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(54) **ORAL COMPOSITION**

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(57) **ABSTRACT**

The present invention relates to a tablet composition comprising a particle and a pharmaceutically acceptable carrier, wherein the particle comprises an amorphous structure and a submicron domain, and wherein the amorphous structure is a molecular solid dispersion of a drug in a polymeric matrix and the submicron domain is a submicron drug particle. The tablet may further comprise a micronized drug particle. The pharmaceutically acceptable carrier comprises a binder, a filler, a lubricant, and optionally a gelling agent, a glidant and an anti-sticking agent.

ORAL COMPOSITION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Non-Provisional application Ser. No. 13/533,410, filed on Jun. 26, 2012 and U.S. Non-Provisional application Ser. No. 13/663,350, filed on Oct. 29, 2012, which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention relates to the compositions and methods of the preparation of an oral solid composition comprising an amorphous structure and a submicron domain, wherein both amorphous structure and submicron domain comprise the same drug, and wherein the oral solid composition shows crystalline property.

BACKGROUND OF THE INVENTION

[0003] Poor water-solubility is known to be a limiting factor bioavailability. Many attempts have been done with the aim to improving the bioavailability of water-insoluble and water-sparingly soluble drugs. Most such formulations were immediate release in nature as this generally maximizes the amount of drug absorbed. Micronization, solid dispersion and micelle-formation are common techniques used to enhance the drug solubility.

[0004] Solid dispersion has been prepared by solvent evaporation, by spray drying, by spraying drug solution onto a carrier, by twin screw extrusion, by melt fusion, by mechanical admixture such as by ball milling and by mechanical admixture at an elevated but non-melting temperature, as described in U.S. Pat. No. 6,706,283.

[0005] Solid dispersion has been suggested by several U.S. patents. U.S. Pat. No. 5,281,420 teaches compositions in dosage form comprising a solid dispersion which is a solidified melt mixture consisting of tebufelone, a poloxamer surfactant and other components. The other components are miscible with a melt mixture of components. U.S. Pat. No. 7,273,624 has taught a composition of an active ingredient embedded amorphously in particular. The author emphasizes that there are essentially no crystalline contents of any constituent in their particular embodiment. U.S. Pat. No. 4,654,296 teaches a solid dispersion composition containing dihydropyridine A uniformly dispersed in hydroxypropylmethyl cellulose. U.S. Pat. No. 5,028,433 teaches a readily absorbable drug formulation by incorporating to a water-soluble or enteric polymer. U.S. Pat. No. 5,514,663 teaches a composition comprising 3-15 mg of sennosides, wherein the sennosides are in a solid dispersion. U.S. Pat. No. 5,631,022 teaches a composition wherein the drug is in a solid dispersion in a water-soluble carrier. U.S. Pat. No. 5,651,983, U.S. Pat. No. 5,843,479 and U.S. Pat. No. 5,656,290 teach a solid dispersion of bisacodyl on a hydrophilic substrate. U.S. Pat. No. 6,174,873 suggests a solid dispersion comprising a carrier selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, phosphatidylcholine, polyoxyethylene hydrogenated castor oil, hydroxypropylmethylcellulose phthalate, carboxymethylethylcellulose, hydroxypropylmethylcellulose, ethyl cellulose and stearic acid.

[0006] Application of solid dispersion on oral extended release tablet for treating diseases has been described in U.S. Pat. No. 6,706,283 and other articles. U.S. Pat. No. 5,162,117 teaches a controlled release tablet of flutamide. The core comprises 20-80 percent of flutamide and a carrier capable of forming a solid dispersion with flutamide. U.S. Pat. No. 5,773,025 teaches a bioavailable sustained release oral solid dosage form comprising agglomerated particles of a therapeutically active medicament in amorphous form.

[0007] Several articles teach tablet composition comprising nano- or submicron particles. U.S. Pat. No. 5,932,245 suggests a dosage formulation that provides for the release of nanoparticles, wherein the nanoparticles have inner phase and outer phase. Both phases are charged. U.S. Pat. No. 5,972,389 teaches a controlled release oral drug dosage form for releasing a vesicle-containing drug into the stomach, duodenum, and intestinal areas which contain Peyer's patches of a patient, wherein said drug is soluble, but is rendered sparingly soluble when contained in said vesicle, and wherein the vesicle is a member selected from the group consisting of a liposome, nanoparticle, nanosphere and nanocapsule. U.S. Pat. No. 7,803,748 teaches a composition of nanoparticles wherein the nanoparticles enhance paracellular transport of at least one bioactive agent and wherein said nanoparticles are further configured in a tablet form with one or more excipients.

