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(54) **PHARMACEUTICAL COMPOSITIONS OF DISPERSIONS OF AMORPHOUS DRUGS MIXED WITH POLYMERS**

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This patent is subject to a terminal disclaimer.

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(60) Provisional application No. 60/300,261, filed on Jun. 22, 2001.

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(58) **Field of Classification Search**
USPC 424/400, 489, 485, 486, 487; 514/313, 514/772.2, 781, 772.3, 772.5
See application file for complete search history.

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(57) **ABSTRACT**

A pharmaceutical composition comprises a dispersion comprising a low-solubility drug and a matrix combined with a concentration-enhancing polymer. At least a major portion of the drug is amorphous in the dispersion. The compositions improve the stability of the drug in the dispersion, and/or the concentration of drug in a use environment.

15 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS OF DISPERSIONS OF AMORPHOUS DRUGS MIXED WITH POLYMERS

This application is a divisional of U.S. application Ser. No. 12/217,700, filed Jul. 8, 2008 now U.S. Pat. No. 8,236,328, which is a continuation of U.S. application Ser. No. 10/175,640, filed Jun. 19, 2002 now abandoned, which is a nonprovisional of U.S. Patent Application Ser. No. 60/300,261 filed Jun. 22, 2001, the priority of all of which is claimed pursuant to 35 USC 120.

BACKGROUND OF THE INVENTION

The invention relates to compositions of a dispersion comprising amorphous drug and a matrix combined with a concentration-enhancing polymer that improves the stability of the drug and/or enhances the concentration of the drug in a use environment.

Low-solubility drugs often show poor bioavailability or irregular absorption, the degree of irregularity being affected by factors such as dose level, fed state of the patient, and form of the drug. Increasing the bioavailability of low-solubility drugs has been the subject of much research. Increasing bioavailability hinges on improving the concentration of the drug in solution to improve absorption.

It is well known that the amorphous form of a low-solubility drug that is capable of existing in either the crystalline or amorphous form may temporarily provide a greater aqueous concentration of drug relative to the equilibrium concentration obtained by dissolution of drug in a use environment. Such amorphous forms may consist of the amorphous drug alone, a dispersion of the drug in a matrix material, or the drug adsorbed onto a substrate. It is believed that such amorphous forms of the drug may dissolve more rapidly than the crystalline form, often dissolving faster than the drug can precipitate from solution. As a result, the amorphous form may temporarily provide a greater-than equilibrium concentration of drug.

While such amorphous forms may show initially enhanced concentration of the drug in a use environment, nevertheless the improved concentration is often short-lived. Typically, the initially enhanced drug concentration is only temporary and quickly returns to the lower equilibrium concentration.

One approach to increase the bioavailability of low-solubility drugs has involved forming amorphous dispersions of drugs with polymers. Examples of attempts to increase drug concentration by forming a dispersion of the drug with a polymer include Lahr et al., U.S. Pat. No. 5,368,864, Kanikanti et al., U.S. Pat. No. 5,707,655, and Nakamichi et al., U.S. Pat. No. 5,456,923.

Curatolo et al., EP 0901786A2, disclose solid amorphous dispersions of poorly water soluble drugs and hydroxypropylmethyl cellulose acetate succinate (HPMCAS). In one embodiment, HPMCAS is a dispersion polymer. Alternatively, a dispersion may be formed of a drug and conventional matrix material such as PVP, HPC or HPMC and then the dispersion is triturated with HPMCAS.

One problem with using the amorphous form of a drug is that the solid drug may not be stable physically in the amorphous form. Often the crystalline form of the drug has a lower free energy, and thus over time, the amorphous drug will tend to crystallize. The rate of crystallization may be influenced by storage conditions, such as temperature and humidity, as well as the constituents of the composition.

polymer and drug may in some cases be unstable. For example, the dispersion may be physically unstable, causing the amorphous drug to separate from the dispersion and/or crystallize. Alternatively, the drug in the amorphous dispersion may be chemically unstable. The drug may degrade over time at moderate temperature and humidity levels or the drug may convert to a lower energy and lower solubility amorphous or crystalline form.

Alternatively, it may be difficult or, in some cases, impossible to form a dispersion of the drug and preferred polymer. In particular, the drug and preferred polymer may not both be amenable to a processing method that results in a dispersion of the drug and preferred polymer. For example, when solvent processing is the preferred method for forming the dispersion, the drug and preferred polymer may not both be soluble to a sufficient extent in an appropriate processing solvent to allow formation of the dispersion. In cases where melt processing is preferred, the drug or polymer or both may suffer unacceptable decomposition upon heating to allow the formation of the preferred composition to be practical.

