Nanoparticulate Formulations of Modafinil

FIELD OF INVENTION

The present invention relates generally to compounds and compositions useful in the treatment of disease states, symptoms, syndromes, and conditions of the central nervous system (CNS). More specifically, the invention relates to nanoparticulate modafinil, its enantiomers such as armodafinil (the single r-isomer of modafinil), polymorphs, and adrafinil pharmaceutical compositions, hereafter referred to as modafinil compositions. The nanoparticulate modafinil compositions have an effective average particle size of less than about 2000 nm.

BACKGROUND OF INVENTION

The following discussion of the background of the invention is merely provided to aid the reader in understanding the invention and is not admitted to describe or constitute prior art to the invention.

A. Background Regarding Nanoparticulate Compositions

Nanoparticulate compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer and is hereby incorporated by reference. The '684 patent does not describe nanoparticulate compositions of modafinil, its enantiomers, or polymorphs.

Methods of making nanoparticulate compositions are described in, for example, U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." All of the above patents are incorporated by reference, as are all the earlier aforementioned patents.

Nanoparticulate compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated

Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for

Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for "Small Scale Mill;" and 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference, as are all the earlier aforementioned patents.

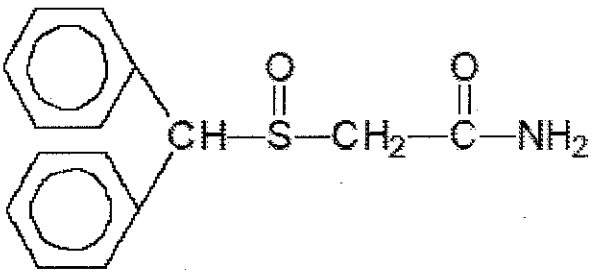
Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas

Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter." which are also hereby incorporated by reference herein

B. Background Regarding Modafinil Compositions

Modafinil has been marketed in 28 countries worldwide for a number of indications. Modafinil is a wakefulness-promoting agent. Modafinil is a racemic compound, activating the central nervous system (CNS), and a selective orexin receptor agonist. The chemical name for modafinil is 2-[(diphenylmethyl) sulfinyl] acetamide or benzhydrylsulphinylacetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36.

modafinil has the chemical structure shown below:



Modafinil is a white to off-white, crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in methanol and acetone.

Modafinil is commercially available in the U.S. under the trade name PROVIGIL® (modafinil) Tablets [C-IV] and is approved for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome (OSAHS), and Shift Work Sleep Disorder (SWSD). It is manufactured and distributed by Cephalon, Inc., and available internationally from various suppliers under the names Alertec, Vigicer, Modalert. PROVIGIL® tablets contain 100 mg or 200 mg of modafinil and the following inactive ingredients: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, and magnesium stearate. For example, PROVIGIL® (modafinil) compositions are described in U.S. Patent Nos. 4,927,855; 5,618,845; and RE 37,516 that are hereby incorporated by reference.

Additionally, Cephalon, Inc. is seeking marketing approval for modafinil under the trade name SPARLON® for the treatment of children and adolescents with ADHD. The proposed formulation has a higher drug/excipient ratio compared to the current marketed product, PROVIGIL, thus allowing for the smaller tablet size. These tablets contain 85, 170, 255, 340, or 425 mg of modafinil and the following inactive ingredients: lactose, croscarmellose sodium, povidone, and magnesium stearate. The film coating for all tablet strengths contains:

hypromellose, titanium dioxide, lactose, polyethylene glycol, and triacetin. In addition, the 170 and 340 mg tablets contain iron oxide yellow, and the 255- and 425-mg tablets contain FD&C Blue#2. Modafinil is a memory-improving and mood-brightening psychostimulant. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines, but it is known that it functions as an alpha 1 adrenoceptor or orexin agonist in the hypothalamus. Modafinil is less likely to cause jitteriness, anxiety, or excess locomotor activity - or lead to a hypersomnolent 'rebound effect' - than traditional stimulants. The normal elimination half-life of modafinil in humans is between about 12 to about 15 hours. It is long acting and does not tend to cause peripheral sympathetic stimulation. Modafinil induces wakefulness in part by its action in the anterior hypothalamus.

At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V.

Narcolepsy is caused by dysfunction of a family of wakefulness-promoting and sleep-suppressing peptides, the orexins. Modafinil activates orexin neurons. Orexinergic neurons are found exclusively in the lateral hypothalamic area. Their activation is associated with enhanced pleasure-seeking and motivation as well as arousal. Orexinergic fibers project to the entire central nervous system. Genetically modified orexin-knockout animals offer a model of human narcolepsy. Narcoleptics suffer profound disturbances in normal sleeping patterns and variable degrees of depression. These symptoms can be reversed with modafinil. Selective orexin receptor agonists of the future may prove useful both to narcoleptics and the population at large.

Modafinil has central alpha 1-adrenergic agonist effects i.e. it directly stimulates the receptors. Modafinil inhibits the reuptake of noradrenaline by the noradrenergic terminals on sleep-promoting neurons of ventrolateral preoptic nucleus (VLPO). More significant, perhaps, is its ability to increase excitatory glutamatergic transmission. This reduces local GABAergic transmission, thereby diminishing GABA(A) receptor signaling on the mesolimbic dopamine terminals.

The optical enantiomers of modafinil have similar pharmacodynamic actions in animals with increased duration and efficacy in humans. Two major metabolites of modafinil, modafinil acid and modafinil sulfone, do not appear to contribute to the CNS-activating properties of modafinil.

Modafinil is a racemic compound, whose enantiomers have different pharmacodynamics and pharmacokinetics. (e.g., the half-life of the *l*-isomer is approximately three times that of the *d*-somer in humans). The enantiomers do not interconvert. Modafinil enantiomers and polymorphs and their methods of preparation are described in U.S. Patent Nos.: 6,992,219; 6,919,378; 6,849,120; 7,057,069; 7,057,068; 7,038,085; 6,998,490; 6,962,717; 6,919,378; 6,919,367; 6,875,893; 6,849,120; 6,833,478; 6,458,384; and 6,489,363 which are hereby incorporated by reference. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration (C_{minss}) of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing. A nanoparticle formulation may shorten the time required to this steady state dosing plateau.

Absorption of modafinil tablets results with peak plasma concentrations (t_{max}) occurring at about 2-4 hours in adults over a 200-600 mg dose range. See, *Cephalon, NDA submission,*NDA 20-717 herein incorporated by reference. The bioavailability of modafinil tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability has not determined due to the aqueous insolubility (<1 mg/mL) of modafinil, which precludes intravenous administration. Food has no effect on overall modafinil bioavailability; however, absorption and (t_{max}) may be delayed by approximately one hour if taken with food. A nanoparticulate formulation may shorten the time required to reach peak plasma concentrations, increase bioavailability, and reduce the absorption (t_{max}) delay associated with fed intake.

Because modafinil and modafinil sulfone are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, phenytoin, and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6 (i.e., 7-10% of the Caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co-administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications. Chronic administration of modafinil 400 mg was found to decrease the systemic exposure to two CYP3A4 substrates, ethinyl estradiol, and triazolam, after oral administration suggesting that CYP3A4 had been induced. Chronic administration of modafinil can increase the elimination of substrates of CYP3A4. Dose adjustments may be

necessary for patients being treated with these and similar medications. A nanoparticulate composition of modafinil may reduce the significance of these drug and enzymic interactions and result in less dosage adjustments of other medications.

A slight decrease (~20%) in the oral clearance (CL/F) of modafinil was observed in a single dose study at 200 mg in 12 subjects with a mean age of 63 years than in matched younger subjects. Due to potential effects from the multiple concomitant medications with which most of the patients were being treated, the apparent difference in modafinil pharmacokinetics may not be attributable solely to the effects of aging. However, the results suggest that the clearance of modafinil may be reduced in the elderly. A nanoparticulate composition of modafinil may improve clearing of the medication in the elderly because of the lower required dosing.

The effectiveness of modafinil in reducing excessive sleepiness has been established in the following sleep disorders: narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). Modafinil may also be used in the treatment to reduce or eliminate symptoms or syndromes or disease states of diseases or disorders, including, but not limited to: dyssomnias, sleep disorders, hypersomnia, including idiopathic hypersomnia and hypersomnia in chronic pain and cancer patients administered opiate analgesics to relieve severe pain, Alzheimer's disease, Parkinson's disease, ischemia, vigilance disorders, Steinert's disease, general depression, extended combat fatigue syndrome, attention-deficit disorder (ADHD), sleep apneas, myotonic dystrophy, multiple sclerosis-induced fatigue, fatigue associated with a disease state, cocaine addiction, heroin addiction, post-anesthesia grogginess, depressive mood related to weak sunlight (sundowning), seasonal affective disorder, food behavior disorders, chemotherapy induced sleepiness, cognitive impairment in schizophrenia, spasticity associated with cerebral palsy, age-related memory decline, idiopathic hypersomnia, jet-lag, depressives who feel sleepy and fatigued on SSRIs, post traumatic stress disorder, emergency response fatigue syndrome. Further uses and methods of treatment incorporating modafinil are described in U.S. Patent Nos.: 6,488,164; 6,456,519; 6,455,588; 6,977,070; 6,348,500; 6,346,548; 5,612,279; 5,401,776; 5,612,379; 5,281,607, 5,719,168; 6,180,678; 6,323,236; 6,566,404; 6,503,950; and 6,488,164 all of which are herein incorporated by reference.

Provigil® is generally prescribed in dosages of 200 mg/day for adult patients and dosages ranging up to 400 mg/day may be tolerated. A nanoparticulate modafinil composition oral dosage range could be reduced, preferably in the 40 mg to 225 mg range as opposed to the present 200-300 mg range seen by Provigil®. The overall range of modafinil formulations is 85 mg to 425 mg. A nanoparticulate modafinil composition could range from about 40 mg to about 400 mg. A

nanoparticulate modafinil composition demonstrates a reduced onset of therapeutic effect of less than about two hours with a T_{max} under about 1.5. A nanoparticle composition would be highly beneficial over the existing formulations where a rapid wakening effect is needed. A nanoparticulate composition could also allow for smaller tablet sizes in pediatric indications allowing for increased ease of swallowing and ease of dosing.

The present invention then, relates to nanoparticulate modafinil compositions comprising modafinil, armodafinil, or adrafinil for the treatment of neurological diseases, conditions, syndromes, and symptoms.

B. Background Regarding Armodafinil

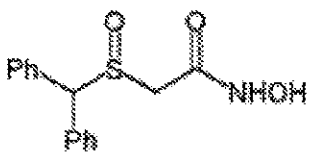
Armodafinil is a wakefulness-promoting agent for oral administration. Armodafinil is the r-enantiomer of modafinil. Armodafinil is not a racemic compound, but is a selective orexin receptor agonist and activates the central nervous system (CNS). The chemical name for armodafinil is (r)-2-((diphenylmethyl)sulfinyl)-acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36.

Armodafinil is an eugeroic drug produced by Cephalon, Inc. under the name NUVIGIL®, and has received FDA approval. Since armodafinil is the r-enantiomer of modafinil, it is expected to act in a substantially similar manner, resulting in similar pharmacologic effects. Armodafinil is exemplied in many of the patents incorporated in the preceding section.

C. Background Regarding Adrafinil

Adrafinil is a wakefulness-promoting agent for oral administration. Adrafinil is a selective orexin receptor agonist. Adrafinil, also known by the name CRL 40028, has as its chemical name 2-(diphenylmethyl) sulfinyl acetohydroxamic acid. The molecular formula is $C_{15}H_{15}NO_3S$ and the molecular weight is 289.35.

Adrafinil has the chemical structure shown below:



Adrafinil is a white to off-white, crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in methanol and acetone.

Adrafinil is not available in the U.S. It is sold over the counter under the name OLMIFON® in the European Union and manufactured and sold by Cephalon, Inc. OLMIFON®

tablets are 300 mg. The manufacture is described in U.S. Patent Nos: 4,066,686; 5,618,845; and 4,177,290, which are hereby incorporated by reference.

Adrafinil is a prodrug; it is primarily metabolized *in vivo* to modafinil (PROVIGIL®), resulting in nearly identical pharmacologic effects. Unlike modafinil, however, it takes time for the metabolite to accumulate to active levels in the bloodstream. Effects usually are apparent within 45-60 minutes when taken orally on an empty stomach.

SUMMARY

The present disclosure relates to nanoparticulate compositions comprising a modafinil, or a salt, or an enantiomer, or a prodrug, or a polymorph, or a derivative thereof. The nanoparticulate compositions comprise modafinil, or a salt, or an enantiomer, or a prodrug, or a polymorph, or a derivative thereof, and at least one surface stabilizer adsorbed on the surface of the nanoparticulate particles. The nanoparticulate composition particles have an effective average particle size of less than about 2000 nm.

