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(71) Applicant (for all designated States except US):
MALLINCKRODT INC. [US/US]; 675 McDonnell
Boulevard, Hazelwood, Missouri 63042 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PARK, Jae Han**
[KR/US]; 1158 Bonhomme Lake Drive, #B, Olivette,
Missouri 63132 (US). **EISENHAUER, Tiffani** [US/US];
618 Lakefield Drive, Columbia, Illinois 62236 (US).
DHANARAJAN, Anish [IN/US]; 926 N. Woodlawn
Ave., Kirkwood, Missouri 63122 (US). **GUPTA, Vishal,**
K. [US/US]; 1141 New Ballwin Oaks Drive, Ballwin,
Missouri 63021 (US). **OVERHOLT, Stephen** [US/US];
5337 Tholozan Avenue, St. Louis, Missouri 63109 (US).

(74) Agents: **SIMAN, Craig, D.** et al.; Mallinckrodt Inc., 675
McDonnell Boulevard, Hazelwood, Missouri 63042 (US).

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(54) Title: METHODS OF PRODUCING STABILIZED SOLID DOSAGE PHARMACEUTICAL COMPOSITIONS CONTAINING MORPHINANS

(57) Abstract: Methods for producing stabilized solid dosage form pharmaceutical compositions are provided. In particular, methods for preparing protected granules containing morphinans, and solid dosage form pharmaceutical compositions produced using the morphinan-protected granules are provided.



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METHODS OF PRODUCING STABILIZED SOLID DOSAGE PHARMACEUTICAL COMPOSITIONS CONTAINING MORPHINANS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/284,651 filed on December 22, 2009, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods of producing stabilized solid dosage forms of morphinan pharmaceutical compositions. In particular, the present invention relates to methods of preparing morphinan-protected granules that may be incorporated into solid dosage forms of morphinan pharmaceutical compositions.

BACKGROUND OF THE INVENTION

[0003] Minimizing the degradation of active pharmaceutical ingredients (APIs) in pharmaceutical compositions is an ongoing challenge in research and development. Degradation may occur from the physical or chemical instability of the API with incompatible pharmaceutical carriers in a pharmaceutical composition, or by reactions of the API with headspace oxygen or residual water in a composition.

[0004] Oxidation is a common mechanism of API degradation in pharmaceutical compositions. The process of oxidative degradation may occur via various mechanisms such as autooxidation, nucleophilic addition, electrophilic addition, or electron transfer. Regardless of the mechanism, degradant compounds formed by the degradation of an API in a pharmaceutical composition may impart potentially harmful properties to the composition.

[0005] If degradants are present in a pharmaceutical composition above the levels prescribed by ICH Guidelines Q3A and Q3B, the degradants must undergo a qualification procedure as part of the approval process required before the use and sale

of the composition is allowed. Qualification of impurities typically involves costly studies using multiple animal models, and introduces considerable risk into the development process. If degradants of a pharmaceutical composition are found to be carcinogenic or teratogenic, the composition will not gain FDA approval, diminishing the opportunity for commercialization of the API.

[0006] As a result, the process of selecting functional carriers for a pharmaceutical composition is particularly challenging. A functional pharmaceutical carrier is typically selected primarily to impart desired performance characteristics to the composition such as an extended release profile. In addition, it is desirable to select functional carriers that are chemically compatible with the API in the composition. In certain compositions, it may be necessary to incorporate functional carriers that may be incompatible with the API in order to achieve a desired performance of the API in the body. In this situation, identifying an effective means to prevent the degradation of the API is an essential part of the development of a successful therapeutic composition.

[0007] For example, the formulation of a solid dosage form of an API may incorporate a release-modifying pharmaceutical carrier in order to achieve a desired release profile after administration of the compound. Polymer carriers such as a polyethylene oxide (PEO) polymer may be incorporated into a pharmaceutical composition to impart an extended release profile to the composition. PEO polymers are produced by a process of radical polymerization process followed by oxidative degradation of the polymer to achieve the desired molecular weight. The resulting PEO polymer carriers may retain residual peroxides and other oxidative species from the production process that may cause the oxidation of the API molecules in any pharmaceutical composition that incorporates PEO polymers. Typically, other excipients such as antioxidants or pH-lowering excipients may be incorporated into the API composition to minimize the degradation of the API in the presence of incompatible carriers such as PEO polymers in the pharmaceutical composition. However, in a solid dosage form composition, this approach is less effective than in other dosage forms such as solutions or suspensions.

[0008] Morphinans, a widespread class of analgesic APIs, are particularly vulnerable to oxidative degradation, especially in compositions that incorporate PEO

polymer carriers or other pharmaceutical carriers that contain residual peroxides or other oxidative species. Because the physiological effects of morphinans are notoriously sensitive to small changes in chemical structure, the formation of degradants may introduce undesirable properties to a pharmaceutical composition in which a morphinan is vulnerable to degradation. For solid dosage forms of morphinan compositions, the introduction of additional antioxidant excipients or pH-lowering excipients to prevent the degradation of the morphinan, particularly when formulated in a solid dosage form, has been relatively ineffective to date.

[0009] A need exists in the art for a method of protecting an API from degradation in a solid dose form of a pharmaceutical composition. In particular, a need exists for a method of stabilizing morphinan APIs, which are especially vulnerable to oxidative degradation, in solid dosage forms of pharmaceutical compositions.

SUMMARY OF THE INVENTION

[0010] Briefly, therefore, one aspect of the disclosure provides a method for the preparation of a solid dosage form pharmaceutical composition comprising a morphinan and at least one other active pharmaceutical ingredient. The method comprises two steps. In the first step, a mixture comprising the morphinan and at least one excipient is granulated in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced thereby forming a morphinan-protected granule. Next, a mixture comprising the morphinan-protected granule, the active pharmaceutical agent, and a release-controlling polymer comprising a polyethylene oxide polymer is granulated to form the solid dosage form pharmaceutical composition comprising a sustained release layer.

[0011] In another aspect of the disclosure, a method for the preparation of a solid dosage form pharmaceutical composition comprising oxycodone and acetaminophen is provided. The method comprises two steps. In one step, a mixture comprising the oxycodone and at least one excipient is granulated in a manner such that the amount of oxycodone exposed on the surface of the granule is substantially reduced thereby forming an oxycodone-protected granule. In the next step, a mixture comprising the oxycodone-protected granule, the acetaminophen, and a release-controlling polymer

comprising a polyethylene oxide polymer is granulated to form the solid dosage form pharmaceutical composition comprising a sustained release layer.

[00012] An additional aspect of the disclosure provides a method for the preparation of a bilayer tablet comprising a sustained release layer and an immediate release layer. The method comprises three steps. In a first step, a mixture comprising oxycodone or hydrocodone and at least one excipient is granulated in a manner such that the amount of oxycodone or hydrocodone exposed on the surface of granule is substantially reduced thereby forming a morphinan-protected granule. In the next step, a mixture comprising the morphinan-protected granule, the acetaminophen, and a release-controlling polymer comprising a polyethylene oxide polymer is granulated to form a sustained release layer. In the final step, a mixture comprising the morphinan-protected granule, the acetaminophen, and at least one excipient is granulated to form the immediate release layer.

[00013] Other features and iterations of the invention are described in more detail below.

DETAILED DESCRIPTION

[00014] The invention provides methods of preparing morphinan-protected granules by combining a morphinan with at least one excipient to form a mixture, and granulating the mixture. The resulting morphinan-protected granules have a physical structure that minimizes the amount of morphinan that is exposed on the surface of the granule. The morphinan-protected granules may stabilize the morphinan against various mechanisms of degradation such as oxidation by substantially decreasing the amount of morphinan exposed on the surface of the granule thereby reducing the degree of contact between the morphinan and the oxidative species in the environment surrounding the granules, including but not limited to carriers and residual water in the composition, and atmospheric oxygen and moisture.

