PHARMACEUTICAL COMPOSITIONS OF 5-HT6 ANTAGONIST"

Field of Invention

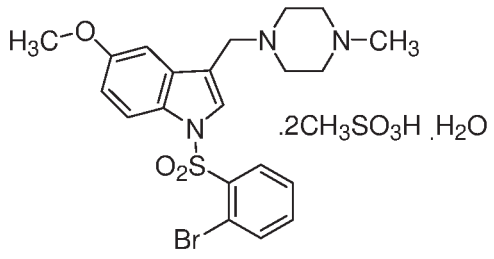
The present invention relates to immediate release (IR) pharmaceutical compositions comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole or a pharmaceutically acceptable salt (s) thereof as an active ingredient and one or more pharmaceutically acceptable excipients and to methods of preparation of said compositions.

Background of Invention

Alzheimer's disease (AD) is the most common cause of dementia worldwide. The exponential rise in the number of cases of AD in the past and the future projection over the next few decades is anticipated to result in great pressure on the social and health-care systems of developed and developing economies alike. AD also imposes tremendous emotional and financial burden to the patient's family and community.

The compound of the present invention is a pure 5-hydroxytryptamine 6 receptor (5-HT_6R) antagonist with high affinity and very high selectivity over closely related serotonin receptor subtypes and improves learning and memory in animals. The 5-HT_6R antagonist, 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole or a pharmaceutically acceptable salt (s) thereof is described in US7875605 which is incorporated by reference.

1-[(2-Bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole dimesylate monohydrate (herein after referred to as Compound 1), which has chemical structure,



is a promising pharmaceutical active agent intended for the symptomatic treatment of Alzheimer's disease and other disorders of memory and cognition like Attention deficient hyperactivity, Parkinson's disease, schizophrenia, lewy body dementia, vascular dementia or frontotemporal dementia. The process for preparing compound 1 on a larger scale is described in WO2015083179A1.

There is a need to develop a suitable dosage form of the compound 1 to treat the patients with AD and other disorders of memory and cognition like Attention deficient hyperactivity, Parkinson's disease, schizophrenia, lewy body dementia, vascular dementia or frontotemporal dementia. In our present invention, we developed IR pharmaceutical compositions of compound 1 having (1) excellent properties of tablet formation, (2) excellent wetting, disintegration, rapid and complete drug release properties, (3) good purity profile and (4) stable formulation for the treatment of AD and other disorders of memory and cognition like Attention deficient hyperactivity, Parkinson's disease, schizophrenia, lewy body dementia, vascular dementia or frontotemporal dementia.

Summary of Invention

In one aspect, the present invention relates to immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

In another aspect, the present invention relates to immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate and one or more pharmaceutically acceptable excipients.

In another aspect, the present invention relates to immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein the pharmaceutical composition comprises binder, diluent, lubricant, glidant, disintegrant and acidifying agent.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate,

(b) from about 36 % to about 97 % of one diluent or total of two diluents;

(c) from about 0.5 % to about 2 % lubricant;

(d) from about 0.5 % to about 1 % glidant;

(e) 0 % to about 10 % binder;

(f) 0 % to about 5 % disintegrant; and

(g) 0 % to about 2 % acidifying agent.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 2 % to about 3 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) about 95 % to about 97 % diluent;

(c) about 1 % lubricant; and

(d) about 0.5 % glidant.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 11 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 61 % to about 87 % of one diluent or total of two diluents;

(c) about 1 % lubricant;

(d) about 0.5 % glidant;

(e) about 2 % disintegrant; and

(f) about 1 % acidifying agent.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 24 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 61 % to about 72 % one diluent or total of two diluents;

(c) from about 1 % to about 1.25 % lubricant;

(d) about 0.5 % glidant; and

(e) about 2 % disintegrant.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 37 % to about 51 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 45 % to about 60 % diluent;

(c) about 1 % lubricant;

(d) about 0.5 % glidant;

(e) about 2 % of disintegrant; and

(f) about 1 % acidifying agent.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 36 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 62 % diluent;

(c) from about 0.5 % to about 1 % lubricant;

(d) about 0.5 % glidant; and

(e) about 2 % disintegrant.

In yet another aspect, the present invention relates to immediate release pharmaceutical composition of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, wherein said composition comprises on a total of 100 % by weight:

(a) from about 11 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 61 % to about 72 % diluent;

(c) about 1 % lubricant;

(d) from about 2 % to about 10 % binder;

(e) about 0.5 % glidant; and

(f) from about 2 % to about 5 % disintegrant.

In yet another aspect, the present invention also relates to methods of preparation of immediate release pharmaceutical compositions.

In yet another aspect the present invention relates to an immediate release tablet, wherein said tablet comprises on a total of 100 % by weight:

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 97 % of one diluent or total of two diluents;

(c) 0 % to about 10 % binder;

(d) from about 0.5 % to about 2 % lubricant;

(e) from about 0.5 % to about 1 % glidant;

(f) 0 % to about 5 % disintegrant; and

(g) 0 % to about 2 % acidifying agent.

In yet another aspect, the present invention relates to immediate release tablet, wherein said tablet comprises on a total of 100 % by weight:

(a) from about 2 % to about 3 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) about 95 % to about 97 % diluent;

(c) about 1 % lubricant; and

(d) about 0.5 % glidant.

In yet another aspect, the present invention relates to immediate release tablet, wherein the said tablet comprises on a total of 100 % by weight:

(a) from about 11 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 61 % to about 87 % of one diluent or total of two diluents;

(c) about 1 % lubricant;

(d) about 0.5 % glidant;

(e) about 2 % disintegrant; and

(f) about 1 % acidifying agent.

