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Pharmacoscintigraphy studies to assess the feasibility of a controlled release formulation of ziprasidone

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ABSTRACT

Ziprasidone, like many BCS Class II drugs with low intrinsic solubility and a strong tendency to crystallize from supersaturated solutions, presents significant technical challenges when developing an oral controlled release dosage form. In order to achieve acceptable bioavailability and prolonged exposures for once-daily dosing, good colonic absorption and a reliable controlled release (CR) technology are necessary. To this end, a novel solubilized drug form — coated crystals made by spray drying (CCSD), was formulated and progressed into human clinical studies. This report describes studies of colonic absorption for the CCSD using the Enterion™ capsule and a pharmacoscintigraphy study in which the CCSD was orally administered via a radiolabelled osmotic tablet formulation. These studies demonstrated that the probability of achieving the required drug solubilization in the colon with the CCSD concept and thereby the desired once daily pharmacokinetic profile was extremely low.

1. Introduction

Ziprasidone (Scheme I) is an atypical antipsychotic agent indicated for the treatment of schizophrenia and mania associated with bipolar disorder. First approved in the U.S. in 2001, it is commercially available as Geodon® immediate release (IR) capsules in 20, 40, 60, and 80 mg strengths for oral use. It is also available as an intramuscular injection form to control acute agitation in schizophrenic patients.

The safety and efficacy of ziprasidone is well established [1–4]. Ziprasidone therapy is initiated with a dose of 20 mg twice-daily and the dose is increased and adjusted based on patient's response. In an expert opinion article [5], three dosing-related issues were identified for ziprasidone. First, higher doses of ziprasidone, e.g., 120–160 mg/day vs. 40–80 mg/day, appear to be more efficacious. Second, this medication needs to be administered twice-daily, which is an issue because compliance in schizophrenia and bipolar disorder is known to be problematic [6,7]. Third, it must be administered with food. Having to take the medicine twice-daily*and* with food compounds the compliance issue. The expert opinion concluded that "if ziprasidone can be dosed once-daily with an established dosing profile, then this treatment will be even more appealing to clinicians." In this paper, we address the technical feasibility of once-daily dosing of ziprasidone.

Two approaches could be considered for a once-daily formulation of ziprasidone: (1) a higher immediate release (IR) dose, viz., administer the total daily dose all at once rather than as divided doses given twice-daily, and (2) a controlled release (CR) formulation. The first approach is less attractive because a high IR dose would result in high peak concentrations, which could potentially lead to a higher incidence of cardiovascular adverse effects. The physicochemical and biopharmaceutical properties of ziprasidone were considered in the context of the second approach, viz. a CR formulation for once-daily dosing. Ziprasidone is poorly water-soluble (free base solubility in pH 6.5 buffered media ~0.3 μg/mL), basic (pKa ~6), and highly lipophilic (clog P = 3.6) [8–10]. These properties combined with a high partition coefficient in bile-salt micelles [11], result in a two-fold increase in absorption of ziprasidone in the fed versus fasted state [12]. However, since no bile-salts are present in the colon to help with absorption of ziprasidone released from a CR dosage form, a solubilized form of ziprasidone is considered necessary for achieving once-daily dosing.

Abbreviations: AUC_{inf}, area under the serum concentration-time profile from time 0 extrapolated to infinite time; BA, bioavailability; C_{max}, maximum serum concentration; T_{max}, time for C_{max}; SCT, swellable core technology; CCSD, coated crystals made by spray drying; IR, immediate release; CR, controlled release; T_{80}, time for 80% of the drug to be released; ICJ, ileocecal junction.

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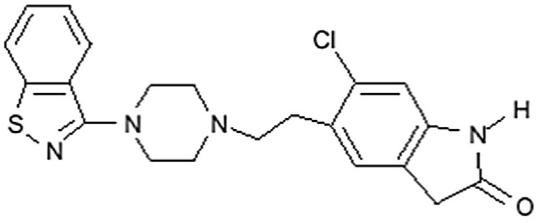

Scheme I. Chemical structure of ziprasidone.

The poor solubility of ziprasidone translates to a dose/solubility ratio of 160 L, and, based on prior in-house experience, would need a solubilization technology coupled with a CR technology to achieve once-daily dosing [13]. The need for solubilization was confirmed by comparing the relative bioavailability (BA) of two CR formulations containing ziprasidone hydrochloride. These formulations were based on osmotic technology and had a short (T_{80} = 6 h) and long (T_{80} = 12 h) delivery duration. They were dosed in the fasted and fed state and compared with Geodon® IR capsules dosed in the fed state. The results showed that the long duration formulation had a low relative BA in the fasted state (as expected) compared to the fed state. Deconvolution of the fed-state data for the long duration CR formulation dosed in the fed state indicated that colonic absorption accounted for approximately 15% of the absorbed dose (data on file, Pfizer Inc.). A human intubation study showed that the fraction absorbed from a ziprasidone solution dosed directly into the duodenum or the ileocecal junction (ICJ) was comparable to that following an oral capsule. However, the fraction absorbed was significantly lower when a ziprasidone suspension was dosed (data on file, Pfizer Inc.). Therefore, the intrinsic permeability of ziprasidone was not anticipated to be a significant issue.

