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(54) Title: PHARMACEUTICAL COMPOSITION OF FINGOLIMOD

(57) Abstract: Present invention relates to a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluents selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant. Invention also relates to process of preparation of solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluents selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant.

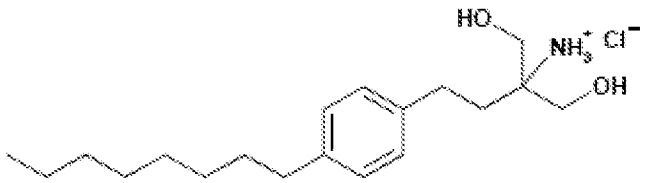
# PHARMACEUTICAL COMPOSITION OF FINGOLIMOD

## FIELD OF INVENTION

Present invention relates to a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluents selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant. Invention also relates to process of preparation of solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluents selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant.

## BACKGROUND

Fingolimod hydrochloride (FTY 720), chemically 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-l,3-diol hydrochloride




is a pharmaceutically active immunomodulating compound. It is a structural analogue of sphingosine and its pharmaceutical activity is associated with its modulating activity towards sphingosine- 1 -phosphate (SIP) receptors. Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate.

The HCl salt form of fingolimod has pH dependent solubility. It is freely soluble in water and in pH 1.0 buffer, very slightly soluble in pH 4.0 buffer and practically insoluble in pH 6.8 buffer.

Fingolimod HCl is approved as Gilenya™, which is a hard-shell capsule filled by a powder comprising 0.56 mg of micronized Fingolimod hydrochloride corresponding to 0.5 mg of Fingolimod per capsule, for once daily administration for the treatment of relapsing remitting multiple sclerosis. Gilenya™ has very fast dissolution profile, which provide dissolution of about 99% in 30 minutes in 500 ml media constituted by 0.1 N HCL + 0.2% SLS, at 100 rpm. (as specified by Office of generic drugs or OGD)

Gilenya™ capsule comprises mannitol as diluent, prepared by direct blending method and capsule additionally comprises small amount of magnesium stearate as a lubricant. Fingolimod HCl was used in a micronized form to ensure content uniformity of the active substance.

It is disclosed in literature that fingolimod reacts with several excipients during compatibility studies and thus mannitol was used as a diluent in Gilenya™ formulation due to the optimum degradation profile. Since, dose of the approved product is very low, and filler or diluent makes most of the part of the composition it is essential to select excipient which is highly compatible with API. (European public assessment report of Gilenya™)

WO 2004/089341 discloses a solid pharmaceutical composition suitable for oral administration comprising various SIP receptor agonists and a sugar alcohol such as mannitol to provide a stable composition and homogenous distribution of API. It also discloses the process such as blending or wet granulation for preparation of pharmaceutical composition. Description does not discloses any compatibility study data of Fingolimod and excipients including sugar alcohols or any other excipients; however applicant has submitted an affidavit in USPTO which discloses that mannitol is most compatible with fingolimod while microcrystalline cellulose, starch and lactose resulted in high impurity when stored for one week at 80° C.

WO2010/055028 discloses crystalline forms and hydrates of fingolimod hydrochloride and pharmaceutical formulations thereof. The solid pharmaceutical formulations comprise the crystalline fingolimod hydrochloride and a sugar alcohol. The sugar alcohol can be, e.g. mannitol, maltitol, inositol, xylitol or lactitol.

WO2009/048993 discloses dosage forms containing S1P modulators and one or more excipients selected from fillers, binders, disintegrants, lubricants, flow regulators, matrix formers, plasticizers, flavouring agents and sweeteners. Patent application discloses that fingolimod is not compatible with most of the excipients due to possibility of Maillard's reaction, which results in impurity during stability hence only those excipients, which show impurity less than 2wt% when stored for one month at 50°C, are selected in the patent application. Patent application also discloses that invention does not comprise some excipients such as reducing sugars, PEG and stearic acid.

WO2011131370, WO2011131369 and WO2011131368 provide alternate strategies such as melting or co-milling of fingolimod with excipient or matrix former to provide homogenous distribution of Fingolimod.

WO201319872 addresses the problem of stability by mixing fingolimod with dry surfactant and then formulating the resulting pre-mix.