In yet another aspect, the present invention relates to immediate release tablet, wherein said tablet comprises on a total of 100 % by weight:

(a) from about 24 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 61 % to about 72 % one diluent or total of two diluents;

(c) from about 1 % to about 1.25 % lubricant;

(d) about 0.5 % glidant; and

(e) about 2 % disintegrant.

In yet another aspect, the present invention relates to immediate release tablet, wherein said tablet comprises on a total of 100 % by weight:

(a) from about 37 % to about 51 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 45 % to about 60 % diluent;

(c) about 1 % lubricant;

(d) about 0.5 % glidant;

(e) about 2 % of disintegrant; and

(f) about 1 % acidifying agent.

In yet another aspect, the present invention relates to immediate release tablet, wherein said tablet comprises on a total of 100 % by weight:

(a) from about 36 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 62 % diluent;

(c) from about 0.5 % to about 1 % lubricant;

(d) about 0.5 % glidant; and

(e) about 2 % disintegrant.

In yet another aspect, the present invention relates to immediate release tablet, wherein said tablet comprises on a total of 100 % by weight:

(a) from about 11 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 61 % to about 72 % diluent;

(c) about 1 % lubricant;

(d) from about 2 % to about 10 % binder;

(e) about 0.5 % glidant; and

(f) from about 2 % to about 5 % disintegrant.

In yet another aspect, the present invention relates to the immediate release pharmaceutical composition of dose ranges from about 5 mg to about 200 mg.

In yet another aspect, the present invention relates to the immediate release pharmaceutical composition, wherein the total weight of the immediate release tablet is from about 100 mg to about 600 mg.

In yet another aspect, the present invention relates to the immediate release pharmaceutical composition, wherein the immediate release pharmaceutical composition comprises,

i) less than 0.5 % of chloro impurity;

ii) less than 0.5 % of unknown impurity;

iii) less than 1 % of total impurity.

In yet another aspect, the present invention relates to the immediate release pharmaceutical composition, wherein the purity of the 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate is about 99.3 %.

In yet another aspect, the present invention relates to the immediate release pharmaceutical composition, wherein the 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate is released about 85 % to about 100 % within 30 minutes.

Detailed description of Invention

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

The term, "pharmaceutically acceptable excipients" as used herein refers to diluents, disintegrants, binders, lubricants, glidants, polymers, coating agents, solvents, co-solvents, preservatives, wetting agents, thickening agents, antifoaming agents, sweetening agents, flavouring agents, antioxidants, colorants, solubulizers, plasticizer or dispersing agents and the like. The pharmaceutical compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable excipients.

The "binder" employed in a composition of the present invention is capable for holding the ingredients together and forming the granules with required mechanical strength. Example of binders includes without limitation, polyvinylpyrrolidone (povidone (PVPK30)), polyethlylene glycol (PEG), saccharides, gelatins, pregelatinized starches, hydroxypropylcellulose, hydroxypropyl methylcellulose (HPMC) and cellulose ethers.

The "diluent" employed in a composition of the present invention is capable for providing bulkiness to obtain a desired immediate release pharmaceutical composition. Preferred diluents are inorganic phosphates such as dibasic calcium phosphate, calcium sulphate or dicalcium phosphate dihydrate; sugars such as lactose, lactose hydrate, lactose monohydrate, lactose anhydrate, sucrose, dextrose, erythritol, lactilol, xylitol, sorbitol, mannitol or malitol; cellulose or cellulose derivatives such as microcrystalline cellulose; Avicel, Avicel PH 101, Avicel PH 102 or Avicel PH 103, maize starch, Starcap-1500, Starlac and isomalt.

The "disintegrant" employed in a composition of the present invention is capable of facilitating the breakup of an immediate release pharmaceutical composition prepared from the composition when placed in contact with an aqueous medium. Preferred disintegrants are alginic acid or sodium alginate; cellulose or cellulose derivatives such as carboxymethylcellulose sodium, croscarmellose sodium, powdered cellulose or croscarmellose; iron exchange resin such as amberlite, gums such as agar, locust bean, karaya, pectin and tragacanth, crospovidone (cross-linked homopolymer of N-vinyl-2-pyrrolidinone, i.e., cross-linked 1-ethenyl-2-pyrrolidinone); sodium starch glycolate or starch.

The "lubricant" employed in a composition of the present invention is capable of preventing the ingredients from clumping together and from sticking to the apparatus on which it is formed, for example, preventing adherence to the face of the upper punch (picking) or lower punch (sticking) of a compression machine. Preferred lubricants are fatty acids or fatty acid derivatives such as calcium stearate, glyceryl monostearate, glyceryl palmitostearate, talc, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid or hydrogenated vegetable oil; polyalkylene glycols such as polyethylene glycol (PEG) or sodium benzoate and the like.

The "glidant" employed in a composition of the present invention is capable for increase in flow, those selected from the group consisting of colloidal silicon dioxide (Aerosil), higher fatty acids, the metal salts, talc, and the like or the mixtures thereof.

The "acidifying agent" employed in a composition of the present invention is capable to increase the acidity, those selected from the group consisting of citric acid, tartaric acid, fumaric acid, hydrochloric acid, maleic acid, acetic acid, nitric acid and the like.

The "coloring agent" (or "colorant") employed in a composition of the present invention may be one or more compounds which impart a desired color to the composition. Addition of a coloring agent may be used, for example, so that tablets of different potencies may be easily distinguished. Example of coloring agent includes but not limited to beta-carotene, indigo carmine, sunset yellow FCF, tartrazine, brilliant blue FCF, titanium dioxide, quinoline yellow, allura red AC, quinizarine green SS and iron oxides, which are accepted universally.

