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Research Article

FORMULATION AND EVALUATION OF FINGOLIMOD CAPSULES

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ABSTRACT

Multiple sclerosis is the most common chronic inflammatory disease of the central nervous system and it is the leading cause of neurological disability in young adults. Fingolimod Hydrochloride is the first oral drug approved by the USFDA. Fingolimod Hydrochloride is available as capsule at the dose of 0.5 mg in the market under the brand name of Gilenya®. The primary aim of the study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of capsules. In the present study five batches of Fingolimod Hydrochloride capsules with the dose of 0.5 mg were formulated and evaluated. Formulation F1, F3, F4 and F5 demonstrated better drug release and the percentage cumulative drug release of innovator and F4 was comparable. The maximum and minimum drug content was found to be 100.50% (F4) and 67.10% (F2) respectively. Stability study of F4 demonstrated no significant changes in appearance, water content, drug content and dissolution profile after each month. Hence, the capsule formulations (F4) of Fingolimod Hydrochloride may be an advantageous alternative for the innovator for the treatment of multiple sclerosis.

Keyword: Fingolimod Hydrochloride, Multiple sclerosis, Pearlitol, Fingolimod capsules

INTRODUCTION

Multiple sclerosis is the most common chronic inflammatory disease of the central nervous system and it is the leading cause of neurological disability in young adults with the prevalence rate of about 2.5 million people worldwide. The latest treatment option for multiple sclerosis is Fingolimod Hydrochloride which is the first oral drug approved by the USFDA. Fingolimod is an immunomodulator which is derived from myriocin, a metabolite isolated from the ascomycete *Isaria sinclairii*, which is a fungus used in traditional Chinese herbal medicine. Chemically, Fingolimod Hydrochloride is 2-amino-2-[2-(4-octylphenyl) ethyl] propane-1, 3-diol hydrochloride with molecular formula $C_{19}H_{33}NO_2$ HCl and chemical structure as shown in Figure 1.[1-3]

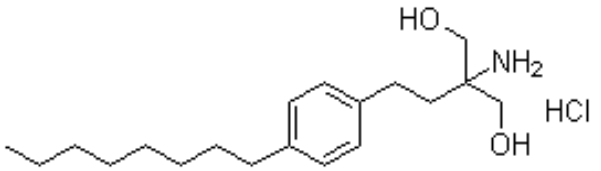

Fig. 1: Chemical structure of Fingolimod Hydrochloride

Fingolimod Hydrochloride is available as capsule at the dose of 0.5 mg in the market under the brand name of Gilenya®. The primary aim of the study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Fingolimod Hydrochloride capsules.

MATERIALS AND METHODS

Fingolimod Hydrochloride, Mannitol, Microcrystalline Cellulose, Magnesium Stearate and all other chemicals used in the study were of analytical grade.

Preformulation studies[4-8]

It is the first step in the rationale development of dosage form. Critical information obtained during preformulation studies can enhance the rapid and successful introduction of new therapeutic entities for humans. Flow property and compatibility study were performed.

Flow property studies

Flow property of pure drug and blend can be determined by angle of repose, compressibility index and hausner ratio.

Angle of repose

A funnel was kept vertically in a stand at a specified height with bottom closed and a paper was placed below on a horizontal surface. Ten grams of sample either API or blend were added to the funnel. The funnel was then opened to release the sample to form a smooth conical heap. Radius and height of the heap was measured. The angle of repose was determined using the formula [Angle of repose (tan θ) = (Height of the heap) / (Radius of the heap)]. Interpretation of flow property of the sample can be done using table 1.

Table1: Interpretation of angle of repose

Angle of Repose	Flow Property
< 25	Excellent
25 - 30	Good
30 - 40	Passable
> 40	Very Poor

Compressibility Index and Hausner Ratio

In a free flowing powder, inter particulate interactions are generally less and greater for poorly flowing powder. Compressibility index and the Hausner ratio measure the propensity of a powder to be compressed and also measures inter particulate interactions. Compressibility index was determined using formula [Compressibility Index = (Tapped Density - Bulk Density)/ (Tapped Density) X 100] and Haussner's ratio was determined using formula [Haussner ratio = (Tapped Density) / (Bulk Density)]. However, bulk density of the sample was determined by pouring a known quantity of sample into a measuring cylinder and measured the volume. Calculate the bulk density using formula [Bulk Density = Mass of the sample / Bulk volume of the sample]. Whereas, tapped density of the sample was determined by tapping the cylinder containing sample from a specific height in a given time. Calculate the tapped density using formula [Tapped Density = Mass of the sample / Tapped volume of the sample]. Interpretation of flow property of the sample was done using table 2.

