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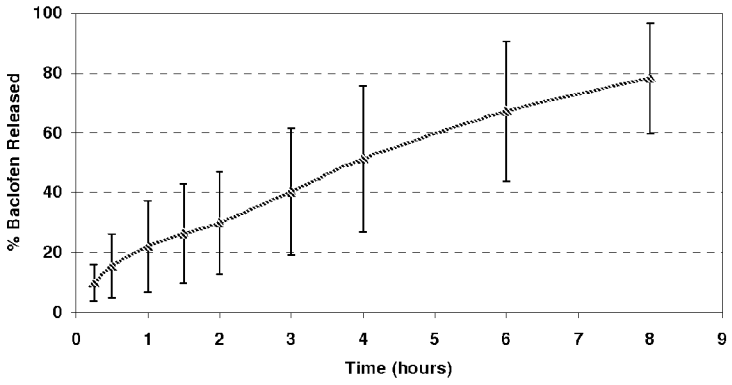

Figure 1

(57) **Abstract**: The disclosure provides multiparticulate systems that give release of active agents with a narrow window of absorption such that there is bioavailability to a patient. The disclosure provides a composition comprising microparticulates comprising a low density excipient and an active agent dispersed therein, wherein the ratio of low-density excipient to active agent is greater than 1:1.

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GASTRORETENTIVE SOLID ORAL DOSAGE FORMS WITH LIPID-BASED LOW-DENSITY EXCIPIENT

Background

[0001] Many active pharmaceutical agents that are orally administered are absorbed in the upper part of the gastrointestinal tract, which constitutes the "window of absorption." The duration of passage of the active agent through this window is limited in time. Consequently, the absorption time itself may be limited. Formulations of active agents that are designed to prolong the exposure of the formulation, and therefore the active, in the upper GI tract may provide a longer period of absorption of the active.

Summary

[0002] This disclosure provides multiparticulate systems for oral delivery of an active agent, which multiparticulate systems can facilitate prolonged release of the active agent over the narrow window of absorption of the upper GI tract.

[0003] The multiparticulate systems using a lipid-based low-density excipient or excipients can provide for increased residence time of an active agent in the upper gastrointestinal (GI) tract as compared to an active agent without a multiparticulate system. Microparticulates of this system can, in some embodiments, float on the surface of the liquid gastric contents, and thus avoid the gastric emptying wave. In addition or alternatively, multiparticulate systems having small particle size can provide for prolonged GI transit time of an active agent as such small particle size allows the microparticulates to become trapped in the folds of the stomach and between the villae of the small intestine. The release profile of the active agent of the multiparticulate systems can be further controlled by incorporation of a control release polymer or a hydrophilic coating or a coating.

[0004] The disclosure provides a composition comprising multiparticulates or microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein the ratio of lipid-based low-density excipient to active agent can be greater than 1:1, and can be at least 1.5:1, or at least 1.7:1, or at least 2:1. The lipid-based low-density excipient has a density that is lower than the density of the gastric fluid in the gastric environment. The lipid-based low-density excipient is a solid or semi-solid material that is meltable. In some embodiments, the composition does not include a gas-generating agent.

[0005] The disclosure also provides a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein the composition does not include a surfactant.

[0006] The release profile of the composition can be assessed by the paddle method with simulated gastric fluid (SGF). In certain embodiments, the composition releases about 10% to about 30% of the drug within about 1 hour. In certain embodiments, the composition releases about 40% to about 60% of the drug within about 6 hours. In certain embodiments, the composition releases about 60% to about 80% of the drug within about 8 hours. In certain embodiments, the composition releases about 40% to about 60% of the drug within about 16 to 24 hours. In certain embodiments, the composition releases about 60% to about 80% of the drug within about 16 to 24 hours.

Brief Description of the Figures

[0007] Figure 1 shows a dissolution profile of baclofen in a multiparticulate system comprising glyceryl behenate.

[0008] Figure 2 shows a dissolution profile of baclofen in a multiparticulate system comprising glyceryl behenate and ethyl cellulose.

[0009] Figure 3 shows a dissolution profile of baclofen in a multiparticulate system comprising glyceryl palmitostearate, methylcellulose, and EUDRAGIT®.

[0010] Figure 4 shows comparisons of dissolution profiles of baclofen in a multiparticulate system comprising glyceryl palmitostearate.

[0011] Figure 5 shows comparisons of dissolution profiles of baclofen in a multiparticulate system comprising glyceryl palmitostearate with addition of EUDRAGIT®.

[0012] Figure 6 shows comparisons of dissolution profiles of baclofen in a multiparticulate system comprising glyceryl behenate with different ratios of glyceryl behenate to baclofen.

[0013] Figure 7 shows comparisons of dissolution profiles of baclofen in a multiparticulate system comprising glyceryl behenate or glyceryl palmitostearate.

[0014] Figure 8 shows comparisons of dissolution profiles of baclofen in a multiparticulate system using a lipid-based low density excipient comprising different particle sizes.

[0015] Figure 9 shows comparisons of dissolution profiles of baclofen in a multiparticulate system comprising glyceryl palmitostearate with different ratios of controlled release polymer.

[0016] Figure 10 shows comparisons of dissolution profiles of baclofen in a multiparticulate system comprising glyceryl palmitostearate with different additives.

[0017] Figure 11 shows a dissolution profile of levodopa in multiparticulate systems comprising glyceryl behenate at different ratios.

[0018] Figure 12, Panel A shows a photograph of a multiparticulate system comprising an active agent, glyceryl palmitostearate, and HPMC taken at the eighth hour after suspension of the multiparticulate system in media.

[0019] Figure 12, Panel B shows a photograph of a multiparticulate system comprising an active agent, glyceryl palmitostearate, HPMC, and EUDRAGIT® taken at the eighth hour after suspension of the multiparticulate system in media.

[0020] Figure 12, Panel C shows a photograph of a multiparticulate system comprising an active agent, glyceryl behenate, HPMC, and EUDRAGIT® taken at the eighth hour after suspension of the multiparticulate system in media.

[0021] Figure 12, Panel D shows a photograph of a multiparticulate system comprising an active agent, glyceryl behenate, ethyl cellulose, and EUDRAGIT® taken at the eighth hour after suspension of the multiparticulate system in media.

Detailed Description

[0022] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0023] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element.

[0024] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0025] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[0026] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0027] The multiparticulate systems using a lipid-based low-density excipient or excipients can provide for increased residence time of active agent in the upper gastrointestinal (GI) tract as compared to an active agent without a multiparticulate system. Microparticulates of this system can, in some embodiments, float on the surface of the liquid gastric contents, and thus avoid the gastric emptying wave. In addition or alternatively, multiparticulate systems having small particle size can provide for prolonged GI transit time of an active agent as such small particle size allows the microparticulates to become trapped in the folds of the stomach and between the villae of the small intestine. The release profile of the active agent of the multiparticulate systems can be further controlled by incorporation of a control release polymer or a hydrophilic coating or a coating.

[0028] The term "microparticulate" refers to discrete particles, which may be solid or semisolid at room temperature, and which are generally of a size of 500 μm or less or 300 μm or less and usually at least 10 μm.

[0029] The term "multiparticulate system" refers to dosage forms comprising a multiplicity of discrete units, each exhibiting some desired characteristics. In these systems, the dosage is divided into a plurality of subunits.

Multiparticulate Systems Using Lipid-based Low-density Excipients

[0030] The disclosure provides a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein the ratio of lipid-based low-density excipient to active agent can be greater than 1:1, and can be at least 1.5:1, or at least 1.7:1, or at least 2:1. The lipid-based low-density excipient has a density that is lower than the density of gastric fluid in the gastric environment.

The lipid-based low-density excipient is a solid or semi-solid material, which material can be meltable at a temperatue compatible with incorporation of active agent into flowable excipient. In some embodiments, the composition does not include a gas-generating agent.

[0031] The disclosure also provides a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein composition does not include a surfactant.

[0032] The release profile of the composition can be assessed by the paddle method with simulated gastric fluid (SGF). In certain embodiments, the composition releases about 10% to about 30% of the drug within about 1 hour. In certain embodiments, the composition releases about 40% to about 60% of the drug within about 6 hours. In certain embodiments, the composition releases about 60% to about 80% of the drug within about 8 hours. In certain embodiments, the composition releases about 40% to about 60% of the drug within about 16 to 24 hours. In certain embodiments, the composition releases about 60% to about 80% of the drug within about 16 to 24 hours.

[0033] Optionally, the microparticulates of the present disclosure can include a controlled release polymer. Thus, in certain embodiments, the microparticulates comprise an active agent, a lipid-based low-density excipient, and a controlled release polymer.

[0034] Where the microparticulates of the present disclosure include a controlled release polymer, the microparticulates can optionally include a hydrophilic coating or a coating. Thus, in certain embodiments, the microparticulates comprise an active agent, a lipid-based low-density excipient, a controlled release polymer and a hydrophilic coating or a coating.

[0035] As noted herein, in certain embodiments of the present disclosure, the multiparticulate systems do not include a gas-generating agent. A "gas-generating agent" refers to a substance known to produce carbon dioxide or sulfur dioxide upon contact with gastric fluid. Examples of gas-generating agents that produce carbon dioxide include sodium or potassium hydrogen carbonate, calcium carbonate, sodium glycine carbonate. Examples of gas-generating agents that produce sulfur dioxide include sulfur sulfite, sodium bisulfite, and sodium metabisulfite.

[0036] As noted herein, in certain embodiments of the present disclosure, the multiparticulate systems do not include a surfactant. A "surfactant" is an amphiphilic molecule consisting of a hydrophobic tail and a hydrophilic head. They are long chain molecules, such as, for example, soaps or detergents. Examples of surfactants include,

the Tween (polyoxyethylene sorbate) family of surfactants (ICI, Wilmington, Del.), the Span (sorbitan long chain carboxylic acid esters) family of surfactants (ICI), the Pluronic (ethylene or propylene oxide block copolymers) family of surfactants (BASF, Parsippany, N.J.), the Labrasol, Labrafil and Labrafac (each polyglycolyzed glycerides) families of surfactants (GatteFosse, St. Priest, France), sorbitan esters of oleate, stearate, laurate or other long chain carboxylic acids, poloxamers (polyethylene-polypropylene glycol block copolymers), other sorbitan or sucrose long chain carboxylic acid esters, mono and diglycerides, PEG derivatives of caprylic/capric acid triglycerides and mixtures thereof.

[0037] Examples of lipid-based low-density excipients, controlled release polymers, hydrophilic coatings, coatings, and active agents are described below.

