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(54) Title: COMPRESSED PHARMACEUTICAL COMPOSITIONS OF ATYPICAL ANTIPSYCHOTICS

(57) Abstract: The present invention relates to compressed pharmaceutical compositions of atypical antipsychotics. Particularly the present invention relates to compressed pharmaceutical compositions of asenapine or pharmaceutically acceptable salts thereof for sublingual, buccal or oromucosal administration. The present invention further relates to processes for preparing such compositions.

COMPRESSED PHARMACEUTICAL COMPOSITIONS OF ATYPICAL ANTIPSYCHOTICS

Field of the Invention

The present invention relates to compressed pharmaceutical compositions of asenapine or pharmaceutically acceptable salts thereof for sublingual, buccal or oromucosal administration. The present invention further relates to processes for preparing such compositions.

Background of the Invention

Schizophrenia is a severe debilitating mental disorder characterized by symptoms such as hallucinations, delusions, disorganized speech, thinking and behavior, reduced motivation and blunted effect. Schizophrenia significantly impairs mental and social functioning and often leads to the development of comorbid diseases. Symptoms of schizophrenia usually begin in late adolescence or early adulthood. In both adults and children, the symptoms of schizophrenia can be divided into positive, negative and cognitive symptoms. Positive symptoms of schizophrenia include loss of contact with reality where patients have beliefs or perceptual experiences not shared by other members of their culture (delusions and hallucinations, respectively) or they engage in bizarre behavior. Negative symptoms such as blunted affect, anhedonia, apathy, and a reduced quantity or content of speech (alogia) are associated with disruptions to normal emotions and behaviors. Cognitive symptoms of schizophrenia are characterized by difficulties in attention, learning, and memory, and a variety of executive functions. Based on the kind of symptoms, schizophrenia can be categorized as paranoid, disorganized, catatonic and undifferentiated schizophrenia. Though exact etiopathology of schizophrenia has not been identified, currently it is believed to be result of combination of both brain vulnerabilities (either inherited or acquired) and life events.

Bipolar disorder is also known as manic-depressive disorder characterized by the presence of one or more episodes of abnormally elevated energy levels, cognition, and mood with or without one or more depressive episodes. It is a condition of severe mood swings that affects an individual for periods of time in a way that interferes with normal functioning. The elevated moods are clinically referred to as mania. Individuals who experience manic episodes may also commonly experience depressive episodes, or symptoms, or a mixed state in which features of both mania and depression are present at the same time. Bipolar disorder has been subdivided into bipolar I, bipolar II,

cyclothymia, and other types, based on the nature and severity of mood episodes experienced. Bipolar I disorder is a mood disorder that is characterized by at least one manic or mixed episode. Genetic factors contribute substantially to the likelihood of developing bipolar disorder, while environmental factors have also been implicated.

Antipsychotic drugs are principally used to treat psychoses particularly schizophrenia and bipolar disorder. Antipsychotics are broadly divided into two groups, the typical (conventional or first generation) antipsychotics and atypical (second generation) antipsychotics respectively. Typical antipsychotic agents act as high affinity antagonists for the type 2 dopamine like receptors with consequences of extrapyramidal side effects such as Parkinsonism, acute muscular dystonia, akathisia and tardive dyskinesia. The introduction of atypical antipsychotic drugs proved to be a significant advancement in the pharmacotherapy of schizophrenia and bipolar disorder. These antipsychotic drugs have enhanced therapeutic action and reduced incidences of extrapyramidal motor control disabilities than typical antipsychotics because they are potent antagonists of serotonin type 2A and type 2 dopamine receptors with higher affinity for the former. Atypical antipsychotics are proved to be effective not only in the treatment of positive symptoms of schizophrenia but also found to be more efficacious against negative as well as cognitive symptoms of schizophrenia than conventional antipsychotics.

Asenapine is an atypical antipsychotic approved in US and Europe for the acute treatment of adults with schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults. Asenapine belongs to the class dibenzo-oxepino pyrroles and is known chemically as (3aRS,12bRS)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenzo[2,3:6,7] oxepino [4,5-*c*]pyrrole (2Z)-2-butenedioate (1:1). It was first disclosed in U.S. Pat. No. 4,145,434 and the process of preparation thereof and the CNS-depressant, antihistamine and antiserotonin activities of the said compound were also described. Though the exact mechanism of action of asenapine is not clear, it is believed to be mediated through a combination of antagonist activity at 5-HT2A and D2 receptors but it has no appreciable activity at muscarinic cholinergic receptors. Asenapine maleate is a white to off-white non hygroscopic powder, slightly soluble in water, sparingly soluble in 0.1M HCl.

