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(54) **Title:** MODIFIED RELEASE PHARMACEUTICAL COMPOSITIONS OF DESVENLAFAXINE

(57) **Abstract:** This present invention relates to modified release pharmaceutical composition comprising Desvenlafaxme, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof. More particularly, the invention relates to modified release pharmaceutical compositions comprising Desvenlafaxme Benzoate and a process for preparation thereof. Further, the invention relates to a modified release pharmaceutical composition comprising Desvenlafaxme Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein C_{max} and AUC of the modified release composition are independent of food effect.

MODIFIED RELEASE PHARMACEUTICAL COMPOSITIONS OF DESVENLAFAXINE

Field Of The Invention:

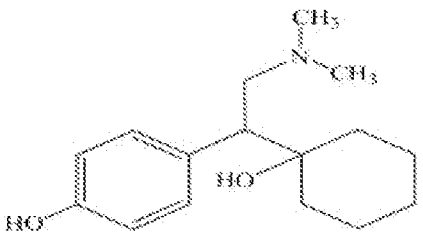
This present invention relates to modified release pharmaceutical compositions comprising Desvenlafaxine and a process for preparation thereof.

Background Of The Invention:

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressant drugs used in the treatment of major depression and other mood disorders. They are also used to treat anxiety disorders, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), chronic neuropathic pain, fibromyalgia syndrome **(FMS),** and for the relief of menopausal symptoms.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) include but not limited to venlafaxine, Desvenlafaxine, milnacipran, duloxetine, sibutramine, levomilnacipran and sibutramine.

Desvenlafaxine is Serotonin-norepinephrine reuptake inhibitors and chemically, Desvenlafaxine is chemically named (±)-l-[2-(dimethylamino)-l-(4-hydroxyphenyl)ethyl]cyclohexanol, is a major metabolite of venlafaxine and has been shown to inhibit norepinephrine and serotonin uptake. Desvenlafaxine, which can also be referred to as O-Desmethylvenlafaxine or desmethylvenlafaxine, is represented by the following structural formula:



O-desmethyl venlafaxine is a major metabolite of venlafaxine and has been shown to inhibit norepinephrine and serotonin uptake.

Desvenlafaxine was exemplified as a fumarate salt in U.S. Pat. No. 4,535,186. However, the fumarate salt of O-desmethyl-venlafaxine has unsuitable physicochemical and permeability characteristics. O-desmethyl-venlafaxine is also exemplified as a free base in International Patent Publication No. WO 00/32555.

U.S. Pat. No. 6,673,838 disclose different crystalline forms of Desvenlafaxine Succinate mainly Form I, II, III and IV. Further it discloses amorphous form of Desvenlafaxine Succinate. U.S. Pat. No. 7,820,716 discloses Form V and Form F of Desvenlafaxine Succinate.

Different salts of Desvenlafaxine have been disclosed in the literature. Succinate salt (U.S. Pat. No. 6,673,838 and US Patent Application No. 20040106576); formate (U.S. Pat. No.7,001,920); hydrochloride (AU Patent Application No. 20080218997); citrate, maleate, mesylate, mandelate, quinic acid salt and tartrate (WO 2010008735); phosphate (WO 2009136756); D-glucuronate and orotate (WO 2009095431); oxalate, Benzoate and lactate (WO 2009053840); saccharinate (WO 2009017813).

Salt formation provides a means of altering the physicochemical and resultant biological characteristics of a drug without modifying its chemical structure. A salt form can have a dramatic influence on the properties of the drug. The selection of a suitable salt is partially dictated by yield, rate and quantity of the crystalline structure. In addition, hygroscopicity, stability, solubility and the process profile of the salt form are important considerations. The identification of a salt form that exhibits a suitable combination of properties can be difficult.

The Succinate monohydrate form of Desvenlafaxine has been incorporated into an extended release hydro-gel tablet, which reduces adverse effects such as nausea, vomiting, diarrhea, and abdominal pain. Formulations describing the use of hydroxypropyl methylcellulose (HPMC) as the hydrogel matrix have been described in U.S. Pat. No. 7,291,347.

US Patent Application No 20050175698 provides an enteric coated multiparticulate form of Desvenlafaxine that reduces undesirable characteristics associated with Desvenlafaxine and the hydrogel formulation thereof. These Desvenlafaxine multiparticulates are composed of Desvenlafaxine Succinate, Desvenlafaxine formate, or combinations thereof. Advantageously, this formulation also allows more convenient dosing to patients who have difficulty swallowing solid foods.

US Patent Application No 20100210719 describes stable amorphous O-desmethylvenlafaxine Succinate solid dispersions with one or more pharmaceutically acceptable carriers.

US Patent Application No 20100330172 discloses matrix controlled-release pharmaceutical formulation comprising Desvenlafaxine Succinate, having an MMD of between about 5 micrometer and about 100 micrometer and matrix rate-controlling pharmaceutically acceptable polymer.

US Patent Application No 20110046231 provides pharmaceutical composition comprising a solid state form of O-desmethylvenlafaxine salt and one or more pharmaceutically acceptable excipients, wherein the salt of O-desmethylvenlafaxine is an oxalate salt, a Benzoate salt or a lactate salt.

US Patent Application No 20070014859 discloses superbioavailable DVS (O-desmethylvenlafaxine Succinate) sustained release composition comprising a core containing at least DVS and a water insoluble filler in an oral dosage unit having a delayed release of at least about one hour and a sustained release over multiple hours to provide a total release of greater than about 85% within about 12 to about 14 hours.

While there are many compositions available to reduce side effects of conventional dosage forms, still there remains a need to develop a controlled release composition of Desvenlafaxine.

Objective Of The Invention:

The main object of invention is to provide modified release pharmaceutical composition of Desvenlafaxine.

Another object of invention is modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

Another object of invention is modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine is upto about 80 microns.

Another object of invention is modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

Another object of invention is modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine is upto about 80 microns such that composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

Another object of invention is modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s).

Another object of invention is modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), such that d_{50} particle size of Desvenlafaxine upto about 80 microns.

Another object of invention is modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type **I** dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

Another object of invention is modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine is upto about 80 microns such that composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type **I** dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

Summary Of The Invention:

The present invention provides modified release pharmaceutical compositions comprising Desvenlafaxine and a process for preparation thereof and their use in medicines. The invention relates to modified release pharmaceutical compositions comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof, which is bioequivalent to extended release composition of Desvenlafaxine Succinate in a bioavailability study in humans. Further, C_{max} and AUC of the modified release composition comprising Desvenlafaxine Benzoate are independent of food effect.

Detailed Description Of The Invention:

The present invention relates to provide modified release pharmaceutical composition of Desvenlafaxine and a process for preparation thereof.