Lipid-based Low-density Excipients

[0038] The embodiments provide a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein the ratio of lipid-based low-density excipient to active agent can be greater than 1:1, and can be at least 1.5:1, or at least 1.7:1, or at least 2:1. The embodiments also provide a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein composition does not include a surfactant.

[0039] An "excipient" refers to a substance added to a composition to further facilitate administration of an active agent. A low density excipient has a density that is lower than the density of the gastric fluid in the gastric environment. In one instance, simulated gastric fluid (SGF) can be used to determine if an excipient is a low density excipient.

[0040] "Lipid" refers to a synthetic or naturally occurring compound that possesses both a lipophilic region and a polar region, commonly referred to as a head group. "Lipid-based" refers to a lipid, or derivative of a lipid that substantially maintains the properties of a lipid.

[0041] Examples of lipid-based low-density excipients can include, but not limited to, waxes, glycerides (e.g., GELUCIRE), fatty acids, mineral oil, and vegetable oil. The lipid-based low-density excipient can be substantially non-crosslinked (i.e., substantially no intramolecular cross-linking).

[0042] In certain embodiments, the lipid-based low-density excipient is in solid or semi-solid form at room temperature and melts with heating at a temperature compatible with incorporate of an active agent of interest. For example, such lipid-based low-density

excipients are normally solid at room temperature and have a melting point of about 30°C or higher. In certain embodiments, a suitable lipid-based low-density excipient has a melting point of about 45 °C or higher. In certain embodiments, a suitable lipid-based low-density excipient has a melting point of up about 65 °C. In certain embodiments, a suitable lipid-based low-density excipient has a melting point of up about 80 °C. In certain embodiments, a suitable lipid-based low-density excipient has a melting point of up about 100 °C.

[0043] In certain embodiments, the ratio of the lipid-based low-density excipient to the active agent is greater than 1:1, and can be at least 1.5:1, or at least 1.7:1, or at least 2:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 3:1; 4:1; 5:1; 6:1; 7:1; 8:1; 9:1; or 10:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 5:1.

[0044] In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 1.1:1; 1.2:1; 1.3:1; 1.4:1; 1.5:1; 1.6:1; 1.7:1; 1.8:1; or 1.9:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 2:1; 2.1:1; 2.2:1; 2.3:1; 2.4:1; 2.5:1; 2.6:1; 2.7:1; 2.8:1; or 2.9:1.

[0045] In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 3:1; 3.1:1; 3.2:1; 3.3:1; 3.4:1; 3.5:1; 3.6:1; 3.7:1; 3.8:1; or 3.9:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 4:1; 4.1:1; 4.2:1; 4.3:1; 4.4:1; 4.5:1; 4.6:1; 4.7:1; 4.8:1; or 4.9:1.

[0046] In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 5:1; 5.1:1; 5.2:1; 5.3:1; 5.4:1; 5.5:1; 5.6:1; 5.7:1; 5.8:1; or 5.9:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 6:1; 6.1:1; 6.2:1; 6.3:1; 6.4:1; 6.5:1; 6.6:1; 6.7:1; 6.8:1; or 6.9:1.

[0047] In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 7:1; 7.1:1; 7.2:1; 7.3:1; 7.4:1; 7.5:1; 7.6:1; 7.7:1; 7.8:1; or 7.9:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 8:1; 8.1:1; 8.2:1; 8.3:1; 8.4:1; 8.5:1; 8.6:1; 8.7:1; 8.8:1; or 8.9:1. In certain cases, the ratio of the lipid-based low-density excipient to the active agent is at least 9:1; 9.1:1; 9.2:1; 9.3:1; 9.4:1; 9.5:1; 9.6:1; 9.7:1; 9.8:1; 9.9:1; or 10:1.

Waxes

[0048] In certain embodiments, the lipid-based low-density excipient is a wax.

[0049] Waxes include a variety of compounds including esters of fatty acids with long chain monohydric alcohols; esters of fatty acids with glycerol; hydrocarbons; and mixtures thereof.

[0050] Waxes can include natural waxes, such as animal waxes, vegetable waxes, and petroleum waxes (i.e., paraffin waxes, microcrystalline waxes, petrolatum waxes, mineral waxes), and synthetic waxes. Examples of waxes include white wax, spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, paraffin wax, microcrystalline wax, petrolatum wax, carbowax, and the like, and mixtures thereof.

[0051] The wax can be a monoglyceryl ester, diglyceryl ester, or triglyceryl ester (glycerides) which is an ester formed from a fatty acid having from about 10 to about 22 carbon atoms and glycerol, wherein one or more of the hydroxyl groups of glycerol is substituted by a fatty acid. Examples of such glycerides include glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl didocosanoate, glyceryl tridocosanoate, glyceryl monodocosanoate, glyceryl monocaproate, glyceryl dicaproate, glyceryl tricaproate, glyceryl monomyristate, glyceryl dimyristate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridecenoate, glyceryl behenate and the like, and mixtures thereof.

[0052] In certain embodiments, the waxes can be selected from Cutina (Hydrogenated castor oil), Hydrobase (Hydrogenated soybean oil), Castorwax (Hydrogenated castor oil), Croduret (Hydrogenated castor oil), Carbowax, COMPRITOL (Glyceryl behenate), Sterotex (Hydrogenated cottonseed oil), Lubritab (Hydrogenated cottonseed oil), Apifil (Wax yellow), Akofine (Hydrogenated cottonseed oil), Softtisan (Hydrogenated palm oil), Hydrocote (Hydrogenated soybean oil), Corona (Lanolin), Gelucire (Macrogolglycerides Lauriques), Precirol (Glyceryl Palmitostearate), Emulcire (Cetyl alcohol), Plurol diisostearique (Polyglyceryl Diisostearate), Geleol (Glyceryl Stearate), and mixtures thereof. In certain embodiments, the wax is COMPRITOL (Glyceryl behenate). In certain embodiments, the wax is Precirol (Glyceryl Palmitostearate).

Glycerides

[0053] Glycerides can include semi-synthetic glycerides, such as those made of saturated C_8-C_{18} fatty acid glycerides (e.g., GELUCIRE). In certain embodiments, the lipid is GELUCIRE® 43/0, which has a melting point around 43°C and HLB value of about 1. Other examples of lipids include GELUCIRE® 44/14 (lauryl macrogol-32 glyceride), GELUCIRE® 50/13 (stearoyl macrogol glyceride), and GELUCIRE® 50/13 (stearoyl macrogol glyceride).

Fatty acids

[0054] In certain embodiments, the lipid-based low-density excipient is a fatty acid. The term fatty acid refers to a group of aliphatic saturated or unsaturated carboxylic acids. The chains are usually unbranched and have 6 to 30, preferably 8 to 22, and in particular 8 to 18, carbon atoms. The saturated fatty acids include, for example, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, margaric acid, stearic acid, nonadecanoic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid and melissic acid. The unsaturated fatty acids may be unsaturated one or more times, in particular unsaturated once, twice, three times, four times, five times or six times. Examples of singly unsaturated fatty acids include palmitoleic acid, oleic acid and erucic acid, of doubly unsaturated fatty acids include sorbic acid and linoleic acid, of triply unsaturated fatty acids include linolenic acid and eleostearic acid, of quadruply unsaturated fatty acids include arachidonic acid, of quintuply unsaturated fatty acids include clupanodonic acid, and of sextuply unsaturated fatty acids include docosahexaenoic acid.

Mineral oil and Vegetable oil

[0055] In certain embodiments, the lipid-based low-density excipient is mineral oil.

[0056] In certain embodiments, the lipid-based low-density excipient is vegetable oil.

Controlled Release Polymers

[0057] As discussed above, the composition can optionally include a controlled release polymer. The controlled release polymer can aid dissolution of an active agent in a lipid-based low-density excipient and can mitigate immediate release of the active agent into the gastric environment.

[0058] A factor to determine the use of a controlled release polymer in the composition is the aqueous solubility of the active agent. If an active agent has a high aqueous solubility, a controlled release polymer can be used in the composition. A "highly aqueous soluble active agent" is soluble in less than or about 250 ml of water over a pH range of about 1 to about 7.5. For example, in the Biopharmaceutics Classification System, based on the United States Pharmacopeia (USP) standards, aqueous soluble drug substances fall in Classes I and III.

[0059] Examples of controlled release polymers include, but not limited to, cellulose derivatives, such as hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC), hydroxypropycellulose (HPC), methylcellulose (MC or METHOCEL),

ethylcellulose (EC), hydroxyethylmethylcellulose (HEMC), ethylhydroxy-ethylcellulose (EHEC), and cellulose acetate.

[0060] Other examples of controlled release polymers include poly(meth)acrylate polymers, such as EUDRAGIT® polymers. Certain EUDRAGIT® polymers include EUDRAGIT® NE grade, EUDRAGIT® NM grade, EUDRAGIT® RL grade, and EUDRAGIT® RS grade. Another example of controlled release polymers includes KOLLIDON®.

[0061] In certain embodiments, when a controlled release polymer is included in the multiparticulate system, the ratio of the controlled release polymer to active agent used in the formulation is at least 1:1. In certain cases, the ratio of the controlled release polymer to the active agent is at least 2:1; 3:1; 4:1; or 5:1.

[0062] In certain embodiments, when a controlled release polymer is included in the multiparticulate system and is applied as a coating, the amount of coating is about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% by weight or coating level.

Hydrophilic Coatings

[0063] Where the composition includes a controlled release polymer, the composition can also optionally include a hydrophilic coating. A hydrophilic coating can help with reducing the agglomerations of controlled release polymers in the multiparticulate systems in the gastric environment. Thus, in multiparticulate systems that comprise a hydrophilic coating, there is also a controlled release polymer.

[0064] Suitable hydrophilic coatings include, for example, poly(meth)acrylates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose and hydroxyethyl cellulose, sugars, starch, and combinations comprising one or more of the foregoing hydrophilic polymers.

[0065] Hydrophilic coatings include poly(meth)acrylates, such as EUDRAGIT® polymers. Examples of EUDRAGIT® polymers include EUDRAGIT® NE grade, EUDRAGIT® NM grade, EUDRAGIT® RL grade, and EUDRAGIT® RS grade.

[0066] In certain embodiments, when a hydrophilic coating is included in the multiparticulate system, the ratio of hydrophilic coating to active agent used in the formulation is at least 1:1. In certain cases, the ratio of the hydrophilic coating to the active agent is at least 2:1; 3:1; 4:1; or 5:1.

[0067] In certain embodiments, when a hydrophilic coating is included in the multiparticulate system and is applied as a coating, the amount of coating is about 1%,

1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% by weight or coating level.

