CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FABRICATION AND *IN VITRO* EVALUATION OF FINGOLIMOD FAST DISSOLVING TABLETS BY USING SOLID DISPERSION TECHNIQUE

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Article Received: November 2022 **Accepted:** November 2022 **Published:** December 2022

Abstract:
The goal of the current study was to increase the solubility and rate of dissolution of Fingolimod using solid dispersion technology. This was accomplished by using amorphous alloys made from high molecular mass polymers, such as PEG 4000 and PEG 6000, which significantly increased solubility compared to the crystalline form. The procedure of physical mixing and solvent evaporation was used to create solid dispersions. Different drug and carrier ratios, including 1:1, 1:2, 1:3 and 1:4 were utilized in the preparation. Pure drug and solid dispersion phase solubility investigations were conducted. It was discovered that Fingolimod's solubility has risen. The drug content was consistent across all batches of solid dispersions and was found to be in the form of fine, free-flowing powders in all cases. Physical and thermal compatibility between the medication and polymer was validated by compatibility investigations like FTIR and DSC analysis. The results generated with pharmacopeial specifications were confirmed by precompression and after compression parameters. All of the solid dispersions of Fingolimod dissolved quickly, with a dissolution rate that was many times higher than that of the comparable pure drug and that followed zero order kinetics. Dissolution rates in solid dispersion were higher than in physical mixes. PEG 6000, a medication, had the quickest dissolution (1:3). In the current work, solid dispersion techniques were effectively used to generate the fast-dissolving tablet formulation of fingolimod, and the solubility and dissolution profiles of drugs with low water solubility, such fingolimod, have improved. In the future, preclinical and clinical analysis will be used to evaluate the therapeutic effectiveness of formulations.

Key words: *Solid dispersion, Fingolimod, PEG 4000, PEG 6000*

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QR code

Please cite this article in press R. Venu Priya et al, ***Fabrication And In Vitro Evaluation Of Fingolimod Fast Dissolving Tablets By Using Solid Dispersion Technique..,*** *Indo Am. J. P. Sci, 2022; 09(12).*

INTRODUCTION:

Poorly water-soluble drugs are allied to slower rate of absorption from oral route; hence dissolution is the rate limiting step for lipophilic drugs [1]. So, there is a necessity to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs [2, 3]. As oral route is considered most natural, uncomplicated, convenient, safe means of administering drugs due to its immense advantages like flexibility in dosage form design, ease of production and low cost e.g. tablets, capsules. But, nearly one third of drugs in development are poorly water soluble, thus these poorly water-soluble drugs show slow drug absorption leading to inadequate and variable bioavailability and gastro intestinal mucosal toxicity of drugs [4]. As these solid dosage forms are convenient for many drugs but they are challenging to formulate if the active substances have poor dissolution rate or low bioavailability. Hence to overcome such problems various techniques have been introduced to enhance the dissolution rate and solubility of the drug[5]. These techniques include physical modification of lipophilic drugs using several carriers like cyclodextrins, carbohydrates, hydrotropes, dendrimers, polyglycolized glycerides, acids [6] and other methods by the use of superdisintegrants, solid dispersions, surfactants, melt granulation, particle size reduction etc [7].

Alteration of the solid state at the particle or molecular level involves a physical change in the drug and is an attractive option for improving drug solubility. Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy. In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits. This solubility benefit can be further enhanced by preparing solid dispersions (SDs). SDs contributes by slowing devitrification, enhancing wettability and modulating the properties of the solvent. The aim of the present study was to examine the solubility and dissolution properties of SDs of Fingolimod, prepared with polymeric additives like polyethylene glycols (PEG 4000 & 6000) of different grades. Fingolimod was chosen as a model candidate because of its low dissolution rate and solubility-limited bioavailability. [8]

Fingolimod is an immunomodulating medication, mostly used for treating multiple sclerosis. Fingolimod is a sphingosine-1-phosphate receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction. Fingolimod is indicated for the treatment of patients aged 10 and above with relapsing forms of multiple sclerosis, which may include clinically isolated syndrome, relapsing-remitting disease, as well as active secondary progressive disease. Fingolimod-phosphate initially activates lymphocyte $S1P_1$ via high-affinity receptor binding, yet subsequently induces $S1P_1$ down-regulation that prevents lymphocyte egress from lymphoid tissues, thereby reducing autoaggressive lymphocyte infiltration into the central nervous system (CNS). Fingolimod is efficiently absorbed, with an oral bioavailability of >90%, and its absorption is unaffected by dietary intake, therefore it can be taken without regard to meals. Steady-state concentrations of fingolimod are achieved within 1-2 months after initiation when it is administered in a single daily dose. The volume of distribution of fingolimod is about 1200±260 L. It is approximately 86% distributed in the red blood cells (RBC). Fingolimod is extensively metabolized, with biotransformation occurring via three main pathways: (i) reversible phosphorylation to fingolimod phosphate; (ii) hydroxylation and oxidation to yield a series of inactive carboxylic acid metabolites; and (iii) formation of non-polar ceramides. About 81% of an oral dose of fingolimod is excreted in the urine in the form of inactive metabolites. Intact fingolimod and its active metabolite account for less than 2.5% of the dose, and can be found excreted in the feces. The half-life of fingolimod and its active metabolite ranges from 6-9 days. Fingolimod (hydrochloride) is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide, which should be purged with an inert gas. The solubility of fingolimod (hydrochloride) in these solvents is approximately 20 mg/ml. Fingolimod hydrochloride is a BCS class II compound based on its low solubility at physiological pH and the high apparent absolute oral bioavailability (93%) observed in humans. [9]

MATERIALS AND METHODS:

Materials

Fingolimod was acquired from NATCO pharmaceuticals Ltd., Hyderabad, where Fingolimod was purchased as a gift sample. The solubilising agent PEG 4000 and PEG 6000 was purchased from Otto Manufacturers. Lactose, PVP K30, talc, and magnesium stearate were purchased from S.D. Fine Chemicals Pvt. Ltd. in Mumbai, India. Each component was of the highest calibre for a lab. The double distillation method was used in the lab to produce the distilled water that was used in the study.

METHODS

Analytical method for the *in vitro* estimation of Fingolimod in the formulations

A primary stock solution of Fingolimod with a concentration of 1000 µg/ml was made using a HCl buffer with a pH of 1.2. Following the proper dilution, a secondary stock solution with a concentration of 10 µg/ml was made from the initial stock solution using the same HCl buffer with a pH of 1.2. The created secondary stock solution's absorption maxima was found to be at 220 nm, which was picked and used for further investigation after being scanned with a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400 nm to 200 nm. Using the same HCl buffer with a pH of 1.2, the secondary stock solution was first diluted to produce a series of concentrations of 5, 10, 15, 20 and 25 µg/ml. Then, the absorbance at the maximum wavelength of 220 nm was determined. Plotting observed absorbencies against matching concentrations resulted in the calibration curve of pure Fingolimod. [10]

Drug and excipients compatibility studies

Drug and excipients used for the formulation of different batch of Fingolimod Fast dissolving tablets were analysed for any possible physical and chemical interactions through FTIR and DSC studies.

