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(19)

(54) VETERINARY COMPOSITIONS

(71) We, BEECHAM GROUP LIMITED, a British company, of Beecham House, Great West Road, Brentford, Middlesex, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to veterinary compositions containing semi-synthetic penicillin suspensions for use in the treatment of mammary disorders in animals, especially bovine mastitis.

Mammary disorders in animals are conventionally treated by the intramammary administration of suspensions or solutions of an antibacterial agent in a suitable vehicle. It has been found that often such antibacterial agents (such as penicillins) are unstable in aqueous vehicles and thus it is necessary to formulate them for intramammary administration in an oily vehicle to produce a product that has an acceptable shelf-life. The oily vehicles used are usually paraffin oils or vegetable oils such as arachis (peanut) oil.

When such products are used during lactation it is important that the antibacterial agent is eliminated as quickly as possible after the treatment has been effected. In this way a minimum of milk is wasted before the level of antibacterial agent in the milk has been reduced to a level acceptable to the health organisations for human consumption.

We have now discovered that semi-synthetic penicillins suspended in a particular class of oily vehicles on intramammary administration to animals give effective treatment of mammary disorders coupled both with a fast milk out rate and also good stability and shelf-life.

Accordingly the present invention provides a veterinary composition for intramammary administration to animals comprising a suspension of a semi-synthetic penicillin in an oily vehicle, the said oily vehicle comprising tri-glycerides, or propylene glycol di-esters, of fatty acids containing 8–10 carbon atoms.

It will be realised by the skilled man that a semi-synthetic penicillin is a penicillin that is normally prepared by the chemical acylation of 6-aminopenicillanic acid, or by an equivalent chemical process. When used herein semi-synthetic penicillin includes a pharmaceutically acceptable salt or ester thereof. Penicillins such as penicillin G and penicillin V which are normally prepared by fermentation are not of course regarded as semi-synthetic penicillins.

The oily vehicle for the semi-synthetic penicillin may comprise a mixture of both tri-glycerides and propylene glycol di-esters of C_{8-10} fatty acids. However, it is normally the case that the oily vehicle will comprise either tri-glycerides of the C_{8-10} fatty acids, or propylene glycol di-esters of the C_{8-10} fatty acids but not both. Preferably these C_{8-10} fatty acids are fully saturated, such as n-caprylic and n-capric acids. Tri-glyceride esters are in general to be preferred to propylene glycol di-esters.

The oily vehicle is conveniently prepared by the commercial fractionating of naturally occurring coconut oil to give mainly C_{8-10} fatty acids followed by esterification of these acids with the chosen alcohol. It will be realised that an oil prepared in this way will contain impurities – oils that do not fall within the class defined above for example – which have not been removed by the fractionating process. We have found that such impurities may be tolerated up to a level of 20% by weight of the total oily vehicle. Thus the oily vehicle will often comprise 80–100% of tri-glycerides, or propylene glycol di-esters of C_{8-10} fatty acids and 0–20% of such esters of other fatty acids.

Additives may also be present in the oily vehicle in minor proportions. Examples of such additives include conventional thickening agents such as 12-hydroxy stearin, aluminium stearate and colloidal silica, and conventional surfactants such as those sold under the Trade Marks "SPAN" and "TWEEN". "SPANS" are

Miglyol 812	to 100

[Miglyol 812 has the approximate composition:

Triglyceride of caproic acid:	3% max.
Triglyceride of caprylic acid:	50–65%
Triglyceride of capric acid:	30–45%
Triglyceride of lauric acid:	5% max.]

The Miglyol was sterilised by membrane filtration, and to this sterilised Miglyol was added the 12-hydroxystearin at 50°C with high shear mixing. The resultant mixture was allowed to cool, and the semi-synthetic penicillins, in sterile form and finely milled, incorporated therein with mixing to give a suspension of the penicillins in the Miglyol. The suspension was then passed through a colloid mill to produce a fine, homogeneous dispersion.

Packs of syringes suitable for intramammary administration were filled with 3 gm. per syringe of the dispersion.

EXAMPLE 2

In order to compare the milk out time and stability of composition A prepared in Example 1 with a standard preparation, a composition B was prepared in an identical manner to A, but the Miglyol 812 was replaced by arachis oil.

3 gm. of A were administered to the mammary gland of a cow, and it was found that the time taken for the penicillin level in the milk to drop below 0.01 micrograms per ml. in all quarters was 60 hours. In contrast, this time was 96 hours using an identical procedure but replacing composition A with composition B.

These results show that a substantial fall in the milk out time can be obtained by replacing a conventional oily vehicle with an oily vehicle according to the invention.

The stability of composition A was then compared with the stability of composition B over a period of 12 months at 37°C. Again, a worthwhile improvement was found with composition A:

	% Penicillin Remaining	
	Ampicillin	**Cloxacillin**
Composition A	99	98
Composition B	89	94

EXAMPLE 3

1 kg. of veterinary composition C, of the following composition, was prepared by the method of Example 1. (The surfactant were mixed into the Miglyol at the same time as the 12-hydroxystearin).

	% by wt.
Sodium Cloxacillin	6.7
12-hydroxystearin	1.0
Tween 80) 58:42 Tween	
Span 80) to Span ratio	3.0
Miglyol 812	to 100

[Span 80 is sorbitan monooleate
Tween 80 is polyoxyethylene (20) sorbitan monooleate]

Packs of syringes suitable for intramammary administration were filled with 3 gm. per syringe of the dispersion.

