NOVEL COATING MATERIAL FOR MEDICAMENTS

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This invention relates to a new coating material useful for prolonging the release of a medicament upon oral administration and medicaments coated with said material.

The coating material of this invention is useful for coating medicaments using any of the conventional coating techniques. For example, it can be used to coat medicament pellets employing a coater pan technique; it can be used to form a pellet of the coating material with the medicament dispersed therein; or a dispersion of medicament in the coating material can be spray dried to coat the medicament.

The coating of small medicament-containing pellets with a fatty material or a fatty material admixed with a waxy material in order to obtain pellets with a size of the order from 0.1 to 2.0 mm. in diameter is known to the art. These pellets are encapsulated and administered to humans to provide for sustained release of the medicament over a long period of time, from about eight to ten hours.

The manufacture of such coated pellets has been complicated by the small size of the pellets and the critical nature of the thickness of the coating in order to obtain a proper release of medicament. Complicating the picture further was the fact that the previous coating materials, for instance glycerin monostearate and beeswax, due to solid state changes of the coatings, such as microcrystallization, i.e., changes of one crystalline form to another, tended to alter the release of the medicament over a period of time, such as slowing down the medicament release. Therefore, in order to solve this problem and obtain products with reliable sustained release characteristics, complicated aging and blending techniques had to be employed. It is an object of this invention to provide a coating material which eliminates these problems.

Further, use of the coating material of this invention enables a continuous application of the coating material to the pellets to be employed during the manufacturing process, a great advantage over the multiple-coating procedures of the prior art.

The coating material of this invention comprises an intimate mixture of a non-toxic, solid hydroxylated lipid material and a non-toxic, solid cellulose derivative. Examples of the lipid material are fatty alcohols having from 12 to 31 carbon atoms, such as for instance 12-hydroxystearyl alcohol, 10-hydroxystearyl alcohol, 9,10-dihydroxystearyl alcohol, 14-hydroxybehenyl alcohol, lauryl alcohol, ceryl alcohol, cetyl alcohol, stearyl alcohol, myristyl alcohol, behenyl alcohol, cetyl alcohol, myristyl alcohol or arachyl alcohol; fatty mono, di or triesters of glycols and glycerols which have at least one free hydroxyl group and are derived from fatty acids of from 12 to 22 carbons, such as glycerol distearate, glycerol mono- and di-esters, propylene glycol monolaurate, ethylene glycol monopalmitate, ethylene glycol mono- and di-hydroxystearate glycerol monobehenate, glycerol monostearate, glycerol didecanoate, propylene glycol monostearate, glycerol mono- and di-hydroxystearate, glycerol tri-12-hydroxystearate,

propylene di-12-hydroxystearate, ethylene glycol di-9,10-dihydroxystearate, glyceryl tri-dihydroxystearate, glyceryl mono-12-hydroxystearate, glyceryl di-12-hydroxystearate, glyceryl di-11-hydroxylmalinate, glyceryl mono-16-hydroxy steareate, glyceryl tri-12-hydroxylaurate, glyceryl tri-12-hydroxy stearate or glyceryl monostearate di-12-hydroxystearate.

Solid esters of either fatty hydrox acids with lower aliphatic alcohols or fatty polyhydric alcohols with lower aliphatic acids, the said esters having a total carbon content of from 12 to 62 carbon atoms are also of value in this combination. Exemplary of such compounds are propyl 9,10-dihydroxystearate, dodecyl 9,10-dihydroxy stearate, 12-hydroxy steararyl butyrate, 12-hydroxy stearyl palmitate, octadecyl 9,10-dihydroxystearate, propyl 13,14-di hydroxy benenate, or octadecyl 12-hydroxy stearate.

Advantageous compounds are glycerol (tri-12-hydroxy stearate, glyceryl di-12-hydroxystearate, glyceryl mono-12-hydroxystearate, behenyl alcohol, stearyl alcohol and 12-hydroxy stearic acid alcohol. A preferred substance is hydrogenated castor oil whose major component is glyceryl tri-12-hydroxystearate.

Exemplary of the cellulose derivative of the combination of this invention are cellulose ethers, such as cellulose, methyl cellulose, propyl cellulose; cellulose esters, as cellulose acetate, cellulose acetate butyrate, cellulose propionate, cellulose caprate, cellulose acetate propionate or cellulose acetate stearate.

The cellulose derivatives preferably are those in which the R moiety of cellulose-R is either an aliphatic acyl of 2 to 22 carbons or an aliphatic alky1 of from 1 to 5 carbons.