According to a first aspect, there is provided a stable nanoparticulate composition comprising: (A) particles comprising modfinil, or a salt, derivative, prodrug, or polymorphy thereof, said particles having an effective average particle size of less than about 2000 nm in diameter; and (B) at least one surface stabilizer.

In one embodiment the present disclosure relates to a composition comprising particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof, wherein the particles consist of a first population of particles and a second population of particles, wherein the ratio of the first population of particles to the second population of particles is about 3:7 by weight, wherein:

(a) the first population of particles comprises coarse particles having a diameter greater than about 240 microns; and

(b) the second population of particles comprises coarse particles having a diameter less than about 240 microns, wherein the second population of particles comprises nanoparticles having a diameter less than about 2000nm.

In another embodiment the present disclosure relates to a composition comprising particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof, wherein the particles consist of a first population of particles and a second population of particles, wherein the ratio of the first population of particles to the second population of particles is about 3:7 by weight, wherein:

(a) the first population of particles comprises coarse particles having a diameter greater than about 220 microns; and

(b) the second population of particles comprises coarse particles having a diameter less than about 220 microns, wherein the second population of particles comprises nanoparticles having a diameter less than about 2000nm.

In certain embodiments of the present disclosure the particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof comprises about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% nanoparticles by weight.

In one embodiment the compositions of the present disclosure are in the form of a tablet or capsule. In one embodiment the compositions of the present disclosure are in an oral controlled release dosage. A preferred dosage form of the disclosure is a solid oral dosage form, although any pharmaceutically acceptable dosage form can be utilized.

In certain embodiments the composition further comprises a cyclodextrin provided that the cyclodextrin is not selected from the group consisting of hydroxylpropylbetacyclodextrin, betacyclodextrinsulfobutylether, and mixtures thereof.

Another embodiment of the disclosure is directed to pharmaceutical compositions comprising a nanoparticulate modafinil, or a salt, or an enantiomer, or a prodrug, or a polymorph, or derivative thereof, and at least one surface stabilizer, a pharmaceutically acceptable carrier, as well as any desired excipients.

One embodiment of the disclosure encompasses a nanoparticulate modafinil composition, wherein the pharmacokinetic profile of the nanoparticulate modafinil is minimally affected by the fed or fasted state of a subject ingesting the composition.

In yet another embodiment, the disclosure encompasses a nanoparticulate modafinil composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

Another embodiment of the disclosure is directed to nanoparticulate modafinil composition combined with one or more additional compounds useful in the treatment of neurological diseases or disorders or syndromes or symptoms.

An additional embodiment of the disclosure is directed to nanoparticle modafinil compositions in combination with one or more additional compounds such as a hypnotic or sedative.

This disclosure further discloses a method of making the inventive nanoparticulate modafinil composition. Such a method comprises contacting the nanoparticulate modafinil, or a salt, or an enantiomer, or a prodrug, or polymorph or derivative thereof, with at least one surface stabilizer for a time and under conditions sufficient to provide a stabilized nanoparticulate modafinil composition.

According to a second aspect, there is provided a method of preparing the composition as defined above comprising contacting particles comprising said modfinil, or a salt, derivative, prodrug, or polymorph thereof, with at least one surface stabilizer for a period of time and under conditions sufficient to provide a nanoparticulate composition comprising modfinil, or a salt, derivative, prodrug, or polymorph thereof, having an effective average particle size of less than about 2000 nm in diameter.

The present disclosure is also directed to methods of treatment including but not limited to, the treatment of neurological diseases or conditions or symptoms or syndromes arising from,

using the novel nanoparticulate modafinil compositions disclosed herein. Such neurological diseases or conditions or symptoms or syndromes include, but are not limited to narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift worker sleep disorder, improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia.

Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate modafinil, or a salt, or an enantiomer, or a prodrug, or polymorph, or derivative thereof. A therapeutically effective amount is an amount that results in a perceived reduction in the symptoms or conditions. Other methods of treatment using the nanoparticulate compositions of the disclosure are known to those of skill in the art.

According to a third aspect, there is provided the use of a composition as defined above in the manufacture of a medicament for preventing and/or treating disease states, symptoms, syndromes, and conditions of the central nervous system (CNS).

The present disclosure also relates to modified release composition having a first component comprising a first population of active ingredient-containing particles and at least one subsequent component comprising a subsequent population of active ingredient-containing particles, wherein each component has a different rate and/or duration of release and wherein at least one of the components comprises modafinil, or a salt, derivative, prodrug, or polymorph thereof. The particles of at least one subsequent component are provided in a modified release (MR) form such as, for example, particles coated with a modified release coating or comprising or incorporated in a modified release matrix material. Upon oral administration to a patient, the composition releases the active ingredient(s) in a bimodal or multimodal manner. The components may optionally comprise one or more additional active ingredients useful in the prevention and treatment of disease states, symptoms, syndromes, and conditions of the CNS and/or one or more pharmaceutically acceptable excipients. According to a fourth aspect, there is provided a pharmaceutical composition comprising a first component of active ingredient-containing particles and at least one subsequent component of active ingredient-containing particles, wherein at least one of said components comprises particles wherein modfinil, or a salt, derivative, prodrug, or polymorph thereof, is the active ingredient and at least one of said components further comprises a modified release coating, a modified release matrix material, or both, such that the composition, following oral delivery to a subject, delivers the active ingredient in a continuous, bimodal or multimodal manner, and wherein at least a population of said modafinil

containing particles are nanoparticles having an effective average particle size of less than 2000 nm in diameter and at least one surface stabilizer. In an embodiment of the present disclosure, at least some of the particles comprise nanoparticles which comprise modafinil, or a salt, derivative, prodrug, or polymorph thereof. In another embodiment of the present disclosure, at least some of the particles are themselves nanoparticles which comprise modafinil, or a salt, derivative, prodrug, or polymorph thereof.

According to a fifth aspect, there is provided a dosage form comprising the composition as defined above.

The first component of the modified release composition may exhibit a variety of release profiles including profiles in which substantially all of the active ingredient contained in the first component is released rapidly upon administration of the dosage form, released rapidly but after a time delay (delayed release), or released slowly over time. In one embodiment, the active ingredient contained in the first component of the dosage form is released rapidly upon administration to a patient. As used herein, "released rapidly" includes release profiles in which at least about 80% of the active ingredient of a component of the dosage form is released within about an hour after administration, the term "delayed release" includes release profiles in which

the active ingredient of a component of the dosage form is released (rapidly or slowly) after a time delay, and the terms "controlled release" and "extended release" include release profiles in which at least about 80% of the active ingredient contained in a component of the dosage form is released slowly.

The subsequent component of the modified release composition may also exhibit a variety of release profiles including an immediate release profile, a delayed release profile or a controlled release profile. In one embodiment, the subsequent component exhibits a delayed release profile in which the active ingredient of the component is released after a time delay. In another embodiment, the subsequent component exhibits a controlled release profile in which the active ingredient of the component is released over a period of about 12 to about 24 hours after administration.

In two-component embodiments in which the components exhibit different release profiles, the release profile of the active ingredients from the composition is bimodal. In embodiments in which the first component exhibits an immediate release profile and the subsequent component exhibits a delayed release profile, there is a lag time between the release of active ingredient from the first component and the release of the active ingredient from the subsequent component. The duration of the lag time may be varied by altering the amount and/or composition of the modified release coating or by altering the amount and/or composition of the modified release matrix material utilized to achieve the desired release profile. Thus, the duration of the lag time can be designed to mimic a desired plasma profile.

In embodiments in which the first component exhibits an immediate release profile and the subsequent component exhibits a controlled release profile, the active ingredients in the first and subsequent components are released over different time periods. In such embodiments, the immediate release component serves to hasten the onset of action by minimizing the time from administration to a therapeutically effective plasma concentration level, and the one or more subsequent components serve to minimize the variation in plasma concentration levels and/or maintain a therapeutically effective plasma concentration throughout the dosing interval. In one such embodiment, the active ingredient in the first component is released rapidly and the active ingredient in the subsequent component is released within a period of about 12 hours after administration. In another such embodiment, the active ingredient in the first component is released rapidly and the active ingredient in the subsequent component is released within a period of about 24 hours after administration. In yet another such embodiment, the active ingredient in the first component is released rapidly and the active ingredient in the subsequent component is released over a period of about 12 hours after administration. In still another such embodiment,

the active ingredient in the first component is released rapidly and the active ingredient in the subsequent component is released over a period of about 24 hours after administration. In yet another such embodiment, the active ingredient in the first component is released rapidly and the active ingredient in the subsequent component is released over a period of at least about 12 hours after administration. In still another such embodiment, the active ingredient in the first component is released rapidly and the active ingredient in the subsequent component is released over a period of at least about 24 hours after administration.

According to a sixth aspect, there is provided the use of a therapeutically effective amount of the composition as defined above in the manufacture of a medicament for preventing and/or treating disease states, symptoms, syndromes, and conditions of the central nervous system (CNS).

The plasma profile produced by the administration of dosage forms of the present disclosure which comprise an immediate release component and at least one modified release component can be substantially similar to the plasma profile produced by the administration of two or more IR dosage forms given sequentially, or to the plasma profile produced by the administration of separate IR and MR dosage forms. The modified release composition of the present disclosure is particularly useful for administering modafinil, or a salt, derivative, prodrug, or polymorph thereof, which is normally administered two times daily. In one embodiment of the present disclosure, the composition delivers the modafinil, or a salt, derivative, prodrug, or polymorph thereof, in a bimodal manner. Upon administration, such a composition produces a plasma profile which substantially mimics that obtained by the sequential administration of two IR doses of modafinil in accordance with a typical treatment regimen.

According to another embodiment of the present disclosure, the composition can be designed to produce a plasma profile that minimizes or eliminates the variations in plasma concentration levels associated with the administration of two or more IR dosage forms given sequentially. In such embodiments, the composition may be provided with an immediate release component to hasten the onset of action by minimizing the time from administration to a therapeutically effective plasma concentration level, and at least one modified release component to maintain a therapeutically effective plasma concentration level throughout the dosing interval. The modafinil, or a salt, derivative, prodrug, or polymorph thereof, may be contained in nanoparticulate particles which comprise also at least one surface stabilizer.

Modified release compositions similar to those disclosed herein are disclosed and claimed in the United States Patent Nos. 6,228,398 and 6,730,325 to Devane et al.

According to a seventh aspect, there is provided a pharmaceutical composition comprising particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof, wherein said particles consist of a first population of particles and a second population of particles, wherein the ratio of said first population of particles to said second population of particles is about 3:7 by weight, wherein: (a) said firs population of particles comprises coarse particles having a diameter greater than about 240 microns; and (b) said second population of particles comprises coarse particles having a diameter less than about 240 microns, wherein said second population of particles comprises nanoparticles having a diameter less than about 2000 nm.

The present disclosure also relates to dosage forms made from the compositions of the present disclosure. According to an eighth aspect, there is provided an oral controlled release dosage form comprising the composition as defined above. In one embodiment, the dosage form is a solid oral dosage form comprising the modified release composition of the present invention. The oral dosage form may utilize, for example, erodable formulations, diffusion controlled formulations and osmotic controlled formulations. In such embodiments, the total dose contained in the dosage form may be release in

a pulsatile or continuous manner. In one such embodiment, a portion of the total dose is released immediately to allow for rapid onset of effect, and the remainder of the total dose is release after a lag time or over a period of time up to about 24 hours.

According to a ninth aspect, there is provided the use of the composition as defined above in the manufacture of a medicament for improving or maintaining bioavailability of modafinil.

According to a tenth aspect, there is provided the use of the composition as defined above in the manufacture of a medicament for treating neurological based disorder selected from the group consisting of narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift worker sleep disorder, improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia, wherein said medicament is to be administered to a patient suffering from said disorder.

According to an eleventh aspect, there is provided a pharmaceutical composition comprising particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof, wherein said particles consist of a first population of particles and a second population of particles, wherein the ratio of said first population of particles to said second population of particles is about 3:7 by weight, wherein: (a) said first population of particles comprises coarse particles having a diameter greater than about 220 microns; and (b) said second population of particles comprises coarse particles having a diameter less than about 220 microns, wherein said second population of particles comprises nanoparticles having a diameter less than about 2000nm.

According to a twelfth aspect, there is provided an oral controlled release dosage form comprising the composition as defined above.

According to a thirteenth aspect, there is provided the use of the composition as defined above in the manufacture of a medicament for improving or maintaining bioavailability of modafinil.

