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(54) **Title**: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

(57) **Abstract**: Controlled release dosage forms are described herein. The controlled release formulations described herein provide prolonged delivery of high dose drugs that are highly water soluble and highly hygroscopic. In specific embodiments, controlled release dosage forms for delivery of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. The controlled release dosage forms described herein may incorporate both controlled release and immediate release formulations in a single unit dosage form.

CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

Technical Field

[0001] This disclosure relates to controlled release drug compositions.

Background

[0002] For some drugs, it is difficult to formulate a controlled release dosage form that maintains an effective concentration of the drug over a sustained period of time. In particular, drugs that are administered at a high dose, drugs having a low molecular weight, and drugs with high water solubility make formulation of a controlled release dosage form challenging. For example, in the context of a controlled release drug formulation produced as a unit dosage form for oral administration, drugs that must be administered at a high dose constrain the amount of rate controlling excipients that can be used in formulating a drug composition that is both capable of sustained delivery of therapeutic doses of the drug and exhibits a size and shape suited to oral administration. Low molecular weight and high-solubility drugs may also readily permeate films and matrices that might otherwise be used to control release, and high solubility drugs are not suited to some drug delivery approaches, particularly where zero-order release kinetics are desired. An example of a drug that is administered at a high dose, has a low molecular weight, and high water solubility, is gamma-hydroxy butyrate (GHB), particularly the sodium salt of GHB.

[0003] Initial interest in the use of GHB as a potential treatment for narcolepsy arose from observations made during the use of GHB for anesthesia. Unlike traditional hypnotics, GHB induces sleep that closely resembles normal, physiologic sleep (Mamelak et al., Biol Psych 1977:12:273-288). Therefore, early investigators administered GHB to patients suffering from disorders of disturbed sleep, including narcolepsy (Broughton et al. in Narcolepsy, NY, NY: Spectrum Publications, Inc. 1976:659-668), where it was found to increase total nocturnal sleep time, decrease nocturnal awakenings and increase Stage 3-4 (slow wave) sleep. Three open-label and two placebo-controlled studies provided a body of evidence demonstrating that improvements in nocturnal sleep were associated with a reduction in cataplexy and

improvements in excessive daytime sleepiness (Broughton et al., Can J. Neurol Sci 1979; 6:1-6, and Broughton et al., Can J. Neurol Sci 1980; 7:23-30).

[0004] An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., J. Muscoloskel. Pain, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., Psychosom. Med., 37, 341 (1975).

[0005] Fibromyalgia patients frequently report symptoms similar to those of patients with post-infectious neuromyasthenia, also referred to as chronic fatigue syndrome (CFS). CFS is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion. They often must function at a level of activity substantially lower than their capacity before the onset of illness. In addition to these key defining characteristics, patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. CFS can persist for years. Compared with fibromyalgia patients, chronic fatigue patients have similarly disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

[0006] Scharf et al. conducted an open-label study to evaluate the effects of GHB on the sleep patterns and symptoms of non-narcoleptic patients with fibromyalgia (Scharf et al., J Rheumatol 1998;25: 1986-1990). Eleven patients with previously

confirmed diagnosis of fibromyalgia who reported at least a 3-month history of widespread musculoskeletal pain in all body quadrants and tenderness in a least 5 specific trigger point sites participated in the study. Results showed that patients reported significant improvements in the subjective assessments of their levels of pain and fatigue over all 4 weeks of GHB treatment as compared to baseline, as well as a significant improvement in their estimates of overall wellness before and after GHB treatment.

[0007] WO 2006/053186 to Frucht describes an open label study of 5 patients with hyperkinetic movement disorders including ethanol responsive myoclonus and essential tremor. Sodium oxybate, a sodium salt of GHB, was reported to produce dose-dependent improvements in blinded ratings of ethanol responsive myoclonus and tremor and was said to be tolerated at doses that provided clinical benefit.

[0008] XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH = 7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration during the night.

[0009] Liang et al. (published U.S. patent application US 2006/0210630 Al) disclose administration of GHB using an immediate release component and a delayed release component. The delayed release component of the formulations taught in Liang et al., however, function in a pH dependent manner.

Brief Description of the Drawings

[0010] FIG. 1 shows the delivery profile of sodium oxybate controlled release formulations as described herein.

[0011] FIG. 2 shows the delivery profile of integrated dosage forms as described herein having an immediate release component and a controlled release component.

[0012] FIG. 3 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

[0013] FIG. 4 provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

[0014] FIG. 5 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

[0015] FIG. 6 provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

[0016] FIG. 7 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by varying the molecular weight of a pore former included within a functional coating.

[0017] FIG. 8 provides a graph illustrating that suitable controlled release profiles from dosage forms prepared according to the present description can be achieved even with functional coatings formed using different grades of the same base polymer material.

[0018] FIG. 9A and FIG. 9B provide graphs illustrating the effects of alcohol on the delivery profile of sustained-release formulations prepared as described herein.

[0019] FIG. 10 provides a graph illustrating the controlled release performance achieved by dosage forms as described herein having functional coatings prepared from aqueous dispersions of ethylcellulose as the base polymer.

[0020] FIG. 11 provides a graph illustrating the controlled release performance achieved by dosage forms as described herein incorporating calcium oxybate as the drug.

[0021] FIG. 12 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment B).

[0022] FIG. 13 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment C).

[0023] FIG. 14. provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E).

Detailed Description

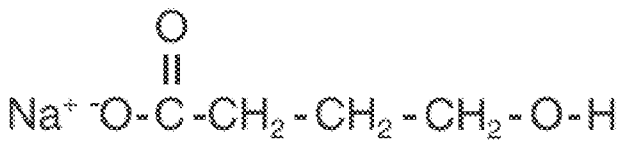
[0024] Formulations and dosage forms for the controlled release of a drug are described herein. Formulations described herein are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dosage form, and in one such embodiment, the controlled release formulation is provided as a coated tablet.

[0025] The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a controlled release (CR) unit dosage form or may be a separate immediate release composition. Therefore, an immediate release (IR) component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the IR component may also be formulated as part of a single dosage form that integrates both the IR and CR components. In such an embodiment, the pharmaceutical formulation may be provided in the form of the coated tablet or capsule.

[0026] In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase “dosed together” refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a

sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

[0027] An example of a drug that may be used with the controlled release dosage forms described herein is GHB. It should be noted that embodiments of controlled release dosage forms comprising GHB, and other drugs, are presented herein for purposes of example only and not for purposes of limitation. The formulations and unit dosage forms provided herein can be utilized to achieve controlled release of GHB, as well as pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The structure of the sodium salt of GHB, sodium oxybate, is given as formula (I):



Methods of making GHB salts are described, for example, in U.S. Patent No. 4,393,236, which is incorporated herein by reference.

[0028] Formulating GHB into a unit dosage form presents various challenges, and such challenges are magnified in the context of formulating a unit dosage form providing controlled release of GHB. For instance, GHB is very soluble, generally requires a relatively high dose, has a low molecular weight, and exhibits a short circulating half-life once administered. Therefore, a controlled release unit dosage form of GHB should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration. However, controlled release formulations typically require the addition of significant amounts of excipients or rate controlling materials to control the delivery of drug, and the presence and need for such materials often limits the drug loading available for a given controlled release technology. Additionally, low molecular weight drugs, such as GHB, typically exhibit high permeability through films and matrices. Even further, high water solubility increases drug mobility and may preclude the use of some approaches utilized to achieved a controlled release dosage form.

[0029] Another challenge to achieving a formulation capable of delivering GHB over a sustained period of time is the fact that some forms of GHB, such as the sodium salt of GHB, sodium oxybate, are extremely hygroscopic. As used herein, the term "hygroscopic" is used to describe a substance that readily absorbs and attracts water from the surrounding environment. The hygroscopic nature of sodium oxybate presents significant challenges to the formulation, production, and storage of dosage forms capable of delivering sodium oxybate over a sustained period of time. Despite the challenges noted, formulations and unit dosage forms providing controlled release of GHB are described herein.

A. Controlled Release Formulations

[0030] As used herein, the term "controlled release" describes a formulation, such as, for example, a unit dosage form, that releases drug over a prolonged period of time. The controlled release compositions described herein may be provided as a unit dosage form suitable for oral administration. In each embodiment of the controlled release compositions described herein, the drug incorporated in such compositions may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB.

[0031] In certain embodiments, the controlled release compositions described herein are formulated as unit dosage forms that deliver therapeutically effective amounts of drug over a period of at least 4 hours. For example, controlled release unit dosage forms as described herein may be formulated to deliver therapeutically effective amounts of drug over a period selected from about 4 to about 12 hours. In specific embodiments, the controlled release dosage forms described herein deliver therapeutically effective amounts of drug over a period selected from about 4, about 5, about 6, about 7, about 8, about 9, about 10 hours, and about 12 hours. In other such embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours, about 6 to about 10 hours, about 6 to about 12 hours, about 7 to about 10 hours, about 7 to about 12 hours, about 8 to about 10 hours, and from about 8 to about 12 hours. In yet other embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 5 to about 9 hours,

about 5 to about 8 hours, about 5 to about 7 hours, and about 6 to about 10 hours, about 6 to about 9 hours, and about 6 to about 8 hours.

[0032] The compositions described herein facilitate production of controlled release dosage forms that provide a substantially constant drug release rate. In one embodiment, the controlled release dosage forms may be formulated to deliver not more than approximately 30% of the drug initially contained within the controlled release dosage form in the first hour post-administration. When referencing the amount of drug initially contained in the controlled release dosage form or "initial drug content" of the controlled release dosage form, for purposes of the present description, such amount refers to the total amount of drug included in the controlled release composition prior to administration to a patient.

[0033] As is detailed herein, the controlled release dosage forms according to the present description include a controlled release component (also referred to as a controlled release "formulation") and, optionally, an immediate release component (also referred to as an immediate release "formulation" or an immediate release "coating"). In specific embodiments, the controlled release dosage forms described herein may be formulated to deliver drug to the gastro-intestinal tract at desired rates of release or release profiles. For example, in some embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 10% to about 60% of the drug initially contained within the controlled release component of the controlled release dosage form during the first two hours post-administration, and not more than about 40% to about 90% of the drug initially contained within the controlled release component of the controlled release dosage form during the first four hours post-administration. In other embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more not more than about 40% of the drug initially contained within the controlled release component in the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release component during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release component during the first four hours post-administration. In still other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 30% of the initial drug content in the controlled release component in the first hour post-administration, not more than

about 60% of the initial drug content in the controlled release component during the first two hours post-administration, and not more than about 90% of the initial drug content of the controlled release component during the first four hours post-administration. In other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 50% of the initial drug content of the controlled release component during the first hour post-administration, between about 50 and about 75% of the initial drug content of the controlled release component after two hours, and not less than 80% of the initial drug content of the controlled release component after four hours post administration. In still other embodiments, a controlled release dosage form as described herein may be formulated release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component during the first hour post-administration, between about 5 and about 30% of the initial drug content of the controlled release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

[0034] Due to the rapid clearance of GHB from the plasma, when GHB is administered in an immediate release formulation, even large doses of the drug (e.g., a dose of between about 2.25 g and 4.5 g) generally result in plasma levels below 10 ug/mL within 4 hours of ingestion. In order to achieve therapeutic efficacy, therefore, a second, equal, dose is often required within 4 hours after administration of the first dose, and some patients may require administration of a second as soon

as 2.5 hours after administration of the first dose. In such an instance, in order to maintain therapeutic efficacy, 4.5 g to 9 g of drug must be administered to the patient in two separate doses within 2 to 5 hours. This also requires that the second dose be administered during the night, which requires that the patient be awakened to take the second dose. The result is that the Cmax/Cmin ratio of GHB over an six hour period can be greater than 4 and is often greater than 8. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 μg/mL. In certain such embodiments, a GHB controlled release dosage form as described herein provides a Cmax to Cmin ratio of GHB over a prolonged period of time after administration selected from less than 3 and less than 2. Therefore, in specific embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. For example, in particular embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 3 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 μg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. In still other embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 μg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours .

[0035] Drug delivery performance provided by the dosage forms described herein can be evaluated using a standard USP type 2 or USP type 7 dissolution apparatus set to 37°C ± 2°C under the conditions described, for example, in the experimental

examples provided herein. The dissolution media may be selected from dissolution media known by those of skill in the art such as at least one of purified water, 0.1N HCl, simulated intestinal fluid, and others.

[0036] In particular embodiments, the controlled release formulations described herein work to reduce inter patient variability in delivery of GHB. In particular, controlled release formulations described herein provide time dependent release of GHB over a sustained period of time. Previous references have described targeted release dosage forms of GHB that function in a pH dependent manner. However, due to inter-subject variability in gastrointestinal pH conditions, delivery of GHB from such dosage forms can be inconsistent. Moreover, because relatively high doses of GHB are typically required for therapeutic effect, unit dosage forms of GHB are also relatively large and may be retained for a period of time in the stomach, which can lead to intra- and inter-patient variability in dose delivery of GHB from pH dependent delivery systems due to variability in gastric retention time. Further, patients with fibromyalgia have an increased chance of also suffering from irritable bowel syndrome (see, e.g., Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder, Int J Colorectal Dis. 2001 Aug;16(4):211-5.) Irritable bowel syndrome is also associated with delayed gastric emptying and variable gastric emptying (see, e.g., Dyspepsia and its overlap with irritable bowel syndrome, Curr Gastroenterol Rep. 2006 Aug;8(4):266-72.) Therefore many patients with fibromyalgia and suffering from irritable bowel syndrome may experience more variability in gastric transit or prolonged gastric transit. By operating in a time dependent manner once placed in an aqueous environment, controlled release formulations described herein offer consistent GHB delivery characteristics and reduce the likelihood of undesirable intra- and inter-patient inconsistencies in dose delivery that may result from variances in gastric retention time that can occur between different patients and different patient populations.

