long-lasting treatment.

In effect, the suppository formulation when inserted at the desired site, such as the vagina or rectum, melts in vivo, due to body heat, forms an emulsion with the water, the resulting emulsion breaks down with oil and aqueous phases separating, and the medicament becomes entrapped in the gel structure of the hydrated hydrophilic polymer which adheres at the desired site.

The hydrated hydrophilic polymer thus aids in retaining medicament at the desired site of action.

The suppository formulation of the invention includes a water-soluble or water-insoluble medicament in an amount within the range of from about 0.1 to about 25% by weight depending upon the particular medicament employed, a hydrocolloid to impart adhesive qualities in an amount within the range of from about 0.5 to about 20% by weight and

preferably from about 1 to about 15% by weight, water in an amount within the range of from about 30 to about 65% and preferably from about 35 to about 50% by weight, and a low-melting suppository base in an amount within the range of from about 25 to about 70% by weight and preferably from about 30 to about 65% by weight, all of the above % being based on the total weight of the pessary or suppository formulation.

In addition, in accordance with the present invention, a method is provided for treating vaginal fungal infections, which method includes the steps of inserting in the vaginal cavity of a mammalian species, such as humans, cats, dogs and the like, in need of such treatment, a therapeutically effective amount of the suppository formulation containing an antifungal agent as described herein and allowing the formulation to slowly melt in the vaginal cavity and adhere to the vaginal membrane.

The medicament which may be employed in the suppository formulation of the invention may be water-soluble or water-insoluble and may include antifungal agents (as described below), antibacterials (such as metronidazole, erythromycin, gentamycin or mupirocin), anti-cancer agents (such as 5-fluorouracil), anti-inflammatory agents (such as hydrocortisone, other known steroids (such as prednisone, prednisolone, triamcinolone, dexamethasone, and betamethasone), hormones (such as oestriol), spermicides (such as D-propanolol or 9-nonoxynol), analgesic and anti-inflammatory agents such as acetaminophen, phenacetin, aspirin,

aminopyrine, sulpyrine, phenylbutazone, mefenamic acid, flufenamic acid, Ibufenac, ibuprofen, indomethacin, colchicine, and Probenecid, and anti-viral gents (such as acyclovir, ribavarin, trifluorothyridine or idoxuridine). The medicament will be present in an amount within the range of from about 0.1 to about 25% and preferably from about 0.2 to about 15% by weight depending upon the particular medicament employed and the desired site of action.

Suppositories containing such medicaments in accordance with the present invention may be administered up to two times per day or any convenient regimen, such as one suppository once or twice a day, preferably one suppository, once a day.

In preferred embodiments, the suppository formulation of the invention will contain one or more antifungal agents, preferably nystatin, or imidazole agents, such as clotrimazole, in sufficient quantities to maintain an effective concentration for sufficient periods of time so as to produce adequate kill of C. albicans. Thus, the suppository formulation will contain from about 0.1 to about 6% by weight antifungal agent, such as nystatin, and preferably from about 1 to about 4% by weight based on the total formulation or from about 3 to about 25% and preferably from about 10 to about 20% by weight antifungal agent such as clotrimazole. In preferred embodiments, the formulation will provide from about 25,000 to about 500,000 and preferably from about 75,000 to about 250,000 units nystatin or from about 5 mg to about

100 mg and preferably from about 15 mg to about 50 mg nystatin per suppository based on a potency of 5000 units/mg nystatin.

Other antifungal agents which may be incorporated in the suppositories of the invention include, but are not limited to amphotericin B, griseofulvin, miconazole, ketoconazole, econazole, and other conventional topically active imidazole antifungal agents which may be administered by suppository dosage form.

The antifungal suppositories such as the nystatin or clotrimazole suppositories may be administered up to two times per day or any convenient regimen, such as one suppository once or twice a day, preferably one suppository once a day.

In addition, the suppositories of the invention may include, together with the antifungal agent, one or more antibacterial agents which may be used to treat bacterial infections in the vaginal cavity, such as, for example, neomycin, gentamycin, tyrothricin, gramicidin, and other conventional topically active antibacterial agents which may be administered by suppository dosage form. The antibacterial agent may be employed in amounts of from about 0.05 to about 5% by weight of the total suppository formulation.