[00015] In addition, if chemically protective excipients including but not limited to antioxidants and pH-adjusting agents are included in the excipient mixture forming the morphinan-protected granule, the morphinan contained within the granule is further protected against degradation. Any oxidative species contained in the environment

surrounding the morphinan-protected granules may react with the chemically protective excipients situated the granules before they can reach the morphinan.

[0016] The morphinan-protected granules may be prepared using any device known in the art, including but not limited to a high-shear wet granulator. The particular device used for granulation may affect the physical properties of the resulting granules, including but not limited to granule size, granule density, and granule porosity, all of which may influence the protective properties of the granule against degradation of the morphinan. Regardless of the granulation method used to form the granules, the distribution of morphinan and excipients within the granules is influenced by at least several factors including but not limited to the size of the morphinan particles relative to the excipient particles in the mixture prior to granulation, the chemical properties of the morphinan and excipients including but not limited to hydrophobicity and ionic charge, and the presence of excipients dissolved in the granulation solution used to prepare the granules.

[0017] The morphinan-protected granules prepared by the methods of the invention may be incorporated into a solid dose form of a pharmaceutical composition, including but not limited to tablet and capsule formulations. In addition to protection against degradation, the inclusion of the morphinan in the form of granules imparts several other advantageous aspects to the resulting composition. Because the morphinan in the granules is protected, the choice of carrier may be selected to satisfy constraints other than compatibility with the morphinan. Carriers in the composition may instead be selected based on factors including but not limited to the cost of the carrier, the desirable modified-release properties imparted by a particular carrier. Further, variation in the characteristics of the morphinan-protected granules including granule size, excipients included in the granules, and the physical structure of the granules may be used to control the release profile or other pharmacokinetic characteristics of pharmaceutical compositions.

[0018] Detailed descriptions of various embodiments of the morphinan protected granules, methods of preparing the morphinan protected granules, and solid dosage forms of pharmaceutical compositions that include the morphinan-protected granules are described in detail below.

(I) *Morphinan-Protected Granules*

[0019] The granules prepared by the methods of the invention stabilize the morphinan contained within the granules by substantially reducing the amount of morphinan exposed on the surface of the granule. In this regard, significantly less of the morphinan is in contact with any oxidative species in the environment outside of the granule, and may additionally provide chemical protection of the morphinan against degradation by surrounding the morphinan with chemically protective excipients including but not limited to antioxidants that are contained within the morphinan-protected granule. The physical structure of the morphinan-protected granule may influence the protective efficacy of the granule against degradation of the morphinan, and further influences the suitability of the granules for inclusion in various solid dose forms of pharmaceutical compositions, including but not limited to tablets and capsules.

(a) *Granule Structure*

[0020] The physical structure of the granule includes the morphinan dispersed within the excipient mixture and granulated in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced. The particular physical structure of any embodiment of a morphinan-protected granule is influenced by at least several factors related to the method of preparing the granules and the particular morphinan and excipients included in the granule. The influence of these factors on the physical structure of the granules is described in detail below.

[0021] In general, the physical structure of the granules may vary from an essentially random spatial distribution of the morphinan and excipients throughout the granules to a highly ordered distribution in which essentially all of the morphinan is contained within a sharply delineated interior region that is surrounded by an exterior region that contains essentially all of the excipients. In an embodiment, the amount of morphinan that is exposed at the surface of the granules is less than about 100% of the total weight of the morphinan in the granules. In other embodiments, the amount of morphinan that is exposed at the surface of the granules is less than about 95%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less

than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, and less than about 5% of the total weight of morphinan in the granule.

[0022] Excipients contained within the granule may provide additional protection against degradation of the morphinan by chemically interacting with degradative compounds surrounding or within the granule. For example, the effectiveness of the excipients at protecting the morphinans in the granule may be enhanced if at least one of the excipients includes but is not limited to an antioxidant, a chelating agent, or a pH-adjusting agent. Various embodiments of the excipients included in the granule are described in detail below.

[0023] The density and porosity of the exterior regions of the granules may influence the effectiveness of the exterior regions at protecting the morphinans in the granules from degradation. Exterior regions having higher densities and lower porosities may be more resistant to penetration by degradative compounds from outside the granule. The densities and porosities of the exterior regions of the granules may be influenced by at least several factors including but not limited to the particular morphinan and excipients included in the granule and the device used to prepare the granule. For example, a granule prepared using a high-shear wet granulator may have a higher density and lower porosity compared to a granule with a similar composition prepared using a fluid bed granulator.

[0024] The d_{90} of the granules in various embodiments may be selected based on the intended use of the granules, in particular the particular solid dosage form in which the granules are to be incorporated. The particular d_{90} of the granule may be influenced by a variety of factors including but not limited to the composition of the granule and the granulation device used to prepare the granules. The d_{90} of the granules may be larger for granule compositions having a higher proportion of excipients including but not limited to binders and fillers relative to other types of excipients.

[0025] In various embodiments, the granules may have an average d_{90} of less than about 2000 μm . In other embodiments, the granules may have an average d_{90} of less than about 1800 μm , less than about 1500 μm , less than about 1000 μm , less than about 900 μm , less than about 800 μm , less than about 700 μm , less than about 600 μm , less than about 500 μm , less than about 400 μm , less than about 300 μm , less than

about 200 μm , less than about 150 μm , and less than about 100 μm . In one exemplary embodiment in which the granules are to be incorporated in a solid dosage form including but not limited to a capsule, the granules may be less than about 1000 μm in average d_{90} . In another exemplary embodiment in which the granules are to be incorporated in a solid dosage form including but not limited to a tablet, the granules may be less than about 800 μm in average d_{90} . In yet another embodiment, the granules may range from about 150 μm to about 200 μm in average d_{90} .

(II) Granule Composition

[0026] The composition of the granules prepared using the methods of the invention include a morphinan and at least one excipient. The particular composition of the granules may influence a variety of properties of the granules including but not limited to the physical structure of the granules, the stability of the morphinan contained within the granule, and the suitability of the granules for incorporation into a particular dry dosage form of a pharmaceutical composition.

[0027] One aspect of the composition that may influence the physical structure of the granules is the d_{90} of the morphinan particles relative to the d_{90} of the excipient particles in the mixture that used to form the granules. As used herein, d_{90} represents the particle diameter at which 90% of the individual particles of a compound are smaller than the specified diameter. Without being bound to any particular theory, when a granulation device including but not limited to a low-shear wet granulator, a high-shear wet granulator, or a fluid bed granulator is used to granulate the mixture of the morphinan and at least one excipient, the compounds having a smaller d_{90} relative to the other compounds in the mixture tend to aggregate near the interior regions of the granules, and the compounds having larger d_{90} tend to aggregate near the exterior regions of the granules, regardless of whether the compound is a morphinan or an excipient.

[0028] As a practitioner skilled in the art may appreciate, for granule compositions in which the morphinan accounts for an extremely low proportion of the total mass of the granule, the size of the morphinan particles relative to the excipient particles may not exert the same influence on the physical structure of the resulting

granules as described previously. By way of a non-limiting example, if a granule is prepared using a mixture containing about 5% morphinan and about 95% excipients by weight, and the d_{90} of the morphinan is larger than the d_{90} of the excipients, the relative scarcity of the morphinan particles may result in a granule in which the individual morphinan particles are surrounded by excipient particles, and the morphinan particles may be located in both the interior region and the exterior region of the granule.

[0029] In one embodiment, the d_{90} of the morphinan is smaller than the d_{90} of the excipients. In another embodiment, the d_{90} of the morphinan is less than about 80% of the d_{90} of the excipients. In yet other embodiments, the d_{90} of the morphinan is less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, or less than about 50% of the d_{90} of the excipients.

[0030] The d_{90} values of the morphinan and the excipients may also be influenced by the capabilities of the particular device used to prepare the granules. Without being bound to any particular theory, when a granulation device including but not limited to a low-shear wet granulator, a high-shear wet granulator, or a fluid bed granulator is used to granulate the mixture of the morphinan and at least one excipient, if the d_{90} of a particular compound falls below a threshold d_{90} , the particles of that compound tend to aggregate before they are granulated, resulting in granules that have a non-homogenous distribution of the compound from granule to granule.

