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Solid dispersions of Myricetin with enhanced solubility: Formulation, characterization and crystal structure of stability-impeding Myricetin monohydrate crystals

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ABSTRACT

Three solid dispersion forms of Myricetin combined with the Polyvinylpyrrolidone were successfully prepared by spray drying method, and characterized by X-ray powder diffraction, thermal analysis, infrared spectroscopy and optical microscopy. Zeta potential measurements provided indications on solid dispersions stability in aqueous suspension related to their storage at elevated temperature and relative humidity, which depends on the Myricetin load. By increase of Myricetin load, the stability of the solid dispersion is impeded due to growth of Myricetin monohydrate crystals. The amorphous dispersions with 10% and 50% Myricetin load are stable and, compared to pure Myricetin, their aqueous solubility is enhanced by a factor of 47 and 13, respectively. The dispersion with 80% Myricetin load is unstable on storage, and this behavior acts in conjunction with the development of Myricetin monohydrate crystals. Single-crystal X-ray diffraction results obtained for Myricetin monohydrate reveal a structure of an infinite 2D network of hydrogen-bonded molecules involving all six hydroxyl groups of Myricetin. The water molecules are positioned in between the infinite chains, and contribute via H-bonds to robust crystal packing. The calculated needle-like morphology of monohydrate form is in agreement with the optical microscopy results. The study shows that the solid amorphous dispersions with up to 50% Myricetin load are a viable option for achieving substantial solubility improvement of Myricetin, and supports their potential use in pharmaceutical applications.

1. Introduction

The use of natural products is considered a viable way for obtaining health benefits or preventing certain diseases [1,2], they are found in plants and microorganism and are known for their antioxidant [3], and free radical scavenging activity [4,5]. Moreover, the natural compounds have shown potential as therapeutic agents against cancer, microbial infection, inflammation and other disease conditions [6–8]. In the past years, the US Food and Drug Administration (FDA) and other regulatory agencies worldwide have approved many natural compounds in the treatment of cancer and infections [9]. Despite of their potential health benefits, many natural products are not effective due to poor solubility and low bioavailability shown in clinical trials [10,11].

Myricetin 3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (Myr) is a natural flavonoid used as a nutritional supplement for increasing vitality and energizing the human body. Besides antioxidant properties [12], this compound shows promising, antiviral, antibacterial and antitumor activity [13,14], and has a great therapeutic potential in diabetes mellitus [15,16]. Recent findings suggest that Myr may have a protective effect against diet-induced obesity and insulin resistance in mice [17]. Similar to other natural compounds, the clinical use is limited by its low aqueous solubility and bioavailability [18]. Different approaches to enhance the solubility and absorption of Myr included complexation with β-cyclodextrins [19,20], microemulsion [21] and cocrystals preparation [22–25]. A more recent molecular docking study attempted screening for possibly more soluble Myr derivatives as candidate drugs for cancer [26].

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In the context of Myricetin's pharmaceutical potential, the aim of this study is to investigate the possibility of enhancing its solubility *via* amorphous solid dispersions by spray-drying technique [27]. Encapsulation of low soluble compounds in polymer matrix by spray drying is one of the strategies to improve the dissolution properties and bioavailability of poorly water-soluble drugs [28,29]. We used the synthetic polymer polyvinylpyrrolidone K30 (PVP-K30) with a degree of polymerization of 30 and molar mass of about 50,000 according to the Fikentscher's equation [30]. Polymers are used as stabilizer or gelling agent in solid dispersions systems [31–35]. Molecular structures of Myr and PVP-K30 are shown in Fig. 1.

The solid-state properties of Myr were recently reported [18], however, a Cambridge Structural Database (CSD) [36] search revealed that only a few crystal structures of similar compounds are known (2205440 [37], FIXROV and FIXROV01 [22], KUZYOU [38], PILCES and PILCIW [39], SIMVOA [40], UNOJAI [41], and that no crystal structure of Myr was reported so far. Also, we report the first crystal structure of Myr monohydrate form, as determined from single-crystal X-ray diffraction.

2. Experimental

2.1. Materials

Nutraceutical compound Myr, was provided by Xi'an Natural Field Bio-technique Co., Ltd, China and used without purification. Polymer PVP-K30 and all solvents of reagent grade were supplied by Merck.

