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In vitro and *in vivo* characterization of amorphous, nanocrystalline, and crystalline ziprasidone formulations

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ABSTRACT

Ziprasidone, commercially available as Geodon® capsules, is an atypical antipsychotic used in the treatment of schizophrenia and bipolar disorder. It is a BCS Class II drug that shows up to a 2-fold increase in absorption in the presence of food. Because compliance is a major issue in this patient population, we developed and characterized solubilized formulations of ziprasidone in an effort to improve absorption in the fasted state, thereby resulting in a reduced food effect. Three formulations utilizing solubilization technologies were studied: (1) an amorphous inclusion complex of ziprasidone mesylate and a cyclodextrin, (2) a nanosuspension of crystalline ziprasidone free base, and (3) jet-milled ziprasidone HCl coated crystals made by spray drying (CCSD) the drug with hypromellose acetate succinate. The formulations were characterized by *in vitro* methods appropriate to each particular solubilization technology. These studies confirmed that ziprasidone mesylate – cyclodextrin was an amorphous inclusion complex with enhanced dissolution rates. The ziprasidone free base crystalline nanosuspension showed a mean particle size of 274 nm and a monomodal particle size distribution. In a membrane permeation test, the CCSD showed a 1.5-fold higher initial flux compared to crystalline ziprasidone HCl. The three formulations were administered to fasted beagle dogs and their pharmacokinetics compared to Geodon® capsules administered in the fed state. The amorphous complex and the nanosuspension showed increased absorption in the fasted state, indicating that solubilized formulations of ziprasidone have the potential to reduce the food effect in humans.

1. Introduction

Ziprasidone (Fig. 1) is a chlorooxyindole class aryl-heterocyclic that is an atypical anti-psychotic agent used in the acute and long-term treatment of schizophrenia and manic symptoms of bipolar disorder (Geodon®, 2009). These are highly debilitating mental disorders – more than 5.7 million Americans suffer from bipolar disorder and 2.4 million Americans suffer from schizophrenia in a year. Ziprasidone binds to a variety of receptors (D_2, D_3, $5HT_{1A}$, $5HT_{2A}$, $5HT_{2C}$, $5HT_{1D}$ and α_1) with low nanomolar affinity. Although its exact mechanism of action is unknown, it is believed to be related to D_2 and $5HT_{2A}$ antagonism (Stahl and Shayegan, 2003). Ziprasidone was first approved in the U.S. in February 2001. The commercially available ziprasidone formulations, which include an oral capsule, an oral suspension, and an immediate-release intramuscular formulation, are marketed worldwide under the trade names of Geodon® or Zeldox®. Over the years, the safety (Daniel, 2003; Patel and Keck, 2006; Zimbroff Dan et al., 2005), efficacy (Greenberg and Citrome, 2007; Harrison and Scott, 2006; Patel and Keck, 2006; Zimbroff Dan et al., 2005), and cost-effectiveness (Bernardo et al., 2006, 2007; Bobes et al., 2004) of ziprasidone have been well established.

Ziprasidone shows up to a 2-fold increase in the rate (*i.e.*, C_{max}) and extent (*i.e.*, AUC_{inf}) of absorption in the presence of a high calorie-high fat meal (Miceli et al., 2000). Studies have shown that calories consumed (rather than the fat content of the meal) and the time between dosing and food intake are important factors in the absorption of ziprasidone (Gandelman et al., 2009; Hamelin et al., 1998; Lincoln et al., 2010). When dosed orally with food, Geodon® exhibits linear pharmacokinetics in the 20–80 mg dose range. Because of this food effect, it is recommended that Geodon® capsules be taken with food (Geodon®, 2009). However, compliance can be a major issue in patients with schizophrenia; it is estimated that around 50% of the patients do not fully comply with the prescribed treatment (Perkins, 2002). Thus, a ziprasidone formulation with no food effect has the potential to enhance

Abbreviations: AUC_{inf}, area under the serum concentration–time profile from time 0 extrapolated to infinite time; AUC_{last}, area under the serum concentration–time profile from time 0 to the time of the last quantifiable concentration (C_{last}); C_{max}, maximum serum concentration; T_{max}, time for C_{max}.

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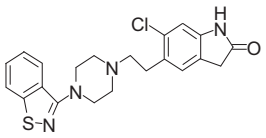

Fig. 1. Chemical structure of ziprasidone.

the effectiveness of this medication in a poorly compliant patient population.

Several review articles have examined food–drug interactions (Melander, 1978; Schmidt and Dalhoff, 2002; Singh, 1999; Toothaker and Welling, 1980; Welling, 1996). Increased oral bioavailability when dosed with food has been attributed to various factors such as micellar solubilization due to bile acids, delayed stomach emptying, decreased hepatic clearance, and increased bile flow leading to reduced presystemic and first pass metabolism (Singh, 1999; Singh and Malhotra, 2004). Ziprasidone HCl is a weak base with a high melting point (304 °C), high lipophilicity ($c\log P = 3.6$), and an intrinsic solubility of 0.3 μg/mL (Friesen et al., 2008; Kim et al., 1998). Based on a partition coefficient into bile salt micelles of about 2200, its solubility in simulated biorelevant fluids was estimated to be 4–5 μg/mL in fasted state media and 10–14 μg/mL in fed state media. We hypothesized that ziprasidone shows solubility and/or dissolution rate-limited absorption in the fasted state, so we attempted to improve the extent of absorption through the use of various solubilization technologies.