Other Coatings

[0068] Certain other suitable coatings that can be used to coat the composition include hydrophobic controlled release polymer coatings, such as ethyl cellulose. Certain other suitable coatings that can be used to coat the composition include enteric coatings, such as EUDRAGIT® L 100 and EUDRAGIT® L 100-55. Certain other suitable coatings that can be used to coat the composition include neutral controlled release polymer coatings, such as EUDRAGIT® NE 30 D and KOLLIDON®.

Particle Sizes for Multiparticulate Systems Using Lipid-based Low-density Excipient

[0069] The multiparticulate system using a lipid-based low-density excipient employs microparticulates with sizes of about 500 μm or less. The microparticulate size is taken when the multiparticulate system comprises an active agent, a lipid-based low-density excipient, an optional controlled release polymer, and an optional hydrophilic coating or coating.

[0070] In certain embodiments, the particle size ranges disclosed herein indicate the particle size range of 90% of the particles in the composition comprising the drug-resin complexes.

[0071] In the discussion herein, if not specified, the lower end of the range is at least 10 μm and can be about 50 μm. In certain embodiments, the particle size is about 480 μm or less. In certain embodiments, the particle size is about 460 μm or less. In certain embodiments, the particle size is about 450 μm or less. In certain embodiments, the particle size is about 440 μm or less. In certain embodiments, the particle size is about 420 μm or less. In certain embodiments, the particle size is about 400 μm or less.

[0072] In certain embodiments, the particle size is about 380 μm or less. In certain embodiments, the particle size is about 360 μm or less. In certain embodiments, the particle size is about 350 μm or less. In certain embodiments, the particle size is about 340 μm or less. In certain embodiments, the particle size is about 320 μm or less. In certain embodiments, the particle size is about 300 μm or less.

[0073] In certain embodiments, the particle size is about 280 μm or less. In certain embodiments, the particle size is about 260 μm or less. In certain embodiments, the particle size is about 250 μm or less. In certain embodiments, the particle size is about 240 μm or less. In certain embodiments, the particle size is about 220 μm or less. In certain embodiments, the particle size is about 200 μm or less.

[0074] In certain embodiments, the particle size is about 180 μm or less. In certain embodiments, the particle size is 160 μm or less. In certain embodiments, the particle size is about 150 μm or less. In certain embodiments, the particle size is about 140 μm or less. In certain embodiments, the particle size is about 120 μm or less.

[0075] In certain embodiments, the particle size range is from about 100 μm to about 450 μm. In certain embodiments, the particle size range is from about 100 μm to about 400 μm. In certain embodiments, the particle size range is from about 100 μm to about 350 μm. In certain embodiments, the particle size range is from about 100 μm to about 300 μm. In certain embodiments, the particle size range is from about 100 μm to about 250 μm. In certain embodiments, the particle size range is from about 100 μm to about 200 μm.

[0076] In certain embodiments, the particle size range is from about 450 μm to about 500 μm. In certain embodiments, the particle size range is from about 400 μm to about 500 μm. In certain embodiments, the particle size range is from about 350 μm to about 500 μm. In certain embodiments, the particle size range is from about 300 μm to about 500 μm. In certain embodiments, the particle size range is from about 250 μm to about 500 μm. In certain embodiments, the particle size range is from about 200 μm to about 500 μm. In certain embodiments, the particle size range is from about 150 μm to about 500 μm.

[0077] In certain embodiments, the particle size range is from about 400 μm to about 450 μm. In certain embodiments, the particle size range is from about 350 μm to about 450 μm. In certain embodiments, the particle size range is from about 300 μm to about 450 μm. In certain embodiments, the particle size range is from about 250 μm to about 450 μm. In certain embodiments, the particle size range is from about 200 μm to about 450 μm. In certain embodiments, the particle size range is from about 150 μm to about 450 μm.

Examples of Combinations of Multiparticulate Systems Using Lipid-based Low-density Excipient

[0078] It will be appreciated from above that the disclosure provides a composition comprising microparticulates comprising an active agent, a lipid-based low-density excipient, an optional controlled release polymer, and an optional hydrophilic coating or coating. Examples of a composition comprising microparticulates comprising an active agent, a lipid-based low-density excipient, an optional controlled release polymer, and an optional hydrophilic coating or coating are described below.

[0079] In certain embodiments, the microparticulates comprise an active agent and glyceryl behenate. In certain embodiments, the microparticulates comprise an active agent and glyceryl behenate, wherein the ratio of glyceryl behenate to active agent is about 5 to 1.

[0080] In certain embodiments, the microparticulates comprise an active agent, glyceryl behenate, and ethyl cellulose.

[0081] In certain embodiments, the microparticulates comprise an active agent, glyceryl behenate, HPMC, and EUDRAGIT®.

[0082] In certain embodiments, the microparticulates comprise an active agent, glyceryl palmitostearate, and HPMC. In certain embodiments, the microparticulates comprise an active agent, glyceryl palmitostearate, and HPMC, wherein the ratio of glyceryl palmitostearate to active agent is about 3 to 1.

[0083] In certain embodiments, the microparticulates comprise an active agent, glyceryl palmitostearate, HPMC, and EUDRAGIT®. In certain embodiments, the microparticulates comprise an active agent, glyceryl palmitostearate, HPMC, and EUDRAGIT®, wherein the ratio of glyceryl palmitostearate to active agent is about 3 to 1.

[0084] In certain embodiments, the microparticulates comprise an active agent, glyceryl palmitostearate, methylcellulose, and EUDRAGIT®.

[0085] The tables below show certain combinations of components for microparticulates. As discussed above, in each of the combinations below, there is at least an active agent dispersed therein, wherein the ratio of lipid-based low-density excipient to active agent is at least 2:1.

Active agent	Lipid-based low-density excipient
baclofen	glyceryl behenate
baclofen	glyceryl palmitostearate

Active agent	Lipid-based low-density excipient	Controlled release polymer
baclofen	glyceryl behenate	ethyl cellulose
baclofen	glyceryl palmitostearate	ethyl cellulose
baclofen	glyceryl behenate	methyl cellulose
baclofen	glyceryl palmitostearate	methyl cellulose
baclofen	glyceryl behenate	HPMC
baclofen	glyceryl palmitostearate	HPMC

Active agent	Lipid-based low-density excipient	Controlled release polymer	Hydrophilic polymer
baclofen	glyceryl behenate	ethyl cellulose	EUDRAGIT®
baclofen	glyceryl palmitostearate	ethyl cellulose	EUDRAGIT®
baclofen	glyceryl behenate	methyl cellulose	EUDRAGIT®
baclofen	glyceryl palmitostearate	methyl cellulose	EUDRAGIT®
baclofen	glyceryl behenate	HPMC	EUDRAGIT®
baclofen	glyceryl palmitostearate	HPMC	EUDRAGIT®

Active agent	Lipid-based low-density excipient
levodopa	glyceryl behenate
levodopa	glyceryl palmitostearate

Active agent	Lipid-based low-density excipient	Controlled release polymer
levodopa	glyceryl behenate	ethyl cellulose
levodopa	glyceryl palmitostearate	ethyl cellulose
levodopa	glyceryl behenate	methyl cellulose
levodopa	glyceryl palmitostearate	methyl cellulose
levodopa	glyceryl behenate	HPMC
levodopa	glyceryl palmitostearate	HPMC

Active agent	Lipid-based low-density excipient	Controlled release polymer	Hydrophilic polymer
levodopa	glyceryl behenate	ethyl cellulose	EUDRAGIT®
levodopa	glyceryl palmitostearate	ethyl cellulose	EUDRAGIT®
levodopa	glyceryl behenate	methyl cellulose	EUDRAGIT®
levodopa	glyceryl palmitostearate	methyl cellulose	EUDRAGIT®
levodopa	glyceryl behenate	HPMC	EUDRAGIT®
levodopa	glyceryl palmitostearate	HPMC	EUDRAGIT®

Active Agents

[0086] The terms "active agent" or “active pharmaceutical agent” refers either to a medicinal substance intended, after administration, to bring about a preventive or therapeutic response, or to a combination of two or more substances of this type.

[0087] In certain embodiments, the active agent has an absorption that occurs mainly in the upper parts of the gastrointestinal tract. These active agents have a limited window of absorption.

[0088] According to the biopharmaceutical classification of drugs in terms of their solubility and intestinal permeability by the FDA, drugs are categorized into four classes. Class I compounds are defined as those with high solubility and high permeability, and are predicted to be well absorbed when given orally. The other classes, Classes II-IV, suffer from low solubility, low permeability, or both and display variable absorption in different regions of the GI tract and as a consequence, their oral bioavailabilities can be affected by the limited absorption window.

[0089] In certain embodiments, the active agent is a compound from Classes II-IV, according to the biopharmaceutical classification of drugs in terms of their solubility and intestinal permeability by the FDA. In certain embodiments, the active agent is a compound from Class I, according to the biopharmaceutical classification of drugs in terms of their solubility and intestinal permeability by the FDA.

[0090] The absorption of active agents can be limited by reduced solubility or lack of solubility of an active agent. In certain embodiments, an active agent has reduced solubility or lack of solubility in gastric fluid or water.

[0091] The absorption of active agents can also be limited by the active transport mechanism in the upper GI tract for absorption. Certain active agents may use active transport mechanism from the upper GI tract, but are poorly absorbed in the large intestine (or colon). As a consequence, the oral bioavailability can be affected by the limited absorptive site. In certain embodiments, an active agent is a compound that uses active transport mechanism in the upper GI tract.

[0092] The active agent can be present as different physical forms. Examples of different physical forms of the active agent include, but are not limited to, pharmaceutically acceptable salts, solvates, co-crystals, polymorphs, hydrates, solvates of a salt, co-crystals of a salt, amorphous, and the free form of the active agent.

[0093] In certain embodiments, the active agent is baclofen. When referring to baclofen, the active agent may be in the salt form or the base form (e.g., free base). Further, baclofen may be in the salt form and one well-known commercially available salt for baclofen is its hydrochloride salt. Some other examples of potentially pharmaceutically acceptable salts include basic salt forms, such as its sodium salt and tetrabutylammonium salt.

[0094] In certain embodiments, the active agent is levodopa or a salt thereof. When referring to levodopa, the active agent may be in the salt form or the free form. Levodopa may be commercially available in the free form.

[0095] Certain active agents that have a limited window of absorption include, but are not limited to, acyclovir, bisphosphonates, captopril, furosemide, metformin, gabapentin, ciprofloxacin, cyclosporine, allopurinol, chlordiazepoxide, cinnarizine, and misoprostol.

Preparation of Microparticulates with Lipid-based Low-density Excipients

[0096] The microparticulates with a lipid-based low-density excipient can be prepared by two methods discussed below, including the granulation method and hot melt extrusion method.

Granulation Method

[0097] The microparticulates with a lipid-based low-density exicipient can be prepared by mixing the components and granulating the mixture. In certain embodiments, the method comprises more than one granulating step. In certain embodiments, the mixture is granulated twice.