Preparation of Fingolimod Hydrochloride capsule

Capsules containing 0.5 mg of Fingolimod Hydrochloride were prepared with a total weight of 50 mg by either wet or dry granulation method. Quantity of Fingolimod Hydrochloride and other excipient are listed in table 3.

Table 2: Interpretation of angle of repose Compressibility Index and Hausner Ratio

S.No.	Flow properties	Compressibility Index (%)	Haussner's Ratio
1	Excellent	< 10	1.00 - 1.11
2	Good	11 - 15	1.12 - 1.18
3	Fair	16 - 20	1.19 - 1.25
4	Passable	21 - 25	1.26 - 1.34
5	Poor	26 - 31	1.35 - 1.45
6	Very Poor	32 - 37	1.46 - 1.59
7	Very Very Poor	> 38	> 1.6

Table 3: Optimized Formula

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Fingolimod Hydrochloride	00.56	00.56	00.56	00.56	00.56
Microcrystalline Cellulose	28.94	-	-	-	-
Mannitol (Pearlitol 100 SD)	20.00	14.68	-	48.94	24.47
Mannitol (Pearlitol 200 SD)	-	34.26	48.94	-	24.47
Magnesium Stearate	00.50	00.50	00.50	00.50	00.50
Purified Water	-	-	Q.S	Q.S	Q.S
Total	50.00	50.00	50.00	50.00	50.00

Dry granulation method

Accurately weighed and sieved (#40 mesh) quantity of Fingolimod Hydrochloride (for both F1 and F2) and microcrystalline cellulose (only for F1) were taken in a polybag. Accurately weighed and sieved (#40 mesh) quantity of mannitol [100 SD] (for both F1 and F2) and mannitol [200 SD] (only for F2) were then added to the above blend in polybag which were then mixed uniformly for 5 minutes. Accurately weighed and sieved (#40 mesh) quantity of magnesium stearate was then added to the above blend and lubricated for 2 minutes. About 50 mg of the above final product was then filled into size 3 capsule.

Wet granulation method

Accurately weighed quantity of Fingolimod Hydrochloride (for F3, F4 and F5) was dissolved in sufficient quantity of water to get a clear solution. The above solution was then used to granulate mannitol [100 SD] (for F3 and F4) or mannitol [200 SD] (for F3 and F5) to get a wet mass. The above wet mass was then passed through #12 mesh and dried in oven for 45 minutes. The dried granules were then passed through #18 mesh and then lubricated with magnesium stearate and passed through #40 mesh for 2 min. About 50 mg of the final product was then filled into size 3 capsule.

Evaluation of Capsules

Weight variation test

Prepared capsules were evaluated for weight variation as per official method.

In-vitro dissolution study

The release rate of Fingolimod Hydrochloride from all 5 formulations and innovator was carried out using USP Type I - Paddle. The dissolution test was performed using 500 ml of 0.1N HCl containing 0.2% SLS, at 37±0.5 ^{0}C for 30 minutes. Exactly after 30 minutes sample was withdrawn and analysed by a validated HPLC method. Chromatographic condition for the HPLC analysis is listed in table 4.

Table 4: Chromatographic conditions for HPLC

Parameter	Specification
Column	Develosil C-8-UG-5 (150×4.6mm) 5um
Flow rate	1.5 ml/min
Wavelength	UV- 220 nm
Column Temp	40 ^{0}C
Injection volume	20 µL
Runtime	10 minutes

Drug content estimation

Ten capsules were taken in a 250 ml volumetric flask containing 160 ml of diluents (water and acetonitrile in the ratio of 50:50 v/v) and then sonicate. Centrifuge the solution at 3500 rpm for 10 minutes. The clear supernatant was separated and used for drug content estimation using validated HPLC method. Chromatographic condition for the HPLC analysis is listed in table 4.

