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In vitro and in vivo evaluation of a fast-disintegrating lyophilized dry emulsion tablet containing griseofulvin

Iman Saad Ahmed, Mona Hassan Aboul-Einien*

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Kasr-El-Eini St., Cairo, Egypt

ARTICLE INFO

Article history:
Received 18 February 2007
Received in revised form
8 April 2007
Accepted 29 May 2007
Published on line 7 June 2007

Keywords:
Griseofulvin
Dry emulsion
Freeze-drying
Lyophilized tablets
In vivo absorption
Bioavailability
Dissolution rate

ABSTRACT

Development of a fast-disintegrating lyophilized dry emulsion (LDE) tablet that enhanced the in vitro dissolution and in vivo absorption of griseofulvin (GF) is presented. The LDE tablets were prepared by freeze-drying o/w emulsions of GF, a drug for which bioavailability is known to be enhanced by fat co-administration. Oil-in-water emulsions were prepared using a gelatin solution (2%, w/v) as the water phase and medium chain triglycerides (Miglyol) or sesame oil as the oil phase. In addition, different emulsifiers were evaluated. The influence of formulation parameters on the disintegration and in vitro dissolution of GF from LDE tablets along with other tablet characteristics were investigated. A significant influence of the emulsifier type on the tablet disintegration time was seen ($p < 0.01$). Results obtained from dissolution studies showed that LDE tablets of GF improved the dissolution rate of the drug compared to the plain drug. The extent of absorption of GF from a selected LDE tablet formulation as compared to an immediate release conventional tablet as reference after single oral dose (125 mg) administration was determined in four healthy subjects using a randomized crossover design. In this study, the rate of absorption of GF from LDE tablet was faster than that from the reference tablet and had significantly higher ($p = 0.02$) peak plasma concentration (more than three times higher) and shortened time to C_{max} by 4 h ($p = 0.014$). The extent of absorption expressed by AUC was 85% larger as compared to the commercial tablet. Stability results, after 6 months storage of LDE tablets at 25 °C and 60% relative humidity, showed a slight increase in disintegration time and residual moisture content, while results from dissolution studies showed slightly slower initial drug release.

1. Introduction

Griseofulvin (GF) is an antifungal drug that is no longer widely used because of its erratic absorption and poor bioavailability. GF belongs, according to the biopharmaceutical classification system (BCS), to Class II of drugs with poor solubility and high permeability for doses of 125 and 250 mg (Amidon et al., 1995; Lindenberg et al., 2004). Class II drugs usually suffer from low bioavailability following oral administration of traditional dosage forms.

Micronized GF also shows an appreciable intersubject variability in the amount of drug absorbed from conventional dosage forms, which often results in clinical failure with GF therapy in many patients (Bates and Sequeira, 1975). Therefore, a new dosage form of micronized GF which allows the drug to be uniformly, rapidly, and maximally absorbed in man is needed and can be applied to similar drugs.

Previous studies indicated that the bioavailability of GF is enhanced when its water solubility is improved or when administered following a meal high in fat or carbohydrate

* *Corresponding author*. Tel.: +20 101648567.
E-mail address: Iman.Saad@Lycos.com (I.S. Ahmed).
0928-0987/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2007.05.114

contents (Kabasakalian et al., 1970; Khalafalla et al., 1981). Therefore, different techniques were applied and reported to enhance the dissolution rate and bioavailability of GF. Micronization or particle size reduction usually results in improvement of dissolution rate and bioavailability of many poorly soluble drugs including GF (Chaumeil, 1998). Similarly, GF solubility was found to increase when solid solutions of GF are used with polyethylene glycol and sodium dodecyl sulfate (Wulff et al., 1995). Increased absorption of GF from emulsified formulations compared to non-emulsified lipid formulations or aqueous suspensions was reported (Bates and Sequeira, 1975; Carrigan and Bates, 1973). In one of these studies, GF was completely absorbed from microsize GF corn oil-in-water emulsions and ultramicrosize commercial tablets compared to only 50% GF absorption from commercial microsize tablets (Bates and Sequeira, 1975). The dissolution rate and the absorption rate of GF are also reported to be significantly increased by its complexation with β-cyclodextrin (Dhanaraju et al., 1998). In this study, an inclusion complex in the molar ratio of 1:2 drug to β-cyclodextrin showed a 95% in vitro release within 45 min and 69% at the end of 5 h whereas in vivo studies in humans showed a fourfold increase in the absorption rate and a relative bioavailability of 73–84% compared to the drug alone. The dissolution rate of GF was also increased by the formation of nanoparticles of GF (below 100 nm) from water dilutable microemulsions (Trotta et al., 2003a), in this study the percent GF dissolved after 500 s from a suspension obtained from microemulsion containing dipotassium glycyrrhizinate (KG) was about four times higher compared to a commercial product.

