Field of invention:

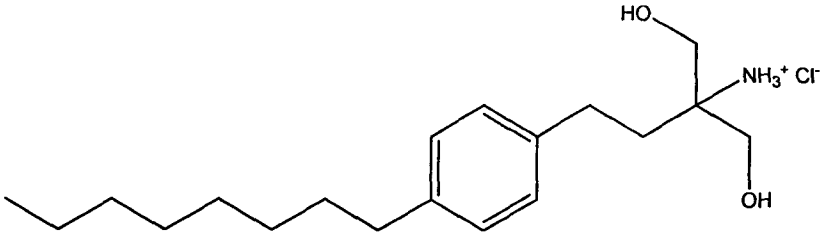
The present invention is directed to oral solid pharmaceutical dosage form comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and method of making thereof.

Background of invention:

2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is an immunosuppressive drug. Accordingly, the compound may be useful in the treatment or prevention of various autoimmune conditions, including multiple sclerosis(MS).

2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride acts as a modulator of sphingosine-1 -phosphate (S1P) receptors, resulting in inhibition of the egress of lymphocytes from lymph nodes and Peyer's patches, and thereby reduces the recirculation of lymphocytes to blood and tissues including the Central Nervous System. 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride has demonstrated significant and consistent effects on Magnetic Resonance Imaging (MRI) measures of inflammation and relapses in study performed in adult patients with relapsing MS (Kappos, et al 2006], Oral 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride for relapsing multiple sclerosis.(N Engl J Med; 355(11):1124-1140).

The structure of the present compound is as follows:



As the pharmaceutical compositions comprising, an active ingredient, 2-amino-2-[2-(4-octyl phenyl)ethyl]propane-1,3-diol hydrochloride pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, the following literatures have been known so far.

2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or pharmaceutical acceptable salt thereof was disclosed in US5604229. 2-amino-2-[2-(4-octylphenyl)ethyl]propane-

1,3-diol hydrochloride is sold by Novartis in capsules under the commercial name of Gilenya as in the treatment of multiple scelorisis.

International Publication No. WO2010055028A2 discloses polymorphs of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride, referred to as form I,II & III and also disclosed the pharmaceutical composition thereof.

International Publication No. WO2004089341A1 discloses the pharmaceutical composition comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride combination with sugar alcohol.

International Publication No. WO2008037421A2 discloses the pharmaceutical composition comprising S1P receptor modulator, wherein the composition comprises a coating comprising one or more polymer resin and one or more metal oxides.

2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is soluble (>10%) in water, 0.9% saline and aqueous buffers at a pH~2.0. It is very soluble or practically insoluble in aqueous buffer at or above pH~3.0.

Henceforth, there is a need in the art to develop a pharmaceutical composition, which enhances the solubility of the API in the stomach.

Advantages of the present Invention:

- Tricalcium phosphate is used as diluent, glidant and buffering agent. Preferably used as diluent. Sodium lauryl sulphate added to increase the solubility, finally it leads to increase in the bioavailability of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (in vitro and in vivo release profile)
- Pregelatinized starch used as capsule binder and diluent, preferably used as capsule binder.
- Pregelatinized starch also enhances the flow properties of blend during capsule filling.
- Pregelatinized starch is used along with stearic acid to enhance the compatibility of the final dosage form

Summary of invention:

The first embodiment of the present invention provides oral solid pharmaceutical composition comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or its pharmaceutically acceptable salts, particularly hydrochloride salt and pharmaceutically acceptable carriers.

The second embodiment of the present invention provides oral pharmaceutical composition comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride combined with at least one surfactant and at least one diluent, and optionally other excipients except sugar alcohols.

The third embodiment of the present invention provides a process for manufacturing the oral solid pharmaceutical composition of 2-amino-2-[2-(4-octylphenyl)ethyl] propane-1,3-diol or its pharmaceutically acceptable salts, particularly hydrochloride salt.

Detailed Description of the Invention:

The first embodiment of the present invention provides oral solid pharmaceutical composition comprising of:

a) 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride,
b) at least one diluent,
c) at least one surfactant,
d) at least one binder,
e) at least one glidant,
f) at least one lubricant.

The second embodiment of the present invention provides oral pharmaceutical composition comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride combined with at least one surfactant and at least one diluent, and optionally other excipients except sugar alcohols.

The excipients are selected to ensure the delivery of consistent amount of 2-

amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and also should contain a convenient unit dosage form to optimize the cost, ease and reliability of the manufacturing process. All the excipients must be inert, organoleptically acceptable, and compatible with the 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride. Generally the excipients used in the solid dosage form include diluents or fillers, binders, surfactants, lubricants, glidants and coating agents.

Diluents are included to increase the bulk of the capsule. The various types of diluents are tricalcium phosphate, lactose and microcrystalline cellulose and the like. Preferably the diluent is tricalcium phosphate.

