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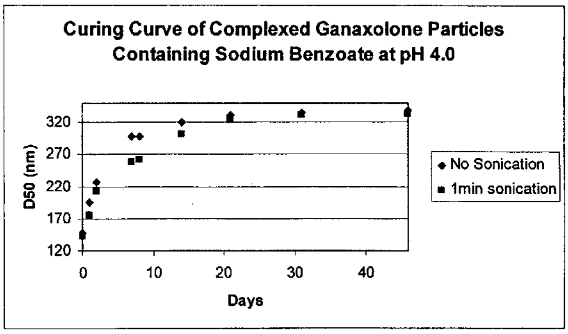
(54) Title: NANOPARTICULATE FORMULATIONS AND METHODS FOR THE MAKING AND USE THEREOF

(57) Abstract: The present invention is directed to size-stabilized drug nanoparticulate compositions and methods of preparation thereof.



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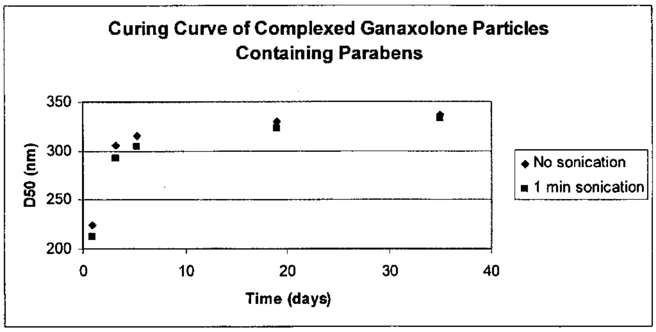

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NANOPARTICULATE FORMULATIONS AND METHODS FOR THE MAKING AND USE THEREOF

FIELD OF THE INVENTION

[0001] Described herein are nanoparticulate formulations of drugs having an aqueous solubility of less than 1mg/ml in a pH of about 7.4 which provide enhanced stability, physical and chemical properties and can provide enhanced pharmacokinetic properties to achieve an optimal balance between pharmacodynamic and side effect profiles in mammals, and dosage forms containing the same, as well as methods of making nanoparticulate drug formulations and their use in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0002] It has been very difficult to formulate therapeutically effective dosage forms specific for drugs having an aqueous solubility of less than 1mg/ml in a pH of about 7.4, across a broad range of therapeutic agents (e.g. medroxyprogesterone acetate, carbamazepine, phenytoin, nifedipine and ganaxolone). Generally, conventional formulations of drugs having an aqueous solubility less than 1mg/ml in a pH of about 7.4 demonstrate variable and low bioavailability and have also shown particularly large exposure differences when the drug is administered in the fed and fasted state. Based upon this difficulty, there exists a need in the art for improved drug formulations and dosage forms for drugs having an aqueous solubility less than 1mg/ml in a pH of about 7.4. Herein are described liquid and solid dosage drug formulations which address this need and which provide improved pharmacokinetic properties which maintain efficacy while reducing side effects and enhancing subject compliance.

[0003] Various methods to improve the solubility and bioavailability of drugs have been used by those skilled in the art. One such method involves the comminuting in size of the drug particles. Small particles have more surface area and therefore dissolve into a fixed amount of media faster. This results in higher oral bioavailability for water insoluble compounds especially those which have restricted areas of absorption in the GI tract, have high first pass clearance (liver metabolism) and have a high dose requirement.

[0004] One way to provide for a small "nano" particle drug formulation is to form a nanoparticle liquid formulation, e.g., nanosuspension. When dealing with nanosuspensions, the less water soluble and more lipophilic the drug, the more difficult it is to obtain a stable small particle "nanosuspension" in polar solvents like water. Particle growth (Otswald Ripening) and aggregation must be minimized in nanoparticulate compositions if the benefit of small particle formulations is to be realized.

[0005] Preparation of nanosuspensions is known in the art. Most current commercial technologies involve the use a water based system to generate small particles (e.g., wet ball milling, precipitation, high pressure homogenization). Many marketed small particle formulations today are prepared utilizing wet ball milling techniques. For example, one common technique entails grinding drug in a milling chamber with grinding media (beads) to produce small particles. For productivity, those skilled in the art appreciate that one wants to mill for as short a period of time needed to make a stable composition and also as concentrated in drug as possible. Recirculation of a tank of drug suspension through a ball mill is the most common technique. As the milling is a high energy process, to avoid contamination from abraded materials (milling chamber and grinding balls), the shortest milling time possible with the lowest energy is the most preferred process. As oral nanoparticulate formulations are formed generally to increase dissolution rates in the gastrointestinal tract, maintaining a constant particle size until the compound is absorbed is the key parameter to monitor.

[0006] The preparation of small particle pharmaceutical compositions (effective particle size (D50) of less than 500 nm) have been described since 1988 (H. Steffen BT Gattefosse No. 81, 1988 pp. 45-53; U.S. Patent No. 4,540,602 (Motoyama, et al.); and U.S. Patent No. 5,145,684 (Liversidge, et al.)). These submicron (nanoparticulate) compositions all describe using non-crosslinked excipients associated with the surface of the small particle to stabilize the composition from significant particle size growth and/or agglomeration. Generally, surface stabilizers fall into two categories: non-ionic (also called stearic stabilizers or modifiers) and ionic stabilizers. The most common non-ionic stabilizers are excipients which are contained in classes known as binders, fillers, surfactants and wetting agents. Limited examples of non-ionic surface stabilizers are hydroxypropylmethyl cellulose, , polyvinylpyrrolidone, Plasdone, polyvinyl alcohol, Pluronics, Tweens and Polyethyleneglycols (PEGs)s. A subset of surface stabilizers commonly used is ionic in nature. These ionic surface stabilizers tend to fall into the class of excipients which are typically used as surfactants and wetting agents. Ionic stabilizers used in the prior art are typically organic molecules bearing an ionic bond such that the molecule is essentially fully charged in the formulation. The two most described ionic surface stabilizers are the long chain sulfonic acid salts sodium lauryl sulfate and dioctyl sodium sulfosuccinate (DOSS). Broad ranges for all surface stabilizers have been claimed in U. S. Patent No. 5,145,684 (the '684 patent) ranging from 0.1% to 90% by weight of the composition. Typically, one adds 20%-150% (wt% of drug) of a nonionic surface stabilizer and 0.2%-5% of an ionic surface stabilizer (wt% of drug) to achieve maximal particle size stabilization from these surface stabilizers. Since 1988, many papers and and patents have published relating to nanoparticulate compositions and various ways to optimize the method of manufacture, use and stability of such compositions.

[0007] In preparing drug nanoparticles via a wet ball milling process as described in the '684 patent, milling suspensions with drug concentrations of 5-30% are typically milled with a hard grinding media in a ball mill to obtain particles with a D50 in the 100-500 nm size range. The literature teaches that particle size reduction using milling is conducted at a sufficient speed and time to obtain a desired particle size. The surface stabilizers are present or added to keep the particle size constant over a variety of stability indicating measurements as compared to the article size (D50) obtained at the end of milling. One of the major issues in wet ball milling is potential residual metals in the composition due to extended milling or energy needed to obtain the desired particle size (Jia, L. Current Nanoscience, 1, pp 237-243 (2005)).

[0008] Enhancing stability has been the focus of much research. Stability is a broad reference and in the pharmaceutical industry is generally recognized as testing needed to determine storage stability (the stability of the formulation under storage over time), purity stability (the purity profile of the formulation over storage conditions), release or dispersion stability (the stability of release or disintegration characteristics for the formulation in water and physiological media). The physiological media for dispersion stability is dependent on the route of administration (simulated gastric and/or intestinal fluid for oral products, saliva for buccal and sub-lingual products, etc). In general any parameter important to the performance or tolerability of a formulation must be monitored for stability.

SUMMARY OF THE INVENTION

[0009] Described herein are compositions, pharmaceutical compositions, methods for treating, methods for formulating, methods for producing, methods for manufacturing, treatment strategies, pharmacokinetic strategies using nanoparticulate formulations of drugs having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4. The drugs that would benefit from this approach are limited to those that can form a cyclodextrin complex.

[0010] The inventors have prepared stable submicron drug particles with particularly advantageous pharmaceutical properties. Stable drug particles described herein comprise a complex of drug and a complexing agent. Additional factors that affect stability and particle size are described herein.

[0011] In certain embodiments, the present invention is directed to drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, and (iii) a complexing agent forming a cyclodextrin inclusion complex when the particles are cured for at least about 3 days. In certain embodiment, the complexing agent may be included in an amount effective to cause an initial increase in the size of the particles, wherein the volume weighted median diameter (D50) of the particles before the initial growth is from about 100 to about 400 nm and the D50 at the end of the curing time is 20% to 300% larger than the D50 measured before the curing period. For example, in certain embodiments, the complexing agent is included in an amount from about 0.1% to about 8%, w/w of the size-stabilized drug particles

[0012] In certain embodiments, the volume weighted diameter (D50) of the complexed particles does not change by more than 10% after a time in consecutive measurements separated by about 72 hours.

[0013] In certain embodiments, the complexed particles increase in effective particle size from about 0% to about 200% upon dispersion in simulated gastric or intestinal fluid as compared to dispersion in water under the same conditions.

[0014] In yet another embodiment, the present invention provides for a pharmaceutical composition comprising the drug complexed particles described above together with at least one pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition may be in the form of a solid dosage form. In other embodiments, the pharmaceutical composition may be in the form of a liquid dosage form, e.g., suspension. When incorporated into a pharmaceutical compositions comprising pharmaceutically acceptable excipients, the amount of drug complexed particles may range from about 1% to about 99%, based on the weight of the entire composition and the amount of pharmaceutically acceptable excipient may range from about 1 to about 99% based on the weight of the total composition.

[0015] In another embodiment, the present invention is directed to size-stabilized drug complexed particles comprising a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 in association with effective amounts of a surface stabilizer and a complexing agent capable of forming a cyclodextrin inclusion complex, the size-stabilized drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm; the drug complexed particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the formulation is dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg drug/mL and placed in a heated bath at 36° to 38° C for 1 hour using a Type I or II dissolution apparatus and a stirring rate of 75 RPM, as compared to the D50 of the drug particles when the formulation is dispersed in distilled water under the same conditions.

[0016] In certain other embodiments, the present invention is directed to a solid pharmaceutical formulation, comprising a plurality of inert beads spray layered with a coating comprising (a) drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, (iii) a complexing agent capable of forming a cyclodextrin inclusion complex; together with effective amounts of (b) a water soluble spacer and (c) an ionic dispersion modulator.

[0017] In another embodiment, the present invention is directed to an orally ingestible tablet, comprising a compressed mixture of (a) drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, (iii) a complexing agent capable of forming a cyclodextrin inclusion complex; together with effective amounts of (b) a water soluble spacer and (c) an ionic dispersion modulator; an inert diluent; and a tableting lubricant.

[0018] In yet another embodiment, the present invention is directed to a size-stabilized nanoparticulate liquid composition comprising a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 in association with effective amounts of a surface stabilizer and a complexing agent capable of forming a cyclodextrin inclusion complex, wherein the volume weighted median diameter (D50) of the size-stabilized particles is from about 50 nm to about 500 nm after curing. The nanoparticulate liquid compositions, may further contain at least one additional pharmaceutically acceptable excipient selected from the group consisting of a hydrophilic polymer, a wetting agent, an ionic dispersion modulator, a water soluble spacer, and any combinations or mixture thereof.

[0019] In certain embodiments, the nanoparticulate liquid composition is converted to a solid nanoparticulate composition by removal of solvent (e.g., via spray drying, spray granulation, spray layering onto inert cores).

[0020] In yet another embodiment, the present invention is directed to a method for preparing stabilized drug particles, comprising: a) reducing the size of drug particles capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 into a size range of about 50 nm to about 200 nm; b) adding an effective amount of a surface stabilizer to the drug particles before, during or after reducing the size of the drug particles to form particles comprising the drug and the surface stabilizer; and c) further stabilizing the particles of step b) by adding an effective amount of a complexing agent capable of forming a cyclodextrin inclusion complex to provide particles that attain a stabilized size such that the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.

[0021] In certain embodiments, the size stabilized particles are prepared by contacting drug particles with a complexing agent such that the size of the particles exhibits an increase in volume weighted median diameter of from about 20% to about 300% and an endpoint is reached such that the particles are size-stabilized. The endpoint can be, e.g., from about 1 to about 20 days.

[0022] In another embodiment, the present invention is directed to a suspension of size-stabilized drug complexed particles comprising a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 in association with effective amounts of a surface stabilizer and a complexing agent capable of forming a cyclodextrin inclusion complex, the size-stabilized drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm; the drug complexed particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the formulation is dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg drug/mL and placed in a vial and heated in a bath at 36° to 38° C for 1-3 hours as compared to the D50 of the drug particles in suspension before dispersion into SGF or SIF.

[0023] In certain embodiments, the size-stabilized drug particles comprise from about 30 to about 95% drug, from about 3 to about 70% surface stabilizer, based on the weight of the size-stabilized drug particles, and from about 0.1% to about 8% complexing agent, based on the weight of the size-stabilized drug particles.

[0024] In certain embodiments where the complexed size stabilized drug particles are spray-layered or spray-dried, the particles further comprise from about 0 to about 40% ionic dispersion modulator and from about 0% to about 60% water soluble spacer, based on the weight of the size-stabilized drug particles. In certain embodiments, the amount of ionic dispersion modulator may range from about 0.1% to 40%. The % weights are not meant to be limiting.

[0025] The present invention is further directed to methods of preparing the compositions disclosed herein, including but not limited to, drug particles, liquid formulations, and solid dosage forms (e.g., immediate release, sustained release, delayed release and pulsatile release).

[0026] The present invention is also directed to methods of treating subjects comprising administering to a subject any of the compositions disclosed herein, including, but not limited to, drug particles, liquid formulations, and oral solid dosage forms (e.g., immediate release, sustained release, delayed release and pulsatile release).

[0027] In certain embodiments, the invention is directed to a solid composition comprising particles comprising a complexed drug; and an effective amount of an ionic dispersion modulator to reduce agglomeration and particle size growth of the particles (e.g. upon storage, dispersion in physiological fluids and water), wherein the volume weighted median diameter (D50) of the particles is from about 100 nm to about 500 nm.

[0028] In certain embodiments, the invention is directed to a solid composition comprising particles comprising a complexed nanoparticulate drug; and an ionic dispersion modulator in an amount of from about 1% to about 50%, w/w, based on the weight of the size stabilized particles, wherein the volume weighted median diameter (D50) of the particles (dispersed in water and/or physiological fluids) is from about 100 nm to about 500 nm.

[0029] In certain embodiments, the excipient comprises a water soluble spacer. The water soluble spacer can be a saccharide or an ammonium salt, a polyethylene glycol or urea that is a solid a temperatures of 50°C or more. The saccharide can be selected from the group consisting of fructose, sucrose, glucose, lactose, mannitol and mixtures thereof. The polyethylene glycol can be selected from PEG 3350, PEG 4000 or PEG 6000.

[0030] In other aspects, the invention is directed to pharmaceutical particles comprising drug or a pharmaceutically acceptable salt thereof, the complexed particles being stable (suitable curing time) such that the volume weighted median diameter (D50) of the particles does not increase by more than about 50% after 28 days storage at room temperature, the volume weighted median diameter (D50) of the particles prior to storage being from about 50 nm to about 500 nm; the particles milled for a sufficient time to achieve the stability. In other aspects, the volume weighted median diameter (D50) of the particles does not change by more than about 25% after 28 days storage at room temperature (25°C) conditions, does not change by more than about 15% after 28 days storage at room temperature, does not change by more than about 10% after 28 days storage at room temperature (25°C) and or does not change by more than about 10% after 4 months storage at 25°C/60% relative humidity and 40°C/75% relative humidity.

[0031] In another embodiment, the present invention is directed to a formulation of solid size-stabilized drug complexed particles comprising a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 comprising (a) drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, (iii) a complexing agent capable of forming a cyclodextrin inclusion complex, the drug complexed particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the formulation is dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg drug/mL and placed in a heated bath at 36° to 38° C for 1-3 hours using a Type I or II dissolution apparatus and a stirring rate of 75 RPM, as compared to the D50 of the drug particles when the formulation is dispersed in distilled water under the same conditions.

[0032] In certain embodiments, the invention is directed to a solid composition (e.g., a powder, immediate release dosage form, or controlled release dosage form) comprising size-stabilized drug particles and at least one pharmaceutically acceptable excipient, the size-stabilized drug particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200%, not more than about 150%, not more than about 100% or not more than about 50%, when the formulation is dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg drug/mL (in any suitable volume, e.g., 15 mL to 1000 mL) and placed in a heated bath at 36° to 38° C without stirring for 1 hour, as compared to the D50 of the drug particles when the formulation is dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the drug particles dispersed in distilled water is from about 50 nm to about 1000 nm, from about 100 nm to about 500 nm, or from about 100 nm to about 350 nm.. The volume weighted median diameter (D50) of the coated beads prior to dispersion can be, e.g., from about 0.1 mm to about 5.0 mm. The solid formulation can be, for example, a powder, a tablet, a capsule, etc.

[0033] In certain embodiments, the present invention is directed to liquid pharmaceutical compositions containing size stabilized drug particles comprising a drug complex exhibiting a D50 after dispersion in SGF or SIF at 36 to 38° C for 1 -3 hours of not greater than about 500 nm, and in certain embodiments having a ratio to D50 after such dispersion in SGF or SIF to the D50 prior to dispersion of less than about 3:1.

[0034] Particle size measurement is generally described and well known to those skilled in the art. The volume weighted median diameter or D50 is a commonly accepted measure of particle size. Sometimes one finds loose aggregates forming upon storage or under physiological fluid testing. Loose aggregates can generally be broken up via sonication. The formation of loose aggregates could impact the pharmacokinetic performance (variability, systemic levels and bioavailability) of a nanoparticulate formulation. The impact of loose aggregation in a formulation or physiological fluid must be ascertained on a compound by compound basis as the performance of a formulation is dependent on a multitude of variables (dose required, site of absorption, solubility, crystalline properties and degree of aggregation) of the drug as well as the whether the formulation is a suspension, immediate release or coated solid formulation protected from gastric fluids. In cases of nanoparticulate formulations of water insoluble drugs it is obvious that any formulation that results in less aggregation (loose or otherwise) or particle growth as measured by an increase in D50 values over time or when exposed to the physiological media that the drug will be subjected prior or during absorption is most preferred (more stable). One could theorize, however, that a nanoparticulate formulation which is formed for a water soluble compound that is being protected from storage degradation might actually benefit from aggregates (longer absorption time due to larger effective particle size). Significant tight aggregation (unreversible) and particle size growth are obviously undersirable as this would effectively loose the advantageous increased kinetic dissolution of the drug.

[0035] Hydroxypropylmethyl cellulose, e.g., HPMC-15 and sodium lauryl sulfate , have also been described as surface stabilizers of drug nanoparticles in water (H. Steffen BT Gattefosse No. 81, 1988 pp. 45-53).

[0036] Preservatives are also sometimes added to nanosuspensions to provide protect the formulation from contamination. For example, Megace ES Suspension® (Parr) is preserved with benzoic acid (as sodium benzoate buffered to pH 4.0 with citric acid and sodium citrate).

[0037] In our U.S. Patent Application No. 11/606,222 entitled “Solid Ganaxolone Formulations and Methods for the Making and Use Thereof” and U.S. Patent Application No.: 11/605,700 entitled “Liquid Ganaxolone Formulations and Methods for the Making and Use

Thereof", both of which were filed on November 28, 2006 and both of which are hereby incorporated by reference, we disclosed ganaxolone formulations which provide enhanced stability, physical and chemical properties and can provide enhanced pharmacokinetic properties to achieve an optimal balance between pharmacodynamic and side effect profiles in mammals, and dosage forms containing the same, as well as methods of making ganaxolone formulations and their use in the treatment of epilepsy-related and other central nervous system disorders. For example, this enhanced stability was achieved via the preparation of particles comprising ganaxolone and a complexing agent, wherein the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm. The complexing agent was disclosed as, for example, a paraben, benzoic acid and mixtures thereof.

Certain definitions

[0038] As used herein, the terms "comprising," "including", "containing" and "such as" are used in their open, non-limiting sense.

[0039] The term "about" is used synonymously with the term "approximately." As one of ordinary skill in the art would understand, the exact boundary of "about" will depend on the component of the composition. Illustratively, the use of the term "about" indicates that values slightly outside the cited values, *i.e.*, plus or minus 0.1% to 10%, which are also effective and safe. Thus compositions slightly outside the cited ranges are also encompassed by the scope of the present claims.

[0040] For purposes of the invention, the term "drug" means any therapeutically active agent capable of forming a cyclodextrin inclusion complex in aqueous based solutions/suspensions. In certain embodiments, such drugs (not as a cyclodextrin inclusion complex) have an aqueous solubility of less than 1mg/ml at a pH of about 7.4.

[0041] "Bioavailability" refers to the degree to which a drug becomes available at the site(s) of action after administration. By way of illustration, the bioavailability of a drug formulation refers to the percentage of the weight of drug dosed that is delivered into the general circulation of the animal or human being studied. The total exposure ($AUC_{(0-\infty)}$) of a drug when administered intravenously is usually defined as 100% bioavailable (F%). "Oral bioavailability" refers to the extent to which drug is absorbed into the general circulation when the pharmaceutical composition is taken orally as compared to intravenous injection. The degree and timing in which an active agent becomes available to the target site(s) after administration is determined by many factors, including the dosage form and various properties, e.g., solubility and dissolution rate of the drug.

[0042] A "blood serum concentration" or "blood plasma concentration" or "serum or plasma concentration or level", typically measured in mg, μg, or ng of a drug per ml, dl, or l of serum or plasma absorbed into the bloodstream after administration. As used herein, measurable plasma concentrations are typically measured in ng/ml orμ g/ml. It is understood that the plasma concentration of a drug may vary significantly between subjects, due to variability with respect to metabolism and/or possible interactions with other therapeutic agents. In accordance with one aspect of the present invention, the blood plasma concentration of drug may vary from subject to subject. Likewise, values such as measured concentration of the active agent in the plasma at the point of maximum concentration (C_{max}) or time to reach maximum plasma concentration (T_{max}), or total area under the plasma concentration time curve ($AUC_{(0-\infty)}$) may vary from subject to subject.

[0043] "$AUC_{(0-\tau)}$ or "exposure or bioavailability" is the area under the curve of a graph of the concentration of the active agent (typically plasma concentration) vs. time (τ), measured from time 0 to τ . $AUC_{(0-\tau)}$ is also used to define the exposure to the drug over a defined period of time. Due to variability, the amount necessary to constitute "a therapeutically effective amount" of drug may vary from subject to subject.

[0044] "Carrier materials" include any commonly used excipients in pharmaceutics and should be selected on the basis of compatibility with drug and the release profile properties of the desired dosage form.

[0045] The term "curing" means treating the drug (either before, during or after particle size reduction) with a complexing agent under suitable conditions to obtain a size stabilized drug product. In certain embodiments, a measurement of stability can be via the comparison of the particle size (e.g., D50) of the uncomplexed drug versus the complexed drug.

[0046] The term "curing time" means a sufficient time until an endpoint is reached such that the properties of the (complexed) drug are stabilized. In certain embodiments, the curing time can be measured as the time until a size stabilized particle size is reached under a specified test condition. For example, a suitable curing time may be such a time wherein the D50 of the (complexed) drug particles do not change or substantially change after time in consecutive measurements separated by approximately 72 hours, e.g., by more than the accuracy of the measuring instrument ± 5%. in 72 hours after the curing period. Preferred curing times are 1-20 days, 2-15 days or 3-10 days. In other embodiments, the a suitable curing time may be such a time wherein the D50 of the (complexed) drug particles do not change or substantially change after time in consecutive measurements over 3 hours at 37°C in simulated gastric and/or simulated intestinal fluid.

[0047] The term "complexed" or "complexed nanopartriculate drug" indicates an association of molecules and/or a particle including drug, a complexing agent and other components which results in better particle size stability of drug particles or some other desirable effect. In some cases, complexing agents initially increase particle size (D50) before imparting stability or other beneficial attributes to the formulation. In certain embodiments, complexed drug or complexed nanoparticulate drug made by adding complexing agents requires a curing time.

[0048] "Complexing agents" are small molecular weight molecules which can form a cyclodextrin inclusion complex and after suitable curing time impart additional stability to the drug. Complexing agents include small compounds under MW 550. Complexing agents include but are not limited to the group consisting of phenol, parabens, ascorbic acid, methyl anthranilate, salicylic acid, acetosalicyclic acid, tocopherol, organic acids, carboxylic acids, aromatic acids, aromatic esters, acid salts of amino acids, benzaldehyde, cinnimaldehyde, imidazole, menthol, thiophenol, m-aminobenzoic acid, anthranilic acid, picolinic acids and alkyl esters thereof, toluidides, sodium benzoate, methylparaben, sodium methylparaben, para-aminobenzoic acid and esters, sorbic and benzoic acids, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, esters, isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures of any of the foregoing.

[0049] "Controlled release" or "modified release", consistent with its use herein, means a dosage form for which the drug release characteristics versus time and/or conditions at the site of dissolution are chosen to accomplish therapeutic or convenience objectives not offered by conventional immediate release dosage forms. Controlled release dosage forms include sustained release, prolonged release, pulsatile release and delayed release forms. Controlled release dosage forms can provide therapeutically effective levels of drug for an extended period of time and therefore provide a longer therapeutic period relative to immediate release forms. Addition of a complexing agent can also impart additional suspension stability during freeze/thaw cycles and boiling if sterilization is needed.

[0050] "Delayed release", consistent with its use herein, means a dosage form that releases a portion or all drug at any time other than immediately after administration and/or at any other location in the gastrointestinal tract more distal to that which would have been accomplished by an immediate release dosage form.

[0051] The term "disintegrate" is the dispersion of the dosage form when contacted with gastrointestinal fluid.. "Disintegration agents or disintegrants" facilitate the breakup or disintegration of a formulation. Examples of disintegration agents include a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, microcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crosspovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate (Explotab®), bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[0052] "Drug absorption" or “absorption” typically refers to the process of movement of drug from site of administration of a drug across a barrier into a blood vessel or the site of action, e.g., a drug moving from the gastrointestinal tract into the portal vein or lymphatic system.

[0053] “Effective particle size” and “particle size” is interchangeably used with “D50”. By “D50”, it is meant that 50% of the particles are below and 50% of the particles are above a defined measurement. D50 can be used to describe different parameters (volume, length, number, area...etc). “Effective particle size” or D50 as used herein indicates the volume-weighted median diameter as measured by a laser/ light scattering method or equivalent, wherein 50% of the particles, by volume, have a smaller diameter, while 50% by volume have a larger diameter. The volume weighted D50 also relates to the percentage of weight of the particle under a certain size. For example a D50 of 500 nm means that 50% of the particulate mass is less than 500 nm in diameter and 50% of the particulate mass is greater than 500 nm in diameter. The effective particle size is measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering (e.g., with a Microtrac UPA 150), laser diffraction and disc centrifugation. For the purposes of the compositions, formulations and methods described herein, effective particle size is the volume median diameter as determined using laser/light scattering instruments and methods, e.g. a Horiba LA-910, or Horiba LA-950. Similarly, “D90” is the volume-weighted diameter, wherein 90% of the particles, by volume, have a smaller diameter, while 10% by volume have a larger diameter and “D10” is the volume-weighted diameter, wherein 10% of the particles, by volume, have a smaller diameter, while 90% by volume have a larger diameter. It is sometimes useful to express the D50 value after sonication for 1 minute or less using about 40 watts of sonicating power at room temperature (25°C).

[0054] An “enteric coating” is a substance that remains substantially intact in the stomach but dissolves and releases the drug in the small intestine and/or colon. Generally, the enteric coating comprises a polymeric material that prevents release in the low pH environment of the stomach but that ionizes or solubilizes at a higher pH, typically a pH of 5 to 7, but at least above 3.0, more or above 5, or even more specifically at a pH of about 5.5 to about 7, and thus dissolves sufficiently in the small intestine and/or colon to release the active agent therein. In some embodiments, the enteric coatings release greater than 50% of the drug that is coated in the small intestine. In other embodiments, the enteric coating provides the release of a substantial portion (greater than 40%) of the coated drug in the mid-small intestine, e.g., the jejunum. Additionally, enteric coatings may comprise a semi-permeable membrane which releases drug slowly in a non pH-dependent manner.

[0055] The term “grinding media” refers to the material used in milling to physically reduce the particle size of a composition. For milling operations, preferred grinding media are spherical balls of yttrium stabilized zirconium oxide, glass or a plastic resin.

[0056] “Gastrointestinal fluid” is the fluid of the gastrointestinal tract of a subject or the saliva of a subject or the equivalent thereof. An “equivalent” of stomach or gastric secretion” is an in vitro fluid having similar content and/or pH as stomach secretions such as simulated gastric fluid (SGF) prepared using USP guidance of about 0.1N HCl solution in water containing about 0.03M NaCl at a pH of around 1.2. In addition, an “equivalent” of intestinal secretion” is an in vitro fluid having similar content and/or pH as intestinal secretions such as simulated intestinal fluid (SIF) prepared using USP guidance is an aqueous phosphate buffer system at pH of 6.7-6.9.

[0057] “Immediate Release” means a dosage form that releases at least 80% of drug within 2 hours of administration, more specifically, within 1 hour of addition to a commonly accepted simulated gastric fluid. Typically an immediate release composition is tested in dissolution apparatus (Type I or II most common) in an amount considered to be therapeutic in patients and a volume of SGF of 500-1000 mL.

[0058] "Ionic Dispersion Modulator" is defined as a salt (not a sulfonic acid), which when added to a complexed small particle composition will reduce the amount of certain ingredient(s) needed to stabilize solid dosage forms or blends when dispersed in water, SGF and SIF.

[0059] "Milling chamber void volume" is the open volume in a milling chamber available to the milling slurry after grinding media has been added. Milling chamber void volume is related to the amount of grinding media (volume %) and the volume of open space when the spherical beads are stacked on one another (grinding media void volume). For 0.2-0.4mm spherical milling grinding media, a range of approx. 36-42% of the volume occupied by the grinding beads is the grinding media void volume. Milling chamber void volume (mL) = Total milling chamber volume (mL) – volume of grinding media (mL) + grinding media void volume (mL).

[0060] "Milling residence time" is the time that a particle is present in the milling chamber over the total time of milling to obtain desired particles. Milling Residence Time (MRT) is defined as: MRT (minutes) = Milling chamber void volume (ml) x total milling time (minutes.)/Milling Slurry Vol. (ml)

[0061] The term "milling slurry" refers to a suspension containing the drug for particle size reduction and other ingredients to facilitate the milling process. The composition of the milling slurry is usually not the final formulation composition.