[0098] In a method of preparation of a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, the method comprises melting a lipid-based low-density excipient to a flowable state; adding an active agent to the molten lipid-based low-density excipient to produce a mixture of the active agent and the lipid-based low-density excipient; cooling the mixture of the active agent and the lipid-based low-density excipient; and granulating the mixture of the active agent and the lipid-based low-density excipient to produce microparticulates. In certain embodiments, the method comprises an additional granulating step. In certain embodiments, the mixture is granulated twice.

[0099] For a composition comprising an optional controlled release polymer or an optional coating, the above method is also used with the addition of adding a controlled release polymer or a coating to the molten lipid-based low-density excipient. Additional controlled release polymer or coating can also be added to the granulated material.

[00100] As discussed above, in the preparation method, a lipid-based low-density excipient is melted to a flowable state. An active agent and optional additives are blended into the molten lipid-based low-density excipient. Gentle stirring of the mixture can be applied. The mixture of the lipid-based low-density excipient, active agent and optional additives is allowed to harden as it cools. The hardened mixture of the lipid-based low-density excipient, active agent and optional additives is then granulated to fine particles.

[00101] Granulation can be performed, for example, with a high shear granulator, twin shell blender or double-cone blender, or a simple planetary mixer. The granulated mixture can be screened through a suitably sized mesh screen. A Fitzmill or Co-mill or

oscillating mill may be used to control granule size. A V-blender or double cone blender may be used for final blending.

[00102] The optional controlled release polymer or optional coating can also be added to the granulated material as a coating. Application of optional controlled release polymer or optional coating is performed with standard procedures. For example, coatings can be applied by using a fluid bed wurster process.

Hot Melt Extrusion Method

[00103] The microparticulates with a lipid-based low-density excipient can be prepared by hot melt extrusion.

[00104] In a method of preparation of a composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, the method comprises mixing a lipid-based low-density excipient and an active agent to produce a mixture of active agent and lipid-based low-density excipient; dry blending the mixture; forcing the mixture through a hot melt extruder to produce extrudates; and grinding the extrudates to produce microparticulates.

[00105] For a composition comprising an optional controlled release polymer or optional coating, the above method is also used with the addition of adding a controlled release polymer or a coating to the mixture before introduction into the hot melt extruder.

[00106] Granulation can be performed, for example, with a high shear granulator, twin shell blender or double-cone blender, or a simple planetary mixer. The granulated mixture can be screened through a suitably sized mesh screen. A Fitzmill or Co-mill or oscillating mill may be used to control granule size. A V-blender or double cone blender may be used for final blending.

[00107] The optional controlled release polymer or optional hydrophilic coating or optional coating can also be added to the granulated material as a coating. Application of optional controlled release polymer or optional hydrophilic coating or optional coating is performed with standard procedures. For example, coatings can be applied by using a fluid bed wurster process.

Methods of Administration

[00108] The compositions can be used as pharmaceutical compositions. The compositions can be used for enteral administration, primarily for oral administration. The preparations can be in solid form, for instance, in capsule, powder, or granule, or tablet form. Alternatively, the composition may be dispersed into a suitable liquid for, e.g., pediatric use.

[00109] A composition in the form of a tablet can be prepared using any suitable conventional pharmaceutical additions routinely used for preparing solid compositions. Examples of such additions include, for example, additional carriers, binders, preservatives, lubricants, glidants, disintegrants, flavorants, dyestuffs, and like substances, all of which are known in the art.

[00110] A composition in the form of a capsule can be prepared using routine encapsulation procedures, for example, by incorporation of multiparticulate system and excipients into a gelatin capsule. A composition in the form of a sachet can be prepared using routine procedures, for example, by incorporation of multiparticulate system and excipients into a sachet.

[00111] Any conventional carrier or excipient may be used in the pharmaceutical compositions. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this regard, the preparation of a suitable pharmaceutical composition for a particular mode of administration is well within the scope of those skilled in the pharmaceutical arts. Additionally, the ingredients for such compositions are commercially-available from, for example, Sigma, P.O. Box 14508, St. Louis, Mo. 63178. By way of further illustration, conventional formulation techniques are described in Remington: The Science and Practice of Pharmacy, 20th Edition, Lippincott Williams & White, Baltimore, Md. (2000); and H. C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th Edition, Lippincott Williams & White, Baltimore, Md. (1999).

[00112] Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, such as microcrystalline cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) talc; (7) excipients, such as cocoa butter and suppository waxes; (8) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (9) glycols, such as propylene glycol; (10) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (11) esters, such as ethyl oleate and ethyl laurate; (12) agar; (13) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (14) pyrogen-free water; (15) isotonic saline; (16) Ringer's solution; (17) ethyl alcohol; (18) phosphate buffer solutions; and (19) other non-toxic compatible substances employed in pharmaceutical compositions.

Methods of Testing Composition for Release of Active Agent

[00113] USP Paddle or Basket Method is the Paddle and Basket Method described, e.g., in U.S. Pharmacopoeia XXII (1990), herein incorporated by reference.

[00114] In the methods below, SGF is Simulated Gastric Fluid. SGF can be prepared, as follows. Dissolve 2.0 g of sodium chloride and 3.2 g of purified pepsin that is derived from procine stomach mucosa, with an activity of 800 to 2500 units per mg of protein in 7.0 ml of hydrochloric acid and sufficient water to make 1000 ml. The test solution has a pH of about 1.2.

Paddle Method

[00115] The release of the active agent from the multiparticulate system can be determined by a testing, for example, by the paddle method. In the paddle method, dissolutions runs were performed using USP type 1 or type 2 dissolution test apparatus with a predetermined paddle speed in Simulated Gastric Fluid (SGF), pH1.2 at 37 $\pm$ 5 ^{o}C. At appropriate time interval, samples were withdrawn and analyzed by HPLC.

Basket Method

[00116] The release of the active agent from the multiparticulate system can be determined by a testing, for example, by the basket method. In the basket method, dissolutions runs were performed using a cylindrical basket covered by a mesh. The basket is immersed in Simulated Gastric Fluid (SGF), pH1.2 at 37 $\pm$ 5 ^{o}C, and rotated at a predetermined speed. At appropriate time interval, samples were withdrawn and analyzed by HPLC.

Representative Profiles

[00117] The release profile of the composition can be assessed by the paddle method with simulated gastric fluid (SGF). In certain embodiments, the composition releases about 10% to about 30% of the drug within about 1 hour. In certain embodiments, the composition releases about 40% to about 60% of the drug within about 6 hours. In certain embodiments, the composition releases about 60% to about 80% of the drug within about 8 hours. In certain embodiments, the composition releases about 40% to about 60% of the drug within about 16 to 24 hours. In certain embodiments, the composition releases about 60% to about 80% of the drug within about 16 to 24 hours.

Examples

[00118] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the embodiments, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or

the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. Standard abbreviations may be used.

Example 1

Preparation of Baclofen/Low-density Excipient Multiparticulate System

[00119] An appropriate amount of low-density excipient was melted at temperature about 20 °C above its melting point. For glyceryl palmitostearate (PRECIROL) as the low-density excipient, the temperature is about 60-70 °C. For glyceryl behenate (COMPRITOL) as the low-density excipient, the temperature is about 70-90 °C.

[00120] Baclofen at various ratios with the low-density excipient was added to the molten low-density excipient with gentle stirring. The mixtures were then cooled to room temperature to form solid mixtures.

[00121] The solid mixtures were granulated to produce fine particulates. Appropriate screens were used to sieve and collect granules that range in size from about 106 to about 300 μm.

Example 2

Preparation of Baclofen/Low-density Excipient/Controlled Release Polymer Multiparticulate System

[00122] An appropriate amount of low-density excipient was melted at temperature about 20 °C above its melting point. For glyceryl palmitostearate (PRECIROL) as the low-density excipient, the temperature is about 60-70 °C. For glyceryl behenate (COMPRITOL) as the low-density excipient, the temperature is about 70-90 °C.

[00123] Baclofen at various ratios with the low-density excipient was added to the molten low-density excipient with gentle stirring. Also, ethyl cellulose or HPMC was added along with the baclofen. The mixtures were then cooled to room temperature to form solid mixtures.

[00124] The solid mixtures were granulated to produce fine particulates. Additional HPMC was added in certain cases. Additional glyceryl behenate was added in certain cases.

[00125] Appropriate screens were used to sieve and collect granules that range in size from about 106 to about 200 μm.

Example 3

Preparation of Baclofen/Low-density Excipient/Controlled Release Polymer/Hydrophilic Polymer Multiparticulate System

[00126] An appropriate amount of low-density excipient was melted at temperature about 20 °C above its melting point. For glyceryl palmitostearate (PRECIROL) as the low-density excipient, the temperature is about 60-70 °C. For glyceryl behenate (COMPRITOL) as the low-density excipient, the temperature is about 70-90 °C.

[00127] Baclofen at various ratios with the low-density excipient was added to the molten low-density excipient with gentle stirring. The mixtures were then cooled to room temperature to form solid mixtures.

[00128] The solid mixtures were granulated to produce fine particulates. Appropriate screens were used to sieve and collect granules that range in size from about 106 to about 200 μm.

[00129] Ethyl cellulose or HPMC was added. EUDRAGIT® was also added.

[00130] The solid mixtures were granulated to produce fine particulates. Appropriate screens were used to sieve and collect granules that range in size from about 106 to about 300 μm.

Example 4

Preparation of Levodopa/Low-density Excipient Multiparticulate System

[00131] Appropriate amount of glyceryl behenate were melted at temperature 20 °C above its melting point (70-90 °C). Levodopa was added to the molten glyceryl behenate while stirring gently. Once the glyceryl behenate/levodopa mixture solidified at room temperature, the solids were grind to fine particulates and appropriate screens were used to sieve. Granules with size range from 106 to 425 μm were collected and encapsulated for dissolution testing.

***In-vitro Release* Procedure for Examples**

[00132] All dissolutions runs were performed using USP type 2 dissolution test apparatus with paddle speed 100 RPM in Simulated Gastric Fluid (SGF), pH1.2 at 37 ± 5 °C. At appropriate time interval, samples were withdrawn and analyzed by HPLC with column Waters Symmetry C18, 4.6 x 150 mm, UV detection at 265 nm, and the injection volume is 50 μL.

Example 5

Dissolution Profile of Baclofen/Low-density Excipient Multiparticulate System

[00133] Figure 1 shows a dissolution profile of a multiparticulate system comprising baclofen and a low-density excipient (COMPRITOL 888ATO) that was obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 106-300 μm. The composition of the multiparticulate system is shown below.