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transforms infrared (FTIR) spectroscopy tests were performed to identify the peaks in the pure API and the excipients used that indicate the existence of a specific functional group. If the functional groups present in the pure drug are replicated in the formulations, the drug and excipients are deemed to be compatible. Both the pure drug and a physical mixture of the drug and all excipients were investigated using FTIR with Fingolimod (optimised formulation). The pellet technique and potassium bromide were employed in the operation (KBr). After the components had been triturated with KBr, a pellet was made by exerting pressure of 100 kg/cm^2 for two minutes. The obtained pellet was investigated in the FTIR 8400S by Shimadzu, Japan. The analysis of the test samples came first, followed by the acquisition of the KBr backdrop. The same steps were performed for the analysis of the drug, each excipient, and the physical mixing of the excipients and the drug. [11]

Differential scanning calorimeter (DSC) investigation:

A Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) apparatus was used for the DSC study. Both a pure drug, Fingolimod, and a mixture (Fingolimod plus excipients), had their DSC thermograms collected. DSC aluminium cells served as the sample container and the reference, respectively. A sample of 2-3 mg was used for analysis. Under nitrogen purge at a rate of 20 ml/min, thermograms were taken over the temperature range of 20°C-200°C at a constant rate of 20°C/min. Figures 3 and 4 show the results. [12]

3.3.2 Fusion-based solid dispersion production

The term "melt method"—which is incorrect unless the starting materials are crystalline—is occasionally used to describe the fusion process. The more inclusive phrase "fusion approach" is therefore adopted. The fusion process was used to make the first solid dispersions made for use in medicinal applications. The polymers polyethylene glycol of two different grades were chosen for the fusing (4000, 6000).

Table 1: Model drug to polymer ratios for fusing

Sl. No	Excipients	Drug: Excipients Ratio
1	PEG 4000	1:1
2		1:2
3		1:3
4		1:4
5	PEG 6000	1:1
6		1:2
7		1:3
8		1:4

Procedure

Model drug and hydrophilic polymers were weighed in accordance with the ratio in trials ranging from 1 to 8 (trials comprising PEG 4000/6000 and the model drug). The metal container was filled with the polymer first, which was then heated to 60 ^{0}C to melt it. To create a homogenous mixture, the model medication was added to the melted bulk and aggressively agitated. The masses were solidified using the same quench cooling technique, and the mass was triturated to minimize the particle size.

The hydrophilic polymers and the model medication were geometrically combined. The mixtures for the geometric mixes were placed in metal containers and together melted at a regulated temperature of 150–160 ^{0}C. To get a homogenous mix, stirring was done continuously. The heating source was turned off for the metal container, and the temperature was allowed to drop to 80 degrees Celsius. A weighed amount of surfactant was added to the half-solidified bulk and agitated to ensure homogeneity. let to cool and solidify by quench cooling. To break up the dense lump, the finished product was pounded in a mortar and pestle. With the use of this micronation of particles, the entire ground mass was passed through sieve number 60 (250 µ) to achieve increased solubility before being physically examined for solubility improvement. [13]

SDS CHARACTERIZATION

A study of physical solubility

First, the probable solubility of the resulting SDs was determined by physically assessing the clarity of the SDs' solutions. Each trial's samples were weighed using the model drug's 50 mg equivalent as a reference. Each sample and 50 mg of the control crystalline model drug were added to a 250 ml volumetric flask. The volumetric flasks received 10 ml aliquots of water, which were added, and were shaken for solubilization. 200 millilitres of water were added, and 30 minutes were spent shaking. allowed to settle, and the liquid supernatant's purity was checked for potential solubility. The optimal ratios were chosen to evaluate analytical solubility. [13]

An analysis of solubility

The solubility investigation was carried out using a custom method created in-house.

Standard preparation

100 cc of methanol were added to 50 mg of the crystalline model substance. To make the concentration 10 ppm, 5 ml was diluted with 250 ml of water.

Sample preparation

A sample (SDs) weighing 50 mg of the model medication was taken.

There was 100 cc of water put to it. After 30 minutes of sonication, the food was cooled to room temperature. Through 0.45 nylon filters, the fluid was filtered. which 5 ml was removed and discarded. To dilute the sample solution to 10 ppm, 250 ml of water were added to 5 ml of sample solution. In a UV spectrophotometer, absorbance measurements for the standard and sample were made at 220nm.

A study of solubility

A subsequent solubility investigation of samples (A) and (B) was conducted to confirm the impact of reduced particle size on these samples' solubility following the reduction of particle size by jet milling. The aforementioned processes were all completed, and solubility was assessed in accordance with accepted testing practices.

Assay

Using a USP-compliant test, the stability of the SDs during the fusion process was determined. In order to assess the effectiveness of the procedure used for SDs, a physical mixture of materials with the same composition as the two SD samples was also submitted for testing. [14]

Formulation of Fingolimod Fast dissolving tablets

Ten distinct formulations (F_1-F_{10}) of fingolimod fast dissolving tablet formulations were created using various ratios of soluble carriers like PEG 4000 and 6000. As a soluble solid dispersion agent, PEG 4000 was employed in different concentrations for formulations F_1 to F_4, PEG 6000 was used in various concentrations for formulations F_5 to F_8, while formulation F_9 to F_{10} combined both carriers. Fingolimod fast dissolving tablets were created using the wet granulation process. Before being used in formulations, all materials were weighed precisely and put through filter #80. Fingolimod, MCC, Mannitol, pregelatinized starch, PEG 4000 and 6000

were just a few of the powders that were triturated and passed through #20 for each composition. Binder utilised was pregelatinized starch. To lower the moisture content and prevent sticking to the sieve, the aggregates created after the addition of the binder were first dried for five to ten minutes. To obtain granules, the aggregates were sent through filter #20. To lower the moisture content of the granules by up to 2-5%, they are dried at 40° C for 20 minutes. Talc and magnesium stearate were utilised as lubricants, and dried granules were combined with the necessary amounts for 2–3 minutes. Prior to compression, the formulations' angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were assessed after lubrication. On a 10-station rotary punching machine (Saimach Pharmaceutical Pvt. Ltd.), using 8 mm concave punches, the evaluated granules were compressed into tablets. Fingolimod, 0.5 mg, is present in each tablet. Table 1 contains the recipes for many formulations, and the same process was used for each formulation. Then, different post-compression parameters were assessed for the generated fast dissolving tablet formulations, including average thickness, weight variation, hardness, friability, drug content study, disintegration, and *in vitro* dissolution experiments. [15, 16]