[0062] The term "milling media" refers to the components of the milling slurry minus the active pharmaceutical ingredient(s).

[0063] The term "milled slurry" refers the milling slurry after it had been reduced to a small particle suspension by milling. The most preferred milling slurries for a liquid dispersion are those that meet particle size and compositions that can be diluted with water and appropriate ingredients to obtain the final formulation. For a solid dosage form, preferred milled slurries are those that can be utilized with minimal manipulation to yield the final solid dosage form.

[0064] "Pharmacodynamics" refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

[0065] "Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

[0066] “Preservatives” are compounds which inhibit microbial growth and are typically added to dispersions to prevent microbes from growing.

[0067] A “pulsatile release” dosage form is a dosage form capable of providing more than one peak blood plasma concentration following a single administration. A “pulsatile release” formulation can contain a combination of immediate release, sustained release, and/or delayed release formulations in the same dosage form.

[0068] “Pharmacokinetic parameters” are parameters which describe the *in vivo* characteristics of the drug over time, including, for example plasma concentration of the drug. Pharmacokinetic parameters include C_{max}, T_{max}, and $AUC_{0-\tau}$ (each discussed above).

[0069] “Solubilizers” include compounds such as triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium doccusate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200 to 600, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide, miglyol, glycerin, glycerol, and the like.

[0070] “Spray Drying” is a process by which a solvent is removed from a composition yielding a dried form of the ingredients in that composition. Drying is effected by spraying the composition through a nozzle into a heated environment containing a vacuum or a flow of air or inert gas. Spray drying can produce amorphous or crystalline powders of drugs or granulations, both which can be converted into a solid dosage form by those skilled in the art.

[0071] “Spray Layering” is a procedure where a solution or suspension containing ingredients are sprayed through a nozzle into a fluidized bed containing particles which are coated with a film containing the composition of the solution or suspension as the solvent is removed by the flow of a heated gas. Spray layering typically involves coating an inert core usually comprised of a sugars and starch or cellulosics or combinations thereof. Such cores are typically 20 to 35 mesh in size. Spray Layering is used extensively for applying coatings (finish or enteric) to solid dosage formulations as well as spherical beads containing a drug for use in a capsule or tablet formulation.

[0072] “Size-stabilized” means the D50 does not substantially change (greater than 50%) after an initial time is defined (e.g., after an appropriate curing time) and up to 4 months storage at room temperature (25°C). For example, the size stabilized drug particles described herein in an aqueous dosage form will not show an increase in effective particle size of greater than 50% over a four month storage period, and preferably no increase in effective particle size of greater than 50% over a two year storage period. Similarly, the size-stabilized drug particles described herein in a liquid or solid form will show an increase in effective particle size of about 0% to about 200% upon dispersion in simulated gastric or intestinal fluid as compared to dispersion in water under the same conditions. In some embodiments, the formulations described herein does not produce any significant amount of unidentified drug degradation impurities up to 4 months storage at room temperature (25°C) at individual levels of about greater than 0.1% by weight as compared to the impurity levels at the initial time designation.

[0073] “Stabilizers” include agents which maintain a desirable attribute of the formulation over a time interval including but not limited to mechanical, chemical and temperature stressing that can be tested in a laboratory setting. Such attributes include stable particle size or homogeneity resulting in concentrations consistent with the labeled potency and maintaining purity. Some but not all of the attributes are listed above.

[0074] “Steady state,” as used herein, is when the amount of drug administered is equal to the amount of drug eliminated within one dosing interval resulting in a plateau or constant plasma drug exposure.

[0075] “Subject” as used herein is any mammal. Subjects include individuals in need of drug treatment (patients) and individuals not in need of drug treatment (e.g. normal healthy volunteers. Humans are preferred subjects and patients.

[0076] “Delayed Release”, consistent with its use herein, means a dosage form that allows at least a one dose reduction in dosing frequency per day as compared to the drug in conventional form, such as a suspension or an immediate release solid dosage form.

[0077] A “therapeutically effective amount” or “effective amount” is that amount of a pharmaceutical agent to achieve a pharmacological effect. The term “therapeutically effective amount” includes, for example, a prophylactically effective amount. An “effective amount” of drug is an amount needed to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. The effective amount of a drug will be selected by those skilled in the art depending on the particular patient and the disease. It is understood that “an effect amount” or “a therapeutically effective amount” can vary from subject to subject, due to variation in metabolism of drug, age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician.

[0078] “Treat” or “treatment” refers to any treatment of a disorder or disease, such as preventing the disorder or disease from occurring in a subject which may be predisposed to the disorder or disease, but has not yet been diagnosed as having the disorder or disease; inhibiting the disorder or disease, e.g., arresting the development of the disorder or disease, relieving the disorder or disease, causing regression of the disorder or disease, relieving a condition caused by the disease or disorder, or reducing the symptoms of the disease or disorder.

Brief Description of the Drawings

[0079] FIGURE 1 is a graph showing the curing curve of sonicated and unsonicated complexed ganaxalone particles at room temperature (25 °C). Figure 1a shows the curing curve of ganaxolone particles complexed with sodium benzoate at pH 4.0. Figure 1b shows the curing curve of ganaxolone particles complexed with parabens.

[0080] FIGURE 2 is a graph showing the D50 vs. Time of paraben complexed and sodium benzoate complexed (at pH 4.0) ganaxolone particles at room temperature (25 °C).

[0081] FIGURE 3 is a graph showing stability plots (D50 vs. Time) of uncomplexed ganaxolone particles with varying milled residence times.

[0082] FIGURE 4 is a graph showing measured D50 values for uncomplexed ganaxolone particles as a function of milling residence time for a typical milling run using a Dyno-Mill Kdl equipped with four 64 Mm polyurethane agitator discs.

[0083] FIGURE 5 is a graph showing particle size distribution (after 1 minute low power sonication) of re-suspended solid dosage forms containing sodium chloride (with and without methylparaben as the complexing agent

DETAILED DESCRIPTION OF THE INVENTION

[0084] Reference will now be made in detail to embodiments of the compositions, formulations, and methods disclosed herein. Examples of the embodiments are illustrated in the following Examples section.

[0085] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the inventions described herein belong. All patents and publications referred to herein are incorporated by reference.

[0086] Many drugs are poorly soluble in water and other pharmaceutically acceptable solvents. As a result of the low aqueous solubility of the drugs of the present invention, there exists a need in the art for drug formulations, which provide increased bioavailability and therapeutic efficacy of the drugs described herein. However, it is known that increasing the maximal systemic levels (Cmax) of an active agent likewise results in the possibility of increased side effects.

[0087] The drug formulations described herein can be administered to a subject by conventional administration routes. Drug oral solid dosage forms and oral aqueous suspensions are included herein. Immediate, modified, controlled, and pulsatile release drug dosages forms are provided herein.

[0088] It is now well-known that drugs which complex with cyclodextrin have the required shape and size to fit at least partially into the cavity of the hydrated cyclodextrin molecule; see, for example, Brauns and Muller European Patent No. 0149197 B1 . and Challa et.al.;"Cyclodextrins in Drug Delivery: An Updated Review". *AAPS PharmSciTech.* 2005; 06(02): E329-E357. Such drugs that can form a cyclodextrin inclusion complex are considered to be within the scope of the invention.

[0089] The drug formulations described herein can comprise drug particles having a D50 of less than about 500 nm. The starting drug composition can be predominantly crystalline, predominantly amorphous, or a mixture thereof. These drug particles can be made by using any method known in the art for achieving particle sizes of less than 500 nm including, for example, milling, homogenization, supercritical fluid fracture or precipitation techniques. Exemplary methods are described in U.S. Pat. Nos. 4,540,602 and 5,145,684, each of which is specifically incorporated by reference.

[0090] Methods of making compositions comprising nanoparticles are also described in U.S. Pat. Nos. 5,518,187; 5,718,388; 5,862,999; 5,665,331; 5,662,883; 5,560,932; 5,543,133; 5,534,270; 5,510,118; 5,470,583 and U.S. Pub. Appl. 2004/0067251, each of which is specifically incorporated by reference.

Milling to Obtain Drug Dispersions Comprising Submicron Particles

[0091] In certain embodiments, the drug is milled in order to obtain submicron particles. The milling process can be a dry process, e.g., a dry roller milling process, or a wet process, i.e., wet-grinding. In some embodiments, this invention is practiced in accordance with the wet-grinding process described in U.S. Pat. Nos. 4,540,602, 5,145,684, 6,976,647 and EPO 498,482, the disclosures of which are hereby incorporated by reference. Thus, the wet grinding process can be practiced in conjunction with a liquid dispersion medium and dispersing or wetting agents such as described in these publications. Useful liquid dispersion media include water, safflower oil, aqueous salt solutions, ethanol, n-butanol, hexane, glycol and the like. The dispersing, and/or wetting agents (alternatively referred to herein and in the prior art as :surface stabilizers") can be selected from known organic and inorganic pharmaceutical excipients such as described in U.S. Pat. Nos. 4,540,602 and 5,145,684, and can be present in an amount of 2.0-70%, preferably 3-50%, and more preferably 5-25% by weight based on the total weight of the drug in the formulation.

[0092] The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in shape, e.g., beads. However, grinding media in the form of other non-spherical shapes are expected to be useful in the practice of this invention.

[0093] The grinding media preferably can have a mean particle size up to about 500 microns. In other embodiments of the invention, the grinding media particles have a mean particle size preferably less than about 500 microns, less than about 100 microns, less than about 75 microns, less than about 50 microns, less than about 25 microns, less than about 5 microns, less than about 3 mm, less than about 2 mm, less than about 1 mm, less than about 0.25 mm, or less than about 0.05 mm. For fine grinding, the grinding media particles preferably are from about 0.05 to about 0.6 mm, more preferably, about 0.1 to about 0.4 mm in size. Smaller size grinding media will result in smaller size drug particles ass compared to the same conditions using larger sized grinding media.

[0094] In selecting material, grinding media with higher density, e.g., glass (2.6 g/cm^3), zirconium silicate (3.7 g/cm^3), and zirconium oxide (5.4 g/cm^3) and 95% zirconium oxide stabilized with yttrium, are generally preferred for more efficient milling. Zirconium oxide, such as 95% Zirconium oxide stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of therapeutic or diagnostic compositions. However, other media, such as stainless steel, titania, agate, glass and alumina, are believed to be useful. In addition, polymeric media having a density typically from about 1 to about 2 g/cm^3 are also expected to be useful.

[0106] If polymeric grinding media is utilized, then the grinding media can comprise particles consisting essentially of the polymeric resin. Alternatively, the grinding media can comprise particles comprising a core having a coating of the polymeric resin adhered thereon. The polymeric resin preferably has a density from 0.8 to 3.0 g/cm^3. Higher density resins are preferred inasmuch as it is believed that these provide more efficient particle size reduction.

[0107] In general, polymeric resins suitable for use herein are chemically and physically inert, substantially free of metals, solvent and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include but are not limited to crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene, styrene copolymers, polycarbonates, polyacetals, such as Delrin™, vinyl chloride polymers and copolymers, polyurethanes, polyamides, poly(tetrafluoroethylenes), e.g., Teflon™, and other fluoropolymers, high density polyethylenes, polypropylenes, cellulose ethers and esters such as cellulose acetate, polyhydroxymethacrylate, polyhydroxyethyl acrylate, silicone containing polymers such as polysiloxanes, and the like. The polymeric polymer can be biodegradable. Exemplary biodegradable polymeric polymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). In the case of biodegradable polymers, contamination from the media itself advantageously can metabolize in vivo into biologically acceptable products which can be eliminated from the body.

[0108] The core material preferably can be selected from materials known to be useful as grinding media when fabricated as spheres or particles. Suitable core materials include but are not limited to zirconium oxides (such as 95% zirconium oxide stabilized with magnesia or yttrium), zirconium silicate, glass, stainless steel, titania, alumina, ferrite, and the like. Preferred core materials have a density greater than about 2.5 g/cm^3. The selection of high density core materials is believed to facilitate efficient particle size reduction.

[0109] Useful thicknesses of the polymeric polymer coating on the core are believed to range from about 1 to about 500 microns, although other thicknesses outside this range may be useful in some applications. The thickness of the polymer coating preferably is less than the diameter of the core.

[0100] The cores can be coated with the polymeric resin by techniques known in the art. Suitable techniques include spray coating, fluidized bed coating, and melt coating. Adhesion promoting or tie layers can optionally be provided to improve the adhesion between the core material and the resin coating. The adhesion of the polymer coating to the core material can be enhanced by treating the core material to adhesion promoting procedures, such as roughening of the core surface, corona discharge treatment, and the like.

[0101] Grinding can take place in any suitable grinding mill. Suitable mills include an airjet mill, a roller mill, a ball mill, an attritor mill, a vibratory mill, a planetary mill, a sand mill and a bead mill. A high energy media mill is preferred when small particles are desired. The mill can contain a rotating shaft.

[0102] The preferred proportions of the grinding media, drug, the optional liquid dispersion medium, and dispersing, wetting or other particle stabilizing agents present in the grinding vessel can vary within wide limits and depends, for example, the size and density of the grinding media, the type of mill selected, the time of milling, etc. The process can be carried out in a continuous, batch or semi-batch mode. In high energy media mills, it can be desirable to fill 80-95% of the volume of the grinding chamber with grinding media. On the other hand, in roller mills, it frequently is desirable to leave the grinding vessel up to half filled with air, the remaining volume comprising the grinding media and the liquid dispersion media, if present. This permits a cascading effect within the vessel on the rollers which permits efficient grinding. However, when foaming is a problem during wet grinding, the vessel can be completely filled with the liquid dispersion medium or an anti-foaming agent may be added to the liquid dispersion.

[0103] The attrition time can vary widely and depends primarily upon the particular drug substance or imaging agent, mechanical means and residence conditions selected, the initial and desired final particle size and so forth. For roller mills, processing times from several days to weeks may be required. On the other hand, milling residence times of less than about 2 hours are generally required using high energy media mills.

[0104] After attrition is completed, the grinding media is separated from the milled drug particulate product (in either a dry or liquid dispersion form) using conventional separation techniques, such as by filtration, sieving through a mesh screen, and the like.

[0105] In one aspect of the invention, the grinding media comprises beads having a size ranging from 0.05-4 mm, preferably 0.1 – 0.4mm. For example, high energy milling of drug with yttrium stabilized zirconium oxide 0.4 mm beads for a milling residence time of 25 minutes to 1.5 hours in recirculation mode at 1200 to 3000 RPM. In another example, high energy milling of drug with 0.1mm zirconium oxide balls for a milling residence time of 2 hours in batch mode. Additionally, the milling temperature should not exceed 50°C as the viscosity of the suspension may change dramatically. Elevated temperatures also may result in precipitation of certain polymers in the milling slurry and will increase wear on the mill seals. If supplies of milled suspension exceeds the void milling chamber volume then this process will require recycling the material to a cooled holding tank and re-milling of the material until the desired particle (D50) size and appropriate properties are achieved in continuous mode and the mill is also jacketed with cooling. In another aspect, the mill can be jacketed to help control internal temperatures in both continuous or batch mode. The milling concentration is from about 10% to about 30% drug by weight vs. the milling media weight. The milling media is defined as the weight of the slurry that is milled minus the weight of the drug in that slurry. In one embodiment, the concentration is 25% drug by weight vs. the milling media (weight). In one embodiment, the milling media contains at least one wetting and/or dispersing agent (alternatively referred to herein and in the prior art as "surface stabilizers") to coat the initial drug suspension so a uniform feed rate may be applied in continuous milling mode. In another embodiment, batch milling mode is utilized with a milling media containing at least one agent to adjust viscosity and/or provide a wetting effect so that the drug is well dispersed amongst the grinding media.

Microprecipitating to Obtain Drug Dispersions comprising nanoparticles

[0106] Drug particles can also be prepared by homogeneous nucleation and precipitation in the presence of a wetting agent or dispersing agent as described in U.S. Patent No. 5,560,932 and U.S. Patent No. 5,665,331, which are specifically incorporated by reference. Such drug particles are storage stable and do not show and appreciable increase in effective particle size over time. This is a method of preparing stable dispersions of drug in the presence of one or more dispersing or wetting agents (alternatively referred to herein and in the prior art as "surface stabilizers") and one or more colloid stability enhancing surface active agents. Such a method comprises, for example: (1) dispersing drug in a suitable liquid media; (2) adding the mixture from step (1) to a mixture comprising at least on dispersing agent or wetting agent such that at the appropriate temperature, the drug is dissolved; and (3) precipitating the formulation from step (2) using an appropriate anti-solvent (e.g., water). The method can be followed by removal of any formed salt, if present, by dialysis or filtration and concentration of the dispersion by conventional means. In one embodiment, the drug particles are present in an essentially pure form and dispersed in a suitable liquid dispersion media. A preferred liquid dispersion medium is water. However, other liquid media can be used including, for example, aqueous salt solutions, oils (e.g., safflower, olive or cremephor), and solvents such as ethanol, t-butanol, hexane, and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art. In this embodiment, the drug particles comprise a discrete phase having been admixed with a dispersing agent or wetting agent. Useful dispersing agents or wetting agents are experimentally determined, but effectively minimize the difference in lipophilicity of drug and the dispersion media by inducing a non-covalent ordered complex between the media, the wetting agent, and drug.

Homogenization to Obtain Drug Dispersions comprising nanoparticles

[0107] In yet another embodiment, the drug particles described herein are produced by high pressure homogenization (see generally U.S. Pat. No. 5,510,118). Such a method comprises dispersing drug particles in a liquid dispersion medium, followed by subjecting the dispersion to repeated homogenization to reduce the particle size of the drug to the desired effective average particle size. The drug particles can be reduced in size in the presence of at least one or more dispersing agents or wetting agents. Alternatively, the drug particles can be contacted with one or more dispersing agents or wetting agents either before or after attrition. Other compounds, such as a diluent, can be added to the drug/dispersing agent composition before, during, or after the size reduction process. In one embodiment, unprocessed drug can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the drug in the liquid medium can vary from about 0.1-60% w/w, and preferably is from 5-30% (w/w). It is preferred, but not essential, that the dispersing agents or wetting agents be present in the premix. The concentration of the dispersing agents or wetting agents can vary from about 0.1 to 90%, and preferably is 1-75%, more preferably 20-60%, by weight based on the total combined weight of the drug and dispersing agents or wetting agents. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise. The premix then can be transferred to the microfluidizer and circulated continuously first at low pressures, then at maximum capacity having a fluid pressure of from about 3,000 to 30,000 psi until the desired particle size reduction is achieved. The particles must be reduced in size at a temperature which does not significantly degrade the drug substance or cause significant particle size growth through solubilization. Next, one of two methods can be used to collect the slurry and re-pass it in a microfluidizer. The "discreet pass" method collects every pass through the microfluidizer until all of the slurry has been passed through before re-introducing it again to the microfluidizer. This guarantees that every substance or particle has "seen" the interaction chamber the same amount of times. The second method re-circulates the slurry by collecting it in a receiving tank and allowing the entire mixture to randomly mix and pass through the interaction chamber.

[0108] If some dispersing agents and/or wetting agents, are not present in the premix, they can be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g.,shaken or stirred.

[0109] The relative amount of drug and dispersing agents and/or wetting agents (alternatively referred to herein and in the prior art as "surface stabilizers")can vary widely. The dispersing agents and/or wetting agents preferably are present in an amount of about 0.1-10 mg per square meter surface area of drug. The dispersing agents or wetting agents can be present in an amount of 0.1-90%, preferably 5-50% by weight based on the total weight of the dry drug particles during the particle size reduction.

[0110] The resulting drug dispersion is storage stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of drug particles can be spray coated onto sugar spheres or beads or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

[0111] The drug particles generated by any of the methods described herein can be utilized in solid or aqueous liquid dosage formulations, such as controlled release formulations, pulsatile dosage forms, multiparticulate dosage forms, solid dose fast melt formulations, lyophilized formulations, tablets, capsules, aqueous dispersions, or aerosol formulations.

The Use of Surface Stabilizers

[0112] In certain preferred embodiments, the drug particles are prepared with the use of one or more materials known in the art as surface stabilizers or modulators (previously or alternatively referred to herein or in the art as wetting and/or dispersing agents) which are, e.g., adsorbed on the surface of the drug compound. The surface stabilizer(s) can be contacted with the drug compound either before, during or after size reduction of the compound. Generally, surface stabilizers fall into two categories: non-ionic (also called steric stabilizers or modifiers) and ionic stabilizers. The most common non-ionic stabilizers are excipients which are contained in classes known as binders, fillers, surfactants and wetting agents. Limited examples of non-ionic surface stabilizers are hydroxypropylmethylcellulose, , polyvinylpyrrolidone, Plasdone, polyvinyl alcohol, Pluronics, Tweens andpolyethylene glycols (PEGs). A subset of surface stabilizers commonly used is ionic in nature. These ionic surface stabilizers tend to fall into the class of excipients which are typically used as surfactants and wetting agents. Ionic stabilizers used in the prior art are typically organic molecules bearing an ionic bond such that the molecule is charged in the formulation. The two most described ionic surface stabilizers are the long chain sulfonic acid salts sodium lauryl sulfate and dioctyl sodium sulfosuccinate (DOSS). Broad ranges for all surface stabilizers have been claimed in U. S. Patent No. 5,145,684 (the '684 patent) ranging from 0.1% to 90% by weight of the composition. Typically, one adds 20%-150% (wt% of drug) of a nonionic surface stabilizer and 0.2%-5% of an ionic surface stabilizer (wt% of drug) to achieve maximal particle size stabilization from these surface stabilizers.

[0113] Conversion of a nanoparticulate composition containing surface stabilizers is most commonly described via a spray drying, spray granulation or spray layering process. These procedures are well known in those skilled in the art. It is also common to add additional excipients prior to removal of solvent in the nanoparticulate suspension to aid in the dispersion of the solid composition in medium in which the solid composition will be exposed (e.g. gastrointestinal fluids) to further prevent agglomeration and/or particle size growth of the small drug particles. An example of such an additional excipient is a water soluble spacer (also referred to as a redispersing agent) which has been described is sucrose (U.S. Patent Application Publication No. 2004/0214746, the disclosure of which is hereby incorporated by reference). Other examples of water soluble spacers include sugars, polyethylene glycols, urea and quarternary ammonium salts.

Obtaining Size Stabilized Particles: Complexing Agents as Particle Growth Stabilizers

[0114] A concern with the preparation of any small particle suspension is the stability of the size-reduced (e.g., milled) particles. After size reduction, the particles after a period of time (e.g., four weeks) may tend to grow and/or agglomerate and result in increased particle size as compared to the particles size immediately after size reduction. When creating small particle formulations (D50 not greater than about 500 nm) most compositions never stabilize and continue to grow until large particles (1-30 microns) are realized. The rate at which these particles grow depends on the composition and the residence time of e.g., milling. The art around producing small particle compositions of organic molecules has focused on various methods and compositions to suppress particle growth or aggregation.

[0115] In contrast, one aspect of the invention is directed to the use of complexing agent(s) which stabilize the size of the particles. The addition of such complexing agent(s) initially provide a rapid particle size growth over a curing period, and then results in size-stabilized particles which have more desirable attributes than the uncomplexed particles.. Generally, the resultant size-stabilized particles have a D50 value of not greater than about 500 nm (the meaning of size-stabilized is defined herein at paragraph [0079]). When combined with particles comprising drugs useful in the present invention (preferably with effective amounts of a surface stabilizer(s), such complexing agents provide added stability and superior physical properties such as storage stability, freeze/thaw stability, heat stability and stability in the physiological medium (e.g., simulated gastrointestinal fluids) that the formulation will be exposed to. This enhanced stability allows the small particle compositions to be exposed to a variety of conditions as mentioned in the previous sentence and/or to be redispersed while maintaining a D50 not greater than about 500 nm. Complexing agents also can minimize the milling time needed to manufacture a stable nanoparticulate formulation and increase the concentration of drug content in various formulations.

[0116] The types of complexing agents were not previously identified in the art as providing such benefits and are small molecular weight molecules (MW less than 550) which can form a cyclodextrin inclusion complex and after suitable curing time impart additional stability to the drug. After suitable curing time, these complexing agents impart additional stability to the drug. Complexing agents include but are not limited to aryl or heteroaryl (N, O, S) aromatic acids and esters and salts thereof. Complexing agents can be substances containing a phenol moiety, an aromatic ester moiety or an aromatic acid moiety.

[0117] Examples of complexing agents include but are not limited to phenol, parabens (e.g., methylparaben, propylparaben, potassium methylparaben, sodium methylparaben), BHT, sorbic acid, ascorbic acid, methyl anthranilate, salicylic acid, acetosalicyclic acid, tocopherol, , organic acids, carboxylic acids, aromatic acids, aromatic esters, acid salts of amino acids, benzaldehyde, cinnimaldehyde, imidazole, menthol, thiophenol, m-aminobenzoic acid, anthranilic acid, picolinic acids and alkyl esters thereof, toluidides, sodium benzoate, benzoic acid, para-aminobenzoic acid and esters, sorbic and benzoic acids, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, propyl/gallate, nordihydroguaiaretic acid, esters, and isomeric compounds thereof, pharmaceutically acceptable salts thereof, mixtures of any of the foregoing, and the like.

[0118] As demonstrated in the appended Examples, this growth in particle size is especially observed, e.g., initially after adding methylparaben with or without propylparaben or benzoic acid/ sodium benzoate. A non-preservative complexing agent providing similar results in the appended Examples is methyl anthranilate.

[0119] The final storage stable particle size of a nanoparticulate suspension as measured by volume-weighted-median (D50) is dependent upon the concentration of the complexing agents and/or milling residence time. When the concentration of complexing agents was kept constant, the post-milling growth of particles correlates closely with residence time. Therefore, certain aspects of the present invention are directed to the unexpected observation that the residence time that the active agent particles (e.g., drug particles) are subjected to during the milling process, has an impact on the variability of the subsequent growth in particles size after milling. The milling residence time is defined by the following equation:

> Milling Residence Time = (milling chamber void volume/milling slurry volume) x milling time (Equation 1).

[0120] Within Equation 1 the void chamber volume is the void space in the mill chamber that can be occupied by the milling slurry. It is calculated by estimating the bead void space in the beads (for 0.4 mm yttrium-stabilized zirconium oxide beads, the bead void space is approximately 36-40% of the beads volume) and void chamber volume is the volume of the milling chamber – the volume of the beads + the bead void space (all in the same volume units). When milling under re-circulating conditions (passing multiple times through a mill by creating a loop between a milling slurry in a vessel and the mill, the disclosed residence times are obtained using flow rates varying from ¼ of the estimated void volume/minute to 3 times (3x) the estimated void chamber volume/minute. Ideally flow rates of 0.5x void chamber volume per minute to 1.5x void volume per minute are used.

[0121] As demonstrated in the Examples section, it has been observed that after obtaining a desired particle size, continued milling which does not significantly reduce the particle size any further, does produce more growth stable particles as compared to the shorter milling residence time when measuring storage stability of the formulation. One factor that may contribute to the growth of the particle size is the association of a complexing agent with a drug particle. It is also possible that this complex can further associate with other particle excipients, e.g., a viscosity enhancing agent or wetting agent (alternatively referred to herein and in the prior art as "surface stabilizers"). These complexes which are initially reversible under sonication, increase over the curing time to become larger, size-stabilized particles. (See FIGURE 1). The curing time is the time needed for the complex to become a size-stabilized particle. The effect of the milling residence time may affect the variability of size growth due to that prolonged milling produces more particles with smoother surfaces that have less area for contact and are less prone to aggregation. To minimize cost and contamination of the formulation by abrasion of grinding media and the portions of the mill in contact with the milling slurry, a preferred embodiment is shorter and lower energy milling by which a size stabilized nanoparticulate composition can be formed by adding a complexing agent. Additional preferred embodiments include nanoparticulate compositions in which addition of a complexing agent allows for more concentrated drug compositions.

[0122] Thus, certain embodiments of the present invention provide pharmaceutical particles comprising complexed drug thereof which exhibit a stable growth profile over time, i.e., the particles provide a D50 ratio of 1.5:1 or less as compared to D50 after 4 months storage (25°C) with the D50 after a suitable curing period. The novel nature of adding a small molecule complexing agent is seen in some embodiments where one can reproducibly increase the particle size by about 20% to 300% within 1-4 weeks curing. After this curing period the particle size is stable for many months.

[0123] In certain embodiments, the invention is directed to a composition comprising particles comprising a drug (preferably with a surface modifier(s) and an effective amount of a complexing agent (added during or within 24-48 hours after particle size reduction) to stabilize the particle growth after an initial particle growth and endpoint is reached (curing time), wherein the volume weighted median diameter (D50) of the particles before the initial growth is from about 50 to about 200 nm and the D50 at the end of the curing time is 20% to 300% larger than the D50 measured before the curing period.

[0124] In further embodiments, the particles have a ratio of D50 values four months storage (25°C) after curing to of about 1.25:1 or less; or about 1.15:1 or less.

[0125] In order for the milled drug particles of the present invention to provide a growth stable profile with drug particles in the 100-500 nm range (D50), the particles have a preferred milling residence time of at least 25 minutes if a complexing agent is added. However, these times are not meant to be limiting. The residence time necessary for obtaining a growth stable formulation can be ascertained by one of skill in the art, given the guidance provided by the present disclosure.

[0126] The resultant particles of the milling process disclosed herein can have a D50 of less than 500nm, less than 400nm, less than 300nm, less than 200nm or less than 100nm. The resultant particles can also have a D90 of less than 1 micron, less than 500nm, less than 400nm, less than 300nm, less than 200nm.

[0127] The end product of the milling processes to obtain growth stable particles can comprise the active agent particles suspended in water (i.e., a suspension).

[0128] Addition of a complexing agent during or preferably post-milling was found to improve the physical stability (storage and dispersed in simulated gastrointestinal fluids) of drug particles formulations (e.g. liquid suspension and solid formulations). The improvement in physical stability is believed to be the result of the formation of complex's of drug particles and the complexing agent which causes an increase in drug particle size. Without being bound by theory, it is hypothesized that the increase in drug particle size in complexing agent containing formulations is achieved through a particle complex forming process. For example, the complexing agent(s) can act as an aggregating for drug particles to form drug-aggregates associated with the complexing agent and possibly other ingredients in the suspension. These aggregates are relatively weak during the early stages (first 2 -3 days) of the complex formation, e.g. in the case of adding methylparaben or methylparaben and propylparaben or parabens and benzoic acid/sodium benzoate to ganaxolone. This is evident as sonication of the formulation in this stage can reduce the particle size of the complex, apparently due to the loose nature of the newly-formed complexes. Over a period of time, these loose aggregates become permanent (irreversible) larger particles. Generally, after no change in particle size growth is observed over 48 hours the curing process is complete. When methyl anthranilate is used as a complexing agent with certain nanoparticulate phenytoin compositions, the curing time is 5-7 days.

