

1

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SPERMICIDAL VAGINAL PHARMACEUTICAL CONCENTRATE FOR PRODUCING NON-AQUEOUS FOAM WITH AEROSOL PROPELLANTS

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ABSTRACT OF THE DISCLOSURE

The invention provides a new composition of matter comprising a major proportion of propylene glycol in a minor proportion of an ethoxylated tallow alcohol, the composition being adapted to incorporation in foam-producing assemblies.

This invention relates to a new and useful non-aqueous foam-producing pharmaceutical substance, and more particularly to such a substance adapted for use as a medicant in a self-propelled dispenser using fluorinated hydrocarbons or other aerosol propellants.

There is a need for a simple, easily used single-dose contraceptive which can be applied as an aerosol foam into the vaginal canal. There has also been a need for a pharmaceutical vehicle for medicants adapted to be injected into human body cavities that can be used either with or without water, depending upon the stability of the ingredients to be incorporated into the preparation. Thus, it is desirable to have a single base that can be used with various enzymes, antibiotics, and medicinal agents, with or without spermicidal agents.

Accordingly, it is a primary object of the present invention to provide a new and useful non-aqueous foam-producing vehicle.

Another object of the invention is to provide a vehicle of the type described in combination with spermicidal substances.

Another object of the present invention is to provide a foam-producing vehicle that can be used either with or without water and various enzymes, antibiotics, and spermicidal agents.

Yet another object of the present invention is to provide a new and useful non-aqueous foam-producing vehicle which contains ethoxylated tallow alcohol as a foaming agent, emulsifier, detergent, wetting agent, and viscosity builder.

A further object of the present invention is to provide a vehicle of the type described which is also spermicidal.

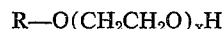
A still further object of the present invention is to provide a vehicle of the type described which is especially suited for use in and in combination with aerosol type applicators for injecting medicants into human body cavities.

A medicinal application of this type is shown and claimed in copending application Ser. No. 407,170, filed Oct. 28, 1964, by the instant inventor, now abandoned.

The non-aqueous foam-producing pharmaceutical substance of the present invention includes a vehicle containing ethoxylated tallow alcohol as a foaming agent, emulsifier, detergent, wetting agent, and viscosity builder. The

2

ethoxylated alcohol is a condensate of pressure-hydrogenated tallow alcohol. The general formula is



with R being a combination of $CH_3(CH_2)_{16}CH_2OH$ (stearyl alcohol 62%), $CH_3(CH_2)_{14}CH_2OH$ (cetyl alcohol 33%), and $CH_3(CH_2)_{12}CH_2OH$ (myristyl alcohol 5%) and the x ranging from three to eleven moles of ethylene oxide.

Propylene glycol U.S.P. may serve as a solvent, preservative, and emollient, and propylhydroxyparaben U.S.P. and methylhydroxyparaben U.S.P. are used as preservatives. In preparing the vehicle, 80 grams of propylene glycol U.S.P. are heated to approximately 50 degrees C. and 0.4 gram of methylhydroxyparaben plus 0.2 grain of propylhydroxyparaben are added and stirred. Two grams of ethoxylated tallow alcohol containing three moles of ethylene oxide, oil-soluble type, are heated to 50 degrees C., and combined with the propylene glycol preservative combination. Ethoxylated tallow alcohol containing from three to eleven moles of ethylene oxide may be used in this formula, depending upon the consistency of foam desired. The product is allowed to cool, and a sufficient amount of propylene glycol U.S.P. is added to make the product weigh 50 grams. Other glycols, as well as glycerol can be used in place of propylene glycol.

Spermicidal preparations are made from this vehicle, as described in the following examples, by dissolving the active ingredients in a sufficient amount of propylene glycol U.S.P. to make 50 grams, and the resulting product is combined with 50 grams of the vehicle to make 100 grams of spermicidal foam concentrate. In some cases, heat must be employed to effect solution. Heat labile substances must be added after cooling.

