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FORMULATION AND EVALUATION OF LEFLUNOMIDE SOLID DISPERSION

Alladi Saritha, Neerati Charan

Corresponding Author: *Dr. Alladi Saritha,Head, dept of pharmaceutics, SSJ College of Pharmacy Hyderabad*

ABSTRACT

In the present study Leflunomide solid dispersions were formulated. Leflunomide was mixed with variousproportions of excipients showed no colour change at the end of two months, proving nodrug-excipient interactions. The precompression blend of Leflunomide soild dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicating good to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, theprepared solid dispersions were compressed into tablets by using rotary tablet punching machine, and 8 mm punch, with the hardness of 4.5kg /cm 2 .The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.25showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation.

KEYWORDS: *Leflunomide, solid dispersions ,PEG 4000,PEG 6000.According to the Biopharmaceutical Classification System (BCS)*

INTRODUCTION

A poorly soluble drug represents a problem for their bioavailability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract (GIT).Solubility behavior of a drug is one of the key factor of its oral bioavailability (1).

When the solid dispersion exposed to aqueous media the carrier can be dissolves the solid dispersion is exposed to aqueous media,the carrier will dissolves and the drug releases as fine colloidal particles in the media. The resulting enhanced surface area shows higher dissolution rate and bioavailability of poorly water soluble drugs. In solid dispersion drug dissolves immediately to saturate the gastrointestinal tract (GIT) fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron to nano size (2,3).

In solid dispersions(SD's) drugs are presented as supersaturated solutions after system dissolution; if drugs are precipitate ,it is as a metastable polymorphic form with higher solubility than the most stable crystal form. (4,5)For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is dictated by the difference in melting temperature between the drug and the carrier,for drugs with high crystal energy shows a higher amorphous compositions can be obtained by choosing of carriers, which show specific interactions with them (6,7) .

MATERIALS

Leflunomide was received as a gift sample from Aurobindo Pharmaceuticals Pvt ltd, Hyderabad. PEG different grade, aerosil, Magnesium stearate were procured from SD fine chemiclas.These all polymers are used in different ratios for different formulations. Isopropyl alcohol is used as solvent were obtained from sigma Aldrich pvt ltd.

EXPERIMENTAL

Formulation Development

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Leflunomide dose was taken as 20mg.Water soluble polymers such as PEG 4000 and PEG 6000 were selected as carriers. Drug and polymers were taken in different ratios stated in the formulation chart (Table 2). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dipersions were mixed with required quantities of diluent, lubricant and glidant (8,9). The blend was evaluated for precompression parameters.

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Table 2 : Formulation table showing various compositions

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	20	20	20	20	20	20	20	20	20
PEG 4000	10	20	30	40					20
PEG 6000					10	20	30	40	20
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Aerosil	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3

The tablets were prepared by using 8 mm flat surfaced punch. The hardness of the tablets was maintained as 4.5 kg/cm^2.

Evaluation of Tablets

Pre compression parameters

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone.

2. Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula. [56]

Bulk density = M/V_0

M = Powder mass

V_0 = apparent unstirred volume

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula. [57]

Tapped density=M/V_f

M =weight of sample power taken

V_f =tapped volume

4. Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100

5. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation. [58]

$H = \rho T / \rho B$

Where ρT = tapped density, ρB = bulk density

Post Compression Parameters

a) Thickness

The thicknes of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed . The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate

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frm the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.
Percentage friability was calculated using the following equation.

$$\text{Friability} = ([w_O - w] / w_O) \times 100$$

Where; w_O = weight of the tablet at time zero before revolution.
w = weight of the tablet after 100 revolutions.

d) Assay

The content of drug in five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in 0.1 N HCl by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 284 nm using UV sectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Leflunomide tablets

Drug release from Leflunomide tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 7.4 medium as the dissolution medium of quantity 900ml. The whole study is being carried out at a temperature of 37^0 C and at a speed of 50rpm.

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 20 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

Evaluation

Characterization Of Precompression Blend: The precompression blend of Etodalascsoilddispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Table6 . Physical properties of precompression blend

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10°	0.53±0.01	0.59±0.01	9.43±0.12	1.09±0.02
F2	25.43°	0.54±0.03	0.60±0.02	9.40±0.13	1.10±0.01
F3	25.41°	0.54±0.02	0.58±0.03	10.01±0.19	1.13±0.06
F4	26.40°	0.51±0.01	0.61±0.06	10.11±0.02	1.16±0.01
F5	27.12°	0.58±0.03	0.63±0.03	10.34±0.13	1.17±0.03
F6	25.31°	0.59±0.03	0.64±0.04	10.12±0.34	1.11±0.06
F7	26.11°	0.56±0.01	0.63±0.01	9.93±0.11	1.13±0.03
F8	26.15°	0.53±0.03	0.58±0.03	10.13±0.02	1.12±0.01
F9	26.10°	0.54±0.01	0.61±0.03	10.20±0.13	1.13±0.03

