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SOLUBILITY AND DISSOLUTION ENHANCEMENT OF LEFLUNOMIDE USING NATURAL POLYMER BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Solid dispersions (SDs) are one of the most promising strategies used to improve the solubility of poorly water soluble drugs. This technology is mainly applied to improve the solubility of Class II and Class IV drugs. Leflunomide is an oral immunomodulatory agent used in the treatment of arthritis and it belongs to the BCS class-II. Many attempts are made in the past to increase its solubility by preparing its solid dispersions. However, very few literature reports are available wherein natural polymers are used for preparation of solid dispersions. In the present work, an attempt is made to increase the solubility of leflunomide by preparing its solid dispersions using natural polymer i.e., guar gum. Various techniques used for preparing solid dispersions are by physical mixture, co-grinding & modified kneading methods using different drug-polymer ratio. Thus prepared solid dispersions were evaluated for drug content & *in-vitro* dissolution studies. The result obtained from above studies indicated that, the solubility and dissolution of leflunomide solid dispersions was improved as compared to pure drug by all the methods employed. Among various methods employed, modified kneading method produced good results compared to physical mixture, co-grinding method. Hence, solid dispersion technology can be used to improve the solubility of leflunomide.

INTRODUCTION

Administration of drug by oral route is the most common & preferred method of delivery due to convenience & ease of taking drug. From a patient's point of view, swallowing a dosage form is a comfortable & a familiar means of administrating dosage form.[1] As a result, patient compliance & hence drug treatment is typically more effective with orally administered dosage form as compared with other routes of administration, for example, parenteral. Although, the oral route of drug administration is preferred, but for many drugs, it can be a problematic & inefficient mode of delivery for a number of reasons. Inadequate drug absorption gives poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route.[2]

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility & poor membrane permeability of the drug molecule. When taking an active agent orally, it must first dissolve in GI fluid before, it can then permeate the membranes of the GI tract to reach systemic circulation.[3] Therefore, a drug with low aqueous solubility will typically exhibit dissolution rate limited absorption & a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two points focus on improving the oral bioavailability of active agents include: (i) enhancing solubility & dissolution rate of poorly water-soluble drugs & (ii) enhancing permeability of poorly permeable drugs. There are various factors responsible for solubilization of drug such as practical size, temperature, pressure, nature of solute & solvent, molecular size, polymorph etc. [4]

Numerous solid dispersion methods have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as solvent evaporation, melt granulation technique, use of surfactant (s) & particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, each of these techniques have its own limitations. [5] On the other hand, formulation of drugs as solid dispersions offers a variety of processing & excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

The Biopharmaceutical Classification System (BCS) defines four classes of drug substances on the basis of their solubility and permeability characteristic are to be considered. BCS Class I (high solubility, high permeability), BCS Class II (low solubility, high permeability), BCS Class III (high solubility, low permeability) & BCS Class IV (low solubility, low permeability). Solid dispersion technologies are particularly promising for improving the oral

absorption and bioavailability of BCS Class II drugs. In solid dispersion drug disperse in the matrix generally a hydrophobic drug is dispersed in a hydrophilic matrix, which forms a solid dispersion. When the solid dispersion is interact with gastrointestinal fluid, the carrier or the polymer which enhance solubility of drug it gets first dissolves & the drug releases as fine colloidal particles. This results in enhanced surface area produces higher dissolution rate & bioavailability of poorly water-soluble drugs. It also sustained the release of drugs, altered solid state properties, enhance release of drugs from ointment & suppository bases & improved solubility & stability.[6]

MATERIAL AND METHOD

Materials: A gift sample of leflunomide was received from Arati Pharmaceutical, Mumbai and all chemicals used were obtained from S.D Fine chemicals, Mumbai of analytical grade.

Method:

Method of preparation: [7-9]

Physical Mixture:

The physical mixture of leflunomide with carrier at four different ratios (1:0.5, 1:1, 1:1.5 & 1:2) was prepared by simple mixing with spatula. This resulting mixture was sieved through a 80 mesh screen. The powder was stored in a screw cap container at room temperature.

