Bulletin of Faculty of Pharmacy, Cairo University 55 (2017) 53–62

Contents lists available at ScienceDirect

Bulletin of Faculty of Pharmacy, Cairo University

journal homepage: www.sciencedirect.com

Original Article

# Dissolution enhancement of leflunomide incorporating self emulsifying drug delivery systems and liquisolid concepts

Nihal M. El-Mahdy El-Sayyad [a,*], Alia Badawi [b], Mohammed Effat Abdullah [a], Nevine Shawky Abdelmalak [b]

[a] Department of Pharmaceutics, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA) University, Egypt
[b] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Egypt

ARTICLE INFO

*Article history:*
Received 1 October 2016
Received in revised form 19 January 2017
Accepted 1 February 2017
Available online 8 February 2017

*Keywords:*
Liquisolid
Dissolution enhancement
Leflunomide
SEDDS
BCS class II

ABSTRACT

The objective of this study is to enhance the dissolution properties of leflunomide, a class BCS-II drug by incorporating the self emulsifying (SE) form of the drug onto liquisolid systems in the form of tablets. Different formulae were prepared by dissolving leflunomide in PEG300 then forming SE systems using tween 80 as surfactant and either sesame oil and paraffin oil then adsorbing on powder excipients to form SE liquisolid powders. The prepared powders showed adequate flowability. The drug and excipients showed compatibility by analysis with DSC, XRD and FTIR. After compression, all tablets showed adequate weight variation, friability and disintegration time with disintegration time ranging between 8.45 ± 0.16 min and 10.7 ± 0.29 min. All liquisolid tablets exhibited higher in vitro dissolution in distilled water compared to physical mixture and the commercial tablets (Arthfree®) with formula containing sesame oil and highest amount of solvent (TS04) exhibiting the highest dissolution profile and it did not change by the change in the pH of the dissolution medium. The tablets showed stability during a 6 months accelerated stability study according to appearance, drug content, disintegration time and dissolution profile. Thus it can be concluded that combining self emulsifying drug delivery technique and liquisolid technology can be a promising tool to enhance the dissolution profile of leflunomide in vitro.


## 1. Introduction

Out of the many routes of administration available, the oral route remains the most popular dosage form among patients as it is easy to use and carry around and causes minimal discomfort for many patients [1]. When the oral drug is swallowed, first dissolution of the drug in vivo occurs to produce a solution and then the dissolved drug is transported across the gastrointestinal membrane [2], Therefore among the many factors that affect bioavailability of any drug, one of the most important factors is gastrointestinal (GI) dissolution and permeability especially for low water soluble drugs which will be released slowly in the gastrointestinal track [3]. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of drug becomes the rate-limiting step in the absorption process [4]. This is manifested in case of class II drugs in the Biopharmaceutics Classification System (BCS) which are hydrophobic, poorly soluble, highly permeable and readily absorbed drugs and class IV drugs which are of low solubility and low permeability [5].

Liquisolid technology is a technique by which a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material [6], thus enhancing the dissolution properties of the drug as defined by Spireas [7]. Liquisolid technology can be applied on solubility and dissolution enhancement especially in Class II and IV drugs. Liquisolid systems have been successfully employed in the dissolution enhancement of poorly soluble drugs like Loratidine [8], Furosemide [9], Carbamazepine [10] and Hydrochlorothiazide [11].

The concept behind the liquisolid technique is when a drug solution or liquid drug is incorporated into a carrier material, initially the liquid is absorbed in the interior of the particles and after saturation, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles takes place. After that, the coating material having high adsorptive properties and large specific surface area is added which gives the liquisolid system the desirable flow characteristics [12].

Lipid formulations have drawn attention in recent years as they have the potential to increase the bioavailability of poorly soluble

Peer review under responsibility of Faculty of Pharmacy, Cairo University.
* Corresponding author.
*E-mail address:* nihal_elmahdy@hotmail.com (Nihal M. El-Mahdy El-Sayyad).

http://dx.doi.org/10.1016/j.bfopcu.2017.02.001
1110-0931/

drugs especially BCS classes II and IV whose bioavailability are limited by their dissolution. Lipid formulations are generally isotropic systems which are classified according to their composition, behavior upon dilution and digestion in the body [13]. Self-emulsifying drug delivery systems (SEDDS) are the isotropic mixtures of oils, surfactants and/or co-surfactants [14]. They rapidly and spontaneously form fine oil in water when exposed into aqueous phases under gentle agitation [15].

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers as it is a simple process and just involves the addition of the liquid formulation onto carriers by mixing and the resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. Solid carriers can be microporous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crosspovidone and crosslinked sodium carboxymethyl methacrylate cellulose [16].

Leflunomide is a disease-modifying antirheumatic drug (DMARD) used in active moderate to severe rheumatoid arthritis and psoriatic arthritis. The chemical name for leflunomide is N-(4′-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. It has an empirical formula $C_{12}H_9F_3N_2O_2$ and a molecular weight of 270.2 [17]. Leflunomide is practically insoluble in water (less than 40 mg/L) and has high bioavailability (around 80%), so belongs to class II of the bio-pharmaceutics classification systems (BCS) [18]. Literature search revealed the absence of any previously published data dealing with enhancing solubilization of leflunomide using liquisolid or SEDDS techniques.

The aim of this work is to enhance the dissolution profile of leflunomide by adsorbing self-emulsifying (SE) systems of leflunomide onto powder carriers to form liquisolid powders which will be compressed into tablets. The enhancement in dissolution of prepared tablets will be compared to the commercial formula Arthfree® 20 mg using similarity factor and will be subjected to accelerated stability studies to assess the stability of the formulation.

## 2. Experimental

### 2.1. Materials

The following materials were used as received: Leflunomide, USP as a gift from EVA Pharma, Egypt (HTRO, USA). Polyethylene glycol 300, methanol, tween 80 and propylene glycol, sesame oil, paraffin oil, monobasic potassium phosphate, sodium chloride, hydrochloric acid and sodium hydroxide were purchased from Merck, Germany. Avicel PH102 and Ac-di-sol were purchased from FMC, USA. Aerosil 200 was purchased from Evonik, France. Purified pepsin and pancreatin were purchased from Sigma Aldrich, USA. All materials used were of analytical grade.

### 2.2. Determination of solubility of leflunomide in the different solvents and oils

Solubility studies of leflunomide were done to test the solubility of leflunomide in the solvents to be used in preparation of liquisolid systems. Specifically, Excess amount of leflunomide was weighed and dissolved in 100 g of each of PEG300, Tween 80, propylene glycol, sesame oil and paraffin oil and were sonicated for 30 min. The resulting solutions were left for 24 h to allow excess amounts to precipitate. The supernatant was analyzed using UV spectrophotometer (Analytic Jena, Germany) at 260 ± 2 nm according to USP 36/NF 31 [19]. The solubility of leflunomide in each solvent was recorded as percentage in solvent w/w.