[0129] The initial target size for the drug particles considered desirable by the inventors was in the range of about 100-200 nm. When milling one gets an Non-linear curve. Initially a large decrease in particle size is obtained per unit milling time which then decreases so that very little particle size change with additional milling occurs.. Longer milling times are generally associated with an increase in residual materials (from the milling chamber lining and balls) in the suspension. On the other hand, the longer a drug is milled, it has been generally found (e.g., with ganaxolone), the more stable it is to particle size growth over time.

[0130] The inventors have found that when adding a preservative to a suspension of drug particles (necessary to preserve the suspension), e.g., ganaxolone in size range of 100-200 nm manufactured using a surface stabilizer(s), it was noticed that the drug particles exhibited a rapid rise in particle size that kept on growing. For example, under high energy ball milling, if one grinds Ganaxolone to 120-170 nm and then adds 0.1% methylparaben and 0.02% propylparaben (very normal preserving levels), a rise in particle size to 300 nm was noted, independent of when the milling process was stopped (i.e., 120 nm sized drug particles grew to 300 nm; and particles milled for less time and having a particles size of 170 nm grew to 300 nm) over a 10 day period or so. In view of this drug particle size growth, the inventors added other preservatives to milled suspension not containing parabens.. Benzalkonium salts were not good (flocculation of particles). Addition of sodium benzoate/benzoic acid showed a slower particle size growth than parabens but also more than doubled over a few weeks. It was thereafter noted that in the case where parabens were added to the ganaxolone drug particle suspension, the particle size of the drug particles stabilized (stopped growing) after a certain period in time and after following for a few months no further changes were noted. Despite this fact, it was noted that the methyl and propyl paraben drug particle suspensions failed when tested for microbial effectiveness. This was not predicted by the inventors as the levels used were within 50% of their solubility limit. Thus, the parabens were not acting as a preservative in the formulation. In fact, a suitable amount of benzoic acid (added as sodium benzoate) was added to the 300 nm drug particle suspension in order to pass preservative testing. It is hypothesized by the inventors that the parabens were tightly bound to the surface and therefore not able to be an effective preservative. This hypothesis is provided for possible explanatory purposes only, and is not meant to be limiting in any way with respect to the appended claims.

[0131] Further studies demonstrated that the addition of methylparaben (and to a lesser degree, propylparaben) gave ganaxolone suspensions more stability than without it. It was thereafter found that adding a non-preservative (methyl anthranilate) caused a rapid rise in particle size which was then stable. This was the first non-preservative that was identified as a "complexing" agent. As one follows the ganaxolone particle size curing period, it was seen that measuring particles size with and without 60 seconds of sonication showed that initially a loose association formed (could be reversed partially by sonication) but after the curing period the particle size of the complexed conmpositions was size stable to storage and dispersion in simulated gastrointestinal fluids.. Further evidence to show that methylparaben was acting in a unique manner in the suspension was seen by filtration. Taking a ganaxolone suspension (170 nm) containing standard surface stabilizers but not methylparaben (uncomplexed) could be filtered through a 450 nm filter and 95% of the particles passed through the filter. After a paraben curing period significant back pressure was seen in filtration and only a few percent of the particles filtered through the 450 nm filter even though at least 60% or more should have. Similar poor filtration was even seen with 1 and 10 um filters. This result indicated that the ionic/non-ionic stabilizers with ganaxolone and parabens form a complicated complex that has a large effective particle size via filtration (even though laser scattering only shows 300 nm particles present).

[0132] The manufacture of size-stabilized drug particles can also be accomplished using a wide range of drugs (as defined herein) and complexing agents other than the parabens. For example, nanoparticles of phenytoin (5,5-diphenylhydantoin) have been complexed with methyl anthranilate to provide initial rapid particle size growth followed by similarly size-stabilized particles.

[0133] A common property of all complexing agents and drugs which are capable of forming a complexed, size-stabilized particulate composition is the ability of these complexing agents and drugs to form a cyclodextrin inclusion complex. It is now understood that a complexing agent, as the term is used in the present application, may be defined as a low molecular weight organic molecule (MW<550) capable of forming a cyclodextrin inclusion complex.

[0134] Different complexing agents affect the drug (e.g., ganaxolone) complex formations differently. For example, methylparaben drug complexes typically take 5 to 7 days to cure while sodium benzoate and/or benzoic acid-drug aggregates take much longer (up to 3 weeks) to cure, as illustrated in Figure 2. Figure 2 shows the particle size growth plots for both methylparaben and propylparaben and sodium benzoate (adjusted to pH 4.0) with drug 100 to 200 nm particles. Both formulations contain 5% drug, 5% HPMC, 1% PVA, 0.1 to 0.2% SLS. The parabens formulation contained 0.1% methylparaben, 0.02% propylparaben and 0.1% simethicone while the sodium benzoate formulation contained 0.17% sodium benzoate, 0.13% citric acid and 0.01% sodium citrate (pH 4.0). It has recently been found that the addition of methyl anthranilate can form a complex which does not change after sonication after 1 day. In the case of methyl anthranilate, approximately 0.05% was added to a non-complexed drug particle suspension at 180 nm and a D50 of 390 nm was seen 72 hours later. Addition of 0.4% methyl anthranilate increased one ganaxolone composition from 220 nm to 480 nm over 3 days which was not reversed by sonication. The 0.4% complexed methyl anthranilate-ganaxolone complex showed no aggregation in SIF or SGF while the uncomplexed ganaxolone composition aggregated significantly. Percentages for liquid formulations are given as wt%/w (weight % / total formulation weight).

[0135] The cured drug-particles appear to have much better physical stability than drug particles that do not contain the complexing agent. Once the drug particle complexes are formed, no further substantial increase in drug particle size is observed. Drug particles of ganaxolone that were milled for less than 2 hours milling residence time and do not contain complexing agents continue to increase gradually in size over a number of months (Figure 3.).

[0136] Complexing agent concentrations also affect the complex curing process. Higher concentrations lead to larger particles and faster curing. For example, two identical drug particle formulations (D50 of 140 nm) with 0.1% and 0.2% methylparaben had D50 values of 190 and 300 nm respectively after the same curing period.

[0137] Parabens are esters of para-hydroxybenzoic acid. Parabens which can be utilized in the present invention include methylparaben, ethylparaben, propylparaben, and butylparaben. Other parabens which can be utilized in the present invention include isobutylparaben, isopropylparaben, benzylparaben. Pharmaceutically acceptable salts, e.g., sodium and potassium salts, can also be utilized in the present invention. Especially preferred parabens for use in the present invention include methylparaben and propylparaben and their sodium salts. If the sodium salts of parabens are utilized an equimolar amount of an organic acid, e.g., citric acid should be added.

[0138] Typically, milled drug particle suspensions are converted into a solid dosage form. Governmental drug regulatory authories such as FDA and requires to justification of all ingredients and their levels in a formulation. Therefore, it is quite uncommon for a preservative to be included in a solid dosage form. With respect to nano-sized dosage forms, commercialized solid dosage forms prepared from a nanosuspension (e.g., TriCor®), Emmend®) and Rapamune®)) do not contain any preservatives. As shown in the examples, complexing agents impart significant stability qualities into solid dosage forms.

[0139] The complexing agent can be present in any suitable amount, e.g., from about 0.001% to about 5%, from about 0.01% to about 2.5%, from about 0.015% to about 1%, from about 0.1% to about 0.5% or from about 0.02% to about 0.1%, based on the weight of the milled slurry.

[0140] Certain embodiments of the invention are directed to minimizing aggregation and/or particle size growth due to the association of the drug particles and the complexing agent when dispersed in simulated gastrointestinal fluids.. These embodiments are directed to pharmaceutical particles comprising drug thereof associated with a complexing agent, the particles exhibiting a ratio of D50 after dispersion in SGF or SIF at 36-38°C for 1-3 hours to D50 prior to dispersion in SGF or SIF of less than about 3:1; less than about 2.7:1, less than about 2.5:1, less than about 2:1, or less than about 1.5:1. In certain embodiments, the invention is directed to pharmaceutical particles comprising drug thereof stabilized with a complexing agent, the complexed particles exhibiting a ratio of D50 after dispersion in SGF or SIF for 1-3 hours to D50 prior to dispersion of from about 1.5:1 to about 3:1; from about 1.8:1 to about 2.7:1 or about 2:1 to about 1.5:1.

[0141] Certain embodiments of the invention are directed to the "cured" complexes which exhibit size stable particle size. These embodiments are directed to pharmaceutical particles comprising drug thereof complexed with a complexing agent, the particles cured for a sufficient time until an endpoint is reached such that the D50 does not change by more than about 5% as measured over 3 days after curing. In other embodiments, the particles are cured for a sufficient time until an endpoint is reached such that the D50 does not change by more than about 12%, more than about 10% , more than about 8% or more than 5% over 1 month after the curing period.

[0142] In further embodiments, the particles are cured for a sufficient time until an endpoint is reached such that the D50 does not change by more than about 5% (over the instrument's variability at the measure particle size) after 20 days after curing, 40 days after curing, 60 days after curing, or 80 days after curing storage conditions of 5°C to 25°C). Cured drug particulate complexes are more desirable as these compositions will provide a more uniform result due to a decreased change in particle size over time, better thermal stability and less aggregation in the gastrointestinal tract.

[0143] The endpoint needed to reach size stabilized particles can be ascertained by one skilled in the art. For example, the endpoint can be reached in about 5 days to about 25 days; in about 5 days to about 7 days, in about 7 days to about 14 days, in about 14 days to about 21 days, or about 10 days to about 15 days.

[0144] In certain embodiments, the particles have a D50 prior to storage of less than 350 nm, less than 250 nm or less than 150 nm. In other embodiments, the particles have a D50 prior to storage of from about 50 nm to about 350 nm, from about 75 nm to about 250 nm or from about 100 nm to about 150 nm.

[0145] The benefits of having a complexed nanosuspension include but are not limited to the following: (1) very stable particle size once cured (e.g., no significant change in particle size after about 2 years); (2) the non-complexed drug suspensions of similar composition are generally less stable in simulated gastric and intestinal fluids, e.g., when incubated at 37° C for 3 hours; (3) the complexed drug suspensions can be boiled and frozen without a significant change in particle size, whereas non-complexed drug suspensions have been found to double in size (e.g., changing in particle size from 140 nm to 330 nm); (4) the milling time can be decreased via the use of a complexing agent to get a storage stable particle size as opposed to obtaining a storage stable particle size by increasing milling time (also less contamination). Milling time is also called residence time and is the time a particle is in the mill when being recirculated through the mill into a large tank. With complexing agents, residence time to obtain a storage stable drug particle suspension may be, e.g., from about 30 to about 35 minutes versus about 1.5 to 2 hours (which translates to a 3-4 time increase in productivity).

[0146] Complexed drug suspensions comprising drug (e.g., Ganaxolone), HPMC, SLS, methylparaben, propylparaben, and PVA were found to provide desirable pharmacokinetic results in animal studies versus uncomplexed Ganaxolone formulations with D50 values 1/3 that of the complexed material. Surprisingly, the total exposure (AUC) was slightly higher with the complexed and higher D50 composition. Previous prior art claims that smaller particle size result in increased bioavailability which is not the case with complexed ganaxolone formulations. The smaller uncomplexed formulation gave higher Cmax values as one would expect with increased dissolution but not higher bioavailability. Higher Cmax levels without an increase in bioavailability is an undersirable attribute for some compounds as higher side effects will be seen without any additional benefit.

[0147] Formulations containing drug complexes as described above may provide a more desireable pharmacokinetic performance (e.g., improved bioavailability, reduction in variability, etc.).

Milling With Simethicone as an Anti-Foaming Agent

[0148] Foaming during the nanosizing of pharmaceutical products can present formulation issues and can have negative consequences for particle size reduction. For example, high levels of foam or air bubbles in the mill can cause a drastic increase in viscosity rendering the milling process inoperable. Even a very low level of air presence can dramatically reduce milling efficiency causing the desired particle size unachievable. This may be due to the resultant air in the mill cushioning the milling balls and limiting grinding efficiency. The air also can form a microemulsion with the milled ingredients which presents many issues with respect to the delivery of an accurate dose and palatability. Addition of a small amount of simethicone is a very effective anti-foaming agent which minimizes milling variability or special handling techniques to avoid the introduction of air into the milling process.

Drugs

[0149] Suitable drugs which can form a cyclodextrin inclusion complex for use in the present invention include, but are not limited to, antineoplastics (anticancer/antitumor agents), sedatives, antiinflammatory steroids (glucocorticoids such as actometasone, betamethasone, beclomethasone, fluocinonide, flunisolide, dexamethasone, cortisone, hydrocortisone, methylprednisolone, mometasone, prednisolone, prednisone, fluticasone, budesonide, and triamcinolone), tranquilizers, anticonvulsants, antivirals, antihistaminics (fexofenadine), vitamins/nutritional factors, emetics (apomorphine), anticoagulants (dicumarol or coumadin), cardiotonics (including the cardiac glycosides such as digoxin or digitoxin), diuretics, carbonic anhydrase inhibitors, non-steroidal analgesic and/or anti-inflammatory agents (NSAID's), androgens (17-methyltestosterone and testosterone), estrogens, anabolic agents (fluoxymesterone and methanstenolone), vasodilators, anxiolytics (e.g, benzodiazepines) antidepressants (sertraline or sulpiride), antipsychotics (ziprasidone, fluspirilene, pimozide and penfluridole), hypnotics (etomidate) and/or steroidal hypnotics/anesthetics (alfaxalone), antifungals, progestins, antiprotozoals, anthelmintics, anesthetics (lidocaine), vasoconstrictors, hypoglycemic (acetohexamide), antibacterials/antibiotics, and anti-infectives, platelet inhibitors, muscle relaxants, antiemetics (dimenhydrinate), radiodiagnostics, antispasmodics, angiotensin converting enzyme inhibitors, antiarrythmics, carbonic anhydrase inhibitors, gastrointestinal agents such as loperamide and cisapride (including H_2-antagonists and other anti-ulcer agents), antihypertensives especially including those useful as anti-glaucoma agents, serotonin antagonists, narcotic antagonists, narcotic agonists, mixed narcotic agonists-antagonists, pharmacologically active proteins such as peptide hormones, prostaglandins (alprostadil, prostacyclin or epoprostenol), dopaminergic agents (L-DOPA), mineral corticoids (desoxycorticosterone), neurosteroids (except for ganaxolone), enzymes, antibodies and other biologically produced substances, anti-Parkinsonism/dopamineric agents and drugs for treating Alzheimer's disease (THA).

[0150] Suitable neurosteroids may include, but are not limited to, beta-hydroxy-delta 5-compounds, such as pregnenolone (PREG) and dehydroepiandrosterone (DHEA), their sulfates, and reduced metabolites such as the tetrahydroderivative of progesterone 3 alpha-hydroxy-5 alpha-pregnane-20-one (3 alpha,5 alpha-THPROG).

[0151] While ganaxolone can indeed form a cyclodextrin inclusion complex, that drug has been described previously in our U.S. Patent Application Nos. 11/606,222 and 11/605,700, both filed on November 28, 2006, the disclosures of which are hereby incorporated by reference in their entirety. However, ganaxolone is therefore excluded from the claims of the present application.

[0152] Suitable antineoplastics for use in the present invention include, but are not limited to chlorambucil, lomustine, melphalan, methotrexate, hexamethylmelamine, teniposide, etoposide, semustine (methyl CCNU), fazarabine (Ara-AC), mercaptopurine, tubulazole, carmofur, carmustine, amsacrine, doxorubicin, bruceantin, diaziquone, dideminin B, echinomycin and PCNU.

[0153] Suitable antiinflammatory steroids (glucocorticoids) for use in the present invention include, but are not limited to actometasone, betamethasone, beclomethasone, fluocinonide, flunisolide, fludrocortisone, dexamethasone, cortisone, hydrocortisone, methylprednisolone, mometasone, prednisolone, prednisone, fluticasone, budesonide, triamcinolone and any pharmaceutically acceptable salts thereof. For example, in certain embodiments the glucocorticosteroid is triamcinolone acetonide.

[0154] Suitable estrogens for use in the present invention include, but are not limited to, 17β-estradiol, 17α-ethynylestradiol (ethinylestradiol), ethynylestradiol 3-methyl ether, estrone, mestranol and estriol. In certain embodiments, the estrogen is a synthetic estrogens such as diethylstilbestrol, benzestrol, dienestrol, hexestrol and the like.

[0155] Suitable progestins for use in the present invention include, but are not limited to, dimethisterone, norethindrone, norethindrone acetate, norgestrel, norethynodrel, ethisterone, medroxyprogesterone acetate and progesterone.

[0156] Suitable immunosuppressive agents for use in the present invention include, but are not limited to, cyclosporine (also known as cyclosporin A).

[0157] Suitable anticonvulsants for use in the present invention include, but are not limited to, phenytoin (5,5-diphenylhydantoin) and carbamazepine.

[0158] Suitable barbiturates for use in the present invention include, but are not limited to, pentobarbital, phenobarbital and secobarbital, which are variously useful as hypnotics, anticonvulsants and sedatives as well.

[0159] Sutiable antivirals for use in the present invention include, but are not limited to, acyclovir, trifluridine, zidovudine, vidarabine and virazole (also known as ribavirin).

[0160] Suitable vitamins/nutritional for use in the present invention include, but are not limited to, factors such as retinol (vitamin A), vitamin A-acetate, cholecalciferol, retinal, retinoic acid (also known as tretinoin or Retin-A™), isotretinoin, etretinate, acitretin and β-carotene, collectively referred to herein as retinoids, as well as other fat-soluble vitamins such as the E, D and K vitamins.

[0161] Beta-blockers suitable for use in the present invention include, but are not limited to, timolol, atenolol, propranolol, nadolol, carteolol, carvedilol, celiprolol, esmolol, labetalol, metoprolol, penbutolol, pindolol and sotalol.

[0162] Diuretics suitable for use in the present invention include, but are not limited to, chlorthalidone, furosemide, spironolactone, and other sulfonamide-type and/or aldosterone antagonist-type diuretics.

[0163] Angiotensin converting enzyme inhibitors (ACE inhibitors) suitable for use in the present invnentio, include but are not limited to, enalaprilic acid (the diacid, sometimes called `enalaprilate`), the ethyl ester of enalaprilic acid (sometimes called enalapril), captopril, lisinopril and SCH-33861.

[0164] Suitable non-steroidal analgesics and/or anti-inflammatory agents for use in the present invention include, but are not limited to, aspirin, ibuprofen, indomethacin, piroxicam, sulindac and flurbiprofen.

[0165] Antibacterials/antibiotics, anti-infectives and/or antifungal/antiprotozoal agents suitable for use in the present invention include, but are not limited to, ampicillin, penicillin G; tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline, minocycline, erythromycin, josamycin, rosamycin, tylosin, troleandomycin and spiramycin, benzalkonium chloride, cetylpyridinium chloride, chlorhexidine, econazole, clotrimazole, oxiconazole, bifonazole, metronidazole (metronidazole benzoate), fenticonazole, miconazole, sulconazole, tioconazole, isoconazole, butoconazole, ketoconazole, doconazole, parconazole, orconazole, valconazole and lombazole, terconazole, itraconazole, ornidazole, carnidazole, ipronidazole, tinidazole and nimorazole, and flubendazole.

[0166] Suitable vasodilators include, but are not limited, to coronary vasodilators such as nitroglycerin, flunarizine, lidoflazine and mioflazine.

[0167] Carbonic anhydrase inhibitors suitable for use in the present invention include, but are not limited to, acetazolamide, chlorzolamide, ethoxzolamine, methazolamide, L-671,152 and MK-927.

[0168] H_2-antagonists suitable for use in the present invention include, but are not limited to, famotidine, burimamide, metiamide, cimetidine and oxmetidine.

[0169] Antihistaminics suitable for use in the present invention include, but are not limited to, astemizole, levocabastine, flunarizine, oxatomide and cinnarizine.

[0170] Anthelmintic agents suitable for use in the present invention include, but are not limited to, thiabendazole, oxibendazole, cambendazole, fenbendazole, flubendazole, albendazole and oxfendazole.

[0171] Serotonin antagonists suitable for use in the present invention include, but are not limited to, ketanserin, ritanserin, altanserin, and mianserin.

[0172] Benzodiazepines suitable for use in the present invention, include but are not limited to, chlordiazepoxide, diazepam, medazepam, oxazepam, lorazepam, flunitrazepam, estazolam, flurazepam, loprazolam, lormetazepam, nitrazepam, quazepam, temazepam and triazolam.

[0173] In certain embodiments, the drug formulations comprise a non-amorphous form of drug comprising drug particles having an effective average particle size by weight of less than about 500 nm. In other embodiments, the drug particles have an effective average particle size by weight of less than about 400 nm, an effective average particle size by weight of less than about 300 nm, an effective average particle size by weight of less than about 200 nm, or an average effective particle size by weight of less than about 100 nm when measured by the above techniques. In yet another embodiment, the drug particles have a particle size distribution wherein the drug particles have an effective particle size by weight of less than about 400 nm and wherein the standard deviation of the particle size distribution is less than about 100 nm.

[0174] In other embodiments, the drug particles by weight have a particle size 500 nm, i.e., less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 200 nm, or less than about 100 nm with less than at least 20%, at least about 15% or at least about 10% of the total particles having a particle size greater than 1 micron.

[0175] In one embodiment, the drug particles have a particle size of around 300 nm with a distribution wherein 90% of the particles by weight have an effective particle size by weight between about 100 nm and 800nm. In another embodiment, the drug particles have a particle size or around 100nm and a distribution wherein 90% of the particles by weight have an effective particle size by weight between about 50 nm and 250 nm.

[0176] In other embodiments, the drug compositions described herein comprise size stabilized drug particles having a particle size by weight of less than 500 nm formulated with drug particles having a particle size by weight of greater than 500 nm. In such embodiments, the formulations have a particle size distribution wherein about 10% to about 100% of the drug particles by weight are between about 100 nm and about 300 nm, about 0% to about 90% of the drug particles by weight are between about 300 nm and about 600 nm, and about 0% to about 30% of the drug particles by weight are greater than about 600 nm. In one embodiment, the formulation has a particle size distribution wherein about 20% of the drug particles by weight are between about 100 nm and about 300 nm, about 40% of the drug particles by weight are between about 300 nm and about 600 nm, and about 30% of the drug particles by weight are greater than about 600 nm. In still another embodiment, the formulation has a particle size distribution wherein about 30% of the drug particles by weight are between about 100 nm and about 300 nm, about 40% of the drug particles by weight are between about 300 nm and about 600 nm, and about 30% of the drug particles by weight are greater than about 600 nm. In yet another embodiment, the formulation has a particle size distribution wherein about 50%% of the drug particles by weight are between about 100 nm and about 300 nm, about 40% of the drug particles by weight are between about 300 nm and about 800 nm, and about 10% of the drug particles by weight are greater than about 800 nm.

[0177] The drug particles generated by the methods described herein can be utilized in solid or aqueous liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, lyophilized formulations, tablets, capsules, aqueous dispersions, or aerosol formulations.

Dosage Forms

[0178] The drug compositions described herein can be formulated for administration to a subject via any conventional means including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, or intramuscular), buccal, intranasal or transdermal administration routes.

[0179] Moreover, the pharmaceutical drug compositions described herein can be formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, aqueous oral suspensions, solid dosage forms including oral solid dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, self-emulsifying dispersions, solid solutions, liposomal dispersions, lyophilized formulations, tablets, capsules, pills, powders, delayed release formulations, immediate release formulations, modified release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations. In some embodiments, drug formulations provide a therapeutically effective amount of drug over an interval of about 30 minutes to about 8 hours after administration, enabling, for example, once-a-day, twice-a-day (b.i.d.), or three times a day (t.i.d.) administration if desired. In one embodiment, the drug particles are formulated into a controlled release or pulsatile solid dosage form for b.i.d. administration. In other embodiments, the drug particles are dispersed in an aqueous dispersion for b.i.d. administration. Generally speaking, one will desire to administer an amount of drug needed to elicit a therapeutic effect in the minimal number of dosings per unit time.

[0180] In certain embodiments of the invention, the stabilized drug particle suspensions are converting to a solid form. There are generally four ways to accomplish this: spray drying; spray layering onto a core (fluidized bed); spray granulation (fluidized bed); or adding more excipients and performing a spheronization extrusion.

[0181] The inventors have found that several issues may arise when removing water from the stabilized drug particle suspension in order to prepare a solid dosage form. For example, there can be particle aggregation in the solid state or particle aggregation (increase in particle size) may occur when the solidified drug particles are re-dispersed into a biological medium.

Spray-Layering

[0182] In a spray layering manufacture, the cores (e.g., inert beads) are sprayed with droplets of the drug particle suspension, e.g., in a Wurster column. The the entire particle should preferably be coated evenly. Then, the water in the suspension has to evaporate before the beads circulated through the Wurster column again. It has been found that uncomplexed drug particles can be spray layered but are generally not stable in SGF and SIF. The complexed (cured particles with a complexing agent) are generally more stable; nevertheless, additional agents are typically added to make spray layering (coating) work give optimal results.

[0183] In general, it is considered by those skilled in the art that it is preferable to make the slurry to be sprayed as concentrated in drug particles as possible. Spray drying manufacture allows the drug concentration to approach 80% or higher. In spray layering manufacture, however, it has been typical to add a lot of sucrose into the drug particle dispersion, which is believed to act as a water soluble spacer separating the drug particles from agglomeration during spraying and re-dispersion.The inventors have found that spray layered ganaxolone drug-complex beads prepared by spray layering without sucrose had good water redispersion, but aggregated more substantially in SGF and SIF. The inventors then determined that adding a small amount of a salt such as sodium chloride dramatically reduced the amount of sucrose needed to help redisperse the beads with good particle size and stability. For example, a 1.5 weight % (as compared to drug) addition of NaCl reduced the amount of sucrose (water soluble spacer 20-fold (from 100% weight of drug to 5% weight of drug) to achieve minimal aggregation when dispersed in SGF. This dramatic effect have been able to provide a greater concentration of drug, thereby allowing more drug to be delivered in one capsule unit. As the stability effects are seen primarily in SGF and SIF, the salt is referred to as an "ionic dispersion modulator" as it seems to have its best effects when redispersing into an ionic medium.

[0184] In certain embodiments, the excipient comprises an ionic dispersion modulator. The ionic dispersion modulator can be a salt such as an organic or inorganic salt. In certain preferred embodiments, the ionic dispersion modulator is an inorganic salt. Suitable inorganic salts include, but are not limited to a magnesium salt, a calcium salt, a lithium salt, a potassium salt, a sodium salt and mixtures thereof. In certain preferred embodiments, the inorganic salt is sodium chloride. In other preferred embodiments, the salt is an organic salt. Suitable organic salts include, but are not limited to a citrate salt, a succinate salt, a fumarate salt, a malate salt, maleate salt, a tartrate salt, a glutarate salt, a lactate salt and mixtures thereof. In yet other embodiments, the ionic dispersion modulator includes one or more of both an inorganic and organic salt.

[0185] The amount of ionic dispersion modulator included in a spray-layering process should be an amount effective to provide a satisfactory redispersibility of the beads with acceptable particle size and stability, without causing the mixture to become a semi-solid. Such an amount typically may comprise from about 0.2% to about 5% as compared to weight of drug in the formulation.

Oral Solid Dosage Forms

[0186] In some embodiments, the solid dosage forms of the present invention may be in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder), a capsule (including both soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or "sprinkle capsules"), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including but not limited to, a fast-melt tablet. Additionally, pharmaceutical formulations of the present invention may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, or three, or four, capsules or tablets.

[0187] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing drug particles with one or more pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the drug particles are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also comprise film coatings, which disintegrate upon oral ingestion or upon contact with diluents. These drug formulations can be manufactured by conventional pharmaceutical techniques.

[0188] In certain aspects, the solid formulation is in the form of a tablet or capsule containing the size stabilized complexed drug particles and at least one surface stabilizer, the size stable drug particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200%, not more than about 150%, not more than about 100%, or not more than about 50%, when the tablets or capsules are dispersed in SGF or SIF (in any suitable volume, e.g., 15 mL to 1000 mL) at a concentration of 0.5 to 1 mg drug/mL at 36° to 38° C using a Type I or II dissolution apparatus and a stirring rate of 75 RPM for 1 hour, as compared to the D50 of the drug particles when the tablets or capsules are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the drug particles when the tablets or capsules are dispersed in distilled water is from about 50 nm to about 1000 nm, from about 100 nm to about 500 nm, or from about 100 nm to about 350 nm.

[0189] In other aspects, the invention is directed to a solid formulation (e.g., a powder, immediate release dosage form, or controlled release dosage form) comprising size stabilized drug particles and at least one pharmaceutically acceptable excipient, the size stabilized drug particles exhibiting a volume weighted median diameter (D50) of less than about 500 nm when the formulation is dispersed in simulated gastric fluid (SGF) for one hour followed by simulated intestinal fluid (SIF) for three additional hours, at a concentration of 0.5 to 1 mg drug/mL (in any suitable volume, e.g., 15 mL to 1000 mL) at a temperature of 36° to 38° C.

In still other aspects, the solid formulation is a tablet or capsule containing the stabilized drug particles and at least one excipient, the stable drug particles exhibiting a volume weighted median diameter (D50) of less than about 500 nm when the tablets or capsules are dispersed in simulated gastric fluid (SGF) for one hour followed by simulated intestinal fluid (SIF) for three additional hours, at a concentration of 0.5 to 1 mg drug/mL (in any suitable volume, e.g., 15 mL to 1000 mL) at a temperature of 36° to 38° C using a Type I or II dissolution apparatus and a stirring rate of 75 RPM.

Preparation of Solid Dosage Forms

[0190] Conventional pharmaceutical techniques for preparation of solid dosage forms include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. See, e.g., Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

Formulation Components

[0191] The pharmaceutical solid dosage forms described herein can comprise the drug compositions described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, complexing agent, ionic dispersion modulator, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000), a film coating is provided around the drug formulation. In one embodiment, some or all of the drug particles are coated. In another embodiment, some or all of the drug particles are microencapsulated. In yet another embodiment, some or all of the drug is amorphous material coated and/or microencapsulated with inert excipients. In still another embodiment, the drug particles not microencapsulated and are uncoated.

[0192] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerin, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcelulose, hydroxypropylmethylcellulose acetate stearate, sugars such as sucrose, microcrystalline cellulose, lactose, mannitol, polyvinylpyrrolidone (PVP), cholesterol, cholesterol esters, sodium caseinate, soy lecithin, taurocholic acid, phosphotidylcholine, cellulose and cellulose conjugates, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[0193] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose (e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, etc.), cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[0194] "Diluents" increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel®; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac® (Amstar); mannitol, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins, and the like. Non water-soluble diluents are compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose, and microcellulose (e.g., having a density of about 0.45 g/cm3, e.g. Avicel, powdered cellulose), and talc. Combinations of one or more diluents can also be used.