The hydrophilic polymers or hydrocolloids which may be present in the suppository formulation of the invention are water-soluble or water-swellable polymeric substances such as cellulosic polymers and gums. The hydrocolloid will preferably comprise cellulose polymers which are cellulose ethers such as methyl cellulose,

cellulose alkyl hydroxylates such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxyethyl cellulose, cellulose alkyl carboxylates such as carboxymethyl cellulose and carboxyethyl cellulose, and alkali metal salts of cellulose alkyl carboxylates, such as sodium carboxymethyl cellulose and sodium carboxyethyl cellulose, or acrylic acid homo- or copolymers or alkali metal salts thereof.

The molecular weight and the degree of ether substitution of the cellulose ether are not critical, and all commercially available products can be used in this invention.

Preferably, the cellulose ether used in this invention has a viscosity, determined for its 2% by weight aqueous solution of 20°C, of 3 to 100,000 centipoises, more preferably 3 to 10,000 centipoises, especially preferably 6 to 6,000 centipoises.

Furthermore, the cellulose ether used in this invention has an ether substitution degree of preferably 0.1 to 6.0, more preferably 0.4 to 4.6.

The degree of ether substitution denotes the average number of ether groups for three hydroxyl groups per glucose unit constituting the cellulose.

The copolymer of acrylic acid used in this invention denotes a copolymer derived from acrylic acid and allyl sucrose, methyl acrylate, methacrylic acid, methyl methacrylate, hydroxyethyl methacrylate, styrene or a vinyl-type ether monomer such as methyl vinyl ether.

The ratio of the comonomer can be varied within the range in which the copolymer is maintained water-soluble or water-swellable. It is generally not more than about 20 mole % based on the copolymer.

A mixture of the homo- or copolymer of acrylic acid readily available on the market with a minor amount (usually, not more than about 20% by weight) of another water-soluble polymer (such as a homo- or copolymer of methacrylic acid or its salt, or polyethylene glycol) can also be used as the acrylic acid homo- or copolymer in this invention.

Suitable pharmaceutically acceptable salts of the acrylic acid homo- or copolymer include alkali metal salts such as sodium or potassium salt and ammonium salts. The degree of neutralizing of the salts is not limited. The acrylic acid homo- or copolymer or its pharmaceutically acceptable salts may have any molecular weight. Desirably, they have a viscosity, measured at 25.0°±0.5°C for an aqueous solution of a sodium salt thereof having a pH of 7 to 7.5 and a concentration of 0.2% by weight as the acrylic acid homo- or copolymer, of generally 360 to 165,000 centipoises, preferably 3,600 to 16,500 centipoises.

The homo- or copolymers of acrylic acid or pharmaceutically acceptable salts thereof in this

invention may be used singly or as a mixture of two or more.

It is to be understood that other known hydrocolloids may be employed in the present invention, including, for example, gum acacia, guar gum, gum tragacanth, gum xanthan, pectin, ammonium or sodium alginate or mixtures thereof.

Preferred hydrocolloids are sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose (such as Celacol HPM or Methocel E or K) or polyacrylic acid (such as Carbopol 934P).

The low-melting suppository base suitable for use in the suppository formulation of the invention will have a melting point of less than 90 to 95°F so that after insertion, it will melt in the vagina or rectum. The suppository base will be of conventional formulation and may include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, fatty acid esters of polyethylene glycol, and mixtures of mono-, di- and triglyerides which are glyceryl esters of mixtures of vegetable C_{12}-C_{18} fatty acids (predominantly lauric acid) derived from palm seed oil such as coconut oil and palm kernel oil) and less than 0.5% surfactant, such as Polysorbate 80 or Cetomacrogol 1000.

The suppository formulation of the invention may also include other conventional ingredients such as amine neutralizing agents, to achieve a pH of from about 4 to about 8.5 in the suppository base-water emulsion and ensure solubilization of the hydrocolloid, for example, polyacrylic acid.

