Title: CENTRAL NERVOUS SYSTEM STIMULANT AND OPIOID ANTAGONIST COMBINATIONS

Abstract: Disclosed in certain embodiments is a pharmaceutical composition comprising at a CNS stimulant and an opioid antagonist.
CENTRAL NERVOUS SYSTEM STIMULANT AND OPIOID ANTAGONIST COMBINATIONS

Field of the Invention

[0001] This application is directed to a combination of a CNS stimulant, e.g., methylphenidate, and an opioid antagonist and methods of administering the composition for the treatment of attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), narcolepsy, cocaine addiction, appetite suppression and depression. Preferably, the combination provides an increased therapeutic effect and reduced abuse potential as compared to either of the drugs used alone.

Background of the Invention

[0002] Attention deficit disorder (ADD) is a learning disorder that relates to developmentally inappropriate inattention and impulsivity, which may be present with hyperactivity (ADHD) or without hyperactivity. ADD is implicated in learning disorders and can influence the behavior of children at any cognitive level. ADD is primarily a disorder experienced by children, but it may be present in adults as well. ADD is estimated to affect 5 to 10% of school-aged children, precipitating half of the childhood referrals to diagnostic clinics, and it is seen 10 times more frequently in boys than girls.

[0003] The primary signs of ADD (with or without hyperactivity) are a subject’s display of inattention and impulsivity. ADHD is diagnosed when the signs of overactivity are obvious. Inappropriate inattention causes increased rates of activity and impersistence or reluctance to participate or respond. A subject suffering from ADD exhibits a consistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. To establish ADD, subjects must suffer clear evidence of interference with developmentally appropriate social, academic, or occupational functioning. Although subjects with ADD (without hyperactivity) may not manifest high activity levels, most exhibit restlessness or jitteriness, short attention span, and poor impulse control. These are qualitatively different from those seen in conduct and anxiety disorders. Inattention is described as a failure to finish tasks started, easy distractibility, seeming lack of attention, and difficulty concentrating on tasks requiring
sustained attention. Impulsivity is described as acting before thinking, difficulty taking turns, problems organizing work, and constant shifting from one activity to another. Impulsive responses are especially likely when involved with uncertainty and the need to attend carefully. Hyperactivity is featured as difficulty staying seated and sitting still, and running or climbing excessively.

[0004] Narcolepsy is characterized by insomnia, including attacks of sleep that may occur suddenly under conditions that are not normally conducive to sleep. Treatments for narcolepsy include administration of tricyclic antidepressants or MAO inhibitors. Alternatively, CNS stimulants, e.g., methylphenidate, have been used. However, as with their use in treating ADD, the use of stimulants is complicated by the risk of abuse and the likelihood of developing tolerance.

[0005] During early studies of the use of CNS stimulants in the treatment of narcolepsy, it was discovered that CNS stimulants produced weight loss, and they have since been used to treat obesity. The stimulants promote weight loss by suppression of appetite, rather than by increasing energy expenditure.

[0006] Cocaine use is associated with its effectiveness to block dopamine transport, which leads to increased dopaminergic stimulation at critical brain sites. The dopaminergic stimulation causes a reinforcing effect and produces increased heart rate and blood pressure, as well as increased arousal, improved performance on tasks of vigilance and alertness, sense of self-confidence and euphoria. Administration of certain CNS stimulants, e.g., methylphenidate, produce subjective effects similar to cocaine by providing an increase in synaptic dopamine primarily by stimulation of presynaptic release of dopamine rather than by blockade of reuptake, as is the case with cocaine.

[0007] Methylphenidate is approved for the treatment of attention deficit/hyperactivity disorders and narcolepsy and has a host of unlabeled uses, e.g., as a treatment for cocaine addiction, and for the treatment of depression in elderly, cancer and post-stroke patients.

[0008] Methylphenidate is commercially available under the tradename Ritalin® (Ciba-Geigy) in 5mg, 10mg and 20mg immediate release tablets and 20mg sustained-release tablets; under the tradename Concerta™ (Alza Pharmaceuticals) as 18mg, 36mg and 54mg
tablets; and under the Tradename Metadate CD® 20mg (Celltech) as a sprinkle dosage form.

[0009] Symptoms of methylphenidate abuse are principally a result of CNS over-stimulation and excessive sympathomimetic effects, and can be characterized by the following: appetite suppression, wakefulness, increased focus/attentiveness, euphoria, vomiting, agitation, tremors, convulsions (possibly followed by a coma), confusion, hallucination, delirium, sweating, flushing, hyperpyrexia, headache, tachycardia, palpitations, cardiac arrhythmias, hypertension and dry mucous membranes.

[0010] Opioid antagonists, e.g., naltrexone, naloxone and nalmefene, typically block or reverse the effect of opioid agonists. Accordingly, opioid antagonists can be used to block euphoric effects that might otherwise be obtained upon administration of opioid agonists to addicts; to determine whether individuals are physically dependent on opioid agonists; and to reverse the effects of opioid agonists on individuals who have overdosed on such drugs. Opioid antagonists have also been used to precipitate abstinence syndrome in subjects physically dependent on opioid agonists.

[0011] Opioid antagonists, e.g., naltrexone and naloxone, have been shown to prevent performance deficit in memory tasks in rats; facilitate learning and retention; enhance attention in animals and humans; improve cognitive performance in attention deficit patients; mediate hyperactivity, inattention and aggression in autistic disorders; significantly decrease alcohol use and improve depression symptoms in depressed patients taking serotonin-reuptake inhibitors (hereinafter "SSRIs"); and decrease food and water intake.

