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Physicochemical and pharmacokinetic characterization of a spray-dried malotilate emulsion

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ABSTRACT

Malotilate (MT) is a hepatoprotective drug administered orally. However, MT was found to be a poorly water-soluble drug with low oral bioavailability. In the present investigation, a novel spray-dried emulsion (SDE) loaded with MT was prepared, and its physicochemical properties were characterized by rheological evaluation, particle size measurement, *in vitro* release, and surface morphology. The pharmacokinetic study of SDE, in comparison to MT suspension with the pure MT powder homogeneously dispersed in 0.5% CMC–Na solution, was also performed in rats after a single oral dose. It was found that SDE exhibited a 2.9-fold higher peak plasma concentration (C_{max}) and 2.3-fold higher area under the curve (*AUC*) than MT suspension.

1. Introduction

As the most widely used lipid-based formulations, emulsion has its utility to improve the dissolution rate and increase the bioavailability of poorly water-soluble drugs by eliminating the dissolution step and amplifying the specific surface area. In addition, emulsion can extend the gastric emptying to provide longer dissolution time. However, creaming, flocculation, coalescence, and phase separation are often observed in emulsion, which gives physicochemical stability problems during storage (Welin-Berger and Bergenstahl, 2000). Besides, compliance problems of emulsion also limit its direct application as the delivery vehicles for oral drugs (Christensen et al., 2002). In order to overcome these drawbacks, self-emulsifying drug delivery system (SEDDS), an isotropic mixture of oils and surfactants and sometimes cosolvents, has been adopted for oral delivery of lipophilic drugs and several products have been commercially available, such as Neoral® (cyclosporine), Sandimmune® (cyclosporine), Norvir® (ritonavir), Fortavase® (saquinavir) and Aptivus® (tipranavir) (Morozowich and Gao, 2009). SEDDS forms fine oil-in-water (O/W) emulsions spontaneously under the digestive motility of the stomach. However, relatively high concentrations of surfactants in SEDDS (usually 30–60%) may cause obvious irritation to gastrointestinal mucosa (Gursoy and Benita, 2004). In addition, lack of general formulation guidance also limited SEDDS to be broadly applied (Buyukozturk et al., 2010).

Recently, dry emulsion (DE), a formulation containing none or small amounts of nonionic surfactants has been suggested as one way to circumvent such disadvantage of conventional emulsions and SEDDS (Shively and Thompson, 1995; Christensen et al., 2001; Jang et al., 2006; Yin et al., 2009). DE formulations are prepared by drying O/W emulsions containing soluble solid carriers (e.g. dextrin (Jang et al., 2006; Yin et al., 2009), lactose monohydrate (Yin et al., 2009), hydroxypropyl methylcellulose (Hansen et al., 2005; Christensen et al., 2001)) and/or insoluble solid carriers (e.g. magnesium aluminometasilate (Hansen et al., 2004)) in aqueous phase. After drying, the solid carriers encapsulate the dispersed lipid phase and form a matrix. The process of solidification of emulsion into DE can be performed by spray drying (Jang et al., 2006; Hansen et al., 2005), lyophilization (Corveleyn and Remon, 1998a,b) or vacuum distillation (Shively, 1993).

DE has been successfully applied as a potential oral drug delivery system for poorly soluble drugs to improve bioavailability (Dollo et al., 2003; Jang et al., 2006; Ge et al., 2008) as well as to improve photostability (Takeuchi et al., 1992; Jang et al., 2006), oxidation stability (Heinzelmann and Franke, 1999) and enzymatic stability (Ge et al., 2008).

Malotilate (MT), diisopropyl 1,3-dithiol-2-ylidenemalonate (Fig. 1), is a liver protein metabolism improved drug used in the treatment of chronic hepatitis and cirrhosis (Bührer et al., 1986;

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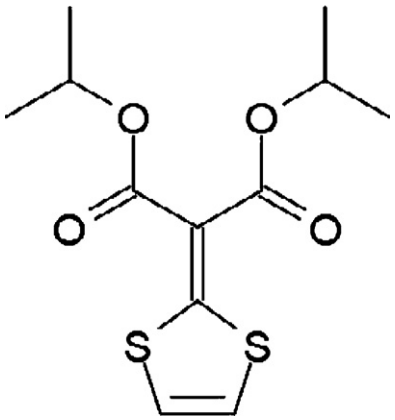

Fig. 1. Chemical structure of malotilate (molecular weight: 288.4).

Ryle and Dumont, 1987). MT is a symmetrical isopropyl ester of a sulphur-containing compound with very poor aqueous solubility. It was easily absorbed from the gastrointestinal (GI) tract after oral administration and undergoes extensive first-pass metabolism (Ryle and Dumont, 1987). Only 2–3% of MT was not eliminated by liver in health human body when administered orally (Bührer et al., 1986). The poor aqueous solubility and extensive first-pass effect resulted in low oral bioavailability of MT. However, very limited studies were reported to enhance the *in vivo* bioavailability of MT. Wu et al. (1999) prepared the amorphous matter of MT using colloidal silica as the carrier to improve the *in vitro* dissolution extent from 16.34 to 44.20% in 60 min. However, no attempt till now was conducted to improve the *in vivo* bioavailability of MT.