[0008] It is known that unstable solid dispersion converts to a crystal form over the time, while nano-particle aggregation or even fusion may happen during the process or storage. Thus, there remains a need for a novel pharmaceutical dosage structure and/or composition comprising an amorphous structure and submicron particle allowing more flexibility for formulation development. A flexible formulation comprising an amorphous structure and submicron particle may allow a reduction of instability during storage or even improved bioavailability compared to conventional tablet dosage forms.

BRIEF SUMMARY OF THE INVENTION

[0009] The inventors have found methods to prepare oral solid compositions comprising an amorphous structure and a submicron domain for water insoluble drugs, wherein the ratio of the amorphous structure to the submicron domain is from 0.1:5 to 1:1, preferably 1:50 to 1:4.

[0010] Accordingly, in one aspect the present invention relates to an oral composition comprising an amorphous structure and a submicron domain, and wherein the amorphous structure is a molecular dispersion of a drug in a solid polymeric matrix and the submicron domain is a submicron drug particle.

[0011] In a further aspect, the present invention relates to a tablet composition comprising a particle and a pharmaceutically acceptable carrier, wherein the particle comprises an amorphous structure and a submicron domain, and wherein the amorphous structure is a molecular solid dispersion of a drug in a polymeric matrix and the submicron domain is a submicron drug particle. The tablet may further comprise a micronized drug particle. The pharmaceutically acceptable carrier comprises a binder, a filler, a lubricant, and optionally a gelling agent, a glidant and an anti-sticking agent. The tablet composition may exhibit crystalline properties as observed under a polarized microscope. The tablet composition is optionally coated with a film for cosmetic or other purposes. And also, the tablet composition may further comprise a sweetener.

[0012] In a further aspect, the invention relates to a method for preparing a particle comprising an amorphous structure

and a submicron domain, wherein the particle is prepared by dissolving a drug and a polymer in a co-solvent, adding a non-solvent to precipitate a portion of the drug, drying and milling of the resulting mass. In an alternative method, the particle is prepared by dissolving a drug and a polymer in a co-solvent, adding a non-solvent to precipitate a portion of the drug, spraying and drying this suspension onto a micronized drug particle. Alternatively, the particle is made by combining a drug solid dispersion and a drug nanoparticle. The particle is blended with other ingredients to form a tablet or encapsulated.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0013] A used herein, the term "drug" means a compound intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. The terms drugs, therapeutics, actives, active ingredient and biological active are inter-changeable.

[0014] "Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

[0015] Singular forms included in the claims such as "a", "an" and "the" include the plural reference unless expressly stated or the context clearly indicates otherwise.

[0016] By "pharmaceutically acceptable" is meant a carrier comprised of a material that is not biologically or otherwise undesirable.

[0017] In the present context, the term "hydrophilic" describes that something 'likes water', i.e. a hydrophilic molecule is one that typically is electrically polarized and capable of forming hydrogen bonds with water molecules.

[0018] The terms "soluble", "slightly soluble", "sparingly-soluble" and "insoluble" are relative. In general, a substance is said to be soluble if more than 0.1 g of the substance dissolves in 100 mL solvent. The present invention can be applied to drugs sparingly soluble in water, drugs slightly soluble in water, drugs very slightly soluble in water and drugs practically insoluble in water. (See Table 1)

TABLE 1

Values for estimating drug solubility based upon "USP definition"

Descriptive Term	Appropriate Volume of Solvent In Milliliters Per Gram of Solute
Very soluble	Less than 1 part solvent needed to dissolve 1 part solute
Freely soluble	From 1 to 10 parts solvent needed to dissolve 1 part solute
Soluble	From 10 to 30 parts solvent needed to dissolve 1 part solute
Sparingly soluble	From 30 to 100 parts solvent needed to dissolve 1 part solute
Slightly soluble	From 100 to 1000 parts solvent needed to dissolve 1 part solute
Very slightly soluble	From 1000 to 10,000 parts solvent needed to dissolve 1 part solute
Practically insoluble	More than 10,000 parts solvent needed to dissolve 1 part solute

[0019] In the present context, the term "amphiphilic" in the present context describes a chemical is able to dissolve in an aqueous medium and an organic solvent. For example, polyvinylpyrrolidone and polyethylene glycol are considered as amphiphilic polymers, as they dissolve in water and in most alcohols.

