METHOD AND COMPOSITION FOR ADMINISTERING AN NMDA RECEPTOR ANTAGONIST TO A SUBJECT

FIELD OF THE INVENTION

The invention relates to compositions containing N-methyl-D- Aspartate receptor (NMDAr) antagonists and methods for using such compositions.

BACKGROUND OF THE INVENTION

Acute and chronic neurological and neuropsychiatric diseases are among the leading causes of death, disability, and economic expense in the world. One of the key challenges in treating these disorders is the high degree of interplay amongst the pathways that control both normal and abnormal neuronal function.

Excitatory amino acid receptors, including the N-Methyl-D-Aspartate (NMDA) receptor, are important mediators of excitatory synaptic transmissions (i.e., stimulation of neurons) in the brain, participating in wide-ranging aspects of both normal and abnormal central nervous system (CNS) function. The NMDA receptor and its associated calcium (Ca2+) permeable ion channel are activated by glutamate, a common excitatory neurotransmitter in the brain and the spinal cord, and the co-agonist glycine. NMDA receptor (NMDAr) activity and consequent Ca2+ influx are necessary for long-term potentiation (a correlate of learning and memory).

Aberrant glutamate receptor activity has been implicated in a large number of CNS-related conditions including, for example, depression and other neuropsychiatric conditions, Parkinson's disease, epilepsy, pain, ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease), and Huntington's disease. In such conditions, the abnormal activation of the NMDA receptor resulting from elevated levels of glutamate may lead to sustained activity of the receptor's ion channel (often lasting for minutes rather than milliseconds), thereby allowing Ca2+ to build-up. This creates both symptomatic and neuro-destructive effects on a patient.

Certain NMDAr antagonists, such as memantine and amantadine, readily cross the blood-brain barrier, achieving similar concentrations in the extra cellular fluid surrounding brain tissue

and systemic serum. Ideally, NMDAr antagonists should be present at a concentration sufficient to reduce the symptoms or damaging effects of the disease in the absence of debilitating side effects. In the present dosage forms however, these drugs, despite having a relatively long half-lives, need to be administered frequently and require dose escalation at the initiation of therapy to avoid side effects associated with initial exposure to the therapeutic agent. This leads to difficulty in achieving adequate patient compliance, which is further exacerbated by the complicated dosing schedules of therapeutic modalities used for neurological or neuropsychiatric disorders.

Thus, better methods and compositions are needed to treat and delay the progression of neurological disorders.

SUMMARY OF THE INVENTION

In general, the present invention provides pharmaceutical compositions that are administered so as to deliver to a subject, an amount of an NMDAr antagonist that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects, particularly CNS side effects. These compositions may be employed to administer the NMDAr antagonist at a lower frequency than presently employed (i.e., once a day (q.d.) versus twice a day (b.i.d) or three times a day (t.i.d)), improving patient compliance and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of the NMDAr antagonist in a shorter period of time. This results in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Furthermore, the compositions of the present invention, by virtue of their design, allow for higher doses of NMDAr antagonist to be safely administered, again increasing the utility of these agents for a variety of indications. Also provided are methods for making, dosing and using such compositions.

The NMDAr antagonist is desirably provided in a controlled or extended release form, with or without an immediate release component in order to maximize the therapeutic benefit of the NMDAr antagonist, while reducing unwanted side effects. In the absence of modified

release components (referred to herein as controlled, extended or delayed release components), the NMDAr antagonist is released and transported into the body fluids over a period of minutes to several hours. In a preferred embodiment, the composition of the invention contains an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, memantine (e.g., 5-80 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®.

NMDAr Antagonists.

The NMDAr antagonist may be an aminoadamantine derivative such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1 -aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below.

Excipients

The excipients used to produce the formulation may include bulking agents, lubricants, glidants, and release controlling agents. Many such materials are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, PA and commonly known to the skilled artisan. The specific excipients used will be determined by the requirements for administration of the dosage, including the targeted dosing frequency, slope of drug release and absorption, and route of administration. In one embodiment, the formulation does not contain a casein salt.

Dosage Form

The NMDAr antagonist may be formulated as a suspension, capsule, tablet, suppository, lotion, patch, or device (e.g., a subdermally implantable delivery device or an inhalation pump). In preferred embodiments, the dosage form is provided for oral administration, e.g. as a capsule.

Release Profile

The compositions described herein are formulated such the NMDAr antagonist has an in vitro dissolution profile that is slower than that for an immediate release (IR) formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or

formulations having substantially the same release profiles as Namenda); and for the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel). These compositions may contain immediate release, sustained or extended release, delayed release components, or combinations thereof. Thus, the present compositions may be formulated such that the fraction of the NMDAr antagonist released is greater or equal to $0.01(0.297 + 0.0153*e^{(0.515*t)})$ and less than $1-e^{(-10.9*t)}$, as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37 ± 0.5^0C, in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist that is released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist is greater or equal to $0.01(0.297 + 0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37 ± 0.5^0C, in water, where t is the time in hours and t is greater than zero and equal or less than 17. Optionally, the fraction of released NMDAr antagonist is greater or equal to $0.01(-2.75 + 2.75*e^{(0.21*t)})$ and less than or equal to $1-e^{(-0.40*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37 ± 0.5^0C, in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist that is released may range between 0.1%-62% in one hour, 0.2%-86 % in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the fraction of NMDAr antagonist that is released may range between 0.6%-33% in one hour, 1.4%-55 % in two hours, 6.9%-91% in six hours, 19.7%-98% in 10 hours, and 31%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH

in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing memantine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium.

In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIGURES 2A-2C and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGURE 2D.

Initial Rate of Release in vivo

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The concentration of the drug in the biological sample may be determined by any standard assay method known in the art. The term "Cmax" refers to the maximum concentration reached by a given dose of drug in a biological sample. The term "Cmean" refers to the average concentration of the drug in the sample over time. Cmax and Cmean may be further defined to refer to specific time periods relative to administration of the drug. The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

Desirably, the NMDAr antagonist is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation and the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation (e.g., Namenda, a

commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, twice per day or once per day form. In such cases, the concentration ramp (or Tmax effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the drug. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (so called IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from 2 hours after administration to 4 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a

substantially constant daily dose (e.g., at a dose ranging between 15 mg and 80 mg, preferably between 20 mg and 65 mg, and more preferably between 20 mg and 45 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Reduced Cmax, Extented Tmax

In a preferred embodiment of this invention, at least 75%, 90%, 95%, 97%, 98%, 99% or even 100% of the NMDAr antagonist is provided in a modified or extended release dosage form and upon the administration of this composition to a subject (e.g., a mammal such as a human), the NMDAr antagonist has a Cmax /C mean of approximately 2.5, 2, 1.5, or 1.0, approximately 1, 1.5, 2 hours to at least 6, 9, 12, 18, 21, 24 hours following such administration. If desired, the release of the NMDAr antagonist may be monophasic or multiphasic (e.g., biphasic). Desirably, 99%, 98%, 95%, 90%, 85%, 80%, 70%, 50%, or 30% of the NMDAr antagonist remains in an extended release dosage form within one hour of such administration.

Dosing Frequency Reduction

The compositions and methods of the instant invention also enable a reduction in the dosing frequency. For example, an NMDAr antagonist ordinarily administered two to four times per day when dosing in an IR form may be provided to the subject once or twice per day using the formulations described herein. In some embodiments, the compositions described herein are administered even less frequently, e.g. every 2 days, every 3 days, every week, or every month.

Non-dose escalation

Immediate release (IR) formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, frequently starting with subtherapeutic amounts of the agent. Although dosing adjustments or individualization may be managed by a physician for a pharmaceutical composition the compositions described herein may be administered at an essentially constant, therapeutically-effective dose from the initiation of therapy, thereby improving patient and caregiver compliance, adherence, and convenience.

Furthermore, the compositions described herein enable the use of higher doses of NMDAr antagonist equal or fewer adverse effects than observed for IR formulations of the same agent, increasing the utility of the NMDAr antagonist for indications described herein.