[0031] In other embodiments, other properties of the morphinan and excipients may influence the physical structure of the granule including but not limited to the hydrophobicity and ionic charge of the morphinan relative to the one or more excipients. As a non-limiting illustrative example, if the morphinan is hydrophobic relative to the excipients and if a polar granulation fluid is used in the granulation process, hydrophobic repulsive forces may tend to situate the morphinan within the interior region of the granules.

[0032] In one embodiment, the composition of the granules includes one morphinan compound. In other embodiments, the composition of the granules may further include one or more additional morphinan compounds within each granule. Any number of different morphinans may be included in the composition of the granules, so

long as all morphinans that are included in the granule are physically and chemically compatible.

[0033] An acid, as defined herein, refers to the acid and any pharmaceutically acceptable salt of the acid.

(a) *Morphinans*

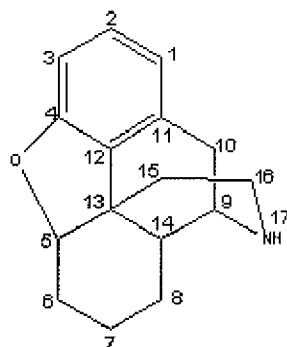
[0034] The compositions of various embodiments of the granules include a morphinan. In one embodiment, the morphinan may be included in the granules in an amount of up to about 90% of the total weight of the granules. In other embodiments, the morphinan may be included in the granules in an amount ranging up to about 80%, up to about 70%, up to about 60%, up to about 50%, up to about 40%, up to about 30%, up to about 20%, up to about 10%, up to about 1%, and up to about 0.5% of the total weight of the granules.

[0035] The morphinan included in various embodiments of the granules may be selected from opium, natural opium derivatives, semi-synthetic opium derivatives, and synthetic opium derivatives. Non-limiting examples of suitable morphinans for various embodiments of the granules include adulmine, allocryptopine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bulbocapnine, buprenorphine, butorphanol, canadine, capaurine, chelerythrine, chelidone, codamine, codeine, coptisine, coreximine, corlumine, corybulbine, corycavamine, corycavine, corydaline, corydine, corytuberine, cularine, cotarnine, cryptopine, cycloartenol, cycloartenone, cyclolaudenol, dehydroreticuline, desomorphine, dextropropoxyphene, dextrorphanol, diacetylmorphine, dicentrine, dihydrosanguinarine, dipropanoylmorphine, epiporphyroxine, ethylmorphine, eupaverine, fagarine, fentanyl, glaucine, homochelidonoine, hydrocodone, hydrocotarnine, hydromorphone, hydroxythebaine, isoboldine, isocorybulbine, isocorydine, isocorypalmine, isoquinoline, laudanidine, laudanine, laudanosine, levorphanol, magnoflorine, meconic acid, methadone, morphine, nalbuphine, nalmefene, naloxone, naltrexamine, α -naltrexol, β -naltrexol, naltrexone, naphthaphenanthridine, narceine, narceinone, narcotoline, narcotine, neopine, nicomorphine, norlaudanosoline, norsanguinarine, noscapine, opium, oripavine, oxycodone, oxymorphone, oxysanguinarine, palaudine, papaverine,

papaveraldine, papaverrubine, perparin, pethidine, phenanthrene, phtalide-isoquinoline, porphyroxine, protopine, pseudocodeine, pseudomorphine, reticuline, salutaridine, sinoacutine, sanguinarine, scoulerine, somniferine, stepholidine, tapentadol, tetrahydroprotoberberine, thebaine, tramadol, and xanthaline. In an exemplary embodiment, the morphinan included in the granules may be selected from oxycodone, oxymorphone, hydrocodone, hydromorphone, nalbuphine, naloxone, buprenorphine, and naltrexone. In another exemplary embodiment, the morphinan in the granules is oxycodone or hydrocodone.

[0036] Any of the morphinans included in the embodiments of the granules may have a (-) or (+) orientation with respect to the rotation of polarized light, depending upon whether the starting substrate has (-) or (+) optical activity, and are referred to herein as (-)-morphinans and (+)-morphinans respectively. More specifically, each chiral center may independently have an R or an S configuration.

[0037] As an illustrative example, an embodiment of the granules may include a morphinan compound possessing a fused carbon ring structure. The ring atoms of the morphinan compound may be numbered as diagrammed in Formula (I) below. Morphinan compounds have asymmetric centers and the core morphinan compound may have at least four chiral carbons including but not limited to C-5, C-13, C-14, and C-9. In various embodiments, the configuration of the chiral carbons C-5, C-13, C-14, and C-9 may be RRRR, RRSR, RRRS, RRSS, RSRR, RSSR, RSRs, RSSS, SRRR, SRSR, SRRS, SRSS, SSRR, SSSR, SSRS, or SSSS, provided that the C-15 and the C-16 carbons are both oriented either on the alpha face or the beta face of the morphinan molecule.



(I)

[0038] In various embodiments of the granules, the morphinan may be provided in any solid form including but not limited to a finely divided solid, a crystal, a particle, a powder, or any other finely divided solid form known in the art. Any finely divided solid form of the morphinan may be used so long as the d_{90} of the morphinan particles are smaller than the d_{90} of the one or more excipients as described above.

(b) Excipients

[0039] Various embodiments of the granules include one or more excipients in addition to the morphinan. In general, the one or more excipients are selected to impart at least one or more desired physical or chemical properties to the granules, including but not limited to adhesion of the particles of the morphinan and excipient compounds in the mixture to facilitate the formation of granules, formation of physical barriers around the morphinans in the granules, and chemical inhibition of various mechanisms of degradation of the morphinans including but not limited to oxidation. Non-limiting examples of the one or more excipients include binders, fillers, antioxidants, pH-adjusting agents, chelating agents, and antimicrobial agents.

[0040] In one embodiment, the one or more excipients may be introduced into the mixture to be granulated in a solid form including but not limited to a crystal, a particle, a powder, or any other finely divided solid form known in the art. In another embodiment, the one or more excipients may be dissolved or suspended in a solvent and sprayed onto the mixture in a granulation device as a binder fluid during granulation.

(i) binders

[0041] In general, binders are excipients included in various embodiments of the granule to impart structural integrity to the granules by binding together the particles making up each granule. Non-limiting examples of binders suitable for the formulations of various embodiments include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides,

oligopeptides, and combinations thereof. The polypeptides may be any arrangement of amino acids ranging from about 100 to about 300,000 Daltons.

[0042] In one embodiment, the binder may be introduced into the mixture to be granulated in a solid form including but not limited to a crystal, a particle, a powder, or any other finely divided solid form known in the art. In another embodiment, the binder may be dissolved or suspended in a solvent and sprayed onto the mixture in a granulation device as a binder fluid during granulation.

(ii) fillers

[0043] Fillers may be included in various embodiments of the granule composition as an excipient to increase the bulk volume of the granules and to impart suitable compressibility characteristics to the granules for subsequent inclusion in solid dosage forms of pharmaceutical compositions including but not limited to tablets. Non-limiting examples of fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. Other non-limiting examples of fillers include dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol.

