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Aminoalkyl methacrylate copolymers for improving the solubility of tacrolimus. I: Evaluation of solid dispersion formulations

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ABSTRACT

The aim of this study was to investigate the effect of Eudragit E®/HCl (E-SD) on the reprecipitation of a poorly water-soluble drug, tacrolimus. To evaluate the inhibition of reprecipitation of E-SD, reprecipitation studies on tacrolimus were conducted using a dissolution test method. Solubility of tacrolimus was measured at regular intervals in a dissolution media, in which tacrolimus was dissolved in ethanol, and the test media contained additives for inhibiting precipitation. Supersaturation profiles of tacrolimus were observed, and were maintained for 24 h only with E-SD. Solid dispersion formulations of tacrolimus prepared with hydroxypropylmethylcellulose (HPMC) or E-SD in different drug/carrier ratios were also investigated. Solid dispersions prepared with E-SD showed higher solubility of tacrolimus compared with that of HPMC. In the E-SD formulation, the drug solubility influences to drug/carrier ratio. The formulation of drug/E-SD (1/5) showed the highest drug solubility. Thus, it may be inferred that a definite drug/carrier ratio exists to increase drug solubility. Further, by mixing E-SD the solid dispersion prepared with HPMC showed enhanced drug solubility.

1. Introduction

Poorly water-soluble drugs, especially Biopharmaceutics Classification System (BCS) Class II substances, show poor *in vivo* absorption due to low solubility in gastrointestinal fluids (Amidon et al., 1995; Lobenberg and Amidon, 2000). In recent years, several solubilizing technologies have been developed to improve the bioavailability of poorly water-soluble drugs (Brouwers et al., 2009). In the field of pharmaceuticals, solid dispersion technology is one of the most common technologies for temporarily increasing drug solubility in gastrointestinal fluids, leading to an improvement in absorption and bioavailability of drugs with low aqueous solubility (Leuner and Dressman, 2000).

Tacrolimus (available as PROGRAF®) is a well-known immunosuppressive agent and a poorly water-soluble drug. Therefore, solid dispersion formulations prepared with hydroxypropylmethylcellulose (HPMC) as a carrier have been adopted to improve *in vivo* drug absorption (Kagayama et al., 1993; Yamashita et al., 2003). HPMC is a commonly used solid dispersion carrier because of its effects on both crystal growth inhibition and prolongation of supersaturated conditions (Gao and Morozowich, 2006).

Though promising, HPMC as a solid dispersion carrier does not always offer optimum solubility to some poorly water-soluble drugs (Brouwers et al., 2009). Supersaturation of solid dispersion formulations in gastrointestinal fluids gradually decreases over time because of reprecipitation of these drugs. Therefore, to improve the solubility of such poorly water-soluble drugs, several studies have been conducted to develop strategies to enhance their dissolution and oral absorption.

The method of preparation of solid dispersion formulations of tacrolimus plays an important role in the solubility and crystallinity of tacrolimus (Joe et al., 2010). Janssens et al. (2010) reported that preparation methods of solid dispersions influenced the degree of supersaturation of drugs. They also investigated the effect of the manufacturing method of solid dispersion formulations on the solubility and miscibility of crystalline drugs and drugs in amorphous polymers, respectively.

A conventional approach to enhance the degree of supersaturation of a drug is to conduct formulation studies such as screening of polymer carriers and using combinations of the drug with a surfactant (Valizadeh et al., 2004; Ghebremeskel et al., 2007; Overhoff et al., 2008; Goddeeris et al., 2008; Janssens et al., 2008; Shinde et al., 2008). Drug/polymer carrier rational formulation study is also conducted to achieve reduction of size and immediate

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disintegration of formulation (capsule or tablet). HPMC acetate succinate (HPMC-AS) inhibits the reprecipitation of poorly water-soluble drugs (Babcock et al., 2003), and solid dispersion formulations prepared with HPMC-AS maintain the supersaturation in the gastrointestinal fluid (Babcock et al., 2003; Curatolo et al., 2009). Therefore, HPMC-AS has been used as a solid dispersion carrier for several poorly water-soluble drugs (Tanno et al., 2004; Nakamichi et al., 2004; Kennedy et al., 2008; Jachowicz and Czech, 2008; Al-Obaidi and Buckto, 2009). Although HPMC-AS induces higher solubility of drugs than solid dispersions prepared with HPMC, HPMC-AS, a well known enteric coating polymer, does not dissolve in acidic media. The improvement in solubility of solid dispersions prepared with HPMC-AS might be limited in natural or basic dissolution media. Our research group, screened excipients for maintaining supersaturation of poorly water-soluble drugs.

We recently found that aminoalkyl methacrylate copolymer E (Eudragit E®) in neutral pH conditions markedly inhibited reprecipitation. In this study, to evaluate the effect of Eudragit E® on the inhibition of reprecipitation of poorly water-soluble drug, a reprecipitation test using dissolution test methods was conducted with tacrolimus. Tacrolimus was chosen as a model compound of poorly water-soluble drug. Further, solid dispersion formulations of tacrolimus were prepared by a conventional solvent evaporation method. Effect of composition parameters on the solubility of tacrolimus was also investigated in terms of drug/polymer ratio and polymer type.

