Research Article

Formulation and In-Vitro Evaluation of Leflunomide Tablet with Enhanced Dissolution

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ABSTRACT

Leflunomide is a pyrimidine synthesis inhibitor belonging to the DMARD (Disease-Modifying Anti-rheumatic Drug) used in pain management associated with rheumatoid arthritis, which shows its maximum effects during morning hours. It is practically insoluble in water, so in turn showing slow dissolution pattern. The aim of this study is to enhance the solubility and dissolution rate of leflunomide by solid dispersion techniques. This is achieved by using different hydrophilic polymers at different ratios such as sodium laurayl sulfate (SLS), urea, gaur gum and polyethelenglycol 4000 (PEG 4000) at different ratios i.e. (1:2), (1:4), (1:6) and (1:8) drug:carrier at one dose 20 mg of leflunomide. The study shows all used carriers (gaur gum, S.L.S, urea and PEG 4000) increased the solubility and the dissolution rate of leflunomide. IR spectroscopy and DSC techniques obviate that all the used carriers are physically compatible with leflunomide. The following formulae: F1, F2, F3 and F4 were selected. These selected formulae were used to prepare leflunomide tablets by direct compression technique. All the prepared leflunomide tablets complied with the pharmacopieal requirements for uniformity of drug content and disintegration time. The release kinetics of leflunomide from solid dispersion formulae & the prepared tablets were evaluated by employing the Korsmeyer peppa's equation.

Keywords: Leflunomide, gaur gum, urea, PEG4000, sodium laurayl sulfate, solid dispersion, enhanced dissolution.

INTRODUCTION

The number of sparingly soluble active pharmaceutical materials has risen sharply in recent years, and the formulation of such entities presents greater challenges to industrial pharmacists. Along with other factors, solubility of active pharmaceutical materials is a key determinant of its oral bioavailability.[1] Solid dispersion (SD) is one of the most promising approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. Solid dispersion can be prepared by various methods such as solvent evaporation, complexation and fusion methods.[1] The mechanisms by which the solubility and dissolution rate of the drug is increased are, firstly, the particle size of a drug is reduced to submicron size or to molecular size in the case where the solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from crystalline to amorphous form, the high energetic state which is highly soluble; finally, the wettability of the particle is improved by the dissolved carrier.[2] Leflunomide is a pyrimidine synthesis inhibitor belonging to the DMARD (disease-modifying anti-rheumatic drug) used in pain management associated with rheumatoid arthritis, which shows its maximum effects during morning hours. It is practically insoluble in water.

MATERIAL AND METHOD

Leflunomide, Gaur gum, Urea, Sodium lauryl sulfate (SLS), Urea, Methanol and Hydrochloric acid were supplied from Arati Pharmaceutical, Mumbai. Poly ethylene glycol 4000 was supplied from S.D.Fine chemicals, Mumbai.

SOLUBILITY STUDY OF LEFLUNOMIDE IN DIFFERENT RATIOS OF CARRIERS

An excess amount of leflunomide was added to 25 ml of 0.1 N HCL solution having different ratios of S.L.S, urea, Gaur gum, Urea& PEG 4000 in stoppered conical flasks. The samples

were sonicated for one hour at room temperature. The stoppered conical flasks were shaken for 24 hours at 37oC to achieve equilibrium in a shaking water bath. The obtained suspensions were filtered and the filtrate was diluted properly with 0.1 N HCL solutions. The diluted solutions were measured spectrophotometrically at wavelength of maximum absorption 260 nm using the same medium as a blank. Each experiment was performed in triplicate.[3]

FORMULATION OF LEFLUNOMIDE SOLID DISPERSIONS

In a present investigation, Leflunomide solid dispersions are mainly getting formulated by following two methods.

1. Co-grinding method (CG)

For co-grinding products (CG), an appropriate amount of leflunomide with different carriers (Gaur gum, S.L.S, urea and PEG4000) were homogenously mixed and triturated to obtain a homogenous mixture. Trituration was carried in a mortar for 10 -15 min to form a homogenous mixture.[4-5]

In this method the solid dispersions are formulated at weight ratios of 1:2, 1:4, 1:6 & 1:8, as represented in Table No.1.

