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Montmorillonite-lipid hybrid carriers for ionizable and neutral poorly water-soluble drugs: Formulation, characterization and *in vitro* lipolysis studies

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ABSTRACT

Lipid-based formulations (LBFs) are a popular strategy for enhancing the gastrointestinal solubilization and absorption of poorly water-soluble drugs. In light of this, montmorillonite-lipid hybrid (MLH) particles, composed of medium-chain triglycerides, lecithin and montmorillonite clay platelets, have been developed as a novel solid-state LBF. Owing to the unique charge properties of montmorillonite, whereby the clay platelet surfaces carry a permanent negative charge and the platelet edges carry a pH-dependent charge, three model poorly water-soluble drugs with different charge properties; blonanserin (weak base, pKa 7.7), ibuprofen (weak acid, pKa 4.5) and fenofibrate (neutral), were formulated as MLH particles and their performance during biorelevant *in vitro* lipolysis at pH 7.5 was investigated. For blonanserin, drug solubilization during *in vitro* lipolysis was significantly reduced 3.4-fold and 3.2-fold for MLH particles in comparison to a control lipid solution and silica-lipid hybrid (SLH) particles, respectively. It was hypothesized that strong electrostatic interactions between the anionic montmorillonite platelet surfaces and cationic blonanserin molecules were responsible for the inferior performance of MLH particles. In contrast, no significant influence on drug solubilization was observed for ibuprofen- and fenofibrate-loaded MLH particles. The results of the current study indicate that whilst MLH particles are a promising novel formulation strategy for poorly water-soluble drugs, drug ionization tendency and the potential for drug-clay interactions must be taken into consideration to ensure an appropriate performance.

1. Introduction

Lipid-based formulations (LBFs) are a well-proven formulation strategy for enhancing the solubilization and oral bioavailability of poorly water-soluble drugs (Feeney et al., 2016; Porter et al., 2008, 2007). LBFs are known to promote oral drug absorption *via* a number of mechanisms, which include (*i*) presenting the poorly water-soluble drug in a pre-dissolved state such that the rate-limiting dissolution step for drug absorption is avoided, (*ii*) enhancing the gastrointestinal solubility of lipophilic drug molecules by stimulating lipid digestion and the secretion of endogenous solubilizing agents (*e.g.* bile salts and phospholipids), (*iii*) possible avoidance of presystemic metabolism *via* the promotion of intestinal lymphatic drug transport, and (*iv*) changes in passive membrane permeability and inhibition of intestinal efflux transporters (Feeney et al., 2016; Porter et al., 2007; Williams et al., 2013).

Despite the many established advantages of LBFs for poorly water-soluble drug delivery, several key limitations have impacted on their commercial application and success to date (Hauss, 2007). Low drug loading levels and compatibility issues between LBFs and capsule shells are two important examples (Cole et al., 2008; Dening et al., 2016b). To circumvent such challenges, solid-state LBFs have attracted significant interest in recent years (Dening et al., 2016b; Tan et al., 2013). In their simplest form, LBFs are adsorbed onto solid carrier materials with large specific surface areas *via* physical mixing. More complex solidification methods such as spray-drying and freeze-drying may be used, with the subsequent benefit of creating specific particle nanostructure which may influence formulation performance (Dening et al., 2016a,b; Tan et al., 2013). The resulting dry solid-state LBF powders may be filled into capsules or alternatively, compressed into tablets (Bremmell et al., 2013). Various solid carrier materials with a wide range of physicochemical properties may be employed to solidify

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LBFs, with silica-based materials and polymers being the most commonly utilized (Dening et al., 2016b; Tan et al., 2013).

Montmorillonite-lipid hybrid (MLH) particles are a novel solid-state LBF first described by Dening et al., 2016a; Dening et al. (2016a). MLH particles are fabricated by spray-drying submicron lipid-in-water emulsions composed of medium-chain triglycerides (MCT) with montmorillonite (MMT) clay platelets as the solid carrier material. MMT is an FDA-approved biocompatible clay material that has been used extensively as an excipient in various pharmaceutical, nutraceutical, cosmetic and food products (Aguzzi et al., 2007; Rowe et al., 2012). Individual MMT platelets are typically 1 nm thick and several hundred nm in diameter, and thus MMT possesses a high specific surface area in the range of 750–800 m^2g^{-1}, making it an ideal solid carrier for LBFs. The clay material has the empirical formula $Al_2O_3{\cdot}4SiO_2{\cdot}H_2O$, and owing to the substitution of some Al^{3+} with Mg^{2+}, it carries an overall negative charge on its hydrophilic platelet surface. The edges of the MMT platelets carry a pH-dependent charge, due to the presence of lattice discontinuities (Joshi et al., 2009a). As a result, MMT platelets may theoretically interact with both cationic and anionic substances. This phenomenon has previously been exploited to achieve controlled drug delivery for various cationic drug molecules directly from MMT (Aguzzi et al., 2007; Joshi et al., 2009a,b; Oh et al., 2013). The recent study by Dening et al. (2016a) established that high lipid loads could be encapsulated within MLH particles. Enhanced lipid digestion kinetics and optimal release of solubilizing free fatty acids (FFAs) from MLH particles was also demonstrated, and MLH particles were proposed as a promising carrier system for poorly water-soluble drugs.

