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STERILE MONO- AND DIGLYCERIDE PHARMACEUTICAL VEHICLE PRODUCT FOR WATER AND/OR OIL-SOLUBLE THERAPEUTIC SUBSTANCES

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The present invention is directed to ester compositions, particularly partial esters of certain lower fatty acids with mono- and poly-hydric alcohols, and also to uses thereof in various fields, such as the pharmaceutical field.

It has been the practice for many years in the drug and pharmaceutical industry to use oils as vehicles or carriers for a variety of preparations. Usually sesame oil or peanut oil is preferred from the standpoint of suitability at an economic price, although products such as modified coconut oil, which is liquid at ice box temperatures and exhibits unusually good oxidative stability, have been used where shelf life and stability are the main factors to consider rather than the cost of the oil vehicle.

In injectables, for parenteral use of drugs, mineral oil has been used as a low priced, stable vehicle oil, but in recent years more and more reservations are forming in regard to this practice. It is believed that mineral oil when used as the vehicle in injectables is inclined to give rise to the formation of nodules, cysts and other undesirable side reactions in the body of the patient.

Still another factor which has motivated a search for better vehicles for such pharmaceutical uses has been the rate of effectiveness and the rate of release of the active medication from such oil vehicles be they vegetable or mineral in origin. Then, too, when such vehicles are used considerable expense and care must be exercised to sterilize and maintain sterile preparations. In some oil vehicles, which have been subjected to the customary standard practice of sterilization, cases have been reported where molds, spores and similar organisms have managed to survive and thrive on the vehicle oil being used, thus vitiating the products.

The present invention is intended and adapted to overcome the defects and disadvantages inherent in compositions previously in use for the above stated purposes, it being among the objects thereof to provide a new material comprising the partial esters of certain fatty acids and certain alcohols, for use in the pharmaceutical as well as in other fields.

It is another object of the invention to devise a class of tailor made vehicles which are adapted to be used as not only the oil phase in such preparations, but also as a medium for maintaining a sterile system over a relatively long period of time.

Still another object of the invention is to provide vehicles which in themselves are germistatic and bacteriostatic and they possess the unique property of retaining moisture which in the sterilization phase will insure the system from the survival of any organism which has heretofore caused trouble.

It is further the purpose of this invention to describe the preparation and use of these tailor made vehicles which have unusually good thermal and oxidative stability and can be stored for years without any fear of deterioration or loss of performance ability.

It is further the purpose of this invention to provide vehicles which in themselves are able to dissolve or retain some moisture and thus provide an oil-water system in homogeneous state.

Still further, it is the purpose of this application to pro-

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vide an application and use of these tailor made vehicle fats which have not been considered and used heretofore and to demonstrate the unique characteristics and advantages of such tailor made vehicles in these applied uses.

Accordingly, in practicing the invention there is provided a series of compounds which are partial esters such as the mono- and di-glycerides of the saturated fatty acids below C_{12} fatty acids, particularly those having even numbers of carbon atoms. Although mono- and di-glycerides of fats and fatty acids are well known and used for food and industrial applications, including pharmaceuticals, it is new and novel to prepare such mono- and di-glycerides of acids C_2 to C_{12} or mixtures thereof, especially those of the C_8 to C_{10} fatty acids of varying mono- and di-glyceride ratios to obtain tailor made vehicles having specific properties to dissolve water and impart the germistatic and bacteriostatic properties which destroy the molds and spores. These same tailor made products appear to have the ability to retain the medication and prolong the effective period of the injectable by controlling the release rate from the vehicle.

Depending upon the amount of hydrophylic and lipophilic properties desired to be built into the product there is synthesized a mono diglyceride of high or low mono content using more or less of a one or more fatty acids in the range of C_2 to C_{12} . For optimum germistatic and bacteriostatic properties applicant prefers to use the C_8 and C_{10} fatty acids, while for hydrophylic properties the C_2 and C_4 acids are more helpful. To maintain the optimum in the germistatic and bacteriostatic properties and still obtain a relatively hydrophylic system, then there is used a high monoglyceride content of the C_8 and C_{10} acids.

The medication that is to be carried by the vehicle is a very important consideration in which type of product is used and which part of the range of C_2 to C_{12} acids is employed or what mono content is obtained in the preparation of the tailor made vehicle for such pharmaceutical use. The fatty acids are preferably obtained from naturally occurring fats and oils. The alcohol used is preferably glycerine although glycols such as propylene glycol can be used and polyols such as pentaerythritol, sorbitol or sugars may be used. The most readily available and flexible polyol, however, is glycerine and since most of the naturally occurring animal and vegetable oils are glycerides there are preferred the mono- and di-glycerides of the partial esters of the C_2 to C_{12} acids.

