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(54) Title: ORAL PHARMACEUTICAL COMPOSITION COMPRISING POSACONAZOLE

(57) Abstract: The present invention relates to a pharmaceutical composition comprising posaconazole in the form of the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates or esters thereof and a dispersion carrier. Furthermore, the composition is obtained using an effective process.

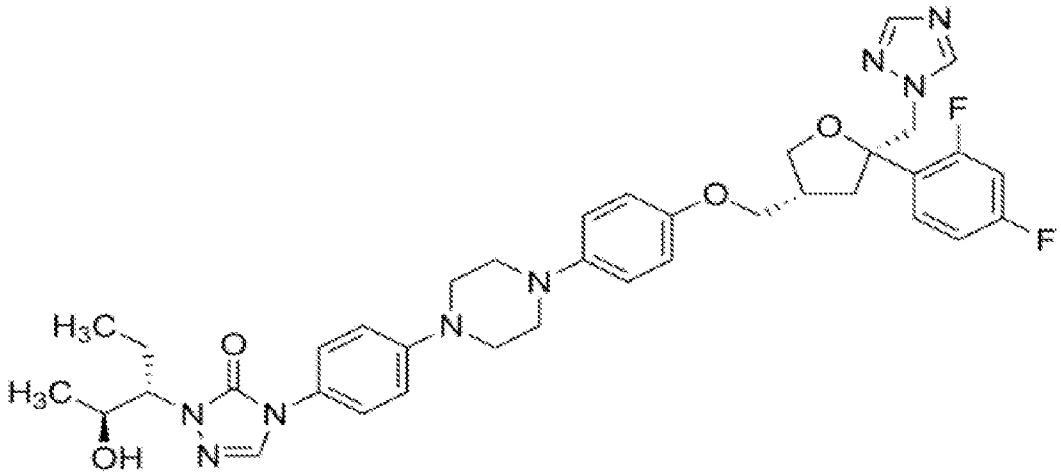
ORAL PHARMACEUTICAL COMPOSITION COMPRISING POSACONAZOLE

Field of the invention

The present invention relates to a pharmaceutical composition comprising posaconazole in the form of the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates or esters thereof and a dispersion carrier. Furthermore, the composition is obtained using an effective process.

Background of the Invention

Posaconazole is a derivative of itraconazole and belongs to the second-generation triazole antifungal agents. The IUPAC name of posaconazole is 4-[4-[4-[4-[[(3R,5R)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(2S,3S)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one. Its chemical structure, shown below (Formula I), has a formula of $C_{37}H_{42}F_2N_8O_4$, with the molecular weight of 700.792 g/mol.



Formula I

Posaconazole is a triazole antifungal agent indicated for the treatment of invasive fungal infections. US5703079 and US5661151 disclose posaconazole molecule. Three crystalline polymorph forms of posaconazole are form I, II and III. They have been described in patent application numbered WO9918097. Posaconazole is marketed by Merck Sharp & Dohme under the trademark Noxafil®.

In the prior art, there are also several patents which disclose posaconazole in oral pharmaceutical dosage forms. However, many of the formulations in the art rely on complex formulation which can add to the cost of the manufacture of the drug and can be subject to malfunction leading to inappropriate administration of the drug.

There still remains a need in the art to provide an improved oral pharmaceutical composition of posaconazole, having high solubility, dissolution rate, and accordingly a high bioavailability and a long-term stability which is also obtained by using an effective process.

Detailed Description of the Invention

The main object of the present invention is to provide high solubility, high bioavailability, high physical and chemical stability and a long shelf life by the help of the selection of excipients in a certain ratio using an effective process.

The term “posaconazole” as used herein refers to posaconazole in the form of the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates, esters or mixture thereof.

According to one embodiment of this invention, the pharmaceutical tablet comprises granules and at least one pharmaceutically acceptable excipient, wherein the granules comprise posaconazole and dispersion carrier.

According to one embodiment of this invention, the total amount of posaconazole in the granule is between 5.0% and 43.0%, between 10.0% and 35.0%, more preferably between 11.0% and 30.0% and between 12.0% and 25.0% by weight of the total composition.

