Advanced Powder Technology 27 (2016) 442–447

Contents lists available at ScienceDirect

Advanced Powder Technology

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

Original Research Paper

Soluble hydrolysis-resistant composite formulation of curcumin containing α-glucosyl hesperidin and polyvinylpyrrolidone

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ARTICLE INFO

Article history:
Received 27 May 2015
Received in revised form 10 December 2015
Accepted 5 January 2016
Available online 2 February 2016

Keywords:
Solubility
Supersaturation
Hydrolytic stability
Polyvinylpyrrolidone

ABSTRACT

We developed a formulation for increasing the water solubility of curcumin (CUR). The new formulation also protected CUR from hydrolytic degradation. A ternary system of CUR/α-glucosyl hesperidin (hesperidin-G)/polyvinylpyrrolidone (PVP) K-30 was prepared by the solvent evaporation method. Although the binary sample of CUR/hesperidin-G showed increased solubility, the effect disappeared within a few hours of storage in aqueous media. In contrast, the ternary system of CUR/hesperidin-G/PVP K-30 (1:10:5, weight ratio) exhibited a long-lasting solubility increase. This supersaturated CUR solution remained stable even after 24 h, as shown by the 2600-fold increase in solubility compared with untreated CUR. The stability of CUR to hydrolytic degradation under alkaline conditions was improved dramatically by adding hesperidin-G and PVP K-30, whereas untreated CUR completely decomposed after a few minutes. The solubilizing effect may arise from the formation of an amorphous solid dispersion, including CUR, and from complex formation between CUR, hesperidin-G, and PVP K-30 in aqueous media. The complex may also protect CUR from hydrolytic degradation.

1. Introduction

Curcumin (CUR) is a yellow pigment derived from the rhizomes of *Curcuma longa*, known as turmeric, and is used in Indian cooking and as a household medicine [1]. In recent years, CUR has gained considerable attention because of its wide range of health-promoting properties, including antioxidant, anti-inflammatory, and antiviral activities, as well as its potential use for the treatment of chronic diseases [2–5]. Despite the attractive pharmacological effects of CUR and its safety at high doses (12 g/day) [6], it has been challenging to use CUR clinically because its low solubility results in low bioavailability [7]. CUR is a hydrophobic molecule with a high log*P* value of ~3.0 [8], and thus it is almost insoluble in water (11 ng/mL at pH 5.0 [9]). CUR is soluble in alkali media, although the compound undergoes rapid hydrolytic degradation at pH values above 7 [10]. Even under intestinal conditions (pH 6.8), the gradual degradation of CUR has been observed [10]. The hydrolysis of CUR has complicated the development of CUR formulations, and it may limit the therapeutic use of CUR.

These physicochemical properties of CUR have motivated many researchers to develop new strategies for increasing the solubility and chemical stability of CUR. To improve these properties, various complexes, such as liposomes, CUR-phospholipid complexes, CUR-cyclodextrin complexes, and micellar formulations, have been reported [9,11–13]. Despite many attempts, an effective strategy for producing stable supersaturated CUR solutions has still not been found. It is important to investigate how CUR complexes confer protection against hydrolytic degradation.

Transglycosylated food additives, such as α-glucosyl hesperidin (hesperidin-G) and α-glucosyl rutin (rutin-G), may improve the solubility and bioavailability of compounds with poor water solubility [14–17]. We have demonstrated that hesperidin-G acts as a pharmaceutical excipient because it dramatically improves the physicochemical properties and the oral absorption efficacy of the drugs flurbiprofen and probucol with no cytotoxicity [18]. The increased solubility may be explained by the formation of a self-associated structure consisting of the transglycosylated compound and the drug, with the flavone skeleton forming a hydrophobic core and the surrounding sugar groups serving as a shell [19]. Rutin-G forms nanostructures in water with an aggregation number of 4 at concentrations above the critical

Abbreviations: CUR, curcumin; DSC, differential scanning calorimetry; hesperidin-G, α-glucosylated hesperidin; PM, physical mixture; PVP, polyvinylpyrrolidone; PXRD, powder X-ray diffraction; rutin-G, α-glucosylated rutin.

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http://dx.doi.org/10.1016/j.apt.2016.01.012
0921-8831/

aggregation concentration [15]. Hesperidin-G and rutin-G may increase the solubility of an insoluble compound such as CUR. Moreover, Gosangari and Dyakonov have reported that the supersaturated conditions for a CUR self-emulsifying drug delivery system could be stabilized by the addition of polyvinylpyrrolidone (PVP) as a precipitation inhibitor [20]. However, there are no reports of combining transglycosylated materials and hydrophilic polymers such as PVP. The hybrid composite structure demonstrated superior properties to the characteristics of a single component for increasing solubility and stability [21,22].

