European Journal of Pharmaceutics and Biopharmaceutics xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Silica encapsulated lipid-based drug delivery systems for reducing the fed/fasted variations of ziprasidone *in vitro*

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ARTICLE INFO

Article history:
Received 10 December 2015
Revised 14 January 2016
Accepted in revised form 18 January 2016
Available online xxxx

Keywords:
Lipid-based drug delivery systems
Self-nanoemulsifying drug delivery systems
Silica–lipid hybrid microparticles
Poorly water-soluble drugs
Ziprasidone
Antipsychotic
Food effect
Solubilization
Solid-dosage forms
Silica nanoparticles

ABSTRACT

Ziprasidone is a poorly water-soluble antipsychotic drug that demonstrates low fasted state oral bioavailability and a clinically significant two-fold increase in absorption when dosed postprandially. Owing to significant compliance challenges faced by schizophrenic patients, a novel oral formulation of ziprasidone that demonstrates improved fasted state absorption and a reduced food effect is of major interest, and is therefore the aim of this research. Three lipid-based drug delivery systems (LBDDS) were developed and investigated: (a) a self-nanoemulsifying drug delivery system (SNEDDS), (b) a solid SNEDDS formulation, and (c) silica–lipid hybrid (SLH) microparticles. SNEDDS was developed using Capmul MCM® and Tween 80®, and solid SNEDDS was fabricated by spray-drying SNEDDS with Aerosil 380® silica nanoparticles as the solid carrier. SLH microparticles were prepared in a similar manner to solid SNEDDS using a precursor lipid emulsion composed of Capmul MCM® and soybean lecithin. The performance of the developed formulations was evaluated under simulated digesting conditions using an *in vitro* lipolysis model, and pure (unformulated) ziprasidone was used as a control. While pure ziprasidone exhibited the lowest rate and extent of drug solubilization under fasting conditions and a significant 2.4-fold increase in drug solubilization under fed conditions, all three LBDDS significantly enhanced the extent of drug solubilization under fasting conditions between 18- and 43-folds in comparison with pure drug. No significant difference in drug solubilization for the fed and fasted states was observed for the three LBDDS systems. To highlight the potential of LBDDS, mechanism(s) of action and various performance characteristics are discussed. Importantly, LBDDS are identified as an appropriate formulation strategy to explore further for the improved oral delivery of ziprasidone.

1. Introduction

Ziprasidone (ZIP) is an orally active atypical antipsychotic drug commonly used for the treatment of schizophrenia and related psychoses (Fig. 1). ZIP was first approved for medical use in the USA in 2001, and is marketed worldwide under the brand names of Geodon® or Zeldox® [1].

Despite its proven efficacy in treating schizophrenia, the oral bioavailability of ZIP is significantly limited by its poor intrinsic aqueous solubility (free base solubility in water = 0.3 μg/mL, pK_a ~ 6) and moderate lipophilicity (log P = 3.6) [2,3]. In addition to displaying low and variable oral absorption under fasting conditions, ZIP also exhibits a significant two-fold increase in absorption when administered postprandially, such that absolute oral bioavailability under fed conditions reaches approximately 60% [4]. Studies have revealed that calorie content of food (>500 calories), rather than fat content, is most important for maximizing ZIP absorption in the postprandial state [5,6]. Further studies have demonstrated that ZIP pharmacokinetics are less than dose-proportional under fasting conditions, meaning that the food effect of ZIP cannot simply be compensated for by doubling the fasted state dose [1,6,7]. Accordingly, the co-administration of ZIP with food is essential to ensure optimal, reliable and dose-proportional oral bioavailability, resulting in predictable symptom control and improved patient tolerability in the clinical setting [6].

The development of a novel ZIP formulation with no food effect or a reduced food effect is of significant interest, given that compliance with medications is a substantial issue for patients with schizophrenia, particularly when complex dosing regimens (e.g. twice daily dosing and take with meals for ZIP) are required [2,8]. Accordingly, numerous formulation strategies have been investigated in recent years as a means of enhancing ZIP absorption under fasting conditions and reducing the influence of food. The various approaches investigated include complexation of amorphous ZIP mesylate with β-cyclodextrins, nanosuspensions

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http://dx.doi.org/10.1016/j.ejpb.2016.01.010
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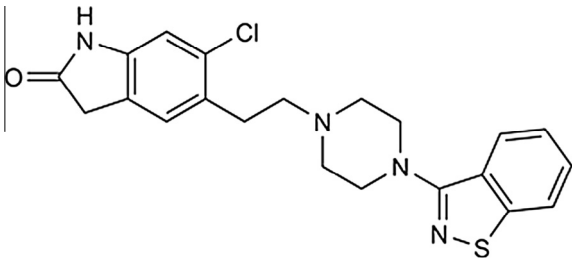

Fig. 1. Chemical structure of ziprasidone.

of crystalline ZIP free base, spray-dried nanocrystalline ZIP HCl, and hydroxypropyl methylcellulose acetate succinate (HPMCAS) matrix formulations of ZIP [2,3,9].