Numerous technologies are available for improving the solubility or dissolution rates of a drug, including prodrugs (Fleisher et al., 1996; Stella and Nti-Addae, 2007), polymorphs, solvates, co-crystals (Babu and Nangia, 2011), salt formation (Serajuddin, 2007), lipid based systems (Hauss, 2007; Humberstone and Charman, 1997; Porter et al., 2008), micellar solubilization including self-emulsifying drug delivery systems (Tang et al., 2007), inclusion complexes (Brewster and Loftsson, 2007), amorphous solid forms such as spray dried dispersions (Friesen et al., 2008), and particle size reduction including nanomilling (Kesisoglou et al., 2007; Merisko-Liversidge et al., 2003; Usha et al., 2010).

In this study, we developed and characterized the following solubilized forms of ziprasidone in an attempt to reduce or eliminate its food effect: an amorphous ziprasidone mesylate – cyclodextrin complex, a suspension containing nanocrystalline ziprasidone free base, and an intimate physical mixture of a jet-milled ziprasidone hydrochloride with a polymeric precipitation inhibitor.

2. Methods and materials

2.1. Materials

Ziprasidone free base, mesylate, and hydrochloride salts were obtained from Pfizer Inc. Sulfobutyl ether β-cyclodextrin sodium (SBECD) was manufactured by Pfizer Inc. under license purchased from CyDex Pharmaceuticals, Inc. (Lenexa, KS, USA). Hypromellose acetate succinate AQOAT®, HG-grade, referred to in this paper by its older name, hydroxypropyl methylcellulose acetate succinate (HPMCAS), was purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Poloxamer 338 (Pluronic® F108) was purchased from BASF Corp. (Mount Olive, NJ, USA). Polysorbate 80 (Tween® 80) and Soybean lecithin (NF grade) were purchased from Spectrum Chemicals (Gardena, CA, USA). All other chemicals, reagents, and solvents were analytical grade and were purchased from commercial suppliers by Pfizer Inc.

Table 1
Summary of solubilized ziprasidone formulations investigated in this study.

Formulation	Acronym	Brief Description
A	Ziprasidone–SBECD complex	Ziprasidone mesylate – sulfobutyl ether β-cyclodextrin inclusion complex
B	Ziprasidone nanosuspension	Ziprasidone free base nanosuspension made by wet-milling
C	Ziprasidone CCSD	Jet-milled ziprasidone HCl crystals coated with hydroxypropyl methylcellulose acetate succinate HG-grade (HPMCAS) as a precipitation inhibitor

2.2. Test formulations and in vitro characterization

Three solubilized formulations, designated as formulations A, B, and C in Table 1, were made and characterized as described below.

2.2.1. Test formulation A

A ziprasidone mesylate – SBECD inclusion complex was prepared by first making an aqueous solution of ziprasidone mesylate and SBECD at a molar ratio of 1:1.3 in a stirred vessel maintained at 75 °C. The solution was then cooled to 40 °C and filtered, under nitrogen, through a 0.45 μm Kleenpak Ultipor N66 filter (Pall Corporation, Port Washington, NY, USA). The filtered solution was dispensed into stainless steel drying trays, lyophilized at −32 °C for at least 96 h, dried at −12 °C until there was a break in the product cake, followed by drying at 25° for 24 h. The dried cake was milled to a powder using a Fitzpatrick M5A mill (The Fitzpatrick Co., Elmhurst, IL, USA) fitted with a 0.0315 in. rasping plate and bar impeller rotating at 1020 rpm.

The stoichiometry of ziprasidone mesylate-SBECD inclusion complex is 1:1 (Kim et al., 1998). A slight excess of SBECD relative to ziprasidone mesylate was selected to ensure that the drug was completely complexed without significantly decreasing the drug loading, which would have resulted in a dosage form of a large size. A crystalline ziprasidone mesylate-SBECD physical mixture was prepared at the same molar ratio of 1:1.3 to serve as a control.

Formulation A and the physical mixture were characterized by light microscopy, powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and SS-NMR to determine the form of the drug in the solid state. In addition, dissolution studies were performed at pH 4.0 and pH 7.4.

2.2.1.1. Light microscopy. Microscopic analyses of ziprasidone mesylate, SBECD, and formulation A were performed using an Olympus BH-2 microscope under bright and dark field.

2.2.1.2. Powder X-ray diffraction (PXRD). PXRD patterns of ziprasidone mesylate, SBECD, a physical mixture of ziprasidone with SBECD, and formulation A were obtained on a D5000 – Siemens Diffractometer with a voltage of 50 kV and a current of 40 mA. Alignment was verified with an aluminum standard before each measurement. Samples were prepared by placing powders in a quartz zero background sample holder and scanned from 3° to 40° 2θ at a rate of 1° per second.

2.2.1.3. Solid-state nuclear magnetic resonance (SS-NMR). Inclusion complexation of ziprasidone with SBECD was confirmed using proton NMR of ziprasidone solubilized in SBECD (Kim et al., 1998). SS-NMR was also used to characterize whether a molecular level interaction between SBECD and ziprasidone was maintained in the solid state lyophilized complex. The details of the methodology and results have been described previously (Hong et al., 2011).