[0012] Opioid antagonists and certain CNS stimulants, e.g., methylphenidate, have common reward pathways and physiological mechanisms of euphoria. Further, it is believed that opioid antagonists increase dopamine levels in brain areas that do not respond to therapy by certain CNS stimulants such as methylphenidate. Accordingly, it would be advantageous to provide compositions and methods for treating attention deficit disorders (ADD, ADHD), narcolepsy, drug addiction, obesity and/or depression that preferably have reduced abuse potential and side effects.
Objects and Summary of the Invention

[0013] It is an object of the present invention to provide a pharmaceutical composition comprising at least one CNS stimulant and at least one opioid antagonist.

[0014] It is an object of certain embodiments of the present invention to provide a combination of a CNS stimulant and an opioid antagonist that provides for a reduction of abuse potential and/or side effects associated with administration of the CNS stimulant alone, while providing a therapeutic benefit for the treatment of attention deficit/hyperactivity disorders, narcolepsy, drug addiction, obesity or depression.

[0015] It is an object of certain embodiments of the present invention to provide a method for treating ADD or ADHD by administering to a patient in need thereof a combination of at least one CNS stimulant and at least one opioid antagonist, wherein the combination is in an effective amount to treat the ADD or ADHD.

[0016] It is an object of certain embodiments of the present invention to provide a method for treating drug addiction (e.g., alcohol, opioid and/or cocaine addiction), narcolepsy, depression and/or obesity by administering to a patient in need thereof a combination of at least one CNS stimulant and at least one opioid antagonist, wherein the combination is in an effective amount to treat the ailment(s).

[0017] It is an object of certain embodiments of the present invention to provide a method for reducing side effects and/or abuse potential associated with CNS stimulant therapy comprising co-administering at least one opioid antagonist with at least one CNS stimulant to a patient in need thereof, whereby a decreased amount of the CNS stimulant is required to achieve a therapeutic effect, as compared to when the CNS stimulant is used alone, thereby resulting in a reduction of side effects and/or abuse potential associated with the CNS stimulant therapy.

[0018] The present invention is related in part to administration of a pharmaceutical composition comprising a CNS stimulant and an opioid antagonist in a single dosage form or the co-administration of a CNS stimulant and an opioid antagonist as separate compositions. The CNS stimulant and opioid antagonist can independently be administered by any
appropriate route, e.g., orally, via implant, parenterally, sublingually, rectally, topically, or via inhalation.

[0019] As used herein, the term “co-administration” means: (i) the administration of a single dosage form containing both the CNS stimulant and the opioid antagonist; or (ii) the administration of the CNS stimulant and the opioid antagonist as separate compositions, either simultaneously or sequentially, by the same route of administration or by a different route of administration to allow the benefit of the combination to be realized.

[0020] The term "parenterally" as used herein encompasses, e.g., subcutaneous, intravenous, intramuscular, intraperitoneal, intradermal, intrarectal injection, intraspinal or infusion techniques.

[0021] The term “topically” as used herein encompasses administration by any transdermal technique known in the art, including, e.g., the use of creams, ointments, emulsions, gels, lotions, solutions, suspensions, aerosols, and transdermal delivery devices such as transdermal patches, transdermal plasters, transdermal discs, and iontophoretic transdermal devices.

[0022] The term “inhalation” as used herein encompasses administration by any technique known in the art for pulmonary or nasal delivery, e.g., aerosols, dry powders, nebulized solutions or infusion.

[0023] The term "sustained release" is defined for purposes of the present invention as the release of the drug from the formulation at a rate which will provide a longer duration of action than a single dose of the normal (i.e., immediate release) formulation. For example, a typical immediate release oral formulation may release the drug, e.g., over a 1 hour interval, as compared to a sustained release oral formulation which may release the drug, e.g., over a 4 to 24 hour interval. Further, a sustained release transdermal system can release the drug contained therein, e.g., over a 1 day to 30 day interval. A sustained release formulation according to the present invention may also have an immediate release portion of drug contained therein to provide a prompt therapeutic effect.
[0024] For purposes of the present invention, the term "central nervous system stimulant" (hereinafter "CNS" stimulant) shall include the base form of the CNS stimulant, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures of any of the foregoing.

[0025] For purposes of the present invention, the term "opioid antagonist" shall include the base form of the antagonist, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures of any of the foregoing.

**Detailed Description**

[0026] In certain embodiments of the present invention, the CNS stimulant is selected from the group consisting of methylphenidate, amphetamine, dextroamphetamine, methamphetamine, phentermine, benzphetamine, phenidimetrazine, diethylpropion, mazindol, fenfluramine, sibutramine, phenylpropanolamine, ephedrine, phenylephrine, mephentermine, norepinephrine, epinephrine, caffeine, doxapram, modafinil, pharmaceutically acceptable salts thereof and mixtures thereof.

[0027] In certain embodiments, the CNS stimulant is methylphenidate or a pharmaceutically acceptable salt thereof, e.g., methylphenidate hydrochloride.

[0028] In certain embodiments of the present invention, the CNS stimulant and opioid antagonist are administered as a combination pharmaceutical composition, wherein both agents are contained in a single dosage form, e.g., an immediate release or sustained release tablet or capsule. In another embodiment of the invention, the CNS stimulant and opioid antagonist are co-administered as separate dosage forms. The co-administration can be simultaneous, or sequential. In sequential administration, the CNS stimulant can be administered and the opioid antagonist can be administered immediately thereafter, or within a specific time period, e.g., several minutes or hours thereafter. Where the CNS stimulant and opioid antagonist are administered separately, the number of doses of each agent given per day may be different, e.g. in the event one agent has a greater duration of action, and can be administered less frequently.
[0029] When the CNS stimulant is methylphenidate or a pharmaceutically acceptable salt thereof, the amount administered per dose is dependent on factors such as, e.g., the route of administration, the formulation containing the drug, and the frequency of administration. Typically, the total oral daily dose of methylphenidate can be from about 1mg to about 60mg, from about 5 mg to about 30 mg, or from about 10mg to about 20mg. The actual amount of drug in each dose can be ascertained by one skilled in the art, taking into account the above factors.