Reduced Time to Therapeutic Concentration and Efficacy

The administration of the compositions described herein at therapeutically effective doses from the initiation of therapy enables the attainment of a steady state level of the agent in a shorter time period (e.g. 20%, 30%, 50%, 70%, 90% less time than for dose-escalated regimens), thus enabling the treatment of more acute disorders such as pain and neuropsychiatric disorders, including depression, agitation, bipolar disorder, and drug dependency, withdrawal, or tolerance.

Conditions Amenable to Treatment

The compositions of the present invention may be employed to treat or reduce the symptoms associated with deregulation in NMDA receptor activity or conditions that would benefit from a reduction in such activity. Further, many NMDAr antagonists have other known activities (e.g. the dopaminergic activity of amantadine, the antiviral activity of rimantadine). The compositions of the present invention are also useful to treat, prevent, or reduce conditions associated with such activities in any subject having or at risk of having a such condition. Exemplary conditions include seizure disorders, pain syndromes, neurodegenerative diseases (including motor neuron diseases, myelopathies, radiculopathies, and disorders of the sympathetic nervous system), dementias, cerebrovascular conditions, movement disorders, brain trauma, cranial nerve disorders, neuropsychiatric disorders, and other disease neuropathies (including viral associated neuropathies, diabetes associated neuropathies, Guillian-Barre syndrome, dysproteinemias, transthyretin-induced neuropathies, and carpal tunnel syndrome).

Alternate Routes of Administration

In one embodiment, the compositions described herein are formulated as tablets or capsules for oral administration or patches for transdermal delivery of the NMDAr antagonist. Alternatively, the compositions may be prepared in other ways for these routes of administration (e.g. as a suspension for oral administration) or specifically for other administrative routes intravenous, topical, intranasal, subtopical transepithelial, subdermal, or inhalation delivery.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described

below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1A is a graph showing the memantine plasma concentration over a period of 24 hours, as predicted by Gastro-Plus software package v.4.0.2, following the administration of a single dose of an immediate release (IR) formulation of memantine (Namenda) or a sustained release formulation of memantine (NPI-6701). The sustained release formulation exhibits a dC/dT during the initial phase that is about 20% of that for the immediate release (IR) formulation.

FIGURE 1B is a graph showing the memantine plasma concentration over a period of 28 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of an immediate release (IR) formulation of memantine (Namenda) and a sustained release formulation of memantine (NPI-6701). When Namenda is administered using a dose escalation regimen pursuant to the manufacturer's US FDA approved label, a steady-state therapeutically effective plasma concentration is reached within about 30 days. The administration of a sustained release formulation of memantine at a constant dose (e.g., 22.5 mg/day) achieves a steady therapeutically effective plasma concentration within about 13 days, a reduction of about 60%..

FIGURE 2A is a graph and a table showing the in vitro dissolution profiles for various sustained release formulations of memantine (NPI-6601, NPI-6701, NPI-6801, NPI-6990, and NPI-6804) and Namenda. Dissolution profiles were obtained with a USP II (Paddle) system using water as a dissolution medium.

FIGURE 2B is a graph showing the dissolution profiles for various sustained release formulations of memantine (NPI-6601, NPI-6701, NPI-6801, NPI-6990, and NPI-6804) and

Namenda obtained with a USP II (Paddle) system using 0.1N hydrochloride solution pH = 1.2 as the dissolution medium.

FIGURE 2C is a graph showing the dissolution profile of memantine formulated as a sustained release form using a neutral (e.g., water) and acidic (pH 1.2) dissolution medium.

FIGURE 2D is a graph and table showing the memantine plasma concentration over a period of 24 hours, as predicted by Gastro-Plus software package v.4.0.2, following the administration of Namenda (10mg b.i.d. or single dose of 20 mg) or various sustained release formulations of memantine (i.e., NPI-6601, NPI-6701, NPI-6801, NPI-6804, and NPI-6990 administered at a single dose of 22.5 mg).

FIGURE 3A is a graph and table showing the dissolution profiles for various sustained released memantine bead/capsule formulations. The experimental dissolution profiles were obtained from a USP II Paddle system using water (pH = 7) as the medium.

FIGURE 3B is a graph and table showing the predicted dissolution profile for a simple two-bead composite capsule (13% of 5001-6991 & 87% of 5001-6992).

FIGURE 4 is a graph showing dissolution profiles for modified release formulations of memantine and an IR formulation of memantine (Namenda).

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain an NMDAr antagonist formulated for extended or modified release to provide a serum or plasma concentration over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma

level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time enabling a increased dosages for appropriate indications.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Preferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1 -aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Patents 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S.P.N. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Patent 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, amino cyclohexanes (i.e., neramexane), ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivatives or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Dosing, PK, & Tox

The pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 5-80 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; amantadine in an amount ranging between 15 and 900 mg/day, 15 mg and 800 mg/day, 15 mg and 700 mg/day, 15 mg and 600 mg/day, 15 and 500 mg/day, 25 and 500 mg/day, 15 and 400 mg/day, 25 and 300 mg/day, 100 and 300 mg/day, or 100 and 200 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary the pharmacokinetic properties (e.g., Tmax and T1/2) of memantine, amantadine, and rimantadine.

Table 1. Pharmacokinetics and Tox in humans for selected NMDAr antagonists

Compound	Human PK (t½) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Tox
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100mg/day	Hallucination
Rimantadine	25	6	100–200 mg/day	Insomnia

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions are known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth

Edition," Lippincott Williams & Wilkins, Philadelphia, PA. Tablets, capsules, pills, powders, granules, dragées, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, extended or modified release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added

from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be 1% to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is

well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S. Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for preparing modified or extended release formulations

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in extended release-formulations include those described in U.S. Patent No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Patent No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Patent No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine,

for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Patent No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle.

Release Profile (Dissolution Rate)

As described above, the NMDAr antagonist may be provided in a modified or extended release form. Extended or modified drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist may be formulated for extended or modified release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist is provided in an extended release dosage form.

Optionally, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIGURES 2A-2C and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is

substantially identical to that shown in FIGURE 2D. The dissolution profile of the composition of the invention may be determined using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C in various dissolution media. In one example, the release fraction is greater or equal to $0.01(0.297 + 0.0153*e^{(0.515*t)})$ and less than $1-e^{(-10.9*t)}$. In another example, the release fraction is greater or equal to $0.01(0.297 + 0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-0.972*t)}$. In both examples, the term "t" is the time in hours and t is greater than zero and equal or less than 17. Thus, the NMDAr antagonist may have an in vitro dissolution profile that ranges between 0.1%-62% in one hour, 0.2%-86 % in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution. Optionally, the release profile may range between 0.1%-20% in one hour, 5%-30 % in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours. Desirably, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium (see FIGURES 2A-2C).

In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate in vivo, Delayed Tmax, Reduced Cmax/Cmean

The NMDAr antagonist is provided as a modified release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist may be provided such that it is released at rate resulting in a Cmax /C mean of approximately 2 or less for approximately 2

hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by US Patent 6,913,768, hereby incorporated by reference.

Thus, upon the administration to a subject (e.g., a mammal such as a human), the NMDAr antagonist has a Cmax /Cmean of approximately 2.5, 2, 1.5, or 1.0 approximately 1, 1.5, 2 hours to at least 6, 8, 9, 12, 18, 21, 24 hours following such administration. If desired, the release of the NMDAr antagonist may be monophasic or multiphasic (e.g., biphasic). One of ordinary skill in the art can prepare compositions with a desired release profile using the NMDAr antagonists and formulation methods known in the art or described below.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., once a day, every 2 days, every 3 days, every week, or every month). While immediate formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose over a set period of time. For example, a composition containing a sustained release formulation of memantine may be administered twice a day, once a day, once every two days, or once every three days in a unit dose containing 10-300 mg, 10-200 mg, 10-100 mg, or 10-50 mg of memantine (e.g.,10 mg, 11.25 mg, 12.5 mg, 15 mg, 20 mg, 22.5 mg, 25 mg, 30 mg, 33.75 mg, 37.5 mg, 40 mg, 45 mg, 50 mg, 60 mg, 65 mg, 67.5 mg, 70 mg, 75 mg, 80 mg, 120mg, 180mg, 240mg or 300 mg).

