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(54) Title: WET GRANULATION FORMULATION FOR A PIPERAZINYLCAMPHORSULFONYL OXYTOCIN RECEPTOR ANTAGONIST

(57) Abstract

The invention describes a process for the preparation of a tablet containing an oxytocin receptor antagonist as active ingredient. The tablet is prepared by forming a powder blend of the active ingredient of 1-(7,7-Dimethyl)-2-endo-(2S-amino-4-(methylsulfonyl)-butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine, or a pharmaceutically acceptable salt thereof, with a first binder and a diluent; wet granulating the powder blend with a solution of a second binder in water to form granules; drying the granules to remove water; and compressing the dried granules into a desired tablet form.

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TITLE OF THE INVENTION

WET GRANULATION FORMULATION FOR A PIPERAZINYL-CAMPHORSULFONYL OXYTOCIN RECEPTOR ANTAGONIST

5 FIELD OF THE INVENTION

This application is a continuation of U.S. Serial No. 08/326,418, filed October 20, 1994, the contents of which are hereby incorporated by reference.

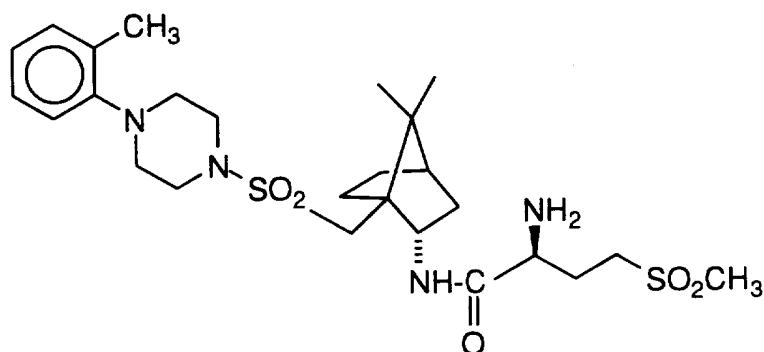
10 The present invention relates to solid dosage formulations and process for manufacture of an oxytocin receptor antagonist. More specifically, the invention relates to a wet granulation formulation of the oxytocin receptor antagonist compound.

BACKGROUND OF THE INVENTION

15 The pharmaceutical industry employs various methods for compounding pharmaceutical agents in tablet formulations. In particular, wet granulation is one of the more prevalent methods. In a typical solid formulation prepared by wet granulation, approximately 20 to 30% of the tablet weight comprises active ingredient and 70 to 20 80% comprises excipients (i.e., inert ingredients, additives).

A number of Piperazinylcamphorsulphonyl oxytocin receptor antagonists have been disclosed as being useful in the treatment of oxytocin-related conditions such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery. These oxytocin receptor 25 antagonist compounds and their utility in treating oxytocin-related disorders are described in EP Patent Publication No. 532,097, published 17 March 1993. The compound disclosed in Example 36 of EP 532,097, i.e., 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)-butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2- 30 methylphenyl)piperazine, is a potent, orally active oxytocin antagonist useful in the treatment of preterm labor and will hereafter be referred to as Compound A.

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Compound A

Preferred crystalline salts of Compound A, as well as an improved process for making Compound A and the crystalline salts of Compound A, are disclosed in EP Patent Publication Number 614,894, published 14 September 1994 and PCT International Application No. WO94/20483, published 15 September 1994. Standard methods for tablet formulation of Compound A, however, suffer difficulties. Because of the bulk of the active ingredient, i.e., Compound A, or a pharmaceutically acceptable salt thereof, and the high dose required to effectively treat the oxytocin-related conditions previously described, numerous problems in formulating a stable, robust tablet occurred. In the 600 mg dosage, almost 80% of the tablet weight is active ingredient and only about 20% of the tablet weight is excipients. This is contrasted with a typical solid formulation wherein the opposite is true, i.e., about 20% is active ingredient and 80% is excipients. Thus, standard methods of preparing a stable solid formulation of Compound A were unsuccessful.

The present invention now provides a wet granulated formulation of Compound A and process therefore wherein the tablet formulation is stable and robust.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of a tablet containing an active ingredient of 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-

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piperazine, or a pharmaceutically acceptable salt thereof, comprising the steps of:

- 5 (1) forming a powder blend of the active ingredient with a first binder and a diluent,
- (2) wet granulating the powder blend with a solution of a second binder in water to form granules,
- (3) drying the granules to remove water, and
- 10 (4) compressing the dried granules into a desired tablet form.