[0030] Opioid antagonists useful in the present invention include, but are not limited to naloxone, naltrexone, nalmefene, cyclazocine, nalorphine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof. Other drugs which exhibit opioid antagonistic effects are also useful in the present invention, e.g., mixed opioid agonist/antagonist agents, such as pentazocine, nalbuphine, buprenorphine, pharmaceutically acceptable salts thereof and mixtures thereof. Naloxone, naltrexone, nalmefene and salts thereof are particularly preferred. In oral dosage forms, naltrexone, nalmefene and salts thereof are particularly preferred. In certain embodiments, the total oral daily dose of opioid antagonist administered can be from about 0.005mg to about 150mg, or from about 1mg to about 50mg. The actual amount of antagonist in each dose can be ascertained by one skilled in the art, taking into account, e.g., the route of administration, the formulation containing the drug, and the frequency of administration.

[0031] In embodiments wherein the opioid antagonist is naloxone or a pharmaceutically acceptable salt thereof, the total oral daily dose can be from about 0.005mg to about 24mg, from about 0.1mg to about 10mg or from about 0.4mg to about 2mg.

[0032] In embodiments wherein the opioid antagonist is naltrexone or a pharmaceutically acceptable salt thereof, the total oral daily dose can be from about 0.005mg to about 150mg, from about 0.1mg to about 75mg or from about 10mg to about 50mg.

[0033] In certain embodiments of the present invention, the pharmaceutical composition(s) can be a dosage form independently selected from the group consisting of oral, sublingual, topical, implantable, inhalable and parenteral dosage forms. When the CNS stimulant and opioid antagonist are present in oral dosage forms, the agents can be combined with excipients, e.g., pharmaceutically acceptable organic or inorganic carrier substances suitable
for oral administration, known in the art. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatins, carbohydrates such as lactose, amylose or starch; magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical compositions can be sterilized, and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like.

[0034] The compositions intended for oral use may be prepared according to any method known in the art. Such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients suitable for the manufacture of tablets. Such excipients include, for example, an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with excipient.

[0035] Aqueous suspensions preferably contain the agent(s) in a mixture that has one or more excipients suitable as suspending agents, for example, pharmaceutically acceptable synthetic gums such as hydroxypropylmethylcellulose or natural gums. Oily suspensions may be formulated by suspending the agent(s) in a vegetable oil or mineral oil. The oily suspensions may contain a thickening agent such as beeswax or cetyl alcohol. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

[0036] The method of treatment and pharmaceutical compositions of the present invention may further include an additional active agent in addition to the CNS stimulant and opioid antagonist. The additional agent can provide increased therapeutic benefit by treating a disease state not being treated by the combination of CNS stimulant and opioid antagonist, or alternatively can augment the intended therapy of the combination.
[0037] The oral pharmaceutical compositions of the present invention can be in the form of tablets, dragees, liquids, drops, gelcaps, troches, lozenges, aqueous or oily suspensions, multiparticulate formulations including dispersible powders, granules, pellets, matrix spheroids, coated inert beads, emulsions, hard or soft capsules, syrups, elixirs, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, etc. The dosage forms of the present invention may preferably include any desired pharmaceutically acceptable excipients known to those skilled in the art.

[0038] In certain embodiments, the CNS stimulant and the opioid antagonist can each independently be released in (i) immediate release form, (ii) sustained release form, or (iii) both immediate and sustained release form. Sustained release may be accomplished in accordance with formulations/methods of manufacture known to those skilled in the art of pharmaceutical formulation, e.g., via the incorporation of a sustained release carrier into a matrix containing the CNS stimulant and opioid antagonist; or via a sustained release coating of a matrix containing the CNS stimulant and opioid antagonist; or a combination thereof.

[0039] The CNS stimulant/opioid antagonist combination can be formulated as a controlled or sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may optionally include a sustained release material which is (i) incorporated into a matrix along with the CNS stimulant and/or opioid antagonist, or (ii) coated on a substrate containing the agent(s). In another embodiment, the composition may include at least one sustained release excipient which provides a sustained release of the CNS stimulant, the opioid antagonist or both the CNS stimulant and the opioid antagonist. The sustained release material preferably provides a sustained release from about 12 to about 24 hours for oral preparations or from about 3 to 7 days for transdermal formulations.

[0040] In certain embodiments of the present invention, the sustained release dosage form may comprise particles containing the active ingredients, wherein the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. The particles may be film coated with a material that permits release of the CNS stimulant and/or antagonist combination at a sustained rate in an aqueous medium. The film coat may be chosen to achieve, in combination with the other stated properties, a desired in-vitro release rate. The sustained release coating formulations of the present invention should be
capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

[0041] In certain embodiments, the particles can comprise immediate release matrices containing the CNS stimulant and/or the opioid antagonist.

[0042] The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the CNS stimulant and/or opioid antagonist in desired areas of the gastrointestinal (GI) tract, e.g., the stomach or small intestine. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

[0043] Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coating and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings that are pH-dependent which may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers, zein, and the like.

[0044] In certain preferred embodiments, a substrate (e.g., tablet core or matrix particle) containing the CNS stimulant and/or without the opioid antagonist is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail, e.g., in U.S. Pat. Nos. 5,273,760 and 5,286,493.
[0045] Other examples of sustained release formulations and coatings that may be used in accordance with the present invention include Assignee's U.S. Pat. Nos. 5,324,351; 5,356,467; and 5,472,712, hereby incorporated by reference in their entirety.

[0046] Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials suited for coating the substrates according to the invention. One preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

[0047] One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

[0048] Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion that can be applied directly onto substrates.