1844/CHE/2011 discloses a solid oral composition comprising fingolimod, pregelatinized starch and stearic acid, but dissolution profile of this composition is slower when compared with Gilenya™ product. Moreover, patent application does not provide any stability study to show compatibility of excipients with Fingolimod.

US20140199382 discloses compositions of fingolimod comprising pregelatinized starch or dicalcium phosphate with sodium starch glycolate and sodium stearyl fumarate which were found stable at 40 °C.

Despite of various prior arts availability to provide solution of one or the other issues associated with fingolimod hydrochloride, still there exists a need for selecting excipient/s for formulating fingolimod, which provides a stable product and provides desired therapeutic effect.

Present invention overcomes all the above mentioned problems by providing a stable solid oral composition having desired content uniformity and dissolution profile.

**SUMMARY OF THE INVENTION**

One aspect of the present invention is to provide a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant.

Another aspect of the present invention is to provide a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, powdered cellulose and a lubricant, wherein said composition provides dissolution of more than 95% in 30 minutes as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS.

Another aspect of the present invention is to provide a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a

lubricant, wherein total impurity of the product is less than 2% when subjected to 80 °C for 72 hrs.

Another aspect of the present invention is to provide a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant, wherein total impurity of the product is less than 1.5% when subjected to 80 °C for 72 hrs.

Another aspect of the present invention is to provide a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof and suitable mixture of first grade of powdered cellulose having average particle size of less than 100 microns with second grade of powdered cellulose having average particle size of more than 120 microns and a lubricant.

Another aspect of the present invention is to provide a solid oral composition consisting of fingolimod or pharmaceutically acceptable salt thereof, powdered cellulose and one or more lubricant, wherein said composition provides dissolution of more than 95% in 30 minutes as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS.

Another aspect of present invention is to provide process of preparation of solid oral composition comprises fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant.

**Figures**

Fig 1: Dissolution profile of compositions according to examples 2, 3 and Gilenya™ in media 1(fig 1a), media 2(fig 1b) and media 3(fig 1c)

Fig 2: Dissolution profile of compositions according to examples 4, 5 and Gilenya™ in media 1(fig 1a), media 2(fig 1b) and media 3(fig 1c)

## DETAIL DESCRIPTION OF THE INVENTION

The following paragraphs detail various embodiments of the invention. For the avoidance of doubt, it is specifically intended that any particular feature(s) described individually in any one of these paragraphs (or part thereof) may be combined with one or more other features described in one or more of the remaining paragraphs (or part thereof). In other words, it is explicitly intended that the features described below individually in each paragraph (or part thereof) represent important aspects of the invention that may be taken in isolation and combined with other important aspects of the invention described elsewhere within this specification as a whole, and including the examples and figures. The skilled person will appreciate that the invention extends to such combinations of features and that these have not been recited in detail here in the interests of brevity.

The use of the terms “a” and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

The term “Fingolimod” as used herein includes fingolimod free base, its pharmaceutically acceptable salt, its polymorphs or its hydrate or fingolimod phosphate. Preferably, fingolimod is fingolimod HCl in anhydrous form. Average particle size of fingolimod or its pharmaceutical acceptable salt used according to

present invention ranges from 1 micron to 50 microns. Preferably, micronized fingolimod or its pharmaceutical acceptable salt with D90 of less than 20 microns is used. Most preferably, D 90 of fingolimod or its pharmaceutical acceptable salt is less than 10 microns as measured using Malvern instrument.

The term "average particle size" or "PSD" as used herein means at least 50% of the molecules have defined particle size as measured by Beckmann Coulter (Coulter LS 230) or Malvern instrument.

The term "product" as used herein means a pharmaceutical composition as prepared according to present application.

The term "powdered cellulose" as defined herein means a cellulose which has degree of polymerization of about 400, preferably from 440 to 2250, and which has not undergone any partial acid hydrolysis. Powdered cellulose is generally available as Arbocel®, Elcema®, Sanacel® and Solka-Floc®. Powdered cellulose may vary in its average particle size ranges from about 50 microns to 200 microns, and bulk density from 0.2 – 0.4 g/cc.