	Per capsule	
Component	%w/w	mg
Baclofen	16.70	60
COMPRITOL 888ATO	83.30	300
Total	100.00	360

Example 6

Dissolution Profile of Baclofen/Low-density Excipient/HPMC/EUDRAGIT® NE30D Muliparticulate System

[00134] Figure 2 shows a dissolution profile of a multiparticulate system comprising baclofen, a low-density excipient (PRECIROL ATO5), methylcellulose (METHOCEL), and EUDRAGIT® that was obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 106-300 μm. The composition of the multiparticulate system is shown below.

Component	%w/w	Amount (mg)
Baclofen	12.50	60.00
PRECIROL ATO5	37.50	180.00
METHOCEL K100MCR	25.00	120.00
EUDRAGIT® NE30D	25.00	120.00
Total	100.00	480.00

Example 7

Dissolution Profile of Baclofen/Low-density Excipient/Ethyl Cellulose Multiparticulate System

[00135] Figure 3 shows a dissolution profile of a multiparticulate system comprising baclofen, a low-density excipient (COMPRITOL 888ATO), and ethyl cellulose (EC 100FP) that was obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 106-300 μm. The composition of the multiparticulate system is shown below.

	Per capsule	
Component	%w/w	%w/w
Baclofen	16.67	60
COMPRITOL 888ATO	50.00	180
EC 100 FP*	16.67	60
COMPRITOL 888ATO*	16.67	60
Total	100.00	360

* EC 100 FP was added in the second granulation with COMPRITOL 888ATO as binder.

Example 8

Comparison of Baclofen/Low-density Excipient Multiparticulate Systems with Different Controlled Release Polymers: EC, HPMC, and EUDRAGIT® S100

[00136] Dissolution profiles of different multiparticulate systems comprising baclofen, a low-density excipient (PRECIROL), and various controlled release polymers were obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 100-300 μm. In the multiparticulate systems being compared in this example, the ratio of PRECIROL to baclofen is 3:1 and the ratio of baclofen to controlled release polymer is 1:1.

[00137] As shown in Figure 4, PRECIROL to baclofen with ratio 3:1 did not demonstrate substantial controlled release property. Addition of EC45 FP and EUDRAGIT® S100 showed slight retardation of baclofen release in the first half hour. Addition of HPMC K100M (CR grade) to the PRECIROL/baclofen multiparticulate system resulted in retardation of baclofen release for about 4-6 hours.

Example 9

Comparison of Baclofen/Low-density Excipient Multiparticulate Systems with Addition of EUDRAGIT® NE30D as a Hydrophilic Polymer

[00138] Dissolution profiles of different multiparticulate systems comprising baclofen, a low-density excipient (PRECIROL), and EUDRAGIT® were obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 100-300 μm. In the multiparticulate systems being compared in this example, the ratio of PRECIROL to baclofen is 3:1 and the ratio of baclofen to controlled release polymer to EUDRAGIT® NE30D is 1:2:2.

[00139] Figure 5 shows the release profiles of PRECIROL/baclofen multiparticulate systems have substantially no controlled release properties but with addition of EUDRAGIT® NE30D, the release of baclofen was slowed down from almost instant release to about 2 hours release. The baclofen release was further slowed down with addition of EC45FP at the first half hour from about 50% to about 30%.

[00140] PRECIROL muliparticulate system with HPMC K100 CR and EUDRAGIT® 30D demonstrates substantial controlled release. The release of baclofen from the HPMC/EUDRAGIT® NE30D system was about 12 hours.

Example 10

Comparison of Baclofen/Low-density Excipient Multiparticulate Systems with Different Levels of Low-density Excipient to Baclofen Ratios

[00141] Dissolution profiles of different multiparticulate systems comprising baclofen and a low-density excipient (COMPRITOL) were obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 100-300 μm. In the multiparticulate systems being compared in this example, the ratio of COMPRITOL to baclofen is 3:1 or 5:1.

[00142] Figure 6 shows that a higher low-density excipient ratio to active agent in the multiparticulate system results in slower release of the active agent. Therefore, by adjusting the ratio of low-density excipient to active agent, the release of active agent can be modulated to a targeted release profile.

Example 11

Comparison of Baclofen/Low-density Excipient Multiparticulate Systems with PRECIROL or COMPRITOL as Low-density Excipient

[00143] Dissolution profiles of different multiparticulate systems comprising baclofen and a low-density excipient (PRECIROL or COMPRITOL) were obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 100-300 μm.

[00144] Figure 7 shows that COMPRITOL has slower baclofen release than PRECIROL. Hence, release profiles of baclofen can be modulated by choice of appropriate low-density excipients with the proper low-density excipient to active agent ratio. In addition, further optimization of the profiles can be done by including controlled release polymers as discussed above.

Example 12

Comparison of Baclofen/Low-density Multiparticulate Systems with Different Particle Sizes

[00145] Dissolution profiles of different multiparticulate systems comprising baclofen and a low-density excipient were obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 100-300 μm and 300-600 μm.

[00146] Figure 8 compares dissolution profiles of multiparticulate systems with particles in a range of 100-300 μm and 300-600 μm.

Example 13

Comparison of Baclofen/Low-density Excipient Multiparticulate Systems with Different Levels of Controlled Release Polymer

[00147] Dissolution profiles of different multiparticulate systems comprising baclofen and a low-density excipient (PRECIROL) were obtained through the procedure according to "*In-vitro Release*." In the multiparticulate systems being compared in this example, the ratio of PRECIROL to baclofen is 3:1 and the ratio of baclofen to controlled release polymer is 1:1, 1:2, or 1:4.

[00148] As shown in Figure 9, higher levels of HPMC K100M CR resulted in slower release of baclofen from the multiparticulate systems. HPMC K100M CR is a hydrophilic controlled release polymer that can form a colloidal gel and can swell in contact with media. Active agent release from a multiparticulate system comprising

HPMC K100M CR can occur through diffusion and erosion of the colloidal gel of HPMC. It was also observed that the units of HPMC formed bigger agglomerates after the capsule shells dissolved.

Example 14

Comparison of Baclofen/Low-density Excipient Multiparticulate Systems with Addition of EUDRAGIT® NE30D

[00149] Dissolution profiles of different multiparticulate systems comprising baclofen and a low-density excipient (PRECIROL) were obtained through the procedure according to "*In-vitro Release*." The particle size of the multiparticulate system is in a range of 106-300 μm. In the multiparticulate systems being compared in this example, the ratio of PRECIROL to baclofen is 3:1 and the ratio of baclofen to controlled release polymer is 1:2 and the ratio of baclofen to EUDRAGIT® is 1:2.

[00150] Figure 10 shows the effects of EUDRAGIT® NE30D on release of baclofen from multiparticulate systems with size range of 106-300 μm. Formulation with PRECIROL shows fast release profile with about 100% release in half hour, while the formulation with PRECIROL and EUDRAGIT® NE30D released about 100% in about 2 hours.

[00151] Multiparticulate systems with the same ratio of active agent to HPMC with and without EUDRAGIT® NE30D showed similar release profiles. This result shows that EUDRAGIT® NE30D did not have significant effect on the controlled release of the multiparticulates at the active agent to HPMC 1:2 ratio level. However, based on observations, the advantage of including EUDRAGIT® NE30D in the formulation is that the extension of agglomerations of HPMC systems was reduced in formulations containing EUDRAGIT® NE30D.

Example 15

Dissolution Profile of Levodopa/Low-density Excipient Multiparticulate System

[00152] Figure 11 shows a dissolution profile of a multiparticulate system comprising baclofen and a low-density excipient (COMPRITOL 888ATO) that was obtained through the procedure according to "*In-vitro Release*." The composition of the multiparticulate system is shown below.

Formulation	5:1 Ratio		3:1 Ratio	
	Per Capsule		Per Capsule	
Ingredient	%w/w	mg	%w/w	mg
Levodopa	16.67	145.0	33.33	145.0
COMPRITOL 888ATO	83.33	725.0	66.67	290.0
Total	100.00	870.0	100.00	435.0

[00153] Figure 11 shows dissolution profiles of different ratio of glyceryl behenate (COMPRITOL) to levodopa. When there is a higher the ratio of COMPRITOL, the release profile shows a slower release. This is an example of a system that can be applied to different pharmaceutical drugs and depending on the solubility of the drug, release profiles can be modulated with different excipient to drug ratio.

Example 16

Studies of Floating Properties

[00154] Four different representative formulations were selected to conduct the floatability studies of the particles. All formulations have particle size range of about 106-300 μm and low-density excipient to active agent ratio of 3:1. Formulation A is PRECIROL based system with an active agent to HPMC ratio of 1:1. Formulation B is PRECIROL based system with a ratio of active agent to HPMC to EUDRAGIT® NE30D of 1:2:2. Formulation C is COMPRITOL based system with a ratio of active agent to HPMC to EUDRAGIT® NE30D of 1:2:2. Formulation D is COMPRITOL based system with a ratio of active agent to ethyl cellulose to EUDRAGIT® NE30D of 1:2:2.

[00155] Formulations A, B, C and D samples were studied for their floatability capacity. There was almost no lag time observed for all formulations. As soon as the multiparticulate systems contact the media, the particles floated to the surface of the media. Photographs of the multiparticulate systems in the floatability studies are shown in the panels of Figure 12. The photographs were taken at the eighth hour in SGF on horizontal shaker at 100 cycles/min at 37 ^{o}C. Based on observations, particles in Formulation A were mostly suspended in the media at the eighth hour. At the eighth hour, a majority of the particles in Formulations B and C were still floating at the surface of the media with some particles appearing in suspensions and few particles sinking. In Formulation D, there were no particles in suspensions or at the bottom of the vials at the eighth hour.

[00156] In summary, Formulation B, C, and D have good floating capacity with majority of the particles remaining in floatation after 8 hours shaking at 100 cycles/min on horizontal shaker at 37°C. It was also observed in other studies (results not shown) that formulations containing low-density excipients/baclofen have excellent floatability and stayed floated for days. In these other studies, higher low-density excipient levels to active agent ratio showed better floatability.

[00157] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

WHAT IS CLAIMED IS:

1. A composition comprising microparticulates comprising a lipid-based low-density excipient and an active agent dispersed therein, wherein the ratio of lipid-based low-density excipient to active agent is greater than 1:1.

2. The composition of Claim 1, wherein the ratio of lipid-based low-density excipient to active agent is greater than 1.5:1

3. The composition of any of Claims 1-2, wherein the composition does not include a surfactant.

4. The composition of any of Claims 1-3, wherein the active agent is a Class II, or Class III or Class IV compound, according to the biopharmaceutical classification of drugs in terms of their solubility and intestinal permeability by the FDA.