### 2.3. Preparation of leflunomide liquisolid tablets

Leflunomide SE systems were prepared by dissolving known weight of leflunomide in PEG 300 as a solvent and Tween 80 as surfactant. Then a known amount of sesame oil or paraffin oil was added in different ratios as mentioned in Table 2 and thoroughly stirred with a magnetic stirrer (IKA, Germany) till one phase was obtained. To each SE formula, Avicel PH102 was added as the carrier material in a mortar and thoroughly mixed with a pestle till a homogeneous mixture was obtained. The amount of Avicel PH102 was calculated so that the liquid loading factor ($L_f$) would be equal to 0.2 in all the formulae prepared. After that Aerosil 200 was added as the coating material so that the ratio between carrier and coating material (R) would be equal to 20 which was stated to be the optimum R for the given materials [21]. Finally the disintegrant Ac-di-sol was added as 2% of the final weight [22]. Physical mixture of the drug and excipients was prepared by mixing a known amount of leflunomide with Avicel PH102, Aerosil 200 and Ac-di-sol in the same ratio as the liquisolid tablets. The tablets were compressed so that each tablet would contain 20 mg of leflunomide. The powders were directly compressed using Korche tablet compression machine (Korche, USA) to form the tablets using oblong punch number 18 on a preset hardness of 15 Kp with a diameter 18 mm and thickness 6.6 mm for all formulae.

The self-emulsification of the prepared systems before addition of solid ingredients was tested by withdrawing 0.5 g from each preparation and was diluted with 5 ml of distilled water and thoroughly agitated. Visual test was used to assess self-emulsification of surfactants in terms of dispersability, ease of emulsification and final appearance using a grading system according to Table 2 [23].

### 2.4. Pre-compression studies

#### 2.4.1. Determination of flowability

The flowability was assessed using measurements of the flow rate and angle of repose for each of the prepared powders by PTG S4 automatic flowability tester (Pharma test, Germany). The flow rate was measured as the time per seconds 100 mg of the powder would take to flow through the orifice of the flowability tester equipment. The angle of repose was measured. The measurements were repeated three times and the average was taken.

#### 2.4.2. Differential scanning calorimetry

DSC Scanning was carried out by Universal Instruments Q20 DSC calorimeter (Universal instruments, USA) by heating the sample of about 5 mg in sealed aluminum dish from ambient temperature to 250 °C at 10 °C/min under atmospheric nitrogen. The drug was scanned individually as well as liquisolid formulae TP04 and TS04 and physical mixtures of drug and powder excipients (DCT) and the resultant thermograms were compared.

#### 2.4.3. Fourier transform infrared spectra analysis (FTIR)

The infrared spectra of solid dispersions were recorded by the potassium bromide method using Fourier transform infrared spectrophotometer (Agilent, USA). A base-line correction was made using dried potassium bromide and then the spectra of leflunomide, liquisolid formulae TP04 and TS04 and physical mixtures of drug and powder excipients (DCT) were obtained.

#### 2.4.4. X-ray diffraction analysis

X-ray diffraction analysis was carried out by X'Pert PRO X-ray Diffraction Instrument (PAN Analytical, USA) by scanning the

self-emulsifying liquisolid formula and physical mixture by using Cu-radiation (λ = 1.524 Å) at 50 K.V, 40 M.A and scanning speed 0.02°/s) The scanning range between 2θ = 2–60°. The drug was scanned individually as well as liquisolid formulae TP04 and TS04. The resultant diffraction charts were obtained and compared.

### 2.5. Post compression studies

#### 2.5.1. Thickness, hardness and weight variation of the compressed tablets

The tablet thickness, diameter and crushing strength (hardness) were measured automatically using the PTB Tablet testing system (Pharma Test, USA) according to USP 36/NF 31. The equipment measurements were taken using two probes that measure thickness and diameter and then pressure force on the tablets was applied and test the force at which the tablets would break is recorded. The measurements were repeated ten times and the average was taken.

#### 2.5.2. Determination of the tablet friability

Friability of the tablets was determined using the PTF Pharma Test friability tester (Pharma Test, USA) according to USP 36/NF 31; ten tablets of each formula were de-dusted and weighed then introduced to the apparatus. The drum of the apparatus was operated for 100 rotations. The tablets are then removed and weighed. The results are presented as percentage friability which is the percentage difference between the weight of tablets before the test and after the test divided by the initial weight of the tablets.

#### 2.5.3. Determination of leflunomide drug content

To measure the contents of leflunomide in each formula of SE liquisolid tablets 20 tablets were taken, crushed and mixed well after which a sample equivalent to 20 mg leflunomide was accurately weighed and dissolved in 100 ml 2% methanol. The solution was sonicated for 10 min to dissolve the active substance then the solution was filtered through a whatman filter paper no 1 (125 mm diameter).The standard solution was prepared by weighing 20 mg leflunomide and dissolving in 100 ml 2% methanol in a volumetric flask. The absorbance of both the test and standard solutions were measured spectrophotometrically at $\lambda_{max}$ of 260 ± 2 nm according to USP 36/NF 31.

#### 2.5.4. Determination of the disintegration time

The time for the compressed tablets to disintegrate was determined using the basket type PTZ disintegration tester (Pharma Test, USA). One tablet was put in each of the six baskets of the apparatus using water as a medium in temperature 37 ± 2 °C. The disintegration time was determined for leflunomide SE liquisolid formulae and directly compressed tablets (DCT) automatically as the time required by the tablets to completely disintegrate. The average time and standard deviation were calculated.

#### 2.5.5. In vitro dissolution studies

The in vitro dissolution studies of the self-emulsifying liquisolid tablets were determined using USP type II dissolution apparatus (Erweka, Germany) using 1000 ml water as dissolution medium at 37 °C ± 2 °C at 100 rpm (USP 36). Six tablets were introduced into the dissolution apparatus cups and 5 ml samples were withdrawn from the dissolution medium at different time intervals for 1 h. The dissolution medium was replaced with 5 ml fresh dissolution medium to maintain sink conditions. The samples were filtered and analyzed spectrophotometrically at $\lambda_{max}$ 260 ± 2 nm according to USP 36/NF 31 to determine the percentage of drug dissolved at each time. The measurements were repeated 3 times and the average was taken. The percentage of the drug dissolved was plotted against the time.

SE liquisolid formula with the highest dissolution profile was selected and compared with leflunomide commercial tablets Arthfree® 20 mg (EvaPharma, Egypt). The percentage of leflunomide dissolved was determined using the same procedure described before. The in vitro dissolution profiles of liquisolid tablets and commercial tablets were compared using similarity factor (f2) . The similarity factor fits the result between 0 and 100. It is 100 when the two dissolution profiles are identical and approaches 0 as the dissimilarity increases. An f2 above 50 indicates that the two profiles are similar. The similarity factor is defined by the following equation [24]

$$f_2 = 50\ \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)\right]^{-0.5} \times 100\right\}$$

where n = the number of time points at which % dissolved was determined: Rt = the % dissolved of one formulation at a given time point, Tt = The % dissolved of the formulation to be compared at the same time point.

The effect of changing pH on the dissolution of SE liquisolid formula was determined by selecting the formula with the highest percentage dissolved and the dissolution studies were determined using the same procedure described before but with changing the dissolution medium. The experiment was done once with gastric fluid pH 1.2 and with simulated intestinal fluid pH 7.2. The dissolution profiles were compared using the similarity factor (f2).

