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Impact of HPMC on inhibiting crystallization and improving permeability of curcumin amorphous solid dispersions

Na Fan, Zhonggui He*, Pingping Ma, Xin Wang, Chang Li, Jin Sun, Yinghua Sun, Jing Li*

Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang, China

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ABSTRACT

The purpose of this paper was to elucidate the impacts of hydroxypropylmethyl cellulose E5 as assistant excipient on inhibiting crystallization and improving membrane permeability in curcumin amorphous solid dispersions that formulated by Eudragit E100. Intermolecular interactions formed between curcumin and polymers were probed using in situ Raman imaging and infrared spectroscopy. The abilities of hydroxypropylmethyl cellulose E5 in inhibiting crystallization and improving membrane permeability were confirmed by fluorescence spectroscopy, dynamic light scattering analysis and in vitro permeability experiment. The results demonstrated hydroxypropylmethyl cellulose E5 was significant in maintaining the amorphous drug concentration owing to the hydrogen bond interactions formed with curcumin, rending its ability to inhibit crystallization by reducing drug droplet size. Furthermore, the addition of hydroxypropylmethyl cellulose E5 in curcumin amorphous solid dispersions promoted drug membrane permeability through lowering the order level of phospholipid bilayer layer.

1. Introduction

The poor solubility of water-insoluble drugs is a limiting factor for achieving good oral bioavailability. Many methods have been used to overcome this issue. For example, Stella introduced a recent "surprising" prodrug bortezomib (marketed as Velcade). Bortezomib was significantly more soluble due to the in situ formation of boronic acid esters by reaction with diol groups of mannitol (Stella & Nti-Addae, 2007). Chaudhari studied the effect of hydroxypropylmethyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) on the model drug fenofibrate. It confirmed that the polymers governed the dissolution of amorphous solid dispersions (ASDs) (Chaudhari & Dave, 2015). Md. Akhlaquer Rahman systematically clarified the oral lipid based formulations improved the bioavailability by increasing the solubility, facilitating gastrointestinal absorption of poorly water-insoluble, lipophilic drug (Rahman, Harwansh, Mirza, Hussain, & Hussain, 2011). Among these methods, ASDs can be considered as the most promising technique (Serajuddin, 1999). ASDs are defined as drug molecules dispersed in hydrophilic carriers and the carriers with different properties can modulate drug release profile. At present, a wide variety of polymers are used in solid dispersions to achieve specific goals. For example, cellulose derivative matrices like carboxymethylcellulose acetate butyrate (CMCAB), hydroxypropylmethyl cellulose acetate succinate (HPMCAS), or cellulose acetate adipate propionate (CAAdP) were applied for quercetin ASDs (Li & Konecke, 2013) and ellagic acid ASDs (Li, Harich, Wegiel, Taylor, & Edgar, 2013). It was also reported that poly(acrylic acid) was applied for increasing the dissolution of the drug, and cellulose derivatives were added to inhibit drug crystallization (Li, Konecke, Wegiel, Taylor, & Edgar, 2013). Therefore, it can be accepted that cellulose derivatives have huge values in assisting the design of ASDs.

Curcumin (Cur, Supplementary data, Fig. S1) is a hydrophobic polyphenol derived from the rhizome of Curcuma longa. Cur exhibits keto–enol tautomerism and its di-keto form and keto–enol form are shown in Fig. S1. The diverse pharmacological and biological properties include anti-oxidant (Sharma, 1976), anti-inflammatory (Motterlini, Foresti, Bassi, & Green, 2000), anti-tumor (Sadzuka, Nagamine, Toyooka, Ibuki, & Sonobe, 2012), anti-cancer (Aggarwal, Kumar, & Bharti, 2003), cardioprotective effects (Imbaby, Ewais, Essawy, & Farag, 2014) and so on. Cur has been investigated in a wide range because of its wide application and good safety (Li, Konecke, Wegiel, Taylor, & Edgar, 2013). However, Cur with characters of moderately hydrophobic (logP 2.5) and low aqueous solubility (11 ng/mL at pH 5.0) (Tønnesen, Másso, & Loftssonb, 2002) degrades very quickly at neutral or alkaline pH (Wang et al., 1997). These disadvantages limit the clinical development of Cur. In order to overcome the challenges, different strategies have been applied (Chen, Ormes, Higgins, & Taylor, 2015). Cur ASDs is one of the most promising strategies due to the high

