J.Padmapreetha et al /J. Pharm. Sci. & Res. Vol. 8(7), 2016, 586-593

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Effect of Kolliphor El on Dissolution Rate of Leflunomide Liquisolid Compacts

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Abstract

Leflunomide is an immunosuppressive disease-modifying antirheumatic drug (DMARD), used in active moderate-to-severe rheumatoid arthritis and psoriatic arthritis. It is highly lipophilic drug which belongs to BCS class II drug and its solubility in water (less than 40 mg/L). The main objective of the present investigation was to develop leflunomide liquisolid compact to improve dissolution rate. Liquisolid compacts were prepared using Kolliphor EL as liquid vehicle, Avicel PH 102 as carrier, aerosil as a coating material and sodium starch glycolate used as a superdisintegrant. The developed formulations were subjected to Fourier transform infrared spectroscopy which showed that there is no interaction between drug and excipients. Both DSC and XRD revealed that leflunomide crystallinity totally lost upon liquisolid formulation which was further confirmed by SEM studies that even though the drug existed in a solid dosage form, it is available in moleculary dispersed state. The powder characteristics were evaluated by different flow parameter to comply with pharmacopoeial limits. Liquisolid tablets were further investigated to hardness, friability and disintegration studies. *In vitro* dissolution profiles of liquisolid formulation were carried out and compared with conventional DCT formulation. The results showed that the selected optimized formulation LFK8 released 73.39% of its content during the first 10 min ($Q_{10\%}$) compared to 18.94 % of conventional DCT formulation. In conclusion, dissolution rate of leflunomide can be enhancing to a greater extent by liquisolid technique.

Key Words: Dissolution; Kolliphor EL; Leflunomide; Liquid load factor; Liquisolid tablets

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids [1]. "Liquisolid compact technique" is successful tool to improve the solubility and dissolution of poorly water soluble drugs and consequently bioavailability [2]. The term liquisolid compacts was derived from powder solution technology that can be used to formulate liquid medication. It refers to solid drugs dispersed in suitable non-volatile liquid vehicles by simple mixing. The liquid medication converted as dry looking, non-adherent, free flowing and readily compactible powder admixtures by blending with selected carriers and coating materials. The appropriate amounts of carrier and coating materials to produce acceptable flowing and compactible powders are calculated using Eqs. (1)- (3), based on the physical properties of powders termed flowable liquid retention potential (ϕ -value) and compressible (Ψ-value) liquid retention potential of the constituent powders. The ratio (R) of the amount of carrier (Q) and coating materials is closely related to the amount of liquid medication (W). The term liquid load factor refers to maximum amount of liquid loads on the carrier material. The carrier:coating ratio (R) is important factor for determining the optimum flowable load factor (L_f) which gives acceptable flowing powders and is characterized by the ratio between (W) and (Q), as shown in Eqs. 1 and 2.

$L_f = \phi_{CA} + \phi_{CO}$ (1/R) (1)

Where, ϕ_{CA} is the flowable liquid retention potential of the carrier and ϕ_{CO} is the flowable liquid retention potential of the coating material.

$L_f = W/Q$ (2)

From Eq.2 the amount of carrier can be calculated and applied to the Eq.(3) to calculate the required amount of the coating (q) material [3].

$R = Q/q$ (3)

In this work leflunomide was used as a model hydrophobic drug to apply liquisolid technique as a tool for drug dissolution enhancement. Leflunomide is used for the treatment of rheumatoid arthritis an illness that affects soft tissues and bones and can cause irreversible joint deformities and functional impairment [4]. It is practically insoluble in water (less than 40mg/L), so belongs to class II of the biopharmaceutical classification systems (BCS) and the studies on solubility enhancement are essential in this compound [5]. To the best of our knowledge no research articles had been published yet to entail improvement of leflunomide dissolution via liquisolid technique.

MATERIALS AND METHODS

Material

Leflunomide was kindly gifted by Alembic pharmaceuticals Ltd. Vadodara, Avicel PH 102, Aerosil 200 was gifted by (FMC biopolymers, USA), Propylene glycol (Loba chemie), Kolliphor EL (BASF - Germany), Tween 80 (RFCL Ltd), PEG 400 (Merck), Sodium starch glycolate (Rouquette -Germany), Magnesium stearate (Otto Kemi), Talc (SD fine chem).

Saturation solubility studies [6]

Solubility studies of leflunomide were performed in Kolliphor EL, PEG 400, propylene glycol, and distilled water. Saturated solutions were prepared by adding excess amount of leflunomide in a screw capped vials containing 5 ml of vehicles. The vials were sealed and shaken on

mechanical shaker for 24 hrs at 37± 2^0C and then settled for another 2 hours. The screw capped vials were centrifuged at 2500 rpm for 20 minutes for further settling of undissolved crystalline material and thereby obtaining a clear supernatant. Supernatant was filtered through membrane filter using 0.45µm filter disk. The drug concentration was determined using UV/Visible spectrophotometer (Schimadzu UV-1700) at 258 nm after appropriate dilution with methanol.