Accordingly, what is still desired is a composition comprising an amorphous drug that is physically and/or chemically stable under typical storage conditions, may be formed via practical processing conditions, and that may enhance the bioavailability of poorly soluble drugs. These needs and others that will become apparent to one of ordinary skill are met by the present invention, which is summarized and described in detail below.

BRIEF SUMMARY OF THE INVENTION

The present invention, in one aspect, relates to pharmaceutical compositions comprising: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer; wherein said composition provides improved stability of said drug relative to at least one of a first control composition consisting of a mixture of said low-solubility drug in undispersed amorphous form and said concentration-enhancing polymer, and a second control composition consisting of a dispersion of said low-solubility drug and said concentration-enhancing polymer.

In a second aspect, the present invention relates to pharmaceutical compositions comprising: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer; wherein at least 10 wt % of said matrix is non-polymeric.

In a third aspect, the present invention relates to pharmaceutical compositions comprising: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer; wherein said concentration-enhancing polymer is non-cellulosic.

In a fourth aspect, the present invention relates to pharmaceutical compositions, comprising: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dis-

enhancing polymer is selected from the group consisting of non-ionizable cellulosic polymers and neutralized acidic polymers.

In a fifth aspect, the present invention relates to pharmaceutical compositions, comprising: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer, wherein said concentration-enhancing polymer is an ionizable cellulosic polymer having at least one of an ester-linked carboxylic acid-functional aromatic substituent and an ether-linked carboxylic acid-functional aromatic substituent.

In a sixth aspect, the present invention relates to pharmaceutical compositions, comprising: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; (b) an amphiphilic, cellulosic concentration-enhancing polymer, said dispersion being free from at least a portion of said amphiphilic, cellulosic concentration-enhancing polymer; (c) said amphiphilic cellulosic concentration-enhancing polymer having at least one hydrophobic substituent selected from the group consisting of ether-linked alkyl substituents, ester-linked alkyl substituents, ether-linked aryl substituents and ester-linked aryl substituents; (d) said amphiphilic cellulosic concentration-enhancing polymer having at least one hydrophilic substituent selected from the group consisting of ether-linked hydroxy alkyl substituents, ester-linked hydroxy alkyl substituents, alkyl ether groups, ester-linked ionizable substituents, and ether-linked ionizable substituents; and (e) provided that when said concentration-enhancing polymer has both the hydrophilic substituents hydroxypropyl and succinate, said polymer is free from both an ether-linked methyl substituent and an ester-linked acetate substituent.

In a preferred embodiment, the drug has improved physical stability in said composition relative to said first control composition.

In another preferred embodiment, at least a major portion of said drug is dissolved in said matrix.

In another preferred embodiment, the drug has a solubility in said matrix that is at least 30% of a concentration of said drug in said matrix.

In another preferred embodiment, the drug has a weight ratio to said matrix of said dispersion of less than 20.

In yet another preferred embodiment, the dispersion has a glass transition temperature that is greater than a glass transition temperature of at least one of said low-solubility drug in undispersed amorphous form and said second control composition.

In another preferred embodiment, the dispersion has a glass transition temperature that is greater than about 50° C. at 50% relative humidity.

In another preferred embodiment, the drug in said dispersion has a crystallization rate that is less than 90% of a crystallization rate of said drug in undispersed amorphous form.

In another preferred embodiment, the drug in said composition has a relative degree of improvement in chemical stability of at least 1.25 relative to at least one of said first control composition and said second control composition.

In still another preferred embodiment, the drug is acid-sensitive and said concentration-enhancing polymer is acidic.

In another preferred embodiment, the drug in said composition consisting of a mixture of said low-solubility drug in undispersed amorphous form and said concentration-enhancing polymer, and a second control composition comprising a dispersion of said drug and said concentration-enhancing polymer.

In another preferred embodiment, at least 10 wt % of said matrix is non-polymeric. Preferred components of said matrix are selected from the group consisting of alcohols, organic acids, organic bases, amino acids, sugars, fatty acid esters, alkyl sulfates, phospholipids, waxes and salts.