* Corresponding authors at: Wenhua road 103, Shenyang Pharmaceutical University, Shenyang, 110016, China.
E-mail addresses: hezhonggui@vip.163.com (Z. He), dddefghijklmn@163.com (J. Li).

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melting point (180 °C) of Cur (Li & Wegiel, 2013). In the current stage, Cur ASDs can be formulated by different polymers, including Eudragit E100 (E100), PVP, CMCAB, HPMC and HPMCAS (Wegiel, Zhao, Mauer, Edgar, & Taylor, 2014).

As cellulose derivatives have potential value as assistant excipient for ASDs, the present paper innovatively introduced HPMC into the design of Cur ASDs formulated by E100 to systemically elucidate the advantages of HPMC that mainly covered its ability in inhibiting Cur crystalline and enhancing membrane permeability in Cur ASDs. E100 is a polybase and proton acceptor, and the average pKa of the basic monomer is 8.4 (Menjoge & Kulkarni, 2007). Cur has pKa values of 10.51, 9.88 and 8.38 (Bernabé-Pineda, Ramírez-Silva, Romero-Romo, González-Vergara, & Rojas-Hernández, 2004). Therefore, ionic interactions were formed between E100 and Cur, resulting in the enhancement of drug dissolution (Wegiel et al., 2014). Herein, the existence of tautomeric Cur in ASDs was vividly showed by Raman imaging plus spectroscopy and the intermolecular interactions were determined by IR spectroscopy. Furthermore, the impact of HPMC on inhibiting crystallization in Cur ASDs was mainly studied by fluorescence spectroscopy and dynamic light scattering analysis. As for membrane permeability experiment, a facile in vitro permeability test was conducted for as-synthesized Cur ASDs. It is believed that impact of HPMC on inhibiting drug crystallization and improving permeability in Cur ASDs that elucidated in this paper can provide valuable instruction for the study of Cur ASDs in future.

2. Materials and methods

2.1. Materials

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

2.2. Preparation of bulk cur ASDs

Cur and the polymer(s) were dissolved in ethanol. Solvent removal was achieved by rotary evaporation. The ASDs with various compositions (Supplementary data, Table S1) were subsequently dried in vacuum oven overnight to remove any residual solvent. The ASDs were ground using a mortar and pestle and then sieved (60 mesh) to obtain uniform particles. The short names for as-synthesized Cur ASDs were listed in Table S1, which were Cur-E100 1:1, Cur-E100 1:2, Cur-E100 1:4, Cur-E100 1:6 or Cur-E100, Cur-E100 1:8, Cur-E100/HPMC1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 4:1, Cur-E100/HPMC 6:1, Cur-E100/HPMC 9:1.

2.3. Intermolecular interactions between cur and polymers

2.3.1. Raman imaging and spectroscopy

The existence form of tautomeric Cur in different ASDs was assessed by Raman imaging and spectroscopy. Samples (Cur-E100 1:6 (Cur-E100), Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 6:1 and Cur-E100/HPMC 9:1) were analyzed in situ through a quartz sight window via a Raman spectrometer (inVia Laser Micro Raman Spectroscopy, Renishaw PLC) equipped with a thermoelectrically cooled CCD detector and a fiber optic probe. Then, the samples were measured at room temperature using a 500 mW laser source with a wavelength of 785 nm.

2.3.2. IR spectroscopy

Infrared spectroscopy (IR, Spectrum 1000, PerkinElmer, USA) spectra of drug, polymers, and Cur ASDs obtained from the spectral region 500–4000 cm^{-1}. Samples were prepared by grounding with KBr gently and respectively.