Co-grinding Complex:

The mixture of leflunomide with carrier at four different ratios (1:0.5, 1:1, 1:1.5 & 1:2) was prepared by grinding the required amount of leflunomide and carriers for 45 min in a mortar with pestle until a homogeneous mixture was obtained. This resulting mixture was sieved through 85 mesh screen. The powder was stored in a screw cap container at room temperature.

Modified Kneading Method:

Solid dispersion of leflunomide with carrier at different ratios (1:0.5, 1:1, 1:1.5 & 1:2) was prepared by modified kneading technique. Drug and polymer were triturate by taking 50:50 ratio of methanol and water in mortar for 45 min. & the slurry was kept in deep freezer for 24 hr and this freeze slurry dried by lyophilizer. Powder was stored in a screw cap container at room temperature.Operating parameters like -40°C, 4kg/test cycle pressure to be maintained.

Evaluation of Prepared Solid Dispersions:

Analysis of Drug Content: [10] The content of leflunomide in each physical mixture, co-grinding & modified kneading complex was determined by using UV spectroscopy. Accurately weighed physical mixture, co-grinding and modified kneading complex in solid

dispersion equivalent to 20 mg of leflunomide was transferred to 100 ml volumetric flask containing 20 ml of methanol & dissolved. The volume was made up to 100 ml with water. The solution was filter through 0.45-µm membrane filter paper. One ml of this solution was diluted 10 times with same solvent and the absorbance was measured at 257 nm.

Dissolution Studies: [11]

The prepared physical mixture, co-grinding & modified kneading complex were subjected to the dissolution study by using USP dissolution apparatus (type II) at 50 RPM at temperature of 37±0.5°C using 900 ml volume of pH 1.2 and pH 7.4 buffers used as the medium, equivalent to 20 mg of drug was taken. Samples of 10 ml were withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 257 nm and the drug release was determined.

Characterization of Solid Dispersion: [12-14]

Infrared Spectroscopy:

The IR spectrum of leflunomide, guar gum & the physical mixture, co-grinding complex, modified kneading complex with guar gum were recorded in the stretching frequency range of 450 to 4000 cm^{-1}. Samples were evaluated by ATR (Attenuated Total Reflectance) Model.

Differential Scanning Calorimeter:

The DSC thermograms of leflunomide, guar gum & the physical mixture, co-grinding complex, modified kneading complex with guar gum were recorded. The samples were separately sealed in aluminum cells and set in PerkinElmer (Pyris 1) DSC. The thermal analysis was performed in a nitrogen atmosphere over a temperature range of 50°C to 250°C.

X- Ray Diffraction:

The X-ray diffraction pattern of leflunomide, guar gum & the physical mixture, co-grinding complex, kneading complex with guar gum were recorded from 5 to 100° at an angle 2θ using diffractometer system.

Dosage Form Development:

The solid dispersion that showed maximum drug release was further formulated as tablets containing solid dispersion equivalent to 20 mg, microcrystalline cellulose & magnesium stearate. The blend was formulated into tablets and evaluated for weight variation test, content uniformity of tablets, friability test, hardness, dissolution study & stability study.

RESULT AND DISCUSSION

Solid dispersions of the leflunomide with guar gum were prepared by physical mixture, co-grinding complex & modified kneading complex in various ratios was represented in Table 1. The prepared solid dispersions of leflunomide were evaluated for drug content & *in-vitro* dissolution studies**.** Data of evaluation study was represented in Table 2. The drug content was found to be high in 1:0.5 (99.15%) as compared to other ratios. The results of FTIR, DSC and XRD confirmed that, there was an interaction occurs due to hydrogen bonding between leflunomide and guar gum, hence the formation of solid dispersion (fig: 1-9). The observed increase in the solubility of leflunomide in solid dispersions is thought to be attributable to the solubilization effect of the guar gum. Fig: 10-15 gives the *in-vitro* dissolution profiles of pure drug of leflunomide & its solid dispersions by different methods. The result indicated that, maximum percentage of drug release was found in modified kneading method in the ratio 1:0.5 (98.86 %) in 120 min. & the dissolution rate of other solid dispersions are also high in contrast to the pure drug (Table-2). As the proportion of guar gum decreased, dissolution rates have been increased. The improvement of dissolution may be due to its hydrophilic nature of the carrier. Thus, it can be concluded that the solubility & dissolution rate of the poorly soluble drug, leflunomide can be improved markedly by using solid dispersion technique and the carrier, guar gum.