[0195] "Plasticizers" are compounds used to soften the microencapsulation material, film coatings or pharmaceutical blends for compression to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. In some embodiments, plasticizers can also function as dispersing agents or wetting agents.

[0196] "Surfactants or Wetting agents" also reffered to as surface stabilizers include compounds such as sodium lauryl sulfate, sodium doccusate, triacetin, vitamin E TPGS, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween® 20, 60 and 80 (ICI Speciality Chemicals)); polyethylene glycols (e.g., Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908®, also known as Poloxamine 9085®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508, a poloxamine) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-IOG® or Surfactant 10-G® (Olin Chemicals, Stamford, Conn.); Crodestas SL-40® (Croda, Inc.); and SA90HCO, which is $C_{18}H_{37}CH_2C(O)N(CH_3)\text{--}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate.The above surfactants are commercially available or can be prepared by techniques known in the art. Many are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference. Wetting agents include surfactants.

[0197] "Antifoaming agents" reduce foaming during processing which can result in coagulation of aqueous dispersions, bubbles in the finished form, or generally impair processing. Exemplary anti-foaming agents include silicon emulsions or sorbitan sesquoleate.

[0198] "Antioxidants" include, e.g., butylated hydroxytoluene (BHT), butylhydroxyanisole (BHA), ascorbic acid, sodium ascorbate, and tocopherol. Combinations of one or more antioxidants can also be used.

[0199] Because the drugs utilized in certain embodiments of the present invention have low solubility, they exhibit a strong correlation between the rate of dissolution and bioavailability. Thus, it is important to optimize the rate of dissolution in biological matrices in order to enhance in vivo drug absorption. In order to release the drug from a solid dosage form matrix as efficiently as possible, disintegrants are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. In some embodiments of the invention, the solid dosage drug formulation has greater than about 1 w% of a disintegrant. In various embodiments of the present invention, the solid dose drug formulations have between about 1 w% to about 11 w% or between about 2 wt% to about 8 wt% disintegrant. In yet other embodiments, the drug formulations have greater than about 2 wt% disintegrant. In some embodiments, combinations of disintegrants provide superior dispersion characteristics compared to single disintegrant at a similar total weight percentage.

[0200] Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or a sodium starch glycolate such as Promogel® or

Explotab®, a cellulose such as a wood product, microcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crosspovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[0201] In one embodiment, Ac-Di-Sol is the disintegrant. The amount of Ac-Di-Sol used in direct compression tableting may vary with typical usage levels between 1 and 3 percent. When added to granulations, generally the same percent is used as with a direct compression formulation. It is often added to both the wet and dried granulations and blends. The amount of Ac-Di-Sol used in capsule formulations generally ranges from 3-6 percent. Reduced interparticle contact within a capsule facilitates the need for elevated levels of disintegrant. Capsules filled on automatic dosater types of equipment, as opposed to semi-automatic or hand-filled machines, are more dense and have a harder structure due to the greater compressional forces needed to form the plug and successfully transfer it into the gelatin or HPMC shell. Greater plug hardness results in greater effectiveness of Ac-Di-Sol.

[0202] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules and in tablet formulation, binders ensure that the tablet remains intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose (e.g. Hypromellose USP Pharmacoat-603), hydroxypropylmethylcellulose acetate stearate (Aqoate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®), microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crosspovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[0203] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations is a function of whether direct compression, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder are used. Formulators skilled in art can determine the binder level for the formulations, but binder usage level of up to 70% in tablet formulations is common.

[0204] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl behenate, glyceryl palmitostearate, glyceryl benzoate, magnesium or sodium lauryl sulfate, mineral oil, hydrogenated vegetable oil such as hydrogenated soybean oil (Sterotex®), higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, Stearowet®, colloidal silica such as Syloid™, Cab-O-Sil®, a starch such as corn starch, silicone oil, a surfactant, and the like.

[0205] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 18000, vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodiu carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[0206] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), butylhydroxyanisole (BHA), sodium ascorbate, Vitamin E TPGS, ascorbic acid, sorbic acid and tocopherol.

[0207] "Erosion facilitators" include materials that control the erosion of a particular material in gastrointestinal fluid. Erosion facilitators are generally known to those of ordinary skill in the art. Exemplary erosion facilitators include, e.g., hydrophilic polymers, electrolytes, proteins, peptides, and amino acids. Combinations of one or more erosion facilitator with one or more diffusion facilitator can also be used in the present invention.

[0208] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms of the present invention. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

[0209] In embodiments directed to solid dosage forms utilizing substrates, the substrates can be, e.g., inert beads, or can be selected from the group consisting of lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol and mixtures thereof.

[0210] In embodiments directed to sustained or delayed dosage forms, the dosage form can be a granulation comprising the drug particles and the controlled release material, (e.g., hydrophobic polymer or pH dependent material), the granulation compressed into a tablet or filled into a capsule.

[0211] In other embodiments directed to sustained or delayed release dosage forms, the dosage form can be a plurality of pharmaceutically acceptable beads coated with the drug particles and overcoated with the controlled release material, (e.g., hydrophobic polymer or pH dependent material), the overcoated beads compressed into a tablet or filled into a capsule.

[0212] In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

Compressed Tablets

[0213] Compressed tablets are solid dosage forms prepared by compacting the bulk blend drug formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will comprise one or more flavoring agents. In other embodiments, the compressed tablets will comprise a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of the drug formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings comprising Opadry® typically range from about 1% to about 3% of the tablet weight. Film coatings for delayed release usually comprise 2-6% of a tablet weight or 7-15% of a spray-layered bead weight. In other embodiments, the compressed tablets comprise one or more excipients.

Capsule Formulations

[0214] A capsule may be prepared, e.g., by placing the bulk blend drug formulation, described above, inside of a capsule. In some embodiments, the drug formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the drug formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the drug formulations are placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments of the present invention, the therapeutic dose is split into multiple (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the drug formulation is delivered in a capsule form. For example, the capsule may comprise e.g., from 0.01 mg to about 5 grams or any dose known to one skilled in the art, such as between about 100 mg to about 600 mg of drug. In some embodiments, the capsule may comprise between about 100 to about 500 mg of drug. In other embodiments, capsule may comprise about 300 mg to about 400mg of drug.

[0215] Another useful capsule has a shell comprising the material of the rate-limiting membrane, including any of the coating materials previously discussed, and filled with drug particles. A particular advantage of this configuration is that the capsule may be prepared independently of the drug particles, thus process conditions that would adversely affect the drug can be used to prepare the capsule. A preferred embodiment is a capsule having a shell made of a porous or a pH-sensitive polymer made by a thermal forming process. An especially preferred embodiment is a capsule shell in the form of an asymmetric membrane; i.e., a membrane that has a thin skin on one surface and most of whose thickness is constituted of a highly permeable porous material. A preferred process for preparation of asymmetric membrane capsules comprises a solvent exchange phase inversion, wherein a solution of polymer, coated on a capsule-shaped mold, is induced to phase-separate by exchanging the solvent with a miscible non-solvent. Examples of asymmetric membranes are disclosed in the European Patent Specification 0 357 369 B1.

[0216] Yet another useful capsule, a "swelling plug device", can be used. Drug particles can be incorporated into a non-dissolving capsule-half of the device, which is sealed at one end by a hydrogel plug. This hydrogel plug swells in an aqueous environment, and, after swelling for a predetermined time, exits the capsule thus opening a port through which the drug can leave the capsule and be delivered to the aqueous environment. Preferred hydrogel-plugged capsules are those which exhibit substantially no release of drug from the dosage form until the dosage form has exited the stomach and has resided in the small intestine for about 15 minutes or greater, preferably about 30 minutes or greater, thus assuring that minimal drug is released in the stomach. Hydrogel-plugged capsules of this type have been described in patent application WO90/19168, which is incorporated herein by reference. A drug swelling plug device may be prepared by loading drug into a non-dissolving half-capsule shell which may be formed from a wide variety of materials, including but not limited to polyethylene, polypropylene, poly(methylmethacrylate), polyvinylchloride, polystyrene, polyurethanes, polytetrafluoroethylene, nylons, polyformaldehydes, polyesters, cellulose acetate, and nitrocellulose. The open end of the capsule shell is then "plugged" with a cylindrical plug formed from a hydrogel-forming material, including but not limited to, a homo- or co-poly(alkylene oxide) cross linked by reaction with isocyanate or unsaturated cyclic ether groups, as described in PCT Application WO 90/09168. The composition and length of the hydrogel "plug" is selected to minimize release of drug to the stomach, to decrease the incidence and/or severity of gastrointestinal side effects. The plugged capsule-half is finally sealed with a water-soluble, e.g., gelatin, capsule-half placed over the hydrogel-plugged end of the drug-containing non-dissolving capsule-half. In an embodiment of the "swelling plug device", the sealed device is coated with a pH-sensitive enteric polymer or polymer mixture, for example cellulose acetate phthalate or copolymers of methacrylic acid and methylmethacrylate. The weight of the enteric polymer coat will generally be from 2 to 20 wt%, preferably from 4 to 15 wt% of the weight of the uncoated sealed capsule. When this preferred "enteric-coated swelling plug device" is ingested orally, the enteric coat prevents release drug in the stomach. The enteric coat dissolves quickly, e.g., within about 15 minutes, in the duodenum, triggering swelling of the hydrogel plug, exiting of the hydrogel plug, and release of the incorporated drug into the gastrointestinal tract at a time greater than about 15 minutes after, and preferably greater than about 30 minutes after, the dosage form has passed from the stomach into the duodenum. Prototype unfilled "swelling plug devices" may be obtained from Scherer DDS Limited, Clydebank, Scotland, under the designation Pulsincap^{TM}.

[0217] In another embodiment, a drug complex formulation comprising a dried drug complex granulation can be filled in a capsule. Drug complex particle suspension comprising 10 to 30 wt% drug, 1 to 10 wt% hydroxypropylmethyl cellulose (Pharmacoat 603), 0.05 to 0.5 wt% sodium lauryl sulfate, 0.015 to 0.2 wt% paraben such as methylparaben, 0.001 to 0.05 wt% simethicone emulsion (30% in water) 0.5 to 5% sucrose and 0.1 to 2% NaCl in water is pumped into a spray granulator using standard parameters known by those skilled in the art. Each wt% of the drug complex particle suspension is based on the total weight of the suspension. The water is evaporated under vacuum at a temperature of 70□C to 90 □C . The resulting drug complex granulation comprises about 50 - 80 wt% of drug based on the total weight of the solid. Additional excipients such as magnesium stearate, Mannitol and a disintegrant can be added for flow and re-dispersion properties. The dispersed solid (in SGF or SIF) generally have a median particle size (D50) of about 50 nm to about 1000 nm, more specifically, about 100 nm to about 500 nm. In one embodiment, the capsule is a swelling plug device. In another embodiment, the swelling plug device is further coated with cellulose acetate phthalate or copolymers of methacrylic acid and methylmethacrylate.

[0218] In yet another embodiment, spray layered drug particles or spray layered drug complex particles are filled in a capsule. An exemplary process for manufacturing the spray layered drug or drug complex particles is the fluidized bed spraying process. Drug suspensions or drug complex suspensions described above are sprayed onto sugar or microcrystalline cellulose (MCC) beads (20-35 mesh) with Wurster column insert at an inlet temperature of 50 to 60 °C and air temp of 30 to 50° C. A 15 to 20 wt% total solids content suspension containing 45 to 80 wt% drug, 10 to 25 wt% hydroxypropylmethyl cellulose, 0.25 to 2 wt% of SLS, 10 to 18 wt% of sucrose, 0.01 to 0.3 wt% simethicone emulsion (30% emulsion) and 0.3 to10% NaCl, based on the total weight of the solid content of the suspension, are sprayed (bottom spray) onto the beads through 1.2 mm nozzles at 10 mL/min and 1.5 bar of pressure until a layering of 400 to 700% wt% is achieved as compared to initial beads weight. The resulting spray layered drug particles or drug complex particles comprise about 30 to 70 wt% of drug based on the total weight of the particles. In one embodiment the capsule is a size 0 soft gelatin capsule In one embodiment, the capsule is a swelling plug device. In another embodiment, the swelling plug device is further coated with cellulose acetate phthalate or copolymers of methacrylic acid and methylmethacrylate.

[0219] In some embodiments the capsule includes at least 250 mg (or at least 300 mg or at least 400 mg) drug and has a total weight of less than 800 mg (or less that 700 mg). The capsule may contain a plurality of drug-containing beads, for example spray layered beads. In some embodiments the beads are 12-25% drug by weight. In some embodiments some or all of the drug containing beads are coated with a coating comprising 6 to 15% (or 8 to 12%) of the total bead weight. Optimization work typically involves lower loading levels and the beads constitute 30 to 60% of the finished bead weight. Instead of or in addition to drug containing beads the capsule may contain a granulated drug composition, wherein the granulated composition comprises drug, or drug, and an ionic dispersion modulator. In some embodiments the compositions additionally comprise a complexing agent and an inorganic or organic salt. For example the granulated composition in some embodiments is comprised of 0.3 to 20% (or 1 to 10% or 1 to 5%) by weight inorganic or organic salt. These granulations also typically contain 5% to30% of a binding agent, 2% to 25% of a water soluble spacing agent and a wetting agent (0.5% to 2 %) of the total composition.

[0220] The capsule may be pulsatile release drug oral dosage form, comprising: (a) a first dosage unit comprising a first drug dose that is released substantially immediately following oral administration of the dosage form to a patient; (b) a second dosage unit comprising a second drug dose that is released approximately 3 to 7 hours following administration of the dosage form to a patient. For pulsatile release capsules containing beads the beads can be coated with a coating comprising 6 to 15% (or 8 to 12%) of the total bead weight. In some embodiments the coating is a coating that is insoluble at pH 1 –to2 and soluble at pH greater than 5.5.

[0221] In certain embodiments the pulsatile release capsule comprises by weight 30 to 50% of the first drug dose and 50 to 70% of the second drug dose. This pulsatile release capsule may contain a plurality of beads in which some beads are immediate release beads and other beads are formulated, for example with the use of a coating, for modified release, typically 3 to 10 hours after administration. In other embodiments the pulsatile release capsule contains a plurality of beads formulated for modified release and drug powder, for example spray granulated drug, for immediate release.

[0222] The particles disclosed above can be prepared according to any of the methods disclosed herein or by the methods described in U.S. Patent Nos. 6,375,986; 6,428,814; 6,432,381; 6,592,903; 6,908,626; or 6,969,529; the disclosures of which are hereby incorporated by reference.

[0223] In certain embodiments, the invention is directed to a pharmaceutical composition comprising particles comprising (i) drug thereof, (ii) a polymer selected from the group consisting of polyvinylpyrrolidone, polysaccharides, copolymers of vinyl acetate and vinyl pyrrolidone, polyvinyl alcohol, copolymers of vinyl acetate and vinyl alcohol, carboxyalkylcelluloses, cellulosic polymers and mixtures thereof; and (iii) a material selected from the group consisting of sodium lauryl sulfate and dioctyl sodium sulfosuccinate (DOSS) and (iv) an ionic dispersion modulator and (v) a water soluble spacer, wherein the D50 of the particles by weight have an effective particle size of less than about 500 nm (or any effective particle size, range, or any other characteristic as disclosed herein), wherein the composition comprises (a) an immediate release component comprising a first portion of the particles and providing an immediate release of the drug or pharmaceutically acceptable salt thereof; and (b) a controlled release component comprising a second portion of the particles and providing a controlled release of the drug or pharmaceutically acceptable salt thereof.

Formulations Containing Coated Drug Particles

[0224] In some embodiments, the spray layered drug particles or spray layered drug complex particles present in drug formulations, such as the capsule formulation described above, is coated. Drug particles can be with a modified release coating, such as an enteric coating using cellulose acetate phthalate or copolymers of methacrylic acid and methylmethacrylate. In one embodiment, the enteric coating may be present in an amount of about 0.5 to15 wt%, more specifically, about 8 to 12 wt%, based on the weight of the spray layered particles. In one embodiment, the spray layered drug particles or spray layered drug complex particles coated with the enteric coatings can be filled in a modified release capsule in which both enteric coated and immediate release drug beads are filled into a soft gelatin capsule. Additional suitable excipients may also be filled with the coated particles in the capsule.

[0225] In another embodiment, mixtures of spray layered drug particles or spray layered drug complex particles coated with the enteric coatings and those without the enteric coatings at appropriate ratios may be encapsulated in a suitable immediate release capsule. The uncoated particles release drug immediately upon administration while the coated particles do not release drug until these particles reach intestine. By controlling the ratios of the coated and uncoated particles, desirable pulsatile release profiles may be obtained. In some embodiments, the ratios between the uncoated and the coated particles are 20/80, or 30/70, or 40/60, or 50/50, w/w to obtain desirable release.

Tablet Spray Layered or Spray Dried Dosage Forms

[0226] In some embodiments, the spray dried drug complex particles or spray layered drug complex particles described above can be compressed into tablets with commonly used pharmaceutical excipients. Any appropriate apparatus for forming the coating can be used to make the enteric coated tablets, e.g., fluidized bed coating using a wurster column, powder layering in coating pans or rotary coaters; dry coating by double compression technique; tablet coating by film coating technique, and the like. See, e.g., U.S. Pat. No. 5,322,655; *Remington's Pharmaceutical Sciences Handbook*: Chapter 90 "Coating of Pharmaceutical Dosage Forms", 1990.

[0227] In various embodiments, the spray dried drug complex particles or spray layered drug complex particles described above and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the drug formulation into the gastrointestinal fluid.

[0228] In other embodiments, the spray dried drug complex particles or spray layered drug complex particles with enteric coatings described above and one or more excipients are dry blended and compressed into a mass, such as a tablet. In one embodiment, the enteric coated particles in the tablet substantially avoids release of drug, for example less than 15 wt%, in the stomach but releases substantially all drug (enterically coated), for example, greater than 80 wt%, in the intestine.

[0229] In yet other embodiments, a pulsatile release drug formulation comprises a first dosage unit comprising a formulation made from drug containing granules made from a spray drying or spray granulated procedure or a formulation made from drug complex containing granules made from a spray drying or spray granulated procedure without enteric coatings and a second dosage unit comprising spray dried drug complex particles or spray layered drug complex particles with enteric coatings. In one embodiment, the first dosage unit and the second dosage unit are wet or dry blended and compressed into a mass to make a pulsatile release tablet. In one embodiment, the weight ratio between the uncoated particles and the coated particles is about –1:4 to 4:1.

[0230] In another embodiment, binding, lubricating and disintegrating agents are blended (wet or dry) to the spray dried drug complex or drug complex spray layered beads to make a compressible blend. The first and the second dosage units are compressed separately and then compressed together to form a bilayer tablet.

[0231] In yet another embodiment, the first dosage unit is in the form of an overcoat and completely covers the second dosage unit.

Microencapsulated Formulations

[0232] In one aspect of the present invention, dosage forms may include microencapsulated drug formulations. In some embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not limited to, complexing agents, ionic dispersion modulators, pH modifiers, erosion facilitators, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[0233] Materials useful for the microencapsulation described herein include materials compatible with drug which sufficiently isolate drug from other non-compatible excipients. Materials compatible with drug of the present invention are those that delay the release of the drug in vivo.

[0234] Exemplary microencapsulation materials useful for delaying the release of the formulations comprising drug include, but are not limited to, hydroxypropyl cellulose ethers (HPC) such as Klucel® or Nisso HPC, low-substituted hydroxypropyl cellulose ethers (L-HPC), hydroxypropyl methyl cellulose ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Methocel®-E, Opadry YS, PrimaFlo, Benecel MP824, and Benecel MP843, methylcellulose polymers such as Methocel®-A, hydroxypropylmethylcellulose acetate stearate Aqoat (HF-LS, HF-LG,HF-MS) and Metolose®, Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®, Polyvinyl alcohol (PVA) such as Opadry AMB, hydroxyethylcelluloses such as Natrosol®, carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC, polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®, monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, Eudragit® NE30D, and Eudragit® NE 40D, cellulose acetate phthalate, sepifilms such as mixtures of HPMC and stearic acid, cyclodextrins, parabens, sodium chloride, and mixtures of these materials.

[0235] In still other embodiments, plasticizers such as polyethylene glycols, e.g., PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for delaying the release of the pharmaceutical compositions is from the USP or the National Formulary (NF). In yet other embodiments, the microencapsulation material is Klucel. In still other embodiments, the microencapsulation material is methocel.

[0236] Microencapsulated drug may be formulated by methods known by one of ordinary skill in the art. Such known methods include, e.g., spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, spray granulation via fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, e.g., complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ polymerization, in-liquid drying, and desolvation in liquid media could also be used. Furthermore, other methods such as roller compaction, extrusion/spheronization, coacervation, or nanoparticle coating may also be used.

[0237] The spinning disk method allows for: 1) an increased production rate due to higher feed rates and use of higher solids loading in feed solution, 2) the production of more spherical particles, 3) the production of a more even coating, and 4) limited clogging of the spray nozzle during the process.

[0238] Spray granulation via a fluid bed is often more readily available for scale-up. In various embodiments, the material used in the spray-granulation encapsulation process is emulsified or dispersed into the core material in a concentrated form, e.g., 10-60 % solids. The microencapsulation material is, in one embodiment, emulsified until about 1 to 3 μm droplets are obtained. Once a dispersion of drug and encapsulation material is obtained, the emulsion is fed as droplets into the heated chamber of the spray granulator. In some embodiments, the droplets are sprayed into the chamber or spun off a rotating disk. The microspheres are then dried in the heated chamber and fall to the bottom of the chamber where they are harvested.

[0239] Roller compaction, which involves dry granulation of single powder or a blended mixture of powders by the use of pressure to form dense compacts (the compacts are subsequently milled to a desired particle size), provides another alternative. It is a simple process that is readily available for use, and does not involved the use of solvents for granulation. Thus, roller compaction eliminates the exposure of sensitive active pharmaceutical ingredients to moisture and drying. Roller compaction can also provide some enhanced stability and taste-masking characteristics to active pharmaceutical by diluting and isolating such components in a granulated matrix of compatible ingredients. Roller compaction also imparts increased density and flow to the powder.

[0240] Extrusion/spheronization is another method that involves wet massing of active pharmaceutical ingredients, followed by the extrusion of the wet mass through a perforated plate to produce short cylindrical rods. These rods are subsequently placed into a rapidly rotating spheronizer to shape the cylindrical rods into uniform spheres. The spheres are subsequently dried using a fluid bed drier and then coated with a functional coating using a fluid bed equipped with a Wurster insert and spray nozzle.

[0241] Coacervation involves microencapsulation of materials such as active pharmaceutical ingredients and involves a three part process of particle or droplet formation, coacerate wall formation, and capsule isolation. This method can produce very small particle size microcapsules (10-70 microns).

[0242] In one embodiment, the drug particles are microencapsulated prior to being formulated into one of the above forms. In still another embodiment, some or most of the drug particles are coated prior to being further formulated by using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000).

Coated or Plasticized Formulations

[0243] In other embodiments, the solid dosage drug formulations are plasticized (coated) with one or more layers. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

[0244] In other embodiments a powder comprising the drug formulations described herein may be formulated to comprise one or more pharmaceutical excipients and flavors. Such a powder may be prepared, for example, by mixing the drug formulation and optional pharmaceutical excipients to form a bulk blend composition. Additional embodiments also comprise a suspending agent and/or a wetting agent. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units. The term "uniform" means the homogeneity of the bulk blend is substantially maintained during the packaging process. In some embodiments, at least about 75% to about 85% of the drug has an effective particle size by weight of less than 500 nm to about 100 nm. In other embodiments, the drug comprises at least 90% drug particles having an effective particle size by weight of less than 500 nm to about 100 nm.

Effervescent Powders

[0245] In still other embodiments, effervescent powders are also prepared in accordance with the present invention. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When salts of the present invention are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence." Examples of effervescent salts include, e.g: sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use and result in a pH of about 6.0 or higher.

[0246] The method of preparation of the effervescent granules of the present invention employs three basic processes: wet granulation, dry granulation and fusion. The fusion method is used for the preparation of most commercial effervescent powders. It should be noted that, although these methods are intended for the preparation of granules, the formulations of effervescent salts of the present invention could also be prepared as tablets, according to known technology for tablet preparation.

Wet and Dry Granulation

[0247] Wet granulation is one of the oldest methods of granule preparation. The individual steps in the wet granulation process of tablet preparation include milling and sieving of the ingredients, dry powder mixing, wet massing, granulation, drying and final grinding. In various embodiments, the drug composition is added to the other excipients of the pharmaceutical formulation after they have been wet granulated.

[0248] Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders, compressing (slugging) and grinding (slug reduction or granulation). No wet binder or moisture is involved in any of the steps. In some embodiments, the drug formulation is dry granulated with other excipients in the pharmaceutical formulation. In other embodiments, the drug formulation is added to other excipients of the pharmaceutical formulation after they have been dry granulated.

Solid Dispersions

[0249] In other embodiments, the drug formulations described herein are solid dispersions. Methods of producing such solid dispersions are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 4,343,789, 5,340,591, 5,456,923, 5,700,485, 5,723,269, and U.S. Pub. Appl 2004/0013734, each of which is specifically incorporated by reference. In some embodiments, the solid dispersions of the invention comprise both amorphous and non-amorphous drug and can have enhanced bioavailability as compared to conventional drug formulations. In still other embodiments, the drug formulations described herein are solid solutions. Solid solutions incorporate a substance together with the active agent and other excipients such that heating the mixture results in dissolution of the drug and the resulting composition is then cooled to provide a solid blend which can be further formulated or directly added to a capsule or compressed into a tablet. Methods of producing such solid solutions are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 4,151,273, 5,281,420, and 6,083,518, each of which is specifically incorporated by reference.

Modified Release Forms, Including Controlled Release and Delayed Release

[0250] The pharmaceutical solid oral dosage forms comprising the drug formulations described herein can be immediate release, or can be further formulated to provide a modified or controlled release of drug.

[0251] In certain embodiments, the controlled release component provides a release selected from the group consisting of sustained release or delayed release.

[0252] In certain embodiments, the controlled release component comprises a coating comprising a hydrophobic material, coated on the second portion of particles.

[0253] In certain embodiments, the controlled release component comprises a matrix comprising the second portion of particles dispersed in a hydrophobic material.

[0254] In certain embodiments, the immediate release component and the controlled release component are independently selected from the group consisting of a tablet, a pill, multiparticulates, a powder, a capsule, a solid dispersion, a solid solution, a pellet, or a granule.

[0255] In certain embodiments, the hydrophobic material is selected from the group consisting of an acrylic polymer, a cellulosic polymer, shellac, zein, fatty alcohols, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, waxes, stearic acid, stearyl alcohol, and mixtures thereof.

[0256] In certain embodiments, the hydrophobic material is an enteric polymer.

[0257] In certain embodiments, the enteric polymer is selected from the group consisting of shellac, acrylic polymers, cellulose derivatives, polyvinyl acetate phthalate and mixtures thereof.

[0258] In certain embodiments, the delayed release component provides a dose of the drug or pharmaceutically acceptable salt thereof delayed by from about 2 hours to about 12 hours after administration.

[0259] In certain embodiments, the delayed release component provides a dose of the drug or pharmaceutically acceptable salt thereof delayed by from about 2 hours to about 8hours after administration.

[0260] In certain embodiments, the delayed component provides a dose of the drug or pharmaceutically acceptable salt thereof delayed by from about 3 hours to about 7 hours after administration.

[0261] In certain embodiments, the controlled release component provides a sustained release of the drug or pharmaceutically acceptable salt thereof for about 2 hours to about 6 hours after administration.

[0262] In certain embodiments, the controlled release component provides a sustained release of the drug or pharmaceutically acceptable salt thereof for about 3 hours to about 10 hours after administration.

[0263] In certain embodiments, the coating further comprises a plasticizer, a colorant, a detackifier, a surfactant, an anti-foaming agent, a lubricant or a mixture thereof.

[0264] In certain embodiments, the immediate release component and the controlled release component independently comprise one or more pharmaceutically acceptable additives from the group consisting of carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combinations thereof.

[0265] The pharmaceutical dosage forms disclosed herein having an immediate release component and a controlled release component in this section (XIII) can provide any pharmacokinetic profile as disclosed herein.

[0266] In some embodiments, the solid dosage forms described herein can be formulated as a delay release dosage form such as and enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine of the gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated. Enteric coatings may also be used to prepare other controlled release dosage forms including extended release and pulsatile release dosage forms.

[0267] An "enterically coated" formulation of drug is intended to mean that some or most of the drug has been enterically coated to ensure that at least some of the drug is released after entering the small intestine, rather than the acidic environment of the stomach. In some embodiments, about 40% to about 60% of the coated drug particles are released in the middle region of the small intestine to minimize interaction with bile acids and minimize food effects. In some embodiments, the enterically coated formulations provide the release of greater than 80% of drug in the small intestine.

[0268] The enteric coating material should be non-toxic and is predominantly soluble in the intestinal fluid, but substantially insoluble in the gastric fluids. Examples include polyvinyl acetate phthalate (PVAP), commercially available under trade names of Opadry® Enteric or Acryl-eze MP from Colorcon®, hydroxypropylmethylcellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), methacrylic acid copolymer, hydroxypropylmethylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, hydroxypropylmethylcellulose hexahydrophthalate, hydroxypropylmethylcellulose phthalate (HPMCP), cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate trimellitate, cellulose acetate butyrate, cellulose acetate propionate, methacrylic acid/methacrylate polymer, methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl methacrylate copolymer, and the like, and combinations comprising one or more of the foregoing enteric polymers. Other examples include natural resins, such as shellac, SANDARAC, copal collophorium, and combinations comprising one or more of the foregoing polymers. Yet other examples of enteric polymers include synthetic resin bearing carboxyl groups. The methacrylic acid: acrylic acid ethyl ester copolymers are commercially available under the trade names of "Eudragit® L", such as Eudragit® L 30-D55 from Degussa.

[0269] Enteric coatings should be applied to a sufficient thickness such that the entire coating does not appreciably dissolve in the gastrointestinal fluids at pH below about 5 after 1 hour, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. In some embodiments the polymers for use in the present invention are anionic carboxylic polymers. In other embodiments, the polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to: Shellac - also called purified shellac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH >7; Acrylic polymers: The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonia methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine; Opadry Enteric are also insoluble in stomach and dissolve in the intestine; Cellulose Derivatives - Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH >6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP psuedolatex with particles <1 μm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethylcellulose acetate succinate include, but are not limited to, AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions; PolyVinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5 and it is much less permeable to water vapor and gastric fluids.