In one embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient. The excipient is present in an amount sufficient to ameliorate or reduce acute toxicity

associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine (e.g., Namenda) or amantadine (e.g., Symmetrel). The use of such composition increases the safety in the administration of such agents, enabling reduced dosing frequency with similar or higher doses of the NMDAr antagonist as compared with the presently available forms of these pharmaceutical products.

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5mg/day) and progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After a period of timeone week acclimation period, subjects are administered with this dose twice daily. Subjects are next administered with a 5 mg and 10mg dosing per day and finally administered with 10 mg Namenda twice daily. FIGURE 2D shows the average serum concentration each day as predicted by the pharmacokinetic software, GastroPlus, from Simulations Plus. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner, without using a dose escalating regimen. As shown in FIGURE 2D, such concentration is predicted to be achieved within thirteen days of the onset of therapy. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of memantine may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Thus in one embodiment, a composition is prepared using the methods described herein, wherein such composition comprises a therapeutically effective amount of memantine or

amantadine and an excipient for administration to a subject without prior administration of a subtherapeutic amount of same active agent (i.e. memantine or amantadine) to the same subject. Specifically, for an indication such as Alzheimer's disease, where a therapeutically effective amount of memantine is typically 20 mg per day, the administration of memantine to the subject is initiated at 22.5 mg per day or more, instead of a subtherapeutic amount (e.g., 5 mg per day as currently indicated in the manufacturer's FDA-approved label for Namenda).

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25% 40% 50% 60% 70% 75% 80% less time than the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

Conditions suitable for treatment according to this invention include seizure disorders, pain syndromes, neurodegenerative diseases (including motor neuron diseases, myelopathies, radiculopathies, and disorders of the sympathetic nervous system), dementias, cerebrovascular conditions, movement disorders, brain trauma, cranial nerve disorders, neuropsychiatric disorders, and other disease neuropathies (including viral associated neuropathies, diabetes

associated neuropathies, Guillian-Barre syndrome, dysproteinemias, transthyretin-induced neuropathies, and carpal tunnel syndrome).

As used herein, seizure disorders include complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions.

Pain syndromes include, for example, headaches (e.g., migraine, tension, and cluster), acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain and inflammatory pain, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy (RSDS).

Neurodegenerative diseases include Alzheimer's disease, Parkinson's Disease, multiple sclerosis, Huntington's Disease, ALS, spinal muscular atrophy, muscular dystrophies prion-related diseases, cerebellar ataxia, Friedrich's ataxia, SCA, Wilson's disease, RP, Gullian Barre syndrome, Adrenoleukodystrophy, Menke's Sx, cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL), Charcot Marie Tooth diseases, neurofibromatosis, von-Hippel Lindau, Fragile X, spastic paraplesia, tuberous sclerosis complex, Wardenburg syndrome, spinal motor atrophies, Tay-Sach's, Sandoff disease, familial spastic paraplegia, myelopathies, radiculopathies, encephalopathies associated with trauma, radiation, drugs and infection, and disorders of the sympathetic nervous system (e.g., Shy Drager (familial dysautonomia), diabetic neuropathy, drug-induced and alcoholic neuropathy).

Dementias include Alzheimer's disease, Parkinson's disease, Pick's disease, fronto-temporal dementia, vascular dementia, normal pressure hydrocephalus, Huntington's disease, and MCI.

Cerebrovascular conditions amenable to treatment according to the present invention include Cerebrovascular disease and strokes (e.g, thrombotic, embolic, thromboembolic, hemorrhagic (including AVM and berry aneurysms), venoconstrictive, and venous).

Included in movement disorders are Parkinson's disease, dystonias, benign essential tremor, tardive dystonia, tardive dyskinesia, and Tourette's syndrome.

Brain trauma as used herein includes traumatic brain and spinal cord injuries as well as brain injuries from radiation.

Cranial nerve disorders include trigeminal neuropathy, trigeminal neuralgia, Menier's syndrome, glossopharangela neuralgia, dysphagia, dysphonia, cranial nerve palsies and Bell's palsy.

Neuropsychiatric disorders include panic syndrome, general anxiety disorder, phobic syndromes of all types, mania, manic depressive illness, hypomania, unipolar depression, depression, stress disorders, PTSD, somatoform disorders, personality disorders, psychosis, and schizophrenia), and drug dependence/additiction (e.g., alcohol, psychostimulants (eg, crack, cocaine, speed, meth), opioids, and nicotine), and drug-induced psychiatric disorders.

Other disease neuropathies that may be treated with the compositions and methods described herein include Guillian-Barre, diabetes associated neuropathies, dysproteinemias, transthyretin-induced neuropathies, neuropathy associated with HIV, herpes viruses (including herpes zoster) or other viral infection, neuropathy associated with Lyme disease, carpal tunnel syndrome, tarsal tunnel syndrome, amyloid-induced neuropathies, leprous neuropathy, Bell's palsy, compression neuropathies, sarcoidosis-induced neuropathy, polyneuritis cranialis, heavy metal induced neuropathy, transition metal-induced neuropathy, drug-induced neuropathy, post-menengitis syndrome, post-polio syndrome, prion diseases, and radiation associated neuropathic syndromes.

Other diseases amenable to treatment with the present invention include fatigue syndromes (e.g., chronic fatigue syndrome and fibromyalgia), ataxic syndromes, olivopontoicerebellar degeneration, striatonigral degeneration, and axonic brain damage.

Because the NMDAr antagonist in the present compositions reaches a therapeutically effective steady state in a shorter period of time than immediate release formulations (e.g., within the course of the first five, seven, nine, ten, twelve, fifteen, or twenty days of administration), the present invention is particularly useful for the treatment of neuropsychiatric disorders such as depression, agitation, anxiety, seizure disorders such as grand mal seizures, status epilepticus,

migraine pain treatment and prophylaxis, Alzheimer's disease, Parkinson's disease, and traumatic brain and spinal cord injury.

Also, the higher doses enabled by the present invention are expected to be of particular importance for dementias including Alzheimer's disease, Parkinson's disease, and vascular dementia, pain syndromes, including headaches and migraines, seizure disorders, movement disorders, and brain trauma.

Furthermore, the ease of use and convenience of a dosage form provided developed to be delivered at once per day or less frequent administration at a therapeutically effective quantity from the onset of therapy is of value in treatment of dementias including Alzheimer's disease and Parkinson's disease, seizure disorders, pain syndromes, and cerebrovascular conditions.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoro-methane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face

mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in US patent 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist is prepared using the OROS® technology, described for example, in U.S. Patent Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S.P.Ns. 6,797,283; 6,764, 697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional methods for making modified release formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Patent Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

Alternatively, the compositions of the present invention may be administered transdermally. Preparation for delivery in a transdermal patch can be performed using methods also known in the art, including those described generally in, e.g., US Patent Nos. 5,186,938 and 6,183,770, 4,861,800, 6,743,211, 6,945,952, 4,284,444, and WO 89/09051, incorporated herein by reference in their entireties. A patch is a particularly useful embodiment with drugs having absorption problems. Patches can be made to control the release of skin-permeable active ingredients over a 12 hour, 24 hour, 3 day, and 7 day period. In one example, a 2–fold daily excess of an NMDAr antagonist is placed in a non-volatile fluid. Given the amount of the agents employed herein, a preferred release will be from 12 to 72 hours.

Transdermal preparations of this form will contain from 1% to 50% active ingredients. The compositions of the invention are provided in the form of a viscous, non-volatile liquid. Preferably, the NMDAr antagonist will have a skin penetration rate of at least 10-9 mole/cm2/hour. At least 5% of the active material will flux through the skin within a 24 hour period. The penetration through skin of specific formulations may be measures by standard methods in the art (for example, Franz et al., J. Invest. Derm. 64:194-195 (1975)). Providing the NMDAr antagonist in the form of patches is useful given that these agents have relatively high skin fluxes.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration.

