(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 July 2009 (09.07.2009)

PCT

(10) International Publication Number
WO 2009/084036 A2

(51) International Patent Classification:
A61K 9/48 (2006.01)

(21) International Application Number:
PCT/IN2008/000843

(22) International Filing Date:
18 December 2008 (18.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3070/CHE/2007 20 December 2007 (20.12.2007) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2009/084036 A2

(54) Title: COMPOSITION FOR TREATMENT OF VIRAL INFECTIONS

(57) Abstract: The present invention relates to stable solid dosage forms of ritonavir and atazanavir/tipranavir and processes for their preparation. In particular, the solid dosage form has improved stability, similar dissolution profile and being bioequivalent to the commercially available formulations of ritonavir and atazanavir.

COMPOSITION FOR TREATMENT OF VIRAL INFECTIONS

FIELD OF INVENTION

The present invention relates to oral solid pharmaceutical compositions for the treatment of viral infections, particularly in the treatment of infections caused by human immunodeficiency virus (HIV); commonly known as the acquired immune deficiency syndrome (AIDS).

More particularly, the present invention relates to solid oral pharmaceutical compositions comprising ritonavir in combination with atazanavir and/or tipranavir and pharmaceutically acceptable excipients.

BACKGROUND OF THE INVENTION AND RELATED PRIOR ART

Treatment of HIV infections, involve the use of numerous pharmacologically active agents which are classified according to their mechanism of action. The agents that are presently in use fall mainly into three classes, namely Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors (PIs). Current therapies for HIV infection involve the use of combination drugs in order to have synergistic effect, as well as to avoid drug resistance.

Ritonavir, a HIV protease inhibitor (PI), is generally used along with other anti-HIV agents to enhance their blood levels. Ritonavir is recommended in the treatment of AIDS along with other anti HIV agents such as atazanavir and/or tipranavir.

Ritonavir is chemically, ((2S, 3S, 5S)-5-(N- (N-((N-Methyl–N-((2-isopropyl–4-thiazolyl)methyl)amino)-carbonyl)-L-valinyl) amino)-2-(N-((5-thiazolyl) methoxy carbonyl) amino)-l,6–diphenyl–3-hydroxyhexane) and is indicated in combination with other anti-retroviral agents for the treatment of HIV-infections.

Atazanavir (also referred to as BMS-232632) is chemically (3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenyl methyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid, is an aza-peptide inhibitor of HIV-1 protease.

Tipranavir (also known as PNU 140690 or U-140690), a non-peptidic HIV protease inhibitor, is chemically 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl] phenyl] -5-(trifluoromethyl) also used in the treatment of HIV infections.

Ritonavir and processes for its preparation are disclosed in U.S. Patent No. 5,541,206, the disclosure of which is herein incorporated by reference. Pharmaceutical compositions comprising ritonavir or a pharmaceutically acceptable salt thereof are disclosed in U.S. Patent Nos. 5,484,801, 5,725,878 and 5,559,158.

Atazanavir and its pharmaceutically acceptable salt forms are disclosed in U.S. Patent Nos. 5,849,911, 6,166,004, and 6,087,383.

U.S. Patent No. 5,852,195 discloses the synthesis, dosage forms of tipranavir and the manner in which it may be used to treat HIV infections. Exemplary fill formulations for soft gelatin capsules are disclosed in U.S. Patent Nos. 6,231,887 and 6,121,313.

Ritonavir is extremely difficult to formulate into suitable oral solid dosage form because of its poor aqueous solubility. It is commercially available as soft gelatin capsule formulation in which it is present in solubilized form. U.S. Patent No. 6,008,228 describes a liquid composition for the administration of several protease inhibitors, among them ritonavir, employing a mixture of mono and diglycerides of C_8-C_{10} saturated fatty acids as organic solvent. Similarly, U.S. Patent No. 6,232,333 discloses pharmaceutical compositions comprising HIV protease inhibitors (especially, ritonavir, lopinavir and mixtures thereof) which have been prepared as a solution in a complex carrier medium comprising several components.

U.S. Patent Application No. 2005/0020517 discloses a combination of therapeutically effective amount of tipranavir or a pharmaceutically acceptable salt thereof, with an inhibitor of Cyp3A4 (such as ritonavir), in further combination with capravirine.

U.S. Patent Application No. 2005/0250764 discloses a soluble stable pharmaceutical composition comprising a solution of an HIV protease inhibitor in combination with suitable pharmaceutical organic solvents, a surfactant and a bioavailability enhancer suitable for the preparation of oral solutions in hard gelatin capsules or soft gelatin capsules.

