PHARMACEUTICAL COMPOSITIONS OF RASAGILINE

ABSTRACT

The invention relates to pharmaceutical compositions of rasagiline, its enantiomer or salts thereof, process of preparation of such compositions and use thereof for treatment of Parkinson's disease, dementia and Alzheimer's disease.

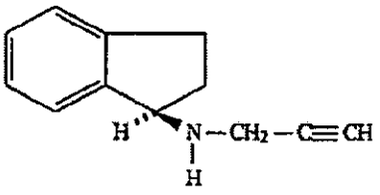
PHARMACEUTICAL COMPOSITIONS OF RASAGILINE

FIELD OF THE INVENTION:

The present invention relates to pharmaceutical compositions of rasagiline, its enantiomer or salts thereof. In particular, the invention relates to stabilizer free pharmaceutical compositions of rasagiline, its enantiomer or salts thereof, process of preparation of such compositions and use thereof for treatment of Parkinson's disease, dementia and Alzheimer's disease.

BACKGROUND OF THE INVENTION:

Rasagiline is a selective irreversible inhibitor of monoamine oxidase enzyme Type-B (MAO-B) and has the chemical name N-propargyl-1(R)-aminoindan ("(R)-PAI"). Its structural formula is:



Rasagiline is an active MAO-B inhibitor while the corresponding S-enantiomer ("(S)-Rasagiline") shows extremely low MAO-B inhibitory activity (U.S. Patent No. 6,316,504). It has also been found that (R)-Rasagiline has a degree of selectivity for MAO-B inhibition surprisingly higher than that of the corresponding racemic form (U.S. Patent No. 6,316,504). The fact that (R)-Rasagiline is more active than the racemic mixture for the inhibition of MAO-B is a reflection of the extremely low activity of (S)-Rasagiline for inhibition of MAO-B (U.S. Patent No. 6,316,504).

Rasagiline, its salts, preparation and use for the treatment of Parkinson's disease, Alzheimer's disease, memory disorders, stroke and other disorders have been the subject of numerous patents, including U.S. Patent Nos. 5,387,612, 5,453,446, 5,457,133, 5,668,181, 5,576,353, 5,532,415, 5,599,991, 5,786,390, 5,519,061, 5,891,923, 5,744,500 and 6,316,504, the contents of which are hereby incorporated by reference.

A formulation of rasagiline mesylate is currently marketed in US in the form of film coated tablets for the treatment of Parkinson's disease either as monotherapy or as an adjunct with other treatments under trade name Azilect® by Teva Pharmaceuticals.

PCT publication No. 95/11016 discloses pharmaceutical formulations of rasagiline.

U.S. Patent No. 6,126,968 subsequently disclosed that the formulations of PCT Publication No. 95/11016 were of unacceptable stability. U.S. Patent No. 6,126,968 then proceeds to offer certain alternative formulations of rasagiline intended to provide improved stability relative to the formulations of PCT Publication No. 95/11016. The tablet of R(+)-N-propargyl-1-aminoindane or pharmaceutical acceptable salt thereof disclosed in the patent comprises at least one alcohol selected from the group consisting of pentahydric and hexahydric alcohols such as mannitol, xylitol and sorbitol.

PCT publication No. 2010/085354 discloses the delayed release composition of rasagiline, wherein the core comprises atleast one antioxidant, preferably citric acid and malic acid.

European Patent No. 0814789 discloses formulations of MAO-B inhibitors which attempt to address some of the known problems. However, the European patent relies on lyophilization of the MAO-B inhibitor formulations which is a costly process and results in high friability of the product, further increasing cost by necessitating costly special blister-pack packaging.

European Patent Application No. 1892233 discloses polymorphic forms of rasagiline oxalate and rasagiline edisilate. The patent application also discloses that mesylate, hydrochloride and phosphate salts of rasagiline show agglomerates after storage even in a closed glass bottle and can also display a slight discoloration and when stored under humid conditions (40°C, 75% relative humidity in an open glass bottle), a sticky powder which is difficult to process forms from said salts of rasagiline.