2. Materials and methods

2.1. Materials

Aminoalkyl methacrylate copolymer (Eudragit® E) was kindly provided by Degussa Co. Inc. (Japan). HPMC (TC-5E) was purchased from Shin-Etsu Co. Inc. (Japan). Tacrolimus and its formulation, Prograf® were provided by Astellas Pharma Inc. (Tokyo, Japan). Hydrochloric acid was purchased from Kanto Chemical (Japan).

2.2. Preparation of Eudragit® E/HCl

Five hundred grams of Eudragit® E, 367.5 g of 10% (w/v) of hydrochloric acid, and 2632.5 g of distilled water were mixed; the mixture was stirred until Eudragit® E was completely dissolved. The resulting solution was lyophilized or spray-dried (spraying volume, 30 g/min; inlet temperature, 145 °C; rotation rate, atomizer at 20,000 ± 500 rpm) using a spray-dryer (L-8; Ohkawara Kakohki Co. Ltd.). Eudragit® E/HCl (abbreviated to E-SD) was obtained as a powder.

2.3. Reprecipitation study

Reprecipitation studies were performed by a co-solvent method in accordance with dissolution test method 2 (paddle method), as described in the Japanese Pharmacopeia (15th edition), using an automatic 6-series dissolution testing device (Toyama Sangyo Co. Ltd., Japan). Three hundred milligrams of additive (HPMC or E-SD) was dissolved in 300 mL of test fluid. To each vessel was added 1 mL of tacrolimus solution (100 mg/mL) in ethanol. The dissolution test medium was maintained at 37 ± 0.2 °C and a paddle speed of 50 rpm throughout the testing period. Samples were taken at regular intervals and centrifuged at 3000 rpm for 15 min. Tacrolimus dissolved in each sample was measured by HPLC (NUCLEOSIL 100-5C8, 4.6 × 150 mm; GL Sciences Inc., Japan). The mobile phase consisted of water, acetonitrile, methanol, and phosphoric acid (460/360/180/1). The column temperature was set at 50 °C, and the flow rate was maintained at 0.45 mL/min. The detection wavelength was 210 nm.

2.4. Preparation of solid dispersion formulation

Tacrolimus was dissolved in ethanol to prepare a 50 mg/mL tacrolimus solution. To this solution was added an adequate amount of a 50 mg/mL of E-SD or HPMC methanol/dichloromethane (1/1) solution. This mixture was transferred to an agate mortar and well kneaded with an agate pestle at room temperature until the solvent was evaporated.

2.5. Powder X-ray diffraction (XRD) measurement

XRD measurement was performed on a powder X-ray diffractometer (Multiflex; Rigaku, Tokyo) using nickel-filtered Cu Kα radiation (acceleration voltage, 40 kV; current, 40 mA). The scanning rate was 4°/min over a 2θ range of 2.5–40° with a sampling interval of 0.02°.

2.6. Differential scanning calorimetry (DSC) measurement

DSC measurements were performed using a DSC instrument (DSC 8230; Rigaku, Tokyo). Ten milligrams of each sample was put into an aluminum pan. The heating rate was at 10 °C/min, and the temperature range was 30–200 °C.

2.7. Measurement of solubility of the solid dispersion formulations

Each solid dispersion of tacrolimus was added to JP 2nd solution (pH 6.8, 12.5 mM KH_2PO_4, 12.5 mM Na_2HPO_4), and stirred using a Vortex mixer. Samples were taken at predetermined time intervals and centrifuged at 3000 rpm for 15 min. The concentration of tacrolimus in each supernatant was measured by HPLC as described in Section 2.3.

2.8. Measurement of particle size distribution

Mean diameter of solid dispersion formulations in JP 2nd solution was measured using photon correlation spectroscopy (Zetasizer 3000HS; Malvern Instruments, Malvern, the United Kingdom). Each solid dispersion of tacrolimus was added to JP 2nd solution (pH 6.8, 12.5 mM KH_2PO_4, 12.5 mM Na_2HPO_4), and stirred using a Vortex mixer. Concentration of tacrolimus in feed was set at 1500 μg/mL.

3. Results and discussion

3.1. Reprecipitation study

To evaluate the effect of E-SD on the inhibition of reprecipitation of tacrolimus, reprecipitation studies were carried out by the co-solvent method (Fig. 1). HPMC was chosen as a control because HPMC is commonly used as a solid dispersion carrier for drugs with low solubility.

Tacrolimus was immediately reprecipitated in the test media in which the no additive was mixed. However, the solubility of tacrolimus was 100% in JP 2nd solution and it was maintained for more than 24 h in E-SD. In the HPMC control, only 20% of tacrolimus was dissolved in the same solution. Therefore, E-SD maintained high solubility of tacrolimus. The solubility of tacrolimus in JP 2nd solution was higher than that in other tested media. Inhibition of reprecipitation by E-SD was influenced by the pH and ionic strength of dissolution test media.