The water insoluble cellulose derivatives are of particular advantage. Advantageous and preferred cellulose derivatives are ethyl cellulose and cellulose acetate butyrate.

The components of the coating material are mixed either by melting the constituents together with intimate mixing or preferably by dissolving the constituted in an organic solvent in which they are sufficiently soluble, such as carbon tetrachloride, ethylene dichloride, chloroform, ethyl acetate or benzene, then evaporating the solvent.

The ratio by weight of lipid material to cellulose material may be varied widely, such as from 1:1 to 20:1. Practically, proportions about 1:1 to about 9:1 are used. A particularly useful combination is hydrogenated castor oil of which the major constituent is glyceryl tri-12-hydroxy stearate and ethyl cellulose preferably in proportions of about 4:1.

The coating material can be dissolved, usually in about 10% solution, in a suitable organic solvent, such as chloroform or alcohol-chloroform mixture and gradually applied by continuous spraying or vaporizing to the medicament-containing pellets which are agitated as the coating material is applied, such as in a coating pan. The pellets are then dried. If desired, the coating material can be applied in successive coats by alternately spraying or vaporizing to the pellets and drying until the desired number of coats have been applied. It is preferred to have the coating a minimum of 2% by weight of the coated pellets. Advantageously the coating will be 5% to 15% by weight of the coated pellets.

Where it is desirable to have the medicament which is coated with the coating material of this invention in a finely divided form, for example, about 500 microns (U.S. 35 mesh) or smaller in size, the medicament in comminuted form 160 mesh (U.S. or smaller) is suspended in a volatile solution of the coating material, for example, the coating material in an organic solvent such as chloroform. The thus formed suspensions is then spray dried to form dry treated particles substantially coated with the coating material. This spray drying may be
carried out in apparatus conventionally used for spray drying and which is well known to the art. The spray drying conditions may vary within wide ranges. It is, however, preferred to use an inlet temperature of the spraying chamber of not more than about 150°C, and an outlet temperature of the spraying chamber of not less than about 50°C. The spray dried material may be used as such or, if desired, can be compressed into a tablet.

Similarly, the coating material of this invention can be employed to provide for a sustained release of medicament by molding pellets using a dispersion of the selected medicament in a melt of the coating material of this invention, this admixture being formed in suitable molds.

The sustained release coating of this invention provides satisfactory sustained release rates of medicament in the gastrointestinal tract. It will be understood that this sustained release of medicament over a period of many hours differs from the result achieved with enteric coatings which protect the medicament during passage through the stomach and then releases all of the medicament at substantially one time.

Further the sustained release rates may be maintained well upon aging. Since the coatings are not very pH sensitive, the medicament release is not affected by the emptying time of the stomach and the varying pH caused thereby. Further, the coatings of this invention are harder than the previously used glyceryl stearate-wax mixtures. For this reason the coated pellets are less liable to erosion in the coating pans as well as more resistant to injury by shock during subsequent commercial handling. In addition the coatings of this invention are less subject to cracking caused by extreme temperature changes, such as from near zero conditions often encountered while shipping to the room temperature conditions of storage.

Pharmaceutical preparations having a medicament coated with the coating material of this invention give good sustained release of medicament with a thinner coat than is possible with the prior art combinations. This is reflected in shorter operating times on each batch of pellets, thereby saving man and machine power as well as coating material.

The variations possible in utilizing the coating combination of this invention will be more apparent from consideration of the following examples:

**Example I**

Nonpareil seed (sugar pellets), 19.2 kg., all passing through a #18 U.S. mesh screen, 90% passing through a #20 U.S. mesh screen, and not more than 1% passing through a #25 U.S. mesh screen are placed in a 36-inch coating pan. A coating solution is prepared consisting of 51.85 gm. of hyoscyamine sulfate, 10.20 gm. of atropine sulfate, and 5.95 gm. of scopolamine hydrobromide which is dissolved in 1500 ml. of 10% gelatin solution. The pan is set in rotation and one-third of the alkaloid coating solution is added by slowly pouring it onto the pellets in order to wet them evenly. Then 400 gm. of coating powder, containing equal parts of starch and sugar, are sprinkled on the wetted mass of nonpareil seeds. The pellets are dried in warm air. The addition of the alkaloid solution, starch, and sugar coating powder and the drying procedure are repeated to apply two additional coats. Two final coatings are added, each coat consisting of 350 ml. of syrup U.S.P. The pellets are thoroughly dried and screened through a #16 mesh screen and on a #25 mesh screen. The yield is approximately 20 kg. The screened pellets make 12.5 liters. Ten liters of the solution are applied in a continuous manner at room temperature. After applying the solution, the pellets are dried with air and one-fourth of the batch is removed.