Simulated gastric fluid was prepared according to USP36 method by dissolving 2.0 g of sodium chloride and 3.2 g of purified pepsin (derived from porcine stomach mucosa, with an activity of 800–2500 units per mg of protein), in 7.0 mL of hydrochloric acid and water up to 1000 mL so the pH would be 1.2. Simulated intestinal fluid was prepared as per USP36 dissolving 6.8 g of monobasic potassium phosphate in 250 mL of water and then adding 77 mL of 0.2 N sodium hydroxide and 500 mL of water. 10.0 g of pancreatin is added and the resulting solution was adjusted with 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of 6.8 ± 0.1 and finally diluted to 1000 ml.

#### 2.5.6. Stability studies

The study was performed on SE liquisolid tablets that showed the highest percentage of leflunomide dissolved. The study was performed under accelerated stability conditions at 40 °C ± 2 °C/75% ± 5% RH for six months according to the ICH guideline (Q1A (R2)) Section 2.1.7.1 [20] and WHO guidelines for stability studies [26] in a stability chamber (Votch, Germany). Samples were withdrawn after one, two, three and six months respectively according to ICH guideline and tested for appearance, hardness, drug content, disintegration time and dissolution profile using the same methods as mentioned before.

The analysis for the drug content and dissolution testing was done using the HPLC (Agilent, USA) method specified in USP 36/NF 31. The standard solution was prepared by dissolving an accurately weighed quantity of leflunomide in a minimum volume of acetonitrile, diluted quantitatively and stepwise if necessary, with mobile phase to obtain a solution having a known concentration of about 1 mg in about 1 ml. The mobile phase was prepared by the addition of water, acetonitrile, and triethylamine in the following ratio (65:35:0.5) to make a 1000 ml mixture then adjusted with phosphoric acid to pH 4, filtered through membrane filter 0.45 μm and degassed. The stationary phase used was L1 (12.5 cm × 4 mm, 5 μm) and the chromatographic conditions were established at a flow rate of 1 ml/min, an injection volume of 10 μl and at 35 °C temperature, detection was done by UV at 260 ± 2 nm (USP 36). The chromatograms were recorded, and the responses

were measured and the quantity of leflunomide was determined by using the following formula:

$$\% \text{ of Leflunomide} = (100C(rU/rS)/20) * 100$$

where, C is the concentration of leflunomide in standard solution, rU and rS are the peak responses of the test and standard solution respectively.

## 3. Results and discussion

### 3.1. Solubility studies and preparation of leflunomide liquisolid tablets and tablets of physical mixture

Leflunomide was selected as the model drug for this study since it is a very poorly water soluble drug(less than 40 mg/L) and a suitable candidate for testing the potential of rapid release using liquisolid concept.

All Solubility studies are summarized in Table 1, leflunomide was found to have the highest solubility in Tween 80 followed by PEG 300 and the least in propylene glycol. Leflunomide was insoluble in distilled water, simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) therefore it can be concluded that pH has no effect on the solubility of leflunomide. Solubility of the leflunomide in sesame oil and paraffin oil was found to be inadequate to directly dissolve the drug. Therefore, the drug was dissolved first in PEG300 as a solvent prior to preparing the SE systems using sesame oil and paraffin oil and Tween 80 as a surfactant.

### 3.2. Preparation of leflunomide liquisolid tablets

The leflunomide SE liquisolid systems were prepared using Avicel PH 102 and Aerosil 200 as the carrier and coating material respectively. Based on previously published data and preformulation studies,the liquid loading factor (Lf) was calculated to be 0.2 and the ratio between carrier and coating material (R) was equal to 20 in all prepared formulations. Avicel PH102 is a grade of microcrystalline cellulose, which is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles [22] which would possess sufficient absorption properties to absorb the liquid portion on its surface and thus it was used as a carrier material. Aerosil 200 is a light, loose, bluish-white coloured, odourless, tasteless, non-gritty amorphous powder. Its small particle size and large specific surface area give it its desirable flow characteristics to improve the flow properties of dry powders [22] and thus would be ideal to be used as a coating material in the liquisolid formulations. The ratios used in this study were according to the ratios used by previous researchers for the same excipients.

**Table 1**
Solubility of leflunomide in different non-volatile solvents, oils and media.

| Solvent | Solubility (% w/w) ± SD |
|---|---|
| Tween 80 | 34.422 ± 0.482% |
| PEG300 | 30.514 ± 0.356% |
| Propylene glycol | 10.167 ± 0.356% |
| Sesame oil | 0.0036 ± 0.0011% |
| Paraffin oil | 0.0039 ± 0.0013% |
| Simulated Gastric fluid (pH 1.2) | 0.0021 ± 0.0001% |
| Simulated Intestinal fluid (pH 7.2) | 0.0022 ± 0.0004% |
| Aqueous media (distilled water) | 0.0025 ± 0.0002% |

As shown in Table 2, Eight formulae of self-emulsifying liquisolid preparations were prepared using Sesame and paraffin oil respectively namely S01-S04 and P01-P04. Quick emulsification of the preconcentrate is necessary for the proper functioning of a self-emulsifying system; therefore emulsification studies were performed to evaluate the ability of the selected surfactants to emulsify maximum amount of selected oils. By following the visual assessment of self-emulsification grading system proposed by Meena et al. [23] upon dilution with water, All the systems form translucent mixtures within 1 min indicating self-emulsification to form grade I SEDDS indicated by their clarity and the time of emulsification, except formulae P01 and S01 that formed turbid solutions with emulsification time of more than one minute. This can be due to the low ratio of PEG300 and Tween 80 to the oil which affected the grade of the emulsion formed. The yellow colour of the SE systems is due to the colour of Tween 80 which is yellowish.

The leflunomide SE liquisolid systems were prepared using Avicel PH 102 and Aerosil 200 as the carrier and coating material respectively. Based on previously published data and preformulation studies,the liquid loading factor (Lf) was calculated to be 0.2 and the ratio between carrier and coating material (R) was equal to 20 in all prepared formulations. Avicel PH102 is a grade of microcrystalline cellulose, which is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles [22] which would possess sufficient absorption properties to absorb the liquid portion on its surface and thus it was used as a carrier material. Aerosil 200 is a light, loose, bluish-white coloured, odourless, tasteless, non-gritty amorphous powder. Its small particle size and large specific surface area give it its desirable flow characteristics to improve the flow properties of dry powders [22] and thus would be ideal to be used as a coating material in the liquisolid formulations. The ratios used in this study were according to the ratios used by previous researchers for the same excipients.

SE formulae were compressed into tablets with formulae shown in Table 3. They were subjected to suitable evaluation tests compared to directly compressible tablet DCT prepared from physical mixture.