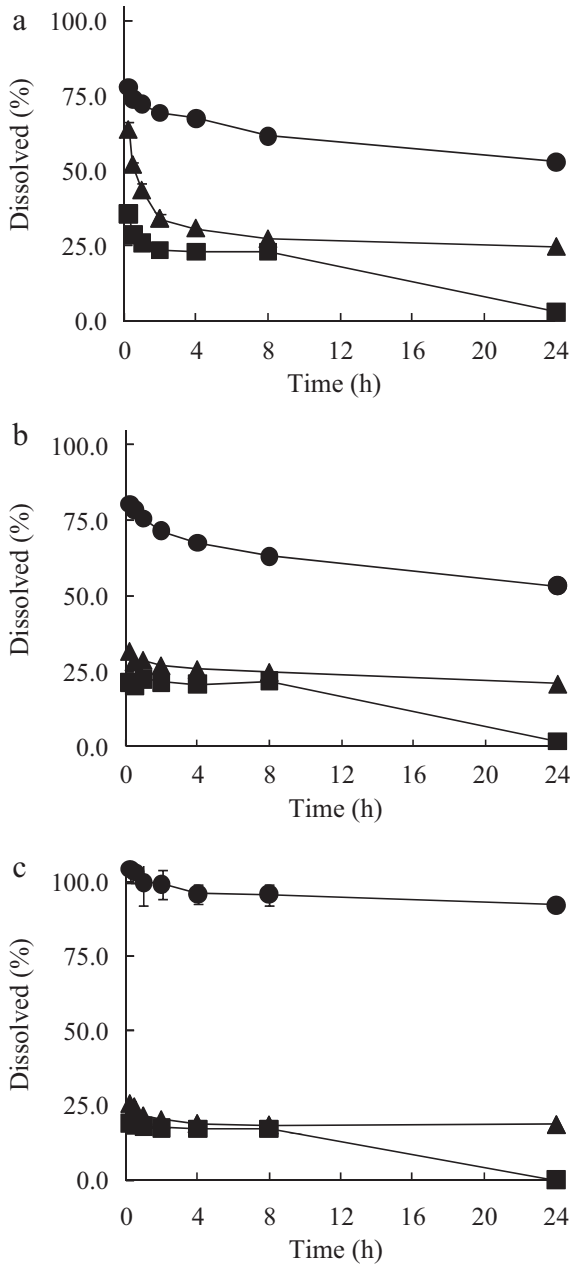

Fig. 1. Reprecipitation profiles of tacrolimus in different test solutions. (a) Water, (b) JP 1st, (c) JP 2nd, (■) no additives, (▲) HPMC, (●) E-SD. Data represent mean and SD ($n = 3$).

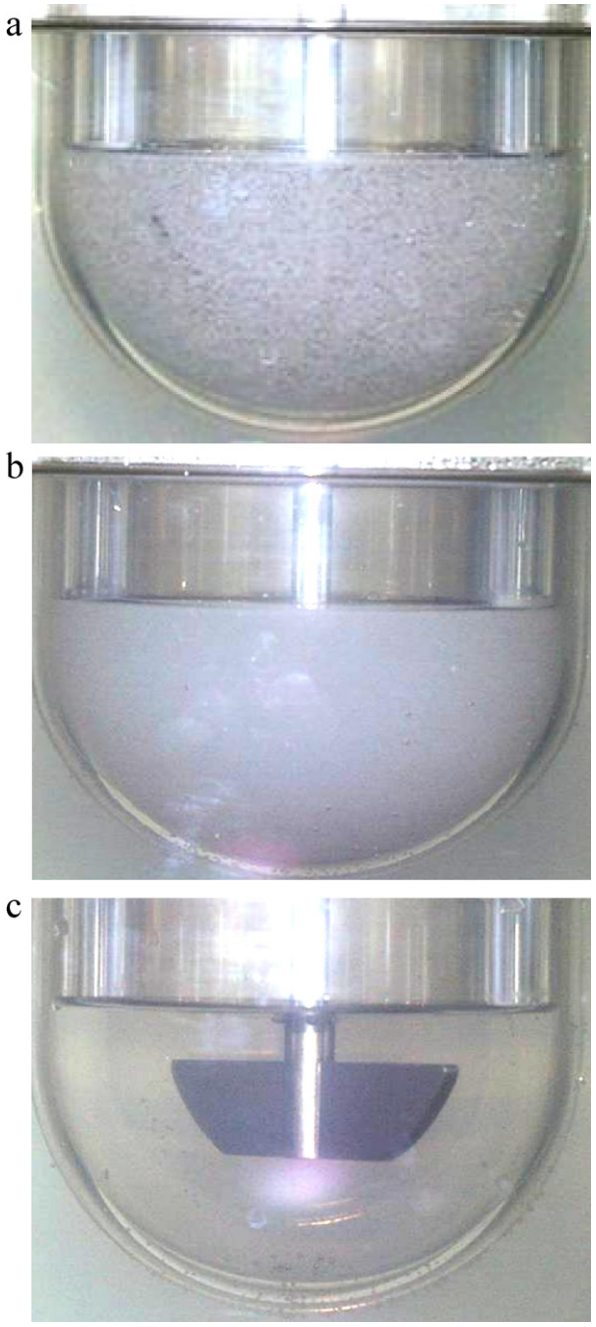

Fig. 2. Representative photographs of dispersion states of tacrolimus in each test solution at 0.25 h. (a) No additive, (b) HPMC, (c) E-SD.