In this work, we develop a water-soluble formulation of CUR with increased stability of the supersaturated state and chemical stability of CUR. A composite formulation of CUR was prepared by using the solvent evaporation method with the transglycosylated compounds hesperidin-G and rutin-G, and PVP, which is a suitable solvent for CUR [23], to evaluate the compatibility of these materials for increasing solubility. The physicochemical properties were evaluated, including solubility, dissolution properties, crystallinity, and thermal behavior. Furthermore, the protective effects of hesperidin-G and PVP to CUR hydrolysis degradation were assessed in a degradation study.

2. Materials and methods

2.1. Materials

CUR (Fig. 1A) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Transglycosylated additives, including hesperidin-G and rutin-G (Fig. 1B and C), were kindly supplied by the Toyo Sugar Refining Co. (Tokyo, Japan). PVP K-30 was a gift from BASF Japan Ltd. (Tokyo, Japan). All other chemicals and solvents were reagent grade or high-performance liquid chromatography (HPLC) grade.

2.2. Preparation of CUR samples with transglycosylated additives and PVP K-30

CUR (50 mg) was completely dissolved in ethanol (99.5%, 30 mL) with sonication, and the transglycosylated additives (500 mg) and PVP K-30 (250 mg) were dissolved in distilled water (30 mL). These solutions were completely mixed with a magnetic stirrer for 1 min at ambient temperature to maintain a specific ratio of CUR to hesperidin-G and PVP K-30. The solvent was removed by using a rotary evaporator (R-3, Büchi, Flawil, Switzerland) under a pressure of 40 bar for 15 min in a water bath at 50 °C. Solidified samples were micronized with a mortar and pestle. A physical mixture (PM) of CUR, transglycosylated additives, and PVP K-30 was also prepared by mortar and pestle at the same ratio as the evaporated samples. All samples were stored in a desiccator with blue silica gel under reduced pressure.

2.3. Solubility study

The apparent solubility of the CUR samples was evaluated. CUR samples containing CUR (50 mg) in distilled water (25 mL) were added to polypropylene conical tubes and incubated at 37 °C with agitation at 100 strokes/min (ML-10, TAITEC Co., Ltd., Saitama, Japan) for 24 h. Test solutions were collected in the initial state and after 24 h incubation. The samples were centrifuged at 15,000*g* to remove residual materials. The concentration of CUR was determined via an absolute calibration curve method by HPLC (SPD-10A, Shimadzu Co., Ltd., Kyoto, Japan) consisting of a pump (LC-10AD) detector (SPD-10A), and column (YMC-Pack Pro C18, 4.6 mm $\varphi \times 75$ mm; YMC Co., Ltd.). The conditions were column temperature, 40 °C; wavelength, 425 nm; injection volume, 10 μL; and flow rate, 1.5 mL/min. The mobile phase was 0.1 wt% phosphoric acid/acetonitrile (55/45).

2.4. Morphology of CUR samples

The morphology of CUR samples was observed by scanning electron microscopy (SEM; TM3030, Hitachi, Tokyo, Japan). The samples were sprinkled onto carbon sticky tape mounted on SEM stubs. The samples were sputtered with a thin layer of platinum under vacuum (MSP-1S, Vacuum Device Inc., Mito, Japan).

2.5. Evaluation of the crystallinity of CUR samples

Powder X-ray diffraction (PXRD; Miniflex600, Rigaku Corporation, Tokyo, Japan) was performed at a scanning rate of 4°/min over

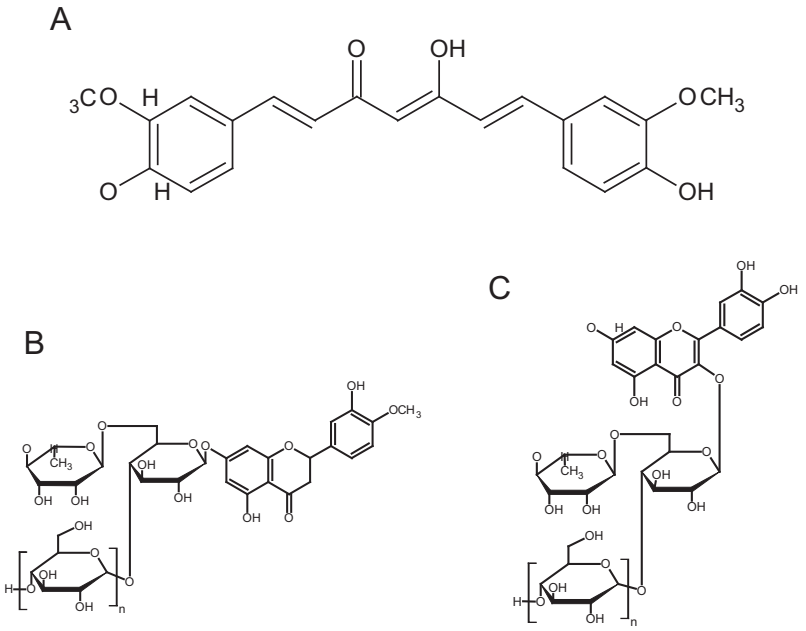

Fig. 1. Chemical structures of (A) CUR, (B) hesperidin-G, and (C) rutin-G.