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FORMULATION, DEVELOPMENT AND EVALUATION OF LEFLUNOMIDE TABLETS

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ABSTRACT

DMARDs (Disease Modifying Anti Rheumatic drug) reduces the rate of damage to the bone and cartilage. They prevent bone and joint damage from occurring secondary to the uncontrolled inflammation. *Leflunomide* is recently introduced immonumodulator inhibits proliferation of activated lymphocytes in patients with Rheumatoid arthritis. Arthritis symptoms are suppressed and radiological progression of disease is retarded. The study was under taken with an aim of Formulation, Development and Evaluation of leflunomide Tablets using excipients. Preformulation study was done on pure drugs and granules and results directed for further course of formulation. Based on preformulation studies different batches of leflunomide were formulated using selected excipients. Granules were evaluated for Loss on drying, Angle of repose, Bulk density, Tapped density, Compressibility Index and Hausner's Ratio. Tablets were tested for weight variation, thickness, hardness, disintegration time, *In-vitro* drug release studies as per specifications.The formulation that has been found to posses ideal characteristics required for leflunomide 10mg, 20mg Tablets, so it was concluded as the final formula for leflunomide 10mg and 20 mg tablets are 150mg, 200 mg respectively made by co-precipitation of drug with PVP.The drug release profile of leflunomide compared with the market sample. From the studies it was concluded that formulation of leflunomide Tablets containing lactose monohydrate, starch, povidone, crospovidone, mg stearate , aerosil taken as ideal or optimized formulation of tablets.

Key Words: Immonumodulator, Bulk density, Tapped density, Compressibility Index.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disorder that causes the immune system to attack the joints, where it causes inflammation (arthritis) and destruction. [(14)] Disease modifying anti-rheumatic drugs reduces the rate of damage to bone and cartilage. ***DMARDs*** have been found to produce durable remissions and delay or halt disease progression.[15] Chemically synthesised DMARDs are Azathioprine, Cyclosporine, D-Penicillamine, Gold, Hydroxychloroquine, and Leflunimide. Solid dosage forms are the most popular category of pharmaceutical formulations. Brockendon is creditor with the discovery of initiating tablet fabrication by compression in 1843. By the end of 19th century tablets were quite popular in European and American markets[1].

Tablets defined as solid Unit pharmaceutical dosage forms containing medicaments with or without suitable recipients & prepared by either compression or moulding.[2] ***Tablets*** are manufactured by wet granulation, Dry granulation or direct compression method. ***Wet granulation*** is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. ***Dry granulation*** involves the formation of slugs. Then the slugs are screened or milled to produce granules. ***Direct compression*** is used to define the process by which tablets are compressed directly from powder blends of active ingredient and suitable recipients, which will flow uniformly in the die cavity & forms a firm compact.[6]Processing Steps Commonly Required In the Various Tablet Granulation Preparation Technique.

Processing steps	**Wet Granulation**	**Dry Granulation**	**Direct Compression**
Raw materials	X	X	X
Weight	X	X	X
Screen	X	X	X
Mix	X	X	
Compress (slug)		X	
Wet mass	X		
Mill	X		
Dry	X		

Mill	X	X	
Mix	X	X	
Compress	X	X	X

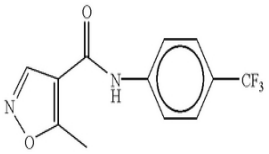
x- steps involved

EXPERIMENTAL INVESTIGATIONS

DRUG PROFILE

LEFLUNOMIDE is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity.

(I)



Molecular formula $C_{12}H_9F_3N_2O_2$

PREFORMULATION STUDY

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. The use of preformulation parameters maximizes the change in formulating an acceptable, safe, efficacious and stable product.[54]

The identification of drug was done by FT-IR Spectroscopy.

Method: Triturate 1-2 mg of the substance to be examined with 300-400 mg, of finely powdered and dried potassium bromide or potassium chloride. These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity. Infrared spectrophotometers are used for recording spectra in the region of 2000 – 500 cm^{-1}. [54]

After identification of drug physical characteristics of leflunomide pure sample are evaluated.

DRUG – EXCIPIENT COMPATIBILITY STUDY:

Leflunomide with various excipients in 1:1 ratio at conditions of (40°C/ 75 % RH & 60°C/ 80% RH) in stability chamber (Newtronic Walk in humidity chamber, India) for one month in open and closed condition. The sample were withdrawn on 1^{st}, 2^{nd} ,3^{rd} , 4^{th} , 5^{th} , 6^{th} , 7^{th}

,14th, 21st ,30th day & physical characteristics like color changing if any was recorded. Evaluation done by HPLC.(54)

FORMULATION OF TABLET

Wet granulation: Sieve drug & excipients through 30 mesh. Dissolve drug & povidone K-30 in 250 ml of isopropyl alcohol, So that co-precipitation occur . Granulate the excipients portion with the prepared solution; mixed for 10 min. Dry the granules in drier at a temperature till of 50-60^{0}c to remove solvent.Pass the semidried granules through 20 mesh of a sifter ensure the entire granules have passed through 20 mesh.Dry the granules to get the moisture content of the granules between 3.0 to 4.0 % by KFR.(karl fisher's reagent).To the final dried lubricate the granules and compressed.

Formulation of tablets.

