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(54) Titre : NOUVELLE FORME GALENIQUE
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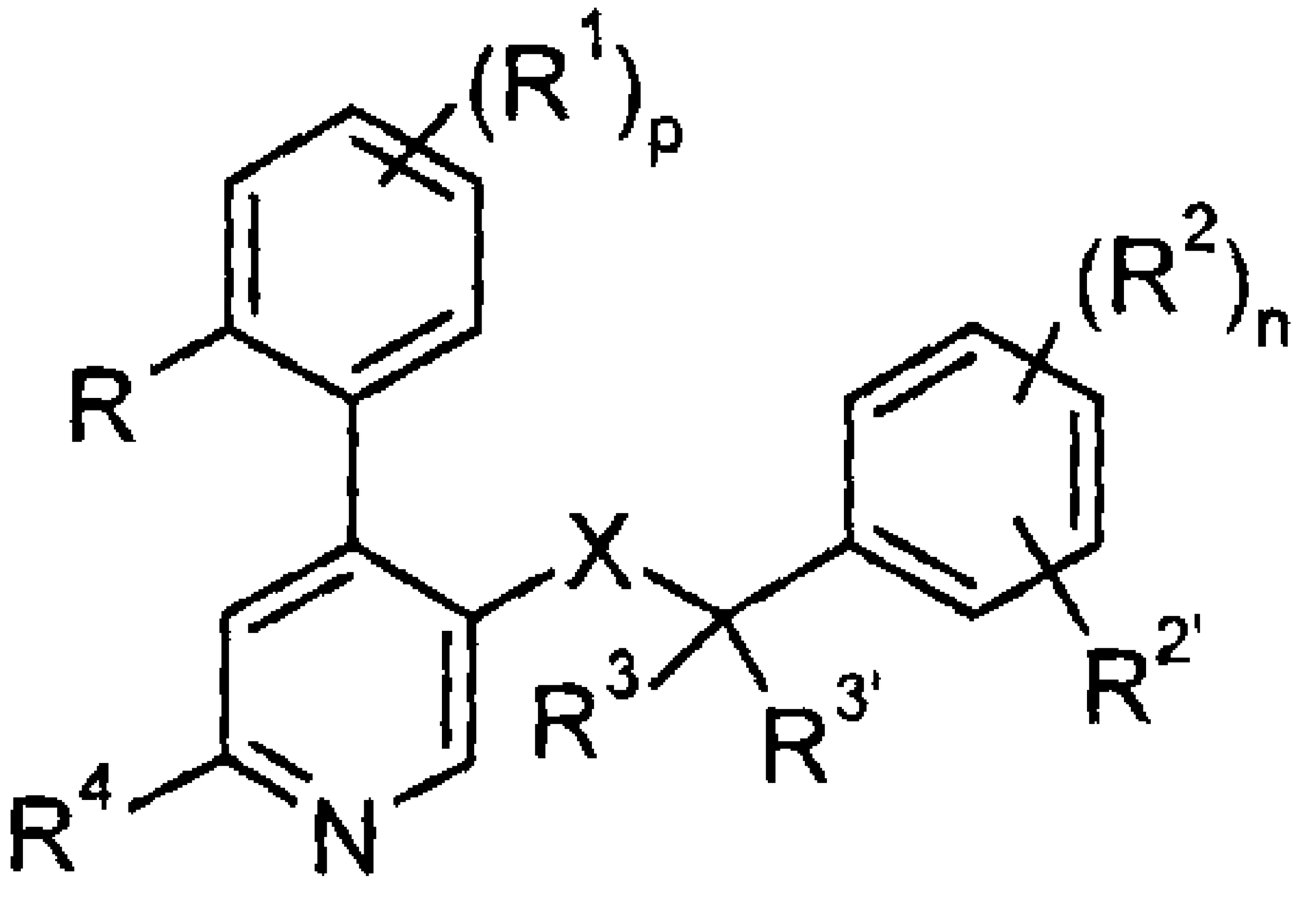


I

(57) Abrégé/Abstract:
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(57) Abrégé(suite)/Abstract(continued):
soluble poloxamer are together processed by hot melt extrusion before mixing with the other ingredients, and wherein the tablet composition may thereafter be coated with a composition comprising an immediate release film coating system and purified water. The invention related also to pharmaceutical compositions, prepared by such method.

