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(54) Title: SOLID PHARMACEUTICAL FORMULATIONS COMPRISING MODAFINIL

**(57) Abrégé/Abstract:**

The present invention is related to compositions of modafinil, including compositions of modafinil and one or more diluents, disintegrants, binders and lubricants, and the processes for the preparation thereof.

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(54) Title: SOLID PHARMACEUTICAL FORMULATIONS COMPRISING MODAFINIL

(57) Abstract: The present invention is related to compositions of modafinil, including compositions of modafinil and one or more diluents, disintegrants, binders and lubricants, and the processes for the preparation thereof.

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## SOLID PHARMACEUTICAL FORMULATIONS COMPRISING MODAFINIL

## FIELD OF THE INVENTION

The present invention is related to compositions of modafinil and processes for the preparation thereof. The present invention relates to compositions that include 5 modafinil and one or more diluents, disintegrants, binders and lubricants. The present invention further relates to processes for the preparing a solid dosage form of a modafinil by wet mixing modafinil and excipients with water.

## BACKGROUND OF THE INVENTION

Modafinil,  $C_{15}H_{15}NO_2S$ , also known as 2-(benzhydrylsulfinyl) acetamide, or 2-10 [(diphenylmethyl) sulfinyl] acetamide, is a synthetic acetamide derivative with wake-promoting activity, the structure of which has been described in French Patent No. 78 05 510 and in U.S. Patent No. 4,177,290 ('290), and which has been approved by the United States Food and Drug Administration for use in the treatment of excessive 15 daytime sleepiness associated with narcolepsy. Modafinil has been tested for treatment of several behavioral conditions in combination with various agents including apomorphine, amphetamine, reserpine, oxotremorine, hypnotics, yohimbine, 5-hydroxytryptophan, and monoamine oxidase inhibitors, as described in the cited 20 patents. A method of preparation of a racemic mixture is described in the '290 patent and a method of preparation of a levorotatory isomer is described in U.S. Patent No. 4,927,855. The levorotatory isomer is reported to be useful for treatment of hypersomnia, depression, Alzheimer's disease and to have activity towards the symptoms of dementia and loss of memory, especially in the elderly.

The primary pharmacological activity of modafinil is to promote wakefulness. 25 Modafinil promotes wakefulness in rats (Touret et al., 1995; Edgar and Seidel, 1997), cats (Lin et al., 1992), canines (Shelton et al., 1995) and non-human primates (Hernant et al, 1991) as well as in models mimicking clinical situations, such as sleep apnea (English bulldog sleep disordered breathing model) (Panckeri et al, 1996) and narcolepsy (narcoleptic canine) (Shelton et al, 1995).

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Modafinil has also been described as an agent with activity in the central nervous system, and as a useful agent in the treatment of Parkinson's disease (U.S. Patent No. 5,180,745); in the protection of cerebral tissue from ischemia (U.S. Patent No. 5,391,576); in the treatment of urinary and fecal incontinence (U.S. Patent No. 5,401,776); and in the treatment of sleep apneas and disorders of central origin (U.S. Patent No. 5,612,379). U.S. Patent No. 5,618,845 describes modafinil preparations of a defined particle size less than about 200 microns. In addition, modafinil may be used in the treatment of eating disorders, or to promote weight gain or stimulate appetite in humans or animals, or in the treatment of attention deficit hyperactivity disorder (ADHD), or fatigue, especially fatigue associated with multiple sclerosis.

Modafinil was known in the art in the form of a therapeutic package, marketed under the name Provigil®. Provigil® is a pharmaceutical product manufactured by Cephalon, Inc. of West Chester, PA and is also marketed by Cephalon, Inc. Provigil® is supplied as tablets containing 100 mg or 200 mg modafinil, with several excipients, including magnesium silicate and talc. In commercial use, modafinil-containing therapeutic packages in the prior art were labeled and otherwise indicated for use in narcolepsy patients.

It is desirable to optimize the formulation of a solid dose form of modafinil, and the methods of their preparation on a commercial scale. In particular, new formulations of modafinil have been discovered which exhibit comparable stability, dissolution rate, hardness, friability, thickness, disintegration, size and shape, and weight variation characteristics to that of Provigil®. Further, it has been discovered that a solid dose forms of modafinil can be prepared, with properties similar to that of Provigil®, without inclusion of magnesium silicate or talc.

In addition, the newly discovered formulations preferably use a minimal number of excipients, and use pharmaceutical grade excipients that are inexpensive, readily available and that facilitate cost-effective manufacture on a commercial scale.

Furthermore, there is a need to improve upon the manufacturing process of the tablet form of modafinil. Improvement in the commercial preparation include minimizing the number of excipients, eliminating the use of organic solvents, reducing the number of steps, and reducing the time and expense of manufacture. The present invention is directed to these, as well as other, important ends.

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**SUMMARY OF THE INVENTION**

The present invention relates to novel compositions of modafinil and the processes for their manufacture. In particular, modafinil is admixed with 5 various excipients to formulate a solid dose of modafinil. In certain embodiments, the solid dose is in tablet form, in other embodiments, it is in capsule form.