[0020] The terms "solid dispersion", "amorphous domain" and "amorphous structure" are interchangeable. Solid dispersion, in the present context, denotes the drug molecules dispersed in a polymeric matrix in a solid state.

[0021] The term "micronized domain" refers to a micronized drug particle sprayed or coated with a solid dispersion-submicron domain mixture.

[0022] In this context, solvent is a liquid that dissolves solids resulting in a solution. Non-solvent is a substance incapable of dissolving a given component of a mixture. Thus, water is a non-solvent to water-insoluble drugs.

The Invention

[0023] The present invention provides an oral composition and methods for preparing such compositions. The oral solid compositions are in the form of particles and tablets and may have one or more of the following characteristics: (1) comprising an amorphous structure of a drug substance, a submicron domain of a drug substance, (2) providing fast or slow release; and (3) optionally coated for appearance, tasking masking, extended-release or delayed-release.

[0024] Accordingly, this invention provides an oral solid composition comprising an amorphous structure and a submicron domain, wherein the amorphous structure comprises drug molecules dispersed in a polymer matrix, and wherein the submicron domain is a submicron drug particle. Further, this invention also provides an oral solid composition essentially consisting of an amorphous structure and a submicron domain, wherein the amorphous structure is a drug molecule dispersed in a polymer matrix, and wherein the submicron domain consists essentially of the same drug, wherein the polymer is amphiphilic and selected from the group consisting of polyvinylpyrrolidone and polyethylene glycol. Under a polarized microscope, the composition shows crystalline properties. The desired ratio of the amorphous structure to the submicron domain, in both compositions, is 0.1:5 to 1:1, and more preferably 1:50 to 1:4. The desired average particle diameter is mesh 12 (1680 microns) and mesh 100 (149 microns), and the most preferred average particle diameter is between mesh 20 (841 microns) and mesh 100 (149 microns). The desired drug solubility in the application is described in paragraph [017].

[0025] In a further aspect, this invention provides an oral tablet composition for pharmaceutical use, comprising a particle described in paragraph [023], wherein the particle may optionally further comprise a micronized drug domain, wherein the tablet composition may further optionally comprise a micronized drug particle and wherein the a pharmaceutically acceptable carrier comprising a binder, a filler, an extended-release aid, glidant and a lubricant alone or in any combinations. The oral tablet composition is optionally film-coated.

[0026] Solvent-based method is one of the popular ways to prepare solid dispersion. In such method, a co-solvent is used to intimately dissolve a drug and carrier molecules together to form a solution, and then the solvent is removed by evaporation. The resulting solid is a dispersion of drug molecules in the carrier molecules. In the present invention, a non-solvent (with respect to the drug; miscible to the solvent) is added to the drug-carrier solution. As the solvency to the drug decreases, the solution becomes saturated and a portion of the

drug precipitates out. At this stage, the solvent is removed by evaporation to achieve a solid state comprising an amorphous structure and submicron domains. Thus, the particle comprising (or essentially consisting of) an amorphous structure and a submicron domain can be obtained by the following steps: dissolving a drug and a polymer in a co-solvent, adding a non-solvent to precipitate a portion of the drug to form a suspension, drying the suspension by air-drying, a spray-dryer or a rotary evaporator, and then milling of the dried mass to form the particles. The amount of the crystalline structure is inversely proportional to the amount of polymer used in the preparation. Alternative method is a direct combination of a drug nano-particle and a drug polymeric dispersion. Under a polarized microscope, the composition shows crystalline properties. The desired ratio of the amorphous structure to the submicron domain is 0.1:5 to 1:1, and more preferably 1:50 to 1:4.