Table 1: Formulation of Solid Dispersions

Mixture code	Carrier	Drug: Polymer ratio	Method used
PM_1	Guar gum	1:0.5	Physical mixture
PM_2	"	1:1	
PM_3	"	1:1.5	
PM_4	"	1:2	
CGC_1	"	1:0.5	Co-grinding complex
CGC_2	"	1:1	
CGC_3	"	1:1.5	
CGC_4	"	1:2	Modified kneading
MKC_1	"	1:0.5	complex
MKC_2	"	1:1	
MKC_3	"	1:1.5	
MKC_4	"	1:2	

Table 2: Evaluation Parameters for the Different Formulations

Sr. No.	Formulation Code	Drug Content (%)	Average % Release at 120 min.	
			pH 1.2	pH 7.4
1	Leflunomide	-	7.51	10.34
2	PM_1(1:0.5)	98.43	79.95	85.53
3	PM_2(1:1)	98.31	77.75	83.80
4	PM_3(1:1.5)	97.37	56.41	71.56
5	PM_4(1:2)	96.16	44.21	59.34
6	CG_1(1:0.5)	95.17	46.32	57.93
7	CG_2(1:1)	94.15	43.17	49.06
8	CG_3(1:1.5)	94.41	36.71	42.06
9	CG_4(1:2)	92.39	27.02	32.62
11	MKM_1(1:0.5)	99.15	84.68	98.86
12	MKM_2(1:1)	98.10	80.16	95.35
13	MKM_3(1:1.5)	98.10	71.38	88.24
14	MKM_4(1:2)	97.24	62.54	72.01