In the preparation of these partial esters any of the usual methods employed will be satisfactory. For example, one of the most effective and readily available products for the purpose of this invention is that prepared from the medium chain length fatty acids which are obtained from the lauric type fats such as coconut, palm kernel, babassu, etc. These kernel oils which are rich in lauric acid all contain various amounts of C_6 to C_{10} fatty acids and are considered an excellent source of such fatty acids. The mono- and di-glycerides prepared from such acids ranging from above 90% mono to below 20% mono, constitute a variety of products having hydrophylic-lipophilic balances covering a range of other properties. In the examples given later in this application the performance differences of the range will be demonstrated. Whether these products are prepared by direct esterification, whether they are molecularly distilled or left with varying amounts of di-, and tri-glycerides or glycerine will depend on the end use being contemplated. The method whereby such partial esters are made to specification does not limit their performance characteristics or their acceptability for the purposes of this invention.

Where short chain acids are desired there are preferably used the anhydrides which are readily available rather than recover such acids from naturally occurring animal

and vegetable fats and oils, although butter oil is a considered source of the C_2 to C_{10} acids especially the C_4 acids. Acetic anhydride and butyric anhydride being readily available and easy to use have been the preferred sources of the short chain acids.

The C_8 and C_{10} acids having the optimum in germistatic and bacteriostatic properties it has been preferred to use these acids where possible or use as much of them as possible to take advantage of their unique properties.

In some cases it is advantageous to use a blend of di- and triglycerides of C_8 and C_{10} fatty acids with varying amounts of di- or mono-glyceride to achieve a compatibility of oil and water soluble components. The inter-solubility of the mono-, di- and tri-glycerides of these acids is thus used to advantage to solubilize and carry oil and water soluble ingredients. The amounts of each used will vary with the formulation desired by the particular firm.

The following are specific examples of the present invention, which are given for the purpose of illustrating the invention, but they should not be construed as a limitation thereon.

Example 1

There is provided a reaction vessel equipped with a magnetic agitator and a packed column. Three openings are provided for a condenser, thermometer and introduction of reactants. A mixture of acids having 6 to 12 carbon atoms in the amount of 1095 gms. and derived from coconut oil is introduced into the reaction vessel together with 900 gms. of 99+ % glycerine. The temperature is raised to 160°–240° C. for 4 hours at atmospheric pressure. The temperature is then held at 240° C. in a vacuum of 1–16 inches of mercury for 40 minutes.

The packed column was used to reflux reactants to the reaction vessel, water vapor being passed to the condenser and receiver. The crude monoglyceride was washed 3 times with water (equal volume), dried, steam deodorized at 149°–160° C. and 10 mm. pressure for 1 hour, and then carbon bleached and filtered. The finished product analyses are:

	Percent
Alpha mono-glyceride	52.2
Free glycerin	1.0
Free fatty acid, as oleic	0.23

This mono-glyceride dissolves 21% of water based on weight of mono.

This product was then evaluated against sesame oil and mineral oil with respect to their ability to hold water, destroy molds and spores and prolonged release of given medication as well as ease of sterilization of the preparations, temperature and time required to obtain sterilization. In all respects the product of this invention proved to be more effective and desirable. On prolonged storage tests and accelerated storage tests the results obtained were more marked and substantiated our original findings.

Example 2

Another product was prepared where the mono-glyceride content was lowered to develop more lipophilic properties. In comparable tests as in Example 1 the product prepared with a lower mono-glyceride content performed in the same manner, but it can carry oil soluble medications at a higher concentration than that of the product made in Example 1. The product was prepared as follows:

In a 3 neck flask, equipped with a magnetic agitator and packed column, 1200 gms. of C_6 through C_{12} acids from coconut oil, having a Free Fatty Acid of 186, were reacted with 510 gms. of 99+ % glycerin for 4 hours at 160° C.–245° C. and atmospheric pressure, and then at 240° C. and 1–16 in. vacuum for 55 minutes more. The packed column was used to reflux reactants to the reaction vessel and pass water vapor to a condenser and receiver. The mono-glyceride was steam deodorized at 140°–153°

C. and 5–10 mm. for 1 hour, and then carbon bleached and filtered. The finished product analyses are:

	Percent
Alpha mono-glyceride	28.7
Free glycerin	3.5
Free fatty acid, as oleic	0.8

This mono-glyceride dissolves 3–3.5% of water based on weight of the mono.

Example 3

A product was prepared from caprylic acid chloride and sucrose in accordance with U.S. Patent 2,948,717. The product of this experiment was then used as the vehicle for an injectable preparation. The tests carried out with the product of Example 1 were repeated with the caprylic product with equally good results.

