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(54) Title: MODIFIED RELEASE ABUSE DETERRENT TABLET

(57) Abstract: The invention relates to a modified release abuse deterrent tablet and a method for preparing the modified release abuse deterrent tablet.

MODIFIED RELEASE ABUSE DETERRENT TABLET

FIELD OF THE INVENTION

The present invention relates to the field of solid oral dosage forms and in particular solid modified release tablets that contain a drug which is subject to abuse. The solid modified release tablets of the present invention contain a plurality of layers or coatings wherein at least one layer or coating comprises a drug which is subject to abuse and at least one polyethylene oxide.

BACKGROUND OF THE INVENTION

Although pharmaceutical dosage forms are designed to be safe and effective in the treatment of various afflictions, they are sometimes misused and subject to illicit use and/or abuse by individuals. Some of the more commonly misused pharmaceutical dosage forms contain opioids, sedatives, stimulants and hypnotics. One of the more common illicit practices is to obtain solid dosage forms such as tablets or capsules and manipulate the solid dosage form, typically by crushing the solid dosage form, to extract the drug and thereby allow the drug to be administered by inhalation or injection.

Due to the increased illicit use of pharmaceutical products there has been an effort to design solid oral dosage forms that will hopefully deter or prevent their misuse and abuse. For example, U.S. Published Patent Application Nos. 2005/0031546; 2009/0081290; 2012/0164220 and 2013/0320592 describe crush resistant opioid dosage forms that contain polyethylene oxide. U.S. Published Patent Application No. 2010/0015223 describes hard opioid matrix tablets that release the opioid drug over extended periods of time and that are difficult to crush.

Polyethylene oxide is a water-soluble resin widely used in the pharmaceutical industry to prepare gastro-retentive tablets, creams, ointments, coatings and abuse deterrent solid oral formulations. Polyethylene oxide is nonionic and commercially available in a wide range of molecular weights which exhibit lubricity, binding, water retention, thickening, thermoplastic and film formation properties. As a thermoplastic material, polyethylene oxide is readily calendared, extruded, injection molded, or casted to form various dosage forms.

Currently, various technologies using polyethylene oxide to prepare abuse deterrent solid oral dosage forms are described in the art, such as hot melt granulation as disclosed in U.S. Patent Nos. 8,114,383; 8,309,060 and 8,337,888, tablet compression and curing of the

formed tablet at elevated temperatures as disclosed in U.S. Published Patent Application No. 2013/025 1802, and injection molding as disclosed in U.S. Patent Nos. 8,603,526; 8,808,745 and 8,821,928. The hot melt and injection molding technologies are complicated and expensive techniques. Due to the complex nature, these methods typically are used to prepare dosage forms that comprise a monolithic or single matrix which exhibit a zero order release profile. These monolithic or single matrix solid formulations cannot provide an initial or immediate release of a therapeutic level of drug followed by a controlled or sustained release of the drug for 8-24 hours. To obtain the initial or immediate release of a therapeutic level of drug from the monolithic or single matrix solid formulations, an immediate release drug coating or layer must be applied to the monolithic or single matrix. Unfortunately, the immediate release drug coating can be easily removed and thereby misused or abused. These monolithic or single matrix solid formulations are also difficult to customize to obtain non-zero order release profiles such as a first order, second order or variations thereof.

There is a need for a simplified manufacturing process for preparing modified release tablets with customizable drug release alternatives that is capable of deterring misuse and abuse. The present invention addresses this need, and others.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an improved abuse deterrent solid oral dosage form that is safe, effective and easy to manufacture.

It is a further object of the present invention to provide a modified release abuse deterrent tablet and a method for manufacturing the abuse deterrent tablet wherein the abuse deterrent tablet can release therapeutic amounts of the drug within 60 minutes, preferably within 45 minutes and most preferably within 30 minutes and provide for controlled or sustained release of the drug for 8-24 hours after administration or in vitro dissolution testing.

Embodiments of the modified release abuse deterrent tablets prepared in accordance with the present invention comprise a plurality of layers and/or coatings, i.e., more than one layers and/or coatings, such as two layers and a coating or two, three, four or more layers wherein each layer or coating that comprises a drug that is subject to abuse also comprises at least one polyethylene oxide. The polyethylene oxide employed in drug containing layers or coatings should have an approximate molecular weight of about 50,000 to about 15,000,000 and preferably about 100,000 to about 7,000,000. The polyethylene oxide employed in each

drug containing layer or coating may be a mixture of two or more polyethylene oxides with different approximate molecular weights. When two or more polyethylene oxides with different approximate molecular weights are employed in a layer or coating, the average approximate molecular weight of the combination of polyethylene oxides should be about 50,000 to about 15,000,000 and preferably about 100,000 to about 7,000,000.

Embodiments of the modified release abuse deterrent tablets prepared in accordance with the present invention may be manufactured using conventional pharmaceutical processes such as wet granulation, dry granulation, or blending to prepare mixtures of the drug that is subject to abuse and at least one polyethylene oxide, compressing the mixtures comprising the drug that is subject to abuse and the at least one polyethylene oxide into a multilayered/coated tablet, and curing the multilayered/coated tablet at an elevated temperature.

The release rate of the drug that is subject to abuse from the modified release abuse deterrent tablets can be tailored to achieve a desired initial burst or immediate release of a therapeutic amount of the drug that is subject to abuse as well as to control or sustain the release of the drug that is subject to abuse over 8-24 hours by employing various amounts and/or various molecular weight polyethylene oxides in each layer of the multilayered/coated tablets. Embodiments of the present invention can obtain the desired initial burst or immediate release of a therapeutic amount of the drug that is subject to abuse by any conventional means known in the pharmaceutical formulation arts such as by applying an immediate release layer or coating to the multilayered/coated modified release abuse deterrent tablets, however, the desired initial burst or immediate release of a therapeutic amount of the drug that is subject to abuse can be obtained by incorporating one or more layers or coatings into the multilayered/coated modified release abuse deterrent tablets wherein the layer or coating providing the desired initial burst or immediate release comprises a mixture of a drug that is subject to abuse and at least one polyethylene oxide.

In an alternative embodiment, modified release abuse deterrent tablets that exhibit a desired initial burst or immediate release of a therapeutic amount of the drug that is subject to abuse employ a plurality of layers or coatings wherein each layer or coating that contains a drug that is subject to abuse also contains at least one polyethylene oxide. These alternative embodiments are free from any drug layer or coating that does not also employ at least one polyethylene oxide.

The modified release abuse deterrent tablets prepared in accordance with the present invention are resistant to crushing by mastication, heating/freezing and particle size reduction with conventional household particle size reduction equipment such as mortars, hammers, coffee grinders or food processors.

Embodiments of the modified release abuse deterrent tablets prepared in accordance with the present invention may further comprise additional pharmaceutical excipients such as rate controlling agents, fillers, binders, lubricants, glidants, antioxidants, chelating agents, pH modifying agents, disintegrants, coloring agents and mixtures thereof.

Embodiments of the modified release abuse deterrent tablets prepared in accordance with the present invention may also further comprise aversive agents such as an irritating agent for the nasal and/or pharyngeal tracts, antagonist agents for the drug that is subject to abuse, bittering agents, visual modifying agents, emetic agents and combinations of the forgoing.

Embodiments of the modified release abuse deterrent tablets prepared in accordance with the present invention may also further comprise an additional active pharmaceutical ingredient or a drug that is not subject to abuse in one or more layers or coatings of the multilayer/coated tablets. Examples of additional active pharmaceutical ingredients or drugs that are not subject to abuse that may be used include, but are not limited to, non-opioid analgesics, antihistamines, decongestants and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of the dissolution profiles for Examples 1A-1D.

Figure 2 is a graph of the dissolution profiles for Examples 2A-2D.

Figure 3 is a graph of the dissolution profiles for Examples 3-5.

Figure 4 is a graph of the dissolution profiles for Examples 6-9.

Figure 5 is a graph of the dissolution profile for Example 10.

Figure 6 is a graph of the dissolution profile for Example 11.

DETAILED DESCRIPTION OF THE INVENTION

Before the present invention is further described, it is to be understood that this invention is not limited to the particular embodiments described. It is also to be understood

that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It should be noted that as used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

The terms "polyethylene oxide" and "polyox" are synonymous and are defined for purposes of the present invention as a homopolymer of repeating ethylene oxide monomers of the formula $(CH_2CH_20)_n$ wherein n represents the average number of ethylene oxide monomers. The terms "polyethylene oxide" and "polyox" are also defined to refer to homopolymers having an approximate molecular weight of at least 50,000, based upon rheological measurements as described in The Handbook of Pharmaceutical Excipients, 5th ed. (2006) at p. 551-552; U.S. Published Patent Application No. 2009/0081290 at paragraphs [0237]-[0241] and DOW Chemical's POLYOX Water Soluble Resins brochures (2002) which are incorporated herein by reference. Homopolymers of repeating ethylene oxide monomers which exhibit an approximate molecular weight of less than 12,000 are referred to herein as polyethylene glycols.

The present invention includes a modified release abuse deterrent tablet and a method for manufacturing the modified release abuse deterrent tablet. The modified release abuse deterrent tablet comprises a plurality of layers and/or coatings. The modified release abuse deterrent tablets comprise at least one layer or coating, preferably more than one layer or coating, comprising a drug that is subject to abuse and at least one polyethylene oxide. As used herein the term "coating" refers to a layer of material that surrounds or encases a separate and distinct layer(s) or core material while the term "layer" refers to a separate and distinct composition region in the tablet. Embodiments of the present invention are multilayered tablets which comprise a plurality of layers, typically but not necessarily arranged in a stratified structure.

Certain embodiments of the modified release abuse deterrent tablets comprise two, three or four layers wherein each layer comprising a drug that is subject to abuse also comprises at least one polyethylene oxide. Further embodiments of the modified release abuse deterrent tablets comprise more than one layer comprising a drug that is subject to abuse and at least one polyethylene oxide and the modified release abuse deterrent tablets are free of any layer or coating containing a drug that is subject to abuse and that that also does not may also comprise at least one polyethylene oxide.

Still further embodiments of the modified release abuse deterrent tablets may also comprise one or more placebo layers or coatings. A placebo layer or coating is a layer or coating comprising one or more pharmaceutical excipients and that does not contain any drug, preferably any drug that is subject to abuse. The placebo layer or coating may be added to separate drug containing layers, to protect the drug containing layers or coatings, to aid in controlling the release of the drug from the dosage form and/or for aesthetic purpose.

Drugs that are subject to abuse include opioids, tranquilizers, sedatives and stimulants. Examples of such drugs can be found on pages 1487-1555 of *Remington, The Science and Practice of Pharmacy,* 21st ed. (2005). Specific examples of the drugs that are subject to abuse and which may be used in the present invention include but are not limited to alfentanil, alimemazine, alprazolam, amphetamine, buprenorphine, butorphanol, clonazepam, codeine, cyclobenzaprine, dexmethylphenidate, dextroamphetamine, dextromethamphetamine, diazepam, dihydrocodeine, dihydromorphine, dronabinol, estazolam, ezopiclone, fentanyl, flurazepam, hydrocodone, hydromorphone, lisdexamfetamine, lorazepam, methobarbital, methylphenidate, methadone, morphine, oxycodone, oxymorphone, phenobarbital, secobarbital, tempazepam, tramadol, triazolam, zaleplon, zopiclone, Zolpidem or pharmaceutically acceptable salts thereof.

In specific embodiments of the present invention, the drug that is subject to abuse comprises an opioid selected from the group consisting of buprenorphine, codeine, dihydrocodeine, dihydromorphine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone or pharmaceutically acceptable salts therefore.

In specific embodiments of the present invention, the drug that is subject to comprises a sedative or tranquilizer selected from the group consisting of alprazolam, clonazepam, diazepam, estazolam, ezopiclone, flurazepam, lorazepam, methobarbital, phenobarbital,

secobarbital, tempazepam, triazolam, zaleplon, zopiclone, Zolpidem, or pharmaceutically acceptable salts therefore.

In specific embodiments of the present invention, the drug that is subject to abuse comprises a stimulant selected from the group consisting of amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, or pharmaceutically acceptable salts therefore.