[0049] In certain embodiments of the present invention, the hydrophobic material comprising the controlled release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminooalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.
[0050] In certain embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0051] In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

[0052] Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as different grades of Eudragit® from Rohm Tech, Inc.

[0053] In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

[0054] The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL or 50% Eudragit® RL and 50% Eudragit® RS or 10% Eudragit® RL and Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used.
[0055] In certain embodiments of the present invention, where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material may further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, may be properly determined after routine experimentation with the particular coating solution and method of application.

[0056] Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethylcellulose utilized in the present invention.

[0057] Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and 1,2-propylene glycol. Other plasticizers that have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of acrylic polymers utilized in the present invention.

[0058] It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

[0059] When a hydrophobic material is used to coat inert pharmaceutical beads such as nu-pariel 18/20 beads, a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.
[0060] Controlled release bead formulations prepared according to the present invention slowly release the therapeutically active agent, e.g., when ingested and exposed to gastrointestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of coating with the hydrophobic material, altering the manner in which the plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

[0061] Substrates coated with a therapeutically active agent of the present invention can be prepared, e.g., by dissolving the therapeutically active agent(s) in water and then spraying the solution onto a substrate, for example, nut pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients can be added prior to coating. The additional ingredients can be used to assist the binding of the agent(s) to the spheroids or beads, and/or to provide color. For example, a product which includes hydroxypropylmethylcellulose, with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the spheroids or beads. The resultant coated substrate, in this example spheroids or beads, may then be optionally overcoated with a barrier agent, to separate the agent(s) from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

[0062] The substrates may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

[0063] The coating solutions of the present invention may contain, in addition to the film-former, plasticizer, and solvent system, a colorant to provide elegance and product
distinction. Color may be added to the solution of the therapeutically active agent instead of, or in addition to the dispersion of hydrophobic material. Any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retardant effect of the coating.

[0064] Plasticized hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In certain embodiments, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of the therapeutically active agent when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

[0065] The release of the therapeutically active agent(s) from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating.

[0066] Release-modifying agents may be, e.g., pore-formers. Pore formers include organic or inorganic materials that can be dissolved, extracted or leached from a coating in an environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose. In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

[0067] The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,899;
4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

[0068] In other embodiments of the present invention, the controlled release formulation is achieved via a matrix having a controlled release coating as set forth above. The present invention may also utilize a controlled release matrix that affords in-vitro dissolution rates of the CNS stimulant and/or opioid antagonist within the preferred ranges and that releases the CNS stimulant and/or opioid antagonist in a pH-dependent or pH-independent manner. The materials suitable for inclusion in a controlled release matrix will depend on the method used to form the matrix.

[0069] For example, a matrix in addition to the CNS stimulant and/or opioid antagonist may include (i) hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins and protein derived materials (ii) digestible, long chain (C₈ -C₅₀, especially C₁₂ -C₄₀), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and iii) polyalkylene glycols. In certain embodiments, the matrix material can melt or soften to the extent necessary to be extruded.

[0070] Of these polymers, acrylic polymers such as Eudragit® RSPO, and cellulose ethers such as hydroxyalkylcelluloses and carboxyalkylcelluloses are preferred. The oral dosage form may contain between about 1% and about 80% (by weight) of at least one hydrophilic or hydrophobic material.

[0071] When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between about 25°C and about 90°C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to about 60% (by weight) of at least one digestible, long chain hydrocarbon.

[0072] Preferably, the oral dosage form contains up to about 60% (by weight) of at least one polyalkylene glycol.

[0073] The hydrophobic material may be selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein,
hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to any of acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses, such as hydroxypropylmethylcellulose, and mixtures of the foregoing.

[0074] Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 30° to about 200°C, preferably from about 45° to about 90°C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and triglycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol, hydrophobic and hydrophilic materials having hydrocarbon backbones, and mixtures thereof. Suitable waxes include, for example, beeswax, glycowax, castor wax or carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30° to about 100°C.

[0075] Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C₈ – C₅₀, especially C₁₂ – C₄₀), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids; mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between about 25° and about 90°C are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to about 60% (by weight) of at least one digestible, long chain hydrocarbon. A combination of two or more hydrophobic materials may be included in the matrix formulations. If an additional hydrophobic material is included, it may be selected
from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid or stearyl alcohol.

[0076] One particular suitable matrix comprises a water soluble hydroxyalkyl cellulose, a C<sub>12</sub>–C<sub>36</sub> (preferably C<sub>14</sub>–C<sub>22</sub>) aliphatic alcohol and, optionally, a polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy (C<sub>1</sub> to C<sub>6</sub>) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose. The amount of the hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of opioid release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In certain embodiments, the aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of CNS stimulant and/or opioid antagonist release required. It will also depend on whether a polyalkylene glycol is present in or absent from the oral dosage form. In the absence of a polyalkylene glycol, the oral dosage form may contain between about 20% and about 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, the combined weight of the aliphatic alcohol and the polyalkylene glycol may be between about 20% and about 50% (by wt) of the total dosage.

[0077] In one embodiment, the ratio of, e.g., the hydroxyalkyl cellulose or acrylic resin to the aliphatic alcohol/polyalkylene glycol is a factor in the release rate of the CNS stimulant and/or the opioid antagonist from the formulation. A ratio of hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

[0078] The polyalkylene glycol may be, for example, polypropylene glycol or more preferably, polyethylene glycol. The average molecular weight of the polyalkylene glycol is preferably between about 1,000 and about 15,000, especially more preferably between about 1,500 and about 12,000.

[0079] Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C<sub>12</sub> to C<sub>36</sub> aliphatic alcohol and, optionally, a polyalkylene glycol.
[0080] In certain embodiments, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

[0081] In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants or glidants that are conventional in the pharmaceutical art.