The term "not detected" as used herein means impurity is below the quantification limit or impurity detected in negligible amount.

The first embodiment of the present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant.

Another embodiment of the present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, powdered cellulose and a lubricant.

A preferred embodiment of the present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, powdered cellulose and a lubricant, wherein said composition provides dissolution of more than 95% in 30 minutes as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS.

It was surprisingly noted that when powdered cellulose is used as a diluent in the composition comprising fingolimod or pharmaceutically acceptable salt thereof, the dissolution of the composition is more than 95% in 30 minutes in OGD media. Even, when analyzed in other media such as Acetate buffer+0.2% SLS or phosphate buffer+0.2% SLS, dissolution was more than 90% in 30 minutes.

Another embodiment of the present invention provides a solid oral composition comprising of fingolimod or pharmaceutically acceptable salt thereof, powdered cellulose and stearic acid as a lubricant, wherein said composition provides dissolution of more than 95% in 30 minutes as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS.

Another embodiment of the present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant, wherein total impurity of the product is less than 2%, when subjected to 80 °C for 72 hrs. Preferably, total impurity is less than 1.5 %, most preferably total impurity is less than 0.2% when subjected to 80 °C for 72 hrs.

While conducting stability studies for formulation of fingolimod with various excipients, high amount of impurity generation was found for most of the formulations, when kept at 80 °C for 72 hrs. Even Gilenya™ formulation, when exposed to 80 °C for 72 hrs, total impurity generation was 2.06%. It was surprisingly noted that the composition with powdered cellulose, dicalcium phosphate or tricalcium phosphate when exposed to same conditions, impurity could not be detected. Even when compositions were subjected to 50 °C in closed vials for 1 month, less than 0.2% of total impurity detected, meaning present invention provides highly stable formulations.

It was surprisingly noted that while using stearic acid in association with powdered cellulose, it does not aid in impurity generation.

Thus, another embodiment of the present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose dicalcium phosphate and tricalcium phosphate; and stearic acid, wherein total impurity of the product is less than 2% when subjected to 80 °C for 72 hrs. Preferably, total impurity is less than 1.5 when subjected to 80 °C for 72 hrs. Preferably, diluent is powdered cellulose.

Another embodiment of the present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof and suitable mixture of first grade of powdered cellulose having average particle size of less than 100 microns with second grade of powdered cellulose having average particle size of more than 120 microns and a lubricant.

It was surprisingly noted that when mixture of two grades of powdered cellulose, one having average particle size of less than on 100 microns and second

having average particle size of more than 120 microns was used in the composition comprising fingolimod or pharmaceutically acceptable salt thereof, flow rate of mixture was improved over the composition where only one grade of powdered cellulose was used. Flow rate was determined by calculating Hausner ratio and compressibility index, as known in the art. Moreover robustness of process and batch to batch consistency of formulation was improved.

Hausner ratio and compressibility index are calculated in present invention according to the formulas:

Compressibility index = Tapped density - bulk density / tapped density X 100

Hausner ratio = Tapped density / Bulk density

Preferable embodiment of present invention provides a solid oral composition comprising fingolimod or pharmaceutically acceptable salt thereof and suitable mixture of first grade of powdered cellulose having average particle size of 50 to 100 microns preferably 70 to 90 microns, most preferably 80 microns with second grade of powdered cellulose having average particle size of 120-200 microns, preferably 140 to 160 microns, most preferably 150 microns and a lubricant.

Ratio of first grade of powdered cellulose having average PSD less than 100 microns to second grade of powdered cellulose having average PSD of more than 120 microns ranges from 1:99 to 99:1. Preferably ratio of first grade of powdered cellulose to second grade of powdered 1: 2, most preferably ratio is 1:1. Particle size of powdered cellulose can be determined by methods known in the art. Particle size mentioned in present application is determined by Beckmann Coulter.

It was noted that formulation of fingolimod HCl with dicalcium phosphate or tricalcium phosphate and a lubricant shows good dissolution profile in OGD media

but not in other media such as Acetate buffer+0.2% SLS or phosphate buffer+0.2% SLS.

It was surprisingly found that addition of an acidifier in the composition improved the dissolution profile in all media.