Devices commonly used for this route of administration are included in US patent 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., US Patent Nos. 3,992,518; 5,660,848; and 5,756,115.

Using the formulations and methods described herein, we have produced numerous formulations of NMDAr antagonists (e.g., memantine and amantadine) having modified release profiles (more than 50). Exemplary formulations are provided in the Examples.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1: Measuring Release Profiles for Aminoadamantanes in vitro

Compositions containing an aminoadamantane were analyzed for release of the aminoadamantane, according to the USP type II apparatus at a speed of 50 rpm. The dissolution media used were water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium was equilibrated to 37±0.5°C.

The USP reference assay method for amantadine was used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) was placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) was added and vortexed for five seconds. The mixture was allowed to stand for approximately five minutes. 3 mL Chloroform was added and vortexed for five seconds. The solution was next centrifuged (speed 50 rpm) for five minutes. The top layer was removed with a disposable pipette. A sample was drawn into 1 cm flow cell and the absorbance was measured at 408 nm at 37°C and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined was plotted against the dissolution time for the sample.

Example 2: Preparation of Memantine-Containing Cores to be Coated with an Enteric Coating

Memantine-containing cores are prepared as follows and as described, for example, in U.S. patent No. 4,606,909. Cores (containing 24% talc) are prepared using 0.97 kg memantine, 0.2 kg sodium laurylsulphate, 0.5 kg microcrystalline cellulose, 5.93 kg saccharose powder, and 2.4 kg talc. Memantine and sodium laurylsulphate are co-comminuted by passage through a grinder using a 0.5 mm sieve. The ground mixture is mixed with microcrystalline cellulose, saccharose, and talc in a planet mixer. 10 kg of the resulting mixture is moistened with 0.8 kg purified water and mixed in a planet mixer until the mixture is slightly lumpy. The moist mixture is extruded through a 0.5 mm sieve. The first kilograms of extrudate passing the sieve is powdery and re-extruded. The resulting extrudates form strings, breaking off in lengths of 10-30 cm. 2 kg of the extruded strings is formed into compact-shaped cores in a marumerizer™ and the resulting compact-shaped cores are dried in a fluidized bed dryer and sieved through a separator (the upper sieve (0.71 mm) and the bottom sieve (0.46 mm). Using the same technique, cores (containing 10% talc) are prepared using 0.97 kg memantine, 0.2 kg sodium laurylsulphate, 1.0 kg microcrystalline cellulose, 6.83 kg saccharose powder, and 1.0 kg talc.

The release of memantine is measured, at a pH 7.5 for the cores containing 24% talc and 10% talc, respectively. The reduction in the talc content from 24% to 10% decreases the release weight of memantine from the core.

An enteric coating suspension, which further delays the release of memantine, is prepared by homogenizing 9.0 kg Eudragit ™ S 12,5 together with 0.135 kg acetyltributylcitrate, 0.9 kg talc, and 7.965 kg isopropanol. 10 kg of the above-described cores containing 10% talc are coated with 4.167 kg of this coating suspension in a fluidized bed and the resulting pellets are covered with talcum. For the preparation of a pharmaceutical dosage form, 1000 of these pellets are filled in a capsule No. 1, such that each of the capsule contains 25 mg memantine.

Example 3: Preparation of Amantadine extended release capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Patent No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg / Capsule
Amantadine	68.34	200.00
OPADRY® Clear YS-3-7011 [1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP [2]	---	---
Sugar Spheres, NF	12.50	54.87
OPADRY® Clear YS-1-7006 [3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE® E-7-7050 [4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules [5]	---	---
TOTAL	100.00%	338.98 mg [6]

[1] A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.

[2] Purified Water, USP is evaporated during processing.

[3] A mixture of hydroxypropyl methylcellulose and polyethylene glycol

[4] Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.

[5] White, opaque, hard gelatin capsule, size 00.

[6] Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules):

Step 1: Prep of Amantadine HCl Beads (bead Build-up #1)	
Component	**Weight (kg)**
Amantadine	12.000
OPADRY® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1	
Component	**Weight (kg)**
Amantadine Beads	8.000
OPADRY® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HCl Beads (Build-up #2)	
Component	**Weight (kg)**
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2	
Component	**Weight (kg)**
Amantadine Beads	10.000
OPADRY® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling -- Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Examples 4-11: Extended release formulation of Rimantidine

The NMDAr antagonist, rimantidine, is formulated for extended release as follows (see, for example, U.S. Patent No. 5,912,013).

Example 4: Core Pellets			
		Weight Percent	**Kilograms**
	MCC	25.0	0.25
	Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
	Tartaric Acid	10.0	0.10
	Sodium Monoglycerate	7.5	0.075
	DSS	0.5	0.005
	Rimantadine	47.0	0.47
	TOTAL	100.0%	1.00 kg
Coating			
	Cellulose Acetate Phthalate (CAP)	60.0	0.60
	Ethylcellulose	25.0	0.25
	PEG-400	15.0	0.15
	TOTAL	100.0%	1.00 kg

Example 5: Coating for Core Pellets from Example 4			
		Weight Percent	**Kilograms**
	Ethacrylic/Methacrylic Acid Esters (Eudragit line of enteric polymers)	85.0	0.85
	Propylene Glycol	14.0	0.14
	Talc	1.0	0.01
	TOTAL	100.0%	1.00 kg
Example 6: Coating for Core Pellets from Example 4			
		Weight Percent	**Kilograms**
	CAP	65.0	0.65
	HPMCP	15.0	0.15
	PEG-400	10.0	0.10
	PEG-8000	10.0	0.10
	TOTAL	100.0%	1.00 kg

Example 7: Core Pellet		
	Weight Percent	**Kilograms**
MCC	25.0	0.25
Mono/Di/Tri-glyceride Mixture	15.0	0.15
Tartaric Acid	10.0	0.10
CAP	10.0	0.10
DSS	0.8	0.008
Rimantadine	39.2	0.392
TOTAL	100.0%	1.00 kg
Coating as in Example 4		

Example 8: Core Pellet as in Example 8, Coating as in Example 5
Example 9: Core Pellet as in Example 8, Coating as in Example 6

Example 10: Coating for Core Pellet as in Example 9		
	Weight Percent	**Kilograms**
Shellac	85.0	0.85
Mineral Oil	13.0	0.13
SLS	0.5	0.005
Talc	1.5	0.015
TOTAL	100.0%	1.00 kg

Example 11: Core Pellet as in Example 4, Coating as in Example 10

Example 12: Preparation of Memantine Controlled Release

Different sustained release tablet formulations of memantine were developed, each of which is associated with a characteristic *in vitro* dissolution profile. As described in further detail below, the sustained release formulations reach a superior pharmacokinetic profile therapeutically. The sustained release profile was achieved using a sustained release matrix or a

sustained release coated tablet. The physical characteristics of the active, a description of the formulation composition, an outline of the small scale production process, and the validated analytical methods are presented below.

Drug Substance Information

API Name	**Memantine**
Molecular Weight	215.8 for HCl salt, 178.3 for free base
Melting Point °C	258 - 295° C
pK_a	10.27
Aqueous Solubility	40 - 45 mg/ml at pH 2 - 9
Stability	$T_{½}$> 24 hours in aqueous buffer, pH 4.0 – 7.4 and rat plasma

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Formulation Composition

	Formulation # 1	**Formulation # 2**
Type of Tablet	Sustained release matrix	Sustained release coated tablet
Memantine HCL (22.5mg)	13.5%	15.25%
Avicel PH102	60.0%	69.0%
Eudragit RS-30D (aqueous dispersion)	15.4%	14.8%
HPMC K100M	10.1%	----
Magnesium Stearate	1.0%	1.0%
Coating: 70% Eudragit RL-30D (aqueous dispersion) 30% Eudragit RS-30D (aqueous dispersion) Talc TEC H_2O	----	Additional 6% coat 21% 9% 9% 2% 59%
Total Tablet Weight	150mg	159mg

Formulation #1: Memantine formulated with a sustained release matrix

Formulation #1 was produced as follows. Memantine was formulated as shown in the table below.