Preparation of leflunomide liquisolid compact and conventional tablet [3]

Leflunomide liquisolid formulations denoted as LFK1 – LFK12 (Table 1) were prepared using Kolliphor EL as liquid vehicle with four different drug: vehicle ratios (1:1, 1:2, 1:3, 1:5). Leflunomide (10 mg/tablet) was dispersed in the liquid vehicle with continuous mixing using mortar and pestle to produce the liquid medication. All liquisolid formulations contained Avicel PH102 as the carrier material and aerosil as the coating material at a three different powder ratio (R) viz. 5, 10 and 20. The appropriate amounts of the carrier and coating materials used in the liquisolid formulation were derived from their ϕ-value and liquid load factors (L_f) as shown in equation (1) – (3). L_f can be calculated by substitute the flowable liquid retention potential of the carrier (ϕ_{CA}) and flowable liquid retention potential of the coating material (ϕ_{CO}) into equation (1). By knowing liquid load factors (L_f) and amount of liquid medication (W) appropriate amounts of carrier material (Q) and coating material (q) (Table 1) can be calculated using Equations (2) and (3). The appropriate amount of carrier Avicel PH 102 was mixed with the drug vehicle suspension. Aerosil was then added to convert the wet mixture into dry powder under continuous mixing. Finally, 5% W/W of sodium starch glycolate as a disintegrant was added into the mixture and mixed for 10 min. the final mixture was compacted on a tabletting machine (10 station minipress). Additionally leflunomide conventional tablets (DCT) were prepared. Table 1 shows the amount of carrier (Q), coating material (q), drug concentration (W/W) and liquid load factor (L_f) used to prepare different liquisolid formulations LFK1-LFK12.

Precompression studies [7]

Flow properties are the prime importance in the formulation of tablet dosage form on industrial scale. Therefore all the prepared liquisolid powders were subjected to undergo the precompression studies such as angle of repose, compressibility index and hausner's ratio.

Angle of repose.

The angle of repose of powder blend was determined by fixed height funnel method. Angle of repose (θ) was calculated using the following equation:

$\theta = \tan\text{-}1\ (h/r)$ (4)

Where h = height of pile, r = radius of the base of the pile. θ = angle of repose.

Compressibility index

The compressibility index of the powder blend was determined by carr's compressibility index. The formula for carr's index is as follows

Carr's index (%)

= [(Tapped density – Bulk density) × 100]/ Tapped density (5)

Hausner's Ratio

Hausner's ratio was calculated from the equation:

Hausner's ratio = Tapped density/ Bulk density (6)

Differential scanning calorimetry

DSC thermograms of leflunomide, Avicel PH 102, Aerosil, and optimized liquisolid formulations were obtained with DSC scanning calorimetry (Model NETZSCHSTA 449F3 STA449F3A-1100-M). Samples (0.733- 2.14 mg) were weighed and transferred into the equipment for analysis in sealed hermetically aluminium pans. The instrument was calibrated with indium before running the samples. Thermal behavior of the samples was investigated at a scanning rate 10.0 K/min, from 0° C to 350° C.

Fourier-transform infrared spectroscopy (FTIR)

FTIR spectroscopy helps to determine any chemical interaction between drug and excipients used in the formulation. FTIR spectra of pure leflunomide and physical mixtures were obtained using JASCO FTIR- 4100 spectrophotometer in the range of 4000-400 cm^{-1}.

Scanning electron microscopy (SEM)

Scanning electron microscopy was performed for optimized formulation using a CARLZEISS SIGMA scanning electron microscope in order to assess the morphological characteristics of the optimized liquisolid formulation.

Post compression studies

The hardness of liquisolid tablets was determined using a Pfizer Hardness Tester (Shreeji chemicals)**.** The mean hardness of each formulation was determined. The friability of prepared liquisolid tablets was determined using a Digital Tablet Friability Tester (Thermonik, Campbell electronics)**.** Disintegration time was measured using a USP Disintegration Tester (Campbell electronics)**.**

Drug content

20 tablets were weighed and finely powdered in glass mortar. An accurately weighed portion of powder equivalent to about 10 mg of powder transferred to 10 ml volumetric flask containing 10 ml of methanol. It was sonicated for 15 min and was filtered through whatmann filter paper. It was then diluted suitably with distilled water with 0.03% SLS. The absorbance of both standard and sample preparation after appropriate dilution were measured in UV spectrophotometer (Model Disso 2000, Lab India) at 258 nm using distilled water with 0.03% SLS.

