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Relative bioavailability of griseofulvin lyophilized dry emulsion tablet vs. immediate release tablet: A single-dose, randomized, open-label, six-period, crossover study in healthy adult volunteers in the fasted and fed states

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ABSTRACT

The oral bioavailability of griseofulvin (GF) formulated as a fast disintegrating lyophilized dry emulsion (LDE) tablet was studied and compared to the commercially available immediate release (IR) tablet, as a reference, in both the fasted and fed states in nine healthy volunteers after a single oral dose (125 mg) in a crossover design. Furthermore the LDE tablets were ingested with and without water under both the fasted and fed states. In the fasted state, the rate of absorption was found to be significantly faster from LDE tablets, in the presence and absence of water, as shown by a higher C_{max} (more than two times higher, $p = 0.0001$) and a shorter t_{max} (by more than 3 h, $p = 0.0001$) compared to IR tablets. The extent of absorption, expressed as AUC, from LDE tablets in the presence and absence of water was 65% and 77% larger and statistically significantly different relative to the mean AUC from IR tablets ($p = 0.006$). In the fed state, C_{max} from LDE tablets ingested with and without water was found to be about 30% and 50% higher, respectively, than the immediate release tablets. A shorter t_{max} was also shown whether LDE tablets were ingested with or without water in the fed state as compared to immediate release tablets. The mean AUC from LDE tablets under fed conditions in the presence of water was about 21% larger and was not statistically significantly different from AUC from immediate release tablets ($p = 0.517$). When ingested without water, AUC from LDE tablets was about 43% larger and statistically significantly different relative to AUC from IR tablets ($p = 0.033$). The mean AUC from the LDE tablet ingested with water under fed conditions relative to AUC from LDE tablet ingested without water was not statistically significantly different ($p = 0.454$). Results show that the food effect of the high fat meal is very pronounced in case of the immediate release tablets, Fulvin, than in case of LDE tablets whether given with or without water.

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1. Introduction

Griseofulvin (GF), a poorly soluble antifungal agent, is slowly, erratically and incompletely absorbed from the gastrointestinal tract in humans (Fell et al., 1978). Clinical failure with griseofulvin therapy is most likely attributed to its poor solubility and appreciable intersubject and intrasubject variation in bioavailability from different commercial products (Bates and Sequeira, 1975a).

According to the biopharmaceutical classification system (BCS), GF belongs to Class II. For class II drugs, the bioavailability is often low and variable due to insufficient dissolution in the gastrointestinal tract (GIT). Furthermore, an increased bioavailability has been observed when a solid dosage form of these substances was taken with a meal (Amidon et al., 1995; Charman et al., 1993; Porter et al., 2004; Sim et al., 2005). The effect of intake of another poorly soluble drug, danazol, with an extra liquid volume has also been studied and shown to increase the oral bioavailability of danazol (Sunesen et al., 2005). Food effects have been reported to result from changes in drug solubility and other factors such as changes in the physiology of the GIT, which include delayed gastric emptying, stimulation of bile flow, changes in GI pH, increase in splanchic blood flow and change of luminal metabolism of a drug substance (Charman et al., 1997; FDA, 2002). It has also been reported that drug–transporter interactions could often be the primary mechanism for the food effect (Wu and Benet, 2005). GF has not been reported to be a substrate or inhibitor for known drug transporters.

Previous studies have shown that the bioavailability of GF is enhanced when its water solubility is improved or when administered following a meal high in fat or carbohydrate content (Kabasakalian et al., 1970; Khalafallah et al., 1981; Ogunbona et al., 1985). These findings have led to the application of different techniques attempting to enhance the dissolution rate and bioavailability of GF. Micronization or particle size reduction (Chaumeil, 1998), solid solutions with polyethylene glycol and sodium dodecyl sulfate (Wulff et al., 1995), emulsified formulations (Bates and Sequeira, 1975b; Carrigan and Bates, 1973), complexation with cyclodextrin (Dhanaraju et al., 1998), formation of nanoparticles from water dilutable microemulsions (Trotta et al., 2003a) have all been reported to increase the dissolution rate and the absorption rate of GF.

In a previous study done by part of this research group, GF was formulated in the form of fast-disintegrating lyophilized dry emulsion (LDE) tablets prepared by freeze-drying o/w emulsions of GF (Ahmed and Aboul-Einien, 2007). LDE tablets developed in this work were found to increase the dissolution rate and oral bioavailability of GF when tested in four subjects under fasting conditions compared to an immediate release conventional tablet as reference. The LDE tablets also shared 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 is to determine in vivo absorption of GF from lyophilized dry o/w emulsion (LDE) tablets and compare it to the in vivo absorption of this drug from commercial immediate release tablets in the fasted and fed conditions in nine healthy volunteers. In this study, bioavailability of GF from LDE tablets was also assessed when the tablets were ingested without water under both the fasted and fed states.

2. Materials and methods

2.1. Materials

Griseofulvin in micronized state (predominantly contains particles of the order of 4 μm in diameter) was purchased from Sigma Chemical Co (St. Louis, 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 the in vivo studies.

2.2. Preparation of LDE tablets

The LDE tablets were prepared according to the method described by Ahmed and Aboul-Einien (2007) to result in a GF dose of 125 mg in each tablet. Briefly, LDE tablets were obtained by freeze-drying o/w emulsion containing GF. A 2% (w/v) gelatin solution was used as the water phase of the emulsion and Miglyol was used as the oil phase. A blend of emulsifiers consisting of Tween 80/Span 80 in the ratio 4:1 was added to the water phase and GF was added to the oil phase. The oil phase was then added to the aqueous phase and homogenized for 3 min at high speed. The resulting emulsion was poured into each of the pockets of a tablet blister pack, kept in a freezer for 24 h and the frozen tablets were freeze dried in a lyophilizer for 24 h. The lyophilized tablets were kept in a dessicator over calcium chloride (0% relative humidity) at room temperature until further use.

2.3. In vivo absorption studies

2.3.1. Study design

The study was carried out to compare the pharmacokinetics of GF from a LDE tablet formulation to a conventional marketed immediate-release tablet formulation (Fulvin, Pharco) following administration of single doses of 125 mg each using a non-blind, three-treatment, three-period, randomized, crossover design under both the fasted and fed states (2×3 crossover). Nine healthy male volunteers participated in the study after giving informed written consent. The subjects ranged in age from 25 to 44 years old (mean 34 years), in height from 165 to 185 cm (mean 170 cm) and in weight from 62 to 82 kg (mean 72 kg). The study was approved by the University Protection of Human Subjects Committee and the protocol complies with the declarations of Helsinki and Tokyo for humans. All subjects were prohibited from taking medications and smoking one week before the beginning of the study to the end of the test. All subjects fasted for at least 10 h before the study day (FDA, 2002). The subjects were randomly assigned to each of the three treatment groups of equal size under the fasted conditions with a one-week washout