S.No	Ingredients/ Batch	F-1	F-2	F-3	FF-4F-4 F-4	F-5	F-6
1.	leflunomide	20mg	20mg	20mg	20mg	20mg	20mg
2.	Lactose monohydrate	110mg	122mg	116g	111g	116g	102g
3.	Maize starch	66g	49mg	35mg	40mg	35g	50g
4.	Polyvinyl pyrrolidinone	----	5mg	5mg	10mg	10mg	10mg
5.	Crospovidone	---	-----	20mg	15g	12g	12g
6.	Aerosil	2mg	2mg	2mg	2mg	2mg	2mg
7	Magnesium stearate	------	-----	-----	2mg	2mg	2mg
8.	PEG-600	-------	------	-----		2mg	2mg

9.	Talc	2mg	2mg	2mg	------	-----	-----
	Total	200mg	200mg	200mg	200mg	200mg	200mg

S.No	Ingredients/ Batch	F-1	F-2	F-3	FF-4F-4 F-4	F-5	F-6
1.	leflunomide	10 mg	10 mg	10mg	10mg	10mg	10 mg
2.	Lactose monohydrate	76mg	88.5mg	83.5mg	81mg	91g	71mg
3.	Maize starch	60mg	45mg	25mg	35mg	36mg	45mg
4.	Polyvinyl pyrrolidinone	---	2.5mg	2.5mg	5mg	5mg	5mg
5.	Crospovidone	---	-----	25mg	15mg	12mg	12mg
6.	Aerosil	2mg	2mg	2mg	2mg	2mg	2mg
7	Magnesium stearate	------	-----	-----	2mg	2mg	2mg
8.	PEG-600	-------	------	-----		2g	2mg
9.	Talc	2mg	2mg	2mg	------	-----	-----
	Total	150mg	150mg	150mg	150mg	150mg	150mg

IN PROCESS EVALUATION – Bulk is evaluated for bulk density, tapped density, Hausner's Ratio, Compressibility Index.

Compression

Setup and operate the compression machine. Check the Upper Punch and Lower Punch and dies before starting the machine for the correctness. Load the blended granules into machine hopper and compress the blended granules into tablets using caplet shaped punches and dies with parameters given in the table. Start the machine by inch mode and check for any noise, continue compression of the blended granules

Specification of punches and dies for compression (10mg)

Upper punches: 9 x 5.3mm oval shape

Lower punches: 9 x 5.3mm

Dies : 9 x 5.3mm

Type of machine: 16 stations

Specification of punches and dies for compression (20mg)

Upper punches: 8 mm circular shape

Lower punches: 8 mm

Dies : 8 mm

Type of machine: 16 stations

EVALUATION OF TABLETS

Dissolution Tablet dissolution was assessed using standard USP 24 apparatus II in 1000 ml of water. The stirring speed was 100 rpm. (Revolution per minutes). Total 6 tablets were taken for test. Temperature was maintained 37ºC ± 0.5ºC through out the experiment. Dissolution study was carried out for 30 minutes. Sampling interval were 10 min, 20 min, 30 min, after collection of sample in each interval, dissolution medium was replenished with the same volume of respective medium. Samples were withdrawn at regular intervals and diluted to 10 ml with corresponding medium and analyzed for drug content by U.V.[60]

Dissolution parameters

1. Medium : purified water (degassed).
2. Quantity : 1000 ml.
3. Apparatus : USP Type II (paddle).

4. Rotational Speed : 100 RPM
5. Time : 10, 20, 30, min or required intervals.
6. Temperature : 37ºC ± 0.5ºC.
7.

Preparation of standard solution

Weigh and transfer accurately about 20 mg of leflunomide into 20 ml of volumetric flask. Make up the volume with methanol then pipette of 2 ml of this solution. Transfer to 200 ml volumetric flask & make up the volume with 200 ml of degasd water .[61]

Preparation of test solution

For 200 mg tablets weigh and drop one tablet in to 1000 ml of degassed water , pipette out 5 ml of this solution then again add 10 ml of degassed water. For 150 mg tablets weigh and drop one tablet in to 1000 ml of degassed water, pipette out 10 ml of this solution .

Procedure: Samplings were done with intervals of 10, 20, 30, minutes, diluted with medium. Filter the samples through 0.45 micrometer filter. Absorbance was seen at wave length of 262nm. [61]

Calculations: (for leflunomide, 200mg)

Cumulative % Drug release =

$$\frac{TA}{SA} \times \frac{SW}{20} \times \frac{2}{200} \times \frac{1000}{20} \times \frac{10}{5} \times 100$$

Calculations: (for leflunomide, 150mg)

Cumulative % Drug release =

$$\frac{TA}{SA} \times \frac{SW}{20} \times \frac{2}{200} \times \frac{1000}{10} \times 100$$

Where,

TA = Test absorption for test solution.

SA = Standard absorption for standard solution.

SW = Weight of standard solution taken. In mg

Average drug content – By HPLC method

Reagents

1. HPLC water.
2. Acetonitrile: HPLC grade.
3. Triethylamine.
4. Phosphoric acid.

Preparation of mobile phase

Take 600 ml of HPLC grade water in suitable container and then add with 348.2 ml of acetonitrile and 5.8 ml of triethylamine. The ratio of 65:35:0.5 mixes properly and degas for 10 minutes.[59]

Chromatographic parameters:

Use suitable high performance liquid chromatograph equipped with following:

1. Column : Hypersil , BDS 48,250*4.6 NO. 48
2. Flow rate : 1.0 ml/mins
3. Wavelength : 210nm
4. Injection volume : 10 µl
5. Diluent : mobile phase

Standard preparation

Weigh and transfer accurately about 50 mg of leflunomide in to 50 ml of volumetric flask. Add 10 ml of acetonitrile . Sonicate to dissolve and make up to the volume with diluent. [59]