***In vitro* drug release study**

The dissolution rates of all formulations were measured in dissolution test apparatus (Tab machines,Mumbai) by tablet dissolution apparatus USP Type II. Dissolution studies were carried out using 900 ml of distilled water with 0.03% sodium lauryl sulphate, as dissolution media, at 50 rpm and at temperature of 37 ± 0.5^0C. Appropriate aliquots were withdrawn at suitable time interval (5, 10, 15, 20, 25, 30 40, 50 and 60 min) and filtered through Whatman filter paper and diluted as per need with distilled water with 0.03% sodium lauryl sulphate. Sink conditions were maintained throughout the study. The samples were then analyzed at λmax of 258 nm by UV/visible spectrophotometer.

Table 1 Formulation of liquisolid systems

Formulation code	Drug concentration in liquid medication (% w/w)	R	L_f	Drug	Liquid Vehicle (mg)	Avicel PH 102Q (mg)	Aerosil 200q (mg)	Unit dose (mg)	F_M
LFK1	50	5	0.45	10	10	44.44	8.888	77.76	0.094
LFK2	33.33	5	0.45	10	20	66.67	13.33	116.65	0.188
LFK3	25	5	0.45	10	30	88.89	17.78	155.55	0.282
LFK4	17	5	0.45	10	50	133.33	26.67	233.32	0.469
LFK5	50	10	0.36	10	10	55.56	5.556	86.02	0.094
LFK6	33.33	10	0.36	10	20	83.33	8.333	129.02	0.188
LFK7	25	10	0.36	10	30	111.11	11.11	172.04	0.282
LFK8	17	10	0.36	10	50	166.67	16.67	258.07	0.469
LFK9	50	20	0.315	10	10	63.492	3.175	91.91	0.094
LFK10	33.33	20	0.315	10	20	95.238	4.762	137.86	0.188
LFK11	25	20	0.315	10	30	126.984	6.349	183.82	0.282
LFK12	17	20	0.315	10	50	190.476	9.524	275.73	0.469
Conventional tablet (LFK8)	-	-	-	10	-	166.67	16.67	208.07	-

RESULTS AND DISCUSSION

Saturation solubility studies

Solubility of leflunomide was determined in a three different liquid vehicles and shown in Table 2. The solubility of leflunomide in distilled water, PEG 400, propylene glycol and kolliphor EL was 0.058, 3.921, 2.071 and 99.474 mg/ml respectively. As shown in Figure 1 the solubility of leflunomide increases in the order of propylene glycol < polyethylene glycol 400 < Kolliphor EL. Solubility of leflunomide was significantly increased in presence of Kolliphor EL i.e. 99.474 mg/ml. So, Kolliphor EL was selected as a non-volatile solvent in preparation of liquisolid compacts.

Table 2 Solubility of leflunomide in various liquid vehicles

S.No	Liquid vehicle	Solubility (mg/ml)
1.	Water	0.058
2.	Propylene glycol	2.071
3.	PEG 400	3.921
4.	Kolliphor EL	**99.474**

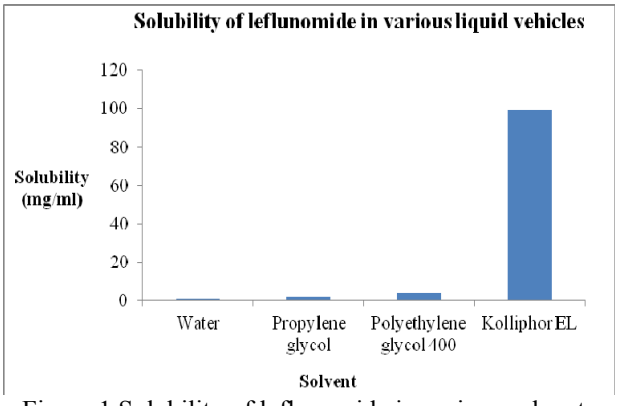


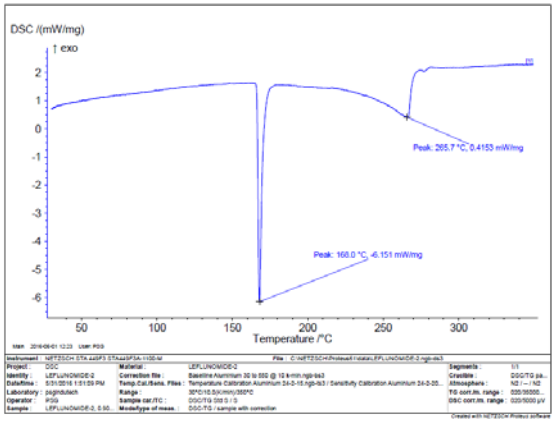
Figure 1 Solubility of leflunomide in various solvents

Precompression studies

The flowing property of a powder is an important part of the industrial production of a tablet dosage form. Optimal flowability is important during tablet formulations to ensure that the flow of powder from hopper to die cavity is uniform and reproducible in order to obtain tablets with uniform weight and drug content. The results of various flow parameters are shown in Table 3. Angle of repose is a characteristic of the internal friction or cohesion of the particles. In general, an angle of repose ≥ 40° indicates a powder with poor flowability [8]. All formulations had an angle of repose within the aforementioned range. Carr's index is a useful parameter in reflecting in interparticulate friction within the powder mass. The powder flowability of leflunomide liquisolid formulations was determined using carr's index and the values ranged between 5 % and 23.08 %. Hausner's ratio was calculated for all the liquisolid formulations and it was found to be between 1.03 and 1.3 indicating that except LFK2 all the formulations possess good flow property and were in accordance with the limit of < 1.25 for good flow.

