European Journal of Pharmaceutics and Biopharmaceutics 129 (2018) 145–153

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Nanocrystal-silica-lipid hybrid particles for the improved oral delivery of ziprasidone *in vitro*

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ARTICLE INFO

Keywords:
Ziprasidone
Lipid-based drug delivery system
Poorly water-soluble drug
Silica-lipid hybrid microparticles
Food effect
Solubilisation
Oral delivery

ABSTRACT

The synergistic effect of nanosizing and lipid-based drug delivery systems (LBDDS) was explored to enhance formulation drug loading levels and improve drug solubilisation in the gastrointestinal environment. A novel formulation combining drug nanocrystals and silica-lipid hybrid (SLH) microparticles as a solid-state LBDDS was developed for the challenging poorly water-soluble drug, ziprasidone. A ziprasidone nanosuspension was fabricated via high-pressure homogenisation, achieving a mean particle size of 280 nm. *In vitro* dissolution studies revealed the nanosuspension to exhibit a significant 2.4-fold increase in the extent of drug dissolution, relative to pure drug. Novel ziprasidone nanocrystal-loaded SLH microparticles (ncSLH) were formulated by freeze-drying a precursor drug-loaded emulsion with drug nanocrystals and silica nanoparticles. Drug loading levels were increased at least 17-fold relative to conventional SLH microparticles, resulting in an increase in crystalline drug content and a change in surface atomic composition. The *in vitro* performance was evaluated by quantifying solubilisation levels during simulated intestinal lipolysis studies. Novel ncSLH significantly improved the *in vitro* fasted state solubilisation of ziprasidone (up to 4.7-fold), thus indicating the potential for such a formulation to overcome some of the various challenges faced by poorly water-soluble, brick-dust drug molecules.

1. Introduction

The oral route is the preferred route of drug administration due to offering the greatest degree of patient acceptance and treatment compliance. Effective oral administration is dependent on the ability of a drug substance to dissolve within the aqueous gastrointestinal fluids and partition across the lipophilic gastrointestinal membrane [1]. In recent years, there has been an increasing number of new drug candidates which exhibit poor aqueous solubility, thus presenting a significant barrier to effective gastrointestinal dissolution and absorption [2]. Rate-limited absorption is generally observed for drugs which have an aqueous solubility of less than 100 μg/mL and commonly leads to poor and variable oral bioavailability, high intra- and inter-subject variability and a lack of dose proportionality [3,4]. Additionally, poorly water-soluble drugs often exhibit increased absorption when they are administered with food [5]. This is termed the positive "pharmaceutical food effect", however, it is inherently variable due to factors such as age, gender and culture, which influence what an individual constitutes as a meal [2]. Consequently, novel formulation approaches are highly desirable to remove food effects and provide optimal oral delivery of hydrophobic pharmaceutical compounds.

Lipid-based drug delivery systems (LBDDS) have the ability to mimic this natural positive food effect by stimulating the physiological processes responsible for the solubilisation and absorption of drugs. Ingested lipids induce the secretion of bile and digestive enzymes from the pancreas and gall bladder, triggering lipid digestion and the formation of various solubilising colloidal species, thereby improving drug absorption and reducing fed/fasted state variations in bioavailability [1]. Furthermore, LBDDS present the drug to the gastrointestinal tract in its molecularly dispersed state, thus avoiding the critical rate-limiting drug dissolution step and facilitating absorption [6].

Silica-lipid hybrid (SLH) microparticles are an example of a promising solid-state LBDDS which have been shown to enhance oral bioavailability for numerous poorly-water soluble drugs including celecoxib [7], ibuprofen [8] and indomethacin [9], albendazole. SLH microparticles are fabricated by stabilising a drug loaded oil-in-water emulsion with silica nanoparticles, followed by solidification to produce porous microparticles with an internal nanostructured matrix [10]. Utilising silica nanoparticles as a stabiliser avoids the need for high quantities of synthetic surfactants, thus eliminating potential safety concerns such as gastrointestinal irritation [11]. Due to comprising of a high lipid surface area which is readily available to lipase

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https://doi.org/10.1016/j.ejpb.2018.05.028
Received 27 March 2018; Received in revised form 14 May 2018; Accepted 22 May 2018
Available online 30 May 2018

enzymes, the porous SLH matrix is significant in enhancing lipid digestion and drug absorption [12]. Dening *et al.* recently explored the incorporation of the challenging brick-dust drug molecule, ziprasidone (ZIP), into SLH microparticles and compared the performance to liquid- and solid-state self-nanoemulsifying drug delivery systems (SNEDDS) [13]. No significant difference in ZIP solubilisation between the fed and fasted state was observed for the various LBDDS, however, SLH microparticles provided > 2-fold increase in drug solubilisation levels compared to SNEDDS, demonstrating the potential of SLH microparticles. Nevertheless, the downfall of using LBDDS for a drug such as ZIP, which exhibits low solubility in both water and lipids, is that only very low levels of drug can be dissolved/encapsulated within the LBDDS. SLH microparticles were capable of encapsulating a maximum ZIP drug load of 0.16% w/w. Therefore, methods of improving LBDDS drug loading levels are of significant interest.

