SUSTAINED RELEASE COMPOSITIONS OF DRUGS

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ABSTRACT

A sustained release pharmaceutical composition has been developed. The composition resists dose dumping when broken, crushed or chewed, which enhances the safety of the dosage form should it be accidentally or intentionally physically compromised. In the preferred embodiment, a drug is modified to increase its lipophilicity. In preferred embodiments the modified drug is homogeneously dispersed within microparticles composed of a material that is either slowly soluble or not soluble in water. In some embodiments the drug containing microparticles coated with one or more coating layers. The sustained release composition retards the release of drug, even if the physical integrity of the formulation is compromised (for example, by chewing or crushing) and the resulting material is placed in 0.1N HCl. However, when administered as directed, the drug is slowly released from the composition as the composition is broken down or dissolved gradually within the GI tract by a combination of diffusion, surfactant action of bile acids, mechanical erosion, and in some embodiments, enzymatic degradation.
SUSTAINED RELEASE COMPOSITIONS OF DRUGS

CROSS REFERENCE TO RELATED APPLICATIONS


BACKGROUND OF THE INVENTION

[0002] The present invention is generally in the field of pharmaceutical compositions, and specifically relates to compositions that are designed to provide a sustained release of drug over time after oral administration.

[0003] Sustained release pharmaceutical formulations, which release drug over an extended period of time, are widely used in the pharmaceutical industry. Such formulations provide several potential advantages to the patient including: (1) the convenience of reduced dosing frequency, (2) optimization of therapy by providing a smoother, more constant, plasma level of drug, and (3) a potential reduction in side effects.

[0004] Several formulations that achieve sustained release of drug when administered orally have been described in the literature. In general, oral sustained release dosage forms can be classified as diffusion-controlled, erosion-controlled or osmotic pressure-controlled. For diffusion based systems, control of drug release is usually achieved by dispersing the drug in an inert insoluble matrix or by coating a drug containing core with an insoluble polymeric film. Erosion controlled formulations can be achieved by dispersing the drug in a slowly soluble carrier material or by coating the drug with a slowly soluble material. Osmotic systems are monolithic in nature and consist of a core containing an osmotically active drug or a drug in combination with an osmotically active salt, surrounded by a semi-permeable membrane containing a small orifice.

[0005] Although many types of sustained release dosage forms have been described, currently available sustained release dosage forms have some inherent disadvantages. Monolithic dosage forms, such as tablets or capsules, can be difficult for some patients to swallow. Since sustained release formulations can be subject to dose dumping when they are crushed, these products come with specific instructions not to break, chew or crush them. While there are some available multiparticulate formulations (such as particles-in-capsule and sachets) that can be administered as particles, for example after sprinkling in applesauce, such formulations are still potentially dangerous if the particles are accidentally chewed, broken or their physical integrity is compromised, thus resulting in the destruction of the sustained release feature.

[0006] It is therefore an object of the present invention to provide a sustained-release, multiparticulate pharmaceutical composition that resists dose dumping when accidentally broken, crushed or chewed.

SUMMARY OF THE INVENTION

[0007] Sustained release pharmaceutical compositions and the methods of making and using the composition have been developed. The compositions can be used to improve the convenience and safety of administration when a sustained release dosage form is desired. In the preferred embodiment, the drug is chemically modified to increase its lipophilicity. In other embodiments, the formulation contains lipophilic or water-insoluble materials or is made using a process which increases the lipophilicity and/or water-insolubility of the composition. In some embodiments, the individual drug-containing microparticles or drug particles are coated with one or more independent coating layers. The compositions retard the release of drug, even if the physical integrity of the dosage form is compromised (for example, by breaking or chewing).

[0008] The compositions achieve a sustained release profile where the drug is released over an extended period of time, typically from 6 to 24 hours. Additional compositions are provided which achieve a small immediate dose that precedes the sustained release of drug. The compositions disclosed herein may optionally include a combination of active pharmaceutical agents.

DETAILED DESCRIPTION OF THE INVENTION

[0010] Disclosed herein are sustained-release pharmaceutical compositions and the method of making and using the compositions.

I. Compositions

[0011] As used herein, “composition” or “compositions” refers to the drug dosage unit for administration to a patient. This may also be used in reference to the final dosage form (tablet or capsule) or to components of the final dosage form (microparticles or coated microparticles).

[0012] Currently available sustained release formulations are subject to dose dumping when chewed or crushed because mechanical destruction of the dosage form exposes the encapsulated drug and allows for immediate dissolution of the drug into aqueous media. Two properties of the dosage form that contribute to this outcome are (1) the ease with which drug is exposed when the compositions are broken or chewed and (2) the high water solubility of the drug salt form.

[0013] In the composition disclosed herein, one or both of these properties are altered in order to achieve a composition which resists dose dumping when chewed or broken. Specifically, in the preferred embodiment, the drug is modified to increase its lipophilicity and, in additional preferred embodiments, is then homogeneously dispersed within a material that is either slowly soluble or not soluble in water and subsequently formulated into microparticles. The drug may be present in the form of discrete particles or may be partially or fully dispersed in the carrier material on a molecular level.
The sustained release composition preferably includes a drug modified to increase its lipophilicity. In other preferred embodiments, the drug is homogeneously dispersed within microparticles composed of a material that is either slowly soluble in water or water insoluble. The compositions slow the release of drug if the dosage form is broken or chewed and the resulting material is swallowed since most of the drug will remain associated with or entrapped within portions of the core material of the microparticles. In some embodiments the drug containing microparticles or individual drug particles are coated with one or more coating layers.

