IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 14, Issue 1 Ver. I (Jan – Feb 2019), PP 77-83
www.Iosrjournals.Org

Enhancement of solubility and dissolution rate of Leflunomide tablets by solid dispersion technique

*T.Tirumala devi*Sk Faheem Ali ,M.Manisha, P.Bhanu prasad, P.Jyothi
Department of pharmaceuitcs, Medarametla anjamma mastanrao college of pharmacy, Acharya nagarjuna university. Narasaraopet-522601. Gnt Dist. Andhra pradesh.
Corresponding Author: T.Tirumala devi

Abstract: *Rheumatoid arthritis is an auto immune disorder that primarily affects joints. The disease causes sewere inflammation of joints,painful joints ;also causes Inflammation around lungs and heart. It increases the risk of heart strokes . The cause of disease is yet unclear predicted to be a combination of genetic and environmental factors. The disease is diagnosed by signs and symptoms and by laboratory tests .Around 41 /1,00,000 people are diagnosed with R.A. As per statistics about 24.5 million people are affected with R.A. About 38,000 deaths are reported in the year 2013.*
Leflunomide is a immuno suppresive disease modifying anti rheumatic drug that show its activity by inhibiting the mitochondrial enzyme ;Di hydro rotatateDehydrogenase .hence leflunomide inhibits reproduction of rapidly dividing cells,Especially lymphocytes. Here we are preparing leflunomide solid dispersion form that enhances its soulubility and dissolution rate.

Keywords: *Rheumatoid arthritis ,Leflunomide, Solid dispersion , solvent evaporation*

Date of Submission: 12-01-2019 Date of acceptance: 27-01-2019

I. Introduction

The oral route is most common and preferred route for drug delivery system, it is convenient and easy ingestion. Moreover patient compliance and drug treatment is more effective with oral administration than other routes of administration.

Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs .Hence the researchers focused on two areas i) to enhance solubility and The main use of solid dispersion technique is to improve the dissolution rate and bioavailability of poorly water soluble drugs. dissolution ii) to increase the permeability of poorly water soluble drugs. Therefore for oral route of administration to increase the dissolution and bio availability by using solid dispersion systems for class-II drugs.

Leflunomide is a pyrimidine synthesis inhibitor belonging to the DMARD (disease-modifying antirheumatic drug) class of drugs, which are chemically and pharmacologically very heterogeneous. Leflunomide was approved by FDA and in many other countries.

II. Methodology

Solvent Evaporation Method: In this method both the drug and carrier are dissolved in a organic solvent. After an entire dissolution the solvent is evaporated. The solid mass is sieved and dried. Example Solid dispersion of furosemide with eudragits was prepared by solvent evaporation method.

Preparation of stock soln :100 mg of Leflunomide was dissolved in methanol 5 ml, volumetric flask make upto 100 ml of Phosphate buffer of pH 7.4 , from this primary stock 10 ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 7.4, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 7.4, to produce 10,20,30,40 and 50 µg/ml respectively.

Preformulation Studies: Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Drug-Excipients compatibility studies : Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

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 diluents.

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
PE 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

Total weight of tablets = 100 mg

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

Materials used in the work

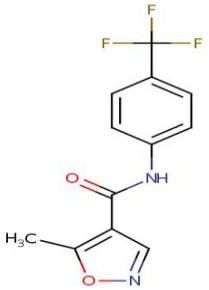
S.No	Materials	Uses
1	Leflunomide	Drug
2	PEG 4000	Carrier,slovent
3	PE 6000	Surfactant
4	PVP K30	Binding agent
5	Magnesium stearate	Lubricating agent
6	Aerosil	Gildant,stabilizer
7	Microcrystalline Cellulose	Adsorbent,disintegrant,diluent
8	Potassium dihydrogenortho phosphate	Buffer
9	Sodium hydroxide	Alkaliniting agent