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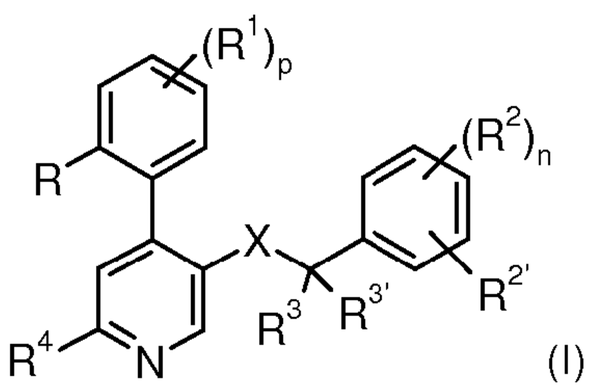
(54) Title: NOVEL DOSAGE FORMULATION



(I)

(57) Abstract: The invention relates to a process for preparing a pharmaceutical tablet composition, wherein the active pharmaceutical ingredient of formula (I) wherein the definitions are described in claim 1 or pharmaceutically acceptable acid addition salts thereof and a water soluble poloxamer are together processed by hot melt extrusion before mixing with the other ingredients, and wherein the tablet composition may thereafter be coated with a composition comprising an immediate release film coating system and purified water. The invention related also to pharmaceutical compositions, prepared by such method.

# NOVEL DOSAGE FORMULATION

The present invention relates to a new process for preparation of galenic compositions and, in particular, to galenic compositions for oral administration of medicaments.

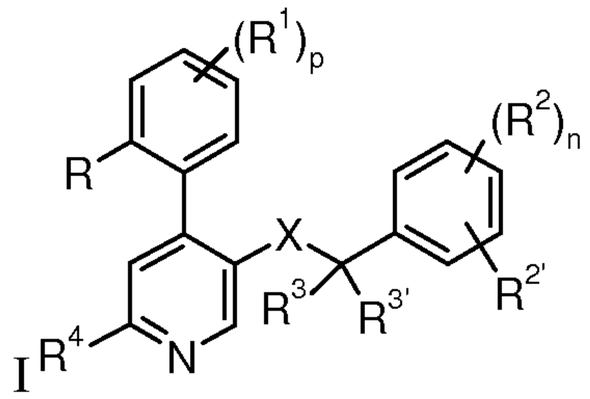
Oral dosage forms are designed to enable sufficient availability of the active compound at its site of action. The bioavailability of a drug depends on several parameters, such as on the physicochemical nature of the active compound, the dosage form, as well as on physiological factors.

Many substances obtained from modern drug discovery are problematic because of insufficient bioavailability. Such molecules often exhibit very low aqueous solubility and limited solubility in oils. Furthermore many substances exhibit significant food effects, i.e., when drugs and certain foods are taken at the same time they can interact in ways that diminish the effectiveness of the ingested drug or reduce the absorption of food nutrients. Additionally, vitamin and herbal supplements taken with prescribed medication can result in adverse reactions.

Some examples of how foods and drugs can interact include:

- § Food can speed up or slow down the action of a medication.
- § Impaired absorption of vitamins and minerals in the body.
- § Stimulation or suppression of the appetite.
- § Drugs may alter how nutrients are used in the body.

Now it has been found that a group of NK-1 receptor antagonists of formula



I I

wherein

R is lower alkyl, lower alkoxy, halogen or trifluoromethyl

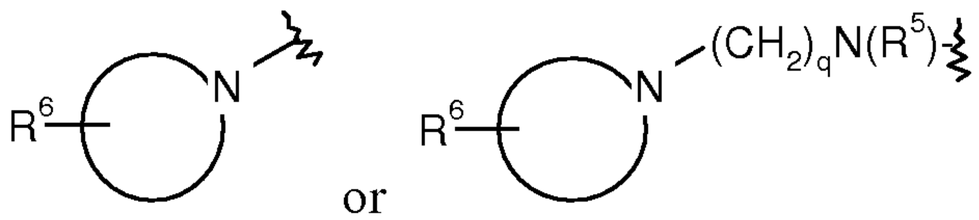
$R^1$ is halogen or hydrogen; and when p is 1, $R^1$ may in addition to the above substituents be taken together with R to form –CH=CH–CH=CH–;