In general, solid dispersion carriers inhibit both the drug nucleation and crystal growth processes because of drug–carrier interactions such as hydrogen bonding and hydrophobic interaction (Al-Obaidi and Buckto, 2009; Valizadeh et al., 2007; Huang et al., 2008; Janssens and Mooter, 2009). Hydrophobic interactions between the drug and E-SD may play an important role in the inhibition of reprecipitation of drug. E-SD is a partially neutralized cationic polymer; thus, the hydrophilic–hydrophobic balance of E-SD in the test solution could be influenced by pH and ionic strength. Therefore, inhibition of the reprecipitation of E-SD may be influenced by the test media conditions.

Fig. 2 shows the dispersion states in JP 2nd solution at 0.25 h after initiation of reprecipitation studies. Tacrolimus was reprecipitated as visible granules in the absence of additive. In the HPMC control, the test media was opalescent in appearance, and visible granules were precipitated with time. On the other hand, in E-SD additive conditions, the test media was clear, with no visible granules observed during test intervals. E-SD thus shows superior inhibition of reprecipitation compared to that of HPMC.

3.2. Preparation of solid dispersion formulations

To investigate the effect of the carrier type and drug/carrier ratio on the improvement of solubility of tacrolimus, solid dispersion formulations were prepared by conventional solvent evaporation methods. All formulations were obtained as powders.

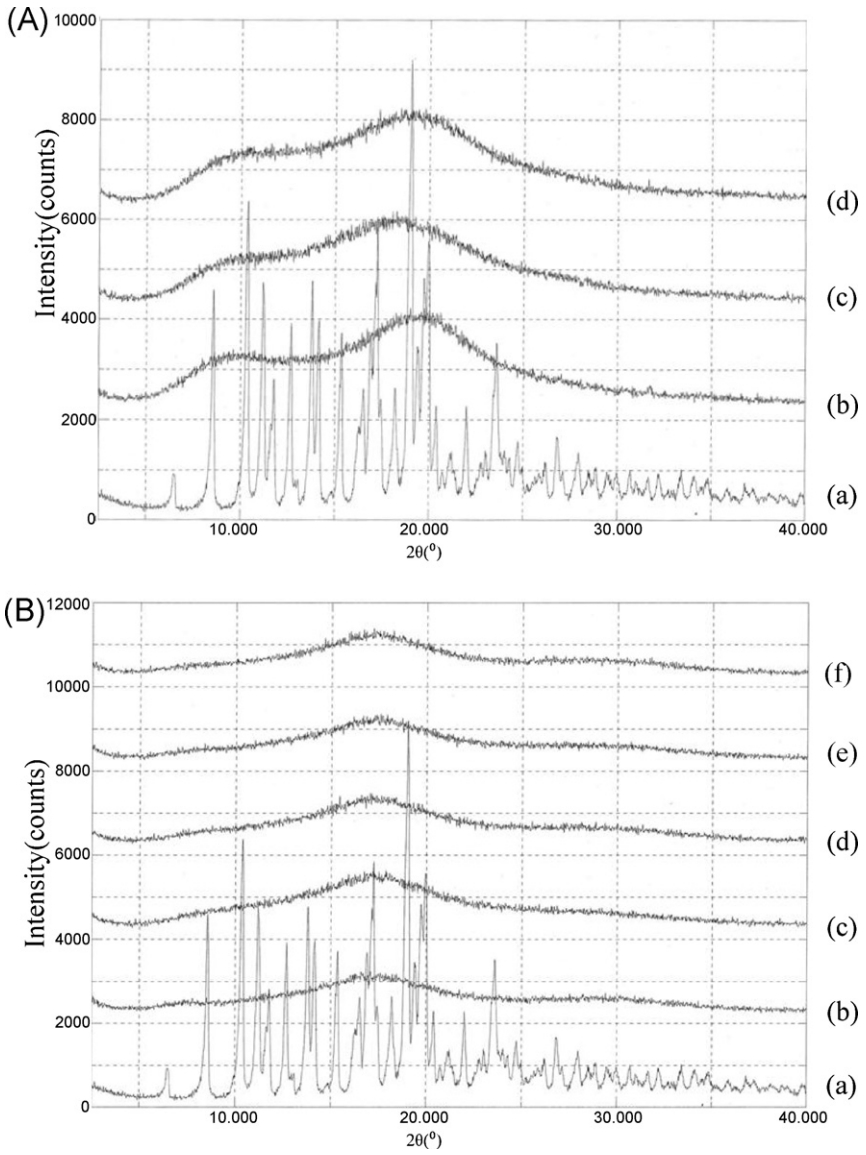

Fig. 3. XRD patterns for solid dispersion formulations of tacrolimus with HPMC (A) and E-SD (B). (a) Tacrolimus crystalline powder; (b) carrier; (c)–(f) solid dispersion formulation with different drug/carrier ratios: (c) 1/1; (d) 1/3; (e) 1/5; and (f) 1/10.