In one embodiment is the process wherein the tablet contains about 23 to 80% by weight of the active ingredient, preferably about 70 to 80% by weight of the active ingredient.

In a class is the process wherein the active ingredient is 1-
15 ((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine hemisulfate salt.

In a subclass is the process further comprising the step of coating the tablet.

20 Illustrative of the invention is the process wherein coating the tablet is accomplished by:

- (1) preparing a mixture of titanium dioxide and talc;
- (2) dry blending the mixture with hydroxypropyl methylcellulose and hydroxypropyl cellulose to form a dry
25 powdered blend;
- (3) adding the dry powdered blend to water to form a slurry;
- (4) adding water to the slurry with stirring to form a suspension; and
- 30 (5) applying the suspension to the tablets.

Exemplifying the invention is the process comprising the steps of:

- (1) forming a powder blend of the active ingredient with a first binder and a diluent from 3 to 25 minutes using a mixer;

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- (2) wet granulating the powder blend by adding a solution of a second binder dissolved in water to the powder blend while mixing over a 1 to 30 minute period to form granules;
- (3) drying the granules to remove water by the use of heated air in a Fluid-bed dryer or tray dryer for 10 minutes to 24 hours;
- (4) milling the dried granules to a uniform size;
- (5) adding and blending a disintegrant with the dried milled particles for 2 to 30 minutes;
- (6) adding and blending a lubricant to the mixture containing the disintegrant for 30 seconds to 20 minutes; and
- (7) compressing the lubricated granules mixture into a desired tablet form.

An illustration of the invention is the process wherein the tablet contains about 23 to 80% by weight of the active ingredient, preferably about 70 to 80% by weight of the active ingredient.

Further illustrating the invention is the process wherein the active ingredient is 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methanesulfonyl)butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine hemisulfate salt.

Additional illustrations of the invention include the process wherein: the diluent is microcrystalline cellulose; the first and second binders are selected from pregelatinized starch or PVP; the disintegrant is croscarmellose sodium; and the lubricant is magnesium stearate. Preferably, the first binder is pregelatinized starch and the second binder is PVP.

An example of the invention is the process further comprising the step of applying a coating to the tablet.

More particularly illustrating the invention is the process wherein coating the tablet is accomplished by:

- (1) preparing a mixture of titanium dioxide and talc;

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- 5
- (2) dry blending the mixture with hydroxypropyl methylcellulose and hydroxypropyl cellulose to form a dry powdered blend;
 - (3) adding the dry powdered blend to water to form a slurry;
 - (4) adding water to the slurry with stirring to form a suspension; and
 - (5) applying the suspension to the tablets.

More specifically exemplifying the invention is the process comprising the steps of:

- 10
- (1) forming a powder blend of the active ingredient, pregelatinized starch and microcrystalline cellulose in a mixer for 3 to 7 minutes;
 - 15 (2) wet granulating the powder blend by adding a solution of a PVP dissolved in water to the powder blend while mixing over a 5-8 minute period to form granules;
 - (3) drying the granules on a tray dryer for 5 to 9 hours to remove water;
 - 20 (4) milling the dried granules to a uniform size using a Quadro Comill type mill;
 - (5) adding and blending the disintegrant, croscarmellose sodium, with the dried milled particles for about 10 minutes;
 - 25 (6) adding and blending magnesium stearate lubricant to the mixture containing the croscarmellose sodium disintegrant with a V blender for 1 to 3 minutes; and
 - (7) compressing the lubricated granules mixture into a desired tablet form.

30 A further illustration of the invention is the process wherein the tablet contains about 23 to 80% by weight of the active ingredient, preferably about 70 to 80% by weight of the active ingredient.

Another example of the invention is the process wherein the active ingredient is 1-((7,7-Dimethyl-2-endo-(2S-amino-4-

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(methylsulfonyl)butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine hemisulfate salt.

Further exemplifying the invention is the process further comprising the steps of:

5

- (1) preparing a mixture of titanium dioxide and talc;
- (2) dry blending the mixture with hydroxypropyl methylcellulose and hydroxypropyl cellulose to form a dry powdered blend;
- 10 (3) forming a slurry by adding the dry powdered blend to water;
- (4) adding water to the slurry with stirring to form a suspension; and
- (5) applying the suspension to the tablets.