A. Drugs to be Formulated

There are many drugs that is desirable to deliver using the compositions described herein.

Exemplary drug agents useful for forming the composition described herein include, but are not limited to, analgesic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticoagulant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; antiinflammatory agents; antimalarial agents; antineoplastic agents; antiparkinsonism drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiviral agents; anxiolytic agents; appetite suppressants; attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antiarrhythmic agents, central nervous system (“CNS”) agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormones; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympathomimetics; peptide drugs; psychostimulants; sedatives; steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonists; and coagulants.

Drugs that are most preferable include those that are currently formulated as sustained or controlled release compositions, where drug release is intended to occur over a prolonged period of time through the gastrointestinal tract, and immediate or burst release is undesirable. Specific examples of agents currently formulated in sustained or controlled release formulations include, but are not limited to, acetaminophen, acetoaminophen, albuterol, alfaxozin, alprazolam, amoxicillin, amphetamine, aspirin, brompheniramine, bupropion, carbamazepine, carbiprod, carbinoxamine, cetirizine, chlorpheniramine, ciprofloxacin, clarithromycin, clavulanate, cloroazepate, celestol, dextrothyroidine, dextromethorphan, dextromethorphan, diclofenac, deflazacort, diltiazem, dipyriramole, disopyramide, divalproex sodium, doxazosin, doxylcine, enalapril, etodolac, felodipine, fexofenadine, fluoxetine, fluvalastin, glipizide, guaifenesin, hyoscynamine, indomethacin, isosorbide dinitrate, isosorbide mononitrate, isradpine, ketoprofen, levodopa, loradatine, lovastatin, meclizine, metformin, methscopolamine, methylphenidate, metoprolol, metronidazole, minocycline, morphine, naproxen, nisac, nicardipine, nifedipine, nisoldipine, nitroglycerin, orphenadrine, oxybutynin, oxycodone, oxymorphone, papaverine, paroxetine, pentoxifyline, phenidinomazine, phenylamine, phenyliso-

The terms “drug”, “active agent”, and “pharmacologically active agent” are used interchangeably herein to refer to a chemical compound that includes a desired pharmacological and/or physiological effect. The terms also encompass pharmaceutically acceptable derivatives of those active agents specifically mentioned herein, including, but not limited to, salts, solvates, hydrates, complexes with one or more molecules, prodrugs, active metabolites, analogs, and the like. When the terms “active agent”, “pharmacologically active agent” and “drug” are used, or when a particular drug, such as oxycodone, is identified, it is to be understood as including the active agent per se as well as pharmaceutically acceptable salts, solvates, hydrates, complexes with one or more molecules, prodrugs, active metabolites, and analogs.

Certain compounds described herein may exist in particular geometric or stereoisomeric forms. The composition disclosed herein contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof, compounds of different spacial conformations, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

As used herein, “pharmacologically acceptable salts” refer to derivatives of the disclosed compounds wherein the parent compound is modified by acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids.

The pharmaceutically acceptable salts of the compounds can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropyl alcohol, or acetonitrile are preferred. Optionally, the salt can also be formed as part of the manufacturing process for the composition. For fatty acid salts such as oleate, myristate, palmitate or stearate, this can be accomplished by melting the fatty acid, optionally along with other waxes, and adding the free base of the drug directly into this melt. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 20th ed., Lippincott Williams & Wilkins, Baltimore, Md., 2000, p. 704, the disclosure of which is hereby incorporated by reference.

Optionally, the composition described herein can include a combination of active pharmaceutical agents.

B. Drug Solubility Modification

In preferred embodiments, the solubility characteristics of a drug are altered prior to incorporation into the formulation. Modification of the drug to produce a more lipophilic derivative serves to reduce the water solubility of
the drug and thus reduces the aqueous extractability. Furthermore, if the drug is made more lipophilic, it can be solubilized in the molten carrier material, rather than physically dispersed in a particulate form. When drug is solubilized in the carrier material it is difficult to extract drug from the resulting intimately dispersed composition.

[0026] The terms “lipophilic derivative” and “lipophilic drug derivative”, as used herein, refer to derivatives of the drug that are less soluble in water than the most soluble salt of the drug. The most soluble salt is selected from either drug alkaline metal salts (for acidic drugs) or salts of the drug with inorganic acids (for basic drugs). The examples of the latter include, but are not limited to, hydrohalates, sulfates, and nitrates.

[0027] Some of the methods that can be used to alter the drug’s lipophilicity are outlined below. It is understood that two or more approaches can be combined to achieve a desired solubility profile.