The therapeutic amounts of the drugs used in the present invention are known in the art and can be found in literature such as Goodman & Gillman's, *The Pharmacological Basis of Therapeutics*, 9th ed. pages 219-222, 361-396, 521-535 and the U.S. Food and Drug Administration's "Approved Drugs and Therapeutic Equivalents" publication (commonly known as "the Orange Book"). For example, typical therapeutic amounts of hydromorphone range from about 1 mg to about 100 mg of the hydrochloride salt, typical therapeutic amounts of morphine range from about 1 mg to about 800 mg, typical therapeutic amounts of oxycodone range from about 1 mg to about 400 mg of the hydrochloride salt, typical therapeutic amounts of hydrocodone range from about 1 mg to about 300 mg of the bitartrate salt, typical therapeutic amounts of oxymorphone range from about 1 mg to about 200 mg of the hydrochloride salt, and typical therapeutic amounts of codeine range from about 1 mg to about 200 mg of the phosphate or sulfate salt.

The polyethylene oxide that may be combined with the drug that is subject to abuse and used to create the individual layers or coatings of the multilayered/coated tablet of the present invention should exhibit an approximate molecular weight or an average approximate molecular weight of about 50,000 to about 15,000,000 and preferably about 100,000 to about 7,000,000. Examples of some polyethylene oxides commercially available from DOW Chemicals that may be used in the present invention are:

Polyox Grade	**Approximate Molecular Weight**
WSRN-10	100,000
WSRN-80	200,000
WSRN-750	300,000
WSR-205	600,000

WSR-1 105	900,000
WSR N-12K	1,000,000
WSR N-60K	2,000,000
WSR 301	4,000,000
WSR Coagulant	5,000,000
WSR-303	7,000,000

The polyethylene oxide or mixtures of polyethylene oxides should comprise about 50% to about 99% of the total weight of each individual layer or coating of the multilayered/coated tablet, preferably about 60% to about 97.5% of the total weight of each individual layer or coating of the multilayered/coated tablet and most preferably about 65% to about 95% of the total weight of each individual layer or coating of the multilayered/coated tablet.

The amount and type of polyethylene oxide employed in each individual layer or coating of the multilayered/coated tablet may be varied to obtain the desired release profile. For example, one layer of the abuse deterrent tablet may contain about 65-90% w/w of a polyethylene oxide with an approximate molecular weight of about 75,000 to 600,000 and a second layer may contain about 65-90% w/w of a polyethylene oxide with an approximate molecular weight of about 500,000 to 15,000,000. In this embodiment, the first layer would release the drug that is subject to abuse at a faster rate than the second layer and the first layer would contribute more of the drug subject to abuse to the initial burst or therapeutic amount released in the first 30-60 minutes following administration.

In one embodiment of the present invention, the modified release abuse deterrent tablet will be a bilayer tablet comprising:

i) a first layer, or layer (A), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (A) exhibits an approximate molecular weight of about 75,000 to about 600,000, preferably about 100,000 to about 500,000 and most preferably about 150,000 to about 400,000; and

ii) a second layer, or layer (B), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (B) exhibits an approximate molecular weight of about 100,000 to about 15,000,000, preferably about 200,000 to about 7,000,000 and most preferably about 300,000 to about 7,000,000.

In another embodiment of the present invention, the modified release abuse deterrent tablet will be a trilayer tablet comprising:

i) a first layer, or layer (A), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (A) exhibits an approximate molecular weight of about 75,000 to about 600,000, preferably about 100,000 to about 500,000 and most preferably about 150,000 to about 400,000;

ii) a second layer, or layer (B), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (B) exhibits an approximate molecular weight of about 100,000 to about 15,000,000, preferably about 200,000 to about 7,000,000 and most preferably about 300,000 to about 7,000,000; and

iii) a third layer, or layer (C), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (C) exhibits an approximate molecular weight of about 75,000 to about 600,000, preferably about 100,000 to about 500,000 and most preferably about 150,000 to about 400,000;

wherein layer (B) is between layer (A) and layer (C). Layers (A) and (C) may have the same or different compositions.

An alternative embodiment of the modified release abuse deterrent trilayer tablet comprises:

i) a first layer, or layer (B), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (B) exhibits an approximate molecular weight of about 100,000 to about 15,000,000, preferably about 200,000 to about 7,000,000 and most preferably about 300,000 to about 7,000,000;

ii) a second layer, or layer (A), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (A) exhibits an approximate molecular weight of about 75,000 to about 600,000, preferably about 100,000 to about 500,000 and most preferably about 150,000 to about 400,000;

iii) a third layer, or layer (D), comprising a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (D) exhibits an approximate molecular weight of about 100,000 to about 15,000,000, preferably about 200,000 to about 7,000,000 and most preferably about 300,000 to about 7,000,000;

wherein layer (A) is between layer (B) and layer (D). Layers (B) and (D) may have the same or different composition.

Layers (A), (B), (C) and (D) in the above embodiments may be replaced with a layer (E) which comprises a mixture of a drug that is subject to abuse such as an opioid, sedative or stimulant, and about 55% to about 95%, preferably about 60% to about 90% and most preferably about 65% to about 85% of one or more polyethylene oxides wherein at least one of the polyethylene oxides in layer (E) exhibits an approximate molecular weight of about 600,000 to about 15,000,000, preferably about 600,000 to about 7,000,000 and most preferably about 900,000 to about 7,000,000.

Other bi- and trilayer embodiments of the present invention may comprise any combination of layers (A), (B), (C), (D) and (E) described above. Preferred embodiments will comprise one or more (A) layers, for example a bilayer tablet may comprise: layer (A) and layer (C) wherein layer (A) and layer (C) are different compositions; layer (A) and layer (D); or layer (A) and layer (E). Similarly, trilayer embodiments may comprise: layer (A) with layers (B) and (E); layer (A), layer (E) and layer (A); layer (A), layer (B) and layer (C) wherein layer (A) and layer (C) are different compositions.

Other multilayer embodiments of the present invention may comprise four, five or more layers wherein the layers are a mixture of the foregoing (A), (B), (C), (D) and (E) layers, preferably with the proviso that at least one layer (A) is present in the multilayer tablet.

Another embodiment of the present invention will comprise a core which comprises two or more layers such as the afore described multilayer tablets and the multilayered cores will be coated, i.e. surrounded, with a coating comprising the composition of layer (A). Certain embodiments of the abuse deterrent tablets of the present invention which employ a coating employ an outer most or final coating that comprising the composition of layer (A).

If a mixture of polyethylene oxides is employed in the individual layers or coatings of the foregoing embodiments, the average approximate molecular weight of the total polyethylene oxide in the particular individual layer or coating should be an average of the approximate molecular weights contributed by each polyethylene oxide to the particular individual layer or coating. For example, if a particular individual layer comprises 15 mg of WSR 1150 (approximate molecular weight of 900,000) and 85 mg of WSR N-750 (approximate molecular weight of 300,000) the average approximate molecular weight for the particular layer is (0.15 x 900,000) + (0.85 x 300,000) or 390,000.

In certain embodiments of the foregoing multilayer/coated tablets that employ a mixture of polyethylene oxides with varying molecular weights, the average approximate molecular weight of the polyethylene oxide in layer or coating:

(A) should exhibit an average approximate molecular weight of about 75,000 to about 600,000, preferably about 100,000 to about 500,000 and most preferably about 150,000 to about 400,000;

(B) should exhibit an average approximate molecular weight of about 100,000 to about 15,000,000, preferably about 200,000 to about 7,000,000 and most preferably about 300,000 to about 7,000,000;

(C) should exhibit an average approximate molecular weight of about 75,000 to about 600,000, preferably about 100,000 to about 500,000 and most preferably about 150,000 to about 400,000;

(D) should exhibit an average approximate molecular weight of about 100,000 to about 15,000,000, preferably about 200,000 to about 7,000,000 and most preferably about 300,000 to about 7,000,000;

(E) should exhibit an average approximate molecular weight of about 600,000 to about 15,000,000, preferably about 600,000 to about 7,000,000 and most preferably about 900,000 to about 7,000,000.

Each of the various layers or coatings (A), (B), (C), (D) and (E) will comprise about 1% to about 99% of the total weight of the final tablet, preferably about 5% to about 90% of the total weight of the final tablet and most preferably about 10% to about 80% of the total weight of the final tablet. In certain embodiments each individual layer or coating of the final tablet should comprise about 10% to about 65% of the total weight of the final tablet, preferably about 20% to about 55% of the total weight of the final tablet and most preferably about 25% to about 50% of the total weight of the final tablet.

The afore-described multilayer/coated tablets may also comprise a placebo layer or coating. For example a placebo layer (P) may be added to the bilayer tablet to create a tablet contain layer (A), layer (B) and layer (P) wherein layer (P) contains one or more pharmaceutical excipients, preferably at least one rate controlling excipient as described below such as hydropropyl cellulose, hydroxypropyl methylcellulose, carbomer or polyethylene oxide which swell or gel in an aqueous environment. The placebo layer (P) will be in contact with layer (B) and reduce the surface area of layer (B) exposed to aqueous environment of the gastrointestinal tract and thereby contribute to delaying or controlling the release of the drug subject to abuse from the dosage form. Similarly one or more placebo layers (P) may be added to the trilayer tablets if desired. In alternative embodiments, the placebo layer (P) may comprise one or more pharmaceutical excipients and be placed between the drug containing layers to separate the layers and prevent any adverse interaction between drug layers.

A placebo coating may also applied to the afore-described multilayer tablets. In certain embodiments, the placebo coating comprises a water soluble material such as a sugar, polymer or wax that will dissolve within less than 10, preferably less than 5 minutes after administration. The placebo coating may be added for aesthetic purposes such as for color or polishing. The placebo coating may also be added to protect the drug in the multilayer tablet from unwanted exposure to moisture or light prior to administration.

The multilayered/coated tablets may be compressed into any tablet shape desired such as round, cylindrical, oval, elliptical or capsule shaped. The individual layers maybe compressed in any manner that allows at least a portion of each individual layer to exhibit an exposed surface on the multilayered tablet. Alternatively, one or more layers of the multilayered tablet may completely surround or encase other layers of the multilayered tablet. In embodiments where a layer completely surrounds or encases another layer, the surrounding or encasing layer may be referred to as a coating while the surrounded or encased layer may be referred to as a core. In certain embodiments the layers of the multilayered tablet are arranged in a horizontal or vertical arrangement similar to a sandwich or layer cake.

In addition to the drug that is subject to abuse and the at least one polyethylene oxide, the layers or coatings of the abuse deterrent tablets may further comprise additional pharmaceutical excipients. Examples of pharmaceutical excipients that may be used include, but are not limited to, rate controlling agents, fillers, binders, lubricants, glidants, antioxidants, chelating agents, pH modifying agents, disintegrants, coloring agents and mixtures thereof. A more detailed description of the pharmaceutical excipients that may also be included in the tablets of the present invention can be found in *The Handbook of Pharmaceutical Excipients*, 5th ed. (2006).

Although the polyethylene oxide of the modified release abuse deterrent tablet of the present invention should impart release controlling properties to the tablets as well as the individual layers or coatings, an additional rate controlling agent may be employed to aid in controlling the release of the drug that is subject to abuse from the final tablet or individual layers or coatings. The additional rate controlling agent that may be used in the present invention includes hydrophobic or hydrophilic materials that delay the release of the drug that is subject to abuse. Examples of hydrophobic materials that may be used as rate controlling agents include, but are not limited to, hydrophobic polymers, waxes, fats, long-chain fatty

acids, fatty alcohols, corresponding esters or ethers, or mixtures thereof. Preferred hydrophobic rate controlling agents include waxes, mono- or di-glycerides of C12-C30 fatty acids and/or Ci_2-C_{30} fatty alcohols or mixtures thereof. Examples of hydrophilic materials that may be used as rate controlling agents include, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose which exhibits a 2% aqueous viscosity at 20° C greater than or equal to 100 mPas·s, hydroxypropylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, carboxymethylcellulose sodium, polyacrylic acid, locust bean gum, starch, guar gum, carrageenan, karaya gum, galactomannan, sodium alginate, tragacanth, xanthan gum and mixtures thereof.