Currently, a widely used PI oral dosage form is soft gelatin capsules containing a fill solution in which the active ingredient is in the dissolved state. The fill solution required to dissolve the PI, often contain excipients that cause discomfort or irritate the gastrointestinal system. Furthermore, only a limited amount of the PI can be dissolved in these dosage forms which therefore limit the amount of the PI loaded in each soft gelatin capsule.

Another problem with these solubilized soft gelatin products, is their storage. They need to be stored in refrigerated conditions, due to the issues related to formulation stability. For subjects residing in economically challenged or developing countries where refrigerators are not as common in households, such storage conditions represent a particularly challenging dilemma.

Further, it has also been observed that upon administration of a PI from soft gelatin capsules there is variability in the blood levels of the active ingredient from subject to subject and even within the same subject. That is, some patients receiving treatment can have very high or very low blood levels of the PI. In turn, this can lead to unwanted adverse events in those patients experiencing high blood levels of the drug or rendering the treatment less effective or ineffective in those patients experiencing low blood levels of the drug.

Currently there is only one product available in the market where ritonavir is formulated along with another anti-HIV agent. In this product, lopinavir is co-formulated with ritonavir. But still much more is desired.

United States Food and Drug Administration have approved the combination of 300 mg of Atazanavir and 100 mg of Ritonavir for the treatment. It has approved Reyataz™ capsule 300 mg to be co-administered with Norvir™ capsule 100 mg for boosting the blood levels of atazanavir. Reyataz™ is a hard gelatin capsule that can be stored at room temperature whereas Norvir™, a soft gelatin capsule needs to be stored under refrigerated conditions.

A single product, which contains ritonavir in combination with another anti-HIV agent like atazanavir or tipranavir, which is stable at ambient conditions and with less pharmacokinetic variations is always desired. A single thermo-stable product will improve the patient compliance, reduce the manufacturing cost and will provide ease of handling to the patient and pharmacist. A single dosage form will provide the same therapeutic efficacy and safety in addition to the above mentioned advantages.

This and other such needs are addressed by the present invention.

SUMMARY OF THE INVENTION

Ritonavir is a poorly water-soluble drug. When administered in the ordinary solution form, major amount of the drug gets precipitated out in the gastro-intestinal tract, instead of getting absorbed. This is due to super-saturation of the drug in gastro-intestinal fluids. One way to prevent precipitation is to add sufficient quantity of surfactant in the composition. Addition of surfactant prevents the precipitation of drug to significant extent but it also delays the drug absorption. Norvir™ capsules contain surfactant to keep the drug in solubilized state and to prevent its precipitation. Since the Norvir™ soft gelatin capsules is in liquid form, it is thermodynamically unstable compared to tablet dosage form.

In the present invention, a method of preventing the precipitation of ritonavir is disclosed; wherein ritonavir is formulated in the form of solid dispersion comprising a matrix of surfactant and hydrophilic polymer into a tablet. In other words, the tablet dosage form contains ritonavir in the form of solid dispersion which releases the drug over the period of 60-90 minutes in gastro-intestinal fluids, thereby preventing the super-saturation and avoiding precipitation. The above ritonavir composition forms one layer of a bi-layer tablet, in which other layer is a rapidly dissolving form comprising of atazanavir and/or tipranavir in combination with other excipients.

In the present invention, pharmaceutical compositions comprising ritonavir in combination with other anti HIV agents such as atazanavir and/or tipranavir are disclosed. The composition contains at least one sugar alcohol or its pharmaceutically acceptable derivative. The composition may optionally contain a pharmaceutically acceptable non-ionic surfactant. Also disclosed are various techniques to prepare the said composition.

OBJECTIVES OF THE INVENTION

The present invention relates to solid oral pharmaceutical compositions comprising ritonavir in combination with atazanavir and/or tipranavir and pharmaceutically acceptable excipients.

More particularly, the present invention relates to a stable solid oral pharmaceutical compositions comprising: a) an effective amount of ritonavir in combination with at least one other anti-HIV agent such as atazanavir and/or tipranavir; b) at least one pharmaceutically acceptable carrier c) at least one pharmaceutically acceptable surfactant and d) optionally other pharmaceutically acceptable customary excipients.

In one embodiment of the present invention, there is provided a bilayer tablet comprising a) ritonavir and atazanavir/tipranavir in combination with b) at least one pharmaceutically acceptable carrier c) at least one acceptable surfactant and d) optionally other pharmaceutically acceptable customary excipients.

Further, the present invention relates to a process for the preparation of a stable solid oral pharmaceutical composition comprising: a) an effective amount of ritonavir in combination with at least one other anti-HIV agent such as atazanavir and/or tipranavir; b) at least one pharmaceutically acceptable carrier c) at least one pharmaceutically acceptable surfactant and d) optionally other pharmaceutically acceptable customary excipients.