[0028] Methods for Increasing Lipophilicity

[0029] In one embodiment, a drug is made more lipophilic by eliminating or reducing the overall charge of the drug molecule. For example, for a basic drug, a water soluble salt (such as hydrochloride, sulfate, or malenate) can be converted to a free base using techniques known in the art. Correspondingly, in the case of an acidic drug, a water soluble salt (such sodium, potassium, or the like) can be converted to a free acid.

[0030] In another embodiment, the drug’s lipophilicity is increased by forming a salt between a drug molecule and a charged compound. In this case the lipophilicity, or water solubility, of the resulting salt can be manipulated by varying the counter-ion. In general, lipophilic acids or amines with chain lengths between C₅-C₂₀ are lipophilic counter-ion candidates. Some specific examples include, but are not limited to, linoleic acid, octanoic acid, lauric acid, stearic acid, palmitic acid, lauryl sulfate, oleic acid, octyl amine, lauryl amine, stearyl amine, palmityl amine, linoleyl amine, and oleyl amine. Other salts which may increase lipophilicity and, hence, lipid solubility relative to the parent drug compound include, but are not limited to, pectinate, tannate, pythate, salicylate, saccharinate, acesulfamate, gallate, and terephthalate salts. The counter-ion used for salt formation may also be polymeric in nature. For example, anionic copolymers based on methacrylic acid and methyl methacrylate sold under the trade name Eudragit® (e.g., Eudragit® L 100 and Eudragit® S 100), acrylic acid polymers, and crosslinked acrylic acid polymers may be used to form a salt with drug molecules. Naturally occurring polymers and their derivatives, for example, carboxymethyl cellulose, may also be used to form a salt with the drug molecules. In the case of polymeric counterions, the number of drug molecules reacted with the polymer to form a salt may or may not be equimolar with respect to the number of salt-forming sites on the polymer chain.

[0031] The formation of a salt composed of a pharmaceutically active agent and a fatty acid or amine can be accomplished by a melt process, with or without the use of a solvent. One or more fatty acids or amines are heated above their melting point and the pharmaceutically active agent, in free base or acid form, is added to the molten fatty acid or amine, respectively, either directly or after dissolution of the active agent in an appropriate solvent. The fatty acid or fatty amine may be present in an equimolar amount or may be present in excess with respect to the free base or free acid of the active agent.

[0032] In another embodiment, a drug is covalently modified to increase its lipophilicity. For example, a lipophilic compound can be covalently attached to a drug molecule via an ester or amide linkage. Such drug derivatives are cleaved in vivo, thus releasing the parent compound.

[0033] C. Drug Containing Microparticles

[0034] In preferred embodiments, drugs are formulated with a carrier material to form microparticles. As used herein, the term “microparticle” refers to a composition including a drug dispersed within a carrier material and “coated microparticle” refers to a composition including a drug containing microparticle or a drug particle coated with one or more coating layers of material. Microparticles and coated microparticles have a size range of 10 to 3000 microns in diameter.

[0035] Within microparticles, drug is preferably homogeneously dispersed in the form of fine particles within the carrier material. More preferably, drug is partially solubilized in molten carrier material or partially dissolved with the carrier material in a mutual solvent during the formulation of the microparticles. Most preferably, drug is completely solubilized in the molten carrier material or completely dissolved with the carrier material in a co-solvent during the formulation of the microparticles. This is accomplished through the selection of materials and the manner in which they are processed.

[0036] Carrier materials appropriate for the fabrication of drug containing microparticles are either slowly soluble in water or insoluble in water, but capable of degrading within the GI tract by means including enzymatic degradation, surfactant action of bile acids and mechanical erosion. As used herein, the term “slowly soluble in water” refers to materials that are not dissolved in water within a period of 30 minutes. Preferred examples include fats, fatty substances, waxes, wax-like substances and mixtures thereof. Suitable fats and fatty substances include fatty alcohols (such as lauryl, myristyl stearyl, cetyl or cetostearyl alcohol), fatty acids and derivatives, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di- and tri-glycerides), and hydrogenated fats. Specific examples include, but are not limited to: hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated castor oil, hydrogenated oils available under the trade name Sterotex®, stearic acid, cocoa butter, glycerol behenate (available under the trade name COMPOTOL® 888®), glycerol dipalmitostearate (available under the trade name PRECIROL®), and stearyl alcohol. Mixtures of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of polyethylene glycol, available under the trade name GELUCIRE® are also suitable fatty materials. Suitable waxes and wax-like materials include natural or synthetic waxes, hydrocarbons, and normal waxes. Specific examples of waxes include beeswax, glycerox, castor wax, carnauba wax, paraffins and candelilla wax. As used herein, a wax-like material is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to 300° C.

[0037] In some cases, it may be desirable to alter the rate of water penetration into the hydrophobic drug containing microparticles. To this end, rate-controlling (wicking) agents may be formulated along with the fats or waxes listed above. Examples of rate-controlling materials include certain starch derivatives (e.g., waxy maleodextrin and drum dried corn starch), cellulose derivatives (e.g., hydroxypropylmethylcellulose, hydroxypropylecelulose, methylcellulose, and carboxymethylcellulose), alginic acid, lactose and talc.
tionally, a pharmaceutically acceptable surfactant (for example, lecithin) may be added to facilitate the degradation of such microparticles.