Surfactants are included to increase the solubility of the drug that finally leads to increase in the bioavailability of the drug. Surfactants may be ionic or nonionic. Ionic surfactants may be anionic, cationic and zwitter ionic. Non-limiting examples include sodium lauryl sulphate, sodium cholate hydrate, poloxomers and docusate sodium and the like. Preferably the surfactant is sodium lauryl sulphate.

Binders are used as a wet granulation excipient to agglomerate the powder mixture of active pharmaceutical ingredient and the other excipients. The binder is selected to improve the flow properties of powder and to improve compatibility. The most commonly used binders are pregelatinized starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose and povidone. Preferably the binder is pregelatinized starch.

Glidants or flow regulators are included to increase the flow properties of the blend. The various types of glidants are dried starch, colloidal silicon dioxide and talc. Preferably the glidant is dried starch.

Lubricants are used in the tablet formulation to reduce the friction during the compression stages and to prevent the sticking of the tablet to the punch faces. Lubricant is selected from stearic acid, vegetable oils(corn oil), mineral oils, polyethylene glycol, inorganic salts(such as sodium chloride),organic salts(sodium benzoate, sodium acetate), and polyvinyl alcohols. Preferably the lubricant is stearic acid.

The third embodiment of the present invention provides a process for manufacturing the oral solid pharmaceutical composition of 2-amino-2-[2-(4-octyl phenyl)ethyl]propane-1,3-diol hydrochloride comprising of:

a) Sifting 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and all excipients and optionally seive,
b) mixing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride, tricalcium phosphate, sodium lauryl sulphate and pregelatinized starch,
c) adding water to the above mixture and drying the granules,
d) sifting the granules through a seive,
e) mixing dried starch to the above granules,
f) blending a stearic acid to the above granules,
g) filling the blend into capsules.

Further embodiment of the present invention provides a process for manufacturing the oral solid pharmaceutical composition of 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride comprising of:

a) Sifting 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and all excipients and optionally seive,
b) mixing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride, tricalcium phosphate, sodium lauryl sulphate and pregelatinized starch,
c) sifting the granules through a seive,
d) mixing dried starch to the above granules,
e) blending a stearic acid to the above granules,
f) filling the blend into capsules.

The oral solid pharmaceutical composition of the present invention may be in the form of tablet, capsule, pellet, preferably capsule.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

Example-1

S No	Components	Mg /Cap
1	2-amino-2-[2-(4-octyl phenyl) ethyl]propane-1,3-diol HCl	0.5
2	Tricalcium phosphate	281.9
3	Sodium lauryl sulphate	3
4	Pregelatinized starch	7.5
5	Purified water	qs
6	Dried starch	3
7	Stearic acid	4.5
	Total Weight	300

Procedure: Accurately weighed 2-amino-2-[2-(4-octyl phenyl) ethyl]propane-1,3-diol hydrochloride, tricalcium phosphate, sodium lauryl sulphate, pregelatinized starch, dried starch and stearic acid were passed through an appropriate mesh. The 2-amino-2-[2-(4-octyl phenyl) ethyl]propane-1,3-diol hydrochloride, tricalcium phosphate, sodium lauryl sulphate and pregelatinized starch were mixed for 15min. Added sufficient quantity of water to the above mixer and mixed with high speed. Dried the above granules. The above dried granules were passed through an appropriate mesh. Added dried starch to the above dried sized granules and blended for 15min. And then added stearic acid to the above blend. Finally the blend is filled into the capsules.

Example-2

S No	Components	Mg /Cap
1	2-amino-2-[2-(4-octyl phenyl) ethyl]propane-1,3-diol HCl	0.5
2	Tricalcium phosphate	281.9
3	Sodium lauryl sulphate	3
4	Pregelatinized starch	7.5
5	Dried starch	3
6	Stearic acid	4.5
	Total Weight	300

Procedure:

Accurately weighed 2-amino-2-[2-(4-octyl phenyl) ethyl]propane-1,3-diol hydrochloride, tricalcium phosphate, sodium lauryl sulphate, pregelatinized starch, dried starch and stearic acid were passed through an appropriate mesh. The 2-amino-2-[2-(4-octyl phenyl) ethyl]propane-1,3-diol hydrochloride, tricalcium phosphate, sodium lauryl sulphate and pregelatinized starch were mixed for 15min. The above granules were passed through an appropriate mesh. Added dried starch to the above dried sized granules and blended for 15min. And then added stearic acid to the above blend. Finally the blend is filled into the capsules.

Dated this day 28th of May 2011.

Authorized Signatory

(Srinivasan Thirumalai Rajan)

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Abstract

The present invention is directed to oral solid pharmaceutical dosage form comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and method of making thereof.