Colloids and Surfaces B: Biointerfaces 161 (2018) 83–93

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

Application of transglycosylated stevia and hesperidin as drug carriers to enhance biopharmaceutical properties of poorly-soluble artemisinin

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ARTICLE INFO

Article history:
Received 6 July 2017
Received in revised form
26 September 2017
Accepted 6 October 2017
Available online 7 October 2017

Keywords:
Cytotoxicity
Physicochemical stability
Drug delivery
Functionalized food additives
Supersaturation solubility

ABSTRACT

Biopharmaceutical properties of poorly water-soluble antimalarial drug, Artemisinin (ART), were improved by formulating amorphous solid dispersions with transglycosylated food additives (Hsp-G and Stevia-G) via co-spray drying. Both the formulated ART/Hsp-G and ART/Stevia-G showed superior dissolution properties with a burst release of more than 95% of drug within 5 min, whereas untreated ART dissolved only 4% in 5 min. The supersaturation solubility of the formulated ART was enhanced by 2-fold as compared with untreated counterpart. The storage stability tests indicated that these formulations chemically stable at room temperature and under low humidity (< 18% RH) conditions. However, high humidity (75% RH) induced re-crystallization and caused changes in the physical appearance of the solid dispersions. In addition, both the food additives and ART formulated samples showed low cytotoxicity to Caco-2 cell line suggesting their good biocompatibility. Thus, the formation of solid dispersions of ART with transglycosylated food additives is a potentially safe and effective approach to enhance the bioavailability of poorly water-soluble ART.

1. Introduction

Oral administration is one of the most common and preferred routes of drug delivery due to easy administration, manufacturing flexibility, and cost-effectiveness [1]. However, the bioavailability and the therapeutic effects of oral dosage forms are hampered by their poor aqueous solubility and dissolution, especially for those active pharmaceutical ingredients (APIs) listed under the Biopharmaceutical Classification System (BCS) class II [2–4]. The solubility of BCS class II drugs in gastric and intestinal fluids plays a vital role in determining their bioavailability, since these drugs have a good absorption and permeation across the intestinal lumen [5,6]. Limited solubility of APIs may result in insufficient and variable absorption, which will lead to unacceptable bioavailability and inadequate clinical efficacy [7]. The low water-solubility often necessitate the application of high doses of APIs in order to achieve a desired therapeutic plasma concentration [8], which may concomitantly lead to side effects such as gastric discomfort, nausea, vomiting and dizziness [9]. Endeavours to enhance the solubility of these therapeutic agents are associated with rapid drug absorption, which eventually improves the bioavailability and reduces clinically relevant doses [10–12].

Numerous pharmaceutical formulation techniques have been employed to overcome the delivery barriers of BCS class II drugs [13–28]. To date, however, the numbers of simple and effective oral formulations of BCS class II drugs that have achieved marketed applications are limited. Therefore, it is essential to explore new types of formulation approaches with market values. Recently, amorphization via formulations of solid dispersions using functionalized food additives have attracted much attention to circumvent the poor aqueous solubility and slow dissolution rate of water-insoluble drugs, since these pharmaceutical excipients are relatively safe and cost-effective [6,29]. Among them, α-glucosyl hesperidin (Hsp-G) and α-glucosyl stevioside (Stevia-G) are particularly noteworthy as potential drug carriers, considering their extreme aqueous solubility augmented by transglycosylation [30,31]. Additionally, Hsp-G has been reported to possess significant anti-inflammatory, hypotensive and analgesic effects [8,32]. Meanwhile, Stevia-G has been used as a sweetener and as a

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https://doi.org/10.1016/j.colsurfb.2017.10.020
0927-7765/

sugar substitute for diabetes and hypoglycemia patients for more than 20 years [33,34]. These functionalized foods have become an important ingredient in daily diets and play a vital role in preventing diseases in countries that face serious aging problem such as Japan[32].

In this study, BCS class II antimalarial drug, Artemisinin (ART), was selected as a model compound, in which ART was formulated with functionalized food additives. Pharmacologically, ART possesses the most rapid action against *Plasmodium falciparum* and *Plasmodium vivax* [35,36]. It has a worldwide demand and is recommended by the World Health Organization (WHO), due to its low toxicity and high efficiency in attacking malaria parasites, such as multidrug resistant and cerebral strains [37–39]. However, ART suffers from poor solubility and short half-life. The poor solubility of ART in water (48 μg/mL at 37 °C) and blood translates into poor bioavailability despite the excellent permeability across intestinal membranes [35,37,40]. The short half-life and high first pass metabolism of ART may cause incomplete clearance of malaria parasites [40]. In order to address these problems, several solubility enhancement studies have been reported previously [36,40–44]. Despite a number of studies on the solubility enhancement of ART, based on our knowledge, there have hitherto been no reports on the application of the functionalized food additives for antimalarial drugs, and also limited studies regarding the physicochemical stability of the amorphous solid dispersions of ART [45,46].