Stability studies

The Fingolimod Hydrochloride capsules of F4 were packed in High-density Polyethylene bottles with Child Resistance Caps (CRC) and induction sealed. These bottles were charged for stability study at 25^{0}C /60 RH and 40^{0}C/75% RH. Sampling time was done at initial, 1st, 2nd and 3rd month and evaluated for appearance, water content, in-vitro dissolution and assay.

RESULTS AND DISCUSSION

The present study was undertaken to formulate Fingolimod Hydrochloride 0.5 mg capsules. The study involves preformulation studies, formulation and evaluation of capsules made with the optimized formulation.

Preformulation Studies

Flow properties

Pure drug and prepared blends were subjected to various flow property tests such as Compressibility index, Hausner's ratio, angle of repose and results are tabulated in Table 5. Blend showed improved flow property than its pure drug. The flow property of the Fingolimod Hydrochloride API was enhanced from passable to good flow.

Table 5: Flow property of drug and blend

Formulation	Compressibility index (%)	Hausner's ratio	Angle of repose $^{(0)}$
Drug	25.36	1.30	32.37
F1	13.48	1.14	26.06
F2	14.99	1.17	28.08
F3	13.88	1.14	25.55
F4	13.89	1.14	24.67
F5	13.63	1.14	27.78

Drug-Excipients compatibility studies

Compatibility studies by accelerated stability testing showed that there was no physical change or interaction between drug and selected excipients (Table 6). Based on the physical compatibility results, and the innovator product composition the above excipients were selected for formulation development.

Table 6: Result of Drug Excipients Compatibility Studies

S. No.	Composition Details	Initial	*28 Days	@14 Days
1	Fingolimod	White to off-white	#NCC	NCC
2	Mannitol(Pearlitol 100 SD)	White to off-white	NCC	NCC
3	Mannitol(Pearlitol 200 SD)	White to off-white	NCC	NCC
4	Microcrystalline cellulose (pH 102)	White to off-white	NCC	NCC
5	Magnesium Sterate	White to off-white	NCC	NCC
6	Fingolimod + Mannitol (Pearlitol 100 SD)	White to off-white	NCC	NCC
7	Fingolimod + Mannitol (Pearlitol 200 SD)	White to off-white	NCC	NCC
8	Fingolimod + MCC (pH 102)	White to off-white	NCC	NCC
9	Fingolimod + Magnesium Sterate	White to off-white	NCC	NCC

#NCC = No Characteristic Change; *28 days at 40°C/75%RH; @14 days at 55°C

Evaluation of capsule

Weight variation

Weight variation of prepared capsule was within 10 % of weight variation limit.

***In-vitro* dissolution studies**

Drug release of all 5 formulations and innovator were listed in Table 7. However, F1, F3, F4 and F5 demonstrated better drug release (Figure 2) and the percentage cumulative drug release of innovator and F4 were comparable.

Assay profile of capsule

The maximum drug content among all 5 formulations was found to be 100.50% (F4) and minimum drug content was found to be 67.10% (F2). Results of drug content uniformity test of all formulations are listed in Table 7. HPLC Chromatograms of Fingolimod Hydrochloride is shown in figure 3.

Stability Studies

Stability study of F4 demonstrated no significant changes in physical parameters, water content, drug content and dissolution profile after each month. Results of stability studies are listed in table 8.

