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Research Article

Exploring the Phase Behavior of Monoolein/Oleic Acid/Water Systems for Enhanced Donezepil Administration for Alzheimer Disease Treatment

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ABSTRACT

Donepezil is a drug usually administered by oral route for Alzheimer disease treatment, but several gastric side effects have been reported as diarrhea, nausea, and anorexia. We explored the phase behavior of lyotropic liquid crystalline (LLC) mesophases composed by monoolein/oleic acid/water for enhanced administration of donepezil. Polarized light microscopy suggested that these systems ranged from isotropic inverse micellar solutions (L_2) to viscous and birefringent reverse hexagonal (H_{II}) mesophases according to the amount of water in the ternary systems. Phase transition was observed from a L_2 phase to H_{II} mesophase after swelling studies, an interesting property to be explored as a precursor of LLC mesophases for mucosal administration that increases its viscosity *in situ*. Mucoadhesive properties of LLC mesophases were characterized using a texture analyzer indicating that these systems can have an increased residence time in the site of absorption. Donepezil-free base was incorporated in the evaluated formulations, and their *in vitro* release was controlled up to 24 h. The phase behavior of the systems demonstrated a great potential for enhanced donepezil administration once these mucoadhesive–controlled release formulations can incorporate the drug and prolong its release, possibly reducing its side effects.

Introduction

Donepezil is a lipophilic drug approved to treat the cognitive manifestations of Alzheimer disease.[1,2] The drug acts as an acetylcholinesterase inhibitor in the brain, enhancing the cholinergic activity and relieving the symptoms related to disease.[3,4] Donepezil has been administered by immediate-release solid oral dosages (tablets and orally disintegration tablets) approved by the Food and Drug Administration in its hydrochloride salt form to increase its solubility in water.[1] Inconveniently, several side effects have been reported as diarrhea, nausea, and anorexia due to the increase in gastric secretion caused by enhanced cholinergic activity through the gastrointestine.[5] These side effects were related to high-peak plasma concentrations (C_{max}) and the rapid drug absorption into the bloodstream resulting in a short time to C_{max}.[6] Donepezil-free base (DPB) has not been considered for conventional drug administration because it is poorly water soluble. However, DPB may be previously dissolved in lipid vehicles and administered as a lipid-based formulation (LBF).[7]

The primary mechanism of LBFs is the enhancement of the drug solubility within gastrointestinal (GI) tract, thereby avoiding solid-state limitations to assure the drug bioavailability.[7] The composition of the LBFs ranges from simple oil solutions to more complex mixtures of oils, surfactants, cosurfactants, and cosolvents.[8] Although lipids have been applied as simple vehicles to drug administration, some amphiphilic lipids as monoglycerides present self-assembly after swell with water.[8-10] This complex phase behavior may be explored to obtain nanostructured colloidal systems.[11,12] The basic concept behind the use of nanotechnology-based systems for controlling drug delivery is its ability to compartmentalize the drug as well as to modify its properties in the biological medium.[12,13] Through drug association with nanostructured colloidal systems, the properties that concern the drug release are determined by the physicochemical properties of the drug delivery system and not by the drug.[13]

Glyceryl monooleate (GMO), also known as monoolein, swells in aqueous medium and forms lyotropic liquid crystalline (LLC) mesophases.[14-16] GMO is a polar lipid formed by the esterification

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reaction of glycerine and oleic acid (OA).[17] It is a nontoxic, biocompatible, and biodegradable lipid.[16,17] Different applications of this monoglyceride have been described in the pharmaceutical field as skin enhancer and emulsifier agent.[18,19] The LLC mesophases formed by GMO have been explored as drug delivery systems to be administered by cutaneous, mucosal, and oral routes.[18,20,21] These mesophases may also be used as mucoadhesive formulations, with which an increased residence time on the site of absorption can be achieved.[22,23] The reverse hexagonal (H_{II}) mesophase of GMO/water is obtained only at high temperatures (85°C), unless a third nonpolar component (e.g., triglyceride, OA, or a "guest" lipophilic compound) is added to the system.[19,24] Borné et al.[24] previously described the isothermal phase diagram of GMO/OA/water at room temperature, and they observed a complex ternary system with different regions of thermodynamic equilibrium single phases and heterogeneous regions of coexisting phases. The largest single-phase region observed was an H_{II} mesophase at low water content.

This work investigated the LLC type II (water-in-oil) GMO/OA/water mesophases for enhanced donepezil administration, searching for systems with mucoadhesive properties and ability to control the release rate of donepezil and possibly reducing its side effects. These novel drug delivery systems for donepezil administration clearly present an opportunity for formulation scientists to overcome the many challenges associated with Alzheimer disease therapy, considering a limited number of therapeutic alternatives available today. The colloidal nanostructured systems were studied by polarized light microscopy (PLM). DPB was incorporated in these systems after a preformulation study (solubility, thermal analysis, and spectroscopic studies). These formulations were evaluated using *in vitro* release studies, and their mucoadhesive properties were investigated using a texture analyzer. Phase transition behavior of a precursor formulation composed by GMO/OA/water was also studied to evaluate the possibility to form an LLC mesophase *in situ* after the administration.