(iii) antioxidants

[0044] Antioxidants are excipients included in various embodiments of the granules to prevent the oxidation of the morphinan in the granules. Suitable antioxidants include, but are not limited to anoxomer, N-acetylcysteine, benzyl isothiocyanate, m-aminobenzoic acid, o-aminobenzoic acid, p-aminobenzoic acid (PABA), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), caffeic acid, canthaxanthin, alpha-carotene, beta-carotene, beta-carotene, beta-apo-carotenoic acid, carnosol, carvacrol, catechins, chlorogenic acid, citric acid and its salts, clove extract, coffee bean extract, p-coumaric acid, 3,4-dihydroxybenzoic acid, N,N'-diphenyl-p-phenylenediamine (DPPD), dilauryl thiodipropionate, distearyl thiodipropionate, 2,6-di-tert-butylphenol, edetic acid, ellagic acid, erythorbic acid, sodium erythorbate, esculetin, esculin, 6-

ethoxy-1,2-dihydro-2,2,4-trimethylquinoline, ethyl maltol, ethylenediaminetetraacetic acid (EDTA) and EDTA salts, eucalyptus extract, eugenol, ferulic acid, flavonoids (e.g., catechin, epicatechin, epigallocatechin (EGC), flavones (e.g., apigenin, chrysin, luteolin), flavonols (e.g., datiscetin, myricetin, daemfero), flavanones, fraxetin, fumaric acid, gallic acid, gentian extract, gluconic acid, glycine, gum guaiacum, hesperetin, alpha-hydroxybenzyl phosphinic acid, hydroxycinnamic acid, hydroxyglutaric acid, hydroquinone, N-hydroxysuccinic acid, hydroxytyrosol, hydroxyurea, rice bran extract, lactic acid and its salts, lecithin, lecithin citrate; R-alpha-lipoic acid, lutein, lycopene, malic acid, maltol, 5-methoxy tryptamine, monoglyceride citrate; monoisopropyl citrate; morin, beta-naphthoflavone, nordihydroguaiaretic acid (NDGA), oxalic acid, palmityl citrate, phenothiazine, phosphatidylcholine, phosphoric acid, phosphates, phytic acid, phytilyubichromel, pimento extract, polyphosphates, quercetin, trans-resveratrol, rosemary extract, rosmarinic acid, sage extract, sesamol, silymarin, sinapic acid, succinic acid, stearyl citrate, syringic acid, tartaric acid, thymol, tocopherols (i.e., alpha-, beta-, gamma- and delta-tocopherol), tocotrienols (i.e., alpha-, beta-, gamma- and delta-tocotrienols), tyrosol, vanillic acid, 2,6-di-tert-butyl-4-hydroxymethylphenol (i.e., Ionox 100), 2,4-(tris-3',5'-bi-tert-butyl-4'-hydroxybenzyl)-mesitylene (i.e., Ionox 330), 2,4,5-trihydroxybutyrophenone, ubiquinone, tertiary butyl hydroquinone (TBHQ), thiodipropionic acid, trihydroxy butyrophenone, tryptamine, tyramine, uric acid, vitamin K and derivatives, vitamin Q10, wheat germ oil, zeaxanthin, or combinations thereof.

[0045] In another embodiment, an antioxidant agent may be subjected to a particle size reduction process including but not limited to grinding, milling, sonication, or hammer milling in order to reduce the d_{90} of the antioxidant agent to a value less than the d_{90} of the morphinan (or other API included in the formulation) prior to granulation. In this embodiment, the reduced d_{90} of the antioxidant agent may result in a distribution of antioxidant agent that is clustered around the morphinan particles, rather than near the outer surface of the granule. A granule having this physical structure may provide comparable protection of the morphinan in the granules against degradation as compared to granules in which the antioxidant agent is situated on the outside of the granule using a significantly lower amount of the antioxidant agent.

[0046] In an exemplary embodiment, the granule composition includes at least one antioxidant including but not limited to citric acid and Na₂EDTA.

(iv) *pH-adjusting agents*

[0047] In various embodiments of the granule composition, a pH-adjusting agent may be included as an excipient to raise or lower the pH of the granule in order to prevent the oxidation of the morphinan in the granules. For example, a pH-adjusting agent including but not limited to citric acid may be incorporated into the composition granule in order to lower the pH of the granule. In this example, a lower pH prevents the oxidation of the granule by various oxidative compounds associated with release-modifying polymer incorporated into a solid dosage form, including but not limited to peroxides.

[0048] In another embodiment, a pH-adjusting agent may be subjected to a particle size reduction process including but not limited to grinding, milling, sonication, or hammer milling in order to reduce the d₉₀ of the pH-adjusting agent to a value less than the d₉₀ of the morphinan prior to granulation. In this embodiment, the reduced d₉₀ of the pH-adjusting agent may result in a distribution of pH-adjusting agent that is clustered around the morphinan particles, rather than near the outer surface of the granule. Non-limiting examples of pH-adjusting agents include citric acid, acetic acid, tartaric acid, malic acid, fumaric acid, lactic acid, phosphoric acid, sorbic acid, benzoic acid, sodium carbonate and sodium bicarbonate.

(v) *chelating agents*

[0049] In various embodiments of the granule composition, a chelating agent may be included as an excipient to immobilize oxidative species including but not limited to metal ions in order to inhibit the oxidative degradation of the morphinan by these oxidative species. Non-limiting examples of chelating agents include lysine, methionine, glycine, gluconate, polysaccharides, glutamate, aspartate, and Na₂EDTA.

(vi) antimicrobial agents

[0050] In various embodiments of the granule composition, an antimicrobial agent may be included as an excipient to minimize the degradation of the morphinan by microbial agents including but not limited to bacteria and fungi. Non-limiting examples of antimicrobials include parabens, chlorobutanol, phenol, calcium propionate, sodium nitrate, sodium nitrite, Na₂EDTA and sulfites including but not limited to sulfur dioxide, sodium bisulfite, and potassium hydrogen sulfite.

(III) Granule Stability

[0051] In various embodiments of the granule composition, the morphinan in the granule is substantially resistant to degradation due to interactions of the morphinan with degradative compounds or conditions present in the environment or in the carriers surrounding the granules in a solid dosage form of a pharmaceutical composition. In one embodiment, the morphinan in the granules is substantially resistant to the formation of degradants resulting from a chemical change in the morphinan brought about during the production and/or storage of the pharmaceutical composition containing the morphinan by the effect of factors including but not limited to light, temperature, pH, water, or reaction with an excipient or carrier included in the pharmaceutical composition. The particular degradants formed in a pharmaceutical composition depend on the particular morphinan and the at least one excipient within the granule, as well as the particular carriers included in the pharmaceutical composition along with the granules.

[0052] Statutory requirements, including but not limited to ICH Guidelines Q3A and Q3B identify maximum allowable amounts of degradants above which the degradants must be reported and subjected to the qualification process described above. According to ICH Guideline Q3B, the amount of any individual degradant must be reported if the amount of degradant exceeds 0.10% of the total API weight for maximum daily doses of 1000 mg of API or below. For APIs having average daily doses of above 1000 mg, degradants in excess of 0.05% of the total API mass must be reported. The ICH guidelines apply throughout the effective shelf life of the pharmaceutical composition.

[0053] Although no standardized method of assessing API stability exists at present, drug developers typically subject potential pharmaceutical compounds to periods of storage at accelerated degradation conditions, typically defined as a temperature of about 40° C and a relative humidity of about 75%. The period of storage time at the accelerated degradation conditions may vary from about 1 day to about 6 months, but is typically about 6 months. In an embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5% of the total mass of the morphinan after about six months of storage at a temperature of about 40° C and a relative humidity of about 75%.

[0054] In an exemplary embodiment, for a pharmaceutical composition incorporating oxycodone as the morphinan and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C and 75% relative humidity. In another exemplary embodiment, for a pharmaceutical composition incorporating oxycodone and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of each of one or more degradants selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C and 75% relative humidity.

(IV) Method of Preparing Granules

[0055] In various embodiments, the granules may be prepared by combining the morphinan with at least one excipient to form a mixture and granulating the mixture in a manner such that the amount of morphinan exposed on the surface of the granules is minimized (thereby forming a morphinan-protected granule).

[0056] Suitable morphinans for the granule embodiments are described in detail in Section (IIa) above, and suitable excipients are described in Section (IIb) above. The mixture may be formed using any suitable method known in the art including but not limited to stirring, shaking, vibrating, and blending. In an embodiment, the morphinan and dry excipients may be charged into a granulation device and mixed prior to the addition of the granulation fluid.