It will be understood that, for the purposes of invention, Desvenlafaxine may be used in the form of base, pharmaceutically acceptable salt(s) or enantiomer(s) or polymorph(s) thereof.

The term "pharmaceutically acceptable salts" refers to salts comprise but not limited to which are prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids, Suitable non-toxic acids include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methane-sulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toulenesufonic acids and the like. Preferably, Desvenlafaxine is in the salt form. More preferably Desvenlafaxine salt is Benzoate, Succinate, glutarate & palmitate.

In another embodiment, Desvenlafaxine Benzoate is in crystalline form or in amorphous form or a mixture thereof. It is to be understood for the purpose of invention that Desvenlafaxine Benzoate may be present in the form of solvates with organic solvents like ethanol, isopropanol or hydrate like monohydrate, dihydrate or enantiomers.

It is to be understood for the purpose of invention, Desvenlfaxine Benzoate can be prepared by methods disclosed in Indian Patent Application no. 0761/KOL/2011 are hereby incorporated in its entirety.

In another embodiment, Desvenlafaxine Benzoate is in crystalline form characterized by a powder X-ray diffraction pattern having at least one peak at about 5.4, 10.75, 16.6, 18.0, 19.2, 23.32 ± 0.2 degrees 2Θsubstantially as depicted in Figure 1.

In another embodiment, Desvenlafaxine Benzoate is in crystalline form characterized by a powder X-ray diffraction pattern having peaks at about 5.4, 10.75, 16.6, 18.0, 19.2, 23.32 ± 0.2 degrees 2Θ substantially as depicted in Figure 1.

In another embodiment, Desvenlafaxine Benzoate is in crystalline form characterized by a powder X-ray diffraction pattern having peaks at about 5.4, 9.5, 10.75, 16.1, 16.6, 17.3, 18.0, 19.2, 20.4, 23.32 ± 0.2 degrees 2Θ substantially as depicted in Figure 1.

In another embodiment, Desvenlafaxine Benzoate is in crystalline form characterized by a powder X-ray diffraction pattern substantially in accordance with Figure 1.

More preferably, Desvenlafaxine Benzoate is in crystalline form characterized by a powder X-ray diffraction pattern having peaks at about 5.4, 9.5, 10.7, 16.1, 16.6, 17.3, 18.0, 19.2, 20.4, 21.5, 23.3, 24.9, 28.3, 29.9 ± 0.2 degrees 2Θ.

Desvenlafaxine Benzoate has solubility in water of greater than 30mg/ml, preferably the aqueous solubility of the Desvenlafaxine Benzoate is at least about 50 mg/ml at 25° C, more preferably, the aqueous solubility of Desvenlafaxine Benzoate is about 60 mg/ml at 25° C.

Desvenlafaxine Succinate has solubility in water of greater than 30mg/ml, preferably the aqueous solubility of the Desvenlafaxine Succinate is about 35 mg/ml at 25° C.

Desvenlafaxine used in pharmaceutical compositions of invention in an amount of which is safe, well tolerated in patients with acceptable adverse effect profiles and are those in common practice and known to person skilled in the art.

Desvenlafaxine used to treat or prevent central nervous system disorders including, but not limited to depression (including but not limited to major depressive disorder, bipolar disorder and dysthymia), fibromyalgia, anxiety, panic disorder, agoraphobia, post traumatic stress disorder, premenstrual dysphoric disorder (also known as premenstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, incontinence (including fecal incontinence, overflow incontinence, passive incontinence, reflex incontinence, stress urinary incontinence, urge incontinence, urinary exertional incontinence and urinary incontinence), pain (including but not limited to migraine, chronic back pain, phantom limb pain, central pain, neuropathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager

can also be used for preventing relapse or recurrence of depression; to treat cognitive impairment; for the inducement syndrome, Raynaud's syndrome, Parkinson's Disease, epilepsy, and others. Compounds and compositions of the present invention of cognitive enhancement in patient suffering from senile dementia, Alzheimer's disease, memory loss, amnesia and amnesia syndrome; and in regimens for cessation of smoking or other tobacco uses.

The dosage amount useful to treat, prevent, inhibit or alleviate each of the aforementioned conditions will vary with the severity of the condition to be treated and the route of administration. The dose and dose frequency will also vary according to age, body weight, response and past medical history of the individual human patient.

Dosage is described in terms of the free base and is adjusted accordingly for the pharmaceutically acceptable salts. In managing the patient, is generally preferred that the therapy be initiated at a lower dose and increased if necessary. Dosages for non-human patients can be adjusted accordingly by one skilled in the art.

A modified release pharmaceutical composition according to the invention comprises but is not limited to tablets (single layered tablets, multilayered tablets, mini tablets, bioadhesive tablets, caplets, matrix tablets, tablet within a tablet, mucoadhesive tablets, modified release tablets, pulsatile release tablets, and timed release tablets), pellets, beads, granules, sustained release formulations, capsules, microcapsules, tablets in capsules, microspheres, matrix formulations, microencapsulation.

The term "modified release" used in pharmaceutical compositions of invention means controlled release, extended release, sustained release, delayed release or combination of any of these techniques. In other words, modified release pharmaceutical composition of inventions may be any formulation technique wherein release of the active substance from the composition is modified to occur at a slower rate than that from an immediate release composition.

In one embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Succinate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipients(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising crystalline form of Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising crystalline form of Desvenlafaxine Benzoate characterized by a powder X-ray diffraction pattern having at least one peak at about 5.4, 10.75, 16.6, 18.0, 19.2, 23.32 ± 0.2 degrees 2Θ substantially as depicted in Figure 1, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising crystalline form of Desvenlafaxine Benzoate characterized by a powder X-ray diffraction pattern having peak at about 5.4, 10.75, 16.6, 18.0, 19.2, 23.32 ± 0.2 degrees 2Θ substantially as depicted in Figure 1, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising crystalline form of Desvenlafaxine Benzoate characterized by a powder X-ray diffraction pattern having peaks at about 5.4, 9.5, 10.75, 16.1, 16.6, 17.3, 18.0, 19.2, 20.4, 23.32 ± 0.2 degrees 2Θ substantially as depicted in Figure 1, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising crystalline form of Desvenlafaxine Benzoate characterized by a powder X-ray diffraction pattern substantially in accordance with Figure 1, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate in crystalline form characterized by a powder X-ray diffraction pattern having peaks at about 5.4, 9.5, 10.7, 16.1, 16.6, 17.3, 18.0, 19.2, 20.4, 21.5, 23.3, 24.9, 28.3, 29.9 ± 0.2 degrees 2Θ, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising amorphous form of Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine glutarate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine palmitate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

The release modifying agent(s) is hydrophilic, hydrophobic or combinations thereof.

In another embodiment, a modified release pharmaceutical composition comprises Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein release modifying agent(s) is from about 1 % to about 95 % based on total weight of composition.