Examples of such neutralizing agents include PEG 15-cocamine (aslo referred to as Ethomeen C-25) diisopropanolamine, triethanolamine, b-dimethyl-aminopropionitrile dodecylamine, morpholine,

In addition, the formulation can include emulsion stabilizers, lubricants and coloring agents. The lubricants include talc, stearic acid, stearate salts and waxes. Examples of emulsion stabilizers include polyethylene glycols 200, 400. 600, 1000, polyvinylalcohols or polypropylene glycols 200, 400, 600 (in amounts of from about 0.05 to about 10% by weight of the total formulation).

A discussion of pessary and suppository base formulations suitable for use herein and methods for preparing same are set out in Remington's "Pharmaceutical Sciences, Sixteenth Edition (Mack Publishing Co., Pa.), pages 1530 to 1533.

Preferred suppository formulations of the invention are set out below.

Ingredient	Mg/Suppository
Medicament	
Nystatin or	5 to 50
Imidazole antifungals, such as clotrimazole, miconazole, econazole or tioconazole	50 to 500
Hydrophilic polymer (sodium carboxymethyl cellulose or hydroxypropyl-methyl cellulose or Carbopol)	10 to 400
Water	600 to 1300
Low melting suppository base	500 to 1900

Preferred suppository bases are Witepsol S55, Witepsol S58, mixtures thereof, or mixtures of either or both with Witepsol W35 and/or Witepsol H15. Witepsol suppository base is a mixture of mono-, di- and triglycerides which are glyceryl esters of mixtures of vegetable fatty acids derived from palm seed oils such as coconut oil and palm kernel oil, and includes C_{12} to C_{18} acids in which lauric acid predominates.

Witepsol W35 has a melting point range of 33.5 to 35.5°C, a solidification point range of 27 to 32°C and a hydroxy value of 40 to 50.

Witepsol H15 has a melting point range of 33.5 to 35.5°C, a solidification point range of 32.5 to 34.5°C and a hydroxy value of 15.

Witepsol S55 has a melting point range of 33.5 to 35.5°C, a solidification point range of 25 to 33°C and a hydroxy value of 50 to 65.

Witepsol S58 has a melting point range of 32 to 33.5°C, a solidification point range of 27 to 29°C and a hydroxy value of 60 to 70.

The suppository formulation of the invention may be prepared by employing conventional pessary and suppository formulating and processing techniques. In a preferred method, the suppository base material is heated to melting and maintained at a temperature not in excess of 45°C until the base is fully melted. The temperature of the mass is reduced to 40°C, a suitable stirrer is introduced and stirring is commenced. Water and optionally neutralizing agent (where the hydrocolloid to be added is an acrylate polymer) are added to form an emulsion having a pH within the range of from about 4 to about 8.5; medicament is then added followed by hydrocolloid. Stirring is continued until a relatively uniform suspension is formed at which time stirring is discontinued, the stirrer is removed and the mass is poured into appropriate molds to form suppositories upon cooling. Throughout the above-described process, the temperature of the mass is maintained above 36-37°C.

The following working Examples represent preferred embodiments of the present invention. Unless otherwise indicated, all temperatures are expressed in degrees Centigrade.

Example 1

An antifungal suppository formulation in accordance with the present invention having the following composition was prepared as described below.

Ingredient	Amount (g)
Nystatin (equivalent to 100 units of drug per mg of product based on a nystatin potency of 5000 units mg^{-1})	0.58
Hydrocolloid (sodium carboxymethyl-cellulose)	0.6
Water	9.4
Low-melting suppository base (Witepsol S58)	19.4

The Witepsol S58 was heated to melting (about 35°) and retained at about 45° until the other components were ready to be added. The temperature of the mass was reduced to 40° by cooling in air with stirring and the resulting liquid was stirred. Water was added and the mixture mixed in a Silverson mixer to form an emulsion. Nystatin was then added followed by hydrocolloid (sodium carboxymethylcellulose). Stirring was continued for 10 minutes until a uniform suspension was formed. Throughout the above procedure, the temperature of

the various mixes was maintained above about 36-37°.

Stirring was then discontinued and the resulting liquid suspension was poured into suitable molds to form 1 g suppositories.