According to one aspect of the present invention, there is provided a composition in the form of a tablet 10 comprising modafinil; one or more diluents, each independently chosen from a starch, a lactose monohydrate or a microcrystalline cellulose; one or more disintegrants, each independently chosen from a pregelatinized starch or a cross-linked sodium carboxymethyl cellulose; a binder; and a 15 lubricant; wherein modafinil comprises from 30-50% by weight of the composition; a diluent is a lactose monohydrate, a second diluent is a microcrystalline cellulose; a disintegrant is a pregelatinized starch, a second disintegrant is a cross-linked sodium carboxymethyl cellulose; the binder is a polyvinyl pyrrolidone, and the 20 lubricant is magnesium stearate; provided the composition does not include magnesium silicate or talc.

According to another aspect of the present invention, there is provided a pharmaceutical composition 25 whose components are selected in accordance with the following table:

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Components	Amount (mg)
Modafinil	100.0
Lactose Monohydrate, NF (Fast Flo #316)	71.75
Microcrystalline Cellulose, NF (Avicel PH 102)	26.0
Pregelatinized Starch, NF (Starch 1500)	27.25
Povidone K29/32, USP	13.0
Croscarmellose Sodium, NF (Ac-Di-Sol)	10.0
Magnesium Stearate, NF	2.0

According to another aspect of the present invention, there is provided a pharmaceutical composition 5 whose components are selected in accordance with the following table:

Components	Amount (mg)
Modafinil	200.0
Lactose Monohydrate, NF (Fast Flo #316)	143.5
Microcrystalline Cellulose, NF (Avicel PH 102)	52.0
Pregelatinized Starch, NF (Starch 1500)	54.5
Povidone K29/32, USP	26.0
Croscarmellose Sodium, NF (Ac-Di-Sol)	20.0
Magnesium Stearate, NF	4.0

According to another aspect of the present invention, there is provided compositions in the form of 10 capsules, wherein the components in said capsules are selected in accordance with the following table:

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Components	Amount (mg)				
	1	2	3	4	5
Modafinil	12.5	25.0	50.0	100.0	200.0
Lactose Monohydrate, NF	99.38	86.88	61.88	11.88	23.75
Povidone K90 D, USP	6.25	6.25	6.25	6.25	12.5
Croscarmellose Sodium, NF (Ac-Di-Sol®)	6.25	6.25	6.25	6.25	12.5
Magnesium Stearate, NF	0.625	0.625	0.625	0.625	1.25

An additional aspect of the present invention include processes for the preparation of modafinil 5 formulations. In particular, the processes involve preparation of a solid dosage form of modafinil, preferably by wet mixing modafinil and excipients with water, followed by drying and milling of the granulated mixture.

Thus, according to another aspect of the present 10 invention, there is provided a process of preparing a solid dosage form of modafinil comprising the steps of: (a) dry blending of modafinil and one or more excipients to form a dry mixture; (b) wetting the dry mixture with purified water to form a wet granulation mixture; (c) drying the wet 15 granulation mixture to form a dried granulation mixture; (d) milling the dried granulation mixture to form a milled granulation mixture; (e) mixing a lubricant in the milled granulation mixture to give a final blended mixture; (f) compressing the final blended mixture in a tablet 20 suitable for oral administration; wherein modafinil is blended with a lactose monohydrate, a microcrystalline cellulose, a pregelatinized starch, a cross-linked sodium

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carboxymethyl cellulose, and polyvinyl pyrrolidone, the lubricant is magnesium stearate, and the solid dosage form does not include magnesium silicate or talc.

According to another aspect of the present  
5 invention, there is provided a process of preparing a solid  
dosage form of modafinil comprising the steps of: (a) dry  
blending of modafinil and one or more excipients to form a  
dry mixture; (b) mixing a lubricant in the dry mixture to  
give a final blended mixture; (c) compressing the final  
10 blended mixture into a tablet suitable for oral  
administration; wherein modafinil is blended with a lactose  
monohydrate, a microcrystalline cellulose, a pregelatinized  
starch, a cross-linked sodium carboxymethyl cellulose, and  
polyvinyl pyrrolidone, the lubricant is magnesium stearate,  
15 and the solid dosage form does not include magnesium  
silicate or talc.

According to another aspect of the invention,  
there is provided the composition as described above for use  
in treating sleepiness, Parkinson's disease, cerebral  
20 ischemia, stroke, sleep apneas, eating disorders, attention  
deficit hyperactivity disorder and fatigue, promotion of  
wakefulness, stimulation of appetite and weight gain, or  
improving cognitive dysfunction.

According to another aspect of the invention,  
25 there is provided a composition comprising components in  
accordance with the following table:

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Ingredient	w/w (%)
Modafinil	40.00
Lactose Monohydrate, NF	28.7
Pregelatinized Starch, NF	10.9
Microcrystalline Cellulose, NF	10.4
Povidone K29/32, USP	5.2
Croscarmellose Sodium, NF	4.0
Magnesium Stearate, NF (Non-Bovine)	0.80

According to another aspect of the invention, there is provided use of the composition as described above 5 in the manufacture of a medicament for treating sleepiness, Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, attention deficit hyperactivity disorder and fatigue, promotion of wakefulness, stimulation of appetite and weight gain, or improving cognitive 10 dysfunction.

According to another aspect of the invention, there is provided use of the composition as described above for treating sleepiness, Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, attention 15 deficit hyperactivity disorder and fatigue, promotion of wakefulness, stimulation of appetite and weight gain, or improving cognitive dysfunction.