2. Solvent evaporation method (SE):

The solvent evaporation method was used to prepare solid dispersions of leflunomide with different carriers (Gaur gum, S.L.S, urea and PEG 4000) at weight ratios of 1:2, 1:4, 1:6 and 1:8drug to carrier as follow (Table No. 2).

Leflunomide and carriers (Gaur gum, S.L.S, urea and PEG 4000) were dissolved in minimum volume of organic solvent (methanol) and the solvent was allowed to evaporate in hot air oven at 45°C±10°C. Then, solid dispersion formulation was crushed, pulverized using a mortar and pestle. The pulverized powder was sieved into defined particle size fraction of 150-200 micrometer for study.[4-5]

Table 1: Formulation of solid dispersion by co-grinding method

S. No.	Mixture code	Carrier	Drug:Polymer ratio
1	SD1	Gaur gum	1:2
2	SD2	Gaur gum	1:4
3	SD3	Gaur gum	1:6
4	SD4	Gaur gum	1:8
5	SD1	Urea	1:2
6	SD2	Urea	1:4
7	SD3	Urea	1:6
8	SD4	Urea	1:8
9	SD1	PEG4000	1:2
10	SD2	PEG4000	1:4
11	SD3	PEG4000	1:6
12	SD4	PEG4000	1:8
13	SD1	SLS	1:2
14	SD2	SLS	1:4
15	SD3	SLS	1:6
16	SD4	SLS	1:8

Table 2: Formulation of solid dispersion by Solvent Evaporation

S. No.	Mixture code	Career	Drug : Polymer ratio
1	SD1	Gaur gum	1:2
2	SD2	Gaur gum	1:4
3	SD3	Gaur gum	1:6
4	SD4	Gaur gum	1:8
5	SD1	Urea	1:2
6	SD2	Urea	1:4
7	SD3	Urea	1:6
8	SD4	Urea	1:8
9	SD1	PEG4000	1:2
10	SD2	PEG4000	1:4
11	SD3	PEG4000	1:6
12	SD4	PEG4000	1:8
13	SD1	SLS	1:2
14	SD2	SLS	1:4
15	SD3	SLS	1:6
16	SD4	SLS	1:8

EVALUATION OF LEFLUNOMIDE SOLID DISPERSIONS

1. Content uniformity analysis

SD (with different carriers) equivalent to 20 mg of leflunomide were weighed and dissolved in 10 ml methanol which added to 100 ml volumetric flask, then complete to the final volume with 0.1N HCL and then were shaken for 10 minutes. The obtained solution was filtered and 3ml of the filtrate were taken and diluted separately to 10 ml with 0.1 N HCL. These diluted samples were measured using UV-Scanning spectrophotometer at 260 nm. The blank was carried out using 0.1 N HCl.[6]

2. *In-vitro* release study

The dissolution rates of pure leflunomide and different formulae that is equivalent to 20 mg of leflunomide were determined in 900 ml of dissolution medium (0.1 N HCL) at 37 °C ± 0.5 °C with a stirrer rotation speed of 75 rpm using the USP Dissolution Apparatus II (paddle type). Aliquots (5 ml) of the sample were withdrawn from dissolution medium at time intervals of 20, 40, 60, 80, 100, and 120 minutes using a pipette. The same volume of 0.1 N HCL was used to replace the samples withdrawn to maintain the sink condition. The samples were suitably filtered, diluted and assayed spectrophotometrically at 260 nm.[7]

FORMULATION OF LEFLUNOMIDE TABLETS

On the basis of evaluation study of solid dispersions, only the solid dispersions formulated wit SLS as a carrier were chosen and compressed into leflunomide tablets as shown in Tables (4). Solid dispersions powder with S.L.S, Micro crystalline cellulose and crosscarmellose sodium were weighted as per formula given in Table: 4, these were then sifted through mesh size 40, transferred to a poly bag and blended for 5 minutes. To this homogeneous blend magnesium stearate pre-sifted through mesh size 60 was added and blended for 2 minutes. The resulted blend was compressed using Tablet compression machine with 10 mm, round, flat-faced single punch. A minimum of 50 tablets was prepared for each formula.[8]