Another embodiment of present invention provides a composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from dicalcium phosphate and tricalcium phosphate; one or more acidifier and a lubricant.

"Acidifier" according to present invention is the substance which provides pH less than 6. Acidifier according to present invention includes amino acids such as Glycine, cysteine or organic acids such as fumaric acid, citric acid, acidified water and the like. Preferably, acidifier is amino acid. Said acidifier not just improves dissolution but also aid into stability of the product.

A preferred embodiment of present invention provides a composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from dicalcium phosphate and tricalcium phosphate; one or more amino acid and a lubricant. Preferably amino acid is selected from glycine and cysteine.

A preferred embodiment of present invention provides a composition consisting of fingolimod or pharmaceutically acceptable salt thereof, diluent selected from dicalcium phosphate and tricalcium phosphate; one or more amino acid and one or more lubricant.

The amount of acidifier to be used in the composition according to present invention ranges from 0.1 to 25%, preferably 1 to 20%, most preferably 1 to 14% of the total weight of the composition.

Another embodiment of the present invention provides a solid oral composition consisting of fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and one or more lubricants. Said composition is either present in the form of granules or blend which is suitably filled in a capsule.

Another embodiment of the present invention provides a solid oral composition consisting of fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; one or more lubricants and optionally one or more acidifier. Said composition is either present in the form of granules or blend which is suitably filled in a capsule.

Another embodiment of the present invention provides a solid oral composition consisting of fingolimod or pharmaceutically acceptable salt thereof, powdered cellulose and one or more lubricant, wherein said composition provides dissolution of more than 95% in 30 minutes as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS. Said composition is either present in the form of granules or blend which is suitably filled in a capsule.

Present invention also provides method of producing composition according to present invention.

Thus, another embodiment of present invention provides a process of preparation of solid oral composition comprising;

1. Mixing/blending fingolimod or pharmaceutically acceptable salt thereof and diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate.

2. Optionally adding one or more acidifier in the mixture of step 1.
3. Adding a lubricant in the mixture obtained in step 1 or 2.
4. Optionally, filling the mixture of step 3 in a capsule or compressing it to form a tablet.

Another embodiment of present invention provides a process of preparation of solid oral composition comprising

1. Mixing first grade of powdered cellulose having average particle size of less than 100 and second grade of powdered cellulose having average particle size of more than 120 microns.
2. Mixing/blending fingolimod or pharmaceutically acceptable salt thereof and powdered cellulose mixture obtained in step 1.
3. Adding a lubricant in the mixture obtained in step 2.
4. Filling the mixture of step 2 or 3 in a capsule or compressing it to form a tablet.

Alternatively, wet granulation or dry granulation/roller compaction methods can also be employed.

The amount of diluent selected from powdered cellulose, dicalcium phosphate or tricalcium phosphate used in the composition according to ranges from 51% to 99.5%, preferably 80% to 99%, most preferably 90% to 99% of the total weight of the composition. Preferably, powdered cellulose is used as diluent.

The amount of lubricant used in the composition according to present invention ranges from 0.01 to 2%, preferably 0.1 to 2% most preferably 0.1 to 1% of the total weight of the composition.

Lubricant according to present invention is magnesium stearate, zinc stearate, calcium stearate, stearic acid, sodium lauryl sulfate or glyceryl behenate and the like, preferably lubricant is stearic acid.

Compositions according to present invention may optionally further comprises one or more surfactant.

Surfactant according to present invention includes sodium lauryl sulfate, docusate sodium, polysorbate, poloxamer, polyoxyethylene alkyl ether, meglumine and the like.

Solid oral composition according to present invention can be in the form of tablet, capsule, powder or sachet. Preferably solid oral composition according to present invention is capsule.

Another embodiment of present invention provides use of the composition prepared according to present invention for treatment of autoimmune disorders including multiple sclerosis.

The invention will be further illustrated by the following examples, however, without restricting its scope to these embodiments.

Example 1:

| **S.No.** | **Ingredients** | **Wt%** |
|---|---|---|
| 1 | Fingolimod Hydrochloride | 1.19 |
| 2 | Powdered Cellulose of average PSD 80 microns | 98.81 |
| Total | | 100.00 |

Fingolimod HCl was co-sifted with powdered cellulose, and then mixture was sifted through 30# sieve for 3 times to ensure proper mixing. Obtained blend was then filled in size "3" capsules.