$R^2$ and $R^{2'}$ are each independently hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano;

and when n is 1, $R^2$ and $R^{2'}$ may in addition to the above substituents form –CH=CH–CH=CH–, unsubstituted or substituted by one or two substituents selected from lower alkyl or lower alkoxy;

$R^3$ and $R^{3'}$ are hydrogen, lower alkyl or taken together with the attached carbon atom form a cycloalkyl group;

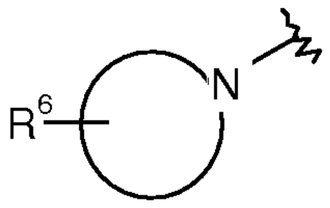
$R^4$ is hydrogen, $–N(R^5)(CH_2)_nOH$, $–N(R^5)S(O)_2$—lower alkyl, $–N(R^5)S(O)_2$—phenyl, $–N{=}CH—N(R^5)_2$, $–N(R^5)C(O)R^5$,



or

$R^5$ is hydrogen, $C_{3-6}$-cycloalkyl, benzyl, or lower alkyl;

$R^6$ is hydrogen, hydroxy, lower alkyl, $–(CH_2)_nCOO—(R^5)$, $–N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, $-(CH_2)_nCN$, $–(CH_2)_nO(CH_2)_nOH$, –CHO or a 5- or 6-membered heterocyclic ring containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, and with one of the carbon atoms in said ring being unsubstituted or substituted with an oxo group, which heterocyclic ring is directly bonded or bonded via an alkylene group to the remainder of the molecule;



is a cyclic tertiary amine which may contain one additional heteroatom selected from the group consisting of oxygen, nitrogen, or sulfur, wherein any sulfur present in the ring is thio or can be oxidized to sulfoxide or sulfur dioxide by which said cyclic tertiary amine is directly attached to the remainder of the molecule or is attached through the linker $-(CH_2)_nN(R^5)-$;

X is $-C(O)N(R^5)-$, $-(CH_2)_mO-$, $-(CH_2)_mN(R^5)-$, $-N(R^5)C(O)-$, or $-N(R^5)(CH_2)_m-$;

n, p, and q are each independently 1 to 4; and

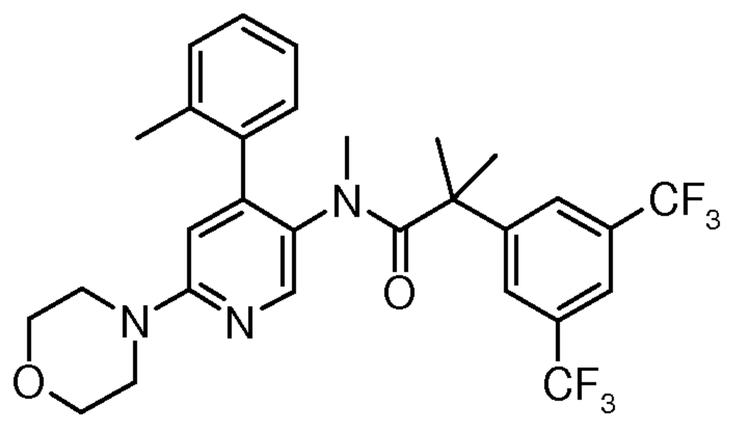
m is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof

in crystalline form, which is practically insoluble in water (for example <0.0001 mg/ml) and in simulated gastric fluid (for example 0.08 mg/ml) at 25°C, may be formulated in a dosage formulation which is suitable and applicable for human patients. Such formulation may overcome the disadvantage of practically insolublility in simulated intestinal fluid fore these compounds. The preferred dosage formulation is a tablet with 400 mg active ingredient.

Compounds of formula I are known compounds and are described in EP 1,035,115 as active NK1 receptor antagonists for the treatment of CNS disorders, such as depression, anxiety and emesis.