Examples of fillers that may be employed in the present invention include, but are not limited to, lactose, starch, dextrose, sucrose, fructose, maltose, mannitol, sorbitol, kaolin, microcrystalline cellulose, powdered cellulose, dextrates, calcium sulfate, calcium phosphate, dicalcium phosphate, lactitol or any combination of the foregoing. The amount of filler that may be employed in the individual layers or coatings of the present invention is generally about 0.5% to about 50% based upon the total weight of the individual layer or coating, preferably about 1% to about 35% based upon the total weight of the individual layer or coating and most preferably about 1% to about 25% based upon the total weight of the individual layer or coating.

Examples of binders that may be employed in the present invention include, but are not limited to, acacia, alginic acid, sodium carboxymethylcellulose sodium, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, starch, polyvinyl alcohol, polyethylene oxide, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose and any combination of the foregoing. The binders may be water soluble materials. The binders also may exhibit a low molecular weight and/or low viscosity when measured in a 2% aqueous solution. The low molecular weight binders typically are polymers with a molecular weight of less than 50,000, preferably less than 30,000, and preferably less than 10,000. The low viscosity binders typically have a viscosity of about 500 mPa·s or lower, preferably about 250 mPa·s or lower and most preferably 150 mPa·s or lower. The amount of binder that may be employed in the individual layers or coatings of the present invention is generally about 0.001% to about 10% based upon the total weight of the individual layer or coating, preferably about 0.001 5% to about 5% based upon the total weight of the individual

layer or coating and most preferably about 0.002% to about 2.5% based upon the total weight of the individual layer or coating.

Examples of lubricants that may be used in the present invention include, but are not limited to, talc, glyceryl monostearates, calcium stearate, magnesium stearate, stearic acid, glyceryl behenate, polyethylene glycol, poloxamer and combinations of the foregoing. The amount of lubricant that may be employed in the individual layer or coating of the present invention is generally about 0.05% to about 15% based upon the total weight of the individual layer or coating, preferably about 0.1% to about 10% based upon the total weight of the individual layer or coating and most preferably about 0.5% to about 5% based upon the total weight of the individual layer or coating.

Examples of glidants that may be used in the present invention include, but are not limited to, colloidal silicon dioxide (CAB-O-SIL®) and Quso (also known as Phila Quartz). The amount of glidant that may be employed in the individual layer or coating of the present invention is generally about 0.1% to about 7.5% based upon the total weight of the individual layer or coating and preferably about 0.5% to about 5% based upon the total weight of the individual layer or coating.

Examples of antioxidants that may be used in the present invention include, but are not limited to, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfate, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfate, sodium sulfate, sodium thiosulfate, sodium dioxide, tocopherol, and mixtures thereof. The amount of antioxidant that may be employed in the individual layer or coating of the present invention is generally about 0.01% to about 20% based upon the total weight of the individual layer or coating, preferably from about 0.1% to about 10% based upon the total weight of the individual layer or coating, and most preferably from about 0.5% to about 5% based upon the total weight of the individual layer or coating.

Examples of chelating agents that may be used in the present invention include, but are not limited to, polyphosphates (e.g., sodium tripolyphosphate, hexametaphosphoric acid, sodium acid pyrophosphate, sodium pyrophosphate, tetra sodium pyrophosphate, sodium hexametaphosphate, sodium metaphosphate); aminocarboxylic acids (e.g., ethylenediaminetetraacetic acid (EDTA), 1,2-bis(2-amino-phenoxy)ethane-N,N,N'N'-tetraacetic acid (EGTA), ethylenebis(oxyethylenenitrilo)tetraacetic acid (BAPTA), N-

(hydroxyethyl)-ethylenediaminetriacetic acid (HEDTA), diethylenetriaminepentaacetic acid (DTPA), N-dihydroxyethylglycine (2-HxG), ethylenebis(hydroxyphenyl-glycine) (EHPG), glutamic acid, aspartic acid, glycine, lysine); 1,3-diketones (e.g., acetylacetone, trifluoroacetylacetone, thenoyltrifluoroacetone, ascorbic acid); hydroxycarboxylic acids (e.g., tartaric acid, citric acid, malic acid, gluconic acid, ferulic acid, lactic acid, glucuronic acid); polyamines (e.g., dietheylenetriamine, triethylenetriamine); aminoalcohols (e.g., triethanolamine, N-hydroxyethylethylene-diamine, aminoethylethanolamine (AEEA); phenols (e.g., disulfopyrocatechol, chromotropic acid); aminophenols (e.g., oxinesulfonic acid); Schiff bases (e.g., disalicylaldehyde 1,2-propylenediimine); tetrapyrroles (e.g., tetraphenylporphin, phthalocyanine); silicates (aluminum calcium silicate, calcium silicate, sodium aluminosilicate sodium calcium aluminosilicate (hydrates), tricalcium silicate); sulfur compounds (e.g., potassium ethyl xanate, sodium diethyldithiocarbamate, diethyl dithiophosphoric acid, thiourea, magnesium sulfate); synthetic macrocyclic compounds (e.g., hexamethyl-[14]-4, l l-dieneN.sub.4, 2.2.2-cryptate); polymers (e.g., polyethyleneimines, polymethacryloylacetone, poly(p-vinylbenzyliminodiacetic acid)), phosphonic acids (e.g., nitrilotrimethylenephosphonic acid, ethylenediaminetetra-(methylenephosphonic acid), hydroxyethylidenediphosphonic acid) or combinations thereof. The amount of chelating agent that may be employed in the individual layer or coating of the present invention is generally about 0.5% to about 15% based upon the total weight of the individual layer or coating, preferably from about 0.75% to about 10% based upon the total weight of the individual layer or coating, and most preferably from about 1% to about 5% based upon the total weight of the individual layer or coating.

Examples of pH adjusting agents that may be used in the present invention include pharmaceutically acceptable acids or bases which may be present to adjust the pH of intermediate compositions used in the preparation of the mixtures used to prepare the individual layer or coating of the present invention, and/or to adjust the pH of the drug environment in an individual layer or coating of the present invention to a desired or optimal pH range. Representative examples of pharmaceutically acceptable acids that may be used include, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid, and mixtures thereof. Representative examples of pharmaceutically acceptable bases that may be used include, but are not limited to, ammonia, ammonium carbonate, diethanolamine, potassium

hydroxide, sodium bicarbonate, sodium carbonate, sodium hydroxide, trolamine, and mixtures thereof.

Examples of disintegrants that may be used in the present invention include, but are not limited to com starch, croscarmellose sodium, crospovidone (POLYPLASDONE® XL-10), sodium starch glycolate (EXPLOTAB® or PRIMOJEL®) or any combination of the foregoing. The amount of disintegrant that may be employed in the individual layer or coating of the present invention is generally about 0.5% to about 10% percent based upon the total weight of the individual layer or coating and preferably about 1% to about 5% based upon the total weight of the individual layer or coating.

Coloring agents that may be used in the present invention include, but are not limited to FD&C-type dyes and lakes, fruit and vegetable extracts, titantium dioxide and mixtures thereof.

In addition to the drug that is subject to abuse and the at least one polyethylene oxide, one or more of the individual layer or coating of the present invention may further comprise an aversive agent such as an irritating agent for the nasal and/or pharyngeal tracts, antagonist agents for the drug that is being abused, bittering agents, visual modifying agents, emetic agents and combinations of the forgoing. Examples of aversive agents that may be used in one or more of the individual layer or coating of the present invention are provided in U.S. Published Patent Application No. 2013/0320592, which is incorporated herein by reference.

Examples of nasal and/or pharyngeal irritants that may be used in the present invention include compounds generally considered pharmaceutically inert, yet can induce irritation. Such compounds include, but are not limited to, surfactants such as sodium lauryl sulfate, poloxamer, sorbitan monoesters and glycerol monooleates and effervescent agents.

Examples of antagonist agents that may be used in the present invention include compounds that block or negate the effect of the drug that is subject to abuse. Examples of antagonist agents for opioids include, but are not limited to, compounds such as naltrexone, naloxone, nalmefene, cyclazacine, levallorphan. Specific examples of antagonist agents and methods for preparing the antagonist agents for incorporation into the tablets of the present invention are provided in U.S. Patent Nos. 7,682,633 and 7,658,939, which are incorporated herein by reference.

Examples of the visual modifying agents include, but are not limited to, the visual modifying agents described in U.S. Patent No. 6,514,531, which are incorporated herein by reference.

Examples of emetic agents that may be used in the present invention include but are not limited to, the emetic agents described in U.S. Patent No. 7,510,726, which are incorporated herein by reference.

The modified release abuse deterrent tablets of the present invention can be made by any means commonly used in the pharmaceutical arts. Embodiments of the present invention can be made by preparing a mixture comprising the drug that is subject to abuse, at least one polyethylene oxide and optionally any desired additional pharmaceutical excipient and/or aversive agent. A separate and distinct mixture will be prepared for each individual layer or coating of the final tablet. Once the individual layer or coating mixtures are prepared, they are separately fed into the die of a tablet press and compressed into the final tablet. For example, a bilayer tablet as described above may be prepared by:

(i) preparing a mixture comprising the components of layer (A);

(ii) feeding the mixture of step (i) into a tablet die;

(iii) preparing a mixture comprising the components of layer (B);

(iv) feeding the mixture of step (iii) into the tablet die containing the mixture of step (i) so that the mixture of step (iii) is layered on top of the mixture of step (i) to create a bilayer composition; and

(v) compressing the bilayer composition of step (iv) to create a multilayer tablet.

The above process may also be used to prepare the tri-, quad- and penta-layer tablets which would further comprise the additional steps of preparing a desired mixture such as described previously for layers (A), (B), (C), (D) and (E) and feeding the prepared mixture into the tablet die prior to the final compression step (v).

In certain embodiments of the present invention, it may be desirable to employ a pre-compression or intermediate compression step wherein the individual mixtures are compressed, typically at a force less than or equal to the final compression force of step (v). The pre-compression step may be conducted before the addition of the subsequent mixture, such as between steps (ii) and (iii) in the above description of the preparation of the bilayer tablet.

The multilayered tablets of the present invention may also be prepared by partial filling or off setting of a layer into the tablet dies to vary the exposed surface of a particular layer. For example a bilayer tablet as described above may be prepared by:

(i) preparing a mixture comprising the components of layer (B);

(ii) feeding the mixture of step (i) into a tablet die;

(iii) compressing the mixture of step (ii) into a tablet;

(iv) preparing a mixture comprising the components of layer (A);

(v) placing the tablet of step (iii) into a larger tablet die;

(vi) feeding the mixture of step (iv) into the larger tablet die containing the tablet of step (iii) so that the mixture of step (iv) covers three sides of the tablet from step (iii); and

(vii) compressing the bilayer composition of step (vi) to create a multilayer tablet wherein only the top portion of layer (B) is exposed to the aqueous environment of a patient's gastrointestinal tract upon administration.

A skilled artisan will appreciate that the individual layer or coating mixtures do not need to be prepared in any particular order and may be prepared in advance of the steps for feeding the mixtures in the tablet die.

The coatings may also be applied to the core, preferably a multilayer core, by compressing coating techniques.

The individual layer or coating mixtures may be prepared by any technique commonly known in the pharmaceutical formulation art such as dry blending the ingredients of the individual layer or coating mixtures or granulating all or part of the ingredients of the individual layer or coating mixtures. If a granulation step is employed, the granules may be prepared by dry granulation or wet granulation techniques. A dry granulation technique may include a slugging step and/or roller compaction step and subsequent milling step.

If a wet granulation technique is employed, the wet granules should be prepared and dried before being added to the tablet die. In one embodiment of the present invention, the individual layer or coating mixtures are prepared by wet granulating the drug that is subject to abuse with a binder and a filler as previously described. The granules are dried and sized. After drying, the granules are mixed with the at least one polyethylene oxide and optionally a lubricant and/or glidant to create the individual layer or coating mixtures that are fed into the tablet die.

In one embodiment, the granules are free of any polyethylene oxide.