Posaconazole is poorly soluble in water. In the stomach, posaconazole has a solubility of about 0.8 mg/ml. At pH 6.4 or higher, the solubility of posaconazole is less than 1 µg/ml. The solubility of crystalline polymorph forms is higher compared to the solubility of amorphous forms. Thus, it would be desirable to have posaconazole available in crystalline polymorph forms (form I, form II, form III) preferably is in crystalline polymorph form I.

As used herein, 'particle size' means the cumulative volume size distribution as tested by any conventionally accepted method such as the laser diffraction method (i.e. Malvern analysis). The term d (0.1) means, the size at which 10% by volume of the particles are finer and d (0.5) means the size at which 50% by volume of the particles are finer and d (0.9) means the size at which %90 by volume of the particles are finer.

Laser diffraction measures particle size distributions by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles.The angular scattering intensity data is then analyzed to calculate the size of the particles responsible for creating the scattering. The particle size is reported as a volume equivalent sphere diameter.

The compositions subjected to the invention comprise micron-sized particles of posaconazole in order to overcome the recognized problems in prior art. This invention provides surprisingly better dissolution rate.

According to one embodiment of the present invention, posaconazole has a d (0.1) particle size which is less than 50 µm, less than 40 µm, less than 30 µm, less than 25 µm, less than 20 µm, less than 10 µm.

According to another embodiment of the present invention, posaconazole has a d (0.5) particle size which is less than 60 µm, less than 50 µm, less than 40 µm, less than 30 µm, less than 25 µm, less than 20 µm, less than 10 µm.

According to another embodiment of the present invention, posaconazole has a d (0.9) particle size which is less than 70 µm, less than 60 µm, less than 50 µm, less than 40 µm, less than 30 µm, less than 25 µm, less than 20 µm, less than 10 µm.

According to another embodiment of the present invention, posaconazole has a d (0.1) particle size is less than 50 µm, d (0.5) particle size is less than 60 µm, d (0.9) particle size is less than 70 µm.

At the present invention, the total amount of the granules in the composition is between 40% and 80%, preferably between 55% and 70%, more preferably between 58% and 68% by weight of the total composition.

At the present invention, the composition comprises posaconazole dissolved or molecularly dispersed in dispersion carriers.

Suitable dispersion carriers are selected from polymers or non-polymers. Suitable polymers are selected from the group comprising hydroxypropyl methylcellulose acetate succinate (HPMC-AS) and their derivatives, hydroxypropyl cellulose, polyvinylpyrrolidone, copolymer of ethyl acrylate or methyl methacrylate (Eudragit L100 55), polyvinylacetal diethylaminoacetate, vitamin E polyethylene glycol succinate, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyoxyl 40 hydrogenated castor oil, hydrogenated castor oil, polyoxyl 15 hydroxystearate, polyoxyl 35 castor oil, polyoxyl castor oil, polyvinyl alcohol/polyethylene glycol graft copolymer, cetearyl ethyl hexanone & isopropyl myristate, gliceryl monostearate, polyethylene glycol or mixtures thereof.

According to one embodiment of the present invention, the selected polymers may have enteric polymer properties. For example; copolymer of ethyl acrylate or methyl methacrylate (Eudragit L100-55), hydroxypropylcellulose-acetate succinate (HPMC-AS) and hydroxypropyl cellulose are enteric polymers.

In this invention, the dispersion carrier is HPMC-AS polymer, in other words, hydroxypropylmethylcellulose-acetate succinate polymer. Furthermore, HPMC-AS polymer may be selected from grade high fine (HF), moderate fine (MF) and low fine (LF). The total amount of HPMC-AS in the granule is between 40.0% and 75.0%, between 42.0% and 65.0%, between 43.0% and 55.0% by weight of granule.

According to one embodiment of the present invention, posaconazole is dissolved in HPMC-AS. It has been surprisingly found that a stable and homogenous solution of posaconazole may be prepared with HPMC-AS to enhance the physical and chemical stability of posaconazole in the present composition.