List of equipment used in the work

S.NO	Equipments	Company
1	Sixteen station rotary tablet punching machine	Cadmach
2	Electronic balance	Shimadzu
3	Digital vernier calipers	Remi equipments Ltd
4	Rotary shaker	Remi equipments Ltd
5	UV/Visible-spectrophotometer	Biochrome
6	Dissolution tester (USP)	Electro Lab TDT-08L
7	Franz diffusion cell	Borosil Glass Works Ltd
8	Modified 2- arm balance	Remi equipments Ltd
9	Digital pH meter	Elico
10	FT-IR spectrophotometer	Bruker
11	Magnetic stirrer	Remi equipments Ltd
12	Incubator /Vacuum oven	Bio technics Ltd
13	Roche Friabilator	Sisco

DRUG PROFILE

Drug name : LEFLUNOMIDE
Iupac name : 5-methyl-N-[4-(trifluoromethyl)phenyl]-1,2-oxazole-4-carboxamide
Synonyms : Arava, Leflunomida, Leflunomide, Leflunomidum, Lefunomide.
Solubility : Soluble in DMSO (54 mg/ml at 25 °C), ethanol (54 mg/ml at 25 °C), and water (<1 mg/ml at 25 °C).
Description : Leflunomide is a pyrimidine synthesis inhibitor belonging to the DMARD (disease-modifying antirheumatic drug) class of drugs, which are chemically and pharmacologically very heterogeneous. Leflunomide was approved by FDA and in many other countries
Melting point : 166.5 °C
CAS NO : 75706-12-6



Molecular formula : C12H9F3N2O2
Molecular weight : Average: 270.2073 Monoisotopic: 270.061612157 g/mol.
Bioavailability : 80%
Half-life : 2 weeks
Protein binding : >99.3%
Dosage forms and dose : tablet(100mg,20mg,10mg)
Category :Antirheumatic Agent Immunosuppressive Agent Enzyme Inhibitors Adjuvant

Evaluation of tablets:
Pre compression parameters: Measurement of Micromeritic Properties of Powders. Hausner's ratio, bulk density and angle of repose has been calculated.

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 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.

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.

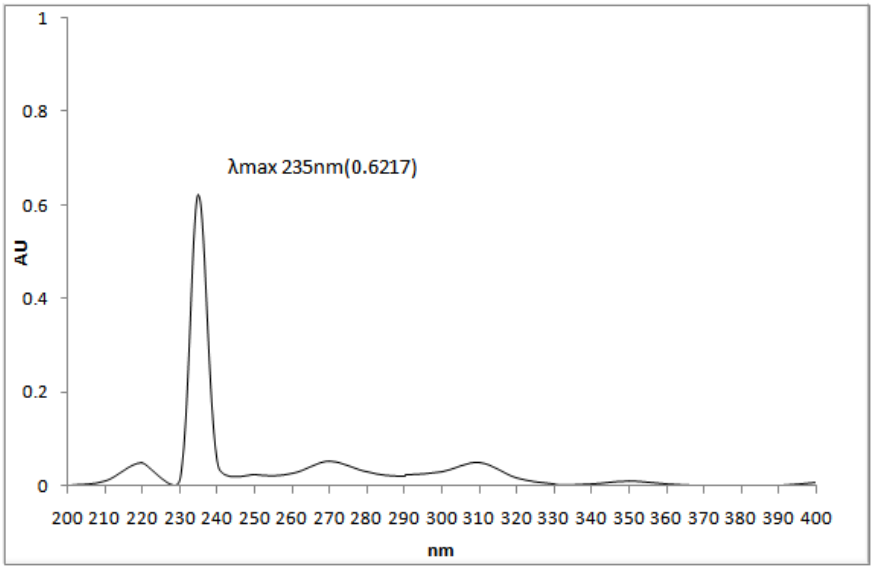
Dissolution test of Leflunomide tablets: Drug release from Leflunomide tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 7.4 medium as the dissolution medium of quantity 900ml. The whole study 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.

III. Result and Discussion

Determination of λ max: The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 235 nm.