Test preparation

Weigh and crush not less than 20 tablets. For 10 mg tablets weigh and transfer 1.5g equivalent wt 100mg into 100 ml volumetric flask. Add 20ml of acetonitrile and sonicate and dilute up to the volume with diluent & filter about 2 ml through 0.45 µm membrane filter. For 20 mg tablets weigh and transfer 1g equivalent wt 100 mg into 100 ml volumetric flask. Add 20ml of acetonitrile and sonicate and dilute up to the volume with diluent. [59

Procedure

Separately inject equal volume of blank. Standard preparation (in 5 replicates) and test preparation (in duplicate) in to the chromatograph and measure the peak area counts for leflunomide . [59]

Calculations: (for leflunomide)

$$\% \text{ W/W of Assay} = \frac{ATA}{ASA} \times \frac{SW}{50} \times \frac{100}{TW} \times AW$$

Where,

ATA = Average peak area counts for test solution.

ASA = Average peak area counts for standard solution.

TW = Weight of test solution taken in mg.

SW = Weight of standard solution taken in mg.

Stability studies

The storage condition used for stability studies are 25 ºC, 60 % ± 5 % RH. 30 ºC, 65 % ± 5 % RH, and 40 ºC, 75 % ± 5 % RH.[62] Stability studies were carried out on the formulation F-6. The tablets of formulation-6 kept in closed high density polyethylene bottle. These were stored at 25 ºC, 60 % ± 5 % RH. 30 ºC, 65 % ± 5 % RH, and 40 ºC, 75 % ± 5 % RH. For 2 months

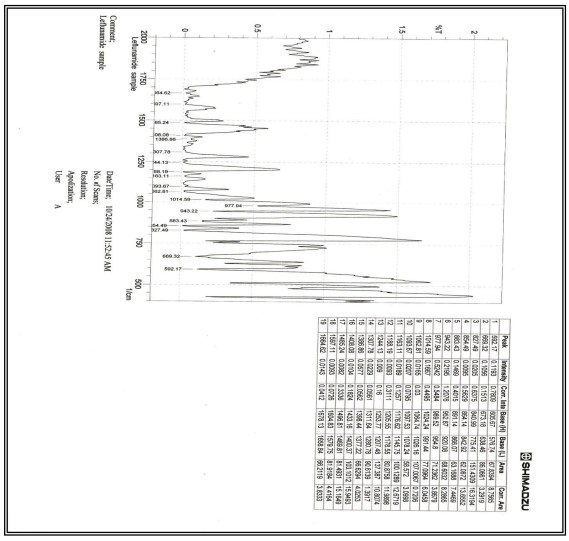
RESULTS AND DISCUSSION

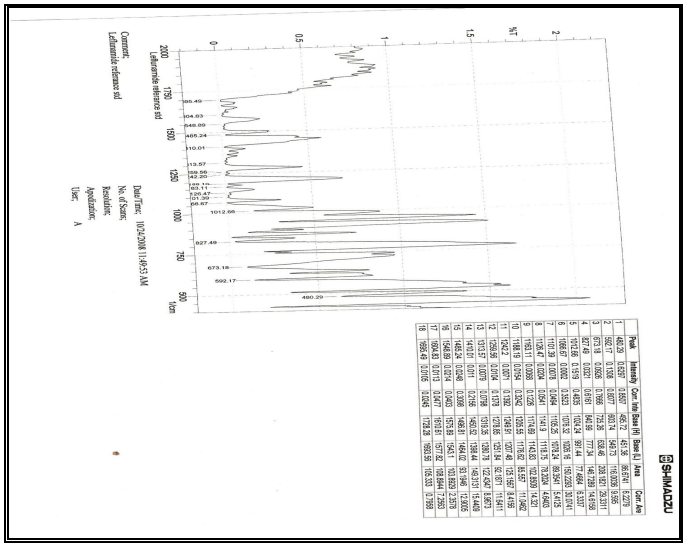
Preformulation studies

The procured sample of leflunomide was tested by Sai mirra innopharm. The drug-excipients compatibility was done at 40ºC/ 75 % RH. 60ºC/ 80 % RH. Open and closed vial methods were used. The result did not show any physical change to the mixture after interval at the end of 30 days. Drug and excipients compatibility assay limits evaluated for readymix and premix by HPLC method. Assay value was within the limits. This fact concluded that the drug and excipients are compatible with each other.

Identification of drug

FT-IR spectrum of leflunomide sample FT-IR spectrum of leflunomide Standard





Physical characteristics	**Result**	**Limit**
Loss on drying	0.16	Not more than 0.3%
solubility	Insoluble in water	Insoluble in water
Residue on ignition	0.5%	Not more than 0.1%
Heavy metals	0.001%	Not more than .002%
Melting range	167^0c	164^0c-168^0c

Assay limit of Readymix

S.No	**Raw materials**	**Assay Value**	**Limit**
1	Leflunomide + Lactose	173.20 mg	159.59± 10%
2	Leflunomide + Starch	315.22 mg	286.58± 10%
3	Leflunomide + PVP	875.71mg	800.68 ± 10%
	Leflunomide +	625.21mg	572.47±10%

4	Crospovidone		
5	Leflunomide + Aerosil	995.21mg	909.44±10%
6	Leflunomide + Mg.Stearate	912.52 mg	909.44±10%

Assay limit of Premix kept at 40°C/ 75%RH & 60°C/ 80%RH

S.No	Raw materials	Assay Value at 40°C/ 75%RH	Assay Value at 60°C/ 80%RH	Limit
1	Leflunomide + Lactose	172.50 mg	172.32 mg	159.59± 10%
2	Leflunomide + Starch	312.62 mg	311.39 mg	286.58± 10%
3	Leflunomide + PVP	870.54mg	870.21mg	800.68 ± 10%
4	Leflunomide + Crospovidone	622.68mg	621.43mg	572.47±10%
5	Leflunomide + Aerosil	993.35mg	993.12mg	909.44±10%
6	Leflunomide + Mg.Stearate	911.50 mg	911.32 mg	909.44±10%

Physiochemical parameters and drug release pattern:

The tablets of leflunomide were prepared by wet granulation method were evaluated for weight variation, drug content, friability, hardness, thickness and drug release pattern for all the formulation 1 to 6.