In one embodiment of the present invention, the process of preparing the stable solid oral pharmaceutical composition comprising ritonavir in combination with atazanavir and/or tipranavir involves wet-granulation, melt-granulation and/or the combined process of melt-granulation and wet granulation.

In a still another embodiment of the present invention, the process of preparing the stable solid oral pharmaceutical composition comprising ritonavir in combination with atazanavir and/or tipranavir involves solid dispersion method in combination with wet granulation/or melt granulation.

Further, an embodiment of the invention provide a pharmaceutical composition comprising ritonavir in combination with atazanavir and/or tipranavir wherein said composition is stable, and can be stored at room temperature.

In an another embodiment, the present invention provides a pharmaceutical composition comprising ritonavir in combination with atazanavir and/or tipranavir having similar *in-vitro* drug release profile as compared to the marketed formulations of ritonavir and atazanavir/tipranavir separately.

Still further, an embodiment of the invention provide a pharmaceutical composition comprising ritonavir in combination with atazanavir and/or tipranavir wherein said composition is bioequivalent to the Norvir™ (Ritonavir Capsules; manufactured by Abbott) and Reyataz™ (Atazanavir Sulfate Capsules, manufactured by BMS).

DETAILED DESCRIPTION INCLUDING PREFERRED EMBODIMENTS OF THE INVENTION:

The present invention relates to solid oral pharmaceutical compositions comprising ritonavir in combination with atazanavir and/or tipranavir and pharmaceutically acceptable excipients.

In the context of the present invention, "pharmaceutical composition", as used herein, means a medicament for use in treating HIV and related diseases in a mammal that comprises ritonavir in combination with atazanavir and/or tipranavir, along with other pharmaceutical excipients appropriate for administration to a mammal.

An embodiment of the present invention provides a stable solid dosage form comprising: [a] a first component comprising: (i) ritonavir or its pharmaceutically acceptable salts; (ii) a pharmaceutical carrier; (iii) a surfactant; and (iv) optionally other pharmaceutically

acceptable excipients; [b] a second component comprising: (i) atazanavir and/or tipranavir or their pharmaceutically acceptable salts; and (ii) pharmaceutically acceptable excipients.

The "dosage form" as used herein include granules, pellets, tablets, bi-layer tablets, tri-layer tablets, mini-tablets, hard gelatin capsules, powder and the like prepared by conventional methods well known to a person skilled in the art and being stable when stored at room temperature.

An embodiment of the present invention provides a stable solid dosage form comprising: [a] a first component comprising ritonavir or its pharmaceutically acceptable salts and [b] a second component comprising atazanavir and/or tipranavir, or their pharmaceutically acceptable salts, wherein said solid dosage form comprises less than about 2% by weight of related substances.

The term "stable" as used herein means the chemical stability of the solid dosage forms and indicates the presence of less than 0.2% w/w of individual impurity and less than 2% w/w of total impurities when measured at 40°C/75%RH, and other conditions well known to a person skilled in the art for atleast three months.

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant. In one embodiment, the dosage form comprises at least one surfactant having a hydrophilic-lipophilic balance (HLB) value of from about 4 to about 10, preferably from about 7 to about 9. Known surfactants like esters of polyethylene glycols, sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; or sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® series) can be effectively employed.

Besides the surfactant having an HLB value of from about 4 to about 10, the dosage form may comprise additional pharmaceutically acceptable surfactants such as polyoxyethylene castor oil derivates, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® series); or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene

polypropylene glycol (Poloxamer® series, from BASF Wyandotte Corp.); or a mono fatty acid ester of polyoxyethylene (20) sorbitan (Tween® series). The sorbitan mono fatty acid esters are preferred, with sorbitan monolaurate and sorbitan monopalmitate being particularly preferred.

The pharmaceutically acceptable "carrier" as used in this invention can be selected from but are not limited to sugar alcohols, for example sorbitol, mannitol, xylitol, arabitol, maltitol, ribitol, dulcitol, lactitol, and the like; organic acids, for example citric acid, succinic acid, tartaric acid, oxalic acid, formic acid and the like and/or polymers such as polyvinyl pyrollidone, cellulose derivatives, gums, methacrylic acid derivatives, alginates, starch derivatives, and the like.

The pharmaceutically acceptable "customary excipients" as used in this invention are selected from the class of diluents, binders, disintegrants, glidants, lubricants, anti-tacking agents etc.

Diluents used in the composition may be one or more selected from the group comprising lactose, cellulose, microcrystalline cellulose, dextrose, calcium phosphate, fructose, maltose, dicalcium phosphate, tricalcium phosphate, and the like.

Binders which include, but are not limited to are alkylcelluloses such as methyl cellulose, ethyl cellulose; hydroxyalkylcelluloses such as hydroxypropylcellulose, hydroxylpropylmethyl cellulose, sodium carboxymethyl cellulose; microcrystalline cellulose, povidone, copovidone, polyvinyl alcohol, sodium alginate, polydextrose and the like.