In an alternative embodiment the granules may comprise at least one polyethylene oxide. If a polyethylene oxide is employed in the granules, the polyethylene oxide should exhibit an approximate molecular weight or average approximate molecular weight of about 75,000 to about 7,000,000, preferably about 85,000 to about 1,000,000 and most preferably about 100,000 to about 500,000.

The process for preparing the modified release abuse deterrent tablets of the present invention also comprises a curing step. The curing step comprises exposing or subjecting the individual layers, coatings and/or the final tablet to a temperature which is at least the softening temperature of said polyethylene oxide for a time period of at least 5 minutes or more. The curing step may occur during the tablet formation by use of a heated tablet die or it may occur after the final tablet is prepared. The curing step may also occur both during the tablet formation and after the formation of the final tablet. When the curing step occurs after formation of the final tablet, it may be performed by heating the tablet die and/or the surrounding environment, however, it is preferred that the final tablet is removed from the die and placed in a heated environment such as an oven or coating apparatus. The final tablet may include any aesthetic coating and the curing step may occur before, during or after the aesthetic coating is applied.

The curing step should be conducted at a temperature that is at least as high as the softening temperature of the polyethylene oxide employed in the tablet. It is believed that the curing at a temperature that is at least as high as the softening temperature of the polyethylene oxide causes the polyethylene oxide particles to at least adhere to each other or even to fuse. The curing step of some embodiments of the present invention occurs at a temperature of about 60°C to about 90°C, preferably about 62° C to about 87°C, and most preferably about 65° C to about 85° C.

The time of the curing step, i.e., exposure to the elevated temperature, will depend on the amount and type of polyethylene oxide present in the modified release abuse deterrent tablets. Typically, the time the required for the curing step is about 5 minutes to about 10 hours, preferably about 15 minutes to about 5 hours and most preferably about 30 minutes to about 4 hours.

In certain other embodiments of the present invention, the curing step occurs in a curing device that is heated by any conventional means such as a heated air supply (inlet); for example, a coating pan or fluidized bed. Such curing devices will hereinafter be called convection curing devices. In such convection curing devices, it is possible to measure the temperature of the inlet air, i.e., the temperature of the heated air entering the convection curing device and/or the temperature of the exhaust air, i.e., the temperature of the air leaving the convection curing device. It is also possible to determine, or at least estimate, the temperature of the formulations inside the convection curing device during the curing step, e.g., by using infrared temperature measurement instruments such as an IR gun, or by measuring the temperature using a temperature probe that was placed inside the curing device near the final tablet.

The curing step may also be conducted by placing the final tablets in an oven set at the desired temperature for the desired time.

After the curing step is completed, the modified release abuse deterrent tablet of the present invention should be resistant to crushing by mastication, heating/freezing and particle size reduction with conventional house hold particle size reduction equipment such as mortars, hammers, coffee grinders or food processors. The ability to resist crushing may be measured by any method commonly used in the pharmaceutical arts. For example, when the cured modified release abuse deterrent tablet of the present invention is subjected to an indentation test it should exhibit a cracking force of at least about 110 N, preferably of at least about 125 N, and most preferably of at least about 150 N. The indentation test can be conducted using a Texture Analyzer such as the TA-XT2 Texture Analyzer (Texture Technologies *Corp.*, 18 Fairview Road, Scarsdale, N.Y. 10583), the details of which are provided in U.S. Published Patent Application No. 2009/0081290, which is incorporated herein by reference.

Alternatively, the ability of the cured modified release abuse deterrent tablet of the present invention to resist crushing may be measured by determining the break strength of the cured modified release abuse deterrent tablet by any method commonly used in the pharmaceutical arts. One method for determining break strength is described in U.S. Published Patent Application No. 2013/0320592, which is incorporated herein by reference. Using the methodology described in U.S. Published Patent Application No. 2013/0320592,

the cured modified release abuse deterrent tablet of the present invention should exhibit a break strength of about 500 N or greater.

The cured modified release abuse deterrent tablet of the present invention may exhibit any desired drug release profile, such as a zero order, first order, second order or any combination thereof. The drug release profile can be adjusted by varying the amount and type of polyethylene oxide in the various layers or coatings of the final tablet as well as the thickness or weight percent of each individual layer present in the final tablet.

In one embodiment, the cured modified release abuse deterrent tablet will release a therapeutic amount of the drug subject to abuse within 60 minutes of administration, preferably within 45 minutes and most preferably within 30 minutes and provide for controlled or sustained release of the drug for 8-24 hours after administration or in vitro dissolution testing.

Alternatively, the cured modified release abuse deterrent tablet will release the drug subject to abuse in a first or second order release profile from 0 to about 2.5 hours after administration, preferably from 0 to about 2 hours and most preferably from 0 to about 1.5 hours when the cured modified release abuse deterrent tablet is subjected to a United States Pharmacopeia (USP) in vitro dissolution test procedure employing either a USP Type I or II apparatus with 900 ml of biorelevant medium such as simulated gastric fluid, simulated intestinal fluid or water, at 50 or 100 rpms and 37° C. After the initial first or second order release, the drug that is subject to abuse will be released from the cured modified release abuse deterrent tablet in a zero order profile or a substantially zero order profile. The terms zero order and substantially zero order refer to the rate of drug release from a dosage form which is independent of the remaining drug concentration in the dosage form, such that the rate is relatively constant over a period of time. A dosage form exhibiting a zero order or substantially zero order release rate would exhibit a relatively straight line in a graphical representation of percent drug released versus time. In certain embodiments of the present invention, a substantially zero order release is defined as a tablet having an amount of drug that is subject to abuse released which is proportional within about 20%, preferably about 15% and most preferably about 10% to elapsed time as measured by USP dissolution test procedure employing either a USP Type I or II apparatus with 900 ml of a biorelevant medium such as simulated gastric fluid, simulated intestinal fluid or water, at 50 or 100 rpms and 37° C. For example, a multilayered tablet that releases 30% of the drug at 4 hours, 45%

of the drug at 6 hours and 60% of the drug at 8 hours would be characterized as exhibiting a zero order release profile from 4 to 8 hours because the amount of drug released at each time point is proportional to the time, i.e., 45% at 6 hours is 1.5 times of the 30% at 4 hours, and 60% at 8 hours is 2 times the 30% at 4 hours. Further, a multilayered tablet that releases 30% of the drug at 4 hours, 52% of the drug at 6 hours and 63% of the drug at 8 hours would be characterized as exhibiting a substantially zero order release profile from 4 to 8 hours because the amount of drug release at each time point is proportional to the time, i.e., 52% at 6 hours is 1.5 ± 20% times of the 30% at 4 hours, and 63% at 8 hours is 2 ± 20% times the 30% at 4 hours.

In certain such embodiments, the cured modified release abuse deterrent tablet of the present invention can be flattened without breaking by application of an external force such as a hammer or a vice. When the cured modified release abuse deterrent tablet of the present invention is flattened to no more than about 60%, no more than about 50%, no more than about 40%, no more than about 30%, or no more than about 20%, of the original thickness of the cured modified release abuse deterrent tablet, the flattened and original modified release abuse deterrent tablet should exhibit similar in vitro dissolution profiles. For example, when a flattened modified release abuse deterrent tablet and a non-flattened modified release abuse deterrent tablet from the same manufacturing lot are subjected to an in vitro USP dissolution procedure employing either a USP Type I or II apparatus with 900 ml of a biorelevant medium such as simulated gastric fluid, simulated intestinal fluid or water, at 50 or 100 rpms and 37° C, the dissolution profile for the flatten modified release abuse deterrent tablet and the non flatten modified release abuse deterrent tablet should deviate by no more than about 25% points, preferably by no more than about 20% points and most preferably by no more than 15% points at any tested time point.

The embodiments of the present invention which employ an opioid as the drug subject to abuse, may also further comprise a non-opioid analgesic such as aspirin, acetaminophen or a non-steroid anti-inflammatory agent such as ibuprofen, naproxen, diclofenac or celecoxib in one or more of the individual layers of the multilayer tablet.

The modified release abuse deterrent tablets of the present invention may also comprise a final aesthetic or color coating if desired. In certain embodiments of the present invention, it may be desirable to apply a placebo film coating such as an aesthetic or color coating to the modified release abuse deterrent tablets prior to the curing step. In addition to

providing an improved aesthetic appearance of color coating, the placebo film coating may also provide an anti-sticking function. A placebo coating which imparts an anti-sticking coating to the modified release abuse deterrent tablets should comprise a film forming polymer, preferably a film forming water soluble polymer that dissolves in less than 45 minute, preferably less than 30 minutes and most preferably less than 20 minutes when placed in 900 ml of water at 37°C. The film forming polymers that may be used in the anti-sticking coating may exhibit a viscosity of about 200 mPa s or less, preferably about 100 mPa s or less and most preferably about 50 mPa s or less at 20°C when a 2% (w/v) aqueous solution is prepared. Examples of the film forming polymers that may be used in the anti-sticking coating include but are not limited to hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hypromellose, polyvinyl alcohol, polyvinylpyrrolidone and mixtures thereof. The preferred the film forming polymers that may be used in the anti-sticking coating are polyvinyl alcohol, polyvinylpyrrolidone or mixtures thereof.

Embodiments of the modified release abuse deterrent tablets of the present invention may be free of any controlled release or release modifying coating.

Embodiments of the modified release abuse deterrent tablets of the present invention may be free of any coating or layer that is free of polyethylene oxide and that contains a drug that is subject to abuse.

The following examples illustrate the present invention and are not intended to limit the scope of the present invention.

EXAMPLE 1

Monolithic matrix tablets with the following compositions were prepared:

Ingredients	1A (55% PEO 303)	1B (55% PEO 301)	1C (55% PEO N80)	1D (55% PEO N750)
Morphine Sulfate	100	100	100	100
Hydroxypropyl Cellulose 75–150 cps	1.36	1.2	1.36	1.36
Microcrystalline Cellulose, 50µ	12.24	11.2	12.24	12.24
Polyethylene Oxide WSR 303	143			
Polyethylene Oxide WSR 301		141.7		
Polyethylene Oxide N 80			143	
Polyethylene Oxide N 750				143

Magnesium Stearate	3.4	2.6	3.4	3.4
Total	260	256.7	260	260

Example 1A was prepared as follows.

331 g of hydroxypropyl cellulose was dissolved in 4,400 g of alcohol to prepare a granulating solution. 24,231 g of morphine sulfate and 2,965 g of microcrystalline cellulose were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 1 hour. The dried granules were milled using a Quadro comill. Two loads of the milled granules were blended with 69,300 g of polyethylene oxide WSR 303 in a 10 cu. ft V-blender. The blend was screened through a Quadro comill and further blended with 1,646 g of screened magnesium stearate to produce the final blend. The blend was compressed into tablets using a 0.3750" round die on a Kilian LX 23 station tablet press at an average hardness of 10 kp. The compressed tablets were cured in a 36" Acela Cota coating pan at 70° C for 1 hour and then coated with an aqueous dispersion of Opadry Color.

Example IB was prepared as follows:

18 g of hydroxypropyl cellulose was dissolved in 450 g of water to prepare a granulating solution. 1620 g of morphine sulfate and 180 g of microcrystalline cellulose were granulated together in a Kitchen-Aid blender using the granulating solution. The resulting granules were dried in a tray oven at 60° C for 7 hour. The dried granules were milled using a Fitz mill at slow speed and knives forward. 56.5 g of the milled granules was blended with 71 g of polyethylene oxide WSR 301 in a plastic bag. 1.3 g of magnesium stearate was screened and added to the plastic bag and blended further to yield the final blend. The blend was compressed into tablets using an 8.7 mm round die on a Globe tablet press at an average hardness of 14 kp. The tablets were cured in a tray oven for 1 hour at 70° C.

Examples 1C and ID were prepared as follows:

318 g of hydroxypropyl cellulose was dissolved in 4,200 g of alcohol to prepare a granulating solution. 23,400 g of morphine sulfate and 2,864 g of microcrystalline cellulose were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 1 hour. The dried granules were milled using a Quadro comill.

For Example 1C, 28.4 g of the milled granules were blended with 35.8 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. The blend was compressed into tablets using a 3/8" round die on a single punch Carver press. The tablets were cured in a tray oven for 1 hour at 70° C.