A preferred compound of formula I is the compound, 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide, having the structural formula



and which exhibits the above noted insolubilities, i.e. <0.0001 mg/ml in water and aqueous buffer solutions of pH 3.0-7.0.

As a main goal to increase bioavailability and decrease side effects, such as food effects in a 400 mg tablet, a new galenic formulation approach was investigated. It has been found that the hot melt extrusion (HME) approach solves the above-mentioned problems.

The object of the present invention is a process for preparing a pharmaceutical tablet composition, wherein the active pharmaceutical ingredient of formula I or pharmaceutically acceptable acid addition salts thereof and a water soluble poloxamer are together processed by hot melt extrusion before mixing with the other ingredients, and wherein the tablet composition may thereafter be coated with a composition comprising an immediate release film coating system and purified water.

It was found that the hot melt extrusion (HME) approach wherein the active ingredient and a water soluble poloxamer, such as, Poloxamer 188 (Lutrol™ F68) a tablet binder and wetability agent are the only components which are processed through the extruder led to a microcrystalline solid dispersion having low particle size, acceptable particle dispersability and dissolution characteristics that when combined with other excipients produced a tablet having the desired drug dissolution characteristics.

The following definitions of general terms used herein apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

The term “lower alkyl” denotes a straight- or branched-chain alkyl group containing from 1 to 7 carbon atoms. Nonlimiting examples of lower alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl, and the like.

The term “alkylene group” means a lower alkyl linker which is bound to a group at either end. Nonlimiting examples of alkylene groups include methylene, ethylene, propylene, and the like.

The term “lower alkoxy” denotes a alkyl group as defined above, which is attached through an oxygen atom. Nonlimiting examples of lower alkoxy groups include methoxy, ethoxy, propoxy, and the like.

The term “cycloalkyl” denotes a saturated carbocyclic group (e.g. a nonaromatic ring) containing 3 to 6 carbon atoms. Nonlimiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "halogen" denotes chlorine, iodine, fluorine, and bromine.

Processing aids are excipients that improve the manufacturability of the formulation by improving for instance the flowability and avoiding sticking. One type of processing aids is "Colloidal silicon dioxide", a submicroscopic fumed silica with a particle size of about 15 nm. It is light, loose, bluish-white-colored, odorless, tasteless nongritty amorphous powder. Nonlimiting examples of colloid silicon dioxides useful in the invention include Aerosil™ 380 and Cab-O-Sil™.

Nonlimiting examples of tablet filler/diluent include starch, modified starch derivatives, cellulose, calcium salts, sugar and sugar alcohols. Starch is a substance consisting of amylase and amylopectin, two polysaccharides based on α-glucose. One type of starch that can be used in the invention is corn starch. Nonlimiting examples of corn starches that can be used in the invention include Pure-Cote™, Pure-Bind™, Pure-Dent™, Pure-Gel™, Pure-Set™, Melojel™, Meritena™, Paygel55™, Perfectamyl™ D6PH, Purity™ 21, Purity™ 826, and Tablet White™.

One type of cellulose that can be used as tablet filler/diluent is microcrystalline cellulose. "Microcrystalline cellulose" (MCC) is a naturally occurring polymer comprised of a glucose units connected by a 1-4β glycosidic bond. MCC can be derived from a special grade of alpha cellulose. Nonlimiting examples of MCC that can be used in the invention include Avicel™, Vivapur™, Vivacel™, Emcocel™. One type of sugar alcohol that can be used as tablet filler/diluent is mannitol. Nonlimiting examples of mannitol that can be used in the invention include Parteck™ M 200.

Different types of disintegrants such as NVP water-swellable polymers, croscarmellose and cellulose derivatives can be used in the invention. An "NVP water-swellable polymer" is an insoluble, swellable homo- or heteropolymer containing N-vinylpyrrolidone, e.g. N-vinyl-2-pyrrolidone.