Preliminary studies revealed an inferior performance of MLH particles loaded with a poorly water-soluble weak base drug in comparison to a control drug-loaded MCT solution during *in vitro* lipolysis. It was hypothesized that the reduced level of drug solubilization was due to cationic drug molecules complexing with the anionic platelet surfaces of MMT. Such an interaction could lead to lower drug bioavailability *in vivo*, and is thus critical to understand. On this basis, the current study sought to assess the impact of drug charge on the performance of MLH particles under simulated digesting conditions *in vitro*. Three model poorly water-soluble drugs were selected based on their charge properties: blonanserin (weak base, pKa 7.7), ibuprofen (weak acid, pKa 4.5) and fenofibrate (neutral). Each drug was loaded into MLH particles, and drug solubilization in the aqueous phase was quantified during *in vitro* lipolysis and compared with various control formulations (*e.g.* pure drug crystals, MCT solution, MCT solution plus MMT platelets and silica-lipid hybrid (SLH) particles). Importantly, this study constitutes the first report of MLH particles as oral drug delivery systems for poorly water-soluble drugs.

2. Materials and methods

2.1. Materials

Blonanserin was purchased from Hangzhou Dayangchem Co. Ltd (China), and ibuprofen and fenofibrate were both purchased from Sigma-Aldrich (Australia). Miglyol 812®, a mixture of medium-chain caprylic/capric (C_8/C_{10}) triglycerides, was purchased from Hamilton Laboratories (Australia). Soybean lecithin (containing >94% phosphatidylcholine and <2% triglycerides) was obtained from BDH Merck (Australia). Pharmaceutical grade MMT clay (Veegum HS®, magnesium aluminium silicate, purified smectite clay) was kindly supplied by A.S. Harrison & Corporation (Australia). Fumed hydrophilic silica nanoparticles with specific surface area 300 m^2g^{-1} (Aerosil® 300 Pharma) were a gift from 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 blonanserin, ibuprofen and fenofibrate in MCT was determined in triplicate at room temperature (20 °C), and was defined as the value attained when consecutive solubility values differed by less than 10%. An excess of each drug was added to centrifuge tubes containing approximately 500 mg MCT. The resulting drug and MCT suspensions were ultrasonicated (Bransonic Model 2510, Danbury, United States) for 60 min to aid drug dissolution, and then covered with foil to protect from light and left agitating. Samples were centrifuged at 20,000 rpm for 30 min at room temperature to precipitate any undissolved drug (Hermle Centrifuge Z36HK, Wehingen, Germany), and methanol was utilized to extract dissolved drug from the supernatant, prior to dilution with mobile phase and quantification of drug content by high performance liquid chromatography (HPLC) as described in Section 2.5. Samples were analyzed every 24 h, with equilibrium solubility typically reached after equilibration times of between 48 and 72 h.

2.3. Preparation of LBFs

2.3.1. Lipid solutions

Based on the results from lipid solubility studies, each drug was loaded in MCT at the same proportion of saturation solubility (*i.e.* 80%) to ensure the same thermodynamic activity. Drug and MCT were weighed into glass vials and vortex-mixed until all drug crystals were dissolved.

2.3.2. MLH particles

MLH formulations were prepared as initially described by Dening et al. (2016a). Briefly, soybean lecithin was dissolved in MCT at 6% w/w. Blonanserin, ibuprofen or fenofibrate was then added to the lecithin/MCT mixture at 80% of drug saturation solubility in MCT, and dissolved with the aid of ultrasonication. Water was added to the resulting lecithin/MCT/drug solution as the continuous phase to form a coarse lipid-in-water emulsion (10% w/v), which was then subsequently homogenized using an Avestin Emulsiflex-C5 Homogenizer (Ottawa, Canada) under a pressure of 1000 bar for five cycles. MMT powder was dispersed in water (2% w/v) and vigorously stirred at room temperature (20 °C) for at least 4 h prior to use to ensure effective hydration of clay platelets. The MMT aqueous dispersion was added to the homogenized emulsion to give a final lipid: MMT ratio of 2:1 w/w and stirred overnight prior to spray-drying with a Büchi Mini Spray Dryer B-290 apparatus (Büchi, Flawil, Switzerland) to form MLH particles under the following conditions: inlet temperature 140 °C, outlet temperature 75 °C, aspirator setting 100, compressed air flow rate set at 4 mm and product flow rate 7 mL/min.

For blonanserin and fenofibrate, the pH of the emulsion/MMT mixture(s) was controlled. For blonanserin, the emulsion/MMT mixture was immediately adjusted to pH ≥ 9.7 using 1 M NaOH. Given the pKa of blonanserin is 7.7, this was to ensure blonanserin remained in its neutral form and did not interact with the MMT platelets during fabrication. For fenofibrate, the pH of the emulsion/MMT mixture was adjusted to approximately 7 to ensure stability of fenofibrate during overnight stirring.