Description

The present invention is related to therapeutic agents which have a coating of a mixture of lipids.

The use of therapeutic agents such as aspirin is widespread as a means for alleviating pain of various types. One problem associated with aspirin for many people is irritation of the stomach. As a result prior art developments have provided polymeric enteric coatings which allow the aspirin particles to pass through the stomach and into the intestines. The more alkaline environment of the intestines dissolves/disrupts the enteric coating allowing the aspirin to be released. Insuring satisfactory coatings (i.e., those that have minimal leakage in the stomach but still release the drug in the intestines) has been a problem continually faced by workers in the field.

Other therapeutic agents are inactivated by the stomach environment (e.g., vitamins, mineral supplements and insulin) and it is desired to have them pass unaltered into the intestines. These agents are also benefited by the present invention.

There are many references concerning polymeric enteric coatings. US-A 3 524 910, August 18, 1970 to Holliday et al. discloses analgesic compositions wherein the analgesic (e.g., aspirin) is coated with ethyl cellulose in a weight amount relative to the amount of analgesic of from 1:22 to 1:50. US-A 3 656 997, April 18, 1972 to Cordes discloses analgesic containing gelatin capsules having a first coating of an enteric material. US-A 3 691 090, September 12, 1972 to Kitajima et al. discloses a method of encapsulating aspirin cores with an enteric polymer. US-A 3 906 086, September 16, 1975 to Guy et al. discloses a particle having an aspirin core and an enteric phthalate coating. US-A 4 308 251, December 29, 1981 to Dunn et al. discloses aspirin tablets containing aspirin, an enteric material and an erosion promoting agent such as corn starch.

Additional references disclosing coatings on analgesics include US-A 2 953 497, September 20, 1960 to Press which discloses analgesic granules having a cellulose acetate phthalate coating; US-A 3 166 476, January 19, 1965 to Lowey which discloses aspirin particles which have a first coating of a material such as gelatin and a second enteric coating; GB-A 1 129 811, October 9, 1968 to Aspro-Nicholas Ltd. which discloses aspirin particles which have a coating of a polysalicylide and possibly a second, unspecified, coating.

Although the use of enteric polymers as disclosed in the above references provide for some stomach protection and release of the drug in the intestines, they are not the final answer. For chronic users of a drug like aspirin minimizing or eliminating stomach damage is a must and this is not achieved by the enteric polymers. The enteric polymers are "pH triggered" and are designed to be disrupted at the pH's found in the intestines, 5–7.5. However, even in the stomach where the pH of the gastric juices is acidic and the enteric should remain intact, most of the stomach muscosal, gastric lining has a higher pH and the enteric coating can be disrupted with stomach irritation the result.

The present invention involves the use of lipids which are not triggered by pH (acidic or neutral) but are broken down by secretions, from the liver anf pancreas, in the intestines. Lipids have been used to coat a variety of drug actives but not in the manner of the present invention.

The use of lipids in many prior references was to provide a sustained release of the drug. US-A 2 921 883, January 19, 1960 to Reese et al. discloses a mixture of a lipid (e.g., glyceryl tri-dihydroxystearate) and a cellulose derivative to provide a sustained release of the medicament. The patentees distinguish their release from that given by an enteric coating. US-A 3 147 187, September 1, 1964 to Playfair discloses a drug mixed with a fat (e.g., glyceryl tristearate), and a swellable gum or proteinaceous material. US-A 4 483 847, November 20, 1984 to Augart discloses a sustained release composition comprising a mixture of high and low melting point lipids and the active ingredient. The intent of the patentee was to achieve sustained release in the gastrointestinal system.

While the prior art discloses a variety of polymeric enteric coatings and lipids, the use of lipids to provide an enteric coating of the type of the present invention has not been disclosed. The present inventors have found that a particular lipid coating provides for release in the intestines while minimizing or eliminating release in the stomach.

It is therefore an object of the present invention to provide therapeutic granules which have a more efficient enteric coating.

It is a further object of the present invention to provide therapeutic granules which have a coating consisting of a mixture of lipids.

These and other objects will become readily apparent from the detailed description which follows. All percentages and ratios herein are by weight unless otherwise specified.

The present invention pertains to enteric coated therapeutic particles wherein the enteric coating is a mixture of two lipids (e.g., glyceryl tristearate) and a second lipid (e.g., sorbitan tristearate) wherein the ratio of the former to the latter is from 1:9 to 1:1, most preferably 1:4 to 2:3.