Table 1: Compositions of different formulations of Fingolimod Fast dissolving tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Drug	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
PEG 4000	0.5	1	1.5	2					0.5	1
PEG 6000	-	-			0.5	1	1.5	2	1	0.5
Mannitol	71	70.5	70	69.5	71	70.5	70	69.5	70	70
MCC	15	15	15	15	15	15	15	15	15	15
Pregelatinized starch	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	100	100	100	100	100	100	100	100	100	100

Evaluation of precompression parameters of dry granules of Fingolimod Fast dissolving tablet formulations

Angle of Repose (θ)

The dry granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where θ was called as angle of repose, h and r were height and radius of the granule heap respectably. According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle greater than 40^0 indicates poor flow. [17]

Bulk density and tapped density

Both the bulk density (BD) and tapped density (TD) of prepared Fingolimod Fast dissolving dry granules of all the formulations were determined using the following formulas. [18]

$$BD = \frac{weight\ of\ the\ dry\ powder}{volume\ of\ the\ packing}$$

$$TD = \frac{weight\ of\ the\ dry\ powder}{tapped\ volume\ of\ the\ packing}$$

Compressibility Index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of granules and the rate at which it packed down. Compressibility index (Carr's index) of prepared Fingolimod Fast dissolving dry granules were calculated by following formula

$$Carr's\ index\ (\%) = \frac{TD-BD}{TD} \times 100$$

According to the specification the Carr's index values "between" 5-15 indicates excellent flow whereas

between 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable whereas between 23-25 indicates poor. "Between" 33-38 indicates very poor and greater than 40 indicates extremely poor. [17]

Hausner's ratio:

The Hausner's ratios of prepared Fingolimod Fast dissolving dry granules were determined by following formula.

$$Hausner's\ ratio\ = \frac{TD}{BD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), whereas greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, glidant need to be added to improves flow. [17]

Evaluation of post-compression parameters of Fingolimod Fast dissolving tablets formulations

Typical thickness

Ten tablets were randomly chosen from each formulation and utilised for thickness measurement. Using digital Vernier callipers (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan), the thickness of each tablet was measured. The results were expressed as the mean values of 10 readings with standard deviations. Tablet thickness should be kept within 5% of the standard value, as per the specification. [18]

Tablet Hardness

Using a Monsanto hardness tester, the hardness of all Fingolimod Fast dissolving tablet formulations was determined (Cad Mach). Ten Fast dissolving tablets with known weights from each formulation were tested for crushing strength, which was measured in kg/cm^2, averaged, and then shown with standard deviation. According to USP requirements, a fast dissolving tablet's hardness value of 3–4 kg is deemed sufficient for mechanical stability. [18]

Friability

Ten tablets from each batch that had previously been weighed were placed in the Roche friabilator (Roche friabilator, Secor India). Tablets were found after a hundred friabilator revolutions. The tablets were then cleaned of dust, and the total weight that remained was noted. This formula was used to determine friability.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

the starting and final weights of the tablets prior to and following the friability test, respectively, were Wi and Wf. Compressible tablets that lose between 0.1% and 0.5% and, at most, 1% of their weight are deemed acceptable. [19]

Weight variation test

The weight variation of each Fingolimod Fast dissolving tablet formulation was assessed in accordance with the USP standard. Using an electronic balance, 20 tablets from each batch were weighed both collectively and individually. Calculations were made on the average weight and % variance of each tablet. The USP standard states that the weight variation tolerance limit for uncoated tablets with an average weight of 130 mg or less is 10%, 7.5% for tablets with an average weight between 130 and 324 mg, and 5% for tablets with an average weight of more than 324 mg. The weight of the tablet must not differ from the average weight by more than two tablets' weight, and no tablet may deviate by more than 15%. [19]

Content uniformity

Twenty tablets were ingested and triturated into powder to test the content homogeneity of all formulations. One tablet's worth of powder was taken, diluted in 100 ml of HCl buffer with a pH of 1.2, and heated at 37^{0}C for 15 to 20 minutes while stirring continuously. The Fingolimod concentration was determined using a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 220 nm after the solution had been cooled, filtered, and appropriately diluted. The average medication content of each formulation was computed after each measurement was made in triplicate. [20]

Wetting time and water absorption ratio

The disintegrating process of the tablet formulation is reflected in the wetting time. The disintegration rate increases as wetting time decreases. Twice-folded tissue paper was placed in a petri dish with an internal diameter of 6.5 cm, 10 ml of phosphate buffer pH 6.8, and 0.1% w/v of methylene blue for the purpose of determining the wetting time. Fingolimod Fast dissolving tablet samples from each formulation were meticulously arranged on the tissue paper in the petri plate. Wetting time was measured as the length of time it took for the dye to reach the tablet's top surface. The standard deviations were also calculated, and measurements were done in triplicate. [21]

The weight (W_b) of the tablet before it is placed on the Petri dish, followed by the observation of the wetting period, can be used to determine the water absorption ratio (R). The wet tablet was taken out and weighed again (Wa). The following equation was used to calculate the water absorption ratio.

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

***In vitro* disintegration time (D_t)**

The USP specifies 2 minutes as the acceptable time limit for tablet disintegration meeting official criteria, whereas 2 minutes for Fast dissolving dosage form when using the disintegration apparatus for oral tablets without the covering plastic discs. The experiment was conducted using a tablet disintegration device (model EI D-16, Electrolab, Mumbai, India). A modified disintegration method was used to conduct an *in vitro* disintegration test on a disintegration tester that was kept at 37°C ± 0.5°C in HCl buffer pH 1.2 (n = 6). The time it took for each tablet to totally break down into smaller particles was observed while the tablets were stored in the basket. [22]

***In vitro* drug release (dissolution) study**

Utilizing an eight station USP Dissolution Rate Test Apparatus Type-II (LABINDIA DS 8000, Mumbai, India.), the *in vitro* dissolution investigation was carried out for all of the formulations. The dissolution medium, a total volume of 900 ml of HCl buffer pH 1.2, was kept at 37°C ± 0.5°C at 50 rpm. At regular intervals, 5ml of aliquots were removed and replaced with an equivalent volume of new dissolving medium. Samples were taken every 5 minutes and then filtered using Whatmann filter paper. Fingolimod released from fast dissolving tablets was determined by spectrophotometric analysis of samples at 220 nm. [23, 24]

Characterization of the *in vitro* drug release profile

The rate of release of Fingolimod from prepared Fast dissolving tablets were analysed by fitting the dissolution data into following exponential equations.

Zero order release equation is calculated by following equation.

$$Q = K_0 \, t$$

Where Q is the amount of drug released at time t and K_0 is the zero-order release rate constant.