[0037] Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (*See, e.g.*, U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience,

yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present description is formulated to deliver more than 90% of the GHB included within the controlled release forumulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

[0038] The controlled release dosage forms described herein may comprise a relatively high concentration of drug that can, in some instances, harm a patient if the formulation releases the drug at a rate that is faster than the intended sustained rate. This rapid release of the drug is sometimes referred to as "dose dumping." To avoid this potential danger, certain embodiments of the controlled release dosage forms described herein may comprise formulations that are resistant to dose dumping. Some users may intentionally attempt to increase the drug release rate of the controlled release dosage form using alcohol (e.g., potential abusers may take the controlled release dosage form prior to, simultaneously with, or after consuming an alcoholic beverage or, alternatively, may seek to extract the drug from the controlled release dosage form by placing the dosage form in solution containing alcohol). Other users may take the dosage form with alcohol, not necessarily in a manner considered abuse of the drug or alcohol, but without regard for the potential risks of dose dumping or contraindication of the two substances. In one embodiment, a controlled release dosage form as disclosed herein may include a coating composition that is resistant to alcohol or that does not dissolve substantially faster in alcohol. In one such embodiment, the controlled release dosage form may comprise the drug sodium oxybate and include a coating composition including ethylcellulose that is resistant to dose dumping in alcohol. In another embodiment, the controlled release dosage form may include a coating composition that is resistant to dose dumping after administration. For example, the controlled release

dosage form may include a coating composition that is resistant to dose dumping in the GI tract after being exposed to gastric fluid and intestinal fluid.

[0039] In certain embodiments, the controlled release formulations described herein are provided as a coated tablet composition having a controlled release core coated by a functional overcoat. The composition of the controlled release core provided in such embodiments facilitates high drug loading, thereby, rendering the coated tablet suitable for formulation and sustained delivery of drugs administered at high doses. The functional overcoat works to control delivery of drug from the controlled release core and maintain the structural integrity of the dosage form over time. In addition to the controlled release core and functional overcoat, the coated tablet composition as described herein may further include a moisture barrier or cosmetic coating disposed over the functional overcoat.

I. Controlled Release Component

[0040] Where the controlled release formulations described herein are formulated as a coated tablet having a controlled release core (CR core), the CR core includes at least one drug substance to be delivered from the controlled release dosage form. The drug included in the CR core may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Examples of suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The CR core is formulated and configured to be suitable for oral administration. In one embodiment, coated tablets as described herein may be administered to provide a dose of GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvate or complex of GHB in a range of about 500 mg to about 12 g of drug in one or more tablets. In particular embodiments, a CR core included in a controlled release dosage form according to the present description may include an amount of drug selected from about 100 mg to about 2,000 mg. In some such embodiments, the amount of drug included in the CR core may be selected from up to about 250 mg, 400 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1,000 mg, 1,100 mg, 1,200 mg, 1,400 mg, 1,500 mg, 1,600 mg, 1,700 mg, 1,800 mg, 1,900 mg, and 2,000 mg. In certain such embodiments, the amount of drug included in a CR core as described herein may range from about 500 mg to about 2,000 mg, such as, for example, about 500 mg to 1,000 mg, about 600 mg to 1,000 mg, about 600 mg to 900 mg, about 600 mg to 800 mg, about 700 mg to 1,000 mg, about 700 mg to

900 mg and about 700 mg to 850 mg. In other such embodiments, the amount of drug included in a CR core as described herein may range from about 700 mg to about 2,000 mg, such as, for example, about 700 mg to 1,500 mg, about 700 mg to 1,400 mg, about 700 mg to 1,300 mg, about 700 mg to 1,200 mg, about 700 mg to 1,100 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg, and about 700 mg to 850 mg.

[0041] In one embodiment, the controlled release dosage form comprises a CR core wherein the relative amount drug in the CR core is at least 90% or greater by weight. In another embodiment, the relative amount of drug in the CR core ranges from between about 90% and 98%, about 91% and 98%, about 92% and 98%, about 93% and 98%, about 94% and 98%, about 95% and 98%, about 96% and 98%, and between about 97% and 98% by weight of the CR core. In yet another embodiment, the relative amount of drug in a CR core may be present at an amount selected from about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and 98% by weight of the CR core. In certain such embodiments, the amount of drug in the CR core may range from about 94 to 98%, 94 to 97%, 94 to 96%, 95 to 98%, 95 to 97%, and 95 to 96.5 % by weight of the CR core.

[0042] In one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with one or more excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment, a CR core as disclosed herein can include one or more binders that are known for use in tablet formulations. In one such embodiment, a CR core may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the CR core included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight. In certain such embodiments, the amount of binder included in the CR core

may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

[0043] The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

[0044] The CR core may also include one or more surfactants. In certain embodiments, the CR core may include a tableted composition that may comprise one or more surfactants selected from, for example, ionic and non-ionic surfactants. In one such embodiment, CR core may include at least one anionic surfactant, including docusate sodium (dioctyl sulfosuccinate sodium salt) and sodium lauryl sulfate. In yet another embodiment, the CR core may include at least one non-ionic surfactant selected from including polyoxyethyelene alkyl ethers, polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate. In specific embodiments, one or more surfactants included in a CR core as disclosed herein may be present, for example, in an amount of up to about 3.0% by weight of the CR core. For example, in certain embodiments, the CR core may include one or more surfactants present in a range selected from about 0.01% to 3%, about 0.01% to 2%, about 0.01% to 1%, about 0.5% to 3%, about 0.5% to 2%, and about 0.5% to 1% by weight of the CR core.

[0045] The CR core included in controlled release dosage form as disclosed herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin,

dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. In another embodiment, a CR core may be prepared by blending a drug and other excipients together, and the forming the blend into a tablet, caplet, pill, or other dosage form according to methods known by those of skill in the art. In certain embodiments, a controlled release formulation as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or triangular. In one such embodiment, the surfaces of the CR core may be flat, round, concave, or convex.

The CR core composition included in a controlled release formulation provided as a coated tablet dosage form as described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and direct compression followed by compression on a conventional rotary tablet press as described in Remington, 20th edition, Chapter 45 (Oral Solid Dosage Forms).

II. Functional Coating Composition

[0046] Where the controlled release formulations as described herein are provided as a coated tablet composition, the CR core is coated with a functional coating. The coating composition works to preserve the integrity of the unit dosage form post administration and serves to facilitate controlled release of drug from the CR core. In certain embodiments, the coating composition is formulated to facilitate controlled release of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In one such embodiment, the coating composition is sufficiently robust to preserve the integrity of the coated tablet pre-and post-administration, yet is subject to disintegration or crushing as it passes through a patient's gastrointestinal tract and after all or substantially all the drug substance contained within the controlled release formulation has been delivered. Such a feature reduces the risk that bezoars formed from intact dosage form shells will form or be maintained within the GI tract of a patient, which may be of particular concern where the drug to be delivered must be administered at high doses using multiple unit dosage forms.

[0047] In one embodiment, a functional coating composition as disclosed herein may control, at least in part, the rate of release of the drug to be delivered from the

CR core into the gastrointestinal tract. In one embodiment, the functional coating composition provides a functional coat that partly or fully covers the CR core included in the controlled release dosage form. In one embodiment, the functional coating composition as disclosed herein may include a polymer or blends of compatible polymers that are water soluble or that are water insoluble and selected to exhibit desired permeability characteristics. In one embodiment, the functional coating composition has a permeability that may be adjusted according the solubility of the drug used in the CR core. In one such embodiment, the functional coating composition may comprise one or more water insoluble polymers that may swell but do not substantially dissolve in the GI tract. For example, in particular embodiments, a functional coating composition as disclosed herein may comprise a rate-limiting film that includes at least one of ethylcellulose, cellulose acetate, such as CA-398. In other embodiments, the functional coating may include combinations of ethylcellulose with ammonio methacrylate copolymers, such as EUDRAGIT RS, EUDRAGIT RL, and combinations thereof. Suitable ethylcellulose materials are readily commercially available, and include, for example, ETHOCEL ethylcellulose polymers. Where ethylcellulose is used to form the functional coating, the physical characteristics of the coating composition and residual shell may be modified by adjusting the molecular weight of the ethylcellulose. For example, different grades of ethylcellulose, including, but not limited to, 4cP, 7cP, 10cP, and 20cP grades, may be used to achieve a coating composition having desired physical characteristics.

[0048] A functional coating composition as disclosed herein may include one or more base polymer and at least one pore-former. In one embodiment, the base polymer content may range from about 50% to about 80% by weight of the coating composition. In certain embodiments, the base polymer may be present in an amount ranging from about 50% to 75%, about 55% to 75%, about 60% to 75%, and about 65% to 75% by weight of the coating composition. In one such embodiment, the base polymer may be present in an amount selected from about 50%, 55%, 60%, 65%, 70%, 75%, and 80% by weight of the coating composition. In cases where a filler material is used (e.g., insoluble, non film-forming material such as magnesium stearate, talc, or fumed silica), these limits apply to the composition of the remaining non-filler components in the film.

[0049] The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In

one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former, such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

[0050] Where used in the functional coating composition, a pore former or a pore-forming agent can be selected to modify the permeability of the coating composition provided over the CR core. For example, the permeability of the functional coating composition may be increased by including one or more pore formers or pore-forming agents in the coating composition. In one embodiment, the pore formers disclosed herein may be soluble in water. In one such embodiment, when a CR dosage form comprising a functional coating composition with at least one pore former is swallowed by a patient and contacted with gastric fluid, the water-soluble pore formers may dissolve and form pores or channels in the coating through which the drug is released. It is possible to use an enteric component as part or all of the pore former in the coating composition. Examples of such materials that may be used as a pore former in the context of the present description include cellulose acetate phthalate, methacrylic acid–methyl methacrylate copolymers, and polyvinyl acetate phthalate. However, incorporating enteric components in the film may result in delivery characteristics that exhibit some level of sensitivity to gastric and intestinal transit times.

[0051] Where included, the amount and nature of the pore former included in the functional coating composition can be adjusted to obtain desired release rate characteristics for a given drug substance. In one embodiment, the functional coating composition may include an amount of pore former that ranges from about 20% to about 50% by weight of the coating composition. For example, the pore former may be present in an amount ranging from about 20% to 45%, about 25% to 45%, about 30% to 45%, and about 35% to 45% by weight of the functional coating composition. In one such embodiment, the pore former may be present in an amount selected from about 20%, 25%, 30%, 35%, 40%, 45%, and 50% by weight of the functional coating composition.

[0052] The functional coating composition as disclosed herein may also comprise one or more plasticizers. In certain embodiments, the functional coating composition may include a plasticizer such as triethyl citrate or dibutyl sebacate. In one such embodiment, a plasticizer may be present in the functional coating composition in an amount ranging from about 5% to 15% by weight relative to the base polymer. In certain embodiments, the functional coating composition may include a plasticizer in an amount selected from about 5%, 8%, 10%, 12%, and 15% by weight relative to the base polymer.

[0053] The functional coating composition as disclosed herein may also include an anti-tack agent. For example, certain embodiments of the functional coating composition may include an anti-tack agent selected from one or more of talc, glyceryl monostearate, and magnesium stearate. Many of the anti-tack agents are also suitable fillers. Addition of fillers, especially magnesium stearate, is one way to make the film more brittle and the dosage form more prone to crushing as it transits through the GI. Depending on forces encountered in the GI, varying the filler level in the film may allow one to adjust the duration, or extent of drug delivered, at which breach of the film and abrupt release of remaining contents occurs.

[0054] The functional coating composition as disclosed herein may be applied to a CR core at a weight that facilitates a suitable combination of sustained drug release and dosage form structural integrity. In certain embodiments, the functional coating composition may be applied at a weight of about 10 to about 100 mg. In particular embodiments, for example, the functional coating may be applied at a weight selected from about 20 to 60 mg, about 20 to 50 mg, about 20 to 40 mg, about 20 to 30 mg, about 30 to 60 mg, about 30 to 50 mg, about 30 to 40 mg,

about 40 to 60 mg, about 40 to 50 mg, and about 50 to 60 mg. These ranges are useful for oval tablets of about 500 mg to about 1000 mg in weight. Alternatively, for a given tablet size or weights, the functional coating composition as disclosed herein may be applied at between about 2.5% and 7.5% of the tablet weight. For example, in one such embodiment, where the tablet is a 2,000 mg oval tablet, a functional coating composition may be applied at a weight ranging from about 50 mg to about 150 mg.

[0055] In addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition. For example, a more rapid release rate will generally be achieved as the amount of a given pore former included in the functional coating composition is increased or the thickness or weight of the coating composition applied over the CR core is decreased. Conversely, a slower or more controlled release may be achieved, generally, as relatively less of a given pore former is included in the functional coating composition or the thickness or weight of the coating composition applied to the CR core is increased. Additionally, in certain embodiments, the release rate of drug from the CR core may be adjusted by modifying the water content of the functional coating composition. For example, increasing the water content of the functional coating composition may increase the release rate of drug the CR core.

[0056] The functional coating compositions as disclosed herein may be applied to a CR core according to conventional coating methods and techniques. In one embodiment, the functional coating composition as disclosed herein may be applied using a conventional perforated pan coater. In another embodiment, the functional coating composition may be applied using an aqueous pan-coating process. In one such embodiment, the use of an aqueous pan-coating process may include the use of a latex dispersion. For example, a latex dispersion such as SURELEASE may be used for an ethylcellulose pan-coating process. In another example, a latex dispersion such as EUDRAGIT RS 30 D may be used in a pan-coating process for ammonio-methacrylates. In yet another embodiment, the functional coating composition may be applied using a solvent-based pan-coating process. In one such embodiment, a solvent-based pan-coating process may include the use of an

alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

[0057] In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

[0058] When a controlled release forumulation or dosage form is provided as a coated tablet, in some embodiments, it may be coated with a moisture barrier or a moisture-resistant coating composition. For example, a controlled release dosage form as disclosed herein comprising GHB as the drug substance may include a moisture barrier. In another example, a moisture barrier may be particularly useful where sodium oxybate is used as the drug substance. In one embodiment, the moisture barrier may be a polyvinyl alcohol-based coating, such as OPADRY AMB (Colorcon Inc., Harleysville, PA). In another embodiment, the moisture barrier may be a hydroxypropyl methylcellulose (HPMC)/wax-based coating, such as AQUARIUS MG (Ashland Aqualon, Wilmington, DE). In yet another embodiment, the moisture barrier may be a HPMC/stearic acid-based coating. The moisture barrier as disclosed herein, in some embodiments, may be formed using a reverse enteric material, such as EUDRAGIT E, and may be coated from alcohol or alcohol/water solutions or from an aqueous latex dispersion. In embodiments where the controlled release dosage form is provided as a tablet of about 500 mg-1000 mg in weight, for example, the moisture barrier coating may be applied at a weight selected from about 10 mg to about 60 mg/tablet and about 25 mg to about 50 mg/tablet. In general, a minimum weight is needed to ensure complete coverage of the tablet in light of imperfections in the tablet surface, and a maximum weight is determined by practical considerations, such as coating time, or by the need for better moisture protection.