The non-ionic nature of the vehicle makes possible the addition of cationic or anionic substances without affecting the foam-producing and barrier action of the ingredients. Propylene glycol is an excellent solvent for many organic chemicals. Its solubility with water in all proportions makes possible the addition of aqueous solutions of spermicidal agents. This vehicle mixes quickly with seminal fluid and vaginal secretions, permitting rapid action of the active ingredients. Its surfactant action spreads the spermicide into all surfaces and crevices. The non-aqueous nature of the vehicle minimizes variations in action due to individual variations of moisture present. The viscous base and foam provide barrier action to passage of sperm through the cervix.

The vehicle itself is spermicidal as shown by the Sanderson-Cramer method of spermicidal evaluation. The vehicle, when diluted with two parts of buffered fructose solution, kills human sperm in twenty seconds. The buffered fructose solution contained three percent fructose, 0.24% anhydrous phosphate, 0.01% monopotassium phosphate, 0.2% sodium chloride, and distilled water (q.s.).

When diluted with an equal volume of propylene glycol U.S.P., the vehicle of the present invention produces a foam with propellants from an aerosol container of the types shown and described in said copending application. A partial emulsification results when the foam concentrate is shaken with fluorinated hydrocarbons or

other aerosol propellants. When released in the manner described in said copending application, an excellent foam is produced. The ratio of vehicle to added propylene glycol can be altered to vary the foam consistency or to compensate for viscosities of added substances. Because of the insolubility of the ethoxylated tallow alcohols in water, the latter can be added to stiffen the foam where it does not affect the stability of added substances.

The formulation has been shown to be non-toxic to the mucosa of the human vagina and cervix. An amount in excess of that ordinarily used, namely 5 grams of the liquid foam concentrate, was applied to the cervical mucosa of six office patients and examination made the next morning. No indications of inflammation were seen, even on repeated application.

The vehicle of the present invention is stable over long periods of time and maintains the stability of added ingredients which are unstable in aqueous vehicles of the prior art.

The following are typical examples of the non-aqueous foam-producing pharmaceutical substance of the present invention:

EXAMPLE 1

A non-aqueous foam-producing vehicle was prepared by heating 80 grams of propylene glycol U.S.P. to 50 degrees C. Then 0.4 gram of methylhydroxyparaben and 0.2 gram of propylhydroxyparaben were added and stirred. Next, 2 grams of ethoxylated tallow alcohol of the general formula $R-O(CH_2CH_2O)_xH$ containing three moles of ethylene oxide of the oil-soluble type were heated to 50 degrees C., and combined with the propylene glycol preservative combination. This mixture was allowed to cool and a sufficient amount of propylene glycol U.S.P. was added to make the product weigh 50 grams.

EXAMPLE 2

The product of Example 1 was prepared in the manner of Example 1 except that the ethoxylated tallow alcohol contained four moles of ethylene oxide.

EXAMPLE 3

The product of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained five moles of ethylene oxide.

EXAMPLE 4

The product of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained six moles of ethylene oxide.

EXAMPLE 5

The product of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained seven moles of ethylene oxide.

EXAMPLE 6

The product of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained eight moles of ethylene oxide.

EXAMPLE 7

The product of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained nine moles of ethylene oxide.

EXAMPLE 8

The product of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained ten moles of ethylene oxide.

EXAMPLE 9

The produce of Example 1 was prepared in accordance with the steps of Example 1 except that the ethoxylated tallow alcohol contained eleven moles of ethylene oxide.

EXAMPLE 10

A product was prepared in accordance with each of the preceding examples except that, in each case, eighty grams of glycerol USP were used in place of the propylene glycol.

EXAMPLE 11

	Grams
Aliphatic polyoxyethylene ether (100% active, Made from commercial tridecyl alcohol and ethylene oxide to give material with an inverse cloud point of approximately 40-42 C. The material is made by standard ethoxylation technique) -----	5
The vehicle of Example 1 -----	50
Propylene glycol q.s. ad -----	100

The aliphatic polyoxyethylene ether provides an excellent spermicide. Its non-ionic nature permits its combination with anionic or cationic agents without any change in spermicidal or antibiotic power. This composition produces an excellent foam when combined with propellants in aerosol containers. The ratio of propylene glycol to vehicle can be altered to produce varied consistency of foam.