According to a fourteenth aspect, there is provided the use of the composition as defined above in the manufacture of a medicament treating neurological based disorder selected from the group consisting of narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift worker sleep disorder, improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia, wherein said medicament is to be administered to a patient suffering from said disorder.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a micrograph of a nanoparticulate modafinil formulation comprising modafinil, 5%w/w; hydroxypropylmethylcellulose, 1.25%w/w; docusate sodium, 0.05%w/w; and deionized water, 93.7%w/w (Formulation 1, Table 1). Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 2 shows a micrograph of a nanoparticulate modafinil Formulation 1. Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 3 shows a micrograph of a nanoparticulate modafinil formulation comprising modafinil, 10%w/w; Plasdone S-630 (povidone), 2.5%w/w; docusate sodium, 0.1%w/w; and deionized water, 87.4%w/w (Formulation 2, Table 1). Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 4 shows a micrograph of a nanoparticulate modafinil formulation comprising modafinil, 10%w/w; hydroxypropylcellulose - super low viscosity (HPC-SL), 2.5%w/w; docusate sodium, 0.1%w/w; and deionized water, 87.4%w/w (Formulation 3, Table 1). Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 5 shows a micrograph of a nanoparticulate modafinil Formulation 3. Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 6 shows a micrograph of a nanoparticulate modafinil formulation comprising modafinil, 10%w/w; Plasdone K29-32 (povidone), 2.5%w/w; sodium lauryl sulphate, 0.1%w/w; and deionised water, 87.4%w/w (Formulation 4, Table 1). Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 7 shows a micrograph of a nanoparticulate modafinil Formulation 4. Microscopy: 100X/1.4 oil phase objective. A 1 μm size reference is noted in the lower right corner.

Figure 8 shows Mean Modafinil Plasma Concentration versus Time Profile.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is described herein using several definitions as set forth below and throughout the application.

As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

As used herein, "therapeutically effective amount of modafinil" means the dosage that provides the specific pharmacological response for which the modafinil is administered in a significant number of subjects in need of the relevant treatment. It is emphasized that a therapeutically effective amount of modafinil that is administered to a particular subject in a particular instance will not always be effective in treating the conditions described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

As used herein, "particulate" refers to a state of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology.

As used herein, "multiparticulate" means a plurality of discrete, or aggregated, particles, pellets, beads, granules or mixture thereof irrespective of their size, shape or morphology. A composition comprising a multiparticulate is described herein as a "multiparticulate composition."

As used herein, "nanoparticulate" refers to a multiparticulate in which the effective average particle size of the particles therein is less than about 2000 nm (2 microns) in diameter. A composition comprising a nanoparticulate is described herein as a "nanoparticulate composition."

As used herein, "effective average particle size" to describe a multiparticulate (e.g., a nanoparticulate) means that at least 50% of the particles thereof are of a specified size. Accordingly, "effective average particle size of less than about 2000 nm in diameter" means that at least 50% of the particles therein are less than about 2000 nm in diameter.

As used herein, "D50" refers to the particle size below which 50% of the particles in a multiparticulate fall. Similarly, "D90" refers to the particle size below which 90% of the particles in a multiparticulate fall.

As used herein with reference to stable particles, "stable" refers to, but is not limited to, one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) the physical structure of the particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) the particles are chemically

stable; and/or (4) where the active ingredient has not been subject to a heating step at or above the melting point of the particles in the preparation of the nanoparticles of the present invention.

As used herein, "poorly water soluble drug" refers to a drug that has a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or less than about 1 mg/ml.

As used herein, "modified release" includes a release which is not immediate and includes controlled release, extended release, sustained release and delayed release.

As used herein, "time delay" refers to the period of time between the administration of a dosage form comprising the composition of the invention and the release of the active ingredient from a particular component thereof.

As used herein, "lag time" refers to the time between the release of the active ingredient from one component of the composition and the release of the active ingredient from another component of the composition.

As used herein, "erodable" refers to formulations which may be worn away, diminished, or deteriorated by the action of substances within the body.

As used herein, "diffusion controlled" refers to formulations which may spread as the result of their spontaneous movement, for example, from a region of higher to one of lower concentration.

As used herein, "osmotic controlled" refers to formulations which may spread as the result of their movement through a semi-permeable membrane into a solution of higher concentration that tends to equalize the concentrations of the formulation on the two sides of the membrane.

As used herein, "modafinil" refers to either a single substantially optically pure enantiomer of modafinil or to a mixture, racemic or otherwise, of enantiomers of modafinil.

I. Nanoparticulate Compositions Comprising Modafinil

The present invention provides a nanoparticulate composition comprising particles which comprise: (A) modafinil, or a salt, derivative, prodrug, or polymorph thereof; and (B) at least one surface stabilizer. Nanoparticulate compositions were first described in U.S. Patent No. 5,145,684. Nanoparticulate active agent compositions are described also in, for example, U.S. Patent Nos. 5,298,262; 5,302,401; 5,318,767; 5,326,552; 5,328,404; 5,336,507; 5,340,564; 5,346,702; 5,349,957; 5,352,459; 5,399,363; 5,494,683; 5,401,492; 5,429,824; 5,447,710; 5,451,393; 5,466,440; 5,470,583; 5,472,683; 5,500,204; 5,518,738; 5,521,218; 5,525,328; 5,543,133; 5,552,160; 5,565,188; 5,569,448; 5,571,536; 5,573,749; 5,573,750; 5,573,783; 5,580,579; 5,585,108; 5,587,143; 5,591,456; 5,593,657; 5,622,938; 5,628,981; 5,643,552;

5,718,388; 5,718,919; 5,747,001; 5,834,025; 6,045,829; 6,068,858; 6,153,225; 6,165,506; 6,221,400; 6,264,922; 6,267,989; 6,270,806; 6,316,029; 6,375,986; 6,428,814; 6,431,478; 6,432,381; 6,582,285; 6,592,903; 6,656,504; 6,742,734; 6,745,962; 6,811,767; 6,908,626; 6,969,529; 6,976,647; and 6,991,191; and U.S. Patent Publication Nos. 20020012675; 20050276974; 20050238725; 20050233001; 20050147664; 20050063913; 20050042177; 20050031691; 20050019412; 20050004049; 20040258758; 20040258757; 20040229038; 20040208833; 20040195413; 20040156895; 20040156872; 20040141925; 20040115134; 20040105889; 20040105778; 20040101566; 20040057905; 20040033267; 20040033202; 20040018242; 20040015134; 20030232796; 20030215502; 20030185869; 20030181411; 20030137067; 20030108616; 20030095928; 20030087308; 20030023203; 20020179758; 20020012675; and 20010053664. Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484; 4,826,689; 4,997,454; 5,741,522; 5,776,496.

As stated above, the effective average particle size of the particles in the nanoparticulate composition of the present invention is less than about 2000 nm (*i.e.*, 2 microns) in diameter. In embodiments of the present invention, the effective average particle size may be, for example, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm in diameter, as measured by light-scattering methods, microscopy, or other appropriate methods.

The nanoparticulate particles may exist in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi amorphous phase, or a mixture thereof.

In addition to allowing for a smaller solid dosage form size, the nanoparticulate composition of the present invention exhibits increased bioavailability, and requires smaller doses of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, as compared to prior conventional, non-nanoparticulate compositions which comprise modafinil. In one embodiment of the invention, the nanoparticulate composition of the present invention has a bioavailability that is about 50% greater than modafinil, or a salt, derivative, prodrug, or polymorph thereof, when administered in a conventional dosage form. In other embodiments, the nanoparticulate composition of the present invention has a bioavailability that is about 40% greater, about 30% greater, about 20% or about 10% greater than modafinil, or a salt, derivative, prodrug, or polymorph thereof, when administered in a conventional dosage form.

The nanoparticulate composition may also have a desirable pharmacokinetic profile as measured following the initial dosage thereof to a mammalian subject. The desirable pharmacokinetic profile of the composition includes, but is not limited to: (1) a C_{max} for modafinil, or a salt, derivative, prodrug, or polymorph thereof, when assayed in the plasma of a mammalian subject following administration that is preferably greater than the C_{max} for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition; and/or (2) an AUC for modafinil, or a salt, derivative, prodrug, or polymorph thereof, when assayed in the plasma of a mammalian subject following administration that is preferably greater than the AUC for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition; and/or (3) a T_{max} for modafinil, or a salt, derivative, prodrug, or polymorph thereof, when assayed in the plasma of a mammalian subject following administration that is preferably less than the T_{max} for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition.

In an embodiment of the present invention, a nanoparticulate composition of the present invention exhibits, for example, a T_{max} for modafinil, or a salt, derivative, prodrug, or polymorph thereof,contained therein which is not greater than about 90% of the T_{max} for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, delivered at the same dosage by a non-nanoparticulate composition. In other embodiments of the present invention, the nanoparticulate composition of the present invention may exhibit, for example, a T_{max} for modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained therein which is not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, delivered at the same dosage by a non-nanoparticulate composition. In one embodiment of the invention, the T_{max} of modafinil, or a salt, derivative, prodrug, or polymorph thereof, when assayed in the plasma of the mammalian subject is less than about 6 to about 8 hours after administration. In other embodiments of the invention, the T_{max} of modafinil, or a salt, derivative, prodrug, or polymorph thereof, is less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after administration.

In an embodiment of the present invention, a nanoparticulate composition of the present invention exhibits, for example, a C_{max} for modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained therein which is at least about 50% of the C_{max} for the same modafinil, or a salt,

derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition. In other embodiments of the present invention, the nanoparticulate composition of the present invention may exhibit, for example, a C_{max} for modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained therein which is at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition.

In an embodiment of the present invention, a nanoparticulate composition of the present invention exhibits, for example, an AUC for modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained therein which is at least about 25% greater than the AUC for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition. In other embodiments of the present invention, the nanoparticulate composition of the present invention may exhibit, for example, an AUC for modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained therein which is at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC for the same modafinil, or a salt, derivative, prodrug, or polymorph thereof, when delivered at the same dosage by a non-nanoparticulate composition.

The invention encompasses a nanoparticulate composition wherein the pharmacokinetic profile of modafinil, or a salt, derivative, prodrug, or polymorph thereof, following administration is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of modafinil, or a salt, derivative, prodrug, or polymorph thereof, absorbed or the rate of absorption when the nanoparticulate composition is administered in the fed versus the fasted state. In conventional modafinil formulations, *i.e.*, NIVADIL®, the absorption of modafinil is increased when administered with food. This difference in absorption observed with conventional modafinil formulations is undesirable. The composition of the invention overcomes this problem.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant as, with poor subject compliance, an increase in the medical condition for which the modafinil is being prescribed may be observed.

The invention encompasses also a nanoparticulate composition comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, in which administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

The difference in absorption of the composition of the invention, when administered in the fed versus the fasted state, preferably is less than about 100%, less than bout 95%, less than about 90%, less than about 85%, less than about 80%, less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

In one embodiment of the invention, the invention encompasses a composition comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, wherein the administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between about 0.80 to about 1.25 (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMEA guidelines, the 90% CI for AUC must be between about 0.80 to about 1.25 and the 90% CI for C_{max} must between about 0.70 to about 1.43.

The nanoparticulate composition of the invention is proposed to have an unexpectedly dramatic dissolution profile. Rapid dissolution of modafinil, or a salt, derivative, prodrug, or polymorph thereof, is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

The compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the modafinil, or a salt, derivative, prodrug, or polymorph

thereof, is dissolved. In other embodiments of the invention, at least about 30% or at least about 40% of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is dissolved within about 5 minutes. In yet other embodiments of the invention, preferably at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is dissolved within about 10 minutes. Finally, in another embodiment of the invention, preferably at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is dissolved within about 20 minutes.

Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; *i.e.*, the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

An additional feature of the nanoparticulate composition of the invention is that particles thereof redisperse so that the particles have an effective average particle size of less than about 2000 nm in diameter. This is significant because, if the particles did not redisperse so that they have an effective average particle size of less than about 2000 nm in diameter, the composition may lose the benefits afforded by formulating the modafinil, or a salt, derivative, prodrug, or polymorph thereof, therein into a nanoparticulate form. This is because nanoparticulate compositions benefit from the small size of the particles comprising the modafinil, or a salt, derivative, prodrug, or polymorph thereof. If the particles do not redisperse into small particle sizes upon administration, then "clumps" or agglomerated particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall well below that observed with the liquid dispersion form of the nanoparticulate composition.

In other embodiments of the invention, the redispersed particles of the invention (redispersed in water, a biorelevant media, or any other suitable liquid media) have an effective average particle size of less than about less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600

nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm in diameter, as measured by light-scattering methods, microscopy, or other appropriate methods. Such methods suitable for measuring effective average particle size are known to a person of ordinary skill in the art.

