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Effectiveness of supersaturation promoting excipients on albendazole concentrations in upper gastrointestinal lumen of fasted healthy adults

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ABSTRACT

Purpose: To evaluate the impact of dosage form relevant levels of a polymeric precipitation inhibitor and of lipid excipients on supersaturation of upper gastrointestinal contents with albendazole, a lipophilic weak base.
Materials and methods: Albendazole concentrations in stomach and in duodenum were evaluated after administration of 1) a suspension in water (Susp-Control), 2) a suspension in water in which hydroxyprolylmethylcellulose E5 (HPMC E5) had been pre-dissolved (Susp-HPMC), and 3) and 4) two contrasting designs of lipid based suspensions dispersed in water (Susp-IIIA and Susp-IV), on a cross-over basis to fasted healthy adults.
Results: Limited, but statistically significant supersaturation of duodenal contents was observed after Susp-HPMC, Susp-IIIA, and Susp-IV; supersaturation was more consistent after Susp-HPMC administration. Based on total albendazole amount per volume, gastric secretions did not significantly alter volumes of bulk gastric contents during the first 40 min post administration of a glass of non-caloric water-based fluid. Albendazole gastric concentrations were higher than in the administered suspensions, but similar for all four formulations. Gastric emptying of albendazole after administration of Susp-Control or Susp-HPMC was slower than after administration of Susp-IIIA or Susp-IV.
Conclusions: Small amounts of HPMC E5 were as effective as lipid excipients in achieving supersaturation of duodenal contents with albendazole, a fast precipitating weak base, in fasted adults. However, compared with the effect of HPMC E5 the effect of lipid excipients was delayed and variable.

1. Introduction

Supersaturation, a thermodynamically unstable condition during which concentrations are temporarily maintained higher than saturation level, may occur in upper gastrointestinal (GI) lumen after administration of salts of weak acids, of weak bases, and of enabling drug products (Brouwers et al., 2009). Optimal intraluminal supersaturation maintenance may provide higher and less variable absorption of poorly soluble drugs, which in turn could reduce the dose requirements and provide wider safety margins for drugs in development. One issue with the assessment of luminal supersaturation and its impact on absorption enhancement relates with the specific phase to which supersaturation refers to, as there are various distinct phases in the lumen including the aqueous phase, the micellar and other colloidal phases of physiological origin (Elvang et al., in press) and the potentially present colloidal phases of non-physiological origin (e.g. nanoparticles or nanodroplets, after oral administration of certain dosage forms). Based on in vitro experiments, there is growing evidence that different phases could be supersaturated at different levels and they may have a different impact on absorption enhancement (e.g. Frank et al., 2014). However, to date, the assay of molecularly dispersed drug in the aqueous phase of intestinal contents so that quantitative information at aspiration time could be derived is not possible. Subsequently, in this investigation supersaturation refers to the sum of aqueous and all colloidal phases that may exist in the medium, both for the data collected in this study and for all relevant prior information which is discussed in relation to this investigation.

In vitro data to date suggest that the period during which supersaturation is maintained varies with the chemical structure of the drug (Box and Comer, 2008), the physical state (solid vs. liquid; crystalline vs. amorphous) and the chemical state (free form vs. salt) of the drug in the supersaturated medium (e.g. Dimopoulou et al., 2016), and the type and amount of excipients which are included in the formulation (e.g. precipitation inhibitors or solubilizing agents). For example, hydroxypropylmethylcellulose (HPMC), a frequently employed polymeric precipitation inhibitor, has been shown to inhibit both

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crystallization (Ilevbare et al., 2013; Hsieh et al., 2014) and particle growth (Patel and Anderson, 2014) in vitro. Similar observations have been made for polyvinylpyrrolidone (PVP) (Lindfors et al., 2008).

To date, the ability of excipients to assist in achieving and maintaining for certain period of time supersaturation of luminal contents in humans has been studied indirectly (by monitoring plasma levels) and primarily under conditions of rapid intragastric dissolution of the dose (Chowdarya and Suresh Babu, 1994; Kapsi and Ayres, 2001; Verreck et al., 2004; Six et al., 2005; Klein et al., 2007; Ouellet et al., 2013) or after administration of solutions, typically, lipid based solutions (Trull et al., 1995; Julianto et al., 2000; Yüksel et al., 2003). In many cases, supersaturation promoting excipients may have to perform in the presence of undissolved drug particles, e.g. in case of supersaturation of gastric contents after administration of a salt of a weak acid, in case of supersaturation of contents of the small intestine after administration of a lipophilic weak base that partially dissolves in the stomach, or after administration of a supersaturation inducing enabling formulation.

The impact of particles on luminal supersaturation in humans has been shown to be substantial for lipophilic weak bases. Based on mean C_{max}/AUC data, absorption rates of SB705498 in fasted adults from immediate release tablets decrease proportionally with the dose, i.e. with the amount of particles arriving in upper small intestine, until they reach a plateau level (Psachoulias et al., 2012). Similarly, based on published C_{max} and AUC data, after administrations of suspensions of posaconazole to fasted adults, mean C_{max}/AUC values estimated after 40 mg and a 400 mg dose were 0.213 h^{-1} and 0.031 h^{-1}, respectively (Walravens et al., 2011; Hens et al., in press). In addition, it is not clear whether lipid solutions are beneficial over lipid suspensions from a human bioavailability perspective, although a canine model has shown suspensions of halofantrine to be beneficial (Porter et al., 2004). It has been speculated that the presence of solid drug may optimize the thermodynamics of drug in lipid solution and, therefore, maintain drug concentrations in the dispersed phases at or near saturation, enhancing the activity with respect to absorption (Porter et al., 2004; Khan et al., 2016).