For Example ID, 28.4 g of the milled granules were blended with 35.8 g of polyethylene oxide WSRN750 and 0.9 g of magnesium stearate together in a plastic bag. The blend was compressed into tablets using a 3/8" round die on a single punch Carver press. The tablets were cured in a tray oven for 1 hour at 70° C.

The cured tablets of Examples 1A-1D and a commercially available morphine sulfate tablet (MS CONTEST lot # WJM-31) were tested with a USP dissolution apparatus type 1 (basket) with 900 mL of water with pH 1.2, 50 rpm, 37° C and exhibited the following dissolution:

Time	MS Contin (Lot#WJM-31)	1A (55% PEO 303)	1B (55% PEO 301)	1C (55% PEO N80)	1D (55% PEO N750)
0	0	0	0	0	0
60	35	20	23	42	25
120	53	33	39	83	44
180	65	46	52	97	63
240	89	74	82	97	79
360	101	89	96	97	96
540	104	96	-	-	-
720	104	99	-	-	-

Graphs of the dissolution profiles for Examples 1A-1D are shown in Figure 1.

EXAMPLE 2

Monolithic matrix tablets with the following compositions were prepared:

Ingredients	2A (80% N750)	2B (80% 3: 1 N750:N80)	2C (80% 1: 3 N750:N80)	2D (80% 1: 1 N750:N80)
Morphine Sulfate	100	100	100	100
Hydroxypropyl Cellulose 75–150 cps	1.36	1.36	1.36	1.36
Microcrystalline Cellulose, 50μ	12.24	12.24	12.24	12.24

Polyethylene Oxide N 80		117.6	352.4	235
Polyethylene Oxide N 750	470	352.4	117.6	235
Magnesium Stearate	3.6	3.6	3.6	3.6
Total	587.2	587.2	587.2	587.2

Example 2A-2D were prepared as follows:

318 g of hydroxypropyl cellulose was dissolved in 4,200 g of alcohol to prepare a granulating solution. 23,400 g of morphine sulfate and 2,864 g of microcrystalline cellulose were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 1 hour. The dried granules were milled using a Quadro comill.

For Example 2A, 28.4 g of the milled granules were blended with 117.5 g of polyethylene oxide WSR N750 and 0.9 g of magnesium stearate together in a plastic bag. The blend was compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 2B, 28.4 g of the milled granules were blended with 88.1 g of polyethylene oxide WSR N750, 29.4 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. The blend was compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 2C, 28.4 g of the milled granules were blended with 29.4 g of polyethylene oxide WSR N750, 88.1 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. The blend was compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 2D, 28.4 g of the milled granules were blended with 58.8 g of polyethylene oxide WSR N80, 58.8 g of polyethylene oxide WSR N750 and 0.9 g of magnesium stearate together in a plastic bag. The blend was compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. The tablets were cured in a tray oven for 3 hour at 80° C.

The cured tablets of Examples 2A-2D and a commercially available morphine sulfate tablet (MS CONTEST lot # WJM-31) were tested with a USP dissolution apparatus type 1

(basket) with 900 mL of water with pH 1.2, 50 rpm, 37° C and exhibited the following dissolution:

Time	MS Contin WJM-31	2 A (80% N750)	2B (80% 3: 1 N750:N80)	2C (80% 1: 3 N750:N80)	2D (80% 1: 1 N750:N80)
0	0	0	0	0	0
60	35	15	15	22	18
120	53	28	29	44	34
180	65	40	43	65	50
240	-	52	56	82	67
360	89	75	83	99	96
540	101	97	98	99	102
720	104	97	98	99	102

Graphs of the dissolution profiles for Examples 2A-2D are shown in Figure 2.

EXAMPLES 3-5

Bilayer tablets with the following compositions were prepared:

Ingredients	Example 3 (80% 1:3 N80:N750)	Example 4 (80% 1:3 N80:301)	Example 5 (80% 1:3 N80: 205)
Layer A			
Morphine Sulfate	25	25	25
Hydroxypropyl Cellulose 75–150 cps	0.34	0.34	0.34
Microcrystalline Cellulose, 50µ	3.06	3.06	3.06
Polyethylene Oxide N 80	117.5	117.5	117.5
Magnesium Stearate	0.9	0.9	0.9
Total	146.8	146.8	146.8
Layer B			
Morphine Sulfate	75	75	75
Hydroxypropyl Cellulose 75–150 cps	1.02	1.02	1.02
Microcrystalline Cellulose, 50µ	9.18	9.18	9.18
Polyethylene Oxide WSR 301		352.5	
Polyethylene Oxide N 205			352.5
Polyethylene Oxide N 750	352.5		

Magnesium Stearate	2.7	2.7	2.7
Total	440.4	440.4	440.4

Examples 3, 4 and 5 were prepared as follows:

318 g of hydroxypropyl cellulose was dissolved in 4,200 g of alcohol to prepare a granulating solution. 23,400 g of morphine sulfate and 2,864 g of microcrystalline cellulose were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 1 hour. The dried granules were milled using a Quadro comill.

For Example 3, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N750 and 0.9 g of magnesium stearate together in a plastic bag. The blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 4, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR 301 and 0.9 g of magnesium stearate together in a plastic bag. The blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 5, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR 205 and 0.9 g of magnesium stearate together in a plastic bag. The blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die

on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

The cured bilayer tablets of Examples 3-5 and a commercially available morphine sulfate tablet (MS CONTIN lot # WJM-31) were tested with a USP dissolution apparatus type 1 (basket) with 900 mL of water with pH 1.2, 50 rpm, 37° C and exhibited the following dissolution:

Time	MS Contin WJM-31	Example 3 (80% 1:3 N80:N750) Bilayer	Example 4 (80% 1: 3 N80:301) Bilayer	Example 5 (80% 1: 3 N80:205) Bilayer
0	0	0	0	0
60	35	21	20	20
120	53	39	35	37
180	65	53	45	49
240		64	52	58
360	89	85	64	75
540	101	94	78	93
720	104	95	87	98

Graphs of the dissolution profiles for Examples 3-5 are shown in Figure 3.

EXAMPLES 6-9

Bilayer tablets with the following compositions were prepared:

Ingredients	Example 6 (80% 1:1 N80:N750) Bilayer	Example 7 (80% 1: 1 N80:205) Bilayer	Example 8 (80% 1: 1 N80:301) Bilayer	Example 9 (80% 3: 1 N80:301) Bilayer
Layer A				
Morphine Sulfate	50	50	50	75
Hydroxypropyl Cellulose 75–150 cps	0.68	0.68	0.68	1.02
Microcrystalline Cellulose, 50µ	6.12	6.12	6.12	9.18
Polyethylene Oxide N 80	235	235	235	352.5
Magnesium Stearate	1.8	1.8	1.8	2.7
Total	293.6	293.6	293.6	440.4
Layer B				
Morphine Sulfate	50	50	50	25
Hydroxypropyl Cellulose 75–150 cps	0.68	0.68	0.68	0.34
Microcrystalline Cellulose, 50µ	6.12	6.12	6.12	3.06

Polyethylene Oxide WSR 301			235	117.5
Polyethylene Oxide N 205		235		
Polyethylene Oxide N 750	235			
Magnesium Stearate	1.8	1.8	1.8	0.9
Total	293.6	293.6	293.6	146.8

Examples 6, 7, 8 and 9 were prepared as follows:

318 g of hydroxypropyl cellulose was dissolved in 4,200 g of alcohol to prepare a granulating solution. 23,400 g of morphine sulfate and 2,864 g of microcrystalline cellulose were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 1 hour. The dried granules were milled using a Quadro comill.

For Example 6, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSRN750 and 0.9 g of magnesium stearate together in a plastic bag. The blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 7, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR 205 and 0.9 g of magnesium stearate together in a plastic bag. The blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 8, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR 301 and 0.9 g of magnesium stearate together in a plastic bag. The

blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

For Example 9, Layer A was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR N80 and 0.9 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 28.4 g of the milled granules with 117.5 g of polyethylene oxide WSR 301 and 0.9 g of magnesium stearate together in a plastic bag. The blends were compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend and then compressed to create the bilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

The cured bilayer tablets of Examples 6-9 and a commercially available morphine sulfate tablet (MS CONTEST lot # WJM-31) were tested with a USP dissolution apparatus type 1 (basket) with 900 mL of water with pH 1.2, 50 rpm, 37° C and exhibited the following dissolution:

Time	MS Contin WJM-31	Example 6 (80% 1:1 N80:N750) Bilayer	Example 7 (80% 1: 1 N80:205) Bilayer	Example 8 (80% 1: 1 N80:301) Bilayer	Example 9 (80% 3:1 N80:301) Bilayer
0	0	0	0	0	0
60	32	22	23	22	24
120	49	42	42	38	46
180	62	62	57	54	69
240	71	79	72	68	87
360	86	97	91	85	96
540	99	99	100	95	98
720	101	99	101	99	98

Graphs of the dissolution profiles for Examples 6-9 are shown in Figure 4.

EXAMPLE 10

Trilayer tablets with the following composition were prepared:

Ingredients	Example 10 (80% 1:2:1 N80:205:N80)

	Trilayer
Layer A	
Morphine Sulfate	25
Hydroxypropyl Cellulose 75-150 cps	0.34
Microcrystalline Cellulose, 50µ	3.06
Polyethylene Oxide N 80	117.5
D&C Yellow # 10 Aluminum Lake	
Magnesium Stearate	0.9
Total	146.8
Layer B	
Morphine Sulfate	50
Hydroxypropyl Cellulose 75-150 cps	0.68
Microcrystalline Cellulose, 50µ	6.12
Polyethylene Oxide N 205	235
Magnesium Stearate	1.8
Total	293.6
Layer C	
Morphine Sulfate	25
Hydroxypropyl Cellulose 75-150 cps	0.34
Microcrystalline Cellulose, 50µ	3.06
Polyethylene Oxide N 80	117.5
D&C Yellow # 10 Aluminum Lake	
Magnesium Stearate	0.9
Total	146.8

The trilayer tablets were prepared as follows:

318 g of hydroxypropyl cellulose was dissolved in 4,200 g of alcohol to prepare a granulating solution. 23,400 g of morphine sulfate and 2,864 g of microcrystalline cellulose were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 1 hour. The dried granules were milled using a Quadro comill.

Layers A and C were prepared by blending 56.8 g of the milled granules with 235 g of polyethylene oxide WSR N80 and 1.8 g of magnesium stearate together in a plastic bag. Layer B was prepared by blending 56.8 g of the milled granules with 235 g of polyethylene oxide WSR 205 and 1.8 g of magnesium stearate together in a plastic bag. The blends were

compressed into tablets using a 0.6732" x 0.3189" oval die on a single punch Carver press. Layer A blend was fed into the die followed by Layer B blend into the same die on top of Layer A blend. Layer C blend was then fed into the die on top of Layer B blend and then compressed to create the trilayer tablets. The tablets were cured in a tray oven for 3 hour at 80° C.

The cured trilayer tablets and a commercially available morphine sulfate tablet (MS CONTEST lot # WJM-31) were tested with a USP dissolution apparatus type 1 (basket) with 900 mL of water with pH 1.2, 50 rpm, 37° C and exhibited the following dissolution:

Time	MS Contin WJM-31	Example 10 (80% 1:2:1 N80:205:N80) Trilayer
0	0	0
60	33	33
120	50	51
180	63	64
240	73	74
360	87	88
540	98	99
720	101	102

A graph of the dissolution profile for Example 10 is shown in Figure 5.