According to another aspect of the invention, there is provided use of the composition as described above 20 in the manufacture of a medicament for the symptomatic treatment of excessive sleepiness in adult patients with

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narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) or shift work disorder (SWSD).

According to another aspect of the invention, there is provided use of the composition as described above 5 for the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) or shift work disorder (SWSD).

According to another aspect of the invention, 10 there is provided the composition as described above, for use in the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) or shift work disorder (SWSD).

15 Other aspects of the present invention include use of the pharmaceutical compositions described herein for the treatment of a disease or disorder in a subject in need thereof. Thus, in embodiments, the invention provides use 20 of the pharmaceutical composition described herein for the treatment of sleepiness, promotion of wakefulness, treatment of Parkinson's disease, treatment of cerebral ischemia, treatment of stroke, treatment of sleep apneas, treatment of eating disorders, stimulation of appetite and weight gain, treatment of attention deficit hyperactivity disorder, 25 treatment of fatigue, or improvement of cognitive dysfunction. Also included are methods for treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compositions of the present invention. Other 30 aspects of the present invention also include commercial packages comprising the pharmaceutical compositions described herein, together with instructions for use.

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**DETAILED DESCRIPTION OF THE INVENTION**

As used herein, "about" refers to a range of values  $\pm 10\%$  of a specified value. For example, "about 20" includes  $\pm 10\%$  of 20, or from 18 to 22.

5 As used herein, "modafinil" refers to modafinil, its racemic mixtures, individual isomers, acid addition salts, such as a metabolic acid of modafinil, benzhydrylsulfinylacetic acids, and its sulfone forms, hydroxylated forms, polymorphic forms, analogs, derivatives, 10 cogeners and prodrugs thereof. Prodrugs are known in the art as compounds that are converted to the active agent (modafinil) in the body of a subject.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, 15 compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk 20 ratio.

As used herein, the term "subject" refers to a warm blooded animal such as a mammal, preferably a human or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and conditions 25 described herein.

As used herein, "therapeutically effective amount" refers to an amount which is effective in reducing, eliminating, treating, preventing or controlling the symptoms of the herein-described diseases and conditions. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or 5 stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, and is intended to include prophylactic treatment.

As used herein, "unit dose" means a single dose which is capable of being administered to a subject, and which can be readily handled and packaged, remaining 10 as a physically and chemically stable unit dose comprising either modafinil, or a pharmaceutically acceptable composition comprising modafinil.

In one embodiment, the present invention provides for compositions of modafinil without magnesium silicate or talc. Other embodiments include compositions of modafinil with one or more diluents, disintegrants, binders and 15 lubricants. Preferably, the excipients meet the standards of the National Formulary ("NF") or United States Pharmacopoeia ("USP"). In a particular embodiment, there is provided a composition consisting of modafinil with one or more diluents, disintegrants, binders and lubricants.

In certain preferred embodiments, the composition comprises modafinil; one or 20 more diluents, each independently chosen from a starch, a lactose monohydrate or a microcrystalline cellulose; one or more disintegrants, each independently chosen from a pregelatinized starch or a cross-linked sodium carboxymethyl cellulose; a binder; and a lubricant. In other preferred embodiments, the binder is a polyvinyl pyrrolidone, and the lubricant is magnesium stearate. In certain more preferred embodiments, a diluent 25 is Fast Flo<sup>®</sup> #316, a second diluent is Avicel<sup>®</sup> PH 102; a disintegrant is Starch 1500<sup>®</sup>, a second disintegrant is Ac-Di-Sol<sup>®</sup>; and the binder is Povidone K-29/32.

The excipients are selected to ensure the delivery of a consistent amount of modafinil in a convenient unit dosage form and to optimize the cost, ease and reliability of the manufacturing process. All excipients must be inert, organoleptically 30 acceptable, and compatible with modafinil. The excipients used in a solid oral formulation, commonly include fillers or diluents, binders, disintegrants, lubricants, antiadherents, glidants, wetting and surface active agents, colors and pigments, flavoring agents, sweeteners, adsorbents, and taste-maskers.

Diluents are typically added to a small amount of the active drug to increase the size of the tablet. The most common diluent is lactose, which exists in two isomeric forms, alpha-lactose or beta-lactose, and can be either crystalline or amorphous. Various types of lactose include spray dried lactose monohydrate (such as 5 Super-Tab<sup>TM</sup> ), alpha-lactose monohydrate (such as Fast Flo<sup>®</sup> ), anhydrous alpha-lactose, anhydrous beta-lactose, and agglomerated lactose. Other diluents include sugars, such as compressible sugar NF, dextrose excipient NF, and dextrose NF. A preferred diluent is lactose monohydrate (such as Fast Flo<sup>®</sup> ). Other preferred diluents include 10 microcrystalline cellulose (such as Avicel<sup>®</sup> PH, and Ceolus<sup>TM</sup> ), and microfine cellulose (such as Elcema<sup>®</sup> ).

Diluents may include starch and starch derivatives. Starches include native starches obtained from wheat, corn, rice and potatoes. Other starches include pregelatinized starch NF, and sodium starch glycolate NF. Starches and starch derivatives also function as disintegrants. Other diluents include inorganic salts, such 15 as dibasic calcium phosphate USP (such as Di-Tab<sup>®</sup> and Emcompress<sup>®</sup> ), tribasic calcium phosphate NF (such as Tri-Tab<sup>®</sup> and Tri-Cafos<sup>®</sup> ), and calcium sulfate NF (such as Compactrol<sup>®</sup> ). Such polyols as mannitol USP, sorbitol NF, and xylitol NF may also serve as diluents. Many diluents also function as disintegrants and binders, and these additional properties must be taken into account when developing a 20 formulation.