[0082] In order to facilitate the preparation of a solid, controlled release, oral dosage form according to the invention, any method of preparing a matrix formulation known to those skilled in the art may be used. A matrix may be prepared, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and the CNS stimulant and/or opioid antagonist; (b) mixing the granules of step (a) with a C_{12} - C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules of step (b). Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/agent(s) with water. In certain embodiments, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the agent(s).

[0083] In yet other alternative embodiments, a spheronizing agent, together with the active ingredient, can be spheronized to form spheroids. Microcrystalline cellulose is a preferred spheronizing agent. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may contain a binder. Suitable binders, such as low viscosity, water soluble polymers, are well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl celluloses, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively), the spheroids may contain a water-insoluble polymer, such as an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating may include a hydrophobic material such as a wax, a fatty alcohol, shellac, zein or mixtures thereof.

[0084] Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a
sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material.

[0085] The additional hydrophobic material may comprise (i) a water-insoluble wax-like thermoplastic substances optionally mixed with (ii) a wax-like thermoplastic substances being less hydrophobic than the substance of (i). In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

[0086] In addition to the above ingredients, a sustained release matrix or matrix multiparticulate formulation may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants or glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

[0087] Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

[0088] The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the CNS stimulant and/or the opioid antagonist together with a hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture may then be extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands can be cooled and cut into multiparticulates. The multiparticulates can then be separated into unit doses. The extrudate may have a diameter of from about 0.1 to about 5 mm and provide sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours.
[0089] An optional process for preparing melt extrusions includes directly metering into an extruder a hydrophobic material, the agent(s), and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and combining a plurality of the particles into a unit dosage form.

[0090] The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit port of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[0091] The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit port. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" ("MEMs") and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" all refer to a plurality of units containing the active agent(s) and excipient produced by melt extrusion. In this regard, the melt-extruded multiparticulates may have a range of from about 0.1 to about 12 mm in length and a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and separated into individual unit doses of the therapeutically active agent(s) without the need of a spheronization step.

[0092] In certain embodiments, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

[0093] In other embodiments, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980), incorporated by reference herein.
[0094] In certain embodiments, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681 (Klimesch, et. al.), described in additional detail above and hereby incorporated by reference.

[0095] Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings may include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the coating may be greater depending upon the physical properties of the particular CNS stimulant and/or opioid antagonist compounds utilized and the desired release rate, among other factors.

[0096] The sustained release formulations of the present invention may slowly release the therapeutically active agent(s), e.g., when ingested and exposed to gastrointestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, e.g., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

[0097] In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the therapeutically active agent(s), which is/are added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent(s) blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent(s) included in the formulation is/are sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

[0098] When the CNS stimulant and/or opioid antagonist are administered by injection, suitable forms of injection include, but are not limited to intravenous, intramuscular, subcutaneous, intraspinal, intraperitoneal, or intradermal administration.

[0099] In certain embodiments, the parenteral dose of the CNS stimulant and/or opioid antagonist can be combined with a pharmaceutically acceptable vehicle for injection or
implantation. For example, the CNS stimulant and/or opioid antagonist can be dissolved in oils, propylene glycol or other solvents commonly used to prepare injectable solutions. Suitable pharmaceutically acceptable vehicles include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and any combinations or mixtures thereof. Examples of aqueous vehicles include sodium chloride for injection, bacteriostatic sodium chloride for injection, Ringers solution, isotonic dextrose for injection, sterile water for injection, bacteriostatic sterile water for injection, dextrose lactated Ringers solution and any combinations or mixtures thereof. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil, peanut oil and any combinations or mixtures thereof. Antimicrobial agents in bacteriostatic or fungistic static concentrations include phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, ethyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride benzethonium chloride and mixtures thereof. Isotonic agents include sodium chloride, dextrose and any combinations or mixtures thereof. Buffers include acetate, phosphate, citrate and any combinations or mixtures thereof. Antioxidants include ascorbic acid, sodium bisulfate and any combinations or mixtures thereof. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone and any combinations or mixtures thereof. Emulsifying agents include Polysorbate 80 (Tween 80). Sequestering or chelating agents of metal ions include ethylenediaminetetraacetic acid. Additional pharmaceutically acceptable vehicles also include ethyl alcohol, polyethylene glycol, glycerin or propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment (e.g., to make the formulation isotonic) and any combinations or mixtures thereof.

[0100] In certain embodiments, the CNS stimulant and/or opioid antagonist can be administered as injectable microparticles (microcapsules and microspheres). The microparticles administered by the methods of the present invention are in a size and distribution range suitable for implantation or injection. The diameter and shape of the microparticles can be manipulated to modify the release characteristics. For example, larger diameter microparticles will typically provide slower rates of release and reduced tissue penetration and smaller diameters of microparticles will produce the opposite effects, relative to microparticles of different mean diameter, but of the same composition. In addition, other particle shapes, such as cylindrical shapes, can also modify release rates by virtue of the
increased ratio of surface area to mass inherent to such alternative geometrical shapes, relative to a spherical shape. The diameter of microparticles may range in size from about 5 microns to about 200 microns in diameter. In a more preferred embodiment, the microparticles range in diameter from about 20 to about 120 microns.