Component Core Tablets - 22.5 mg - Formulation 1292-22.5-10A	% Comp. Solid weight	mg/tablet Solid weight	Total weight (g)
Granulation from 1292-12 - 150 grams			
Memantine HCl	13.51	22.5	22.79
Avicel ® PH102	60.04	100.0	101.28
Eudragit RS-30D (30% w/v aqueous dispersion)	15.37	25.6	25.92
Extragranular Excipient			
HPMC K100M	10.08	16.8	17.00
Magnesium Stearate	1.01	1.6	1.7
Total	**100.0**	**166.5**	**168.7 (solid weight)**

API is bag blended with Avicel PH102 and sieved through an 18-mesh screen. The mix is next dried in a low shear mixer. The blend is wet massed with Eudragit and the granulation is dried in an oven at 40-45° C for 12 hours. The granulation is next pass dried through an Alexanderwerk Mill set up with 0.8mm screen, producing the intermediate active blend. HPMC was sieved through a 30 mesh screen. The screened HPMC was premixed with an equal amount of the intermediate active blend, referred to herein as 1292-12 and bag blended for two minutes. The blend was next lubricated with Magnesium Stearate in a low shear blender. A sample from this blend was collected for LOD (Loss on Drying) testing on Computrac MAx 2000 set at 105^{0}C. The final blend is then compressed and tables are punched using a D3B set up with 0.25

inch standard round concave punch tooling. The dissolution profile of this formulation is provided in Figure 6 (% Label claim vs. time).

Formulation 2: Memantine Formulated Using A Sustained Release Coated Matrix

Component Core Tablets - 22.5 mg -	% Comp. Solid weight	mg/tablet Solid weight	Total weight (g)
Memantine HCl active	15.25	22.5	93.80
Avicel ® PH102	68.96	101.75	424.20
Eudragit RS-30D (30% w/v aqueous dispersion)	14.79	21.83	303.3*
Extragranular Excipient			
HPMC K100M	10.08	16.8	17.00
Magnesium Stearate	1.01	1.6	1.7
Total	100.0	166.5	168.7 (solid weight)

* 303.3g of Eudragit RS-30D aqueous dispersion contains 91g of solid polymer and 212.3g of liquid.

Memantine HCl is first bag blended with Avicel PH102 for one minute. The dry blend is sieved through an 18 mesh screen into a poly bag and bag blended for one minute. The mixture is loaded into a low-shear mixer and dried for two minutes. The blend was wet massed with Eudragit and the granulation was next dried in an oven at 40-45° C for 12hours. The dried granulation is next passed through an Alexanderwerk Mill set up with a 0.8mm screen. Sieved magnesium stearate (30-mesh) was next added to the milled mix and bag blended. The final blend was next compressed and tablets were punched using a D3B 0.25 inch standard round punch.

The coat tablet was prepared as follows. To prepare the coat, Eudragit RL-30D & Eudragit RS-30D was added to bubble free purified water while vortexing. TEC is next added and mixed for >30 minutes. Talc is slowly added and mixed to obtain homogenous dispersion. The coating desertion was next screened through 60-mesh sieve. The coating parameters are as follows (O'Hara Lab II-X 15"pna): inlet temp: 37-40°C; outlet temp: 25-28°C; air flow rate: 150-175 CFM; pan speed: 8-9 rpm; and spray distance: 6-8".

Tablets were next coated. The exhaust temperature and coating speed (weight change/minute) were first calibrated and tables were coated for a set amount of time. Tablets were allowed to roll for 3 minutes at a constant temperature (37-40°C) and tablets were next cooled and transferred to a forced air oven (40°C) for 24 hours to dry.

Example 13: Film-Coated Formulation

Film-coated tablets were formulated by coating a memantine tablet with or without an Opadry® subcoat and with a Surelease® overcoat. 2% Opadry® based coating with 2% Surelease® overcoat presented a desired release profile.

Example 14: Matrix Core Tablet

Matrix Core tablets were formulated as shown in the table below. (Appearance = good, weight = 167 mg; hardness= 5.1 kg; friability 100 revs: 0.6%). Low coating weight gain was associated with rapid hydration of coating, whereas high coating weight gain was associated with slow hydration of coating.

Granulation	%w/w	mG/Tablet
Memantine HCL	14	22.5
Avicel PH102	60	100.0
Eudragit RS-30D	15	25.6
Extragranular		
Methocel K100M*	10	16.8
Mg Stearate	1	1.6
Total	100	166.5

Coated beads or granules were compressed into a tablet. A honeycomb-like structure is established during compression. The tablet disintegrates into beads and granules, whose individual properties then control release of memantine. A HPMC subcoat may optionally be used. Water penetrates the Surelease coating, which remains intact therefore trapping the HPMC subcoat between the core and the external coating. The water-soluble HPMC subcoating hydrates. While it is water soluble it is a large molecular weight polymer which cannot diffuse out through the water insoluble ethycellulose coating. Release of drug will not occur until water reaches the core. The delay should therefore vary as a function of the amount of HMPC in the tablet. Water reaches the outside surface of the core and memantine dissolves. High water solubility establishes a high concentration gradient. Dissolved memantine next diffuses through the hydrated HPMC layer and the porous ethylcellulose coating. Accordingly, a high level of ethylcellulose coating controls the release rate by the external coating whereas a lower level of ethylcellulose coating results in erosion, sloughing off of the hydrated HPMC, and the control of release being governed by the matrix bead.

Example 15: In vitro dissolution profile of Sustained Release Formulations of Memantine

Various sustained release formulations of memantine were prepared as follows.

Matrix Tablet Formulation 5001-6601

Memantine HCL (22.5mg)	13.51%
Avicel PH102	60.04%
Eudragit RS-30D (30% w/w aqueous dispersion)	15.37%
HPMC K100M	10.08%
Magnesium Stearate	1.00%
Total Component Weight	166.5mg

Coated Tablet Formulation 5001-6701

Memantine HCL (22.5mg)	13.21%
Avicel PH102	58.72%
Eudragit RS-30D (30% w/w aqueous dispersion)	15.03%
HPMC K100M	9.86%
Magnesium Stearate	0.98%
Surelease® Clear, (Formulation E-7-19010, Colorcon)	2.20%
Total Component Weight	170.2mg

Coated Tablet Formulation 5001-680

Memantine HCL (22.5mg)	12.73%
Avicel PH102	56.55%
Eudragit RS-30D (30% w/w aqueous dispersion)	14.48%
HPMC K100M	9.50%
Magnesium Stearate	0.94%
Opadry® Clear, (Formulation YS-1-7006, Colorcon)	3.00%
Surelease® Clear, (Formulation E-7-19010, Colorcon)	2.80%
Total Component Weight	176.2mg

Coated Tablet Formulation 5001-6804

Memantine HCL (22.5mg)	12.64%
Avicel PH102	55.98%
Eudragit RS-30D (30% w/w aqueous dispersion)	14.33%
HPMC K100M	9.40%
Magnesium Stearate	0.93%
Opadry® Clear, (Formulation YS-1-7006, Colorcon)	3.00%
Surelease® Clear, (Formulation E-7-19010, Colorcon)	3.80%
Total Component Weight	178mg

Coated Bead Formulation 5001-6990

20% Memantine HCL (22.5mg) & Eudragit RS-30D (30% w/w aqueous dispersion)	75%
Opadry® Clear, (Formulation YS-1-7006, Colorcon)	2.00%
Surelease® Clear, (Formulation E-7-19010, Colorcon)	10%
Total Component Weight	NA

Coated Bead Formulation 5001-6991

20% Memantine HCL (22.5mg) & Eudragit RS-30D (30% w/w aqueous dispersion)	65%
Opadry® Clear, (Formulation YS-1-7006, Colorcon)	10.00%
Eudragit RS-30D coat(30% w/w aqueous dispersion)	25%
Total Component Weight	NA

Coated Bead Formulation 5001-6992

20% Memantine HCL (22.5mg) & Eudragit RS-30D (30% w/w aqueous dispersion)	55%
Opadry® Clear, (Formulation YS-1-7006, Colorcon)	10.00%
Eudragit RS-30D coat(30% w/w aqueous dispersion)	35%
Total Component Weight	NA

Coated Bead Formulation 5001-6993

20% Memantine HCL (22.5mg) & Eudragit RS-30D (30% w/w aqueous dispersion)	53%
Opadry® Clear, (Formulation YS-1-7006, Colorcon)	30.00%
Surelease® Clear, (Formulation E-7-19010, Colorcon)	17%
Total Component Weight	NA

Exemplary in vitro dissolution profiles of sustained release formulations of memantine and Namenda are shown in FIGURES 2A-2C and 3A-3B. The dissolution profiles of the sustained release memantine formulations in neutral medium (FIGURE 2A) are substantially identical to their dissolution profiles in an acidic dissolution medium (FIGURE 2B).