Initially, attempts were made to develop a conventional oral solid dosage form of asenapine, however, low bioavailability (<2%) caused by extensive first-pass metabolism necessitated the need to explore alternative routes of administration. Attempts to provide asenapine in the form of intranasal, transdermal and injectable dosage forms were also made; however these routes of administration are not patient friendly and are likely to face non-compliance. A sublingual formulation of asenapine was developed in an attempt to circumvent the hepatic first-pass metabolism of the molecule and improve its bioavailabilty. The absolute bioavailability of asenapine is about 35% when administered sublingually. Asenapine, as asenapine maleate is therefore currently marketed in the form of sublingual tablets of 5 mg and 10 mg strengths under the brand name Saphris in the US and Sycrest in Europe by N.V. Organon. These sublingual tablets need to be placed under the tongue and left to dissolve completely. Eating and drinking needs to be avoided for 10 minutes after administration.

U.S. Patent No. 5,763,476 covering the above sublingual product states that oral doses of asenapine may have cardiovascular side effects and further provides a sublingual or buccal pharmaceutical composition thereof which is manufactured by freeze-drying an aqueous suspension of asenapine, gelatin and mannitol in pre-formed aluminium blister pockets. The patent further discusses use of the composition in treating or managing diseases including mental disorders, such as tension, excitation, anxiety, psychosis and schizophrenia.

Sublingual or buccal formulations are designed to cause absorption of the active through the oral mucosa so that the active directly enters into the systemic circulation thereby avoiding the first pass metabolism. Freeze-dried formulations are commonly employed for sublingual administration to obtain improved bioavailability and rapid onset of action. In the case of asenapine as well the marketed product is a freeze-dried formulation. Freeze-drying technique, however, is a cumbersome, time consuming and expensive process. Moreover, freeze dried formulations tend to lack mechanical strength and fracture easily during handling and packaging.

A need, therefore, exists for an alternative dosage form of asenapine for sublingual, buccal or oromucosal delivery that can be prepared by simple, less time consuming and less expensive processes or equipments.

The present inventors after rigorous experimentation have developed pharmaceutical compositions of asenapine or pharmaceutically acceptable salts thereof for sublingual, buccal or oromucosal administration that have adequate mechanical strength, desired taste, requisite disintegration time and desired in-vitro dissolution and bioavailability. Such compositions are compressed dosage forms comprising asenapine or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient. The compositions of the present invention are manufactured by simple and cost effective manufacturing process and are stable.

Summary of the Invention

The present invention relates to compressed pharmaceutical compositions of asenapine or pharmaceutically acceptable salts thereof for sublingual, buccal or oromucosal administration comprising asenapine or pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient. Such compressed compositions may be in the form of monolithic, bilayered or multilayered dosage forms. The present invention further relates to processes for preparing such compositions.

Detailed Description of the Invention

The present inventors after, thorough research, have developed compressed dosage form of asenapine or pharmaceutically acceptable salt thereof for sublingual, buccal or oromucosal absorption of the active that has adequate mechanical strength, requisite disintegration time, desired in-vitro dissolution and bioavailability. In one embodiment, the compositions of the present invention are stable under ambient and accelerated storage conditions. Furthermore, in the pharmaceutical compositions of the present invention, the bitter, unpleasant or otherwise undesirable taste of the active is masked, without compromising on its stability, release and absorption requirements. The compositions of the present invention are prepared by simple and cost-effective process.

Pharmaceutical composition of the present invention comprises asenapine or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient wherein the composition is in the form of a compressed dosage form.

Asenapine may be incorporated in the compositions of the present invention in the form of free base or pharmaceutically acceptable salts, prodrugs, active metabolites, polymorphs, amorphous form, crystalline forms, combination of crystalline and amorphous forms, solvates, hydrates, enantiomers, optical isomers, tautomers or racemic mixtures thereof. In one embodiment, asenapine in the form of maleate salt is incorporated in the compositions of the present invention.