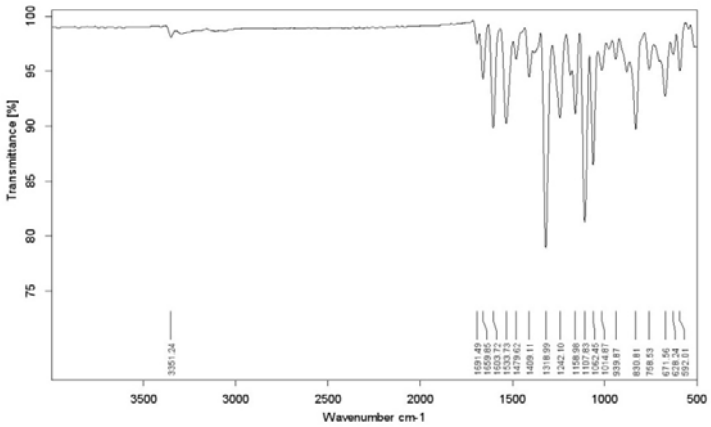

Fig. 1: FTIR spectrum of Leflunomide

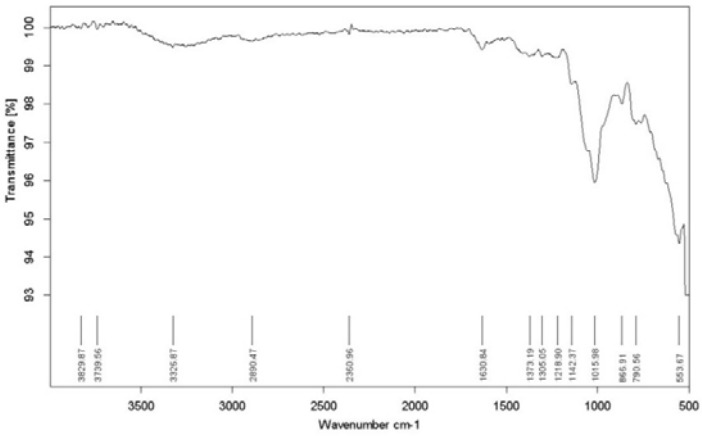

Fig. 2: FTIR spectrum of Guar gum

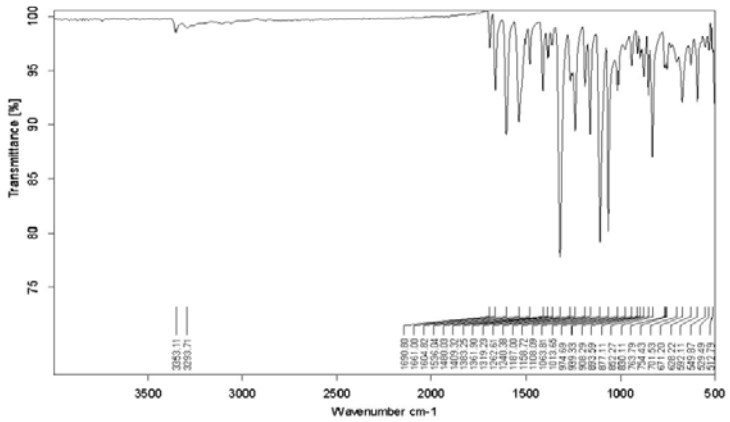

Fig. 3: FTIR spectrum of Solid dispersion

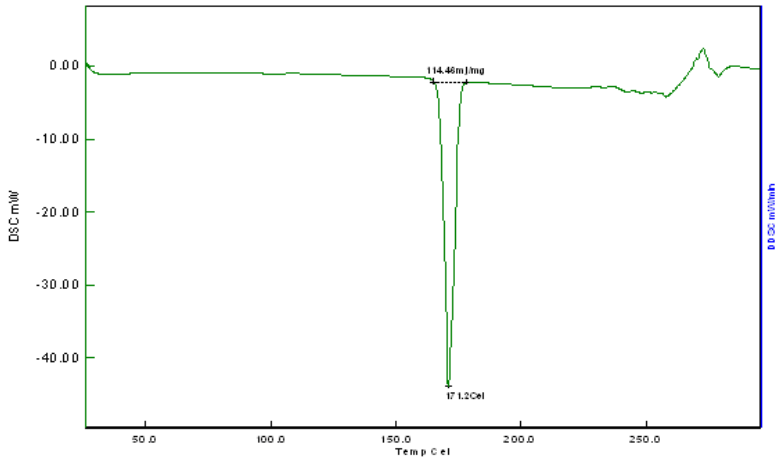

Fig. 4: DSC Thermogram of Leflunomide

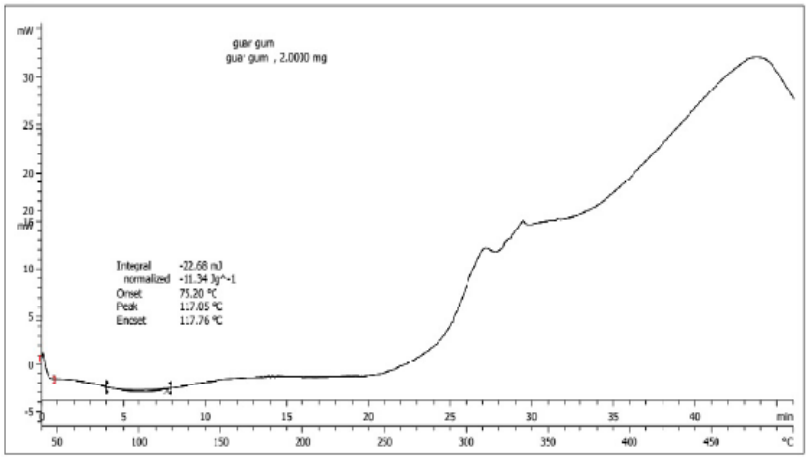