"Pharmaceutically acceptable acid addition salts" embraces salts with inorganic or organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric

acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

"Water-soluble poloxamers" are block copolymers of ethylene oxide ,i.e. polyoxyethylene (POE) and propylene oxide, i.e. polyoxypropylene (POP) that are soluble in water and are used as wetting agents in pharmaceutical formulations. Nonlimiting examples of poloxamers useful in the present invention include Lutrol F68 (poloxamer 188).

"Extrusion" is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions.

The present invention provides a composition which comprises a hot melt extrudate that comprises a compound of formula I and a water-soluble poloxamer. In particular, the invention provides a composition comprising a hot melt extrudate that comprises a compound of formula I, such as 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramidehydrochloride and a water-soluble poloxamer, such as Lutrol F68.

The new pharmaceutical tablet composition comprises

| | |
|---|---|
| a) an active ingredient of formula I | 30-60 % |
| b) a water soluble poloxamer | 10-20 % |
| c) a filler | 20-30 % |
| d) a disintegrant | 1-10 % |
| e) processing aid and | 0-5 % and |
| f) glidant | 0-5 %, and if desired |
| g) immediate release film coating system | 2 -5 % of the tablet weight |
| h) purified water | |

| **An example of a representative formulation composition comprises the ingredients** | **mg/Tablet** |
|---|---|
| 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide hydrochloride | 400.00 |
| Lutrol F68 | 133.35 |
| Microcrystalline Cellulose(Avicel PH102) | 162.65 |
| Parteck M 200(Mannitol) | 30.00 |
| Polyplasdone XL | 16.00 |
| Colloidal Silicon Dioxide(Aerosil 380) | 16.00 |
| Corn Starch | 30.00 |
| Magnesium Stearate | 12.00 |
| Total Weight of Kernel | 800.00 |

An example of a representative coating composition comprises

Opadry™ Yellow 03K 12429

25.00

Purified Water 131.25

Total Weight of Film Coated Tablet 825.00

Manufacturing Process:

The process for preparing a pharmaceutical tablet composition according to the present invention comprises the following steps:

1) blending the active pharmaceutical ingredient with a water soluble Poloxamer™,

2) preparing the hot melt extrudates using the powder blend from step 1,

3) passing the extruded material through a sieving machine in order to get milled material, whereby more than one sieving step maybe necessary in order receive material in the desired particle size range,

4) blending the milled extrudate from step 3 in a first step with the filler(s) and disintegrant,

5) preparing the final blend by blending the mixture form step 4 with the processing aid and glidants, and

6) compressing the final blend prepared in step 5 to tablets.

More specifically, the process comprises the following steps:

- About 50 % of the active pharmaceutical ingredient/drug substance is placed in a blender, e.g. PK, Bin or Bohle mixer.
- The water soluble poloxamer is added and then the remainder of the drug substance is added.
- The material is mixed for about 30 minutes.
- The powder mix from step 3 is transferred into the hot melt extruder (e.g. Leistritz) using a hopper-feeder (e.g. K-Tron Soder) and the powder mix is passed through the hot melt extruder.
- The hot melt extrusion product is collected at room temperature.
- Thereafter the extruded material is first passed through a sieving machine, e.g. FitzMill set using slow speed knives forward through a #3 screen and then at medium speed knives forward through a #2 screen.
- About 50 % of the milled material is placed in a PK blender or equivalent along with the filler (e.g. Avicel PH 102 or Parteck M 200, after passing through a #40 mesh screen), Corn Starch, the disintegrant (e.g. Polyplasdone XL) and other excipients (e.g. Aerosil, 380 after passing through a # 12 mesh screen), and thereafter the remaining milled material is added and mixed for 30 minutes.
- About 50% of the powder mixture is removed and the glidant (e.g. Magnesiun Stereate, after passing through a #40 mesh screen) is added to the remaining material in the blender and the balance of the powder mixture is readded and mixed for 5 minutes, and
- The final blend is compressed to tablets, using for instance 0.738" x 0.344" oval shaped punches.