[0057] Any suitable granulation device known in the art may be used to prepare the granules. As previously discussed, the particular granulation device selected for the preparation of the granules may influence the physical properties of the resulting granules. Non-limiting examples of suitable devices for the preparation of the granules include a low-shear wet granulator, a high-shear wet granulator, a fluid-bed granulator, a roller compactor, a vertical granulator, an oscillating granulator, a gelatinizer, a pelletizer, and a spheronizer. The granulation device may be selected in order to prepare granules having the desired granule physical characteristics described in Section (II) above.

[0058] In an exemplary embodiment, a high-shear wet granulator is used to prepare the granules. The high-shear wet granulator may be capable of preparing granules having properties that enhance the protective effect of the granule, including but not limited to higher granule densities and lower granule porosities relative to granules prepared by other devices. Further, the high-shear wet granulator is capable of preparing granules with a d_{90} that is larger than other granulation devices, resulting in granules suitable for inclusion in a wider variety of solid dosage forms of morphinan compositions.

[0059] In the same exemplary embodiment, the morphinan and the excipients in dry form of the composition are introduced into the wet high shear granulator in order to form the mixture. After the morphinan and the dry excipients are essentially homogeneously distributed within the granulator, a granulation fluid is sprayed into the granulator. In various embodiments, the granulation fluid may be any volatile, non-toxic granulation fluid known in the art. Non-limiting examples of suitable granulation fluids include water, ethanol, isopropanol, and combinations thereof. In other embodiments, one or more of the excipients may be mixed with the granulation fluid prior to spraying the granulation fluid into the granulator. In an exemplary embodiment, a binder including but not limited to pregelatinized starch may be dissolved into the granulation fluid including but not limited to water to form a granulation solution, and the granulation solution may be sprayed into the granulator in order to prepare the granules.

[0060] In an additional embodiment, the wet granules prepared in the high shear wet granulator may be dried using a drying device, resulting in dried granules having a

water content of less than about 2% of the total weight of the granules. Any suitable drying device known in the art may be used to dry the wet granules, including but not limited to an oven, a vacuum oven, and a rotary drum dryer.

(V) Solid Dosage Forms Incorporating Granules

[0061] The morphinan-protected granules prepared by various embodiments may be incorporated into various solid dosage pharmaceutical compositions. Non-limiting examples of solid dosage pharmaceutical compositions incorporating embodiments of the morphinan granules include granules, tablets, and capsules. Non-limiting embodiments of tablets include uncoated tablets, coated tablets, mini-tablets, orally disintegrating tablets, and bilayer tablets. Non-limiting embodiments of capsules include hard capsules and multi-layer capsules. Depending on the selection of particular formulation, the solid dosage pharmaceutical composition may have release characteristics including but not limited to rapid release, sustained release, extended release, slow release, time release, and combinations thereof.

[0062] In an exemplary embodiment, solid dosage form pharmaceutical compositions are made via a two step process. First, the morphinan-protected granule is formed. The morphinan-protected granule is then mixed with excipients and other active pharmaceutical ingredients, which are then granulated to form the solid dosage form pharmaceutical composition. The solid dosage form pharmaceutical composition may include additional APIs. In an exemplary embodiment, the solid dosage form pharmaceutical composition comprises a morphinan and acetaminophen. In additional embodiments, the solid dosage form pharmaceutical composition may comprise sustained release (SR) and immediate release layers (IR). Typically, the SR and IR layers both include the morphinan and acetaminophen. In each of the foregoing embodiments, the SR layer typically comprises a release-controlling polymer comprising a polyethylene oxide polymer.

(a) Compositions of Solid Dosage Forms

[0063] Various embodiments of the solid dosage pharmaceutical compositions incorporating the morphinan-protected granules may include one or more

pharmaceutically acceptable carriers in addition to the granules. Pharmaceutically acceptable carriers suitable for embodiments of the solid dosage pharmaceutical compositions may include but are not limited to binders, fillers, lubricants, diluents, non-effervescent disintegrants, effervescent disintegrants, flavor-modifying agents, sweeteners, dispersants, coloring agents, taste masking agents, release-controlling polymers and combinations thereof.

(i) binders

[0064] Non-limiting examples of binders suitable for the formulations of various embodiments include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof. The polypeptide may be any arrangement of amino acids ranging from about 100 to about 300,000 Daltons.

(ii) fillers

[0065] Non-limiting examples of fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. Other non-limiting examples of fillers include dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol.

(iii) lubricants

[0066] Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and light mineral oil.

(iv) *diluents*

[0067] Diluents suitable for use include but are not limited to pharmaceutically acceptable saccharides such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, and sorbitol; polyhydric alcohols; starches; pre-manufactured direct compression diluents; and mixtures of any of the foregoing.

(v) *non-effervescent and effervescent disintegrants*

[0068] Non-limiting examples of non-effervescent disintegrants include starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, and tragacanth. Suitable effervescent disintegrants include but are not limited to sodium bicarbonate in combination with citric acid, and sodium bicarbonate in combination with tartaric acid.

(vi) *flavor-modifying agents*

[0069] Suitable flavor-modifying agents include but are not limited to synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits, and combinations thereof. Other non-limiting examples of flavor-modifying agents include cinnamon oils, oil of wintergreen, peppermint oils, clover oil, hay oil, anise oil, eucalyptus, vanilla, citrus oils such as lemon oil, orange oil, grape and grapefruit oil, fruit essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, and apricot.

(vii) *sweeteners*

[0070] Non-limiting examples of sweeteners include glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; *Stevia rebaudiana* (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol,

mannitol, sylitol, hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof.

(viii) dispersants

[0071] Dispersants may include but are not limited to starch, alginic acid, polyvinylpyrrolidones, guar gum, kaolin, bentonite, purified wood cellulose, sodium starch glycolate, isoamorphous silicate, and microcrystalline cellulose as high HLB emulsifier surfactants.

(ix) coloring agents

[0072] Suitable coloring agents include but are not limited to food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors or dyes, along with their corresponding lakes, and certain natural and derived colorants may be suitable for use in various embodiments.

(x) taste-masking agents

[0073] Taste-masking agents include but are not limited to cellulose hydroxypropyl ethers (HPC) such as Klucel®, Nisswo HPC and PrimaFlo HP22; low-substituted hydroxypropyl ethers (L-HPC); cellulose hydroxypropyl methyl ethers (HPMC) such as Seppifilm-LC, Pharmacoat.RTM, Metolose SR, Opadry YS, PrimaFlo, MP3295A, Benecel MP824, and Benecel MP843; methylcellulose polymers such as Methocel® and Metolose®; Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel.RTM., Aqualon®-EC, Surelease; Polyvinyl alcohol (PVA) such as Opadry AMB; hydroxyethylcelluloses such as Natrosol®; carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aualon®-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® RD100, and Eudragit® E100; cellulose acetate phthalate; sepifilms such as mixtures of

HPMC and stearic acid, cyclodextrins, and mixtures of these materials. In other embodiments, additional taste-masking agents contemplated are those described in U.S. Pat. Nos. 4,851,226, 5,075,114, and 5,876,759, each of which is hereby incorporated by reference in its entirety.

(xi) *release-controlling polymers*

[0074] Release-controlling polymers may be included in the various embodiments of the solid dosage pharmaceutical compositions incorporating the granules. In one embodiment, the release-controlling polymers may be used as a tablet coating. In other embodiments, including but not limited to bilayer tablets, a release-controlling polymer may be mixed with the granules and other excipients prior to the formation of a tablet by a known process including but not limited to compression in a tablet mold. Suitable release-controlling polymers include but are not limited to hydrophilic polymers and hydrophobic polymers.