15

An additional illustration of the invention is a solid dosage form containing an active ingredient of 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine, or a pharmaceutically acceptable salt thereof, wherein the dosage form is prepared by the process.

20

DETAILED DESCRIPTION OF THE INVENTION

Granulation is the process of adding water to a powder mixture until granules are formed. The granulation step may be varied from 2 to 30 minutes, preferably 2 to 10 minutes, most preferably 4 to 8 minutes. Preferably, the granules are dried using a fluid bed dryer or tray dryer. Milling of the dried granules is accomplished using a Quadro Comill or Fitz mill. The lubrication step is the process of adding lubricant to the mixture; the lubrication step may be varied from 30 seconds to 20 minutes, preferably about 1 minute.

30

The disclosed process may be used to prepare solid dosage forms, particularly tablets, for medicinal administration.

The term "tablet," as used herein, is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes,

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whether coated or uncoated. Substances which may be used for coating include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), titanium dioxide, talc, sweeteners and colorants.

The term "active ingredient," as used herein includes both
5 the free base Compound A, as well as the pharmaceutically acceptable salts thereof.

Preferred diluents include: lactose, microcrystalline cellulose, calcium phosphate(s), mannitol, powdered cellulose, pregelatinized starch and other suitable diluents (see, e.g., Remington's
10 Pharmaceutical Sciences, 18th Edition, 1990, p. 1635).

Microcrystalline cellulose is particularly preferred. Specifically, microcrystalline cellulose NF, especially Avicel PH101, the trademarked name for microcrystalline cellulose NF manufactured by FMC Corp. is preferred.

15 Preferred binders include pregelatinized starch, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone (PVP) and other known binders (see, e.g., Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1635-1636. Most preferably, pregelatinized starch and/or PVP are employed
20 as binders. Specifically, starch pregelatinized NF 1500 manufactured by Colorcon Corporation and PVP 29/33 manufactured by TSP Technologies are most preferred.

The disintegrant may be one or more of several starches, clays, celluloses, algins, gums or crosslinked polymers known to those
25 skilled in the art. (See, e.g., Remington's Pharmaceutical Sciences, 18th Edition, 1990, p. 1637). Preferably, one or more of several modified starches or modified cellulose polymers, such as microcrystalline cellulose and croscarmellose sodium, are used. Croscarmellose sodium Type A, commercially available under the trade name "Ac-di-sol," is
30 particularly preferred.

Preferred lubricants include magnesium stearate, calcium stearate, stearic acid, surface active agents such as sodium lauryl sulfate, propylene glycol, sodium dodecane sulfonate, sodium oleate sulfonate and sodium laurate mixed with stearates and talc, sodium stearyl

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famerate and other known lubricants (see, e.g., Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1636-1637). Especially preferred is magnesium stearate.

The active ingredient, Compound A, can be prepared according to the methods disclosed in EP Patent Publication No. 532,097, published 17 March 1993, EP Patent Publication No. 614,894, published 14 September 1994 and PCT International Application No. WO94/20483, published 15 September 1994.

The pharmaceutically acceptable salts of Compound A may also be employed in the instant invention. Examples of pharmaceutically acceptable salts include the sulfate, tartrate, hydrochloride, maleate and phosphate salts. Preferably, crystalline salts of Compound A are employed. The crystalline sulfate salt, specifically the crystalline hemisulfate salt, is particularly preferred. The salts may be prepared by methods known in the art; the crystalline salts may be prepared according to the methods taught in EP Patent Publication No. 614,894, published 14 September 1994 and PCT International Application No. WO94/20483, published 15 September 1994.

The pharmaceutical compositions of the present invention comprise 23 to 80% by weight of an active ingredient which is Compound A, i.e., 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine, or a pharmaceutically acceptable salt thereof; 0 to 77% by weight of a first binder; 0 to 77% by weight of a diluent; 0 to 5% by weight of a second binder; 0 to 6% by weight of a disintegrant; and 0 to 5% by weight of a lubricant.

More specifically, the first and second binders are selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, pregelatinized starch or PVP; the diluent is selected from lactose, microcrystalline cellulose, calcium phosphate, mannitol, powdered cellulose or pregelatinized starch; the disintegrant is selected from microcrystalline or croscarmellose sodium; and the lubricant is selected from magnesium stearate, calcium stearate, steric acid or a surface active agent.