FIGURE 2C is a graph showing effect of medium on the release profile of memantine from matrix tablets. Testing was performed using the R&D method using Apparatus 2 at 50 RPM. Three media were employed: Vessels 1&2 = Water; Vessels 3&4 = pH 1.2 Buffer; Vessels 5&6 = pH 1.2 Buffer for 2 hours, then pH adjusted to 6.8. There were no significant differences in the profiles for the first two hours or between the profile obtained in a pH 1.2 buffer and water. The switch to a buffer having a pH 6.8, however, slowed down release. Accordingly, optimal media testing may be water (pH of a solution containing approximately 22.5 mg Memantine HCl in water is 7.7, consistent with a dilute solution of a base that has a pKa of about 9-10).

Formulation of Memantine HCl SR capsules as coated pellets (22.5 mg)

Memantine was formulated as shown in the table below.

Ingredients	Qty/ unit (mg)
Memantine Hydrochloride	22.5
HPMC 5 cps	9.5
Non-pareils (Celpheres)	90.0
Isopropyl alcohol	q.s.
Dichloromethane	q.s
Total	122.0

The memantine pellets were next coated using a Wurster coater. The Ethylcellulose: HPMC ratios of coating formulation I and coating formulation II were 9:1 and 8:2, respectively (see table below).

Ingredients	%	
	Coating Formula I	Coating Formula II
Ethylcellulose 7 cps	8. 10	6.46
HPMC 5cps	0.92	1.61
Miglyol 812 N	0.42	0.32
Isopropyl alcohol	72.54	67.31
Dichloromethane	18.02	24.30
Coating levels (%)	**8.7, 11.2, 13.0 & 16.5**	**8.0, 11.6, 14.4 & 16.11**

Once coated, the memantine pellets were encapsulated by hand filling, such . Each capsule contained 22.5 mg of memantine. The capsule size was '3.'

The dissolution profiles of the above formulations were next determined with a USP II (Paddle) system, using water (500 mL) as a dissolution medium at 50 rpm. Different coating levels (%w/w) were employed. The release profile of each memantine capsule (22.5 mg) was determined at 1, 2, 4, 6, 8, and 12 hours (see tables below).

Release Data of Memantine HCl SR Capsules 22.5 mg filled with pellets coated with Coating formula I at different coating levels (% w/w)

Time (hours)	8.70%	11.20%	13%	16.50%
0	0	0	0	0
1	11	8	6	4
2	34	23	18	11
4	69	51	41	28
6	82	68	57	42
8	88	76	67	54
12	95	86	80	68

Release Data of Memantine HCl SR Capsules 22.5 mg filled with pellets coated with *Coating formula II* at different coating levels (% w/w)

Time (Hours)	8%	11.60%	14.40%	16.60%
0	0	0	0	0
1	30	14	11	5
2	65	39	31	17
4	93	69	63	40
6	99	83	76	57
8	100	90	86	65
12	100	99	95	83

Drug release was sustained up to 12 hours, in a non-linear fashion. In most cases, pellets showed faster release after 2 hours. To linearise the release profile up to 12 hours with around 100% drug release, drug layering and coating compositions may be varied.

Example 16: Predicted Plasma Profile of Memantine Sustained Release

Using the formulations and dissolution profiles described in Example 14, the serum concentrations resulting from single or multiple administrations of memantine were calculated using the pharmacokinetic software, GastroPlus, from Simulations Plus (see FIGURE 2D). The administration of either of the sustained release formulations achieves a therapeutically effective steady state serum concentration much sooner than with Namenda (13 days versus 30 days from the start of treatment therapy). Furthermore, the initial slope of the sustained release formulation is less than the slope obtained with the immediate release formulation.

Example 17: Patch Providing Extended Release of Memantine

As described above, extended release formulations of an NMDA antagonist may be formulated for topical administration. Memantine transdermal patch formulations may be prepared as described, for example, in U.S.P.Ns. 6,770,295 and 6,746,689, hereby incorporated by reference.

For the preparation of a drug-in-adhesive acrylate, 5 g of memantine is dissolved in 11 g of ethanol and is added to 20 g of Durotak 387-2287 (National Starch & Chemical, U.S.A.). The drug gel is coated onto a backing membrane (Scotchpak 1012; 3M Corp., U.S.A.) using a coating equipment (e.g., RK Print Coat Instr. Ltd, Type KCC 202 control coater). The wet layer thickness is 400 μm. The laminate is dried for 20 minutes at room temperature and then for 30 minutes at 40°C. A polyester release liner is laminated onto the dried drug gel. The sheet is cut into patches and stored at 2-8 °C until use (packed in pouches). The concentration of memantine in the patches ranges between 5.6 and 8 mg/cm^2.

Example 18: Patch Providing Extended Release of Memantine

A patch allowing the extended release of memantine may be prepared as follows. The matrix patch is composed of 1 mm thick polyolefin foam (as an occlusive backing) coated with an acrylate matrix that includes a mixture of memantine and an intradermal-penetration agent in an acrylate polymer. The matrix is prepared by mixing memantine (20 weight percent); acrylate polymer (Durotak.RTM. 387-2052, 75 weight percent); intradermal-penetration agent; aluminumacetylacetonate (Al(ACAC)$_3$, 0.4 weight percent, as a crosslinker); and ethanol until homogeneous. The homogeneous mixture is then coated on polyolefin foil with a hand-coater machine to an average thickness of about 270 μm. The coated foil is dried for about one hour at about 50°C to evaporate the ethanol. The resulting patch weighs approximately 50 g/m^2 dry.

Example 19: Determination of Increased-Dose Tolerability for Memantine SR formulations

A study to determine safety and tolerability of increased dosing for Memantine SR is described below. The study results are expected establish a maximum administerable dose greater than 20 mg when given once per day, as well as confirm tolerability of a non-dose escalating dosing regimen (i.e., administration of substantially identical doses of memantine throughout the term of dosing).

Purpose	Multiple Dose Tolerability
Dosage:	11.25 , 22.5, 33.75, 45.0, 56.25, 67.5, 78.75 and 90.0 mg memantine SR
Concurrent Control:	Placebo
Route:	Oral
Subject Population:	Healthy, drug-naive male subjects
Structure:	Placebo-controlled, Sequential dose escalation in
Study Sites:	Single center
Blinding:	Open label
Method of Subject Assignment:	Subjects in each Cohort will be randomized to either active drug (n=8-10) or placebo (n=2)
Total Sample Size:	80-100 subjects
Primary Efficacy Endpoint:	None
Adverse Events:	Monitored with reports by clinic personnel at least 2 or 3 times per day throughout the study, as well as volunteered by subjects.
Blood Collection	Blood sampling and plasma preparations at the following time points: Day 1:0, 1, 2, 3, 4, 6, 7, 8, 10, 12, 14, 16, 20 Days 2-6: pre-dose trough Day 7: 0, 1, 2, 3, 4, 6, 7, 8, 10, 12, 14, 16, 20, 24, 48, 72, 96, 120, 144, and 168 hours
Analysis	Adverse events (including dizziness, headache, confusion, constipation, hypertension, coughing), tolerability, Pharmacokinetics

Example 20: Determination of Increased-Dose Tolerability for Amantadine SR formulations

A study to determine safety and tolerability of increased dosing for Amantadine SR is described below. The study results are expected establish a maximum administerable dose greater than 200 mg when given once per day, as well as confirm tolerability of a non-dose

escalating dosing regimen (i.e., administration of substantially identical doses of memantine throughout the term of dosing).