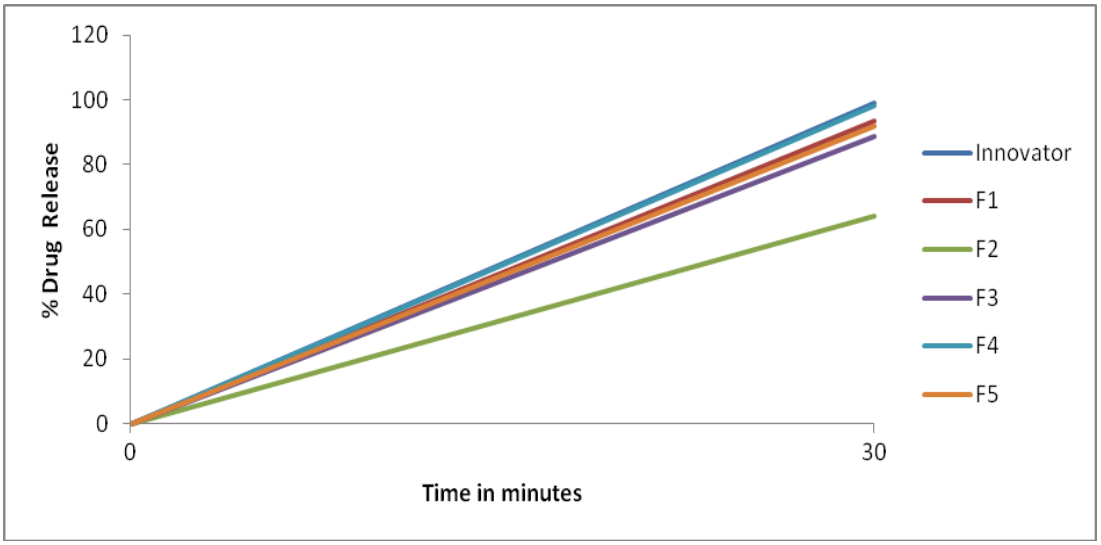

Fig. 2: In-vitro drug release profile

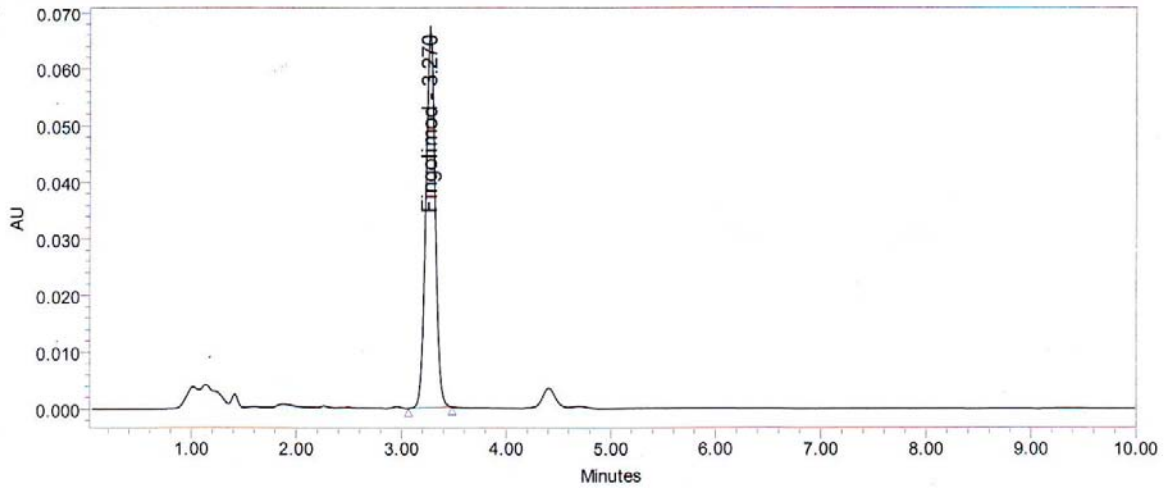

Fig. 3: Chromatograms of Fingolimod Hydrochloride

Table 7: Comparative assay profile from F1-F5

Assay	F1	F2	F3	F4	F5
	97.88	67.1	88.15	100.5	91

Table 8: Results of Stability Studies

Test parameters	Initial Value	40⁰C/75 RH			25⁰C /60 RH		
		1 Month	2 Month	3 Month	1 Month	2 Month	3 Month
Appearance*	White	White	White	White	White	White	White
Water content (%)	0.160	0.151	0.189	0.464	0.179	0.205	0.272
Dissolution (%)	98.1	97.6	97.5	97.0	97.8	97.2	97.0
Assay (%)	100.5	99.4	95.6	95.5	99.4	99.0	98.8

*White color powder filled in size 3 capsules containing yellow color body and green color capsule

CONCLUSION

From the study it was concluded that the Fingolimod Hydrochloride was formulated as capsule by using mannitol (Pearlitol 100 SD) and magnesium stearate showed better dissolution profile which was comparable to the innovator. Moreover, 3 month stability study showed no significant changes in appearance, drug content, water content, dissolution profile and assay. Hence, the capsule formulations (F4) of Fingolimod Hydrochloride may be an advantageous alternative for the innovator for the treatment of multiple sclerosis.

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