5. The composition of any of Claims 1-3, wherein the active agent is baclofen.

6. The composition of any of Claims 1-3, wherein the active agent is levodopa.

7. The composition of any of Claims 1-3, wherein the lipid-based low-density excipient is a wax.

8. The composition of any of Claims 1-3, wherein the lipid-based low-density excipient is glyceryl palmitostearate or glyceryl behenate.

9. The composition of any of Claims 1-3, wherein the lipid-based low-density excipient is a semi-synthetic glyceride made of a saturated C_8-C_{18} fatty acid glyceride.

10. The composition of any of Claims 1-3, wherein the lipid-based low-density excipient has a melting point of above about 30 ^oC.

11. The composition of any of Claims 1-3, wherein the ratio of lipid-based low-density excipient to active agent is at least 5:1.

12. The composition of any of Claims 1-3, wherein the microparticulates have a size range of about 500 μm or less.

13. The composition of any of Claims 1-3, wherein the microparticulates have a size range of about 300 μm or less.

14. The composition of any of Claims 1-3, further comprising a controlled release polymer.

15. The composition of Claim 14, wherein the controlled release polymer is a cellulose derivative.

16. The composition of Claim 15, wherein the cellulose derivative is hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC), hydroxypropycellulose (HPC), methylcellulose (MC), ethylcellulose (EC), hydroxyethylmethylcellulose (HEMC), or ethylhydroxy-ethylcellulose (EHEC).

17. The composition of Claim 15, wherein the cellulose derivative is hydroxypropylmethylcellulose (HPMC), methylcellulose (MC), or ethylcellulose (EC).

18. The composition of Claim 14, wherein the ratio of controlled release polymer to active agent is at least 1:1.

19. The composition of Claim 14, wherein the ratio of low-density excipient to active agent is at least 3:1.

20. The composition of Claim 18, wherein the ratio of controlled release polymer to active agent is at least 1:1.

21. The composition of Claim 14, further comprising a hydrophilic coating.

22. The composition of Claim 21, wherein the hydrophilic coating is selected from poly(meth)acrylates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and hydroxyethyl cellulose, sugars, and starch.

23. The composition of Claim 21, wherein the hydrophilic coating is EUDRAGIT®.

24. The composition of Claim 23, wherein the EUDRAGIT® is selected from EUDRAGIT® NE grade, EUDRAGIT®™ NM grade, EUDRAGIT® RL grade, and EUDRAGIT® RS grade.

25. The composition of Claim 21, wherein the ratio of lipid-based low-density excipient to active agent is at least 3:1.

26. The composition of Claim 21, wherein the ratio of controlled release polymer to active agent is at least 1:1.

27. The composition of Claim 21, wherein the ratio of hydrophilic coating to active agent is at least 1:1.

28. A composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein, wherein

the ratio of lipid-based low-density excipient to active agent is at least 5:1;

the lipid-based low-density excipient is glyceryl behenate;

the size range of the microparticulates is less than about 300 μm.

29. A composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein, and ethyl cellulose, wherein

the ratio of lipid-based low-density excipient to active agent is at least 2:1;

the size range of the microparticulates is less than about 300 μm.

30. A composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein, ethyl cellulose, and EUDRAGIT®, wherein

the ratio of lipid-based low-density excipient to active agent is at least 2:1;

the lipid-based low-density excipient is glyceryl behenate;

the size range of the microparticulates is less than about 300 μm.

31. A composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein, and HPMC, wherein

the ratio of lipid-based low-density excipient to active agent is at least 3:1;

the lipid-based low-density excipient is glyceryl palmitostearate;

the size range of the microparticulates is less than about 300 μm.

32. A composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein, HPMC, and EUDRAGIT®, wherein

the ratio of lipid-based low-density excipient to active agent is at least 3:1;

the lipid-based low-density excipient is glyceryl palmitostearate;

the size range of the microparticulates is less than about 300 μm.

33. A composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein, methocel, and EUDRAGIT®, wherein

the ratio of lipid-based low-density excipient to active agent is at least 2:1;

the lipid-based low-density excipient is glyceryl palmitostearate;

the size range of the microparticulates is less than about 300 μm.

34. A method of preparing a composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein; wherein the ratio of lipid-based low-density excipient to active agent is at least 1:1; the method comprising:

melting a lipid-based low-density excipient;

adding an active agent to the molten lipid-based low-density excipient to produce a mixture of the active agent and the lipid-based low-density excipient;

cooling the mixture of the active agent and the lipid-based low-density excipient; and

granulating the mixture of the active agent and the lipid-based low-density excipient to produce multiparticulates.

35. The method of Claim 34, further comprising an additional granulating step.

36. A composition produced by the method of any one of Claims 34 and 35.

37. A method of preparing a composition comprising microparticulates comprising a lipid-based low density excipient and an active agent dispersed therein; wherein the ratio of lipid-based low-density excipient to active agent is at least 1:1; the method comprising:

mixing a lipid-based low-density excipient and an active agent to produce a mixture of active agent and lipid-based low-density excipient;

dry blending the mixture;

forcing the mixture through a hot melt extruder to produce extrudates; and

grinding the extrudates to produce microparticulates.

38. A composition produced by the method of Claim 37.

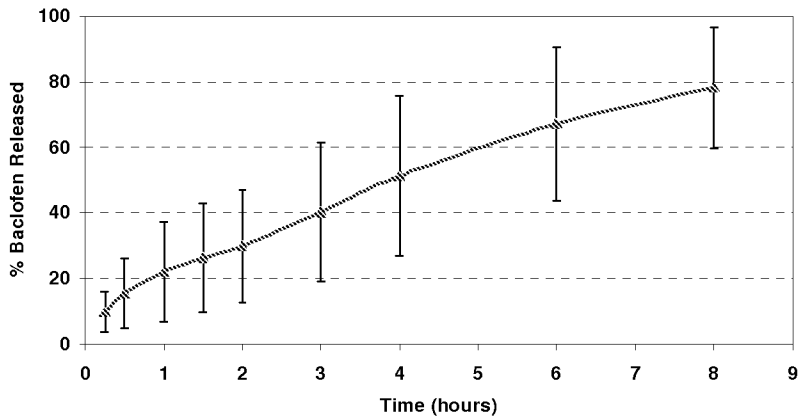

Figure 1

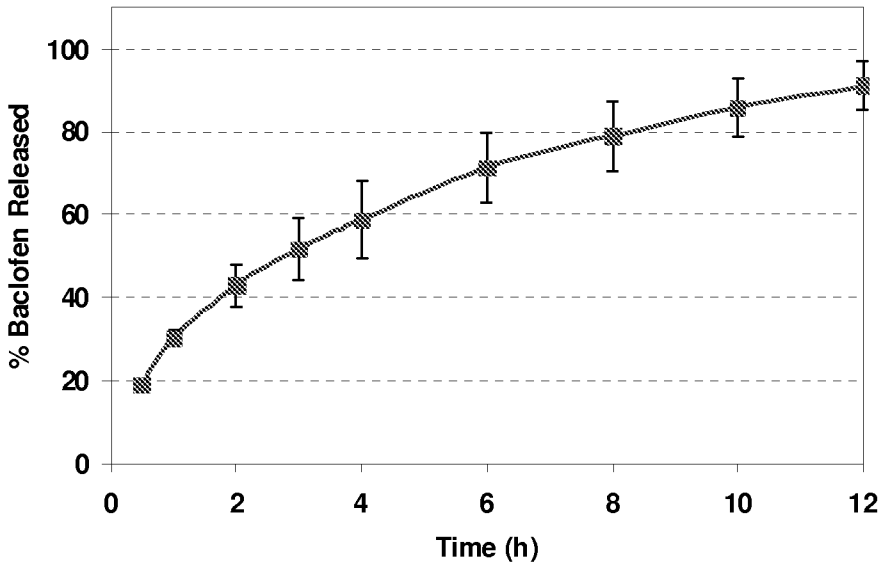

Figure 2

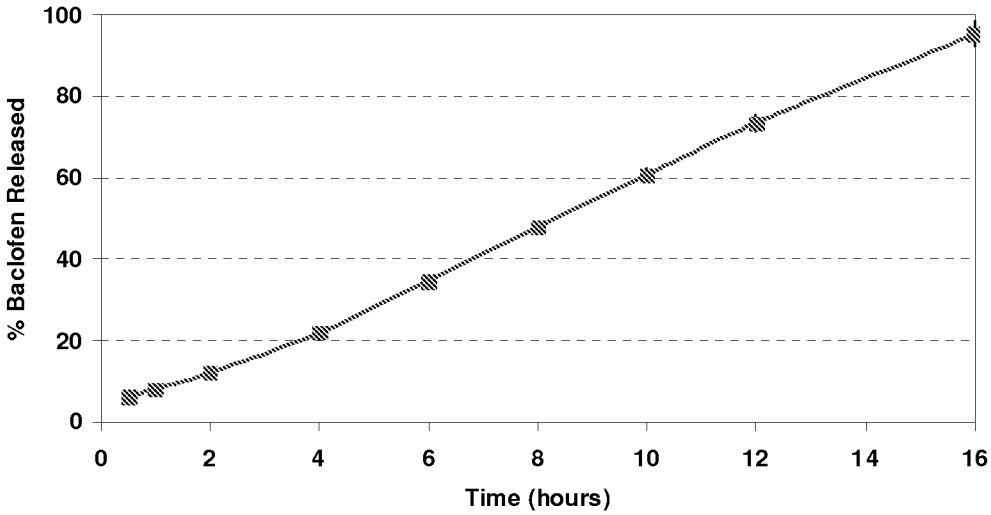
100
80
60
40
20
0
% Baclofen Released
0
2
4
6
8
10
12
14
16
Time (hours)