In another embodiment, a modified release pharmaceutical composition comprises Desvenlafaxine Succinate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein release modifying agent(s) is present in an amount less than about 55% based on total weight of composition.

In another embodiment, a modified release pharmaceutical composition comprises Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein release modifying agent(s) is from about 1 % to about 95 % based on total weight of composition.

The hydrophilic release modifying agent(s) according to invention comprises but not limited cellulose derivatives, alginic acid derivatives, polysaccharides, alkylene oxides or mixtures thereof.

Preferably, hydrophilic release modifying agent(s) comprises celluloses or their salts or derivatives thereof, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose, alginic acid or their salts and derivatives thereof, carbomer (Carbopol(TM)), polyethyleneoxide, xanthan gum, guar gum, locust bean gum, poly vinyl acetate, polyvinyl alcohol, lactose.

The hydrophobic release modifying agent(s) according to the invention comprises but not limited to hydrogenated vegetable oils, polymethacrylates, ethyl cellulose or mixtures thereof.

Preferably, hydrophobic release modifying agent(s) comprises Ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, Polyacrylate dispersion 30% as described in Ph. Eur., Polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly(hexyl methacrylate). Poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl actylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate, glycerol distearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

The average particle size of the particles of Desvenlafaxine or a pharmaceutically acceptable salt thereof, in the modified release pharmaceutical composition of the invention is between about 5 microns to about 120 microns, preferably between about 7 microns to about 100 microns and more preferably about 10 microns to about 80 microns.

The terms "average particle size", '¾ $_0$" and "mass mean diameter" can be used interchangeably.

The average particle size, i.e. the average equivalent diameter, is defined as the diameter where 50 mass % of the particles of the Desvenlafaxine have a larger equivalent diameter, and the other 50 mass-% have a smaller equivalent diameter.

The "average particle size" also refers to the median particle diameter based on mass (i.e. the particle diameter where one half of the mass of particles is contributed by particles with a lesser diameter and one half of the mass of particles is contributed by particles with a greater diameter).

The particle size can be measured using various commonly available methods such as measurement using light (eg. light-scattering methods or turbidimetric methods), sedimentation methods (eg. pipette analysis using an Andreassen pipette, sedimentation scales, photo-sedimentometers or sedimentation in a centrifugal force), pulse methods (eg. Coulter counter), or sorting by means of gravitational or centrifugal force.

It is to be understood for the purpose determining particle size of Desvenlafaxine or pharmaceutically acceptable salts like Succinate or Benzoate in pharmaceutical compositions, the methods comprising but not limited to isolating, crushing, extracting, separating and precipitating can be commonly employed. Determining particle size of Desvenlafaxine or pharmaceutically acceptable salts like Succinate or Benzoate in pharmaceutical compositions is well within the scope of present invention.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine is upto about 80 microns.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine Benzoate is from about 10 microns to about 80 microns.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Succinate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine Succinate is upto about 80 microns.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Succinate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine Succinate is upto about 50 microns.

In another embodiment, a modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s).

In another embodiment, a modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), such that d_{50} particle size of Desvenlafaxine is upto about 80 microns.

In another embodiment, a modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically

acceptable excipient(s), wherein release of Desvenlafaxine is predominantly modified by coating.

In another embodiment, a modified release pharmaceutical composition having release of Desvenlafaxine in two or more steps at different release rates, which comprises a) a modified release part A comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) and b) a modified release part B comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s).

In another embodiment, a modified release pharmaceutical composition having release of Desvenlafaxine in two or more steps at different release rates, which comprises a) a modified release part A comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) and b) a modified release part B comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein part A is coated with part B.

In another embodiment, a modified release pharmaceutical composition is bi-layer tablet comprises a sustained release layer comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s); and immediate release layer comprising Desvenlafaxine and one or more pharmaceutically acceptable excipient(s).

In another embodiment, a modified release pharmaceutical composition is multi-layered tablet.

In another embodiment, a modified release pharmaceutical composition comprises a inert core which is loaded with drug layer comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein Desvenlafaxine Benzoate layer being further coated with one or more release modifying layer comprising release modifying agent(s) and one or more pharmaceutically acceptable excipient(s).

In another embodiment, a modified release pharmaceutical composition comprises a inert core which is loaded with drug layer comprising Desvenlafaxine Succinate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s)

wherein Desvenlafaxine Succinate layer being further coated with one or more release modifying layer comprising release modifying agent(s) and one or more pharmaceutically acceptable excipient(s).

The inert core comprises but not limited to sugar sphere or pellets, microcrystalline cellulose sphere, sugar/starch core or any suitable material.

In another embodiment drug layer and release modifying layer may be separated by one or more separating layers.

The separating layer comprises one or more pharmaceutically acceptable excipients and one or more hydrophilic agent(s), hydrophobic agent(s) or combination thereof.

The hydrophilic agent(s) according to invention comprises but not limited to cellulose derivatives, alginic acid derivatives, polysaccharides, alkylene oxides or mixtures thereof.

Preferably, hydrophilic agent(s) comprises celluloses or their salts or derivatives thereof, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose, alginic acid or their salts and derivatives thereof, carbomer (Carbopol(TM)), polyethyleneoxide, xanthan gum, guar gum, locust bean gum, poly vinyl acetate, polyvinyl alcohol, lactose.

The hydrophobic agent(s) according to the invention comprises but not limited to hydrogenated vegetable oils, polymethacrylates, ethyl cellulose or mixtures thereof.

Preferably, hydrophobic agent(s) comprises Ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, Polyacrylate dispersion 30% as described in Ph. Eur., Polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly(hexyl methacrylate). Poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl actylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl

alcohol; and fatty acid esters such as glyceryl monostearate, glycerol distearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

The term 'pharmaceutically acceptable excipient(s)' used in pharmaceutical compositions of invention comprise but not limited to diluents, binders, pH stabilizing agents, disintegrants, surfactants, glidants and lubricants.

The amounts of excipient(s) employed will depend upon how much active agent is to be used. One excipient(s) can perform more than one function.

Binders as used in the invention comprises but are not limited to, starches such as potato starch, wheat starch, corn starch; microcrystalline cellulose such as products known under the registered trademarks Avicel, Filtrak, Heweten or Pharmacel; celluloses such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose (HPMC), ethyl cellulose, sodium carboxy methyl cellulose; natural gums like acacia, alginic acid, guar gum; liquid glucose, dextrin, povidone, syrup, polyethylene oxide, polyvinyl pyrrolidone, poly-N-vinyl amide, polyethylene glycol, gelatin, poly propylene glycol, tragacanth, combinations thereof and other materials known to one of ordinary skill in the art and mixtures thereof.

Fillers or diluents, as used in the invention comprises but not limited to confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, fructose, lactitol, mannitol, sucrose, starch, lactose, xylitol, sorbitol, talc, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic or tribasic, calcium sulphate, and the like can be used.