The remainder of the batch, containing three-fourths of the coated pellets, further is coated with 1.5 l. of fat-cellulose solution. After applying the solution, the pellets are dried with air and two-thirds of the remaining batch removed.

The remainder of the batch, containing one-fourth of the original pellets, is further coated with 1.0 l. of fat-cellulose solution. After applying the solution, the pellets are dried with air.

The three groups of pellets thus formed are placed in a single container and thoroughly mixed to provide a uniform mixture. Size No. 4 gelatin capsules are then filled with the thus mixed pellets to provide a total dosage of 0.4 mg. of mixed alkaloids per capsule. Each capsule contains about 350 pellets.

Each No. 4 capsule provides the desired body level of belladonna alkaloids in about one-half hour. The coated pellets continue to provide sufficient belladonna alkaloids to maintain this desired body level for approximately ten hours.

**Example II**

Pellets coated with belladonna alkaloids and overcoated with syrup are prepared and screened as in Example I. The screened pellets, approximately 20 kg., are returned to a coating pan and coated with 1.2 l. of a fat-cellulosic coating solution made by admixing 1000 gm. of hydrogenated castor oil, 250 gm. of ethyl cellulose and sufficient chloroform to make 12.5 liters.

The coating solution is applied gradually and continuously until the coating operation is completed. The pellets are dried with air and screened through a #16 mesh screen and on a #25 mesh screen. The pellets are thoroughly mixed and filled into size No. 4 gelatin capsules to provide a total dosage of 0.4 mg. of mixed alkaloids per capsule. Each capsule contains about 350 pellets. Each No. 4 capsule provides the desired body level of belladonna alkaloids in about one-half hour. The coated pellets continue to maintain this desired body level for approximately ten hours.

**Example III**

Nonpareil seeds (sugar pellets), 18.3 kg., like those used in Example I are placed in a 36-inch coating pan. A coating solution is prepared by dissolving 1.2 kg. of chlorprophenyridamine maleate in 2.3 l. of 10% gelatin solution. The pan is set in rotation and approximately 150 ml. of the coating solution is added by slowly pouring it onto the pellets to evenly wet them. The pellets are dried in warm air. The addition of the coating solution and the drying procedure are repeated until the solution is exhausted. When all of the coating solution has been applied, two final coats consisting of 150 ml. syrup U.S.P. are applied. The pellets are thoroughly dried and screened through a #16 mesh screen and a #25 mesh screen. The yield is approximately 20 kg.

The screened pellets are returned to a coating pan and coated with the fat-cellulosic coating solution as in Example I.

The three groups of pellets thus formed are placed in a single container and thoroughly mixed to provide a uniform mixture.

Size No. 3 gelatin capsules are then filled with the thus mixed pellets to provide a total dosage of 8 mg. of chlorprophenyridamine maleate per capsule. Each capsule contains about 450 pellets.

Each No. 3 capsule provides the desired body level of chlorprophenyridamine maleate in about one-half hour. The pellets continue to provide sufficient chlorprophenyridamine maleate to maintain this desired body level for approximately ten hours.
Example IV

Pellets coated with chlorphenpyridamine maleate and overcoated with syrup are prepared and screened as in Example III. The yield is 20 kg.

Eighteen kilograms of the screened pellets are returned to a coating pan and coated with 10.8 l. of a fat-cellulosic coating solution made by admixing 1001 gm. of hydrogenated castor oil, 250 gm. of ethyl cellulose and sufficient chloroform to make 12.5 liters. The coating solution is applied gradually and continuously until the coating operation is completed. The pellets are dried with air and screened through a #16 mesh screen and on a #25 mesh screen.

The remaining 2 kg. of the originally produced pellets overcoated with syrup are screened through a #16 mesh screen and on a #25 mesh screen. The fat-cellulosic coated pellets are then thoroughly mixed with the pellets which are not fat-cellulosic coated in a ratio of 9:1 to provide a uniform mixture.

Size No. 3 gelatin capsules are filled with the thus mixed pellets to provide a total dosage of 8 mg. of chlorphenpyridamine maleate per capsule. Each capsule contains about 450 pellets.

Each No. 3 capsule provides the desired body level of chlorphenpyridamine maleate in about one-half hour. The coated pellets continue to provide sufficient chlorphenpyridamine maleate to maintain this desired body level for approximately ten hours.