Disintegrants are included in tablet formulations to break the tablets into particles of the active pharmaceutical ingredient and excipients which will facilitate dissolution of the active ingredient and enhance bioavailability of the active ingredient. Starch and starch derivatives, including cross-linked sodium salt of a carboxymethyl 25 ether of starch (such as sodium starch glycolate NF, Explotab<sup>®</sup> , and Primogel<sup>®</sup> ) are useful disintegrants. A preferred disintegrant is pregelatinized starch, such as Starch 1500<sup>®</sup> . Another preferred disintegrant is cross-linked sodium carboxymethyl cellulose (such as Croscarmellose Sodium NF, Ac-Di-Sol<sup>®</sup> ). Other disintegrants include cross-linked polyvinylpyrrolidone (such as Crospovidone NF), 30 microcrystalline cellulose (such as Avicel<sup>®</sup> PH).

Binders are used as a wet granulation excipient to agglomerate the active pharmaceutical ingredient and the other excipients. A binder is selected to improve powder flow and to improve compactibility. Binders include cellulose derivatives

such as microcrystalline cellulose NF, methylcellulose USP, carboxymethylcellulose sodium USP, hydroxypropyl methylcellulose USP, hydroxyethyl cellulose NF, and hydroxypropyl cellulose NF. Other binders include polyvidone, polyvinyl pyrrolidone, gelatin NF, natural gums (such as acacia, tragacanth, guar, and pectin),  
5 starch paste, pregelatinized starch NF, sucrose NF, corn syrup, polyethylene glycols, and sodium alginate, ammonium calcium alginate, magnesium aluminum silicate, polyethylene glycols. A preferred binder is polyvinyl pyrrolidone, in particular, Povidone USP, and preferably, povidone K-29/32.

Lubricants are used in tablet formulation to prevent sticking of the tablet to the  
10 punch faces and to reduce friction during the compression stages. Lubricants typically include vegetable oils (such as corn oil), mineral oils, polyethylene glycols (such as PEG-4000 and PEG-6000), salts of stearic acid (such as calcium stearate and sodium stearyl fumarate), mineral salts (such as talc), inorganic salts (such as sodium chloride), organic salts (such as sodium benzoate, sodium acetate, and sodium oleate)  
15 and polyvinyl alcohols. A preferred lubricant is magnesium stearate.

In other embodiments, modafinil comprises from about 30-50% by weight of the composition. Preferably, the composition comprises a diluent which is a lactose monohydrate, a second diluent which is a microcrystalline cellulose; a disintegrant which is a pregelatinized starch, a second disintegrant which is a cross-linked sodium  
20 carboxymethyl cellulose; a binder which is a polyvinyl pyrrolidone, and a lubricant which is magnesium stearate.

In certain other preferred embodiments, the lactose monohydrate is from about 25-35% of the composition by weight; the microcrystalline cellulose is from about 5-15%, the pregelatinized starch is from about 5-15%, the cross-linked sodium  
25 carboxymethyl cellulose is from about 1-10%, the polyvinyl pyrrolidone is from about 1-10%, and the magnesium stearate is from about 0.2-2.0%.

In certain more preferred embodiments, the lactose monohydrate is Fast Flo® #316; the microcrystalline cellulose is Avicel® PH 102; the pregelatinized starch is Starch 1500®, the cross-linked sodium carboxymethyl cellulose is Ac-Di-Sol®; and the  
30 polyvinyl pyrrolidone is Povidone K-29/32.

In a particularly preferred embodiment, modafinil is about 40.0% of the composition by weight, Fast Flo® #316 is about 28.7%, the Avicel® PH 102 is about 10.4%, the Starch 1500® is about 10.9%, the Ac-Di-Sol® is about 4.0%, the Povidone K-29/32 is about 5.2% and the magnesium stearate is about 0.8%.

In other embodiments, the compositions comprise at least one unit dose of modafinil. In a further embodiment, the compositions comprise one unit dose of modafinil. Preferably the unit dose is in a solid dose form, and more preferably is a tablet. In particular, the tablet can include 10, 25, 50 and preferably 100 mg of modafinil in a 250 mg tablet. In other embodiments, the tablet can include 200 mg of modafinil in a 500 mg tablet, 300 mg of modafinil in a 750 mg tablet, and 400 mg modafinil in 1000 mg tablet. Similarly, a capsule may contain 10, 25, 50, or 100 mg of modafinil in a 125 mg capsule or 200 mg of modafinil in a 250mg capsule.

In a second embodiment, the present invention provides for a process of preparing a solid dosage form of modafinil by wet mixing modafinil and excipients with water, drying and milling the granulated mixture. In certain embodiments, the final mixture is compressed into a tablet. In other embodiments, the final mixture is encapsulated. In particular, the process comprises the steps of:

- (a) dry blending of modafinil and one or more excipients to form a dry mixture;
- (b) wetting the dry mixture with water, preferably with purified water, to form a wet granulation mixture;
- (c) drying the wet granulation mixture to form a dried granulation mixture;
- (d) milling the dried granulation mixture to form a milled granulation mixture;
- (e) mixing a lubricant in the milled granulation mixture to give a final blended mixture;
- (f) preparing the final blended mixture in a solid dosage form suitable for oral administration.

