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The effect of HPMCAS functional groups on drug crystallization from the supersaturated state and dissolution improvement

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ABSTRACT

The inhibitory effect on drug crystallization in aqueous solution was evaluated using various forms of hydroxypropyl methylcellulose acetate succinate (HPMCAS). HPMCAS suppressed crystallization of carbamazepine (CBZ), nifedipine (NIF), mefenamic acid, and dexamethasone. The inhibition of drug crystallization mainly derived from molecular level hydrophobic interactions between the drug and HPMCAS. HPMCAS with a lower succinoyl substituent ratio strongly suppressed drug crystallization. The inhibition of crystallization was affected by pH, with the CBZ crystallization being inhibited at a higher pH due to the hydrophilization of HPMCAS derived from succinoyl ionization. The molecular mobility of CBZ in an HPMCAS solution was evaluated by 1D-^{1}H NMR and relaxation time measurements. CBZ mobility was strongly suppressed in the HPMCAS solutions where strong inhibitory effects on CBZ crystallization were observed. The mobility suppression of CBZ in the HPMCAS solution was derived from intermolecular interactions between CBZ and HPMCAS leading to an inhibition of crystallization. The effect of HPMCAS on the drug dissolution rate was evaluated using an NIF/HPMCAS solid dispersion. The dissolution rate of NIF was increased when HPMCAS with a higher succinoyl substituent ratio was used.

1. Introduction

Most recently developed drug candidates are poorly water-soluble (Hauss, 2007; Lipinski, 2002). Poor solubility impedes the development of new drug candidates, and the formulation of such drugs requires improvement of drug solubility and an increased ability to be absorbed through the small intestine. Apparent drug solubility has been improved by drug encapsulation into complexes such as cyclodextrin (Higashi et al., 2009, 2010), micelles (Francis et al., 2003; Kawakami et al., 2006), and emulsions (Itoh et al., 2002). Encapsulation of a poorly water-soluble drug into the hydrophobic environment of a colloidal micelle enables the solubilization required to achieve higher concentrations in aqueous solution. Meanwhile, solubilization of a drug does not always lead to an improvement in drug permeation, because encapsulated drugs cannot permeate membranes (Miller et al., 2012; Ueda et al., 2012; Yano et al., 2010). On the other hand, supersaturated solutions of poorly water-soluble drugs have been reported to be efficient at improving drug permeation through the small intestine (Brouwers et al., 2009, 2007; Mellaerts et al., 2008). Supersaturated drug solutions can be prepared by dissolving amorphous or salt forms of the drug (Brouwers et al., 2007; Gupta et al., 2004; Hancock and Parks, 2000).

The supersaturated state is metastable and a drug can be easily crystallized from such a solution. Thus, a drug crystallization inhibitor is required to maintain a supersaturated state. Ideally, the inhibitor would not suppress drug diffusion in the aqueous solution, such as that achieved by cyclodextrin, micelles, and emulsions. It has been reported that drug crystallization from supersaturated solutions could be inhibited by polyvinylpyrrolidone (PVP) (Abu-Diak et al., 2011; Konno et al., 2008), methacrylate copolymers (Eudragit®) (Abu-Diak et al., 2011; Jung et al., 1999), hydroxypropyl methylcellulose (HPMC) (Konno et al., 2008), and hydroxypropyl methylcellulose acetate succinate (HPMCAS) (Friesen et al., 2008; Konno et al., 2008; Tanno et al., 2004). Supersaturated solutions stabilized by these polymers have been reported to be effective at improving drug permeation through a model of the small intestine (Miller et al., 2012; Ueda et al., 2012).

Solid dispersion is one of the formulations used to prepare supersaturated solutions of poorly water-soluble drugs. An amorphous drug could be easily crystallized in the solid state (depending on temperature, humidity, or water adsorption) because of the higher energy of the amorphous state relative to that of the crystalline state (Gupta et al., 2004; Hancock and Parks, 2000). In a solid dispersion, drug molecules are dispersed into a polymer matrix and prevented from crystallizing. It was reported that the crystallization from solid dispersion with PVP, HPMC, or HPMCAS could be strongly inhibited in high humidity conditions or in the dissolution medium (Alonzo et al., 2010; Crowley and Zografi, 2003; Konno and Taylor, 2008).

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Table 1
Substituent ratios of HPMCAS and HPMC (average number/glucose ring unit).

Polymer	—CH_3	—$CH_2CH(CH_3)OH$	—$COCH_3$	—$COCH_2CH_2COOH$
AS-LF	1.87	0.25	0.48	0.37
AS-MF	1.88	0.24	0.52	0.26
AS-HF	1.89	0.25	0.67	0.18
AS-1	1.87	0.24	0.70	0.10
AS-2	1.46	0.25	0.54	0.70
AS-3	1.41	0.25	0.57	0.35
AS-4	1.43	0.25	0.73	0.47
AS-5	1.43	0.25	0.84	0.24
HPMC	1.90	0.25	–	–

The methods used to prepare solid dispersions could affect the molecular state and dissolution characteristics of a drug (Sugimoto et al., 1998; Won et al., 2005). In addition, a suitable choice of polymer is essential for solid dispersion. Polymer that can improve drug dissolution and the subsequent permeation should be chosen based on the properties of both the solution and the solid states. Drug crystallization from the supersaturated solution should be efficiently suppressed in the presence of the polymer. Polymer structure, especially the functional groups, has been reported to affect the preservation of the supersaturated state (Ilevbare et al., 2012).