The "active ingredient" defined in this invention is 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole dimesylate monohydrate.

The term "about" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. The term "about" as used herein refers to a defined range of the value by ± 10 %. For example, about 2 % means 1.8 % to 2.2 %, about 5 % means 4.5 % to 5.5 %, about 10 % means 9 % to 11 % and about 40 % means 36 % to 44 %.

The term, "pharmaceutically acceptable salt" as used herein refers to salts of the active ingredient and are prepared by reaction with the appropriate acid or acid derivative, depending on the particular substituents found on the compounds described herein. The pharmaceutically acceptable salt includes but not limited to dimesylate monohydrate salt, dihydrochloride salt, oxalate salt, tartrate salt and the like. Preferably, the pharmaceutically acceptable salt is dimesylate monohydrate salt and dihydrochloride salt. More preferably, the pharmaceutically acceptable salt is dimesylate monohydrate salt.

The term, "patient" as used herein refers to an animal. Preferably the term "patient" refers to mammal. The term mammal includes animals such as mice, rats, dogs, rabbits, pigs, monkeys, horses and human. More preferably the patient is human.

The term, "immediate release composition" refers to a composition of an active ingredient which disintegrates rapidly and releases greater than 85 % at 30 minutes.

The term "impurity" as used herein refers to any component of a drug substance that is not the chemical entity defined as the drug substance and in addition, for a drug product, any component that is not a formulation ingredient.

The immediate release pharmaceutical compositions of the present invention can be used for treatment or prevention of Alzheimer's disease and other disorders of memory and cognition like Attention deficient hyperactivity, Parkinson's disease, schizophrenia, lewy body dementia, vascular dementia or frontotemporal dementia. The immediate release pharmaceutical composition of the instant invention can be administered orally, in an effective amount, to a mammalian (especially human) subject to treat or prevent the aforementioned disorders.

The effective dosage of the immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-

1H-indole dimesylate monohydrate is about 5 mg to about 200 mg. The immediate release pharmaceutical composition can be administered 1 to 3 times per day, based on condition of the patients. The total weight of immediate release pharmaceutical composition of the present invention is from about 100 mg to 600 mg.

The compound 1 belongs to class I as per BCS classification based on our experimental results and hence particle size of the compound 1 does not effect in the treatment of the patient.

In one embodiment the present invention relates to the immediate release pharmaceutical composition comprising:

Ingredient	Range (% w/w)	Preferred Range (% w/w)
Compound 1 (Active ingredient)	2 – 60	10 - 50
Diluent	36 – 97	40 - 90
Binder	0-10	3 - 5
Disintegrant	0 – 5	2 - 4
Lubricant	0.5 – 2	0.5 - 1
Glidant	0.5 – 1	0.5 - 1
Acidifying agent	0 – 2	0 - 1

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 2 % to about 3 % by weight of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole dimesylate monohydrate.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 10 % to about 40 % by weight of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 20 % to about 40 % by weight of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 30 % to about 50 % by weight of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 30 % to about 60 % by weight of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprising; about 40 % to about 80 % by weight of diluent

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprising about 70 % to about 90 % by weight of diluent.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprising about 20 % to about 40 % by weight of diluent.

In yet another embodiment, the present invention relates to immediate release pharmaceutical composition in the form of tablet or capsule.

In yet another embodiment, the present invention relates to an immediate release tablet, wherein the tablet comprises,

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 97 % of microcrystalline cellulose;

(c) from about 0.5 % to about 2 % magnesium stearate;

(d) from about 0.5 % to about 1 % colloidal silicon dioxide;

(e) 0 % to about 5 % crospovidone; and

(f) 0 % to about 2 % citric acid.

In yet another embodiment, the present invention relates to an immediate release tablet, wherein the tablet comprises,

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 97 % of microcrystalline cellulose;

(c) from about 0.5 % to about 2 % magnesium stearate;

(d) from about 0.5 % to about 1 % colloidal silicon dioxide;

(e) 0 % to about 10 % povidone;

(f) 0 % to about 5 % crospovidone; and

(g) 0 % to about 2 % citric acid.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 40 % to about 80 % by weight of microcrystalline cellulose.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 70 % to about 90 % by weight of microcrystalline cellulose.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 20 % to about 40 % by weight of microcrystalline cellulose.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 2 % by weight of crospovidone.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 1 % by weight of citric acid.

In yet another embodiment, the present invention relates to the immediate release pharmaceutical composition comprises about 4 % by weight of povidone.

In other aspect, the present invention relates to the use of the immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients for the treatment of Alzheimer's disease, memory and cognition disorders selected from Attention deficient hyperactivity disorder, Parkinson's disease, schizophrenia, lewy body dementia, vascular dementia or frontotemporal dementia.

In yet another aspect, the instant invention relates to the method of treatment of Alzheimer's disease, memory and cognition disorders selected from Attention deficient hyperactivity disorder, Parkinson's disease, schizophrenia, lewy body dementia, vascular dementia or frontotemporal dementia comprising administering to a patient a therapeutically effective amount of the immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

Methods of preparation of immediate release pharmaceutical composition

In another aspect, the instant invention relates to the process for the preparation of the immediate release pharmaceutical composition comprising 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole or a pharmaceutically acceptable salt thereof.

The preparation of the immediate release pharmaceutical composition includes two methods, a) direct compression method and b) wet granulation method.