[0075] Suitable hydrophilic polymers include, but are not limited to, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose ethers, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, nitrocellulose, crosslinked starch, agar, casein, chitin, collagen, gelatin, maltose, mannitol, maltodextrin, pectin, pullulan, sorbitol, xylitol, polysaccharides, ammonia alginate, sodium alginate, calcium alginate, potassium alginate, propylene glycol alginate, alginate sodium carmellose, calcium carmellose, carrageenan, fucoidan, furcellaran, arabicgum, carrageensgum, ghaftigum, guar gum, karayagum, locust beangum, okragum, tragacanthgum, scleroglucangum, xanthangum, hypnea, laminaran, acrylic polymers, acrylate polymers, carboxyvinyl polymers, copolymers of maleic anhydride and styrene, copolymers of maleic anhydride and ethylene, copolymers of maleic anhydride propylene or copolymers of maleic anhydride isobutylene), crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, diesters of polyglucan, polyacrylamides, polyacrylic acid, polyamides, polyethylene glycols, polyethylene oxides, poly(hydroxyalkyl methacrylate), polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, polystyrenes, polyvinylpyrrolidone, anionic and cationic hydrogels, and combinations thereof.

[0076] Non-limiting examples of suitable hydrophobic polymers include cellulose acetate butyrate, cellulose acetate ethylcarbamate, cellulose acetate heptanoate, cellulose acetate methylcarbamate, cellulose acetate octanoate, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate succinate, cellulose acetate trimaleate, cellulose acetaldehyde dimethyl acetate, cellulose butyrate, cellulose dimethylaminoacetate, cellulose disuccinate, cellulose dipalmitate, cellulose dicaprylate, cellulose propionate, cellulose propionate succinate, cellulose trioctanoate, cellulose tripropionate, cellulose trimellitate, cellulose tripalmitate, cellulose trivalerate, cellulose valerate palmitate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, ethylhydroxy ethylcellulose, hydroxy propyl methylcellulose phthalate, methyl cellulose, methyl ethyl cellulose, propyl cellulose, sodium carboxymethyl starch, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, methacrylic acid copolymers, methacrylic acid ester copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylate), poly(methacrylate), poly(methyl methacrylate), poly(ethylacrylate), poly(ethyl methacrylate), poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, ammonio methacrylate copolymers, lecithins, aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, hydrogenated vegetable oil, 12-hydroxystearyl alcohol, glyceryl monopalmitate, glyceryl dipalmitate, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, myristyl alcohol, stearic acid, stearyl alcohol, polyethyleneglycols, zein, shellac, bee's wax, carnauba wax, glyceryl behenate, Japan wax, paraffin, spermaceti, synthetic waxes, and combinations thereof.

(b) *Methods of Producing Solid Dosage Forms*

[0077] The solid dosage pharmaceutical compositions may be produced using any suitable method known in the art. The particular production method selected may depend on the desired type of solid dosage form and the desired release profile.

(i) *production of tablet compositions*

[0078] The pharmaceutical compositions in the form of a tablet may be produced using any suitable method known in the art including but not limited to direct compression, wet granulation, dry granulation, and combinations thereof. In one embodiment, the morphinan-protected granules may be combined with the one or more carriers and granulated into tablet granules using any of the known granulation devices described previously. In this same embodiment, the tablet granules formed from the combination of the morphinan-protected granules and the one or more carriers may be optionally blended with one or more additional carriers including but not limited to lubricants, and the resulting tablet blend may be compressed into a tablet form. In another embodiment, one or more carriers incorporated into the tablet granules may include a release-controlling polymer to impart a modified release profile to the resulting tablet.

[0079] In yet another embodiment, a bilayer tablet may be formed by producing a first tablet blend and a second tablet blend using a tablet granulation and blending process similar to those previously described. In this embodiment, the first tablet blend may include a disintegrant in order to impart a rapid release profile to the resulting tablet produced using the first tablet blend. The second tablet blend of this embodiment may include a release-controlling polymer to impart a modified release profile to the resulting tablet produced using the second tablet blend. The first tablet blend and the second tablet blend may be loaded into a tableting device including but not limited to a bilayer tablet press, and pressed into a bilayer tablet in which the first layer may have a rapid release profile and the second layer may have a modified release profile.

[0080] In yet another embodiment, the morphinan-protected granules may be coated with a release-controlling polymer prior to incorporating the morphinan-protected granules into a solid tablet form in order to impart a modified release profile to the resulting tablet. In an additional embodiment, the solid tablet form may be coated with a release-controlling polymer to impart a modified release profile. Other combinations of the embodiments described above may be used to produce additional embodiments having a desired release profile or other desired performance characteristic including but not limited to masked taste, acceptable tongue-feel and mouth-feel, and enhanced stability.

(ii) *production of capsule compositions*

[0081] The pharmaceutical compositions in the form of a capsule may be produced using any suitable method known in the art including but not limited to direct loading into two-piece telescoping hard capsules. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, and hard cellulose capsules. In one embodiment, the capsule form of the pharmaceutical compositions may be produced by loading the morphinan-protected granules in to the hard capsule and sealing the capsule. In other embodiments, the morphinan-protected granules may be coated with a release-controlling polymer to impart a modified release profile to the hard capsule composition. In yet other embodiments, a fraction of the morphinan-protected granules may be coated with a release-controlling polymer and combined with the remaining uncoated morphinan-protected granules prior to loading the granules into the hard capsule.

(VI) *Exemplary Embodiments*

[0082] Exemplary embodiments of a granule and a solid dose pharmaceutical composition are described below.

(a) *Oxycodon-Protected Granule*

[0083] An exemplary embodiment of a granule includes oxycodone, microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid. The overall composition of the exemplary oxycodone-protected granule embodiment is listed in Table 2 below. In this embodiment, the granules may be formed using the wet granulation method described in Example 1 below. In this embodiment, the oxycodone granules have a granule d₉₀ ranging from about 100 μm to about 400 μm, and contain less than about 2% water by weight.

(b) *Bilayer Oxycodone/APAP Tablet*

[0084] An exemplary embodiment of a solid dose pharmaceutical composition may be a bilayer tablet that includes the oxycodone-protected granules described

above. The exemplary bilayer tablet may be formed using the method described in Example 2 below. The two layers of the bilayer tablet in this embodiment include an instant-release (IR) layer and a sustained release (SR) layer. The overall compositions of the IR layer and the sustained release layer of the exemplary bilayer tablet embodiment are listed in Table 1 below. The stability of the oxycodone in the exemplary bilayer tablet composition that incorporates oxycodone in a granular form is significantly better than a similar bilayer tablet composition that incorporates oxycodone in an unprotected powder form, as described in Example 2 below.

TABLE 1: Composition of Exemplary Bilayer Tablet Composition

Compound	Dry Wt. (% total)	
	IR Layer	SR Layer
Protected oxycodone granules	16.00%	7.4%
APAP	67.25%	42.5%
MCC	5.00%	
Hydroxypropyl cellulose	8.00%	2.4%
Cross carmellose sodium	3.00%	
Silicon dioxide	0.50%	0.5%
Magnesium stearate	0.25%	1.0%
MCC		1.2%
Polyethylene oxide polymer		45.0%

EXAMPLES

[0085] The following examples demonstrate various aspects of the invention.

Example 1: Incorporation of Protected Oxycodone Granules into Bilayer Tablet Composition

[0086] To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan granules into a solid dosage form, the following experiment was conducted.

[0087] Powdered oxycodone HCl, microcrystalline cellulose (MCC), and citric acid powder (an antioxidant) were mixed together and charged into a high-shear granulator. An aqueous solution containing pregelatinized starch (PGS) and Na₂EDTA (an antioxidant) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 2% water remained in the granules. The dried granules had particle sizes ranging from about 100 – 300 μ m. The composition of the protected oxycodone granules is summarized in Table 2:

TABLE 2: Composition of Protected Oxycodone Granules

Compound	Dry Weight (% tot. wt.)
Oxycodone HCl	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

[0088] The oxycodone-protected granules were divided into two groups to be incorporated into batches of instant release (IR) granules and into batches of sustained release (SR) granules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed protected oxycodone granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 3:

TABLE 3: Composition of IR and SR Granules

Compound	Dry Wt. (% total wt.)	
	IR Layer	SR Layer
Protected oxycodone granules	16.1%	14.2%
APAP	67.8%	81.2%
MCC	5.0%	
Hydroxypropyl cellulose	8.1%	4.5%
Cross carmellose sodium	3.0%	

[0089] The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 4:

TABLE 4: Composition of IR and SR Blends

Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	99.25%	
SR granules		52.30%
Silicon dioxide	0.50%	0.50%
Magnesium stearate	0.25%	0.10%
MCC		1.20%
Polyethylene oxide polymer		45.00%

[0090] The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 29% of the IR blend and about 71% the SR blend by weight.