All the values represent mean ± Standard deviation (SD), n=3

Evaluation of Tablets

Physical Evaluation of Leflunomide solid dipersion tablets: The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 7.All the tablets of different batches complied with the official requirement of

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weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.6 to 5 kg/cm^2 and the friability values were less than 0.561% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.71-4.91cm. All the formulations satisfied the content of the drug as they contained 98-100% of Leflunomide and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table7 .Physical Evaluation of Leflunomide tablets

Formulation code	Weight variation (mg)	Thickness (cm)	Diameter	Hardness (Kg/cm^2)	Friability (%)	Content uniformity(%)
F1	103±1	4.76±0.01	8.12±0.01	4.5±0.7	0.420	99±0.12
F2	104±2	4.74±0.04	8.14±0.02	4.2±0.5	0.341	99±0.3
F3	101±1	4.71±0.01	8.01±0.01	4.6±0.6	0.363	100±0.1
F4	104±2	4.80±0.06	8.03±0.03	4.8±0.5	0.561	100±0.3
F5	105±3	4.81±0.04	8.04±0.04	4.8±0.4	0.482	99±0.6
F6	104±1	4.74±0.05	8.09±0.05	4.4±0.6	0.513	99±0.4
F7	105±1	4.76±0.03	8.11±0.03	5 ± 0.1	0.412	98±0.9
F8	104±2	4.71±0.04	8.09±0.06	4.6±0.2	0.432	99±0.1
F9	108±3	4.73±0.03	8.03±0.02	4.5±0.3	0.512	100±0.1

In Vitro Release Studies

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 7.4 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hrs and analysed after appropriate dilution by using UV Spectrophotometer at 235nm.

Table8 :Invitro dissolution data for formulations F1 – F4 by using PEG 4000 Polymer.

Time(MIN)	% Drug release			
	F1	F2	F3	F4
0	0	0	0	0
5	26.73	16.73	12.56	7.73
10	31.06	20.4	16.57	11.56
20	44.9	25.9	18.9	16.56
30	57.06	35.56	27.73	18.9
40	75.56	44.9	42.4	22.73
50	94.9	54.4	47.9	36.06
60		79.9	66.56	48.4

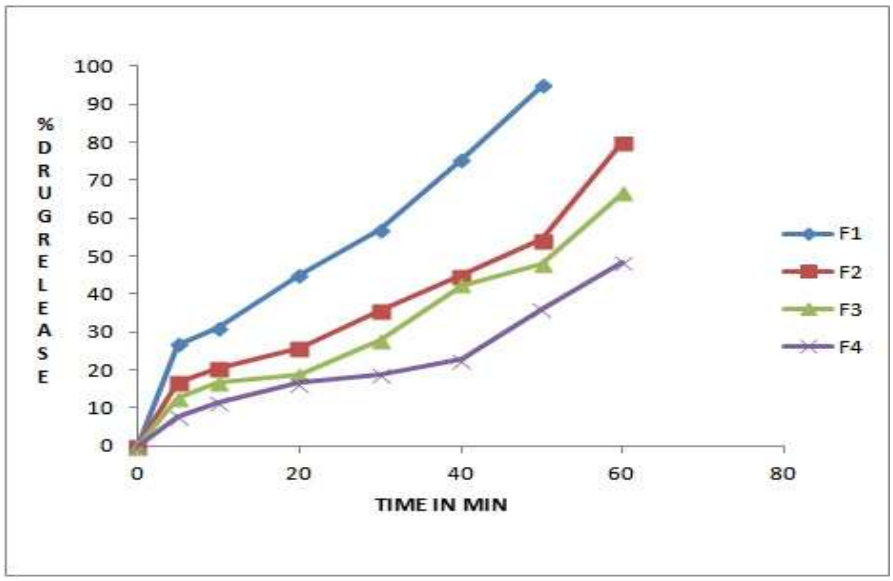

Fig1 :Invitro dissolution data for formulations F1 – F4 by using PEG 4000 Polymer

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Table-2:Invitro dissolution data for formulations F5– F8 by using PEG 6000 Polymer.