[0038] Proteins which are water insoluble, such as zein, are preferred carrier materials for the formation of drug containing microparticles. Additionally, proteins, polysaccharides and combinations thereof which are water soluble can be formulated with drug into microparticles and subsequently cross-linked to form an insoluble network.

[0039] Certain polymers may also be used as carrier materials in the formulation of drug containing microparticles. Suitable polymers include ethylcellulose and other natural or synthetic cellulose derivatives. Polymers which are slowly soluble and form a gel in an aqueous environment, such as hydroxypropyl methylcellulose or polyethylene oxide, may also be suitable as carrier materials for drug containing microparticles.

[0040] Encapsulation or incorporation of drug into carrier materials to produce drug containing microparticles can be achieved through known pharmaceutical formulation techniques. To create a composition that protects drug from exposure upon mechanical disruption (e.g., breaking or chewing), the drug is intimately dispersed within the carrier material. In the case of formulation in fats, waxes or wax-like materials, the carrier material is heated above its melting temperature and the drug is added to form a mixture including drug particles suspended in the carrier material, drug dissolved in the carrier material, or a mixture thereof. Microparticles can be subsequently formulated through several methods including, but not limited to, the processes of congealing, extrusion, spray chilling or aqueous dispersion. In a preferred process, wax is heated above its melting temperature, drug is added, and the molten wax-drug mixture is congealed to form solid, spherical particles via a spraying or spinning disk process. Alternatively, the molten wax-drug mixture can be extruded and spheronized to form pellets or beads. Detailed descriptions of these processes can be found in “Remington—The science and practice of pharmacy”, 20th Edition, Jannaro et al., (Phila., Lippincott, Williams, and Wilkens, 2000). Detailed descriptions of the spinning disk process can be found in U.S. Pat. Nos. 3,015,128 and 7,261,529.

[0041] For some carrier materials it may be desirable to use a solvent evaporation technique to produce drug containing microparticles. In this case drug and carrier material are co-dissolved in a mutual solvent and microparticles can subsequently be produced by several techniques including, but not limited to, forming an emulsion in water or other appropriate media, spray drying, using a spinning disk process or by evaporating off the solvent from the bulk solution and milling the resulting material.

[0042] In addition to modification of the drug itself, processing conditions can be used to influence the dispersion of the drug within water-insoluble or slowly water-soluble material. For example, in the case where the water insoluble or slowly soluble material is melted and drug is fully or partially dissolved under stirring conditions, the temperature, agitation rate and time of processing will influence the degree of dissolution achieved. More specifically, a more homogenous dispersion may be achieved with a higher temperature, faster stirring rate and longer processing time. Ultrasound can also be applied to the molten mixture to increase the degree of dispersion and/or the rate of dissolution of the drug.

[0043] In some embodiments, drug in a particulate form is homogenously dispersed in a water-insoluble or slowly water soluble material. To minimize the size of the drug particles within the composition, the drug powder itself may be milled to generate fine particles prior to formulation. The process of jet milling, known in the pharmaceutical art, can be used for this purpose. In some embodiments drug in a particulate form is homogeneously dispersed in a wax or wax like substance by heating the wax or wax like substance above its melting point and adding the drug particles while stirring the mixture. In this case a pharmaceutically acceptable surfactant may be added to the mixture to facilitate the dispersion of the drug particles.

[0044] For formulations including a pharmaceutically active agent in the free base form and one or more fatty acids, a homogeneous molten mixture, in which the drug particles are completely dissolved, can be achieved in the following manner. The one or more fatty acid(s) are heated above their melting point but below the melting point of the active agent. The active agent in free base form is mixed with the molten fatty acid until a clear, homogeneous mixture is formed. The active agent may be added in the solid form or may first be dissolved in an appropriate solvent. Optionally, one or more fats, fatty substances, waxes, and/or wax-like substances are co-melted into the mixture, either before the addition of the active agent or following the addition of the active agent. It is believed that a clear solution is formed due to the formation of a salt between the free base of the active agent and the one or more fatty acids present in the formulation. An analogous composition may be formed using the free acid of the active agent, one or more fatty amines, and, optionally, one or more fats, fatty substances, waxes, and/or wax-like substances.

[0045] D. Coated Drug Containing Microparticles

[0046] In some embodiments, drug containing microparticles or drug particles are encapsulated. Drug containing microparticles can be encapsulated in water insoluble materials, slowly water soluble materials, or materials with pH dependent solubilities.

[0047] In general, any coating procedure which provides a contiguous coating on each microparticle without significant agglomeration of particles may be used. Coating procedures known in the pharmaceutical art including, but not limited to, fluid bed coating processes and microencapsulation may be used to obtain appropriate coatings. Detailed descriptions of these processes can be found in “Remington—The science and practice of pharmacy”, 20th Edition, Jannaro et al., (Phila., Lippincott, Williams, and Wilkens, 2000).