Example V

Hydrogenated castor oil 8
Ethyl cellulose (15 cps.) 2
Chloroform, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example I, to a 6% increase in weight of the pellets. These pellets are filled directly into gelatin capsules with no uncoated medicament necessary.

Example VI

Hydrogenated castor oil 6%
Ethyl cellulose (15 cps.) 3%
Chloroform, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example I, to a 6% increase in weight of the pellets.

Example VII

Hydrogenated castor oil 9
Ethyl cellulose (15 cps.) 1
Chloroform, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example I, to a 6% increase in weight of the pellets.

Example VIII

Glyceryl distearate 8
Ethyl cellulose (30 cps.) 2
Ethyl alcohol, q.s. 100% volume.

This solution is applied to medicated sugar pellets at 60° C, following the procedure of Example I, to an 8% increase in weight of the pellets.

Example IX

Glyceryl tri-12-hydroxystearate 4
Glyceryl distearate 4
Ethyl cellulose (15 cps.) 2
Ethyl alcohol, q.s. 100% volume.

Example X

Hydrogenated castor oil 6
Glyceryl distearate 6
Ethyl cellulose (15 cps.) 3
Ethyl alcohol, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at 60° C, following the procedure of Example I, to a 10% increase in weight of the pellets.

Example XI

Hydrogenated castor oil 12
Cellulose acetate butyrate 3
Chloroform, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at 60° C, following the procedure of Example I, to a 10% increase in weight of the pellets.

Example XII

Hydrogenated castor oil 6.7
Cellulose acetate butyrate 3.3
Chloroform, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example I, to a 6% increase in weight of the pellets.

Example XIII

Glyceryl distearate 12
Cellulose acetate butyrate 3
Ethyl alcohol, q.s. 100% volume.

The above solution is applied to medicated sugar pellets at 60° C, following the procedure of Example I, to a 6% increase in weight of the pellets.

Example XIV

Behenyl alcohol 5
Cellulose acetate butyrate 5
Ethyl alcohol: chloroform (3:1), q.s. 100% volume.

The above solution is applied to medicated sugar pellets at 60° C, following the procedure of Example I, to a 10% increase in weight of the pellets.

Example XV

Stearyl alcohol 5
Cellulose acetate butyrate 5
Ethyl alcohol: chloroform (3:1), q.s. 100% volume.

The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example I, to a 7% increase in weight of the pellets.

Example XVI

12-hydroxy stearyl alcohol 5
Cellulose acetate butyrate 5
Ethyl alcohol: chloroform (3:1), q.s. 100% volume.

The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example I, to a 9% increase in weight of the pellets.

Example XVII

Hydrogenated castor oil 5.6
Ethylene glycol monohydroxy stearate 2.4
Cellulose acetate butyrate 2.0
Chloroform, q.s. 100% volume.
The above solution is applied to medicated sugar pellets at room temperature, following the procedure of Example II, to a 9% increase in weight of the pellets.

What is claimed is:

1. A coating material for medicaments to prolong the release of the medicament in the gastrointestinal tract which comprises an intimate mixture of a non-toxic, solid hydroxylated lipid material selected from the group consisting of a fatty alcohol having from 12 to 31 carbon atoms; a fatty ester of a glycol which has at least one free hydroxyl group with a fatty acid of from 12 to 22 carbon atoms; a fatty ester of a glycerol which has at least one free hydroxyl group with a fatty acid of from 12 to 22 carbon atoms; a solid ester of a fatty hydroxyl acid with a lower aliphatic alcohol, the said ester having a total carbon content of from 12 to 62 carbon atoms; a solid ester of a fatty polyhydric alcohol with a lower aliphatic acid, the said ester having a total carbon content of 12 to 62 carbon atoms; and a non-toxic, solid cellulose derivative represented by cellulose-R in which the R moiety is a member selected from the group consisting of an aliphatic acyl group of from 1 to 5 carbon atoms and an aliphatic acyl group of from 2 to 22 carbon atoms, the ratio by weight of said lipid material to said cellulose material being from about 1:1 to about 9:1.

2. A coating material in accordance with claim 1 characterized in that the ratio by weight of said lipid material to said cellulose material is about 4:1.

3. A coating material for medicaments to prolong the release of the medicament in the gastrointestinal tract which comprises an intimate mixture of hydrogenated castor oil and ethyl cellulose, the ratio by weight of hydrogenated castor oil to ethyl cellulose being from about 1:1 to about 9:1.