[0270] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflec A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[0271] In other embodiments, the drug formulations described herein are delivered using a pulsatile dosage form. In such a pulsatile release drug oral dosage form, a first dose of the drug is released followed by a second dose of the drug released approximately 3 to 7 hours following administration of the dosage form. For example, such pulsatile dosage forms may comprise: (a) a first dosage unit comprising a first dose of drug that is released substantially immediately following oral administration of the dosage form to a patient; (b) a second dosage unit comprising a second dose of drug that is released approximately 3 to 7 hours following administration of the dosage form to a patient.Pulsatile dosage forms comprising the drug formulations described herein may be administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, those described in U.S. Pat. Nos. 5,011,692, 5,017,381, 5,229,135, and 5,840,329, each of which is specifically incorporated by reference. Other dosage forms suitable for use with the drug formulations are described in, for example, U.S. Pat. Nos. 4,871,549, 5,260,068, 5,260,069, 5,508,040, 5,567,441 and 5,837,284, all of which are specifically incorporated by reference. In one embodiment, the controlled release dosage form is pulsatile release solid oral dosage form comprising at least two groups of particles, each containing the drug formulation described herein. The first group of particles provides a substantially immediate dose of drug upon ingestion by a subject. The first group of particles can be either uncoated or comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 70%, and more preferably from about 40% to about 70%, by weight of the total dose of the drug in said formulation, in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ingredient in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. Suitable coatings include one or more differentially degradable coatings such as, by way of example only, pH sensitive coatings (enteric coatings) such as acrylic resins (e.g., Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, and Eudragit® NE30D, Eudragit® NE 40D®) either alone or blended with cellulose derivatives, e.g., ethylcellulose, or non-enteric coatings having variable thickness to provide differential release of the drug formulation.

[0272] Many other types of controlled release systems known to those of ordinary skill in the art and are suitable for use with the drug formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, plyanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman et al., *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725, 4,624,848, 4,968,509, 5,461,140, 5,456,923, 5,516,527, 5,622,721, 5,686,105, 5,700,410, 5,977,175, 6,465,014 and 6,932,983, each of which is specifically incorporated by reference.

[0273] In another embodiment, a modified release dosage formulation may comprise a combination of: (a) a compressed tablet core comprising complexed drug particles, a surface stabilizer, an ionic dispersion modifier, a water soluble spacer, a pharmaceutically acceptable water swellable polymer, and an osmotic agent; and (b) an outer coating layer which completely covers the tablet core and comprises a pH sensitive coating. An optional sealing coat may be applied to the compressed tablet core and an optional coating layer comprising an enteric coating agent may be applied under the outer coating layer as an inner coating or as an overcoat over the outer coating layer. The tablet core may be compressed using a smooth faced tablet die. In one embodiment, the active agent is drug.

[0274] The osmotic agent in this dosage form is any non-toxic pharmaceutically acceptable water soluble compound which will dissolve sufficiently in water and increase the osmotic pressure inside the tablet core. Suitable osmotic agents include simple sugars and salts such as sodium chloride, potassium chloride, magnesium sulfate, magnesium sulfate, magnesium chloride, sodium sulfate, lithium sulfate, urea, inositol, sucrose, lactose, glucose, sorbitol, fructose, mannitol, dextrose, magnesium succinate, potassium acid phosphate and the like. The preferred osmotic agent for the tablet core is a simple sugar such as anhydrous lactose in the range of 0-50% by weight, based on the weight of the compressed, uncoated tablet.

[0275] The water swellable polymer may be any pharmaceutically acceptable polymer which swells and expands in the presence of water to slowly release drug. These polymers include polyethylene oxide, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and the like. In a preferred embodiment, the water swellable polymer will be polyethylene oxide (obtained from Union Carbide Corporation under the trade name Polyox WSR Coagulant or Polyox WSR N 80). These materials form a viscous gel in water or other solvent system at a sufficient concentration to control the release of the drug. This will generally require a concentration of the pharmaceutically acceptable, water swellable polymer of about 0-50% by weight of the compressed, uncoated tablet.

[0276] The outer coating comprises a pH sensitive coating which functions as an enteric polymer in that it does not begin to dissolve until pH conditions in excess of the pH of the stomach region are encountered. The pH sensitive coating is the same type of material that is described above. The pH sensitive coating may be present in an amount of about 0.5-15 wt%, more specifically, about 8 – 12 wt%, based on the weight of the coated tablet core.

[0277] Certain controlled release formulation may release less than about 20 wt% of drug in the formulation is released within the first three hours after administration and more than about 60 percent of drug between 3 and 10 hours. Other controlled release drug formulation may release less than about 50 percent within the first three hours after administration and about 50 percent of drug between 3 and 10 hours.

[0278] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[0279] A particularly suitable methacrylic copolymer is Eudragit L®, particularly L-30D® and Eudragit 100-55®, manufactured by Rohm Pharma, Germany. In Eudragit L-30D®, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH values present in the small intestine.

[0280] In some embodiments, materials include shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof. In other embodiments, materials include Eudragit® series E, L, RL, RS, NE, L, L300, S, 100-55, cellulose acetate phthalate, Aquateric, cellulose acetate trimellitate, ethyl cellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, polyvinyl acetate phthalate, and Cotteric.

[0281] In other aspects, the invention is directed to an oral solid dosage form comprising (i) a controlled release component comprising a first portion of particles comprising drug; and a controlled release material, and (ii) an immediate release component comprising a second portion of particles comprising drug, the first and second portion of drug particles having a volume weighted median diameter (D50) of from about 50 nm to about 1000 nm, from about 100 nm to about 450 nm, or from about 100 nm to about 350 nm. The ratio of drug in controlled release to immediate release can be, e.g., from about 4:1 to about 1:4, from about 3:2 to about 2:3, or about 1:1. The controlled release component can be in any form, including but not limited to (i) a plurality of pharmaceutically acceptable beads coated with the first portion of drug particles and overcoated with the controlled release material (optionally a film coat comprising a material such as hydroxypropylmethylcellulse or polyvinyl alcohol can be included on the beads prior to coating with the drug particles), (ii) a plurality of matrices comprising the first portion of drug particles dispersed in the controlled release material, (iii) a tablet comprising the first portion of drug particles dispersed in the controlled release material, or (iv) a granulation comprising the first portion of drug particles and the controlled release material. The immediate release component can be in any form, including bit not limited to (i) plurality of pharmaceutically acceptable beads coated with the second portion of drug particles, (ii) a plurality of matrices comprising the second portion of drug particles dispersed in an excipient, (iii) a tablet comprising the second portion of drug particles dispersed in excipient, or (v) a granulation comprising the second portion of drug particles and excipient. Alternatively, the immediate release component can be included in the dosage form in powder form.

[0282] In certain embodiments, the controlled release component and the immediate release component are contained in a capsule.

[0283] In other embodiments, the controlled release component is a tablet and the immediate release component is coated onto the tablet.

[0284] In further embodiments, the controlled release component and the immediate release component are in a bi-layer tablet.

[0285] In still other embodiments, the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of drug particles and overcoated with the controlled release material and the immediate release component comprises a plurality of pharmaceutically acceptable beads coated with the second portion of drug particles, the controlled release component and immediate release component contained in a capsule.

[0286] In another aspect, the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of drug particles and overcoated with the controlled release material and the immediate release component comprises a tablet comprising the second portion of drug particles dispersed in an excipient, the controlled release component and immediate release component contained in a capsule.

[0287] In still another embodiments, controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of drug particles and overcoated with the controlled release material and the immediate release component comprises a granulation comprising the second portion of drug particles and an excipient, the controlled release component and immediate release component contained in a capsule.

[0288] In another embodiment, the controlled release component comprises a plurality of pharmaceutically acceptable beads coated with the first portion of drug particles and overcoated with the controlled release material, and the immediate release component comprises a granulation comprising the second portion of drug particles and an excipient, the controlled release component dispersed in the immediate release component in the form of a compressed tablet.

[0289] In further embodiments, the controlled release component comprises a compressed tablet and the immediate release component is compression coated over the controlled release tablet.

[0290] In embodiments directed to drug coated beads, controlled release material can be coated onto the drug layered bead in an amount, e.g., from about 3% to about 25%, or from about 10% to about 20%, based on the total weight of the component.

[0291] In certain embodiments, the dosage forms of the present invention provide pulsatile release of two or more doses of drug. The dosage form can provide an immediate release dose after administration and at least one additional dose at a time after administration selected from the group consisting of 3-8 hours, 6-10 hours, 10-14 hours, 14-18 hours, 16-20 hours and 22-24 hours.

[0292] In certain embodiments, the invention is directed to an oral solid dosage form comprising drug particles and a controlled release material, the drug particles having a volume weighted median diameter (D50) of from about 50 nm to about 1000 nm, the dosage form providing a controlled release of the drug to provide a therapeutic effect for about 8 to about 24 hours after administration.

[0293] In other embodiments, the invention is directed to an oral solid dosage form comprising particles comprising drug; and a pH dependent polymer, the drug particles having a volume weighted median diameter (D50) from about 50 nm to about 1000 nm, the dosage form providing a delayed release of the drug for a time period from about 2 to about 12 hours after administration.

[0294] The dosage forms can be prepared according to any of the methods disclosed herein or by the methods described in U.S. Patent Nos. 5,209,746; 5,213,808; 5,221,278; 5,260,068; 5,260,069; 5,308,348; 5,312,390; 5,318,588; 5,340,590; 5,391,381; 5,456,679; 5,472,708; 5,508,040; 5,840,329; 5,980,508; 6,214,379; 6,228,398; 6,248,363; 6,514,518; 6,569,463; 6,607,751; 6,627,223; 6,730,325; 6,793,936; 6,902,742 and 6,923,988, the disclosures of which are hereby incorporated by reference.

Liquid Formulations

[0295] In some embodiments, pharmaceutical drug formulations are provided comprising the drug particles described herein and at least one dispersing agent or suspending agent for oral administration to a subject. The drug formulation may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained. As described herein, the aqueous dispersion can comprise amorphous and non-amorphous drug particles of consisting of multiple effective particle sizes such that drug particles having a smaller effective particle size are absorbed more quickly and drug particles having a larger effective particle size are absorbed more slowly. In certain embodiments the aqueous dispersion or suspension is an immediate release formulation. In another embodiment, an aqueous dispersion comprising amorphous drug particles is formulated such that about 50% of the drug particles are absorbed within about 3 hours after administration and about 90% of the drug particles are absorbed within about 10 hours after administration. In other embodiments, addition of a complexing agent to the aqueous dispersion results in a larger span of drug containing particles to extend the drug absorption phase such that 50-80% of the particles are absorbed in the first 3 hours and about 90% are absorbed by about 10 hours.

[0296] A suspension is "substantially uniform" when it is mostly homogenous, that is, when the suspension is composed of approximately the same concentration of drug at any point throughout the suspension. Preferred embodiments are those that provide concentrations essentially the same (within 15%) when measured at various points in a drug aqueous oral formulation after shaking. Especially preferred are aqueous suspensions and dispersions, which maintain homogeneity (up to 15% variation) when measured 2 hours after shaking. The homogeneity should be determined by a sampling method consistent with regard to determining homogeneity of the entire composition. In one embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 45 seconds. In yet another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 30 seconds. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[0297] In some embodiments, the drug powders for aqueous dispersion described herein comprise size stabilized drug particles having an effective particle size by weight of less than 500 nm formulated with drug particles having an effective particle size by weight of greater than 500 nm. In certain embodiments, the formulations have a particle size distribution wherein about 10% to about 100% of the drug particles by weight are between about 75 nm and about 500 nm, about 0% to about 90% of the drug particles by weight are between about 150 nm and about 400 nm, and about 0% to about 30% of the drug particles by weight are greater than about 600 nm. The drug particles describe herein can be amorphous, semi-amorphous, crystalline, semi-crystalline, or mixture thereof.

[0298] In one embodiment, the aqueous suspensions or dispersions described herein comprise drug particles or drug complex at a concentration of about 20 mg/ml to about 150 mg/ml of suspension. In another embodiment, the aqueous oral dispersions described herein comprise drug particles or drug complex particles at a concentration of about 25 mg/ml to about 75 mg/ml of solution. In yet another embodiment, the aqueous oral dispersions described herein comprise drug particles or drug complex at a concentration of about 50 mg/ml of suspension. The aqueous dispersions described herein are especially beneficial for the administration of drug to infants (less than 2 years old), children under 10 years of age and any patient group that is unable to swallow or ingest solid oral dosage forms.

[0299] Liquid drug formulation dosage forms for oral administration can be aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, and syrups. See, e.g., Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 754-757 (2002). In addition to drug particles, the liquid dosage forms may comprise additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, (g) at least one flavoring agent, and (h) a complexing agent. In some embodiments, the aqueous dispersions can further comprise a crystalline inhibitor.

[0300] Examples of disintegrating agents for use in the aqueous suspensions and dispersions include, but are not limited to, a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®; a cellulose such as a wood product, microcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crosspovidone; a cross-linked polyvinylpyrrolidone; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a clay such as Veegum® HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[0301] Dispersing/suspending agents and/or viscosity modulating agents include materials that control the diffusion and homogeneity of a drug through liquid media or a granulation method or blend method. In some embodiments, these agents also facilitate the effectiveness of a coating or eroding matrix. Viscosity enhancing agents" are agents which are typically added to a particulate dispersion to increase the viscosity and prevent or slow settling of the particles. Viscosity enhancing agents in solid dosage forms are used on occasion to form a gel matrix as water permeates the solid dosage form and can delay the release of the pharmaceutically active ingredient(s). In some embodiments, the dispersing agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, for example, hydrophilic polymers, electrolytes, Tween® 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropylcellulose ethers (e.g., HPC, HPC-SL, and HPC-L), hydroxypropylmethylcellulose and hydroxypropylmethylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetatestearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (Plasdone®, e.g., S-630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)). In other embodiments, the dispersing agent is selected from a group not comprising one of the following agents: hydrophilic polymers; electrolytes; Tween ® 60 or 80; PEG; polyvinylpyrrolidone (PVP); hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L); hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M, and Pharmacoat® USP 2910 (Shin-Etsu)); carboxymethylcellulose sodium; methylcellulose; hydroxyethylcellulose; hydroxypropylmethyl-cellulose phthalate; hydroxypropylmethylcellulose acetate stearate; non-crystalline cellulose; magnesium aluminum silicate; triethanolamine; polyvinyl alcohol (PVA); 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde; poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); or poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®).

[0302] Wetting agents (including surfactants) suitable for the aqueous suspensions and dispersions described herein are known in the art and include, but are not limited to, acetyl alcohol, glycerol monostearate, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80® (ICI Specialty Chemicals)), and polyethylene glycols (e.g., Carbowaxs 3350® and 1450®, and Carpool 934® (Union Carbide)), oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, vitamin E TPGS, sodium taurocholate, simethicone, phosphotidylcholine and the like.

[0303] Typically amounts of preservatives needed to pass anti-microbial effectiveness testing as described by USP and EU methodology are used to test appropriate preservative levels. Suitable preservatives for the aqueous suspensions or dispersions described herein include, for example, potassium sorbate, parabens (e.g., methylparaben and propylparaben) and their salts, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl alcohol or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride. Preservatives, as used herein, are incorporated into the dosage form at a concentration sufficient to inhibit microbial growth. In one embodiment, the aqueous liquid dispersion can comprise methylparaben and propylparaben in a concentration ranging from about 0.01% to about 0.3% methylparaben by weight to the weight of the aqueous dispersion and 0.005% to 0.03% propylparaben by weight to the total aqueous dispersion weight. In yet another embodiment, the aqueous liquid dispersion can comprise methylparaben 0.05to about 0.1 weight% and propylparaben from 0.01-0.02 weight % of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion can comprise sodium benzoate 0.05to about 0.1 weight % of the aqueous dispersion and pH adjusted from 3.5 to 5.0.

[0304] Suspensions or dispersions described herein include, but are not limited to, methyl cellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, Plasdone® S-630, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the viscosity enhancing agent will depend upon the agent selected and the viscosity desired.

[0305] Examples of natural and artificial sweetening agents suitable for the aqueous suspensions or dispersions described herein include, for example, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof. In one embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.0001% to about 10.0% the weight of the aqueous dispersion. In another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.0005% to about 5.0 % wt% of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about .0001% to 0.1 wt%, from about 0.001% to about 0.01 weight%, or from 0.0005 % to 0.004% of the aqueous dispersion.

[0306] In addition to the additives listed above, the liquid drug formulations can also comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers.

[0307] In certain embodiments, the invention is directed to an oral liquid dosage form comprising from about 2.5% to about 5% size stabilized drug complex particles, from about 2% to about 5% hydroxypropylmethyl cellulose, about 0.5% to about 1.5% polyvinyl alcohol, from about 0.1% to about .03% sodium lauryl sulfate, from about 0.005% to about 0.02% simethicone, from about 0.01% to about 0.03% sucralose, from about 0.05% to about 0.1% methylparaben, from about 0.01% to about 0.02% propylparaben, from about 0.05 to about 0.1% sodium benzoate, from about 0.05% to about 0.15% citric acid, from about 0.005 to about 0.1% sodium citrate and from about 0.002% to about 0.004% flavoring, the liquid having a pH of about 3.8 to about 4.2, wherein all percentages are weight percent to the total liquid formulation weight.

[0308] In certain embodiments, the invention is directed to an oral liquid dosage form comprising size stabilized complexed drug particles and at least one pharmaceutically acceptable excipient, the particles suspended in a pharmaceutically acceptable liquid vehicle, wherein the volume weighted median diameter (D50) after a suitable curing time does not change by more than about 15% after 10 days storage at room temperature, by more than about 12% after 10 days storage at room temperature, by more than about 10% after 10 days storage at room temperature, by more than about 8% after 10 days storage at room temperature, by more than about 15% after 20 days of storage at room temperature, by more than about 15% after 40 days of storage at room temperature, by more than about 15% after 60 days of storage at room temperature, or by more than about 15% after 80 days of storage at room temperature. In certain aspects, the volume weighted median diameter (D50) of the size stabilized drug complex particles prior to storage is from about 100 nm to about 500 nm, or from about 100 nm to about 350 nm.

[0309] In certain embodiments, the invention is directed to an oral liquid dosage form wherein the volume weighted median diameter (D50) of the size stablized drug complex particles do not change by more than about 15% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes, does not change by more than about 15% when placed in a glass vial and heated in a 100° C oil bath for 4 hours, does not change by more than about 10% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes, does not change by more than about 5% when placed in a glass vial and heated in a 100° C oil bath for 20 minutes, or does not change when placed in a glass vial and heated in a 100° C oil bath for 20 minutes (within the accuracy of the particle size measurement procedure).

[0310] In still further embodiments, the invention is directed to an oral liquid dosage form the volume weighted median diameter (D50) of the size stabilized drug complex particles does not change by more than about 25% when placed in a HDPE container and frozen and thawed three or more times with the time frozen for each cycle being at least 12 hours. The frozen temperature can be any suitable freezing temperature, e.g., from about -80°C to about -20°C.

[0311] In certain embodiments, the oral liquid dosage form is prepared by contacting drug particles with a complexing agent, wherein the size of the particles exhibits an increase in volume weighted median diameter (D50) of from about 20% to about 300% and reaching an endpoint such that the particles are size stablized.

[0312] In certain solid formulations, the size stabilized drug complex particles are dispersed in a liquid to form a suspension and the suspension is spray coated onto the plurality of substrates, or spray granulated with the plurality of substrates. In further embodiments the drug particles are dispersed in a liquid to form a suspension and the suspension is spray dried to form a powder which is then granulated and added to a capsule or granulated and compressed into a tablet.. The suspension can be, e.g., about 5% to about 35%, or about 15% to about 25% total solids. The drug concentration in the solids can be, e.g., from about 20% to about 80%.

[0313] In embodiments directed to liquid dosage forms, the liquid dosage form can be include at least one excipient selected from hydroxypropylmethylcellulose, sodium lauryl sulfate, methyl anthranilate, sodium benzoate, citric acid, sodium citrate, simethicone, sucralose and flavoring. For example, the liquid dosage form can comprise about 5% drug, about 5% hydroxymethylcellulose (2910), about 0.1% sodium lauryl sulfate, about 0.4% methylanthranilate about 0.1% sodium benzoate, about 0.12% citric acid, about 0.06% sodium citrate, about 0.01% simethicone, and 0.02% sucralose. These ingredients and % amounts are not meant to be limiting.

Emulsions

[0314] In some embodiments, the pharmaceutical drug formulations described herein can be self-emulsifying drug delivery systems (SEDDS). Emulsions are dispersions of one immiscible phase in another, usually in the form of droplets. Generally, emulsions are created by vigorous mechanical dispersion. SEDDS, as opposed to emulsions or microemulsions, spontaneously form emulsions when added to an excess of water without any external mechanical dispersion or agitation. An advantage of SEDDS is that only gentle mixing is required to distribute the droplets throughout the solution. Additionally, water or the aqueous phase can be added just prior to administration, which ensures stability of an unstable or hydrophobic active ingredient. Thus, the SEDDS provides an effective delivery system for oral and parenteral delivery of hydrophobic active ingredients. SEDDS may provide improvements in the bioavailability of hydrophobic active ingredients. Methods of producing self-emulsifying dosage forms are known in the art include, but are not limited to, for example, U.S. Pat. Nos. 5,858,401, 6,667,048, and 6,960,563, each of which is specifically incorporated by reference.

[0315] Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butyleneglycol, dimethylformamide, sodium lauryl sulfate, sodium doccusate, cholesterol, cholesterol esters, taurocholic acid, phosphotidylcholine, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Intranasal Formulations

[0316] Intranasal formulations are known in the art and are described in, for example, U.S. Pat. Nos. 4,476,116, 5,116,817 and 6,391,452, each of which is specifically incorporated by reference. Drug formulations prepared according to these and other techniques well-known in the art are prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, Ansel, H. C. et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, Sixth Ed. (1995). Preferably these compositions and formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. These ingredients are known to those skilled in the preparation of nasal dosage forms and some of these can be found in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 21st edition, 2005, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters, emulsifiers or dispersing agents, preservatives, surfactants, gelling agents, complexing agents or buffering and other stabilizing and solubilizing agents may also be present. Preferably, the nasal dosage form should be isotonic with nasal secretions.

Buccal Formulations

[0317] Buccal formulations comprising the drug formulations described herein may be administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, U.S. Pat. Nos. 4,229,447, 4,596,795, 4,755,386, and 5,739,136, each of which is specifically incorporated by reference. In addition, the buccal dosage forms described herein can further comprise a bioerodible (hydrolyzable) polymeric carrier that may also serves to adhere the dosage form to the buccal mucosa. The buccal dosage form is fabricated so as to erode gradually over a predetermined time period, wherein drug delivery is provided essentially throughout. Buccal drug delivery, as will be appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow drug absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. With regard to the bioerodible (hydrolysable) polymeric carrier, it will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not comprised, and the carrier is compatible with drug and any other components that may be present in the buccal dosage unit. Generally, the polymeric carrier comprises hydrophilic (water-soluble and water-swellable) polymers that adhere to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B.F. Goodrich, is one such polymer). Other components may also be incorporated into the buccal dosage forms described herein include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like.

Transdermal Formulations

[0318] Transdermal formulations described herein may be administered using a variety of devices which have been described in the art. For example, such devices include, but are not limited to, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,710,795, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,972,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,077,407, 4,201,211, 4,230,105, 4,292,299, 4,292,303, 5,336,168, 5,665,378, 5,837,280, 5,869,090, 6,923,983, 6,929,801 and 6,946,144, each of which is specifically incorporated by reference in its entirety. In some embodiments, the transdermal delivery device used with the drug formulations described herein can comprise a power source, radio frequency, or a brief electrical current to micro-electrodes in the skin creating “channels” or “pores” in the stratum corneum to facilitate the delivery of the drug formulation, such methods are known in the art and are described in, for example U.S. Pat. Nos. 6,611,706, 6,708,060, and 6,711,435, each of which is specifically incorporated by reference in its entirety. In other embodiments, the transdermal delivery device can comprise a means for porating the stratum corneum, e.g., micro-lancing, application of sonic energy, or hydraulic puncturing, to facilitate the delivery of the drug formulation, such methods are known in the art and are described in, for example, U.S. Pat. Nos. 6,142,939 and 6,527,716, each of which is specifically incorporated by reference in its entirety. The pores described by the methods herein are typically about 20-50 microns in depth and to not extend into areas of innervation or vascularization.

[0319] The transdermal dosage forms described herein may incorporate certain pharmaceutically acceptable excipients which are conventional in the art. In general, the transdermal formulations described herein comprise at least three components: (1) a drug complex formulation; (2) a penetration enhancer; and (3) an aqueous adjuvant. In addition, transdermal formulations can include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation can further comprise a woven or non-woven backing material to enhance drug absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

Injectable Formulations

[0320] Size stabilized drug complex formulations suitable for intramuscular, subcutaneous, or intravenous injection may comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propylene glycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Drug formulations suitable for subcutaneous injection may also contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, benzoic acid, benzyl alcohol, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged drug absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin. Drug suspension formulations designed for extended release via subcutaneous or intramuscular injection can avoid first pass metabolism and lower dosages of drug will be necessary to maintain plasma levels in therapeutic range. In such formulations, the particle size of the drug particles and the range of the particle sizes of the drug particles can be used to control the release of the drug by controlling the rate of dissolution in fat or muscle.

Sterile Drug Formulations

[0321] Some of the drug formulations described herein can be sterile filtered. This property obviates the need for heat sterilization, which can harm or degrade drug, as well as result effective particle size growth.

[0322] Sterile filtration can be difficult because of the required small particle size of the composition. However, this method is suitable and commonly used for dispersions comprising nanoparticles. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize conventional suspensions of micron-sized drug because the drug particles are too large to pass through the membrane pores.

[0323] Because some of the size stabilized drug-complex formulations described herein can be sterilized via autoclaving, and because the formulations can have a very small drug effective average particle size, some sterilized drug formulations are suitable for parenteral administration. Additionally, a sterile drug formulation is particularly useful in treating immunocompromised patients, infants or juvenile patients, patients with head trauma and the elderly.

Combination Therapies

[0324] The compositions and methods described herein may also be used in conjunction with other well known therapeutic reagents that are selected for their particular usefulness against the condition that is being treated. In general, the compositions described herein and, in embodiments where combinational therapy is employed, other agents do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

[0325] The particular choice of compounds used will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. The compounds may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of compounds used. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

[0326] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, can be modified in accordance with a variety of factors. These factors include the disorder from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, the dosage regimen actually employed can vary widely and therefore can deviate from the dosage regimens set forth herein.

[0327] The pharmaceutical agents which make up the combination therapy disclosed herein may be a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. The two-step administration regimen may call for sequential administration of the active agents or spaced-apart administration of the separate active agents. The time period between the multiple administration steps may range from, a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent. Circadian variation of the target molecule concentration may also determine the optimal dose interval.

[0328] In some embodiments, the drug formulation is administered with at least one other agent, e.g., an anti-convulsant agent, an anti-anxiety agent or an anti-depression agent.

Controlled Exposure Profiles

[0329] In certain embodiments, about 40% of the drug is released from the dosage form within about 3 hours and about 95% of the drug is released from the dosage form within about 10 hours after administration. In yet another embodiment, about 30% of the drug is released from the dosage form within about 3 hours and about 90% of the drug is released from the dosage form within about 10 hours after administration. . In yet another embodiment, about 80% of the drug is released from the dosage form within about 2 hours and about 90% of the drug is released from the dosage form within about 10 hours after administration.

Reduced fed/fasted effects associated with the administration of drug

[0330] It is generally known in the art that if a positive fed/fasted effect is seen with a pharmaceutical agent, it is typically related to the dose of the active agent administered such that a lower dose of an active agent will have a lower ratio of $AUC_{(fed)}/AUC_{(fasted)}$ and a higher dose of an active agent will have a higher ratio of $AUC_{(fed)}/AUC_{(fasted)}$. In addition, it is known that dosage forms which substantially eliminate the effects of food on the therapeutic window (levels for efficacy vs. levels giving side effects) are safer than those dosage forms which do not. Thus dosage forms that provide reduced fed/fasted effects provide decreased risks and reduce the potential for side effects, thereby increasing subject safety and compliance. Fed/ fasted conditions are in accordance with FDA guidelines for testing drug exposure in the fed and fasted states.

[0331] Conventional formulations of drug display large fed/fasted effects in a manner that is not limited to dose dependency. The drug formulations described herein are less effected by the fed or fasted state of the subject being administered the formulation. The systemic exposure of the drug formulations described herein is less sensitive to the type of meal ingested than conventional drug formulations. This means that there is a reduced difference in the $AUC_{(0-\tau)}$ values of drug when the drug formulations are administered in the fed versus the fasted state at therapeutically effective doses. Thus, described herein are drug formulations that can substantially reduce the effect of food on the pharmacokinetics of drug. In one embodiment, the drug formulation is an aqueous dispersion that when administered to a child under 12 yeas old or adult not capable of swallowing a solid formulation, provides a ratio of the $AUC_{(0-\infty)}$ or $AUC_{(0-\tau)}$ values of drug, when administered in the fed versus the fasted state, of less than about 4. In another embodiment, the drug formulation is a solid oral dosage form that when administered to a human over twelve years old provides a the ratio of the $AUC_{(0-\tau)}$ values of drug, when administered in the fed versus the fasted state, of less than about 3. In still another embodiment, the drug formulation is a solid oral dosage form that when administered to a human over twelve years old provides a ratio of the $AUC_{(0-\tau)}$ values of drug, when administered in the fed versus the fasted state, of less than about 2. In yet another embodiment, the drug formulation is a solid oral dosage form that when administered to a human over twelve years old provides a ratio of the $AUC_{(0-\tau)}$ values of drug, when administered in the fed versus the fasted state, of less than about 1.5. In still another embodiment, the drug formulation is a solid oral dosage form that when administered to a human over twelve years old provides a ratio of the $AUC_{(0-\tau)}$ values of drug, when administered in the fed versus the fasted state, ranging from about 3 to about 1.5. In another embodiment, the drug formulation is a solid oral dosage form that when administered to a human over twelve years old provides a ratio of the $AUC_{(0-\tau)}$ values of drug, when administered in the fed versus the fasted state, of about 2.

Dose Amounts

[0332] The drug formulations described herein are administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. In human therapy, the dosage forms described herein preferably deliver drug formulations that maintain a therapeutically effective amount of drug at steady state while reducing the side effects associated with an elevated C_{max} blood plasma level of drug.