Physicochemical properties of the solid dispersion formulations were evaluated by XRD and DSC studies.

Fig. 3 shows the XRD diffraction patterns of the samples. Crystalline tacrolimus showed diffraction peaks. On the other hand, all solid dispersion formulations showed hollow patterns, and diffraction peaks related to crystalline tacrolimus were not observed. Next, crystalline tacrolimus exhibited an endothermic peak at around 130 °C, corresponding to melting of tacrolimus (Fig. 4). The solid dispersion formulations displayed only broad featureless peaks. These results obtained from XRD and DSC measurements suggest that tacrolimus exists in an amorphous state in all formulations regardless of the carrier type and drug/carrier ratio.

3.3. Solubility of solid dispersions

To investigate the improvement in solubility of tacrolimus, related to the effect of inhibition of reprecipitation by E-SD, the solubility of solid dispersion formulations was examined. Fig. 5(a) shows the results of solubility of solid dispersion formulations. Tacrolimus dissolved completely in the solid dispersion formulation at a concentration of 333 μg/mL. This concentration used was identical to that used in the reprecipitation study.

In the HPMC formulations, the drug/carrier ratio did not affect the solubility of tacrolimus. In both tacrolimus/HPMC (1/1 and 1/3) formulations, the solubility of tacrolimus was between 70 and 85 μg/mL. On the other hand, the solubility of tacrolimus in E-SD formulations drastically increased with an increase in the amount of E-SD. In the tacrolimus/E-SD (1/3) formulation, almost 100% of tacrolimus dissolved, and the solubility was maintained for more than 6 h.

To evaluate the effect of E-SD on the improvement in solubility of tacrolimus, additional studies were conducted at tacrolimus concentrations of 1500 and 5000 μg/mL, respectively.

Fig. 5(b) shows the solubility of tacrolimus at 1500 μg/mL. The solubility of tacrolimus in the HPMC control was similar to that at 333 μg/mL. Thus, no improvement in solubility was observed