Fig. 5: DSC thermogram of Guar gum

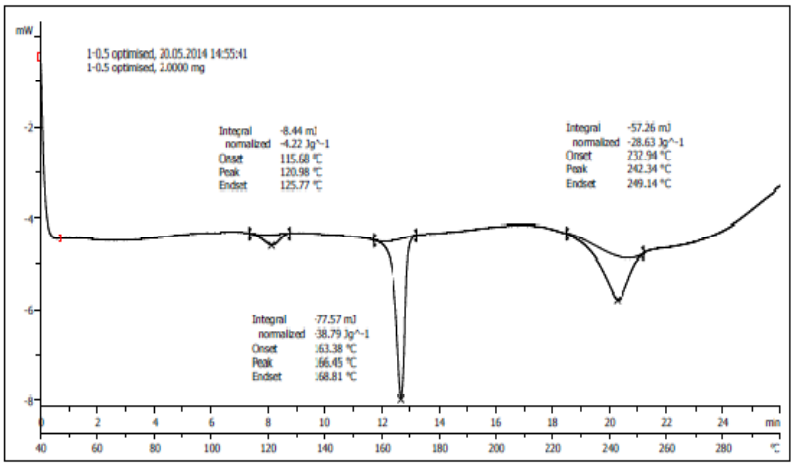

Fig. 6: DSC thermogram of Solid Dispersion

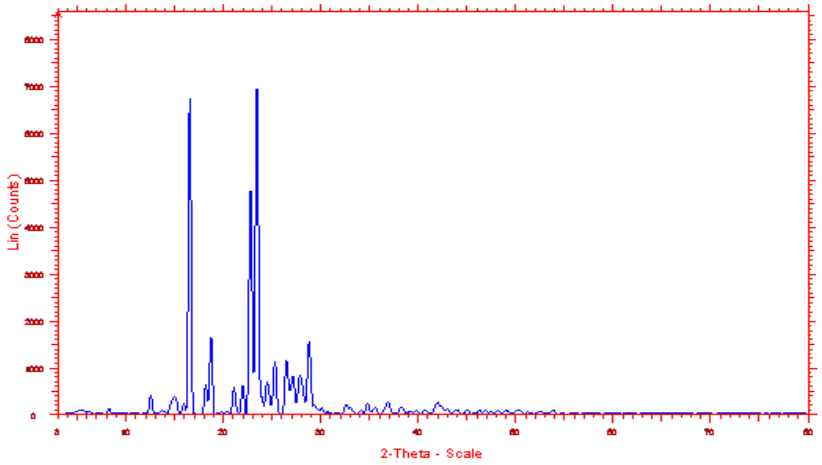

Fig. 7: XRD pattern of Leflunomide

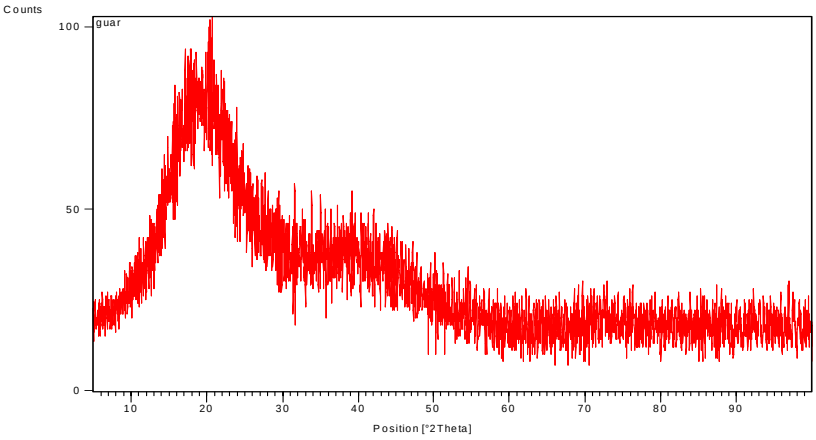

Fig. 8: XRD pattern of Guar gum

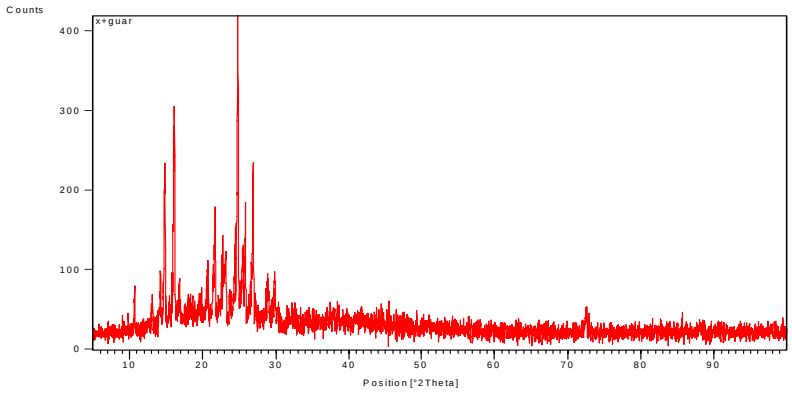

Fig. 9: XRD pattern of Solid Dispersion