The essential as well as optional components of the invention claimed herein are set forth in the paragraphs which follow. In the present application the following terms have the meanings given.

"Pharmaceutically-acceptable" or "pharmacologically-acceptable", as used herein, means that the ingredients used in the compositions are suitable for use in contact with the tissue of humans, without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

The term "comprising", as used herein, means that various other compatible components, including both active and inert ingredients, can be conjointly employed in the composition of this invention. The term "comprising" thus encompasses and includes the more restrictive terms "consisting essentially of".

By "compatible" herein is meant that the components of the present invention are capable of being

commingled without interacting in a manner which would substantially decrease the efficacy of the therapeutic under ordinary use conditions.

THERAPEUTIC ACTIVE CORE

The therapeutic actives materials useful in the present invention may include vitamins, mineral supplements, insulin and preferably nonsteroidals which have analgesic and/or antipyretic and/or anti-inflammatory properties. Aspirin is an example of such a material and is the preferred material. However, there are numerous and other materials which can be used. These include calcium carbaspirin, chloline salicylate, salicylic acid, naproxen, ibuprofen, fenoprofen and mixtures thereof.

The uncoated therapeutic particles generally contain 50% to 100%, prefereably from 85% to 95% of the therapeutic active material.

Optional components which may be used include diluents, binders, disintegrents, lubricants, glidents, buffering adjuvants and direct acting adjuvants. Numerous pharmaceutically acceptable and compatible materials can be found in various pharmacological references. Two such references are Pharmaceutical Dosage Forms: Tablets, Vol. 1, Ed. H. A. Lieberman and L. Lachman, Mercel Dekker, Inc., 1980 and "Proposed Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Drugs", Federal Register, July 8, 1977.

Exemplary material of the above types include dicalcium phosphate and lactose as diluents; gelatin and polyvinylpyrrolidone as binders; corn starch, sodium starch glycolate and cellulosics as disintegrents; stearates as lubricants; fumed silica as glidents; glycine and other amino acids, bicarbonate salts, carbonate salts, magnesium and aluminum hydroxides, aluminium glycinate, citrate salts and borate salts as buffering adjuvants; and caffeine, ascorbic acid and other vitamins, antihistamines and other cough, cold, allergy bronchodilator and antiasthmatic drugs as direct acting adjuvants.

These optional components individually may be present at a level of from about 0% to about 50%, preferably from about 5% to about 15% of the uncoated particles.

Lipid Coating

The enteric (the accepted usage of this term means allowing passage through the stomach and into the intestines) coating used with the present particles is a combination of lipid materials.

The first lipid is selected from the group consisting of glyceryl tristearate, (GTS), commonly referred to as "tristearin", preferably the β′ form, glyceryl tripalmitate, monopalmityl distearyl triglyceride, dipalmityl monostearyl triglyceride and mixtures thereof. This lipid material is water permeable and is important in allowing the active ingredient to be released in the intestines. This lipid generally comprises from 5% to 50%, preferably from 15% to 45%, most preferably from 25% to 40%, of the total lipid coat.

The second lipid is selected from the group consisting of sorbitan tristearate, hexaglycerol hexapalmitate, hexaglycerol hexastearate, decaglycerol decapalmitate, decaglycerol decastearate and mixtures thereof. The preferred material is sorbitan tristearate. This lipid, or mixture, is present at a level of from 50% to 95%, preferably from 55% to 85%, most preferably from 60% to 75% of the total lipid coating.

The total lipid coating generally comprises from 3% to 45% of the coated particle, preferably from 10% to 30%, most preferably from 15% to 25%. These levels are far lower than prior art lipid coating levels designed to bypass the stomach.

Optional components which may be used in the lipid coating include a variety of materials. One such material is a conventional polymeric enteric material. Suitable materials include hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, acrylic anionic polymers (e.g., Eudragit™ – a polymer based on polymethacrylic acid and acrylic acid esters and polyvinyl acetyl phthalate offered by Rohm Pharma).

If present the polymeric enteric comprises from 5% to 60% preferably from 10% to 25% of the total lipid coating.

Other optional components useful in the lipid coating include such things as cholesterol and acetylated monoglycerides as plasticizers.

Another execution within the scope of the present invention involves coating the therapeutic active material with a polymeric enteric material prior to the application of the lipid coating. If used in this manner the polymer material comprises from 3% to 20%, preferably from 5% to 12% of the total coated particles. This coating may help to release the therapeutic active in the intestines but also provides for a smoother, better surface to apply the lipids.