In one embodiment, the preparation of immediate release pharmaceutical composition using direct compression method comprises the following steps:

a) weighing the active ingredient and one or two diluent (s) and sieving through sieve number 40;
b) mixing the sieved active ingredient and one or two diluent (s);
c) weighing the lubricant, glidant, disintegrant and acidifying agent and sieving through sieve number 40;
d) adding the mixture obtained in step (c) into step (b) and blending the mixture for 5-20 minutes to form homogenous mixture; and
e) compressing the lubricated blend to obtain the required dosage form.

The above obtained dosage forms can be optionally coated with polymers, solvents and coloring agents by methods known in the art.

In another embodiment, the preparation of immediate release pharmaceutical composition using wet granulation method comprises the following steps:

a) weighing the active ingredient, diluents and super disintegrant;
b) sieving the weighed materials through sieve number 40;
c) blending the sieved active ingredient, diluents and super disintegrant for 10 minutes in an octagonal blender;
d) weighing the binder and dissolve in required quantity of purified water;
e) transferring the active ingredient, diluents and super disintegrant into RMG;
f) adding binder solution dropwise to RMG to form cohesive mass;
g) drying the blend in a tray drier at 50 °C;
h) passing the blend through # 18 mesh to form granules;
i) weighing the lubricant and glidant and pass through sieve number 40;
j) adding the mixture obtained in step (h) to step (i) and blend for 10 minutes in an octagonal blender; and

k) compressing the lubricated blend to obtain the required dosage form.

The above obtained dosage forms can be optionally coated with polymers, solvents and coloring agents by methods known in the art.

Abbreviations:

AUC	:	Area under the curve
C_{max}	:	Maximum plasma concentration
HDPE	:	High density polyethylene
HPMC	:	Hydroxypropyl methylcellulose
HPLC	:	High performance liquid chromatography
kg	:	Kilogram
LC-MS/MS	:	Liquid chromatography/ Tandem mass spectrometry
mg	:	Milligram
mL	:	Milliliter
ng	:	Nanogram
N	:	Normality
rpm	:	Rotation per minute
RMG	:	Rapid mixer granulator
T_{max}	:	Time of maximum plasma concentration
$T_{1/2}$	:	Half-life
°C	:	Degree Celsius
% W/W	:	Percent weight/weight
UV	:	Ultra violet

Examples

The following Examples are provided to illustrate preferred embodiments of the invention and are not intended to limit the scope of the present invention.

Example 1: Pharmaceutical composition of Compound 1 IR tablets.

By using range of ingredients (% w/w) in below mentioned table and procedures explained in above mentioned preparation methods, the IR tablets of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1H-indole dimesylate monohydrate are prepared.

Ingredient	Range (% w/w)
Compound 1	2 – 60
Binder	0 – 5
Diluent	36 - 97
Disintegrant	0 – 4
Lubricant	0.5 – 2
Glidant	0.5 – 1
Acidifying agent	0 – 2

Example 2:

Preparation of IR tablet using direct compression method:

Composition of 5 mg dose IR tablet:

Ingredient	% w/w	mg/tablet
Compound 1	2.47	7.41[#]
Microcrystalline cellulose (Avicel PH 102)	96.03	288.09
Magnesium stearate	1	3
Colloidal silicon dioxide (Aerosil®)	0.5	1.5
Total	100	300

[#] equivalent to 5 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound).

Method of preparing IR tablet:

All the ingredients were accurately weighed (Compound 1 of 2.47 %, Avicel PH 102 of 96.03 %) and sieved using sieve number 40. The sieved compound 1 and Avicel PH 102 were blended for 10 minutes in an octagonal blender. The mixture obtained was added to magnesium stearate (1%) and aerosil (0.5 %) and blended for 10 minutes in an octagonal blender. The lubricated blend was compressed using 9 mm round concave punches and dies on rotary compression machine to obtain 300 mg tablet.

The examples 3 to 52 are prepared by following the method of preparation of example 2 by using appropriate amount of active ingredient, diluent(s), disintegrant, lubricant and with/without acidifying agent.

Examples 3 to 16:

Compositions of 25 mg dose IR tablets:

	Example 3		Example 4	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	12.34	37.02#	14.81	37.02#
Microcrystalline cellulose (Avicel PH 102)	86.16	258.48	83.69	209.23
Magnesium stearate	1	3	1	2.5
Colloidal silicon dioxide (Aerosil®)	0.5	1.5	0.5	1.25
Total	100	300	100	250

equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

5

	Example 5		Example 6	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	37.03	37.03#	12.42	37.26#
Microcrystalline cellulose (Avicel PH 102)	61.47	61.47	84.08	252.24
Magnesium stearate	1	1	1	3
Colloidal silicon dioxide (Aerosil®)	0.5	0.5	0.5	1.5
Crospovidone	-	-	2	6
Total	100	100	100	300

equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 7		Example 8	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	16.93	37.25#	16.93	37.25#
Microcrystalline cellulose (Avicel PH 102)	79.57	175.05	81.57	179.45
Magnesium stearate	1	2.2	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1	0.5	1.1

Crospovidone	2	4.4	-	-
Total	100	220	100	220

[#] equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 9		Example 10	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	16.93	37.25[#]	16.93	37.25[#]
Microcrystalline cellulose (Avicel PH 102)	40.78	89.72	-	-
Lactose Monohydrate	40.79	89.73	-	-
Dibasic calcium phosphate dihydrate	-	-	81.57	179.45
Magnesium stearate	1	2.2	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1	0.5	1.1
Total	100	220	100	220