Table 3 Precompression studies of prepared liquisolid powders

S.No	Formulation code	Angle of repose	Carr's index	Hausner's ratio
1.	LFK1	13.63	6.67	1.07
2.	LFK2	14.04	23.08	1.3
3.	LFK3	14.47	14.29	1.17
4.	LFK4	27.96	9.09	1.1
5.	LFK5	14.26	11.0	1.13
6.	LFK6	22.64	7.69	1.08
7.	LFK7	23.67	9.5	1.11
8.	LFK8	27.63	6.25	1.07
9.	LFK9	15.95	13.33	1.15
10.	LFK10	19.98	11.11	1.13
11.	LFK11	32.01	5.0	1.05
12.	LFK12	38.15	5.0	1.05



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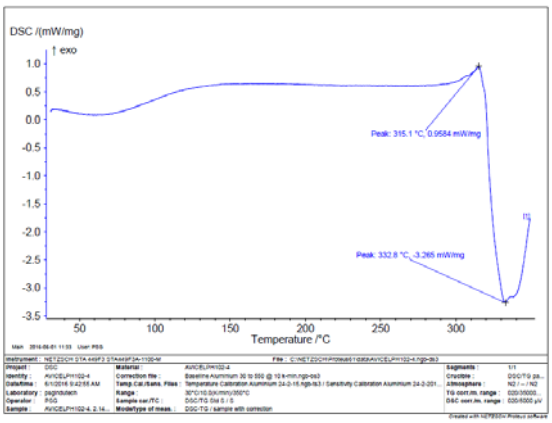

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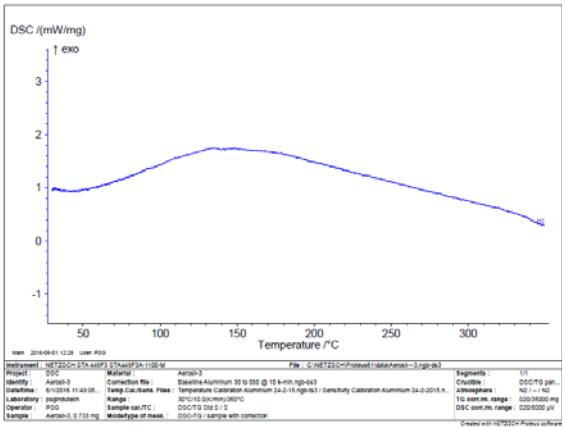
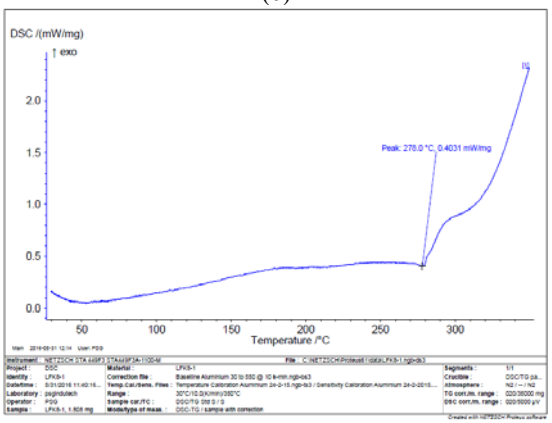
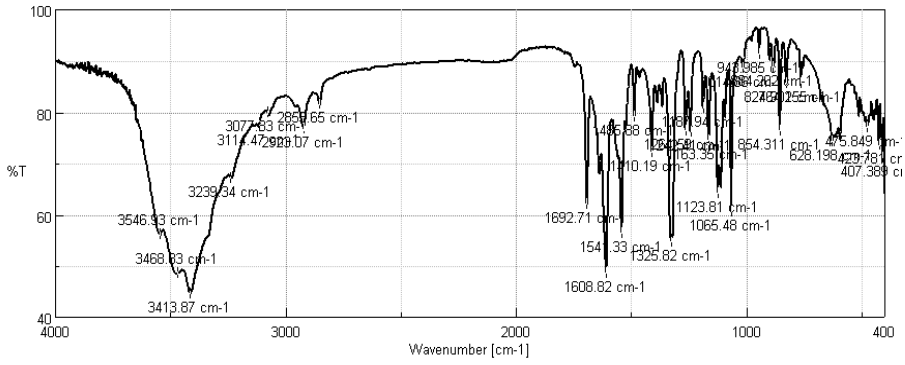


(b)