Fig6 : Spectrum showing absorption maxima



Instrument performance.
Model: UV-Vis Spectrophotometer
Number: 19-1950-21-0002
Spectral band width: 1.00nm

Calibration curve of Leflunomide :
The standard curve of Leflunomide was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 7.4 phosphate buffer.
The standard graph values of Leflunomide are tabulated as below-

Table5 : Standard Graph values of Leflunomide at 235 nm in pH 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
10	0.198
20	0.396
30	0.601
40	0.804
50	0.998

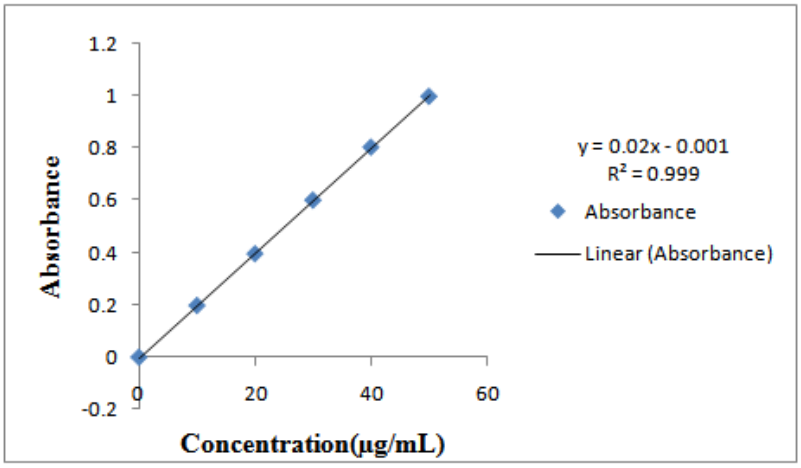


Fig no 7: standard curve of leflunomide

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 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	4.74±0.05	8.09±0.05	4.4±0.6	0.513	99±0.4
	F7	4.76±0.03	8.11±0.03	5 ± 0.1	0.412	98±0.9
	F8	4.71±0.04	8.09±0.06	4.6±0.2	0.432	99±0.1
	F9	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

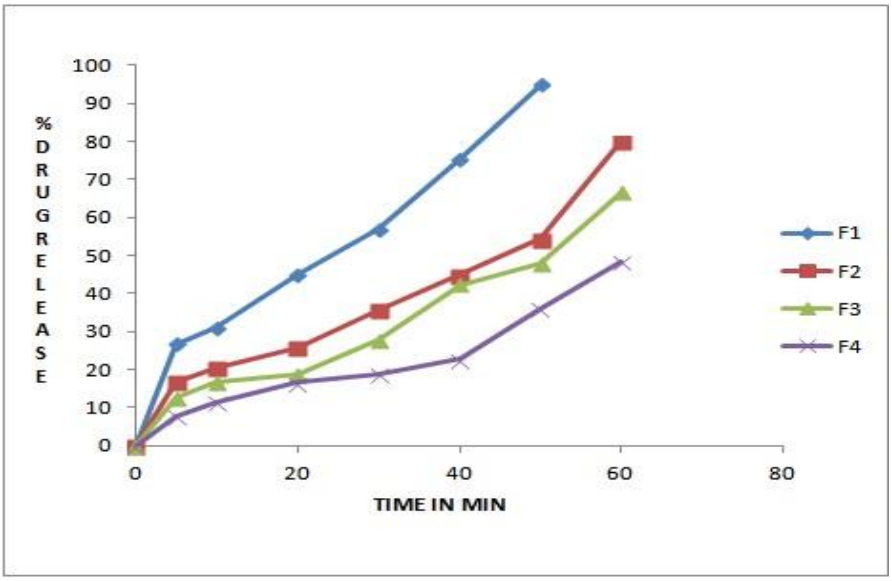
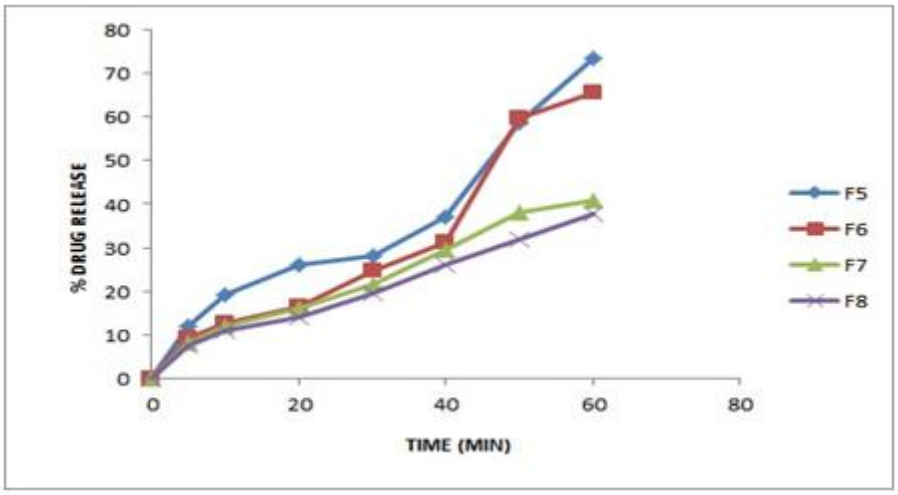