According to one embodiment of the present invention, the ratio of posaconazole to HPMC-AS is in the range of between 4:1 to 1:4 by weight, preferably between 3:1 to 1:3 by weight. This ratio is important in order to provide stability in the present composition.

According to another embodiment of the present invention, the dispersion carrier is copolymer of ethyl acrylate or methyl methacrylate (Eudragit L100 55).

According to one embodiment of the present invention, the granules comprise at least one surfactant.

The present composition may comprise any of a variety of anionic, cationic, nonionic, amphoteric, zwitterionic surfactants.

Suitable surfactants are selected from the group comprising alpha tocopherol, docusate sodium, glyceryl monooleate, glyceryl monostearate, macrogol 15 hydroxystearate, phospholipids, poliyoxylglycerides, polyethylene glycol, triacetin, sodium lauryl sulphate, sorbitan esters, potassium cetylphosphate, ethylene glycol distearate, sodium dodecanoate, dioctyl sodium sulfosuccinate, sodium stearate, benzalkonium chlorides, polysorbates, poloxamers, polyoxyethylene castor oil derivatives, bile salts, lecithin, 12-Hydroxystearic acid-polyethylene glycol copolymer, sodium dodecanesulfonate, sodium oleyl sulfate, and sodium laurate, alkyltrimethylammonium bromides or mixtures thereof.

According to one embodiment of the present invention, the total amount of surfactant in the granules is between 0.1% to 5.0% by weight of granule.

In the present invention, the pharmaceutical composition is suitable for oral administration. Dry oral dosage is used for having effective antifungal activity and bioavailability. Suitable dosage forms are selected from the group comprising tablets, capsules, granules, powders, pellet and unit dose packets. In this invention, the composition is in the form of a tablet. In certain embodiments, oral dosage forms have a drug loading capacity of at least 20 mg per oral dosage form.

According to one embodiment of the present invention, the composition further comprises at least one pharmaceutically acceptable excipient which is selected from the group comprising disintegrants, fillers, lubricants, glidants, coating agents or mixtures thereof.

Suitable disintegrants are selected from the group comprising crospovidone, low-substituted cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose,

crosslinked sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, hydroxymethyl starch or mixtures thereof.

Suitable fillers are selected from the group comprising microcrystalline cellulose, sucrose, starches derived from wheat, corn rice and potato, gelatin and tragacanth, alginic acid, sodium carboxymethylcellulose sodium alginate, ammonium calcium alginate, polyvinylpyrrolidone, methylcellulose, sodium croscarmellose or mixtures thereof.

Suitable lubricants are selected from the group comprising magnesium stearate, calcium stearate, sodium stearyl fumarate, potassium stearate, stearic acid, high melting point waxes, sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols or mixtures thereof.

Suitable glidants are selected from the group comprising colloidal silicon dioxide, water soluble excipient, hydrophilic polymers, silicon dioxide or mixtures thereof, preferably glidant is colloidal silicon dioxide.

Suitable coating agents are selected from the group comprising polymethacrylates preferably copolymer of ethyl acrylate or methyl methacrylate (Eudragit L100 55), hydroxypropyl methylcellulose, triethyl citrate, lactose monohydrate, hydroxypropyl cellulose, polyvinyl alcohol (PVA), polyethylene glycol (PEG), talc, polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat® IR), ethylcellulose dispersions (Surelease®), polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, titanium dioxide, iron oxide, water or mixtures thereof.

The selected coating agents may have enteric coating properties. The enteric coating is achieved with the help of enteric polymers on oral administration that prevents active agent's dissolution or disintegration in the gastric environment.

According to another embodiment of the present invention, the pharmaceutical tablet comprises;

40.0-80.0% by weight of granule

15.0-38.0% by weight of microcrystalline cellulose

1.0-10.0% by weight of crospovidone

0.01% - 3.0% by weight of magnesium stearate

1.0% - 15.0% by weight of coating agent

According to another embodiment of the present invention, the granule comprises;
5.0-43.0% by weight of posaconazole
40.0-75.0% by weight of HPMC-AS
Optionally, 0.1-5.0% by weight of surfactant

According to one embodiment of the present invention, the process of preparing granule is hot melt extrusion, direct compression, spray drying, wet granulation, dry granulation or mixtures thereof. Preferably it is spray drying or hot melt extrusion.