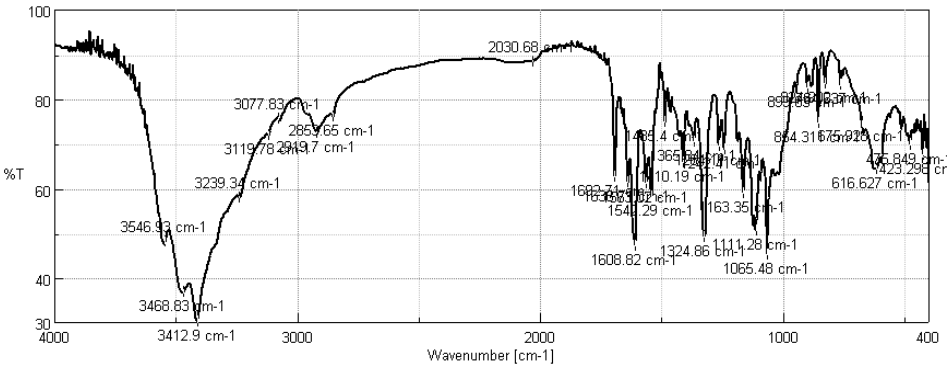


(d)

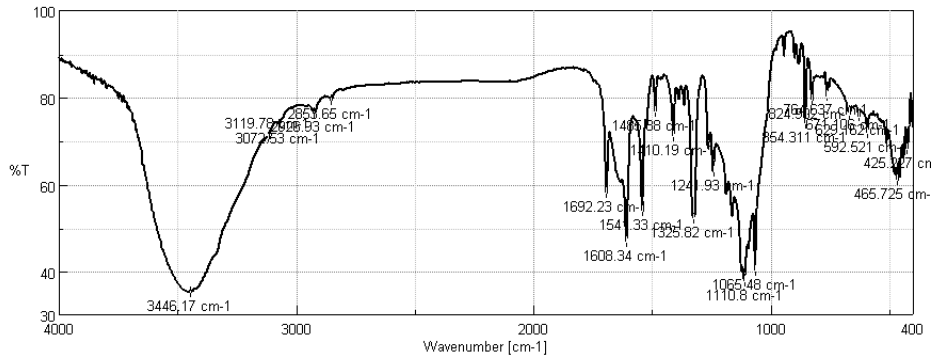
Figure 2 DSC thermograms of a) Leflunomide b) Aerosil c) Avicel PH 102 d) Optimized formulation LFK8



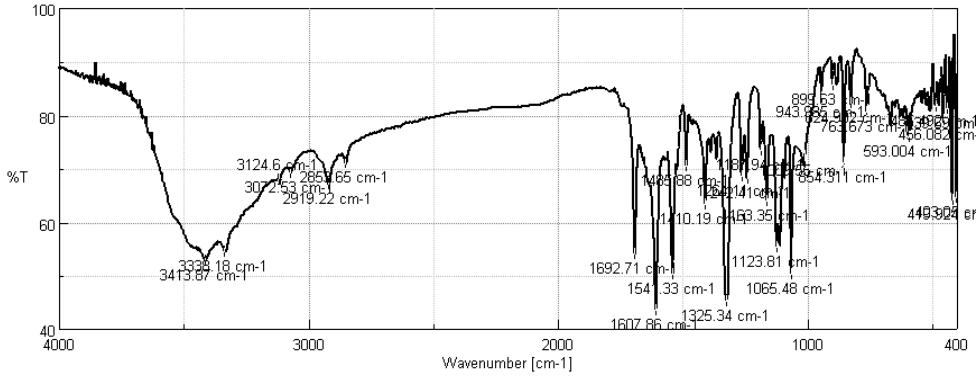
a) Leflunomide



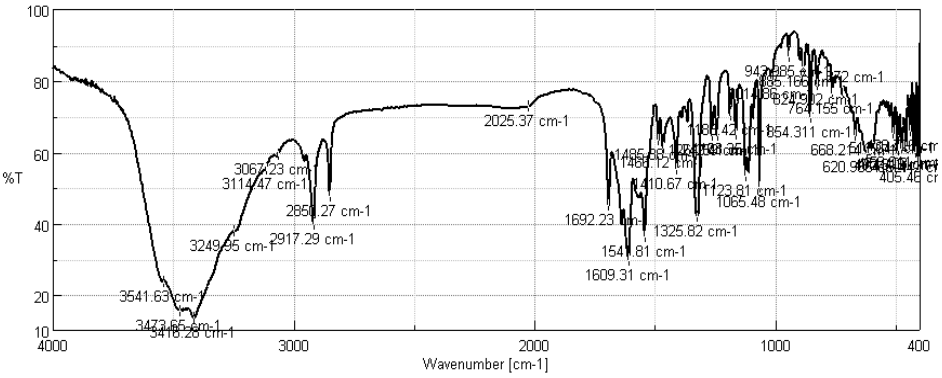
b) Leflunomide +Microcrystalline cellulose PH 102