[0333] In various other embodiments of the present invention, the amount of drug administered to a subject via a solid dosage form is the amount known in the art to achieve a therapeutically effective concentration of drug in the bloodstream of a human or animal in need thereof. For example, the amount of drug may range from about 0.01 micrograms to about 6gm. In other embodiments, the amount of drug may range from about 0.1mg to about 1000mg. In other embodiments, the amount of drug may range from about 1mg to about 500mg, from about 50 mg to about 800 mg or from about 300 mg to about 700 mg. In one embodiment, a drug formulation is administered in a solid dosage form at a concentration of about 250 mg to about 650 mg. In another embodiment, the drug formulation is administered in a solid dosage form at concentration of about 300-400 mg. In another aspect, the solid oral dosage form can be administered twice a day (b.i.d). In yet another aspect, the solid oral dosage form is a controlled release dosage form administered b.i.d. providing a pulsatile release of drug such that the C_{max} of blood plasma drug is reduced to avoid adverse effects while simultaneously reducing fed/fasted effects and maintaining total exposure ($AUC_{(0-\infty)}$).

[0334] A therapeutically effective concentration of an oral aqueous suspension or dispersion comprising a drug formulation described herein, administered according to the methods described herein, is typically in the range of about 20 mg/ml to about 150 mg/ml final concentration. In one embodiment, a drug formulation is administered as an aqueous oral suspension at a concentration of about 25 mg/ml to about 100 mg/ml final concentration. In another embodiment, a drug formulation is administered as an aqueous oral suspension at a concentration of about 50 mg/ml final concentration. The aqueous oral suspensions comprising a drug formulation described herein can be administered both as a single dose per day or given multiple times within a 24 hour period. In one aspect, the aqueous oral suspension can be administered three times a day (t.i.d). In another aspect, the aqueous oral suspension can be administered twice a day (b.i.d.).

[0335] Contemplated compositions of the present invention provide a therapeutically effective amount of drug over an interval of about 30 minutes to about 8 hours after administration, enabling, for example, once-a-day, twice-a-day, three times a day, and etc. administration if desired.

[0336] In further embodiments, greater than about 95%; or greater than about 90%; or greater than about 80%; or greater than about 70% of the drug dosed by weight is absorbed into the bloodstream within 8 hours after administration.

[0337] In other embodiments, the pharmaceutical formulations provide a release profile for an immediate release dosage form of the drug, whereby using methods described in Example 29, whereby about 80% (or about 70% or about 90%) of the drug is released from the dosage form within about 1 hours in SGF and for a delay release drug dosage form about 60% of the (or preferably 70% or 80%) is released from the composition within about 3 hours in SGF.

Pharmacokinetic Analysis

[0338] Plasma concentrations of drug referenced herein are intended to mean total drug concentrations including both free and bound drug. Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods.

Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of the drug formulation described herein. Aqueous dispersions of drug are size stable at temperatures from 4°C to 40°C for at least 4 months.

[0339] Certain drug compositions and formulations described herein display enhanced pharmacokinetic (PK) and pharmacodynamic (PD) profiles and/or minimized side effects as compared to conventional drug formulations known in the art.

[0340] Certain formulations described herein reduce the risk of drug side effects (e.g., ataxia, sedation and somnolence) relative to conventional drug formulations. In certain embodiments improved performance compared to conventional drug formulations can be seen on acute doses. In other embodiments, maximal benefit of the drug formulations described herein can be seen at steady state.

[0341] Any hypotheses provided herein are for possible explanatory purposes only, and is not meant to be limiting in any way with respect to the appended claims. All U.S. patent references discussed in the specification are hereby incorporated by reference.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0342] This invention is further illustrated by the following examples that should not be construed as limiting. Those of skill in the art of pharmaceutical formulation will readily appreciate that certain modifications to the examples described herein may be needed, particularly for changes in formulation batch size. Any methods, materials, or excipients which are not particularly described will be generally known and available to those skilled in the drug design and assay and pharmacokinetic analysis.

[0343] The particle size data, for examples in which a ganaxolone or phenytoin particle size is reported, were obtained using a Horiba LA-910 Laser Light Scattering Particle Size analyzer (Horiba Instruments, Irvine, California) and reported as volume weighted median (D50). Studies of ganaxolone or phenytoin particles in liquids, beads, powders and immediate release dosage forms in SGF and SIF are performed by dispersing an appropriate amount of the ganaxolone or phenytoin formulation into 20 mL (unless otherwise specified) of SGF or SIF in a vial to obtain a measuring concentration of ganaxolone or phenytoin of about 0.5 mg/mL. For example, in one embodiment, 200 mg of a ganaxolone suspension formulation containing 5 wt% of ganaxolone and appropriate levels of HPMC, PVA, SLS, and complexing agents was dispersed into 20 mL of SGF or SIF in a vial for measurement. The vial is immersed in an oil bath kept at 36 to 38°C for 3h. The sample is assessed visually for signs of flocculation and particle size is measured on a Horiba LA-910 to obtain D50 values.

[0344] Compositions/formulations are expressed weight percent (%wt) of the total composition for liquid suspensions and as weight percent (%wt) to the drug (API) for solid compositions unless specified otherwise

Abbreviations

[0345] The following abbreviations are used in the examples below. Other abbreviations used in the examples will be understood by those of skill in the art of pharmaceutical formulations.

GNX	Ganaxolone
HDPE	High Density Polyethylene
HPMC	Hydroxypropylmethylcellulose-2910
PVA	Polyvinyl alcohol (USP)
SLS	Sodium Lauryl Sulfate
DOSS	Sodium docusate
SGF	Simulated gastric fluid USP
SIF	Simulated intestinal fluid USP
WT	Weight
rt	room temperature
D50	Volume weighted median particle size
MCC	Microcrystalline Cellulose
API	Active Pharmaceutical Ingredient

Example 1

Preparation of USP Simulated Gastric and Intestinal Fluid

Simulated Intestinal Fluid (SIF)

[0346] Monobasic potassium phosphate (6.8 g) and sodium hydroxide (0.616g) are added into 250 ml of distilled water in a 1000 ml volumetric flask and swirled until dissolved. 700 ml distilled water is added and the pH checked. The pH is adjusted to pH 6.8 +/- 0.1 by adding either 0.2N sodium hydroxide or 0.2N hydrochloric acid and the volume is brought to 1000 ml.

Simulated Gastric Fluid (SGF)

[0347] Sodium chloride (2 g), 750 ml distilled water, and 7.0 ml of concentrated hydrochloric acid are added into a 1000 ml volumetric flask. The flask is swirled to mix and the volume brought to 1000 ml with distilled water. The pH should be approx. 1.2.

Example 2

Particle Size Measurement Method

[0348] The following methods and settings for particle size measurement were used for all D50 values for ganaxolone and phenytoin.

Particle Size Method Using Horiba Laser Scattering Particle Size Distribution Analyzer LA-910

[0349] Particle size measurement using Horiba laser scattering particle size distribution analyzer is generally well known for those skilled in the art. It is important that the parameters be kept constant when measuring different samples if they are used for comparison purposes. For ganaxolone and phenytoin nanoparticulate compositions, instrument settings and sample preparation method are described below:

Instrument Settings and Parameters:

Measure Conditions: Circulation = 4; ultrasonic time = 1; agitation = 1; sampling times: red laser = 10, blue lamp = 2; preferred % transmittance: blue lamp = 75-80%; blank: red laser = 10, blue lamp = 2. For D50 values after sonication, the sonication power is set to low and the sonication time is 1 minute.

Display settings:

Form of distribution: standard (Gaussian) = 10 iterations; RR Index = 1.15-010; distribution base: volume; size class = passing (underclass).

Example 2A
Sample Preparation and Particle Size (D50) Determination

[0350] For concentrated nanoparticle drug suspensions, dilute the nanoparticulate composition with deionized water to approximately 5 mg/mL API concentration. Shake well for 15-30 seconds. Add 120 mL of deionized water to thechamber, turn agitation and recirculation settings on. Transfer the nanoparticulate suspension via a pipette tothe sample chamber in sufficient quantity to reach the transmittance range of 75-80% blue lamp. If a suspension or stability indicating dispersion is at a concentration of approximately 0.5 mg/ml do not further dilute if not necessary and use directly for particle size measurement. Transfer the sample to be measured via a pipette to up to the desired transmittance range (75-80% blue lamp). Take a measurement and collect the D50 value. This will be the unsonicated particles size. Sonicate for 1 min and take a measurement again to collect D50 value. This will be the particle size after 1 minute sonication. One can also use this procedure obtain other particle size parameters such as D10 or D90 values.

Example 2B
General Particle Size Method for Solid Formulations Containing Insoluble Excipients

[0351] Use the following method if measuring formulations where insoluble excipients are added: Calculate the amount of insoluble excipients that will be present in the measurement of the composition and conduct the particle size experiment using these insoluble excipients and the same conditions as will be used in the measurement of D50 with the composition. Blank the instrument and drain. Measure the particle size (D50) of the composition as described above. This process subtracts any particle size interference from the insoluble excipients. In the case where the only insoluble excipient are MCC cores, pipette the dispersed suspension (excluding MCC cores) to the Horiba chamber containing 120 ml distilled water. Measure the particle size as per method 2A.

Examples 3A-B (Dispersion Testing)

Example 3A
Dispersion Testing for Aggregation of Liquid and Solid Nanoparticulate Compositions

[0352] General method: The solid or liquid nanoparticulate composition is placed in a 25 ml HDPE vial with HDPE cap and is diluted with 15-20 ml of simulated gastric or intestinal fluid to achieve a final API concentration of approx 0.5 mg/ml. The vial is agitated manually for until completely dispersed (generally 15-30 seconds). The vial is then placed in a heated oil bath at 36-38 °C unstirred unless specified otherwise until the desired test time. The vial is removed from the bath and inspected visually for signs of flocculation. After shaking the contents of the vial for 15-30 seconds manually, the particle size is determined (D50) using a Horiba-LA-910 particle analyzer as described in Example 2. A comparison of D50 values (e.g. after and before addition to SGF or SIF) is used to define the degree of particle aggregation or growth. Initial D50 values before addition to the dispersion media is used as the initial for liquid compositions. Initial D50 value for a solid compositions is the D50 of the liquid composition prior to removal of liquid (e.g. a spray suspension of API prior to spray drying, spray granulation or spray layering).

Example 3B
Dispersion of Tablets and Capsules (Immediate and Delayed Release) of Nanoparticlate Compositions

[0353] Place the drug solid dosage form in a type I (e.g, beads and capsules) or type II (e.g., tablets) dissolution apparatus with basket at 36-38 °C containing SGF at 0.5 to 1.0 mg/ ml API concentration for the immediate release component. Stir at 75 RPM and sample at 1 hour for the particle size. Measure the particle size as described as Example 2. For a controlled release release dosage, follow the preparation above but incubate in SGF for 2 hours, replace the SGF with SIF (0.5 to 1 mg/mL API concentration) and incubate for an additional 3 hours. Measure the particle size (D50) as described in Example 2.

Example 4

Preparation of Complexed Ganaxolone Nanoparticulate Compositions in the Presence of a Complexing Agent

[0354] The purpose of this example is to show that the complexing agent can be present during milling to obtain complexed ganaxolone nanoparticles.

[0355] Ganaxolone was wet milled in a 600 ml chamber using a DYNO-Mill KDL equipped with four 64 mm polyurethane agitator discs. The mill was operated at 3000 RPM or a tip speed of 10 m/sec. The mill was loaded with 88 vol% of 0.4 mm yttrium stabilized zirconium oxide beads. The milling slurry (1200 g) contained 25 wt% ganaxolone (Marinus Pharmaceuticals Inc., Connecticut, USA), 5 wt% hydroxypropyl methylcellulose (Pharmacoat 603), 0.0333 wt% 30% simethicone emulsion, 0.3 wt% sodium lauryl sulfate and 0.2 wt% methylparaben. This slurry was circulated through the mill via a peristaltic pump and returned to a cooled reservoir where it was re-circulated through the mill. The mill was operated in this recirculation mode, keeping the slurry temperature at 35 – 40 °C, for a total of 410 minutes (90 minutes residence time). The product slurry was filtered through a 20 micron polypropylene cartridge filter. The mill was flushed with 300 mL of the milling media (milling slurry minus ganaxolone). The total weight of the milled slurry was 1185 g. The concentration of ganaxolone was determined to be 20.5% by HPLC. The particle size (D50) measured on a Horiba LA 910 was 0.164 μm unsonicated /0.153 μm after 1 minute sonication. After 7 days at room temperature, the particle size increased to 0.320 μm (unsonicated) /0.309 μm (after 1 minute sonication). This formulation was then used in different studies as described in other examples. The D50 did not change by more than 10% after this curing period for the duration of all other studies conducted with this formulation.

Examples 5A-C
Preparation of Ganaxolone Nanoparticulate Suspension Without a Complexing Agent

Example 5A: (Residence time 75 minutes)

[0356] The purpose of this example is to demonstrate preparation of an aqueous ganaxolone dispersion without a complexing agent.

[0357] Ganaxolone milling slurry (1200 g) having the same composition as described in Example 4 without methylparaben was milled as in Example 4 for 75 minutes of residence time. After filtration through a 20 micron polypropylene cartridge filter and milled was flushed with 300 mL of milling media, milled ganaxolone slurry (1271 g) was obtained. The concentration of ganaxolone was 21.25% by HPLC. The particle size (D50) measured on a Horiba LA 910 was 0.103 μm (unsonicated) / 0.102 μm (after 1min sonication). D50 increased slightly after storage under refrigerated conditions. This formulation was used in other examples.

Example 5B (Residence time 24 minutes)

[0358] Powdered ganaxolone aqueous dispersion (1200 g) comprising a mixture of 30 wt% ganaxolone and 5 wt% HPMC, 0.2 wt% sodium lauryl sulfate and 100 ppm simethicone was milled in a DYNO Mill KDL as described for Example 5A. After 24.0 minutes of residence time, D50 was 163 nm.

Example 5C (Residence time 50.8 minutes)

[0359] Powdered ganaxolone aqueous dispersion (1200 g) comprising a mixture of 15 wt% ganaxolone and 3 wt% HPMC was milled in a DYNO Mill KDL as described for Example

5A. During milling, 2 portions of 0.05% w/w sodium lauryl sulfate were added to keep the milling slurry fluid. After 50.8 minutes of residence time, D50 was 116 nm.

Example 6

Preparation of Uncomplexed Ganaxolone Nanoparticulate Suspension Containing HPMC, SLS and Simethicone

[0360] Powdered ganaxolone aqueous dispersion (1500 g) comprising a mixture of 25 wt% ganaxolone, 5 wt% HPMC, 0.1 wt% sodium lauryl sulfate and 0.028 wt% simethicone 30% emulsion (all based on total weight of the dispersion in deionized water) was milled in a DYNO Mill KDL as described in Example 5. After 43 minutes of residence time, the D50 was 0.113 μm (unsonicated)/0.112 (after 1 minute sonication). The final ganaxolone concentration was 22.6% by HPLC. This formulation was used in Example 12.

Example 7

Preparation of Uncomplexed Ganaxolone Nanoparticulate Suspension Containing HPMC and Sodium Lauryl Sulfate and Stability

[0361] Powdered ganaxolone in deionized water (180 g) containing a 30 wt% ganaxolone (Marinus Pharmaceuticals Inc., Connecticut, USA), 3 wt% HPMC, and 0.1% wt sodium lauryl sulfate (all based on total weight of suspension) was milled in a DYNO Mill KDL (Willy A. Bachofen A. G., Maschinenfabrik, Basel, Switzerland) with a 300 mL glass batch chamber and utilizing 0.1 mm zirconium oxide beads (260 mL, 85% of the chamber volume). The milling was conducted for 120 min at a tip speed of 22.5 m/s. The particle size (D50) after milling was 0.106 μm unsonicated. The milled slurry (150g) was diluted with 150 g of deionized water containing 7 wt% HPMC and 0.1wt% SLS to give a 15 wt% gnx suspension. A sample of this 15 wt% slurry was further diluted using 100 g of the slurry and 500 g of deionized water containing 5% HPMC and 0.1% SLS to give a final concentration of 2.5% ganaxolone in 5% HPMC, 0.1% SLS and water. The particle size (D50) remained unchanged at room temperature (25 °C) after 4 months. This ganaxolone nanoparticle suspension underwent flocculation upon incubation in SGF and SIF (shown below) using the method as described in Example 3. This material was used in one oral dog pharmacokinetics study (Example 27, formulation 27A) to show pharmacokinetics of an uncomplexed ganaxolone suspension (D50 of 110 nm) which demonstrated good storage stability but aggregation in simulated gastric and intestinal fluids.

	Initial	SGF 90 min	SIF 90 min
D50 (µm) unsonicated/1min sonication	0.110	0.390/0.118	0.535/0.134
Visual observation		Flocculation	Flocculation

Example 8

Preparation of Uncomplexed Phenytoin Nanoparticulate Suspension Containing HPMC, SLS and Simethicone

[0362] The purpose of this study was to prepare a nanoparticulate suspension of a structurally different water insoluble compound capable of forming a cyclodextrin inclusion complex (Phenytoin, 5,5-diphenylhydantoin) to further exemplify the benefits of stabilizing nanoparticulate compositions with a complexing agent.

A milling slurry (164 g) containing by weight percent 20 wt% Phenytoin 5% wtHPMC, 0.1wt% SLS, 0.03 wt% simethicone 30% emulsion and 74.87% deionized water was milled in the same manner as described in Example 7 for 35 minutes using 0.3 mm zirconium oxide balls (260 ml, 85% of chamber volume). The particle size (D50) after milling was 0.150 µm unsonicated/0.127 µm after 1 min sonicatation.

[0363]

Examples 9A-B

Preparing Phenytoin Nanoparticulate Compositions With and Without a Complexing Agent

[0364] The purpose of this example was to create complexed and uncomplexed phenytoin nanoparticulate suspensions to further exemplify the benefits of a complexing agent and an ionic dispersion modulator in forming more stable solid nanoparticulate compositions.

Example 9A
Uncomplexed Phenytoin Nanoparticulate Comositions

[0365] A milling slurry (1500 g) comprising a mixture of 20% wt phenytoin,5 wt% HPMC (Pharmacoat 603), 0.1 wt% SLS and 0.028 wt% simethicone 30% emulsion was milled in a DYNO Mill KDL as described in Example 6 for a residence time of 26 minutes(total milling time of 145 minutes) to obtain 1419.6 g of milled suspension after filtration. The D50 after milling was 0.141 µm unsonicated and 0.128 µm after 1 minute sonication. The uncomplexed composition after 5 days at room temperature had a D50 of 0.169 µm unsonicated/0.144 µm after 1 minute sonication.

Example 9B
Complexed Phenytoin Nanoparticulate Compositions

[0366] To a portion of the milled phenytoin suspension (496.1 g) of Example 9A was added a methyl anthranilate (2 g, 0.4%) as a complexing agent. The milled material with the complexing agent was allowed to cure for 5 days. The D50 for the complexed material after 5 days of curing time was 0.206 µm unsonicated/177 µm after 1 minute sonication.

[0367] The complexed and uncomplexed suspensions were used to create solid dose nanoparticlate phenytoin compositions described in Examples 18 and 24.

Example 10
Stability Studies of Complexed and Uncomplexed Aqueous Phenytoin Nanoparticulate Compositions in SGF and SIF

[0368] This example demonstrates that enhanced stability of a phenytoin nanoparticulate suspension in USP simulated gastric and intestinal fluids can be obtained by addition of a complexing agent.

[0369] A sample of the uncomplexed phenytoin nanoparticle suspension (17g) prepared in Example 8 was added methyl anthranilate (71.4 mg, 0.42%) and the suspension was allowed to cure for 5 days at room temperature (25°C).

[0370] As described in Example 8, the initial D50 value for the uncomplexed suspensions were 0.162 µm unsonicated/0.123 µm after 1 minute sonication, whereas the initial D50 value for the complexed supensions were 0.169 µm unsonicated/0.159 µm after 1 min sonication.

[0371] The uncomplexed and complexed suspensions were incubated side by side in SGF and SIF using the method described in Example 3. The uncomplexed composition visibly flocculated and settled to the bottom of the vials after 1 hour whereas the complexed composition remained dispersed in both conditions for the 3 hour period. Additionally, the complexed composition in both SGF and SIF showed less particle size changes when examining both unsonicated and sonicated D50 values to initial values as well as demonstrating less loose aggregation (difference between D50 unsonicated and sonicated for 1 minute). The results are shown in Table 1.

Table 1

D50 values for Complexed and Uncomplexed Aqeous Phenytoin Nanoparticulate Compositions Before and After Incubation in SGF and SIF

Entry	Methyl anthranilate (%wt/Phenytoin)	Initial D50 (µm) unsonicated/1 min sonication	D50 (µm) unsonicated/1 min sonication after 3 hours incubation	Incubation Medium
1	2.1	0.169/0.159	0.302/0.219	SGF
2	2.1	0.169/0.159	0.316/0.211	SIF
3	0	0.162/0.123	0.868/0.322	SGF
4	0	0.162/0.123	1.18/0.298	SIF

Examples 11A-C
Comparative Stability Studies of Complexed and Uncomplexed Ganaxolone Nanoparticle Suspensions

[0372] This example demonstrates the enhanced stability of ganaxolone nanoparticulates complexed with methylparaben compared with uncomplexed ganaxolone nanoparticulates after incubation in SGF, SIF, heating to 100°C and conducting several freeze/thaw cycles.

Example 11A (Stability in SGF and SIF at 36-38°C)

[0373] The complexed ganaxolone nanosuspension of Example 4 and uncomplexed ganaxolone nanosuspension of Example 5A after a curing time (for complexed preparations) of at least 7 days of storage at room temperature (20-25°C) were incubated side by side in SGF and SIF using the method described in Example 3. The D50 of the complexed formulation (Entry 1, Table 2) increased only slightly (< 23% unsonicated and 9% after 1minute sonication) from its initial values. In contrast, the D50 of the uncomplexed formulation (Entry 2, Table 2) increased at least 560% unsonicated and 153% after 1 minute sonication from its initial values. The 1.5-fold increase in D50 after sonication indicates the formation of either strong aggregation or particle growth. Similar trends were observed after doubling the amount of HPMC and SLS versus ganaxolone (Entries 3-4, table 2). Doubling the HPMC and SLS amounts versus ganaxolone was achieved by diluting a 5 g sample from Examples 4 and 5 with 5 g of deionized water containing 5 wt% HPMC, 0.3 wt% SLS and 0.033 wt% simethicone (30% emulsion).

Table 2

	Comparative gastric and intestinal stability studies of methylparaben complexed (initial D50: 0.320 μm unsonicated/0.309 μm after 1 minute sonication) and uncomplexed (initial D50: 0.136 μm unsonicated/0.112 μm 1 minute sonication) ganaxolone nanaoparticle suspensions				
Entry	HPMC %(wt/GNX)	SLS %(wt/GNX)	Methylparaben %(wt/GNX)	D50 (μm) No Sonication/1 min sonication	Test conditions[1]
1	24.4	1.46	0.98	0.382/0.324	A
				0.394/0.326	B
2	23.5	1.41	0	0.897/0.290	A
				7.36/0.283	B
3	47.1	2.82	0	0.828/0.258	A
				0.933/0.267	B
4	48.8	2.93	0.98	0.350/0.314	A
				0.353/0.313	B

[1] Incubation conditions: A, SGF, 36-38 °C, 3h; B. SIF, 36-38 °C, 3h see Example 3 for method.

Example 11B (D50 Stability of Complexed and Uncomplexed Ganaxolone liquid Nanoparticulate Compositions After Heating at 100°C)

[0374] The milled compositions of Example 4 (complexed) and Example 5A (uncomplexed) (approximately 2g each) were placed in 25 mL glass vials and sealed with a plastic cap. The vials were heated in a 100°C oil bath. The D50 of the complexed formulation did not change after heating for 4h (both unsonicated and 1 minute sonication) (Table 3). In contrast, D50 of the uncomplexed suspension continued to grow over the 4 hour period and doubled in size from initial values as shown in Table 3.

Table 3

Changes in D50 values for Complexed and Uncomplexed Liquid Ganaxolone Nanoparticulate Compositions			
Suspension Formulation	Initial D50 (μm) unsonicated/after 1 min sonication	D50 (μm) after 20 min at 100°C unsonicated/after 1 min sonication	D50 (μm) after 4h at 100°C unsonicated/after 1 min sonication
Methylparaben complexed	0.320/0.298	0.326/0.311	0.320/0.310
Uncomplexed	0.149/0.140	0.246/0.207	0.317/0.302

Example 11C (Stability of Complexed and Uncomplexed Ganaxolone Compositions After Freeze/Thaw Cycles)

[0375] Ganaxolone formulations of Example 4 (complexed) and Example 5A (uncomplexed) were tested for freeze thaw stability as follows:

[0376] Ten grams of each formulation was placed into a 25 ml HDPE scintillation vial with HDPE cap. These were placed into a 500 ml glass beaker containing approx. 1 inch of Styrofoam packing (to slow freezing process) and placed into an insulated carton containing crushed dry ice. The vials were stored overnight and then thawed at room temperature for 1 hour. This process was repeated until 3 freeze/thaw cycles had been completed. The D50 was measured and compared to control material stored at room temperature in the same container closure system. The D50 of the complexed formulation did not change after 3 freeze/thaw cycles (Table 4). In contrast, D50 of the uncomplexed formulation increased 450% (unsonicated) and 144% (1 minute sonication) after the same treatment (Table 4).

Table 4

Particle size (D50) before and after freezing/thaw cycles for complexed ganaxolone particles and uncomplexed ganaxolone particles

Formulation	Initial D50 (μm) unsonicated/after 1 min sonication	D50 (μm) after 3 freeze/thaw cycles unsonicated/after 1 min sonication
Methylparaben complexed	0.320/0.298	0.319/0.310
Uncomplexed	0.149/0.140	0.822/0.341

Example 12

Stability of Complexed Ganaxolone Aqueous Nanoparticulate Suspensions in SGF and SIF

[0377] Aliquots of the uncomplexed ganaxolone suspension from Example 6 were diluted with either diluent A or diluent B (diluent composition listed in tabular form below) in 1:2 ratio (Example 6 Suspension/Diluent) to provide two 75 mg/ml ganaxolone nanoparticle suspension; One with 0.1 wt% methylparaben and 0.02 wt% propylparaben as complexing agents (Diluent A) and the other with 0.09 wt% sodium benzoate as the complexing agent with pH adjusted to 4 by the sodium citrate buffer (Diluent B). Additionally both formulations contained the following: 5 wt% HPMC, 1 wt% PVA, 0.1 wt% SLS. The two formulations were allowed to cure for at least 5-7 days (paraben complexed formulation) and 20 days (sodium benzoate complexed formulation) to reach a stable particle size (D50) of 0.314 μm (unsonicated) /0.311 μm (after 1 minute sonication) for the paraben complexed formulation and 0.321 μm (unsonicated)/0.314 μm (after 1 minute sonication) for the sodium benzoate complexed formulation at a pH of 4.

	Diluent A	Diluent B
Ingredients	% wt	%wt
Hypromellose (Pharmacoat 603)	5.00	5.00
Polyvinyl Alcohol	1.50	1.50
Sodium Lauryl Sulfate	0.10	0.10
Methylparaben	0.15	0.00
Propylparaben	0.03	0.00
sodium benzoate	0.00	0.14
citric acid anhydrous	0.00	0.18
Sodium citrate	0.00	0.014
Deionized water	93.22	93.07
Total:	100.00	100.00

[0378] The complexed ganaxolone nanoparticulate suspensions as described above were incubated in SGF and SIF at 36-38°C for 3h as in the method described in Example 3. The results are listed in Table 5 which showed virtually no increase in particle size (D50) after incubation in SGF and SIF.

Table 5

Test results in SGF and SIF for Complexed and Uncomplexed Aqueous Nanoparticulate Ganaxolone Compositions

Entry	Complexing agent/amount (% wt of total formulation)	Initial D50 (μm), unsonicated /after 1min sonication	D50 (μm) after incubation in SGF for 3h, no sonication/ after 1 min sonication	D50 (μm) after incubation in SIF for 3h no sonication/ after 1 min sonication
A	Methylparaben/0.1% Propylparaben/0.02%	0.314 /0.311	0.326 /0.313	0.344 /0.330
B	Sodium benzoate/0.09% Citric acid/0.12% Sodium citrate/0.093%	0.321/0.314	0.322/0.312	0.329/0.313

[a] The composition of the test formulations are: 7.5 wt% ganaxolone, 5 wt% HPMC, 1 wt% PVA, 0.1 wt% SLS in addition to the amounts of complexing agents and pH adjusting agents listed in Table 5

Example 13

SGF Stability of Methyl Anthranilate Complexed versus Uncomplexed Ganaxolone Nanoparticulate Suspensions

[0379] To the uncomplxed ganaxolone nanoparticulate suspension prepared as in Example 6 was added 0.1 wt% or 0.4 wt% methyl anthranilate. All suspensions (with and without methyl anthranilate as the complexing agent) were kept at room temperature to allow sufficient curing time to obtain complexed particles. The complexed suspensions were tested in SGF with the uncomplexed control as per Example 3. The results are shown in Table 6 below. The complexed formulation showed virtually no change from initial after incubation in SGF. In contrast, the uncomplexed control showed 3-fold increase in D50 unsonicated and 1.6-fold after 1 min sonication.

Table 6

D50 values for Complexed (methyl anthranilate) and Uncomplexed Aqueous Ganaxolone Nanoparticulate Compositions in SGF

Formulation Type	Initial D50 (µm) unsonicated/after 1 min sonication	D50 (µm) in SGF unsonicated/ after 1 min sonication
Uncomplexed	0.215/0.188	0.656/0.312
Complexed with 0.1 wt% Methyl Anthranilate	0.311/0.306	0.363/0.306
Complexed with 0.4 wt% Methyl Anthranilate	0.480/0.460	0.541/0.465

Example 14

Preparation of Pharmaceutically Useful Complexed Ganaxolone Suspension Formulations (50 mg/mL) from Milled Uncomplexed Ganaxolone Nanoparticulate Suspensions

[0380] This example illustrates the dilution to 50 mg/mL ganaxolone nanoparticulate suspension formulations.

Method A (one-step dilution):

An uncomplexed ganaxolone nanoparticulate suspension of known ganaxolone concentration prepared as described in Example 5A is diluted with appropriate amount of diluent containing appropriate levels of excipients and other necessary components such as preservatives, complexing agents, flavoring, sweetener and antifoaming agent to achieve 50 mg/mL drug concentration.

Method B (two-step dilution):

An uncomplexed ganaxolone nanoparticulate suspension prepared as described in Example 5A is first diluted to an intermediate drug concentration (ca. 80 mg/mL) with appropriate amount of diluent containing appropriate levels of surface stabilizers excipients and all necessary components such as preservatives, complexing agents, antifoaming agents, flavoring and sweeteners. For example, for a milled uncomlexed ganaxolone nanoparticulate suspension with an initial (milling slurry) ganaxolone concentration of 25 wt% is diluted by mixing one part of the milled suspension with two parts of the diluent to obtain an intermediate concentration of complexed ganaxolone nanoparticulate suspension of about 8 wt%. The precise ganaxolone concentration is then determined by appropriate assay (e. g. HPLC). The final dilution to 50 mg/mL ganaxolone is performed with appropriate an amount of diluent containing the correct levels of all excipients and other components.