Lubricants as used in the invention comprises but not limited to Mg, Al ,Ca or Zn stearate, polyethylene glycol, glyceryl behenate, mineral oil, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oil and talc.

Glidants comprises but not limited to, silicon dioxide; magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate, calcium silicate, magnesium silicate, colloidal silicon dioxide, silicon hydrogel and other materials known to one of ordinary skill in the art.

Disintegrants comprises but not limited to starches; clays; celluloses; alginates; gums; cross-linked polymers, e.g., cross-linked polyvinyl pyrrolidone or crospovidone, e.g., POLYPLASDONE XL, cross-linked sodium carboxymethylcellulose or croscarmellose sodium, e.g., AC-DI-SOL from FMC; and cross-linked calcium carboxymethylcellulose; soy polysaccharides; and guar gum. Use of disintegrant according to the invention facilitates in the release of drug in the latter stage and thereby completely releasing the drug from the dosage form.

The pharmaceutical composition may optionally contain a surface-active agent. The preferred agent is copolymers composed of a central hydrophobic chain of polyoxypropylene (poly (propylene oxide)) and polyoxyethylene (poly (ethylene oxide)) that is well known as poloxamer. However, other agents may also be employed such as dioctyl sodium sulfosuccinate (DSS), triethanolamine, sodium lauryl sulphate (SLS), polyoxyethylene sorbitan and poloxalkol derivatives, quaternary ammonium salts or other pharmaceutically acceptable surface-active agents known to one ordinary skilled in the art.

The pharmaceutical composition can be formed by various processes known in the art but not limited to such as by dry granulation, wet granulation, melt granulation, direct compression, double compression, extrusion spheronization, layering and the like. The solvent(s) used in wet granulation include all the solvents well known in the art or the mixtures thereof.

In another embodiment, a modified pharmaceutical composition of invention comprises one or more coating comprising but not limited to modified release coating, sustained release coating, extended release coating, enteric coating, partial enteric coating or leaky enteric coating, bioadhesive coating and similar coatings known in the art. These coatings may help the pharmaceutical composition to release the drug at and for the required time.

These coatings comprise coating agent(s) selected from hydrophilic or hydrophobic agent(s) or the combinations thereof.

The hydrophobic agent(s) in the coating comprises but not limited to Ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer

type A, B and C as described in USP, Polyacrylate dispersion 30% as described in pH. Eur., Polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly(hexyl methacrylate). Poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl actylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate, glycerol distearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

The hydrophilic agent(s) in the coating comprises but not limited to celluloses or their salts or derivatives thereof, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose, alginic acid or their salts and derivatives thereof, carbomer (Carbopol(TM)), polyethyleneoxide, xanthan gum, guar gum, locust bean gum, poly vinyl acetate, polyvinyl alcohol, lactose, PVA these hydrophilic polymers also act as pore forming agent.

These coating comprises one or more excipients selected from the group comprising coating agents, opacifiers, taste-masking agents, fillers, polishing agents, colouring agents, antitacking agents and the like.

The pharmaceutical composition can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan and hot melt (extrusion) coating. Such methods are well known to those skilled in the art.

In another embodiment, a stable modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Succinate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein composition releases about 75% of Desvenlafaxine Succinate in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein $\mathbf{d_{50}}$ particle size of Desvenlafaxine is upto about 80 microns such that composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein $\mathbf{d_{50}}$ particle size of Desvenlafaxine Benzoate is from about 5 microns to about 80 microns such that composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment, a modified release pharmaceutical composition comprises from about 10 % to about 50% by weight of Desvenlafaxine Succinate and less than about 60 % of release modifying agent(s) based upon total weight of composition, wherein $\mathbf{d_{50}}$ particle size of Desvenlafaxine Succinate is upto about 50 microns such that composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment, a modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further

coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment, a modified release pharmaceutical composition comprises a matrix core comprising Desvenlafaxine, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) wherein the matrix core being further coated with one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein d_{50} particle size of Desvenlafaxine is upto about 80 microns such that composition releases about 75% of Desvenlafaxine in 16 hours measured using USP Type I dissolution apparatus in 900 ml of 0.9% NaCl in water at 100 rpm.

In another embodiment of the invention is a method of lowering the incidence of nauseau, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus resulting from the oral administration of venlafaxine, Desvenlafaxine, or a salt of Desvenlafaxine other than Desvenlafaxine Benzoate to a patient. The method includes orally administering to a patient in need thereof a therapeutically effective amount of Desvenlafaxine Benzoate.

In another embodiment of the invention is a method of lowering the incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus resulting from the oral administration of Desvenlafaxine Benzoate to a patient. The method includes orally administering to a patient in need thereof a therapeutically effective amount of a sustained release oral dosage form comprising Desvenlafaxine Benzoate having a peak blood plasma level of less than about 225 ng/ml.

Desvenlafaxine Benzoate may also be provided in combination with venlafaxine. The dosage of venlafaxine is preferably about 75 mg to about 350 mg/day and more preferably about 75 mg to about 225 mg/day. Still more preferably the dosage of venlafaxine is about 75 mg to about 150 mg/day. The ratio of Desvenlafaxine to

venlafaxine will vary from patient to patient depending upon a patient's response rate, but generally will be at least 6:1 Desvenlafaxine to venlafaxine.

Desvenlafaxine Benzoate is less fluffy than that of Desvenlafaxine Succinate. So, the dusting is less during manufacturing of the drug product and which gives ease of handling the drug substance as compared to the Succinate and there is a minimum chance of drug loss during manufacturing process and hence gives an advantage over Succinate salt. Further, the particle size distribution of Desvenlafaxine Benzoate drug substance is smaller as compared to Desvenlafaxine Succinate drug substance. Hence, the distribution of drug substance in the drug product is uniform and gives no chance of variation in content uniformity of the final drug product/dosage form.

Due to its advantegeous properties, lower concentration of rate controlling polymers or release modifying polymers is required for Desvenlafaxine Benzoate as compared to Desvenlafaxine Succinate in matrix tablet formulation to achieve the similar drug release profile and also to make the bioequivalent product with Pristiq®.

Pristiq® is the brandname for the extended release composition of Desvenlafaxine Succinate, 50 mg and 100 mg marketed by Wyeth Pharmaceuticals Inc. (Now Pfizer) Philadelphia, PA 19101.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein the modified release composition provides C_{max} (peak plasma levels) of upto about 225 ng/ml.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s), wherein the modified release composition provides C_{max} (peak plasma levels) of upto about 300 ng/ml.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof, wherein **Cmax** and AUC of the modified

release composition are within the limit of 80 % to 125 % of **Cmax** and AUC of the extended release composition of Desvenlafaxine Succinate.