Deals with results of all formulations 1 to 6 and experiments and their discussions. F(1) is made by without coprecipitation method i.e. 150mg , 200mg respectively; invitro dissolution studies showing that poor dissolution due to poor aqueous solubility of drug, So need to improve our method. In next batch F(2) we used PVP, leflunomide coprecipitates formation

using common solvent and formulated. In-vitro dissolution studies showing that aqueous solubility improved, but thephysical parameters hardness , disintegration time ,flow properties were not meet the specifications . So need to improve in further batches f(3) , F(4) , F(5) , F(6). F(6) is the final batch for both 150mg, 200mg tablets because it meets all the specification & in vitro dissolution profile also improved containing drug and PVP in ratio (1: 0.5). In vitro Comparative studies with marketed samples both 150mg 200mg has been done. Comparative studies indicate that using co-precipitation, aqueous solubility was relatively improved for both the strengths.

Characterization of Trial Blends

For 200 mg tablet

B.No	Bulk density*	Tapped density*	Loss on Drying in %*	Compressibility Index*	Hausner Ratio*	Angle of Repose(^{o})*
T1	0.525 ±. 0.023	0.625 ± 0.014	1.25 ± 0.011	22.22 ± 0.012	1.1904 ± 0.017	32^{o}±2
T2	0.535 ± 0.008	0.613 ± 0.022	1.22 ± 0.014	16.25 ± 0.023	1.145 ± 0.014	30^{o}±3
T3	0.567 ± 0.021	0.630 ± 0.011	1.17 ± 0.018	15.41± 0.018	1.11 ± 0.012	30^{o}±2
T4	0.507 ± 0.015	0.612 ± 0.017	1.15 ± 0.016	17.62 ± 0.013	1.2071 ± 0.016	28^{o}±3
T5	0.588 ± 0.015	0.642 ± 0.018	1.21 ± 0.011	16.51 ± 0.019	1.091 ± 0.015	26^{o}± 2
T6	0.575 ± 0.019	0.639 ± 0.016	1.19 ± 0.013	18.32 ± 0.016	1.111 ± 0.024	26^{o}±3

For 150 mg tablet

B.No	Bulk density*	Tapped density*	Loss on Drying in %*	Compressibility Index*	Hausner Ratio*	Angle of Repose(^{o})*

T1	0.531 ± 0.020	0.660 ± 0.012	1.14 ± 0.011	19.54 ± 0.015	1.241 ± 0.019	31°±2
T2	0.529 ± 0.006	0.645 ± 0.020	1.19 ± 0.014	18.25 ± 0.019	1.215 ± 0.030	32°±3
T3	0.531 ± 0.018	0.648 ± 0.014	1.21 ± 0.018	17.58± 0.021	1.223 ± 0.010	30°±2
T4	0.528 ± 0.015	0.655 ± 0.016	1.22 ± 0.016	19.25 ± 0.027	1.259± 0.021	27°±3
T5	0.532 ± 0.012	0.652 ± 0.014	1.12 ± 0.011	16.26 ± 0.014	1.142 ± 0.018	25°± 2
T6	0.530 ± 0.015	0.650 ± 0.018	1.15 ± 0.013	16.34 ± 0.028	1.114 ± 0.028	25°±3

Physical Characteristics of Finished products. (200mg)

S.No	Formulation no	Thickness (mm)	Hardness (kg/cm2)	Average weight (mg)	Friability (%)	DT Min.-sec.
1.	F-1	3.85-3.96	7.0-8.0	199.5-200.5	0.04	3m - 10s
2.	F-2	3.82-3.98	7.5-8.5	198.4-201.4	0.06	3m -15s
3.	F-3	3.81-3.95	4.4-4.6	199.8-202.6	0.41	1m – 5s
4.	F-4	3.86-3.98	5.5-5.8	199.6-202.2	0.25	2m – 4s
5.	F-5	3.82-3.96	5.6-5.9	198.5-20I.3	0.21	2m – 5s
6.	F-6	3.81-4.00	5.4-5.7	197.5-201.8	0.19	2m – 2s

Physical Characteristic of Finished products (150mg)

S.No	Formulation no	Thickness (mm)	Hardness (kg/cm2)	Average weight (mg)	Friability (%)	DT Min.-sec.
1.	F-1	3.24-3.30	5-5.5	148.9-151.5	0.03	3m - 05s
2.	F-2	3.22-3.26	5.4-5.6	146.5-150.2	0.04	3m -12s
3.	F-3	3.28-3.30	3.2-4.0	147.5-152.8	0.16	1m – 10s
4.	F-4	3.24-3.28	3.5-4.0	148.5-153.8	0.22	1m – 45s
5.	F-5	3.22-3.30	3.0-4.0	149.5-152.5	0.26	2m – 10s
6.	F-6	3.24-3.28	3.5-3.8	149.0-152.4	0.24	2m – 5s

Average Drug Content. (150mg)