Redispersibility can be tested using any suitable means known in the art. See *e.g.*, the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

The nanoparticulate composition of the present invention exhibits dramatic redispersion of the particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media, such that the effective average particle size of the redispersed particles is less than about 2000 nm. Such biorelevant aqueous media can be any aqueous media that exhibits the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," Pharm. Res., 14 (4): 497-502 (1997). It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 N, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 N HCl or less, about 0.01 N HCl or less, about 0.001 N HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and

mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 N HCl, 0.01 N HCl, and 0.1 N HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 N HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

As stated above, the composition comprises also at least one surface stabilizer. The surface stabilizer can be adsorbed on or associated with the surface of the particles containing modafinil, or a salt, derivative, prodrug, or polymorph thereof. Preferably, the surface stabilizer adheres on, or associates with, the surface of the particles, but does not react chemically with the particles or with other surface stabilizer molecules. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The relative amounts of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, and surface stabilizer present in the composition of the present invention can vary widely. The optional amount of the individual components can depend, upon, among other things, the particular drug selected, the hydrophilic-lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer. The concentration of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined weight of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, and surface stabilizer(s), not including other excipients. The concentration of the surface stabilizer(s) can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, and surface stabilizer(s), not including other excipients.

The choice of a surface stabilizer(s) for the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is non-trivial and required extensive experimentation to realize a desirable formulation. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate compositions comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, can be made.

Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, anionic, cationic, ionic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-

methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl

ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where n>1;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethyl-chloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000).

The compositions of the invention can comprise, in addition to modafinil, or a salt, derivative, prodrug, or polymorph thereof, one or more compounds useful in treating treatment of disease states, symptoms, syndromes, or conditions of the CNS.

The composition may also be administered in conjunction with such a compound. These other active compounds preferably include those useful for treatment of bodily conditions such as headaches, fevers, soreness, and other like conditions that are generally occasioned with conditions of the CNS. Such active compounds should be present in a manner, as determined by one skilled in the art, such that they do not interfere with the therapeutic effect of modafinil, or a salt, derivative, prodrug, or polymorph thereof.

The composition of the present invention may comprise also one or more binding agents, filling agents, diluents, lubricating agents, emulsifying and suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, perfuming agents, and other excipients. Such excipients are known in the art. In addition, prevention of the growth of microorganisms can be ensured by the addition of various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. For use in injectable formulations, the composition may comprise also isotonic agents, such as sugars, sodium chloride, and the like and agents for use in delaying the absorption of the injectable pharmaceutical form, such as aluminum monostearate and gelatin.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose®

DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

The composition of the present invention may comprise also a carrier, adjuvant, or a vehicle (hereafter, collectively, "carriers").

In one method, particles comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, are dispersed in a liquid dispersion medium in which the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is poorly soluble. Mechanical means are then used in the presence of grinding media to reduce the particle size to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion medium is water. The particles can be reduced in size in the presence of at least one surface stabilizer. The particles comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode. One skilled in the art would understand that it may be the case that, following milling, not all particles may be reduced to the desired size. In such an event, the particles of the desired size may be separated and used in the practice of the present invention.

Another method of forming the desired nanoparticulate composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble modafinil, or a salt, derivative, prodrug, or polymorph thereof, in the presence of surface stabilizer(s) and one or more colloid stability-enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving modafinil, or a salt, derivative, prodrug, or polymorph thereof, in a suitable solvent; (2) adding the

formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

A nanoparticulate composition may be formed also by homogenization. Exemplary homogenization methods are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing particles comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size to the desired effective average particle size. The particles can be reduced in size in the presence of at least one surface stabilizer. The particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the composition before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

Another method of forming the desired nanoparticulate composition is by spray freezing into liquid (SFL). This technology comprises injecting an organic or organoaqueous solution of modafinil, or a salt, derivative, prodrug, or polymorph thereof, and surface stabilizer(s) into a cryogenic liquid, such as liquid nitrogen. The droplets of the drug-containing solution freeze at a rate sufficient to minimize crystallization and particle growth, thus formulating nano-structured particles. Depending on the choice of solvent system and processing conditions, the particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the particles.

As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to create equivalent nanostructured particles with greatly enhanced surface area.

URF comprises taking a water-miscible, anhydrous, organic, or organoaqueous solution of modafinil, or a salt, derivative, prodrug, or polymorph thereof, and surface stabilizer(s) and applying it onto a cryogenic substrate. The solvent is then removed by means such as lyophilization or atmospheric freeze-drying with the resulting nanostructured particles remaining.

Another method of forming the desired nanoparticulate composition is by template emulsion. Template emulsion creates nano-structured particles with controlled particle size distribution and rapid dissolution performance. The method comprises preparing an oil-in-water emulsion and then swelling it with a non-aqueous solution comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, and surface stabilizer(s). The size distribution of the particles is a direct result of the size of the emulsion droplets prior to loading of the emulsion with

the drug. The particle size can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water are removed, and the stabilized nano-structured particles are recovered. Various particle morphologies can be achieved by appropriate control of processing conditions.

The invention also provides a method comprising the administration of an effective amount of a nanoparticulate composition comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof.

The composition of the present invention can be formulated for administration parentally (*e.g.*, intravenous, intramuscular, or subcutaneous), orally (*e.g.*, in solid, liquid, or aerosol form, vaginal), nasally, rectally, ocularly, locally (*e.g.*, in powder, ointment, or drop form), buccally, intracisternally, intraperitoneally, or topically, and the like.

The nanoparticulate composition can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, depots, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.*

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Solid dosage forms for oral administration include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin,

polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to modafinil, or a salt, derivative, prodrug, or polymorph thereof, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

One of ordinary skill will appreciate that a therapeutically effective amount of modafinil, or a salt, derivative, prodrug, or polymorph thereof, can be determined empirically. Actual dosage levels of modafinil, or a salt, derivative, prodrug, or polymorph thereof, in the nanoparticulate compositions of the invention may be varied to obtain an amount of the drug that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered modafinil, or a salt, derivative, prodrug, or polymorph thereof, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of modafinil, or a salt, derivative, prodrug, or polymorph thereof, or such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the modafinil, or a salt, derivative, prodrug, or polymorph thereof; the duration of the treatment; active compound used in

combination or coincidental with modafinil, or a salt, derivative, prodrug, or polymorph thereof; and like factors well known in the medical arts.

II. Controlled Release Compositions Comprising Modafinil, or a Salt, Derivative, Prodrug, or Polymorph Thereof

The effectiveness of pharmaceutical compounds in the prevention and treatment of disease states depends on a variety of factors including the rate and duration of delivery of the compound from the dosage form to the patient. The combination of delivery rate and duration exhibited by a given dosage form in a patient can be described as its *in vivo* release profile and, depending on the pharmaceutical compound administered, will be associated with a concentration and duration of the pharmaceutical compound in the blood plasma, referred to as a plasma profile. As pharmaceutical compounds vary in their pharmacokinetic properties such as bioavailability, and rates of absorption and elimination, the release profile and the resultant plasma profile become important elements to consider in designing effective therapies.

The release profiles of dosage forms may exhibit different rates and durations of release and may be continuous or pulsatile. Continuous release profiles include release profiles in which a quantity of one or more pharmaceutical compounds is released continuously throughout the dosing interval at either a constant or variable rate. Pulsatile release profiles include release profiles in which at least two discrete quantities of one or more pharmaceutical compounds are released at different rates and/or over different time frames. For any given pharmaceutical compound or combination of such compounds, the release profile for a given dosage form gives rise to an associated plasma profile in a patient. When two or more components of a dosage form have different release profiles, the release profile of the dosage form as a whole is a combination of the individual release profiles and may be described generally as "multimodal." The release profile of a two-component dosage form in which each component has a different release profile may described as "bimodal," and the release profile of a three-component dosage form in which each component has a different release profile may described as "trimodal."

Similar to the variables applicable to the release profile, the associated plasma profile in a patient may exhibit constant or variable blood plasma concentration levels of the pharmaceutical compounds over the duration of action and may be continuous or pulsatile. Continuous plasma profiles include plasma profiles of all rates and duration which exhibit a single plasma concentration maximum. Pulsatile plasma profiles include plasma profiles in which at least two higher blood plasma concentration levels of pharmaceutical compound are separated by a lower blood plasma concentration level and may be described generally as "multimodal." Pulsatile

plasma profiles exhibiting two peaks may be described as "bimodal" and plasma profiles exhibiting three peaks may be described as "trimodal." Depending on, at least in part, the pharmacokinetics of the pharmaceutical compounds included in the dosage form as well as the release profiles of the individual components of the dosage form, a multimodal release profile may result in either a continuous or a pulsatile plasma profile upon administration to a patient.

In one embodiment, the present invention provides a multiparticulate modified release composition which delivers modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, in a pulsatile manner. The nanoparticles are of the type described above and comprise also at least one surface stabilizer.

In another embodiment, the present invention provides a multiparticulate modified release composition which delivers modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, in a continuous manner. The nanoparticles are of the type described above and comprise also at least one surface stabilizer.

In yet another embodiment, the present invention provides a multiparticulate modified release composition in which a first portion of modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, is released immediately upon administration and one or more subsequent portions of modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, are released after an initial time delay.

In yet another embodiment, the present invention provides solid oral dosage forms for once-daily or twice-daily administration comprising the multiparticulate modified release composition of the present invention.

In still another embodiment, the present invention provides a method for the prevention and/or treatment of disease states, symptoms, syndromes, and conditions of the CNS comprising the administration of a composition of the present invention.

In an embodiment, the present invention provides a multiparticulate modified release composition in which the particles forming the multiparticulate are nanoparticulate particles of the type described above. The nanoparticulate particles may, as desired, contain a modified release coating and/or a modified release matrix material.

According to one aspect of the present invention, there is provided a pharmaceutical composition having a first component comprising active ingredient-containing particles, and at least one subsequent component comprising active ingredient-containing particles, each subsequent component having a rate and/or duration of release different from the first component wherein at least one of the components comprises particles containing modafinil, or a salt, derivative, prodrug, or polymorph thereof. In an embodiment of the invention, the particles that

form the multiparticulate may themselves contain nanoparticulate particles of the type described above which comprise modafinil, or a salt, derivative, prodrug, or polymorph thereof, and also at least one surface stabilizer. In another embodiment of the invention, nanoparticulate particles of the type described above which comprise modafinil, or a salt, derivative, prodrug, or polymorph thereof, and also at least one surface stabilizer themselves are the drug-containing particles of the multiparticulate. The drug-containing particles may be coated with a modified release coating. Alternatively or additionally, the drug-containing particles may comprise a modified release matrix material. Following oral delivery, the composition delivers modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, in a pulsatile manner. In one embodiment, the first component provides an immediate release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, and the one or more subsequent components provide a modified release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same. In such embodiments, the immediate release component serves to hasten the onset of action by minimizing the time from administration to a therapeutically effective plasma concentration level, and the one or more subsequent components serve to minimize the variation in plasma concentration levels and/or maintain a therapeutically effective plasma concentration throughout the dosing interval.

The modified release coating and/or the modified release matrix material cause a lag time between the release of the active ingredient from the first population of active ingredient-containing particles and the release of the active ingredient from subsequent populations of active ingredient-containing particles. Where more than one population of active ingredient-containing particles provide a modified release, the modified release coating and/or the modified release matrix material causes a lag time between the release of the active ingredient from the different populations of active ingredient-containing particles. The duration of these lag times may be varied by altering the composition and/or the amount of the modified release coating and/or altering the composition and/or amount of modified release matrix material utilized. Thus, the duration of the lag time can be designed to mimic a desired plasma profile.

Because the plasma profile produced by the modified release composition upon administration is substantially similar to the plasma profile produced by the administration of two or more IR dosage forms given sequentially, the modified release composition of the present invention is particularly useful for administering modafinil, or a salt, derivative, prodrug, or polymorph thereof.

According to another aspect of the present invention, the composition can be designed to produce a plasma profile that minimizes or eliminates the variations in plasma concentration

levels associated with the administration of two or more IR dosage forms given sequentially. In such embodiments, the composition may be provided with an immediate release component to hasten the onset of action by minimizing the time from administration to a therapeutically effective plasma concentration level, and at least one modified release component to maintain a therapeutically effective plasma concentration level throughout the dosing interval.

The active ingredients in each component may be the same or different. For example, the composition may comprise components comprising only modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, as the active ingredient. Alternatively, the composition may comprise a first component comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, and at least one subsequent component comprising an active ingredient other than the modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, suitable for co-administration with modafinil, or a salt, derivative, prodrug, or polymorph thereof, or a first component containing an active ingredient other than modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, and at least one subsequent component comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same. Indeed, two or more active ingredients may be incorporated into the same component when the active ingredients are compatible with each other. An active ingredient present in one component of the composition may be accompanied by, for example, an enhancer compound or a sensitizer compound in another component of the composition, in order to modify the bioavailability or therapeutic effect thereof.

As used herein, the term "enhancer" refers to a compound which is capable of enhancing the absorption and/or bioavailability of an active ingredient by promoting net transport across the GIT in an animal, such as a human. Enhancers include but are not limited to medium chain fatty acids; salts, esters, ethers and derivatives thereof, including glycerides and triglycerides; non-ionic surfactants such as those that can be prepared by reacting ethylene oxide with a fatty acid, a fatty alcohol, an alkylphenol or a sorbitan or glycerol fatty acid ester; cytochrome P450 inhibitors, P-glycoprotein inhibitors and the like; and mixtures of two or more of these agents.