Prior art formulations suggest that use of sugar alcohols or polyols is required in order to develop stable formulations of rasagiline. However, when consumed in relatively large amount, sugar alcohols such as lactose, mannitol, are known to cause gastro-intestinal disturbances. The most common side effect is the possibility of bloating and diarrhea when sugar alcohols are eaten in excessive amounts. There is also some evidence that sugar alcohols, much like fructose can cause a 'laxative effect' and weight gain has also been seen when these products are overeaten. The American Diabetes Association claims that sugar alcohols are acceptable in a moderate amount but should not be eaten in excess. Some people with diabetes, especially Type I diabetics have found that their blood sugars rise if sugar alcohols are eaten in uncontrolled amounts. Moreover, the 'lactose-intolerant' patient group having inability to digest lactose may result in aggravation of gastro-intestinal symptoms.

Moreover, poor physico-chemical and formulation characteristics of many salts of rasagiline possess limitations and challenge in developing a stable formulation.

Thus, there exists a need to provide a formulation of rasagiline which are suitable for all patient population and also such formulations, without employing any sugar alcohol or polyols or any other stabilizer, ought to remain stable over the storage period.

SUMMARY OF THE INVENTION:

In one general aspect, there is provided a pharmaceutical composition of rasagiline, its enantiomer or salts thereof comprising one or more pharmaceutical excipients, wherein said composition is free of sugar alcohols or polyols or any other stabilizer.

In another general aspect, there is provided a pharmaceutical composition of rasagiline besylate or its enantiomer comprising one or more pharmaceutical excipients, wherein said composition is free of sugar alcohols or polyols.

In another general aspect, there is provided a pharmaceutical composition of rasagiline besylate or its enantiomer comprising one or more pharmaceutical excipients, wherein said composition is free of stabilizer.

In another general aspect, there is provided a pharmaceutical composition of rasagiline, its enantiomer or salts thereof, wherein said composition is free of sugar alcohols/ polyols/any other stabilzer and it retains at least 80% of the potency of rasagiline, its enantiomer or salts thereof in the pharmaceutical composition after storage for three months at 40^0 C and 75% relative humidity.

In another general aspect, there is provided a pharmaceutical composition of rasagiline besylate, its enantiomer thereof, wherein said composition is free of sugar alcohols/ polyols/any other stabilzer and it retains at least 80% of the potency of rasagiline, its enantiomer or salts thereof in the pharmaceutical composition after storage for three months at 40^0 C and 75% relative humidity.

In another general aspect, there is provided a pharmaceutical composition of rasagiline, its enantiomer or salts thereof, wherein the composition is prepared by dissolving rasagiline, its enantiomer or salts thereof alone or in combination with atleast one polymer in suitable solvent and adsorbing the resultant solution on to atleast one pharmaceutically acceptable excipient and formulated in to suitable dosage forms by methods known in the art.

Embodiments of the present invention may include one or more of the following features for example the pharmaceutical composition may further include one or more pharmaceutical acceptable excipients. The pharmaceutical acceptable excipients may include fillers/diluents, binders, polymers, disintegrants, lubricants, glidants, sweeteners, taste masking agents and flavors.

In another general aspect, there is provided a pharmaceutical composition comprising rasagiline, its enantiomer or salts thereof have 90th volume percentile particle size (D90) greater than about 250 µm.

Alternatively, rasagiline, its enantiomer or salts thereof may have particle size distribution wherein 10th volume percentile particle size (D10) is greater than about 20 µm, the 50th volume percentile particle size (D50) is greater than

about 100 µm, D(90) is greater than about 250 µm, or any combination thereof.

In another general aspect, there is provided a pharmaceutical composition comprising rasagiline, its enantiomer or salts thereof have water content less than 6%.

In another general aspect, there is provided a method of treating Parkinson's disease, dementia and Alzheimer's disease in patient comprising administering to said subject a pharmaceutical composition of rasagiline, its enantiomer or salts thereof comprising one or more pharmaceutical excipients, wherein said composition is free of sugar alcohols or polyols or any other stabilizer.

The details of one or more embodiments of the present invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description.

DETAIL DESCRIPTION OF THE INVENTION:

The inventors of the present invention have found that it is possible to formulate stable formulations of rasagiline without using amino sugars or polyols or any other stabilizer and such formulation retains at least 80% of the potency of rasagiline, its enantiomer or salts thereof in the pharmaceutical composition after storage for three months at 40^0 C and 75% relative humidity. Additionally, the inventors have found that formulations containing besylate salt of rasagiline may exhibit significant stability and in particular, possess good formulation characteristics.