Example 2:

| S.No. | Ingredients | Wt% |
|---|---|---|
| 1 | Fingolimod Hydrochloride | 1.19 |
| 2 | Powdered Cellulose (50: 50 mixture of 80 microns and 150 microns average PSD) | 98.81 |
| Total | | 100.00 |

Powdered cellulose of average PSD 80 microns and powdered cellulose of average PSD 150 microns were mixed in ratio of 1:1. Fingolimod HCl was co-sifted with powdered cellulose mixture and mixed geometrically, and then mixture was sifted through 30# sieve for 3 times to ensure proper mixing. Obtained blend was then filled in size "3" capsules.

Example 3:

| S.No. | Ingredients | Wt% |
|---|---|---|
| 1 | Fingolimod Hydrochloride | 1.19 |
| 2 | Powdered Cellulose (50: 50 mixture of 80 microns and 150 microns average PSD) | 98.31 |
| 3 | Stearic acid | 0.50 |
| Total | | 100.00 |

Powdered cellulose of average PSD 80 microns and powdered cellulose of average PSD 150 microns were mixed in ratio of 1:1. Fingolimod HCl was co-sifted with powdered cellulose mixture and mixed geometrically, and then mixture was sifted through 30# sieve for 3 times to ensure proper mixing. 40# passed Stearic acid was added to obtained blend and mixed. Final mixture was then filled in size "3" capsules.

Example 4:

| S.No. | Ingredients | Wt% |
|---|---|---|
| 1 | Fingolimod Hydrochloride | 0.93 |
| 2 | Dicalcium Phosphate | 99.07 |
| Total | | 100.00 |

Fingolimod HCl was co-sifted with dicalcium phosphate and mixed geometrically, and then mixture was sifted through 60# sieve for 3 times to ensure proper mixing. Blend was then filled in size "3" capsules.

Example 5:

| S.No. | Ingredients | Wt% |
|---|---|---|
| 1 | Fingolimod Hydrochloride | 0.93 |
| 2 | Dicalcium Phosphate | 96.07 |
| 3 | Cysteine Hydrochloride | 2.00 |
| 4 | Glyceryl behenate | 1.00 |
| Total | | 100.00 |

Fingolimod HCl was co-sifted with dicalcium Phosphate and cysteine and mixed geometrically, and then mixture was sifted through 60# sieve for 3 times to ensure proper mixing. Glyceryl behenate was mixed and final blend was filled in size "3" capsules.

Example 6:

| S.No. | Ingredients | Wt% |
|---|---|---|
| 1 | Fingolimod Hydrochloride | 0.93 |
| 2 | Tricalcium Phosphate | 99.07 |
| Total | | 100.00 |

Fingolimod HCl was co-sifted with tricalcium phosphate and mixed geometrically, and then mixture was sifted through 60# sieve for 3 times to ensure proper mixing to prepare blend.

**Dissolution profile:**

Dissolution of the compositions prepared from Example 2 to 5 and Gilenya™ (Batch No S0035), was checked in various media, as summarized in table 1.

Media 1 (OGD media): 0.1 N HCl + 0.2% SLS; basket; 100rpm, 500 ml.

Media 2: pH 4.5 Acetate buffer + 0.2% SLS; basket; 100rpm, 500 ml

Media 3: pH 6.8 phophate buffer + 0.2% SLS; basket; 100 rpm; 500 ml

Comparative dissolution profiles of various formulations are given below and represented in figs 1 to 3.

| Example/time | 0 | 5 | 10 | 15 | 20 | 30 | 45 |
|---|---|---|---|---|---|---|---|
| **Media 1** | | | | | | | |
| Gilenya™ | 0 | 89 | 96 | 97 | 98 | 99 | 99 |
| Example 2 | 0 | 86 | 94 | 95 | 97 | 98 | 99 |
| Example 3 | 0 | 96 | 101 | 102 | 105 | 105 | 105 |
| **Media 2** | | | | | | | |
| Gilenya™ | 0 | 72 | 85 | 90 | 93 | 97 | 99 |
| Example 2 | 0 | 77 | 86 | 91 | 93 | 95 | 97 |
| Example 3 | 0 | 79 | 89 | 93 | 94 | 96 | 97 |
| **Media 3** | | | | | | | |
| Gilenya™ | 0 | 81 | 89 | 91 | 92 | 94 | 99 |
| Example 2 | 0 | 72 | 83 | 87 | 90 | 93 | 95 |
| Example 3 | 0 | 76 | 85 | 88 | 89 | 92 | 93 |