[#] equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 11		Example 12	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	16.93	37.25[#]	16.93	37.25[#]
Microcrystalline cellulose (Avicel PH 102)	40.78	89.72	40.78	89.72
Lactose Monohydrate	-	-	40.79	89.73
Starch (Starlac)	40.79	89.73	-	-
Magnesium stearate	1	2.2	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1	0.5	1.1
Total	100	220	100	220

[#] equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 13		Example 14	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	16.93	37.25#	16.93	37.25#
Microcrystalline cellulose (Avicel PH 102)	40.78	89.72	81.57	179.45
Starch (Starlac)	40.79	89.73	-	-
Magnesium stearate	1	2.2	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1	0.5	1.1
Total	100	220	100	220

equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 15		Example 16	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	16.93	37.25#	16.93	37.25#
Microcrystalline cellulose (Avicel PH 102)	-	-	80.57	177.25
Starch (Starlac)	81.57	179.45	-	-
Magnesium stearate	1	2.2	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1	0.5	1.1
Citric acid	-	-	1	2.2
Total	100	220	100	220

equivalent to 25 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

Examples 17 to 38:

Compositions of 50 mg dose IR tablets:

	Example 17		Example 18	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05#	29.62	74.05#
Microcrystalline cellulose (Avicel PH 102)	66.63	166.58	-	-
Isomalt	-	-	68.88	172.2

Magnesium stearate	1.25	3.12	1	2.5
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Crospovidone	2	5	-	-
Total	100	250	100	250

[#] equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 19		Example 20	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05[#]	28.8	72[#]
Starch (Starlac)	68.88	172.2	-	-
Microcrystalline cellulose (Avicel PH 113)	-	-	69.45	173.63
Magnesium stearate	1	2.5	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Total	100	250	100	250

[#] equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 21		Example 22	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	28.8	72[#]	29.62	74.05[#]
Microcrystalline cellulose (Avicel PH 102)	69.45	173.63	-	-
Lactose Monohydrate	-	-	68.63	171.58
Magnesium stearate	1.25	3.12	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Total	100	250	100	250

[#] equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 23		Example 24	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05[#]	28.8	72[#]
Starch (Starcap 1500)	68.63	171.58	-	-
Microcrystalline cellulose (Avicel PH 101)	-	-	69.45	173.63
Magnesium stearate	1.25	3.12	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Total	100	250	100	250

[#] equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 25		Example 26	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05[#]	29.62	74.05[#]
Dextrose Monohydrate	68.88	172.2	-	-
Mannitol	-	-	68.88	172.2
Magnesium stearate	1	2.5	1	2.5
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Total	100	250	100	250

[#] equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 27		Example 28	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	37.03	74.06[#]	29.62	74.05[#]
Microcrystalline cellulose (Avicel PH 102)	61.47	122.94	-	-
Dicalcium phosphate dihydrate	-	-	68.63	171.58

Magnesium stearate	1	2	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1	0.5	1.25
Total	100	200	100	250

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 29		Example 30	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05#	29.62	74.05#
Microcrystalline cellulose (Avicel PH 101)	68.63	171.58	-	-
Lactose Monohydrate	-	-	66.63	166.58
Magnesium stearate	1.25	3.12	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Crospovidone	-	-	2	5
Total	100	250	100	250

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 31		Example 32	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05#	29.62	74.05#
Starch (Starcap 1500)	-	-	66.63	166.58
Dicalcium phosphate dihydrate	66.63	166.58	-	-
Magnesium stearate	1.25	3.12	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Crospovidone	2	5	2	5
Total	100	250	100	250

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 33		Example 34	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	29.62	74.05#	29.62	74.05#
Lactose Monohydrate	66.63	166.58	-	-
Microcrystalline cellulose (Avicel 101)	-	-	66.63	166.58
Magnesium stearate	1.25	3.12	1.25	3.12
Colloidal silicon dioxide (Aerosil®)	0.5	1.25	0.5	1.25
Crospovidone	2	5	2	5
Total	100	250	100	250

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 35		Example 36	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	24.83	74.5#	33.86	74.5#
Microcrystalline cellulose (Avicel PH 102)	71.67	215	62.64	137.8
Magnesium stearate	1	3	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.5	0.5	1.1
Crospovidone	2	6	2	4.4
Total	100	300	100	220

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 37		Example 38	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	12.35	74.1#	49.67	74.51#
Microcrystalline cellulose (Avicel PH 102)	84.15	504.9	49.83	70.24

Magnesium stearate	1	6	1	1.5
Colloidal silicon dioxide (Aerosil®)	0.5	3	0.5	0.75
Crospovidone	2	12	2	3
Total	100	600	100	150

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

Example 39 to 43:

Composition of 75 mg dose IR tablets:

	Example 39		Example 40	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	37.25	111.75#	50.79	111.74#
Microcrystalline cellulose (Avicel PH 102)	59.25	177.75	45.71	100.56
Magnesium stearate	1	3	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.5	0.5	1.1
Crospovidone	2	6	2	4.4
Total	100	300	100	220

equivalent to 75 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 41		Example 42	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	50.8	111.76#	50.8	111.76#
Microcrystalline cellulose (Avicel PH 102)	46.7	102.74	47.7	104.94
Magnesium stearate	1	2.2	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1	0.5	1.1
Citric acid	1	2.2	-	-
Total	100	220	100	220

equivalent to 75 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 43	
Ingredient	(% w/w)	mg/tablet
Compound 1	50.8	111.76[#]
Starch (Starlac)	47.7	104.98
Magnesium stearate	1	2.2
Colloidal silicon dioxide (Aerosil®)	0.5	1.1
Total	100	220

[#] equivalent to 75 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

Examples 44 to 50:

Composition of 100 mg dose IR tablets:

	Example 44		Example 45	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	49.36	148.08[#]	49.37	148.11[#]
Microcrystalline cellulose (Avicel PH 102)	49.14	147.42	49.13	147.39
Magnesium stearate	1	3	1	3
Colloidal silicon dioxide (Aerosil®)	0.5	1.5	0.5	1.5
Total	100	300	100	300

[#] equivalent to 100 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 46		Example 47	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	59.24	148.1[#]	37.03	148.12[#]
Microcrystalline cellulose (Avicel PH 102)	39.26	98.15	61.47	245.88
Magnesium stearate	1	2.5	1	4
Colloidal silicon dioxide	0.5	1.25	0.5	2

(Aerosil®)				
Total	100	250	100	400

[#] equivalent to 100 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 48		Example 49	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	49.67	149.01[#]	59.6	149[#]
Microcrystalline cellulose (Avicel PH 102)	47.33	141.99	36.9	92.25
Magnesium stearate	0.5	1.5	1	2.5
Colloidal silicon dioxide (Aerosil®)	0.5	1.5	0.5	1.25
Crospovidone	2	6	2	5
Total	100	300	100	250

[#] equivalent to 100 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

	Example 50	
Ingredient	(% w/w)	mg/tablet
Compound 1	24.7	148.2[#]
Microcrystalline cellulose (Avicel PH 102)	71.8	430.8
Magnesium stearate	1	6
Colloidal silicon dioxide (Aerosil®)	0.5	3
Crospovidone	2	12
Total	100	600

[#] equivalent to 100 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

Examples 51-52:

Composition of 150 mg and 200 mg dose IR tablets:

	Example 51		Example 52	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	49.67	223.52*	49.67	298.02#
Microcrystalline cellulose (Avicel PH 102)	46.83	210.73	46.83	280.98
Magnesium stearate	1	4.5	1	6
Colloidal silicon dioxide (Aerosil®)	0.5	2.25	0.5	3
Crospovidone	2	9	2	12
Total	100	450	100	600

* equivalent to 150 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

equivalent to 200 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

Example 53:

Preparation of IR tablet using wet granulation method

Composition of 50 mg IR tablet:

Ingredient	% W/W	mg/tablet
Compound 1	24.67	74#
Microcrystalline cellulose (Avicel PH 102)	66.83	200.5
Povidone	4.0	12
Crospovidone	3.0	9
Magnesium stearate	1.0	3
Colloidal silicon dioxide (Aerosil®)	0.5	1.5
Total	100	300

equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free base compound)

Method of preparing IR tablet:

All the ingredients were accurately weighed (Compound 1 of 24.67%, Avicel PH 102 of 66.83% and crospovidone of 3%) and sieved using sieve number 40. The sieved compound 1, Avicel PH 102 and crospovidone were blended for 10 minutes in an octagonal blender. The mixture obtained was transferred into RMG and added povidone binder solution (povidone (4 %) was dissolved in purified water) dropwise to RMG to form cohesive mass. The blend obtained was dried in a tray drier at 50 °C. Dried blend was passed through # 18 mesh to form granules. The granules obtained were mixed with magnesium stearate and aerosil and the mixture was blended for 10 minutes in an octagonal blender. The lubricated blend was compressed using 9 mm round concave punches and dies on rotary compression machine to obtain 300 mg tablet.

Examples 54-55:

The following examples are prepared by following the method of preparation of example 53.

Composition of 50 mg IR tablets:

	Example 54		Example 55	
Ingredient	(% w/w)	mg/tablet	(% w/w)	mg/tablet
Compound 1	24.67	74[#]	24.67	74[#]
Microcrystalline cellulose (Avicel PH 102)	65.83	197.5	64.83	194.5
Povidone (PVP K30)	4.0	12	-	-
HPMC	-	-	5.0	15
Sodium starch glycolate	4.0	12	-	-
Croscarmellose sodium	-	-	4.0	12
Magnesium stearate	1	3	1	3
Aerosil	0.5	1.5	0.5	1.5
Total	100	300	100	300

[#] equivalent to 50 mg of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole (free Base compound)

Example 56:

Dissolution studies of IR tablets

The dissolution studies were conducted for the immediate release tablets of the instant invention to demonstrate the % release of active ingredient at different time intervals.

Protocol:

Dissolution was carried out in accordance with the United States pharmacopeia general procedures using dissolution apparatus II (paddle method). The IR tablet was placed in 900 mL of simulated gastric fluid (pH 1.2), 0.1N hydrochloric acid or water at 37 °C with a paddle speed of 50 rpm/ 100 rpm and measuring the amount of active ingredient dissolved (especially, using UV at 255 nm or using HPLC, wavelength 220 nm) at 15 and 30 minutes.

Results:

The dissolution studies data of the IR tablets are tabulated below.