WHAT WE CLAIM IS:—

1. A veterinary composition for intramammary administration to animals comprising a suspension of a semi-synthetic penicillin in an oily vehicle, the said oily vehicle comprising tri-glycerides, or propylene glycol di-esters, of fatty acids containing 8—10 carbon atoms.

2. A composition according to claim 1, wherein the semi-synthetic penicillin is ampicillin, amoxycillin, carbenicillin, ticarcillin, cloxacillin, flucloxacillin, dicloxacillin, oxacillin, talampicillin, nafcillin, methicillin, or carfecillin.

3. A composition according to claim 1, wherein the semi-synthetic penicillin is a mixture of ampicillin and cloxacillin, amoxycillin and cloxacillin, or ticarcillin and flucloxacillin.

4. A composition according to claims 1, 2 or 3, wherein the oily vehicle comprises tri-glycerides or propylene glycol di-esters of n-caprylic and n-capric acids.

5. A veterinary composition for intramammary administration to animals comprising a suspension of ampicillin, cloxacillin or a salt thereof in an oily vehicle, the said oily vehicle comprising tri-glycerides or propylene glycol di-esters, of fatty acids containing 8 to 10 carbon atoms.

6. A composition according to claim 5, comprising a suspension of cloxacillin or a salt thereof in an oily vehicle, the said oily vehicle comprising tri-glycerides, or propylene glycol di-esters, of n-caprylic and n-capric acids.

7. A composition according to claim 5 or 6, containing 0.1 to 8% of a surfactant, which surfactant comprises polyoxyalkylene sorbitan fatty acid esters and sorbitan fatty acid esters in a weight ratio of 80:20 to 40:60.

8. A veterinary composition for intramammary administration to animals comprising a suspension of ampicillin and cloxacillin, or salts thereof, in an oily vehicle, the said oily vehicle comprising tri-glycerides, or propylene glycol di-esters, of fatty acids containing 8 to 10 carbon atoms.

9. A composition according to claim 8, wherein the fatty acids are n-caprylic and n-capric acids.

10. A composition according to claim 8 or 9, containing 0.1 to 8% of a surfactant, which surfactant comprises polyoxyalkylene sorbitan fatty acid esters and sorbitan fatty acid esters in a weight ratio of 80:20 to 40:60.

11. A veterinary composition substantially as described in Example 1.

12. A veterinary composition substantially as described in Example 3.

13. A process for the preparation of veterinary composition according to claim 1, which process comprises suspending the semi-synthetic penicillin in the oily vehicle.

14. A method of treatment of mammary disorders in non-human animals, which method comprises the intramammary administration

* C L M S *

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The stability of composition A was then compared with the stability of composition B over a period of 12 months at 37°C. Again, a worthwhile improvement was found with composition A:

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2. A composition according to claim 1, wherein the semi-synthetic penicillin is ampicillin, amoxycillin, carbenicillin, ticarcillin, cloxacillin, flucloxacillin, dicloxacillin, oxacillin, talampicillin, nafcillin, methicillin, or carfecillin.

3. A composition according to claim 1, wherein the semi-synthetic penicillin is a mixture of ampicillin and cloxacillin, amoxycillin and cloxacillin, or ticarcillin and flucloxacillin.

4. A composition according to claims 1, 2 or 3, wherein the oily vehicle comprises tri-glycerides or propylene glycol di-esters of n-caprylic and n-capric acids.

5. A veterinary composition for intramammary administration to animals comprising a suspension of ampicillin, cloxacillin or a salt thereof in an oily vehicle, the said oily vehicle comprising tri-glycerides or propylene glycol di-esters, of fatty acids containing 8 to 10 carbon atoms.

6. A composition according to claim 5, comprising a suspension of cloxacillin or a salt thereof in an oily vehicle, the said oily vehicle comprising tri-glycerides, or propylene glycol di-esters, of n-caprylic and n-capric acids.

7. A composition according to claim 5 or 6, containing 0.1 to 8% of a surfactant, which surfactant comprises polyoxyalkylene sorbitan fatty acid esters and sorbitan fatty acid esters in a weight ratio of 80:20 to 40:60.

8. A veterinary composition for intramammary administration to animals comprising a suspension of ampicillin and cloxacillin, or salts thereof, in an oily vehicle, the said oily vehicle comprising tri-glycerides, or propylene glycol di-esters, of fatty acids containing 8 to 10 carbon atoms.

9. A composition according to claim 8, wherein the fatty acids are n-caprylic and n-capric acids.

10. A composition according to claim 8 or 9, containing 0.1 to 8% of a surfactant, which surfactant comprises polyoxyalkylene sorbitan fatty acid esters and sorbitan fatty acid esters in a weight ratio of 80:20 to 40:60.

11. A veterinary composition substantially as described in Example 1.

12. A veterinary composition substantially as described in Example 3.

13. A process for the preparation of veterinary composition according to claim 1, which process comprises suspending the semi-synthetic penicillin in the oily vehicle.

14. A method of treatment of mammary disorders in non-human animals, which method comprises the intramammary administration

of an effective amount of a composition according to any one of the claims 1 to 4.

15. A method of treatment of mammary disorders in non-human animals, which method comprises the intramammary administration of an effective amount of a composition according to any one of the claims 5, 6, 7 or 12.

16. A method of treatment of mammary disorders in non-human animals, which method comprises the intramammary administration of an effective amount of a composition according to any one of the claims 8, 9, 10 or 11.

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