In yet another preferred embodiment, the matrix has at least one polymeric component. Preferred components of said matrix are selected from the group consisting of polyethylene glycols, polyoxyethylene glycols, polyethylene-polypropylene glycol copolymers, polyethylene oxides, polyvinylpyrrolidone, polyvinyl alcohols, polyethylene-vinyl alcohol copolymers, polyvinyl alcohol polyvinyl acetate copolymers, carboxylic acid-functionalized polymethacrylates, amine-functionalized polymethacrylates, proteins, xanthan gum, carrageenan, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxy methyl cellulose, chitosan, chitin, polydextrose, dextrin and starch.

In another preferred embodiment, the drug is substantially amorphous in said dispersion.

In another preferred embodiment, the dispersion is substantially homogeneous.

In another preferred embodiment, the dispersion is completely homogeneous.

In another preferred embodiment, the composition is a solid mixture in which said concentration-enhancing polymer is suspended as a separate phase within said dispersion.

In another preferred embodiment, the composition is a mixture of particles of dispersion and particles of concentration-enhancing polymer.

In another preferred embodiment, the mixture is formed by at least one of dry-granulation and wet-granulation.

In another preferred embodiment, the dispersion and said concentration-enhancing polymer are each in separate regions.

In another preferred embodiment, the compositions further comprise a blend of concentration-enhancing polymers selected from the group consisting of ionizable cellulosic polymers, non-ionizable cellulosic polymers, ioniziable non-cellulosic polymers, non-ionizable non-cellulosic polymers, and neutralized acidic polymers.

In still another preferred embodiment, the concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

In another preferred embodiment, the concentration-enhancing polymer is an ionizable cellulosic polymer such as polymers selected from the group consisting of hydroxypropyl methyl cellulose succinate, cellulose acetate succinate, methyl cellulose acetate succinate, ethyl cellulose acetate succinate, hydroxypropyl cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate succinate, hydroxypropyl cellulose butyrate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl

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In another preferred embodiment, the concentration-enhancing polymer is a non-ionizable cellulosic polymer, such as polymers selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose, and blends thereof.

In another preferred embodiment, the concentration-enhancing polymer is an ionizable, non-cellulosic polymer, such as polymers selected from the group consisting of carboxylic acid functionalized polymethacrylates, carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates, amine-functionalized polymethacrylates, proteins, and carboxylic acid functionalized starches, and blends thereof.

In another preferred embodiment, the concentration-enhancing polymer is a non-ionizable, non-cellulosic polymer such as polymers selected from the group consisting of vinyl polymers and copolymers having at least one substituent selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido; vinyl copolymers of at least one hydrophilic, hydroxyl-containing repeat unit and at least one hydrophobic, alkyl- or aryl-containing repeat unit; polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed form, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol polypropylene glycol copolymers, polyvinyl pyrrolidone, and polyethylene polyvinyl alcohol copolymers, and blends thereof.

In yet another preferred embodiment, the concentration-enhancing polymer is selected from the group consisting of hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, ethyl picolinic acid cellulose acetate, carboxy methyl cellulose, carboxy ethyl cellulose, ethyl carboxy methyl cellulose, and blends thereof.

In another preferred embodiment, the amphiphilic, cellu-

nate, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxyethyl methyl cellulose, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate, and blends thereof.

In still another preferred embodiment, at least a portion of said concentration-enhancing polymer is neutralized. In other preferred embodiments, concentration-enhancing polymer is a neutralized acidic polymer.

In still another preferred embodiment, the composition when administered to a use environment provides a dissolution area under the concentration versus time curve for a time period of at least 90 minutes during the 270 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition comprising an equivalent amount of undispersed amorphous drug alone.

In another preferred embodiment, the composition when administered to a use environment provides a maximum concentration of said drug in said use environment that is at least 1.25-fold a maximum concentration of said drug provided by a control composition comprising an equivalent amount of undispersed amorphous drug alone.

In another preferred embodiment, the composition when administered to an animal provides a relative bioavailability of at least 1.25 relative to a control composition comprising an equivalent amount of undispersed amorphous drug alone.

In another preferred embodiment, the composition when administered to a use environment provides a dissolution area under the concentration versus time curve for a time period of at least 90 minutes during the 270 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition comprising an equivalent amount of said dispersion but with no concentration-enhancing polymer.

