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Storage stability and solubilization ability of HPMC in curcumin amorphous solid dispersions formulated by Eudragit E100

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ABSTRACT

The present study elucidated the advantages of using hydroxypropyl methylcellulose E5 (HPMC) as auxiliary excipient in maintaining storage stability and solubilization ability for curcumin amorphous solid dispersion (Cur ASDs) formulated by Eudragit E100 (E100). Polarized light microscopy and in vitro dissolution experiment was applied for confirming the ability of HPMC on inhibiting crystallization thereby maintaining storage stability in Cur ASDs. Meanwhile, as a non-ionic surfactant, HPMC can form micelles in pH 1.0 hydrochloric acid and played a role in solubilization ability on Cur. Critical micelle concentration (CMC), molar solubilization ratio (MSR) and micelle-water partition coefficient K_{mc} of surfactants (HPMC, E100/HPMC 1:1 and E100/HPMC 6:1) in pH 1.0 hydrochloric acid were calculated to determine the solubilization ability of surfactants. The results showed that the solubilization ability of E100/HPMC 6:1 was the best and the solubilization mechanism of E100/HPMC 6:1 was also different from HPMC and E100/HPMC 1:1.

1. Introduction

Curcumin (Cur) is a hydrophobic polyphenol derived from the rhizome of turmeric (Curcuma longa). At present, Cur has attracted great attention for its diverse pharmacological and biological properties, such as anti-tumor (Wegiel, Zhao, Mauer, Edgar, & Taylor, 2013), anticancer (Mitsionis & Vaimakis, 2012), anti-inflammatory (Mir et al., 2011), anti-oxidant (Sharma, 1976), cardioprotective effects (Imbaby, Ewais, Essawy, & Farag, 2014) and so on. Meanwhile, it has reported that Cur has good safety for long-term use (Hegge, Vukicevic, Bruzell, Kristensen, & Tonnesen, 2013; Li, Konecke, Wegiel, Taylor, & Edgar, 2013). However, just like a lot of new chemical entities with promising therapeutic activity have characters of low aqueous solubility and bioavailability (Gao et al., 2012; Sugano et al., 2010), Cur is moderately hydrophobic (logP 2.5) and has low aqueous solubility (11 ng/mL at pH 5.0) (Aguiar, Carpena, Molina-Bolívar, & Carnero Ruiz, 2003; Kadota et al., 2016), which leads to low aqueous solubility and bioavailability of Cur. In addition, Cur degrades very quickly at neutral or alkaline pH (Basu Ray, Chakraborty, & Moulik, 2006), which can further limit its usage (Wegiel, Zhao, Mauer, Edgar, & Taylor, 2014). Various strategies have been employed to design soluble formulations of Cur, including liposomes, nanoparticles, amorphous solid dispersions (ASDs) (Chuah et al., 2014; Li et al., 2013) and cyclodextrin complexation (Gangurde et al., 2015). Cur ASDs is one of the most promising strategies due to the high melting point (180°C) of Cur and the strong crystal lattice energy can disrupt its crystalline structure (Li et al., 2013). In the current study, Cur ASDs are formulated with single polymer or binary polymers by the methods of solvent evaporation, spray drying, hot melt extrusion and antisolvent precipitation (Janssens et al., 2010; Mustapha et al., 2017). For instance, single polymer such as polyoxyethylene pyrrolidone K30 (PVP), Eudragit E100, polyethylene glycol (PEG) have been used for enhancing solubility and dissolution of Cur (Li, Lee, Shin, Chen, & Park, 2015; Paradkar, Ambike, Jadhav, & Mahadik, 2004). At the same time, binary polymers such as Eudragit EPO and hydroxypropylmethyl cellulose E50 (HPMC) were also applied for preparing Cur ASDs (Li et al., 2017).