2.2. Optimization and preparation of solid dispersions

In order to develop a formulation with obvious concentration of Myr and PVP-K30, with high stability and enhanced dissolution, three solid dispersions (SD) were prepared using the spray drying method [42,43]. Myr was combined with polymer in three formulation with decreasing concentration of polymer. Myr and PVP-K30 (10:90 w/w; 50:50 w/w; 80:20 w/w) were dissolved in ethanol, and the solution were dried using a Buchi Mini Spray Dryer B-290 (Supplementary Table S1). The inlet and outlet temperature, the feed rate and the air flow were recorded continuously during each run.

2.3. Preparation of single crystals of Myricetin monohydrate

An amount of 10 mg from the Myr was dissolved in 6 ml of mixture dioxane: methanol (1:1) ratio, with magnetic stirring. The resulting solution was filtered and allowed to slowly evaporate at ambient temperature. After two weeks, dark-yellow, block-like crystals were obtained, which were analyzed by single-crystal X-ray diffraction.

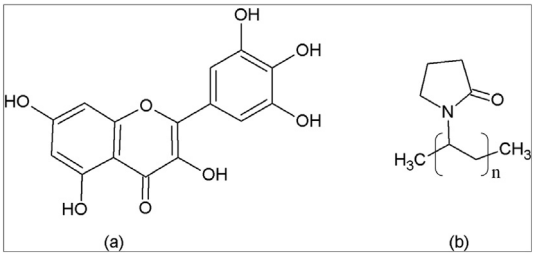

Fig. 1. Structures of (a) Myr, $C_{15}H_{10}O_8$, MW = 318.2351 g/mol, and (b) PVP-K30 $(C_6H_9NO)_n$.

3. Characterization of solid dispersions

3.1. X-ray powder diffraction

X-ray powder diffraction patterns (XRPD) were recorded using Shimatzu XRD-6000 diffractometer, (Shimadzu Corporation, Japan), equipped with a CuKα radiation (40 kV and 30 mA). All samples was scanned between 3 and 40° in 2θ scan range, with a step size of 0.02° and a scan speed of 2°/min.

3.2. Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out with a differential scanning calorimeter Shimadzu DSC-60 (Shimadzu Corporation, Japan), at a heating rate of 10 °C min^{-1}, in the range of 30–400 °C.

Thermogravimetric analysis (TGA) was performed with a Shimadzu DTA/DTG-60H apparatus, at the same heating rate. In both types of measurements, the nitrogen flow rate was 70 cm^3/min. For data collection and analysis, the Shimadzu TA-60WS software was used.

3.3. Fourier transform-infrared spectroscopy

Infrared absorption spectra were recorded using a JASCO 6200 Fourier Transform-Infrared spectrometer (Jasco Inc., MD, USA). Small amounts (~1 mg) of each solid sample were previously mixed with 150 mg of KBr powder and compressed in pellets. The spectra were recorded in the spectral domain 400–4000 cm^{-1}, with a resolution of 4 cm^{-1} and 256 scans. A background spectrum of the KBr pellet was recorded under the same instrumental conditions and subtracted from each sample spectrum. Data analysis was performed using Spectra Analysis software.

3.4. Dissolution and stability studies

Powder dissolution experiments were performed with μDISS Profiler™ apparatus (pION Inc., MA, USA) in order to assess the dissolution rate and the apparent solubility of amorphous Myr formulations in deionized water (pH 5.8). The system consists of an integrated diode array spectrophotometer connected to a fiber optic UV probe located directly in the reaction vessel and measures the concentration as a function of time. Measurements of dissolution kinetics and equilibrium solubility were carried out at 255–280 nm, and the concentrations of Myricetin were calculated by means of a standard curve.

In order to study the accelerated stability of the solid dispersions, the samples were placed in open vials, in a Memmert Humidity Chamber, stored at 40 ± 2 °C and controlled humidity 75± 5% RH. The physicochemical properties of these dispersions were evaluated after 2 months, to assess their stability against crystallization.

3.5. Zeta potential

For zeta potential measurements the particles were dispersed in water and ultrasonicated for 1 min. Zeta potential was measured with a Zetasizer NanoZS90 instrument (Malvern Instruments) at 25 °C. The average Zeta-potential and standard deviation were calculated based on three measurements for each sample.

3.6. Optical microscopy

Differential interference contrast (DIC) and transmission microscopy images were obtained with an inverted Zeiss Axio