EXAMPLE 12

	Grams
Aliphatic polyoxyethylene ether (100% active, described in Example 11) -----	5
Lactic acid 85% U.S.P. -----	0.5
Distilled water -----	10
Vehicle of Example 1 -----	50
Propylene glycol U.S.P. q.s. ad -----	100

Sufficient acid has been added to this product to produce a pH of 4.0 which increases the spermicidal power because it produces a condition resembling the vaginal pH of 4.5. Water has been added to aid in the ionization of the acid because the effect of acids in spermicides depends upon the extent to which they ionize.

EXAMPLE 13

	Grams
Aliphatic polyoxyethylene ether (100% active, described in Example 11) -----	5
Papain -----	1
Vehicle of Example 2 -----	50
Propylene glycol U.S.P. q.s. ad -----	100

Other papainases that could be used with this vehicle are bromelin and ficin. As is known in the art, bromelin and papain intra-vaginally are dilatatory, and possibly indicated in dysmenorrhea as well for removing cervical mucous plugs to permit intrauterine placement of radio-opaque materials in roentgenographic studies. Water has been omitted in Example 13 to increase the stability of the enzyme. Stability studies have shown that these enzymes retain over 50% of their proteolytic activity against standard substrates when left at room temperature for six months.

EXAMPLE 14

	Grams
Aliphatic polyoxyethylene ether (100 active, described in Example 11) -----	5
Trypsin -----	1
Vehicle of Example 3 -----	50
Propylene glycol U.S.P. q.s. ad -----	100

Other pancreatic enzymes that could be used in the foam concentrate include cathepsins and chymotrypsin.

EXAMPLE 15

	Grams
Aliphatic polyoxyethylene ether of Example 11 -----	5
Desoxyribonucleases (a Dornase proteolytic enzyme) -----	1
Vehicle of Example 4 -----	50
Propylene glycol U.S.P. q.s. ad -----	100

EXAMPLE 16

	Grams
Aliphatic polyoxyethylene ether (100% active, described in Example 11) -----	5
Bacterial protease from <i>B. Subtilis</i> -----	1
Vehicle of Example 5 -----	50
Propylene glycol U.S.P. q.s. ad -----	100

Other proteases from microbiological sources included those from *Pseudomonas*, *Clostridia*, and fungi. Hyaluronidase also has been used. The proteolytic enzymes described in Examples 13 through 16 enhance the mucolytic action upon sperm as well as vaginal and cervical mucous, allowing the spermicide to reach the sperm better. The cleansing and anti-inflammatory, antibiotic-enhancing, fibrinolytic, mucolytic, and debriding properties of such enzymes is known. Thus, they can be used in vehicles of the present invention for intravaginal infestations such as vaginitis, leukorrhea, trichomonas, moniliasis, as well as for hygienic and prophylactic purposes by incorporating them alone or in combination with suitable antiseptics, germicides, antibiotics, and peptizing agents such as carbamide. Water has been omitted in Examples 13 through 16 to increase the stability of the enzymes and antibiotics. Stability studies have shown that enzymes retain over 50% of their proteolytic activity against standard substrates when left at room temperature for six months.

EXAMPLE 17

	Grams
Aliphatic polyoxyethylene ether of Example 11 ----	5
Lactic acid 85% U.S.P. -----	0.5
Tyrothricin -----	0.5
Vehicle of Example 6 -----	50
Distilled water -----	10
Propylene glycol U.S.P. q.s. ad -----	100

This combination was formulated for instances where a contraceptive is desired in combination with trichomonal or other antibiotic or where the latter is desired alone in an aerosol foam treatment. It is known that Tyrothricin and Chlortetracycline are more active protozoal agents than streptomycin, chloramphenicol, or penicillin. Tyrothricin possesses many advantages over other antibiotics for use in the vehicle of the present invention. It is odorless and has remarkable stability, being stable in aqueous solutions and propylene glycol for long periods even at summer temperatures. Its solution in propylene glycol may be autoclaved without significant loss of activity. Its solubility in propylene glycol and its compatibility with many organic and inorganic substances makes it uniquely useful with a spermicidal composition. Lactic acid has been added to this composition to maintain a healthier flora in the vagina. As is known, the treatment of trichomonas vaginalis is directed toward cleanliness and maintenance of acid pH in the vagina. Water has been added to the formula to aid in the ionization of the acid.