S. No	Examples	Time (minutes)	% of Active ingredient release	S. No	Examples	Time (minutes)	% of Active ingredient release
1	Example 2	15	97	19	Example 25	15	98
		30	97			30	97
2	Example 3	15	108	20	Example 26	15	104
		30	105			30	103
3	Example 4	15	85	21	Example 27	15	102
		30	97			30	106
4	Example 6	15	103	22	Example 30	15	104
		30	106			30	104
5	Example 7	15	103	23	Example 32	15	98
		30	103			30	100
6	Example 12	15	103	24	Example 33	15	102
		30	104			30	101
7	Example 13	15	97	25	Example 37	15	98
						30	96
		30	100	26	Example 38	15	98
						30	102
8	Example 14	15	100	27	Example 40	15	101
		30	100			30	101
9	Example 15	15	102	28	Example 41	15	100
		30	102			30	100
10	Example 16	15	96	29	Example 42	15	100
		30	97			30	100
11	Example 17	15	102	30	Example 43	15	106
		30	101			30	108
12	Example 18	15	98	31	Example 47	15	82
		30	98			30	94
13	Example 19	15	100	32	Example 48	15	105
		30	99			30	105
14	Example 20	15	102	33	Example 50	15	101
						30	99
		30	107	34	Example 51	15	98

S. No	Examples	Time (minutes)	% of Active ingredient release	S. No	Examples	Time (minutes)	% of Active ingredient release
						30	96
15	Example 21	15	107	35	Example 52	15	99
						30	99
		30	106	33	Example 53	15	99
16	Example 22	15	101			30	99
		30	103	34	Example 54	15	100
17	Example 23	15	99			30	100
		30	99	35	Example 55	15	101
18	Example 24	15	105			30	101
		30	105				

Example 57:

Stability study of IR tablets

The stability study was conducted to assess the stability of the immediate release tablets and the impurity profile of the instant invention under different storage conditions.

The stability studies were carried out at ambient temperature, 40 °C / 75 % RH and 60 °C oven for 6 months.

Protocol:

The immediate release tablets are packed in HDPE bottles with polyethylene liners with desiccant for a period of 6 months at different storage conditions. The samples were analyzed for purity using HPLC.

Results:

Dissolution:

The dissolution data of examples for different time points at accelerated storage conditions are tabulated below.

S. No	Examples	Time (minutes)	% of Active ingredient release			
			Day 1	1 month	3 months	6 months
1	Example 18	30	106	106	90	104
2	Example 20	30	91	99	89	97
3	Example 21	30	98	99	103	102
4	Example 22	30	99	100	103	99
5	Example 37	30	96	99	100	102
6	Example 38	30	102	101	100	99

7	Example 50	30	99	99	99	99

Conclusion:

We observed no significant variation in dissolution of the IR tablets after storing for 6 months at accelerated storage conditions (*i.e,* temperature 40 ± 2 °C at 75 ± 5 % relative humidity (RH)).

Purity:

The purity of IR tablet on day 1 is tabulated below.

S. No	Example number	Dose (mg)	Purity of active ingredient (%)	Chloro impurity (%)	Maximum unknown impurity (%)	Other unknown impurities (%)	Total impurities (%)
1	18	75	99.64	0.19	0.06	0.11	0.36
2	20	75	99.66	0.19	0.06	0.09	0.34
3	22	75	99.64	0.20	0.06	0.10	0.36

The purity of IR tablets under different storage conditions at the end of 6 months is tabulated below.

S. No	Example number	Dose (mg)	Storage conditions	Purity (%)	Chloro impurity (%)	Maximum unknown impurity (%)	Other impurities (%)	Total impurities (%)
1	18	75	60 °C Oven	99.38	0.21	0.09	0.32	0.62
2	18	75	40 °C / 75 % RH	99.63	0.19	0.06	0.12	0.37
3	20	75	40 °C / 75 % RH	99.64	0.19	0.06	0.11	0.36
4	22	75	60 °C Oven	99.37	0.20	0.08	0.35	0.63
5	22	75	40 °C / 75 % RH	99.62	0.20	0.06	0.12	0.38

Conclusion:

We observed no significant variation in purity of the active ingredient under different storage conditions. As evident from the above stability data the active ingredient in immediate release tablets of instant invention is stable at least six months under accelerated storage condition.

Example 58:

***In-vivo* pharmacokinetic study of IR tablets**

The dog pharmacokinetic study is conducted to confirm the dissolution data of Compound 1.

Experimental procedure of dog pharmacokinetic study

Male beagle dogs (10 ± 2 kg) were used as experimental animals. Each dog was housed in individual cages. Animals were fasted over night before oral dosing (p.o) and food pellets were allowed 2 hours post dosing. Two beagle dogs (~11 mg/kg) were dosed orally with IR tablets prepared by pharmaceutical compositions disclosed in Example 48.

At each time point, blood (0.5 mL) was collected through cephalic vein. Collected blood was transferred into a labeled eppendroff tube containing 10 µL of heparin as anticoagulant. Typically blood samples were collected at following time points: Pre dose, 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 12, 24, 30 and 48 hours post dose (n=2). Blood was centrifuged at 4000 rpm for 10 minutes. Plasma was separated and stored at -20 °C until analysis. The concentrations of active ingredient were quantified in plasma by validated LC-MS/MS method using suitable extraction technique. The active ingredient was quantified in the calibration range around 0.2-200 ng/mL.

Pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-t} and $T_{1/2}$ were calculated by using standard non-compartmental model Phoenix WinNonlin 6.2 version Software package.

The results of this study are tabulated below.

Strain/ Gender	Dose (mg/kg)	Dosage form	C_{max} (ng/mL)	T_{max} (hours)	AUC_{0-t} (ng.hour/mL)	$T_{1/2}$ (hours)
Beagle dog	~11	Tablet	60 ± 16	1.25±0.35	251 ± 27	5.97±0.40

We claim:

1. An immediate release pharmaceutical composition on a total of 100% by weight comprises:

a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole or a pharmaceutically acceptable salt thereof;

b) from about 36 % to about 97 % diluent or total of two diluents; wherein the diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, dibasic calcium phosphate, lactose, lactose hydrate, lactose anhydrate, mannitol, starch and isomalt;

c) from about 0.5 % to about 2 % lubricant; wherein the lubricant is magnesium stearate;

d) from about 0.5 % to about 1 % glidant; wherein the glidant is colloidal silicon dioxide; e) 0 % to about 10 % binder; wherein the binder is selected from group consisting of povidone or hydroxypropyl methylcellulose;

f) 0 % to about 5 % disintegrant; wherein the disintegrant is selected from crospovidone, sodium starch glycolate and croscarmellose sodium; and

g) 0 % to about 2 % acidifying agent; wherein the acidifying agent is citric acid.