Figure 3

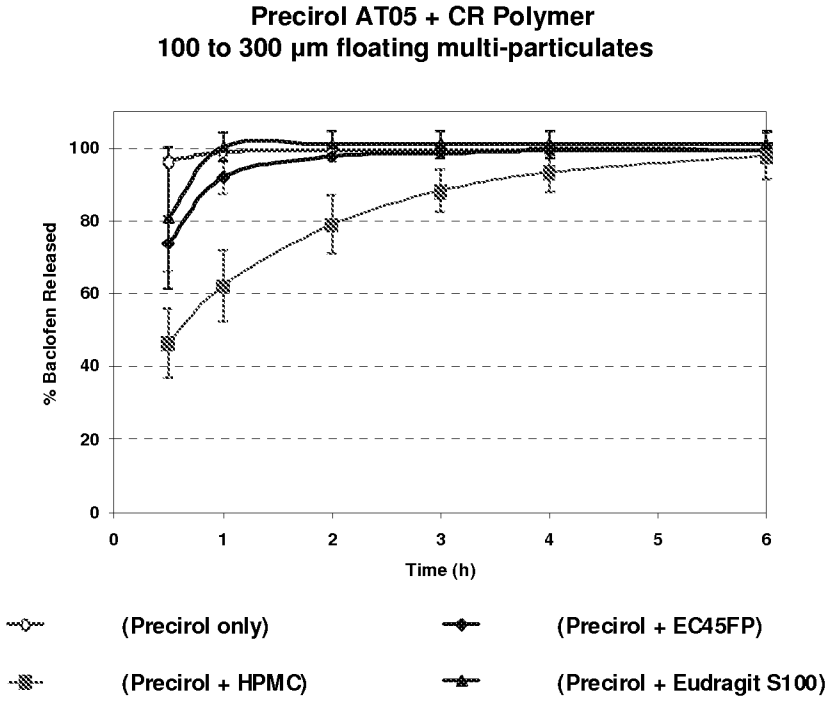
Precirol AT05 + CR Polymer
100 to 300 µm floating multi-particulates
% Baclofen Released
100
80
60
40
20
0
0
1
2
3
4
5
6
Time (h)
(Precirol only)
(Precirol + EC45FP)
(Precirol + HPMC)
(Precirol + Eudragit S100)

Figure 4

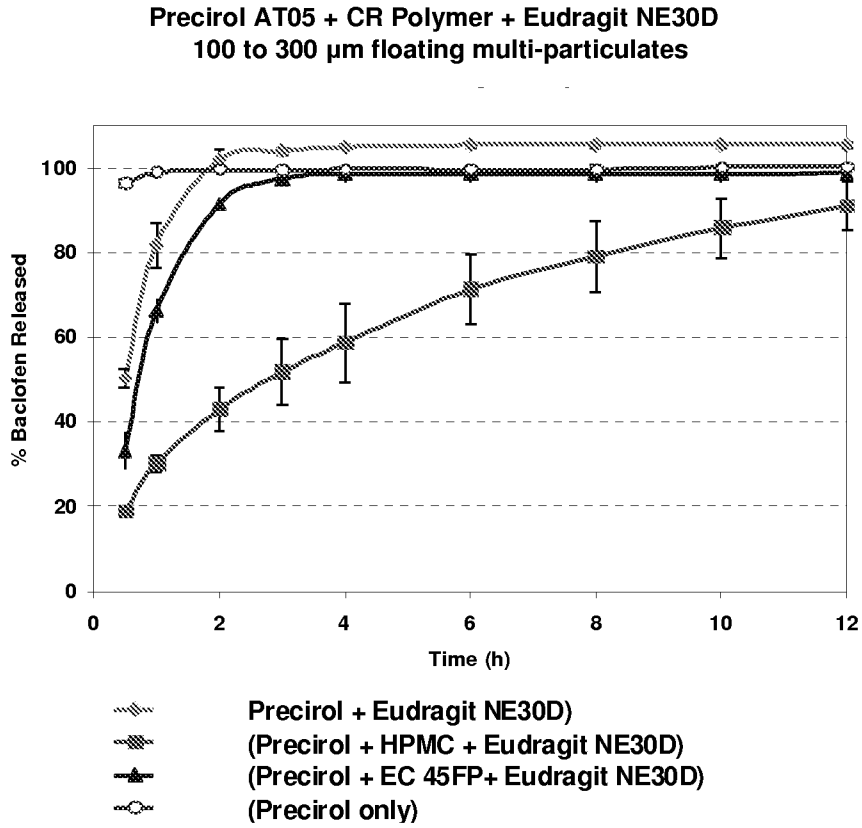
Precirol AT05 + CR Polymer + Eudragit NE30D
100 to 300 µm floating multi-particulates
% Baclofen Released
0
20
40
60
80
100
0
2
4
6
8
10
12
Time (h)
Precirol + Eudragit NE30D)
(Precirol + HPMC + Eudragit NE30D)
(Precirol + EC 45FP+ Eudragit NE30D)
(Precirol only)

Figure 5

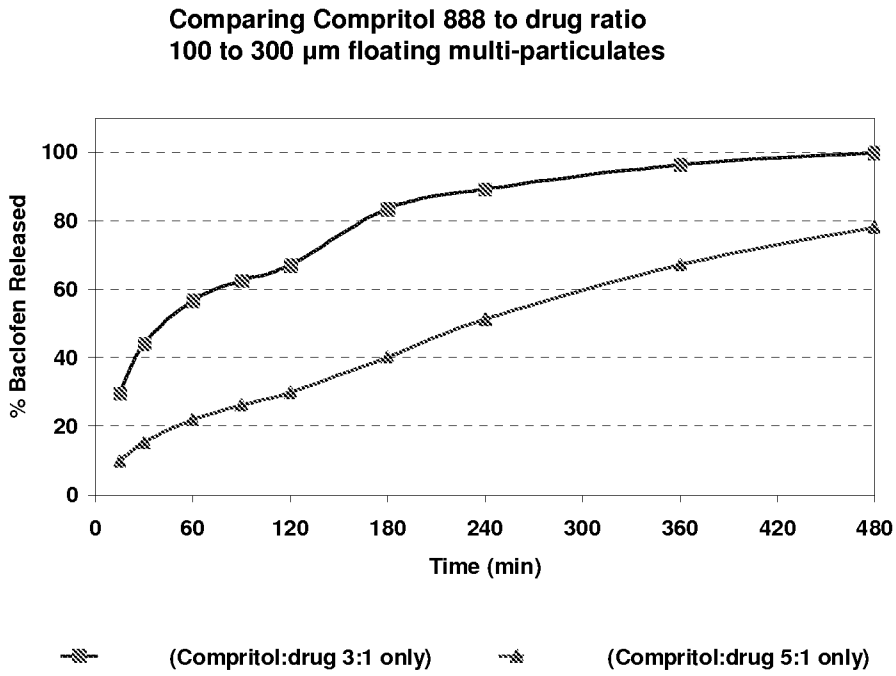
Comparing Compritol 888 to drug ratio
100 to 300 µm floating multi-particulates
% Baclofen Released
100
80
60
40
20
0
0
60
120
180
240
300
360
420
480
Time (min)
(Compritol:drug 3:1 only)
(Compritol:drug 5:1 only)

Figure 6

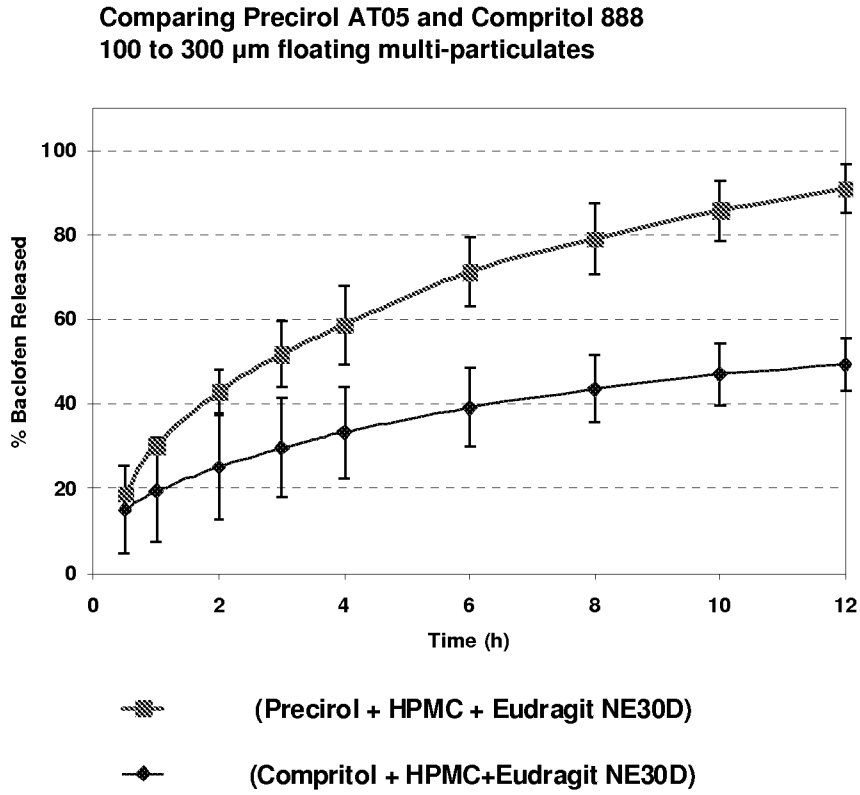
Comparing Precirol AT05 and Compritol 888
100 to 300 µm floating multi-particulates
% Baclofen Released
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (h)
(Precirol + HPMC + Eudragit NE30D)
(Compritol + HPMC+Eudragit NE30D)

Figure 7

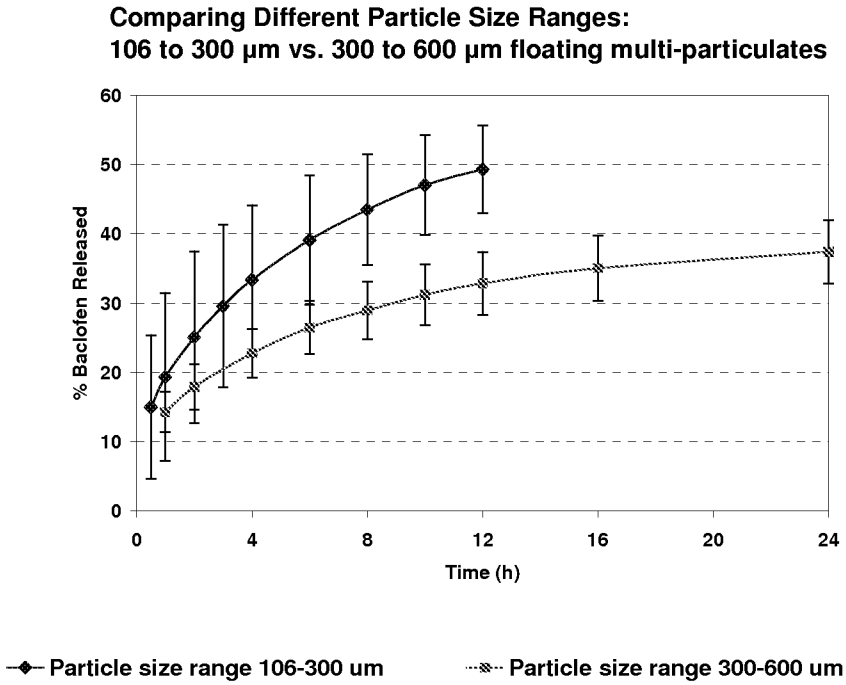
Comparing Different Particle Size Ranges:
106 to 300 µm vs. 300 to 600 µm floating multi-particulates
% Baclofen Released
0
10
20
30
40
50
60
0
4
8
12
16
20
24
Time (h)
Particle size range 106-300 um
Particle size range 300-600 um