Optional components useful with polymeric enterics include surface active agents, particularly nonionic agents, and plasticizers such as triethyl citrate, triacetin, castor oil and acetylated monoglyceride.

The total coated particles of the present invention may be of any size but are preferably in the size range of 0.3 mm to 3 mm, most preferably from 0.5 mm to 1 mm. This preferred range provides for rapid exit of the particles from the stomach.

METHOD OF MANUFACTURE

The present coated particles may be made according to the process outlined in US-A 4 182 778, January 8, 1980 to Hall et al. A specific example is set forth below.

Commercially available (Monsanto Chemical Co.) aspirin granules are screened to provide granules with a diameter range of 0.6 to 0.85 mm. Said granules are then coated with the lipid using a Wurster fluidized bed coater (Glatt Air Techniques, Inc., Model WSG5) with a 17.78 cm column diameter.

Two thousand grams of sieved granules are palced in the Wurster coater. The lipid coat components, 265 grams of sorbitan tristearate and 88

grams of glyceryl tristearate are melted and then mixed with a solvent (isopropyl alcohol) at a level of about 40% by weight of the total coating solution and maintained in a liquid state during the coating application via agitation and heat. The coating solution is applied at a rate of 56 ml/min. air at 45 psig (310.3 kPa gauge). The bed is fluidized with 115 SCFM (3256.3 standard liters/min.) air at 39°C inlet temperature. The exit air temperature under these conditions is about 34°C. The coating operation is continued until all the coating solution is used up.

Alternative processes do not involve the use of the solvent or a different solvent level. If no solvent is used, the temperature of the lipid mixture should be increased to maintain the lipids in liquid form.

FIELD OF USE

The particles of the present invention can be used in tablets, capsules or in any other convenient form. The therapeutic agents are well recognized for treating a wide variety of human ailments. With aspirin and many other nonsteroidals a usual dosage is from about 100 to about 650 mg, preferably from about 200 to about 500 mg.

The following non-limiting examples illustrate the compositions of the present invention.

EXAMPLE I

Aspirin particles about 0.5 mm to 1.0 mm, in diameter were coated with a mixture of sorbitan tristearate, 60%, and glyceryl tristearate, 40%, according to the method described hereinbefore. The lipid coating amounted to 25% of the total coated particle. When exposed to a 0.1 NHC aqueous solution as outlined in the Pharmacopeial Forum, pp. 2072–2073 (U.S. Pharmacopeial Convention, Inc.), the particles released none of the coated aspirin.

When in the particles described above, sorbitan tristearate is replaced by hexaglycerol hexapalmitate, hexaglycerol hexastearate, decaglycerol decapalmitate, decaglycerol decastearate and mixtures of these or mixtures with sorbitan tristearate similar results are achieved.

Similarly when glyceryl tristearate is replaced by glyceryl tripalmitate, monopalmityl distearyl triglyceride, dipalmityl monostearyl triglyceride and mixtures of these or mixtures with glyceryl tristearate similar results are achieved.

EXAMPLE II

Aspirin particles of the same type as those of Example I were first coated with a coating of cellulose acetate phthalate (CAP) plasticized with castor oil. This plasticized polymeric coating amounted to 10% of the total coated particle. On top of the CAP coating was applied a coating of a mixture of sorbitan tristearate, 60%, and glyceryl tristearate, 40%. This lipid coating amounted to 15% of the total coated particle.

This particle performed in the same manner as those of Example I.

EXAMPLE III

Particles similar to those of Example I were prepared with the lipid coating amounting to 15% of the total coated particles. The ratio of sorbitan tristearate to glyceryl tristearate was 75:25. These particles performed in the same manner as those of Example I.

EXAMPLE IV

When in Example I aspirin is replaced by insulin, vitamins or mineral supplements, the lipid allows for the therapeutic agent to bypass the stomach and be released in the intestines.

Claims

1. Therapeutic active particles comprising a therapeutic active material having a lipid coating of a mixture of:
   a) a lipid selected from the group consisting of glyceryl tristearate, glyceryl tripalmitate, monopalmityl distearyl triglyceride, dipalmityl monostearyl triglyceride and mixtures thereof;
   b) a lipid selected from the group consisting of sorbitan tristearate, hexaglycerol hexapalmitate, hexaglycerol hexastearate, decaglycerol decapalmitate, decaglycerol decastearate and mixtures thereof,

wherein the lipid coating comprises from 3% to 45% of the coated particle and the ratio of a:b is from 1:9 to 1:1.