Disintegrants used in the composition may be one or more selected from the group comprising starch and its derivatives, croscarmellose sodium, croscarmellose calcium, polacrillin potassium, gums such as alginic acid, sodium alginate, cross-linked polyvinylpyrrolidone, cellulose derivatives such as microcrystalline cellulose and its salts, microfine cellulose, low-substituted hydroxypropylcellulose and mixtures thereof. Most preferably, disintegrants are cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose and cross-linked sodium carboxymethylcellulose.

Glidants can be selected from the group consisting of: silicon dioxide, colloidal silicon dioxide, fumed silicon dioxide, sodium aluminosilicate, calcium stearate, magnesium stearate, zinc stearate, stear-o-wet, wherein colloidal silicon dioxide is the preferred glidant.

Lubricants may be one or more selected from the group consisting of magnesium stearate, calcium stearate, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oil, sodium benzoate, polyethylene glycol, talc etc and the like.

METHOD OF PREPARATION

Various methods can be used for manufacturing the solid dosage forms according to the invention. These methods comprise the preparation of a solid solution of the HIV protease inhibitor or the combination of HIV protease inhibitors in a matrix of the water-soluble carrier and the surfactant, and shaping into the required tablet form. Alternatively, the solid solution product may be subdivided to granules, e.g. by grinding or milling, and the granules may subsequently be compacted to tablets.

An embodiment of the present invention provide for a process for preparation of a stable solid dosage form, comprising: [a] (i) blending ritonavir, a carrier, a surfactant, and other pharmaceutically acceptable excipients, (ii) optionally granulating and/or compressing the blend to form a first component; [b] (i) blending atazanavir and/or tipranavir, and one or more pharmaceutically acceptable excipients, (ii) optionally granulating and/or compressing the blend to form the second component and [c] blending/compressing both components to form a solid dosage form.

Granulation can be carried out by either dry granulation, wet granulation and/or melt granulation. Wet granulation and melt granulation are usually preferred. Melt granulation with solvent evaporation or solution evaporation being preferred processes.

Usually, the melt temperature is in the range of about 70 to about 250°C., preferably from about 80°C to about 180°C., most preferred from about 100°C to about 140°C. The melting and/or mixing takes place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders,

intermeshing screw extruders or else multi-screw extruders, preferably twin screw extruders, which can be co-rotating or counter-rotating and, optionally, be equipped with kneading disks.

Shaping of the extrudate conveniently is carried out by a calendar with two counter-rotating rollers with mutually matching depressions on their surface. A broad range of tablet forms can be attained by using rollers with different forms of depressions. Alternatively, the extrudate is cut into pieces, either before (hot-cut) or after solidification (cold-cut).

Apart from melt granulation, wet granulation can also be used for the preparation of the oral pharmaceutical composition of the invention. According to this procedure, the dry active ingredient, pharmaceutically acceptable carriers, surfactants, & other customary excipients are blended, for example, in a planetary mixer or a rapid mixer granulator. The powders are wetted with a granulating liquid like water, isopropyl alcohol or acetone or dichloromethane and other hydro-alcoholic solvents such as isopropyl alcohol-water mixture. Binders may be included in the granulating liquid. The moist mass is granulated, e.g., by forcing through a screen of suitable mesh size, dried, and, if desired, the particles further reduced in size. Granulates are then compressed in conventional manner, using lubricants, glidants, etc., as required, into a bilayer tablet.

An embodiment of the present invention provides a process for the preparation of a stable solid dosage form, said process comprising: [a] (i) dissolving ritonavir, surfactant and optionally other excipients in a solvent to prepare a solution and then drying to prepare a solid dispersion; (ii) blending the same with other pharmaceutically acceptable excipients, (iii) optionally granulating and/or compressing said blend to form a first component; [b](i) blending atazanavir and/or tipranavir, and one or more pharmaceutically acceptable excipients, (ii) optionally granulating and/or compressing the blend to form the second component and [c] blending/compressing the two components to form a solid dosage form.

According to the present invention, solid dispersion technique is also used in the preparation of the solid dosage form of the anti-HIV agents. The said technique comprises drying a solution of ritonavir or atazanavir/tipranavir alone or in combination with one or more

pharmaceutically acceptable carrier. The process may include optionally further drying of the drug solution/dispersion.

The solution of ritonavir alone or in combination with atazanavir/tipranavir can be obtained by dissolving the drug in a suitable solvent. The solvent which can be used can be any solvent from the various classes of solvents such as for example alcohols, glycols, acids, water, aprotic polar solvents or mixtures thereof. Preferably, organic solvents such methylene chloride, isopropyl alcohol, acetone, dichloromethane, methanol, ethanol and the like in various ratios without any limitations are included within the scope of the present invention.