In certain preferred embodiments, the final blended mixture is compressed into tablets. In other preferred embodiments, the final blended mixture is enclosed in a capsule.

Specifically, in step (a), modafinil is blended with all excipients in the final formulation, other than the lubricant. In particular, modafinil is thoroughly dry blended with the diluent(s), disintegrant(s) and binder to form a uniform dry mixture. Blenders appropriate for large scale dry blending include twin shell blenders, double cone blenders, and ribbon blenders. Ribbon blenders have the advantage of being used in continuous-production procedures. High-speed, high shear mixers may also be used and offer the advantage of shorter mixing times. The dry mixture may also be

granulated, milled into a fine powder, passed through a mesh screen, or micronized, if necessary. Preferably, the dry blending was performed in high shear granulators.

The resulting dry mixture is then wetted with a wetting agent to form a wet granulation mixture in step (b). The wetting agent is typically added over time, 5 usually from about 1 to about 15 minutes, with continuous mixing. Typically, the wetting agent is added to the blender used in the dry blending step. Preferably the wet granulation is carried out in a high shear granulator. In certain embodiments, the wetting agent is an aqueous-based solution. Preferably, the wetting agent is water without any additional solvents, and in particular, without organic solvents. More 10 preferably, the water is purified water. The type and amount of wetting agent, rate of addition of wetting agent, and the mixing time influences the structure of the granules. The different types of granules, such as pendular, funicular, capillary, etc., can be manipulated to achieve the desired density, porosity, texture and dissolution pattern of the granules, which in turn, determines the compressibility, hardness, disintegration 15 and consolidation characteristics of the dried mixture.

The wet granulation mixture is then dried in step (c) to form a dried granulation mixture with an appropriate moisture content. In certain embodiments, the drying means include a fluid bed or tray dryers. Fluid bed drying yield shorter drying times, in the range from 1 to 3 hours, while tray drying averages 10 to 13 hours. Preferably, 20 the wet granulation mixture is dried in a fluid bed, for preferably about 1-3 hours. Fluid bed drying has the added advantages of better temperature control and decreased costs. The method of drying, drying time, and moisture content are critical to avoid decomposition, chemical migration, and other adverse physical characteristics of dried mixture which can affect the dosage form performance.

25 The dried granulation mixture is subsequently milled in step (d) to form a milled granulation mixture. The particle size of the dried granulation mixture is reduced to achieve an appropriate particle size distribution for the subsequent processes. In certain embodiments, milling is achieved using a high shear impact mill (such as Fitzpatrick) or a low shear screening mill (such as Comil). The dried 30 granulation mixture may also be screened to select the desired granule size.

In the next step (e), the lubricant was blended with the dried granulation mixture to give a final blended mixture. In certain embodiments, a V blender or bin blenders are used. A preferred blender is a V-shell PK blender. A gentle blending is preferred, such that each granule covered with the lubricant, while minimizing the

breaking up of the granules. Increased breaking of the granules results in fine powder, or "fines". A high fine content results in variations of weight and density during compression into a tablet, as well as increases the need for cleaning of the compression machinery.

5 The final blended mixture is then prepared in a solid dosage form suitable for oral administration. Solid dosage forms include tablets, capsules, pills, troches, cachets, and the like. In one embodiment, the final blended mixture is compressed into a tablet. The compression machinery typically contains two steel punches within a steel die cavity. The tablet is formed when pressure is exerted on the dried granulation 10 mixture by the punches in the cavity, or cell. Tableting machines include single-punch machines, rotary tablet machines, gravity feed, and powder assisted machines. Preferably, gravity feed or powder assisted machines are used. Rotary machines operating at high speeds suitable for large-scale production include double rotary machines and single rotary machines. Tablets can also include sugar-coated tablets, 15 film-coated tablets, enteric-coated tablets, multiple-compressed tablets, controlled-release tablets, tablets for solution, effervescent tablets or buccal and sublingual tablets.

Compressed tablets may be characterized by a number of specifications, including diameter size, shape, thickness, weight, hardness, friability, disintegration 20 time, and dissolution characteristics. The compositions of the current invention preferably have similar properties to that of Provigil®. The tablets preferably have weights, friability and dissolution rates in accordance with USP standards. The preferred hardness and thickness ranges of various sized tablets are shown below in Table 1:

25

Amount of Modafinil (mg)	Hardness (Kp)	Thickness (inches)
100	4 - 14	0.132 - 0.171
200	7 - 21	0.163 - 0.219
300	9 - 22	0.197 - 0.248
400	10 - 22	0.268 - 0.249

In another embodiment, the final blended mixture is enclosed in capsules, preferably hard gelatin capsules. The hard gelatin capsules are commercially available, and are generally made from gelatin, colorants, optionally an opacifying

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agent such as titanium dioxide, and typically contain 12-16% water. The hard capsules can be prepared by filling the longer end of the capsule with the final blended mixture, and slipping a cap over the top using mG2, Zanasi, or Höfliger and Karg (H&K) machines.