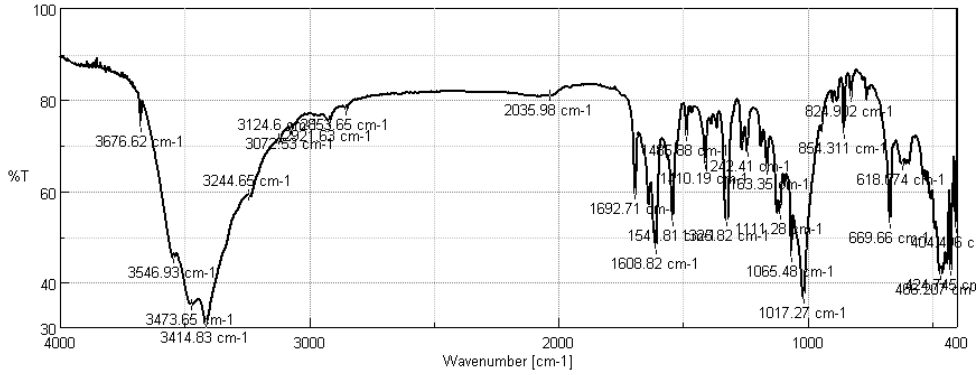
c) Leflunomide+Aerosil



d) Leflunomide+Sodium starch glycolate



e) Leflunomide+Magnesium stearate



f) Leflunomide+Talc

g)

Figure 3. Fourier-transform infrared spectroscopy (FT-IR) of a) leflunomide b) Physical mixtures – leflunomide + Microcrystalline cellulose PH 102, c) Physical mixtures –Leflunomide +Aerosil d) Physical mixtures –Leflunomide + Sodium starch glycolate e) Physical mixtures – Leflunomide +Magnesium stearate f) Physical mixtures –Leflunomide +Talc

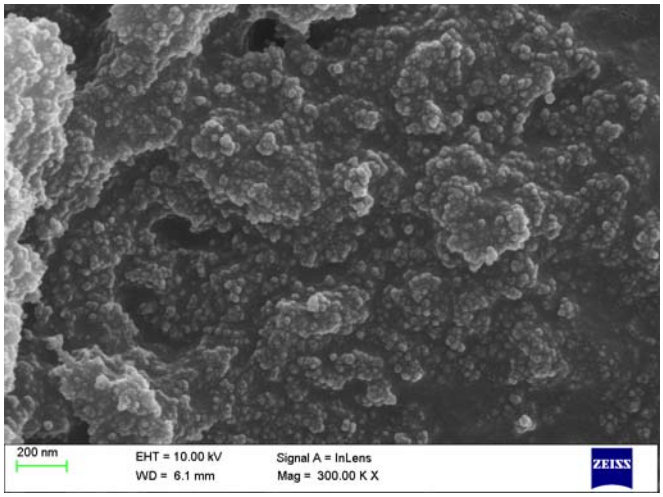


Figure 4.Scanning electron photomicrograph of optimized liquisolid formulation LFK8 prepared magnified at 300 KX

Differential scanning calorimetry (DSC)

DSC was used for the investigation of any interaction between the drug and its excipients. Figures 2 (a), 2 (b), 2 (c) and 2 (d) show the thermogram for leflunomide, aerosil, Avicel PH 102 and liquisolid mixture. The thermogram of leflunomide showed a sharp endothermic peak at 168° C corresponding to its melting point. For liquisolid mixture the endothermic peak of the drug completely disappeared indicating that the drug is completely solubilized and molecularly dispersed with excipients within liquisolid system. This ensures that the drug was moleculary dispersed state in the liquisolid system.

Fourier-transform infrared spectroscopy (FTIR)

Determination of interaction between drug and excipients were studied using FTIR analysis. FTIR of leflunomide and drug loaded physical mixtures were studied with potassium bromide pellet technique using JASCO FTIR 4100 instrument in the range of 4000-400 cm^{-1} and the resolution was 2 cm^{-1} range are shown in Figure 3.

Major peak of leflunomide c=o stretching of secondary amides was found at 1693 cm^{-1}. NH bonding of secondary amide appeared at 1541 cm^{-1}. CH_3 two distinct bonds occurred at 2923 and 2854 cm^{-1}. Amide N-H stretch 3414 and 3469 cm^{-1} were also found with leflunomide. All other relevant peaks of leflunomide were also appeared in the spectrum. Drug loaded physical mixtures of leflunomide were also shown the peaks of secondary amide N-H, amide c=o and and $-CH_3$. It clearly proved that, there was no interaction between drug sample of leflunomide and excipients.

Scanning electron microscopy (SEM)

The SEM photographs presented in Figure 4. Further proved the results of both DSC and XRD. The photomicrograph of the optimized liquisolid system signifies the complete disappearance of the leflunomide crystals, a fact that indicates that the drug was completely solubilised in liquisolid system which contributes to the improved drug dissolution properties.