Pharmaceutically effective amount of asenapine is employed in the composition of the present invention. The term "effective amount" refers to an amount effective to achieve desired therapeutic and/or beneficial effect in schizophrenia, bipolar disorder, psychotic disorders, tension, excitation or anxiety. In one embodiment, asenapine is incorporated in the compositions of the present invention in an amount of about 0.01 weight % to about 95 weight %, based on the total weight of the composition. In yet another embodiment, asenapine is incorporated in the compositions of the present invention in an amount of about 0.02 weight % to about 85 weight %, based on the total weight of the composition. In a further embodiment, asenapine is incorporated in the compositions of the present invention in an amount of about 0.05 weight % to about 80 weight %, based on the total weight of the composition. In one embodiment, the compositions of the present invention may be administered at a dose of about 0.01 mg to about 150 mg of asenapine for antipsychotic, antihistamine or antiserotonin action. In a further embodiment, the compositions of the present invention may be administered at a dose of about 0.1 mg to about 120 mg of asenapine. In another embodiment, the compositions of the present invention may be administered at a dose of about 0.5 mg to about 100 mg of asenapine. In a further embodiment, the compositions of the present invention may be administered at a dose of about 5 mg or 10 mg of asenapine for antipsychotic, antihistamine or antiserotonin action.

Asenapine may be in the form of, but not limited to, powder, granules, pellets, beads, or the like. The asenapine granules may be prepared by methods such as, but not limited to, wet granulation, melt granulation, dry granulation or roll compaction or the like. In one aspect of the present invention granulations, such as, but not limited to, aqueous, hydroalcoholic or alcoholic granulations may be employed. In another aspect of the present invention, pellets of asenapine may be prepared using extrusion spheronization. In another aspect of the present invention, asenapine can be loaded on an inert carrier.

The inert carrier can be selected from, but not limited to, beads, pellets, spheres or similar particles that do not contain an active ingredient. Non-limiting examples of inert carriers include microcrystalline cellulose, sugar or silicon dioxide. In a yet another embodiment, asenapine, in the powder form, may be incorporated in the composition of the present invention. In another embodiment, asenapine, in the powder form, may be blended, coated or treated with at least one pharmaceutically acceptable excipient.

The pharmaceutical formulation of the present invention further comprises at least one pharmaceutically acceptable excipient such as, but not limited to, binders, disintegrants, superdisintegrants, diluents, surfactants, solubilizers, pH modifiers, flavors, sweeteners, colorants, salivating agents, souring agents, glidants, lubricants, absorption enhancers, mucoadhesive agents, taste-modifiers or the like.

Disintegrants that may be employed include, but are not limited to, crospovidone, microcrystalline cellulose, calcium silicate, starch and the like or combinations thereof. Examples of superdisintegrants that may be employed include, but are not limited to, natural, modified or pregelatinized starch, crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, effervescent disintegrating systems and the like or combinations thereof. Effervescent disintegrating systems that may be employed include a gas generating agent and an acid source. Suitable acid source that may be employed as part of effervescent disintegrating system includes, but is not limited to, citric acid, citric acid anhydrous, maleic acid and the like or combinations thereof. Gas generating agents that may be used in the present invention include, but are not limited to, sodium bicarbonate, sodium glycine carbonate, potassium bicarbonate, ammonium bicarbonate, sodium bisulfite, sodium metabisulfite, and the like or combinations thereof. Examples of suitable binders that may be employed include, but are not limited to, starch, pregelatinized starch, polyvinyl pyrrolidone, copovidone, cellulose derivatives, such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose and carboxymethyl cellulose and their salts and the like or combinations thereof. Examples of suitable diluents include, but are not limited to, starch, microcrystalline cellulose, lactose, xylitol, mannitol, maltose, polyols, fructose, dicalcium phosphate, directly compressible composites, and the like or any combinations thereof. Directly compressible composites that may be employed include, but are not limited to, directly compressible coprocessed composite of calcium silicate and mannitol and the like.