A promising formulation approach that has not yet been adequately investigated for ZIP is the use of lipid-based drug delivery systems (LBDDS). For poorly water-soluble drugs such as ZIP, LBDDS have the ability to mimic food effects on drug absorption, thereby enhancing fasted state bioavailability and reducing variations in drug absorption between the fed and fasted states [10,11]. Of the various LBDDS, self-nanoemulsifying drug delivery systems (SNEDDS) have received significant attention in recent years. SNEDDS is isotropic mixtures of oil, surfactant, cosolvent and drug spontaneously emulsified in aqueous media to form fine nanoemulsions [12]. Such delivery systems present poorly water-soluble drug in a molecularly dispersed state, and hence the rate-limiting dissolution step in drug absorption is avoided [13,14]. While numerous studies have demonstrated the significant potential of SNEDDS, their commercial application is challenged by potential physicochemical instability during storage [13,15]. As a result, solid-state LBDDS, such as solid SNEDDS, have attracted growing interest owing to their ability to combine the advantages of the original LBDDS with those of solid dosage forms, namely improved stability [16,17]. An alternative solid-state LBDDS to solid SNEDDS are silica–lipid hybrid (SLH) microparticles, as first detailed by Tan et al. [18]. SLH microparticle systems combine the solubilizing effects of lipids with the stabilizing/protective effects of silica nanoparticles, and have been extensively investigated for enhancing the oral delivery of various poorly water-soluble drugs [18–20].

In this study, we developed and characterized the following LBDDS in an attempt to reduce the influence of food on ZIP solubilization *in vitro*: SNEDDS, solid SNEDDS and SLH microparticles. For comparison, ZIP-loaded silica particles were also developed. The performance of the developed formulations was evaluated under simulated digesting conditions using an *in vitro* lipolysis model, and we hypothesized that LBDDS may improve the solubilization of ZIP under fasting conditions and reduce variations in ZIP solubilization between the fed and fasted states.

2. Materials and methods

2.1. Materials

Ziprasidone free base (ZIP) was purchased from Tecoland Corporation (USA). Capmul MCM® (glyceryl mono- and di-caprylate) and Caprol PGE 860® (decaglycerol mono- and di-oleate) were gifts from Abitech Corporation (USA). Tween 80® (polysorbate 80), ethanol and polyethylene glycol (PEG) 400 were purchased from ChemSupply (Australia). Maisine 35-1, Labrafil M 1944 CS®, Gelucire 44/14® and Labrasol® were obtained from Gattefossé (France). Hamilton Laboratories (Australia) supplied Miglyol 812®, and Cremophor EL® and Cremophor RH40® were supplied by Sigma–Aldrich (Australia). Soybean lecithin (containing >94% phosphatidylcholine and <2% triglycerides) was obtained from BDH Merck (Australia). Fumed hydrophilic silica nanoparticles (average primary particle diameter 7 nm, specific surface area 380 $m^2 g^{-1}$) (Aerosil 380®) were supplied by Evonik Degussa (Germany). Sodium taurodeoxycholate (NaTDC), trizma maleate, type X-E L-α-lecithin (consisting of approximately 60% pure phosphatidylcholine), 4-bromophenylboronic acid (4-BPB), calcium chloride dihydrate and sodium hydroxide pellets were purchased from Sigma–Aldrich (Australia). Porcine pancreatin extract (activity equivalent to 8× USP specification) was supplied by MP Biomedicals (Australia). All chemicals and solvents were of analytical grade and used as received. High purity (Milli-Q) water was used throughout the study.

2.2. Lipid solubility studies

The equilibrium solubility of ZIP in various lipid excipients was determined at room temperature. An excess of ZIP powder (10–50 mg) was added to centrifuge tubes containing approximately 1 g of lipid excipient. The drug-lipid suspensions were ultrasonicated (Bransonic Model 2510, USA) for 90 min, and then covered with foil and left rotating at room temperature for seven days. Samples were centrifuged at 20,000 rpm (i.e. 29,060*g*) for 30 min at room temperature to precipitate any undissolved drug (Hermle Centrifuge Z36HK, Germany). Dissolved drug was extracted from the supernatant using methanol, prior to dilution with mobile phase and quantification of ZIP content by high performance liquid chromatography (HPLC).

2.3. Preparation of formulations

2.3.1. SNEDDS preconcentrate

Based on the results from lipid solubility studies, Capmul MCM® and Tween 80® were selected for SNEDDS formulation. The screening of candidate SNEDDS was performed by mixing the selected lipid and surfactant in different weight ratios ranging from 1:9 to 9:1 w/w in glass vials. Water was added to the lipid/surfactant mixtures (100-fold dilution). Visual observations were made for phase clarity and flowability, and nanoemulsions that were clear or slightly bluish in appearance were selected for further characterization. Nanoemulsions were assessed for droplet size by dynamic light scattering (DLS) (Malvern Zetasizer Nano ZS, UK), and an optimal SNEDDS was selected based on having the smallest droplet size and lowest polydispersity index (PDI).

SNEDDS was prepared by mixing lipid and surfactant at the selected ratio of 1:6 w/w in a glass vial, followed by ultrasonication to aid mixing and generate an isotropic SNEDDS preconcentrate. Drug-loaded SNEDDS was prepared by weighing the required amount of ZIP into the SNEDDS preconcentrate to give a final drug content of 0.5% w/w. The drug-loaded SNEDDS was ultrasonicated for 60 min to aid drug dissolution within the preconcentrate. The mixture was protected from light and stored at room temperature until use.

2.3.2. Solid SNEDDS

Aerosil 380® silica nanoparticles were utilized as the solid carrier for preparation of solid SNEDDS. Drug-loaded SNEDDS was dispersed in water (1:10 w/w) to form a fine nanoemulsion after sonication for 10 min. The dispersed SNEDDS was then mixed with an equal volume of 5% w/v silica dispersion to give a final SNEDDS: silica ratio of 2:1 w/w. The resulting mixture was kept stirring at room temperature for 1 h, prior to spray-drying with a Büchi Mini Spray Dryer B-290 apparatus (Büchi, Switzerland) to form dry, powdery solid SNEDDS under the following conditions: inlet tem-