2. Therapeutic active particles according to claim 1 wherein the therapeutic active material is a nonsteroidal.

3. Therapeutic active particles according to claim 2 wherein the lipid coating is from 10% to 30% of the coated particle.

4. Therapeutic active particles according to claim 2 wherein the coated particles are from 0.3 to 3 mm in diameter.

5. Therapeutic active particles according to claim 2 wherein the a lipid is glyceryl tristearate and the b lipid is sorbitan tristearate.

6. Therapeutic active particles according to claim 5 wherein the ratio of a:b is from 1:4 to 2:3.

7. Therapeutic active particles according to claim 6 wherein the therapeutic active material is aspirin.

8. Therapeutic active particles according to claim 6 wherein the lipid coating is from 10% to 30% of the coated particle.

9. Therapeutic active particles according to claim 2 wherein the therapeutic active material has a first coating of a polymeric enteric material and the lipid coating is over the polymeric material.

10. Therapeutic active particles according to claim 9 wherein the polymeric enteric coating is from 3% to 20% of the coated particle.

11. Therapeutic active particles according to claim 2 which have a polymeric enteric coating mixed in with the lipid coating.

12. Therapeutic active particles according to claim 1 wherein the therapeutic active material is se-

grams of glyceryl tristearate are melted and then mixed with a solvent (isopropyl alcohol) at a level of about 40% by weight of the total coating solution and maintained in a liquid state during the coating application via agitation and heat. The coating solution is applied at a rate of 56 ml/min. air at 45 psig (310.3 kPa gauge). The bed is fluidized with 115 SCFM (3256.3 standard liters/min.) air at 39°C inlet temperature. The exit air temperature under these conditions is about 34°C. The coating operation is continued until all the coating solution is used up.

Alternative processes do not involve the use of the solvent or a different solvent level. If no solvent is used, the temperature of the lipid mixture should be increased to maintain the lipids in liquid form.

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The particles of the present invention can be used in tablets, capsules or in any other convenient form. The therapeutic agents are well recognized for treating a wide variety of human ailments. With aspirin and many other nonsteroidals a usual dosage is from about 100 to about 650 mg, preferably from about 200 to about 500 mg.

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1. Therapeutic active particles comprising a therapeutic active material having a lipid coating of a mixture of:
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   b) a lipid selected from the group consisting of sorbitan tristearate, hexaglycerol hexapalmitate, hexaglycerol hexastearate, decaglycerol decapalmitate, decaglycerol decastearate and mixtures thereof,

wherein the lipid coating comprises from 3% to 45% of the coated particle and the ratio of a:b is from 1:9 to 1:1.

2. Therapeutic active particles according to claim 1 wherein the therapeutic active material is a nonsteroidal.

3. Therapeutic active particles according to claim 2 wherein the lipid coating is from 10% to 30% of the coated particle.

4. Therapeutic active particles according to claim 2 wherein the coated particles are from 0.3 to 3 mm in diameter.

5. Therapeutic active particles according to claim 2 wherein the a lipid is glyceryl tristearate and the b lipid is sorbitan tristearate.

6. Therapeutic active particles according to claim 5 wherein the ratio of a:b is from 1:4 to 2:3.

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10. Therapeutic active particles according to claim 9 wherein the polymeric enteric coating is from 3% to 20% of the coated particle.

11. Therapeutic active particles according to claim 2 which have a polymeric enteric coating mixed in with the lipid coating.

12. Therapeutic active particles according to claim 1 wherein the therapeutic active material is se-

lected from the group consisting of insulin, vitamins, mineral supplements and mixtures thereof.

Patentansprüche

1. Therapeutisch wirksame Partikel, umfassend ein therapeutisch wirksames Material mit einem Lipidüberzug einer Mischung aus;
a) einem Lipid, ausgewählt aus der Gruppe, bestehend aus Glyceryltristearat, Glyceryltripalmitat, Monopalmityldistearyltriglycerid, Dipalmitylmonostearyltriglycerid und deren Mischungen, und
b) einem Lipid, ausgewählt aus der Gruppe bestehend aus Sorbitantristearat, Hexaglycerolhexapalmitat, Hexaglycerolhexastearat, Decaglyceroldecapalmitat, Decaglyceroldecastearat und deren Mischungen,
wobei der Lipidüberzug 3 bis 45% des beschichteten Partikels umfaßt und das Verhältnis von a:b 1:9 bis 1:1 beträgt.