Examples of lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, talc, sodium stearyl fumarate and the like or combinations thereof. The formulations of the present invention may also include a glidant such as, but not limited to, colloidal silica, colloidal silicon dioxide, silica gel, precipitated silica, and the like or combinations thereof. The said compositions may also include salivating agents such as, but not limited to, micronized polyethylene glycol, citric acid, citric acid anhydrous, sodium chloride or precipitated micronized silica, and the like or combinations thereof to improve the disintegration properties of the said compositions. Examples of solubilizers include, but are not limited to cetostearyl alcohol, cholesterol, diethanolamine, ethyl oleate, ethylene glycol palmitostearate, glycerin, polysorbate, polysorbate 20, polysorbate 80, polyethylene glycol, glyceryl monostearate, isopropyl myristate, lecithin, medium-chain glyceride, monoethanolamine, oleic acid, propylene glycol, polyoxyethylene alkyl ether, poloxamer, poly (oxyethylene)-poly(oxypropylene) block copolymers, polyoxyethylene castor oil glycoside, polyethylene sorbitan fatty acid ester, polyoxyethylene stearate, propylene glycol alginate, sorbitan fatty acid ester, macrogol glycerides, caprylcaproyl macrogol glycerides, stearic acid, sunflower oil, polyethylene glycol triethanolamine, cyclodextrins such as β-cyclodextrin, hydroxypropyl β-cyclodextrin, and the like or mixtures thereof. Examples of surfactants include, but are not limited to, cationic, anionic or zwitterionic surfactants such as, but not limited to, sodium docusate, glyceryl monooleate, polyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, sorbic acid, sorbitan fatty acid ester, and the like or mixtures thereof. Souring agents include, but are not limited to, monosodium fumarate and/or citric acid and the like or combinations thereof. The compositions of the present invention may further optionally comprise a pH modifier or buffering agent such as, but not limited to, benzoic acid, sodium benzoate, tartaric acid, citric acid, citric acid anhydrous, fumaric acid, sodium citrate, potassium citrate, phosphoric acid and the like or combinations thereof.

Absorption enhancers include, but are not limited to, sodium caprate, sodium glycocholate, chitosans, polysorbate 80, Cremophor® EL, D-α-tocopheryl polyethylene glycol succinate, and the like or combinations thereof. Mucoadhesive agents, that may be employed include, but are not limited to, cellulose derivatives such as, but not limited to, hydroxyethylcellulose, hydroxypropylcellulose, methyl cellulose, sodium carboxymethylcellulose and the like; poly (acrylic acid) polymers such as, but not limited

to, carbopol and the like; natural polymers such as, but not limited to, shellac, tragacanth, pectin, lectin, sodium alginate, acacia, guar gum, karaya gum and the like; alginate-polyethylene glycol acrylate (alginate-PEGAc), poloxamer, pluronics, polyacrylates; polymethacrylates, vinyl derivatives or polymers and copolymers thereof such as, but not limited to, poly (vinyl pyrrolidone), poly (vinyl alcohol) and the like. Further, the compositions of the present invention comprise at least one sweetener such as, but not limited to, aspartame, stevia extract, glycyrrhiza, saccharine, saccharine sodium, acesulfame, sucralose and dipotassium glycyrrhizinate; and/or one or more flavors, such as, but not limited to, mint flavour, orange flavour, lemon flavors, strawberry aroma, vanilla flavour, raspberry aroma, cherry flavor, tutty frutty flavor, magnasweet 135, key lime flavor, grape flavor, trusil art 511815, and fruit extracts. Taste-modifiers that may optionally be incorporated in the compositions of the present invention include, but are not limited to, water soluble, water dispersible, water insoluble polymeric or non-polymeric agents and the like or combinations thereof. Water soluble, water dispersible, water insoluble polymeric or non-polymeric agents include, but are not limited to, cellulose derivatives, saccharides or polysaccharides, polyhydric alcohols, poly (oxyethylene)-poly(oxypropylene) block copolymers (poloxamers), vinyl derivatives or polymers or copolymers thereof, acrylic acid derivatives, fats, oils, waxes, fatty acids, fatty acid esters, long chain monohydric alcohols and their esters, phospholipids, terpenes, and the like or any combinations thereof. The pharmaceutically acceptable excipient is present in the composition of the present invention in an amount of about 1% to about 95% by weight of the dosage form. In one embodiment, the active is blended, coated or granulated with at least one taste-modifier. In another embodiment, the active is complexed or blended with at least one cyclodextrin such as, but not limited to, β-cyclodextrin, hydroxypropyl β-cyclodextrin.

The pharmaceutical composition of the present invention of asenapine is a compressed dosage form. Such a compressed dosage form can be prepared by methods such as, but not limited to, direct compression, wet granulation, dry granulation, roll compaction, extrusion spheronization, melt granulation, melt extrusion, fluid bed coating, spray coating, compression coating and the like. In one embodiment the pharmaceutical compositions of the present invention for sublingual, buccal or oromucosal administration can be in the form of, but not limited to, orally or rapidly disintegrating or dissolving

tablets, minitablets, pellets or lozenges or mucoadhesive tablets or pellets, pellets in capsule or minitablets in capsule.