In accordance with the present invention, there is provided a pharmaceutical composition of rasagiline, its enantiomer or salts thereof comprising one or more pharmaceutical excipients, wherein the composition is free of sugar alcohols or polyols or any other stabilizers.

The term 'rasagiline' is used in broad sense to include not only the rasagiline per se but also its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof, and their crystalline and amorphous forms.
Racemic, S(-) or R(+) enantiomers of rasagiline, and especially the enantiomer R(+) of rasagiline is particularly preferred. Particularly preferred salts of rasagiline or its enantiomer are besylate, mesylate, maleate, fumarate, tartrate, hydrobromide, esylate, tosylate, benzoate, oxalate, edisilate, phosphate, hydrochloride, acetate, sulphate.

The term 'sugar alcohols' used hereinbefore and throughout the description hereinafter refers to polyhydric sugar and its derivatives e.g. lactose, mannitol, xylitol, fructose, maltitol, isomaltitol, erythritol, lactitol and Sorbitol and the term 'polyols' used hereinbefore and throughout the description hereinafter refers to excipients containing more than four alcoholic (–OH) groups.

The term 'stabilizers' used hereinbefore and throughout the description hereinafter refers to citric acid, tartaric acid, lactic acid, butyl hydroxyl toluene, butyl hydroxyl anisole, EDTA and the like.

The inventors of the present invention have also found that particle size distributions have a beneficial effect on the uniformity of the solid

pharmaceutical composition of Rasagiline. Coarser particle size of rasagiline, its enantiomer or salts thereof provides better uniformity, flowability compared to the finer particle size and suitable for pharmaceutical formulations.

In accordance with the present invention, there is provided a pharmaceutical composition of rasagiline, its enantiomer or salts thereof have 90th volume percentile particle size (D90) greater than about 250 µm, or any combination thereof.

In an embodiment, rasagiline, its enantiomer or salts thereof may have particle size distribution, wherein 10th volume percentile particle size (D10) is greater than about 20 µm, the 50th volume percentile particle size (D50) is greater than about 100 µm, and D(90) is greater than about 250 µm, or any combination thereof.

In a further embodiment, rasagiline, its enantiomer or salts thereof may have particle size D(90) greater than 250 microns, and D(50) greater than 150 microns.

In an embodiment, the pharmaceutical composition of rasagiline, its enantiomer or salts thereof have water content less than 6%, preferably less than 4%.

In accordance with the present invention, there is provided a process for the preparation of pharmaceutical composition of rasagiline, its enantiomer or salts thereof, wherein said, process comprises the steps of dissolving rasagiline, its enantiomer or salts thereof alone or in combination with atleast one polymer in suitable solvent (s) and adsorbing the resultant solution on

atleast one pharmaceutically acceptable excipient and formulated in to suitable dosage forms by methods known in the art.

In an embodiment of the invention, the process for the preparation of pharmaceutical composition of rasagiline, its enantiomer or salts thereof, comprises the steps of

i). Preparing granulate comprising rasagiline dispersion along with at least one filler and optionally other excipients, by wet granulation;

ii). Drying said granulate;

iii). Blending said granulate of step (ii) with extra-granular excipient;

iv). Compressing said blended granulate of step (iii) to get the tablet;

and

v). Optionally coating said tablet with a film coating material.

Suitable solvents that may be used for preparing the dispersion include organic, aqueous, or a mixture thereof. Organic solvents may be aliphatic alcohols such as methanol, ethanol, n-propanol, and isopropanol; aliphatic ketones such as acetone and methyl ethyl ketone; aliphatic carboxylic esters such as ethyl acetate; aromatic hydrocarbons such as toluene and xylene; aliphatic hydrocarbons such as hexane; aliphatic nitriles such as acetonitrile; chlorinated hydrocarbons such as dichloromethane; aliphatic sulfoxides such as dimethyl sulfoxide; and the like, as well as mixtures comprising at least one of the foregoing organic solvents. Aqueous solvents include solvent comprising water and/or a water-miscible organic solvent such as a lower alcohol, acetonitrile, tetrahydrofuran, dimethylacetamide, dimethyl formamide, and the like. Combination of various solvents can also be used.