The kernels may be coated as follows:

1) In a stainless steel container a complete film coating system, e.g. the Opadry Yellow, is dispersed in purified water by mixing for 45 minutes until completely dispersed to form a coating suspension,

2) The kernels are placed into a perforated coating pan and heated with inlet air of 45° +/- 5°C with intermittent jogging until the exhaust air reaches 40° +/- 5°C,

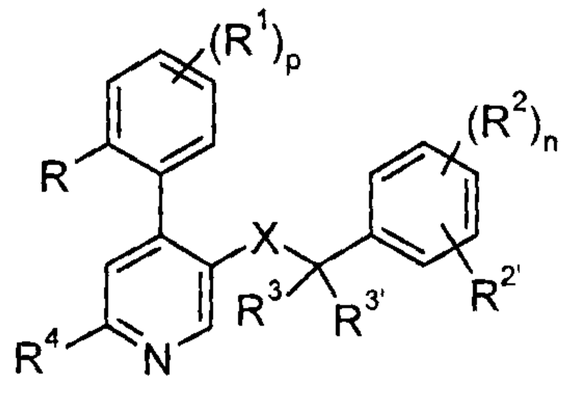
3) Thereafter the inlet temperature is increased to 60° +/-5°C and the kernels coated with the coating suspension stirring continuously and using an air spray system applying a certain amount of the film coat (approx. 2 to 5 % of the tablet weight) on a dry basis per tablet,

4) The coated tablets are dried by jogging until the moisture content is less than 2%, and

5) The tablets are cooled to room temperature and stored in a tight double polyethylene-lined container.

**CLAIMS:**

1. A process for preparing a pharmaceutical tablet composition, wherein the active pharmaceutical ingredient of formula I



I

wherein

R is lower alkyl, lower alkoxy, halogen or trifluoromethyl

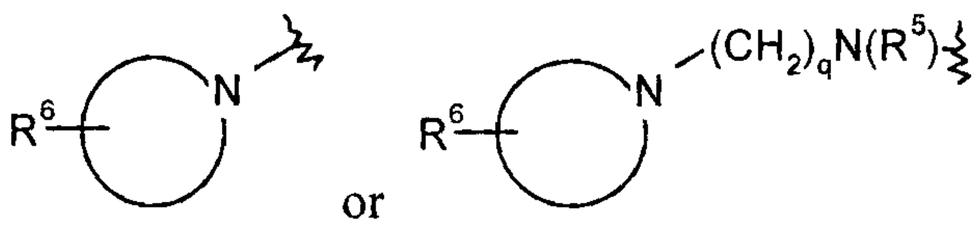
$R^1$ is halogen or hydrogen; and when p is 1, $R^1$ is one of the above substituents, or is taken together with R to form –CH=CH–CH=CH–;

$R^2$ and $R^{2'}$ are each independently hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano;

and when n is 1, $R^2$ and $R^{2'}$, each are one of the above substituents, or form –CH=CH–CH=CH–, unsubstituted or substituted by one or two substituents selected from lower alkyl or lower alkoxy;

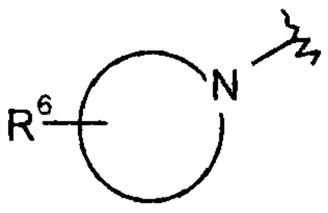
$R^3$ and R3' are hydrogen, lower alkyl or taken together with the attached carbon atom form a cycloalkyl group;

$R^4$ is hydrogen, $–N(R^5)(CH_2)_nOH$, $–N(R^5)S(O)_2$—lower alkyl, $–N(R^5)S(O)_2$—phenyl, –N=CH—$N(R^5)_2$, $–N(R^5)C(O)R^5$,



$R^5$ is hydrogen, $C_{3-6}$-cycloalkyl, benzyl, or lower alkyl;

$R^6$ is hydrogen, hydroxy, lower alkyl, $-(CH_2)_nCOO—(R^5)$, $-N(R^5)CO$-lower alkyl, hydroxy-lower alkyl, $-(CH_2)_nCN$, $-(CH_2)_nO(CH_2)_nOH$, –CHO or a 5- or 6-membered heterocyclic ring containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, and with one of the carbon atoms in said ring being unsubstituted or substituted with an oxo group, which heterocyclic ring is directly bonded or bonded via an alkylene group to the remainder of the molecule;



is a cyclic tertiary amine which contains no additional heteroatom or one additional heteroatom selected from the group consisting of oxygen, nitrogen, or sulfur, wherein any sulfur present in the ring is thio or is oxidized to sulfoxide or sulfur dioxide by which said cyclic tertiary amine is directly attached to the remainder of the molecule or is attached through the linker