In a further embodiment the pharmaceutical formulation of the present invention is in the form of a monolithic tablet. In another embodiment, the pharmaceutical formulation is in the form of multilayered tablet. In one embodiment, the composition of the present invention is a bilayered tablet. In another embodiment, the bilayered pharmaceutical composition of the present invention comprises one active layer and the other layer or the second layer devoid of the active. In one embodiment, both the layers of the bilayered tablet composition comprise the active. In another embodiment, one active layer of the bilayered tablet composition comprises more active than another. In a further embodiment, the composition of the present invention is in the form of a bilayered tablet wherein one layer comprises asenapine or pharmaceutically acceptable salt thereof in an amount of more than 50% by weight of the dose of asenapine to be delivered and the other layer comprises the remaining dose of asenapine. In another embodiment, the composition of the present invention is in the form of a bilayered tablet wherein one layer comprises asenapine or pharmaceutically acceptable salt thereof in an amount of more than 75% by weight of the dose of asenapine to be delivered and the other layer comprises the remaining dose of asenapine. In a further embodiment, the composition of the present invention is in the form of a bilayered tablet wherein one layer comprises asenapine or pharmaceutically acceptable salt thereof in an amount of more than 85% by weight of the dose of asenapine to be delivered and the other layer comprises the remaining dose of asenapine. In another embodiment, the bilayered tablet composition of the present invention comprises in one active layer more than about 90% by weight of the dose of asenapine to be delivered and the other layer comprises the remaining dose of asenapine. In another embodiment, the bilayered tablet composition of the present invention comprises in one active layer more than about 95% by weight of the dose of asenapine to be delivered and the other layer comprises the remaining dose of asenapine. In a further embodiment, the pharmaceutical composition of the present invention is in the form of a tablet-in-tablet dosage form or compressed core with compression coated type of dosage form or inlay tablet type of dosage form.

In one embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates within about 3 minutes as per USP in-vitro disintegration

test. In a further embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates within about 2 minutes as per USP in-vitro disintegration test. In another embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates within about 60 seconds as per USP in-vitro disintegration test. In a further embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates within about 45 seconds as per USP in-vitro disintegration test. In another embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates within about 30 seconds as per USP in-vitro disintegration test. In yet another embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates in more than 30 seconds as per USP in-vitro disintegration test. In yet another embodiment, the compressed pharmaceutical formulation of asenapine of the present invention disintegrates in more than 45 seconds as per USP in-vitro disintegration test.

In one embodiment, one layer of the bilayered tablet formulation of the present invention comprising all the active or more amount of the active than the other layer is a rapidly disintegrating layer and the other layer not comprising the active or comprising less amount of active than the other layer is a slow disintegrating layer. The two layers of the bilayered tablet of the present invention have different in-vitro disintegration times as measured by USP in-vitro disintegration test.

In another embodiment, in a tablet-in-tablet or inlay tablet type of dosage form, the outer tablet or outer compressed coating is rapidly disintegrating one, while the inner tablet or compressed core can be a slow disintegrating one. In another embodiment, outer tablet or outer compressed coating disintegrates rapidly and the inner tablet or compressed core disintegrates slowly. In yet another embodiment, outer tablet or outer compressed coating disintegrates rapidly and the inner tablet or compressed core disintegrates slowly.

In one embodiment, the in vitro disintegration time of the compositions of the present invention is measured as per United States Pharmacopoeia (USP e.g. USP35). The disintegration time is measured in vivo by placing the compressed dosage form e.g. tablet in the sublingual, buccal or oromucosal cavity, and measuring, using a stopwatch,

the time that elapses between the beginning of the measurement and the moment when the tablet has completely disintegrated under the action of saliva and without chewing. In one embodiment, the later disintegrating part or the slow disintegrating part of the compressed pharmaceutical composition of asenapine or pharmaceutically acceptable salt thereof retains the dosage form at the desired site in the oral cavity for sublingual, buccal or oromucosal administration. In a further embodiment, the composition of the present invention releases asenapine or pharmaceutically acceptable salt thereof immediately for absorption across the oral mucosa. In another embodiment, the composition of the present invention releases asenapine or pharmaceutically acceptable salt thereof in a modified manner for absorption across the oral mucosa.