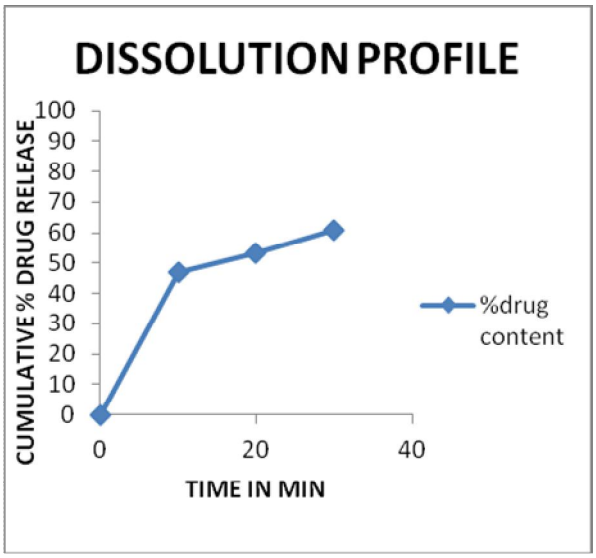
S.No.	Formulation no	leflunomide %
1.	F-1	72.50
2.	F-2	94.56
3.	F-3	94.36
4.	F-4	99.27
5.	F-5	99.34
6.	F-6	99.39

Average Drug Content. (200 mg)

S.No.	Formulation no.	leflunomide %
1.	F-1	73.40
2.	F-2	95.24
3.	F-3	95.25
4.	F-4	99.74
5.	F-5	99.25
6.	F-6	99.29

Dissolution Profile (200mg)

F1



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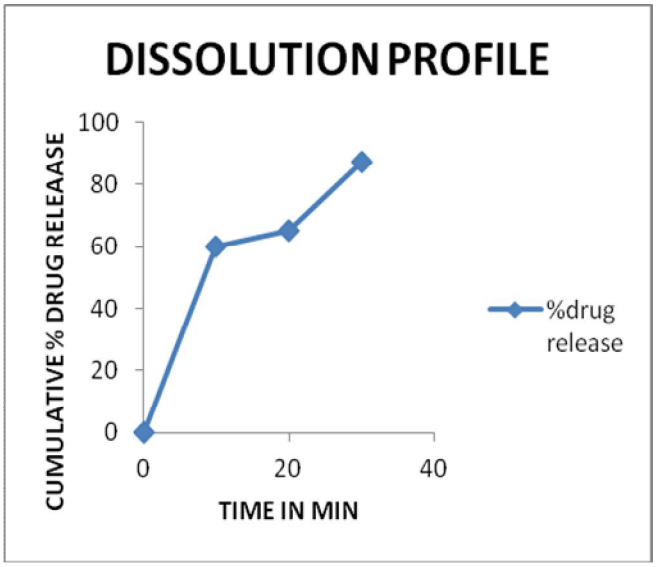

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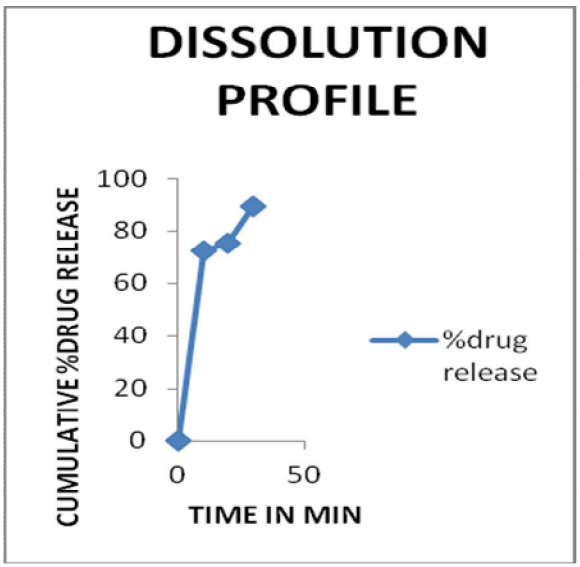

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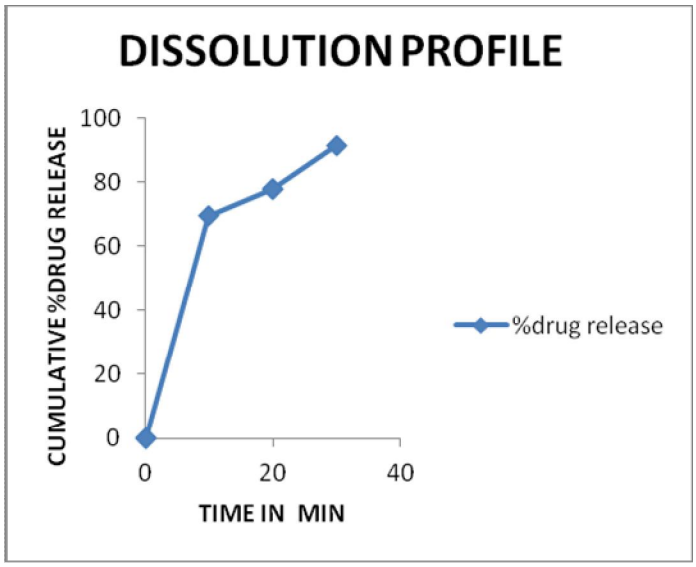