The first order equation is calculated by following equation.

$$\log(100 - Q) = log100 - K_1 \, t$$

Where, K_1 is the first order release rate constant. [25, 26]

Stability studies of best formulation

The short-term stability studies of best formulation of Fingolimod Fast dissolving tablet were carried out according to ICH guidelines. The best formulation was subjected to accelerated stress condition at 40 °C ± 2 °C/ 75% ± 5% RH for 90 days. After that period the product was evaluated for friability, hardness, weight variation, thickness, drug content and *in vitro* drug release study. [27, 28]

RESULTS AND DISCUSSION:

Drug-Excipient Compatibility studies by FTIR:

According to the results of the FTIR research, the peaks in the Fingolimod spectrum are caused by CH stretching (Alkane) at 2918.76 cm^{-1}, C=C (Aromatic) at 1600.47 cm^{-1}, C-C (Loop) at 1471.28 cm^{-1}, N-H (Stretch) at 3259.60 cm^{-1}, C-N vibration at 1339.43 cm^{-1}, C-O streching at 1240.48 cm^{-1} and Broad OH (streching) at 3259.60 cm^{-1}. These values complied with the values that had been reported. The CH stretching (Alkane) at 2919.16 cm^{-1}, C=C (Aromatic) at 1647.74 cm^{-1}, C-C (Loop) at 1472.52 cm^{-1}, N-H (Stretch) at 3261.05 cm^{-1}, C-N vibration at 1339.15 cm^{-1}, C-O streching at 1195.63 cm^{-1} and Broad OH (streching) at 3261.05 cm^{-1} exhibit peaks in the FTIR spectra of the optimised formulation (Fingolimod with all the Excipients). Therefore, it is clear from the fact that all of the characteristic peaks that were present in the spectra of pure drugs were almost exactly replicated in the same region in the spectra of the best formulations of Fingolimod Fast dissolving tablet that there is no meaningful interaction between the drugs and the excipients. **Figures 1 and 2** display the FTIR spectra of the medication Fingolimod in its purest form and the finest formulations.