**Table 2**
Composition of different self-emulsifying liquisolid systems.

| Formula | Oil used | Leflunomide (g) | PEG 300 (g) | Tween 80 (g) | Oil (g) | Visual assessment of self-emulsification upon addition of distilled water | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Appearance | Time of emulsification | Grade |
| S01 | Sesame oil | 1.00 | 1.00 | 1.50 | 1.50 | Slightly less clear, yellowish white | 1 min and 10 s | II |
| S02 | | 1.00 | 1.00 | 2.00 | 1.50 | Clear, light yellow | Less than 1 min | I |
| S03 | | 1.00 | 1.00 | 2.50 | 1.50 | Clear, light yellow | Less than 1 min | I |
| S04 | | 1.00 | 1.00 | 3.00 | 1.50 | Clear, light yellow | Less than 1 min | I |
| P01 | Paraffin oil | 1.00 | 1.00 | 1.50 | 1.50 | Slightly less clear, yellowish white | 1 min and 15 s | II |
| P02 | | 1.00 | 1.00 | 2.00 | 1.50 | Clear, light yellow | Less than 1 min | I |
| P03 | | 1.00 | 1.00 | 2.50 | 1.50 | Clear, light yellow | Less than 1 min | I |
| P04 | | 1.00 | 1.00 | 3.00 | 1.50 | Clear, light yellow | Less than 1 min | I |

**Table 3**
Composition of self-emulsifying liquisolid formulae compressed into tablets (composition per tablet).

| Formula | Leflunomide (mg) | Amount of Oil, Surfactant and solvent (mg) | Avicel pH102 (mg) | Aerosil 200 (mg) | Ac-di-sol (mg) | Total weight/tablet (mg) |
|---|---|---|---|---|---|---|
| TS01 | 20.00 | 80.00 | 500.00 | 25.00 | 12.76 | 637.76 |
| TS02 | 20.00 | 90.00 | 550.00 | 27.50 | 14.03 | 701.53 |
| TS03 | 20.00 | 100.00 | 600.00 | 30.00 | 15.31 | 765.31 |
| TS04 | 20.00 | 110.00 | 650.00 | 32.50 | 16.58 | 829.08 |
| TP01 | 20.00 | 80.00 | 500.00 | 25.00 | 12.76 | 637.76 |
| TP02 | 20.00 | 90.00 | 550.00 | 27.50 | 14.03 | 701.53 |
| TP03 | 20.00 | 100.00 | 600.00 | 30.00 | 15.31 | 765.31 |
| TP04 | 20.00 | 110.00 | 650.00 | 32.50 | 16.58 | 829.08 |
| DCT | 20.00 | – | 700.00 | 35.00 | 15.40 | 770.40 |

### 3.3. Pre-compression studies

#### 3.3.1. Determination of flowability

Flowability is the ability of a powder to flow through equipment reliably. The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms. Poor flowability can lead to the inability to feed powder into the dies of a rotary tablet press, and can also cause tablet weight variation [27]. According to USP 36/NF31 flow properties can be assessed by measuring angle of repose and flow through an orifice .USP defines angle of repose as the "constant, three dimensional angle, relative to the horizontal base, assumed by a cone-like pile of material," which is formed when the powder is passed through a funnel-like container, Flow rate through an orifice is generally measured as the mass of material per unit time flowing from any of a number of types of containers (cylinders, funnels, hoppers). It is considered a more direct measure of flow than measurements such as angle of repose or Hausner ratio, because it more closely simulates flow of material from processing equipment such as from a tablet press hopper into a die [27]. According to the flow rate and angle of repose, all powders prepared possessed excellent to good flowability properties with a θ value ranging from 27.5° to 33.4° indicating their ability to flow effectively from the processing equipment.

#### 3.3.2. Differential scanning calorimetry

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation; it is very important to establish the existence of any incompatibilities to ensure the success of the subsequent stability studies.

Fig. 1 shows the DSC thermograms of pure leflunomide, physical mixture, SE liquisolid systems prepared with sesame oil and paraffin oil respectively. Fig. 1A shows a sharp endothermic peak at 166.49 °C which corresponds to the melting point of leflunomide [18]. It is evident that the excipients and the drug do not show any incompatibility indicated by the presence of this characteristic peak in the physical mixture thermogram at 166.58 °C (Fig. 1B). The thermogram of SE liquisolid formula prepared with sesame oil is shown in Fig. 1C and the SE liquisolid formula prepared with paraffin oil is shown in Fig. 1D. Both of them show the absence of the distinctive peak of the leflunomide. Differential scanning calorimetry was tested to detect if there is an incompatibility between leflunomide and different excipients present in the directly compressed formula and liquisolid formula. It is evident that the excipients and the drug do not show any incompatibility indicated by the presence of the peak as the distinct melting endotherm of leflunomide in the physical mixture thermogram. Both thermograms of SE liquisolid systems prepared with sesame oil and paraffin oil show the absence of the distinctive peak of the leflunomide indicating that the drug is in a completely solubilized state in the SE system [28]. This might be due to the formation of a solid solution in the liquisolid powdered system, i.e. the drug was molecularly dispersed within the liquisolid matrix. This disappearance of drug peaks upon formulation into a liquisolid system who declared that the complete suppression of all drug thermal features undoubtedly indicates the formation of an amorphous solid solution [29]. The total disappearance of the drug melting peak indicates that drug amorphization had taken place [30].

#### 3.3.3. Fourier transform infrared spectroscopy (FTIR)

Incompatibilities were further tested with Fourier transform infrared spectroscopy (FTIR) which was used to identify leflunomide and detect incompatibilities between leflunomide and the excipients used in the liquisolid formulae prepared. The IR spectra

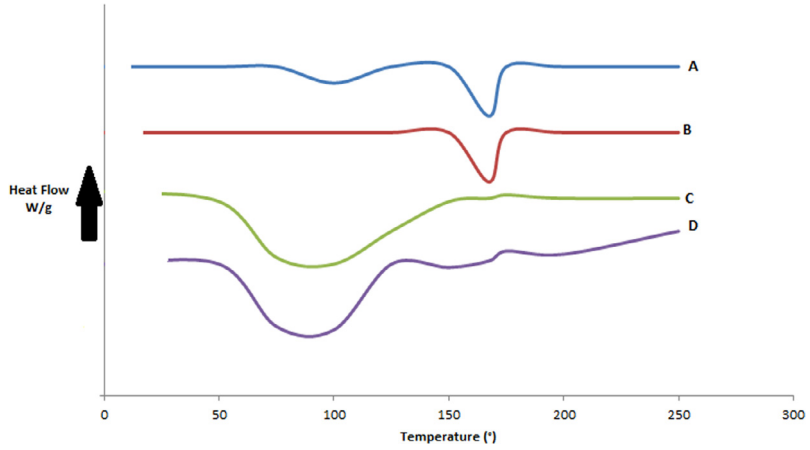


**Fig. 1.** DSC thermograms of pure drug (A), physical mixture(B) and SE liquisolid formulae. A: Pure leflunomide. B: Physical mixture of drug and powder excipients (DCT). C: SE liquisolid formula prepared with sesame oil(TS04). D: SE liquisolid formula prepared with paraffin oil (TP04).