The term "**Cmax**" as used herein, means maximum plasma concentration of Desvenlafaxine produced by the ingestion of the modified release composition of invention or the marketed Pristiq® (Extended Release Composition of Desvenlafaxine Succinate) composition. C_{max} or peak plasma level may be used interchangeably.

The term "AUC" as used herein, means area under the plasma concentration-time curve of Desvenlafaxine produced by the ingestion of the modified release composition of invention or the marketed Pristiq® (Extended Release Composition of Desvenlafaxine Succinate).

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein, T_{max} of the modified release composition is comparable to **Tmax** of the extended release composition of Desvenlafaxine Succinate.

The term "**Tmax**" as used herein, means time to the maximum observed plasma concentration of Desvenlafaxine produced by the ingestion of the modified release composition of invention or the marketed Pristiq® (Extended Release Composition of Desvenlafaxine Succinate).

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein, $\mathbf{T_{max}}$ of the modified release composition is less than about 8 hours.

In another embodiment, **Cmax** and AUC were comparable for the modified release composition of Desvenlafaxine Benzoate when administered after a high-fat meal and under fasting condition as the ratios falls between 80-125%.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof wherein C_{max} and AUC of the modified release composition are independent of food effect.

In another embodiment, a modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof, which is bioequivalent to Pristiq® tablet in a bioavailability study in humans.

A modified release pharmaceutical composition of the present invention can be used to treat or prevent central nervous system disorders including, but not limited to depression (including but not limited to major depressive disorder, bipolar disorder and dysthymia), fibromyalgia, anxiety, panic disorder, agoraphobia, post traumatic stress disorder, premenstrual dysphoric disorder (also known as premenstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, incontinence (including fecal incontinence, overflow incontinence, passive incontinence, reflex incontinence, stress urinary incontinence, urge incontinence, urinary exertional incontinence and urinary incontinence), pain (including but not limited to migraine, chronic back pain, phantom limb pain, central pain, neuropathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager can also be used for preventing relapse or recurrence of depression; to treat cognitive impairment; for the inducement syndrome, Raynaud's syndrome, Parkinson's Disease, epilepsy, and others. Compounds and compositions of the present invention of cognitive enhancement in patient suffering from senile dementia, Alzheimer's disease, memory loss, amnesia and amnesia syndrome; and in regimens for cessation of smoking or other tobacco uses. Additionally, compounds and compositions of the present invention can be used for treating hypothalamic amenorrhea in depressed and non-depressed human females.

The following examples are illustrative of the present invention, and the examples should not be considered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art, in the light of the present disclosure, and the accompanying claims.

X -RD Stability Study

The X-ray diffraction pattern for Desvenlafaxine Benzoate was measured using X-ray diffractometer.

X-RD pattern for Desvenlafaxine Benzoate is depicted in Figure 1.

Example 1:

S.NO.	NAME OF INGREDIENTS	% W/W
Intragranular		
1	Desvenlafaxine Benzoate	36.58
2	Hypromellose	31.73/4
3	Povidone	6.10
4	Purified Water USP/ IPA	q.s
5	Dibasic calcium phosphate / Microcrystalline Cellulose NF	18.12
Extragranular		
6	Aerosil	3.00
7	Magnesium Stearate/Stearic Acid	2.00
Film Coating		
8	Opadry	2.50
9	Purified Water USP/ IPA/DCM	q.s

Procedure:

1. Aqueous/Non-aqueous granulation of Desvenlafaxine Benzoate, Hypromellose and Dibasic calcium phosphate/ MCC using Povidone as binder.
2. Dry the granules at 50±5°C till desired LOD is achieved.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling
5. Aqueous /Non-aqueous film coating.

Example 2:

S.NO.	NAME OF INGREDIENTS	% W/W
Intragranular		
1	Desvenlafaxine Benzoate	36.58
2	Hypromellose	20.00
3	Povidone	6.10
4	Purified Water/IPA	qs
5	Dibasic calcium phosphate/ Microcrystalline Cellulose	17.82
Extragranular		
6	Aerosil	3.00
7	Magnesium Stearate/Stearic Acid	2.00
Release Modifying Coating		
9	Hypromellose	7.00
10	Ethyl cellulose	5.00
11	IPA/DCM	q.s
Film Coating		
12	Opadry	2.50
13	Purified Water USP/ IPA/DCM	qs

Procedure:

1. Aqueous /Non-aqueous granulation of Desvenlafaxine Benzoate, Hypromellose and Dibasic calcium phosphate/ MCC using Povidone as binder.
2. Dry the granules at 50±5°C till desired LOD is achieved.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling
5. Non- Aqueous coating with a build up of l-10%w/w.
6. Aqueous /Non-aqueous film coating.

Example 3:

S.NO	NAME OF INGREDIENT	% W/W
Intragranular		
1	Desvenlafaxine Glutarate/Palmitate	36.58
2	Hypromellose	18.30
3	Povidone	6.10
4	Microcrystalline Cellulose / Dibasic calcium phosphate	13.22
5	Purified Water	q.s
Extragranular		
6	Hypromellose	18.30
7	Colloidal Silicon Dioxide	3.00
8	Stearic acid	2.00
Film Coating		
9	Opadry	2.50
10	Purified Water USP/ IPA/DCM	q.s

Procedure:

1. Aqueous /Non-aqueous granulation of Desvenlafaxine Glutarate/Palmitate, Hypromellose and Dibasic calcium phosphate / MCC using Povidone as binder.
2. Dry the granules at 50±5°C till desired LOD is achieved.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling.
5. Aqueous /Non-aqueous film coating.

Example 4:

S.NO	NAME OF INGREDIENT	% W/W
Immediate release layer		
1	Desvenlafaxine Benzoate	4.87
2	Povidone	4.87
3	Purified Water	--
4	Dibasic calcium phosphate / Microcrystalline Cellulose	11.50
5	Colloidal Silicon Dioxide	1.00
6	Magnesium Stearate	1.00
Sustained release layer		
7	Desvenlafaxine Benzoate	31.70
8	Eudragit or Ethylcellulose	25.00
9	Purified Water	q.s
10	Dibasic calcium phosphate / Microcrystalline Cellulose	13.56
11	Colloidal Silicon Dioxide	2.00
12	Magnesium stearate	2.00
Film Coating		
13	Opadry	2.50
14	Purified Water USP/ IPA/DCM	q.s

Procedure:

Immediate release layer

1. Aqueous /Non-aqueous granulation of Desvenlafaxine Benzoate and Dibasic calcium phosphate/ MCC using Povidone as binder.

2. Dry the granules at 50±5°C till desired LOD is achieved.
3. Add Colloidal Silicon Dioxide and Magnesium stearate and mix well.