In the present investigation we evaluated the impact of dosage form relevant level of a polymeric precipitation inhibitor and of lipid excipients on supersaturation of human upper GI contents by using albendazole as the drug model, under conditions where solid particles of the drug are present during gastric residence. Albendazole (ABZ) is one of the WHO Essential medicines and is commercially available for oral administration at a single dose of 400 mg with the objective being to maintain effective luminal concentrations in the entire gastrointestinal lumen, due its specific pharmacological action (prescription drug information on http://home.intekom.com/pharm/smith_kb/zentel.html). Albendazole is a lipophilic weak base [pka 2.80 (Jung et al., 1998) with logP 3.46 (Rivera et al., 2007)]. Based on in vitro data (Morrison et al., 2014) and rat data (Tanaka et al., 2014), albendazole is expected to precipitate fast upon entering the upper small intestine. Albendazole solubility decreases from ≈500 μg/ml in pH 1.2 to ≈2 μg/ml in pH 4.1 and ≈1.5 μg/ml in pH 7.0 (Paulekuhn et al., 2013), i.e. albendazole solubility is low, even under conditions of extensive ionization. Therefore, in the present investigation lower than the pharmacologically relevant single dose was studied (50 instead of 400 mg), because the impact of supersaturation promoting excipients, if any, is expected to be increased in presence of fewer particles (Psachoulias et al., 2012; Walravens et al., 2011; Hens et al., in press) and easier to be detected.

Polymeric precipitation inhibitors have not been studied extensively with ABZ. In a rat study, the impact of methylcellulose 50 at a high dose level (0.5% solution) had been evaluated with practically no effect on luminal supersaturation (Tanaka et al., 2014). In this study, hydroxypropylmethylcellulose was selected as model polymeric precipitation inhibitor (Ilevbare et al., 2013; Hsieh et al., 2014; Patel and Anderson, 2014). The impact of lipid excipients on albendazole absorption has been studied in preclinical species (Mukherjee and Plakogiannis, 2010; Meena et al., 2012). In those studies only Type III lipid based formulations were tested (Pouton, 2006). It is not clear on whether suspensions or solutions were tested; significant differences exist between the two papers in the ABZ solubility values in the same lipid excipient. Although some of the excipients were similar with those employed in the present investigation, exact compositions of lipid based formulations were different. The amounts of excipients required for the observed substantial effect on plasma levels in preclinical species (Mukherjee and Plakogiannis, 2010; Meena et al., 2012) was much higher than the amounts which could be considered for human administration, based on their current Generally Recognized As Safe (GRAS) status. Aside objective of this study was to collect baseline data for developing in vitro methodologies for predicting the impact of GI transfer on formulation performance without the complicating process of luminal digestion. To this end, a Type III lipid based formulation (consisting of glyceride, surfactant and cosolvent) and a Type IV lipid based formulation (consisting of surfactant and cosolvent) were to be tested (Pouton, 2006) and compositions were identical with those recently used with another lipophilic API, fenofibrate (Griffin et al., 2014).

To simulate a typical administration of a dosage form with a glass of water, luminal performance of ABZ in the present human aspiration study was evaluated after the administrations of 50 mg ABZ in the following forms:

- Suspension in 240 ml table water (Susp-Control).
- Suspension in 240 ml table water in which 5 mg of hydroxyprolylmethylcellulose (HPMC E5) had been pre-dissolved (0.1% of the ABZ dose) (Susp-HPMC).
- Suspension of a Type IIIA (1.0 g) lipid based formulation (Pouton, 2006) in 240 ml table water (Susp-IIIA), and.
- Suspension of a Type IV (0.6 g) lipid based formulation (Pouton, 2006) in 240 ml table water (Susp-IV).

2. Materials and methods

2.1. Materials

Albendazole free base clinical grade material (purity 100%) was provided by GSK (Ware, UK). Based on six representative commercial clinical micronized batches, the mass median diameter ranged between 2.9 μm and 3.9 μm (average 3.4 μm) and the % by volume of particles smaller than 10 μm ranged from 90.4 to 96.0% (average 93%) (GSK data on file). Hydroxypropylmethylcellulose E5 (Pharmacoat, HPMC E5, from GSK, Ware, UK), Miglyol 812 N [Caprylic/Capric (C8–C10) triglycerides, from Sasol, Hamburg, Germany], Cremophor RH 40 (BASF, Ludwigshafen, Germany) and Polysorbate 80 (Sigma Aldrich, Saint Louis, U.S.A) were all appropriate for human use. Acetonitrile and water of HPLC grade were from Sigma Aldrich (Saint Louis, U.S.A.). All other materials were of analytical grade.

2.2. Methods

2.2.1. Human study

The study was performed in the Red Cross Hospital of Athens after receiving approval by the Executive and Scientific Committees of the Hospital (AP 26665, 17 October 2014). It was a randomized cross-over four period four treatment study. Eight healthy male adults with a mean age of 26 years (range 21–34 years) gave informed consent and participated in the study.

2.2.2. Inclusion criteria

Willingness of the subject to participate as indicated by his signed informed consent, age 18–50 years, weight within 20% of ideal body weight as determined by Metropolitan Life Tables, verification of