[0048] The water-insoluble coating materials may be any of a large number of natural or synthetic film-formers used singly, in admixture with each other, and in admixture with plasticizers, pigments and other substances to alter the characteristics of the coating. A water-insoluble but water-permeable diffusion barrier may consist of ethyl cellulose, methyl cellulose and mixtures thereof. The water-permeable diffusion barrier may also include ammonio methacrylate copolymers sold under the trade name EUDRAGIT® (Rohm Pharma), such as EUDRAGIT RS, EUDRAGIT RL, EUDRAGIT NE and mixtures thereof. Other synthetic polymers, for example, polyvinyl acetate (available under the trade name KOLLICOAT®), can also be used to form water-insoluble but permeable coatings.

[0049] The coating may also include a water-insoluble but enzymatically degradable material. In some instances the substrates of digestive enzymes are naturally water-insoluble and can be utilized in the formulation without further processing. Solid esters of fatty acids, which are hydrolyzed by
lipases, can be spray coated onto microparticles or drug particles. Mixtures of waxes (beeswax, carnauba wax, etc.) with glycerol monostearate, stearic acid, palmitic acid, glycerol monopalmitate and cetyl alcohol will also form films that are dissolved slowly or broken down in the GI tract. Zein is an example of a naturally water-insoluble protein. It can be coated onto drug containing microparticles or drug particles by spray coating or by wet granulation techniques. In addition to naturally water-insoluble materials, some substrates of digestive enzymes can be treated with cross-linking procedures, resulting in the formation of non-soluble networks. Many methods of cross-linking proteins, initiated by both chemical and physical means, have been reported. One of the most common methods to obtain cross-linking is the use of chemical cross-linking agents. Examples of chemical cross-linking agents include aldehydes (glutaraldehyde and formaldehyde), epoxy compounds, carbodiimides, and genipin. In addition to these cross-linking agents, oxidized and native sugars have been used to cross-link gelatin (Cortesi, R., et al., Biomaterials 19 (1998) 1641-1649). Cross-linking can also be accomplished using enzymatic means; for example, transglutaminase has been approved as a GRAS substance for cross-linking seafood products. Finally, cross-linking can be initiated by physical means such as thermal treatment, UV irradiation and gamma irradiation.

To produce a coating layer of cross-linked protein surrounding drug containing microparticles or drug particles, a water soluble protein can be spray coated onto the microparticle and subsequently cross-linked by the one of the methods described above. Alternatively, drug containing microparticles can be microencapsulated within protein by coacervation-phase separation (for example, by the addition of salts) and subsequently cross-linked. Some suitable proteins for this purpose include gelatin, albumin, casein, and gluten.

Polysaccharides can also be cross-linked to form a water-insoluble network. For many polysaccharides, this can be accomplished by reaction with calcium salts or multivalent cations which cross-link the main polymer chains. Pectin, alginate, dextran, amylose and guar gum are subject to cross-linking in the presence of multivalent cations. Complexes between oppositely charged polysaccharides can also be formed; pectin and chitosan, for example, can be complexed via electrostatic interactions. Insoluble coatings can be formed on particles in this fashion. It should be noted that in many cases polysaccharides are broken down specifically by enzymes produced by bacteria within the colon.

In some cases a water-insoluble but enzymatically degradable coating including both a protein and a polysaccharide can be produced if the components are oppositely charged polyelectrolytes. Under the proper temperature, pH, and concentrations, the two polymers can interact through their opposite electrical charges and form a water-insoluble complex. If a core particle is present at the time the complex phase separates, it will be coated. For example, gelatin and gum arabic can be coated onto a core particle utilizing this process. Optionally, the complex can be made irreversibly insoluble by subsequent cross-linking induced by chemical or physical means.

Coating materials may also include a pH sensitive polymer which is insoluble in the acid environment of the stomach, and soluble in the more basic environment of the GI tract. Such a coating is thus an enteric coating, creating a dosage form designed to prevent drug release in the stomach. Preventing drug release in the stomach has the advantage of reducing side effects associated with irritation of the gastric mucosa, and of minimizing exposure of drug to very low pH. Avoiding release within the stomach can be achieved using enteric coatings known in the art. The enteric coated formulation remains intact or substantially intact in the stomach, however, once the formulation reaches the small intestines, the enteric coating dissolves and exposes either drug-containing carrier particles or drug-containing carrier particles coated with extended release coating.

The enteric coated particles can be prepared as described in "Pharmaceutical dosage forms tablets", eds. Liberman et. al. (New York, Marcel Dekker, Inc., 1989), "Remington—The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, Md., 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et. al., (Media, Pa. Williams and Wilkins, 1995). Examples of suitable coating materials include, but are not limited to, cellulose polymers, such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and certain methacrylic resins that are commercially available under the trade name EUDRAGIT® (Rohm Pharma). Additionally the coating material may contain conventional carriers such as plasticizers, pigments, colorants, glidants, stabilization agents, and surfactants.

In some cases it may be desirable to coat the particles with a coating which is soluble in aqueous solutions but insoluble in hydroalcoholic solutions. In this case the coating material may or may not have pH sensitive solubility in aqueous solutions.

In some cases it may be desirable to combine coating materials to produce a tailored release of drug. For example, combinations of insoluble polymers and pH dependent polymers can produce a pH dependent sustained release profile. Combinations of insoluble polymers (e.g., ethylcellulose), water-soluble polymers (e.g., HPMCC or PEG) and pH dependent swellable polymers (e.g., carboxyvinylpolymer) have also been reported to produce pH dependent sustained release profiles (See, for example, Journal of Controlled Release, 2006, 111:309-315).

