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

aDepartment of Pharmaceutics, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA) University, Egypt
bDepartment of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Egypt

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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 disintegration 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.

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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
articles 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, crospovidone 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 C₁₂H₉F₃N₂O₂ 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 liquisol 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 Aarthree® 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. Pured 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 280 ± 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 sesam 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) would be equal to 0.2 in all the formulæ 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 disintegant 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 Korché tablet compression machine (Koché, 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 formulæ.

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 54 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 liquidsolid formule 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, liquidsolid formule 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
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