$-(CH_2)_nN(R^5)–$;

X is $–C(O)N(R^5)–$, $–(CH_2)_mO–$, $–(CH_2)_mN(R^5)–$, $–N(R^5)C(O)–$, or $–N(R^5)(CH_2)_m–$;

n, p, and q are each independently 1 to 4; and

m is 1 or 2;

or pharmaceutically acceptable acid addition salts thereof and a water soluble Poloxamer™ are together processed by hot melt extrusion before mixing with the other ingredients.

2. The process for preparing the pharmaceutical tablet composition according to claim 1, wherein after the mixing of the ingredients, the tablet composition is coated with a composition comprising an immediate release film coating system and purified water.

3. The process for preparing the pharmaceutical tablet composition according to claim 1 or 2, comprising the following steps:

1) blending the active pharmaceutical ingredient with the water soluble Poloxamer™,

2) preparing the hot melt extrudates using the powder blend from step 1,

3) passing the extruded material through a sieving machine in order to get milled material.

4) blending the milled extrudate from step 3 in a first step with the filler(s) and disintegrant,

5) preparing the final blend by blending the mixture form step 4 with the processing aid and glidants, and

6) compressing the final blend prepared in step 5 to tablets.

4. The process for preparing the pharmaceutical tablet composition according to claim 3, wherein more than one sieving step is necessary in order to receive material in the desired particle size range.

5. A pharmaceutical tablet composition prepared according to the process defined in any one of claims 1 to 4 comprising:

| | |
|---|---|
| a) an active ingredient of formula I | 30-60% |
| b) a water soluble poloxamer | 10-20% |
| c) a filler | 20-30% |
| d) a disintegrant | 1-10% |
| e) processing aid and | 0-5% and |
| f) glidant | 0-5%, and if desired |
| g) immediate release film coating system | 2 -5% of the tablet weight |

h) and purified water.

6. The pharmaceutical tablet composition according to claim 5, wherein the tablet contains 400 mg of an active ingredient of formula I.

7. The pharmaceutical tablet composition according to claim 5, wherein the active ingredient is 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide.

8. The pharmaceutical tablet composition according to claim 5, wherein the water soluble poloxamer is a block copolymer of ethylene oxide (POE) or propylene oxide (POP).

9. The pharmaceutical tablet composition according to claim 8, wherein the water soluble poloxamer is Lutrol™ F68.

10. The pharmaceutical tablet composition according to claim 5, wherein the filler is a mixture of corn starch, microcrystalline cellulose and sugar alcohol.

11. The pharmaceutical tablet composition according to claim 10, wherein the filler is pure-Cote™ or Pure-Bind™ or Pure-Dent™ or Pure Gel™ or Pure-Set™ or Melojel™ or Meritena™ or Paygel55™ or perfectamylD6PH™ or Purity 21™ or Purity 826™ or Tablet White™ and Avicel™ or Vivapur™ or Vivacel™ or Emcocel™ or Parteck™ M 200.