[0027] The pharmaceutical tablet composition according to the present invention can be obtained by (1) blending and then (2) compressing the particle comprising the amorphous structure and submicron domains with a pharmaceutically acceptable carrier. In this invention, the composition can be an extended release tablet or an immediate-release tablet. The composition may further comprise a sweetener and another drug. Under a polarized microscope, the composition shows crystalline properties. The desired ratio of the amorphous structure to the submicron domain is 0.1:5 to 1:1, and more preferably 1:50 to 1:4. The composition may also optionally film-coated for functional or cosmetic purposes. The functional purposes of the film include moisture-barrier, extended-release, delayed-release, taste-masking etc.

[0028] In one embodiment, the oral solid composition essentially consisting of an amorphous structure and a submicron domain, wherein the amorphous structure comprising a drug and a polymer, and wherein the submicron domain essentially consisting of a drug. The desired ratio of the amorphous structure to the submicron domain is 0.1:5 to 1:1, and more preferably 1:50 to 1:4. The polymer is preferred to be amphiphilic, the preferred polymer is selected from the group consisting of polyethylene glycol and polyvinylpyrrolidone. In another embodiment, the solubility of the polymer is preferred to be pH sensitive. Examples include but not limited to amino methacrylate copolymer and poly(methacylic acid-co-methyl methacrylate). The preferred average diameter of the submicron domain is about 100 nm or smaller. The preferred average diameter of the particle is from mesh 20 to mesh 100. And, there is a preference for the solubility of the drug, please, see paragraph [017].

[0029] In the tablet embodiments, the oral tablet compositions comprising: (1) a drug particle essentially consisting of an amorphous structure and a submicron domain and (2) a carrier, wherein the ratio of the amorphous structure to the submicron domain is 1:50 to 1:4, wherein the amorphous structure is evenly distributed in the submicron domain, the average diameter of the oral particle is from mesh 20 to mesh 100. In such embodiments, the amorphous structure comprises a drug and an amphiphilic polymer, wherein the submicron domain essentially consists of a drug. The preferred amphiphilic polymer is polyvinylpyrrolidone. There is a preference for the solubility of the drug. [Paragraph 017] In one tablet embodiment, more than 100 parts water is needed to dissolve 1 part drug. In another tablet embodiment, more than 1000 parts water is needed to dissolve 1 part drug. In a further tablet embodiment, more than 10,000 parts water is needed to dissolve 1 part drug.

[0030] In a particular embodiment, the oral tablet compositions comprising: (1) a particle comprising an amorphous structure and a submicron domain and (2) a carrier, wherein the amorphous structure comprises a drug and a polyvinylpyrrolidone, wherein the amorphous structure is evenly distributed in the submicron domain, wherein the submicron domain essentially consists of a drug, wherein the ratio of the amorphous structure to the submicron domain is from 1:50 to 1:4, wherein the average diameter of the oral particle is from mesh 20 to mesh 100, wherein more than 100 parts water is needed to dissolve 1 part drug. In this embodiment, the tablet composition may also comprise a micronized drug particle. Such composition may also be designed for high drug loads, such that the amount of the drug in the oral tablet composition is more than 30%, 50% and 70%. The carrier comprises a binder, a filler (or a diluent), a disintegrant, a lubricant, a glidant, an anti-sticking agent, optionally a gelling agent, optionally a gas-producing ingredient and optionally an acid-soluble polymer. The oral tablet composition is optionally coated with an enteric film.

[0031] In a specific embodiment, the oral tablet composition comprises: (1) a drug particle essentially consisting of an amorphous structure and a submicron domain and (2) a carrier, wherein the ratio of the amorphous structure to the submicron domain is 1:50 to 1:4, wherein the amorphous structure is evenly distributed in the submicron domain, wherein the average diameter of the oral particle is from mesh 20 to mesh 100, wherein the drug is ezetimibe. In this embodiment, the tablet composition may also comprise a micronized drug particle. Such composition may also be designed for high drug loads, such that the amount of the drug in the oral tablet composition is more than 30%, 50% and 70%. The carrier comprises a binder, a filler (or a diluent), a disintegrant, a lubricant, a glidant, an anti-sticking agent, optionally a gelling agent, optionally a gas-producing ingredient and optionally an acid-soluble polymer. The oral tablet composition is optionally coated with an enteric film.