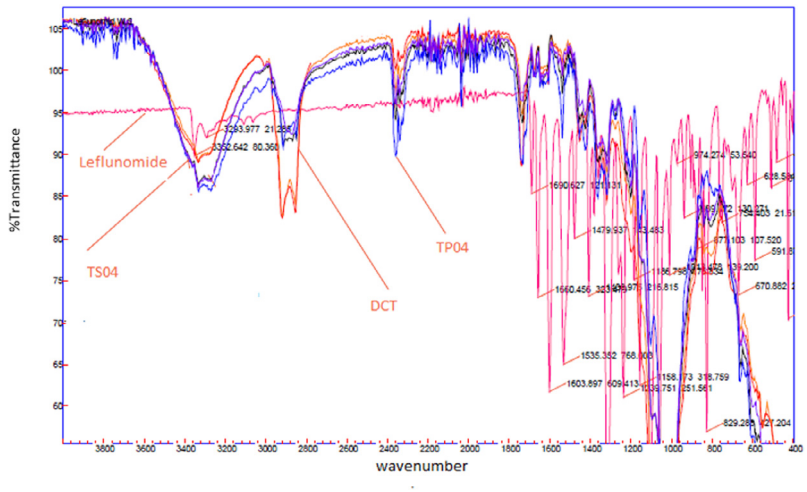


**Fig. 2.** FTIR spectra of pure drug, physical mixture (DCT) and SE liquisolid formulae (TS04 and TP04).

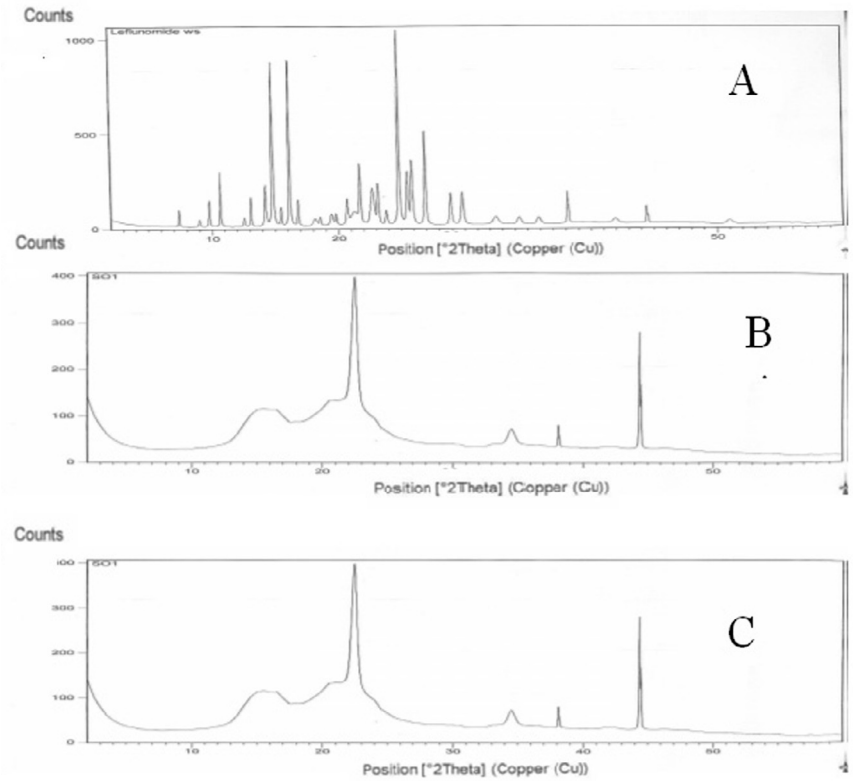


**Fig. 3.** XRD diffractograms of pure drug and SE liquisolid formulae. A: Pure leflunomide. B: SE liquisolid formula prepared with sesame oil (TP04). C: SE liquisolid formula prepared with paraffin oil (TS04).

of pure leflunomide and SE liquisolid formulae present in Fig. 2 show the same clear sharp characteristic peak at 3358 cm-1 attributed to NH peak of amide, a sharp doublet peak appearing at 2924 cm-1 in spectrum is assigned to CH stretching vibration and HC═N─O sharp peak present in isoxazole ring appears at 1690 cm-1 in the leflunomide spectra. The IR spectrum of leflunomide also show a sharp peak at 1604 cm-1 assigned to C═O of amide and a peak at 1504 cm-1 attributed to C═C which indicates that the formulae do not show any well-defined interaction between leflunomide and excipients. This indicates that the drug is compatible with the formulation components [31]

### 3.3.4. X-ray diffraction analysis

The X-ray diffraction analysis as it is used to detect polymorphic changes and changes in crystal habit. As shown in Fig. 3, The absence of the sharp characteristic peaks of leflunomide in the diffractograms of SE liquisolid systems indicate that leflunomide have transformed from the crystalline state to the molecular or sol-

ubilized form. This lack of crystallinity can be due to the complete solubilization of leflunomide in the liquid vehicle which is absorbed in the carrier material and adsorbed onto the coating material [32].

### 3.4. Post compression studies

#### 3.4.1. Thickness, hardness and weight variation

The results in Table 4 indicate that the tablets have the acceptable thickness, hardness and diameter. The average weight variation falls within the limit of the theoretical weight as USP 36/NF 31 states that not more than two of the individual weights deviate from the average weight by more than 7.5% and none deviates by more than 10%.

#### 3.4.2. Determination of the tablet friability

The results of the friability test of the tablets as shown in Table 4 indicate that the liquisolid tablets have adequate friability as they are all below 1% as per the USP 36/NF 31 and thus can withstand chipping and abrasion by tumbling in the rotating cylinder.

#### 3.4.3. Determination of leflunomide drug content

The results of drug content for all formulae fall within the limit specified by the USP 36/NF 31 which should be greater than or

**Table 4**
Average thickness, hardness, diameter, weight, friability, drug content and disintegration time of SE liquisolid tablets.

| Formula name | Average flow rate (mg/s) | Angle of repose (°) | Flowability properties | Average thickness (mm) | Average diameter (mm) | Average hardness (Kp) | Average weight (mg) | Friability (%) | Drug Content (%) | Average Disintegration time (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| TS01 | 34.2 ± 0.2 | 29.31 ± 0.78 | Excellent | 6.52 ± 0.09 | 18.29 ± 0.02 | 14.2 ± 0.72 | 658.20 ± 4.40 | 0.25 ± 0.12 | 102.21 ± 0.92 | 8.45 ± 0.16 |
| TS02 | 36.6 ± 0.1 | 28.10 ± 0.46 | Excellent | 6.41 ± 0.05 | 18.32 ± 0.04 | 14.7 ± 0.62 | 719.99 ± 4.70 | 0.17 ± 0.03 | 104.32 ± 5.69 | 9.12 ± 0.25 |
| TS03 | 32.6 ± 0.3 | 27.29 ± 0.75 | Excellent | 6.75 ± 0.10 | 18.25 ± 0.05 | 14.9 + 0.56 | 790.95 ± 8.20 | 0.28 ± 0.13 | 103.16 ± 3.87 | 9.37 ± 0.22 |
| TS04 | 33.5 ± 0.4 | 30.37 ± 0.28 | Good | 6.45 ± 0.04 | 18.42 ± 0.03 | 14.5 ± 0.31 | 843.01 ± 5.40 | 0.35 ± 0.17 | 101.21 ± 2.31 | 10.54 ± 0.19 |
| TP01 | 37.4 ± 0.7 | 29.75 ± 0.93 | Excellent | 6.61 ± 0.08 | 18.43 ± 0.04 | 15.1 ± 0.43 | 660.38 ± 2.13 | 0.39 ± 0.19 | 103.21 ± 3.98 | 8.96 ± 0.23 |
| TP02 | 38.5 ± 0.5 | 28.42 ± 0.12 | Excellent | 6.33 ± 0.07 | 18.28 ± 0.03 | 14.9 ± 0.51 | 727.62 ± 8.70 | 0.29 ± 0.13 | 102.47 ± 2.43 | 9.53 ± 0.42 |
| TP03 | 34.7 ± 0.6 | 28.76 ± 0.98 | Excellent | 6.54 ± 0.05 | 18.45 ± 0.02 | 15.5 ± 0.61 | 783.20 ± 3.40 | 0.35 ± 0.16 | 101.3 ± 1.74 | 9.42 ± 0.35 |
| TP04 | 34.4 ± 0.4 | 29.68 ± 1.24 | Good | 6.52 ± 0.09 | 18.29 ± 0.02 | 15.0 ± 0.21 | 844.17 ± 6.50 | 0.22 ± 0.05 | 99.24 ± 3.45 | 10.77 ± 0.29 |
| DCT | 34.1 ± 0.2 | 28.23 ± 0.53 | Good | 6.52 ± 0.01 | 18.29 ± 0.03 | 10.0 ± 0.61 | 658.20 ± 3.50 | 0.14 ± 0.06 | 104.36 ± 3.21 | 5.24 ± 0.24 |