2. Therapeutisch wirksame Partikel gemäß Anspruch 1, worin das therapeutisch wirksame Material ein nicht-steroides Material ist.

3. Therapeutisch wirksame Partikel gemäß Anspruch 2, worin der Lipidüberzug 10 bis 30% des beschichteten Partikels beträgt.

4. Therapeutisch wirksame Partikel gemäß Anspruch 2, worin die beschichteten Partikel einen Durchmesser von 0,3 bis 3 mm haben.

5. Therapeutisch wirksame Partikel gemäß Anspruch 2, worin das Lipid a) Glyceryltristearat und das Lipid b) Sorbitantristearat ist.

6. Therapeutisch wirksame Partikel gemäß Anspruch 5, worin das Verhältnis von a:b 1:4 bis 2:3 beträgt.

7. Therapeutisch wirksame Partikel gemäß Anspruch 6, worin das therapeutisch wirksame Material Aspirin ist.

8. Therapeutisch wirksame Partikel gemäß Anspruch 6, worin der Lipidüberzug 10 bis 30% des beschichteten Partikels beträgt.

9. Therapeutisch wirksame Partikel gemäß Anspruch 2, worin das therapeutisch wirksame Material einen ersten Überzug aus einem polymeren enterischen Material hat und sich der Lipidüberzug über dem polymeren Material befindet.

10. Therapeutisch wirksame Partikel gemäß Anspruch 9, worin der polymere enterische Überzug 3 bis 20% des beschichteten Partikels beträgt.

11. Therapeutisch wirksame Partikel gemäß Anspruch 2, welche eine polymeren enterischen Überzug haben, der mit dem Lipidüberzug gemischt ist.

12. Therapeutisch wirksame Partikel gemäß Anspruch 6, worin das therapeutisch wirksame Material ausgewählt ist aus der Gruppe bestehend aus Insulin, Vitaminen, Mineralsupplementen und deren Mischungen.

Revendications

1. Particules thérapeutiques actives comprenant une substance thérapeutique active possédant un enrobage lipidique d'un mélange de :
a) un lipide choisi dans le groupe constitué par le tristéarate de glycéryle, le tripalmitate de glycéryle, le monopalmityl-distéaryl-triglycéride, le dipalmityl-monostéaryl-triglycéride et leurs mélanges;
(b) un lipide choisi dans le groupe constitué par le tristéarate de sorbitanne, l'hexapalmitate d'hexaglycérol, l'hexastéarate d'hexaglycérol, le décapalmitate de décaglycérol, le décastéarate de décaglycérol et leurs mélanges,
dans lesquelles l'enrobage lipidique constitue de 3% à 45% de la particule enrobée et le rapport a:b est de 1:9 à 1:1.

2. Particules thérapeutiques actives selon la revendication 1, dans lesquelles la substance thérapeutique active est un non stéroïde.

3. Particules thérapeutiques actives selon la revendication 2, dans lesquelles l'enrobage lipidique constitue de 10% à 30% de la particule enrobée.

4. Particules thérapeutiques actives selon la revendication 2, dans lesquelles les particules enrobées ont un diamètre de 0,3 à 3 mm.

5. Particules thérapeutiques actives selon la revendication 2, dans lesquelles le lipide a) est le tristéarate de glycéryle et le lipide b) est le tristéarate de sorbitanne.

6. Particules thérapeutiques actives selon la revendication 5, dans lesquelles le rapport a:b est de 1:4 à 2:3.

7. Particules thérapeutiques actives selon la revendication 6, dans lesquelles la substance thérapeutique active est l'aspirine.

8. Particules thérapeutiques actives selon la revendication 6, dans lesquelles l'enrobage lipidique constitue de 10% à 30% de la particule enrobée.

9. Particules thérapeutiques actives selon la revendication 2, dans lesquelles la substance thérapeutique active possède un premier enrobage d'une substance entérique polymère et l'enrobage lipidique recouvre la substance polymère.

10. Particules thérapeutiques actives selon la revendication 9, dans lesquelles l'enrobage entérique polymère constitue de 3% à 20% de la particule enrobée.

11. Particules thérapeutiques actives selon la revendication 2, qui possèdent un enrobage entérique polymère mélangé dans l'enrobage lipidique.

12. Granulés thérapeutiques actifs selon la revendication 1, dans lesquels la substance thérapeutique active est choisie dans le groupe constitué par l'insuline, les vitamines, les suppléments minéraux et leurs mélanges.