Conclusion: It was found that composition of example 2 and 3 wherein powdered cellulose has been used provide dissolution of more that 95% as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS. Also in other two media, dissolution was found more than 90%.

| Example/Time | 0 | 5 | 10 | 15 | 20 | 30 | 45 |
|---|---|---|---|---|---|---|---|
| **Media 1** | | | | | | | |
| Gilenya™ | 0 | 89 | 96 | 97 | 98 | 99 | 99 |
| Example 5 | 0 | 83 | 89 | 91 | 92 | 93 | 95 |
| Example 4 | 0 | 57 | 72 | 85 | 88 | 92 | 92 |
| **Media 2** | | | | | | | |
| Gilenya™ | 0 | 72 | 85 | 90 | 93 | 97 | 99 |
| Example 5 | 0 | 64 | 76 | 81 | 84 | 87 | 90 |
| Example 4 | 0 | 38 | 55 | 65 | 70 | 80 | 83 |
| **Media 3** | | | | | | | |
| Gilenya™ | 0 | 81 | 89 | 91 | 92 | 94 | 94 |
| Example 5 | 0 | 54 | 84 | 88 | 92 | 93 | 94 |
| Example 4 | 0 | 25 | 42 | 51 | 58 | 81 | 82 |

Conclusion: It was found that addition of cysteine with dicalcium phosphate in formulation comprising fingolimod resulted in improvement of dissolution profile in all the specified media.

**Degradation profile:**

Formulation blends prepared in example 1-3, example 6, and Gilenya™, were exposed to 80°C for 72 Hours. Degradation profile of the formulations is summarized in table 1.

**Table 1**

| Formulation | Total impurity in % (at 80°C for 72 hrs) |
|---|---|
| Example 1 | Not detected |
| Example 2 | Not detected |
| Example 3 | Not detected |
| Example 6 | Not detected |
| Gilenya™ | 2.06 |

Conclusion: It can be concluded from data presented in table 1 that compositions of example 1, 2 and 3 are more stable than marketed formulation Gilenya™ and subjected to mentioned conditions.

Formulation blends prepared in example 1 to 3 were exposed to 50°C, in closed vials for 1 month. Degradation profile of the formulations is summarized in table 2.

**Table 2**

| Formulation | Total impurity in % |
|---|---|
| Example 1 | 0.06 |
| Example 2 | 0.06 |

| | |
|---|---|
| Example 3 | 0.05 |

Conclusion: It can be concluded from data presented in table 2 that composition of example 1, 2 and 3 are stable even when subjected to 50°C for 1 month.

Flow Rate

To determine flow rate of the powder, Haunser ratio and Compressibility Index of the powder were determined for example 1 and 3. Results are summarized in Table 3

**Table 3**

| Powder | Hausner ratio | Compressibility Index |
|---|---|---|
| Powdered cellulose (80 microns) of example 1 | 1.93 | 48.28 |
| Powdered cellulose (80 microns + 150 microns) of Example 2 | 1.53 | 34.48 |
| Powdered cellulose (80 microns + 150 microns) + stearic acid of Example 3 | 1.50 | 33.33 |

Conclusion: It can be concluded that suitable mixture of one grade of powdered cellulose having average PSD less than 100 microns with another grade of powdered cellulose having average PSD more than 120 microns has better flow rate as compared to only one grade of powdered cellulose.