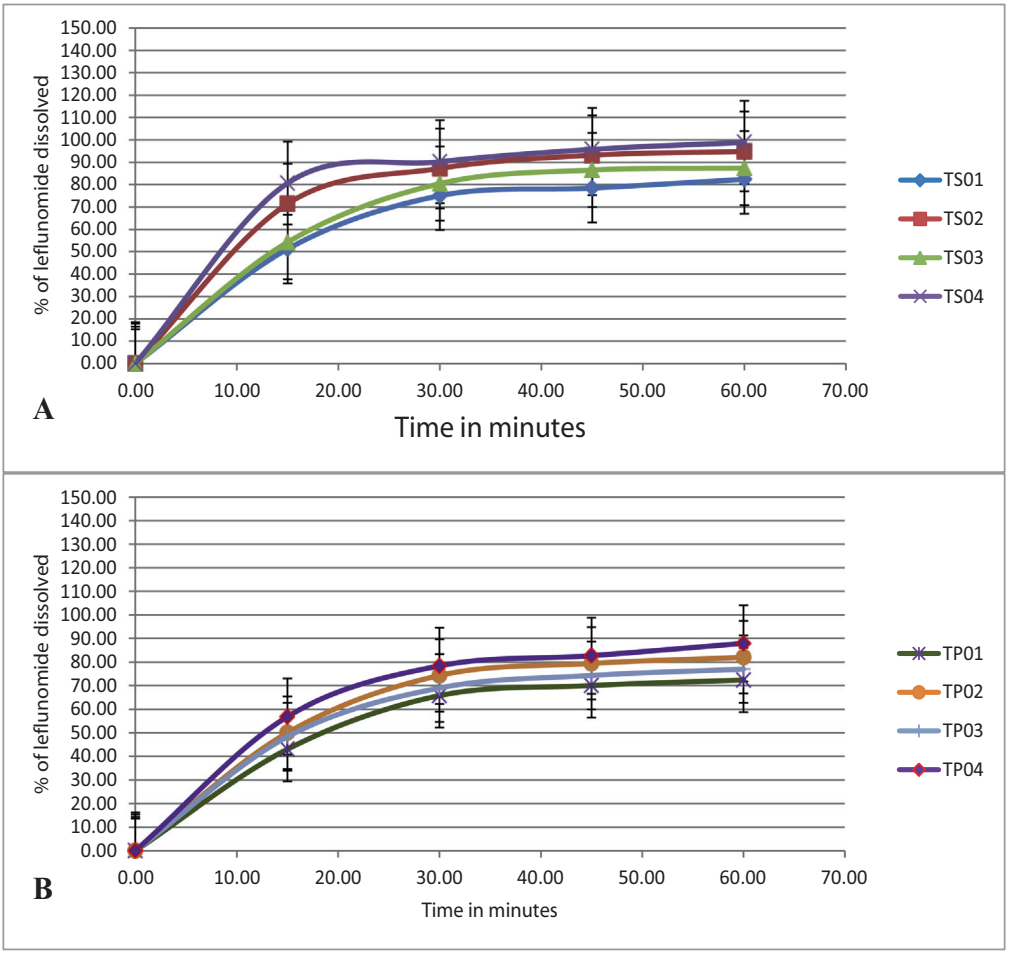


**Fig. 4.** Dissolution profiles of leflunomide from the prepared SE liquisolid formulae. A: Liquisolid formulae prepared with sesame oil (TS01-TS04)B: Liquisolid formulae prepared with paraffin oil (TP01-TP04).

equal 90% w/w and less than or equal 110% w/w and thus the preparation and compression method can be considered as acceptable.

*3.4.4. Determination of the disintegration time*

All the prepared batches had a disintegration time ranging between 8.45 ± 0.16 min and 10.7 ± 0.29 min (Table 4). The average disintegration time of liquisolid tablets is higher when compared to the directly compressed tablets. This can be attributed to the fact that the liquid ingredients may act as a binder to the solid ingredients and thus increasing the average disintegration time. Worth noting that, it was observed that tablets did not disintegrate but gradually eroded during the dissolution study.

*3.4.5. In vitro dissolution studies*

Fig. 4(A&B) shows the dissolution profile of the eight SE liquisolid formulae prepared with paraffin oil and sesame oil respectively. Formulae TS01 to TS04 prepared with sesame oil has shown higher dissolution profile than formulae TP01 to TP04 prepared with paraffin oil .All SE liquisolid formulae prepared show dissolution profiles conforming to the USP36/NF 31 [19] regulation which states that for the dissolution time test to be conforming not less than 75% of the labeled amount should dissolve in 30 min except formulae TP01 and TP03. Fig. 5 illustrates the dissolution profile of TP04 and TS04 (showing highest dissolution profile amongst tested formulae) compared to DCT which is the directly compressed tablets prepared from physical mixture and the commercial formula Arthfree®. The percentage of the drug dissolved after 15 min in TS04 SE liquisolid prepared with sesame oil was 80.64 ± 2.49% and compared with 52.39 ± 0.78% and 69.51 ± 0.52% for the directly compressed mixture(DCT) and the commercial formula Arthfree® respectively. At the end of the 60th min, the percentage of leflunomide dissolved was 98.86 ± 0.34% for TS04 and 81.34 ± 2.12% and 90.25 ± 0.82% for DCT and Arthfree® respectively.

The results of the dissolution studies indicate that all the SE liquisolid systems have higher percentage dissolved and dissolution rates than the directly compressed tablets probably due to small particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase. Another reason might be due to amorphization or solubilization of leflunomide in liquisolid tablets which was indicated by DSC and XRD studies. Formulae S01 to S04 prepared with sesame oil has shown higher dissolution profile than formulae P01 to P04 prepared with paraffin oil as shown in Fig. 4(A-B). This can be attributed to the nature of the oil itself and the characteristics of the emulsion formed.

A direct relationship between the liquid portion amount and the percentage of leflunomide dissolved was found which can be due to increased solubilization of the drug and the formation of a more stable emulsion. This is shown as formulae TS04 and TP04 which have the highest solvent amount (liquid portion is 110 mg/tablet) also display the highest percentage dissolved and dissolution rate among other formulae. By comparing between formulae TS04 and TP04 that displayed the highest dissolution profile, formula TS04 prepared with sesame oil has higher percentage dissolved and dissolution rate than formula TP04 (Fig. 5).