In those embodiments in which more than one drug-containing component is present, the proportion of modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained in each component may be the same or different depending on the desired dosing regime. The modafinil, or a salt, derivative, prodrug, or polymorph thereof, present in the first component and in subsequent components may be any amount sufficient to produce a therapeutically effective plasma concentration level. The modafinil, or a salt, derivative, prodrug, or polymorph thereof,

may be present either in the form of one substantially optically pure stereoisomer or as a mixture, racemic or otherwise, of two or more stereoisomers. In one embodiment, the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is present in the composition in an amount of from about 0.1 to about 500 mg. In another embodiment, the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is present in the composition in an amount of from about 1 to about 100 mg. In yet another embodiment, the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is present in the first component in an amount of from about 0.5 to about 60 mg. In still another embodiment, the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is present in the first component in an amount of from about 2.5 to about 30 mg. If in subsequent components, the modafinil, or a salt, derivative, prodrug, or polymorph thereof, is present in amounts within similar ranges to those described for the first component.

The time release characteristics for the delivery of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from each of the components may be varied by modifying the composition of each component, including modifying any of the excipients and/or coatings which may be present. In particular, the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, may be controlled by changing the composition and/or the amount of the modified release coating on the particles, if such a coating is present. If more than one modified release component is present, the modified release coating for each of these components may be the same or different. Similarly, when modified release is facilitated by the inclusion of a modified release matrix material, release of the active ingredient may be controlled by the choice and amount of modified release matrix material utilized. The modified release coating may be present, in each component, in any amount that is sufficient to yield the desired delay time for each particular component. The modified release coating may be present, in each component, in any amount that is sufficient to yield the desired time lag between components.

The lag time and/or time delay for the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from each component may also be varied by modifying the composition of each of the components, including modifying any excipients and coatings which may be present. For example, the first component may be an immediate release component wherein modafinil, or a salt, derivative, prodrug, or polymorph thereof, is released immediately upon administration. Alternatively, the first component may be, for example, a time-delayed immediate release component in which modafinil, or a salt, derivative, prodrug, or polymorph thereof, is released substantially in its entirety immediately after a time delay. The subsequent component may be, for example, a time-delayed immediate release component as just described or, alternatively, a time-

delayed sustained release or extended release component in which modafinil, or a salt, derivative, prodrug, or polymorph thereof, is released in a controlled fashion over an extended period of time.

As will be appreciated by those skilled in the art, the exact nature of the plasma concentration curve will be influenced by the combination of all of these factors just described. In particular, the lag time between the delivery (and thus also the onset of action) of modafinil, or a salt, derivative, prodrug, or polymorph thereof, in each component containing modafinil, or a salt, derivative, prodrug, or polymorph thereof, may be controlled by varying the composition and coating (if present) of each of the components. Thus by variation of the composition of each component (including the amount and nature of the active ingredient(s)) and by variation of the lag time, numerous release and plasma profiles may be obtained. Depending on the duration of the lag time between the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from each component and the nature of the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from each component (i.e. immediate release, sustained release etc.), the plasma profile may be continuous (i.e., having a single maximum) or pulsatile in which the peaks in the plasma profile may be well separated and clearly defined (e.g. when the lag time is long) or superimposed to a degree (e.g. when the lag time is short).

The plasma profile produced from the administration of a single dosage unit comprising the composition of the present invention is advantageous when it is desirable to deliver two or more pulses of active ingredient without the need for administration of two or more dosage units.

Any coating material which modifies the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, in the desired manner may be used. In particular, coating materials suitable for use in the practice of the present invention include but are not limited to polymer coating materials, such as cellulose acetate phthalate, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, ammonio methacrylate copolymers such as those sold under the trademark Eudragit® RS and RL, poly acrylic acid and poly acrylate and methacrylate copolymers such as those sold under the trademark Eudragit® S and L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium carmellose, sodium carboxymethyl starch, polyvinyl alcohol, hydroxyethyl cellulose, methyl cellulose, gelatin, starch, and cellulose based cross-linked polymers--in which the degree of crosslinking is low so as to facilitate adsorption of water and expansion of the polymer matrix, hydoxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, aminoacryl-methacrylate copolymer (Eudragit® RS-PM, Rohm & Haas), pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable

hydrophilic polymers) poly(hydroxyalkyl methacrylate) (mol. wt. ~5k-5,000k), polyvinylpyrrolidone (mol. wt. ~10k-360k), anionic and cationic hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (mol. wt. ~30k-300k), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, Polyox® polyethylene oxides (mol. wt. ~100k-5,000k), AquaKeep® acrylate polymers, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, sodium starch glucolate (e.g. Explotab®; Edward Mandell C. Ltd.); hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro cellulose, carboxymethyl cellulose, cellulose ethers, polyethylene oxides (e.g. Polyox®, Union Carbide), methyl ethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, collagen, starch, maltodextrin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of methacrylic acid or methacrylic acid (e.g. Eudragit®, Rohm and Haas), other acrylic acid derivatives, sorbitan esters, natural gums, lecithins, pectin, alginates, ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as arabic, karaya, locust bean, tragacanth, carrageens, guar, xanthan, scleroglucan and mixtures and blends thereof. As will be appreciated by the person skilled in the art, excipients such as plasticisers, lubricants, solvents and the like may be added to the coating. Suitable plasticisers include for example acetylated monoglycerides; butyl phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalyl ethyl glycolate; glycerin; propylene glycol; triacetin; citrate; tripropioin; diacetin; dibutyl phthalate; acetyl monoglyceride; polyethylene glycols; castor oil; triethyl citrate; polyhydric alcohols, glycerol, acetate esters, gylcerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidised tallate, triisoctyl trimellitate, diethylhexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate.

When the modified release component comprises a modified release matrix material, any suitable modified release matrix material or suitable combination of modified release matrix materials may be used. Such materials are known to those skilled in the art. The term "modified release matrix material" as used herein includes hydrophilic polymers, hydrophobic polymers and mixtures thereof which are capable of modifying the release of modafinil, or a salt, derivative,

prodrug, or polymorph thereof,, dispersed therein in vitro or in vivo. Modified release matrix materials suitable for the practice of the present invention include but are not limited to microcrystalline cellulose, sodium carboxymethylcellulose, hydoxyalkylcelluloses such as hydroxypropylmethylcellulose and hydroxypropylcellulose, polyethylene oxide, alkylcelluloses such as methylcellulose and ethylcellulose, polyethylene glycol, polyvinylpyrrolidone, cellulose acteate, cellulose acetate butyrate, cellulose acteate phthalate, cellulose acteate trimellitate, polyvinylacetate phthalate, polyalkylmethacrylates, polyvinyl acetate and mixture thereof.

A modified release composition according to the present invention may be incorporated into any suitable dosage form which facilitates release of the active ingredient in a pulsatile manner. In one embodiment, the dosage form comprises a blend of different populations of active ingredient-containing particles which make up the immediate release and the modified release components, the blend being filled into suitable capsules, such as hard or soft gelatin capsules. Alternatively, the different individual populations of active ingredient-containing particles may be compressed (optionally with additional excipients) into mini-tablets which may be subsequently filled into capsules in the appropriate proportions. Another suitable dosage form is that of a multilayer tablet. In this instance the first component of the modified release composition may be compressed into one layer, with the subsequent component being subsequently added as a subsequent layer of the multilayer tablet. The populations of the particles making up the composition of the invention may further be included in rapidly dissolving dosage forms such as an effervescent dosage form or a fast-melt dosage form.

In one embodiment, the composition comprises at least two components containing modafinil, or a salt, derivative, prodrug, or polymorph thereof: a first component and one or more subsequent components. In such embodiment, the first component of the composition may exhibit a variety of release profiles including profiles in which substantially all of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained in the first component is released rapidly upon administration of the dosage form, released rapidly but after a time delay (delayed release), or released slowly over time. In one such embodiment, the modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained in the first component is released rapidly upon administration to a patient. As used herein, "released rapidly" includes release profiles in which at least about 80% of the active ingredient of a component is released within about an hour after administration, the term "delayed release" includes release profiles in which the active ingredient of a component is released (rapidly or slowly) after a time delay, and the terms "controlled release" and "extended release" include release profiles in which at least about 80% of the active ingredient contained in a component is released slowly.

The subsequent component of such embodiment may also exhibit a variety of release profiles including an immediate release profile, a delayed release profile or a controlled release profile. In one such embodiment, the subsequent component exhibits a delayed release profile in which modafinil, or a salt, derivative, prodrug, or polymorph thereof, is released after a time delay.

The plasma profile produced by the administration of dosage forms of the present invention which comprise an immediate release component comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof,, or nanoparticles containing the same, and at least one modified release component comprising modafinil, or a salt, derivative, prodrug, or polymorph thereof,, or nanoparticles containing the same, can be substantially similar to the plasma profile produced by the administration of two or more IR dosage forms given sequentially, or to the plasma profile produced by the administration of separate IR and modified release dosage forms. Accordingly, the dosage forms of the present invention can be particularly useful for administering modafinil, or a salt, derivative, prodrug, or polymorph thereof, where the maintenance of pharmacokinetic parameters may be desired but is problematic.

In one embodiment, the composition and the solid oral dosage forms containing the composition release modafinil, or a salt, derivative, prodrug, or polymorph thereof, such that substantially all of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained in the first component is released prior to release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from the at least one subsequent component. When the first component comprises an IR component, for example, it is preferable that release of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, from the at least one subsequent component is delayed until substantially all modafinil, or a salt, derivative, prodrug, or polymorph thereof, in the IR component has been released. Release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from the at least one subsequent component may be delayed as detailed above by the use of a modified release coatings and/or a modified release matrix material.

When it is desirable to minimize patient tolerance by providing a dosage regime which facilitates wash-out of a first dose of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from a patient's system, release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from subsequent components may be delayed until substantially all of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, contained in the first component has been released, and further delayed until at least a portion of the modafinil, or a salt, derivative, prodrug, or polymorph thereof, released from the first component has been cleared from the patient's system. In one embodiment, release of the modafinil, or a salt, derivative, prodrug, or polymorph

thereof, from subsequent components of the composition is substantially, if not completely, delayed for a period of at least about two hours after administration of the composition. In another embodiment, the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, from subsequent components of the composition is substantially, if not completely, delayed for a period of at least about four hours after administration of the composition.

As described hereinbelow, the present invention also includes various types of modified release systems by which modafinil, or a salt, derivative, prodrug, or polymorph thereof, may be delivered in either a pulsatile or continuous manner. These systems include but are not limited to: films with modafinil, or a salt, derivative, prodrug, or polymorph thereof,, or nanoparticles containing the same, in a polymer matrix (monolithic devices); systems in which modafinil, or a salt, derivative, prodrug, or polymorph thereof,, or nanoparticles containing the same, is contained by a polymer (reservoir devices); polymeric colloidal particles or microencapsulates (microparticles, microspheres or nanoparticles) in the form of reservoir and matrix devices; systems in which modafinil, or a salt, derivative, prodrug, or polymorph thereof, or nanoparticles containing the same, is contained by a polymer which contains a hydrophilic and/or leachable additive e.g., a second polymer, surfactant or plasticizer, etc. to give a porous device, or a device in which the release of modafinil, or a salt, derivative, prodrug, or polymorph thereof, may be osmotically controlled (both reservoir and matrix devices); enteric coatings (ionizable and dissolve at a suitable pH); (soluble) polymers with (covalently) attached pendent molecules of modafinil, or a salt, derivative, prodrug, or polymorph thereof, and devices where release rate is controlled dynamically: e.g., the osmotic pump.

The delivery mechanism of the present invention can control the rate of release of modafinil, or a salt, derivative, prodrug, or polymorph thereof. While some mechanisms will release modafinil, or a salt, derivative, prodrug, or polymorph thereof, at a constant rate, others will vary as a function of time depending on factors such as changing concentration gradients or additive leaching leading to porosity, etc.

Polymers used in sustained release coatings are necessarily biocompatible, and ideally biodegradable. Examples of both naturally occurring polymers such as Aquacoat® (FMC Corporation, Food & Pharmaceutical Products Division, Philadelphia, USA) (ethylcellulose mechanically spheronised to sub-micron sized, aqueous based, pseudo-latex dispersions), and also synthetic polymers such as the Eudragit® (Röhm Pharma, Weiterstadt.) range of poly(acrylate, methacrylate) copolymers are known in the art.

Reservoir Devices

A typical approach to modified release is to encapsulate or contain the drug entirely (*e.g.*, as a core), within a polymer film or coat (*i.e.*, microcapsules or spray/pan coated cores).