[0059] As will be readily appreciated, the controlled release dosage form can be further provided with a cosmetic top coat. In one embodiment, a top-coat may be

applied to an existing coating composition such as a moisture barrier. In certain embodiments, a cosmetic top-coat may include at least one of HPMC and copovidone. For example, when the controlled release dosage form includes a coated tablet comprising sodium oxybate as the drug, a top-coat including HPMC, such as for example an HPMC material selected from one or more of HPMC E3, E5, or E15, may be applied over a moisture barrier to improve the effectiveness of the moisture barrier by reducing any seepage of sodium oxybate and water from the surface of the coated tablet.

B. Immediate Release Formulations

[0060] The controlled release formulations described herein can be dosed together with an immediate release (IR) formulation. In one embodiment, the IR formulation may be provided as a separate formulation or dosage form that may be dosed together with a dosage form provided by a controlled release dosage form as described herein. The IR formulation may be provided in any suitable form, such as a dry powder formulation, a tablet or capsule unit dosage form, or a liquid formulation such as a solution or suspension formulation. As used herein, "immediate release" refers to a drug formulation that releases more than about 95% of the drug contained therein within a period of less than one hour after administration. In particular embodiments, the IR component of the compositions described herein release more than about 95% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration. In other embodiments, the IR component of the compositions described herein release more than about 80% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration.

[0061] In certain embodiments, the IR formulation is provided as an immediate release component of a controlled release dosage form as described herein. In one such embodiment, the IR component is provided as a coating over a controlled release component or formulation as desribed herein. A unit dosage form that integrates both controlled release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time.

Furthermore, where the drug to be delivered is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, dosing controlled release and immediate release formulations together may avoid the disadvantages of the current GHB dosing regimens, which can result in highly pulsatile plasma concentrations.

I. Immediate Release Component

[0062] When the immediate release formulation is provided as an integrated IR component of a controlled release dosage form, the amount of drug included in the IR component may range from about 10% to 50% by weight of the total drug included in the integrated dosage form. As used herein, "integrated dosage form" refers to a single unit dosage form that includes both immediate release and controlled release components as described herein. For example, where the drug to be delivered from the immediate release and controlled release formulations incorporated into an integrated dosage form is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB in some embodiments, the drug included in the IR component may comprise about 10% to about 50% by weight of the total drug included in the unit dosage form. In one such embodiment, the drug included in the IR component of an integrated dosage form may comprise about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by weight of the total drug included in the unit dosage form. For example, an integrated dosage form as described herein may contain 1000 mg sodium oxybate, wherein 100 mg to 500 mg sodium oxybate (10% to 50% by weight) is contained within and delivered from the IR component and 500 mg to 900 mg sodium oxybate (50% to 90% by weight) is contained within and delivered from the CR component.

[0063] Where the IR component is provided as a coating over a controlled release dosage form, in certain embodiments, the drug included in the IR component may account for between about 75% and 98% by weight of the IR formulation. In the context of describing an IR component provided over a controlled release dosage form as described or disclosed herein, the controlled release dosage forms referred to include the controlled release formulations described herein, including, in specific embodiments, CR cores coated with a functional coating as described herein. Again, the drug included in such an embodiment may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of

GHB. In certain embodiments, the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

[0064] An IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a tableted overcoat according to conventional tablet coating and binding methods. Alternatively, an IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a film coating, such as, for example, from a solution containing a suitable amount of drug and film former. In one such embodiment, wherein sodium oxybate is the drug included in the IR component, the coating forming the IR component may be coated over a controlled release dosage form from a coating solution that utilizes an alcohol and water solvent. For example, a suitable immediate release coating may be formed using a 20% solution of sodium oxybate in a 60%/40% (w/w) alcohol/water solution that contains a suitable film-former.

[0065] Where the IR component is provided as a film coat and includes one or more film-formers, suitable film formers may be selected from, for example, copovidone, hydroxypropyl cellulose, HPMC, and hydroxymethyl cellulose materials. An IR component containing sodium oxybate as the drug can be applied as a suspension or as a solution by adjusting the water content of the coating mixture. For a suspension, little or no water is added to the alcohol, and the example film formers should be suitable. To prepare a solution, however, the water content of the solvent is increased, for example to 40%, and a smaller set of film formers would be suitable due to the precipitation of most common film formers in the presence of sodium oxybate solution. Hypromellose is one of several potential film formers that is suitable. It is further possible, with more difficulty, to apply the sodium oxybate from an aqueous solution; however, the same limitations on film former applies, and processing is complicated by the hygroscopic nature of the drug. In one embodiment, the IR component useful for use in a controlled release dosage form as described herein includes 91% sodium oxybate and 9% hypromellose (HPMC E-15) that is applied from a solution containing 20% sodium oxybate and 2% HPMC E-15 in a 60/40 w/w ethanol/water solvent.

[0066] Where the IR component of an integrated dosage form is provided as a coating over the controlled release dosage form, the coating forming the IR

component may further include one or more of an anti-tack agent and a plasticizer to facilitate processing and to improve film properties. Furthermore, addition of one or more surfactants, such as sodium lauryl sulfate, may improve the dissolution of IR coatings that contain hydrophobic components (such as anti-tack agents or water-insoluble film formers).

[0067] In embodiments where the IR component is provided as a coating over a controlled release forumlation as described herein, the IR component may be positioned directly over the functional coating of the controlled release formulation. Where desired or necessary based on the drug to be delivered from the IR component and controlled release forumulation included in such an integrated dosage form, the outer surface of the IR component may then be coated with a moisture barrier layer. For example, where the drug delivered by the integrated dosage form is highly hygroscopic, such as, for example, sodium oxybate, a moisture barrier layer over the immediate release coating forming the IR component may be provided.

[0068] The formulation and structure of integrated dosage forms as described herein can be adjusted to provide a combination of immediate release and controlled release performance that suits a particular dosing need. In particular, the formulation and structure of integrated dosage forms as described herein can be adjusted to provide any combination of the immediate release and controlled release performance characteristics described herein. In particular embodiments, for example, the drug delivered from an integrated dosage form as described herein is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, and the integrated dosage form sustains delivery of GHB over a period of from about 4 to about 10 hours. In one such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug as the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours. In another such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45

minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug after the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours.

[0069] Moreover, the ratio of drug release from the IR component and CR component can be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. A dosage form as described herein that integrates both IR and CR components may be formulated to deliver as much as 2,000 mg of a desired drug, such as GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvates or complex of GHB. In particular embodiments, the total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg. For example, in certain such embodiments, the total amount of drug may be selected from between about 500 mg and 1,400 mg, about 500 mg and 1,200 mg, about 500 mg and 1,100 mg, about 600 mg and 1,200 mg, about 600 mg and 1,100 mg, about 600 mg and 1,000 mg, about 600 mg and 950 mg, about 600 mg and 850 mg, about 600 mg and 750 mg, about 750 mg and 1,200 mg, about 750 mg and 1,100 mg, about 750 mg and 1,000 mg, about 750 mg and 950 mg, and about 750 mg and 850 mg. In an integrated IR/CR dosage form, the relative amounts of drug delivered from the IR component and CR components may be adjusted as desired as well. In particular embodiments, the ratio of drug released from the IR component to drug released from the CR component is from about 1:2 to about 1:4. In certain embodiments, such ratio is selected from about 1:2, 1:2.5, 1:3, 1:3.5 and 1:4.

[0070] In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form maybe formulated and configured such that start-up of delivery of drug from the controlled release composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would

also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag time is desired, the delay may be accomplished or adjusted by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

Examples

Example 1 – *Controlled Release Core*

[0071] A granulation used to form CR cores as described herein was manufactured in a 25 L high shear granulator according to the formula in Table 1A. Klucel EXF was divided into two equal portions; half of the Klucel EXF was dissolved in the ethanol, and half was dry blended with sodium oxybate. The material was initially granulated with 10% w/w ethanol and then titrated with another 3.5% w/w ethanol solution to achieve desired granule growth. A suitable wet mass was obtained at a total ethanol concentration of 13.5% w/w. The wet granules were divided into two sub lots and then each sub lot was dried in a 5-liter Niro fluid bed dryer. The dried granules were combined and milled through a COMIL equipped with a 14 mesh screen. Granulation parameters and particle size distribution are shown in Tables 1B and 1C, respectively.

[0072] The granulation was then combined with 2% magnesium stearate lubricant, and tablets were compressed on a 16-station press fitted with chrome-plated 0.325" x 0.705" modified oval tooling. The average tablet hardness was 10.7 kiloponds.

Table 1A. Controlled Release Core Tablet Formulation

	Ingredient(s)	% w/w	mg/tablet
1	Sodium Oxybate	96.0	750.0
2	Hydroxypropyl cellulose, NF (Klucel EXF)	2.0	15.6
3	Ethanol, USP (200 proof)*	*13.5*	
4	Magnesium Stearate, NF	2.0	15.6
	TOTAL	**100.0**	**781.2**

* Granulation solvent, removed during drying step

Table 1B. Granulation Parameters

WET GRANULATION		
GRANULATION SOLUTION ADDITION RATE (G/MIN)	250	
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES	
IMPELLER SPEED (RPM)	300	
CHOPPER SPEED (RPM)	1800	
DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET TEMPERATURE (°C)	70	70
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE AT END OF DRYING (°C)	47	48
LOD (% WT LOSS)	0.84	0.92

Table 1C: Screen Analysis of Milled Granulation

Screen size US Std mesh	Opening size microns	Wt Retained (%)
20	850	2.1
40	420	10.4
60	250	19.8
80	180	25.0
120	125	22.9
200	75	12.5
Pan	<45	7.3

Example 2 – *Functional Coating*

[0073] Tablets from Example 1 were coated with a solution prepared according to the formulation in Table 2A. The ethylcellulose was first added to a 95/5 w/w mixture of ethanol and water and stirred until dissolved. Next, the hydroxypropyl cellulose and dibutyl sebacate were added and stirred until completely dissolved. 4.7 kg of tablets from Example 1 were then charged to an 8" pan Driam tablet coater and coated with the solution to 5.1 wt% gain (40 mg/tablet). The tablets were then dried for 5 minutes in the coater, and then finally cooled in the pan to an exhaust temperature below 30ºC.

[0074] The dissolution profile was measured in de-ionized water using USP Apparatus 2 set to 37°C ± 2°C with paddles at 50 rpm. Samples were analyzed by HPLC. As shown in FIG. 1, the coated tablets exhibited controlled release with duration of approximately 6 hours. The dosage form released 12% of its contents after 1 hour, 34% after 2 hours, 71% after 4 hours, 93% after 6 hours, and 99% after 8 hours.

Table 2A. Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/ tablet
5	Sodium Oxybate tablet core		95.13	781.25
6	Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80	14.80
7	Dibutyl sebacate	5.0	0.24	2.00
8	Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82	23.20
9	Ethanol, USP (200 proof)*			
10	Purified water*			
	TOTAL	**100.0**	**100.00**	**821.25**

* Coating solvent, removed during processing

Table 2A. Coating Parameters for Driam 8" Pan Coater

CR COATING	AVERAGE	RANGE
INLET TEMPERATURE (°C)	46	42-55
EXHAUST TEMPERATURE (°C)	43	41-46

INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2.0
SPRAY RATE (G/MIN)	35	32-37
PAN SPEED (RPM)	6	5-7

Example 3 – *Immediate-Release Overcoat*

[0075] A solution of 20% sodium oxybate as active and 2.0% hypromellose E-15 (HPMC E-15) as film-former was prepared in 60/40 (w/w) ethanol/water. The coating solution was manufactured by first dissolving the HPMC E15 in water, then adding the ethanol and sodium oxybate. 3kg of 750-mg strength sustained-release tablets from Example 2 were charged to a Driam tablet coater equipped with an 8" pan and preheated to 40°C. The entire coating solution was applied according to the parameters listed in Table 3A. The tablet weight gain was monitored every 5 minutes, and the coating was stopped when the entire solution was sprayed (the theoretical weight gain is 33.5%). The tablets were dried for 15 minutes; the tablets did not lose any weight during the 15 minute drying time, and so it was assumed that the drying was complete. The tablets were then cooled in the pan to an exhaust temperature of <30°C.

[0076] Analysis by HPLC revealed an overall potency of 961 mg, and thus a drug overcoat potency of 211 mg. Dissolution testing using USP Apparatus 2 set to 37°C ± 2°C with paddles at 50 rpm, shown in FIG. 2, demonstrates substantially the entire immediate-release overcoat is dissolved in 15 minutes and that controlled release is maintained for approximately 6 hours thereafter. Higher amounts of drug can be applied to the immediate release overcoat by using higher amounts of coating solution and extending the coating time accordingly.

Table 3A. Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (°C)	59	55-63
EXHAUST TEMPERATURE (°C)	51	50-53
PRODUCT TEMPERATURE (°C)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

[0077] The following examples illustrate aspects of the sustained-release coating formulation with several evaluations using tablets from Example 1.

Example 4 – *Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating*

[0078] One means of controlling dissolution is by adjustment of the coating thickness, or amount of film applied to each tablet. This was illustrated with a film consisting of 33% poloxamer 188 (P188) and 67% ethylcellulose 10cPs (EC-10). The coating solution was prepared by dissolving 3.59 grams of EC-10 and 1.77 grams of P188 in a mixture of 80 grams denatured alcohol ("alcohol") and 4 grams de-ionized water. (Denatured alcohol, S-L-X manufactured by W. M. Barr, is approximately a 50/50 w/w blend of methanol and ethanol.)

[0079] Twelve tablets from Example 1 were coated in a Caleva Mini-coater/Drier 2 under parameters listed in Table 4A. Periodically, the tablets were removed and weighed to determine film weight. Three tablets were removed at times corresponding to 21 mg, 30 mg, 40 mg, and finally 60 mg weight gain.

[0080] The dissolution profiles were measured with USP Apparatus 7 (Vankel Bio-dis) set to 37°C ± 2°C and using a dipping rate of 30/minute, tablets fixed in plastic holders and intervals corresponding to 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, and 14h (each interval is 50 ml volume). The tubes were analyzed by conductivity, and results are calculated as percent of total amount. The results demonstrate that controlled release is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Table 4A. Standard Parameters for Sustained-Release Coating in Caleva Mini-Coater/Drier 2

Parameter	Setting
Batch size	3-12 Tablets
Inlet temperature	40ºC
Air flow setting	70-85%
Solution flow rate	18 ml/hr
Agitator setting	32
Atomization pressure	0.5 bar
Gun position	Adjusted to achieve desired deposition

Example 5 – *Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating*

[0081] Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting of 7% solids in 95/5 alcohol/water. The results shown in FIG. 4 demonstrate that controlled release over a relevant time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6 – *Effect of Poloxamer Level in Functional Coating*

[0082] In addition to adjustment of membrane weight, another useful means of controlling release rate or duration is by adjustment of the pore-former content of the

formulation. Following procedures of Example 4, two additional solutions consisting of (a) 25% P188 by weight / 75% EC-10 by weight and (b) 40% P188 by weight / 60% EC-10 by weight were prepared as 7% (w/w) solutions in 95/5 alcohol/water. In each of the two separate coatings, four tablets from Example 1 were coated to 41 mg. The dissolution profiles are shown in FIG. 5, along with that of the 40 mg set of Example 4 for comparison. The results demonstrate that poloxamer level can be adjusted at least over the range of 25%-40% by weight, while still providing controlled release of the drug.

