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Medicated Suppository

This invention relates to a medicated suppository for vaginal or rectal application. In particular the invention relates to a medicated suppository capable of releasing the contained medicament evenly over the walls of the vaginal or rectal cavity. The invention is a triglyceride based suppository and is additionally comprised of a medicament, a gel forming agent and a gel dispersing agent.

The administration of medicaments in the form of suppositories is known in the art. In general usage, however, it has been found that upon liquefaction of the suppository some of the fluid containing the medicament flows out of the vaginal or rectal cavity leaving less of the medicament available for the intended therapeutic use. To counteract this loss of medicament, higher concentrations of the medicament are sometimes employed. As a result, the patient is exposed to higher doses of the medicament than are actually required for successful treatment. In addition, the cost of the therapy is of necessity higher due to the use of excess medicament.

The suppository of the present invention is comprised of a triglyceride as the carrier, a gel forming agent and a gel dispersing agent in combination with a medicament. The desired therapeutic effect is achieved by a diffusion of the medicament throughout the vaginal or rectal cavity by means of the dispersing agent and the adhesive properties of the gel forming agent which combine to prevent the liquified suppository from flowing out of the vaginal or rectal cavity. The availability of the medicament is thus increased by the resultant increase in the surface of absorption and the extension of the time during which the medicament resides in the vaginal or rectal cavity. The unique combination of ingredients results in a homogeneous composition which is capable of distributing the

medicament throughout the vaginal or rectal cavity. This results in the administration of smaller doses of the medicament than those required in conventional suppositories.

According to the present invention, a triglyceride is employed as the carrier in the suppository. Mixtures of mono-, di- and triglycerides of the fatty acids $C_{10}H_{20}O_2$ to $C_{18}H_{30}O_2$ (hard fat commonly known in the art as Adeps solidus) may be employed. The triglyceride is present in an amount of about 60- 87% by weight.

As the gel forming agent materials such as polygum, guar, alkali metal and alkaline earth metal salts of alginic acid, polygel and xanthan may be employed. The gel forming agent is present in an amount of about 5-25% by weight.

As the gel dispersing agent materials such as stearyl heptanoate, purcelline oil, mixtures of triglycerides of saturated fatty acids, partial fatty acid glycerol esters and surface active agents such as Tween* may be employed. The gel dispersing agent is present in an amount of about 4-8% by weight.

The formulation may be employed with one or more of a number of known medicaments including antibiotics such as tetracycline hydrochloride, erythromycin, neosporin, achromycin and chloromycetin, for example; antimycotics such as econazole nitrate, miconazole nitrate and clotrimazole, for example; anti-inflammatory agents such as aspirin, clocortolone pivalate, hydrocortisone, tolmetin sodium and indomethacin, for example; estrogens; trichomonacids; anti-inflammatory agents and disinfectants. The amount of medicament present in the suppository will depend upon the particular medicament employed; however, amounts of about 4-15% by weight of a given medicament may be employed.

*"Tween" is a registered Trade Mark.

In certain formulations better homogenicity may be obtained by the use of a stabilizer for the colloidal suspension. Colloidal silicon dioxide and urea can be used as the stabilizing agent. In those cases where the medicament is only moderately soluble in the suppository formulation, a solubilizing agent such as sorbitan monostearate or polyethylene glycol may be employed. With certain medicaments, it may be necessary to employ a preservative such as benzoic acid, for example, or an anti-oxidant such as butylated hydroxytoluene, for example, in the formulation.

The suppository of the present invention is generally prepared by first mixing the gel forming agent and the medicament in a suitable vessel and micronizing the mixture. The medicament is added in portions; after each addition the granules are pressed through a sieve and the mixing is continued for several minutes. In a separate vessel the fatty acid triglyceride and the gel dispersing agent are melted together at a temperature of about 50-60°C. The melt is cooled to about 40°C. The two mixtures are combined with stirring and the combined mixture is then homogenized for about 10 minutes at a temperature between 38-40°C. The mixture is then cooled to about 36-39°C and placed in a suppository shell. If a stabilizing agent is to be employed in the suppository, it is generally added to the mixture of the fatty acid triglyceride and the gel dispersing agent after the melt has been cooled. The solubilizing agents and preservatives, when employed, can be added at various stages during the procedure.

Although the suppository of the present invention may be prepared in a variety of shapes, the preferred shape is an egg-shaped ovule. The suppository has a weight between 1 and 3 g. The preferred weight is about 2.2-2.7 g.

A more detailed description of the process according to the invention is described in Procedure 1.

Procedure 1

A. Polygel (24 Kg) is placed in a mixing vessel. Econazole nitrate (8 Kg) is added in portions and the mixture is micronized and mixed for 5 minutes. After each addition of econazole nitrate, the granules are pressed through an 0.4 mm sieve and then mixed for 10 minutes.