[0101] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

**EXAMPLE 1**

[0102] Sustained Release Methylphenidate Hydrochloride formulations containing naltrexone hydrochloride are prepared with the formula in Table 1 below:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amt/Unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate HCl</td>
<td>7.5</td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>72.35</td>
</tr>
<tr>
<td>Povidone</td>
<td>5.0</td>
</tr>
<tr>
<td>Eudragit RS30D (solids)</td>
<td>10.0</td>
</tr>
<tr>
<td>Triacetin</td>
<td>2.0</td>
</tr>
<tr>
<td>Naltrexone HCl</td>
<td>1.0</td>
</tr>
<tr>
<td>Stearyl Alcohol</td>
<td>25.0</td>
</tr>
<tr>
<td>Talc</td>
<td>3.25</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.25</td>
</tr>
<tr>
<td>Opadry Pink Y-S-14518A</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>132.35</strong></td>
</tr>
</tbody>
</table>

[0103] In this example, the naltrexone hydrochloride is added to the formulation during the granulation process. The process is set forth below:

1. Dissolve the Naltrexone HCl in water
2. Disperse the Triacetin into the Naltrexone HCl solution and incorporate the Eudragit RS30D into the dispersion

4. Milling: Discharge the granulation and pass through a mill with approximately 1 mm openings (18 mesh screen).

5. Waxing: Melt the stearyl alcohol at about 70 degrees C and add to the milled granulation using a high shear mixer. Allow to cool at room temperature on trays or a fluid bed.

6. Milling: Pass the cooled granulation through a mill with approximately 18 mesh screen.

7. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

8. Compression: Compress the granulation into tablets using a Kilian tablet press.

9. Film Coating: Disperse the Opadry into water and apply an aqueous film coat to the tablets using a rotary pan.

EXAMPLE 2

[0104] Methylphenidate salt /naltrexone salt sustained release osmotic tablets are produced with the formula set forth in Table 2 below:

Table 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amt/unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Layer:</strong></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate HCL</td>
<td>7.5</td>
</tr>
<tr>
<td>Naltrexone HCL</td>
<td>1.0</td>
</tr>
<tr>
<td>Polyethylene oxide</td>
<td>142.74</td>
</tr>
<tr>
<td>Povidone</td>
<td>8.8</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.76</td>
</tr>
<tr>
<td><strong>Displacement Layer:</strong></td>
<td></td>
</tr>
<tr>
<td>Polyethylene oxide</td>
<td>85.96</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>40.50</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose</td>
<td>6.75</td>
</tr>
<tr>
<td>Ferric Oxide</td>
<td>1.35</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.34</td>
</tr>
<tr>
<td>BHT</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Semipermeable Wall:</strong></td>
<td></td>
</tr>
<tr>
<td>Cellulose acetate</td>
<td>38.6</td>
</tr>
</tbody>
</table>
[0105] The dosage form having the above formulation is prepared according to the following procedure:

[0106] First, the methylphenidate hydrochloride, the naltrexone hydrochloride dihydrate, poly(ethylene oxide) possessing a 200,000 average molecular weight, and polyvinylpyrrolidone having a 40,000 average molecular weight are added to a mixer and mixed for 10 minutes. Then, denatured anhydrous alcohol is added to the blended materials with continuous mixing for 10 minutes. Then, the wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 20 hours, and then passed through a 16 mesh screen. Next, the granulation is transferred to the mixer, mixed and lubricated with magnesium stearate.

[0107] Then, the displacement or push composition for pushing the methylphenidate HCL/naltrexone HCL composition from the dosage form is prepared as follows: first 3910 g of hydroxypropylmethylcellulose possessing a 11,200 average molecular weight is dissolved in 45,339 g of water. Then, 101 g of butylated hydroxytoluene is dissolved in 650 g of denatured anhydrous alcohol. Next, 2.5 kg of the hydroxypropylmethylcellulose aqueous solution is added with continuous mixing to the butylated hydroxytoluene alcohol solution. Then, binder solution preparation is completed by adding with continuous mixing the remaining hydroxypropylmethylcellulose aqueous solution to the butylated hydroxytoluene alcohol solution.

[0108] Next, 36,000 g of sodium chloride is sized using a Quadro Comil® mill equipped with a 21 mesh screen. Then, 1200 g of ferric oxide is passed through a 40 mesh screen. Then, the screened materials, 76,400 g of pharmaceutically acceptable poly(ethylene oxide) possessing a 7,500,000 average molecular weight, and 2500 g of hydroxypropylmethylcellulose having a 11,200 average molecular weight are added to a Glatt® Fluid Bed Granulation’s bowl. The bowl is attached to the granulator and the granulation process is initiated for effecting granulation. Next, the dry powders are air suspended and mixed for 10 minutes. Then, the binder solution is sprayed from 3 nozzles onto the powder. The granulating is monitored during the process as follows: total solution spray rate of 800 g/min; inlet temperature 43°C and air flow 4300 m³/hr. At the end of solution spraying, 45,033 g of the resultant coated granulated particles are subjected to a drying process for 35 minutes.
[0109] The coated granules are sized using a Quadro Comil® mill with an 8 mesh screen. The granulation is transferred to a Tote® Tumbler, mixed and lubricated with 281.7 g of magnesium stearate.

[0110] Next, the drug composition comprising the methylphenidate hydrochloride/naltrexone hydrochloride and the push composition are compressed into bilayer tablets on a Kilian® Tablet press. First, the drug composition is added to the die cavity and precompressed; then, 135 mg of the push composition is added and the layers are pressed under a pressure head of 3 metric tons into a 11/32 inch (0.873 cm) diameter contacting layer arrangement.

[0111] The bilayered arrangements are coated with a semipermeable wall. The wall forming composition comprises 100% cellulose acetate having a 39.8% acetyl content. The wall-forming composition is dissolved in acetone:water (95:5 wt:wt) cosolvent to make a 4% solid solution. The wall-forming composition is sprayed onto and around the bilayers in a 24 inch (60 cm) Vector® Hi-Coater. Next, one 20 mil (0.508 mm) exit passageway is drilled through the semipermeable wall to connect the drug methylphenidate layer with the exterior of the dosage form. The residual solvent is removed by drying for 72 hours at 45°C and 45% humidity. Next, the osmotic dosage systems are dried for 4 hours at 45°C to remove excess moisture.