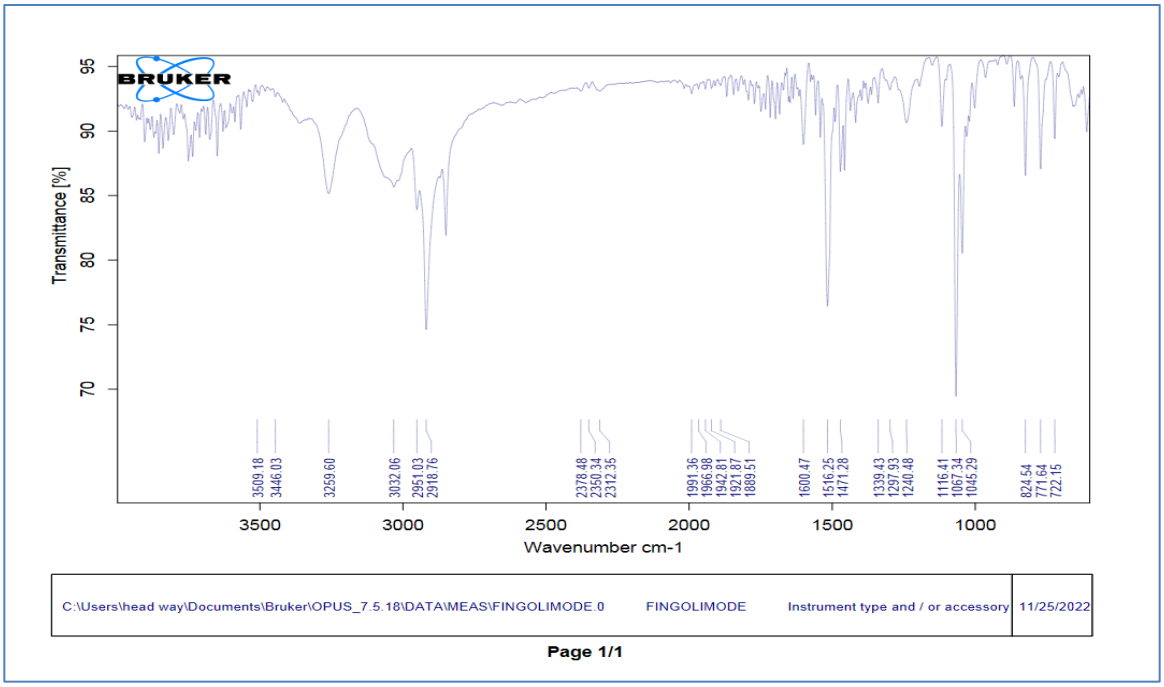

Fig. 1: FT-IR spectra of Fingolimod Pure drug

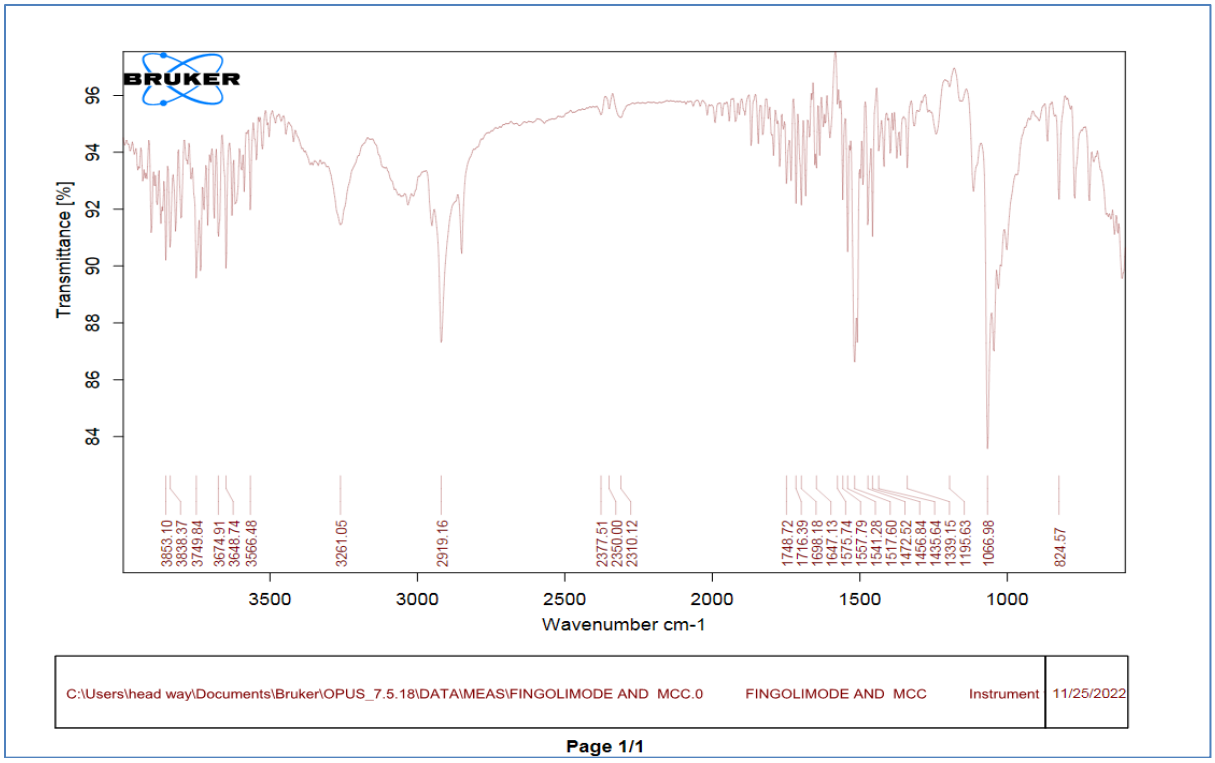

Fig. 2: FT-IR spectra of physical mixture of Fingolimod with excipients

DSC Studies:

To rule out any potential drug and polymer thermal interaction, a DSC thermogram of fingolimod and a physical mixture of fingolimod with excipients utilised in the formulation of fast-dissolving tablets were obtained. This study compared the endothermic peaks that appeared in the physical mixture of the drug and excipients used to create fast-dissolving

tablets with the pure drug. It was noted that the endothermic peak for Fingolimod appeared at 104.5°C and in the physical mixture at 104.2°C. Due to excipients like PEG 4000 and other excipients like mannitol and MCC, respectively, the DSC thermogram of the physical mixture of fingolimod showed the presence of an endothermic peak at 65.4 ºC and 151.2 ºC. According to the aforementioned DSC investigations, the formulation is thermodynamically stable because it required approximately the same amount of heat as the pure medication and the inclusion of various excipients in the drug didn't result in any thermal changes. Additionally, no endothermic to exothermic peak shifting was observed. Figures 3 and 4 display the DSC thermograms for fingolimod and the physical mixture of fingolimod and excipients used to create fast-dissolving tablets.

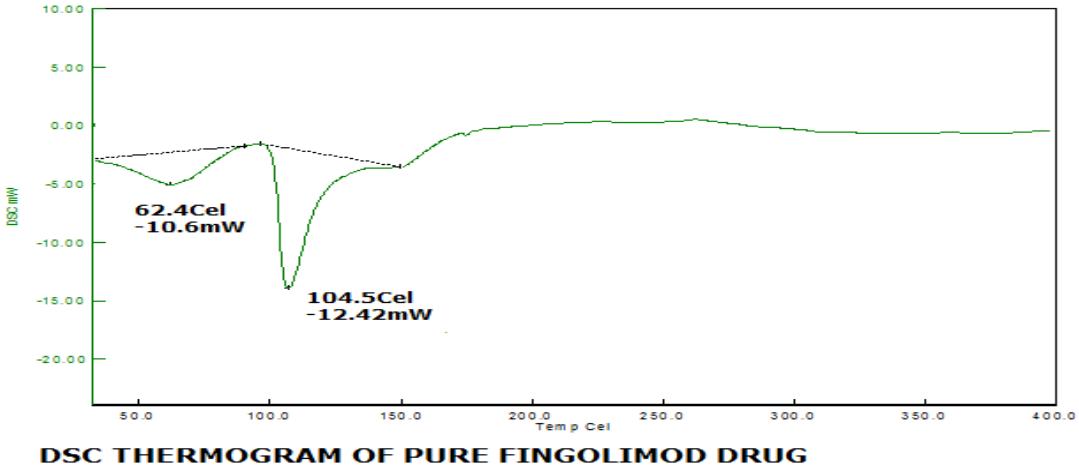

Fig. 3: DSC thermogram of Fingolimod pure drug

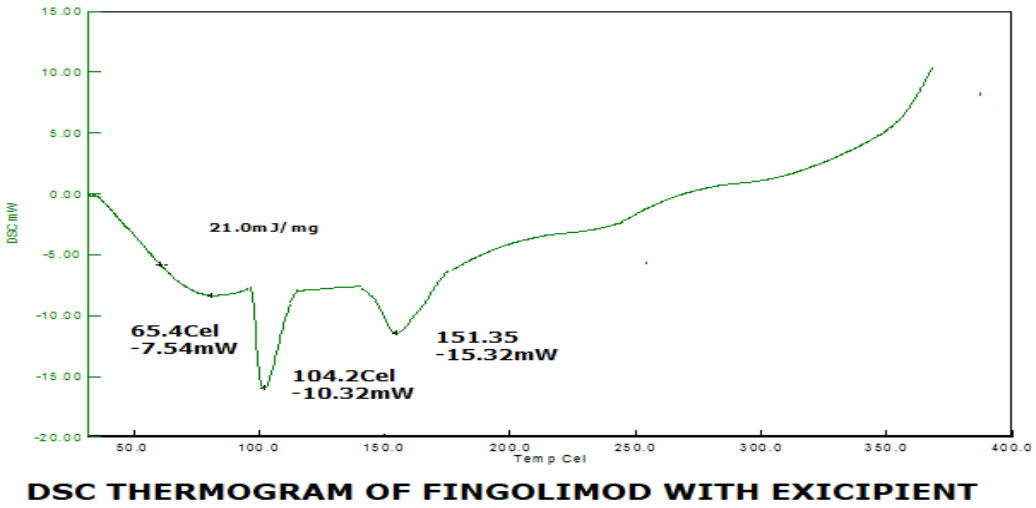

Fig. 4: DSC Thermogram of optimized Fingolimod Fast dissolving tablets

Characterizing The Resultant SDs From The Fusion Method
A study of physical solubility

Table 2: Qualitative solubility of selected SDs

Sl.no	Excipients	Drug: Excipients Ratio	Remarks
1	PEG 4000	1:1	1:3 ratio showed increase in solubility
2		1:2	
3		1:3	
4		1: 4	
5	PEG 6000	1:1	1:3 ratio showed increase in solubility
6		1:2	
7		1:3	
8		1:4	

The combination of these ratios that produced the best results during physical observation was submitted for quantitative estimation.

A quantitative assessment of solubility

The table contains the results of a solubility study performed on a subset of samples using an internal process.