In order to get the solid dispersion of drug, the solvent have to be dried or removed from the drug solution. The solvent(s) can be removed from the solution by techniques known in the art which includes but are not limited to distillation, evaporation, oven drying, tray drying, rotational drying, spray drying, freeze-drying, fluid bed drying, flash drying, spin flash drying and the like

Dosage forms according to the invention may be provided as dosage forms consisting of several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer. Multilayer forms have the advantage that two active ingredients which are incompatible with one another can be processed, or that the release characteristics of the active ingredient(s) can be controlled. For example, it is possible to provide an initial dose by including an active ingredient in one of the outer layers, and a maintenance dose by including the active ingredient in the inner layer(s).

Multilayer tablets types may be produced by compressing two or more layers of granules. Alternatively, multilayer dosage forms may be produced by a process known as "co-extrusion". In essence, the process comprises preparation of at least two different melt compositions as explained above, and passing these molten compositions into a joint co-extrusion die. The shape of the co-extrusion die depends on the required drug form. For example, dies with a plain die gap, called slot dies, and dies with an annular slit are suitable.

Optionally, the compressed tablets can be film-coated. A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. If desired, the film-coat may be an enteric coat.

As per the disclosed invention, the exemplary compositions are given below to further illustrate the embodiments of the invention without limiting it. The composition disclosed herewith can be a tablet or a capsule or a powder. The granulation for these dosage forms are carried out by either melt-granulation or wet-granulation or the combination of wet granulation and melt granulation.

Example 1

Unit Composition:

S. No.	Ingredient	mg/unit
1	Ritonavir	100.00
2	Sorbitol	500.00
3	Sorbitan monolaurate	84.00
4	Glyceryl monostearate	150.00
5	Colloidal Silicone Dioxide	12.00
6	Atazanavir sulfate (equivalent to 300 mg Atazanavir)	341.70
7	Lactose monohydrate	168.30
8	Crospovidone	20.00
9	Sodium stearyl fumarate	12.00
10	Magnesium stearate	6.00
11	Purified water (To be evaporated)	---
	Tablet Weight	**1394.00**

Brief Manufacturing Process:

1. Atazanavir sulfate, Lactose monohydrate and crospovidone were sifted through sieve of mesh no. 40 using mechanical sifter.
2. The material of step 1 was transferred to rapid mixer and granulator and mixed at slow speed for about 30 minutes. This powder mix was further granulated with purified water and the wet material was dried in fluidized bed dryer. The dried material was then sifted using mechanical sifter fitted with sieve of mesh no. 30.

3. Magnesium stearate was sifted through sieve of mesh no. 40 and added to the sifted material of step 2 in a bin blender and blended for about 5 minutes
4. Ritonavir, sorbitol, glyceryl monostearate and colloidal silicon dioxide were passed through the sieve no. 40 and mixed with sorbitan monolaurate in a stainless steel jacketed vessel. The material mix was heated with mixing till a uniform translucent paste was formed.
5. The material of step 4 was allowed to cool and then milled through the multi-mill fitted with the 0.5 mm screen.
6. Sodium stearyl fumarate was sifted through the sieve of mesh no. 40 and mixed with the milled material of step5
7. The blends of step 3 and step 6 were compressed separately into a bilayer tablet using bilayer tablet compression machine.

Example 2

Unit Composition:

S. No.	Ingredient	mg /unit
1	Ritonavir	100.00
2	Copovidone	650.00
3	Sorbitan monolaurate	84.00
4	Colloidal Silicone Dioxide	12.00
5	Atazanavir sulfate (equivalent to 300 mg Atazanavir)	341.70
6	Lactose monohydrate	168.30
7	Crospovidone	20.00
8	Sodium stearyl fumarate	12.00
9	Magnesium stearate	6.00
10	Sodium chloride	200.00
11	Purified water (To be evaporated)	---
Tablet Weight		**1594.00**

Brief Manufacturing Process:

1. Atazanavir sulfate, Lactose monohydrate, crospovidone were sifted through sieve of mesh no. 40 using mechanical sifter.
2. The material of step 1 was transferred to rapid mixer and granulator and mixed at slow speed for about 30 minutes. This powder mix was further granulated with

purified water and the wet material was dried in fluidized bed dryer. The dried material was then sifted using mechanical sifter fitted with sieve of mesh no. 30.