The percentage dissolved of leflunomide in commercial tablets were lower than liquisolid SE formula TS04 while it was higher than liquisolid formula TP04 prepared with paraffin oil and directly compressed tablets (DCT) (Fig. 5). The similarity factor (f2) was calculated to determine if SE liquisolid tablets TS04 dissolution profile would be similar to the commercial tablets. According to similarity factor (f2) calculation, the dissolution profile of SE liquisolid tablet TS04 is not similar to the commercial tablet dissolution profile ($f2 < 50$). The dissolution profile of formula TS04 was studied in different pH media to study the effect of pH of gastrointestinal

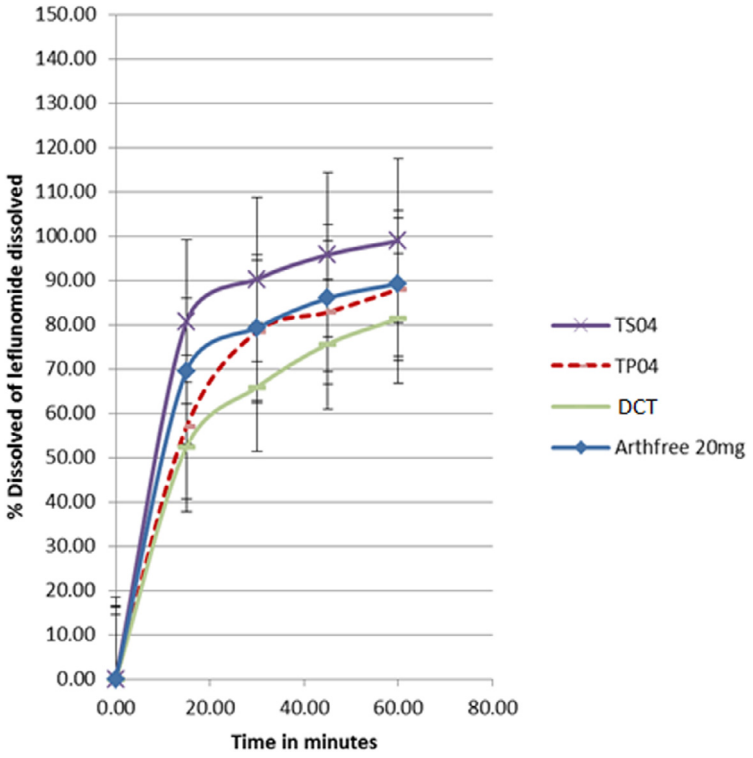


**Fig. 5.** Dissolution Profiles of leflunomide from SE formulae prepared Using paraffin oil TP04, Sesame oil TS04, commercial tablets(Arthfree® 20 mg) and Directly compressible tablets DCT.

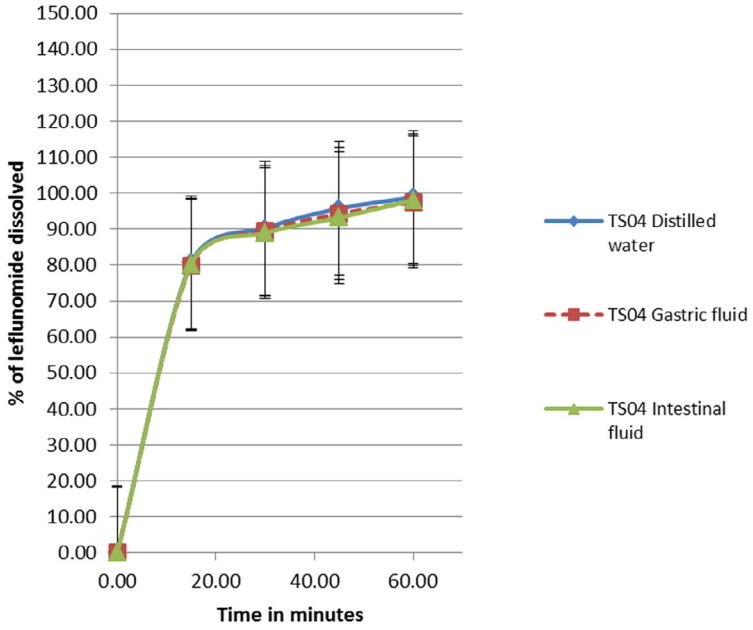


**Fig. 6.** Dissolution Profiles of leflunomide from the prepared SE liquisolid formula TS04 in different media with different pH values.

fluids on the dissolution properties of leflunomide in SE liquisolid systems (Fig. 6). It was found that the dissolution profile of leflunomide in simulated gastric fluid and intestinal fluid are similar to the dissolution profile in distilled water ($f2 > 50$). Thus it can be concluded that changing the pH has no significant difference on the dissolution profile of SE liquisolid formulae of leflunomide which agree with the solubility of leflunomide in gastric and intestinal fluids (Table 1) which showed no significant difference from the solubility in water. As formula TS04 prepared with sesame oil showed the best dissolution profile and adequate tablet properties it was selected for further studying the effect of aging on the tablets.

*3.4.6. Stability studies*

The stability of a drug product is defined by the rate of change over time of key measures of quality on storage under specific conditions of temperature and humidity. The ICH [25] specify the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. Accelerated stability studies where done on the SE liquisolid formula that showed the maximum percentage drug dissolved (TS04). The study indicates that there is no major difference in hardness (12.98 ± 0.22 kp), drug content (98.25 ± 0.68%) and disintegration time (12.34 ± 0.35 min) after storing the formulation for six months under accelerated storage conditions tested with ANOVA ($(P < 0.05)$. The tablets appearance did not change over the course of the study. The dissolution profile of fresh and aged leflunomide liquisolid compacts show no significant effect on drug release as $f2 > 50$ (Fig. 7). Thus, the tested formulation was stable during the course of this study. Thus, SE liquisolid formula can be considered as a novel, effective and a commercially viable alternative to the currently existing leflunomide formulations.

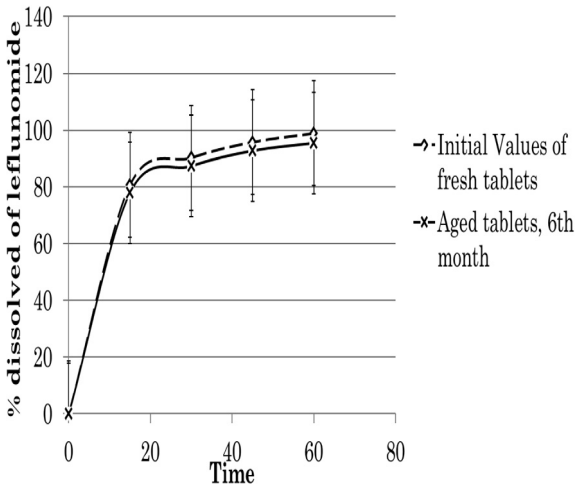


**Fig. 7.** Dissolution Profiles of fresh and incubated tablets of formula TS04 during accelerated stability study.

## 4. Conclusion

Leflunomide as a BSCII drug exhibits high permeability through biological membranes, but its absorption after oral administration is limited by its low dissolution rate due to its very low aqueous solubility. Hence, the use of the liquisolid technique was chosen to enhance the dissolution properties of leflunomide .On the basis of the previous findings, it can be concluded that combining self-emulsifying drug delivery technique and liquisolid technology can be a promising tool to enhance the dissolution of BCS-II drug leflunomide and thus increase its bioavailability and conformance to USP standards. All leflunomide self-emulsifying liquisolid systems prepared with sesame oil or paraffin oil upon dilution with distilled water formed clear homogeneous emulsions indicating self-emulsifying ability of these systems upon dilution. All SE liquisolid formulae possessed adequate flow and adequate tablet characteristics. Excipients have shown compatibility indicated by FTIR and DSC. The drug was completely solubilized in the PEG300 as indicated by XRD and DSC which can be the cause of increased dissolution profile of leflunomide which increased as the liquid portion of the SE liquisolid systems increased. Dissolution of SE liquisolid systems prepared with sesame oil was higher than systems prepared with paraffin oil. SE liquisolid systems prepared with sesame oil showed higher percentage of leflunomide dissolved than commercial tablets and their dissolution profile

showed no significant difference upon changing the dissolution medium to simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2). It has also shown stability and the dissolution profile, hardness and disintegration did not show any significant difference upon storage during the accelerated stability study. Finally it can be concluded that liquisolid concept can be applied successfully for leflunomide self-emulsifying systems to produce tablets with enhanced in vitro dissolution of leflunomide and thus it may improve its bioavailability in vivo. However, Biological, bioequivalence, and clinical studies are needed to validate these in vitro findings.