Table 3: Selected sample solubility research results

Sl. No	Batch	Solubility (mg/ml)
1	Model drug	0.015
2	Model drug + PEG (4000) (1:3)	0.035
3	Model drug + PEG (6000) (1:3)	0.054

Precompression parameters

The values for the angle of repose were discovered to be between 20.14±0.35 to 22.41±0.32. The results for LBD and TBD are 0.396±0.002 to 0.534±0.002 and 0.454±0.003 to 0.598±0.002, respectively. Carr's index and Hausner's ratio are calculated using these numbers. The values of the Carr's index were discovered to be between 9.47% and 14.53%. This shows that granules have excellent flow characteristics. The granules had the necessary flow quality for compression, as shown by the Hausner's ratio values, which were determined to be in the range of 1.09-1.16. Between 98.45±0.79-101.4±0.85% of fingolimod was determined to have a consistent drug content percentage, which was within acceptable bounds. Wet granulation is a common and more advantageous process for creating the tablet granules than other ones. An accumulation of separate particles linked together by bonds with a finite strength is referred to as a granule. In a heterogeneous formulation, physical characteristics of the granules, such as their surface area, shape, hardness, and size, can have a considerable impact on the rate of drug dissolution and, consequently, their total bioavailability. For all formulations, the angle of repose of the granules after mixing with magnesium stearate and talc was less than 25º, indicating excellent granule flow qualities. For all formulations, the compressibility index is likewise under 16%, which points to the granules' good flow characteristics. Granules with formulas F_1 and F_{10} have larger bulk densities than those with other formulations, which suggests that the formulations include more particles. In table 4, all pre-compression parameter values that were obtained for all formulations are listed.

Table 4: Evaluation of precompression parameters of Fingolimod Fast dissolving dry granules

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	Carr's index (%)	Hausner's ratio	Drug Content (%)
F_1	0.406±0.003	0.475±0.003	22.21±0.22	14.53	1.16	99.05±0.78
F_2	0.396±0.002	0.454±0.003	21.30±0.21	12.77	1.15	99.35±0.66
F_3	0.487±0.003	0.538±0.002	22.41±0.32	9.47	1.10	98.51±0.97
F_4	0.534±0.002	0.598±0.002	21.32±0.22	10.70	1.12	99.52±0.43
F_5	0.473±0.003	0.529±0.001	20.14±0.35	10.58	1.12	99.70±0.88
F_6	0.479±0.002	0.521±0.003	21.32±0.22	08.06	1.09	98.45±0.79
F_7	0.487±0.002	0.543±0.002	22.14±0.13	10.31	1.11	99.28±0.85
F_8	0.465±0.002	0.512±0.003	21.23±0.32	09.17	1.10	99.50±0.97
F_9	0.494±0.003	0.547±0.002	22.25±0.23	09.69	1.11	101.4±0.85
F_{10}	0.463±0.002	0.524±0.001	21.26±0.22	13.55	1.13	99.35±0.74

All values are expressed as mean± SD; (n=3)

Post-compression parameters

Each formulation batch's tablet morphology was revealed by microscopic testing to be homogeneous, white, circular, and free of fractures. There were no signs of the typical tablet abnormalities such capping, picking, or chipping. The range of tablet thicknesses was determined to be 3.21±0.26-3.81±0.28mm. The tablets' diameter ranges from 3.02 to 3.15 mm. All of the tablets had consistent weights with small standard deviation values. The range of hardness that can be measured is 2-4 Kg/cm2. Tablet hardness increased as compression force and super-disintegrant usage were both reduced. This guarantees all batches will have good handling characteristics. In all formulations, the percentage of friability is less than 1%, ensuring that the tablets were mechanically stable. The formulations' fast-dissolving tablet disintegration times, which vary from 1 to 3 minutes, are within acceptable bounds. All of the formulations' wetting times were determined to be between 87 and 132 seconds. The formulation F_8 had the lowest wetting values and the formulation F_1 had the highest wetting values. In table 5, the post compression values for all formulations were displayed.

Table 5: Evaluation of Post-compression parameters of Fingolimod Fast dissolving tablets

F. No.	Average hardness (kg/cm^2)	Average Weight Variation (%)	Average friability (% w/w)	Average thickness (mm)	Disintegration time (sec)	Wetting time (sec)
F_1	3.69±0.25	3.21±0.24	0.48±0.23	3.35±0.32	168	132
F_2	3.48±0.32	4.32±0.35	0.55±0.15	3.25±0.41	152	115
F_3	3.26±0.40	3.44±0.52	0.71±0.24	3.44±0.30	145	103
F_4	2.18±0.34	3.32±0.41	0.74±0.25	3.62±0.31	121	92
F_5	3.75±0.16	3.30±0.37	0.56±0.22	3.81±0.28	165	128
F_6	3.51±0.36	3.36±0.37	0.65±0.31	3.40±0.25	154	109
F_7	2.62±0.22	3.51±0.24	0.72±0.35	3.21±0.26	138	101
F_8	2.29±0.36	3.53±0.21	0.78±0.34	3.34±0.21	101	85
F_9	3.63±0.42	3.72±0.41	0.67±0.28	3.52±0.45	108	98
F_{10}	3.05±0.51	3.25±0.35	0.65±0.21	3.67±0.32	104	87

All values are expressed as average± SD; (n=3)

Using a USP type-II paddle type dissolution device, the in vitro drug release properties were investigated for a duration of 25 to 30 minutes in HCl buffer pH 1.2 dissolution media. Increasing the carrier concentration enhanced the rate of dissolution, which revealed an ideal dissolution profile at a drug:polymer ratio of 1:3, but above 3% as the hardness decreased, it was thought to be the ideal concentration. When both carrier grades (PEG 4000 & 6000) are combined at a total concentration of 3%, the dissolving profile is improved and the medication is released virtually completely after 25 minutes. Formulation F_9 releases 99.86% of the medication within 25 minutes at a carrier (PEG 4000 & 6000) concentration of 3% (1% PEG 4000 and 2% PEG 6000). Mannitol and MCC function well together as diluents since they are both better hydrophilic diluents, and this combination was used in all of the formulations.

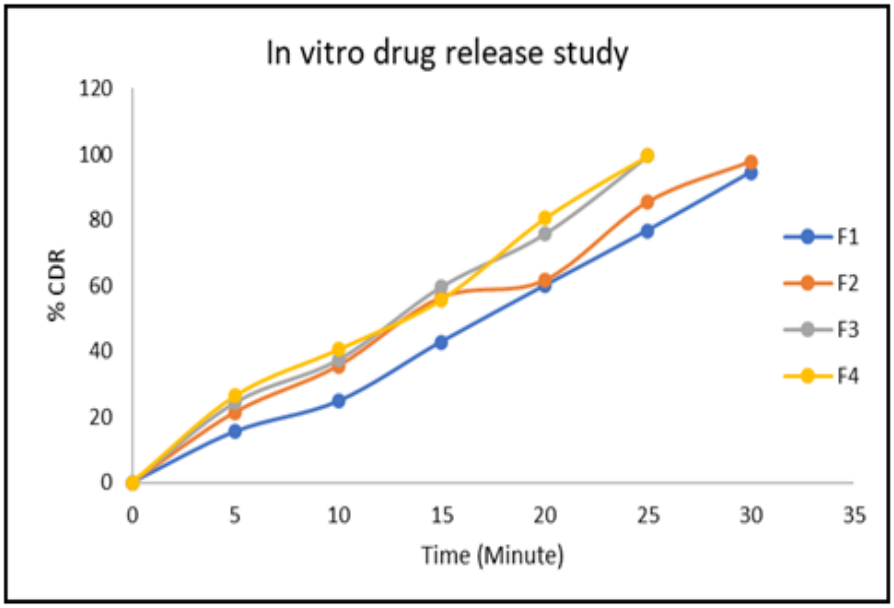

Fig. 5: *In vitro* dissolution data for formulations (F_1-F_4) by using PEG 4000 Polymer.