**EXAMPLE 3**

[0112] Hydrocodone 5 mg/naltrexone 0.0625 mg sustained release capsules are prepared with the formula set forth in Table 3 below:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amt/unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate HCl</td>
<td>5.0</td>
</tr>
<tr>
<td>Naltrexone HCl</td>
<td>0.0625</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>8.15</td>
</tr>
<tr>
<td>Stearic Alcohol</td>
<td>24.00</td>
</tr>
<tr>
<td>Eudragit RSPO</td>
<td>82.79</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
</tr>
</tbody>
</table>

[0113] The formulation above is prepared according to the following procedure:
1. Pass the stearyl alcohol flakes through an impact mill.
2. Blend the Methylphenidate HCl, Naltrexone HCl, stearic acid, stearyl alcohol and the Eudragit RSPO in a suitable blender/mixer.
3. Continuously feed the blended material into a twin screw extruder at elevated temperatures, and collect the resultant strands on a conveyor.
4. Allow the strands to cool on the conveyor.
5. Cut the strands into 1 mm pellets using a pelletizer.
6. Screen the pellets for fines and oversized pellets to an acceptable range of about 0.8 - 1.4 mm in size.
7. Fill into capsules with a fill weight of 120 mg/capsule (fill into size 2 capsules).

**EXAMPLE 4**

[0114] Methylphenidate 5 mg/naltrexone 0.0625 mg sustained release capsules are prepared according to the following procedure:

[0115] Initially, immediate release methylphenidate beads are prepared with the formula set forth in Table 4 below:

**Table 4**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount/Unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate HCl</td>
<td>5.0</td>
</tr>
<tr>
<td>Opadry® Clear YS-1-19025A</td>
<td>1.25</td>
</tr>
<tr>
<td>NuPareil (Sugar beads) 30/35 mesh</td>
<td>59.35</td>
</tr>
<tr>
<td>Opadry® Butterscotch YS-1-17307A</td>
<td>1.90</td>
</tr>
<tr>
<td>Total</td>
<td>62.5</td>
</tr>
</tbody>
</table>

Process

1. Drug layering solution: Dissolve hydrocodone HCl and Opadry Clear in water.
2. Drug loading: Spray the drug solution onto NuPareil beads in a fluid bed dryer.
Sustained Release Beads are then prepared with the formula set forth in Table 5 below:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount/Unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate IR Beads (5mg/62.5mg)</td>
<td>53.08</td>
</tr>
<tr>
<td>Eudragit® RS 30 D (solids)</td>
<td>5.04</td>
</tr>
<tr>
<td>Eudragit® RL 30 D (solids)</td>
<td>0.27</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>1.05</td>
</tr>
<tr>
<td>Cab-O-Sil®</td>
<td>0.27</td>
</tr>
<tr>
<td>Opadry® Clear YS-1-19025A</td>
<td>2.79</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>62.5</strong></td>
</tr>
</tbody>
</table>

**Process**

1. Controlled release coating solution: Homogenize triethyl citrate in water. Add the dispersion to Eudragit® RS 30 D and Eudragit® RL 30 D then add Cab-O-Sil® to mixture.
2. Seal coat solution: Dissolve Opadry® Clear in water.
3. Coating: Apply the control release coating solution followed by the seal coat solution onto Methylphenidate HCl IR beads using a fluidized bed bottom-spray technique.
4. Curing: Place the coated beads on tray and cure in oven for 24 hours at 45°C.

To develop Methylphenidate/Naltrexone sustained release beads 0.0625mg of Naltrexone per unit can be included in the above formulation. It can be dissolved together with the Methylphenidate HCl in the purified water before being sprayed onto the NuPareil beads.

In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.
What is claimed is:

1. A pharmaceutical composition comprising at least one CNS stimulant and at least one opioid antagonist.

2. The pharmaceutical composition according to claim 1, wherein said CNS stimulant is selected from the group consisting of methylphenidate, amphetamine, dextroamphetamine, methamphetamine, phentermine, benzphetamine, phenmetrazine, diethylpropion, mazindol, fenfluramine, sibutramine, phenylpropanolamine, ephedrine, phenylephrine, mephentermine, norepinephrine, epinephrine, caffeine, doxapram, modafinil, pharmaceutically acceptable salts thereof, and mixtures of any of the foregoing.

3. The composition according to claim 2, wherein said CNS stimulant is methylphenidate or a pharmaceutically acceptable salt thereof.

4. The composition according to claim 3, wherein said methylphenidate or pharmaceutically acceptable salt thereof is in an amount of from about 1mg to about 60mg.

5. The composition according to claim 4, wherein said methylphenidate or pharmaceutically acceptable salt thereof is in an amount of from about 10 to about 20mg.

6. The composition according to claim 3, wherein said CNS stimulant is methylphenidate hydrochloride.

7. The composition according to claim 2, wherein said CNS stimulant is a mixture of dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulphate and amphetamine sulphate.

8. The composition according to claim 1, wherein said opioid antagonist is selected from the group consisting of naloxone, naltrexone, nalmefene, cycloclam, nalorphine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.
9. The composition according to claim 8, wherein said opioid antagonist is in an amount of from about 0.005mg to about 150mg.

10. The composition according to claim 8, wherein said opioid antagonist is in an amount of from about 1mg to about 50mg.

11. The composition according to claim 8, wherein said opioid antagonist is naltrexone or a pharmaceutically acceptable salt thereof.

12. The composition according to claim 11, wherein naltrexone or pharmaceutically acceptable salt thereof is present in an amount of from about 0.005mg to about 150mg.