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In a specific embodiment, the first binder is pregelatinized starch; the diluent is microcrystalline cellulose; the second binder is PVP; the disintegrant is croscarmellose sodium; and the lubricant is magnesium stearate.

5 The pharmaceutical compositions of the present invention are preferably in the form of tablets. The tablets may be, for example, from 50 mg to 1.0 g in net weight, preferably 100 to 900 mg net weight, more preferably 200 to 870 mg net weight.

10 Preferred pharmaceutical compositions comprise about 23 to 80% by weight of the active ingredient, about 9 to 27% by weight of pregelatinized starch; about 9 to 51% by weight of microcrystalline cellulose; about 1 to 5% by weight of PVP 29/32; about 0.5 to 6% by weight of croscarmellose sodium; and about 0.1 to 5% by weight of magnesium stearate.

15 More preferred pharmaceutical compositions in accordance with the present invention comprise: about 65.2 to 76.71 % by weight of the active ingredient; about 9.39 to 27% by weight of pregelatinized starch; about 9.39 to 27% by weight of microcrystalline cellulose; about 1.0 to 5.0 % by weight of PVP 29/32; about 1.0 to 6% by weight of croscarmellose sodium; and about 0.5 to 5% by weight of magnesium stearate.

Preferred pharmaceutical compositions as envisioned for commercial development are as follows:

Tablets of 100 mg potency free base:

25 about 23.5% by weight of active ingredient; about 19% by weight of pregelatinized starch; about 50.9% by weight of microcrystalline cellulose; about 2% by weight of PVP 29/32; about 1.5% by weight of croscarmellose sodium; and about 1% by weight of magnesium stearate.

30 Tablets of 200 mg potency free base:

about 23.5% by weight of active ingredient; about 19% by weight of pregelatinized starch; about 50.9% by weight of microcrystalline cellulose; about 2% by weight of PVP 29/32; about

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1.5% by weight of croscarmellose sodium; and about 1% by weight of magnesium stearate.

Tablets of 600 mg potency free base:

about 76.71% by weight of active ingredient; about 9.39%

5 by weight of pregelatinized starch; about 9.39% by weight of microcrystalline cellulose; about 2% by weight of PVP 29/32; about 1.5% by weight croscarmellose sodium; and about 1% by weight of magnesium stearate.

The tablets of the 200 mg potency are preferably
10 formulated in an 850 mg tablet containing 425 μ l purified water per tablet. The 600 mg potency tablets are preferably formulated in an 850 mg tablet containing 510 μ l purified water per tablet.

In a particularly preferred embodiment, the tablet
15 formulations of the instant invention are coated. In the pharmaceutical compositions envisioned for commercial development described above, the tablets of 200 mg and 600 mg potency free base are coated with about 0.78% by weight of hydroxypropyl methylcellulose; about 0.78% by weight of hydroxypropyl cellulose; about 0.31% by weight titanium dioxide; and about 0.078% by weight of purified talc.

20 In a most preferred embodiment, the active ingredient in the above-described pharmaceutical compositions is the hemisulfate salt of Compound A.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation
25 ingredients selected from a wide variety of excipients (also referred to as "additives") known in the pharmaceutical formulation art. According to the desired properties of the tablet, any number of additives may be selected, alone or in combination, based upon their known uses in preparing tablet compositions. Such additives include, but are not
30 limited to, diluents, binders, compression aids, disintegrants, lubricants, flavors, flavor enhancers, sweeteners and preservatives.

The pharmaceutical compositions of the present invention are useful in the therapeutic treatment of oxytocin-related disorders

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such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being
5 limitations on the scope or spirit of the invention.