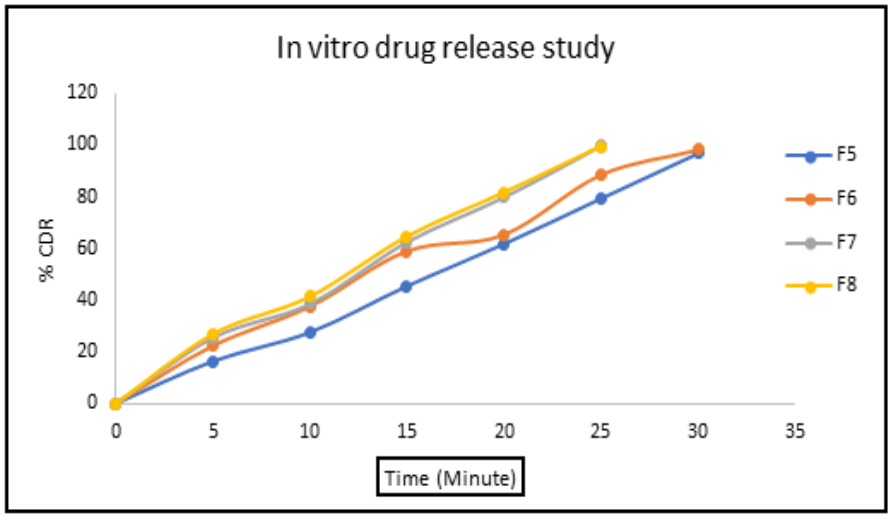

Fig. 6: *In vitro* dissolution data for formulations (F_5-F_8) by using PEG 6000 Polymer.

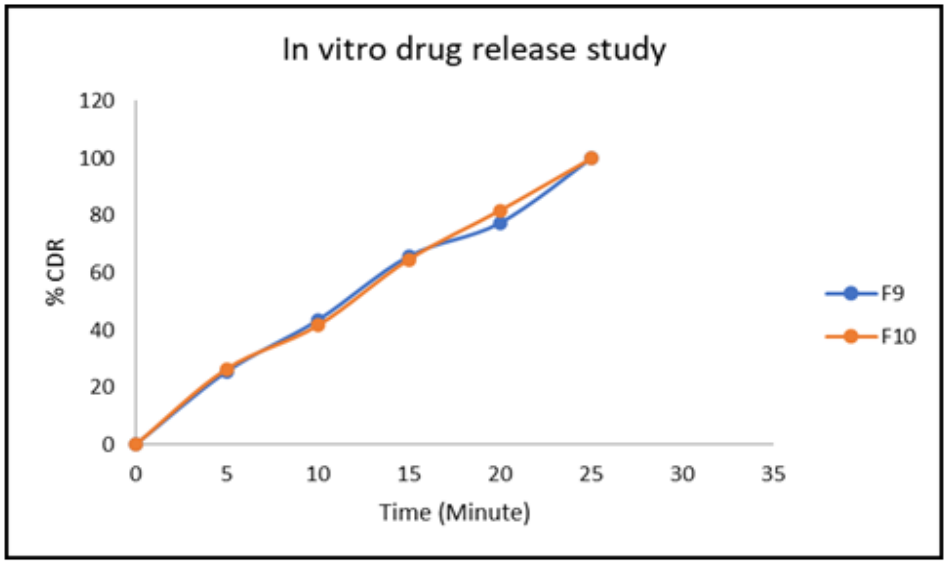

Fig 7: *In vitro* dissolution data for formulations (F_9-F_{10}) by using both PEG 4000 & 6000 Polymer.

The optimised formulation F_7's *in vitro* dissolution study findings were put to the test for several kinetic release investigations, including zero order and first order kinetic models. The results' regression values were examined. The best formulation F_7 with zero order and first order kinetic model underwent *in vitro* drug release kinetic investigations. Because it has the highest R^2 value, it was determined from the R^2 value that the *in vitro* release kinetics model follows zero order kinetics.