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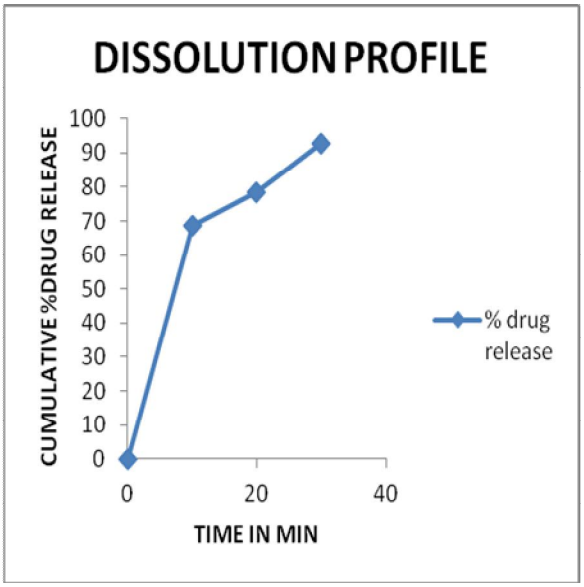

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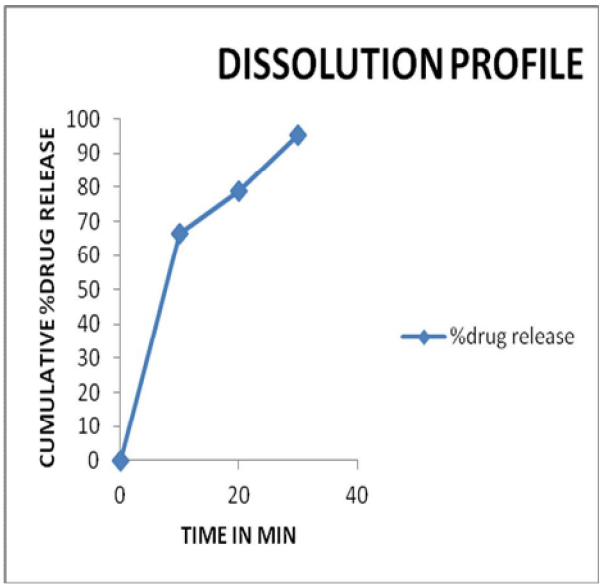
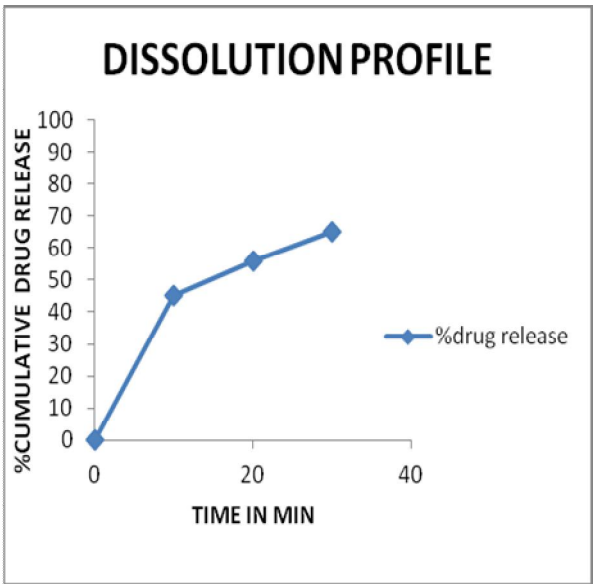


Dissolution Profile (150mg)

F1



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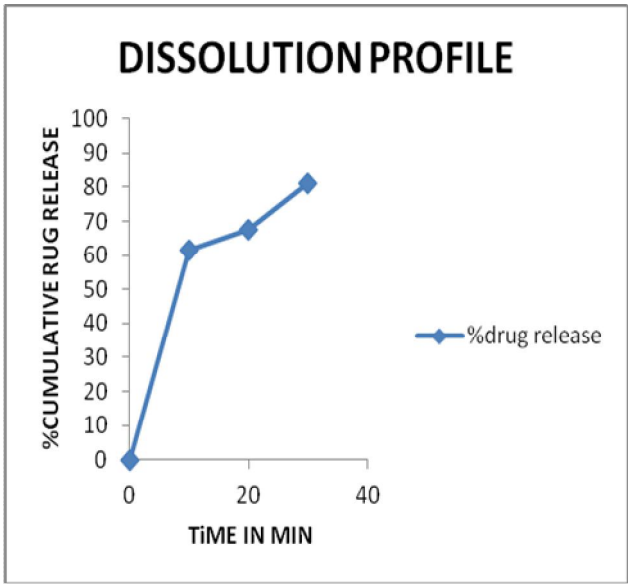

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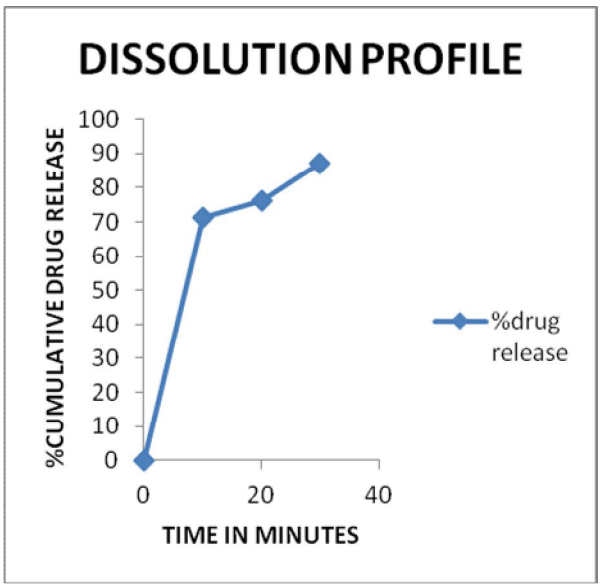