The present paper introduced HPMC into the design of Cur ASDs formulated by E100 due to cellulose derivatives have potential value as assistant excipient for ASDs. Ionic interactions can be formed between E100 and Cur because E100 is a polybase and proton acceptor (Pradhan, Kim, Yong, & Kim, 2016). And the ionic interactions between E100 and Cur can improve dissolution of Cur (Bernabé-Pineda, Ramírez-Silva, Romero-Romo, González-Vergara, & Rojas-Hernández, 2004; Wegiel et al., 2014). It also has reported that cellulose derivatives like HPMC or hydroxypropylmethyl cellulose acetate succinate (HPMCAS) are playing important roles in inhibiting crystallization, thus maintaining stability of ASDs during the storage (Avalle, Pygall, Gower, & Midwinter, 2011; Tajarobi, Abrahmsen-Alami, Carlsson, & Larsson,

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2009). At the same time, as a non-ionic surfactant, HPMC consists of hydrophilic part and lipophilic part. Therefore, HPMC can significantly reduce surface tension of the system and has abilities of wetting, emulsifying, dispersion, foaming, solubilization and so on. When the concentration of surfactant molecules in solution reaches a certain level, the surfactant molecules will form micelles with lipophilic-oriented inward and hydrophilic-oriented outward. The minimum concentration at which micelles begin to form is the critical micelle concentration (CMC). The solubilization ability of surfactant to dissolve drugs is very important (Gaucher, Satturwar, Jones, Furtos, & Leroux, 2010). After the surfactant forms micelles in aqueous solution, the solubility of the insoluble organic substance is significantly increased. Surfactant micelles can not only increase the dissolved amount of the drug, increase the absorption and enhance the physiological activity, but also isolate the drug in the micelle from the oxygen and effectively prevent the oxidation of the drug. HPMC, E100/HPMC 1:1 and E100/HPMC 6:1 also has these abilities.

In our study, Cur ASDs were prepared by binary polymers of E100 and HPMC. Herein, the dissolution of Cur ASDs in pH 1.0 hydrochloric acid was studied by polarized light microscopy and in vitro dissolution experiment. Furthermore, the storage stability experiment was used to demonstrate the ability of HPMC on maintaining stability during the storage of Cur ASDS. Pyrene probe fluorescence spectrophotometry was used to determine the CMC of surfactants including HPMC, E100/HPMC 1:1 and E100/HPMC 6:1. The solubilization ability of HPMC, E100/HPMC 1:1 or E100/HPMC 6:1 was described by Molar Solubilization Ratio (MSR) and micellar/water partition coefficient K_{mc}. The solubilization mechanisms were studied by the method of steady-state fluorescence spectrophotometry.

2. Materials and methods

2.1. Materials

Cur with purity of more than 99.8% was purchased from meilunbio Co., Ltd. (Dalian, China). Eudragit E100 (E100) was kindly provided by Evonik Co., Ltd. (Germany). Hydroxypro-pylmethyl cellulose E5 (HPMC) was obtained from Anhui Shanhe Pharmaceutical Excipients Co., Ltd. (Huainan, China). Other chemical agents were provided by Tianjin Bodi Chemical Holding Co., Ltd. (Tianjin, China).

2.2. Preparation of Cur ASDs

Single polymer (E100) or binary polymers (E100/HPMC with weight ratio of 1:1, 3:1, 6:1, 9:1, respectively) were dissolved in ethanol. In the meantime, Cur was completely dissolved in ethanol on a 80℃ water bath. The weight ratio between drug and excipient was designed as 1:6. The above solution was mixed and the solvent ethanol was completely removed by rotary evaporation. The Cur ASDs were dried in vacuum oven overnight to remove any residual solvent. The Cur ASDs were ground using a mortar and pestle and then sieved (60 mesh) to obtain particles that named as Cur-E100, Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 6:1 and Cur-E100/HPMC 9:1.

2.3. Drug dissolution

2.3.1. Polarized light microscopy

To vividly present and confirm the wetting behavior of Cur ASDs, polarized light microscopy (PLM) (Olympus Co., Tokyo, Japan) was applied for observing sample powder with or without one drop of dissolution medium. The magnification was set at 10 × 40 times.