Quality control studies

All the prepared tablets complied with the pharmacopoeial required specifications for the weight variation, hardness, friability, and disintegration time. Results are represented in Table 4. Hardness test showed an average hardness of liquisolid tablets ranging from 2.5-4.5 Kg/cm^2. The percentage friability for all the formulations was below 1 %. This indicates acceptable resistance was shown by liquisolid tablets to withstand handling. Disintegration time was found to be in the range of 244-818 sec for liquisolid preparations. Disintegration time test revealed that the liquisolid tablet formulae LFK4 and LFK8 disintegrated in less than 5 min (4.06 and 4.08 minutes)

***In vitro* dissolution studies**

The dissolution profiles of leflunomide liquisolid tablets are shown in Figures. 5 (a), 5(b) and 5 (c).

In this work, drug concentration of liquisolid formulations is constant but the vehicle concentration will be varied as 1:1, 1:2, 1:3 and 1:4.

In order to investigate the effect of vehicle concentration in liquid medication (1:1,1:2,1:3 and 1:4) on the dissolution rate of leflunomide from liquisolid preparations, the fraction of molecularly dispersed or dissolved drug in liquid medication of the prepared liquisolid formulations.

F_M is calculated according to the equation (7) and the results are presented in Table 1. The F_M of the conventional leflunomide tablets was taken to be zero, since no liquid vehicle was used during preparation of these tablets.

$$F_M = C_L / C_d \quad (7)$$

Where C_L is the saturation solubility of leflunomide in the liquid vehicle and C_d is the drug concentration in the liquid medication. By comparison of the fraction of molecularly dispersed or dissolved drug (F_M) in liquid medication of the prepared liquisolid formulations, it is documented that F_M is directly proportional to the drug dissolution rate [9, 3].

The drug particles in liquisolid formulation were dispersed in selected liquid vehicle, which enhances the wetting properties of the drug particles followed by surface area of the drug particles available for dissolution increased enormously.

After disintegration of the liquisolid tablet the primary particles of liquisolid were suspended in the dissolution medium contained drug particles in a moleculary dispersed state but in conventional tablet surface exposed for dissolution are very limited due to the hydrophobicity of the drug particles.

Accordingly, the higher dissolution rates observed in liquisolid formulations may be attributed to significantly larger surface area of the molecular dispersed drug particles. Since the drug particles in liquisolid formulations are in a state of molecular dispersion its saturation solubility (c_s) might be increased. As shown in Table 2 leflunomide has higher solubility in Kolliphor EL compared to propylene glycol and polyethylene glycol 400. Theoretically the liquisolid tablets formulated with Kolliphor EL should have better dissolution rate. Apparently formulations with higher vehicle concentration which have 46.9 % of drug available in solubilised form promote higher dissolution rate than the formulations with lower vehicle concentration. It was proven that F_M is directly proportional to the drug dissolution rate.

It was evident that formula LFK8 has the highest dissolution pattern in both the rate and the extent of drug dissolved. The percentage of leflunomide dissolved from LFK8 reached 92.81% after 60 min, while the DCT had a maximum leflunomide content (43.09%) dissolved after 60 min. The percent of drug dissolved from each formula after 10 min (Q_{10}) and drug release rate (D_R) were taken as a measure of the extent and rate of drug dissolved from the prepared tablets, respectively as presented in Table 5.

The results in the Table 5 clearly confirm that the liquisolid tablet formula LFK8 had highest percentage of drug dissolved in the first 10 minutes; it dissolved 73.39 % of its leflunomide content during first 10 min. As well, it is clear from the Table 5 that LFK8 had the highest leflunomide dissolution rate of all the formulae.

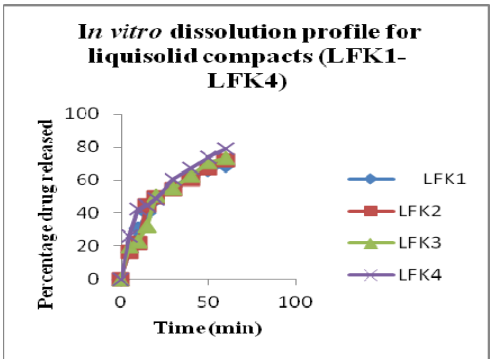
The most important observation is that Table 5 and Figure 6 suggest that all the formulae had higher drug dissolution rates (D_R) and larger amounts of drug dissolved in the first 10 min (Q_{10}) than directly compressed tablets. Therefore, they proved that the liquisolid technique can be a promising alternative for the formulation of water-insoluble drug into rapid release tablets.