Example 7 – *Effect of Hydroxypropyl Cellulose Level in Functional Coating*

[0083] In a fashion similar to Example 6, the effect of HPC level in the functional coating was evaluated over the range of 30% - 50% by weight. Three separate coating solutions were prepared with 30%, 40%, and 50% HPC-EF; 5% DBS; and the balance EC-10. All solutions were prepared with 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The dissolution profiles shown in FIG. 6 demonstrate controlled release of the drug was achieved with HPC levels of at least 30-50% by weight.

Example 8 – *Effect of Hydroxypropyl Cellulose Molecular Weight when used in Functional Coating*

[0084] Hydroxypropyl cellulose is supplied in several molecular weight grades, many of which may be suitable for use as pore-formers in ethylcellulose films. Two such grades (Klucel “EF” and “JF”, supplied by Ashland) corresponding to 80,000 daltons and 140,000 daltons were evaluated with other components fixed. Following procedures of Example 4, solutions were prepared with 40% HPC, 5% DBS, and 55% EC-10 (all percentages by weight) using 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The results shown in FIG. 7 demonstrate a modest effect of molecular weight and that the two grades tested provide for acceptable release profiles.

Example 9 – *Effect of Ethylcellulose Molecular Weight or Viscosity*

[0085] Another consideration is the molecular weight, or viscosity, of ethylcellulose. Two grades were evaluated, corresponding to 4cPs and 10cPs viscosity for a 5% solution. Following procedures of Example 4, two solutions were prepared corresponding to 58.5 wt% ethylcellulose (EC-4 or EC-10), 36.5 wt% HPC-EF, and 5.0 wt% DBS having 7% w/w total components in 95/5 alcohol/water. Tablets from Example 1 were coated to 40 mg/tablet weight gain, and dissolution profiles are shown as FIG. 8. The results indicate both grades of ethylcellulose provide for acceptable profiles, and suggest that other ethylcellulose grades (such as 20cPs) may also be acceptable.

Example 10 – *Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets*

[0086] Co-administration of sustained-release dosage forms with alcoholic beverages is a relevant concern, as ethanol is known to dissolve certain rate-controlling components that would not otherwise be dissolved. In some dosage forms, this may lead to dose-dumping. As ethanol is rapidly absorbed in the stomach, a relevant test involves dissolution of the dosage form in vodka (40% ethanol nominal) for 2 hours (representing gastric retention time), followed by normal dissolution in de-ionized water.

[0087] This test was performed on sustained-release tablets from Example 9 (36.5 wt% HPC EF, 5 wt% DBS, 58.5 wt% EC-4). The analysis of sodium oxybate by conductivity was corrected for the different response in vodka vs. de-ionized water. The results shown in FIG. 9A indicate that dissolution is slower in Vodka, and that no dose-dumping occurred.

[0088] Likewise, a similar test was performed on sustained-release tablets with a film comprised of 33 wt% P188 and 67 wt% EC-10. Those results, shown in FIG. 9B, also indicate slower release in vodka and no dose-dumping.

Example 11 – *Aqueous Coating of Controlled Release Film*

[0089] Due to the hygroscopic nature of sodium oxybate, coating the rate-controlling film from an alcoholic solution is desirable. However, use of ethylcellulose aqueous dispersions is attractive for environmental and cost considerations. A film consisting of 30 wt% HPC EF and 70 wt% Surelease

(aqueous ethylcellulose dispersion) was deposited on tablets from Example 1 as follows. First, 1.37 grams of HPC EF was dissolved in 22.6 grams de-ionized water. This was then poured into 32.5 grams of Surelease E-7-19040-clear while stirring. Eight tablets were coated in the Caleva Mini-coater/Drier 2 with flow rate of 15 ml/hr and 58ºC inlet temperature. Samples removed at 24 mg and 40 mg were then tested for dissolution, with no post-coating heat treatment. The results are shown in FIG. 10.

Example 12 – *Calcium Oxybate Controlled Release*

[0090] A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in US 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325" x 0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as Figure 11. These results using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13 – *Clinical Evaluation of Controlled Release Dosage Forms*

[0091] An open-ended, randomized, crossover study was conducted to evaluate controlled release dosage forms as described herein. The controlled release dosage forms were formulated to deliver sodium oxybate and were compared to a sodium oxybate oral solution (commercially available as Xyrem® (sodium oxybate) oral solution). The study was conducted in healthy male and female volunteers.

[0092] Four different sodium oxybate formulations were administered to patients. The first, designated herein as Treatment A, was the sodium oxybate oral solution

containing 375 mg/ml sodium oxybate. Treatments B through E, as designated herein, involved administration of three controlled release dosage forms (Treatments B through D), with one of the controlled release dosage forms being used to administer two different doses of sodium oxybate (Treatments D and E). The controlled release dosage forms administered as Treatment B included 750 mg sodium oxybate per dosage form and were produced with a CR core and functional overcoat as described in Example 1 and Example 2, the controlled release dosage forms administered as Treatment C included 750 mg sodium oxybate per dosage form and were produced as described in Example 1 and Example 4, and the controlled release dosage forms administered as Treatments D and E included 1,000 mg sodium oxybate per dosage form and were produced with a CR core (750 mg sodium oxybate), functional overcoat, and IR overcoat (250 mg sodium oxybate) as described in Examples 1 through 3.

[0093] Patients were divided into two groups. The first group received Treatment A, Treatment B, and Treatment C over the course of the clinical study, with a washout period between each treatment. Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments B and C were administered to each patient only at time zero, with each treatment being administered as 8 tablets, providing a total dose of 6 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 29 patients received Treatment A, a total of 19 patients received Treatment B, and a total of 19 patients received Treatment C. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in Figure 12 (Treatment A and Treatment B) and Figure 13 (Treatment A and Treatment C), and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 5.

Table 5: Summary of PK Parameters for Treatments A, B, C

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
			Treatment A			
N	29	29	29	29	29	29
Mean	1.22	0.60	4.50 (0.5, 4.75)	130.79	350.84	351.20
SD	0.27	0.13		31.52	116.74	116.74
CV%	21.93	22.61		24.10	33.27	33.24
Mean	1.19	0.58		127.37	333.33	333.72
			Treatment B			
N	18	18	19	19	19	18
Mean	0.62	1.22	2.00 (1.50, 5.00)	41.78	188.23	196.25
SD	0.16	0.40		18.40	103.60	102.50
CV%	26.44	32.58		44.03	55.04	52.23
Mean	0.59	1.17		38.46	163.80	173.33
			Treatment C			
N	19	19	19	19	19	19
Mean	0.74	0.99	2.50 (1.00, 5.00)	50.49	221.64	222.60
SD	0.16	0.23		15.83	106.85	106.80
CV%	22.25	22.93		31.35	48.21	47.98
Mean	0.72	0.96		48.10	200.08	201.12

[0094] The second group was administered Treatment A, Treatment D, and Treatment E during over the course of the clinical study, with a washout period between each treatment. Again, Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments D and E were administered to each patient only at time zero. Patients receiving Treatment D were administered 4 tablets at time zero, providing a total dose of 4 g sodium oxybate, and patients receiving Treatment E were administered 8 tablets at time zero, providing a total dose of 8 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 30 patients received Treatment A, and a total of 30 patients received Treatments D and E. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in Figure 14, and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 6.

Table 6: Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
			Treatment A			
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV%	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
			Treatment D			
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV%	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55
			Treatment E			
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV%	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

[a] Tmax is summarized as median (min, max).

[0095] It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

Claims

1. A controlled release dosage form for oral administration, the controlled release dosage form comprising:

a controlled release formulation comprising at least one drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB; and

wherein less than 30% of the at least one drug included in the controlled release formulation is released from the controlled release formulation during the first hour after administration.

2. The controlled release dosage form of claim 1, wherein less than 60% of the at least one drug included in the controlled release formulation is released within two hours after administration, and wherein less than 80% of the at least one drug included in the controlled release formulation is released within four hours after administration, and wherein greater than 90% of the at least one drug included in the controlled release formulation is released within 12 hours after administration.

3. The controlled release dosage form of either of claim 1 and claim 2, wherein the at least one drug is selected from calcium, lithium, potassium, sodium and magnesium salts of GHB.

4. The controlled release dosage form of any preceding claim, wherein the at least one drug comprises sodium oxybate.

5. The controlled release dosage form of any preceding claim, wherein the dosage form further comprises an immediate release component comprising the at least one drug, and further wherein greater than 90% of the at least one drug included in the immediate release component is released from the immediate release component within the first hour after administration.

6. The controlled release dosage form of any preceding claim, wherein the controlled release dosage formulation begins to release the at least one drug within 1 hour after administration.

7. The controlled release dosage form of either of claim 5 and claim 6, wherein the immediate release formulation comprises at least one drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB.

8. The controlled release dosage form of any of claims 5 through 7, wherein the at least on drug included within the immediate release formulation comprises at least one drug selected from calcium, lithium, potassium, sodium and magnesium salts of GHB.

9. The controlled release dosage form of any of claims 5 through 8, wherein the immediate release formulation comprises sodium oxybate.

10. The controlled release dosage form of any of claims 5 through 9, wherein the immediate release formulation is applied as a coating over the controlled release formulation.

11. The controlled release dosage form of any preceding claim, wherein the controlled release formulation comprises a controlled release core comprising the at least one drug, wherein the controlled release core is coated with at least one coating composition that is formulated to control the release rate of the at least one drug after administration.

12. The controlled release dosage form of claim 11, wherein the at least one coating composition comprises at least one polymer.

13. The controlled release dosage form of either of claim 11 and 12, wherein the at least one coating composition comprises at least one pore-former.

14. The controlled release dosage form of any of claims 11 through 13, wherein the at least one coating composition comprises at least one polymer and at least one pore-former.

15. The controlled release dosage form of any of claims 11 through 14, wherein the at least one coating composition comprises ethylcellulose.

16. The controlled release dosage form of either of claim 13 and claim 15, wherein the pore-former is at least one of a polyethylene glycol, poloxamer, polyvinyl alcohol, copovidone, povidone, a water soluble sugar, a water soluble organic acid, such as carboxylic acids and their salts, and a hydroxyalkyl cellulose selected from hydroxyethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

17. The controlled release dosage form of any of claims 11 through 16, wherein the at least one coating composition comprises at least one plasticizer.

18. The controlled release dosage form of any of claims 11 through 17, wherein the at least one coating composition comprises at least one anti-tack agent.

19. The controlled release dosage form of any of claims 5 through 18, wherein the controlled release dosage form comprises an immediate release formulation and the immediate release formulation comprises between 10% and 50% by weight of the total sodium oxybate in the controlled release dosage form.

20. The controlled release dosage form of any of claims 5 through 19, wherein the controlled release dosage form comprises an immediate release formulation and the immediate release formulation comprises between 50% and 90% by weight of the total sodium oxybate in the controlled release dosage form.

21. The controlled release dosage form of any of claims 5 through 20, wherein the immediate release formulation further comprises at least one pharmaceutically acceptable excipient.

22. The controlled release dosage form of any of claims 5 through 21, wherein the pharmaceutically acceptable excipient comprises at least one of copovidone, plasacryl, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and hydroxymethyl cellulose.

23. A controlled release dosage form for oral administration, the controlled release dosage form comprising:

a controlled release formulation comprising at least one pharmaceutically active ingredient selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB ;

at least one coating composition applied over the controlled release formulation; and

an immediate release formulation comprising at least one pharmaceutically active ingredient selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, wherein the immediate release formulation is applied over the coating composition.

24. The controlled release dosage form of claim 23, wherein the controlled release formulation further comprises at least one pharmaceutically acceptable excipient.

25. The controlled release dosage form of claim 24, wherein the at least one pharmaceutically acceptable excipient comprises at least one of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers, cross-linked polyacrylates, polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil, methylcellulose, magnesium aluminum silicate, and sodium alginate.

26. The controlled release dosage form of claim 24, wherein the at least one pharmaceutically acceptable excipient comprises at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

27. The controlled release dosage form of claim 24 wherein the at least one pharmaceutically acceptable excipient comprises at least one of docusate sodium, sodium lauryl sulfate, benzalkonium chloride, benzethonium chloride, cetrimide, alkyltrimethylammonium bromide, polyoxyethyelene alkyl ethers,

polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate.

28. The controlled release dosage form of any of claims 23 through 27, wherein the at least one coating composition comprises at least one polymer.

29. The controlled release dosage form of any of claims 23 through 28, wherein the at least one coating composition comprises at least one pore-former.

30. The controlled release dosage form of any of claims 23 through 29, wherein the at least one coating composition comprises at least one polymer and at least one pore-former

31. The controlled release dosage form of any of claims 23 through 30, wherein the at least one coating composition comprises ethylcellulose.

32. The controlled release dosage form of any of claims 29 through 31, wherein the at least one pore-former is at least one of a polyethylene glycol, poloxamer, polyvinyl alcohol, copovidone, povidone, a water soluble sugar, a water soluble organic acid, such as carboxylic acids and their salts, and a hydroxyalkyl cellulose selected from hydroxyethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

33. The controlled release dosage form of any of claims 23 through 32, wherein the at least one coating composition comprises at least one plasticizer.

34. The controlled release dosage form of any of claims 23 through 33, wherein the at least one coating composition comprises at least one anti-tack agent.

35. The controlled release dosage form of any of claims 23 through 34, wherein the immediate release formulation further comprises at least one pharmaceutically acceptable excipient.

36. The controlled release dosage form of claim 35, wherein the pharmaceutically acceptable excipient comprises at least one of copovidone, glyceryl monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and hydroxymethyl cellulose.

37. The controlled release dosage form of claim 23, wherein the immediate release formulation further comprises an overcoat layer.

38. The controlled release dosage form of claim 23, wherein both the immediate release formulation and the controlled release core formulation comprise a pharmaceutically active ingredient comprising sodium oxybate.