E. Dosage Forms

There are a number of drug compositions that meet the criteria outlined above. In one embodiment a drug is homogeneously dispersed, in a fine particulate form, within a water-insoluble or slowly water soluble material and the mixture is formulated into microparticles. In another embodiment a drug is partially dissolved within a water-insoluble or slowly water soluble material during the manufacturing process, for example, by mixing at a temperature above the melting point of the carrier material, and the mixture is formulated into microparticles. In yet another embodiment a drug is fully dissolved within a water-insoluble or slowly water soluble material during the manufacturing process, for example, by mixing at a temperature above the melting point of the carrier material, and the mixture is formulated into microparticles. In still a further embodiment, the drug containing microparticles, where the drug is homogeneously dispersed in a particulate form, or has been partially or fully dissolved within the carrier material during the manufacturing process, are coated with one or more coatings to form coated microparticles.
The microparticles, coated microparticles, or a mixture thereof are formed into a solid dosage form suitable for oral administration. For example, microparticles or coated microparticles can be incorporated into hard capsules, dispersed within a soft gelatin capsule, or combined with appropriate excipients and tableted by compression.

Dosage forms can include one or more drugs. If the drugs are compatible, several different drugs can be incorporated into the same microparticle composition or coated microparticle composition. The drugs can be incorporated into separate microparticle compositions where a first drug is formulated into microparticle compositions or coated microparticle compositions described herein and one or more additional drugs are incorporated into microparticle compositions or coated microparticle compositions described herein, sustained release compositions known in the art or immediate release compositions known in the art. The compositions including the different drugs are formulated into a single solid dosage form suitable for oral administration, for example, they can be incorporated into a gelatin capsule, or combined with appropriate excipients and compressed into a tablet form.

An immediate release dose can be incorporated into the formulation in several ways. Immediate release microparticles can be made utilizing standard methodologies and formulated along with sustained release microparticle and/or coated microparticle compositions in a suitable oral dosage form. Alternatively, a coating containing drug which is available for immediate release can be placed on a tablet including sustained release microparticle and/or coated microparticle compositions plus appropriate excipients. Additionally, an immediate dose of drug can be granulated or blended with rapidly dissolving excipients and subsequently compressed (1) as one layer of bi-layer tablets in which the sustained release microparticle and/or coated microparticle compositions are compressed as the outer layer, or (2) as the outer layer of compression-coated tablets in which the sustained release microparticle and/or coated microparticle compositions are compressed as the inner core, or (3) into tablets in which sustained release microparticle and/or coated microparticle compositions are embedded.

Optional excipients present in the oral dosage form including abuse deterrent microparticles or coated microparticles include, but are not limited to diluents, binders, lubricants, disintegrants, colorants, plasticizers and the like. Diluents, also termed “fillers,” are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets. Examples of diluents include cellulose, dry starch, microcrystalline cellulose, dicalcium phosphate, calcium sulfate, sodium chloride, confectioner’s sugar, compressible sugar, dextrose, dextrin, dextrose, sucrose, mannitol, powdered cellulose, sorbitol, and lactose. Binders are used to impart cohesive qualities powered materials and can include materials such as starch, gelatin, sugars, natural and synthetic gums, polyethylene glycol, ethylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, waxes and polyvinyl pyrrolidone. Lubricants are used to facilitate tablet manufacture; examples of lubricants include talc, magnesium stearate, calcium stearate, hydrogenated vegetable oils stearic acid, sodium stearyl fumarate, sodium benzoate, sodium acetate, leucine, sodium oleate, sodium lauryl sulfate, magnesium lauryl sulfate and polyethylene glycol. Disintegrants can be added to pharmaceutical formulations in order to facilitate “breakup” or disintegration after administration. Materials used for this purpose include starches, clays, celluloses, algin, gums, and cross-linked polymers. A plasticizer may be included in coating materials to alter their mechanical properties. Examples of plasticizers include benzyl benzoate, chlorobutanol, dibutyl sebacate, diethyl phthalate, glycerin, mineral oil, polyethylene glycol, sorbitol, triacetin, triethyl citrate, glycerol, etc. In addition to the additives above, coloring and flavoring agents may also be incorporated into the composition.

II. Methods of Administration

It is assumed that upon oral ingestion of the intact composition, drug is released as the formulation is gradually broken down or dissolved within the GI tract by a combination of diffusion, surfactant action of bile acids, mechanical erosion, and, in some embodiments, enzymatic degradation. This is a result of the unique ability of the human digestive system to efficiently break down or solubilize a variety of materials. The process within the GI tract that results in the digestion of food and the absorption of nutrients is well known. Following mastication within the mouth, food passes into the stomach where it is mixed with digestive juices. This fluid contains the proteolytic enzyme pepsin which, following activation by the low pH within the stomach, begins the process of cleaving ingested proteins into smaller peptide fragments. Food then enters the small intestine in the form of macromolecular aggregates, where it is digested into molecules near or in a form capable of being absorbed. This digestion is accomplished through the action of various enzymes which are produced in the pancreas and flow into the upper portion of the large intestine, the duodenum. The enzymes synthesized in the pancreas include proteases, amylases and lipases; these enzymes are capable of breaking down proteins, starches and fats, respectively. The digestion of fats is further facilitated by the secretion of bile into the duodenum since bile salts, which contain both hydrophobic and hydrophilic portions, are capable of emulsifying lipids into minute droplets in order to increase the surface area available for digestion by lipases. The material which remains following passage through the small intestine enters the large intestine. Bacteria capable of breaking down carbohydrates not digested in the small intestine (such as cellulose) are present in large numbers this region of the digestive tract. Finally, in addition to microbial fermentation, the large intestine functions to absorb water and electrolytes and to form and store feces until they are excreted.