Particle size reduction is an attractive formulation approach for poorly water-soluble drugs. Modification of particle size, particularly in the nanometre range, significantly increases dissolution rate $\left(\frac{dx}{dt}\right)$ as a direct result of increased surface area (A) according to the Noyes-Whitney equation (Eq. (1)). Additional factors which influence the dissolution rate of a compound include the saturation solubility (C_s), concentration in the bulk solution (C), the diffusion coefficient (D) and thickness of the concentration gradient (δ) [14].

$$\frac{dx}{dt} = \left(\frac{DA}{\delta}\right)(c_s - c) \quad (1)$$

Another major advantage of drug nanoparticles is their ability to reduce fed/fasted state variations in absorption [15,16]. As a result of the small particle size and increased surface area, the drug is subject to rapid dissolution regardless of fed or fasted state [17]. This phenomenon was investigated by Thombre et al. whereby a ZIP free base nanosuspension significantly enhanced drug absorption in the fasted state, indicating the potential to reduce the influence of food on bioavailability. It is important to note that this nanosuspension attained a high ZIP drug load of 210 mg/mL, which is suitable for patient use [18].

The current study aims to combine drug nanosizing and SLH formulation approaches to produce nanocrystal-loaded SLH microparticles (ncSLH) (Fig. 1). As a challenging poorly water-soluble drug, ZIP will be further explored as both nanosizing and LBDDS approaches have previously been individually analysed. The oral absorption of ZIP is extremely low due to exhibiting poor aqueous solubility (approximately 0.3 μg/mL in pH 6.5 buffered media) and moderate lipophilicity (log P = 3.6) [19]. The physicochemical properties of ZIP suggest that it is a "brick-dust" molecule due to its extensive intramolecular hydrogen bonding network and high melting point (226 °C), making it a particularly difficult molecule to reformulate [20]. Additionally, ZIP exhibits a significant two-fold positive food effect such that when administered postprandially, absolute oral bioavailability reaches 60% [19,21]. The performance of the dual action ncSLH formulation studied herein, will be evaluated using an *in vitro* intestinal lipolysis model to determine whether the benefits of a LBDDS for ZIP can be retained whilst improving the drug load within the formulation via incorporation of ZIP nanocrystals. It was hypothesised that ZIP nanocrystals will allow for an enhanced drug load in SLH microparticles, and that such formulations will achieve higher solubilisation levels *in vitro*.

2. Materials and methods

2.1. Materials

Ziprasidone free base (ZIP) was purchased from Tecoland Corporation (California, USA). Capmul MCM® (glyceryl mono- and dicaprylate) was a gift from Abitec Corporation (Wisconsin, USA). Hydrophilic fumed silica nanoparticles (Aerosil 300®) were supplied by Evonik Degussa (Essen, Germany). Soybean lecithin was purchased from BDH Merck (Sydney, Australia) and Polysorbate 80 (Tween 80®) was purchased from ChemSupply (Adelaide, Australia). Sodium hydroxide (NaOH), Trizma maleate, sodium chloride, calcium chloride dihydrate, egg lecithin (consisting of 60% phosphatidylcholine from dried egg yolk), sodium taurodeoxycholate (NaTDC) and 4-bromophenylboronic acid (4-BBA) were obtained from Sigma Aldrich (Sydney, Australia). Poloxamer 407 (Pluronic F-127®) was also obtained from Sigma Aldrich (Missouri, USA). Porcine pancreatin extract was purchased from MP Biomedicals (Illkirch, France). All chemicals and solvents were of analytical grade. High purity Milli-Q water was used during the study.

2.2. Preparation of formulations

2.2.1. ZIP nanosuspension

A 1% w/v ZIP free base nanosuspension was prepared by adapting the methods established by Thombre et al. and Teeranachaideekul et al. [18,22]. A drug suspension was prepared by adding pure ZIP to an aqueous dispersion of Pluronic F-127, Tween 80 (both 0.04% w/v) and soybean lecithin (0.02% w/v) under magnetic stirring. High pressure homogenisation (Avestin EmulsiFlex-C5 Homogenizer, Canada) was applied at 500 bar and 1000 bar for two cycles each, followed by 20 homogenisation cycles at 1500 bar. The nanosuspension was stored at 4 °C until use.

2.2.2. ZIP nanocrystals

To produce ZIP nanocrystals, the ZIP nanosuspension (100 mL) was frozen using liquid nitrogen and freeze-dried (Martin Christ Alpha 1–2 LD Plus Freeze Dryer, Germany) at a collector temperature of −55 °C and vacuum pressure of 0.090 mbar for 24 h. The nanosuspension was stirred for 1 h with mannitol (2% w/w) as a cryoprotectant prior to

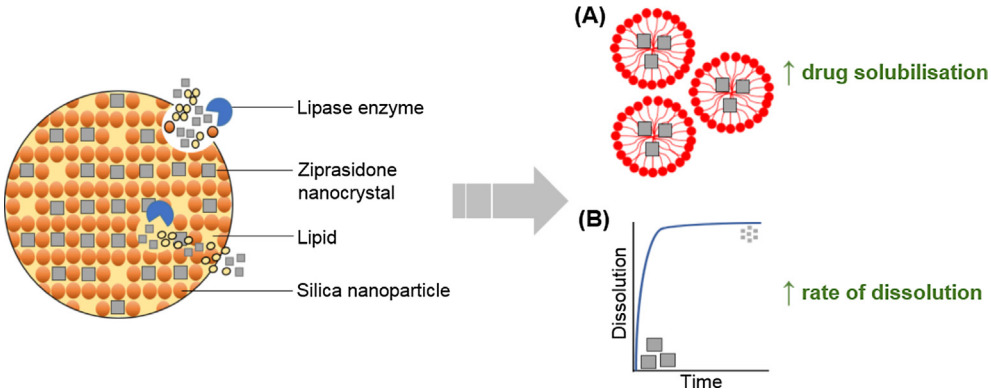

Fig. 1. Schematic of ncSLH mechanism which combines the advantages of (A) lipids to improve drug solubilisation by stimulating the formation of highly solubilising colloidal species, such as micelles, and (B) nanocrystals which enhance the rate of drug dissolution due to attaining a high surface area.