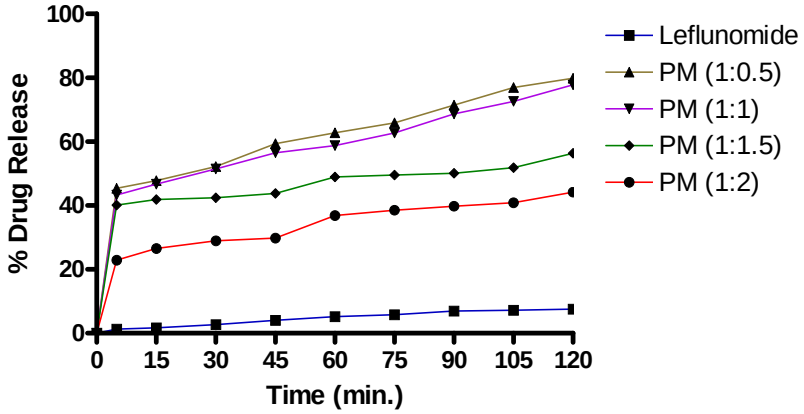

Fig. 10: *In-vitro* dissolution profile of Leflunomide & physical mixture with Guar gum (1:0.5, 1:1, 1:1.5 and 1:2) in pH 1.2

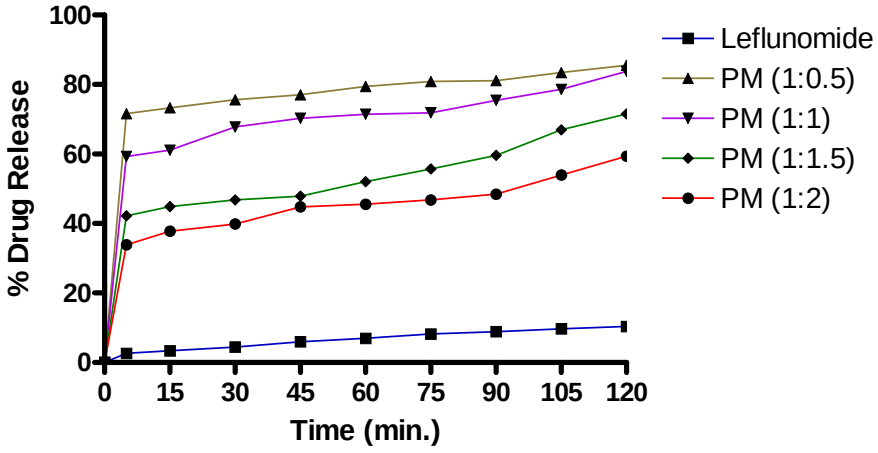

Fig.11: *In-vitro* dissolution profile of Leflunomide & physical mixture with Guar gum (1:0.5, 1:1, 1:1.5, 1:2) in pH 7.4