According to one embodiment of the present invention, granules is obtained by spray drying which is a method of producing a dry powder from a liquid by rapidly drying with a hot gas. This is the preferred method for drying many pharmaceuticals. The method provides desired stability in the tablet. Solvent is used in the process.

Suitable solvents are selected from the group comprising dichloromethane, 0.1N HCl, methanol, ethanol, isopropyl alcohol, benzyl alcohol, propylene glycol, polyethylene glycol, glycerine, cyclomethicone, glycerine triacetate, diethylene glycol monoethyl ether, glycerol formal, propylene carbonate or mixtures thereof.

The pharmaceutical tablet comprises 40.0-80.0% by weight of granule, 15.0-38.0% by weight of filler, 1.0-10.0% by weight of disintegrant, 0.01% - 3.0% by weight of lubricant, 1.0-15.0% by weight of coating agent. The formulation is produced using spray drying method.

The process for preparing the pharmaceutical tablet processed spray drying comprise the following steps:

a) mixing posaconazole, at least one polymer, optionally surfactant
b) dissolving the mixture in dichloromethane or HCl or ethanol or methanol or mixtures thereof
c) drying the mixture using spray drying method
d) obtaining granules
e) mixing the granules, filler and disintegrant until homogeneous
f) adding lubricant and glidant and mixing
g) then, pressing the mixture into tablets
h) coating the tablets with a coating

According to another embodiment of the present invention, granules are obtained that at the end of the hot melt extrusion, extrudates form is converted to granules.

According to another embodiment of the present invention, a d (0.9) particle size of obtained extrudate using hot melt extrusion is less 250 µm, more preferably it is less 200 µm. The size of the extrudate provides surprisingly better solubility and stability.

Hot-melt extrusion (HME) technology is prominent in the pharmaceutical industry. HME offers the potential of shorter and more efficient times to the final product, through reduction of the processing steps involved. HME is used to disperse active agent in a matrix at the molecular level, thus forming solid solutions. This method is used for poorly soluble active agent and desired dissolution rate and stability are obtained.

Hot-melt extrusion is a technique for manufacturing amorphous solid dispersions in which the active agent is melted or dissolved within a dispersion carrier and mixed to produce and stabilize. Functional excipients, such as surfactants, are often added to further aid in processability or improve the dissolution rate of the formulation.

In addition, the modular concept of the individual screw elements and use of different heating zones along the process barrel allows individual adaptation of the processing section to different product and formulation requirements.

According to one embodiment of the present invention, the below-described heating temperatures are used at zones during the hot melt extrusion. The temperature is chosen according to the properties of the dispersion carriers and posaconazole.

Table 1: The temperatures of the zones during the hot melt extrusion

Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8
20-80 °C	40-100 °C	70-140 °C	80-150 °C	85-155 °C	90-160 °C	95-165 °C	100-170 °C

Preferably heating is limited to provide a temperature no greater than the fluxing temperature of the mixture comprising posaconazole, dispersion carriers to insure homogeneity of the composition.

Preferably the heating temperature is chosen between 25°C and 60°C at zone 1, between 50°C and 90°C at zone 2, between 80°C and 130°C at zone 3, between 100°C and 145°C at zone 4, between 100°C and 150°C at zone 5, between 110°C and 150°C at zone 6, between 110°C and 155°C at zone 7, between 120°C and 160°C at zone 8.

The temperature ranges given above aresuitable for this invention to provide high solubility, high physical and chemical stability.

Cooling temperature is provided by using glycol at 23 °C.

The pharmaceutical tablet comprises 40.0-80.0% by weight of granules, 15.0-38.0% by weight of microcrystalline cellulose, 1.0-10.0% by weight of crospovidone, 0.01% - 3.0% by weight of magnesium stearate, 1.0-15.0% by weight of coating agent. The tablet form of the composition is produced using hot melt extrusion.