39. The controlled release dosage form according to any preceding claim, wherein the dosage form delivers the at least one drug in a manner that provides a Cmax to Cmin ratio of the at least one drug selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

40. The controlled release dosage form according to any preceding claim, wherein not more than about 10% to 60% of the at least one drug initially contained within the controlled release formulation is released during the first two hours post-administration, and not more than about 40% to 90% of the drug initially contained within the controlled release formulation is released during the first four hours post-administration.

41. The controlled release dosage form according to any preceding claim, wherein not more than about 30% of the at least one drug initially contained within the controlled release formulation is released during the first hour post-administration, not more than about 60% of the at least one drug initially contained within the controlled release formulation is released during the first two hours post-administration, and not more than about 90% of the at least one drug initially contained within the controlled release formulation is released during the first four hours post-administration.

42. The controlled release dosage form according to any preceding claim, wherein not more than about 50% of the at least one drug initially contained within the controlled release formulation is released during the first hour post-administration, not more than about 50% to about 75% of the at least one drug initially contained within the controlled release formulation is released during the first two hours post-administration, and not more than about 80% of the at least one drug initially contained within the controlled release formulation is released during the first four hours post-administration.

43. The controlled release dosage form according to any preceding claim, wherein not more than about 20% of the at least one drug initially contained within the controlled release formulation is released during the first hour post-administration, between about 5% to about 30% of the at least one drug initially contained within the controlled release formulation is released during the first two hours post-administration, between about 30% to about 50% of the at least one drug initially contained within the controlled release formulation is released during the first four hours post-administration, between about 50% to about 70% of the at least one drug initially contained within the controlled release formulation is released during the first six hours post-administration, and not more than 80% of the at least one drug initially contained within the controlled release formulation is released during the first 10 hours post administration.

44. The controlled release dosage form according to any preceding claim, wherein not more than about 20% of the at least one drug initially contained within the controlled release formulation is released during the first hour post-administration, between about 20% and about 50% of the at least one drug initially contained within the controlled release formulation is released during the first two hours post-administration, between about 50% and about 80% of the at least one drug initially contained within the controlled release formulation is released during the first four hours post-administration, and not more than about 85% of the at least one drug initially contained within the controlled release formulation is released during the first eight hours post-administration.

45. A method for delivering a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, the method comprising;

delivering to a patient in need thereof, one or more dosage forms according to any of the preceding claims.

46. A method according to claim 45, wherein delivery of the one or more dosage forms provides a Cmax to Cmin ratio of the drug selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours

47. A method according to either of claims 45 and 46, wherein not more than about 10% to 60% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first two hours post-administration, and not more than approximately 40% to 90% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first four hours post-administration.

48. A method according to either of claims 45 and 46, wherein not more than about 30% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first four hours post-administration.

49. A method according to either of claims 45 and 46, wherein not more than about 50% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first hour post-administration, not more than about 50% to about 75% of the drug

initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first two hours post-administration, and not less than about 80% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released after the first four hours post-administration.

50. A method according to either of claims 45 and 46, wherein not more than about 20% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first hour post-administration, between about 5% to about 30% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first two hours post-administration, between about 30% to about 50% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first four hours post-administration, between about 50% to about 70% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first six hours post-administration, and not less than 80% of the drug initially contained within controlled release formulation of the one or more controlled release dosage forms is released after the first 10 hours post administration.

51. A method according to either of claims 45 and 46, wherein not more than about 20% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first hour post-administration, between about 20% and about 50% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first two hours post-administration, between about 50% and about 80% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released during the first four hours post-administration, and not less than about 85% of the drug initially contained within the controlled release formulation of the one or more controlled release dosage forms is released after the first eight hours post-administration.

52. A controlled release dosage form for oral administration, the controlled release dosage form comprising:

a controlled release core;

a functional coating composition; and

a moisture barrier layer;

wherein the functional coating composition is disposed over the controlled release core, and wherein the moisture barrier layer is disposed over the functional coating composition.

53. The controlled release dosage form of claim 52, wherein the controlled release dosage form comprises:

(a) a controlled release core comprising:

a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB;

at least one binder; and

at least one lubricant;

(b) a functional coating composition comprising:

at least one base polymer; and

at least one pore-former; and

(c) a moisture barrier layer.

54. The controlled release dosage form of claim 53, wherein the at least one binder is selected from one of or any combination of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers, cross-linked polyacrylates, polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil, methylcellulose, magnesium aluminum silicate, and sodium alginate, and the lubricant is selected from one of or any combination of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

55. The controlled release dosage form of claim 52 or 53, wherein the controlled release core optionally comprises at least one surfactant at least one filler.

56. The controlled release dosage form of claim 55, wherein the at least one surfactant is selected from one of or any combination of docusate sodium, sodium lauryl sulfate, benzalkonium chloride, benzethonium chloride, cetrimide, alkyltrimethylammonium bromide, polyoxyethyelene alkyl ethers, polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate, and the at least one filler is selected from one of or a combination of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose

57. The controlled release dosage form according to any of claims 53 through 56, wherein the at least one pore former is selected from one of or any combination of polyethylene glycol, poloxamer, polyvinyl alcohol, copovidone, povidone, a water soluble sugar, a water soluble organic acid, such as carboxylic acids and their salts, and a hydroxyalkyl cellulose selected from hydroxyethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

58. The controlled release dosage form of any of claims 53 through 57, wherein the functional coating composition optionally comprises at least one plasticizer selected from triethyl citrate and dibutyl sebacate and at least one anti-tack agent selected from talc, glyceryl monostearate, and magnesium stearate.

59. The controlled release dosage form according to any of claims 53 through 58, wherein the moisture barrier layer is selected from a polyvinyl alcohol-based coating, a hydroxypropyl methylcellulose/wax-based coating, a hydroxypropyl methylcellulose/stearic acid-based coating, and reverse enteric material.

60. The controlled release dosage according to any of claims 53 through 59, wherein the relative amount drug present in the controlled release core is at least 90% or greater by weight of the controlled release core.

61. The controlled release dosage form according to any of claims 53 through 60, wherein the relative amount of drug present in the controlled release core is selected from a range of about 90% to about 98%, about 91% to about 98%, about 92% to about 98%, about 93% to about 98%, about 94% to about 98%, about 95% to about 98%, about 96% to about 98%, and between about 97% to about 98% by weight of the controlled release core.

62. The controlled release dosage form according to any of claims 53 through 60, wherein the relative amount of drug present in the controlled release core is selected from about 94 to about 98%, about 94 to about 97%, about 94 to about 96%, about 95 to about 98%, about 95 to about 97%, and about 95 to about 96.5 % by weight of the controlled release core.

63. The controlled release dosage form according to any of claims 53 through 60, wherein the relative amount of drug present in the controlled release core is selected from about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and 98% by weight of the controlled release core.

64. The controlled release dosage form according to any of claims 53 through 64, wherein the amount of binder present in the controlled release core is about 1% to about 10% by weight of the controlled release core.

65. The controlled release dosage form according to any of claims 53 through 64, wherein the amount of binder present in the controlled release core is selected from about 1% to about 2%, about 1% to about 3%, about 1% to about 4%, about 1% to about 5%, about 1% to about 6%, about 1% to about 7%, about 1% to about 8%, about 1% to about 9% and about 1% to about 10% by weight of the controlled release core.

66. The controlled release dosage form according to any of claims 53 through 64, wherein the amount of binder present in the controlled release core is selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight of the controlled release core.

67. The controlled release dosage form according to any of claims 53 through 66, wherein the amount of lubricant present in the controlled release core is about 0.5% to about 5% by weight of the controlled release core.

68. The controlled release dosage form according to any of claims 53 through 67, wherein the amount of lubricant present in the controlled release core is selected from about 0.5% to about 2%, about 1% to about 2%, about 1% to about 3%, about 2% to about 3%, and about 2% to about 4% by weight of the controlled release core.

69. The controlled release dosage form according to any of claims 53 through 68, wherein the amount of lubricant present in the controlled release core is selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight of the controlled release core.

70. The controlled release dosage form according to any of claims 55 through 69, wherein the amount of surfactant present in the controlled release core is 3.0% or less by weight of the controlled release core.

71. The controlled release dosage form according to any of claims 55 through 70, wherein the amount of surfactant present in the controlled release core is selected from about 0.01% to about 3%, about 0.01% to about 2%, about 0.01% to about 1%, about 0.5% to about 3%, about 0.5% to about 2%, and about 0.5% to about 1% by weight of the controlled release core.

72. The controlled release dosage form according to any of claims 53 through 71, wherein the amount of base polymer present in the functional coating composition is about 50% to about 80% by weight of the functional coating composition.

73. The controlled release dosage form according to any of claims 53 through 72, wherein the amount of base polymer present in the functional coating composition is selected from about 50% to about 75%, about 55% to about 75%,

about 60% to about 75%, and about 65% to about 75% by weight of the functional coating composition.

74. The controlled release dosage form according to any of claims 53 through 73, wherein the amount of base polymer present in the functional coating composition is selected from about 50%, 55%, 60%, 65%, 70%, 75%, and 80% by weight of the functional coating composition.

75. The controlled release dosage form according to any of claims 53 through 74, wherein the amount of pore-former present in the functional coating composition is about 20% to about 50% by weight of the functional coating composition.

76. The controlled release dosage form according to any of claims 53 through 75, wherein the amount of pore-former present in the functional coating composition is selected from about 20% to about 45%, about 25% to about 45%, about 30% to about 45%, and about 35% to about 45% by weight of the functional coating composition.

77. The controlled release dosage form according to any of claims 53 through 76, wherein the amount of pore-former present in the functional coating composition is selected from about 20%, 25%, 30%, 35%, 40%, 45%, and 50% by weight of the functional coating composition.

78. The controlled release dosage form according to any of claims 58 through 77, wherein the amount of plasticizer present in the functional coating composition is about 5% to about 15% by weight relative to the base polymer.

79. The controlled release dosage form according to any of claims 58 through 78, wherein the amount of plasticizer present in the functional coating composition is selected from about 5%, 8%, 10%, 12%, and 15% by weight relative to the base polymer.

80. A controlled release dosage form according to any of claims 52 through 79 further comprising an immediate release component comprising a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, wherein the immediate release component is disposed over the functional coating composition, wherein the moisture barrier layer is disposed over the functional coating composition, and wherein the immediate release component provides immediate release of the at least one drug upon administration to the gastro-intestinal tract.

81. The controlled release dosage form of claim 80, wherein the immediate release component further comprises at least one pharmaceutically acceptable excipient.

82. The controlled release dosage form of any of claim 81, wherein the at least one pharmaceutically acceptable excipient included in the immediate release comprises one or more of at least one anti-tack agent, at least one plasticizer, at least one surfactant.

83. The controlled release dosage form according to any of claims 80 through 82, wherein the amount of drug present in the immediate release component is about 10% to about 50% by weight of the total drug included in the unit dosage form.

84. The controlled release dosage form according to any of claims 80 through 83, wherein the amount of drug present in the immediate release component is selected from about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by weight of the total drug included in the unit dosage form.

85. The controlled release dosage form according to any of claims 80 through 84, wherein the amount of drug present in the immediate release component is between about 75% and about 98% by weight of the immediate release component.

86. The controlled release dosage form according to any of claims 80 through 85, wherein the amount of drug present in the immediate release component is selected from a range of about 75% to about 98%, about 80% to about 98%, about 85% to about 98%, about 90% to about 98%, and about 95% to about 98% by weight of the immediate release component.

87. The controlled release dosage form according to any of claims 52 through 86, wherein the dosage form delivers the drug in a manner that provides a C_{max} to C_{min} ratio of the at least one drug selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours. up to about 9 hours, and up to about 10 hours.

88. The controlled release dosage form according to any of claims 52 through 86, wherein the dosage form delivers the drug in a manner that provides a C_{max} to C_{min} ratio of the at least one drug selected from less than 3 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

89. The controlled release dosage form according to any of claims 52 through 86, wherein the dosage form delivers the drug in a manner that provides a C_{max} to C_{min} ratio of the at least one drug selected from less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

90. The controlled release dosage form according to any of claims 52 through 89, wherein, after administration, the dosage form provides plasma concentrations of the drug of at least 10 µg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

91. The controlled release dosage form according to any of claims 52 through 90, wherein not more than about 10% to about 60% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first two hours post-administration, and not more than about 40%

to about 90% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first four hours post-administration.

92. The controlled release dosage form according to any of claims 52 through 90, wherein not more than about 30% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first four hours post-administration.

93. The controlled release dosage form according to any of claims 52 through 90, wherein not more than about 50% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first hour post-administration, not more than about 50% to about 75% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first two hours post-administration, and not less than about 80% of the drug initially contained within the controlled release core of the controlled release dosage form is released after the first four hours post-administration.

94. The controlled release dosage form according to any of claims 52 through 90, wherein not more than about 20% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first hour post-administration, between about 5% to about 30% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first two hours post-administration, between about 30% to about 50% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first four hours post-administration, between about 50% to about 70% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first six hours post-administration, and not less than about 80% of the drug

initially contained within the controlled release core of the controlled release dosage form is released after the first 10 hours post administration.

95. The controlled release dosage form according to any of claims 52 through 90, wherein not more than about 20% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first hour post-administration, between about 20% and about 50% of the drug initially contained within the controlled release core of the controlled release dosage form is released during the first two hours post-administration, between about 50% and about 80% of drug initially contained within the controlled release core of the controlled release dosage form is released during the first four hours post-administration, and not less than about 85% of the drug initially contained within the controlled release core of the controlled release dosage form is released after the first eight hours post-administration.

96. The controlled release dosage form according to any of claims 52 through 90, wherein about 90% or more of the drug initially contained within the controlled release core of the controlled release dosage form is released within about 4 to 10 hours of administration.

97. The controlled release dosage form according to any of claims 52 through 90, wherein about 90% or more of the drug initially contained within the controlled release core of the controlled release dosage form is released within a period of time selected from about 4, about 5, about 6, about 7, about 8, about 9, about 10, and about 12 hours post-administration.

98. The controlled release dosage form according to any of claims 52 through 97, wherein more than about 95% of the drug initially contained within the immediate release component of the dosage form is released within a period of time selected from less than 45 minutes post-administration, less than 30 minutes post-administration, and less than 15 minutes post-administration.

99. The controlled release dosage form according to any one of claims 52 through 97, wherein more than about 80% of the drug initially contained within the

immediate release component is released within a period of time selected from less than 45 minutes post-administration, less than 30 minutes post-administration, and less than 15 minutes post-administration.