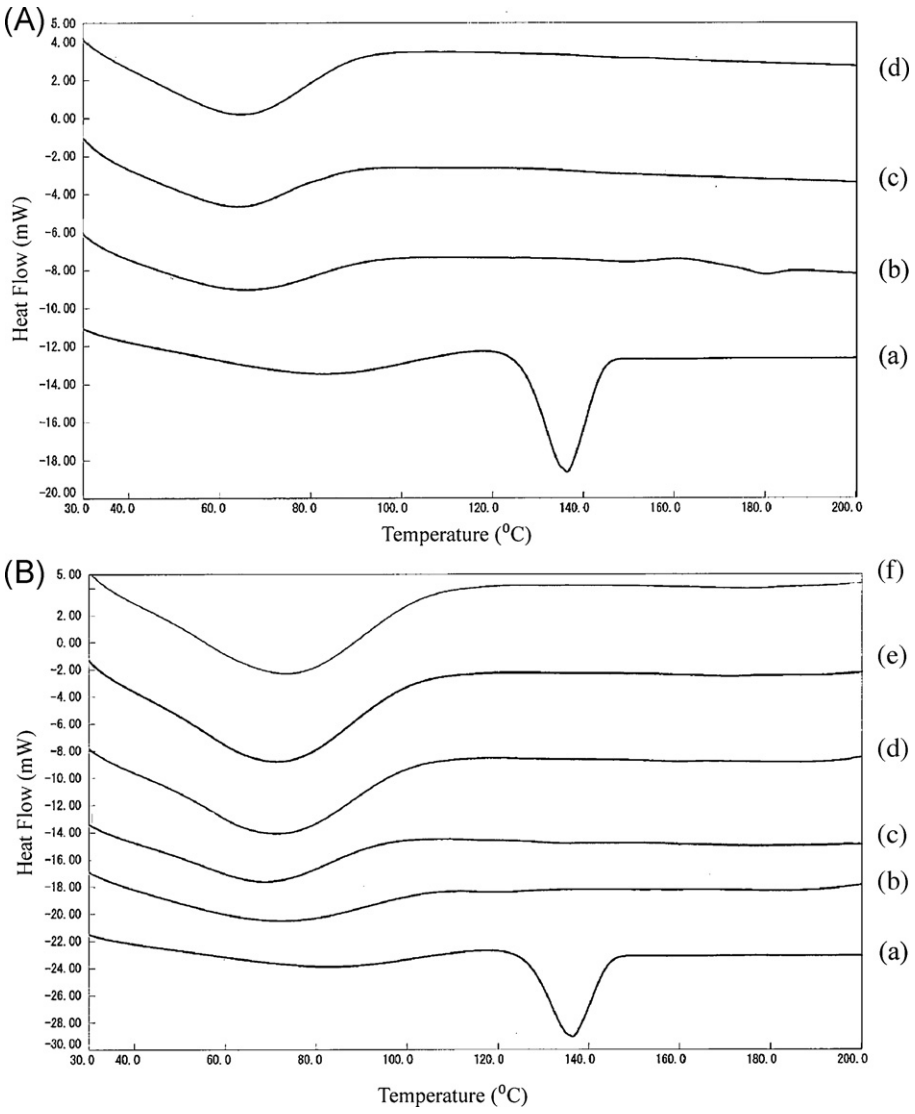

Fig. 4. DSC thermograms of the solid dispersion formulations of tacrolimus with HPMC (A) and E-SD (B). (a) Tacrolimus crystalline powder; (b) carrier; (c)–(f) solid dispersion formulation with different drug/carrier ratios: (c) 1/1; (d) 1/3; (e) 1/5; and (f) 1/10.

in the HPMC control at higher concentrations of tacrolimus. However, the solubility of tacrolimus increased in E-SD formulations. At 0.25 h, the solubility of tacrolimus/E-SD (1/3) and tacrolimus/E-SD (1/5) was 1205 μg/mL and 1466 μg/mL, respectively. However, the solubility of tacrolimus decreased to 611 μg/mL in the 1/10 formulation. The solubility of tacrolimus gradually decreased in all drug/carrier ratios with time. To investigate the soluble state of tacrolimus in JP 2nd solution, dynamic light scattering measurement was performed for tacrolimus/E-SD formulations. Table 1 summarized the mean particle size of each formulation in JP 2nd solution at 0.25 h. With increasing E-SD adding ratio, particle size was dramatically decreased. Compared with HPMC control, E-SD formulations showed smaller particle size distribution. Because of the small particle size in test media, E-SD formulations showed clear appearance in test media. This result suggests that the E-SD formulations form micelle-like structure to enhance poorly water-soluble drugs like tacrolimus, and the mechanism underlying the enhancement of solubility may be different from HPMC case.

Table 1
Particle size distribution of solid dispersion formulations in JP 2nd solution.

Formulation	Intensity average (nm)			
	Area (%)	Mean (nm)	Width (nm)	Average (nm)
Drug/HPMC = 1/3	100.0	1126.6	1670.4	1126.6
Drug/E-SD = 1/3	99.8	369.8	413.6	369.1
Drug/E-SD = 1/5	58.7	25.3	24.9	59.6
	41.3	106.4	130.1	
Drug/E-SD = 1/10	85.3	10.5	10.2	38.4
	14.7	201.0	86.1	

Finally, Fig. 5(c) shows the solubility of tacrolimus at a concentration of 5000 μg/mL. The solubility of the tacrolimus/E-SD (1/5) formulation was almost 100%. However, the 1/10 formulation showed lower solubility. These results suggest that E-SD has the ability to improve the solubility of tacrolimus when an appropriate drug/carrier ratio is used.

3.4. Effect of addition of E-SD to the tacrolimus-HPMC solid dispersion formulation on tacrolimus solubility

In the previous section, it was clarified that E-SD enhanced the solubility of tacrolimus as a solid dispersion carrier. In this