The polymer that may be used for preparing drug dispersion includes water soluble and/or water insoluble polymer.

Suitable polymers that may be used for preparing the dispersion include, but are not limited to, copovidone, ethylcellulose, hydroxypropyl cellulose, hydroxyl propyl methyl cellulose, polyvinyl alcohol, methylcellulose, polyethylene oxide, polyvinylpyrrolidone, povidone, starch, or sodium carboxymethylcellulose and the like.

The pharmaceutical composition of rasagiline, its enantiomer or salts thereof can be prepared by any suitable method known in the art such as direct compression, dry granulation or wet granulation using aqueous and/or non-aqueous solvents, fluidized bed granulation, melt extrusion, melt granulation, spray coating, freeze drying, spray drying and solution evaporation.

The pharmaceutical composition can be formulated into tablets, pellets, wafers, granules, micro-granules, powders, capsules, lozenges, films, chewables, pellets in capsule, granules in capsule or any other dosage form suitable for oral administration.

In an embodiment, the pharmaceutical composition is provided as a tablet, which can be film coated with one or more coating agents. Usable coating agents are hypromellose, polyvinyl alcohol, sodium carboxymethyl cellulose and various methacrylic acid polymers. The coating may also contain further such as plasticizers, pigments, pore forming materials.

In another embodiment, the composition containing rasagiline, its enantiomer or salts thereof can be developed into fast-releasing and delayed-releasing compositions by methods known to the person skilled in the art.

Pharmaceutically acceptable excipients for use in the pharmaceutical composition of rasagiline comprise one or more diluents, fillers/bulking agents,

binders, disintegrants, lubricants, glidants, sweeteners/taste masking agents, colorants and flavors.

In a preferred embodiment, the pharmaceutically acceptable excipients for use in the pharmaceutical composition of rasagiline contains less than five alcohol (-OH) groups.

Suitable diluents/fillers or bulking agents which includes, but are not limited to, saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols having less than five alcohol (-OH) groups, and other bulking agents such as dibasic calcium phosphate and powdered cellulose and derivatives thereof and combinations thereof, preferably dibasic calcium phosphate and/or microcrystalline cellulose.

Suitable binders which includes, but are not limited to, acacia, alginic acid, carbomer copolymer, carbomer interpolymer, copovidone, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, glucose (liquid), guar gum, hydroxypropyl cellulose, polyvinyl alcohol, maltose, methylcellulose, polyethylene oxide, polyvinylpyrrolidone, povidone, starch, or sodium carboxymethylcellulose and the like.

Suitable disintegrants which includes, but are not limited to, croscarmellose sodium, crospovidone, sodium starch glycolate, corn starch, potato starch, maize starch, pregelatinized starch and modified starches, calcium silicates, low substituted hydroxy- propylcellulose.

Suitable lubricants and glidants which may include, but are not limited to, stearic acid and its derivatives or esters like sodium stearate, magnesium

stearate, calcium stearate and sodium stearyl fumarate; talc and colloidal silicon dioxide.

Suitable taste masking agents may include one or more of polymers, surfactants, sweeteners and flavors. Examples of polymers include one or more of cellulose acetate, polymethacrylates, cellulose derivatives such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxylethyl cellulose; and the like. Examples of sweeteners include but not limiting to one or more of aspartame, saccharin, sucralose, glycyrrhizin; and the like.

Suitable sweeteners that may be used, comprises saccharides such as aspartame, sugar derivatives having less than five alcohol (–OH) groups. Other examples of sweeteners comprise sodium saccharin; aspartame; sugarless sweeteners including glycerol, hydrogenated starch hydrolysates, alone or in combination.