EXAMPLE 11

Trilayer tablets with the following composition were prepared:

Ingredients	Example 11 (82.5% 1: 2:1 N80:205:N80) Tri-layer
Layer A	**(mg)**
Intra Granular	
Morphine Sulfate	**25**
Hydroxypropyl Cellulose 75–150 cps	**0.3**
Polyethylene Oxide N 80	**1.0**
Extra Granular	
Polyethylene Oxide N 80	**29.96**
Polyethylene Oxide N 205	**92.87**
D&C Yellow # 10 Aluminum Lake	**0.02**

Magnesium Stearate	**0.85**
Total	**150**
Layer B	
Intra Granular	
Morphine Sulfate	**50**
Hydroxypropyl Cellulose 75-150 cps	**0.6**
Polyethylene Oxide N 80	**2.0**
Extra Granular	
Polyethylene Oxide N 205	**245.7**
Magnesium Stearate	**1.7**
Total	**300**
Layer C	
Intra Granular	
Morphine Sulfate	**25**
Hydroxypropyl Cellulose 75-150 cps	**0.3**
Polyethylene Oxide N 80	**1.0**
Extra Granular	
Polyethylene Oxide N 80	**122.81**
D&C Yellow # 10 Aluminum Lake	**0.04**
Magnesium Stearate	**0.85**
Total	**150**
Core Tablet Weight (mg)	**600**
Opadry II White (85F18422)	**20**
Coated Tablet Weight (mg)	**620**

The trilayer tablets were prepared as follows:

374 g of hydroxypropyl cellulose was dissolved in 4,970 g of alcohol to prepare a granulating solution. 30,426 g of morphine sulfate and 1,200 g of polyethylene oxide WSR N80 were granulated together in a 150 L high shear mixer using the granulating solution. The resulting granules were dried in a tray oven at 45° C for 30 minutes. The dried granules were milled using a Quadro comill.

Layer A was prepared by blending 3,945 g of the milled granules with 4,494 g of polyethylene oxide WSR N80, 13,931 g of polyethylene oxide WSR 205, 3 g of D&C Yellow # 10 Aluminum Lake were blended in 3 cu. ft. V-Blender. The blend was screened through a

Quadro Comill and further blended with 127 g of screened magnesium stearate to produce the final Layer A blend.

Layer B was prepared by blending 7,890 g of the milled granules with 36,855 g of polyethylene oxide WSR 205 were blended in 5 cu. ft. V-Blender. The blend was screened through a Quadro Comill and further blended with 255 g of screened magnesium stearate to produce the final Layer B blend.

Layer C was prepared by blending 3,945 g of the milled granules with 18,422 g of polyethylene oxide WSR N80, 6 g of D&C Yellow # 10 Aluminum Lake were blended in 3 cu. ft. V-Blender. The blend was screened through a Quadro Comill and further blended with 127 g of screened magnesium stearate to produce the final Layer C blend.

The blends were compressed into tablets using a 0.616" x 0.292" oval die on an Elizabeth-Hata Tri-layer tablet press. Layer A blend was fed into the die. Layer B blend was fed in to the same die on top of the Layer A blend. Layer C Blend was then fed into the same die on top of the Layer B blend. The three blends were compressed to create the trilayer tablet. The trilayer core tablets were film coated with Opadry II White aqueous dispersion in a 36" Acela-cota perforated coating pan. The Opadry II White coated tablets were cured in a tray oven for 2 hour at 80° C to yield the final product.

The cured coated trilayer tablets and a commercially available morphine sulfate tablet (MS CONTIN lot # WJM-31) were tested with a USP dissolution apparatus type 1 (basket) with 900 mL of water with pH 7, 100 rpm, 37° C and exhibited the following dissolution:

Time	MS Contin WJM-31	Example 11 (82.5%) Trilayer
0	0	0
60	25	16
120	39	31
180	48	43
360	69	66
540	83	85
720	92	93
900	98	94
1080	99	95
1440	100	95

A graph of the dissolution profile for Example 11 is shown in Figure 6

EXAMPLE 12

The bilayer tablets of Examples 3-9 can be prepared by replacing the morphine sulfate with the following opioids:

	Opioid	Layer A	Layer B
Example 12A	Oxycodone	20 mg	20 mg
Example 12B	Oxymorphone	20 mg	20 mg
Example 12C	Hydromorphone	16 mg	16 mg
Example 12D	Hydrocodone	15 mg	15 mg

The oxycodone, oxymorphone and hydromorphone were used as an equivalent amount of the hydrochloride salt while the hydrocodone was used as an equivalent amount of the bitartrate salt.

EXAMPLE 13

The bilayer tablets of Examples 3-9 can be prepared by replacing the morphine sulfate with the following stimulants:

	Stimulants	Layer A	Layer B
Example 13A	Methylphenidate	18 mg	18 mg
Example 13B	Dexmethylphenidate	20 mg	20 mg
Example 13C	Mixed amphetamines	10 mg	10 mg
Example 13D	Dextroamphetamine	5 mg	5 mg
Example 13E	Lisdexamfetamine	20 mg	20 mg

The methylphenidate and dexmethylphenidate were used as an equivalent amount of the hydrochloride salt. The mixed amphetamine was used as an equivalent amount of the sulfate and saccharate salt. The lisdexamfetamine was used as an equivalent amount of the dimesylate salt.

EXAMPLE 14

The bilayer tablets of Examples 3-9 can be prepared by replacing the morphine sulfate with the following sedatives:

	Sedatives	Layer A	Layer B
Example 14A	Zolpidem	6.25 mg	6.25 mg
Example 14B	Ezopiclone	1 mg	1 mg
Example 14C	Zaleplon	5 mg	5 mg

The Zolpidem was used as an equivalent amount of the tartrate salt.

EXAMPLE 15

The trilayer tablets of Examples 10 and 11 can be prepared by replacing the morphine sulfate with the following opioids:

	Opioid	Layer A	Layer B	Layer C
Example 15A	Oxycodone	20 mg	20 mg	20 mg
Example 15B	Oxymorphone	10 mg	10 mg	10mg
Example 15C	Hydromorphone	10 mg	10 mg	10 mg
Example 15D	Hydrocodone	10 mg	10 mg	10 mg

The oxycodone, oxymorphone and hydromorphone were used as an equivalent amount of the hydrochloride salt while the hydrocodone was used as an equivalent amount of the bitartrate salt.

EXAMPLE 16

The trilayer tablets of Examples 10 and 11 can be prepared by replacing the morphine sulfate with the following stimulants:

	Stimulants	Layer A	Layer B	Layer C
Example 16A	Methylphenidate	18 mg	18 mg	18 mg
Example 16B	Dexmethylphenidate	15 mg	15 mg	15 mg
Example 16C	Mixed amphetamines	7.5 mg	10 mg	7.5 mg

Example 16D	Dextroamphetamine	5 mg	5 mg	5 mg
Example 16E	Lisdexamfetamine	20 mg	20 mg	20 mg

The methylphenidate and dexmethylphenidate were used as an equivalent amount of the hydrochloride salt. The mixed amphetamine was used as an equivalent amount of the sulfate and saccharate salt. The lisdexamfetamine was used as an equivalent amount of the dimesylate salt.

EXAMPLE 17

The trilayer tablets of Examples 10 and 11 can be prepared by replacing the morphine sulfate with the following sedatives:

	Sedatives	**Layer A**	**Layer B**	**Layer C**
Example 17A	Zolpidem	3.125 mg	6.25 mg	3.125 mg
Example 17B	Ezopiclone	0.5 mg	1 mg	0.5 mg
Example 17C	Zaleplon	2.5 mg	5 mg	2.5 mg

The Zolpidem was used as an equivalent amount of the tartrate salt.

EXAMPLE 18

The trilayer tablet of Example 11 was tested in an open label, randomized, single dose, three way crossover bioequivalence study with MS CONTIN® 100 mg tablet as the reference product. 47 healthy adult human subjects (24 males and 23 females) were enrolled in the study and 38 subjects (21 males and 17 females) completed the study.

The trilayer tablet of Example 11 and the MSCONTIN® 100 mg tablet were administered to the subjects after a 10 hour overnight fast with 240 ml of water. There was a seven day wash out period between administrations and subjects were not allowed to eat for four hours following administration.

The trilayer tablet of Example 11 was also administered to the same subject population under fed conditions following a seven day period washout period. The subjects in the fed arm of the study were given a standard high fat, high calorie breakfast following a 10

hour overnight fast **30** minutes prior to administration of the trilayer tablet with **240** ml of water.

The subjects were also administered a **50** mg naltrexone tablet **12** hours prior to dosing, approximately **0.75** hours prior to dosing and approximately **12** hours after dosing with **120** ml of water, to reduce the risk of any opioid related adverse events.

Blood samples were collected **60** minutes prior to dosing, and **0.5, 0.75, 1. 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 30, 36** and **48** hours after dosing. The blood samples were analyzed to determine the plasma concentrations of morphine and its active metabolite, morphine-**6**-glucoronide, using validated analytical methods in accordance with FDA guidelines.

The pharmacokinetic parameters from this study were reported as follows:

	Trilayer Tablet of Ex. 11 (Fasting) (N=42)	**Trilayer Tablet of Ex. 11 (Fed) (N=39)**	**MS CONTIN® (Fasting) (N=41)**
	Arithmetic Mean ± SD (%CV)		
AUC_{0-t} (ng.hr/mL)	367.44±127.44 (34.68)	422.53±143.32 (33.92)	395.27±139.45 (35.28)
AUC_{0-inf} (ng.hr/mL)	390.11±137.29 (35.19)	437.21±147.53 (33.74)	421.08±149.64 (35.54)
C_{max} (ng/mL)	38.71±16.68 (43.09)	43.08±16.31 (37.86)	35.38±11.48 (32.44)
T_{max} (hr)	2.59±1.44 (55.72)	5.60±3.01 (53.79)	2.72±1.44 (53.06)

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations, which is not specifically disclosed herein. Thus, for example, in each instance herein, any of the terms "comprising," "consisting essentially of and "consisting of may be replaced with either of the other two terms. The terms and expressions that have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of

excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

We claim:

1. An abuse deterrent tablet comprising:
    a) at least one layer or coating comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 75,000 to about 600,000; and
    b) at least one layer or coating comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 100,000 to about 15,000,000.

2. The tablet as defined in claim 1 wherein the tablet is a bilayer tablet or a trilayer tablet.

3. The tablet as defined in claim 2 wherein the tablet is a trilayer tablet comprising:
    a) a first layer comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 75,000 to about 600,000;
    b) a second layer comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 100,000 to about 15,000,000; and
    c) a third layer comprising either: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 75,000 to about 600,000, or (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 100,000 to about 15,000,000.

4. The tablet as defined in claim 1 wherein the drug that is subject to abuse is an opioid, sedative or stimulant.

5. The tablet as defined in claim 4 wherein the drug that is subject to abuse is an opioid.

6. The tablet as defined in claim 5 wherein the opioid is selected from the group consisting of buprenorphine, codeine, dihydrocodeine, dihydromorphine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone or pharmaceutically acceptable salts therefore.

7. The tablet as defined in claim 1 wherein a therapeutic amount of the drug that is subject to abuse is released within 60 minutes of administration and exhibits a controlled or sustained release of the drug for 8-24 hours after administration.

8. The tablet as defined in claim 1 wherein a therapeutic amount of the drug that is subject to abuse is released within 45 minutes of administration and exhibits a controlled or sustained release of the drug for 8-24 hours after administration.

9. The tablet as defined in claim 1 wherein a therapeutic amount of the drug that is subject to abuse is released within 30 minutes of administration and exhibits a controlled or sustained release of the drug for 8-24 hours after administration.

10. The tablet as defined in claim 1 wherein the drug that is subject to abuse is released in a first or second order release profile from 0 to about 2.5 hours and zero order or substantially zero order profile thereafter when tested according to a United States Pharmacopeia (USP) in vitro dissolution procedure employing either a USP Type I or II apparatus with 900 ml of biorelevant medium.

11. The tablet as defined in claim 1 wherein the drug that is subject to abuse is released in a first or second order release profile from 0 to about 2.0 hours and zero order or substantially zero order profile thereafter when tested according to a United States Pharmacopeia (USP) in vitro dissolution procedure employing either a USP Type I or II apparatus with 900 ml of biorelevant medium.

12. A method for preparing a modified release abuse deterrent tablet comprising the steps of:

a) preparing a mixture comprising (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 75,000 to about 600,000;

b) feeding the mixture of step (a) into a tablet die;

c) preparing a mixture comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 100,000 to about 15,000,000;

d) feeding the mixture of step (c) into the tablet die containing the mixture of step (a) so that the mixture of step (c) is layered on top of the mixture of step (a) to create a layer composition;

e) compressing the layer composition of step (d) to create a multilayer tablet; and

f) curing the multilayer tablet of step (e) for at least 5 minutes at a temperature of about 60° C to about 90° C.