Sustained release layer

1. Aqueous/Non-aqueous granulation of Desvenlafaxine Benzoate, Dibasic calcium phosphate / MCC using Methacrylic acid or Ethylcellulose as sustained release polymer.
2. Dry the granules at 50±5°C till desired LOD is achieved
3. Add Colloidal Silicon Dioxide and Magnesium stearate and mix well.
4. Compress both the layers of Immediate and Sustained release part using suitable punch tooling.
5. Aqueous /Non-aqueous film coating.

Example 5:

S.NO.	NAME OF INGREDIENT	% W/W
1	Desvenlafaxine Succinate	36.58
2	Hypromellose / Xanthan gum	40.00
3	Microcrystalline Cellulose / Dibasic calcium phosphate	15.92
4	Colloidal Silicon Dioxide	3.00
5	Stearic acid / Magnesium Stearate	2.00
	Film Coating	
6	Opadry	2.50
7	Purified Water USP/ IPA/DCM	qs

Procedure:

1. Desvenlafaxine Succinate and Hypromellose or Xanthum gum are dry mixed.
2. Add Microcrystalline Cellulose / Dibasic calcium phosphate to step 1 and mix well.
3. Add Colloidal Silicon Dioxide to Step 3 and mix well.
4. Lubricate the blend with Stearic acid or Magnesium Stearate.

5. Compress the granules using suitable punch tooling.
6. Aqueous /Non-aqueous film coating.

Example 6:

S.NO.	NAME OF INGREDIENTS	% W/W
Intragranular		
1	Desvenlafaxine Succinate	36.58
2	Hypromellose	20.00
3	Povidone	6.100
4	Purified Water/IPA	qs
5	Dibasic calcium phosphate/ Microcrystalline Cellulose	17.82
Extragranular		
6	Aerosil	3.00
7	Magnesium Stearate/Stearic Acid	2.00
Release Modifying Coating		
9	Hypromellose	7.00
10	Ethyl cellulose	5.00
11	IPA/DCM	q.s
Film Coating		
12	Opadry	2.50
13	Purified Water USP/ IPA/DCM	qs

Procedure:

1. Aqueous /Non-aqueous granulation of Desvenlafaxine Succinate, Hypromellose and Dibasic calcium phosphate/ MCC using Povidone as binder.
2. Dry the granules at 50±5°C till desired LOD is achieved.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling
5. Non- Aqueous coating with a build up of l-10%w/w.
6. Aqueous /Non-aqueous film coating.

Example 7:

S.NO	NAME OF INGREDIENT	% W/W
Part-A		
1	Desvenlafaxine Succinate	4.87
2	Povidone	4.87
3	Purified Water	–
4	Dibasic calcium phosphate / Microcrystalline Cellulose	11.50
5	Colloidal Silicon Dioxide	1.00
6	Magnesium Stearate	1.00
Part-B		
7	Desvenlafaxine Succinate	31.70
8	Eudragit or Ethylcellulose	25.00
9	Purified Water	q.s
10	Dibasic calcium phosphate / Microcrystalline Cellulose	13.56
11	Colloidal Silicon Dioxide	2.00

12	Magnesium stearate	2.00
Film Coating		
13	Opadry	2.50
14	Purified Water USP/ IPA/DCM	q.s

Procedure:

Part A

1. Aqueous /Non-aqueous granulation of Desvenlafaxine Succinate and Dibasic calcium phosphate/ MCC using Povidone as binder.
2. Dry the granules at 50±5°C till desired LOD is achieved.
3. Add Colloidal Silicon Dioxide and Magnesium stearate and mix well.

Part B

4. Aqueous /Non-aqueous granulation of Desvenlafaxine Succinate, Dibasic calcium phosphate / MCC using Methacrylic acid or Ethylcellulose as sustained release polymer.
5. Dry the granules at 50±5°C till desired LOD is achieved
6. Add Colloidal Silicon Dioxide and Magnesium stearate and mix well.
7. Compress both the layers of Part A and Part B part using suitable punch tooling.
8. Aqueous /Non-aqueous film coating.

Example 8:

S.NO.	NAME OF INGREDIENT	% W/W
1	Desvenlafaxine Succinate	36.58
2	Ethyl Cellulose	40.00
3	Microcrystalline Cellulose / Dibasic calcium phosphate	15.92
4	Colloidal Silicon Dioxide	3.00
5	Stearic acid / Magnesium Stearate	2.00

	Film Coating	
6	Opadry	2.50
7	Purified Water USP/ IPA/DCM	q.s

Procedure:

1. Desvenlafaxine Succinate and Ethyl Cellulose are dry mixed.
2. Add Microcrystalline Cellulose / Dibasic calcium phosphate to step 1 and mix well.
3. Add Colloidal Silicon Dioxide to Step 3 and mix well.
4. Lubricate the blend with Stearic acid or Magnesium Stearate.
5. Compress the granules using suitable punch tooling.
6. Aqueous /Non-aqueous film coating.

Example 9:

S.NO.	NAME OF INGREDIENT	% W/W
Sugar Hardening		
1	Sugar sphere	98.00
2	HPMC	2.00
3	DCM/IPA	Qs
	Total	100.00
Drug Loading		
4	Sugar spheres	40.00
5	Desvenlafaxine Succinate	42.00
6	HPMC	2.75
7	Talc	5.00
8	Aerosil	5.00

9	Glyceryl monostearate	5.00
10	IPA/DCM	q.s
11	Total wt.	100.00
Release Modifying coating		
12	HPMC	16.00
13	Ethyl cellulose	48.00
14	Triethyl citrate	16.00
15	Talc	16.00
16	DCM:IPA	q.s
	Total	100.00

Procedure -

1. Hardening of sugar spheres carried out.
2. Mix Desvenlafaxine Succinate, HPMC, talc & Aerosil.
3. Coat the mixture of Step 2 on sugar spheres of step 1 using DCM/IPA solution to form drug layer.
4. Release Modifying coating of HPMC, ethyl cellulose, talc and triethyl citrate loaded on Drug layer of Step 3.

Example 10:

	Ingredients	***%w/w***
Intragranular		
1	Desvenlafaxine Benzoate	***36.52***
2	Hypromellose	***40.24***
3	Povidone	***4.88***
4	Isopropyl Alcohol	***q.s***

Extragranular		
5	Microcrystalline Cellulose	*8.36*
6	Colloidal Silicon Dioxide	*3.66*
7	Talc	*1.95*
8	Stearic Acid	*1.95*
Film Coating		
9	Opadry	*2.44*
10	Purified water	*q.s*

Procedure:

1. Non-aqueous granulation of Desvenlafaxine Benzoate and Hypromellose using Povidone as binder.
2. Dry the granules at 55±5°C till desired LOD is achieved.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling
5. Aqueous film coating.