Experimental Data

Materials

Donepezil hydrochloride (DPH) in raw material was supplied by Megafine Pharma Limited (Maharashtra, India). OA (≥99%) was purchased from Sigma-Aldrich (St. Louis, MO). The GMO used was of commercial grade (Myverol 18-99; Quest International, Hoffman States, IL). All other reagents were of analytical grade.

HPLC Analysis

Samples were analyzed using HPLC from Shimadzu (Kyoto, Japan). Analysis was carried out using a validated method previously described by Ruela et al.[25] using a C_{18} end-capping column 150.0 × 4.6 (i.d.) with 4-μm particle size. The mobile phase was a mixture of 5-mM monobasic potassium phosphate buffer (pH 3.0) with 0.5% of triethylamine and methanol (55:45). The flow rate of the mobile phase was 1.0 mL min^{-1}, injection volume was 50 μL, and UV detection was carried out at 268 nm. The samples were filtered using a 0.45-μm syringe filter composed of hydrophilic polytetrafluoroethylene. The retention time of the donepezil was approximately 7.9 min. The total run time was 15 min.

Preformulation

Donepezil-Free Base

DPB was obtained from hydrochloride salt using a liquid–liquid extraction procedure. For this, a dispersion of DPH was prepared in an alkaline solution (2 N NaOH), and DPB was extracted using toluene under vigorous shaking. DPB was recovered after the evaporation of the solvent to dryness at room temperature.

The characterization of the raw materials (DPH and DPB) was performed by a stability indicating–assay method by liquid chromatography coupled to tandem mass spectrometry[25] (LC-MS/MS; Shimadzu, Kyoto, Japan) in positive electrospray mode, and data acquisition was performed in total ion current mode. The mobile phase was a mixture of 0.2% acetic acid pH 3.2 and methanol (60:40), flow rate of 0.4 mL min^{-1}, and the injection volume was 5 μL. The infrared analysis of DPH and DPB was performed using a Fourier transform infrared spectrometer Shimadzu model Prestige 21 (Kyoto, Japan). An attenuated total reflectance sampling accessory (model GladiATR 300, Pike Technologies) was used, and the spectra were collected with no further processing of the samples. X-ray diffraction (Ultima IV model, Rigaku, Tokyo, Japan) measurements were carried out at room temperature under the following conditions: graphite monochromated Cu-Kα radiation (λ = 1.542 Å), voltage of 40 kV, current of 30 mA, and rate scan of 0.25°/min between 3° and 50° of the 2θ range. Thermal analysis using differential scanning calorimetry (DSC 1 model; Mettler Toledo TM, Barueri, São Paulo, Brazil) and thermogravimetric analysis (Seiko 6000 model; Exstar TG/DTA, Chiba, Japan) were carried out at a temperature ramp from 30°C to 350°C at 2°C min^{-1}.

Solubility

Solubility measurements of DPB and DPH were performed at 25°C to determine the strategy to incorporate donepezil in the formulations. The assays were firstly performed in aqueous media. For this, an excess amount of drug was added to each vehicle and shaken for 24 h. The supernatant was taken, filtered, and analyzed by HPLC. The relative solubility of DPB and DPH in oil vehicles (isopropyl myristate, isopropyl palmitate, soybean oil, olive oil, OA, and mineral oil) was visually inspected. For this, DPB and DPH were dispersed at 10% w/w in oil vehicles and classified in the following scale: soluble (without crystals), partially soluble (few crystals are precipitated), and practically insoluble (large amounts of crystals are precipitated).

OA/Water Partition of DFB

The partition of DPB in the system OA/water was characterized considering that these 2 phases are poorly miscible. Two milliliters of saturated solution of DPB in water was stirred for 2 h with 2 mL of OA previously saturated with water. Samples were centrifuged at 3,400 rpm for 15 min. The aqueous phase was analyzed by HPLC before (C_1) and after (C_2) the partition studies. The partition coefficient (K) was calculated according to the following equation and expressed as log K:

$$K = \frac{C_1 - C_2}{C_2}$$

Formulations

The phase behavior, physicochemical properties, and release from the LLC mesophases were studied from different proportions of GMO/OA/water. The compositions are shown in Table 1. The formulations were prepared by direct mixing of GMO, OA, and water at room temperature. DFB was previously dissolved in OA (66.7 mg/g) to assure its incorporation in the formulations. Drug concentration in these formulations was 16.7 mg/g. The systems were allowed to equilibrate at room temperature for at least 7 days before the evaluations. A control formulation without GMO was prepared by dissolving DPB (10.0 mg) in OA (150.0 mg). PLM using