100. The controlled release dosage form according to any one of claims 52 through 97, wherein more than about 90% of the drug initially contained within the immediate release component is released over a period of time selected from less than one hour post-administration, less than 45 minutes post-administration, less than 30 minutes post-administration, and less than 15 minutes post-administration, wherein as the immediate release component is released, the controlled release core begins release of the drug contained within the control release core.

101. The controlled release dosage form according to any one of claims 52 through 97, wherein more than about 90% of the drug initially contained within the immediate release component is released over a period of time selected from less than one hour post-administration, less than 45 minutes post-administration, less than 30 minutes post-administration, and less than 15 minutes post-administration, wherein after the immediate release component is released, the controlled release core begins release of the drug contained within the control release core.

102. A method for delivering a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, the method comprising;

delivering to a patient in need thereof, one or more dosage forms according to any of claims 52 through 101.

103. A method according to claim 102, wherein delivery of the one or more dosage forms provides a Cmax to Cmin ratio of the drug selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours

104. A method according to either of claims 102 and 103, wherein not more than about 10% to 60% of the drug initially contained within the controlled release

core of the one or more controlled release dosage forms is released during the first two hours post-administration, and not more than approximately 40% to 90% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first four hours post-administration.

105. A method according to either of claims 102 and 103, wherein not more than about 30% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first two hours post-administration, and not more than about 90% of the drug initially contained within controlled release core of the one or more controlled release dosage forms is released during the first four hours post-administration.

106 A method according to either of claims 102 and 103, wherein not more than about 50% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first hour post-administration, not more than about 50% to about 75% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first two hours post-administration, and not less than about 80% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released after the first four hours post-administration.

107. A method according to either of claims 102 and 103, wherein not more than about 20% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first hour post-administration, between about 5% to about 30% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first two hours post-administration, between about 30% to about 50% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first four hours post-

administration, between about 50% to about 70% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first six hours post-administration, and not less than 80% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released after the first 10 hours post administration.

108. A method according to either of claims 102 and 103, wherein not more than about 20% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first hour post-administration, between about 20% and about 50% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first two hours post-administration, between about 50% and about 80% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released during the first four hours post-administration, and not less than about 85% of the drug initially contained within the controlled release core of the one or more controlled release dosage forms is released after the first eight hours post-administration.

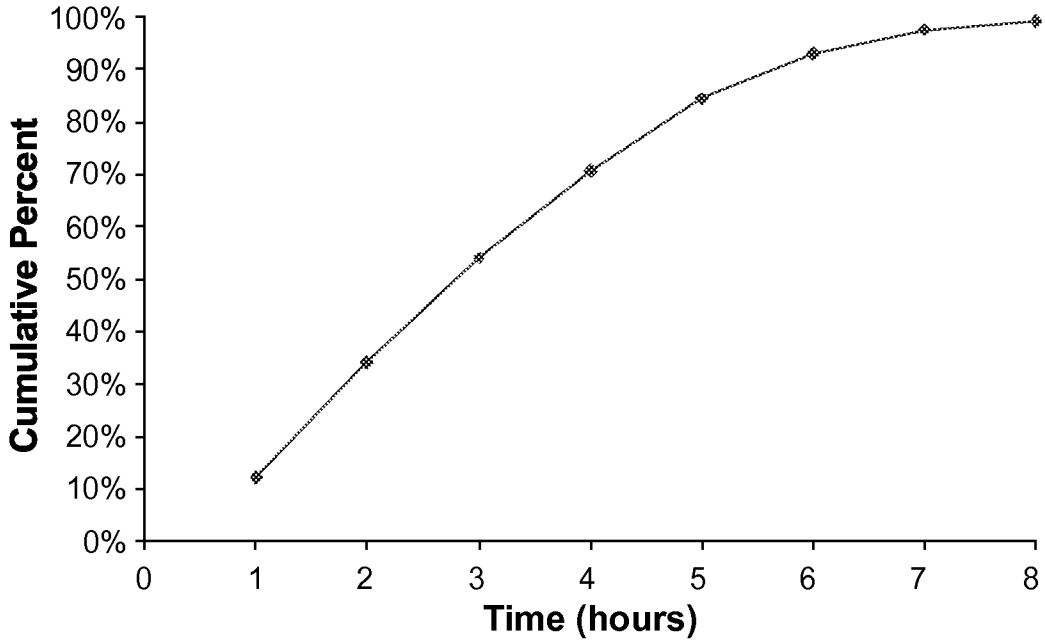
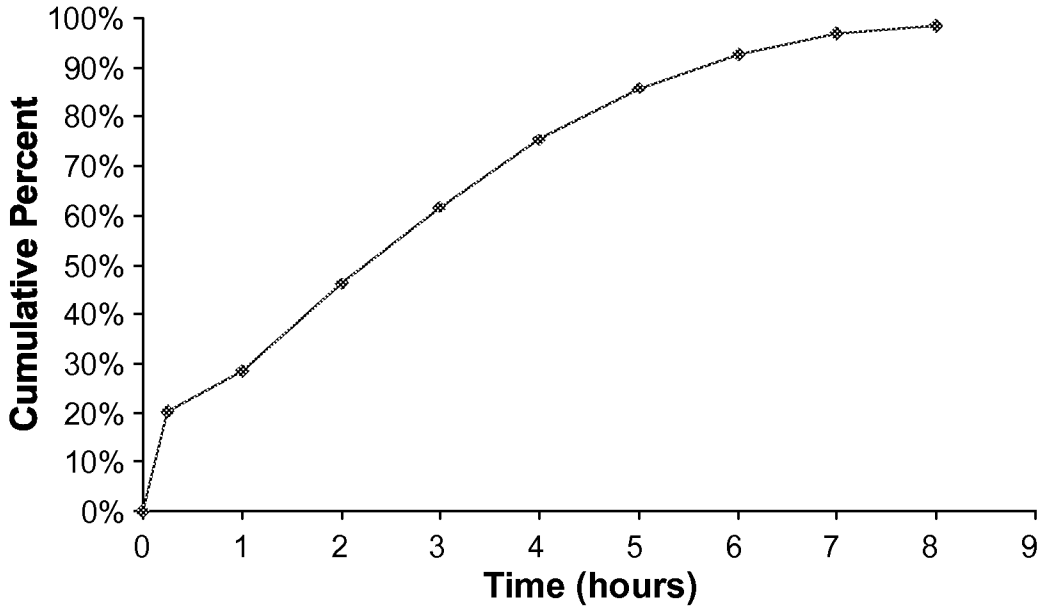

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 1


Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
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3
4
5
6
7
8
9
Time (hours)

FIG. 2

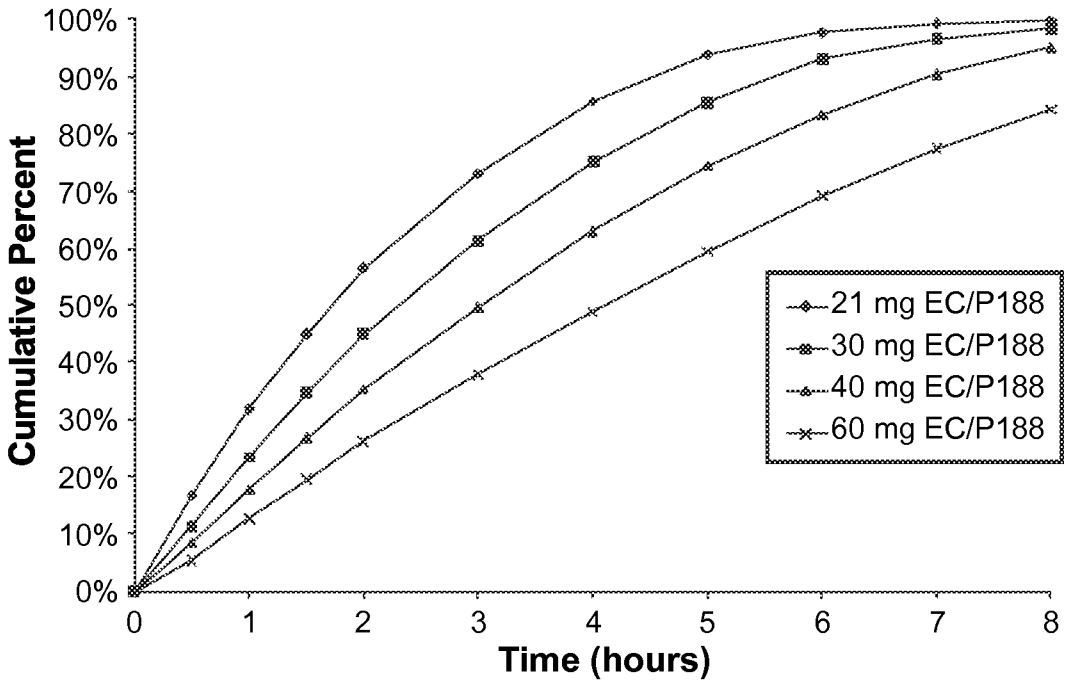
Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3

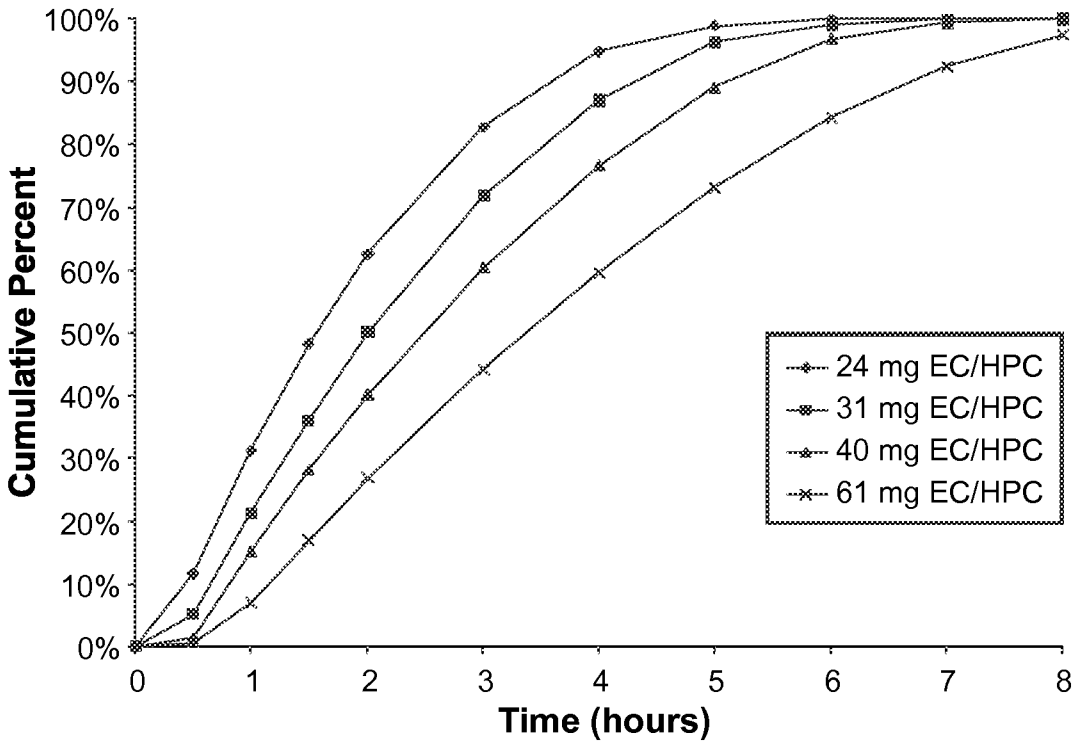
Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4

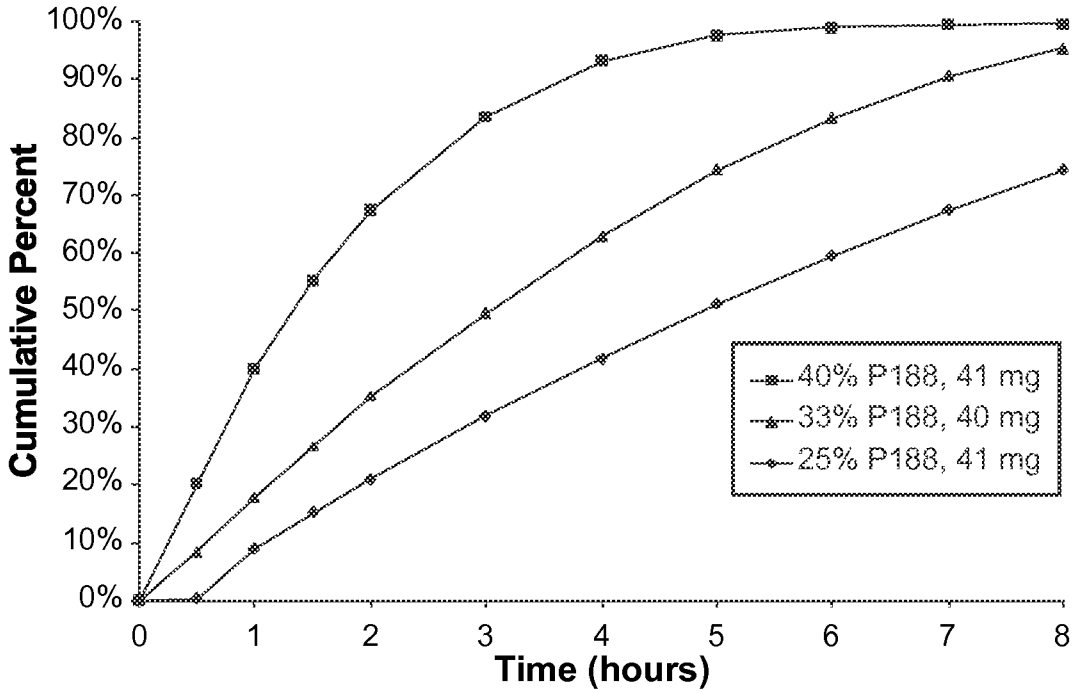
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5