2. The immediate release pharmaceutical composition as claimed in claim 1, wherein said composition comprises on a total of 100 % by weight:

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 97 % of one diluent or total of two diluents; wherein the diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, dibasic calcium phosphate, lactose, lactose hydrate, lactose anhydrate, mannitol, starch and isomalt;

(c) from about 0.5 % to about 2 % lubricant; wherein the lubricant is magnesium stearate;

(d) from about 0.5 % to about 1 % glidant; wherein the glidant is colloidal silicon dioxide;

(e) 0 % to about 10 % binder; wherein the binder is selected from group consisting of povidone or hydroxypropyl methylcellulose;

(f) 0 % to about 5 % disintegrant; wherein the disintegrant is selected from crospovidone, sodium starch glycolate and croscarmellose sodium and

(g) 0 % to about 2 % acidifying agent; wherein the acidifying agent is citric acid.

3. The immediate release pharmaceutical compositions as claimed in claim 1 or claim 2, wherein the composition on a total of 100 % by weight is selected from the group consisting of:

1) (a) from about 2 % to about 3 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, (b) from about 95 % to about 97 % diluent, (c) about 1 % lubricant and (d) about 0.5 % glidant;

2) (a) from about 11 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, (b) from about 61 % to about 87 % of one diluent or total of two diluents, (c) about 1% lubricant, (d) about 0.5 % glidant, (e) about 2 % disintegrant and (f) about 1 % acidifying agent;

3) (a) from about 24 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, (b) from about 61 % to about 72 % one diluent or total of two diluents, (c) from about 1 % to about 1.25 % lubricant, (d) about 0.5 % glidant and (e) about 2 % disintegrant;

4) (a) from about 37 % to about 51 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, (b) from about 45 % to about 60 % diluent, (c) about 1 % lubricant, (d) about 0.5 % glidant, (e) about 2 % of disintegrant and (f) about 1 % acidifying agent;

5) (a) from about 36 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate, (b) from about 36 % to about 62 % diluent, (c) from about 0.5 % to about 1 % lubricant, (d) about 0.5 % glidant and (e) about 2 % disintegrant; and

6) (a) from about 11 % to about 38 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate; (b) from about 61 % to about 72 % diluent; (c) from about 2 % to about 5 % binder; (d) about 1 % lubricant; (d) about 0.5 % glidant and e) from about 2 % to about 4 % disintegrant.

4. The immediate release pharmaceutical composition as claimed in any one of the claims 1 to 3, wherein the dosage of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-

piperazinyl)methyl]-1H-indole or a pharmaceutically acceptable salt thereof is about 5 mg to about 200 mg.

5. The immediate release pharmaceutical composition as claimed in any one of the claims 1 to 4, wherein the composition is in the form of tablet or capsule.

6. The immediate release pharmaceutical composition as claimed in any one of the claims 1 to 3, the composition having:

i) less than 0.5 % of chloro impurity;
ii) less than 0.5 % of unknown impurity;
iii) less than 1 % of total impurity.

7. The immediate release pharmaceutical composition as claimed in any one of the claims 1 to 3, wherein the purity of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate is about 99.3 %.

8. The immediate release pharmaceutical composition as claimed in any one of the claims 1 to 3, the composition having:

i) about 99.3 % purity of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;
ii) less than 0.5 % of chloro impurity;
iii) less than 0.5 % of unknown impurity;
iv) less than 1 % of total impurity.

9. The immediate release pharmaceutical composition as claimed in any one of the claims 1 to 3, wherein the 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate is released about 85 % to about 100 % within 30 minutes when tested with the rotating paddle at 100 rpm with 900 mL of dissolution media, 01N hydrochloric acid or water at 37°C.

10. The immediate release tablet composition as claimed in claim 1, wherein said composition on a total of 100% by weight comprises:

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 97 % of one diluent or total of two diluents; wherein the diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, dibasic calcium phosphate, lactose, lactose hydrate, lactose anhydrate, mannitol, starch and isomalt;

(c) from about 0.5 % to about 2 % lubricant; wherein the lubricant is magnesium stearate;

(d) from about 0.5 % to about 1 % glidant; wherein the glidant is colloidal silicon dioxide;

(e) 0 % to about 10 % binder; wherein the binder is selected from group consisting of povidone or hydroxypropyl methylcellulose;

(f) 0 % to about 5 % disintegrant; wherein the disintegrant is selected from crospovidone, sodium starch glycolate and croscarmellose sodium; and

(g) 0 % to about 2 % acidifying agent; wherein the acidifying agent is citric acid.

11. The immediate release tablet composition as claimed in claim 10, wherein the composition on a total of 100% by weight comprises:

(a) from about 2 % to about 60 % 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl]-1H-indole dimesylate monohydrate;

(b) from about 36 % to about 97 % of microcrystalline cellulose;

(c) from about 0.5 % to about 2 % magnesium stearate;

(d) from about 0.5 % to about 1 % colloidal silicon dioxide;

(e) 0 % to about 5 % povidone;

(f) 0 % to about 4 % crospovidone; and

(g) 0 % to about 2 % citric acid.

12. The immediate release tablet composition as claimed in claim 10 or claim 11, wherein the total weight of immediate release tablet is from about 100 mg to 600 mg.