The various factors that can affect the diffusion process may readily be applied to reservoir devices (e.g., the effects of additives, polymer functionality (and, hence, sink-solution pH) porosity, film casting conditions, etc.) and, hence, the choice of polymer must be an important consideration in the development of reservoir devices. Modeling the release characteristics of reservoir devices (and monolithic devices) in which the transport of modafinil, or a salt, derivative, prodrug, or polymorph thereof, is by a solution-diffusion mechanism therefore typically involves a solution to Fick's second law (unsteady-state conditions; concentration dependent flux) for the relevant boundary conditions. When the device contains dissolved active agent, the rate of release decreases exponentially with time as the concentration (activity) of the agent (i.e., the driving force for release) within the device decreases (*i.e.*, first order release). If, however, the active agent is in a saturated suspension, then the driving force for release is kept constant until the device is no longer saturated. Alternatively the release-rate kinetics may be desorption controlled, and a function of the square root of time.

Transport properties of coated tablets, may be enhanced compared to free-polymer films, due to the enclosed nature of the tablet core (permeant) which may enable the internal build-up of an osmotic pressure which will then act to force the permeant out of the tablet.

The effect of de-ionized water on salt containing tablets coated in poly(ethylene glycol) (PEG)-containing silicone elastomer, and also the effects of water on free films has been investigated. The release of salt from the tablets was found to be a mixture of diffusion through water filled pores, formed by hydration of the coating, and osmotic pumping. KCl transport through films containing just 10% PEG was negligible, despite extensive swelling observed in similar free films, indicating that porosity was necessary for the release of the KCl which then occurred by trans-pore diffusion. Coated salt tablets, shaped as disks, were found to swell in de-ionized water and change shape to an oblate spheroid as a result of the build-up of internal hydrostatic pressure: the change in shape providing a means to measure the force generated. As might be expected, the osmotic force decreased with increasing levels of PEG content. The lower PEG levels allowed water to be imbibed through the hydrated polymer, while the porosity resulting from the coating dissolving at higher levels of PEG content (20 to 40%) allow the pressure to be relieved by the flow of KCl.

Methods and equations have been developed, which by monitoring (independently) the release of two different salts (e.g., KCl and NaCl) allowed the calculation of the relative magnitudes that both osmotic pumping and trans-pore diffusion contributed to the release of salt

from the tablet. At low PEG levels, osmotic flow was increased to a greater extent than was trans-pore diffusion due to the generation of only a low pore number density: at a loading of 20%, both mechanisms contributed approximately equally to the release. The build-up of hydrostatic pressure, however, decreased the osmotic inflow, and osmotic pumping. At higher loadings of PEG, the hydrated film was more porous and less resistant to outflow of salt. Hence, although the osmotic pumping increased (compared to the lower loading), trans-pore diffusion was the dominant release mechanism. An osmotic release mechanism has also been reported for microcapsules containing a water soluble core.

Monolithic Devices (Matrix Devices)

Monolithic (matrix) devices may be used for controlling the release of a drug. This is possibly because they are relatively easy to fabricate compared to reservoir devices, and the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device is not present. In such a device, the active agent is present as a dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrixes, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug (0 to 5% W/V), the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% W/V), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug.

It is common to add a plasticizer (e.g., a poly(ethylene glycol)), a surfactant, or adjuvant (i.e., an ingredient which increases effectiveness), to matrix devices (and reservoir devices) as a means to enhance the permeability (although, in contrast, plasticizers may be fugitive, and simply serve to aid film formation and, hence, decrease permeability - a property normally more desirable in polymer paint coatings). It was noted that the leaching of PEG increased the permeability of (ethyl cellulose) films linearly as a function of PEG loading by increasing the porosity, however, the films retained their barrier properties, not permitting the transport of electrolyte. It was deduced that the enhancement of their permeability was as a result of the effective decrease in thickness caused by the PEG leaching. This was evidenced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a

PEG loading of 50% W/W: plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis: the magnitude of which decreased towards zero with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusional flows during the early stages of the experiment (the flow of the drug and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up. Caffeine, when used as a permeant, showed negative lag times. No explanation of this was forthcoming, but it was noted that caffeine exhibited a low partition coefficient in the system, and that this was also a feature of aniline permeation through polyethylene films which showed a similar negative time lag.

The effects of added surfactants on (hydrophobic) matrix devices has been investigated. It was thought that surfactant may increase the release rate of a drug by three possible mechanisms: (i) increased solubilization, (ii) improved 'wettability' to the dissolution media, and (iii) pore formation as a result of surfactant leaching. For the system studied (Eudragit® RL 100 and RS 100 plasticized by sorbitol, flurbiprofen as the drug, and a range of surfactants) it was concluded that improved wetting of the tablet led to only a partial improvement in drug release (implying that the release was diffusion, rather than dissolution, controlled), although the effect was greater for Eudragit® RS than Eudragit® RL, while the greatest influence on release was by those surfactants that were more soluble due to the formation of disruptions in the matrix allowing the dissolution medium access to within the matrix. This is of obvious relevance to a study of latex films which might be suitable for pharmaceutical coatings, due to the ease with which a polymer latex may be prepared with surfactant as opposed to surfactant-free. Differences were found between the two polymers with only the Eudragit® RS showing interactions between the anionic/cationic surfactant and drug. This was ascribed to the differing levels of quaternary ammonium ions on the polymer.

Composite devices consisting of a polymer/drug matrix coated in a polymer containing no drug also exist. Such a device was constructed from aqueous Eudragit® lattices, and was found to provide a continuous release by diffusion of the drug from the core through the shell. Similarly, a polymer core containing the drug has been produced and coated with a shell that was eroded by gastric fluid. The rate of release of the drug was found to be relatively linear (a function of the rate limiting diffusion process through the shell) and inversely proportional to the shell thickness, whereas the release from the core alone was found to decrease with time.

Microspheres

Methods for the preparation of hollow microspheres have been described. Hollow microspheres were formed by preparing a solution of ethanol/dichloromethane containing the drug and polymer. On pouring into water, an emulsion is formed containing the dispersed polymer/drug/solvent particles, by a coacervation-type process from which the ethanol rapidly diffused precipitating polymer at the surface of the droplet to give a hard-shelled particle enclosing the drug dissolved in the dichloromethane. A gas phase of dichloromethane was then generated within the particle which, after diffusing through the shell, was observed to bubble to the surface of the aqueous phase. The hollow sphere, at reduced pressure, then filled with water which could be removed by a period of drying. No drug was found in the water. Highly porous matrix-type microspheres have also been described. The matrix-type microspheres were prepared by dissolving the drug and polymer in ethanol. On addition to water, the ethanol diffused from the emulsion droplets to leave a highly porous particle. A suggested use of the microspheres was as floating drug delivery devices for use in the stomach.

Pendent devices

A means of attaching a range of drugs such as analgesics and antidepressants, etc., by means of an ester linkage to poly(acrylate) ester latex particles prepared by aqueous emulsion polymerization has been developed. These lattices, when passed through an ion exchange resin such that the polymer end groups were converted to their strong acid form, could self-catalyze the release of the drug by hydrolysis of the ester link.

Drugs have been attached to polymers, and also monomers have been synthesized with a pendent drug attached. Dosage forms have been prepared in which the drug is bound to a biocompatible polymer by a labile chemical bond e.g., polyanhydrides prepared from a substituted anhydride (itself prepared by reacting an acid chloride with the drug: methacryloyl chloride and the sodium salt of methoxy benzoic acid) were used to form a matrix with a second polymer (Eudragit® RL) which released the drug on hydrolysis in gastric fluid. The use of polymeric Schiff bases suitable for use as carriers of pharmaceutical amines has also been described.

Enteric films

Enteric coatings consist of pH sensitive polymers. Typically the polymers are carboxylated and interact very little with water at low pH, while at high pH the polymers ionize

causing swelling or dissolving of the polymer. Coatings can therefore be designed to remain intact in the acidic environment of the stomach, protecting either the drug from this environment or the stomach from the drug, but to dissolve in the more alkaline environment of the intestine.

Osmotically controlled devices

The osmotic pump is similar to a reservoir device but contains an osmotic agent (e.g., the active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane. Such a device, called an elementary osmotic pump, has been described. Pressure is generated within the device which forces the active agent out of the device via an orifice of a size designed to minimize solute diffusion, while preventing the build-up of a hydrostatic pressure head which can have the effect of decreasing the osmotic pressure and changing the dimensions of the device. While the internal volume of the device remains constant, and there is an excess of solid or saturated solution in the device, then the release rate remains constant delivering a volume equal to the volume of solvent uptake.

Electrically stimulated release devices

Monolithic devices have been prepared using polyelectrolyte gels which swell when, for example, an external electrical stimulus is applied causing a change in pH. The release may be modulated by changes in the applied current to produce a constant or pulsatile release profile.

Hydrogels

In addition to their use in drug matrices, hydrogels find use in a number of biomedical applications such as, for example, soft contact lenses, and various soft implants, and the like.

Methods of Using Modified Release Compositions Comprising Modafinil

According to another aspect of the present invention, there is provided a method for treating a patient suffering from disease states, symptoms, syndromes, and conditions of the CNS comprising the step of administering a therapeutically effective amount of the composition of the present invention in solid oral dosage form. Advantages of the method of the present invention include a reduction in the dosing frequency required by conventional multiple IR dosage regimes while still maintaining the benefits derived from a pulsatile plasma profile or eliminating or minimizing the variations in plasma concentration levels. This reduced dosing frequency is advantageous in terms of patient compliance and the reduction in dosage frequency made

possible by the method of the present invention would contribute to controlling health care costs by reducing the amount of time spent by health care workers on the administration of modafinil.

In the following examples, all percentages are weight by weight unless otherwise stated. The term "purified water" as used throughout the Examples refers to water that has been purified by passing it through a water filtration system. It is to be understood that the examples are for illustrative purposes only, and should not be interpreted as restricting the spirit and breadth of the invention as defined by the scope of the claims that follow.

Several exemplary nanoparticulate modafinil tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather to provide exemplary tablet formulations of nanoparticulate modafinil that can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

Formulation #1

Exemplary Nanoparticulate Modafinil Tablet Formulation #1	
Component	g/Kg
Nanoparticulate Modafinil	about 40 to about 500
Hypromellose, USP	about 10 to about 70
Docusate Sodium, USP	about 1 to about 10
Sucrose, NF	about 100 to about 500
Sodium Lauryl Sulfate, NF	about 1 to about 40
Lactose Monohydrate, NF	about 50 to about 400
Silicified Microcrystalline Cellulose	about 50 to about 300
Crospovidone, NF	about 20 to about 300
Magnesium Stearate, NF	about 0.5 to about 5

Formulation #2

Exemplary Nanoparticulate Modafinil Tablet Formulation #2	
Component	g/Kg
Nanoparticulate Modafinil	about 100 to about 300
Hypromellose, USP	about 30 to about 50
Docusate Sodium, USP	about 0.5 to about 10

Sucrose, NF	about 100 to about 300
Sodium Lauryl Sulfate, NF	about 1 to about 30
Lactose Monohydrate, NF	about 100 to about 300
Silicified Microcrystalline Cellulose	about 50 to about 200
Crospovidone, NF	about 50 to about 200
Magnesium Stearate, NF	about 0.5 to about 5

Formulation #3

Exemplary Nanoparticulate Modafinil Tablet Formulation #3	
Component	G/Kg
Nanoparticulate Modafinil	About 200 to about 225
Hypromellose, USP	About 42 to about 46
Docusate Sodium, USP	About 2 to about 6
Sucrose, NF	About 200 to about 225
Sodium Lauryl Sulfate, NF	About 12 to about 18
Lactose Monohydrate, NF	About 200 to about 205
Silicified Microcrystalline Cellulose	About 130 to about 135
Crospovidone, NF	About 112 to about 118
Magnesium Stearate, NF	About 0.5 to about 3

5

Formulation #4

Exemplary Nanoparticulate Modafinil Tablet Formulation #4	
Component	g/Kg
Nanoparticulate Modafinil	about 119 to about 224
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 119 to about 224
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 119 to about 224

Silicified Microcrystalline Cellulose	about 129 to about 134
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

The invention provides a method of increasing bioavailability of a modafinil, or a salt, or an enantiomer, or a prodrug, or a polymorph, or derivative thereof, in a subject. Such a method comprises orally administering or injecting intravenously to a subject an effective amount of a composition comprising a nanoparticulate modafinil. The nanoparticulate modafinil composition, in accordance with standard pharmacokinetic practice, would typically have a bioavailability that is about 50% greater than a conventional dosage form, about 40% greater, about 30% greater, about 20% or about 10% greater.

The compositions of the invention are useful in the treatment of nervous system conditions, or diseases, or syndromes, or their symptoms. The invention relates to nanoparticulate modafinil, its enantiomers such as armodafinil (the single r-isomer of modafinil), polymorphs, and adrafinil pharmaceutical compositions, hereafter referred to as modafinil compositions.

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present inventions without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modification and variations of the invention provided they come within the scope of the appended claims and their equivalents.

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. Patent, are specifically incorporated by reference.

Example 1

This example demonstrates the preparation of compositions comprising nanoparticulate modafinil compositions, or a salt, or an enantiomer, or a prodrug, or a polymorph, or derivative thereof.