5 In an alternative embodiment, the present invention provides for a process of preparing a solid dose form of modafinil by dry mixing modafinil with the excipients. In certain embodiments, the mixture is compressed into a tablet. In other embodiments, the mixture is encapsulated. In particular, the process comprises the steps of:

10 (a) dry blending of modafinil and one or more excipients to form a dry mixture;

(b) mixing a lubricant in the dry mixture to give a final blended mixture;

(c) preparing the final blended mixture in a solid dosage form suitable for oral administration.

15 In certain preferred embodiments, the final blended mixture is compressed into tablets. In other preferred embodiments, the final blended mixture is enclosed in a capsule.

20 Specifically, in step (a), modafinil is blended with all excipients in the final formulation, other than the lubricant. Preferably, modafinil is thoroughly dry blended with the diluent(s), disintegrant(s) and a binder to form a uniform dry mixture. Blenders appropriate for large scale dry blending include twin shell blenders, double cone blenders, V blenders or bin blenders. A preferred blender is a V-shell PK blender. High-speed, high shear mixers may also be used. The dry mixture may also be granulated, milled into a fine powder, passed through a mesh screen, or micronized, 25 if necessary.

In the next step (b), the lubricant was blended with the dry mixture to give a final blended mixture. In certain embodiments, a V blender or bin blenders are used. A preferred blender is a V-shell PK blender.

30 The final blended mixture is then prepared in a solid dosage form suitable for oral administration. Solid dosage forms include tablets, capsules, pills, troches, cachets, and the like. In one embodiment, the final blended mixture is compressed into a tablet. In another embodiment, the final blended mixture is enclosed in capsules, preferably hard gelatin capsules.

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Other aspects of the invention also include use of these compositions for the treatment of a disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compositions of the present invention. In particular, the present compositions are useful in the treatment of 5 sleepiness, promotion of wakefulness, treatment of Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, stimulation of appetite and weight gain, treatment of attention deficit hyperactivity disorder and fatigue, and improvement of cognitive dysfunction.

**Examples**

10 The materials, methods, and examples presented herein are intended to be illustrative, and not to be construed as limiting the scope or content of the invention. Unless otherwise defined, all technical and scientific terms are intended to have their art-recognized meanings.

**Example 1: Formulation of a 100 mg Modafinil Tablet**

15

Components	Amount per tablet (mg)
Modafinil	100.0
Lactose Monohydrate, NF (Fast Flo #316)	71.75
Microcrystalline Cellulose, NF (Avicel PH 102)	26.0
Pregelatinized Starch, NF (Starch 1500)	27.25
Povidone K29/32, USP	13.0
Croscarmellose Sodium, NF (Ac-Di-Sol)	10.0
Magnesium Stearate, NF	2.0
<b>Total Tablet Weight</b>	<b>250.0</b>

**Example 2: Formulation of a 200 mg Modafinil Tablet**

Components	Amount per tablet (mg)
Modafinil	200.0
Lactose Monohydrate, NF (Fast Flo #316)	143.5
Microcrystalline Cellulose, NF (Avicel PH 102)	52.0
Pregelatinized Starch, NF (Starch 1500)	54.5
Povidone K29/32, USP	26.0
Croscarmellose Sodium, NF (Ac-Di-Sol)	20.0
Magnesium Stearate, NF	4.0
<b>Total Tablet Weight</b>	<b>500.0</b>

**Example 3: Large Scale Preparation (250 kg) of Modafinil Formulation****Step (a): Dry Mixture**

5 Pass Modafinil (100.00 kg), Lactose Monohydrate NF (71.75 kg), Pregelatinized Starch NF (27.25 kg), Microcrystalline Cellulose NF (26.00 kg), Croscarmellose Sodium NF (10.00 kg) and Povidone K29/32 USP (13.00 kg) through a #10 mesh screen. Add the screened material to a 600 liter Collette mixer. Mix for 6 minutes at low speed, without a chopper.

**10 Step (b): Wet Granulation Mixture**

To a stainless steel tank, add Purified Water USP (100.00 kg). While mixing the dry mixture at low speed, pump the purified water into the Collette mixer at a rate of 14 kg/min. After the water has been added, continue to mix the wet granulation mixture at low speed and low chopper for 30 additional seconds. Additional mixing, 15 and/or additional water may be required to achieve the desired consistency. Discharge the wet granulation mixture from the Collette bowl into a suitable transport vessel.

**Step (c): Drying Wet Granulation Mixture**

Spread the wet granulation evenly, and not to exceed 2 inches in depth, on 2 drying racks lined with 40 lb. Kraft paper. Place the racks in G&G Steam Heated

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Oven. Dry the wet granulation mixture at  $60^{\circ}\text{C} \pm 2^{\circ}\text{C}$  until a L.O.D. of 1.0 – 2.1% is reached.

*Step (d): Milling the Dried Granulation Mixture*

Pass the dried granulation mixture through an auger feed Fitz®mill (Model 5 DAS06), with knives forward, at medium speed, through a 2 $\text{\AA}$  screen.

*Step (e): Mixing a Lubricant*

Add the dried granulation mixture from the previous step to a 20-cubic foot V-shell PK blender (Model C266200). Pass Magnesium Stearate NF (2.00 kg) through a 10-mesh screen into a properly prepared container. Add approximately half of the 10 Magnesium Stearate to each side of the PK blender and blend for 5 minutes.