Table 3: Evaluation parameters for the Different Solid dispersion Formulations

S. No.	Formulation code	Drug Content (%)		Average % Release at 120 min. 0.1 N HCl	
		Co-grinding	Solvent Evaporation	Co-grinding	Solvent Evaporation
1	Leflunomide	---	---	38.54	37.89
2	SD1-GG (1:2)	119	61	65.14	64.24
3	SD2-GG (1:4)	82	82	74.95	69.79
4	SD3-GG (1:6)	95	118	76.14	74.36
5	SD4-GG (1:8)	147	119	74.45	75.12
6	SD1-Urea (1:2)	100	82	73.48	65.14
7	SD2-Urea (1:4)	108	91	75.13	71.23
8	SD3-Urea (1:6)	89	108	77.12	78.24
9	SD4-Urea (1:8)	60	108	79.48	80.48
10	SD1-PEG (1:2)	70	70	54.65	62.14
11	SD2-PEG (1:4)	121	98	64.63	68.78
12	SD3-PEG (1:6)	115	109	72.14	72.14
13	SD4-PEG (1:8)	94	129	75.87	80.24
14	SD1-SLS (1:2)	113	103	92.14	94.48
15	SD2-SLS (1:4)	112	116	98.14	98.26
16	SD3-SLS (1:6)	116	138	101.16	100.01
17	SD4-SLS (1:8)	120	101	105.66	102.64

Table 4: The suggested formulae of leflunomide tablets

Formulae	Ingredients (mg)				
	Solid Dispersion Formulae	Magnesium stearate	Micro crystalline cellulose	Crosscamelose sodium	Total weight
F1	60	1	157	12	230
F2	100	1	117	12	230
F3	140	1	77	12	230
F4	180	1	37	12	230

PREFORMULATION STUDY OF LEFLUNOMIDE FORMULATIONS [9-10]

1. Density

The bulk density and tap density were determined by following formula:

Bulk density = weight of powder/ volume of powder in measuring cylinder.

Tap density = weight of powder / Tapped volume of powder in measuring cylinder.

Procedure: The 2gms of powder was introduced into a 10 ml of measuring cylinder. Then for bulk density, firstly note down the initial volume, then tapping was continued for tap density determination until no further change in volume was noted.

2. Angle of Repose

The angle of repose was determined by using fix funnel method. The accurately weighted powder was allowed to flow through the funnel. The funnel is adjusted to a stand at definite height. The radius of powder and height of heap of cone was measured. The angle of repose was then calculated by following formula.

$$\tan \theta = h / r$$
$$\theta = \tan^{-1} (h/r)$$

Where,

θ = angle of repose

h = height of the heap

r = radius of the heap

3. Compressibility Index

The flow ability of powder can be determine by comparing the bulk density and tapped density of powder. Carr's index was calculated by:

Carr's index **=** (tap density – bulk density) ×100 / tap density

4. Hausner ratio

Hausner ratio of each tablet blend was also calculated by using following formula:

Formula= tapped density / bulk density

EVALUATION OF LEFLUNOMIDE TABLETS[9-11]

The prepared tablets from each formula were subjected to the following Quality control tests

1. Tablet thickness

The thickness was measured by placing tablet between two arms of the Varnier calipers. 5 tablets were taken and their thickness was measured.

2. Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

3. Tablet friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = \frac{W0 - W}{W0} \times 100$$

4. Content uniformity analysis

Ten tablets from each formula were powdered and were mixed. An amount equivalent to 20 mg of leflunomide was taken and was dissolved in 50 ml methanol which added to 500 ml volumetric flask, then complete to the final volume with 0.1N HCL. The flask was shaken for 10 minutes. The obtained solution was filtered and 1ml of the filtrate were taken and diluted separately to 3 ml with 0.1N HCL. This diluted sample was measured using UV- Scanning spectrophotometer at 260 nm. Blank tablets without the drug were prepared and were subjected to the same analytical procedure to serve as the blank for spectrophotometric determination.

5. Disintegration time

One tablet was placed in each of the six tubes of the basket and the apparatus was operated, using 0.1N HCL maintained at 37^{o}C as the immersion fluid at the end of the time, the basket was lifted from the fluid, and the tablets were observed till disintegration of all tablets completely. The test was carried out according to USP and the disintegration time of each of six individual tablets was determined using tablet disintegration test apparatus.