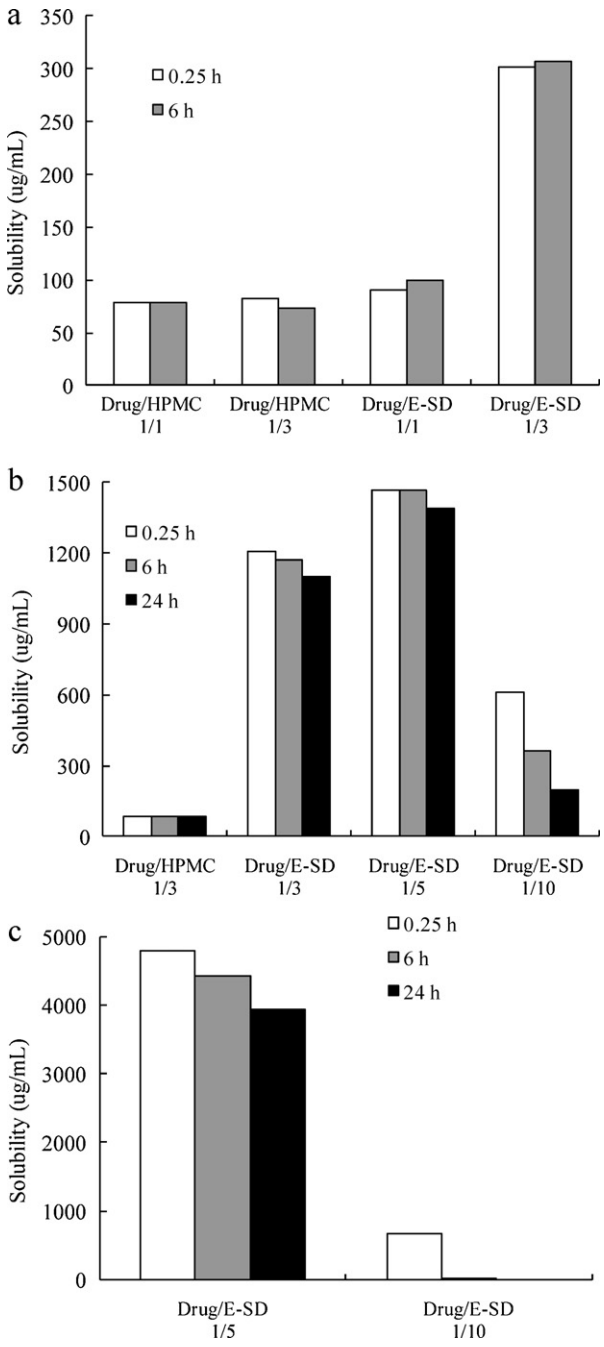

Fig. 5. Solubility of tacrolimus with different concentration conditions: (a) 333 μg/mL, (b) 1500 μg/mL and (c) 5000 μg/mL.

section, we investigated the effect of solubility enhancement by adding E-SD to the tacrolimus/HPMC solid dispersion formulation. In this study, tacrolimus was used at concentrations of 300 and 1500 μg/mL.

Figs. 6 and 7 show the results of the observations and solubility at 300 μg/mL. The tacrolimus/HPMC/E-SD (1/3/1) formulation was slightly turbid in appearance. With an increase in the E-SD adding ratio, solutions became clear, and approximately 80% of tacrolimus was dissolved and maintained for more than 6 h.

Figs. 8 and 9 show the results at 1500 μg/mL of tacrolimus used. At 0.25 h, the clarity of solution increased with an increase in the E-SD additive ratio. On the other hand, in the tacrolimus/HPMC/E-SD

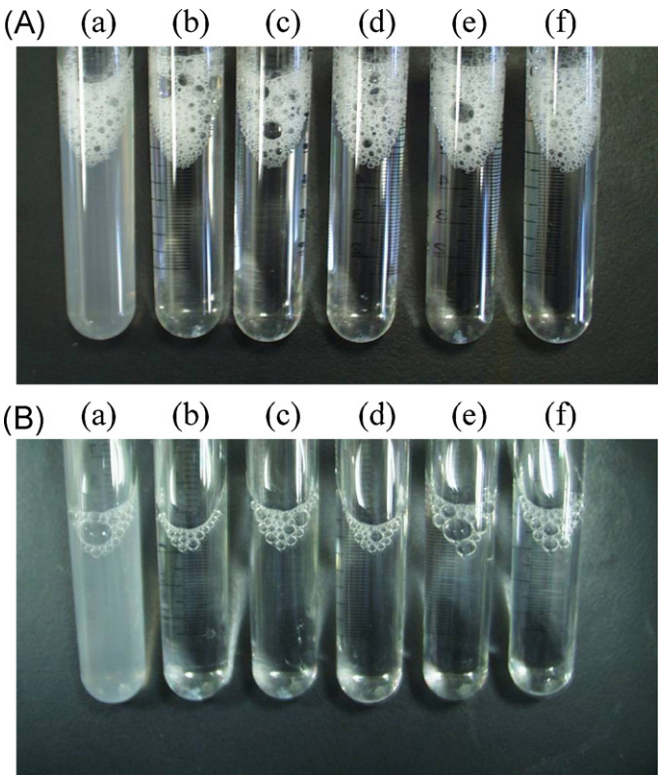

Fig. 6. Representative photographs of dispersion states of tacrolimus. 300 μg/mL at (A) 0.25 h and (B) 24 h. Drug/HPMC/E-SD ratios: (a) 1/3/1; (b) 1/3/3; (c) 1/3/5; (d) 1/3/7; (e) 1/3/9; (f) 1/3/10.

(1/3/9 and 1/3/10) formulations, solutions became turbid at 24 h, and solubility became decreased with time. A similar trend was observed in the solubility of tacrolimus with an increase in the E-SD content. The solubility of tacrolimus increased to approximately 80%.

These results suggest that the addition of E-SD to tacrolimus/HPMC solid dispersion formulations improves the solubility of tacrolimus. A definite E-SD additive ratio also exists to increase tacrolimus solubility.

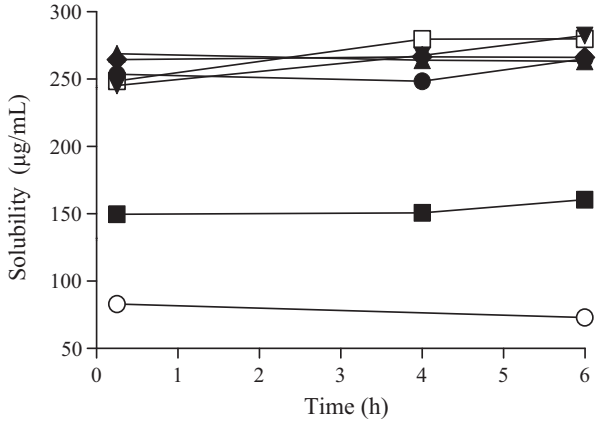

Fig. 7. Solubility of tacrolimus with different E-SD mixing conditions at 300 μg/mL (○) Drug/HPMC/E-SD = 1/3/0, (■) Drug/HPMC/E-SD = 1/3/1, (▲) Drug/HPMC/E-SD = 1/3/3, (●) Drug/HPMC/E-SD = 1/3/5 (♦) Drug/HPMC/E-SD = 1/3/7, (▼) Drug/HPMC/E-SD = 1/3/9, (□) Drug/HPMC/E-SD = 1/3/10.