Purpose	Multiple Dose Tolerability
Dosage:	100, 200, 300, 400, 500, 600, 700, and 800 mg amantadine SR
Concurrent Control:	Placebo
Route:	Oral
Subject Population:	Healthy, drug-naive male subjects
Structure:	Placebo-controlled, Sequential dose escalation
Study Sites:	Single center
Blinding:	Open label
Method of Subject Assignment:	Subjects in each Cohort will be randomized to either active drug (n=8) or placebo (n=2)
Total Sample Size:	80-100 subjects
Primary Efficacy Endpoint:	None
Adverse Events:	Monitored with reports by clinic personnel at least 2 or 3 times per day throughout the study, as well as volunteered by subjects.
Blood Collection	Blood sampling and plasma preparations at the following time points: Day 1:0, 1, 2, 3, 4, 6, 7, 8, 10, 12, 14, 16, 20 Days 2-6: pre-dose trough Day 7: 0, 1, 2, 3, 4, 6, 7, 8, 10, 12, 14, 16, 20, 24, 48, 72, 96, 120, 144, and 168 hours
Analysis	Adverse events (including dizziness, headache, confusion, constipation, hypertension, coughing), tolerability, Pharmacokinetics

Example 21: Treating NMDA-Receptor Related Disorders with Controlled Release Formulations

A patient diagnosed with dementia of the Alzheimer's type is administered 22.5 mg of memantine in a sustained release formulation (e.g., formulated as described in Example 13) once a day. Memantine plasma concentrations can be determined using HPLC coupled to mass spectrometric detection as described in Periclou et al., Annals of Pharmacotherapy 38:1389-94 (2004). A therapeutically effective steady state serum concentration is reached within ten days of the start of this therapy.

Example 22: Treating Major Depression

A patient diagnosed with Major Depression is administered 22.5 mg or more, up to a maximum tolerated dose (as determined using the protocol in Example 20) of memantine formulated as described in Example 13, once daily. A therapeutically effective steady state serum concentration is reached within ten days of the start of this therapy.

Example 23: Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered a daily dose of 400 mg of a sustained released amantadine formulation. Improvements in dyskinesia are measured using UPDRS scoring.

Example 24: Clinical Trial to Compare Memantine SR formulation to Namenda® in Patients with Alzheimer's Disease or Refractory Depression.

Protocol Objective:	Confirm the improvement in onset to efficacy for a QD, non-dose escalating treatment regimen
Inclusion Criteria:	Chosen from the following indications: Alzheimer's – moderate to severe AD patients (see Tariot et al., JAMA 291:317-24 (2004)) Refractory depression/MADD – unresponsive to SSRIs, HamD 20-24. (see Mann N Engl J Med 353:1819-34 (2005), Berman Biol Psychiatry 47:351-4 (2000), Gauthier et al., Int J Geriatr Psychiatry 20, 459-64 (2005))
Dosage:	22.5 mg (20 mg delivered) Memantine SR given once per day from the onset of therapy;
Concurrent Control:	10 mg Memantine IR given twice per day after

	manufacturer's recommended dose escalation
Route:	Orally or transdermally
Blinding:	Double blinding
Total Sample Size:	120 patients and 120 controls for each indication group
Primary Efficacy Endpoint:	HAMD, MADRS, NPI measured at weekly visits
Secondary Efficacy Endpoint:	Fatigue

In each of the above active controlled, double blind trial, the time required to reach a steady state plasma therapeutic level for Memantine SR is compared to that of memantine IR. Patients are screened against the inclusion criteria and admitted to the trial population. After a 4 week washout of interfering medications, patients are scored at baseline and administered the test medication in a blinded fashion using an over-encapsulation procedure. Measurements of the endpoints are made at weekly intervals on each patient.

Based on our computer simulations, patients receiving a full dose of Memantine SR are expected to reach steady state in 8 days, rather than the 40 days required in patients being administered memantine IR. Thus, beneficial effects are expected earlier in their treatment course.

Example 25: Clinical Trial to Assess Efficacy of Amantadine SR formulation in Patients with Multiple Sclerosis.

Protocol Objective:	Confirm the improvement in depression, neuropsychiatric complications, and fatigue for a QD, non-dose escalating treatment regimen of amantadine
Inclusion Criteria:	MS – relapsing/remitting on interferon treatment with concomitant fatigue (see Bashki et al., Mult Scler 6:181-5 (2000), Siegert et al., J Neurol Neurosurg Psychiatry 76:469-75 (2005))
Dosage:	400 mg Amantadine SR given once per day from the onset of therapy.
Concurrent Control:	Placebo
Route:	Orally
Blinding:	Double blinding
Total Sample Size:	40 patients and 40 controls
Primary Efficacy Endpoint:	HAMD, MADRS, NPI measured at weekly visits
Secondary Efficacy Endpoint:	Fatigue

In each of the above active controlled, double blind trial, Amantadine SR is compared to placebo to measure the effect. Patients are screened against the inclusion criteria and admitted to the trial population. After a 4 week washout of interfering medications, patients are scored at baseline and administered the test medication in a blinded fashion using an overcapsulation procedure. Measurements of the endpoints are made at weekly intervals on each patient.

Patients receiving the Amantadine SR are expected to show an improved score in the test criteria correlating to an improvement in depression or fatigue.

Example 26: Clinical trial to Assess Efficacy of Amantadine SR formulation in Patients with drug induced dyskinesia.

Title:	High Dose Amantadine for the treatment of Drug-Induced Dyskinesia
Study Phase:	II
Purpose	This study will evaluate the effects of amantadine on Parkinson's disease symptoms and on dyskinesias (involuntary movements) that develop as a result of long-term levodopa treatment. Amantadine inhibits the activity of glutamate which is thought to be elevated in patients with Parkinson's disease. The study objective is to test the hypothesis that blockade of glutamate receptors by high doses of amantadine will lessen the severity of Parkinsonian signs and levodopa-associated motor response complications in PD patients to a greater extent than current amantadine doses and dose forms.
Name of Drug:	Amantadine SR
Dosage:	400mg QD
Concurrent Control:	Symmetrel (amantadine immediate release)
Route:	Oral
Subject Population:	Patients with relatively advanced Parkinson's disease and dyskinesias who are between 30 and 80 years of age having a URPDS-3 score of between 16 and 20. Candidates are screened with a complete medical history and physical examination, neurological evaluation, blood and urine tests, and electrocardiogram (ECG).
Structure:	Two arm study, treatment and placebo arms.
Study Sites:	Multiple
Blinding:	Double blind
Method of Subject Assignment:	Random
Total Sample Size:	40 patients per arm
Study Term	Two weeks
Primary Efficacy Endpoint:	Parkinsonian symptoms and choreiform dyskinesias are scored every 10 minutes by a masked neurologist using an abbreviated UPDRS-3 rating scale. A modified abnormal movement scale (AIMS) describing involuntary movements in all extremities and trunk and face on a scale from 1-4.

Secondary Efficacy Endpoints:	Efficacy is assessed using validated motor function scales. Safety is monitored by means of frequent clinical evaluations and laboratory tests.
Adverse Events:	Standard battery of AE assessments collected throughout study period
Blood Collection:	To determine blood levels of amantadine, samples are drawn intermittently throughout the study.
Analysis:	Standard assays to determine concentration of amantadine in blood samples.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS:

What is claimed is:

1. A composition comprising a modified release coating or matrix and an N-methyl-D-aspartate (NMDA) receptor antagonist, wherein said NMDA receptor antagonist has an in vitro dissolution profile in water that is substantially identical to its in vitro dissolution profile in a dissolution medium having a pH of 1.2 and wherein said dissolution profile ranges between 0.1-20% in one hour, 5-30 % in two hours, 40-80% in six hours, greater than or equal to 70% in 10 hours, and greater than or equal to 90% in 12 hours as measured using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37 ± 0.5^{0}C.