4. A coating material in accordance with claim 3 characterized in that the ratio by weight of hydrogenated castor oil to ethyl cellulose is about 4:1.

5. A coating material for medicaments to prolong the release of the medicament in the gastrointestinal tract which comprises an intimate mixture of hydrogenated castor oil and cellulose acetate butyrate, the ratio by weight of hydrogenated castor oil to cellulose acetate butyrate being from about 1:1 to about 9:1.

6. A coating material in accordance with claim 5 characterized in that the ratio by weight of hydrogenated castor oil to cellulose acetate butyrate is about 4:1.

7. A coating material for medicaments to prolong the release of the medicament in the gastrointestinal tract which comprises an intimate mixture of 12-hydroxystearyl alcohol and ethyl cellulose, the ratio by weight of 12-hydroxystearyl alcohol to ethyl cellulose being from about 1:1 to about 9:1.

8. A coating material in accordance with claim 7 characterized in that the ratio by weight of 12-hydroxystearyl alcohol to ethyl cellulose is about 4:1.

9. A coating material for medicaments to prolong the release of the medicament in the gastrointestinal tract which comprises an intimate mixture of 12-hydroxystearyl alcohol and cellulose acetate butyrate, the ratio by weight of 12-hydroxystearyl alcohol to cellulose acetate butyrate being from about 1:1 to about 9:1.

10. A coating material in accordance with claim 9 characterized in that the ratio by weight of 12-hydroxystearyl alcohol to cellulose acetate butyrate is about 4:1.

11. A coating material for medicaments to prolong the release of the medicament in the gastrointestinal tract which comprises an intimate mixture of glyceryl tri-12-hydroxy stearate and ethyl cellulose, the ratio by weight of glyceryl tri-12-hydroxy stearate to ethyl cellulose being from about 1:1 to about 9:1.

12. A coating material in accordance with claim 11 characterized in that the ratio by weight of glyceryl tri-12-hydroxy stearate to ethyl cellulose is about 4:1.

13. A pharmaceutical preparation providing a prolonged release of the contained medicament in the gastrointestinal tract which comprises a medicament protected by a coating comprising an intimate mixture of a non-toxic, solid hydroxylated lipid material selected from the group consisting of glyceryl tri-12-hydroxy stearate, glyceryl mono-12-hydroxy stearate, behenyl alcohol, stearyl alcohol and 12-hydroxy stearic acid, and a non-toxic, solid cellulose derivative selected from the group consisting of ethyl cellulose, methyl cellulose, propylene cellulose acetate, cellulose acetate butyrate, cellulose propionate, cellulose caprate, cellulose acetate propionate and cellulose acetate stearate, the ratio by weight of said lipid material to said cellulose material being from about 1:1 to about 9:1.

14. A pharmaceutical preparation in accordance with claim 12 characterized in that the ratio by weight of said lipid material to said cellulose material is about 4:1.

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UNITED STATES PATENT OFFICE

Certificate

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Davis R. Reese and Joseph V. Swintosky

Application having been made jointly by Davis R. Reese and Joseph V. Swintosky, the inventors named in the patent above identified, and Smith Kline & French Laboratories, Philadelphia, Pennsylvania, a corporation of Pennsylvania, the assignee, for the issuance of a certificate under the provisions of Title 35, Section 256 of the United States Code, deleting the name of the said Davis R. Reese from the patent as a joint inventor, and a showing and proof of facts satisfying the requirements of the said section having been submitted, it is this 19th day of February 1963, certified that the name of the said Davis R. Reese is hereby deleted from the said patent as a joint inventor with the said Joseph V. Swintosky.

[SEAL]

EDWIN L. REYNOLDS,
First Assistant Commissioner of Patents.
UNITED STATES PATENT OFFICE

Certificate


Davis R. Reese and Joseph V. Swintosky

Application having been made jointly by Davis R. Reese and Joseph V. Swintosky, the inventors named in the patent above identified, and Smith Kline & French Laboratories, Philadelphia, Pennsylvania, a corporation of Pennsylvania, the assignee, for the issuance of a certificate under the provisions of Title 35, Section 236 of the United States Code, deleting the name of the said Davis R. Reese from the patent as a joint inventor, and a showing and proof of facts satisfying the requirements of the said section having been submitted, it is this 19th day of February 1963, certified that the name of the said Davis R. Reese is hereby deleted from the said patent as a joint inventor with the said Joseph V. Swintosky.

[SEAL]

EDWIN L. REYNOLDS,
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