2.3.3. Effect of polymer on the equilibrium solubility of cur

The equilibrium solubility of Cur was determined by adding an excess amount of Cur to 1 mL pH enzyme-free simulated gastric fluid (pH 1.0 hydrochloric acid) with the presence of 500 μg/mL pre-dissolved polymer(s) in Eppendorf tubes (EP tubes). The EP tubes were equilibrated at 37 °Cfor 48 h in an agitating water bath. Samples were then ultracentrifuged to separate excess crystalline Cur particles from the supernatant. Ultracentrifugation was performed at 12000 rpm for 10 min. High performance liquid chromatography (HPLC) analysis was performed using an HITACH HPLC (Tokyo, Japan). The chromatographic separation was performed with a C18 Column. A water (22%), methanol (77%) and glacial acetic acid (1%) mixture was used as mobile phase, and the flow rate was 1 mL/min. The ultraviolet detection wavelength was 428 nm. All measurements were performed in triplicate at room temperature.

2.4. The impact of HPMC on inhibiting crystallization

2.4.1. Fluorescence spectroscopy

Fluorescence spectroscopy was used to reflect the nature of phase separation phenomena occurring in solution. Herein, 50 μL Cur ethanol solution with the concentration of 10, 20, 30, 40, 50, 60, 70, 80, 90 μg/mL were added to 50 μL pH 1.0 hydrochloric acid with the presence of 500 μg/mL pre-dissolved polymer(s) in 96-well plates. Fluorescence measurements were made using a Microplate reader (ThermoFisher scientific, USA). The excitation wavelengths used were settled in the range of 200 ~ 500 nm, the emission wavelength was 520 nm.

2.4.2. The effect of polymer(s) on amorphous drugs concentration

The effect of polymer(s) on amorphous Cur concentration was determined by adding 100 μL Cur supersaturated ethanol solution (Cur supersaturated ethanol solution was obtained from the supernatant when dissolving an excess amount of Cur in ethanol solution until the existence of Cur crystals at the bottom) to 400 μL pH 1.0 hydrochloric acid with the presence of 500 μg/mL pre-dissolved polymer(s) in EP tubes. A batch of samples was immediately filtered with an oil microporous membrane (0.45 μm) and measured by HPLC, while another batch of samples was filtered after standing for 2 h and then measured by HPLC. All samples were performed in triplicate. The polymer solutions in the test included E100, HPMC, E100/HPMC 1:1, E100/HPMC 3:1, E100/HPMC 6:1 and E100/HPMC 9:1, and the working conditions of HPLC were the same as described in Section 2.5.

2.4.3. Dynamic light scattering (DLS)

The particle size of each sample was determined by DLS (Nano ZS90, Malvern, Worcestershire, UK). It can not only be used for nanosuspension, but also for evaluating particle size with nanometer level. The following procedure was applied for sample preparation. Briefly, 0.5 mL saturated ethanol solution of Cur was pipetted into 2 mL polymer(s) aqueous solution (pH 1.0 hydrochloric acid) with 500 μg/mL pre-dissolved polymer(s). The parameters included: (1) Equilibrium time 10s; (2) 13 of number of runs; (3) 5 of run duration (s); (4) 3 of number of measurements; (5) 1 of delay between measurements (s).

2.4.4. In vitro dissolution

Cur and Cur ASDs (containing 4 mg Cur) were dissolved in 250 mL pH 1.0 hydrochloric acid by using small cup method with a RC806D dissolution tester (Tianjin, China). The experiment was carried out for 2 h with working conditions of 37 °C and 50 rpm. Aliquots (5 mL) were withdrawn at appropriate time intervals and replaced with 5 mL of fresh dissolution medium after each sampling to maintain constant volume. For convenience, the sample medium was analyzed using UV-1120 (Shimadzu, Japan) at the wavelength of 425 nm after going