2. The composition of claim 1, wherein at least 95% of said NMDA receptor antagonist in said composition is provided in a controlled release dosage form.

3. The composition of claim 2, wherein at least 99% of said NMDA receptor antagonist in said composition is provided in a controlled release dosage form.

4. The composition of claim 3, wherein 100% of said NMDA receptor antagonist in said composition is provided in a controlled release dosage form.

5. The composition of claim 1, wherein said NMDA receptor antagonist is an aminoadamantine derivative.

6. The composition of claim 5, wherein said aminoadamantane derivative is memantine, rimantadine, or amantadine.

7. The composition of claim 6, wherein said aminoadamantane derivative is memantine.

8. The composition of claim of claim 1, wherein said NMDA receptor antagonist is not amantadine or dextromethorphan.

9. The composition of claim 1, wherein said composition is formulated for oral, topical, transepithelial, subdermal, or inhalation delivery.

10. The composition of claim 1, wherein said composition is formulated as a lotion or patch.

11. A composition comprising a modified release coating or matrix and memantine, wherein memantine has an in vitro dissolution profile ranging between 0-60% one hour, 0-86% in two hours, 0.6-100% in six hours, 3-100% in 10 hours, and 8-100% in 12 hours as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C, in water.

12. The composition of claim 11, wherein memantine has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50% or more in 10 hours, and 90% or more in 12 hours as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C, in water.

13. The composition of claim 11, wherein at least 95% of memantine in said composition is provided in a controlled release dosage form.

14. The composition of claim 13, wherein at least 99% of memantine in said composition is provided in a controlled release dosage form.

15. The composition of claim 14, wherein 100% of memantine in said composition is provided in a controlled release dosage form.

16. The composition of claim 11, wherein less than 15% of memantine is released at 15 minutes.

17. The composition of claim 11, wherein less than 15% of memantine is released at 30 minutes.

18. The composition of claim 11, wherein at least 60% of said memantine is released as measured at 6 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5°C, in a dissolution medium having a pH of 1.2.

19. The composition of claim 11, wherein said composition is formulated for oral, topical, transepithelial, subdermal, or inhalation delivery.

20. The composition of claim 19, wherein said composition is formulated as a lotion or patch.

21. A composition comprising memantine and a sustained release coating or matrix, wherein the fraction of released memantine is greater or equal to $0.01(0.297 + 0.0153*e^{(0.515*t)})$ and less than $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37 ± 0.5^0C, in water, wherein t is the time in hours and wherein t is greater than zero and equal or less than 17.

22. The composition of claim 21, wherein the fraction of released memantine is greater or equal to $0.01(0.297 + 0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37 ± 0.5^0C, in water, wherein t is the time in hours and wherein t is greater than zero and equal or less than 17.

23. The composition of claim 21, wherein at least 95% of memantine in said composition is provided in an extended release dosage form.

24. The composition of claim 23, wherein at least 99% of memantine in said composition is provided in an extended release dosage form.

25. The composition of claim 24, wherein 100% of memantine in said composition is provided in an extended release dosage form.

26. The composition of claim 21, wherein less than 5% of memantine is released in one hour.

27. The composition of claim 21, wherein said composition is formulated for oral, topical, transepithelial, subdermal, or inhalation delivery.

28. The composition of claim 21, wherein said composition is formulated as a lotion or patch.

29. The use of a composition comprising an NMDA receptor antagonist in the manufacture of a medicament for the treatment of a neurologic or neuropsychiatric condition, wherein said NMDA receptor antagonist is provided in a modified release dosage form and is to be administered at a substantially identical dose from the start of therapy.

30. The use of claim 29, wherein said composition is any one of the compositions of claims 1-28.

31. The use of claim 29, wherein said condition is selected from the group consisting of seizure disorders, pain syndromes, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, brain trauma, cranial nerve disorders, neuropsychiatric disorders, other disease neuropathies, fatigue syndromes, ataxic syndromes, and axonic brain damage.

32. The useof claim 29, wherein said condition is Parkinson's disease, multiple sclerosis, epilepsy, pain, depression, agitation, Alzheimer's disease, amyotrophic lateral sclerosis, or neuropathic pain.

33. The use of claim 29, wherein said composition is to be administered no more than once every 24 hours.

34. The use of claim 29, wherein said composition, upon administration, reaches a therapeutically effective steady state plasma concentration in a subject within fifteen days.

35. The use of claim 29, wherein said composition, upon administration, reaches a therapeutically effective steady state plasma concentration in a subject within five days of said administration.

36. The use of claim 29, wherein said composition is to be administered to a subject no more than once every 24 hours and wherein said NMDA receptor antagonist reaches a therapeutically effective steady state plasma concentration in a subject in less than 30 days.

37. The use of claim 29, wherein, upon administration of said composition to a subject, the mean plasma concentration profile of the NMDA receptor antagonist has an slope from 2 hours to 4 hours after administration less than 50% of that for an IR formulation of the same NMDA receptor antagonist at the same administered dose.

38. The use of claim 29, wherein said NMDA receptor antagonist is an aminoadamantane.

39. The use of claim 38, wherein said aminoadamantane is memantine, amantadine, or rimantadine.

40. The use of claim 39, wherein said aminoadamantane is memantine.

41. The use of claim 40, wherein memantine is to be administered at a daily dose ranging between 5 and 100 mg.

42. The use of claim 41, wherein memantine is to be administered at a daily dose ranging between 2 and 80 mg.

43. The use of claim 42, wherein memantine is to be administered at a daily dose ranging between 5 and 80 mg.

44. The use of claim 43, wherein the daily dose of memantine ranges between 5 and 40 mg .

45. The use of claim 43, wherein the daily dose of memantine ranges between 20 and 50 mg.

46. The use of claim 45, wherein the daily dose of memantine ranges between 20 and 40 mg.

47. The use of claim 29, wherein subject to be administered said composition has not been administered said NMDA receptor antagonist, within one week of onset of therapy, at a dose that is lower than said dose used during therapy.

48. A method of preparing a pharmaceutical composition for the treatment of a condition associated with a deregulation in NMDA receptor activity by providing a matrix or coated core to provide sustained release of a NMDA receptor antagonist, wherein said NMDA receptor antagonist is present in sufficient quantity to treat said condition, using a therapy that involves administering to a subject substantially identical doses of said NMDA receptor antagonist from the onset of said therapy.

49. The method of claim 48, further comprising providing a mixture containing a NMDA receptor antagonist to provide an immediate release of a NMDA receptor antagonist, wherein the weight of said mixture is less than 5% than the total weight of said matrix or coated core and mixture.

50. The method of claim 48, wherein said NMDA receptor antagonist is memantine.

51. The method of claim 48, wherein said NMDA receptor antagonist is not amantadine or dextromethorphan.

52. The method of claim 48, wherein said matrix core is a wax, insoluble matrix polymer, water soluble matrix materials, or mixtures thereof.

53. The method of claim 48, wherein said coated core is a core of NMDA receptor antagonist coated with a pharmaceutically acceptable polymer including diffusion barrier polymers with or without porosity enhancers selected from the group consisting of ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials, sugars, lactose, sucrose, fructose and mannitol, salts, sodium chloride, potassium chloride, organic acids, fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers, hydroxypropyl celluose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

54. The method of claim 48, further comprising compressing said core and said mixture into a tablet form and wherein said core and said mixture are dispersed throughout said tablet.

55. The method of claim 48, wherein said core and said mixture are combined and compressed into a tablet form such that said core and said mixture form a multilayer tablet form.

56. The method of claim 48, wherein said core and said mixture are combined into a capsule or a patch.

57. The use of a composition comprising an NMDA receptor antagonist in the manufacture of a medicament for the treatment of a neurologic or neuropsychiatric condition, wherein said composition is provided in a modified release dosage form and is administered at a substantially identical dose from the start of therapy, no more than once every 24 hours.

58. The use of claim 57, wherein said composition is manufactured according to claim 46.