EXAMPLE 1

Procedure for Manufacturing 600 mg Potency Tablets of Compound A

10

<u>Ingredients</u>	<u>Per Tablet</u>	<u>Per 2600 Tablets</u>
Active Ingredient (Crystalline hemisulfate salt 15 of Compound A)	652.2 mg	1695.72 g
Starch Pregelatinized NF 1500	79.78 mg	207.43 g
20 Microcrystalline Cellulose NF Avicel PH 101	79.78 mg	207.43 g
Magnesium Stearate Impalpable Powder NF	8.5 mg	22.1 g
25 Croscarmellose Sodium NF	12.75 mg	33.15 g
PVP 29/32	17.0 mg	44.2 g
30 Water Purified	510 µl	1326 ml

The active ingredient (equivalent to 600 mg anhydrous free
base per tablet) was mixed with the starch pregelatinized NF 1000 and
microcrystalline cellulose NF in a high Fielder 10/25 mixer for 3
35 minutes. The PVP 29/32 was dissolved in the water and this solution
added to the powder mixture with the mixer running over a period of
1.5 to 3.0 minutes then granulated for 4.5 minutes to form granules.
The wet granules were dried at about 47°C (range 46 to 48°C) in a tray

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dryer for 5.0 hours. The dried granules were then milled using a Quadro Comill to achieve fine granules. After milling, croscarmellose sodium NFS (disintegrant) was added to the fine granules and mixed in a V blender for 10 minutes. Magnesium stearate impalpable powder NF
 5 (lubricant) was added to this blend through a 60 mesh stainless steel screen and blended in the V blender for 1 minute. The lubricated mixture was compressed to provide tablets of 600 mg active ingredient (free base equivalent).

10

EXAMPLE 2

Procedure for Manufacturing 600 mg Potency Coated Tablets of Compound A

15	<u>Ingredients</u>	<u>Per Tablet</u>	<u>Per 2600 Tablets</u>
	Hydroxypropyl Methylcellulose USP (HPMC)	6.8 mg	17.68 g
20	Hydroxypropyl Cellulose NF with < 0.3% Silica (HPC)	6.8 mg	17.68 g
	Titanium Dioxide USP	2.72 mg	7.072 g
25	Talc USP Purified	0.68 mg	1.768 g
	Water Purified	To 170 µl	To 442 ml

The titanium dioxide and talc, USP were mixed and passed
 30 through a 60 mesh stainless steel screen. This mixture was mixed with HPMC and HPC to form a dry blend. The dry blend was added to water (147 ml) which was previously heated to 90°C with mild agitation to ensure that the blend is wetted to form a slurry. The remainder of the water (up to 442.0 ml) was added to the slurry at ambient
 35 temperature with gentle agitation to form a suspension. The suspension was then applied to the tablets from Example 1 using the following guidelines to provide the coated tablets.

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Pan: suitable size

Pan Speed: 20 RPM

Nozzles: 2850 liquid/120 air

Inlet Temperature: 85°C

5 Bed Temperature: 47°C

Spray Rate: ca. 2.0 g/minute/kg Tablets

EXAMPLE 3

10	<u>Active Ingredients</u>	<u>Per Tablet</u>	<u>Per 7000 Tablets</u>
	Active Ingredient (Crystalline hemisulfate salt of Compound A)	217.39 mg	1521.73 g
15	Starch Pregelatinized NF 15000	161.5 mg	1130.5 g
20	Microcrystalline Cellulose NF Avicel PH 101	432.86 mg	3030.02 g
	Magnesium Stearate Impalpable Powder NF	8.5 mg	59.5 g
25	Croscarmellose Sodium NF	12.75 mg	89.25 g
	PVP 29/32	17.0 mg	119 g
30	Water Purified	425 µl	2975 ml

35 The active ingredient (equivalent to 200 mg anhydrous free base per table) was mixed with starch pregelatinized NF 1500 and microcrystalline cellulose NF in a Fielder mixer at slow speed for 5 minutes, then at fast speed for 2 more minutes. PVP 29/32 was dissolved in water and the resulting solution added to the powder mixture in the fielder with the mixture running over a period of 3 to 5 minutes, then granulating for 8 minutes to form granules. The wet granules were dried at about 47°C (range 46-48°C) for 8.63 hours. The

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dried granules were then milled using a Quadro Comill to achieve fine granules. After milling, croscarmellose sodium NF (disintegrant) was added to fine granules and mixed in a V Blender for 10 minutes. Magnesium stearate impalpable powder NF (lubricant) was added to this
5 blend through a 60 mesh stainless steel screen and blended in the V blender for 1 minute. The lubricated mixture was compressed to provide tablets of 200 mg active ingredient (free base equivalent).