In some embodiments, an immediate release of drug is achieved within the stomach in order to provide rapid therapeutic onset.

The pharmaceutical drug composition is administered orally. The appropriate dosage formulations can be obtained by calculation of the pharmacokinetics of the formulation, then adjusting using routine techniques to yield the appropriate drug levels based on the approved dosage forms. Any suitable amount of drug containing microparticles or coated microparticles can be included in the final formulation. The selection of a suitable amount of drug containing microparticles depends on the dosage desired and is readily determined by those skilled in the art.

In addition to oral administration, some embodiments may also be administered by other routes, including,
but not limited to, rectal and nasal administration. Some embodiments may also be suitable for formulation as oral liquids.

[0067] The present composition and method of making and using the composition will be further understood by reference to the following non-limiting examples.

EXAMPLE 1

Preparation of Lipophilic Oxycodone Derivative

Oxycodone Free Base

[0068] The free base of oxycodone can be prepared from its hydrochloride salt by the following method: Oxycodone hydrochloride is dissolved in water and sodium carbonate was added in the amount required to neutralize hydrochloric acid. Methylene chloride is added in order to extract the formed oxycodone free base. The obtained organic layer is dried over sodium sulfate and methylene chloride is evaporated using rotary evaporator. The obtained oxycodone free base is purified by crystallization.

EXAMPLE 2

Preparation of Drug Containing Microparticles

[0069]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Composition of Formulation A</th>
<th>Composition of Formulation B</th>
<th>Composition of Formulation C</th>
<th>Composition of Formulation D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone Base</td>
<td>5 g</td>
<td>5 g</td>
<td>10 g</td>
<td>5 g</td>
</tr>
<tr>
<td>Myristic Acid</td>
<td>—</td>
<td>—</td>
<td>50 g</td>
<td>30 g</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>34 g</td>
<td>34 g</td>
<td>—</td>
<td>10 g</td>
</tr>
<tr>
<td>Yellow</td>
<td>10 g</td>
<td>—</td>
<td>10 g</td>
<td>10 g</td>
</tr>
<tr>
<td>Beeswax</td>
<td>5 g</td>
<td>10 g</td>
<td>20 g</td>
<td>10 g</td>
</tr>
</tbody>
</table>

Procedure:

[0070] 1. Fatty acid (myristic or stearic acid) was melted in an erlenmeyer flask in a silicone oil bath at 100°C. Note the composition was subjected to stirring and was kept under an argon blanket for this and all subsequent steps.

2. Oxycodone base was introduced into the molten fatty acid and the melt was stirred until all oxycodone base dissolved and a clear liquid was formed.

3. Yellow beeswax was added and melted under constant stirring.

4. Carnauba wax was added and melted under constant stirring.

5. The resulting homogeneous molten solution was poured onto aluminum foil and allowed to solidify at room temperature.

6. The bulk wax obtained was combined with dry ice and subjected to size reduction in a mortar and pestle.

7. The dry ice was allowed to dissipate and the particles were sieved to obtain various size ranges. Particles 20-40 mesh in size (400-841 micron) were subjected to testing.

EXAMPLE 3

Release of Drug from Crushed Microparticles

[0071] In vitro testing was conducted in order to assess the influence of the crushing of the microparticles produced in Example 2 on the release in simulated stomach conditions. A currently marketed sustained release formulation of oxycodone, OxyContin®, was also subjected to crushing and dissolution for comparison purposes.

[0072] Microparticles (Formulations A, B, C or D, all 20-40 mesh in starting particle size) or tablets were crushed using a glass mortar & pestle. The resulting crushed material was placed in a dissolution vessel equipped with paddles (USP Apparatus II). 900 mL of 0.1N HCl pre-warmed to 37°C was added to the vessels and stirring was conducted for 15 minutes. After 15 minutes the amount of oxycodone released was determined. See Table 2.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>OxyContin Formulations</th>
<th>% Released in 15 minutes in 0.1N HCl (x = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OxyContin® (40 mg Tablet)</td>
<td>95.6 +/- 2.7</td>
<td></td>
</tr>
<tr>
<td>Formulation A (microparticles containing 40 mg oxycodone HCl equivalent)</td>
<td>31.6 +/- 2.6</td>
<td></td>
</tr>
<tr>
<td>Formulation B (microparticles containing 40 mg oxycodone HCl equivalent)</td>
<td>19.7 +/- 1.4</td>
<td></td>
</tr>
<tr>
<td>Formulation C (microparticles containing 20 mg oxycodone HCl equivalent)</td>
<td>14.8 +/- 1.1</td>
<td></td>
</tr>
<tr>
<td>Formulation D (microparticles containing 20 mg oxycodone HCl equivalent)</td>
<td>18.2 +/- 1.6</td>
<td></td>
</tr>
</tbody>
</table>

[0073] As illustrated in the table above, the microparticle compositions of Example 2 release only a fraction of the total drug load in simulated stomach conditions when crushed. In contrast, a currently marketed sustained release composition, OxyContin®, releases approximately 96% of the drug load when crushed and exposed to identical conditions.