Example 4

A monoester of pentaerythritol and a mixture of caproic and caprylic acids was prepared having about 45% monoester. This product, too, demonstrated the same unique properties with respect to its ability to perform as the product of Example 1.

Example 5

Still another partial ester of propyleneglycol and capric acids was prepared and tested. This, too, was comparable to Example 4 in its satisfactory performance.

Example 6

A mixed glyceride ester was prepared of a mixture of acetic, butyric and caprylic acids having about 50% monoester content. The product performed similarly to Example 4.

Example 7

A mono-, di-ester of sorbitol was prepared from a mixture of acids having 4 to 10 carbon atoms obtained from butter oil and palm kernel oil. The product was similar in properties to that found in Examples 4–6.

Example 8

There was prepared the mixed mono-glycerides of caproic, caprylic and capric acids by the usual methods. It was admixed in a 1 to 1 ratio with the fatty acid triglyceride of a mixture of acids having 6 to 12 carbon atoms, as described in Pat. No. 2,914,456. The product performed equally as well as the foregoing products. It had the highly desirable quality of being able to carry both oil soluble and water soluble components.

Example 9

Similarly to Example 8, a product was made from a mixture of the ethyl ester of caprylic acid with the mono-glyceride of a mixture of caprylic and capric acids. The properties of the product were equally satisfactory.

Example 10

Some of the partial esters which are effective for the present invention may be made by rearrangement and alcoholysis. For example, triacetin, tricaprylin and glycerine were rearranged to give a mixed partial ester of acetic and capric acids. The product showed the same essential performance as those of the other examples.

There are important advantages inherent in the products and the uses described and claimed herein. Those who are versed in the art will readily understand the underlying principle of the invention. By using the short and medium chain length saturated fatty acids in the preparation of these partial esters not only is advantage taken of their hydrophylic characteristics as a means of carrying water in the vehicle, but also their inherent germistatic and bacteriostatic properties which can be used to advantage in the maintaining of sterile preparations is utilized. Within this whole area of C_2 to C_{12} fatty acids, partial esters, numerous tailor made esters can be prepared to

satisfy the specific requirements of solubility, stability, sterility, etc. which may be needed for the drug industry.

In the biochemical and bacteriological tests performed special emphasis was placed on the organisms commonly encountered in drug preparations especially the parenteral drugs. Molds, spores and bacteria of the classes known as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* and the like have been especially troublesome and common to most preparations. Effectiveness against these organisms both Gram positive and Gram negative was considered a major achievement in overcoming the shortcomings of the prior art.

What is claimed is:

1. A method for preparing for sterilization and maintaining sterility of a therapeutic composition and for imparting germistatic and bacteriostatic properties which destroy mold and spores which comprises dissolving a water and/or oil-soluble therapeutic substance in an essentially mono- and di-glyceride partial ester of at least one 2 to 12 carbon atom saturated fatty acid with a polyhydric alcohol, sterilizing, and introducing the sterilized composition into an environment where molds, spores and similar organisms manage to survive and thrive.

2. A method according to claim 1 characterized in that said alcohol has from 2 to 6 hydroxyl groups.

3. A method according to claim 1 characterized in that said ester contains also an ester of said acids with a lower monohydric alcohol having 2 to 8 carbon atoms.

4. A method according to claim 1 characterized in that said composition contains at least 1 to 30% of water.

5. A method according to claim 1 characterized in that said composition is adapted to be miscible with oil soluble and water soluble substances.

6. A method according to claim 1 characterized in that said alcohol is glycerin.

7. A method according to claim 1 characterized in that said acids are a mixture of caprylic and capric.

8. A method according to claim 1 characterized in that the content of said ester is at least about 20%.

9. A method according to claim 1 characterized in that said acids have 6 to 10 carbon atoms.

10. A method according to claim 1 characterized in that said acids have even numbers of carbon atoms.

11. A sterile pharmaceutical vehicle product for water- and/or oil-soluble therapeutic substances consisting essentially of an essentially mono- and di-glyceride partial ester of at least one 2 to 12 carbon atom saturated fatty acid with a polyhydric alcohol, having dissolved therein a water and/or oil-soluble therapeutic substance.

12. A product according to claim 11 characterized in that there is present ester of a lower monohydric alcohol,

13. A product according to claim 11 characterized in that said alcohol is glycerin.

14. A product according to claim 11 characterized in that said acid is a mixture of caprylic and capric.

15. A product according to claim 11 characterized in that said acid is a mixture taken from the class consisting of those having 2 and 4 carbon atoms with an acid taken from the class consisting of those having 6, 8 and 10 carbon atoms.

16. A product according to claim 12 characterized in that said monohydric alcohol is ethanol.

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