EXAMPLE 4

10

Procedure for Making 200 mg Potency Coated Tablets of Compound A

	<u>Ingredients</u>	<u>Per Tablet</u>	<u>Per 7000 Tablets</u>
15	HPMC USP	6.8 mg	47.6 g
	HPC with < 0.3% Silica	6.8 mg	47.6 g
	Titanium Dioxide USP	2.72 mg	19.04 g
20	Talc	0.68 mg	4.76 g
	Water	To 170 µl	To 1190.0 ml

25 Using essentially the procedure of Example 2 and applying the suspension to the tablets from Example 3, 200 mg potency coated tablets were formed.

30 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, modifications, deletions or additions of procedures and protocols described herein, as come within the scope of the following claims and their equivalents.

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WHAT IS CLAIMED IS:

1. A process for the preparation of a tablet containing an active ingredient of 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine, or a pharmaceutically acceptable salt thereof, comprising the steps of:
- 5
- (1) forming a powder blend of the active ingredient with a first binder and a diluent,
 - 10 (2) wet granulating the powder blend with a solution of a second binder in water to form granules,
 - (3) drying the granules to remove water, and
 - (4) compressing the dried granules into a desired tablet form.

15
2. The process of Claim 1, wherein the tablet contains about 70 to 80% by weight of the active ingredient.
3. The process of Claim 1, comprising the steps of:
- 20
- (1) forming a powder blend of the active ingredient with a first binder and a diluent from 3 to 25 minutes using a mixer;
 - (2) wet granulating the powder blend by adding a solution of a second binder dissolved in water to the powder blend while mixing over a 1 to 30 minute period to form granules;
 - 25 (3) drying the granules to remove water by the use of heated air in a Fluid-bed dryer or tray dryer for 10 minutes to 24 hours;
 - (4) milling the dried granules to a uniform size;
 - 30 (5) adding and blending a disintegrant with the dried milled particles for 2 to 30 minutes;
 - (6) adding and blending a lubricant to the mixture containing the disintegrant for 30 seconds to 20 minutes; and

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- (7) compressing the lubricated granules mixture into a desired tablet form.

4. The process of Claim 3, wherein the tablet contains
5 about 70 to 80% by weight of the active ingredient.

5. The process of Claim 3, wherein the diluent is microcrystalline cellulose; the first and second binders are selected from pregelatinized starch or PVP; the disintegrant is croscarmellose sodium;
10 and the lubricant is magnesium stearate.

6. The process of Claim 5, wherein the active ingredient is 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)-butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine hemisulfate salt, the first binder is
15 pregelatinized starch and the second binder is PVP.

7. The process of Claim 3, comprising the steps of:

- 20 (1) forming a powder blend of the active ingredient, pregelatinized starch and microcrystalline cellulose in a mixer for 3 to 7 minutes;
- (2) wet granulating the powder blend by adding a solution of a PVP dissolved in water to the powder blend while mixing
25 over a 5-8 minute period to form granules;
- (3) drying the granules on a tray dryer for 5 to 9 hours to remove water;
- (4) milling the dried granules to a uniform size using a Quadro Comill type mill;
- 30 (5) adding and blending the disintegrant, croscarmellose sodium, with the dried milled particles for about 10 minutes;

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- 5 (6) adding and blending magnesium stearate lubricant to the mixture containing the croscarmellose sodium disintegrant with a V blender for 1 to 3 minutes; and
- (7) compressing the lubricated granules mixture into a desired tablet form.

8. The process of Claim 7, wherein the tablet contains about 70 to 80% by weight of the active ingredient.

10 9. The process of Claim 7, wherein the active ingredient is 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)-butyramido)bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine hemisulfate salt.

15 10. The process of Claim 7, further comprising coating the tablet by:

- (1) preparing a mixture of titanium dioxide and talc;
- 20 (2) dry blending the mixture with hydroxypropyl methylcellulose and hydroxypropyl cellulose to form a dry powdered blend;
- (3) forming a slurry by adding the dry powdered blend to water;
- (4) adding water to the slurry with stirring to form a suspension; and
- 25 (5) applying the suspension to the tablets.

30 11. A solid dosage form containing an active ingredient of 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine, or a pharmaceutically acceptable salt thereof, wherein the dosage form is prepared by the process of Claim 1.