*Step (f): Compression into Tablets*

Add the blended granulation mixture form the previous step to Kikusui tablet press for compression into capsule-shaped tablets. The compression equipment can be outfitted to make tooling for a 100 mg tablet (0.496 x 0.218 inches), a 200 mg tablet 15 (0.625 x 0.275 inches, bisected), 300 mg tablet (0.715 x 0.315 inches) and a 400 mg tablet (0.750 x 0.330 inches).

*Alternative Step (f): Filling into capsules*

Add the blended granulation mixture form the previous step to H & K 400 machine for filling the appropriate size capsules.

**Example 4: Formulation of Modafinil Capsules**

Components	Amount per capsule (mg)				
Modafinil	12.5	25.0	50.0	100.0	200.0
Lactose	99.38	86.88	61.88	11.88	23.75
Monohydrate, NF					
<i>Povidone K90 D, USP</i>	6.25	6.25	6.25	6.25	12.5
Croscarmellose	6.25	6.25	6.25	6.25	12.5
Sodium, NF (Ac-Di-Sol®)					
Magnesium Stearate, NF	0.625	0.625	0.625	0.625	1.25
<b>Total Capsule Weight</b>	<b>125.0</b>	<b>125.0</b>	<b>125.0</b>	<b>125.0</b>	<b>250.0</b>

Although the present invention has been described in considerable detail, those skilled in the art will appreciate that numerous changes and modifications may be made to the embodiments and preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all equivalent variations as fall within the scope of the invention.

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CLAIMS:

1. A composition in the form of a tablet comprising modafinil; one or more diluents, each independently chosen from a starch, a lactose monohydrate or a microcrystalline cellulose; one or more disintegrants, each independently chosen from a pregelatinized starch or a cross-linked sodium carboxymethyl cellulose; a binder; and a lubricant;

wherein modafinil comprises from 30-50% by weight of the composition;

10 a diluent is a lactose monohydrate,

a second diluent is a microcrystalline cellulose;

a disintegrant is a pregelatinized starch,

a second disintegrant is a cross-linked sodium carboxymethyl cellulose;

15 the binder is a polyvinyl pyrrolidone, and

the lubricant is magnesium stearate;

provided the composition does not include magnesium silicate or talc.

2. The composition of Claim 1, wherein the lactose monohydrate is Fast Flo® #316, the microcrystalline cellulose is Avicel® PH 102; the pregelatinized starch is Starch 15000®, the cross-linked sodium carboxymethyl cellulose is Ac-Di-Sol®; and the polyvinyl pyrrolidone is Povidone K-29/32.

25 3. The composition of Claim 1, wherein the lactose monohydrate is from 25-35% of the composition by weight; the microcrystalline cellulose is from 5-15%, the pregelatinized

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starch is from 5-15%, the cross-linked sodium carboxymethyl cellulose is from 1-10%, the polyvinyl pyrrolidone is from 1-10%, and the magnesium stearate is from 0.2-2.0%.

4. The composition of Claim 3, wherein the lactose  
5 monohydrate is Fast Flo® #316; the microcrystalline  
cellulose is Avicel® PH 102; the pregelatinized starch is  
Starch 1500®, the cross-linked sodium carboxymethyl  
cellulose is Ac-Di-Sol®; and the polyvinyl pyrrolidone is  
Povidone K-29/32.

10 5. The composition of Claim 4 wherein modafinil is  
40.0% of the composition by weight, Fast Flo® #316 is 28.7%,  
the Avicel® PH 102 is 10.4%, the Starch 1500® is 10.9%, the  
Ac-Di-Sol® is 4.0%, the Povidone K-29/32 is 5.2% and the  
magnesium stearate is 0.8%.

15 6. The composition of Claim 5, wherein the tablet  
weight is 250 mg.

7. The composition of Claim 6, comprising 100 mg of modafinil.

8. The composition of Claim 5, wherein the tablet  
20 weight is 500 mg.

9. The composition of Claim 8, comprising 200 mg of modafinil.

10. A process of preparing a solid dosage form of modafinil comprising the steps of:

25 (a) dry blending of modafinil and one or more  
excipients to form a dry mixture;

(b) wetting the dry mixture with purified water to form a wet granulation mixture;

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(c) drying the wet granulation mixture to form a dried granulation mixture;

(d) milling the dried granulation mixture to form a milled granulation mixture;

5 (e) mixing a lubricant in the milled granulation mixture to give a final blended mixture;

(f) compressing the final blended mixture in a tablet suitable for oral administration;

wherein modafinil is blended with a lactose  
10 monohydrate, a microcrystalline cellulose, a pregelatinized starch, a cross-linked sodium carboxymethyl cellulose, and polyvinyl pyrrolidone, the lubricant is magnesium stearate, and the solid dosage form does not include magnesium silicate or talc.

15 11. The process of Claim 10, wherein the dry blending of step (a) and wet granulation of step (b) is carried out in a high shear granulator.

12. The process of Claim 10, wherein drying of the wet granulation mixture in step (c) is carried out in tray  
20 dryers or in a fluid bed.

13. The process of Claim 12, wherein the wet granulation mixture is dried in the fluid bed for 1-3 hours or the tray dryers for 10-13 hours.

14. The process of Claim 13, wherein the wet granulation mixture is dried in the fluid bed for 1-3 hours.

15. The process of Claim 10, wherein the dried granulation mixture is milled in step (d) using an impact mill or a low shear mill.

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16. The process of Claim 10, wherein the lubricant and the milled granulation mixture in step (e) are blended using a V blender or bin blenders.