In one of the embodiment of the present invention, the dosage form may be optionally coated. Surface coating may be employed for aesthetic purposes or for dimensionally stabilizing the compressed dosage form. The coating may be carried out using any conventional technique employing conventional pharmaceutically acceptable polymers. The terms "tablet" and "tablet composition" and "tablet formulation" are used synonymously within the context of the present invention. These terms should be construed to include a compacted or compressed powder composition obtained by compressing or otherwise forming the composition to form a solid having a defined shape. The tablet may vary in shape such as oval, triangle, almond, peanut, parallelogram, round, pentagonal, hexagonal, and trapezoidal. The preferred shapes are round, oval and parallelogram forms.

The present invention discloses a process for preparing the compressed pharmaceutical formulation of asenapine or pharmaceutically acceptable salts thereof comprising: (a) blending asenapine or pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient; (b) lubricating the blend of step (a); and (c) compressing the lubricated blend of step (b) to form tablets for buccal, sublingual or oromucosal administration. The present invention discloses a process for preparing the compressed pharmaceutical formulation of asenapine or pharmaceutically acceptable salts thereof comprising: (a) blending asenapine or pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient; (b) dry or wet granulating the blend of step (a) to form granules; (c) lubricating the blend of step (b);

and (d) compressing the lubricated blend of step (c) to form for buccal, sublingual or oromucosal administration.

The present invention discloses a process for preparing the compressed pharmaceutical formulation of asenapine or pharmaceutically acceptable salts thereof comprising: (a) blending asenapine or pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient; (b) lubricating the blend of step (a) to form the active layer; (c) blending at least one pharmaceutically acceptable excipient with lubricant to form layer devoid of active agent; (d) compressing the active layer of step (b) and the layer devoid of the active agent of step (c) to form a bilayered tablet for buccal, sublingual or oromucosal administration. The present invention discloses a process for preparing the compressed pharmaceutical formulation of asenapine or pharmaceutically acceptable salts thereof comprising: (a)blending more than 50% by weight, in a further embodiment more than 75% by weight, in yet another embodiment more than 85% by weight, in a still further embodiment more than 90% by weight, in still another embodiment more than 95% by weight, of the dose of asenapine to be delivered with at least one pharmaceutically acceptable excipient; (b) lubricating the blend of step (a) to form the first active layer; (c) blending the remaining dose of asenapine and at least one pharmaceutically acceptable excipient; (d) lubricating the blend of step (c) to form the second active layer; (e) compressing the first active layer of step (b) and the second active layer of step (d) to form a bilayered tablet for buccal, sublingual or oromucosal administration. The present invention discloses a process for preparing the compressed pharmaceutical formulation of asenapine or pharmaceutically acceptable salts thereof comprising: (a)blending more than 50% by weight, in a further embodiment more than 75% by weight, in yet another embodiment more than 85% by weight, in a still further embodiment more than 90% by weight, in still another embodiment more than 95% by weight, of the dose of asenapine to be delivered with at least one pharmaceutically acceptable excipient; (b) granulating the blend of step (a) with at least one binder to form granules (c) blending the granules of step (b) with the remaining excipients and then lubricant to form the first active layer; (d) blending the remaining dose of asenapine and at least one pharmaceutically acceptable excipient; (e) granulating the blend of step (d) with at least one binder to form granules (f) blending the granules of step (e) with the remaining excipients and then lubricant to form the second active layer (g) compressing

the first active layer of step (c) and the second active layer of step (f) to form a bilayered tablet for buccal, sublingual or oromucosal administration.

The present invention discloses a process for preparing the compressed pharmaceutical formulation of atypical antipsychotic agent such as asenapine or pharmaceutically acceptable salts thereof comprising: (a) blending at least one pharmaceutically acceptable excipient with lubricant and compressing the blend to form compressed tablet devoid of active agent; (b) blending the active agent with at least one pharmaceutically acceptable excipient, lubricating the blend, and compressing the lubricated blend in the form of coating over the compressed tablet of step (a) to form tablet in tablet dosage form for buccal, sublingual or oromucosal administration.

The present invention further provides a method for the treatment of tension, excitation, anxiety or psychotic disorders such as but not limited to schizophrenia, bipolar disorder, and the like comprising administering to the patient in need thereof compressed pharmaceutical formulations of the present invention comprising asenapine or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient. In another embodiment, there is provided use of the compressed pharmaceutical formulation of the present invention comprising asenapine or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient for the manufacture of a medicament for the treatment of tension, excitation, anxiety or psychotic disorders such as but not limited to schizophrenia, bipolar disorder, and the like. In a still further embodiment of the present invention the compressed pharmaceutical compositions of the present invention may be adapted to deliver one or more active agents in addition to asenapine or pharmaceutically acceptable salts thereof. In another embodiment of the present invention the compressed pharmaceutical formulation of the present invention may be co-administered with compositions of other active agents, such as, but not limited to, lithium, valproate, dimebon and the like.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. Details of the present invention, including its objects and advantages, are provided in the non-limiting exemplary illustrations below.