Figure 8

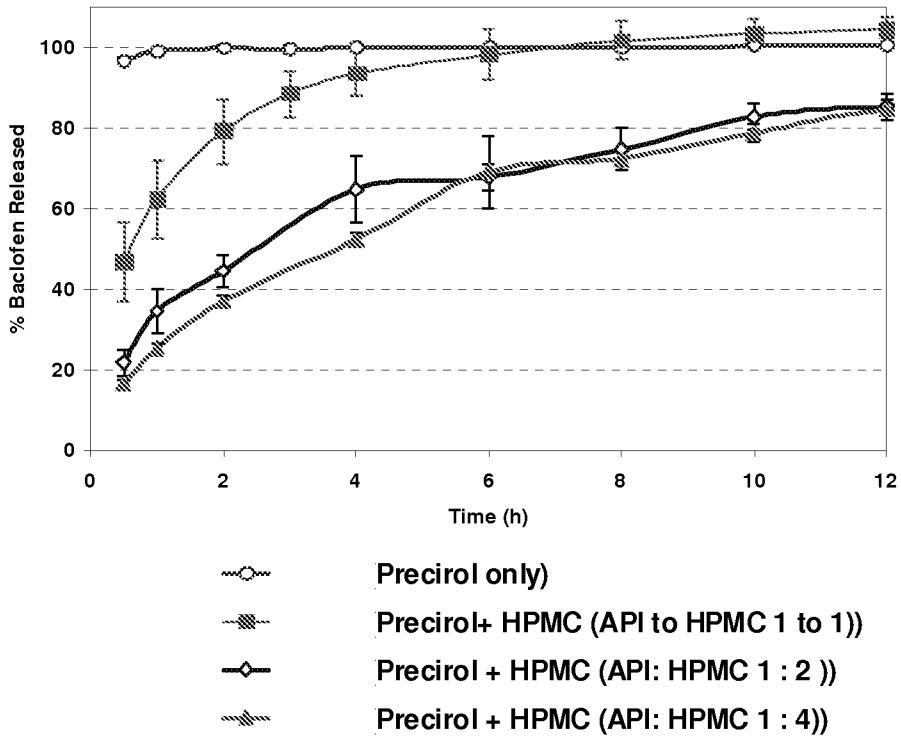
% Baclofen Released
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (h)
Precirol only)
Precirol+ HPMC (API to HPMC 1 to 1))
Precirol + HPMC (API: HPMC 1 : 2))
Precirol + HPMC (API: HPMC 1 : 4))

Figure 9

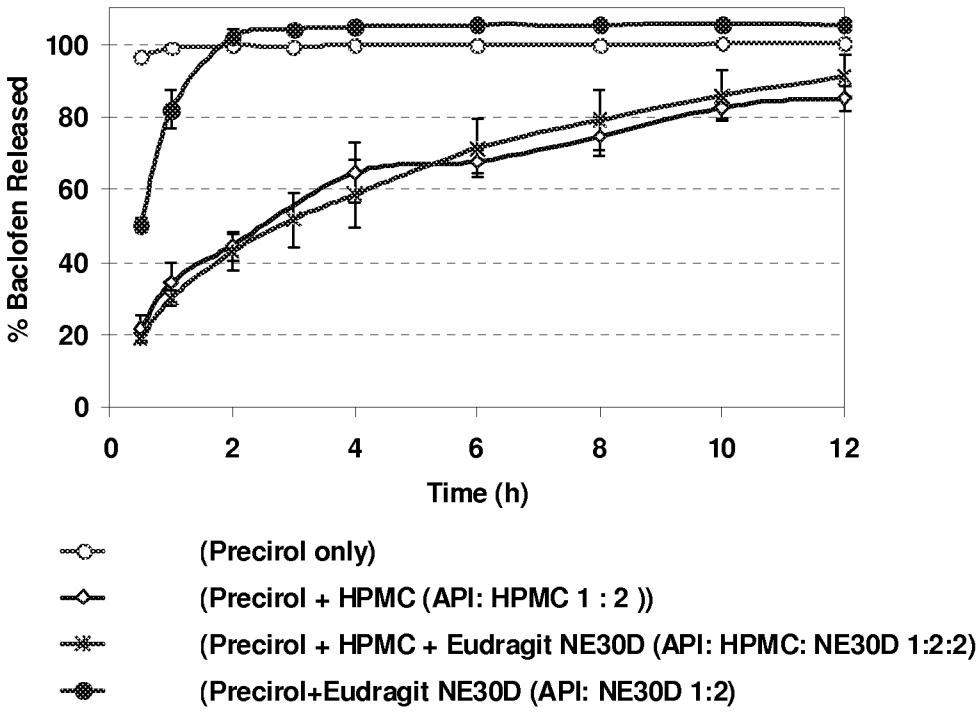
% Baclofen Released
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (h)
(Precirol only)
(Precirol + HPMC (API: HPMC 1 : 2))
(Precirol + HPMC + Eudragit NE30D (API: HPMC: NE30D 1:2:2)
(Precirol+Eudragit NE30D (API: NE30D 1:2)

Figure 10

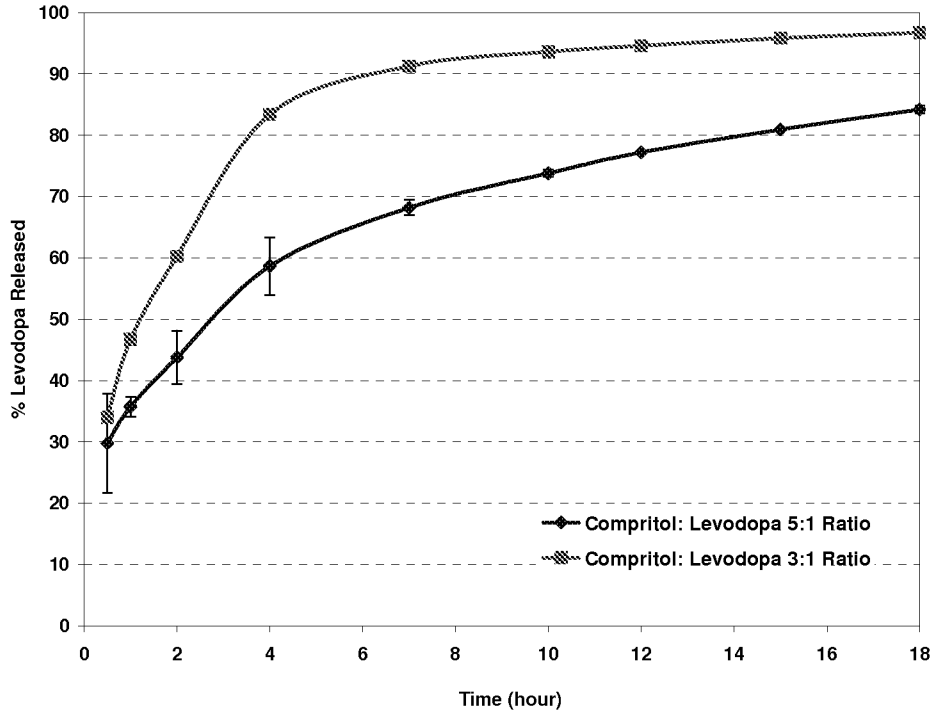
100
90
80
70
60
50
40
30
20
10
0
% Levodopa Released
0
2
4
6
8
10
12
14
16
18
Time (hour)
Compritol: Levodopa 5:1 Ratio
Compritol: Levodopa 3:1 Ratio

Figure 11

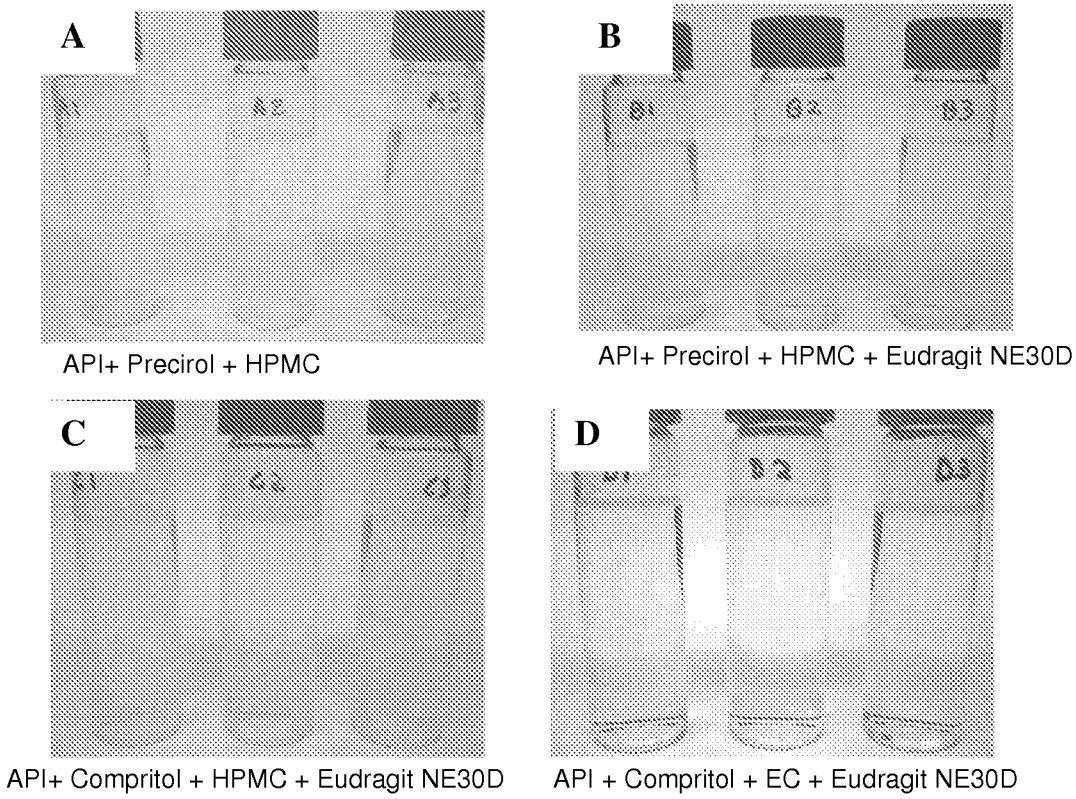
A
API+ Precirol + HPMC
B
API+ Precirol + HPMC + Eudragit NE30D
C
API+ Compritol + HPMC + Eudragit NE30D
D
API + Compritol + EC + Eudragit NE30D

Figure 12