The granules comprise 10.0-43.0% by weight of posaconazole, 52.0-75.0% by weight of HPMC-AS, 0.1-5.0% by weight of surfactant.

The process for preparing pharmaceutical tablet processed hot melt extrusion comprises the following steps;

a) dry mixing HPMC-AS, posaconazole and optionally surfactant until a homogeneous mixture is obtained,
b) heating the mixture prepared at step(a) thereby forming a melt,
c) cooling the melt formed at step(b),
d) converting extrudates form to granules
e) mixing filler and disintegrant in separate tank
f) adding the granules into step (e) mixture and mixing
g) then, pressing the mixture into tablets
h) coating the tablets.

In this invention, between steps (b) and (c) the melt is extruded to provide an extrudate with a desired cross-sectional shape.

It is important the feed rate and screw rate value in order to provide homogeneity in the extrudate, also it provides in the composition.

Also, the value of screw rate thus provides minimizing the risk ofthermal degradation of the posaconazole. The following values give the best stability result for the composition.

The temperature of the hot melt extrusion is set in the range of about 40° C to about 160° C and the rotation speed of the screw is set in the range of about 150 to about 280 rpm.

According to one embodiment of the present invention, screw speed during hot melt extrusion process is between 150rpm and 280 rpm. Also, screw speed during hot melt extrusion process is between 150 rpm and 180 rpm, 180 rpm and 220 rpm, 220 rpm and 250 rpm, 250 rpm and 280 rpm.

According to one embodiment of the present invention, feed rate during hot melt extrusion process is between 15 g/min and 30 g/min. Also, feed rate during hot melt extrusion process is between 15 g/min and 18 g/min, 18 g/min and 20 g/min, 20 g/min and 25 g/min, 25 g/min and 28 g/min, 28 g/min and 30 g/min.

According to one embodiment of the present invention, torque value during hot melt extrusion process is between 25% and 27%.

According to another preferred embodiment of the present invention, said formulation is obtained by means of a hot melt extrusion not involving any liquid solvent during the granulation phase.

The compositions of the invention may be developed into tablet comprising immediate release, extended release, sustained release, controlled release, modified release and delayed release or combination thereof. Such compositions may be prepared using rate controlling polymers.

Example 1: Tablet composition prepared by hot melt extrusion

	amount (w/w)
Granules	40.0% - 80.0%
Fillers	15.0% - 38.0%
Disintegrants	1.0% - 10.0%
Lubricants	0.01% - 3.0%
Glidants	0.01% - 3.0%
Coating agents	2.0% - 13.0%
Total	**100**

Example 2: Tablet composition prepared by hot melt extrusion

	amount (w/w)
Granules	56.0% - 68.0%
Microcrystalline cellulose	27.0% - 38.0%
Disintegrants	2.0% - 10.0%
Lubricants	0.01% - 3.0%
Glidants	0.01% - 3.0%
Coating agents	2.0% - 13.0%
Total	**100**

Example 3: Tablet composition prepared by hot melt extrusion

	amount (w/w)
Granules	56.0% - 70.0%
Microcrystalline cellulose	15.0% - 38.0%
Crospovidone	1.0% - 20.0%
Magnesium stearate	0.01% - 5.0%
Colloidal silicon dioxide	0.01% - 3.0%
Coating agents	2.0% - 10.0%
Total	**100**

Example 4: Tablet composition prepared by spray drying

	amount (w/w)
Granules	40.0% - 78.0%
Fillers	15.0% - 35.0%
Disintegrants	1.0% - 10.0%
Lubricants	0.1% - 3.0%
Glidants	0.01% - 3.0%
Coating agents	2.0% - 15.0%
Total	**100**

Example 5: Tablet composition prepared by spray drying

	amount (w/w)
Granules	50.0% - 70.0%
Microcrystalline cellulose	15.0% - 30.0%
Crospovidone	1.0% - 35.0%
Lubricants	0.1% - 3.0%
Glidants	0.01% - 3.0%
Coating agents	2.0% - 15.0%
Total	**100**