Example 2

Nystatin suppositories (1 g each) of the following composition were prepared following the procedure of Example 1 except neutralizing agent was added with the water so that a pH of 6 was achieved with the emulsion and Witepsol S55 was used as the suppository base.

Ingredient	Amount (g)
Nystatin (equivalent to 100 units of drug per mg of product based on a nystatin potency of 5000 units mg^{-1})	0.58
Hydrocolloid (polyacrylic acid - Carbopol 934P)	0.5
Water	17.7
Low melting suppository base (Witepsol S55)	10
Neutralizing agent (PEG 15-cocamine-Ethomeen C-25)	1.25

Examples 3 to 5

Clotrimazole suppositories of the following composition were prepared following the procedure similar to that described in Example 1.

Ingredient	Amount (g) Ex. 3	Ex. 4	Ex. 5
Clotrimazole	0.5	0.5	0.5
Hydrocolloid (sodium carboxymethyl cellulose	0.06	0.3	0.2
Water	0.9	0.9	1.1
Low melting suppository base (Witepsol S58)	1.9	1.7	1.7

Example 6

Clotrimazole suppositories of the following composition were prepared following the procedure similar to that described in Example 2 except polyethylene glycol 400 (stabilizer-emulsifier) was added with the water.

Ingredient	Amount (g)
Clotrimazole	0.5
Hydrocolloid (Na carboxymethyl cellulose)	0.06
Water	0.9
Low melting suppository base (Witepsol S58)	1.8
Polyethylene glycol 400	0.2

CLAIMS

1. A bioadhesive suppository formulation comprising a medicament in an amount within the range of from about 0.1 to about 25% by weight of the total formulation, a hydrocolloid in an amount within the range of from about 0.5 to about 20% by weight of the formulation, water in an amount within the range of from about 30 to about 65% by weight of the formulation, and a low-melting suppository base, whereupon shortly after insertion of said suppository at the desired site of action, said suppository base melts and forms an emulsion from which said hydrocolloid and medicament are released to adhere to and be retained at the desired site of action.

2. The formulation as defined in Claim 1 wherein the medicament is an antifungal agent.

3. The formulation as defined in Claim 2 wherein the antifungal agent is nystatin, clotrimazole, amphotericin B, miconazole, ketoconazole or griseofulvin.

4. The formulation as defined in Claim 3 wherein the suppository formulation contains from about 25,000 to about 500,000 units of nystatin.

5. The formulation as defined in Claim 1 wherein said hydrocolloid is a cellulose polymer.

6. The formulation as defined in Claim 1 wherein said cellulose polymer is a cellulose ether, a cellulose alkyl hydroxylate, a cellulose alkyl carboxylate or an alkali metal salt of a cellulose alkyl carboxylate, an acrylic acid homo- or copolymer or salt thereof, or mixtures thereof.

7. The formulation as defined in Claim 1 wherein said hydrocolloid is sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose or polyacrylic acid.

8. The formulation as defined in Claim 2 wherein said antifungal agent has an average particle size of within the range of from about 1 to about 50 microns.

9. The formulation as defined in Claim 1 wherein said water is present in an amount within the range of from about 35 to about 50% by weight of said formulation.

10. The formulation as defined Claim 1 further including one or more antibacterial agents in an amount of from about 0.05 to about 5% by weight.

11. The formulation as defined in Claim 10 wherein said antibacterial agent is neomycin, gentamycin, gramicidin or tyrothricin.

12. The formulation as defined in CLaim 7 wherein such hydrocolloid is polyacrylic acid and including an amine neutralizing agent.

13. The formulation as defined in Claim 1 including an emulsion-stabilizer.

14. A method for treating candidiasis in the vaginal cavity which comprises administering to the vaginal cavity of a mammalian species in need of treatment a therapeutically effective amount of the suppository formulation as defined in Claim 2 and allowing the formulation to melt in the vaginal cavity and adhere to the vaginal membrane.

15. The method as defined in Claim 4 wherein the suppository formulation contains

nystatin in an amount of from about 15 to about 25 mg per suppository based on a potency of 5000 units per mg and is administered in a single dose once daily.

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