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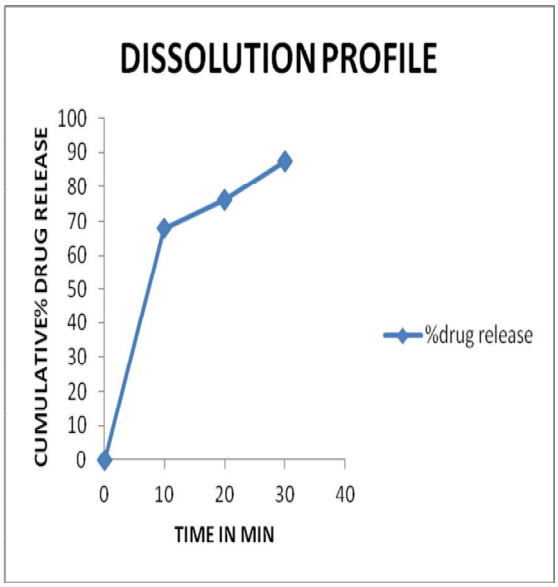

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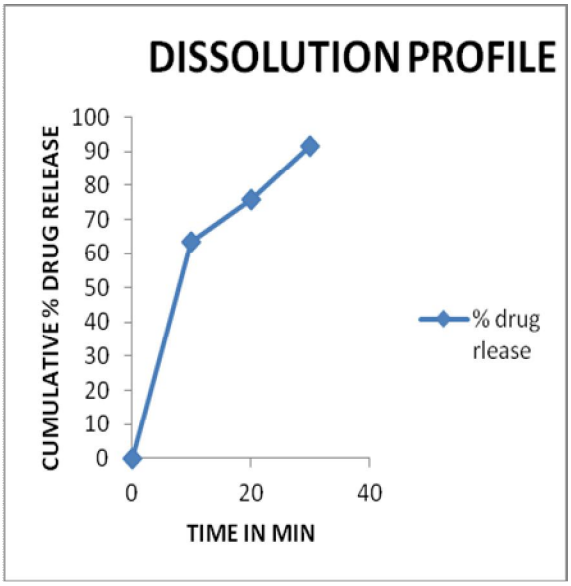
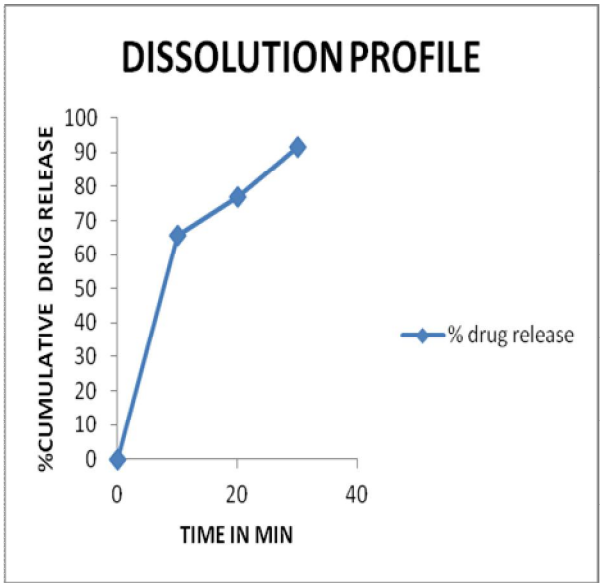