Example 6: Granule composition of the invention

	amount (w/w)
Posaconazole	5.0% - 43.0%
Dispersion carrier	40.0% - 75.0%
Total	**100**

Example 7: Granule composition of the invention

	amount (w/w)
Posaconazole	5.0% - 43.0%
HPMC-AS (grade HF, MF, LF)	40.0% - 75.0%
Surfactants	0.1% - 5.0%
Total	**100**

Example 8: Granule composition of the invention

	amount (w/w)
Posaconazole	5.0% - 43.0%
Eudragit L100-55	40.0% - 75.0%
Surfactants	0.1% - 5.0%
Total	**100**

Example 9: Granule composition of the invention

	amount (w/w)
Posaconazole	10.0% - 35.0%
HPMC-AS (grade HF, MF, LF) and hydroxypropyl cellulose	40.0% - 75.0%
Surfactants	0.1% - 5.0%
Total	**100**

Example 10: Granule composition of the invention

	amount (w/w)
Posaconazole	5.0% - 43.0%
HPMC-AS (gradeHF,MF,LF) and hydroxypropyl cellulose	40.0% - 75.0%
Total	**100**

Process for the preparation of the granules according to example 1,2,3 comprises;

a) Dry mixing HPMC-AS, posaconazole and optionally surfactant until a homogeneous mixture is obtained,
b) heating the mixture prepared at step(a) thereby forming a melt,
c) cooling the melt formed at step(b),
d) converting extrudate form to granules

Process for the preparation of the tablet composition by hot melt extrusion according to example 1, 2, 3 comprises;

e) mixing filler and disintegrant in a separate tank
f) adding the granules into step (e) mixture
g) Then, pressing the mixture into tablets
h) coating the tablets.

Process for the preparation of the granules according to example 4 and 5 comprises;

a) mixing posaconazole with at least one polymer and optionally a surfactant
b) dissolving the mixture in dichloromethane or HCl or ethanol or methanol or mixtures thereof
c) drying the mixture using spray drying
d) obtaining granules

Process for the preparation of the tablet composition by spray drying according to example 4 and 5 comprises;

e) mixing the granules, filler and disintegrant until a homogeneous mixture is obtained
f) adding magnesium stearate
g) Then, pressing the mixture into tablets
h) Coating the tablets with coating

CLAIMS

1. A pharmaceutical tablet comprising granules and at least one pharmaceutically acceptable excipient, wherein the granules comprise posaconazole and dispersion carrier.

2. The pharmaceutical tablet according to claim 1, wherein the total amount of posaconazole in the granules is 5.0% and 43.0% by weight of the total composition.

3. The pharmaceutical tablet according to claim 1, wherein said posaconazole is in crystalline polymorph form.

4. The pharmaceutical tablet according to claim 1, wherein d (0.1) particle size is less than 50 µm, d (0.5) particle size is less than 60 µm, d (0.9) particle size is less than 70 µm.

5. The pharmaceutical tablet according to claim 1, wherein the total amounts of granules in the composition is between 40% and 80% by weight of the total composition.

6. The pharmaceutical tablet according to claim 1, wherein the dispersion carrier in the granule is hydroxypropyl methylcellulose acetate succinate.

7. The pharmaceutical tablet according to claim 1 or 6, wherein the ratio of posaconazole to hydroxypropyl methylcellulose acetate succinate is in the range of between 4:1 to 1:4 by weight, preferably between 3:1 to 1:3 by weight.

8. The pharmaceutical tablet according to claim 7, wherein the total amount of hydroxypropyl methylcellulose acetate succinate in the granule is between 40.0% and 75.0% by weight of granule.

9. The pharmaceutical tablet according to claim 1, wherein the dispersion carrier in the granule is copolymer of ethyl acrylate or methyl methacrylate or mixtures thereof.

10. The pharmaceutical tablet according to any preceding claims, wherein the granules comprising at least one surfactant.