[0032] In all tablet embodiments, the tablet composition is optionally film-coated for moisture barrier, appearance and modified-release.

[0033] In all embodiments, the particle essentially consisting of an amorphous structure and a submicron domain is prepared by dissolving the drug and a polymer in a co-solvent, adding a non-solvent to precipitate a portion of drug, drying and then milling of the resulting mass. Alternatively, the particle essentially consisting of an amorphous structure and a submicron domain is simply prepared by adding a drug polymeric dispersion onto a drug nanoparticle.

[0034] The present invention can be applied to drugs sparingly soluble in water, drugs slightly soluble in water, drugs very slightly soluble in water and drugs practically insoluble in water. Examples include but not limited to acetaminophen, alprazolam, atorvastatin calcium, betamethasone acetate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, buprenorphine hydrochloride, butoconazole nitrate, caffeine, calcitriol, carbamazepine, carprofen, celecoxib, cilostazol, clarithromycin, clobetasol Propionate, clofibrate, clopidogrel bisulfate, clotrimazole, dactinomycin, danazol, dapsone, desoximetasone, dexamethasone acetate, dextromethorphan, diazepam, efavirenz, erythromycin estolate, erythromycin ethylsucci-

nate, erythromycin, estradiol, ethinyl estradiol, ethotoin, ezetimibe, felodipine, fexofenadine hydrochloride, flurbiprofen, fluvoxamine maleate, gemfibrozil, haloperidol, ibuprofen, idarubicin hydrochloride, indapamide, indomethacin, isofluorophate, isotretinoin, ivermectin, lansoprazole, leflunomide, levonorgestrel, lidocaine, loratadine, lovastatin, medroxyprogesterone acetate, metaxalone, methocarbamol, nabumetone, naproxen, niacin, nifedipine, norethindrone acetate, omeprazole, oxandrolone, oxybenzone, oxymetholone, paclitaxel, perphenazine, phenobarbital, phenyloin, pimozide, pitavastatin, prednisolone, prednisolone tebutate, proclorperazine, progesterone, propoxyphene napsylate, risperidone, ritonavir, lopinavir, and simvastatin.

[0035] In all tablet embodiments discussed, the carrier comprises a binder, a filler (or a diluent), a disintegrant, a lubricant, a glidant, an anti-sticking agent, optionally a retarding agent, optionally a gas-producing ingredient, and optionally an acid-soluble polymer. The amount of an excipient employed will depend upon how much active agent is to be used. One excipient can perform multi-functionally.

[0036] Binders include, but are not limited to, starches such as potato starch, wheat starch, corn starch; microcrystalline cellulose; celluloses such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, sodium carboxy methylcellulose; natural gums like acacia, alginic acid, guar gum; liquid glucose, dextrin, povidone, syrup, polyethylene oxide, polyvinyl pyrrolidone, poly-N-vinyl amide, polyethylene glycol, gelatin, poly propylene glycol, tragacanth, combinations thereof and other materials known to one of ordinary skill in the art and mixtures thereof.

[0037] Fillers or diluents, which include, but are not limited to sugar, dextrates, dextrin, dextrose, fructose, lactitol, mannitol, sucrose, starch, lactose, xylitol, sorbitol, talc, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic or tribasic, calcium sulphate, and the like can be used.

[0038] Disintegrants which include but are not limited to crospovidone; carboxyalkyl celluloses, low substituted hydroxypropyl cellulose, crosslinked carboxyalkylcellulose and their alkali salts; pregelatinized starch, dried starch, sodium starch glycolate; resins; and mixtures thereof.

[0039] Lubricants may be selected from, but are not limited to, those conventionally known in the art such as magnesium, aluminum or calcium or zinc stearate, polyethylene glycol, glyceryl behenate, mineral oil, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oil and talc.

[0040] Glidants include, but are not limited to, silicon dioxide; magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate, calcium silicate, magnesium silicate, colloidal silicon dioxide, silicon hydrogel and other materials known to one of ordinary skill in the art.

[0041] Retarding agent is any substance retards the drug release to produce the controlled-release effect. Examples of retarding agent include but not limited to wax, gelling agent, and many other water-insoluble materials. In the invention, gelling agent is the key retarding agent. In this invention, gelling agent is a water-swellable polymer.