EXAMPLE 18

	Grams
Aliphatic polyoxyethylene ether of Example 11 ----	5
Tyrothricin -----	0.5
Papain -----	1
Vehicle of Example 7 -----	50
Propylene glycol q.s. ad -----	100

The proteolytic enzymes used in Examples 13 through 16 may be used in this formula. This formula combines the specific treatment of antibiotics for *Trichomonas* with a mucolytic enzyme, such as papain and hyaluronidase. Water has been omitted because of the instability of the proteolytic enzyme in this vehicle.

The formulae given in Examples 11 through 18 were tested for spermicidal activity using the Sanderson-Cramer method of spermicidal testing on human sperm. All sperm were killed in twenty seconds at a 1:50 dilution with the buffered fructose solution discussed hereinbefore. Results

can be expected in vivo that do not show in this test because of the enhanced action of the added enzymes and acids. No appreciable difference in spermicidal action was noted with the addition of antibiotics in vitro.

EXAMPLE 19

	Grams
Aliphatic polyoxyethylene ether of Example 11 ----	5
Hydrocortisone alcohol, micronized -----	1
Vehicle of Example 8 -----	50
Propylene glycol q.s. ad -----	100

Hydrocortisone can be used along with the contraceptive when its anti-inflammatory action is desired. The relative insolubility and its high degree of activity of the alcohol form make it useful, especially where the systemic effects of the glucocorticoid are not desired.

EXAMPLE 20

	Grams
Aliphatic polyoxyethylene ether of Example 1 ----	5
Hydrocortisone alcohol, micronized -----	1
Neomycin sulfate, micronized -----	0.5
Vehicle of Example 1 -----	50
Glycerol q.s. ad -----	100

This formula combines the anti-inflammatory qualities of Hydrocortisone with the anti-pyrogenic action of neomycin plus contraceptive.

EXAMPLE 21

	Grams
Aliphatic polyoxyethylene ether of Example 11 ----	5
Sulfanilamide, micronized -----	10
Vehicle of Example 1 -----	50
Propylene glycol q.s. ad -----	100

Other sulfonamides may be used in place of the sulfanilamide or a combination of two or more may be used. This formula is useful in the post-operative care of the cervix and for secondary invasions of trichomonas vaginalis.

EXAMPLE 22

	Grams
Aliphatic polyoxyethylene ether of Example 11 ----	5
Sulfanilamide, micronized -----	10
Neomycin sulfate, micronized -----	0.5
Vehicle of Example 1 -----	50
Propylene glycol U.S.P. q.s.d. ad -----	100

This formula can be used when the action of a sulfonamide along with an antibiotic is desired plus contraceptive. Another sulfonamide or sulfonamides may be used as well as antibiotics.

EXAMPLE 23

	Grams
Aliphatic polyoxyethylene ether of Example 11 ----	5
Povidone iodine NND -----	1
Vehicle of Example 1 -----	50
Propylene glycol q.s. ad -----	100

The addition of the iodine compound aids in the treatment of non-specific vaginitis and *Candida albicans*, *Monilia*, and *Trichomonas vaginalis* along with a contraceptive.

EXAMPLE 24

Examples were prepared in accordance with each of the thirteen preceding examples (11-23) except that in each case the aliphatic polyoxyethylene ether was omitted.

While the particular embodiments of the present invention herein described in detail are fully capable of attaining the objects and providing the advantages hereinbefore stated, it is to be understood that they are merely illustrative of the presently preferred embodiments of the invention and that no limitations are intended to the specific embodiments herein described other than as defined in the appended claim.

I claim:
 1. A spermicidal vaginal pharmaceutical concentrate for producing non-aqueous foam with aerosol propellants comprising:

- 80 grams of propylene glycol;
- 0.4 gram of methylhydroxyparaben;
- 0.2 gram of propylhydroxyparaben;
- 2 grams of ethoxylated tallow alcohol containing from three to eleven moles of ethylene oxide of the oil-soluble type; said composition of matter being non-aqueous, thereby constituting a stable vehicle for proteolytic enzymes and antibiotics.

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