EXAMPLE 4

Preparation of Coated Drug Containing Microparticles

[0074] The drug-containing particles from Example 2 are spray coated with cellulose acetate phalate.

EXAMPLE 5

Preparation of Capsules for Oral Administration

[0075] The drug containing microparticles from Example 2 and/or the coated microparticles from Example 3 are blended with a lubricant and incorporated into standard gelatin capsules.

[0076] Modifications and variations of the present invention will be obvious to those skilled in the art.
We claim:

1. An orally administrable sustained release pharmaceutical composition comprising a therapeutically effective amount of microparticles consisting of

(a) a lipophilic drug or lipophilic derivative of a drug other than a drug prone to abuse and

(b) one or more carrier materials selected from the group consisting of fats, fatty substances, waxes, wax-like substances and mixtures thereof

wherein the drug is dispersed within the one or more carrier materials, and the release of a portion of incorporated drug is retarded when the physical integrity of the composition is compromised and the compromised composition is exposed to 0.1N HCl.

2. An orally administrable sustained release pharmaceutical composition comprising a therapeutically effective amount of microparticles consisting of a lipophilic derivative of a drug other than a drug prone to abuse dispersed within one or more carrier materials which are either slowly soluble in water or insoluble in water, wherein the release of a portion of incorporated drug is retarded when the physical integrity of the composition is compromised and the compromised composition is exposed to 0.1N HCl.

3. The composition of claim 1 or 2, wherein the portion of the drug released immediately when the physical integrity of the composition is compromised is less than 80% of the total amount of drug incorporated into formulation.

4. The composition of claim 1 or 2, wherein the lipophilic derivative of a drug is a free base or a free acid of the drug.

5. The composition of claim 1 or 2, wherein the lipophilic derivative of a drug is a salt comprising the ionized drug and a counter-ion.

6. The composition of claim 1 or 2, wherein the lipophilic derivative of a drug is an ester or amide formed between the drug and a fatty acid.

7. The composition of claim 5 wherein the counter-ion is selected from the group consisting of stearic acid, palmitic acid, myristic acid, and mixtures thereof.

8. The composition of claim 5 wherein the counter-ion is selected from the group consisting of methacrylic acid-methyl methacrylate copolymers, acrylic acid polymers, crosslinked acrylic acid polymers and carboxymethylcellulose.

9. The composition of claim 2 wherein the microparticles consist of drug dispersed in a material selected from the group consisting of fats, fatty substances, waxes, wax-like substances and mixtures thereof.

10. The composition of claim 1 or 2 comprising one or more carrier materials selected from the group consisting of stearic acid, palmitic acid, and mixtures thereof.

11. The composition of claim 1 or 2 comprising one or more carrier materials selected from the group consisting of beeswax, cannauba wax, hydrogenated oil, and mixtures thereof.

12. The composition of claim 1 or 2 wherein the carrier materials are selected from the group consisting of myristic acid, palmitic acid, stearic acid, cannauba wax, beeswax and mixtures thereof.

13. The composition of claim 2 wherein the microparticles consist of a drug dispersed in a carrier material selected from the group consisting of naturally water insoluble proteins, naturally water insoluble polysaccharides, naturally water insoluble lipids and phospholipids, cross-linked water soluble proteins, cross-linked water soluble polysaccharides and combinations thereof.

14. The composition of claim 1 or 2 wherein the individual microparticles are coated with one or more independent layers.

15. The composition of claim 14 wherein the coated layer(s) comprise a material selected from the group consisting of naturally water insoluble polysaccharides, naturally water insoluble lipids and phospholipids, cross-linked proteins, cross-linked polysaccharides, mixtures of waxes and fatty substances, and combinations thereof.

16. The composition of claim 15 wherein the coated layer(s) comprise a material selected from the group of pH dependent coatings, water insoluble diffusion barrier coatings, water soluble coatings and combinations thereof.

17. The composition of claim 1 or 2 wherein the lipophilic derivative is dissolved in the carrier material in a molten state to result in a uniform dispersion within the carrier material.

18. The composition of claim 1 or 2 wherein the lipophilic derivative is dissolved in a co-solvent along with a carrier material to result in a uniform dispersion within the carrier material.

19. The composition of claim 1 or 2 wherein the individual microparticles are further formulated into a tablet or capsule for oral administration.

20. The composition of claim 19 wherein the individual microparticles contain one or more drugs.

21. The composition of claim 19 wherein the tablet or capsule further comprises one or more drugs formulated as an immediate release dose, a sustained release dose, a delayed release dose, or a combination thereof.

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