[0091] The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Example 2: Oxidative Stability Assessment of Bilayer Tablet Composition

[0092] To assess the effect of incorporating a morphinan in the form of protected granules into a solid dosage therapeutic composition on the oxidative stability of the composition, the following experiment was conducted.

[0093] Unprotected bilayer tablets were formed using a process similar to that described in Example 1, except that powdered oxycodone HCl, rather than protected oxycodone granules, were incorporated into the IR and SR granules formed using the fluid bed granulation device. Protected bilayer tablets formed using protected oxycodone granules as described in Example 1 were also obtained. The unprotected bilayer tablets were similar in composition to the protected bilayer tablets, except that the unprotected bilayer tablets lacked antioxidant excipients and oxycodone-protected granules, although the overall oxycodone contents of the two formulations of bilayer tablet were comparable.

[0094] A batch of protected bilayer tablets and a batch of unprotected tablets were placed into an environmental chamber and exposed to accelerated stability conditions. In particular, all bilayer tablets were kept in the environmental chamber at a temperature of 55° C and a relative humidity of 80% for a period of six days. For the remainder of the first month and for the duration of a second month, the bilayer tablets were exposed to a temperature of 40° C and a relative humidity of 75%.

[0095] After six days, one month, and two months in the environmental chamber, samples of the protected and unprotected formulations were removed from the chamber and submitted to mass spectrographic analysis to determine the presence of three oxidative degradants of oxycodone: dihydroxy oxycodone, oxycodone n-oxide, and 10-hydroxy oxycodone. The results of these analyses are summarized in Table 5 below:

TABLE 5: Oxidative Stability of Unprotected vs. Protected Formulations of Bilayer Tablets

Degradation Conditions			Amount of Degradant Formed (% weight of oxycodone)					
			Di-hydroxy oxycodone		10-hydroxy oxycodone		Oxycodone n-oxide	
Time (days)	Temp. (° C)	Relative Humidity (%)	Not Protected	Protected	Not Protected	Protected	Not Protected	Protected
6	55	80	0.20	0.00	0.04	0.00	0.12	0.03
30	40	75	0.05	0.01	0.01	0.00	0.12	0.01
60	40	75	0.11	0.02	0.03	0.00	0.21	0.03

[0096] The protected formulation of the bilayer tablets that incorporated the oxycodone-protected granules had significantly lower levels of all degradants after exposure to all environmental conditions. No 10-hydroxy oxycodone was measured at any environmental condition for the protected formulation of the bilayer tablet.

[0097] The results of this experiment demonstrated that the formation of oxidative degradants of oxycodone was significantly inhibited by the incorporation of the oxycodone in the form of protected granules. In particular, the bilayer tablets formed using the protected oxycodone granules were significantly more stable than similar bilayer tablets formed using unprotected oxycodone powder.

Example 3: Effect of Granule Composition on Oxidative Stability

[0098] To assess the effect of various granule compositions on the oxidative stability of the morphinan encapsulated in the granules, the following experiment was conducted.

[0099] Granules containing oxycodone and various combinations of excipients were formed using methods similar to those described in Example 1. The specific compositions of the granules are summarized in Table 6:

TABLE 6: Composition of IR and SR Granules

Compound	Granule Composition (%w/w)				
	1	2	3	5	6
Oxycodone	30	30	30	30	30
MCC	65	64.95	62.2	64.95	62.2

HPC	5	4.6	4.6		
BHA		0.05		0.05	
EDTA		0.4	0.4	0.4	0.4
Ascorbic Acid			2.8		2.8
PGS				4.6	4.6

[0100] For granule compositions 1, 2, and 3 the HPC and EDTA were dissolved in a granulation solution and applied to a dry mixture of the remaining ingredients. For granule compositions 5 and 6, the PGS and EDTA were dissolved in a granulations solution and applied to a dry mixture of the remaining ingredients.

[0101] The resulting granules were stored at accelerated stability conditions for a period of 4 weeks at 40° C and 75% relative humidity. Samples of the granules were taken just before storage and after one, two, and four weeks of storage at accelerated stability conditions and subjected to mass spectrographic analysis as described in Example 2 to determine the presence of oxidative degradants of oxycodone. The results of the analyses of the samples taken after four weeks of storage are summarized in Table 7 below:

TABLE 7: Oxidative Stability of Granule Formulations

Compositi on	Impurity After 4 Weeks at Accelerated Degradation Conditions (% wt of oxycodone)	
	6-a-Oxycodol	Noroxycodone
1	0.11	0.01
2	0.11	0.02
3	0.33	0.13
5	0.11	0.00
6	0.29	0.14

[0102] The impurities for granule compositions 1, 2, and 5 were all of comparable low amounts, indicating that the granulation of the oxycodone resulted in a protective effect from oxidative degradation. This protective effect was achieved even in granule composition 1, which did not include any antioxidant excipients. However, granule compositions 3 and 6, which contained ascorbic acid, resulted in much higher levels of

oxidative impurities after 4 weeks of storage at accelerated stability conditions, indicating that the ascorbic acid may produce oxidative products that result in the long-term degradation of the oxycodone.

[0103] The results of this experiment demonstrated the protective effect of granulation against the oxidative degradation of oxycodone, so long as ascorbic acid was not included in the granule composition.

Example 4: Effect of Granulation Composition on Oxidative Stability of Solid Dose Oxycodone/APAP Formulations

[0104] To assess the effect of encapsulation on the oxidative stability of the morphinan in various solid dose formulations, the following experiment was conducted.

[0105] Solid dose tablets were formed using the methods described in Example 2. The solid dose tablets contained the oxycodone either in the protected granular form described in Example 3, or as the same ingredients in a powdered form rather than as granules. In both cases, the oxycodone and excipients were combined with APAP and polyethylene oxide (PEO) polymer. Each tablet contained 10% of the oxycodone granule compositions described in Example 3, in either granulated or powdered form, 46.8% APAP, and 43.2% PEO polymer on a weight basis.

[0106] The protected and unprotected tablet formulations were stored at accelerated stability conditions for a period of 4 weeks at 40° C and 75% relative humidity. Samples of the tablets were taken just before storage and after one, two, and four weeks of storage at accelerated stability conditions and subjected to mass spectrographic analysis as described in Example 2 to determine the presence of oxidative degradants of oxycodone. The results of these analysis of the samples taken after four weeks of storage are summarized in Table 8 below:

TABLE 8: Effect of Granulation on Oxidative Stability of Tablet Formulations

Compositi on Combined with APAP and PEO Polymer	Impurity After 4 Weeks at Accelerated Degradation Conditions (% wt of oxycodone)			
	6-a-Oxycodol		Noroxy	
	Protected granules	Unprotected	Protected Granules	Unprotected

1	0.20	.74	0.03	.27
2	0.22	.51	0.05	.28
3	0.60	1.25*	0.11	.14*
5	0.17	.49	0.01	.18

* measured at two weeks after storage

[0107] All of the protected tablet formulations, in which the oxycodone was granulated using methods similar to those described in Example 1 formed significantly lower levels of impurities after storage for 4 weeks at accelerated stability conditions compared to tablets containing non-granulated oxycodone and the same excipients

[0108] The results of this experiment demonstrated that granulating the oxycodone and excipients prior to incorporating the granules in a tableting process resulted in tablets with superior stability compared to tablets formed using the same oxycodone and excipients in a loose powder form, independent of the particular composition of excipients in the formulation.