The main objective of the present study is to employ DE as the carrier for improving the dissolution rate and increasing the bioavailability of MT. The physicochemical properties of the liquid emulsion prepared by high pressure homogenization and DE obtained by spray-drying were characterized. In addition, *in vivo* pharmacokinetic study of the spray-dried emulsions (SDE) loaded with MT was performed, in comparison with MT suspension, to demonstrate the oral bioavailability enhancement of SDE.

2. Materials and methods

2.1. Materials

Malotilate (mean particle size about 150–300 μm) was purchased from Yabang Pharmaceuticals Co., Ltd. (Changzhou, China). Malotilate reference standard and indomethacin reference standard were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Labrafac® CC, Peceol® and Labrafil® M 1944CS were obtained from Gattefosse Corp. (Lyon, France). Glucidex® 12 was obtained from Roquette Freres (Lestrem, France). Crodamol® EO and Crodamol® IPM were obtained from Croda (Yorkshire, England). Neobee M-5 was obtained from Stepan Company (Illinois, USA). Peanut oil was purchased from Yihai Kerry Foodstuffs Marketing Co., Ltd. (Shenzhen, China). Soybean oil was purchased from Huanye Pharmaceuticals Co., Ltd. (Guangzhou, China). PVA-0486 was purchased from Sinopharm Chemical Reagent Beijing Co., Ltd. (Beijing, China). Methanol of HPLC grade was from Merck (Darmstadt, Germany). All other chemical reagents were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

2.2. Solubility studies

The equilibrated solubilities of MT were determined in various oils (e.g. Crodamol EO, Crodamol IPM, Labrafac CC, peanut oil, soybean oil, Labrafil M 1944CS, Neobee M-5 and Peceol). Excess amount of MT was shaken with each oil by ZD-85 shaker (Guohua Instrument Co., Ltd., China) at 37 °C. Following equilibration (2 days), samples were centrifuged at 14,000 rpm for 10 min in a Sigma centrifuge (Model 1-15 K, Germany). Aliquot portions of the supernatant liquid were collected and filtered through a 0.45 μm filter, and then the concentrations of MT in various oils were analyzed by HPLC method. All samples were prepared in triplicates.

The HPLC system consisted of a Shimadzu LC-10AD pump and a SPD-10A UV detector (Kyoto, Japan). The analysis was carried out on a Waters ODS column (5 μm, 4.6 mm × 150 mm) which was held at 30 °C. The isocratic mobile phase was a mixture of methanol, water and 40% acetic acid (77:22.5:0.5, v/v/v) and was pumped at a flow rate of 1.0 ml/min with UV monitoring at 362 nm.

Table 1
Compositions of the homogenized emulsion.

Formulation	g/100 ml
Malotilate	4.11
Labrafac CC	6.32
PVA	6.80
Glucidex	10.33
Water	To 100 ml

2.3. Stabilizer selection by surface tension determination

The surface tension analyses were carried out with the Wilhelmy Plate method using a DCAT 21 Tensiometer (DataPhysics Instrument GmbH, Germany). This method utilized the interaction of a platinum plate (9.95 mm × 9.95 mm × 0.20 mm) with the surface being tested. In the plate method the liquid was raised until the contact between the surface and the plate was registered. All the experiments were performed at 25 °C, using the following instrumental parameters: small vessel 30 ml, motor speed 1 mm/s, and immersion depth 3 mm. Samples were prepared by dispersing selected oil phase into the aqueous solutions containing different concentrations of the stabilizer candidate (e.g. HPMC, PVA, PVP), using an Ultra-Turrax T18 stirrer (Jahnke & Kunkel, Staufen, Germany) at 14,000 rpm for 3 min. All samples were determined in triplicates.

2.4. Preparation of the emulsions

Labrafac CC with MT dissolving in it (650 mg/g) was dispersed in an aqueous solution containing stabilizer and Glucidex using an Ultra-Turrax T18 stirrer at 14,000 rpm for 3 min. Compositions of the liquid emulsion formulation were provided in Table 1. The obtained coarse emulsion (CE) was then homogenized *via* a high pressure homogenizer (Avestin Emulsiflex-05, Avestin Inc., Ottawa, Canada) at 30 °C. 10 cycles at 1600 bar were applied to obtain the homogenized emulsion (HE).

In order to enhance the physical stability of liquid emulsion, the prepared HE was subsequently spray dried using a mini spray-dryer equipped with a high performance cyclone (Büchi B-290: Büchi Labortechnik AG, Switzerland) and a 0.7-mm nozzle. The following standard operating conditions were used: inlet temperature, 155 °C; aspirator setting, 100% (40 m^3/h); spray flow rate, 600 l/h; pump setting, 5 ml/min; these conditions resulted in an outlet temperature around 100 °C. The content of MT in dry emulsion was 149.1 mg/g. Stability data by HPLC determination showed that no significant change in drug content was observed, which confirmed that the homogenization and spray drying process did not cause any significant chemical degradation of MT in lab-scale batch process.