B. In a separate vessel adeps solidus (Witepsol* H 19; 64.72 Kg), adeps solidus (Wecobee FS; 269.18 Kg) and stearyl heptanoate (21.82 Kg) are added together and the mixture is melted at 50-60°C. The melt is cooled to 40°C, colloidal silicon dioxide (4.32 Kg) is added and the mixture is homogenized for 5 minutes. This mixture is then combined with the mixture prepared in A above with stirring and the resulting mixture is homogenized for 10 minutes at 38-40°C under vacuum. The homogenate is then cooled to 36-39°C *in vacuo* and placed in a multiplast container.

The following are examples of suppositories falling within the present invention.

Example 1

	mg/suppository
Econazole nitrate	150.0
Polygel	300.0
Colloidal silicon dioxide	27.0
Adeps solidus (Witepsol H 19)	404.2
Adeps solidus (Wecobee FS)	1682.4
Stearyl heptanoate	136.4

* "Witepsol" is a registered Trade Mark.

Example 2

	mg/suppository
Metronidazole	350.0
Alginate	350.0
Colloidal silicon dioxide	27.0
Adeps solidus (Novata 299)	413.0
Adeps solidus (Wecobee FS)	1410.0
Softigen 701	150.0

Example 3

Estriol	0.5
Benzoic acid	0.8
Butylated Hydroxytoluene	0.5
Polygel	300.0
Polyethylene glycol 400	60.0
Polyethylene glycol 1000	300.0
Sorbitan monostearate (Span*60)	215.0
Adeps solidus (Witepsol S 55)	1823.2

Example 4

Sulfathiazole	170.0
Sulfacetamide	145.0
Sulfabenzamide	180.0
Urea	32.0
Polygel	300.0
Adeps solidus (Witepsol H 12)	1873.0
Gel dispersing agent	Q.S.**

* "Span" is a registered Trade Mark.

** To provide 4-8% by weight.

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Example 5

	mg/suppository
Chlorquinaldol	200.0
Oxychinolin sulfate	10.0
Polygum (Guar)	350.0
Colloidal silicon dioxide	25.8
Adeps solidus (Witepsol H 19)	429.7
Adeps solidus (Wecobee FS)	1547.0
Stearyl heptanoate	137.5

The suppositories prepared according to the above examples liquefy in body fluids in less than thirty minutes at about 37°C.

The above examples are provided by way of illustration and are not meant to limit the scope of the present invention, the scope of which is defined by the appended claims.

The adeps solidus "Witepsol H 19" mentioned above melts at 33.5-35.5°C and has a hydroxyl value of 20-30. The adeps solidus "Wecobee FS" mentioned above melts at 38-42°C and has a hydroxyl value not more than 10.

CLAIMS

1. A medicated suppository comprising about 60-87% by weight of a mixture of triglycerides of the fatty acids $C_{10}H_{20}O_2$ to $C_{18}H_{30}O_2$; 5-25% by weight of a gel forming agent; 4-8% by weight of a gel dispersing agent and 4-15% by weight of a medicament.

2. The medicated suppository of Claim 1 wherein the gel forming agent is selected from polygum, guar, alkali metal and alkaline earth metal salts of alginic acid, polygel and xanthan.

3. The medicated suppository of Claim 1 or 2 wherein the gel dispersing agent is selected from stearyl heptanoate, purcelline oil, mixtures of triglycerides of saturated fatty acids, partial fatty acid glycerol esters and surfactants.

4. The medicated suppository of Claim 1,2 or 3 wherein the medicament is selected from econazole nitrate, miconazole nitrate and clotrimazole.

5. The medicated suppository of Claim 1 which comprises 5.56% by weight of econazole nitrate, 11.11% by weight of polygel, 1.0% by weight of colloidal silicon dioxide, 14.97% by weight of an adeps solidus melting at 33.5-35.5°C and having a hydroxyl value of 20-30, 62.31% by weight of an adeps solidus melting at 38-42°C and having a hydroxyl value not more than 10, and 5.05% by weight of stearyl heptanoate.

6. A suppository base comprising 60-87 parts by wt of a mixture of triglycerides of the fatty acids $C_{10}H_{20}O_2$ to $C_{18}H_{30}O_2$; 5-25 parts by wt of a gel forming agent and 4-8 parts by wt of a gel dispersing agent; these three constituents totalling 85-96 parts by wt.

7. The suppository base of Claim 6 wherein the gel forming agent is selected from polygum, guar, alkali metal and alkaline earth metal salts of alginic acid, polygel and xanthan.

8. The suppository base of Claim 6 or 7 wherein the gel dispersing agent is selected from stearyl heptanoate, purcelline oil, mixtures of triglycerides of saturated fatty acids, partial fatty acid glycerol esters and surfactants.

9. The medicated suppository of claim 1, comprising constituents substantially as specified in the foregoing Example 1, 2, 3, 4 or 5.