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Ternary dispersions to enhance solubility of poorly water soluble antioxidants

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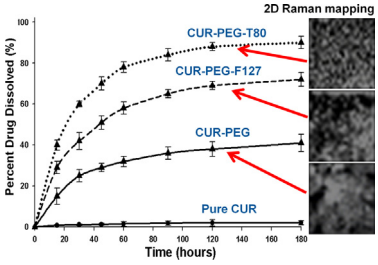
HIGHLIGHTS

- Binary dispersions of curcumin and hesperetin prepared with PVP and PEG polymers.
- PVP caused greater amorphization in the drugs compared to PEG.
- Ternary dispersions – surfactant (Pluronic F127, Tween 80) added to polymer.
- Surfactants enhanced interaction of polymer with drug, hence better dispersion.
- Significant increase in dissolution and stability of ternary dispersions of drugs.

GRAPHICAL ABSTRACT



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ABSTRACT

The main aim of this study was to enhance the solubility and dissolution rate of the two poorly water-soluble antioxidants, curcumin (CUR) and hesperetin (HSP). Binary dispersions of the two drugs in the polymer, polyvinylpyrrolidone (PVP) or polyethylene glycol (PEG) matrix were prepared. A surfactant (Pluronic F127 or Tween 80) was also combined with the polymer to develop ternary solid dispersions to further improve the dissolution properties of CUR and HSP. The FTIR study suggested hydrogen bonding between PVP and the drugs and minor intermolecular interactions between PEG and drugs. PVP showed better amorphizing nature than PEG as inferred from the DSC and XRD study. The surfactants added in the ternary dispersions further enhanced the intermolecular interaction of the polymers with the drugs. The 2D micro-Raman spectroscopic mapping showed that after adding the surfactants in the ternary dispersions, CUR and HSP were more uniformly distributed in the PEG matrix. The solubility and dissolution rates of CUR and HSP were increased by dispersing them in the polymer matrix and the increase was dramatic when the surfactant was added to the dispersion system. The intermolecular interactions between drug and carriers led to better dispersion of drug in the polymer matrix and reduction in the size of drug particles; increase in the amorphous nature, decrease in surface tension and increase in the wettability which resulted in enhanced solubility and dissolution of the ternary dispersions. The ternary dispersions also presented better long term stability in terms of the amorphous nature and the dissolution properties.

1. Introduction

The phytochemicals curcumin and hesperetin are widely spread in nature and easily extracted from a lot of different plants. Curcumin is a polyphenol extracted from the rhizome of the herb

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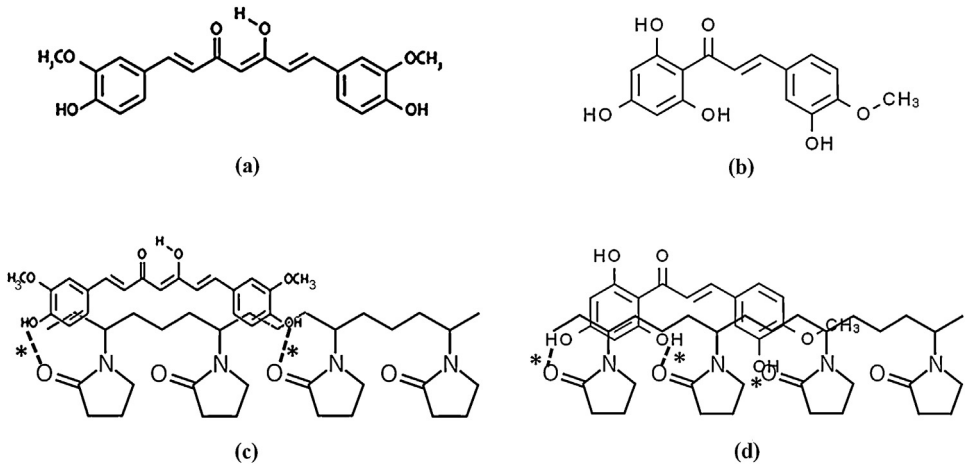

Fig. 1. The chemical structure of the drugs (a) curcumin, (b) hesperetin, and the possible hydrogen bond formation between the hydroxyl group (-OH) of (c) curcumin and (d) hesperetin with carbonyl group of PVP (>C=O).