Other approaches include increasing the dissolution rate and bioavailability of GF by the use of bioadhesive polymer (Khalid et al., 1997), the formation of GF nanoparticles made with poly-ε-caprolactone (Zili et al., 2005), and the preparation of GF nanosuspensions from triacetin-in-water emulsion (Trotta et al., 2003b). In one study, 50% GF was dissolved for spray dried GF/Poloxamer 407 particles within 15 min, compared to 18% for spray dried GF only particles and 7% for the drug alone. In this study, the absolute oral bioavailability of GF from spray dried GF/Poloxamer particles in rats was 6.92% compared to 3.94% from the oral administration of the drug alone (Wong et al., 2006). Spray-dried o/w emulsions administered as redispersible emulsions (Takeuchi et al., 1992; Christensen et al., 2001; Dollo et al., 2003) or compressed as tablets (Hansen et al., 2005) were also reported to improve the oral bioavailability of GF and other drugs such as vitamin E acetate, hydrochlorthiazide, and Lu 28–179; however, these techniques suffered from a number of disadvantages, such as the difficulty to preserve the initial emulsion lipid droplet size following redispersion; also, powders obtained from spray dried o/w emulsions are usually bulky, cohesive and suffer from poor flowability, which makes it difficult to handle without additional processing.

Freeze-dried o/w emulsion tablets made of maltodextrin and medium chain triglycerides were also evaluated and were found to release 35.1% hydrochlorthiazide after 10 min compared to 24.1% from a conventional tablet (Corveleyn and Remon, 1998). Freeze-dried emulsion tablets have the advantage of sharing the properties of freeze-dried dosage forms, such as rapid reconstitution, good preservation, and stability. The tablets also disintegrate rapidly in the mouth upon contact with saliva and therefore do not need to be swallowed, which usually results in improving patient's compliance and acceptability.

The purpose of this study was to investigate the in vitro dissolution and in vivo absorption of GF from lyophilized dry o/w emulsion (LDE) tablets. We also report on the preparation, characterization, and stability of LDE tablets. LDE tablets could be useful for the delivery of poorly soluble drugs for which fat co-administration results in improving bioavailability or for which an increased oral bioavailability is observed when incorporated in o/w emulsions.

2. Materials and methods

2.1. Materials

Griseofulvin in micronized state (predominantly contains particles of the order of 4 μm in diameter), micronized gelatine, glycine and sorbitol were purchased from Sigma Chemical Co (St. Louis, USA). Fractionated coconut oil which is medium chain triglycerides of caprylic and capric acids (Miglyol 812 N®) was provided by Condea (Witten, Germany) and sesame oil from Sigma–Aldrich Co. (UK). Polyoxyethylene sorbitan monoeleate (Tween 80) and sorbitan monoeleate 80 (Span 80) were obtained from Nintech-Brixworth (Northants, UK). Hydroxypropylmethylcellulose (HPMC, Methocel® K100LV) was obtained from Colorcon Ltd. (West point, PA, USA). HPLC-grade methanol and acetonitrile were supplied by Fisher Chemicals (USA). All water used was distilled de-ionized water. All other chemicals were of reagent grade and used as received. Fulvin 125 mg (Pharco, Egypt) was used as a reference tablet in in vivo studies.

2.2. Preparation of LDE tablets

The LDE tablets were obtained by freeze-drying o/w emulsions containing GF. Solutions containing 2% (w/v) gelatin in water were used as the water phase of the emulsions. Miglyol or sesame oil was used as the oil phase. GF was added to the oil phase with stirring to obtain a suspension of GF in oil. The emulsifiers used (HPMC or a blend of Tween 80/Span 80 in the ratio 4:1) were added to the aqueous phase with stirring until completely dissolved. Glycine and sorbitol were also added in equal amounts to the aqueous phase of two of the emulsion formulations. The oil phase was then added to the water phase and homogenized for 3 min at high speed (25,000 rpm) using a Diax 900 homogenizer (Heidolph-Instruments GMDH & Co., Kelheim, Germany). The detailed compositions of the prepared emulsions are listed in Table 1. The resulting emulsions were poured into each of the pockets of a tablet blister pack to result in a GF dose of 125 mg in each tablet. The tablet blister packs, each containing ten tablets, were then transferred to a freezer at −22 °C and kept in the freezer for 24 h. The frozen tablets were placed in a lyophilizer for 24 h using a Novalyphe-NL 500 Freeze Dryer (Savant Instruments, Holbrook, NY, USA) with a condenser temperature of −45 °C and a pressure of 7×10^{-2} mbar. A total of 200 tablets were prepared for each formulation in two separate runs. The lyophilized tablets were