12. The pharmaceutical tablet composition according to claim 5, wherein the processing aid is colloidal silicon dioxide.

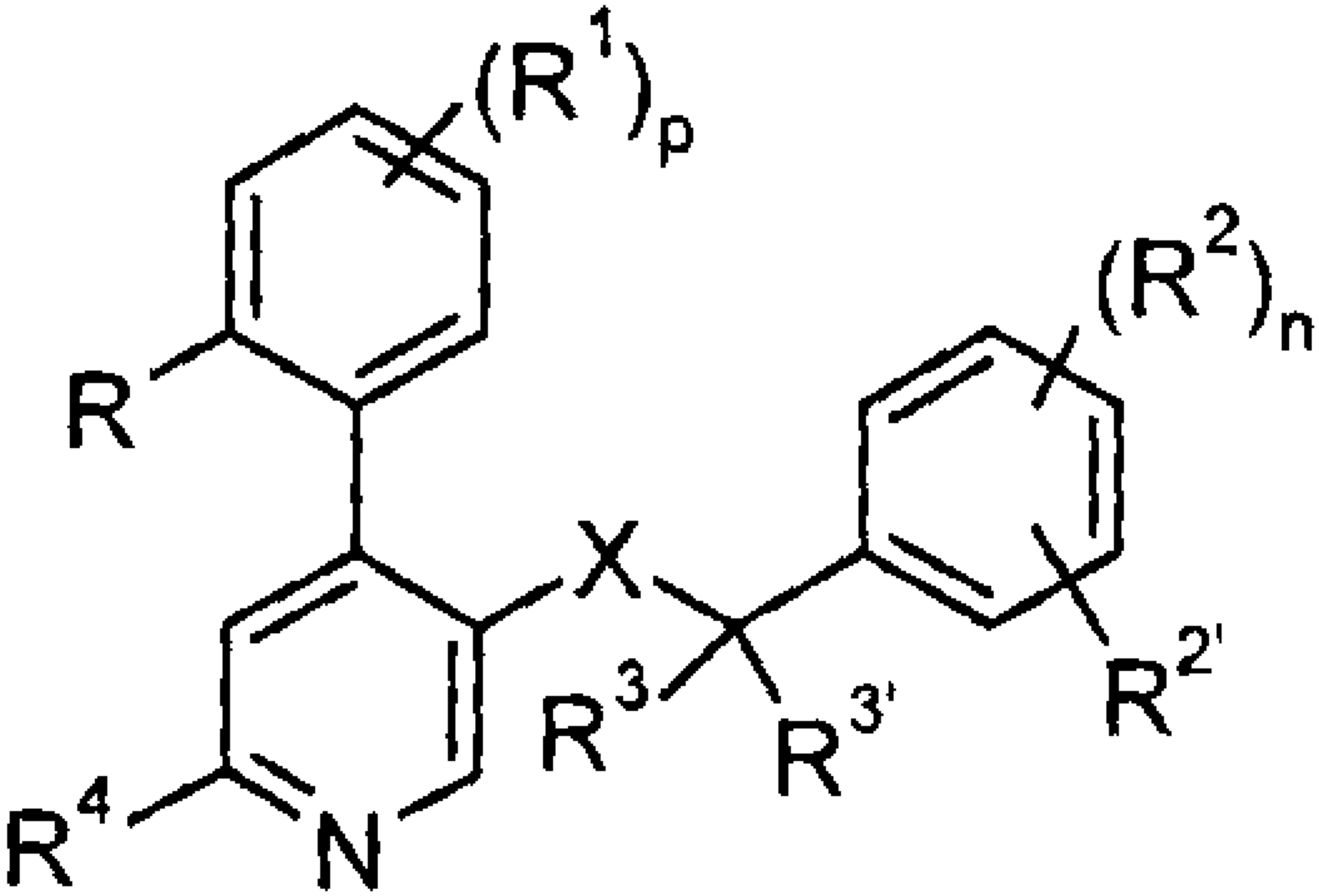
13. The pharmaceutical tablet composition according to claim 12, wherein the processing aid is Aerosil™ 380 or Cab-O-Sil™.

14. The pharmaceutical tablet composition according to claim 5, wherein the disintegrant is polyplasdone™ XL.

15. The pharmaceutical tablet composition according to claim 5, wherein the glidant is magnesium stearate.

16. A pharmaceutical tablet composition according to claim 5, comprising:

| | |
|---|---|
| - 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide hydrochloride | 400.00 mg |
| - Lutrol™ F68 | 133.35 mg |
| - Microcrystalline Cellulose(Avicel™ PH102) | 162.65 mg |
| - Parteck™ 200 (Mannitol) | 30.00 mg |
| - Polyplasdone™ XL | 16.00 mg |
| - Colloidal Silicon Dioxide(Aorosil™ 380) | 16.00 mg |
| - Corn Starch | 30.00 mg |
| - Magnesium Stearate | 12.00 mg |
| - Opadry™ Yellow 03K 12429 | 25.00 mg |
| - and Purified Water | 131.25 ml. |

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