13. The composition according to claim 11, wherein naltrexone or pharmaceutically acceptable salt thereof is present in an amount of from about 0.1mg to about 5mg.

14. The composition according to claims 1-13, wherein said composition is a dosage form selected from the group consisting of an oral, sublingual, topical, implantable, inhalable and parenteral dosage form.

15. The composition according to claim 13, wherein said oral dosage form is a tablet.

16. The composition according to claim 13, wherein said oral dosage form is a capsule.

17. The composition according to claim 1, further comprising at least one sustained release excipient which provides a sustained release of said CNS stimulant.

18. The composition according to claim 1, further comprising at least one sustained release excipient which provides a sustained release of said opioid antagonist.

19. The composition according to claim 1, further comprising a sustained release excipient which provides a sustained release of said CNS stimulant and said opioid antagonist.

20. The composition according to claim 17-19, wherein said sustained release excipient
provides a sustained release from about 12 to about 24 hours.

21. A method for treating attention deficit with or without hyperactivity disorder comprising administering to a patient in need thereof an effective amount of a combination comprising at least one CNS stimulant and at least one opioid antagonist.

22. A method for treating narcolepsy comprising administering to a patient in need thereof a combination comprising at least one CNS stimulant and at least one opioid antagonist, said combination in an effective amount to treat narcolepsy.

23. A method for treating depression comprising administering to a patient in need thereof a combination comprising at least one CNS stimulant and at least one opioid antagonist, said combination in an effective amount to treat depression.

24. A method for treating obesity comprising administering to a patient in need thereof a combination comprising at least one CNS stimulant and at least one opioid antagonist, said combination in an effective amount to treat obesity.

25. A method for treating drug addiction comprising administering to a patient in need thereof a combination comprising at least one CNS stimulant and at least one opioid antagonist, said combination in an effective amount to treat drug addiction.

26. The method of claim 25, wherein said drug addiction is selected from the group consisting of alcohol addiction, opioid addiction and cocaine addiction.

27. The method of claims 21-26, wherein said combination of CNS stimulant and said opioid antagonist are administered as a single dosage form.

28. The method of claims 21-26, wherein said CNS stimulant and said opioid antagonist are administered as separate dosage forms.

29. The method of claim 28, wherein said CNS stimulant and said opioid antagonist are administered simultaneously.
30. The method of claim 28, wherein said opioid antagonist is administered after said CNS stimulant.

31. The method of claim 28, wherein said CNS stimulant is administered after said opioid antagonist.

32. The method of claim 28, wherein said CNS stimulant and said opioid antagonist are independently selected from the group consisting of an oral, sublingual, topical, implantable and parenteral dosage form.

33. The method of claims 21-26, wherein said CNS stimulant is selected from the group consisting of methylphenidate, cocaine, amphetamine, dextroamphetamine, methamphetamine, phentermine, benzphetamine, phendimetrazine, diethylpropion, mazindol, fenfluramine, sibutramine, phenylpropanolamine, ephedrine, phenylephrine, mephentermine, norepinephrine, epinephrine, caffeine, doxapram, modafinil, pharmaceutically acceptable salts thereof and mixtures of any of the foregoing.

34. The method of claim 33, wherein said CNS stimulant is methylphenidate or a pharmaceutically acceptable salt thereof.

35. The method of claim 34, wherein said methylphenidate or pharmaceutically acceptable salt thereof is in an amount of from about 1mg to about 60mg.

36. The method of claims 35, wherein said methylphenidate or pharmaceutically acceptable salt thereof is in an amount of from about 10 to about 20mg.

37. The method of claim 34, wherein said CNS stimulant is methylphenidate hydrochloride.

38. The method of claim 33, wherein said CNS stimulant is a mixture of dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulphate and amphetamine sulphate.

39. The method of claims 21-26, wherein said opioid antagonist is selected from the
group consisting of naloxone, naltrexone, nalmefene, cyclazocine, nalorphine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

40. The method of claim 39, wherein said opioid antagonist is in an amount of from about 0.005mg to about 150mg.

41. The method of claim 39, wherein said opioid antagonist is in an amount of from about 1mg to about 50mg.

42. The method of claim 39, wherein said opioid antagonist is naltrexone or a pharmaceutically acceptable salt thereof.

43. The method of claim 42, wherein said naltrexone or pharmaceutically acceptable salt thereof is present in an amount of from about 0.005mg to about 150mg.

44. The method of claim 42, wherein said naltrexone or pharmaceutically acceptable salt thereof is present in an amount of from about 0.1mg to about 5mg.

45. The method of claim 32, wherein said oral dosage form is a tablet.

46. The method of claim 32, wherein said oral dosage form is a capsule.

47. The method of claims 21-26, wherein said CNS stimulant is administered in combination with at least one sustained release excipient.

48. The method of claims 21-26, wherein said opioid antagonist is administered in combination with at least one sustained release excipient.

49. The method of claims 21-26, wherein said CNS stimulant and said opioid antagonist are administered in combination with at least one sustained release excipient.

50. The method of claims 47-49, wherein said sustained release excipient provides a sustained release from about 12 to about 24 hours.
51. A method for reducing side effects associated with CNS stimulant therapy comprising co-administering at least one opioid antagonist with at least one CNS stimulant to a patient in need thereof, whereby a decreased amount of said CNS stimulant is required to achieve a therapeutic effect as compared to the CNS stimulant used alone, thereby resulting in a reduction of side effects associated with said CNS stimulant therapy.

52. A method for reducing abuse potential associated with CNS stimulant therapy comprising co-administering at least one opioid antagonist with at least one CNS stimulant to a patient in need thereof, whereby a decreased amount of said CNS stimulant is required to achieve a therapeutic effect as compared to the CNS stimulant used alone, thereby resulting in a reduction of abuse potential associated with said CNS stimulant therapy.