In this article, we focused on substituent groups of HPMCAS. HPMCAS is a derivative of HPMC and has a strong inhibitory effect on crystallization (Konno et al., 2008; Tanno et al., 2004). A spray-dried solid dispersion with HPMCAS achieved higher drug concentrations for prolonged periods (Curatolo et al., 2009; Friesen et al., 2008). Since the HPMCAS-induced improvement in drug concentration was not derived from solubilization, but rather from a strong inhibition of drug crystallization, a solid dispersion with HPMCAS could improve the dissolution properties and subsequent Caco-2 permeation of poorly water-soluble drugs (Ueda et al., 2012). In this study, the effect of HPMCAS substituent level on inhibition of crystallization and improvement of drug dissolution was evaluated. The relationship between the substituent ratio of HPMCAS and the inhibitory effect of drug crystallization was discussed. The molecular states of poorly water-soluble drugs in HPMCAS solutions of varying substituent levels were evaluated by NMR measurements. Finally, the relationship between the inhibition of drug crystallization and the dissolution rate of poorly water-soluble drugs from solid dispersion was discussed in terms of substituent level of HPMCAS.

2. Materials and methods

2.1. Materials

HPMC and HPMCAS (Shin-Etsu AQOAT®) were kindly donated by Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan). AS-LF, MF, and HF are commercially available grades of HPMCAS. Non-commercial grades that have various substitution levels (AS-1, AS-2, AS-3, AS-4, and AS-5) were specially synthesized by Shin-Etsu Chemical Co. Ltd. Carbamazepine (CBZ) was purchased from Tokyo Chemical Industry (Tokyo, Japan). Nifedipine (NIF), mefenamic acid (MFA), and dexamethasone (DEX) were purchased from Wako Chemicals Co. (Tokyo, Japan). All materials were reagent grade. Chemical structures of HPMC, HPMCAS, CBZ, NIF, MFA, and DEX are represented in Fig. 1. Table 1 shows the molar ratio of substituents in HPMC and HPMCAS. The average molecular weight of HPMC and HPMCAS ranged from 15,000 to 24,000.

2.2. Evaluation of drug concentration in polymer solution

Each drug (100 mg) was dissolved in 1 mL of dimethyl sulfoxide (DMSO). The DMSO solution was added to each polymer solution

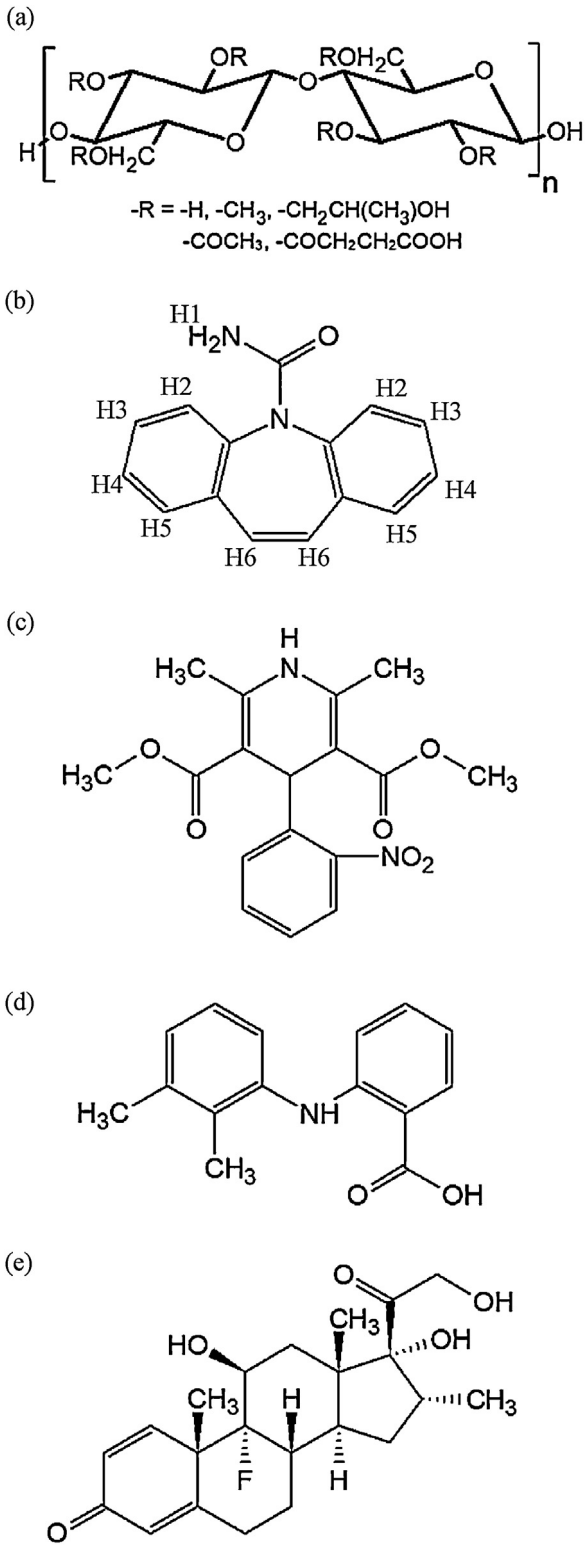

Fig. 1. Chemical structures of (a) HPMCAS, (b) CBZ, (c) NIF, (d) MFA, and (e) DEX. Proton numbering of CBZ represents the peak assignment in ^{1}H NMR spectra.

(0.05 M phosphate buffer, pH 5.6–8.0) at a DMSO concentration of 2% (v/v) for CBZ, 0.5% (v/v) for NIF, 1% (v/v) for MFA, and 1% (v/v) for DEX. Concentrations of HPMC and HPMCAS were 3 mM and 12 mM, defined as the concentration of glucose units in the polymer chain. The sample solutions were shaken in a 37.0 °C water bath at 150 rpm. The solutions were filtered through a cellulose ester membrane filter (0.45 μm) after a 1-day incubation. The concentration