11. The pharmaceutical tablet according to claim 10, wherein at least one surfactant is selected from the group comprising alpha tocopherol, docusate sodium, glyceryl monooleate, glyceryl monostearate, macrogol 15 hydroxystearate, phospholipids, poliyoxylglycerides, polyethylene glycol, triacetin, polysorbate, sodium lauryl sulphate, sorbitan esters , potassium cetylphosphate, ethylene glycol distearate, sodium dodecanoate, dioctyl sodium sulfosuccinate, sodium stearate, benzalkonium chlorides, polysorbates, poloxamers, polyoxyethylene castor oil derivatives, bile salts, lecithin, 12-Hydroxystearic acid-polyethylene glycol copolymer, sodium dodecanesulfonate, sodium oleyl sulfate, and sodium laurate, alkyltrimethylammonium bromides or mixtures thereof.

12. The pharmaceutical tablet according to claim 11, wherein the total amounts of surfactants in the granule is between 0.1% and 5.0% by weight of granule.

13. The pharmaceutical tablet according to any preceding claims, further comprising at least one pharmaceutically acceptable excipient which is selected from the group comprising disintegrants, fillers, lubricants, glidants, coating agents or mixtures thereof.

14. The pharmaceutical tablet according to any preceding claims, the tablet comprising;
40.0-80.0% by weight of granule
15.0-38.0% by weight of microcrystalline cellulose
1.0-10.0% by weight of crospovidone
0.01% - 3.0% by weight of magnesium stearate
1.0% - 15.0% by weight of coating agent

15. The pharmaceutical tablet according to claim 14, the granule comprising;
5.0-43.0% by weight of posaconazole
40.0-75.0% by weight of hydroxypropyl methylcellulose acetate succinate
Optionally, 0.1-5.0% by weight of surfactant

16. The pharmaceutical tablet according to any preceding claims, wherein said granules obtained by hot melt extrusion, direct compression, spray drying, wet granulation or dry granulation or mixtures thereof.

17. The pharmaceutical tablet according to claim 16, wherein the granules obtained by spray drying or hot melt extrusion.

18. The pharmaceutical tablet according to claim 17, wherein the granules are obtained at the end of the hot melt extrusion as an extrudate.

19. The pharmaceutical tablet according to claim 18, wherein said extrudate has d (0.9) particle size less than 250 µm, more preferably less than 200 µm.

20. The pharmaceutical tablet according to claim 17, wherein granule is obtained by spray drying.

21. The pharmaceutical tablet according to claim 20, wherein a solvent is used in the spray drying process.

22. The pharmaceutical tablet according to claim 21, wherein the solvent is selected from the group comprising dichloromethane, 0.1N HCl, ethanol, isopropyl alcohol, benzyl alcohol, propylene glycol, polyethylene glycol, glycerine, cyclomethicone, glycerine triacetate, diethylene glycol monoethyl ether, glycerol formal, propylene carbonate or mixtures thereof.

23. A process for preparing the pharmaceutical tablet according to claim 17, comprising the following steps;

a) mixing posaconazole with at least one polymer, optionally a surfactant
b) dissolving the mixture in dichloromethane or HCl or ethanol or methanol or mixtures thereof
c) drying the mixture using spray drying
d) obtaining granule
e) mixing the granule, filler and disintegrant until homogeneous
f) adding magnesium stearate
g) then, pressing to form tablet
h) coating the tablet with coating

wherein the granules are obtained by spray drying.

24. A Process for preparing the pharmaceutical tablet according to claim 17, comprising the following steps;

a) dry mixing hydroxypropyl methylcellulose acetate succinate, posaconazole, optionally surfactant until homogeneous,
b) heating the admixture prepared at step(a) thereby forming a melt,
c) cooling the melt formed at step(b),
d) converting extrudates form to granules
e) mixing microcrystalline cellulose and crospovidone in separate tank
f) adding the granules into step (e) mixture
g) then, pressing to form tablet
h) coating the tablets with coating agents

wherein the granules are obtained by hot melt extrusion.