## References


[1] I.R. Ibrahim, M.I.M. Ibrahim, M.S.D. Al-Haddad, The influence of consumers' preferences and perceptions of oral solid dosage forms on their treatment, Int. J. Clin. Pharm. 34 (5) (2012) 32–72.

[2] M.A. Alam, F.I. Al-Jenoobi, A.M. Al-mohizea, Commercially bioavailable proprietary technologies and their marketed products, Drug Discov. Today 18 (19–20) (2013) 936–949.

[3] R. Lobenberg, G.L. Amidon, Modern bioavailability, bioequivalence and biopharmaceutics classification system. New approaches to international regulatory standards, Eur. J. Pharm. Biopharm. 50 (1) (2000) 3–12.

[4] M.J. Habib, Pharmaceutical Solid Dispersion Technology, Technomic publication company Inc, Lancaster, USA, 2000.

[5] J. Cook, W. Addicks, Y.H. Wu, Application of the biopharmaceutical classification system in clinical drug development–an industrial view, AAPS J. 10 (2) (2008) 306–310.

[6] S. Spireas, Liquisolid systems and methods for preparing same, United States Patent US6423339 B1, 2000.

[7] S. Spireas, S.M. Bolton, Liquisolid systems and methods of preparing same, United States Patent US5800834 A, 1998.

[8] M. El-Hammadi, N. Awad, Investigating the use of liquisolid compacts technique to minimize the influence of pH variations on loratadine release, AAPS PharmSciTech 13 (1) (2012) 53–58.

[9] B. Akinlade, A. Elkordy, E. Essa, S. Elhaggar, Liquisolid systems to improve the dissolution of furosemide, Scientia Pharmacuetica 78 (2010) 325–344.

[10] Y. Javadzadeh, B. Jafari-Navimipour, A. Nokhodchi, Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine), Int. J. Pharm. 341 (1–2) (2007) 26–34.

[11] K.A. Khaled, Y.A. Asiri, Y.M. El-Sayed, In vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs, Int. J. Pharm. 222 (1) (2001) 1–6.

[12] R. Fahmy, M. Kassem, Enhancement of famotidine dissolution rate through liquisolid tablet formulation: in vitro and In vivo evaluation, Eur. J. Pharm. Biopharm. 69 (3) (2008) 993–1003.

[13] C.W. Pouton, C.J.H. Porter, Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies, Adv. Drug Deliv. Rev. 60 (6) (2008) 625–637.

[14] A.C. Koåník, M.G. Sznitowksa, Solubility of ocular therapeutic agents in self emulsifying oils I. Self emulsifying oils for ocular drug delivery: solubility of Indomethacin, Acta Pol. Pharm. 66 (6) (2009) 709–713.

[15] S. Gupta, R. Kesarla, A. Omri, Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems, ISRN Pharm. (2013), http://dx.doi.org/10.1155/2013/848043.

[16] B. Tang, G. Cheng, J.C. Gu, C.H. Xu, Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms, Drug Discov. Today (2008) 606–612.

[17] S. Sweetman, Martindale: the complete drug reference. Electronic Version, Pharmaceutical Press, London, 2013.

[18] D. Vega, A. Petragalli, D. Fernandez, J.A. Ellena, Polymorphism on leflunomide: stability and crystal structures, J. Pharm. Sci. 95 (5) (2006) 1075–1083.

[19] The United States pharmacopeia 36/National Formulary 31, Rockville, USA, 2012.

[20] ICH harmonized triparitate guideline: validation of analytical procedures: text and methodology Q2(R1), in: International Confrence on Harmonization of technical requirements for registration of pharmacueticals for human use, 2005.

[21] Y. Javadzadeh, M.R. Siahi, S. Asnashaari, A. Nokhodshi, Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties, Acta Pharm. 57 (1) (2007) 99–109.

[22] R.C. Rowe, P.J. Sheskey, S.C. Owen, Handbook of Pharmaceutical Excipients, fifth ed., Pharmaceutical press, London, 2006.

[23] A.K. Meena, K. Sharma, M. Kandaswamy, S. Rajagopal, R. Mullangi, Formulation and in-vitro characterization of self nano emulsifying drug delivery system of cinnarizine, Acta Pharm. 62 (4) (2012) 563–580.

[24] Y. Javadzadeh, H. Shariati, E. Movahhed-Danesh, A. Nokhodchi, Effect of some commercial grades of microcrystalline cellulose on flowability, compressibility, and dissolution profile of piroxicam liquisolid compacts, Drug Dev. Ind. Pharm. 35 (2) (2009) 243–251.

[25] ICH harmonized triparitate guideline, stability testing of new drug substances and products Q1A (R2), in: International Confrence on Harmonization of technical requirements for registration of pharmacueticals for human use, 2003.

[26] World Health Organization (WHO), Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, WHO Technical Report Series, No. 953, 2009.

[27] G.E. Amidon, P.J. Secreast, D. Mudie, Particle, powder, and compact characterization, in: Y. Qui, Y. Chen, G. Zhang (Eds.), Developing Solid Oral Dosage Forms Pharmaceutical Theory and Practice, Academic press, MA, USA, 2009, pp. 163–183.

[28] Y. Chen, C. Chen, J. Zheng, Z. Chen, Q. Shi, H. Liu, Development of a solid supersaturatable self-emulsifying drug delivery system of docetaxel with improved dissolution and bioavailability, Biol. Pharm. Bull. 34 (2) (2011) 278–286.

[29] J.A. McCauley, H.G. Brittain, Thermal method of analysis, in: H.G. Brittain (Ed.), Physical Characterization of Pharmaceutical Solids, Drugs and Pharmaceutical Sciences, Marcel Dekker Inc, New York, 2005, pp. 223–250.

[30] P. Mura, M.T. Fauci, P.L. Parrini, Effect of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties, Drug Deliv. Ind. Pharm. 27 (2) (2011) 119–128.

[31] B. Chen, Z. Wang, G. Quan, X. Peng, X. Pan, R. Wang, et al., In vitro and in vivo evaluation of ordered mesoporous silica as a novel adsorbent in liquisolid formulation, Int. J. Nanomed. 7 (2012) 199–209.

[32] S.K. Niazi, Handbook of Preformulation: Chemical, Biological and Botanical Drugs, Informa Heathcare, USA, 2007.