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12. A pharmaceutical composition comprising by weight, about 23 to 80% by weight of an active ingredient which is 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)bicyclo-(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine, or a
5 pharmaceutically acceptable salt thereof; 0 to 77% by weight of a first binder; 0 to 77% by weight of a diluent; 0 to 5% by weight of a second binder; 0 to 6% by weight of a disintegrant; and 0 to 5% by weight of a lubricant.
13. The pharmaceutical composition of Claim 12,
10 wherein the first and second binders are selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, pregelatinized starch or PVP; the diluent is selected from lactose, microcrystalline cellulose, calcium phosphate, mannitol, powdered cellulose or pregelatinized starch; the
15 disintegrant is selected from microcrystalline cellulose or croscarmellose sodium; and the lubricant is selected from magnesium stearate, calcium stearate, steric acid or a surface active agent.
14. The pharmaceutical composition of Claim 13,
20 comprising by weight, about 23 to 80% by weight of the active ingredient, about 9 to 27% by weight of pregelatinized starch, about 9 to 51% by weight of microcrystalline cellulose, about 1 to 5% by weight of PVP 29/33, about 0.5 to 6% by weight of croscarmellose sodium and about 0.1 to 5% by weight of magnesium stearate.
15. The pharmaceutical composition of Claim 14,
25 comprising by weight, about 65.2 to 76.71% by weight of the active ingredient, about 9.39 to 27% by weight of pregelatinized starch, about 9.39 to 27% by weight of microcrystalline cellulose, about 1.0 to 5.0%
30 by weight of PVP 29/32, about 1.0 to 6% by weight of croscarmellose sodium and about 0.5 to 5% by weight of magnesium stearate.
16. The pharmaceutical composition of Claim 15,
comprising by weight, about 76.71% by weight of the active ingredient,

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about 9.39% by weight of pregelatinized starch, about 9.39 by weight of microcrystalline cellulose, about 2% by weight of PVP 29/32, about 1.5% by weight croscarmellose sodium and about 1% by weight of magnesium stearate.

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17. The pharmaceutical composition of Claim 16, further comprising a coating of about 0.78% by weight of hydroxypropyl methylcellulose, about 0.78% by weight of hydroxypropyl cellulose, about 0.31% by weight titanium dioxide and
10 about 0.078% by weight of purified talc.

18. The pharmaceutical composition of Claim 16, wherein the active ingredient is 1-((7,7-Dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)bicyclo(2.2.1)heptan-1-yl)methane-
15 sulfonyl)-4-(2-methylphenyl)piperazine hemisulfate salt.

19. A tablet prepared from the pharmaceutical composition of Claim 16.

20. The pharmaceutical composition of Claim 14, comprising about 23.5% by weight of active ingredient; about 19% by weight of pregelatinized starch; about 50.9% by weight of microcrystalline cellulose; about 2% by weight of PVP 29/32; about 1.5% by weight of croscarmellose sodium; and about 1% by weight of
25 magnesium stearate.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/13342

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/20, 9/28, 31/495; A01N 43/60

US CL : 424/465,474; 514/255

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/465,474; 514/255

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y ---- A	EP, A, 0 614 894 (MERCK & CO. INC.) 14 September 1994, pages 1, 16 and 17.	1, 2 and 11-13 ----- 3-10 and 14-20
Y --- A	EP, A, 0 532 097 (MERCK & CO. INC.) 17 March 1993, pages 1, 2, 13 and 14.	1, 2 and 11-13 ----- 3-10 and 14-20
A	US, A, 4,806,359 (RADEBAUGH ET AL) 21 February 1989, see entire document.	1-10
A	US, A, 5,073,380 (BABU ET AL) 17 December 1991, see entire document.	1-10

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Further documents are listed in the continuation of Box C.

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See patent family annex.

* Special categories of cited documents:	*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A document defining the general state of the art which is not considered to be of particular relevance	*X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G document member of the same patent family
*O document referring to an oral disclosure, use, exhibition or other means	
*P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 JANUARY 1996

Date of mailing of the international search report

31 JAN 1996

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/13342

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STNCAS, STNEXPRESS-structure search

search terms: 1-7,7-dimethyl-2-endo-2s-amino-4-methyl-sulfonyl-butyramido-bicyclo-2.2.1-heptan-1-yl-methane sulfonyl-4-2-methylphenyl-piperazine, piperazinylcamphorsulphonyl and oxytocin receptor antagonists, wet granulation, binder, tablet