13. The method as defined in claim 12 further comprising the steps of preparing a mixture comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 75,000 to about 600,000, or a mixture comprising: (i) a drug that is subject to abuse and (ii) about 55% to about 95% of one or more polyethylene oxides having an approximate molecular weight or an average approximate molecular weight of about 100,000 to about 15,000,000, and feeding said mixture into the tablet die containing the mixtures of step (a) and step (c) so the mixture of this further step is layered on top of the mixture of step (c) to create a layer composition.

14. The method as defined in claim 12 wherein the drug that is subject to abuse is an opioid, sedative or stimulant.

15. The method as defined in claim 14 wherein the drug that is subject to abuse is an opioid.

16. The method as defined in claim 15 wherein the opioid is selected from the group consisting of buprenorphine, codeine, dihydrocodeine, dihydromorphine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone or pharmaceutically acceptable salts therefore.

17. The method as defined in claim 12 wherein a therapeutic amount of the drug that is subject to abuse is released from the cured multilayer tablet within 60 minutes of administration and exhibits a controlled or sustained release of the drug for 8-24 hours after administration.

18. The method as defined in claim 12 wherein a therapeutic amount of the drug that is subject to abuse is released from the cured multilayer tablet within 45 minutes of administration and exhibits a controlled or sustained release of the drug for 8-24 hours after administration.

19. The method as defined in claim 12 wherein a therapeutic amount of the drug that is subject to abuse is released from the cured multilayered tablet within 30 minutes of administration and exhibits a controlled or sustained release of the drug for 8-24 hours after administration.

20. The method as defined in claim 12 wherein the drug that is subject to abuse is released from the cured multilayer tablet in a first or second order release profile from 0 to about 2.5 hours and zero order or substantially zero order profile thereafter when tested according to a United States Pharmacopeia (USP) in vitro dissolution procedure employing either a USP Type I or II apparatus with 900 ml of biorelevant medium.

21. The method as defined in claim 12 wherein the drug that is subject to abuse is released from the cured multilayer tablet in a first or second order release profile from 0 to about 2.0 hours and zero order or substantially zero order profile thereafter when

tested according to a United States Pharmacopeia (USP) in vitro dissolution procedure employing either a USP Type I or II apparatus with 900 ml of biorelevant medium.

Figure 1

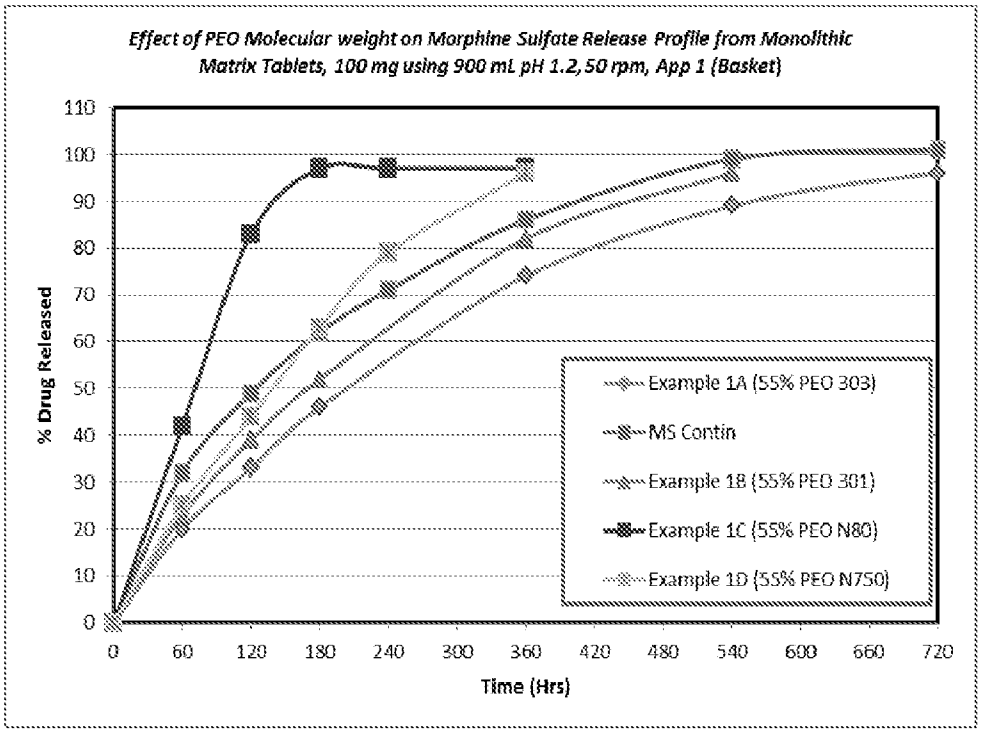

Effect of PEO Molecular weight on Morphine Sulfate Release Profile from Monolithic Matrix Tablets, 100 mg using 900 mL pH 1.2, 50 rpm, App 1 (Basket)
% Drug Released
Time (Hrs)
0
10
20
30
40
50
60
70
80
90
100
110
0
60
120
180
240
300
360
420
480
540
600
660
720
Example 1A (55% PEO 303)
MS Contin
Example 1B (55% PEO 301)
Example 1C (55% PEO N80)
Example 1D (55% PEO N750)

Figure 2

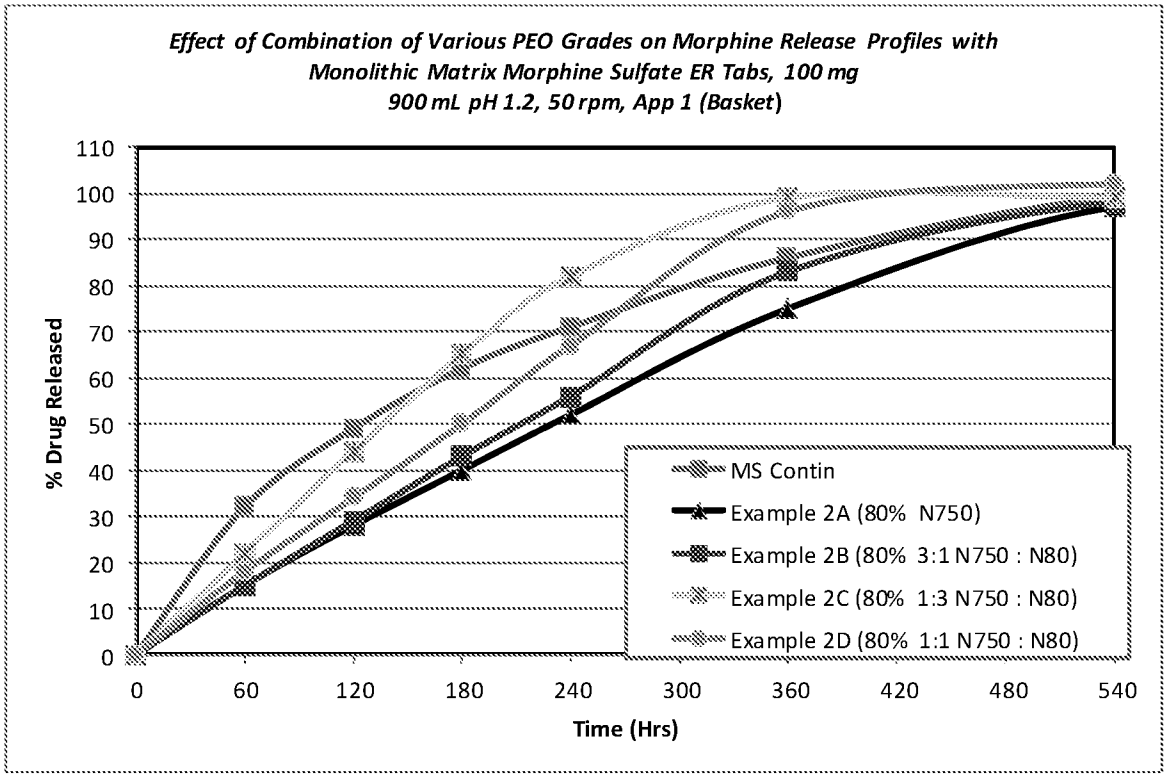

Effect of Combination of Various PEO Grades on Morphine Release Profiles with Monolithic Matrix Morphine Sulfate ER Tabs, 100 mg
900 mL pH 1.2, 50 rpm, App 1 (Basket)
% Drug Released
Time (Hrs)
0
10
20
30
40
50
60
70
80
90
100
110
0
60
120
180
240
300
360
420
480
540
MS Contin
Example 2A (80% N750)
Example 2B (80% 3:1 N750 : N80)
Example 2C (80% 1:3 N750 : N80)
Example 2D (80% 1:1 N750 : N80)

Figure 3

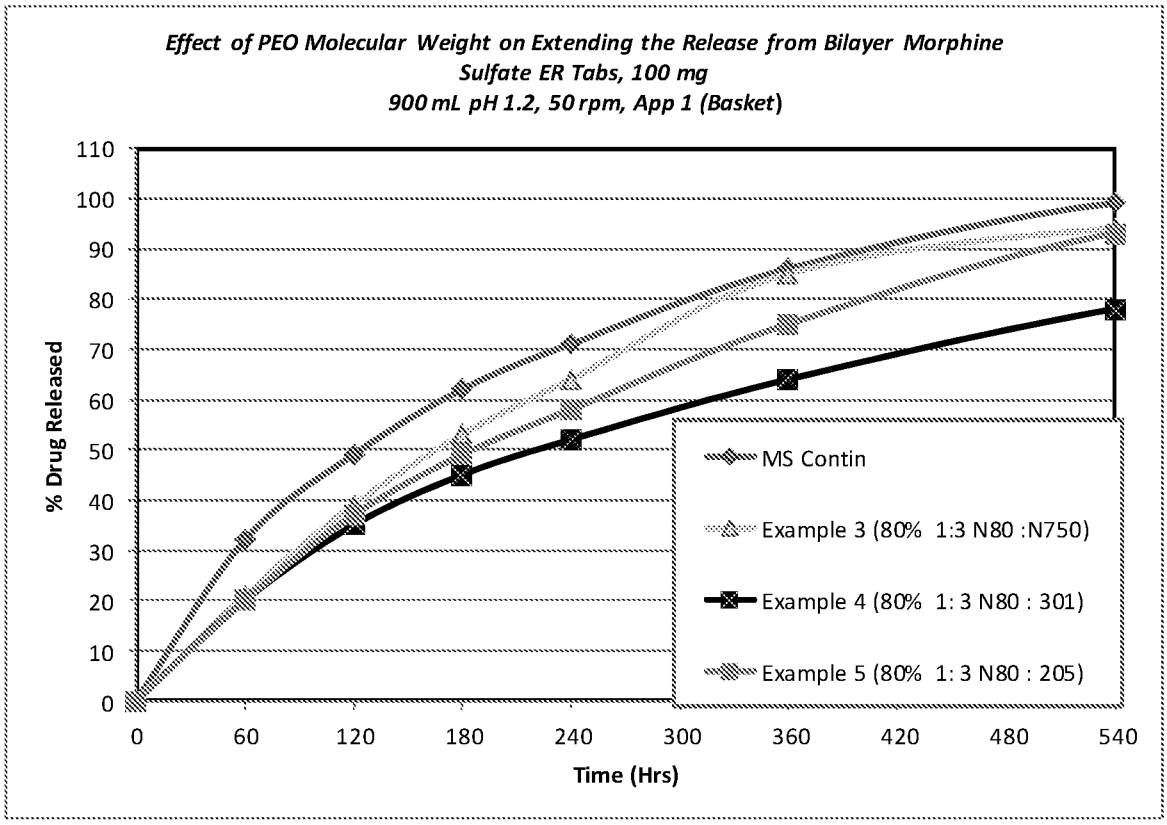

Effect of PEO Molecular Weight on Extending the Release from Bilayer Morphine Sulfate ER Tabs, 100 mg
900 mL pH 1.2, 50 rpm, App 1 (Basket)
% Drug Released
Time (Hrs)
0
10
20
30
40
50
60
70
80
90
100
110
0
60
120
180
240
300
360
420
480
540
MS Contin
Example 3 (80% 1:3 N80 :N750)
Example 4 (80% 1: 3 N80 : 301)
Example 5 (80% 1: 3 N80 : 205)