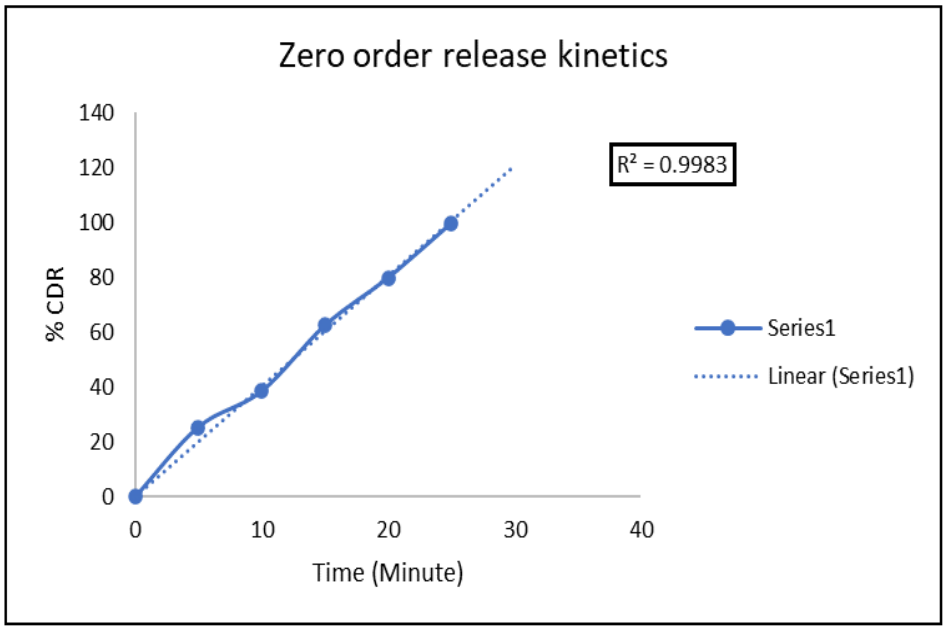

Fig. 8: Zero order release kinetic study of best formulation

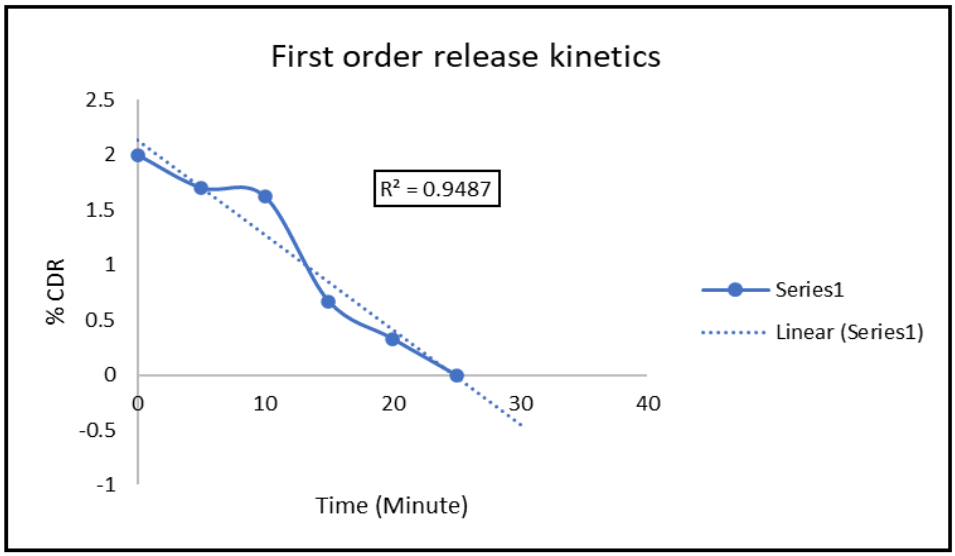

Fig. 9: First order release kinetic study of best formulation

Different physical characteristics of tablets were compared, including their friability, hardness, weight fluctuation, thickness, drug content, in vitro release research of the best fresh formulation (F_7), and investigation of their accelerated stability. The test satisfies the stability requirements. It was found that there has been very little change to the physical properties and *in vitro* release of the best tablet. The comparative physicochemical properties at different interval of time are presented in **table 6** and comparative release profile has been represented in **figure 10.**

Table 6: Comparative physicochemical properties of F_7 at accelerated conditions (40 ºC ± 2 ºC/ 75% ± 5% RH)

Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
Physical appearance	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
Weight variation	3.51±0.24	3.64±0.12	3.74±0.42	3.82±0.65
Hardness	2.62±0.22	2.52±0.31	2.45±0.16	2.36±0.34
Friability	0.72±0.35	0.74±0.01	0.76±0.04	0.80±0.05
Wetting time (Sec)	101±0.45	106±0.28	110±0.42	115±0.55
Drug content	99.28±0.85	98.34±1.16	96.39±1.05	95.29±1.42
D_t (Sec)	138±2.25	142±2.65	148±1.52	154±2.24

All values are expressed as mean± SD; (n=3)

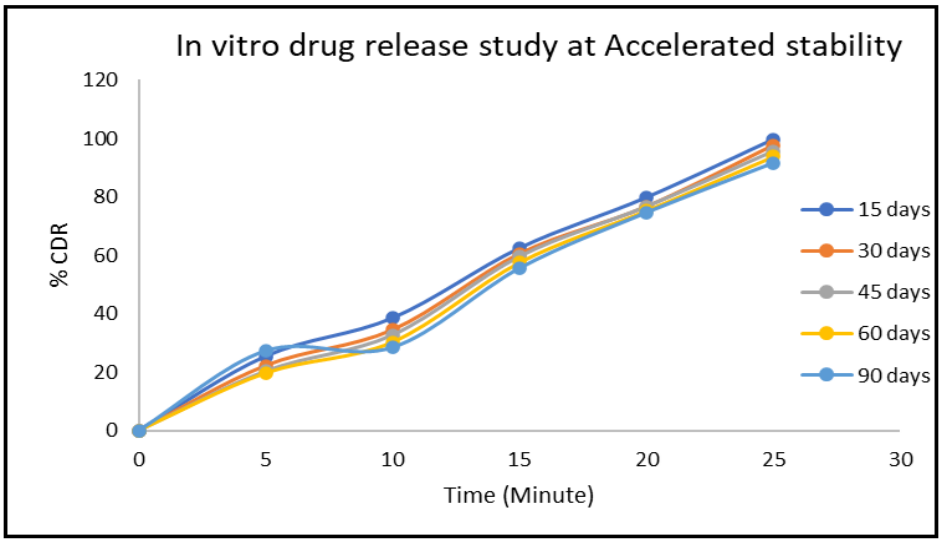

Fig. 10: *In vitro* release study of best formulation (F_7) at stressed condition

CONCLUSION:

The goal of the current study was to use the solid dispersion approach to increase the dissolution rates of the poorly soluble medication Fingolimod. A realistic way to further improve the solubility benefit attained by amorphous systems is by solid dispersion. The formulation of solid solutions or dispersions of amorphous Fingolimod into a matrix for rapidly dissolving tablets using Fingolimod as a model candidate. The solubility of the amorphous alloys produced utilizing high molecular mass polymers like PEG 4000 and PEG 6000 was significantly improved compared to the crystalline version. Physical and thermal compatibility between the medication and polymer was validated by compatibility investigations like FTIR and DSC analyses. The results generated with pharmacopeial specifications were confirmed by precompression and after compression parameters. The increase in drug wettability may have contributed to the higher dissolving rates of physical combinations than those of pure drugs. Dissolution rates in solid dispersion were higher than in physical mixes. PEG 6000, a medication, had the quickest dissolution (1:3). There was no further improvement in the drug's solubility and dissolution profile after increasing the concentration of soluble carriers like PEG 4000 and PEG 6000, and utilizing both grades of PEG had no appreciable impact either. The optimal formulation was discovered to follow zero order kinetics in the kinetic investigation of drug release profile. The field of amorphous medicines has a lot of potential. It is conceivable to commercially employ these molecularly disordered systems in pharmaceuticals by having a complete grasp of the relationship between the glassy behavior and product performance, as well as a thorough comprehension of the thermodynamic and kinetic properties. Solid dispersion technology holds up the tremendous promise of accelerating the drug release profile of weakly water-soluble medicines, despite challenges like scale-up and manufacturing expense must be overcome. The fast-dissolving tablet formulation of Fingolimod was thus successfully created in the current study using solid dispersion techniques, and the solubility and dissolution characteristics of drugs like fingolimod that are weakly water-soluble have improved. In the future, preclinical and clinical analyses will be used to evaluate the therapeutic effectiveness of formulations.

ACKNOWLEDGMENT

The Hyderabad-based NATCO drugs Ltd., is grateful to the authors for giving free samples of medication and superdisintegrant so they could conduct their research. The chairman and principal of the Anwarul Uloom College of Pharmacy in Hyderabad, Telengana, are also acknowledged by the authors for granting permission to conduct the research.

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