[0042] Gas-producing ingredients include but are not limited to calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium sulfite, sodium bisulfite, sodium metabisulfite, citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, their salts, and mixtures thereof.

[0043] An acid-soluble polymer may be included in the composition. The preferred acid-soluble polymer is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate.

[0044] Sweeteners may also be added to the composition. Examples of sweeteners include but not limited to glucose, stevia extracts, acesulfame potassium, aspartame, neotame, saccharin and sucralose.

[0045] The pharmaceutical dosage form of the invention may also be optionally coated with moisture-barrier film, sugar coating, enteric coating, bioadhesive coating and other coatings known in the art. These coatings help pharmaceutical formulations to release the drug at the required site of action. In one example, the additional coating prevents the dosage from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small intestine or colon (e.g., an enteric coating).

[0046] These coatings comprise one or more excipients selected from a group consisting of coating agents, plasticizers, channeling agents, opacifiers, taste-masking agents, fillers, polishing agents, coloring agents, anti-tacking agents and the like.

[0047] Coating agents which are useful in the coating process, include, but are not limited to, polysaccharides such as maltodextrin, alkyl celluloses such as methyl or ethyl cellulose, cellulose acetate, hydroxyalkylcelluloses (e.g. hydroxypropylcellulose or hydroxypropylmethylcelluloses); polyvinylpyrrolidone, acacia, corn, sucrose, gelatin, shellac, cellulose acetate phthalate, lipids, synthetic resins, acrylic polymers, OPADRY® coating systems, polyvinyl alcohol (PVA), copolymers of vinylpyrrolidone and vinyl acetate (e.g. marketed under the brand name of PLASDONE®) and polymers based on methacrylic acid such as those marketed under the brand name of EUDRAGIT®. These may be applied from aqueous or non-aqueous systems or combinations of aqueous and non-aqueous systems as appropriate.

[0048] Additives can be included along with the film formers to obtain satisfactory films. These additives can include plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol (PEG) and the like, channeling agents such as surfactants, short-chain water-soluble polymers, salts and the like, antitacking agents such as talc, stearic acid, magnesium stearate and colloidal silicon dioxide and the like, fillers such as talc, precipitated calcium carbonate, polishing agents such as Beeswax, carnauba wax, synthetic chlorinated wax and opacifying agents such as titanium dioxide and the like. All these excipients can be used at levels well known to the persons skilled in the art.

EXAMPLES OF INVENTION

[0049] The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modifications without deviating from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention.

Example 1

[0050] Duloxetine hydrochloride and polyvinylpyrrolidone are co-dissolved in methanol. Homogenization is applied to the mixture, as purified water is added gradually till the solution turns to turbid. The suspension is then spray-died,

and passed through a 20 mesh screen. The screened particle is then mixed with a pharmaceutically acceptable carrier, compressed into a tablet.

Example 2

[0051] A portion of metaxalone and polyvinylpyrrolidone are co-dissolved in methanol. Homogenization is applied to the mixture, as purified water is added gradually till the solution turns to turbid. The suspension is then spray-died, and passed through a 20 mesh screen. The screened particle is then mixed with another portion of metaxalone and a pharmaceutically acceptable carrier, compressed into a tablet.

Example 3

[0052] A portion of clopidogrel bisulfate and polyvinylpyrrolidone are co-dissolved in methanol. Homogenization is applied to the mixture, as purified water is added gradually till the solution turns to turbid. The suspension is then spray-died, and passed through a 20 mesh screen. The screened particle is then mixed with another portion of metaxalone and a pharmaceutically acceptable carrier, compressed into a tablet.

Example 4

[0053] Duloxetine hydrochloride and polyvinylpyrrolidone are co-dissolved in methanol. Homogenization is applied to the mixture, as purified water is added gradually till the solution turns to turbid. The suspension is then spray-died, and passed through a 20 mesh screen. The screened particle is then mixed with bupropion hydrochloride and a pharmaceutically acceptable carrier, compressed into a tablet.