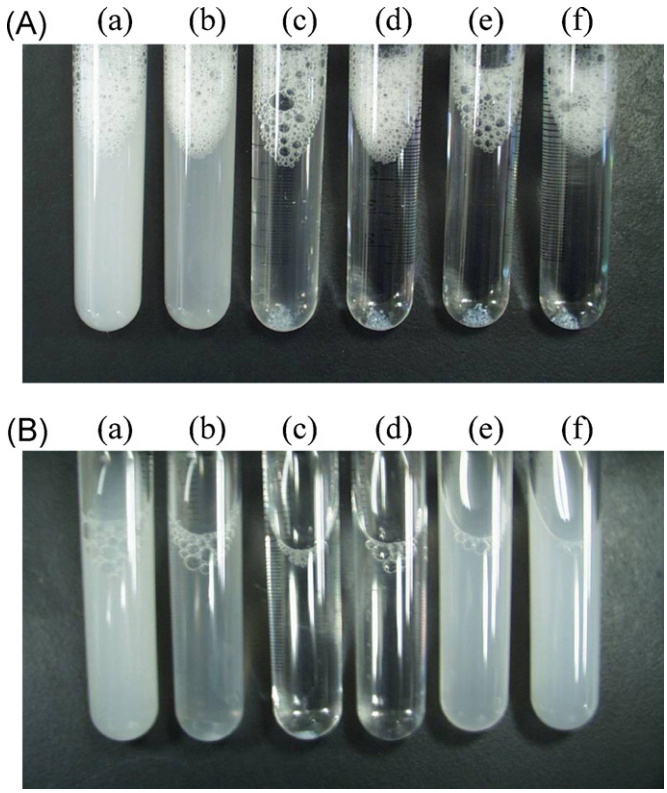

Fig. 8. Representative photographs of dispersion states of tacrolimus. 1500 μg/mL at (A) 0.25 h and (B) 24 h. Drug/HPMC/E-SD ratios: (a) 1/3/1; (b) 1/3/3; (c) 1/3/5; (d) 1/3/7; (e) 1/3/9; (f) 1/3/10.

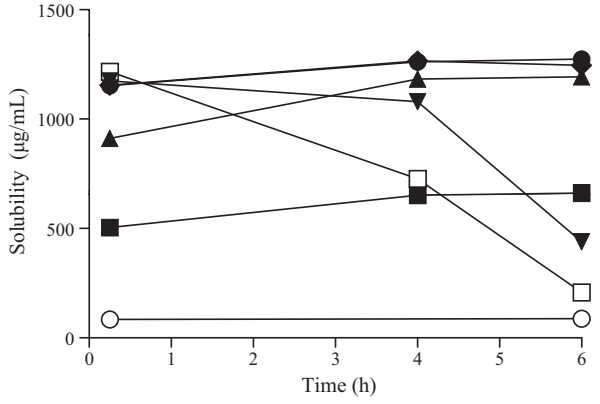

Fig. 9. Solubility of tacrolimus with different E-SD mixing conditions at 1500 μg/mL (○) Drug/HPMC/E-SD = 1/3/0, (■) Drug/HPMC/E-SD = 1/3/1, (▲) Drug/HPMC/E-SD = 1/3/3, (●) Drug/HPMC/E-SD = 1/3/5, (♦) Drug/HPMC/E-SD = 1/3/7, (▼) Drug/HPMC/E-SD = 1/3/9, (□) Drug/HPMC/E-SD = 1/3/10.

4. Conclusion

E-SD inhibited reprecipitation of tacrolimus in several dissolution test fluids. Ionic strength and pH influenced the degree of supersaturation of tacrolimus. Solid dispersion formulations of tacrolimus were prepared with several drug/E-SD ratios, and it was observed that tacrolimus existed in the amorphous state in all formulations. In the drug/E-SD (1/5) formulation, the highest degree of supersaturation of tacrolimus was maintained for a prolonged time. An optimum drug/carrier ratio has to be maintained for this increase. The degree of supersaturation of E-SD was affected physicochemical properties of dissolution test media (ionic strength, pH) and polymer concentration. Also solid dispersion formulation of E-SD existed as very small particles. These characters were similar to polymer micelles. It is speculated that the solubilizing mechanism of E-SD is like a polymer micelle formulations. Now the solubilizing mechanism of E-SD has been investigating. In this research it was shown that E-SD has possibility to increase solubility of poorly water soluble API.

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