3. Magnesium stearate was sifted through sieve of mesh no. 40 and added to the sifted material of step 2 in a bin blender and blended for about 5 minutes
4. Ritonavir, copovidone, Sorbitan monolaurate and colloidal silicon dioxide were mixed in rapid mixer and granulator. The mixed mass was then passed through the melt extruder maintained at about 120°C.
5. The extrudes of step 4 were cooled and milled through the mill fitted with the 0.5 mm screen.
6. Sodium chloride and sodium stearyl fumarate were sifted through the sieve of mesh no. 40 and mixed with the milled material of step5.
7. The blends of step 3 and step 6 were compressed separately into a bilayer tablet using bilayer tablet compression machine.

Example 3

Unit Composition:

S. No.	Ingredient	mg /unit
1	Ritonavir	100.00
2	Xylitol	500.00
3	Sorbitan monolaurate	84.00
4	Glyceryl monostearate	150.00
5	Colloidal Silicone Dioxide	12.00
6	Atazanavir sulfate (equivalent to 300 mg Atazanavir)	341.70
7	Lactose monohydrate	168.30
8	Crospovidone	20.00
9	Sodium stearyl fumarate	12.00
10	Magnesium stearate	6.00
11	Purified water (To be evaporated)	---
12	Methanol (To be evaporated)	---
Tablet Weight		**1394.00**

Brief Manufacturing Process:

1. Atazanavir sulfate, Lactose monohydrate and crospovidone were sifted through sieve of mesh no. 40 using mechanical sifter.
2. The material of step 1 was transferred to rapid mixer and granulator and mixed at slow speed for about 30 minutes. This powder mix was further granulated with

purified water and the wet material was dried in fluidized bed dryer. The dried material was then sifted using mechanical sifter fitted with sieve of mesh no. 30.

3. Magnesium stearate was sifted through sieve of mesh no. 40 and added to the sifted material of step 2 in a bin blender and blended for about 5 minutes
4. Ritonavir, xylitol, glyceryl monostearate, sorbitan monolaurate and colloidal silicon dioxide were added to the methanol in a stainless steel vessel and mixed till uniform clear slurry was formed.
5. The slurry of step 4 was then dried under vacuum in tray dryer and the dried material was milled through the multi-mill fitted with the 0.5 mm screen.
6. Sodium stearyl fumarate was sifted through the sieve of mesh no. 40 and mixed with the milled material of step 5.
7. The blends of step 3 and step 6 were compressed separately into a bilayer tablet using bilayer tablet compression machine.

Example 4

Unit Composition:

S. No.	Ingredient	mg /unit
1	Ritonavir	100.00
2	Copovidone	653.80
3	Sorbitan monolaurate	83.90
4	Colloidal Silicone Dioxide (part 1)	12.30
5	Atazanavir sulfate (equivalent to 300 mg Atazanavir)	341.70
6	Lactose monohydrate	168.30
7	Crospovidone	34.00
8	Magnesium stearate	6.00
9	Sodium stearyl fumarate	20.00
10	Sodium chloride	220.00
11	Colloidal Silicone Dioxide (part 2)	10.00
12	Purified water (To be evaporated)	---
13	Methylene chloride (To be evaporated)	---
Tablet Weight		**1650.00**

Brief Manufacturing Process:

1. Atazanavir sulfate, lactose monohydrate and crospovidone were sifted trough mechanical sifter fitted with sieve of mesh no. 40 (ASTM).

2. The sifted material of step 1 was then charged into rapid mixer and granulator where it was mixed for 15-20 minutes at slow speed. This mixture was then subject to granulation by the addition of water which was about 30% w/w of the powdered blend. The wet mass was then dried in fluidized bed dryer and the dried material was passed through the sieve of mesh no. 30.
3. Magnesium stearate was sifted through sieve of mesh no. 40 and blended with the granules of step 2 in bin blender for about 5 minutes.
4. Ritonavir and sorbitan monolaurate were dissolved in methylene chloride in a stainless steel vessel.
5. Copovidone and colloidal silicon dioxide (part 1) were sifted through the sieve of mesh no. 40 using mechanical sifter
6. The material of step 5 was then added to the Ritonavir solution of step 4 and mixed till clear uniform dispersion was formed.
7. The dispersion of step 6 was then dried under vacuum at about 40-50°C in tray dryer till the residual solvent content is below 600 ppm. The dried material was then milled using multi mill fitted with 0.5 mm screen
8. Sodium stearyl fumarate, sodium chloride and colloidal silicon dioxide (part 2) were sifted through the sieve of mesh no. 40 and mixed with the milled material of step7 in bin blender and mixed for about 10 minutes
9. The blends of step 3 and step 8 were compressed separately in bilayer tablet compression machine to form bilayer tablets.