Table 4 Post compression studies of prepared liquisolid formulations

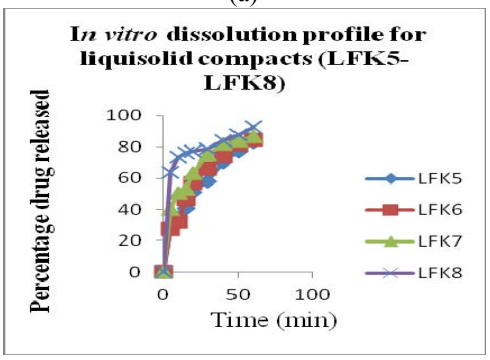
Formulation code	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (sec)	% Drug Content
LFK1	4.1	0.87	444	93.24
LFK2	3.2	0.46	569	96.12
LFK3	3.6	0.44	818	96.65
LFK4	3.2	0.44	244	97.56
LFK5	4.5	0.80	460	93.57
LFK6	3.2	0.83	470	98.45
LFK7	2.8	0.47	306	94.17
LFK8	2.5	0.43	245	98.44
LFK9	4.5	0.42	394	95.33
LFK10	4.2	0.40	305	96.47
LFK11	3.7	0.40	383	93.08
LFK12	3.6	0.73	405	99.25

Table 5.Perecentage of leflunomide dissolved after 10 min and 10-min dissolution rates from the conventional directly compressed leflunomide tablets

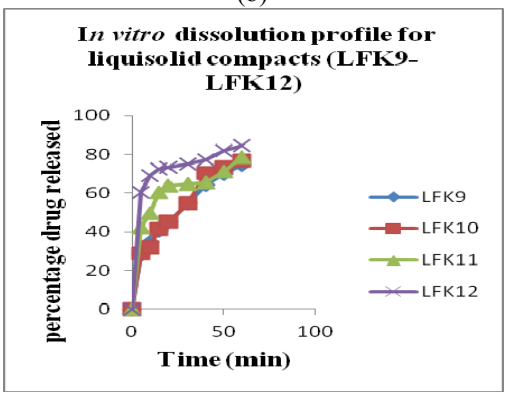
S.No	Formulation code	$Q_{10\%}$	D_R (µg/min)
1.	LFK1	30.69	613.80
2.	LFK2	21.80	436.00
3.	LFK3	22.91	458.20
4.	LFK4	42.51	850.20
5.	LFK5	35.07	701.40
6.	LFK6	32.23	644.60
7.	LFK7	50.58	1011.60
8.	LFK8	**73.39**	**1467.80**
9.	LFK9	34.59	691.80
10.	LFK10	31.77	635.40
11.	LFK11	49.69	993.80
12.	LFK12	69.12	1382.40
13.	Conventional DCT	18.94	378.80



(a)



(b)



(c)

Figure 5: (a) I*n vitro* dissolution profile for liquisolid compacts (LFK1-LFK4). (b) I*n vitro* dissolution profile for liquisolid compacts (LFK5-LFK8). (c) I*n vitro* dissolution profile for liquisolid compacts (LFK9-LFK12)

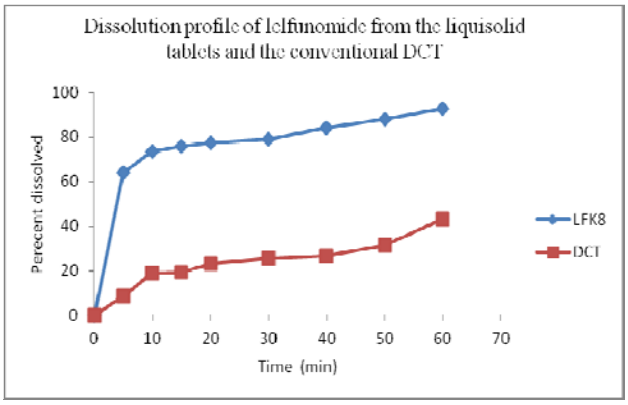


Figure 6. Dissolution profiles of leflunomide from the liquisolid tablet and the conventional DCT

CONCLUSION

In conclusion, this study showed that liquisolid technique could be a promising approach in improving dissolution of poorly water soluble drugs and formulating immediate release solid dosage forms. Kolliphor EL proved to be promising liquid vehicle for formulation of liquisolid preparations. Leflunomide tablets formulated from drug: vehicle ratio (1:5) was found to be superior in terms of dissolution properties in comparison with other liquisolid formulation. The improvement in the dissolution characteristics of a liquisolid technique changes the properties of leflunomide particles by simply dispersing the drug particles in the non-volatile liquid vehicle which in turn increase the wetting properties and surface area of drug particles and hence improve the dissolution profiles.

ACKNOWLEDGEMENT:

The authors are very thankful to KMCH College of pharmacy, Coimbatore for providing us facilities for the experiment work and research. I would like to thank Alembic Pharmaceutical Limited, Vadodara (India), for providing gift samples. I extend my sincere thanks to Mr.V.Guruprasad, Deputy Manager, formulation and development, Biocon limited, Bengaluru for providing the solvents, carrier and coating materials.

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