**Claims:**

1. A solid pharmaceutical composition comprising fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and a lubricant.
2. A solid pharmaceutical composition consisting of fingolimod or pharmaceutically acceptable salt thereof, diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate; and one or more lubricant.
3. The solid pharmaceutical composition according to claim 1 or 2, wherein diluent is powdered cellulose.
4. The solid pharmaceutical composition according to claim 3, wherein powdered cellulose is present in an amount of 51 % to 99.5 % of total composition.
5. The solid pharmaceutical composition according to claim 4, wherein powdered cellulose comprises mixture of (a) powdered cellulose having average particle size of less than 100 microns and (b) powdered cellulose having average particle size of more than 120 microns.
6. The solid pharmaceutical composition according to claim 5, wherein powdered cellulose having average particle size of less than 100 microns and powdered cellulose having average particle size of more than 120 microns are present in ratio of 1: 2, preferably, 1:1.
7. The solid pharmaceutical composition according to claim 6, wherein said composition provides dissolution of more than 95% in 30 minutes as measured using rotating basket method at 100rpm in 500ml of dissolution medium constituted by water with 0.1N HCl and 0.2% SLS.
8. The solid pharmaceutical composition according to claim 1 wherein diluent is selected from dicalcium phosphate and tricalcium phosphate.
9. The solid pharmaceutical composition according to claim 8, wherein composition comprises one or more acidifier.

10. The solid pharmaceutical composition according to claim 9, wherein acidifier is amino acid.
11. The solid pharmaceutical composition according to claim 10, wherein amino acid is selected from glycine and cysteine.
12. The solid pharmaceutical composition according to any of the preceding claims wherein total impurity of the product is less than 2% when subjected to 80 °C for 72 hrs.
13. The solid pharmaceutical composition according to any of the preceding claims, wherein lubricant is selected from magnesium stearate, zinc stearate, calcium stearate, stearic acid and glyceryl behenate.
14. The solid pharmaceutical composition according to claim 13, wherein lubricant is stearic acid.
15. A process of preparation of solid pharmaceutical composition as claimed in any of the preceding claims, wherein the process comprising of

    1. Mixing/blending fingolimod or pharmaceutically acceptable salt thereof and diluent selected from powdered cellulose, dicalcium phosphate and tricalcium phosphate.
    2. Optionally adding one or more acidifier in the mixture of step 1.
    3. Adding a lubricant in the mixture obtained in step 1 or 2.

16. A solid pharmaceutical composition comprising fingolimod or pharmaceutically acceptable salt thereof as herein described with reference to the examples and figures accompanying the specification.