Example 5

[0054] Duloxetine hydrochloride and polyvinylpyrrolidone are co-dissolved in methanol. Homogenization is applied to the mixture, as purified water is added gradually till the solution turns to turbid. The suspension is then spray-died, and passed through a 20 mesh screen. The screened particle is then mixed with a tranquilizer and a pharmaceutically acceptable carrier, compressed into a tablet.

Example 6

[0055] A portion of a metaxalone polymeric dispersion is mixed with a portion of metaxalone nanoparticles, dried and milled to the desired particle size. The milled particle is blended with a carrier and compressed into a tablet.

We claim:

1. An oral tablet composition comprising: (1) a drug particle essentially consisting of an amorphous structure and a submicron domain and (2) a carrier, wherein the ratio of the amorphous structure to the submicron domain is 1:50 to 1:4, and wherein the average diameter of the oral particle is from mesh 20 to mesh 100.

2. The oral tablet composition as claimed in claim **1**, wherein the amorphous structure comprises a drug and an amphiphilic polymer, wherein the submicron domain essentially consists of a drug.

3. The oral tablet composition as claimed in claim **2**, wherein the amphiphilic polymer is polyvinylpyrrolidone.

4. The oral tablet composition as claimed in claim **3**, wherein more than 100 parts water is needed to dissolve 1 part drug.

5. The oral tablet composition as claimed in claim **3**, wherein more than 1000 parts water is needed to dissolve 1 part drug.

6. The oral tablet composition as claimed in claim **3**, wherein more than 10,000 parts water is needed to dissolve 1 part drug.

7. An oral tablet composition comprising: (1) a drug particle essentially consisting of an amorphous structure and a submicron domain and (2) a carrier, wherein the ratio of the amorphous structure to the submicron domain is 1:50 to 1:4, wherein the average diameter of the oral particle is from mesh 20 to mesh 100, wherein more than 100 parts water is needed to dissolve 1 part drug; wherein the amorphous structure comprises a drug and polyvinylpyrrolidone, and wherein the submicron domain essentially consists of a drug.

8. The oral tablet composition as claimed in claim **7**, wherein the oral tablet composition comprises a micronized drug particle.

9. The oral tablet composition as claimed in claim **7**, wherein the amount of the drug in the oral tablet composition is more than 30%.

10. The oral tablet composition as claimed in claim **7**, wherein the amount of the drug in the oral tablet composition is more than 50%.

11. The oral tablet composition as claimed in claim **7**, wherein the amount of the drug in the oral tablet composition is more than 70%.

12. The oral tablet composition as claimed in claim **7**, the carrier comprises a binder, a filler, a disintegrant, a lubricant, and optionally a gelling agent, a glidant and an anti-sticking agent.

13. The oral tablet composition as claimed in claim **12**, the carrier optionally comprises an acid-soluble polymer and the oral tablet composition is optionally coated with an enteric film.

14. The oral tablet composition as claimed in claim **13**, the acid-soluble polymer is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate.

15. The oral tablet composition as claimed in claim **10**, the carrier comprises a binder, a filler, a disintegrant, a lubricant, and optionally a gelling agent, a glidant and an anti-sticking agent.

16. The oral tablet composition as claimed in claim **15**, the disintegrant is selected from the group consisting of crospovidone; carboxyalkyl celluloses, low substituted hydroxypropyl cellulose, crosslinked carboxyalkylcellulose and their alkali salts; pregelatinized starch, dried starch, sodium starch glycolate; resins; and mixtures thereof.

17. The oral tablet composition as claimed in claim **15** the carrier optionally comprises an acid-soluble polymer and the oral tablet composition is optionally coated with an enteric film.

18. The oral tablet composition as claimed in claim **15**, the carrier optionally comprises a gas-producing ingredient.

19. The oral tablet composition as claimed in claim **18**, the gas-producing ingredient is selected from the group consisting of calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium sulfite, sodium bisulfite, sodium metabisulfite, citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, their salts, and mixtures thereof.

20. An oral tablet composition comprising: (1) a drug particle comprising an amorphous structure and a submicron

domain and (2) a carrier, wherein the ratio of the amorphous structure to the submicron domain is 1:50 to 1:4, wherein the average diameter of the oral particle is from mesh 20 to mesh 100, wherein the oral tablet composition optionally comprises a micronized drug particle, and wherein the drug is ezetimibe.

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