[0109] Having described the invention in detail, it will be apparent that modifications and variations are possible. Those of skill in the art should, in light of the present disclosure, appreciate that many changes could be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth is to be interpreted as illustrative and not in a limiting sense.

CLAIMS

What is claimed is:

1. A method for the preparation of a solid dosage form pharmaceutical composition comprising a morphinan and at least one other active pharmaceutical ingredient, the method comprising:
 - (a) granulating a mixture comprising the morphinan and at least one excipient in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced thereby forming a morphinan-protected granule; and
 - (b) granulating a mixture comprising the morphinan-protected granule, the active pharmaceutical agent, a release-controlling polymer comprising a polyethylene oxide polymer to form the solid dosage form pharmaceutical composition comprising a sustained release layer.
2. The method of claim 1, wherein the active pharmaceutical agent is acetaminophen.
3. The method of claim 1, wherein the morphinan comprises up to about 90% of the total weight of the morphinan-protected granule formed in step (a).
4. The method of claim 1, wherein the morphinan is chosen from adulmine, allocryptopine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bulbocapnine, buprenorphine, butorphanol, canadine, capaurine, chelerythrine, chelidonine, codamine, codeine, coptisine, coreximine, corlumine, corybulbine, corycavamine, corycavine, corydaline, corydine, corytuberine, cularine, cotarnine, cryptopine, cycloartenol, cycloartenone, cyclolaudenol, dehydroreticuline, desomorphine, dextropropoxyphene, dextrorphanol, diacetylmorphine, dicentrine, dihydrosanguinarine, dipropanoylmorphine, epiporphyroxine, ethylmorphine, eupaverine, fagarine, fentanyl, glaucine, homochelidonine, hydrocodone, hydrocotarnine, hydromorphone, hydroxythebaine, isoboldine, isocorybulbine, isocorydine, isocorypalmine, isoquinoline, laudanidine, laudanine, laudanidine, levorphanol, magnoflorine, meconic acid, methadone, morphine, nalbuphine, nalmeferine, naloxone, naltrexamine, α -naltrexol, β -naltrexol, naltrexone, naphthaphenanthridine,

- narceine, narceinone, narcotoline, narcotine, neopine, nicomorphine, norlaudanoline, norsanguinarine, noscapine, opium, oripavine, oxycodone, oxymorphone, oxysanguinarine, palaudine, papaverine, papaveraldine, papaverrubine, perparin, pethidine, phenanthrene, phtalide-isoquinoline, porphyroxine, protopine, pseudocodeine, pseudomorphine, reticuline, salutaridine, sinoacutine, sanguinarine, scoulerine, somniferine, stepholidine, tapentadol, tetrahydroprotoberberine, thebaine, tramadol, and xanthaline.
5. The method of claim 1, wherein the d_{90} of the morphinan is less than the d_{90} of the excipient in the morphinan-protected granule, or the d_{90} of the morphinan is less than about 80% of the d_{90} of the excipient in the morphinan-protected granule.
 6. The method of claim 1, wherein less than about 90% of the morphinan is exposed on the surface of the morphinan-protected granules.
 7. The method of claim 1, wherein the morphinan-protected granules have a d_{90} of less than about 2000 micrometers.
 8. The method of claim 1, wherein the granulation in step (a) and (b) is done using a device chosen from a low-shear wet granulator, a high-shear wet granulator, a fluid-bed granulator, a roller compactor, a vertical granulator, an oscillating granulator, a gelatinizer, a pelletizer, a spheronizer, and combinations thereof.
 9. The method of claim 1, wherein the excipient in step (a) or (b) is chosen from a filler, an antioxidant, a pH-adjusting agent, a chelating agent, an antimicrobial agent, a release-controlling polymer, and combinations of any of the foregoing excipients.
 10. The method of claim 1, further comprising step (c) which includes granulating a mixture comprising the morphinan-protected granule, the active pharmaceutical agent, and at least one excipient to form an immediate release layer.
 11. The method of claim 1, wherein the morphinan is substantially resistant to oxidative degradation.
 12. The method of claim 1, wherein the solid dosage form pharmaceutical composition is chosen from granules, uncoated tablets, coated tablets, mini-

tablets, bilayer tablets, orally disintegrating tablets, hard capsules, and multilayer capsules.

13. The method of claim 1, wherein the morphinan is hydrocodone and the active pharmaceutical agent is acetaminophen.

14. A method for the preparation of a solid dosage form pharmaceutical composition comprising oxycodone and acetaminophen, the method comprising:
 - (a) granulating a mixture comprising the oxycodone and at least one excipient in a manner such that the amount of oxycodone exposed on the surface of the granule is substantially reduced thereby forming an oxycodone-protected granule; and
 - (b) granulating a mixture comprising the oxycodone-protected granule, the acetaminophen, and a release-controlling polymer comprising a polyethylene oxide polymer to form the solid dosage form pharmaceutical composition comprising a sustained release layer.
15. The method of claim 14, wherein the oxycodone comprises up to about 90% of the total weight of the oxycodone-protected granule formed in step (a).
16. The method of claim 14, wherein the d_{90} of the oxycodone is less than the d_{90} of the excipient in the oxycodone-protected granule, or the d_{90} of the oxycodone is less than about 80% of the d_{90} of the excipient in the oxycodone-protected granule.
17. The method of claim 14, wherein less than about 90% of the oxycodone is exposed on the surface of the oxycodone-protected granules.
18. The method of claim 14, wherein the oxycodone-protected granules have a d_{90} of less than about 2000 micrometers.
19. The method of claim 14, wherein the granulation in step (a) and (b) is done using a device chosen from a low-shear wet granulator, a high-shear wet granulator, a fluid-bed granulator, a roller compactor, a vertical granulator, an oscillating granulator, a gelatinizer, a pelletizer, a spheronizer, and combinations thereof.
20. The method of claim 14, wherein the excipient in step (a) or (b) is chosen from a filler, an antioxidant, a pH-adjusting agent, a chelating agent, an antimicrobial agent, a release-controlling polymer, and combinations of any of the foregoing excipients.

21. The method of claim 14, further comprising step (c) which includes granulating a mixture comprising the oxycodone-protected granule, the acetaminophen, and at least one excipient to form an immediate release layer.
22. The method of claim 14, wherein the oxycodone is substantially resistant to oxidative degradation.
23. The method of claim 14, wherein the solid dosage form pharmaceutical composition contains less than about 0.5 % w/w of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C and 75% relative humidity.
24. The method of claim 14, wherein the solid dosage form pharmaceutical composition contains less than about 0.5 % w/w of each of any one or more degradants selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C and 75% relative humidity.
25. The method of claim 14, wherein the solid dosage form pharmaceutical composition is chosen from granules, uncoated tablets, coated tablets, mini-tablets, mini-tablets, bilayer tablets, orally disintegrating tablets, hard capsules, and multilayer capsules.
26. The method of claim 23, wherein the solid dosage form pharmaceutical composition is a bilayer tablet.
27. The method of claim 26, wherein the excipients in step (a) comprise at least one antioxidant, binder, and diluent, the excipients in step (b) comprise binder and glidant, and the excipients in step (c) comprise binder, glidant, disintegrant, and lubricant.
28. A method for the preparation of a bilayer tablet comprising a sustained release layer and an immediate release layer, the method comprising:
 - (a) granulating a mixture comprising oxycodone or hydrocodone and at least one excipient in a manner such that the amount of oxycodone or hydrocodone exposed on the surface of granule is substantially reduced thereby forming a morphinan-protected granule;

- (b) granulating a mixture comprising the morphinan-protected granule, the acetaminophen, and a release-controlling polymer comprising a polyethylene oxide polymer to form the sustained release layer; and
- (c) granulating a mixture comprising the morphinan-protected granule, the acetaminophen, and at least one excipient to form the immediate release layer.