Suitable flavors that may be used, comprise citric acid, cinnamon, wintergreen, eucalyptus, spearmint, peppermint, menthol, anise as well as fruit flavors such as apple, pear, peach, vanilla, strawberry, cherry, apricot, orange, watermelon, banana and the like; bean-derived flavors, such as coffee, cocoa and the like or mixtures thereof.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1

Table 1

Sr. No.	Name of Ingredient	Qty Mg/Tablet
1	Rasagiline besylate (Eq to 1 mg of base)	1.92
2	Dibasic Calcium Phosphate anhydrous	85.58
3	Pregelatinized Starch	10.00
4	Microcrystalline cellulose	100.00
5	Colloidal silicon dioxide	1.00
6	Stearic acid	1.50
8	Isopropyl alcohol	q. s.
	Total	**200.00**

Process: Drug solution was prepared by dissolving drug in Isopropyl Alcohol. The drug solution was adsorbed onto mixture of Dibasic calcium phosphate anhydrous, Microcrystalline Cellulose & Pregelatinized Starch in rapid mixture granulator following by drying in fluidized bed dryer at temperature of about 60 °C. Dried granules were sized through suitable screen following by blending with extra-granular Colloidal silicon dioxide and lubricating with stearic acid. Finally lubricated blend was compressed to form tablets and packed in Alu-Alu Blisters and charged for stability study.

Example 2

Table 2

Sr. No.	Name of Ingredient	Qty Mg/Tablet
1	Rasagiline besylate (Eq to 1 mg of base)	1.92
2	Dibasic Calcium Phosphate anhydrous	100.00
3	Microcrystalline cellulose	75.08
3	Pregelatinized Starch	20.00
4	Collodal silicon dioxide	1.00
5	Stearic acid	2.00
6	Purified water	qs
	Total	**200.00**

Process: Drug solution was prepared by dissolving drug in purified water. The drug solution was adsorbed onto mixture of Dibasic calcium phosphate anhydrous, microcrystalline cellulose & Pregelatinized Starch in rapid mixture granulator following by drying in fluidized bed dryer at temperature of about 60 °C. Dried granules were sized through suitable screen following by blending with extra-granular Colloidal silicon dioxide and lubricating with stearic acid. Finally lubricated blend was compressed to form tablets and packed in Alu-Alu Blisters and charged for stability study.

Example 3

Table 3

Sr. No.	Name of Ingredient	Qty Mg/Tablet
1	Rasagiline besylate (Eq to 1 mg of base)	1.92
2	Povidone	2.00
2	Dibasic Calcium Phosphate anhydrous	98.00
3	Pregelatinized Starch	20.00
4	Microcrystalline cellulose	75.08
5	Colloidal silicon dioxide	1.00
6	Stearic acid	2.00
8	Isopropyl alcohol	q. s.
	Total	**200.00**

Process: Drug solution was prepared by dissolving drug and povidone in Isopropyl Alcohol. The drug solution was adsorbed onto mixture of Dibasic calcium phosphate anhydrous, Pregelatinized Starch & Microcrystalline Cellulose in rapid mixture granulator following by drying in fluidized bed dryer at temperature of about 60 °C. Dried granules were sized through suitable screen following by blending with extra-granular Colloidal silicon dioxide and lubricating with stearic acid. Finally lubricated blend was compressed to form tablets and packed in Alu-Alu Blisters and charged for stability study.

Example 4

Table 4

Sr. No.	Name of Ingredient	Qty Mg/Tablet
1	Rasagiline besylate (Eq to 1 mg of base)	1.92
2	Dibasic Calcium Phosphate anhydrous	85.58
3	Pregelatinized Starch	10.00
4	Microcrystalline cellulose	100.00
5	Collodal silicon dioxide	1.00
6	Stearic acid	1.50
7	Isopropyl alcohol	qs
	Total	**200.00**

Process: Drug solution was prepared by dissolving drug in Isopropyl alcohol. The drug solution was adsorbed onto mixture of Dibasic calcium phosphate anhydrous, Pregelatinized Starch and part of microcrystalline cellulose in rapid mixture granulator following by drying in fluidized bed dryer at temperature of about 60 °C. Dried granules were sized through suitable screen following by blending with extra-granular microcrystalline cellulose and Colloidal silicon dioxide and lubricating with stearic acid. Finally lubricated blend was compressed to form tablets and packed in Alu-Alu Blisters and charged for stability study.

Dated this 16th Day of May 2013.

Signature:

Mr. Chirag Soni
Senior Manager,
Global-IP,
Cadila Healthcare Limited.