Example 11:

	Ingredients	*%w/w*
Intragranular		
1	Desvenlafaxine Succinate	*37.26*
2	Hypromellose	*46.34*
3	Povidone	*4.88*
4	Isopropyl Alcohol	*q.s*
Extragranular		
5	Microcrystalline Cellulose	*1.52*
6	Colloidal Silicon	*3.66*

	Dioxide	
7	Talc	*1.95*
8	Stearic Acid	*1.95*
Film Coating		
9	Opadry	*2.44*
10	Purified water	*q.s*

Procedure:

1. Non-aqueous granulation of Desvenlafaxine Succinate and Hypromellose using Povidone as binder.
2. Dry the granules at 55±5°C till desired LOD is achieved.
3. Add the Extra granular part and mix well.
4. Compress the granules using suitable punch tooling
5. Aqueous film coating.

Example 12:

	Ingredients	***%w/w***
Intragranular		
1	Desvenlafaxine Succinate	*36.24*
2	Hypromellose	*43.0 -57.0*
3	Colloidal Silicon Dioxide	*0.5-2.0*
4	Talc	*0.5-2.0*
5	Magnesium Stearate	*0.5-2.0*
Extragranular		
6	Microcrystalline Cellulose	***3.0-5.76***

7	Colloidal Silicon Dioxide	***0.5-2.0***
8	Talc	***0.5-2.0***
9	Magnesium Stearate	***0.5-2.0***
Film Coating		
10	Opadry	2.0-3.0
11	Purified water	***q.s***

Procedure:

1. Compact Desvenlafaxine Succinate, Hypromellose, Colloidal Silicon Dioxide, Talc and Magnesium Stearate in a roller compactor.
2. Sift and size the granules using comminuting mill to desired granules size.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling
5. Aqueous film coating.

Example 13:

	ingredients	***%w/w***
Intragranular		
1	Desvenlafaxine Benzoate	*37.56*
2	Hypromellose	*30.00-53.00*
3	Talc	*0.5-2.0*
4	Stearic Acid	*0.5-2.0.*
Extragranular		
5	Microcrystalline Cellulose	*5.00-16.44*
6	Colloidal Silicon Dioxide	*0.5-5.0*

7	Talc	***0.5-2.0***
8	Stearic Acid	***0.5-2.0***
Film Coating		
9	Opadry	1.94 -3.0
10	Purified water	***q.s***

Procedure:

1. Compact Desvenlafaxine Benzoate, Hypromellose, Talc and Stearic Acid in a roller compactor.
2. Sift the granules using comminuting mill to desired granules size.
3. Add the Extragranular part and mix well.
4. Compress the granules using suitable punch tooling
5. Aqueous film coating.

***In-Vitro* Dissolution Study:**

Table 1 given below shows the dissolution profile of Desvenlafaxine Benzoate Modified Release Tablets of Example 1 of the present invention carried out in 900 ml of 0.9% NaCl in water for 24 hours using Apparatus **USP-I** (Basket) at 100 rpm speed. The release profile (cumulative % of drug released) is given in Table 1.

Table 1:

Time In Hrs	**Cumulative % Drug Release For Example 1**
1	Not More Than 20%
4	30-50%
8	50-70%
16	Not Less Than 75%

Table 2 given below shows the dissolution profile of Desvenlafaxine Succinate Modified Release Tablets of Example 5 of the present invention carried out in 900 ml of 0.9% NaCl in water for 24 hours using Apparatus USP-I (Basket) at 100 rpm speed. The release profile (cumulative % of drug released) is given in Table 1.

Table 2:

Time In Hrs	Cumulative % Drug Release For Example 5
1	Not More Than 20%
4	30-50%
8	50-70%
16	Not Less Than 75%

In -vivo Bioavailability Study:

An Open Label, Balanced, Randomized, Single-Dose, Three-Treatment, Three-Sequence, Three-Period Crossover Oral Bioequivalence Study Of Reference product (Treatment A) PRISTIQ® (Extended release composition of Desvenlafaxine Succinate) 100 mg of Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101 and Test product (Treatment B) Desvenlafaxine Benzoate Modified Release Tablet 100 mg formulated as per Example 13 under fasting conditions and food effect study of Desvenlafaxine Benzoate Modified Release Tablet 100 mg formulated as per example 13 administered under fasting (Treatment B) and fed (Treatment C) conditions in Healthy, Adult, Human Male Subjects.

The study was designed to demonstrate the similar clinical efficacy compared to Pristiq®. The *in-vivo* bioavailability study in fasting state shows the results as shown in the Table 3 below:

Table 3: Comparative pharmacokinetic parameters of Example 13 vs Pristiq® 100 mg in Fasted state

Product Name	***AUC (0- t) ng. hr /ml***	***AUC (0-∞) ng. hr /ml***	***C_{max} ng /ml***	***$T_{max\ (hrs)}$***
Desvenlafaxine Benzoate MR Tablets 100 mg	5429.332	6140.836	249.504	5.943
Pristiq 100 mg	5762.351	6096.586	263.630	6.257

Conclusions:

Bioequivalence between Treatment A and B administered under fasting conditions:

The 90% Confidence Interval of the relative geometric mean of C_{max}, AUQo-t) and $AUC_{(0-\infty)}$ were found to be within the limit of 80 % to 125 %. Based on the results obtained, Desvenlafaxine Benzoate Modified Release Tablet lOOmg formulated as per Example 13 and PRISTIQ® (Extended release composition of Desvenlafaxine Succinate) 100 mg of Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101, are found to be bioequivalent in healthy human adult male subjects under fasting conditions.

Food effect (Treatment B vs C) on Desvenlafaxine Benzoate Modified Release Tablet lOOmg:

Administration of Desvenlafaxine Benzoate Modified Release Tablets 100 mg with food had a minimal effect on drug absorption, resulting in an approximate 2 hour delay in T_{max}. C_{max} and AUC were comparable for Desvenlafaxine Benzoate Modified Release Tablets 100 mg when administered after a high-fat meal and under fasting condition as the ratios

falls between 80-125%. Food is not expected to have significant clinical effect on the absorption **(Cm_ax** and **AUC)** of Desvenlafaxine from Desvenlafaxine Benzoate Modified Release Tablets 100 mg. Desvenlafaxine Benzoate Modified Release Tablets 100 mg can be administered without regard to food.

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CLAIMS

1. A modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof.

2. The modified release pharmaceutical composition of claim 1, wherein Desvenlafaxine Benzoate is crystalline.

3. The modified release pharmaceutical composition of claim 2, wherein Desvenlafaxine Benzoate is characterized by a powder X-ray diffraction pattern having at least one peak at about 5.4, 10.75, 16.6, 18.0, 19.2, 23.32 ± 0.2 degrees 2Θ.

4. The modified release pharmaceutical composition of claim 2, wherein Desvenlafaxine Benzoate is characterized by a powder X-ray diffraction pattern substantially in accordance with Figure 1.