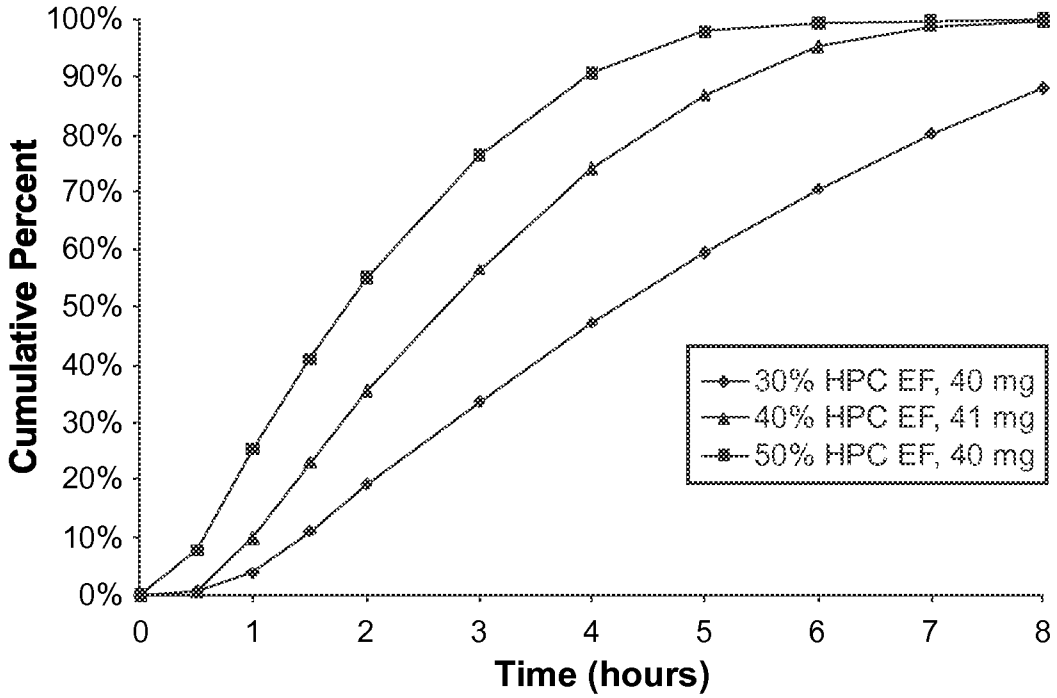
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6

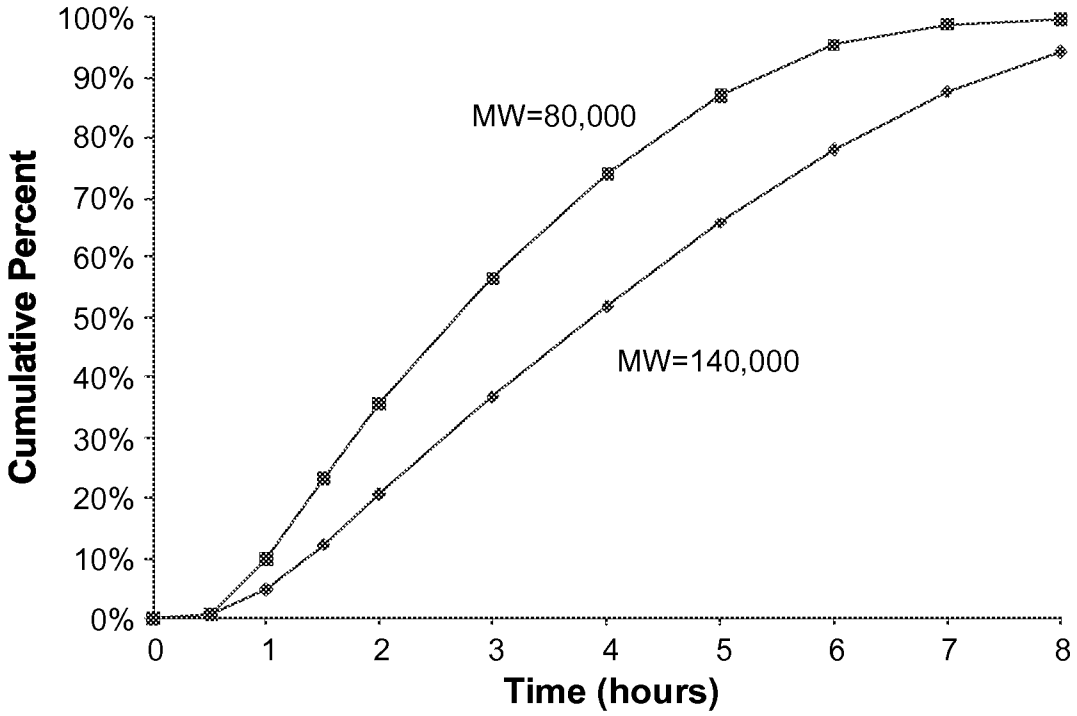
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
MW=80,000
MW=140,000
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 7

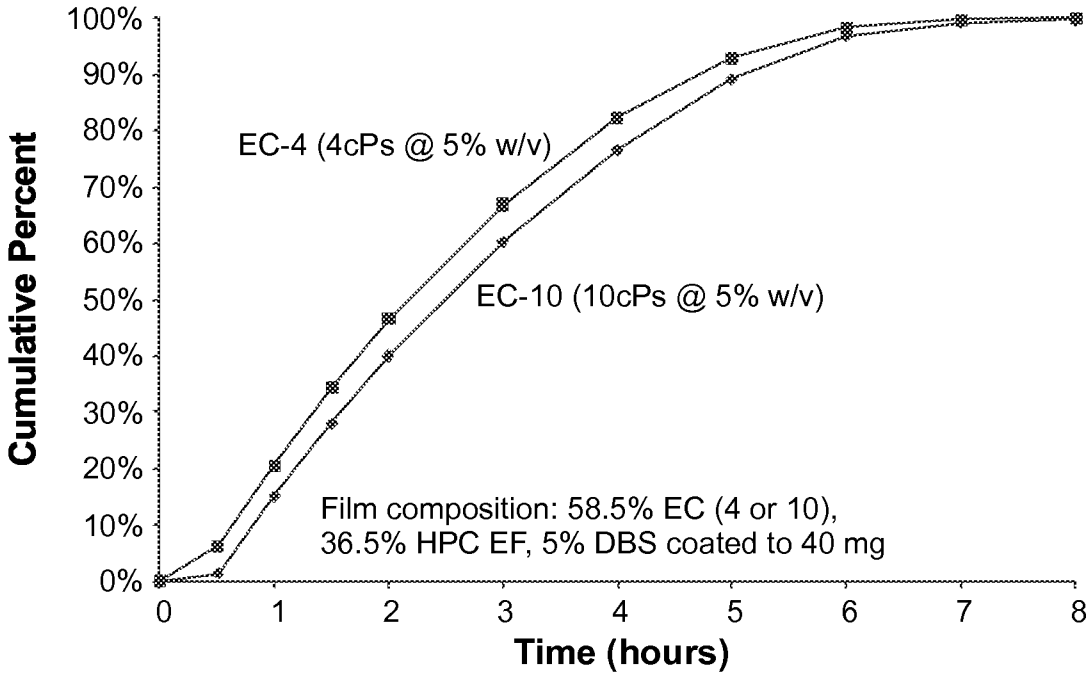
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 8

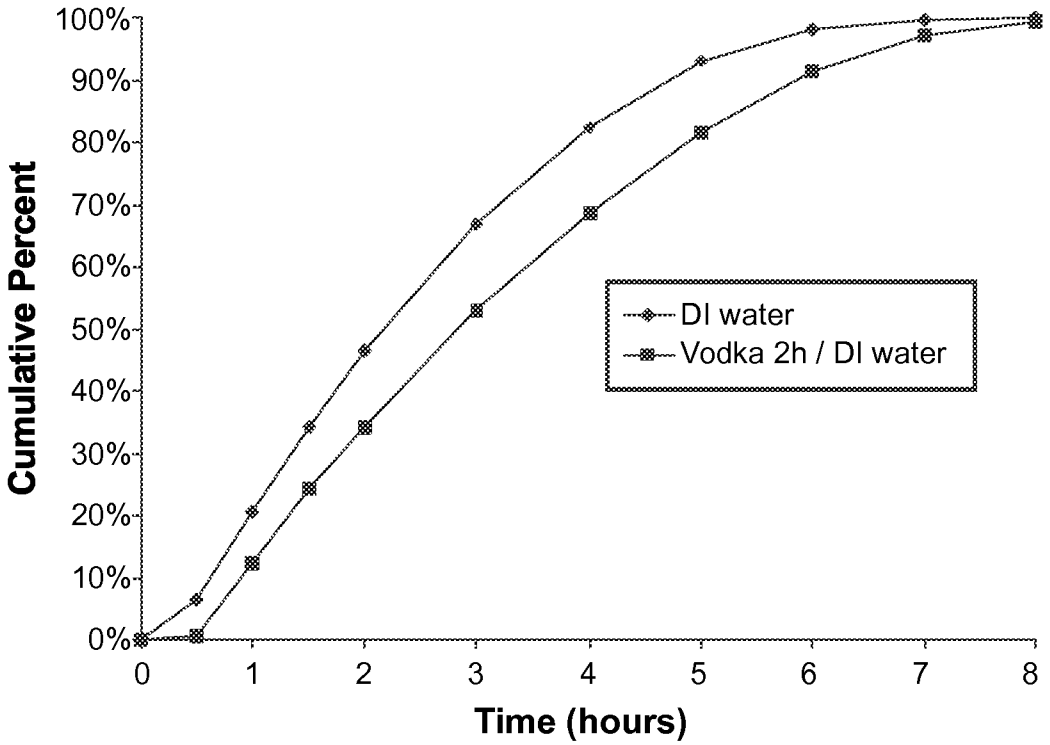
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A

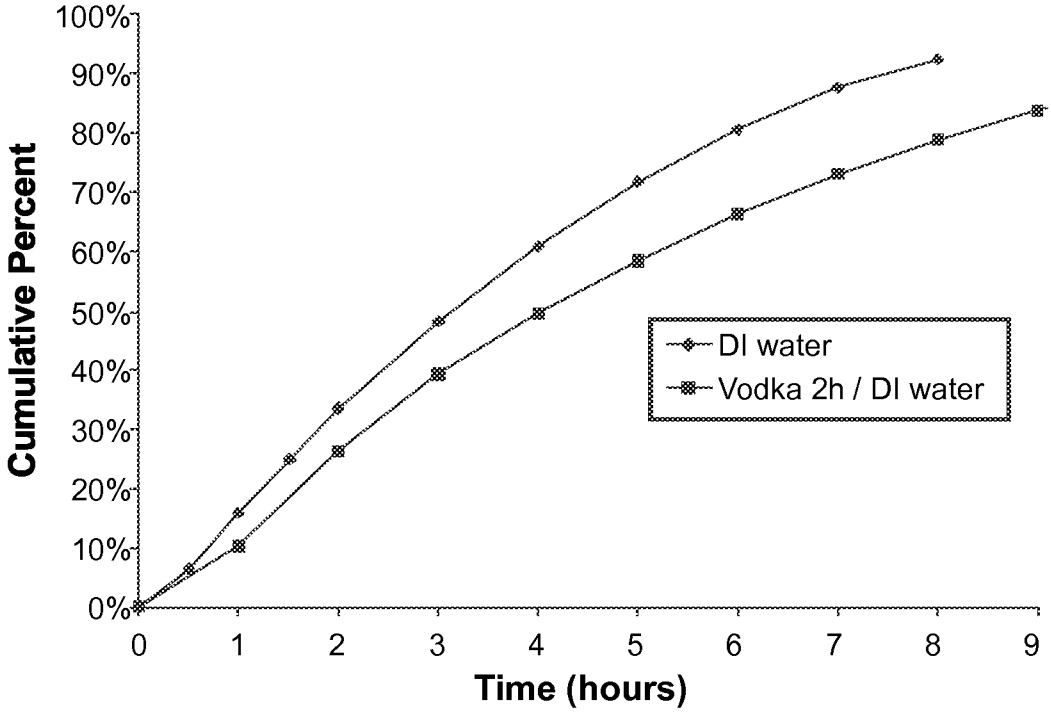
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B

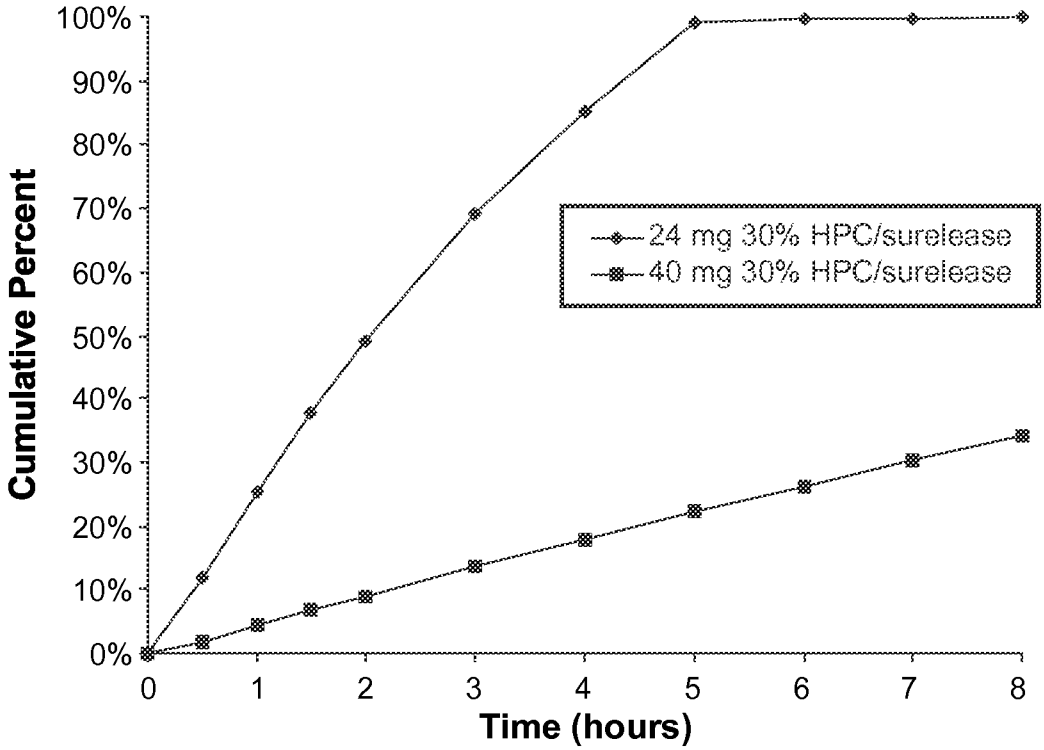
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10