Stability Study:

The stability of the resultant tablets obtained from Example 4 was evaluated. Tablets were packed in HDPE bottle, sealed and closed with child resistant closures. The packed bottles were loaded in the stability chambers maintained at 40°C/75% RH. The samples were withdrawn after 1 and 3 months. The results of the stability studies are given below:

Tests	**Initial**	**1 month at 40°C /75 % RH**	**3month at 40°C /75 % RH**
Assay (Ritonavir)	102.5	103.7	103.1
Assay (Atazanavir)	96.04	96.17	93.66
Water Content	5.6 %	4.9%	4.7%
Related Substances (Ritonavir layer)			
Impurity – B	0.05	0.05	0.07

Impurity – F	0.09	0.09	0.11
Impurity – K	0.01	0.02	0.02
Impurity – L	0	0.01	0.01
Maximum Unknown	0.09	0.09	0.09
Total Impurities	**0.71**	**0.67**	**0.77**
Related Substances (Atazanavir layer)			
Impurity – 2	0.07	0.07	0.08
Impurity – 4	0.01	0.01	0.01
Impurity – 5	0	0	0
Impurity – 8	0.02	0.02	0.02
Maximum Unknown	0.06	0.06	0.09
Total Impurities	**0.28**	**0.30**	**0.37**

The stability data reported in the above table indicates that both atazanavir and ritonavir layers of the tablets are stable at 40°C /75% RH when packed in HDPE bottles. Thus it can be predicted that the resultant tablets have good stability at room temperature and the formulation need not be stored under the refrigerated conditions.

Example 5 [Coating Composition]

S. No.	Ingredient	mg /unit
1	Hydroxypropyl methylcellulose 6cps	30.00
2	Polyethlene glycol 400	1.50
3	Polyethlene glycol 8000	1.50
4	Purified water (To be evaporated)	-

Brief Manufacturing Procedure:

1. Hydroxypropyl cellulose, polyethylene glycol was dispersed in water and stirred for about 30-40 minutes.
2. The tablets of composition disclosed in the example 4 were further coated with the coating dispersion of step 1 using perforated coating pan.

Dissolution Study

The dissolution profile of the resulting coated tablets as per Example 5 was studied for Atazanavir portion in 1000 ml of 0.025 N HCl, using USP–II apparatus at 50 rpm. The sampling was carried out at 10, 20, 30 and 45 minutes. The dissolution profile was then compared with that of marketed product Reyataz™ which is a hard gelatin capsule. The results are depicted in the table below:

Time Point (minutes)	**Atazanavir/Ritonavir Tablets [Example 5] [Atazanavir part]**	**Reyataz™**
10	91.8	88.3
20	96.8	98.3
30	97.2	99.5
45	97.5	100.2

For Ritonavir portion, dissolution was evaluated in 900 ml of 0.1 N HCl with 25 mM Polyoxyethylene10laurylether, using USP–II apparatus at 50 rpm. The sampling was carried out at 10, 20, 30, 45, 60, 90 and 120 minutes. The dissolution profile was then compared with that of marketed product Norvir™ which is a soft gelatin capsule. The values are listed in the following table:

Time (minutes)	**Atazanavir/ Ritonavir Tablets [Example 5] [Ritonavir part]**	**Norvir™**
10	19.0	88.6
20	38.2	95.9
30	60.2	97.0
45	78.8	97.0
60	93.7	97.2
90	101.3	97.3

The results of the dissolution studies shows that the dissolution profile of atazanavir portion is similar to that of Reyataz™ tablets while in case of ritonavir, the dissolution profile is entirely different for the two formulations. This is largely due to entirely different

formulation design of the two products. The slow dissolution of ritonavir over 60-90 minutes was desired in order to avoid the super-saturation in the gastro-intestinal fluids as discussed earlier.

BIOEQUIVALENCE STUDY

A two-way crossover bioequivalence study was carried out using the tablets of composition of Example 5 and using Reyataz™ and Norvir™ capsules as the reference products. During the study each volunteer received either tablets of composition of Examples 5 or Reyataz™ and Norvir™ capsules together. The study was planned to evaluate the bioequivalence of atazanavir from Reyataz™ in the presence Ritonavir from Norvir™ capsules with the atazanavir from the bilayer tablet of atazanavir/ritonavir (composition of Examples 5). The study was carried out in thirty six healthy volunteers in fed conditions. The study was monitored in terms of the AUC and C_{max} achieved for atazanavir with the test product and reference products.

The 90% confidence intervals for the ratios of the log transformed mean values for C_{max} and AUC for the test and reference product (T/R ratio) is a measure of the bioequivalence between the test and reference product.

The results of the study are depicted in the table below:

Parameter	**Log Transformed T/R (%) ratio of least square means**
AUC_{0-t}	108.66
$AUC_{0-\infty}$	105.65
C_{max}	110.16

The results indicate that blood levels of atazanavir obtained with bilayer tablets are similar to that obtained when Reyataz™ is administered along with Norvir™ capsules and the proposed formulation is bioequivalent to the reference product.