Four different formulations with multiple samples, detailed in Table 1, Column 3, were synthesized and evaluated. The first formulation (1) comprising modafinil was milled in the 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see *e.g.*, U.S, Patent No. 6,431,478) along with 500 micron PolyMill® attrition media (Dow Chemical Co.), at a media

load of about 89%. The Formulation Number 1 was milled at a speed of 2500 RPM for 60 minutes. Formulations 2-4 comprising modafinil were milled in the 50 ml chamber with 'smooth agitator' of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see *e.g.*, U.S, Patent No. 6,431,478) along with 500 micron PolyMill® attrition media (Dow Chemical Co.), at a media load of about 89%. The Formulation Numbers 2-4 were milled at a speed of 1600 RPM for 120 minutes.

Following milling, the modafinil particles were evaluated using a Lecia DM5000B microscope and Lecia CTR 5000 light source (Laboratory Instruments & Suppiles (I) Ltd. Ashbourne CO Meath ROI). Observations are presented in Table 1, Column 4. Successful formulations, as determined by microscopy observation, are noted in Column 5. Additionally or alternatively, the particle size of the milled modafinil particles may be measured, using deionized, distilled water and a particle size analyzer, such as a Horbia LA910 particle size analyzer. After particle size analysis, a "successful composition," may define formulations in which the initial mean and/or D50 milled modafinil particle size is less than about 2000 nm. Particles may additionally be analyzed before and after a 60 second sonication.

TABLE 1

Formulation Number	Number of Samples	Formulation	Microscopy observation	Figure	Successful formulation
1	2	Modafinil, 5%w/w; Hydroxypropyl methylcellulose, 1.25%w/w; Docusate Sodium, 0.05%w/w; and Deionized Water, 93.7%w/w	There were no signs of flocculation or crystal growth. Brownian motion was evident and nano-particulates were present along with a number of unmilled drug crystals. The sample was difficult to photograph due to a large depth of view.	1, 2	YES
2	1	Modafinil, 10%w/w; Plasdone S-630 (Povidone), 2.5%w/w; Docusate Sodium, 0.1%w/w; and Deionized Water, 87.4%w/w	Brownian motion was present with nanoparticulates clearly visible, no gellation or flocculation was present.	3	YES
3	2	Modafinil, 10%w/w; Hydroxypropyl	The sample for the microscopy shows that nanoparticulates are present.	4,5	YES

		cellulose - super low viscosity (HPC-SL), 2.5%w/w; Docusate Sodium, 0.1%w/w; and Deionized Water, 87.4%w/w	Brownian motion is also visible with no signs of flocculation or gelation.		
4	2	Modafinil, 10%w/w; Plasdone K29-32 (Povidone), 2.5%w/w; Sodium Lauryl Sulphate, 0.1%w/w; and Deionized Water, 87.4%w/w	The sample for the microscopy shows that nanoparticulates are present. Brownian motion is also visible with no signs of flocculation or gelation taken place.	6,7	YES

In the accompanying figures, the nanoparticulates of the invention appear as grey or black spots distributed across the field of view, while the larger bright (white) shapes which can be seen in some of the micrographs are what appear to be partially unmilled drug particles.

The following mixture was milled under the same conditions as Formula 1 above (attrition media PolyMill 500, 89% media load): Modafinil 10%w/w; Pharmacoat 603 (HPMC) 2%w/w; docusate sodium; 0.1%w/w; deionised water 87.9%w/w. Particle size analysis of the resulting composition was carried out on a Horbia LA910 particle size analyzer. Particle size data pre and post sonication is set out in Table 2A.

TABLE 2A

Sizing parameter	Value without sonication (nm)	Value following 60 sec sonication (nm)
Mean	207	228
D50	200	219
D90	273	295
D95	300	329
Median	200	219
Mode	206	212

Four additional formulations, detailed in Table 2B, are synthesized and evaluated. The first formulation (5) comprising is milled in the 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see *e.g.*, U.S, Patent No. 6,431,478) along with 500 micron

PolyMill® attrition media (Dow Chemical Co.), at a media load of about 89%. The Formulation Number 5 is milled at a speed of 2500 RPM for 60 minutes. Formulations 6-8 are milled in the 50 ml chamber with 'smooth agitator' of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see *e.g.*, U.S, Patent No. 6,431,478) along with 500 micron PolyMill® attrition media (Dow Chemical Co.), at a media load of about 89%. The Formulation Numbers 6-8 are milled at a speed of 1600 RPM for 120 minutes.

Following milling, the modafinil particles are evaluated using a Lecia DM5000B microscope and Lecia CTR 5000 light source (Laboratory Instruments & Suppiles (I) Ltd. Ashbourne CO Meath ROI). Additionally or alternatively, the particle size of the milled modafinil particles may be measured, using deionized, distilled water and a particle size analyzer, such as a Horbia LA910 particle size analyzer. After particle size analysis, a "successful composition," may define formulations in which the initial mean and/or D50 milled modafinil particle size is less than about 2000 nm. Particles may additionally be analyzed before and after a 60 second sonication.

TABLE 2B

Formulation Number	Formulation
5	Nanoparticle Modafinil, 3.5%w/w; Coarse Modafinil (>240 microns), 1.2%w/w; Hydroxypropyl methylcellulose, 1.25%w/w; Docusate Sodium, 0.05%w/w; and Deionized Water, 94.0%w/w
6	Nanoparticle Modafinil, 3.5%w/w; Coarse Modafinil (>240 microns), 1.2%w/w; Plasdone S-630 (Povidone), 2.5%w/w; Docusate Sodium, 0.1%w/w; and Deionized Water, 92.7%w/w
7	Nanoparticle Modafinil, 3.5%w/w; Coarse Modafinil (>240 microns), 1.2%w/w; Hydroxypropyl cellulose - super low viscosity (HPC-SL), 2.5%w/w; Docusate Sodium, 0.1%w/w; and Deionized Water, 92.7%w/w
8	Nanoparticle Modafinil, 3.5%w/w; Coarse Modafinil (>240 microns), 1.2%w/w; Plasdone K29-32 (Povidone), 2.5%w/w; Sodium Lauryl Sulphate, 0.1%w/w; and

	Deionized Water, 92.7%w/w

Example 2

A 100 mg/ml modafinil dispersion was prepared according to the following formulation:

TABLE 3

Component	*Amount (% w/w)*
*Modafinil**	*10.09*
Pharmacoat 603 (HPMC)	*3.98*
Docusate sodium	*0.02*
Deionised water	*85.91*

* amount of active ingredient adjusted for purity to achieve 100 mg/ml

The equipment used was as per Example 1, the process conditions being mill speed of 2400rpm, for a total mill time of 90min.

Particle size analysis – Stability

$T_{\#}$ = particle size measured after # days after preparation of dispersion, i.e. T_1 = particle size measurements taken after 1 day, etc; T_0 = particle size as measured on the day of manufacture. All particle size figures are in nm. Sonication: sample sonicated for 60sec prior to particle amalysis yes (Y) / no (N). Conditions: S_1 = 5°C; S_2 = 25°C and 60% relative humidity; and S_3 = 40°C and 75% relative humidity.

TABLE 4

	Conditions	Mean	D50	D90	D95	Mode	Median	Sonication
T_0	Ambient	214	202	292	333	207	202	N
		228	216	309	350	211	215	Y
T_1	S_1	241	227	323	368	214	227	N

		268	259	364	403	272	259	Y
	S_2	245	230	326	375	215	230	N
		271	261	371	415	273	261	Y
	S_3	237	208	334	414	209	208	N
		291	265	391	464	273	265	Y
T_3	S_1	201	194	262	291	187	194	N
		204	198	260	288	188	198	Y
	S_2	230	215	312	361	210	215	N
		246	231	331	382	215	231	Y
	S_3		209	386		208	209	N
			261	469		254	261	Y
T_7	S_1	232	216	313	360	211	216	N
		214	198	304	358	186	195	Y
	S_2	252	231	341	410	215	231	N
		390	208	357	578	208	208	Y
	S_3							N
								Y
T_{14}	S_1	226	209	326	386	209	209	N
		272	263	373	417	273	263	Y
	S_2	563	213	406	2831	209	213	N
		841	269	1053	5453	246	269	Y
	S_3	2035	286	7725	10775	246	286	N
		2353	316	8276	10724	275	316	Y
T_{23}	S_1	225	204	324	386	206	204	N
		227	265	380	430	274	265	Y
	S_2	1098	267	3121	7443	245	267	N
		1445	292	5435	8801	276	292	Y
	S_3	4629	336	12153	21518	276	336	N
		3834	361	11393	15509	278	381	Y

Example 3

The purpose of this example is to determine the pharmacokinetics of modafinil when administered orally as 200 mg NanoCrystalTM dispersions and as 200 mg Provigil® to fasted male beagle dogs.

This study was a single dose two way crossover study conducted in 6 beagle dogs. There was at least a 7 day washout between each treatment period. The test formulation was modafinil Nanocrystal® (100 mg/g) (10%w/w) NCD (Batch No: TESR-1148-009). The reference formulation was modafinil tablets (Provigil®) (Batch No: BN 5E39).

Blood samples were collected before dosing and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), 45 minutes (±5 minutes), 1 hour (±5 minutes), 1.25 hours (±5 minutes), 1.5 (±5 minutes), 1.75 hours (±5 minutes), 2 hours (±5 minutes), 3 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes) and 12 hours (±10 minutes) after dosing. On Study Day 0, following an overnight fast (14-18 hrs), each animal received 200mg modafinil administered as 2g NanoCrystalTM dispersion by oral gavage. On Study Day 8, following an overnight fast (14-18 hrs), each animal received 200 mg modafinil administered as Provigil tablets by oral administration.

Modafinil was measured in dog plasma samples by a validated LC MS/MS method incorporating a liquid-liquid extraction method by BioClin Research Laboratories. The limit of quantitation of the modafinil plasma assay was 100ng/mL (assay range 100-5000ng/mL).

The pharmacokinetic evaluation was conducted by PK Pharma Innovations Limited. The pharmacokinetic parameters were calculated using WinNonlin™, Version 4.0.1 (Pharsight Corporation, USA).

The following pharmacokinetic parameters were derived from the plasma concentrations versus time data for modafinil, using non-compartmental methodology:-

- AUC_{inf} ($AUC_{0-\infty}$) - Area under the curve from time of dosing extrapolated to infinity as AUC_{0-t} + C_{last}/ lambda z, where AUC_{0-t} is the area under the curve from time of dosing to the last evaluable concentration, C_{last} is the last evaluable plasma concentration and lambda z is the elimination rate constant associated with the terminal portion of the curve.
- AUC_{last} (AUC_{0-t}) - Area under the curve from the time of dosing to the time of the last quantifiable concentration calculated using the linear trapezoidal rule where AUC (t_1-t_2) = $\delta t * (c_2+c_1)/2$.
- Maximum plasma concentration (C_{max}) and its corresponding time (t_{max}) were recorded from the observed plasma concentration-time profiles.
- Relative bioavailability of the test treatment (Trt A) to the reference (Trt B) based on AUC (test/reference and expressed as a percentage).
- Half Life ($t_{1/2}$) was calculated as ln2/ Lambda z.

– Lambda z (K_{el}) - First order rate constant associated with the terminal (log-linear) portion of the curve estimated via linear regression of time vs. log concentration. For each regression analysis, an adjusted r^2 was computed as follows: Adjusted $r^2 = 1 - ((1-r^2)*(n-1)) / (n-2)$, where r^2 is the square of the correlation coefficient and n is the number of points used in the regression. Linear regression analyses of time versus log plasma concentration was conducted using a manual iterative procedure including increasing numbers of samples from the last three quantifiable plasma concentrations up to and including C_{max}. The regression with the largest adjusted r^2 was selected to estimate lambda z as -1 times the estimated slope of the regression line.

As there were no significant deviations from the amount of modafinil administered in each of the administrations or the actual sampling times at which blood draws were obtained, pharmacokinetic analysis was based on nominal amounts administered and nominal sampling times.

The data was summarized using descriptive statistics. Arithmetic means, standard deviations, and coefficients of variation were calculated for the pharmacokinetics parameters listed. For each parameter, the median, minimum and maximum values were presented. No formal statistical analysis was performed.

The mean, treatment and individual subject concentrations versus time profiles were also prepared. All graphs were prepared using WinNonlin and are presented on their normal scales.

A full listing of modafinil plasma pharmacokinetic parameters and graphical displays are presented in the report appendices. The mean plasma pharmacokinetic parameters are presented in Table 5 below (mean ± standard deviation and CV% values presented) with the mean pharmacokinetic profile illustrated in Figure 8.