Example 15

Preparation of Solid Nanoparticulate Particles via Rotary Evaporator Drying and Composition Optimization for Solid Nanaoparticulate Compositions

[0381] This method was applied for ganaxolone nanoparticulate composition optimization. The method described below can be generally applied to other water insoluble nanoparticulate compositions.

General Method for Drying Aqueous Nanoparticulate Compositions to Solids

[0382] A general method for drying small samples of complexed and uncomplexed nanoparticulate compositions for solid dose optimization studies is as follows: One gram of complexed or uncomplexed nanaoparticulate suspension was placed in a 25 ml glass scintillation vial then fitted onto a Buchi rotary evaporator R-124. The vial was rotated at 150-175 rpm and the water bath temperature set at 70°-90°C. Full vacuum was applied (2 to 4 mbar) over a 2 minute period and continued for 20 to 25 minutes until all visible signs of moisture were gone. This method yields vials containing solids which are used for incubation studies.

[0383] During optimization for a solid composition, additional components were added to the nanoparticulate suspensions prior to drying as follows: The components were weighed into the vial first and 0.5 g of deionized water was added to dissolve or disperse the component(s). To this solution/suspension was added 1.0 g of the nanoparticulate suspension. The contents of the vial were swirled manually for 15-30 seconds followed by evaporation of water as described above.

Example 16

Stability of Complexed and Uncomplexed Solid Ganaxolone Nanoparticulate Compositions in SGF and SIF

[0384] Complexed and uncomplexed aqueous ganaxolone milled suspensions from Examples 4 and 5A respectively were used and additional components were added and removal of water was conducted as by the method described in Example 15.

[0385] D50 changes from the initial values with and without sonication are listed in Table 7. Incubation in SGF and SIF were conducted using the method described in Example 3. Complexed Ganaxolone nanoparticles showed 2-4 fold increase in unsonicated D50 values versus initial values. No change in sonicated D50 values was observed. Uncomplexed ganaxolone nanoparticles showed a 27-fold increase in unsonicated D50 values versus initial values and still showed a 7-9-fold increase in sonicated D50 values versus initial values. For the complexed formulation, addition of sucrose prior to drying reduced aggregation and/or particle size growth (2-fold increase in D50 unsonicated in SIF versus initial and no increase in D50 values sonicated or unsonicated in SGF from initial). In contrast, the uncomplexed formulation with sucrose added still showed unsonicated D50 increasing > 18-fold versus initial values, and at least a doubling of the D50 from initial values with sonication.

TABLE 7

Comparative Incubation Results in SGF and SIF of Dried Ganaxolone Nanoparticulate Compositions: Methylparaben Complexed (Initial D50: 0.310 μm unsonicated/0.298 μm after 1minute sonication) versus Uncomplexed (Initial D50: 0.147 μm unsonicated/ 0.140 μm after 1 minute sonication).

Entry	Sucrose % (wt/GNX)	HPMC (wt/GNX)	SLS % (wt/GNX)	Methylparaben % (wt/GNX)	D50 (μm) No sonication/1 min sonication	dispersing conditions[1]
1	0	47.1	2.82	0	4.02/1.12	SGF, 3h
					4.13/1.24	SIF, 3h
2	0	48.8	2.93	0.98	0.636/0.314	SGF, 3h
					1.28/0.322	SIF, 3h
3	103.8	46.7	2.8	0.98	0.383/0.292	SGF, 3h
					0.588/0.304	SIF, 3h
4	104.4	47.1	3.1	0	2.72/0.293	SGF, 3h
					5.46/0.301	SIF, 3h

[1] All conditions run as in Example 3

Examples 17A-B
Effect of an Ionic Dispersion Modulator in Complexed and Uncomplexed Ganaxolone Nanoparticulate Solid Compositions

[0386] This example shows the effect of various amounts of an ionic dispersion modulator (e.g., sodium chloride) on stabilizing and reducing the amount of sucrose needed to reduce changes in D50 values (from initial) when dispersed in SGF and SIF.

Example 17A
Preparation of Solid Ganaxolone Nanoparticulate Compositions Containing an Ionic Dispersion Modulator by Rotary Evaporator Drying

[0387] The following is an example of preparing solid complexed and uncomplexed ganaxolone nanoparticulate compositions listed in Table 8 by the method of Example 15. Other compositions listed in Table 8 were prepared using the same procedure by adding the appropriate amount of salt and sucrose unless otherwise specified in Table 8.

[0388] The following components were placed in a 25 ml glass scintillation vial: 5.13 mg of sucrose crystals and 12.5 mg of 25 wt % sodium chloride solution. Deionized water (0.5 g) was then added to dissolve the sucrose crystals and to achieve a homogeneous solution.

[0389] The complexed ganaxolone suspension (1 g) of Example 4 containing 20.5 wt% ganaxolone, 5.0 wt% HPMC, 0.3 wt% sodium lauryl sulfate, 0.2 wt% methylparaben 0.03 wt% simethicone (30% emulsion in water) was then added to the vial and the mixture was swirled to mix well. The contents in the vial were then dried per Example 15. This produced the composition listed in Table 8, Entry 7.

Table 8

Compositions Demonstrating benefits of an Ionic Dispersion modulator

Entry[c]	Nanopartriculate Ganaxolone Suspension (g)	NaCl solution (25 wt %)	Sucrose (g)	Deionized water (g)
1	1.0	0.3	0	0.5
2	1.0	0.1	0	0.5
3	1.0	0.050	0	0.5
4	1.0	0.025	0	0.5
5	1.0	0.0125	0	0.5
6	1.0	0.0125	0.01025	0.5
7	1.0	0.0125	0.00513	0.5
8	1.0	0.0164	0	0.5
9	1.0	0.050[a]	0	0.5
10	1.0	0	0	0.5
11[b]	1.0	0.050[a]	0	0.5

[a] Salt was added as solid;
[b] The nanoparticle slurry was from Example 5A;
[c] Complexed Ganaxolone suspension from Example 4 was used in Entry Nos. 1-10.

Example 17B
Dispersion Results of Dried Comlexed and Uncomplexed Ganaxolone Nanoparticles in both SGF and SIF

[0390] Table 9 shows the degree of aggregation of solid nanoparticulate complexed and uncomplexed ganaxolone compositions incubated in SGF and SIF. The Entry number in Table 9 corresponds to the compositions given in Table 8.

[0391] Sodium chloride as an ionic dispersion modulator is very effective in preventing aggregation in SGF and SIF when used with a complexed nanoparticle formulation. Addition of an ionic dispersion modulator also allows the complexed solid nanoparticulate formulation to have a higher drug concentration by requiring less of a water soluble spacer (e.g. sucrose) to achieve minimal aggregation. This ability to create more stable and concentrated solid formulation is needed in preparing commercially viable compositions of drugs requiring a high dose.

[0392] Addition of an ionic dispersion modulator allows for more concentrated drug compositions.

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Table 9

Effect of an Ionic Dispersion Modulator on the Dispersion of Dried Ganaxolone Compositions (With and Without a Complexing Agent) in Simulated Gastric and Intestinal Fluid (SGF and SIF)

Entry	HPMC %wt/ GNX	SLS % wt/ GNX	Simethicone 30% emulsion %wt/ GNX	Methyl-paraben %wt/ GNX	NaCl %wt/ GNX	Sucrose %wt/ GNX	D50(μm) unsonicated/1 min sonication	Dispersion conditions[1]
10	24.4	1.46	0.15	0.98	0	0	13.2/0.332	A
							0.286	B
9	24.4	1.46	0.15	0.98	24.4	0	0.344/0.319	A
11	23.5	1.41	0.14	0	23.5	0	22.7/8.9	A
5	24.4	1.46	0.15	0.98	1.5	0	3.17/0.337	A
							4.45/0.353	C
6	24.4	1.46	0.15	0.98	1.5	5	0.364/0.316	A
							0.396/0.322	C
							0.490/0.331	D
							0.561/0.329	E
7	24.4	1.46	0.15	0.98	1.5	2.5	0.395/0.323	A
							0.370/0.312	C
							0.416/0.326	D
							0.533/0.331	E
8	24.4	1.46	0.15	0.98	2.0	0	0.548/0.334	A
							0.506/0.326	C

Table 9 Cont'd

Effect of an Ionic Dispersion Modulator on the Dispersion of Dried Ganaxolone Compositions(With and Without a Complexing Agent) in Simulated Gastric and Intestinal Fluid (SGF and SIF)

Entry	HPMC %wt/ GNX	SLS % wt/ GNX	Simethicone 30% emulsion %wt/ GNX	Methyl-paraben %wt/ GNX	NaCl %wt/ GNX	Sucrose %wt/ GNX	D50(μm) unsonicated/1 min sonication	Dispersion conditions[1]
4	24.4	1.46	0.15	0.98	3.0	0	0.355/0.319	A
							0.367/0.315	C
							0.485/0.329	D
							0.609/0.334	E
3	24.4	1.46	0.15	0.98	6.1	0	0.338/0.314	A
							0.429/0.337	C
2	24.4	1.46	0.15	0.98	12.2	0	0.353/0.317	A
							0.367/0.318	C
9	24.4	1.46	0.15	0.98	24.4	0	0.440/0.322	D
							0.459/0.324	E
1	24.4	1.46	0.15	0.98	36.6	0	0.346/0.315	A
							0.372/0.317	C

[1] Dispersion conditions: A, SGF, 5 min, rt; B, deionized water, 5 min, rt; C, SIF, 5 min, rt; D, SGF, 3h, 36-38 °C, stirred; E, SIF, 3h, 36-38 °C, stirred.

Example 18

Effect of an Ionic Dispersion Modulator (Sodium Chloride) on Complexed and Uncomplexed Nanoparticulate Phenytoin Solid Compositions

[0393] The complexed and uncomplexed phenytoin nanoparticulate suspensions of Example 9, were diluted (1:1 by weight, 5 g of each) with deionized water containing 6.25 wt% HPMC and 0.125 wt% SLS to obtain phenytoin nanoparticulate suspensions containing 10 wt% phenytoin, 5.625 wt% HPMC, 0.1125 wt% SLS for rotary evaporated drying. The suspensions (0.5 g) containing appropriate amount of urea and/or sodium chloride were dried on a Buchi rotary evaporator using the method described in Example 15 to obtain dried phenytoin nanoparticulte powders. The dried phenytoin nanoparticulate powders were incubated in SGF per Example 3. The results are shown in Table 10 below:

Table 10

Effect of an Ionic Dispersion Modulator (NaCl) on the Dispersion of Rotary Evaporated Solid Complexed and Uncomplexed Phenytoin Nanoparticulate Compositions in SGF.

Entry	HPMC %wt/ API	SLS %wt/ API	Methyl anthranilate %wt/ API	Sucrose %wt/ API	Urea %wt/ API	NaCl %wt/ API	D50 (μm) after incubation in SGF (36°-38°C, 70 minutes)	
							Unsonicated	1 min sonication
1[a]	56.25	1.125	2	0	0	0	5.87	0.299
2[a]	56.25	1.125	2	0	100	0	3.493	0.273
3[a]	56.25	1.125	2	0	0	5	8.914	0.353
4[a]	56.25	1.125	2	10	0	5	23.64	5.961
5[a]	56.25	1.125	2	0	8	5	0.405	0.249
							0.283 (DI water)	0.206 (DI water)
6[a]	56.25	1.125	2	0	8	0	3.894	0.287
							0.290 (DI water)	0.216 (DI water)
7[a]	56.25	1.125	2	0	0	20	0.325	0.228
8[b]	56.25	1.125	0	0	8	5	16.642	1.926

[a] Prepared from methyl anthranilate (0.4 wt%) complexed phenytoin nanoparticulate suspension with initial D50 (μm) of 0.211(unsonicated)/0.187(after1 min sonication) ; [b] Prepared from uncomplexed phenytoin nanoparticulate suspension with initial D50 (μm) of 0.161(unsonicated)/0.141 (after 1 min sonication).

In the above example, urea was identified as a water soluble spacer.

Examples 19-20

[0394] Examples 19-20 below demonstrate that certain complexed ganaxolone spray dried and spray layered compositions containing an ionic dispersion modulator have less aggregation in SGF and SIF (unsonicated) by a factor of greater than 10-fold. Additionally the examples below show less aggregation for certain complexed phenytoin nanoparticulate formulations than for uncomplexed.

Example 19

Preparation of Complexed Ganaxolone Nanoparticulate Suspension for Spray Layering and Spray Drying

[0395] Complexed ganaxolone nanoparticulate suspensions for spray layering and spray drying were prepared by milling a slurry (7000 g) containing 28.3 wt% ganaxolone, 3 wt% HPMC, 0.15 wt% SLS and 0.033 wt% simethicone (as a 30% emulsion) as described in Example 6. After milling, a complexing agent (methylparaben sodium, 12.60 g), SLS (11.52 g), citric acid anhydrous (13.91g) and deionized water (3972.93 g) were added and stirred for 20 minutes. After stirring, the suspension was packaged in a HDPE container and kept at room temperature (25 °C) to cure. After a curing time of 2 weeks, additional components (e.g. sucrose, PEG, salt) were added and diluted with water to desired concentration for spray layering or spray drying. D50 values were 0.336µm (unsonicated)/0.332 µm (after 1 min sonication).

Examples 20A-C

Spray Layered Complexed and Uncomplexed Ganaxolone Nanoparticulate Composition

[0396] The spray-layered complexed and uncomplexed ganaxolone nanaparticulate compositions of Examples 20A-C were prepared using the following method:

[0397] A Mini Glatt 8560 (Glatt Air Techniques, Ramsey, NJ) was configured for fluid bed coating using a 0.5 mm Schlick nozzle with a Wurster column (3.5 cm x 9.5 cm) set 10 mm above the bottom of the chamber floor. The temperature of the bed was monitored with an internal probe. A peristaltic pump was used to introduce the spray solutions through the nozzle. The unit was first pre-heated for one hour at 56 °C. The bed chamber was opened and 40 g of MCC beads (Celphere, CP-305) was introduced and a pressure of 0.36 bar was used to fluidize the bed. To minimize electrostatic charges, water was immediately sprayed (atomization pressure 0.26 bar). After 1-2 minutes of spraying, the feed line was switched to a stirred vessel containing the ganaxolone spray slurry.

[0398] Examples 20A and 20B demonstrate optimization of SGF dispersion testing results of a complexed ganaxolone spray layered composition (immediate release) for dog pharmacokinetics described below in Example 27. Example 20C describes spray layering of an uncomplexed ganaxolone nanoparticulate composition.

[0399] The ingredients contained in the solid composition of each of the compositions of Examples A-C are shown in Table 11A.

Table 11A

Solid composition of spray layered ganaxolone nanoparticulate compositions (complexed vs uncomplexed)

Spray	Solid Composition (%wt of total solid excluding MCC cores)										
Form	GNX	HPMC	SLS	PEG 400	PEG 4000	Sucrose	Sodium chloride	Methyl paraben sodium	Citric acid	Methyl paraben	Simethicone
20A	69.54	20.05	2.37	3.92	0	0	3.13	0.46	0.50	0	0.02
20B	49.99	12.30	0.26	0	3.16	33.36	0.64	0	0	0.28	0.02
20C	68.16	16.04	0.96	0	14.81	0	0	0	0	0	0.03

[0400] The dispersion testing results for each of the compositions of Examples 20A-C are shown in Table 11B.

Table 11B

Dispersion Results in SGF or Water

Spray Formulation	Initial D50 (μm) unsonicated/1 min sonication	Dispersion D50 (μm) unsonicated/1 min sonication	Testing Conditions[A]
20A	0.339/0.332	6.67 /0.369	SGF,
20B	0.356/0.346	0.395 /0.370	SGF,
		0.366/0.343	Deionized water, rt, 5 min
20C	0.170/0.160	0.202/0.196	water, rt, 5 min
		5.57/0.392	SGF,

[A] Conditions were 36-38°C for 3 hours unless specified otherwise.

Example 20A (Complexed Ganaxolone Spray Formulation)

[0401] A total of 38.1 g of the ganaxolone spray slurry was sprayed over 39 minutes (average spray rate approximately 1 ml/min). The bed temperature ranged from 45 to 49°C. The spray layered beads were dried for an additional 7 minutes after the spraying was completed. Spray layered beads (47 g) were isolated. Theoretical loading of layered solid: 19.7%.

Example 20B (Complexed Ganaxalone Spray Formulation)

[0402] A total of 80 g of slurry was sprayed onto 40 g of MCC beads (Celphere CP-305) over a period of 105 minutes to obtain 63 g of spray layered beads (57.5% loading). The bed temperature was maintained at 43-47°C and inlet air temperature was 54 °C.

Example 20C (Uncomplexed Ganaxolone Spray Formulation)

[0403] This spray formulation was prepared by adding PEG 4000 (3 wt% of total formulation) to the uncomplexed ganaxolone nanoparticulate suspension of Example 5A. A total of 93 g of slurry was sprayed onto 40 g of MCC beads (Celphere CP-305) over a period of 110 minutes to obtain 58 g of spray layered beads (45% loading). The bed temperature was maintained at 36-44°C and inlet air temperature was 48 °C.

Examples 21A-B

Spray Dried Complexed and Uncomplexed Ganaxolone Nanoparticulate Composition

Example 21A

Spray Dried Complexed Ganaxolone Nanoparticulate Compositions

[0404] To the complexed ganaxolone nanoparticle suspension of Example 19 was added sucrose, and sodium chloride. The mixture was diluted with deionized water to obtain the following composition suitable for spray drying: 14.47 wt% Ganaxolone, 1.91 wt% HPMC, 0.96 wt% SLS, 2.15 wt% sucrose, 1.43 wt% NaCl, 0.04 wt% methylparaben and 0.006 wt% simethicone 30% emulsion. This slurry (478 g) was spray dried on a Buchi B-191 Mini Spray Drier to obtain 63.4 g of dry ganaxolone nanoparticle powder. The process parameters were as the following: average spray rate: 5.3 g/min; outlet temperature: 64-66°C; inlet temperature: 108-114°C; airflow: 85% aspiration. D50 values for the ganaxolone nanoparticles were 0.329 µm unsonicated/0.318 µm after 1 minute sonication upon re-dispersion in water. D50 values in SGF were 0.317 µm unsonicated/0.306 µm 1 minute sonication.

Example 21B
Spray Dried Uncomplexed Ganaxolone Nanoparticulate Composition

[0405] To an uncomplexed ganaxolone nanoparticle suspension milled in a similar fashion as described in Example 6 was added PEG 3350 and diluted with deionized water to obtain the following composition: 22.88 wt% Ganaxolone, 4.78 wt% HPMC, 0.19 wt% SLS, 4.31 wt% PEG 3350 and 0.032 wt% simethicone 30% emulsion. This slurry was spray dried on a Buchi B-191 Mini Spray Drier in a similar fashion as described in above Example 20a to obtain dry ganaxolone nanoparticulate powder in 62% yield. D50 of the ganaxolone nanoparticles was 0.249 µm unsonicated/0.220 µm after 1 minute sonication upon re-dispersion in water. D50 in SGF was 4.71 µm unsonicated/2.54 µm after 1 minute sonication.

Example 22
Preparation of an Enteric Coated (Controlled Release) Complexed Ganaxolone Formulation)

[0406] The complexed spray layered beads prepared as described in Example 20B is spray coated with an enteric coating formulation having the following composition:

Component	Amount (g)
Eudragit L30 D-55 (Degussa)	96
Triethyl citrate	4
Talc	8
Water	95

[0407] The coating process is carried out as follows:

[0408] Charge 140 g of spray layered IR beads and 1 g talc to the pre-heated mini Glatt, which has been configured with a 3.5 cm x 9.5 cm Wurster column and a 0.5 mm Schlick nozzle as described in Examples 20A-C. The thermostat on the Glatt is set to 40 °C and the drying air pressure to 0.20 bar.

[0409] Eudragit enteric coating formulation is introduced to the mini Glatt via a peristaltic pump that is positioned in close proximity. The coating formulation is well stirred during the coating. The Eudragit slurry is added at 2.5 ml/min with an atomization pressure of 0.92 bar. The bed temperature is maintained between 26 and 28 °C.

[0410] After completion of the coating process, the coated beads are allowed to cool for 5 minutes. After cooling, one hundred and thirty grams (130g) of the Eudragit slurry is coated onto the beads. This amounts to 18.4% of coating solids. The weight of the coated beads isolated is 166 g.

Example 23

Preparation of Solid Complexed Ganaxolone Particles via Spray Granulation

[0411] A Mini Glatt (Glatt Air Techniques, Ramsey, NJ) is configured for top spray with a fluid bed. A 0.5 mm Schlick-type nozzle is inserted above the fluid bed. Then, 50 g of lactose monohydrate (Kerry) is added and fluidized with 0.27 bar pressure. The apparatus is heated to 50°C for approximately 30 min with bed fluidization pressure of 0.20 – 0.25 bar.

[0412] A ganaxolone slurry comprising 14 wt% ganaxolone, 3.5 wt% HPMC, 8 wt% sucrose, 0.08 wt% methylparaben, 0.07 wt% sodium benzoate, 0.14% citric acid, 0.9 wt% PEG 4000, 0.4 wt% sodium chloride is introduced by a peristaltic pump through the top-mounted nozzle.

[0413] The spray pressure ranges from 0.27 to 0.35 bar and the bed temperature is held at 40 – 45 °C while spraying at 1 to 2 ml/min. The fine powered lactose becomes granular during the spraying. A total of 36 g of 21% solids is sprayed, for a solids loading of 20%.

Examples 24A-D

A Spray Layered Complexed and Uncomplexed Phenytoin Nanoparticulate Composition

[0414] A Mini Glatt 8560 was configured for spray layering as described in Examples 20 A-C. The unit was pre-heated at 60 °C. The bed chamber was opened and 75 g of MCC beads (Celphere, CP-305) was introduced and a pressure of 0.30-0.32 bar was used to fluidize the bed. To minimize electrostatic charges, water was immediately sprayed (atomization pressure

1 bar). After 1-2 minutes of spraying, the feed line was switched to a stirred vessel containing the phenytoin spray slurry. The bed temperature was maintained at 36-41°C during spraying. The spray layered beads were incubated in SGF per Example 3 and the testing results are shown in Table 12.

Example 24A (Uncomplexed Phenytoin Spray Composition)

[0415] This formulation was prepared by adding sucrose (5.4 g), sodium chloride (0.2 g), SLS (0.06 g) and deionized water to the uncomplexed phenytoin nanoparticulate suspension of Example 9 (100.0 g). It was sprayed at 2.5 ml/min. After completion of the spray layering, 96.8 g of spray layered beads were obtained. The loading was 29%.

Example 24B (Complexed Phenytoin Spray Composition)

[0416] This formulation was prepared and spray layered as described for the above formulation 24A except using the complexed phenytoin nanoparticulate of Example 9. After completion of spraying, 101.1 g of spray layered beads was obtained. The loading was 34.8%.

Example 24C (Uncomplexed Phenytoin Spray Composition)

[0417] This formulation was prepared by adding a solution of urea (0.8 g), sodium chloride (0.5 g) in deionized water (2 g) to the uncomplexed phenytoin nanoparticulate suspension of Example 9 (50.0 g). The resultant suspension was diluted with deionized water (50 g) containing 6.25 wt% HPMC, 0.125 wt% SLS and 0.08 wt% simethicone 30% emulsion. This suspension was spray layered onto 75 g of the MCC beads (Celphere CP-305) as described for spray formulation 24A. After completion, phenytoin spray layered beads (87.2 g) was obtained. The loading of phenytoin on the beads was 16.2%.

Example 24D (Complexed Phenytoin Spray Composition)

[0418] This formulation was prepared and spray layered onto 75 g of MCC cores as described above for Formulation 24C except using the complexed phenytion nanoparticulate suspension of Example 9. After completion of the spray layering, 86.8 g of spray layered beads was obtained. The loading was 15.7%.

Table 12

Spray Formul-ation	Solid Composition as % weight to Drug						D50 (μm) after incubation SGF per Example 3 unless specified otherwise	
	HPMC	SLS	Methyl anthranilate	Urea	Sucrose	NaCl	Un-sonicated	1 min sonicat-io
24A	25.0	0.8	0	0	27.0	1.0	23.34	5.51
24B	25.0	0.8	2	0	27.0	1.0	8.55	0.291
24C	56.25	1.125	0	8	0	5	9.13	0.289
							3.74 (DI water)	0.223 (DI water)
24D	56.25	1.125	2	8	0	5	0.320	0.267
							0.304 (DI water)	0.205 (DI water)

Dispersion SGF testing results of spray layered uncomplexed and complexed phenytoin nanoparticulate compositions[1]

[1] Initial D50 (μm) values: 0.192 (unsonicated)/0.141 (after 1 min sonication) for the uncomplexed and 0.209 (unsonicated)/0.177 (after 1 min sonication) for the complexed phenytoin nanoparticulate composition.

[0419] The purpose of the following examples is to describe preparation and testing of various solid dosage forms comprising drug nanoparticles.

Example 25

Pharmacokinetics of Nanoparticulate Formulations in Beagle Dogs

[0420] Purpose-bred Beagle dogs are obtained and housed in a USDA-approved facility in accordance with AAALAC guidelines. Expected dog weights are from 8 to 12.0 kg at the beginning of the evaluation, and are weighed prior to each period of the study. Animals are block randomized into groups of 3 per treatment. Each study will test a complexed drug composition. Fasted animals are fasted overnight without water prior to each study day. Designated fed dogs are fed a can (about 400 g) of Alpo "Chunky with Beef for Dogs," which has 55% of total calories from fat, approximately 45 minutes prior to dosing. If the liquid suspension is to be administered without dilution, the dose is given via oral gavage followed by a 7.5 to 10 ml/kg water flush. Standard laboratory chow and water are offered ad libitum 4 h after dosing. To eliminate the variability of drug absorption among the dogs, all studies should be conducted in a randomized crossover design. Approximately 2 milliliters of blood sample are withdrawn with a 21G needle and via direct venipuncture sampling at predose, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 24 h and 48 h. Blood is immediately transferred to a potassium EDTA blood collection tube (VACUTAINER, Becton Dickinson, Franklin Lakes, NJ, USA) and is stored on ice until the samples are centrifuged at 2500-4000 rpm for 15 min. The plasma is transferred to polypropylene tubes, and samples are stored at -70°C until analyzed by a suitable method (e.g.liquid chromatography/tandem weight spectrometry).

Example 26

Dog Pharmacokinetics with Complexed and Uncomplexed Aqueous Ganaxolone Nanoparticulate Compositions

[0421] The uncomplexed ganaxolone formulation 26A from Example 7 (final composition of 2.5 wt% ganaxolone, 5 wt% HPMC, 0.1 wt% SLS,) showed an approx. 3 and 2-fold increase in Cmax and AUC in the Fed and fasted state respectively. The uncomplexed ganaxolone formulation 26B prepared from a concentrated slurry as in Example 6 (final composition of 5 wt% ganaxolone, 5 wt% HPMC, 0.2 wt% SLS and 1 wt% Polyvinyl alcohol (PVA) (all based on total weight of formulation) . Uncomplexed formulation 26B gave a decrease in Cmax levels and AUC by about 50% as compared to uncomplexed formulation 26A . Administering the complexed ganaxolone formulation prepared from a concentrated slurry as in Example 6 (final composition of 5 wt% ganaxolone, 5 wt% HPMC, 0.1wt% SLS, 1 wt% PVA, 0.1 wt% methylparaben, 0.02 wt% propyl paraben, 0.09 wt% sodium benzoate, 0.12 wt% citric acid and 0.0093 wt% sodium citrate) gave the most desirable pharmacokinetic performance by achieving optimal bioavailability and reduced variability and Cmax. Achieving a high bioavailability (AUC) with a larger particle size (2-fold higher due to complexing agent and curing) was surprising as bioavailability is thought to increase as the particle size decreases. In the case of Ganaxolone, complexed compositions of the type in formulation 26C allow for greater overall exposure while minimizing sedation due to high Cmax values.

TABLE 13

Comparative PK results in beagle dogs for ganaxolone suspension formulations at comparable dose levels (5 mg/kg)					
Formulation Reference	Particle Size (D50)	PVA/ Complexing Agent (Methylparaben)	C_{max} (ng/mL)	$AUC_{0\text{-}72\ hr}$ (ng*h/mL)	Food Intake
Formulation 26A	110nm	None/None	448 ±96	2422±1059	Fasted
Formulation 26A	110nm	None/None	1194 ±104	4637 ±2600	Fed
Formulation 26B	140nm	Yes/None	268 ±36	1643 ±295	Fasted
Formulation 26B	140nm	Yes/None	640 ±92	3525±1190	Fed
Formulation 26C	320nm	Yes/Yes	243 ±40	1855 ± 321	Fasted
Formulation 26C	320nm	Yes/Yes	642 ± 40	5512 ± 681	Fed

EXAMPLE 27

Pharmacokinetic Analysis of Solid Ganaxolone Nanoparticulate Compositions in Beagle Dogs.

[0422] The following example demonstrates that in cases where loose aggregation can be totally reversed by sonication, a measurable difference in pharmacokinetic performance can be seen. Although the impact of loose aggregates on pharmacokinetic performance will be dependent on specific compounds, this example illustrates with immediate release complexed ganaxolone spray layered beads in gelatin capsules that the most preferred embodiments are those that demonstrate the smallest changes in D50 values measured unsonicated versus after 1 min sonication.

[0423] The solid ganaxolone formulations from Example 20A and 20B were placed into gelatin capsules to deliver a 5mg/kg dose of ganaxolone to beagle dogs in the fasted state. The fasted state was chosen as this condition tends to show more pharmacokinetic differences in nanoparticulate formulations of water insoluble drugs. These formulations were chosen as they were part of the solid dose optimization process and exhibited different degrees of loose aggregation. As can be seen below in Table 14, a 3-fold improvement in bioavailability (AUC) was seen with solid complexed ganaxolone capsules versus capsules containing solid complexed ganaxolone that demonstrated more loose aggregation in SGF.

Table 14

Formulation Reference	D50 (μm) in SGF Unsonicated/ after 1 min sonication	C_{max} (SD)(ng/mL)	AUC $_{0\text{-}72h}$ (SD)(ng*h/mL)
Formulation 20A	6.67/0.369	150 (94)	756 (332)
Formulation 20B	0.395/0.370	135 (40)	2294 (1574)

SD = Standard Deviation

Example 28
Immediate Release Capsules With and Without Complexing Agent

[0424] Suspensions (1200 grams) in water containing 25 wt% ganaxolone, 5.0% wt% hydroxypropyl methylcellulose (Pharmacoat 603), 0.0333 wt% of 30% simethicone emulsion, and 0.2 wt% sodium lauryl sulfate, either with 0.05 wt% methylparaben (capsule Ex. 1) or with no methylparaben (capsule Ex. 2, 5.2 wt% of HPMC instead of 5 wt%) are prepared. Each wt% is based on the total weight of the suspension.