In another preferred embodiment, the composition when administered to a use environment provides a maximum concentration of said drug in said use environment that is at least 1.25-fold a maximum concentration of said drug provided by a control composition comprising an equivalent amount of said dispersion but with no concentration-enhancing polymer.

of at least 1.25 relative to a control composition comprising an equivalent amount of said dispersion but with no concentration-enhancing polymer.

In another preferred embodiment, the drug is selected from the group consisting of antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, anti-atherosclerotic agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

In another preferred embodiment, the drug is a glycogen phosphorylase inhibitor selected from the group consisting of [R—(R*S*)]-5-chloro-N-[2-hydroxy-3-{methoxymethylamino}-3-oxo-1-(phenylmethyl)propyl-1H-indole-2-carboxamide and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl-)-3-oxypropyl]amide.

In another preferred embodiment, the drug is a cholesterol ester transfer protein inhibitor selected from the group consisting of [2R,4S]-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, [2R,4S]-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, and [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

In a seventh aspect, the present invention relates to methods of administering a drug comprising co-administering to a patient in need of said drug: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer; wherein said dispersion provides improved stability of said drug relative to at least one of a first control composition consisting of a mixture of said low-solubility drug in undispersed amorphous form and said concentration-enhancing polymer, and a second control composition consisting of a dispersion of said low-solubility drug and said concentration-enhancing polymer.

In a preferred embodiment, the dispersion is administered separately from said concentration-enhancing polymer.

In another preferred embodiment, the dispersion and said concentration-enhancing polymer are administered at approximately the same time.

In another preferred embodiment, the dispersion and said concentration-enhancing polymer are present in a single dosage form.

The present invention also relates to, in an eighth aspect, methods of administering a drug comprising co-administering to a patient in need of said drug: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer;
wherein at least 10 wt % of said matrix is non-polymeric.

In a ninth aspect, the present invention relates to methods a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer; wherein said concentration-enhancing polymer is non-cellulosic.

In a tenth aspect, the present invention relates to methods of administering a drug comprising co-administering to a patient in need of said drug: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer, wherein said concentration-enhancing polymer is selected from the group consisting of non-ionizable cellulosic polymers and neutralized acidic polymers.

In an eleventh aspect, the present invention relates to methods of administering a drug comprising co-administering to a patient in need of said drug: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; and (b) a concentration-enhancing polymer, said dispersion being free from at least a portion of said concentration-enhancing polymer, wherein said concentration-enhancing polymer is an ionizable cellulosic polymer having at least one of an ester-linked carboxylic acid-functional aromatic substituent and an ether-linked carboxylic acid-functional aromatic substituent.

In a twelfth aspect, the present invention relates to methods of administering a drug comprising co-administering to a patient in need of said drug: (a) a solid dispersion comprising a low-solubility drug and a matrix, wherein at least a major portion of said drug in said dispersion is amorphous; (b) an amphiphilic, cellulosic concentration-enhancing polymer, said dispersion being free from at least a portion of said amphiphilic, cellulosic concentration-enhancing polymer; (c) said amphiphilic cellulosic concentration-enhancing polymer having at least one hydrophobic substituent selected from the group consisting of ether-linked alkyl substituents, ester-linked alkyl substituents, ether-linked aryl substituents and ester-linked aryl substituents; (d) said amphiphilic cellulosic concentration-enhancing polymer having at least one hydrophilic substituent selected from the group consisting of ether-linked hydroxy alkyl substituents, ester-linked hydroxy alkyl substituents, alkyl ether substituents, ester-linked ionizable substituents, and ether-linked ionizable substituents; and (e) provided that when said concentration-enhancing polymer has both the hydrophilic substituents hydroxypropyl and succinate, said polymer is free from both an ether-linked methyl group and an ester-linked acetate group.

The solid compositions of the present invention are combinations comprising (1) a dispersion of a low-solubility drug and matrix and (2) concentration-enhancing polymer(s). "Combination" as used herein means that the drug/matrix dispersion and concentration-enhancing polymer may be in physical contact with each other or in close proximity but are not mixed at the molecular level so as to form a solid molecular dispersion. In other words, although the drug/matrix dispersion and the concentration-enhancing polymer may be mixed, they remain as separate phases retaining their own physical properties such as melting points or glass-transition temperatures. Thus, the dispersion of the drug and matrix is free from at least a portion, if not all, of the concentration-enhancing polymer.

Alternatively, the drug/matrix dispersion and concentra-

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