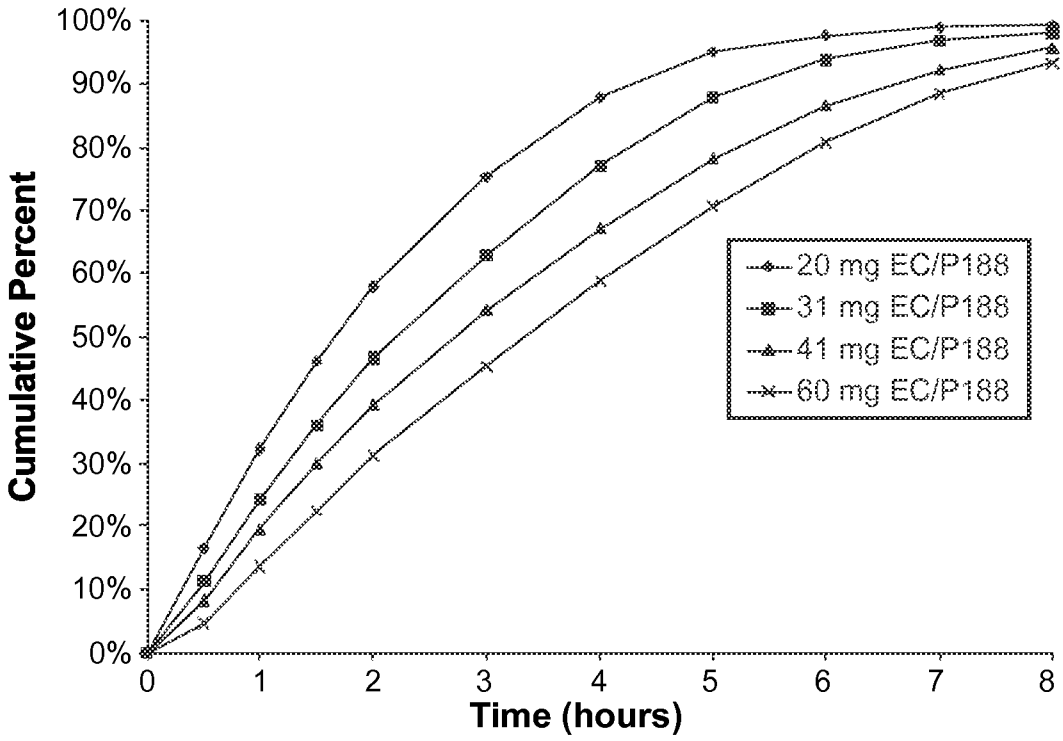
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
20 mg EC/P188
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11

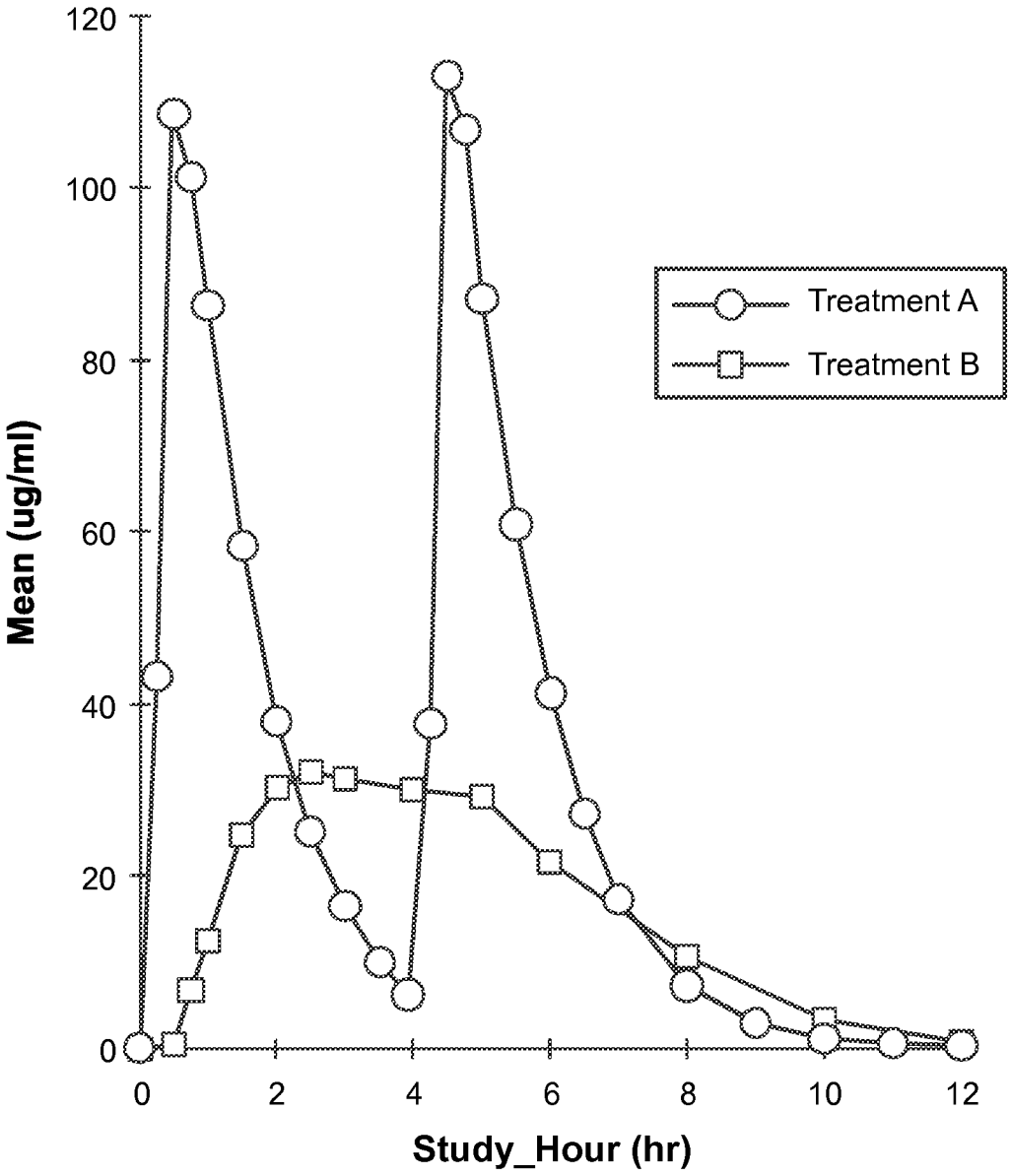
120
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12

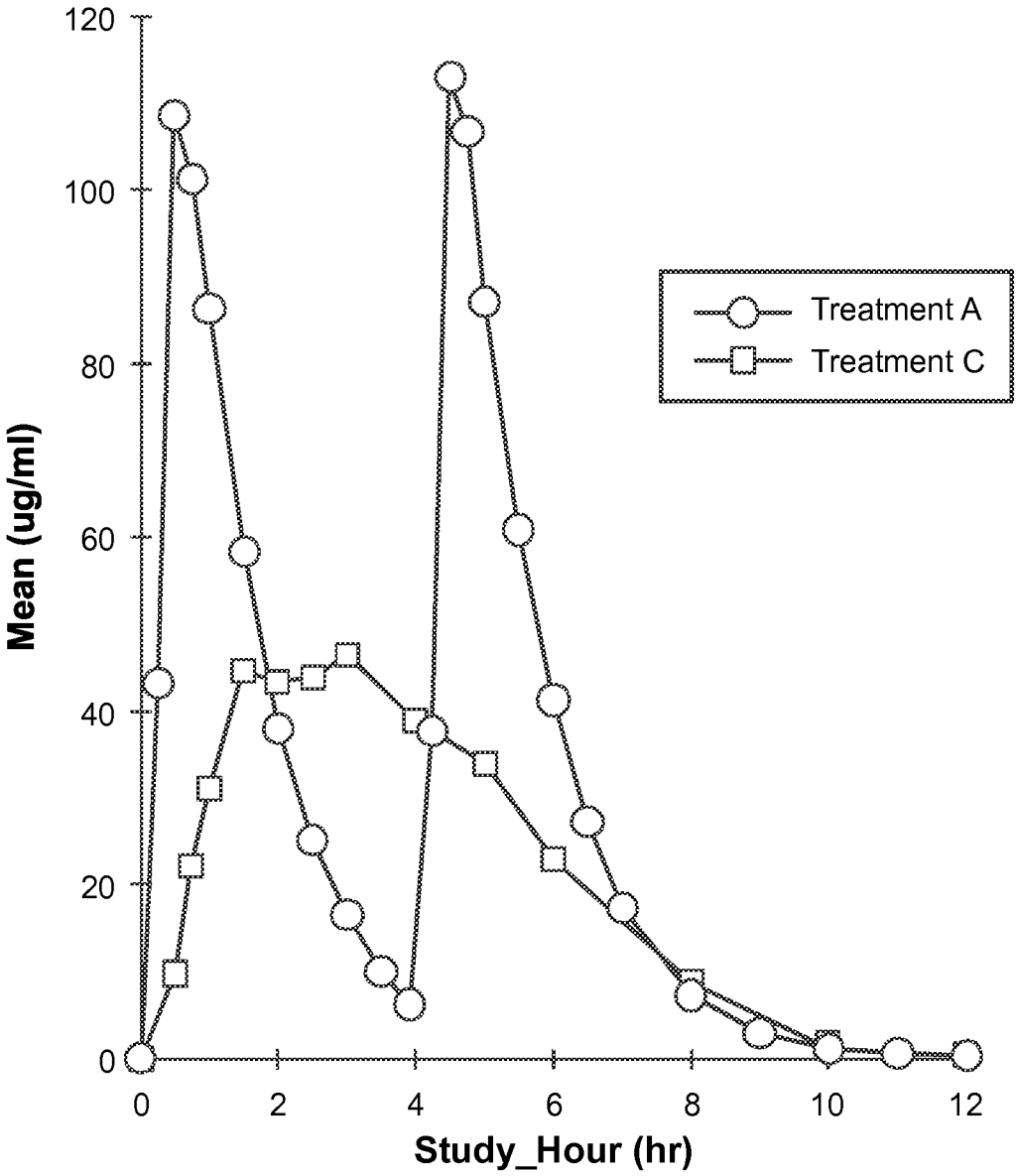
120
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13

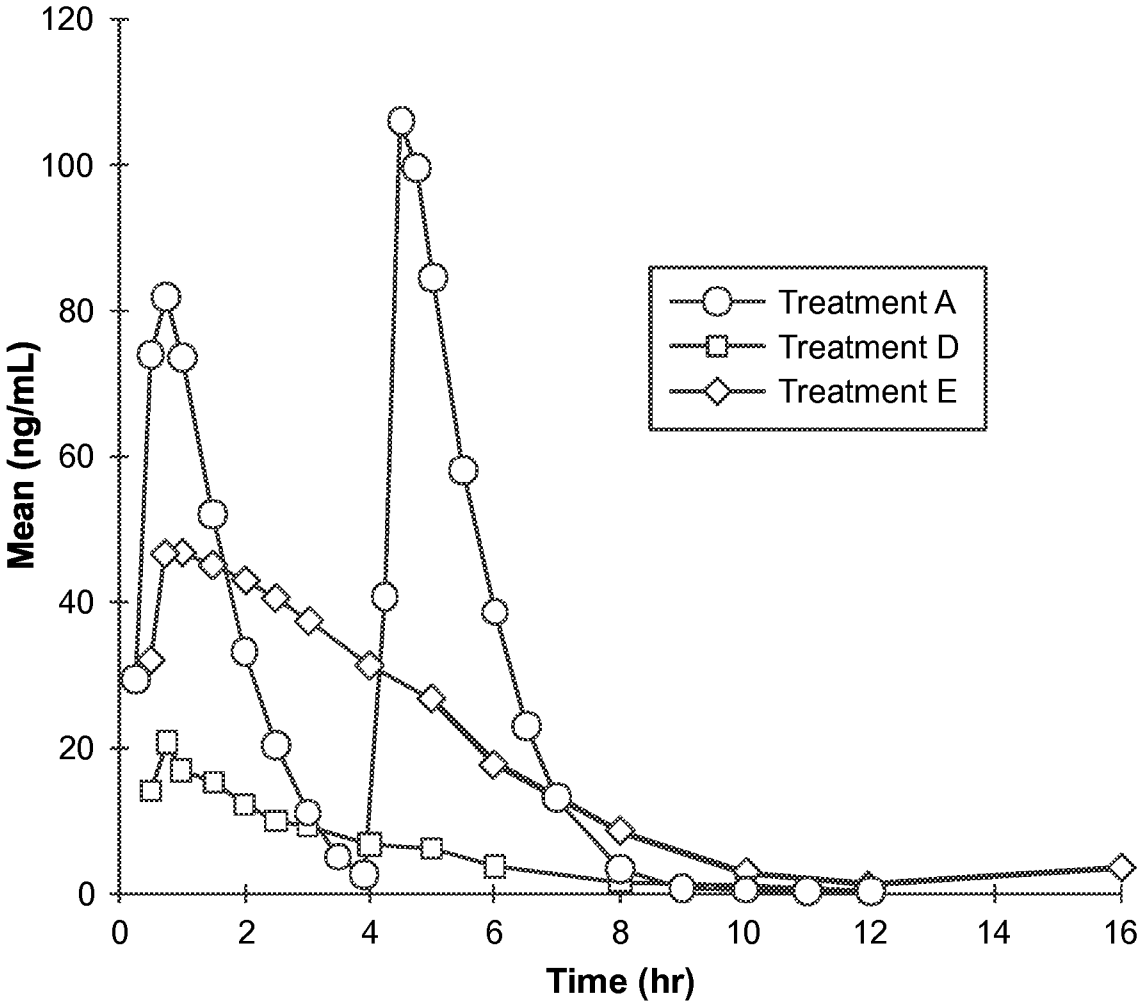
120
100
80
60
40
20
0
Mean (ng/mL)
0
2
4
6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/29802

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/52 (2011.01)
USPC - 424/457
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)
USPC - 424/457

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/468 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: release, GHB, first hour, controlled, immediate, moisture

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2006/0018933 A1 (Vaya et al.) 26 January 2006 (26.01.2006) para [0032]-[0033], [0061]-[0079], [0093]-[0094]	1-3, 23-28, 38 ---------- 37, 52-56
Y	US 2006/0210630 A1 (Liang et al.) 21 September 2006 (21.09.2006) para [0080], [0090]	37, 52-26
A	US 2006/0024365 A1 (Vaya et al.) 02 February 2006 (02.02.2006) entire document	1-3
A	US 2008/0292700 A1 (Nghiem et al.) 27 November 2008 (27.11.2008) entire document	1-3
A	US 2008/0069871 A1 (Vaughn et al.) 20 March 2008 (20.03.2008) entire document	1-3
P/A	US 2010/0112056 A1 (Rourke et al.) 06 May 2010 (06.05.2010) entire document	1-3, 23-28, 37-38, 52-56

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
23 May 2011 (23.05.2011)	27 MAY 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/29802

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-22, 29-36, 39-51 and 57-108
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.