Fig 1

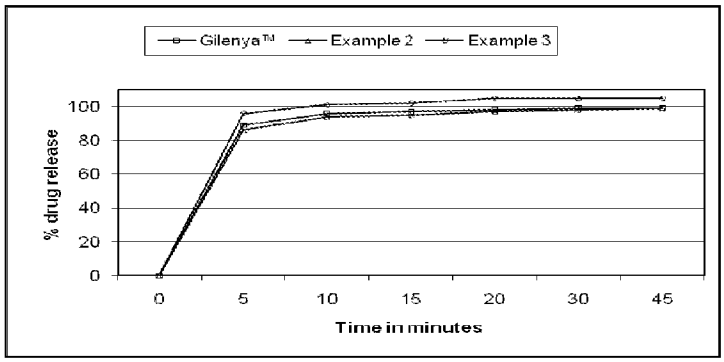



Fig 1a

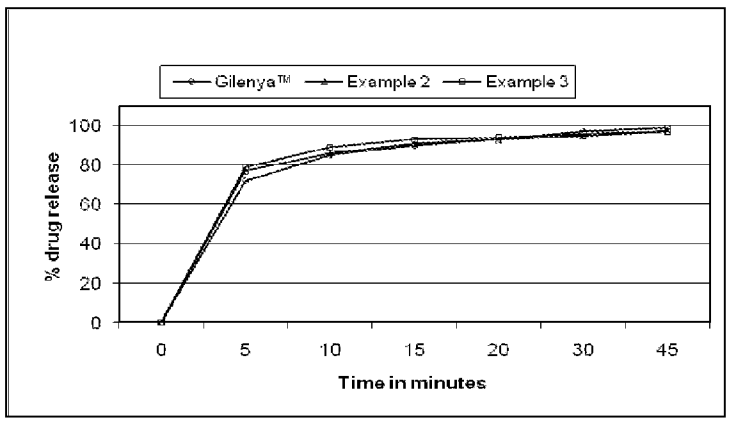



Fig 1b

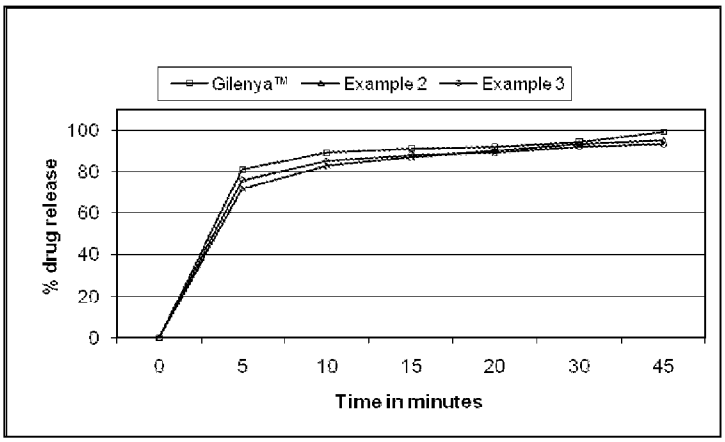



Fig 1c

Fig 2

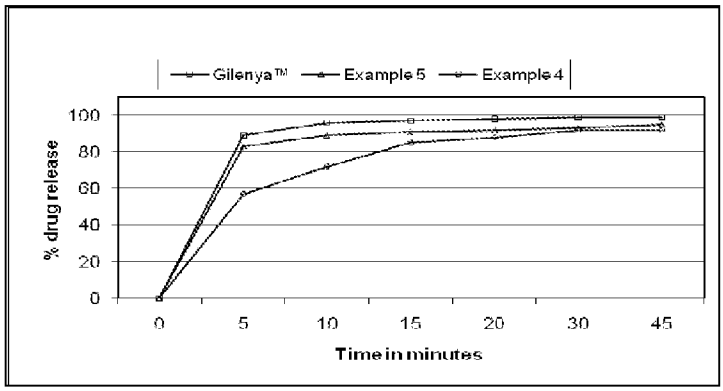



Fig 2a

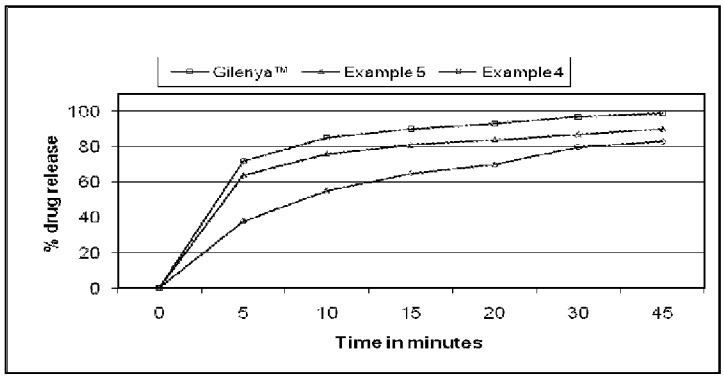



Fig 2b

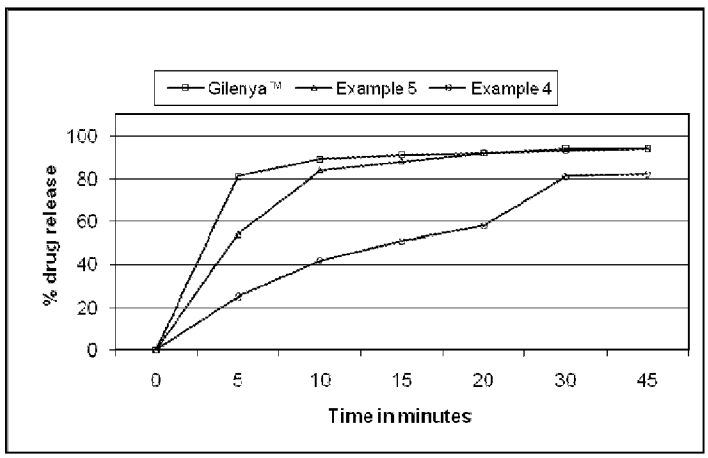



Fig 2c