5. The modified release pharmaceutical composition of claim 2, wherein Desvenlafaxine Benzoate is characterized by a powder X-ray diffraction pattern having peaks at about 5.4, 10.75, 16.6, 18.0, 19.2, 23.32 ± 0.2 degrees 2Θ.

6. The modified release pharmaceutical composition of claim 5, wherein Desvenlafaxine Benzoate is characterized by powder X-ray diffraction pattern having peaks at about 5.4, 9.5, 10.7, 16.1, 16.6, 17.3, 18.0, 19.2, 20.4, 21.5, 23.3, 24.9, 28.3, 29.9 ± 0.2 degrees 2Θ.

7. The modified release pharmaceutical composition of claim 1, wherein d_{50} particle size of Desvenlafaxine Benzoate is from about 5 microns to about 80 microns.

8. The modified release pharmaceutical composition of claim 1, wherein said composition releases about 75% of Desvenlafaxine Benzoate in 16 hours measured using USP Type **I** dissolution apparatus in 900 ml of 0.9% NaCl in water, at 100 rpm.

9. The modified release pharmaceutical composition of claim 1, wherein Desvenlafaxine Benzoate is amorphous.

10. A modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof, wherein C_{max} and AUC of the modified release composition are within the limit of 80 % to 125 % of C_{max} and AUC of the extended release composition of Desvenlafaxine Succinate.

11. A modified release pharmaceutical composition comprising Desvenlafaxine Benzoate, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s) thereof, wherein C_{max} and AUC of the modified release composition are independent of food effect.

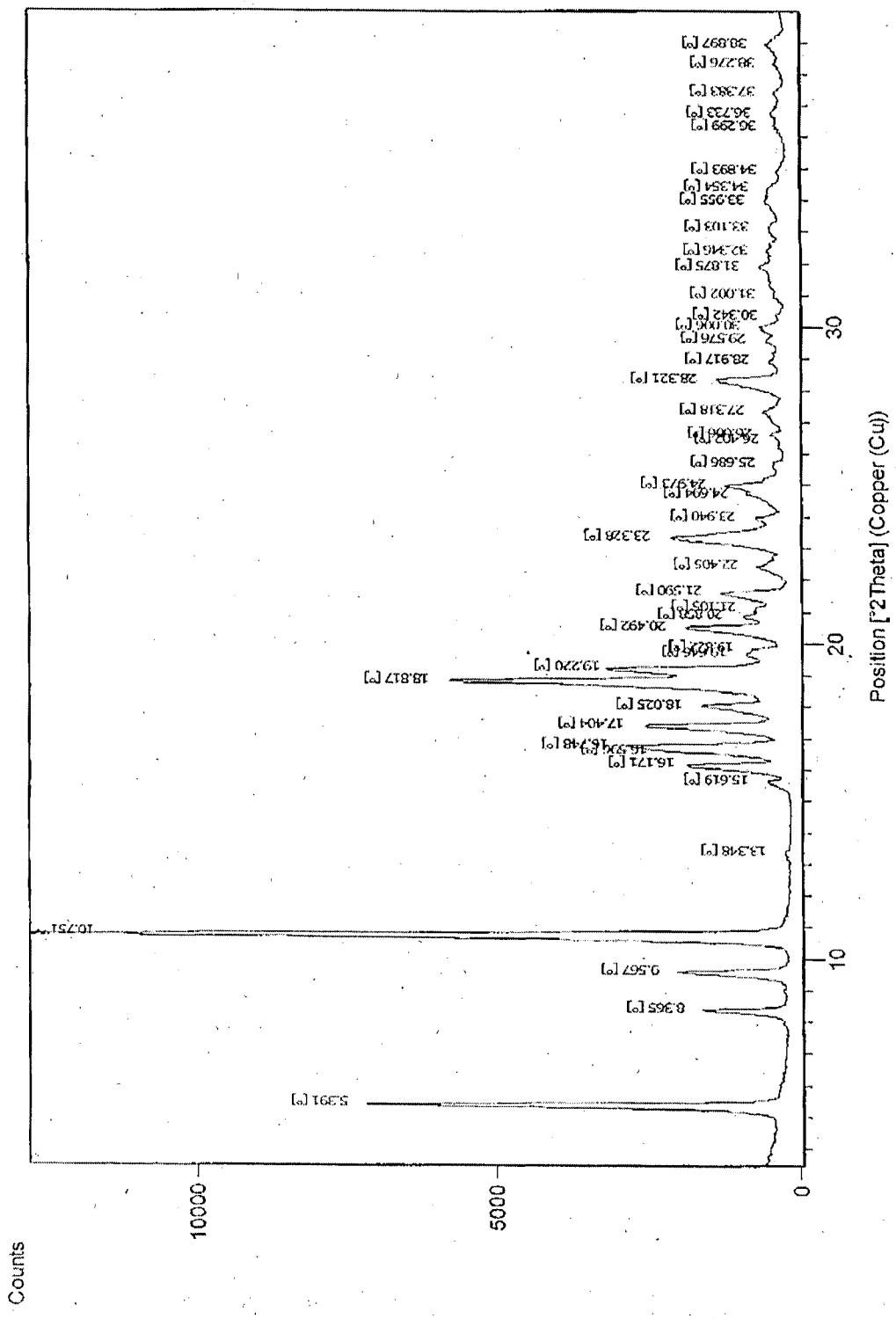
Counts
10000
5000
0
Position [°2Theta] (Copper (Cu))
10
20
30
5.391 [°]
8.365 [°]
9.567 [°]
10.751 [°]
13.348 [°]
15.619 [°]
16.172 [°]
17.404 [°]
18.025 [°]
18.817 [°]
19.220 [°]
20.492 [°]
21.590 [°]
22.405 [°]
23.328 [°]
23.940 [°]
25.686 [°]
27.318 [°]
28.321 [°]
28.917 [°]
29.576 [°]
30.342 [°]
31.002 [°]
31.875 [°]
33.103 [°]
33.955 [°]
34.354 [°]
34.893 [°]
36.299 [°]
36.733 [°]
37.383 [°]
38.276 [°]
38.897 [°]

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051761

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/133 A61K31/137
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/053840 A2 (ACTAVIS GROUP PTC EHF [IS] ; SEBASTIAN SONNY [IN] ; PATTABHI RAMAN BUDDH) 30 April 2009 (2009-04-30) claims 1,2 example 2 page 5, lines 14-20 page 32, lines 8-25 -----	1-11
X	WO 2009/049354 A1 (ALPHAPHARM PTY LTD [AU] ; MOONEY BRETT ANTONY [AU] ; KERAMIDAS PANAGIOTA) 23 April 2009 (2009-04-23) page 5, lines 30-35 page 6, lines 28-37 page 7, lines 5-18 page 8, lines 26-27 -----	1,7

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2012	30/08/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051761

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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