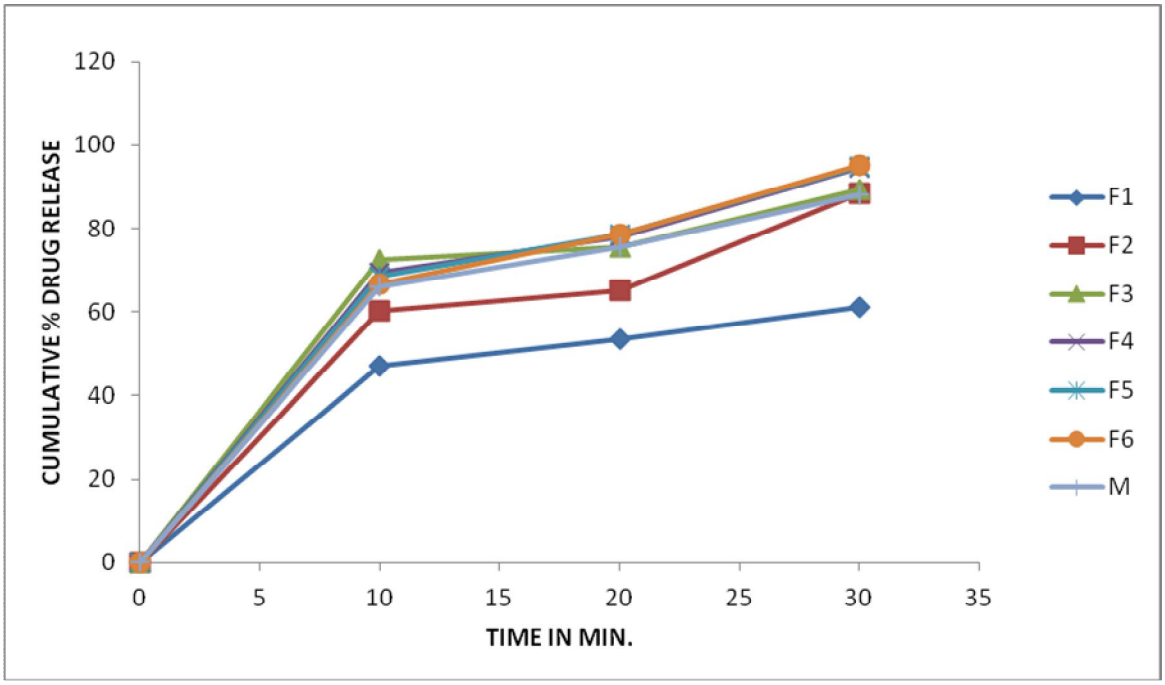
F6



Dissolution Profile of Leflunomide in (F1-F6) (200mg) with marketed tablet

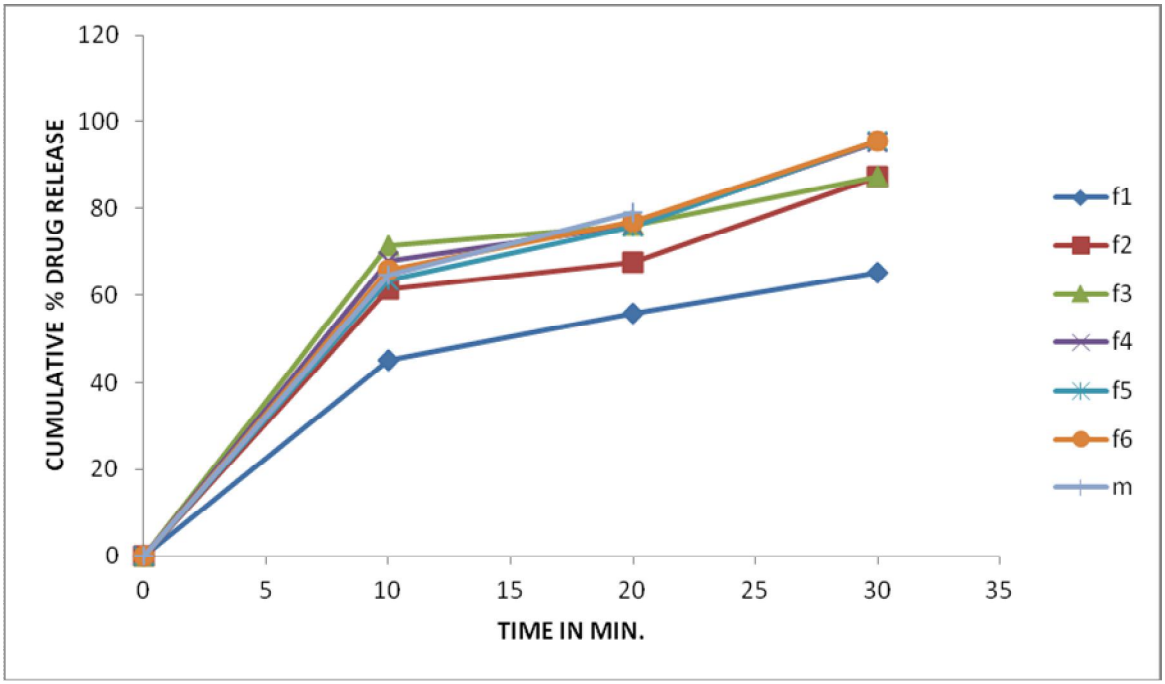
S.No	Time in minutes	Cumulative % Drug Release.						
		F-1	F-2	F-3	F-4	F-5	F-6	M
1.	00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

2.	10	47.01	60.23	72.33	69.51	68.55	66.52	65.91
3.	20	53.37	65.22	75.44	77.91	78.51	78.51	75.58
4.	30	60.99	88.37	89.31	94.48	94.88	95.32	88.05



Dissolution Profile of Leflunomide in (F1-F6) (150mg) with marketed tablet

S.No	Time in minutes	Cumulative %Drug Release						
		F-1	F-2	F-3	F-4	F-5	F-6	M
1.	00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.	10	45.25	61.45	71.45	67.82	63.45	65.85	64.68
3.	20	55.80	67.55	76.25	76.25	75.95	76.90	78.93
4.	30	65.29	87.25	87.29	95.22	95.48	95.68	86.04



For stability:

Optimized batch were taken and subjected for stability, we observed on stability data, optimized batch passes the tests.

Effect on physical properties of tablet at various Storage Conditions.

S.No	Properties	Initial	Storage conditions					
			25°C, 60% ± 5% RH		30°C, 65% ± 5%RH		40°C, 75% ± 5% RH	
			One month	Two month	One month	Two month	One month	Two month
1.	Colour	white colour	white colour	white colour	white colour	white colour	white colour	white colour
2.	Average weight (mg)	199.5-201.8	199.4-201.2	198.9-200.8	199.1-201.0	198.5-200.6	199.0-200.9	198.2-200.3
3.	Hardness	5.5-6.2	5.3-6.0	5.0-6.8	5.3-6.0	5.0-6.8	5.3-6.0	5.0-6.8

	Kg/cm2							
4.	Disintegration Time in (mins)	2.4-3.4	2.8-3.8	2.2-3.0	2.8-3.8	2.2-3.0	2.8-3.8	2.2-3.0
5.	Assay	99.29	99.10	99.02	99.07	99.01	99.03	99.00

CONCLUSION

The Formulation 6 has been found to possess ideal characteristics required for leflunomide tablets that meet all physical specifications. In -vitro dissolution studies concluded that aqueous solubility of leflunomide was improved using co-precipitation of leflunomide with PVP. Using co-precipitation in-vitro dissolution meet the specifications. So it was concluded as the final formula for leflunomide 20 mg tablet is 200mg containing leflunomide to PVP ratio (1:0.5).It was concluded as the final formula for leflunomide 10 mg tablet is 100 mg containing leflunomide to PVP ratio (1:0.5).

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