[0425] The ganaxolone particles are milled using conditions as described in Example 4. For formulations with complexing agent (Capsule Form 1), ganaxolone nanoparticles having a particle size (D50) of about 120 nm as measured by Horiba LA 910 particle size analyzer are obtained immediately after milling. This volume-weighted-median particle size grows to about 220 nm after 7 days of curing at ambient temperature, indicating that ganaxolone complex is formed. The D50 does not change after this curing period for the duration of the study. For Capsule Form 2 (without complexing agent), ganaxolone nanoparticles having the same particle size (D50) (about 120 nm) are obtained immediately after milling.

[0426] Sucrose (48.5 g) and NaCl (6.5 g) (together about 13 wt% of solids) and water (800 ml) is added to each of the ganaxolone suspensions for Capsule Form 1 and 2 and the resulting mixtures are homogenized for 20 minutes for spray drying. The compositions of the mixtures to be spray dried are given in Table 15.

Table 15

Composition of spray mixture prior to spray layering				
	Capsule Example 1		Capsule Example 2	
	Ganaxolone Complex		Ganaxolone (No Paraben)	
Component	Weight, gram	Wt% /total solid wt, %	Weight, gram	Wt% based on total solid weight, %
Ganaxolone	300	71.7	300	71.4
HPMC	60	14.3	62.4	14.9
Simethicone	0.12	0.03	0.12	0.03
SLS	2.4	0.57	2.4	0.57
Methylparaben	0.60	0.14	0	0
Sucrose	48.5	11.6	48.5	11.5
Sodium chloride	6.5	1.6	6.5	1.5
Total	418.12	100	419.92	100

[0427] For each of Capsule Form 1 and 2, 100 grams of microcrystalline cellulose (MCC) beads (e.g. Celphere, 30/35 mesh) are added to a Glatt GPCG-3 fluidized bed with Wurster column insert (4 inch), inlet temperature of about 55°C and air temp of about 40°C (total air volume approx. 175 cubic cm/hr). About 2000 grams of each spray mixture are sprayed (bottom spray) through 1.2 mm nozzles at 11 ml/min and 1.5 bar of pressure until a layering of about 400 wt% is achieved as compared to initial beads weight. The theoretical compositions of the spray layered ganaxolone complex particles (Capsule Form 1) and ganaxolone particles (Capsule Form 2) are shown in Table 16.

Table 16

Composition of spray layered particles after spray drying				
	Capsule Form 1		Capsule Form 2	
	Ganaxolone Complex		Ganaxolone (No Methyl Paraben)	
Component	Weight, gram	Wt% /total solid wt, %	Weight, gram	Wt% based on total solid weight, %
Ganaxolone	300	57.9	300	57.7
HPMC	60	11.6	62.4	12.0
Simethicone	0.12	0.02	0.12	0.02
SLS	2.4	0.46	2.4	0.46
Methylparaben	0.60	0.12	0	0
Sucrose	48.5	9.4	48.5	9.3
NaCl	6.5	1.25	6.5	1.25
MCC beads	100	19.3	100	19.2
Total	518.12	100	519.92	100

[0428] The spray layered ganaxolone complex particles (Capsule Form 1) or ganaxolone particles (Capsule Form 2) are then filled into gelatin capsules with a fill weight of 518-520 mg coated beads to achieve a 300 mg dose.

Example 29 Delayed Release Capsules

[0429] Drug complexed particles (e.g., prepared as set forth for the ganaxolone nanoparticles in the above examples) spray-layered onto inert beads (500 g) are loaded directly into a rotary granulator/coater (Freund CF-360 granulator) for enteric coating. The rotating particle bed is sprayed with a coating solution containing 50 wt% Eudragit® L 30-D55, 2.5 wt% talc, 1.5 wt% dibutyl sebecate, 20 wt% ethanol, 23.5 wt% isopropyl alcohol, and 2.5 wt% water. A coating level of about 8 wt% is achieved. The ganaxolone content in each coated bead is about 53.4 wt% based on the total weight of the coated beads.

[0430] A suitable amount of the coated beads are hand-filled into gelatin capsule shells, respectively, to form modified release capsules. These particulates are substantially insoluble in the stomach due to the enteric coating but substantially soluble in the intestine.

Example 30
Coated Tablets

[0431] To spray-dried drug complexed particles (e.g., prepared as set forth for the ganaxolone nanoparticles in Example 21, Prosolv 90, Ganaxolone spray granulate, and Dipotassium Phosphate Powder are added sequentially into a Bohle Bin Blender (BL07C, Warminster, Pennsylvania, USA) and blended for 10 ± 0.1 minutes at 11 ± 1 rpm. Additional Prosolv 90 and Sodium Starch Glycolate are added and blended for 10 ± 0.1 minutes at 11 ± 1 rpm. The material is then milled and then passed through a 0.5 mm screen (35 Mesh).

Blend Component	*Weight*	*% w/w*
Silicified Microcrystalline Cellulose, NF (Prosolv 90)	*4.255 kg*	*37.0*
Sodium Starch Glycolate, NF, EP	*0.230 kg*	*2.00*
Sodium Chloride	*0.287 kg*	*2.5*
Magnesium Stearate	*0.0575 kg*	*0.5*
Dipotassium Phosphate Powder, USP, PE	*0.230 kg*	*2.00*
Drug spray granulate	*6.44 kg*	*56.0*
Totals	*11.5 kg*	*100.0*

[0432] The drug blend is loaded into a tablet compressing machine, such as a Fette 1200 B Tool Tablet Press (TP06) or equivalent, and tablets are formed using oval upper and lower punches.

[0433] Optionally, an enteric coat is applied to the tablet cores as follows: The enteric coating comprising Opadry® Enteric from Colorcon® and the over coat comprising Opadry® clear applied sequentially as aqueous coating suspensions using a coating pan. The tablet cores are preheated to 46°C (Exhaust air temperature). The pan speed is adjusted to provide adequate tablet flow and the coating suspensions are sprayed onto the tablets at an atomizing air pressure of 18 – 30 psi; an inlet air temperature of 60 – 70°C for over coat, and of 42 – 50°C for the enteric coat; an exhaust air temperature of 40 to 50°C for the over coat and 30 to 35°C for the enteric coat; a spray rate of 15 to 50 ml/ min.; and an inlet air flow of 175 to 300 CFM. One of skill in the art will understand that the processing parameters for coating are dependent in part upon the size of the batch to be coated and can be adjusted accordingly. The enteric coating should be applied so that a tablet core weight gain of 8 – 15% w%/ tablet core weight is achieved. Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, a methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, or a combination comprising one or more of the foregoing enteric polymers may be used in place of the Opadry Enteric coating.

[0434] In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

What is claimed is:

1. Drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, and (iii) a complexing agent forming a cyclodextrin inclusion complex when the particles are cured for at least about 3 days.

2. The drug complexed particles of claim 1, wherein the complexing agent is included in an amount effective to cause an initial increase in the size of the particles, wherein the volume weighted median diameter (D50) of the particles before the initial growth is from about 100 to about 400 nm and the D50 at the end of the curing time is 20% to 300% larger than the D50 measured before the curing period.

3. The drug complexed particles of claim 1, wherein the surface stabilizer is at least one non-ionic material selected from the group consisting of binders, fillers, surfactants/wetting agents; and/or at least one ionic surface stabilizer.

4. The drug complexed particles of claim 2, wherein the complexing agent is selected from the group consisting of phenol, parabens, ascorbic acid, methyl anthranilate, salicylic acid, acetosalicyclic acid, tocopherol, organic acids, carboxylic acids, aromatic acids, aromatic esters, acid salts of amino acids, benzaldehyde, cinnimaldehyde, imidazole, menthol, thiophenol, m-aminobenzoic acid, anthranilic acid, picolinic acids and alkyl esters thereof, toluidides, sodium benzoate, para-aminobenzoic acid and esters, sorbic and benzoic acids, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, esters, isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures of any of the foregoing.

5. The drug complexed particles of claim 4, wherein the complexing agent is selected from the group consisting of methylparaben, propylparaben, potassium methylparaben, sodium methylparaben, methyl anthranilate, benzoic acid, sodium benzoate, and any combinations or mixtures thereof.

6. The drug complexed particles of claim 4, which comprise from about 0.1% to about 8%, w/w of the complexing agent.

7. The drug complexed particles of claim 5, wherein the surface stabilizer is selected from the group consisting of cellulosics, polyvinylpyrrolidones, polyethylene glycols, pluronics and any combinations or mixtures thereof.

8. The drug complexed particles of claim 5, wherein the surface stabilizer is selected from the group consisting of hydroxypropymethylcellulose, polyvinyl alcohol, docusate sodium, sodium lauryl sulfate, polyvinylpyrrolidone, Plasdone, and mixtures thereof.

9. The drug complexed particles of claim 2, wherein the volume weighted diameter (D50) of the complexed particles does not change by more than 10% after a time in consecutive measurements separated by about 72 hours.

10. The drug complexed particles of claim 2, wherein the complexed particles increase in effective particle size from about 0% to about 200% upon dispersion in simulated gastric or intestinal fluid as compared to dispersion in water under the same conditions.

11. The drug complexed particles of claim 2, wherein the D50 after the endpoint is reached is less than about 500nm.

12. A pharmaceutical composition, comprising the drug complexed particles of claim 1 together with at least one pharmaceutically acceptable excipient.

13. The pharmaceutical composition of claim 12, which is in a form of a solid dosage form.

14. The pharmaceutical composition of claim 12, which is in a form of a liquid suspension.

15. A method of treatment, comprising administering an effective dose of the pharmaceutical composition of claim 13 to a human or animal in need thereof.

16. A method of treatment, comprising administering an effective dose of the pharmaceutical composition of claim 14 to a human or animal in need thereof.

17. Size-stabilized drug complexed particles comprising a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 in association with effective amounts of a surface stabilizer and a complexing agent capable of forming a cyclodextrin inclusion complex, the size-stabilized drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm; the drug complexed particles exhibiting an increase in volume weighted median diameter (D50) of from 0% to not more than about 200% when the formulation is dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg drug/mL and placed in a heated bath at 36° to 38° C for 1 hour using a Type I or II dissolution apparatus and a stirring rate of 75 RPM, as compared to the D50 of the drug particles when the formulation is dispersed in distilled water under the same conditions.

18. The size-stabilized drug complexed particles of claim 16, wherein the surface stabilizer is at least one non-ionic material selected from the group consisting of binders, fillers, surfactants/wetting agents; and/or at least one ionic surface stabilizer; and the complexing agent is selected from the group consisting of phenol, parabens, ascorbic acid, methyl anthranilate, salicylic acid, acetosalicyclic acid, tocopherol, organic acids, carboxylic acids, aromatic acids, aromatic esters, acid salts of amino acids, benzaldehyde, cinnimaldehyde, imidazole, menthol, thiophenol, m-

aminobenzoic acid, anthranilic acid, picolinic acids and alkyl esters thereof, toluidides, sodium benzoate, para-aminobenzoic acid and esters, phosphoric acids, sorbic and benzoic acids, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, esters, isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures of any of the foregoing.

19. A pharmaceutical composition, comprising the drug complexed particles of claim 17 together with at least one pharmaceutically acceptable excipient.

20. The pharmaceutical composition of claim 19, which is in a form of a solid dosage form.

21. The pharmaceutical composition of claim 19, which is in a form of a liquid suspension.

22. The size-stabilzed drug complexed particles of claim 17, wherein the complexig agent is selected from the group consisting of methylparaben, propylparaben, potassium methylparaben, sodium methylparaben, methyl anthranilate, benzoic acid, sodium benzoate, and any combinations or mixtures thereof.

23. The size-stabilized drug complexed particles of claim 15, wherein the complexig agent is methyl anthranilate.

24. A method of treatment, comprising administering an effective dose of the pharmaceutical composition of claim 20 to a human or animal in need thereof.

25. A method of treatment, comprising administering an effective dose of the pharmaceutical composition of claim 21 to a human or animal in need thereof.

26. The size-stabilized drug complexed particles of claim 17, which comprise from about 0.1% to about 8%, w/w of the complexing agent.

27. The pharmaceutical composition of claim 20, which is an oral solid dosage form providing an immediate, delayed, sustained, or pulsatile release of the drug when orally administered to a human or animal.

28. The pharmaceutical composition of claim 27, wherein the oral solid dosage form is a tablet or a capsule.

29. The pharmaceutical composition of claim 19, wherein the drug complexed particles are spray-layered along with effective amounts of a water soluble spacer and an ionic dispersion modulator onto a plurality of inert beads.

30. The pharmaceutical composition of claim 29, wherein the ionic dispersion modulator is in an amount effective to provide a satisfactory redispersibility of the beads with acceptable particle size and stability.

31. The composition of claim 29, wherein the ionic dispersion modulator is an organic or inorganic salt selected from the group consisting of magnesium salt, a calcium salt, a lithium salt, a potassium salt, a sodium salt, a citrate salt, a succinate salt, a fumarate salt, malate salt, maleate salt, a tartrate salt, a glutarate salt, a lactate salt and mixtures thereof.

32. A method for preparing stabilized drug particles, comprising:
    a) reducing the size of drug particles capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 into a size range of about 50 nm to about 200 nm;
    b) adding an effective amount of a surface stabilizer to the drug particles before, during or after reducing the size of the drug particles to form particles comprising the drug and the surface stabilizer; and

c) further stabilizing the particles of step b) by adding an effective amount of a complexing agent capable of forming a cyclodextrin inclusion complex to provide particles that attain a stabilized size such that the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.

33. The method of claim 32, wherein the complexing agent can be added to the stabilized drug particles of step b) to provide particles that attain a stabilized size such that the volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm.

34. The method of claim 33, further comprising spraying layering inert beads with a suspension of the stabilized drug particles together with a water soluble spacer and an ionic dispersion modulator in an amount effective to reduce the amount of water soluble spacer needed to redisperse the spray-layered beads.

35. The method of claim 34, wherein the water soluble spacer comprises from about 0 to about 60% and the ionic modulator comprises from about 0 to about 40% of the spray-layered particles, by weight stabilized drug particles.

36. The method of claim 35, wherein the ionic dispersion modulator is selected from the group consisting of an organic salt, an inorganic salt, and mixtures thereof.

37. The method of claim 36, wherein the inorganic salts is selected from the group consisting of a magnesium salt, a calcium salt, a lithium salt, a potassium salt, a sodium salt and mixtures thereof; and the organic salt is selected from the group consisting of a citrate salt, a succinate salt, a fumarate salt, a malate salt, maleate salt, a tartrate salt, a glutarate salt, a lactate salt and mixtures thereof.

38. A method of treatment, comprising administering the composition of claim 33 to a human or animal in need thereof.

39. A solid pharmaceutical comopsition, comprising a plurality of inert beads spray layered with a coating comprising (a) drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, (iii) a complexing agent capable of forming a cyclodextrin inclusion complex; together with effective amounts of (b) a water soluble spacer and (c) an ionic dispersion modulator.

40. The pharmaceutical comopsition of claim 39, further comprising one or more pharmaceutically acceptable excipients.

41. The pharmaceutical comopsition of claim 40, which is a liquid suspension of said coated inert beads.

42. The pharmaceutical comopsition of claim 40, wherein a therapeutically effective dose of the coated inert beads are incorporated into a hard gelatin capsule.

43. The pharmaceutical comopsition of claim 42, wherein the coated inert beads are further over-coated with a coating which imparts a sustained or delayed release of the drug from the formulation when the formulation is exposed to simulated gastrointestinal fluid.

44. The pharmaceutical comopsition of claim 42, wherein a portion of the coated inert beads incorporated into the hard gelatin capsule are in immediate release form and a portion of the inert beads incorporated into the hard gelatin capsule are in modified release form selected from the group consisting of sustained release, delayed release and a mixture of the foregoing, to provide a pulsatile release of drug from the formulation when the formulation is exposed to simulated gastrointestinal fluid.

45. An orally ingestible tablet, comprising a compressed mixture of (a) drug complexed particles having a volume weighted median diameter (D50) from about 50 nm to about 500 nm, each of the particles comprising in association (i) a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4, (ii) a surface stabilizer, (iii) a complexing agent capable of forming a cyclodextrin inclusion complex; together with effective amounts of (b) a water soluble spacer and (c) an ionic dispersion modulator; an inert diluent; and a tableting lubricant.

46. The orally ingestible tablet of claim 45, further comprising one or more excipients which impart a sustained or delayed or pulsatile release of the drug from the formulation when the formulation is exposed to simulated gastrointestinal fluid.

47. A size-stabilized nanoparticulate liquid composition comprising a drug capable of forming a cyclodextrin inclusion complex and having an aqueous solubility of less than 1 mg/ml in a pH of about 7.4 in association with effective amounts of a surface stabilizer and a complexing agent capable of forming a cyclodextrin inclusion complex, wherein the volume weighted median diameter (D50) of the size-stabilized particles is from about 50 nm to about 500 nm after curing.

48. The nanoparticulate liquid composition of claim 47, wherein the composition further contains at least one additional pharmaceutically acceptable excipient selected from the group consisting of a hydrophilic polymer, a wetting agent, an ionic dispersion modulator, a water soluble spacer, and any combinations or mixture thereof.

49. The nanoparticulate liquid composition of claim 47, wherein the liquid composition is converted to a solid nanoparticulate composition by removal of solvent.

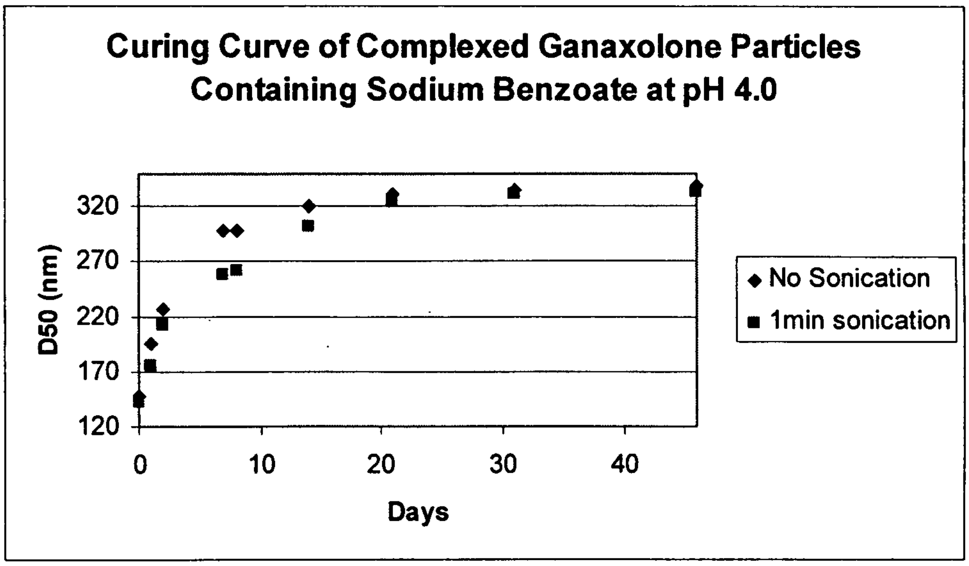


Figure 1a

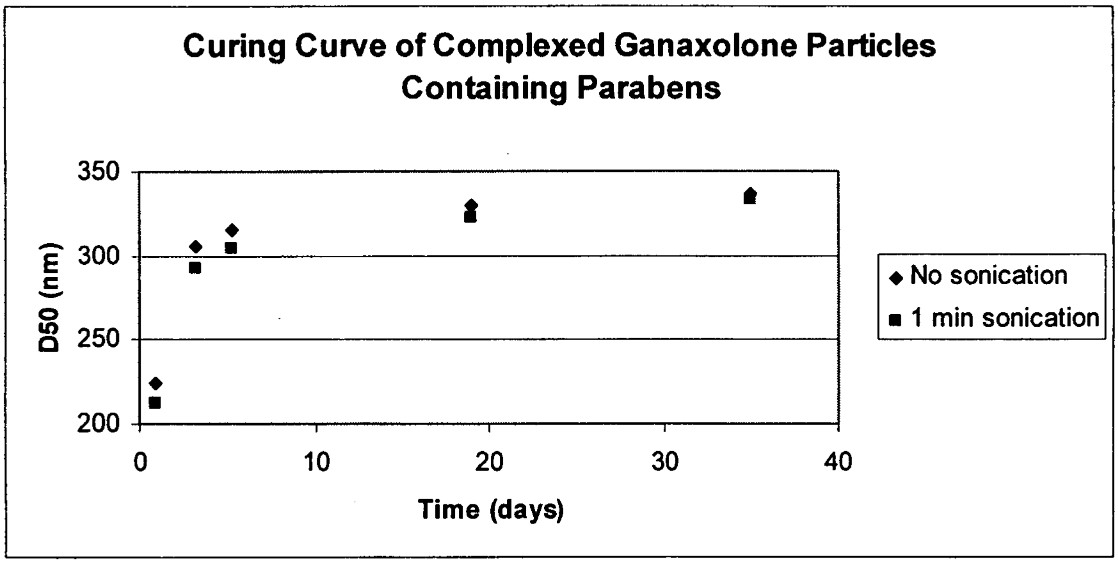


Figure 1b

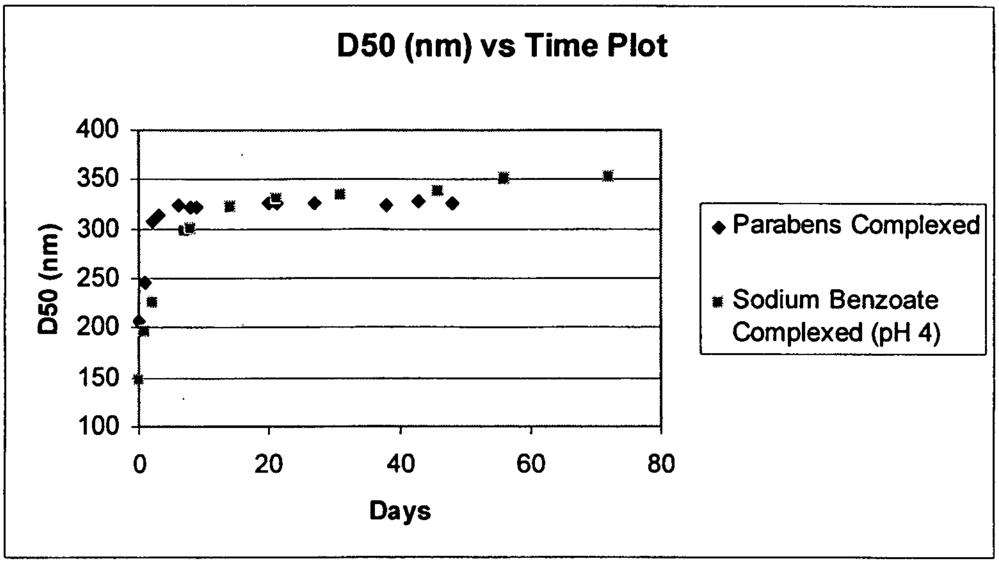

D50 (nm) vs Time Plot
400
350
300
250
200
150
100
D50 (nm)
0
20
40
60
80
Days
◆ Parabens Complexed
✱ Sodium Benzoate Complexed (pH 4)

Figure 2

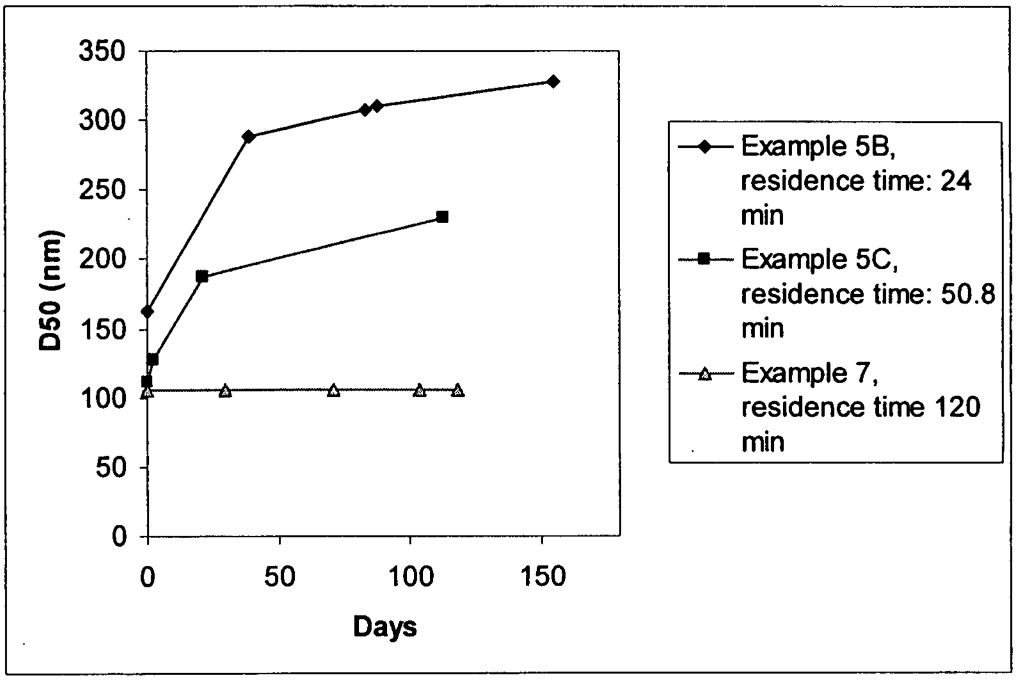
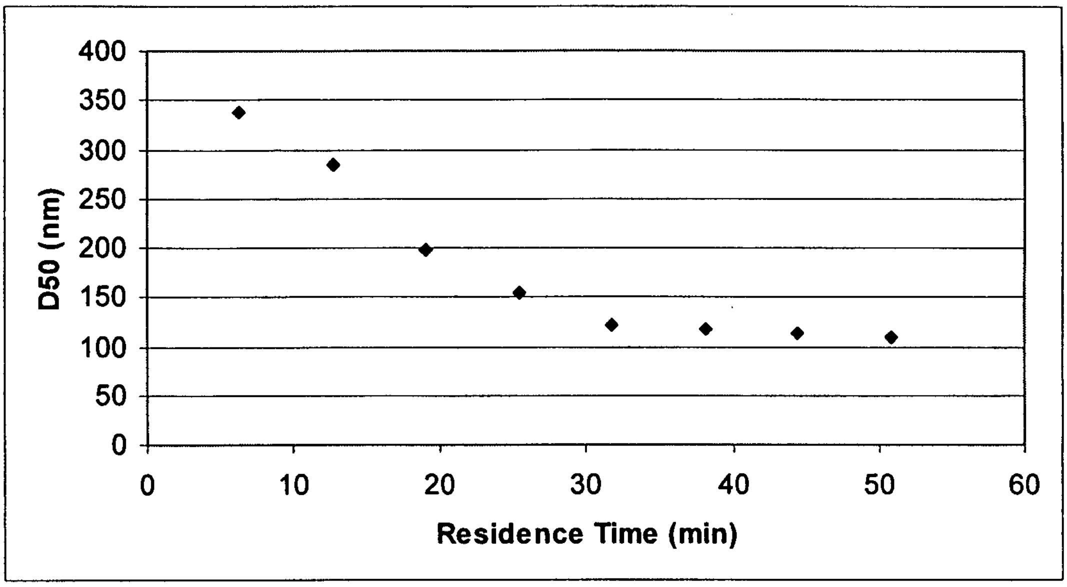

350
300
250
200
150
100
50
0
D50 (nm)
0
50
100
150
Days
Example 5B, residence time: 24 min
Example 5C, residence time: 50.8 min
Example 7, residence time 120 min

Figure 3


400
350
300
250
200
150
100
50
0
D50 (nm)
0
10
20
30
40
50
60
Residence Time (min)

Fi
gure 4

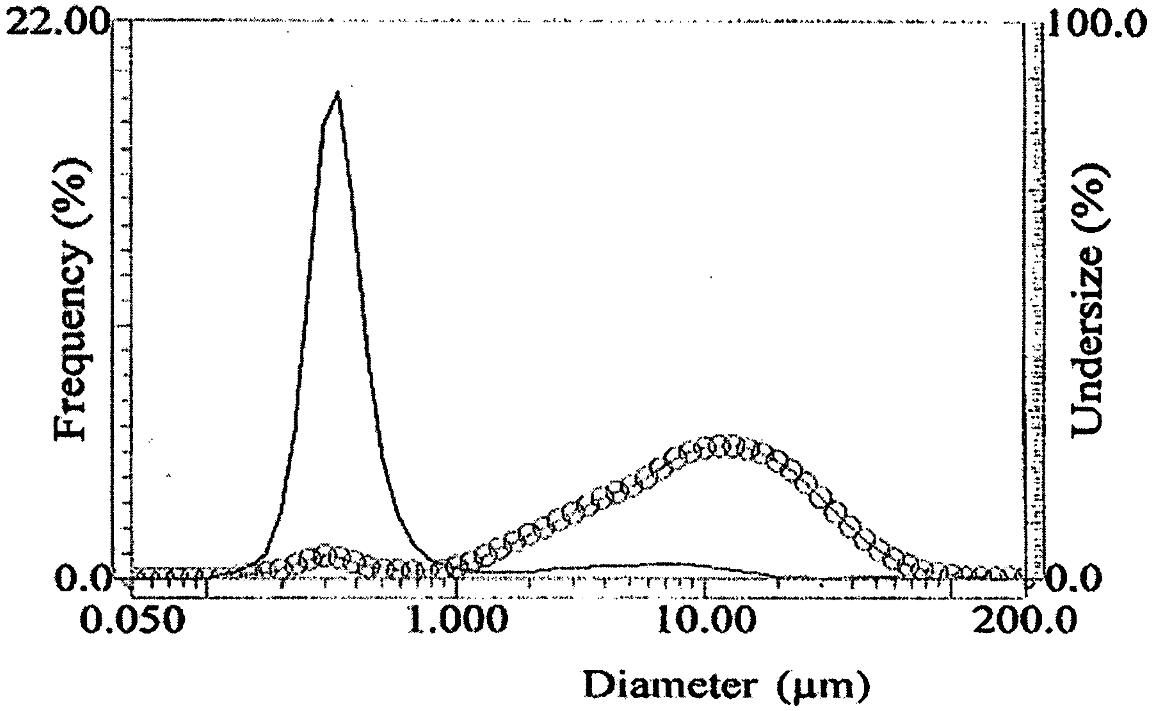

22.00
0.0
Frequency (%)
100.0
0.0
Undersize (%)
0.050
1.000
10.00
200.0
Diameter (μm)

Figure 5