WE CLAIM:

1. A stable solid dosage form comprising:

[a] a first component comprising:

(i) ritonavir or its pharmaceutically acceptable salts;

(ii) a pharmaceutical carrier;

(iii) a surfactant; and

(iv) optionally other pharmaceutically acceptable excipients;

[b] a second component comprising:

(i) atazanavir and/or tipranavir or their pharmaceutically acceptable salts; and

(ii) pharmaceutically acceptable excipients.

2. A stable solid dosage form comprising:

[a] a first component comprising ritonavir or its pharmaceutically acceptable salts; and

[b] a second component comprising atazanavir and/or tipranavir, or their pharmaceutically acceptable salts;

wherein, said solid dosage form comprises not more than about 0.5% by weight of individual impurity and not more than 2% by weight of total impurities after three months at 40°C and 75% relative humidity.

3. The stable solid dosage form according to claim 1, wherein said pharmaceutically acceptable excipients are selected from a group consisting of diluents, binders, desiccants, disintegrants, stabilizers, lubricants, glidants, plasticizers and preservatives.

4. The stable solid dosage form according to claim 1 or 2, wherein said solid dosage form is a tablet or a hard gelatin capsule.

5. The stable dosage form according to claim 4, wherein said tablet is in the form of bilayer tablet or compression coated tablet.

6. The solid dosage form according to claim 1, wherein said pharmaceutical carrier is selected from the group consisting of sorbitol, mannitol, xylitol, arabitol, maltitol, ribitol, dulcitol, lactitol, citric acid, succinic acid, tartaric acid, oxalic acid, formic acid, polyvinyl

pyrollidone, cellulose derivatives, gums, methacrylic acid derivatives, alginates, sodium chloride, potassium chloride and starch derivatives.

7. The solid dosage form according to claim 1, wherein said surfactant is selected from the group consisting of sodium dodecyl sulphate, sorbitan monolaurate, sorbitan monopalmitate, poloxamers and Tween™.

8. A process for preparation of a stable solid dosage form, said process comprising:

[a] (i) blending ritonavir, a carrier, a surfactant, and other pharmaceutically acceptable excipients,

(ii) optionally granulating and/or compressing the blend to form a first component;

[b] (i) blending atazanavir and/or tipranavir, and one or more pharmaceutically acceptable excipients,

(ii) optionally granulating and/or compressing blend from previous step to form a second component; and

[c] blending/compressing both components to form said solid dosage form.

9. A process for the preparation of a stable solid dosage form, said process comprising:

[a] (i) dissolving ritonavir, surfactant and optionally other excipients in a solvent to prepare a solution and then drying said solution to prepare a solid dispersion;

(ii) blending said dispersion with other pharmaceutically acceptable excipients,

(iii) optionally granulating and/or compressing said blend to form a first component;

[b] (i) blending atazanavir and/or tipranavir, and one or more pharmaceutically acceptable excipients;

(ii) optionally granulating and/or compressing blend from previous step to form a second component; and

[c] blending/compressing the two components to form said solid dosage form.

10. The process according to claim 8 or 9, wherein said granulation is carried out by dry granulation, wet granulation and/or melt granulation.

11. The process according to claim 9, wherein the solvent used for the preparation of solid dispersion is selected from a group consisting of methylene chloride, isopropyl alcohol, acetone, dichloromethane, methanol, ethanol, water and their mixtures.

12. A stable solid dosage form comprising:

[a] a first component comprising:

(i) ritonavir or its pharmaceutically acceptable salts;

(ii) copovidone;

(iii) sorbitan monolaurate; and

(iv) optionally other pharmaceutically acceptable excipients;

[b] a second component comprising:

(i) atazanavir and/or tipranavir or their pharmaceutically acceptable salts;

(ii) lactose

(iii) crospovidone; and

(iv) optionally, other pharmaceutically acceptable excipients,

wherein said dosage form may optionally be coated.

13. A stable solid dosage form comprising:

[a] a first component comprising ritonavir or pharmaceutically acceptable salts; and

[b] a second component comprising atazanavir and/or tipranavir, or their pharmaceutically acceptable salts,

wherein, atazanavir component of said solid dosage form exhibit similar *in-vitro* dissolution profile when compared with commercially available Reyataz™ formulation.

14. A stable solid dosage form comprising:

[a] a first component comprising ritonavir or pharmaceutically acceptable salts; and

[b] a second component comprising atazanavir and/or tipranavir, or their pharmaceutically acceptable salts,

wherein, the individual components of said solid dosage form are bio-equivalent to commercially available Norvir™ and Reyataz™ formulations respectively.

15. A stable solid dosage form comprising ritonavir, atazanavir and/or tipranavir and other pharmaceutically acceptable excipients as exemplified by the disclosed examples.