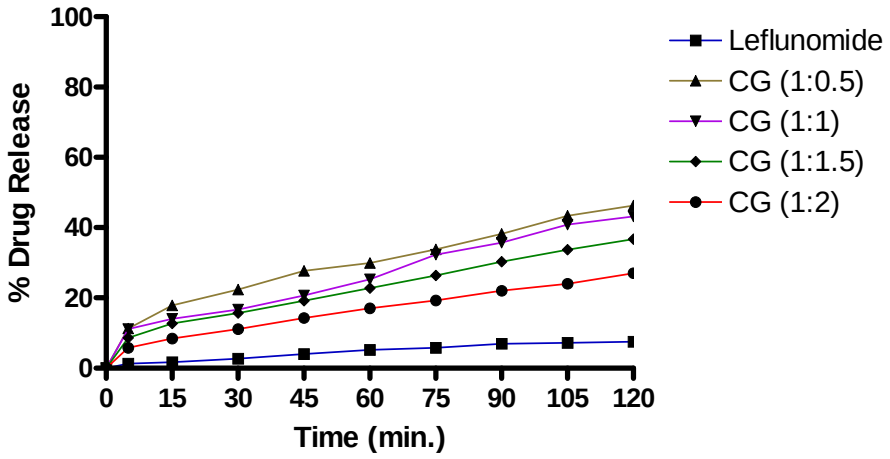

Fig. 12: *In-vitro* dissolution profile of Leflunomide & co-grinding complex with Guar gum (1:0.5, 1:1, 1:1.5, 1:2) in pH 1.2

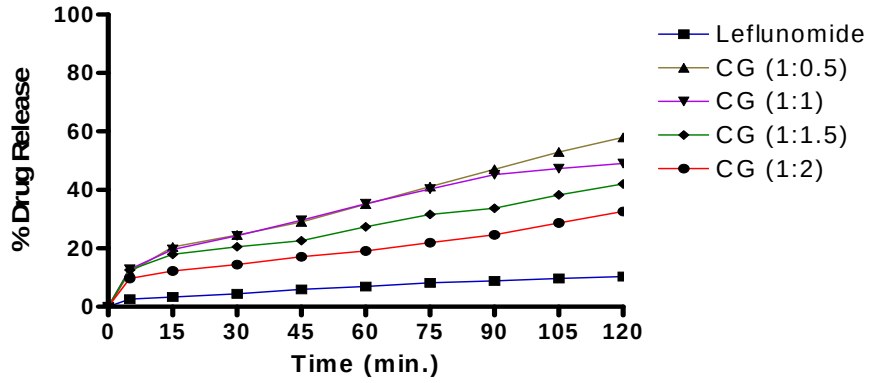

Fig. 13: In-vitro dissolution profile of Leflunomide & co-grinding complex with Guar gum (1:0.5, 1:1, 1:1.5, 1:2) in pH 7.4

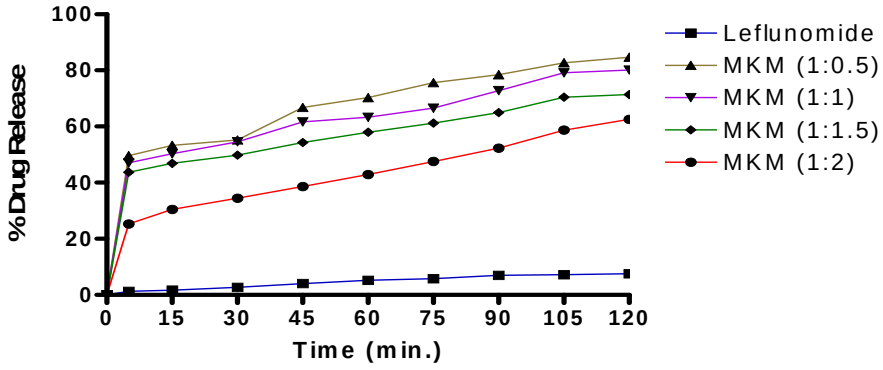

Fig. 14: *In-vitro* dissolution profile of Leflunomide & modified kneading complex with Guar gum (1:0.5, 1:1, 1:1.5, 1:2) in pH 1.2

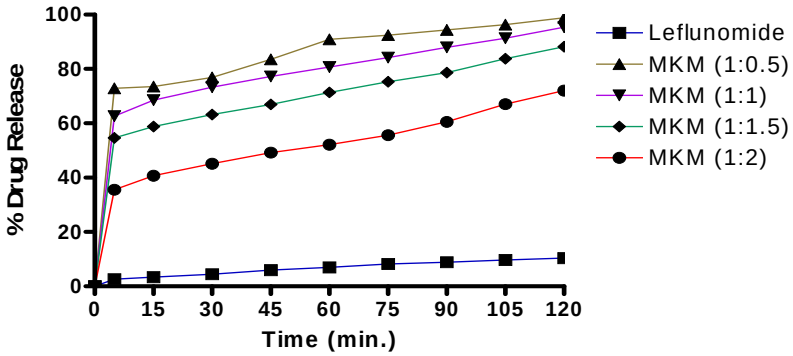

Fig. 15: *In-vitro* dissolution profile of Leflunomide & modified kneading complex with Guar gum (1:0.5, 1:1, 1:1.5, 1:2) in pH 7.4