6. *In-vitro* release study of leflunomide tablets

The *in-vitro* release study of leflunomide tablets and leflunomide commercial tablet were investigated adopting the USP rotating paddle

apparatus II. The dissolution medium (900 ml) was 0.1N HCL. Each tablet was placed in a flask containing the used medium; the paddle was rotated at 75 r.p.m. at a constant temperature 37^{o}C. Aliquots, each of 5 ml were withdrawn from the release medium at intervals 20, 40, 60, 80, 100 and 120 minutes. The same volume of the used medium replaced all samples. The samples were filtered, diluted and measured spectrophotometrically at 260 nm. The concentration of the drug was determined from the previously constructed standard calibration curve. The procedure was repeated three times and the mean reading was taken.

CONCLUSION

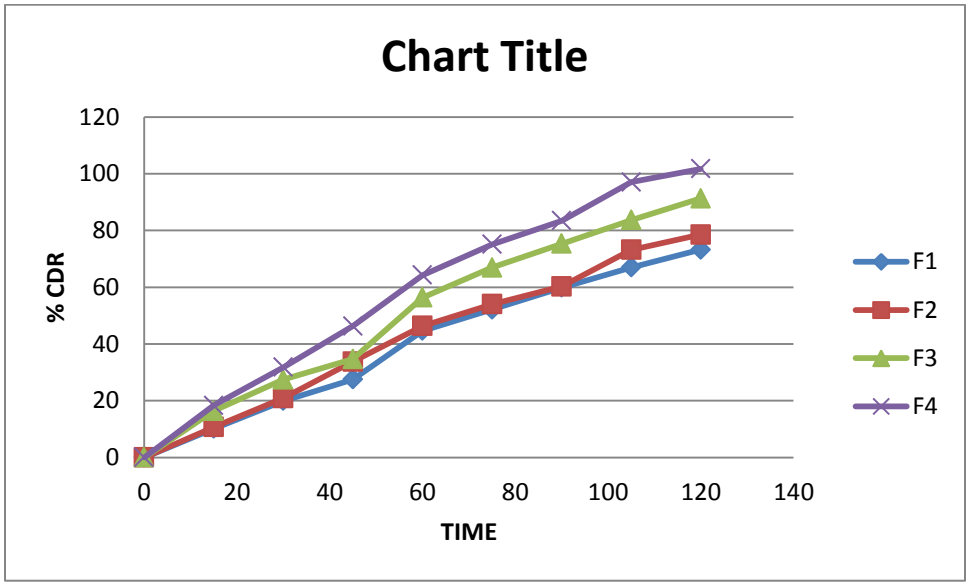
All the studied carriers (S.L.S, urea, PEG 4000 and gaur gum) increased the solubility and the dissolution rate of leflunomide. All the prepared leflunomide tablets gave % release higher than the commercial tablet. The maximum in-vitro release of leflunomide from the prepared tablet was found in **F4** formulation. With respect to the same, from the current investigation we also found that out of four types of carriers SLS gives an enhanced dissolution as compare to any other carriers which are investigated in current study. Hence it is concluded that with the help of hydrophilic carrier systems and by using solid dispersion technique solubility of Leflunomide was get enhanced in aqueous system.

Table 5: Preformulation Study of Leflunomide Formulation

Formulae	Bulk density	Tap density	Carr`s index (%)	Hausner`s ratio	Angle of repose
F1	0.45	0.54	27.55	1.78	37 ^{o}
F2	0.54	0.79	31.64	1.46	40 ^{o}
F3	0.53	0.70	24.28	1.32	36 ^{o}
F4	0.40	0.48	16.66	1.2	39 ^{o}

Table 6: Evaluation Study of Optimized Batch of Leflunomide Tablet

S. No.	Parameters	F1	F2	F3	F4
1	**Thickness (cm)**	0.5	0.5	0.5	0.5
2	**Hardness (kg/cm^2)**	2.5	2.5	3	3
3	**Friability (%)**	0.36	0.62	0.33	0.39
4	**Disintegration time (min)**	32.24	30.11	27.14	24.40
5	**% drug content**	39.6	42.5	49.35	54.95
6	**% CDR of 120 min**	73.21	78.55	91.29	101.73



In-vitro release of leflunomide tablet from all the different formulae in 0.1 N HCl

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