Time(MIN)	% Drug release			
	F5	F6	F7	F8
0	0	0	0	0
5	11.86	8.18	9.21	7.51
10	19.01	11.86	12.60	10.90
20	26.16	16.06	16.43	15.55
30	28.22	21.44	24.83	23.80
40	36.99	29.62	31.32	30.29
50	58.81	59.77	37.95	31.98
60	73.55	65.59	40.90	37.58

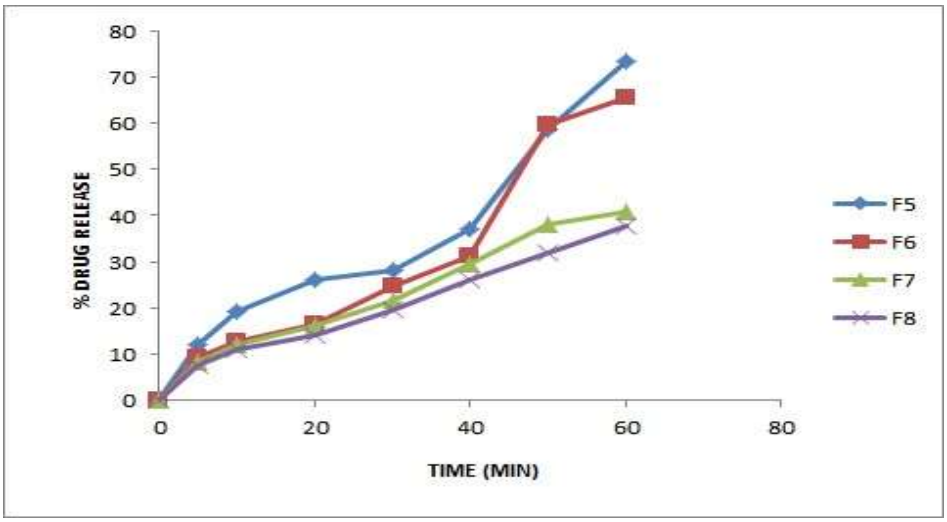

Fig11 :Invitro dissolution data for formulations F5– F8 by using PEG 4000 Polymer

Table10 :Invitro dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer.

Time(MIN)	% Drug release
	F9
0	0
5	7.51
10	10.90
20	15.55
30	23.80
40	28.29
50	34.98
60	39.58

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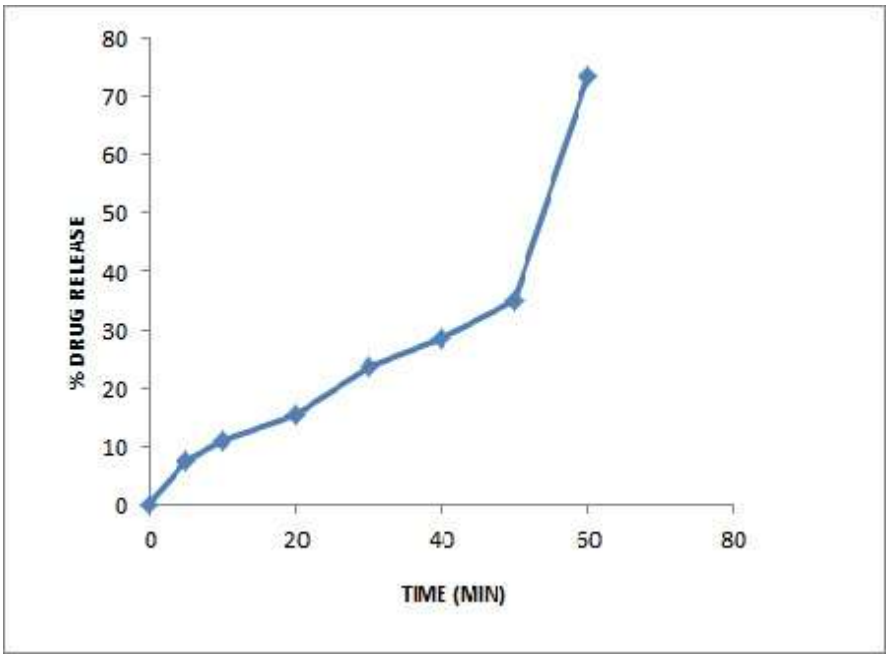

Fig12 :Invitro dissolution data for formulations F9 by using PEG 4000 & 6000 Polymer.

Among all the formulations F1 formulation containing, Drug and Peg 4000 in the ratio of 1:0.25 showed good result that is 94.95 % in 50 minutes. As the concentration of polymer increases the drug release was decreased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F1 formulation is the better formulation. The formulation containing combination of PEG 4000& 6000 was also not producing desired percentage drug release. The formulation is following zero order release kinetics.

CONCLUSION

Leflunomide belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects.

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