This work focuses on formulating amorphous solid dispersions to improve the biopharmaceutical properties such as aqueous solubility and dissolution rate, and physicochemical stability of ART. The amorphization of the drug was achieved by encapsulating the drug particles within functionalized food additives (Hsp-G and Stevia-G) via co-spray drying. These two food additives have been chosen as potential drug carriers by virtue of their superior aqueous solubility, relative safety and cost-effectiveness.The solid dispersions of ART with food additives were achieved via spray drying due to the advantages of this technique compared with other drug loading techniques [47].

2. Materials and methods

2.1. Materials

Artemisinin (ART) was obtained from Junda Pharmaceuticals, Co. Zhenjiang, China, and α-glucosyl hesperidin (Hsp-G) and α-glucosyl stevioside (Stevia-G) were purchased from Toyo Sugar Refining Co., Ltd, Tokyo, Japan. Activ-vial® was supplied by CSP technologies, Auburn, AL, USA. Hydrochloric acid (HCl) was from Merck KGaA, Darmstadt, Germany, ethanol was from Fisher Scientific Ltd., Leics, UK and deionized water was acquired by reverse osmosis with a MilliQ system (Millipore, Roma, Italy). All other reagents and solvents used in the study were reagent grade and were used without further purification.

2.2. Spray drying

Solid dispersions of ART/Hsp-G and ART/Stevia-G were formulated by using a BÜCHI B-290 mini spray dryer (BÜCHI Labortechnik AG, Flawil, Switzerland) operating in an inert loop mode with nitrogen purge flow. In order to formulate ART/Hsp-G (1:10 w/w) and ART/Stevia-G (1:10 w/w), typically, 2 g of ART was dissolved in 250 mL of mixture of ethanol/water (8:2 v/v), to which 20 g of Hsp-G or Stevia-G was subsequently added. The mixture was stirred overnight prior to spray drying. The inlet temperature was maintained at 120 °C. The resulting outlet temperature at the aforesaid operating condition was approximately 70–80 °C. The fine liquid suspensions were fed to the spray dryer via a peristaltic pump at a feed rate of 6.0 ml/min and sprayed into the chamber from a nozzle with 406 μm diameter at a pressure of 0.12-0.15 MPa. All the samples were dried in desiccators with silica beads under reduced pressure for 1 day before characterization. Spray dried samples was denoted by S.D.

2.3. Physical mixture

The physical mixtures were prepared by thoroughly mixing the crystalline ART and food additives in a turbula mixer (Turbula® T2F) at 49 rpm for 30 min until a homogeneous mixture was obtained. This physical mixture was characterized immediately after harvesting the sample from the glass vessels at the end of the mixing process. Physical mixture was denoted as P.M.

2.4. Powder X-ray diffraction (PXRD)

The crystallinity of the formulated samples was characterized by PXRD. The PXRD was performed using a D8-ADVANCE (BRUKER, Madison, WI) X-ray diffractometer in steps of 0.028° using monochromatized Cu Kα radiation (λ = 0.1542 nm) as X-ray source and scanned over an angular range from 5° to 50° (2θ). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 10 mA; scanning speed, 2°/min. PXRD holders were used to support samples and all the measurements were performed at room temperature.

2.5. Differential scanning calorimetry (DSC)

The thermal behaviour of the loaded powder samples were analyzed by using differential scanning calorimetry (DSC). The DSC was performed concurrently using a SDT 2960 simultaneous TGA-DSC thermo-gravimetric analyzer (TA Instrument Co., New Castle, DE, USA). Samples of 10 mg were weighted directly into platinum pans in each experiment, with an empty platinum pan being the control. Before each analysis, the sample pans were washed with ethanol and heated with flame jet to remove any residues. The samples were heated from room temperature to 180 °C under nitrogen purge flow at 100 mL/min with a heating rate of 10 °C/min. All data handling was performed using the Universal Analysis 2000 software package (TA Instruments).

2.6. Scanning electron microscopy (SEM)

The morphology of the powder samples was examined by a high resolution scanning electron microscope (SEM, JSM-6700F, JEOL, Tokyo, Japan) operating at 5 keV in secondary electron image (SEI) and lower electron image (LEI) mode. Prior to analysis, samples were mounted on double-sided adhesive copper tapes and coated with gold for 1 min in a sputter coater (Cressington Sputter Coater 208HR, Ted Pella, Inc., Watford, UK).

2.7. Contact angle measurement

The contact angle measurements were carried out using the sessile-drop technique with contact angle analyzer KSV CAM 100 (KSV instruments Ltd, Helsinki, Finland). Approximately 50 mg of powders were compressed into tablets by a hydraulic press at a pressure of 75 MPa for 1 min. A water droplet was placed on the compact surface using a microsyringe and subsequently was photographed to determine the contact angles. Each sample was measured in replicates of three ($n = 3$) to ensure reproducibility. All the measurements were carried out at room temperature.