Figure 4

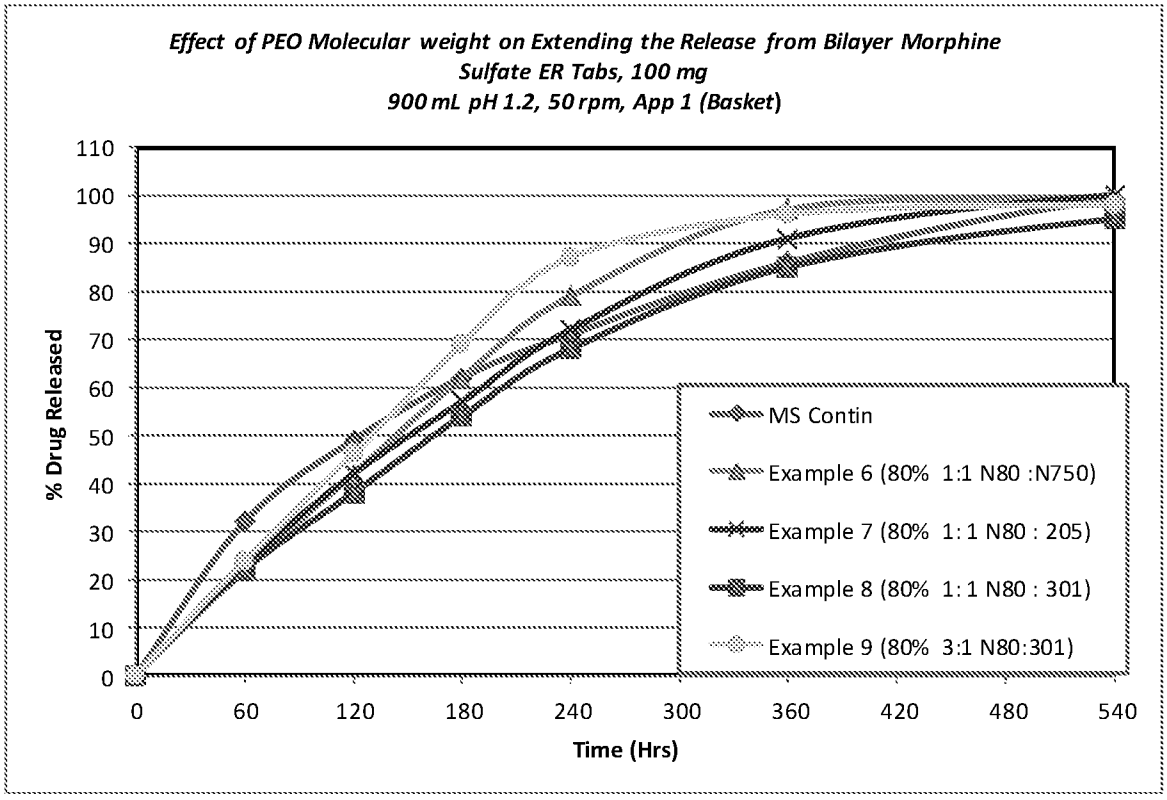

Effect of PEO Molecular weight on Extending the Release from Bilayer Morphine Sulfate ER Tabs, 100 mg
900 mL pH 1.2, 50 rpm, App 1 (Basket)
% Drug Released
Time (Hrs)
0
10
20
30
40
50
60
70
80
90
100
110
0
60
120
180
240
300
360
420
480
540
MS Contin
Example 6 (80% 1:1 N80 :N750)
Example 7 (80% 1:1 N80 : 205)
Example 8 (80% 1:1 N80 : 301)
Example 9 (80% 3:1 N80:301)

Figure 5

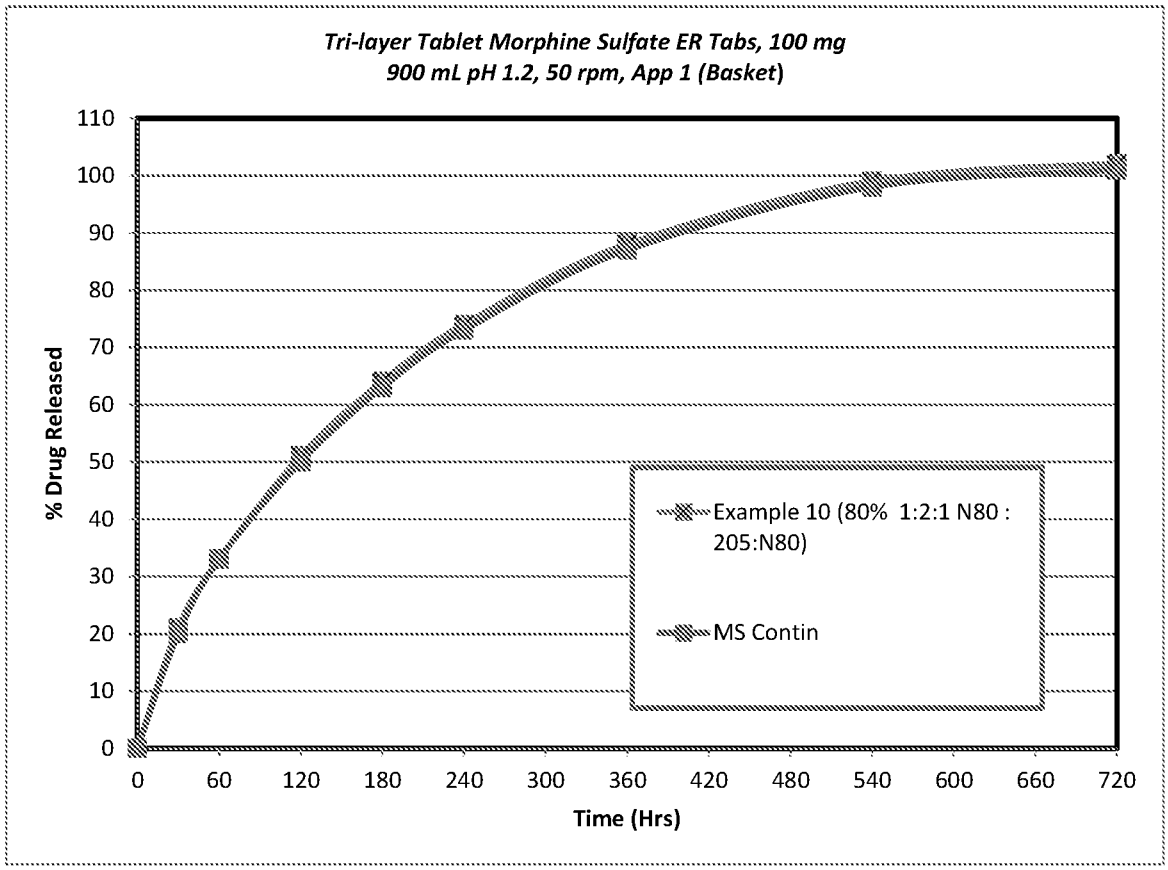
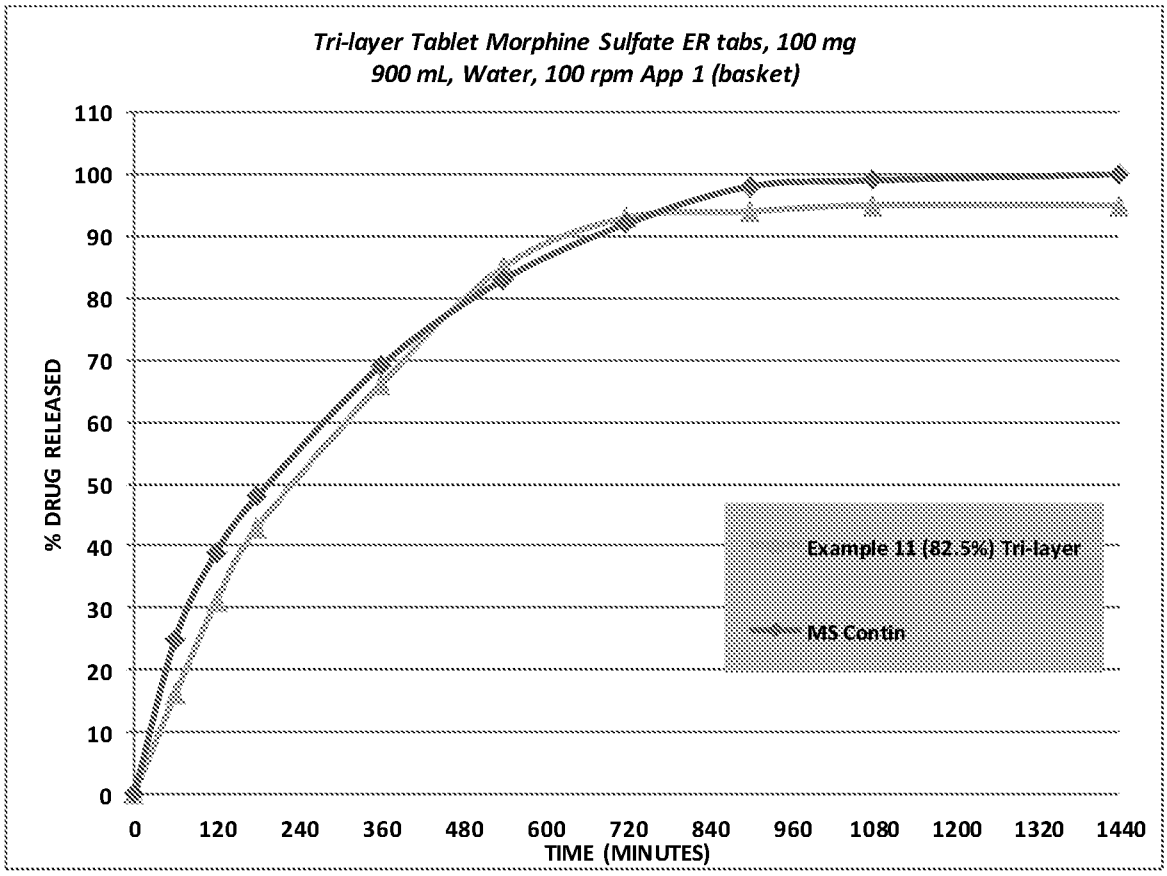

Tri-layer Tablet Morphine Sulfate ER Tabs, 100 mg
900 mL pH 1.2, 50 rpm, App 1 (Basket)
% Drug Released
110
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360
420
480
540
600
660
720
Time (Hrs)
Example 10 (80% 1:2:1 N80 : 205:N80)
MS Contin

Figure 6


Tri-layer Tablet Morphine Sulfate ER tabs, 100 mg
900 mL, Water, 100 rpm App 1 (basket)
% DRUG RELEASED
110
100
90
80
70
60
50
40
30
20
10
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
TIME (MINUTES)
Example 11 (82.5%) Tri-layer
MS Contin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2016/062010

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/22 *(2006.01)*
A61K 47/30 *(2006.01)*
A61P 25/36 *(2006.01)*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/22, 47/30, A61P 25/36

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, CIPO, ChemlDplus Advanced, DEPATISnet, DWPI, Depatisnet, EAPATIS, ESP@CE, ESP@CENET, KIPRIS, MEDLINE, NCBI, PAJ, PatSearch, PubMed, RUPTO, STN, USPTO, WIPO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 9 044 402 B2 (EGALET LTD.) 02.06.2015, abstract, col. 3-6, 13-14, 20, 31-32, claims 6-9, 12	1-21
Y	WO 2009/089494 A2 (CHARLESTON LABORATORIES, INC.) 16.07.2009, abstract, claims 1, 18, 24-32	1-21
Y	WO 2008/060964 A2 (OREXIGEN THERAPEUTICS, INC. et al.) 22.05.2008, claims 1,3, 21-22, 26-28, 46	2-3, 13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2017 (30.01.2017)	06 March 2017 (06.03.2017)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37	Authorized officer D.Igumnov Telephone No. 495 531 65 15