Curcuma longa [1] and has been widely investigated for its anti-cancer [2,3], anti-inflammatory [4] and antioxidant [5] effects. Hesperetin is a flavonoid that exists ubiquitously in plants, fruits and flowers [6]. Hesperetin also acts as a potential antioxidant [7], anti-inflammatory agent [8] and anticancer agent [9]. Despite these medicinal benefits, both curcumin and hesperetin (shown in Fig. 1(a) and (b)) have a low bioavailability due to their poor aqueous solubility and slow dissolution rate in the aqueous gastro-intestinal fluids, which greatly restricts their use in therapy [1,10]. Manju et al. reported curcumin to be practically insoluble in water with the solubility of 0.27 μg/ml [11]. Solubility of hesperetin at 25 °C was shown to be 4.5×10^{-6} M (1.36 μg/ml) by Liu and Chen [12], and 3.3×10^{-6} M (1 μg/ml) by Tommasini et al. [13], which was stated to be in very good agreement with the Merck Index. Improving the solubility and dissolution of such drugs is one of the challenges in the pharmaceutical industry today. An increase in the dissolution rate may be achieved by increasing the surface area. One of the most common approaches to enhance the solubility and dissolution rate is by the formation of solid dispersions [14,15]. In these formulations, the drug can be dissolved or homogeneously dispersed as fine particles in a carrier. According to Serajuddin [15], the advantage of solid dispersion is that when the carrier is dissolved the drug is released as very fine colloidal particles and because of the large surface area, the dissolution rate is enhanced. Fine dispersion increases the available surface area and also prevents aggregation of individual drug particles so that wetting and dissolution can occur more rapidly [16]. In most cases, the drug is in the amorphous state, thus, resulting in an improved dissolution rate [17]. Amorphous drugs are however thermodynamically unstable and tend to recrystallize over time but the carrier reduces molecular mobility and thus, impedes nucleation and crystal growth [14].

The present research focuses on the development of a new carrier system for curcumin (CUR) and hesperetin (HSP). Although extensive research has been done on solid dispersions focussing predominantly on binary mixtures but more complex carrier systems remain unexplored. In this study, a surfactant has been combined with a polymer to develop ternary solid dispersions to improve the dissolution properties of CUR and HSP. Here we show that by adding small amount of surfactant, we can improve the dissolution of the drug substantially without the need to add large amounts of polymer, which will be useful when higher drug loading is desired.

First of all, both CUR and HSP were combined with an amorphous polymer polyvinylpyrrolidone (PVP) and a semi-crystalline polymer polyethylene glycol (PEG), to form the binary systems. These polymers are used extensively in pharmaceutical technology as drug carriers and are the most used drug carriers for solid dispersion preparations [18–21]. They were selected due to their strong hydrophilic properties and their capability to form molecular adducts with many compounds. The presence of hydroxyl or carbonyl groups in the repeat units of these polymers tend to increase the water solubility [22–25] and stability [24,26] of the drug and also improve its bioavailability [27]. In the second step, ternary systems were prepared by adding a surfactant to the previous drug-polymer systems. The non-ionic surfactants such as Pluronic F127 (F127) and Tween 80 (T80), were incorporated in the solid dispersions of CUR and HSP with PVP and PEG. The surfactants lower the interfacial surface tension of poorly water-soluble drug particles making the dispersion of the drug inside the polymer matrix easier. Moreover, they increase the drug affinity for aqueous media, thus improving the dissolution and have the potential to maintain a supersaturated solution upon dissolution of a drug. Therefore, the main aims of this work are to prepare and to characterize the physicochemical properties of the binary and ternary systems and to evaluate the effect of interactions between drugs and carriers on drug dispersion in the matrix and consequently its solubility, dissolution rate and the long term stability.

2. Materials and methods

2.1. Materials

Curcumin, hesperetin, polyvinylpyrrolidone (MW 40,000), polyethylene glycol (MW 4000), Pluronic F127 and Tween 80 were obtained from Sigma–Aldrich, Singapore. All the reagents used were of technical grade.

2.2. Method

Pure drug powder and polymers were dissolved in solvent (ethanol) and the solid dispersions were obtained by evaporation of the solvent, followed by vacuum drying. Firstly, a 5 mg/ml drug solution was prepared by dissolving 250 mg of the drug in 50 ml of ethanol and later 250 mg of the polymer (PVP or PEG) was added to the prepared drug solution. The mixture was stirred and sonicated to obtain a homogenous solution, which was poured into a 250 ml round bottom flask to be attached to a rotary evaporator. The flask was immersed partly in a water bath at 40 °C and set to a rotation