17. The process of Claim 10, wherein the tablets are  
5 compressed in gravity or power-assisted tablet presses.

18. The process of Claim 10, wherein the lactose monohydrate is Fast Flo® #316, the microcrystalline cellulose is Avicel® PH 102, the pregelatinized starch is Starch 1500®, the cross-linked sodium carboxymethyl cellulose is Ac-Di-Sol®, and the polyvinyl pyrrolidone is Povidone K-29/32.  
10

19. The process of Claim 18, wherein modafinil is 40.0% of the final blended mixture by weight, Fast Flo® #316 is 28.7%, the Avicel® PH 102 is 10.4%, the Starch 1500® is 15 10.9%, the Ac-Di-Sol® is 4.0%, the Povidone K-29/32 is 5.2%, and the magnesium stearate is 0.8%.

20. A process of preparing a solid dosage form of modafinil comprising the steps of:

(a) dry blending of modafinil and one or more 20 excipients to form a dry mixture;

(b) mixing a lubricant in the dry mixture to give a final blended mixture;

(c) compressing the final blended mixture into a tablet suitable for oral administration;

25 wherein modafinil is blended with a lactose monohydrate, a microcrystalline cellulose, a pregelatinized starch, a cross-linked sodium carboxymethyl cellulose, and polyvinyl pyrrolidone, the lubricant is magnesium stearate,

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and the solid dosage form does not include magnesium silicate or talc.

21. The process of Claim 20, wherein the lactose monohydrate is Fast Flo® #316, the microcrystalline cellulose is Avicel® PH 102, the pregelatinized starch is Starch 1500®, the cross-linked sodium carboxymethyl cellulose is Ac-Di-Sol®, and the polyvinyl pyrrolidone is Povidone K-29/32.

22. The process of Claim 21, wherein modafinil is 40.0% of the final blended mixture by weight, Fast Flo® #316 is 28.7%, the Avicel® PH 102 is 10.4%, the Starch 1500® is 10.9%, the Ac-Di-Sol® is 4.0%, the Povidone K-29/32 is 5.2%, and the magnesium stearate is 0.8%.

23. The composition of Claim 3, for use in treating sleepiness, Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, attention deficit hyperactivity disorder and fatigue, promotion of wakefulness, stimulation of appetite and weight gain, or improving cognitive dysfunction.

24. The composition of Claim 1 wherein the components are selected in accordance with the following table:

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Components	Amount (mg)
Modafinil	100.0
Lactose Monohydrate, NF (Fast Flo #316)	71.75
Microcrystalline Cellulose, NF (Avicel PH 102)	26.0
Pregelatinized Starch, NF (Starch 1500)	27.25
Povidone K29/32, USP	13.0
Croscarmellose Sodium, NF (Ac-Di-Sol)	10.0
Magnesium Stearate, NF	2.0

25. The composition of Claim 1 wherein the components are selected in accordance with the following table:

Components	Amount (mg)
Modafinil	200.0
Lactose Monohydrate, NF (Fast Flo #316)	143.5
Microcrystalline Cellulose, NF (Avicel PH 102)	52.0
Pregelatinized Starch, NF (Starch 1500)	54.5
Povidone K29/32, USP	26.0
Croscarmellose Sodium, NF (Ac-Di-Sol)	20.0
Magnesium Stearate, NF	4.0

5

26. Compositions in the form of capsules, wherein the components in said capsules are selected in accordance with the following table:

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Components	Amount (mg)				
	1	2	3	4	5
Modafinil	12.5	25.0	50.0	100.0	200.0
Lactose Monohydrate, NF	99.38	86.88	61.88	11.88	23.75
Povidone K90 D, USP	6.25	6.25	6.25	6.25	12.5
Croscarmellose Sodium, NF (Ac-Di-Sol®)	6.25	6.25	6.25	6.25	12.5
Magnesium Stearate, NF	0.625	0.625	0.625	0.625	1.25

27. The composition according to any one of Claims 1-9 or 23 to 26 wherein the modafinil is the levorotatory isomer 5 of modafinil.

28. The process according to any one of Claims 10 to 22 wherein the modafinil is the levorotatory isomer of modafinil.

29. A composition comprising components in accordance 10 with the following table:

Ingredient	w/w (%)
Modafinil	40.00
Lactose Monohydrate, NF	28.7
Pregelatinized Starch, NF	10.9
Microcrystalline Cellulose, NF	10.4
Povidone K29/32, USP	5.2
Croscarmellose Sodium, NF	4.0
Magnesium Stearate, NF (Non-Bovine)	0.80

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30. Use of the composition of Claim 3 in the manufacture of a medicament for treating sleepiness, Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, attention deficit hyperactivity disorder and fatigue, promotion of wakefulness, stimulation of appetite and weight gain, or improving cognitive dysfunction.

5 31. Use of the composition of Claim 3 for treating sleepiness, Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, attention deficit 10 hyperactivity disorder and fatigue, promotion of wakefulness, stimulation of appetite and weight gain, or improving cognitive dysfunction.

15 32. Use of the composition of Claim 29 in the manufacture of a medicament for the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) or shift work disorder (SWSD).

20 33. Use of the composition of Claim 29 for the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) or shift work disorder (SWSD).

25 34. The composition of Claim 29, for use in the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) or shift work disorder (SWSD).

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