2.3.2. In vitro dissolution

Drug release experiment was performed using the small cup method (50 rpm, 37 °C, and 250 mL dissolution medium) with a RC806D dissolution tester (Tianjin, China). Cur and Cur ASDs (containing 4 mg Cur) were dissolved in 250 mL pH 1.0 hydrochloric acid. At appropriate time intervals, aliquots (5 mL) of samples were withdrawn and replaced with 5 mL of fresh dissolution medium to maintain constant volume. After going through 0.45 μm microporous membrane, the sample medium was analyzed using UV-1120 (Shimadzu, Japan) at the wavelength of 425 nm. All samples were performed in triplicate.

2.4. Storage stability experiment

Cur ASDs were stored for six months and in vitro dissolution experiments of these samples were carried out. The method of in vitro dissolution experiments was the same as Section 2.3.2.

2.5. Effect of HPMC on Cur ASDs

2.5.1. The CMC of HPMC, E100/HPMC 1:1 and E100/HPMC 6:1

Pyrene probe fluorescence spectrophotometry was used to determine the CMC of HPMC. Pyrene stock solution was prepared by ethanol at a concentration of 6×10^{-6} mol/L. Different concentrations of surfactant solution (HPMC, E100/HPMC 1:1 and E100/HPMC 6:1) were prepared with pH 1.0 hydrochloric acid solution. Afterwards, the experiment was carried out step by step. Firstly, 100 μL pyrene stock solution was placed into Eppendorf tubes (EP tubes) and then ethanol was completely dried. Secondly, 1 mL different concentrations of surfactant solution were added to EP tubes respectively. Thirdly, the EP tubes were shaken in a constant temperature water bath for 4 h and then placed at 25℃ for 12 h. Finally, 50 μL solution was put in 96-well plates and fluorescence measurements were made using a Microplate reader (ThermoFisher scientific, USA). The excitation wavelength used was settled at 335 nm, the emission wavelength was set as 373 nm and 384 nm and the corresponding fluorescence intensity was named as I_1 and I_3, respectively. The value of I_3/I_1 was plotted against the surfactant concentration.

2.5.2. The solubilization ability of HPMC, E100/HPMC 1:1 and E100/HPMC 6:1 on Cur

Molar Solubilization Ratio (MSR) was used to quantitatively describe the ability of a surfactant solution to solubilize a particular solute. Mohammad et al. proposed MSR can be obtained by plotting concentration of the surfactant solution against drug concentration. When the units of drug concentration and surfactant concentration were mmol /L, the slope of profile was MSR (Mir et al., 2011). The solubilization ability of HPMC, E100/HPMC 1:1 and E100/HPMC 6:1 on Cur was determined by adding an excess amount of Cur to 3 mL pH 1.0 hydrochloric acid with different concentrations (0.5, 1, 1.4, 1.6, 1.8, 2, 2.5 times of CMC) of surfactant solution (HPMC, E100/HPMC 1:1 and E100/HPMC 6:1) in EP tubes. The EP tubes were equilibrated at 37 °C for 48 h in an agitating water bath. Samples were then ultracentrifuged to separate excess crystalline Cur particles from the supernatant. Ultracentrifugation was performed at 13,000 rpm for 5 min. At last, the samples were analyzed using UV-1120 (Shimadzu, Japan) at the wavelength of 425 nm.

2.5.3. The solubilization mechanisms of HPMC, E100/HPMC 1:1 and E100/HPMC 6:1 on Cur

Steady-state fluorescence spectrophotometry was used to study the solubilization mechanisms of HPMC, E100/HPMC 1:1 and E100/HPMC 6:1 on Cur. Cur stock solution was prepared by ethanol at a concentration of 200.4 μg/mL. The initial step was to add 200 μL Cur stock solution to EP tubes and then dried ethanol completely. Afterwards, 1 mL pH 1.0 hydrochloric acid with different concentrations (0.5, 1.0, 1.4, 1.6, 1.8, 2.0, 2.5 times of CMC) of surfactant solution (HPMC, E100/HPMC 1:1 and E100/HPMC 6:1), water and n-hexane were added into EP tubes. After that, the EP tubes were sonicated for 6 h and were placed at 25℃ for 12 h. Finally, 50 μL solution was put in 96-well plates