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Molecular-level elucidation of saccharin-assisted rapid dissolution and high supersaturation level of drug from Eudragit® E solid dispersion

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ABSTRACT

In this work, the effect of saccharin (SAC) addition on the dissolution and supersaturation level of phenytoin (PHT)/Eudragit® E (EUD-E) solid dispersion (SD) at neutral pH was examined. The PHT/EUD-E SD showed a much slower dissolution of PHT compared to the PHT/EUD-E/SAC SD. EUD-E formed a gel layer after the dispersion of the PHT/EUD-E SD into an aqueous medium, resulting in a slow dissolution of PHT. Pre-dissolving SAC in the aqueous medium significantly improved the dissolution of the PHT/EUD-E SD. Solid-state ^{13}C NMR measurements showed an ionic interaction between the tertiary amino group of EUD-E and the amide group of SAC in the EUD-E gel layer. Consequently, the ionized EUD-E could easily dissolve from the gel layer, promoting PHT dissolution. Solution-state ^{1}H NMR measurements revealed the presence of ionic interactions between SAC and the amino group of EUD-E in the PHT/EUD-E/SAC solution. In contrast, interactions between PHT and the hydrophobic group of EUD-E strongly inhibited the crystallization of the former from its supersaturated solution. The PHT supersaturated solution was formed from the PHT/EUD-E/SAC SD by the fast dissolution of PHT and the strong crystallization inhibition effect of EUD-E after aqueous dissolution.

1. Introduction

Solid dispersions (SDs), where drugs are dispersed into a polymer matrix in an amorphous state, are practical formulations for improving the solubility and bioavailability of poorly water-soluble drugs (Baghel et al., 2016). Various polymers such as derivatives of vinyl (Mistry et al., 2015), cellulose (Ueda et al., 2012; Yun et al., 2014), polyethylene glycol (Zhu et al., 2013), and methacrylate (Kojima et al., 2012; Moustafine et al., 2013) have been used as SD carriers. The presence of these polymers in SDs efficiently inhibits the recrystallization of the amorphous drug during storage. Furthermore, they suppress the crystal nucleation and growth of drugs from the drug-supersaturated solutions formed by the dissolution of the SD, leading to the long-term maintenance of the drug-supersaturated solution (Ilevbare et al., 2012; Schram et al., 2015).

The drug supersaturation level attained by SD dissolution strongly depends on the dissolution rate and the drug crystallization inhibition effect of polymers used in the SDs. Highly water-soluble polymers demonstrate high dissolution rates in an aqueous medium, while the hydrophobicity of polymers plays an important role in the crystallization inhibition of hydrophobic drugs from the drug-supersaturated solution (Ueda et al., 2014). On the other hand, SDs with polymers that exhibit poor water-solubility limit the dissolution of the drug despite the strong inhibitory effect of drug crystallization (Sun and Lee, 2013, 2015). The preparation methods of SDs (Mahmah et al., 2014; Sóti et al., 2015), the drug/polymer compositions (Chauhan et al., 2014; Konno et al., 2008), and the addition of other excipients such as polymers and surfactants (Chen et al., 2015; Ohyagi et al., 2017) have been investigated in order to obtain a drug-supersaturated solution with a high supersaturation level.

The aminoalkyl methacrylate copolymer, Eudragit® E (EUD-E), is basic because of its amino group and has been applied for taste-masking and enteric coating. Furthermore, it has attracted significant attention as a carrier polymer for SDs. EUD-E effectively stabilizes the amorphous state of drugs in their SD as well as the drug supersaturated solution formed after aqueous dispersion (Saal et al., 2017; Ueda et al., 2015). Reportedly, the in vivo absorption of poorly water-soluble drugs can be significantly enhanced because of the stable drug-supersaturated state with a high supersaturation level (Kojima et al., 2012). However, the drug solubility improvement by the EUD-E SD is limited only to the acidic condition because of the low solubility of EUD-E in neutral and basic solutions. Further improvement of the solubility of EUD-E at neutral pH is expected to enhance the absorption of drugs through the small intestinal membrane. Yoshida et al. (2012) achieved a high drug concentration in neutral pH solutions using EUD-E/hydrochloride as the SD carrier, which was prepared by spray-drying of the

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hydrochloride solution containing EUD-E. In a previous study, we succeeded in preparing a ternary SD in a single process where the excipient saccharin (SAC) was cryogenically ground with the drug and EUD-E. This ternary SD significantly improved the dissolution rate even in neutral solutions and the supersaturation level of probucol, which was used as a model poorly water-soluble drug (Higashi et al., 2016). These results were attributed to ionic interactions between the amino group of EUD-E and the amide group of SAC in the ternary SD (Higashi et al., 2016). The protonated EUD-E, which is the same molecular state of EUD-E in an acidic solution, contributed to the rapid dissolution of probucol/EUD-E/SAC SD in neutral solutions and the subsequent high supersaturation level of probucol. However, the enhancement mechanism of drug dissolution and supersaturation level was speculated simply based on the solid-state characterization. Therefore, an investigation of the molecular state of each component during and after the dissolution process in an aqueous medium is necessary to understand the mechanism of formation of drug-supersaturated solutions from the drug/EUD-E/SAC ternary SD.

Nuclear magnetic resonance (NMR) has been widely used to directly investigate the molecular states of samples, regardless of their state (i.e., either as a solution, suspension, or in the solid state) (Berendt et al., 2006; Hasegawa et al., 2015; Paudel et al., 2014). Intermolecular interactions in the drug/EUD-E and drug/EUD-E/SAC SDs have been evaluated by solid-state ^{13}C NMR including relaxation time measurements (Higashi et al., 2016; Kojima et al., 2012; Ueda et al., 2015). Solution-state ^{1}H NMR, including high-resolution magic-angle spinning have been also applied to detect the intermolecular interactions between the drug and EUD-E in the drug-supersaturated solution (Higashi et al., 2014; Kojima et al., 2012).