CONCLUSION

The solid dispersions of leflunomide with the guar gum as carrier were prepared & evaluated. From the results of FTIR, DSC and XRD we concluded that there was an interaction between the drug and carrier, hence the formation of solid dispersion (Fig. 1-6). The solubility and dissolution studies have shown that there is a possibility of improved solubility of leflunomide through solid dispersion with natural polymer viz., guar gum. A maximum increase in dissolution rate was obtained with Leflunomide: guar gum solid dispersion with a weight ratio of 1:0.5 prepared by modified kneading complex (Table-2) though physical mixtures & co-grinding complex showed faster dissolution rate when compared with that of pure drug.

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REFERENCES

1. Keraliya AR, Soni GT, Thakkar TV, Gandhi RT, Patel CR. Formulation & Physical Characterization of Microcrystals for Dissolution Rate Enhancement of Tolbutamide. Int J Pharm Sci 2010 ; 1(1):69-77.
2. Dora CP, Singh SK, Development & Characterization of Nanoparticals of Glibenclamide by Solvent Displacement Method. Acta Poloniae Pharma Drug Res 2010; 67(3):283-292.
3. AbdElbary AA, Maher ME. *In vitro & in vivo* Evaluation of Glibenclamide using Surface Solid Dispersion (SSD) Approach. Br J Pharmacol Toxicol 2011; 2(1):51-62.

4. Bhanja SB, Ellaiah P, Martha SK. Sahu A. Pandhy SK. Preparation & Evaluation of Solid Dispersions of Poorly Soluble Drug Repaglinide. Asian J Biochem Pharm Res 2011; 3(1):2231-2560.
5. Hyma P, Ravikanth N, Reddy CH. Improvement of Solubility & Dissolution Rate of Pioglitazone by Solid Dispersion Technique. Int J Pharm Sci 2012; 3(6):423-431.
6. Reddy KK, Rao NB, Reddy RK. Study on Effect of Excipients in Enhancing the Solubility of Nateglinide by Solid Dispersion. Asain J Pharm Technol 2012; 2(1):04-07.
7. Kumar S, Rai U, Singh R, Srivastava VP. Solubility Enhancement of Dicyclomine using Solid Dispersion Techniques. World J of Pharm Res 2013; 2(2):445-458.
8. Aruna MS, Babu AK, Thadanki M, Gupta ME. Solid Dispersions-An Approach to Enhance the Dissolution Rate of Irbesartan. Int J of Res in Pharm and Chem 2011; 1(4):780-788.
9. Pawar AR, Choudhari PD. Novel Techniques for Solubility, Dissolution Rate & Bioavailability Enhancement of Class II & IV Drugs. Asian J of Biomed & Pharm Sci 2012; 2(13):9-14.
10. Reddy M KK, Rao BN, Reddy KR. Study on Effect of Excipients in Enhancing the Solubility of Nateglinide by Solid Dispersions. Asian J Pharm Tech 2012; 2(1):4-7.
11. Indian Pharmacopoeia, Controller of Publications, Government of India, Ministry of Health and Welfare, New Delhi, 1996,Vol.II, A-82-84.
12. Kumar S, Parkash C, Kumar P, Singh SK. Application of some Novel Techniques for Solubility Enhancement of Mefenamic acid, a Poorly Water Soluble Drug. Int J of Pharm Sci and Drug Res 2009; 1(3):164-171.
13. Willard HH, Merritt LL, Dean JA, Settle FA. Instrumental Methods of Analysis. 7th ed. New Delhi: CBS publishers and distributors; 1986, 287-762.
14. Jain S, Sandhu P, Gurjar M, Malvi R. Solubility Enhancement by Solvent Deposition Technique: An Overview. Asian J of Pharm & Clin Res 2012; 5(4):15-19.