Examples:

Example 1: Bilayered orally disintegrating sublingual tablet of asenapine maleate

Ingredients	mg/tab
Layer 1	
Asenapine maleate equivalent to asenapine 5mg base	7.03
Mannitol, USP	18
Crospovidone, USP/NF	15
Colloidal silicon dioxide, USP/NF	2
Microcrystalline cellulose, USP/NF	27.47
Copovidone, USP/NF	2
Aspartame, USP/NF	2
Strawberry flavour	0.5
Magnesium stearate, USP/NF	1
Total	**75**
Layer 2	
Mannitol, USP	20
Crospovidone, USP/NF	5
Colloidal silicon dioxide, USP/NF	2
Microcrystalline cellulose, USP/NF	30
Copovidone, USP/NF	3
Sodium carboxymethyl cellulose, USP/NF	10
Aspartame, USP/NF	2
Strawberry flavour	1
Magnesium stearate, USP/NF	2
Total	**75**

Procedure: Asenapine maleate was thoroughly blended with all the excipients of layer 1 except lubricant in a blender to get a uniform powder mix. This mix was then lubricated using magnesium stearate to form lubricated blend of layer 1. All excipients except the lubricant of layer 2 were dry mixed separately. This mix was then lubricated with magnesium stearate to form lubricated blend of layer 2. Lubricated blends of layer 1 and

layer 2 were then compressed together into a bilayered tablet. The tablets had the desired disintegration time, friability, hardness and palatability.

Example 2: Orally disintegrating sublingual tablet of asenapine maleate

Ingredients	mg/tab
Asenapine maleate equivalent to 10 mg asenapine base	14.06
Microcrystalline cellulose, USP/NF	30.94
Directly compressible coprocessed composite of calcium silicate and mannitol	40
Copovidone, USP/NF	3
Crospovidone, USP/NF	5
Acesulfame, Ph.Eur.	3
Colloidal silicon dioxide, USP/NF	2
Bubble gum flavor	1
Magnesium stearate, USP/NF	1
Total	**100**

Procedure: All the above excipients except the lubricant were blended. The blend was then lubricated and compressed into into tablets. The tablets had the desired disintegration time, friability, harness and palatability.

Example 3: Orally disintegrating buccal tablet of asenapine maleate

Ingredients	mg/tab
Asenapine maleate equivalent to 5 mg asenapine base	7.03
Hydroxy propyl β–cyclodextrin, USP/NF	15
Microcrystalline cellulose, USP/NF	75.97
Directly compressible coprocessed composite of calcium silicate and mannitol	35
Crospovidone, USP/NF	12
Sucralose, USP/NF	2
Orange flavour	1
Magnesium stearate, USP/NF	2
Total	**150**

Procedure: Asenapine was blended with hydroxy propyl β–cyclodextrin. Such treated asenapine was blended with other excipients except the lubricant in a blender. This blend was then lubricated and compressed into tablets. The tablets had the desired disintegration time, friability, hardness and palatability.

Example 4: Orally disintegrating sublingual tablet of asenapine maleate

Ingredients	**mg/tab**
Asenapine maleate equivalent to 5 mg asenapine base	7.03
Polyvinylpyrrolidone, USP	4
Anhydrous citric acid, USP/NF	10
Sodium bicarbonate, USP	10
Mannitol, USP	52.97
Colloidal silicon dioxide, USP/NF	2
Crospovidone, USP/NF	10
Aspartame, USP/NF	2
Peppermint flavour	1
Magnesium stearate, USP/NF	1
Total	**100**

Procedure: All the ingredients except the lubricant were blended. The blend was then lubricated and compressed into tablets. The tablets had desired disintegration time, friability, hardness and palatability.