Numerous technologies are available for improving the solubility or dissolution rates of a drug, including polymorphs/solvates/co-crystals [14], salt formation [15], lipid based systems [16–18], inclusion complexes [19], amorphous solid forms such as spray dried dispersions [9], and particle size reduction including nanomilling [20–22]. Solubilized forms of ziprasidone commonly result in supersaturated drug concentrations, and the drug has a strong tendency to convert to the free base form and precipitate out of these solutions at intestinal pHs [23,24]. Typically, a higher degree of supersaturation results in faster precipitation kinetics. In these cases, the use of precipitation inhibitors may be used to maintain supersaturation for a longer period of time.

Enhanced bioavailability has been demonstrated with physical mixtures of ziprasidone hydrochloride and hydroxypropylmethylcellulose acetate succinate (HPMCAS) [25]. The solubilized form utilized in this study is an intimate physical mixture of crystalline ziprasidone and HPMCAS created by spray-drying a suspension of the drug in a solvent-based solution of the polymer (coated-crystals made by spray-drying (CCSD)). The drug form was ziprasidone hydrochloride dihydrate, i.e., the same form as present in Geodon®, the only difference being that the crystals were jet-milled in order to maximize dissolution rate.

CCSDs can be formulated into several platform CR technologies, including hydrophilic matrix tablets, osmotic tablets, and multiparticulates. Toward the purpose of developing a once-daily ziprasidone formulation, this paper details the use of the swellable-core technology (SCT) tablet, a push–pull osmotic pump tablet comprised of a coated bilayer tablet with a laser drilled hole [26]. The SCT tablet was strongly desirable due to the zero-order release profile, independence of release to surrounding media (including pH, bile concentration, ionic strength, or ethanol content), and the ability to handle the dose required for ziprasidone.

The pharmaceutical industry has developed several tools to justify or aid in the development of modified release dosage forms. Several techniques such as intubation studies, the HF Capsule, and the InteliSite® Capsule have been used to assess drug absorption at specific sites in the gastrointestinal tract [27–32]. Gamma-scintigraphy is an imaging technique that has been used for the in vivo monitoring of dosage forms [33–35]. It was first used in 1966 as a clinical tool for the assessment of gastric emptying times [36], and subsequently in 1976 [37,38] for the assessment of pharmaceutical dosage forms (capsule disintegration). Visualization is achieved by the incorporation of a short half-life gamma-emitting radionuclides e.g. technetium-99m(^{99m}Tc) and indium-111(^{111}In) into the drug product. A gamma camera is used to detect the gamma rays, and record these as primary counts which are represented as an image. Analysis of these images can be performed in both a qualitative (e.g. assessment of the time taken for a dosage form to transit through the regions of the gastrointestinal tract, and anatomical location of events such as disintegration) and a quantitative (e.g. determination of a percentage vs time profile for tablet erosion) manner, depending on the objectives of the study. Pharmacoscintigraphy, entailing a combination of gamma-scintigraphy to visualize the dosage form during transit during a traditional pharmacokinetic study, has been a powerful tool used to study the transit of orally administered dosage forms and correlate the regional absorption of a drug delivered from a CR formulation [33,34,39,40].

A strongly-precedented technology used in pharmacoscintigraphy studies is the Enterion™ capsule [41,42]. It contains a radiotracer port which allows real-time monitoring of the position of capsule in the gastrointestinal tract by gamma-scintigraphy. The capsule can be remotely triggered to deliver a bolus of a liquid or solid formulation when it arrives at the desired location in the gastrointestinal tract (e.g., jejunum, ileocecal junction, or colon). The data from Enterion™ studies has been routinely used to assess the feasibility of developing a CR formulation.

In this paper, we describe two pharmacoscintigraphy studies conducted to assess the colonic absorption of a jet-milled ziprasidone hydrochloride CCSD. Two different drug loadings (35% and 44%) were studied. The lower drug loading might be expected to have a better performance because of the higher proportion of the precipitation-inhibiting polymer. In contrast, the higher drug loading would be desirable from a pharmaceutical development perspective as it would result in a reasonable sized final dosage form. The lower drug loading was studied at two doses (5 mg and 20 mg) to assess whether the enabling technology had a dose proportional impact on drug absorption. In the first study, the Enterion™ capsule was used to deliver ziprasidone solutions and CCSDs directly to the ascending colon to understand the absorption of the drug forms. In the second study, we assessed the performance of an SCT tablet containing the ziprasidone CCSD. The non-disintegrating SCT tablets were radiolabeled using a "drill and fill" method to enable the study of their gastrointestinal transit through gamma-scintigraphy in conjunction with the pharmacokinetics.

2. Materials and methods

2.1. Materials

Ziprasidone hydrochloride dihydrate was provided by Pfizer Inc. Hypromellose acetate succinate, referred to in this paper as hydroxypropyl methylcellulose acetate succinate (HPMCAS) AQOAT®, HG grade was purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). All the excipients in the clinical formulations were of compendial grade and obtained through the Inventory Management group at Pfizer Inc. All other chemicals, reagents, and solvents were of analytical grade and were purchased from commercial suppliers by Pfizer Inc. The following materials required for dose preparation at the clinical site were sourced directly by Pharmaceutical Profiles Ltd., Nottingham, UK (now Quotient Clinical): Amberlite® IRP-69 resin (Rohm & Haas, Philadelphia, PA), indium-111 chloride solution (Mallinkrodt Pharmaceuticals, Dublin, Ireland), and Surgical Simplex P Bone Cement (Stryker Corp., Kalamazoo, MI). The Enterion™ capsules were supplied by Hansatech Ltd.