TABLE 5

PK Parameters **(Mean ± SD – CV%)**	**Trt 1** **200mg Modafinil Nanocrystal®** **(100 mg/g) (10% w/w) NCD†** **dosed by oral gavage** ***n*6**	**Trt 2** **200mg Provigil® tablets** **dosed by oral administration** ***n*6**
Relative Bioavailability (%) CV% (Based on AUC_{inf})	128.649±47.123* 36.6	-
Relative Bioavailability (%) CV% Based on AUC_{last}	134.626±38.630 28.7	-

Relative Cmax (%) CV%	140.306±73.964 52.7	-
AUCinf (ug/mL·h) CV%	37.095±11.075 29.9	28.867±9.150* 31.7
AUC_{last} (ug/mL·h) CV%	35.821±11.328 31.6	27.494±8.533 31.0
Cmax (ug/mL) CV%	8.650±2.245 25.9	7.411±3.534 47.7
Tmax (h) CV% Median Range	1.917±0.719 37.5 2.00 0.75-3.00	2.167±0.665 30.7 1.88 1.50-3.00
Thalf (h) CV%	1.616±0.483 29.9	1.933±0.709* 36.7

†Dosed as 2g NCD

*n5

The treatments administered in this study were as follows:

Trt 1 - 200mg Modafinil Nanocrystal® (100 mg/g) (10%w/w) NCD† dosed by oral gavage (administered as 2g of NCD) (test)

Trt 2 – 200mg Provigil® tablets dosed by oral administration (reference)

Plasma samples were collected prior to dosing, and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), 45 minutes (±5 minutes), 1 hour (±5 minutes), 1.25 hours (±5 minutes), 1.5 (±5 minutes), 1.75 hours (±5 minutes), 2 hours (±5 minutes), 3 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes) and 12 hours (±10 minutes) post-dosing.

Modafinil was measured in dog plasma samples by a validated LC MS/MS method incorporating a liquid - liquid extraction method. The limit of quantitation of the modafinil plasma assay was 100ng/mL (assay range 100-5000ng/mL).

The relative bioavailability and the relative Cmax of the test, NCD dispersion was 129±47% and 140±74% compared to that of the reference, Provigil tablet respectively. The extent of absorption as determined by AUC was 35.8±11.3ug/mL.h and 27.5±8.5ug/mL.h following administration of the NCD dispersion and the Provigil tablets respectively. The maximum concentration determined was 8.7±2.2ug/mL and 7.4±3.5ug/mL following administration of the NCD dispersion and the Provigil tablets respectively.

The median time to reach peak concentration was approximately 2h following administration of both the test and reference formulations.

In conclusion, the oral gavage administration of 200mg Modafinil Nanocrystal (100 mg/g) (10%w/w) NCD resulted in a mean 29% increase in the extent and a mean 40% increase in the rate of absorption of modafinil compared with the oral administration of 200mg Modafinil in the form of Provigil tablets.

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present inventions without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modification and variations of the inventions provided they come within the scope of the appended claims and their equivalents.

The terms and expressions which have been employed are used as terms of descriptions and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been illustrated by specific embodiments and optional features, modification and/or variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope on this invention.

In addition, where features or aspects of the invention are described in terms of Markush group or other grouping of alternatives, those skilled in the art will recognized that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

All references, patents, and/or applications cited in the specification are incorporated by references in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by the reference in its entirety individually.

WHAT IS CLAIMED IS:

1. A stable nanoparticulate composition comprising: (A) particles comprising modfinil, or a salt, derivative, prodrug, or polymorph thereof, said particles having an effective average particle size of less than about 2000 nm in diameter; and (B) at least one surface stabilizer.

2. The composition of claim 1, wherein said particles are in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi amorphous phase, or a mixture thereof.

3. The composition of claim 1 further comprising one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

4. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

5. The composition of claim 1, wherein the composition comprises:

(a) about 40 to about 500 g/kg modfinil;
(b) about 10 to about 70 g/kg hypromellose;
(c) about 1 to about 10 g/kg docusate sodium;
(d) about 100 to about 500 g/kg sucrose;
(e) about 1 to about 40 g/kg sodium lauryl sulfate;
(f) about 50 to about 400 g/kg lactose monohydrate;
(g) about 50 to about 300 g/kg silicified microcrystalline cellulose;
(h) about 20 to about 300 g/kg crospovidone; and
(i) about 0.5 to about 5 g/kg magnesium stearate.

6. The composition of claim 5, further comprising a coating agent.

7. The composition of claim 1, wherein the composition comprises:

(a) about 100 to about 300 g/kg modfinil;
(b) about 30 to about 50 g/kg hypromellose;
(c) about 0.5 to about 10 g/kg docusate sodium;
(d) about 100 to about 300 g/kg sucrose;
(e) about 1 to about 30 g/kg sodium lauryl sulfate;
(f) about 100 to about 300 g/kg lactose monohydrate;

(g) about 50 to about 200 g/kg silicified microcrystalline cellulose;

(h) about 50 to about 200 g/kg crospovidone; and

(i) about 0.5 to about 5 g/kg magnesium stearate.

8. The composition of claim 7, further comprising a coating agent.

9. The composition of claim 1, wherein the composition comprises:

(a) about 200 to about 225 g/kg modfinil;

(b) about 42 to about 46 g/kg hypromellose;

(c) about 2 to about 6 g/kg docusate sodium;

(d) about 200 to about 225 g/kg sucrose;

(e) about 12 to about 18 g/kg sodium lauryl sulfate;

(f) about 200 to about 205 g/kg lactose monohydrate;

(g) about 130 to about 135 g/kg silicified microcrystalline cellulose;

(h) about 112 to about 118 g/kg crospovidone; and

(i) about 0.5 to about 3 g/kg magnesium stearate.

10. The composition of claim 9, further comprising a coating agent.

11. The composition of claim 1, wherein the composition comprises:

(a) about 119 to about 224 g/kg modfinil;

(b) about 42 to about 46 g/kg hypromellose;

(c) about 2 to about 6 g/kg docusate sodium;

(d) about 119 to about 224 g/kg sucrose;

(e) about 12 to about 18 g/kg sodium lauryl sulfate;

(f) about 119 to about 224 g/kg lactose monohydrate;

(g) about 129 to about 134 g/kg silicified microcrystalline cellulose;

(h) about 112 to about 118 g/kg crospovidone; and

(i) about 0.5 to about 3 g/kg magnesium stearate.

12. The composition of claim 11, further comprising a coating agent.

13. The composition of claim 1, additionally comprising one or more active compounds useful for the prevention and treatment of disease states, symptoms, syndromes, and conditions of the central nervous system (CNS).

14. The composition of claim 1 wherein said particles contain a reservoir which contains modfinil, or a salt, derivative, prodrug, or polymorph thereof, said reservoir being enclosed by a semi-permeable membrane which allows for water to be imbibed into said particles, thus generating pressure which forces said modfinil, or a salt, derivative, prodrug, or polymorph thereof, out of said particles.

15. The composition of claim 14 wherein said reservoir further comprises an osmotic agent.

16. A method of preparing the composition of claim 1 comprising contacting particles comprising said modfinil, or a salt, derivative, prodrug, or polymorph thereof, with at least one surface stabilizer for a period of time and under conditions sufficient to provide a nanoparticulate composition comprising modfinil, or a salt, derivative, prodrug, or polymorph thereof, having an effective average particle size of less than about 2000 nm in diameter.

17. Use of a composition according to claim 1 in the manufacture of a medicament for preventing and/or treating disease states, symptoms, syndromes, and conditions of the central nervous system (CNS).

18. A pharmaceutical composition comprising a first component of active ingredient-containing particles and at least one subsequent component of active ingredient-containing particles, wherein at least one of said components comprises particles wherein modfinil, or a salt, derivative, prodrug, or polymorph thereof, is the active ingredient and at least one of said components further comprises a modified release coating, a modified release matrix material, or both, such that the composition, following oral delivery to a subject, delivers the active ingredient in a continuous, bimodal or multimodal manner, and wherein at least a population of said modafinil containing particles are nanoparticles having an effective average particle size of less than 2000 nm in diameter and at least one surface stabilizer.

19. The composition of claim 18 wherein each component comprises particles in which modafinil, or a salt, derivative, prodrug, or polymorph thereof, is the active ingredient.

20. The composition of claim 18, wherein the first component comprises an immediate release component and at least one subsequent component comprises a modified release component.

21. The composition of claim 18, wherein the active ingredient-containing particles are erodable.

22. The composition of claim 18 wherein said composition further comprises an enhancer.

23. A dosage form comprising the composition of claim 14.

24. The dosage form of claim 23 comprising a blend of active ingredient-containing particles contained within a hard gelatin or soft gelatin capsule.

25. The dosage form of claim 23, wherein the active ingredient-containing particles are in the form of mini-tablets and the capsule contains a mixture of said mini-tablets.

26. The dosage form of claim 23 in the form of tablet.

27. The dosage form of claim 23 wherein the particles containing modafinil, or a salt, derivative, prodrug, or polymorph thereof, are provided in a rapidly dissolving dosage form.

28. The dosage form of claim 26 wherein the tablet is a fast-melt tablet.

29. Use of a therapeutically effective amount of the composition of claim 18 in the manufacture of a medicament for preventing and/or treating disease states, symptoms, syndromes, and conditions of the central nervous system (CNS).

30. The composition of claim 18 wherein the modified-release coating comprises a pH-dependent polymer coating for releasing a pulse of the active ingredient in said patient following a time delay of about 6 to about 12 hours after administration of said composition to said patient.

31. The composition according to any one of claims 1 to 15, 18 to 22, and 30 wherein said modafinil is the r-isomer of modafinil.

32. The method according to any one of claims 16, 17, and 29 wherein said modafinil is the r-isomer of modafinil.

33. The dosage form according to any one of claims 23 to 28 wherein said modafinil is the r-isomer of modafinil.

34. A pharmaceutical composition comprising particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof, wherein said particles consist of a first population of particles and a second population of particles, wherein the ratio of said first population of particles to said second population of particles is about 3:7 by weight, wherein:

(a) said first population of particles comprises coarse particles having a diameter greater than about 240 microns; and

(b) said second population of particles comprises coarse particles having a diameter less than about 240 microns, wherein said second population of particles comprises nanoparticles having a diameter less than about 2000nm.

35. The composition according to claim 34 wherein said particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof comprises about 10% nanoparticles by weight.

36. The composition according to claim 35 wherein said particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof comprises about 40%, 50%, 60%, 70%, or 80% nanoparticles by weight.

37. The composition according to claim 34 wherein the composition is in the form of a tablet or capsule.

38. The composition according to claim 34 further comprising one or more pharmaceutical acceptable excipients.

39. The composition according to claim 38 where in the one or more pharmaceutical acceptable excipients comprises one or more binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

40. An oral controlled release dosage form comprising the composition according to any one of claims 34 to 36.

41. The composition according to claim 34 further comprising cyclodextrin provided that said cyclodextrin is not selected from the group consisting of hydroxylpropylbetacyclodextrin, betacyclodextrinsulfobutylether, and mixtures thereof.

42. Use of the composition of claim 41 in the manufacture of a medicament for improving or maintaining bioavailability of modafinil.

43. Use of the composition of claim 41 in the manufacture of a medicament for treating neurological based disorder selected from the group consisting of narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift worker sleep disorder, improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia, wherein said medicament is to be administered to a patient suffering from said disorder.

44. A pharmaceutical composition comprising particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof, wherein said particles consist of a first population of particles and a second population of particles, wherein the ratio

of said first population of particles to said second population of particles is about 3:7 by weight, wherein:

(a) said first population of particles comprises coarse particles having a diameter greater than about 220 microns; and

(b) said second population of particles comprises coarse particles having a diameter less than about 220 microns, wherein said second population of particles comprises nanoparticles having a diameter less than about 2000nm.

45. The composition according to claim 44 wherein said particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amorphous forms or mixtures thereof comprises about 10% nanoparticles by weight.

46. The composition according to claim 45 wherein said particles of modafinil, enantiomers, polymorphs, hydrates, solvates, amoiphous forms or mixtures thereof comprises about 40%, 50%, 60%, 70%, or 80% nanoparticles by weight.

47. The composition according to claim 44 wherein the composition is in the form of a tablet or capsule.

48. The composition according to claim 44 further comprising one or more pharmaceutical acceptable excipients.

49. The composition according to claim 48 where in the one or more pharmaceutical acceptable excipients comprises one or more binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

50. An oral controlled release dosage form comprising the composition according to any one of claims 44 to 46.

51. The composition according to claim 44 further comprising cyclodextrin provided that said cyclodextrin is not selected from the group consisting of hydroxylpropylbetacyclodextrin, betacyclodextrinsulfobutylether, and mixtures thereof.

52. Use of the composition of claim 51 in the manufacture of a medicament for improving or maintaining bioavailability of modafinil.

53. Use of the composition of claim 51 in the manufacture of a medicament treating neurological based disorder selected from the group consisting of narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift worker sleep disorder, improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia, wherein said medicament is to be administered to a patient suffering from said disorder.