Example 5: Bilayered orally disintegrating sublingual tablet of asenapine maleate

Ingredients	**mg/tab**
Active Layer 1	
Asenapine maleate (95% of dose equivalent to asenapine 10mg base)	13.357
Mannitol, USP	32.143
Starch, USP/NF	6.8
Microcrystalline cellulose, USP/NF	8
Hydroxypropylcellulose, USP/NF	0.2
Polaxomer 188, USP/NF	1

Citric acid anhydrous, USP/NF	1
Sodium starch glycolate, USP/NF	12
Sucralose, USP/NF	2
Colloidal silicon dioxide, USP/NF	0.5
Sodium stearyl fumarate, USP/NF	1.5
Peppermint flavor	1.5
Total (Active layer 1)	**80**
Layer 2	
Asenapine maleate (5% of dose equivalent to asenapine 10mg base)	0.703
Mannitol, USP	74.197
Hydroxypropylcellulose, USP/NF	0.75
Sucralose, USP/NF	0.75
Colorant	0.1
Colloidal silicon dioxide, USP/NF	0.5
Peppermint flavor	1.5
Sodium stearyl fumarate, USP/NF	1.5
Total (Active layer 2)	**80**
Total Tablet Weight	**160**

Procedure: For active layer 1, asenapine maleate was thoroughly blended with mannitol and part of sodium starch glycolate. The blend was then granulated with hydroalcoholic solution of hydroxypropylcellulose. The granules were then dried and blended with the remaining ingredients, and lubricated in a blender to get a blend of active layer 1. For active layer 2, asenapine maleate was thoroughly blended with mannitol and then granulated with hydroalcoholic solution of hydroxypropyl cellulose. The granules were dried and blended with the remaining ingredients, and lubricated in a blender to get a blend of active layer 2. Lubricated blends of layer 1 and layer 2 were then compressed together into a bilayered tablet. The tablets had the desired disintegration time, friability, hardness, in-vitro dissolution and palatability.

CLAIMS

We claim:

1. A pharmaceutical composition of asenapine or pharmaceutically acceptable salt thereof for sublingual, buccal or oromucosal administration comprising asenapine or pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient; wherein the composition is in the form of a compressed dosage form.

2. The pharmaceutical composition of claim 1 wherein said asenapine is in the form of free base, pharmaceutically acceptable salt, prodrug, active metabolite, polymorph, amorphous form, crystalline form, combination of crystalline and amorphous form, solvate, hydrate, enantiomer, optical isomer, tautomer or racemic mixture thereof.

3. The pharmaceutical composition of claim 1 wherein the composition comprises asenapine maleate.

4. The pharmaceutical composition of claim 1 wherein the composition is in the form of a monolithic tablet.

5. The pharmaceutical composition of claim 1 wherein the composition is in the form of a multilayered tablet.

6. The pharmaceutical composition of claim 1 wherein the composition is in the form of a bilayered tablet.

7. The pharmaceutical composition of claim 6 wherein the composition is in the form of a bilayered tablet comprising one active layer and second layer devoid of the active.

8. The pharmaceutical composition of claim 6 wherein the composition is in the form of a bilayered tablet comprising two active layers.

9. The pharmaceutical composition of claim 8 wherein the composition is in the form of a bilayered tablet comprising one active layer comprising more than 50% by weight of the dose of asenapine to be delivered and the second active layer comprising remaining dose of asenapine.

10. The pharmaceutical composition of claim 1 wherein the composition is in the form of a tablet-in-tablet dosage form or compressed core with compression coated type of dosage form or inlay tablet type of dosage form.

11. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable excipient is binder, disintegrant, superdisintegrant, diluent, surfactant, solubilizer, pH modifier, flavorant, sweetener, colorant, salivating agent, souring agent, glidant, lubricant, absorption enhancer, mucoadhesive agent, or taste-modifier.

12. The pharmaceutical composition of claim 1 wherein the dosage form disintegrates within about 3 minutes as per USP in-vitro disintegration test.

13. The pharmaceutical composition of claim 1 wherein the dosage form disintegrates after about 45 seconds as per USP in-vitro disintegration test.

14. The pharmaceutical composition of claim 1 wherein the dosage form disintegrates after about 30 seconds as per USP in-vitro disintegration test.

15. The pharmaceutical composition of claim 1 wherein the dosage form disintegrates within about 30 seconds as per USP in-vitro disintegration test.

16. The pharmaceutical composition of claim 1 wherein the compressed dosage form is prepared by direct compression, wet granulation, dry granulation, roll compaction, extrusion spheronization, melt granulation, melt extrusion, fluid bed coating, spray coating, or compression coating.

17. The pharmaceutical composition of claim 1 wherein the composition is in the form of orally or rapidly disintegrating or dissolving tablets, minitablets, pellets or lozenges, mucoadhesive tablets, pellets, pellets in capsule or minitablets in capsule.

18. The pharmaceutical composition of claim 1 wherein the composition further comprises an additional active agent.