Fig10 : Invitro dissolution data for formulations F1 – F4 by using PEG 4000 Polymer

Table9 :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



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

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.

IV. Conclusion

- ✓ The standard curve of Leflunomide was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 7.4 phosphate buffer.
- ✓ Leflunomide was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.

- ✓ Solid dispersions were prepared with various concentrations of carriers, the prepared 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 1:0.25 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.
- ✓ By conducting further studies like Invivo studies , preclinical and clinical studies we can commercialise the product.

Note: The enhancement of soulibility and dissolution profile of drug shows rise in bio availability and reduce its side affects.

References

[1]. TheFreeDictionary > oral administration of medication Citing: Mosby's Medical Dictionary, 8th edition. 2009
[2]. Sarode Ashish,Wang Peng,Cote Catherine,Worthen David R. Low-Viscosity hydroxypropylcellulose(HPC) grades SL and SSL:versatile pharmaceutical polymers for dissolution enhancement, controlled release, and pharmaceutical processing.AAPS Pharm Sci Tech.2013;14(1):151-159.
[3]. Dr.K.L.Senthilkumar and Y.sirisha. Enhancement of dissolution rate studies on solid dispersion of Aceclofenac. International Journal of Pharma and Bio Sciences. 2011; 2 (2):70-76.
[4]. P.Kumar, S.Kumar, A.kumar, M.Chander.Physicochemical Characterization of Solid Dispersion of Cefdinir with PVP K-30 and PEG 4000.International journal of pharmaceutical sciences and nanotechnology.2010; 3(2):948-956.
[5]. Tantishaiyaku V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone Int J Pharm.,1999;30(2):143-51.
[6]. Newa M,Bhandari KH,Lee DX,Sung JH,Kim JA,Yoo BK,Woo JS,Choi HG,Yong CS.Drug.Dev Ind.Enhanced dissolution of ibuprofen using solid dispersion with polyethylene glycol 20000. Pharm.2008; 34(10):1013-21.
[7]. Jiang YR,Zhang ZH,Xia HJ,Jia XB.Study on solid dispersion -based tanshinone II(A). Zhongguo Zhong, Yao Za Zhi .2013; 38(2):174-8.
[8]. Ashish L.Sarode,Harpreet Sandhu,Navnit Shah,Waseem Malick,Hossein Zia. Hot melt extrusion (HME) for amorphous solid dispersions: Predictive tools for processing and impact of drug–polymer interactions on supersaturation.Europian Journal of Pharmaceutical Sciences.2013;48(3):371-384.

IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) is UGC approved Journal with Sl. No. 5012, Journal no. 49063.

T.Tirumala devi " Enhancement of solubility and dissolution rate of Leflunomide tablets by solid dispersion technique" IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 14.1 (2019): 77-83.