In this study, we evaluated the dissolution of the drug from the drug/EUD-E/SAC ternary SD and the molecular states in the obtained supersaturated solution. Phenytoin (PHT) was used as a model for poorly water-soluble drugs, as the solubility of probucol used in the previous study was too low to be analyzed. The effect of SAC addition on the dissolution of the drug/EUD-E SD was investigated to clarify the dissolution mechanism of the ternary SD in more detail. Both solution- and solid-state NMR measurements were obtained to investigate the molecular states of PHT, EUD-E, and SAC during the dissolution process and after the SD was dissolved in an aqueous medium. Finally, the mechanism of improvement in the dissolution of PHT and supersaturation level from the EUD-E SDs owing to the coexistence of SAC was discussed based on the revealed molecular states.

2. Materials and methods

2.1. Materials

PHT and SAC were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). EUD-E was generously supplied by Evonik Japan Co., Ltd. (Tokyo, Japan). The molecular structures and peak assignments of PHT, EUD-E, and SAC for NMR spectra are shown in Fig. 1.

2.2. Preparation of the SD

PHT, EUD-E, and SAC were mixed in weight ratios of PHT/EUD-E = 1:6, EUD-E/SAC = 6:2, and PHT/EUD-E/SAC = 1:6:2 in glass vials using a vortex mixer for 3 min to prepare the physical mixtures (PMs). Each PM (3 g) was ground using a vibrational rod mill (TI-500ET, CMT Co., Ltd., Fukushima, Japan) at −180 °C for 90 min to obtain the SDs, because the glass transition temperature of EUD-E is 52.6 °C (Qi et al., 2008). The grinding temperature was controlled by circulating liquid nitrogen around the milling cell. All SDs showed halo patterns in their powder X-ray diffraction spectra, confirming the amorphization of PHT and SAC in the SDs (Fig. S1).

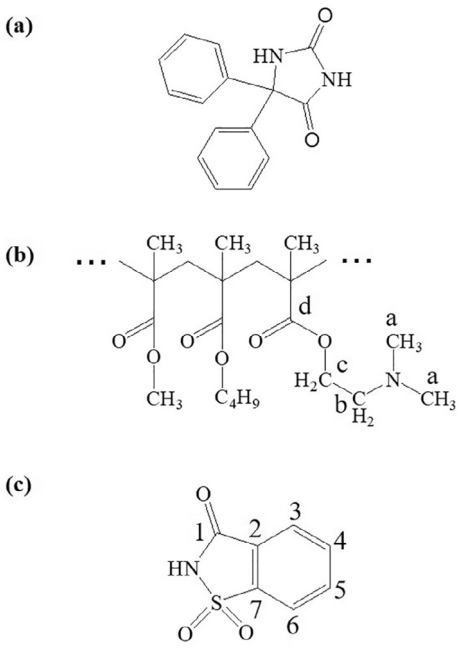

Fig. 1. Chemical structures of (a) phenytoin (PHT), (b) Eudragit® E PO (EUD-E), and (c) saccharin (SAC). The numbering in the EUD-E and SAC structures corresponds to the peak assignments in their NMR spectra.

2.3. Dissolution test

As the basic polymer EUD-E shows pH-dependent dissolution behavior, phosphate buffer (0.1 M, pH 6.8) was used as an aqueous medium to control the pH in all experiments unless specified otherwise. Dissolution tests were performed at 37.0 ± 0.5 °C using a NTR-VS6P (Toyama Sangyo, Osaka, Japan) apparatus with a paddle speed of 100 rpm. Each sample containing 28 mg of PHT (700 μg/mL) and 168 mg of EUD-E (4200 μg/mL) was dispersed either in 40 mL of a non-SAC solution or a SAC solution of 1400 μg/mL. The solution was sampled at defined time points and then filtered through a cellulose ester membrane (pore size, 0.45 μm). The same volume of the medium was replaced after each sampling. PHT concentration was determined by HPLC. In order to determine the EUD-E concentration, solution-state ^{1}H NMR spectra were taken. The sample solution was freeze-dried using a DRC-1100 freeze dryer (Tokyo Rikakikai Co., Ltd., Tokyo, Japan). The freeze-dried powder was then dissolved in hydrochloride solution (1.0 M) containing trimethylsilyl propionate (TSP) as an internal NMR reference. The concentration of EUD-E was determined from the area of the ^{1}H peak corresponding to the tertiary amino group of EUD-E against that of the TSP peak.

2.4. Evaluation of PHT crystallization inhibition in EUD-E solution

PHT (70 mg) was dissolved in 1 mL of dimethyl sulfoxide (DMSO). This solution was then added to the 4200 μg/mL EUD-E solution, 1400 μg/mL SAC solution, and 4200/1400 μg/mL EUD-E/SAC solution at a DMSO concentration of 1% (v/v). The mixed solutions were shaken in a water bath at 150 rpm and 37 °C. The solution was sampled at defined time intervals and then filtered through a cellulose ester membrane filter (pore size, 0.45 μm). The concentration of PHT in the filtrate was determined using HPLC.

2.5. Evaluation of EUD-E gel layer formation

200 mg of the EUD-E powder was put into a punch and a die (diameter: 10 mm), and compressed with 4 MPa for 30 s. The thickness of the compressed tablet was 2.7 mm. The tablet was then immersed either