An aminoalkyl methacrylate copolymer, Eudragit® E (EUD-E), has gained tremendous attention as a solid dispersion carrier because it efficiently stabilizes drugs in the amorphous state. Furthermore, EUD-E remarkably enhances drug dissolution in water. This review focuses on the interaction between drugs and EUD-E in solution, which contributes to the enhancement of drug concentration. Studies examining interactions between acidic drugs and EUD-E in organic solvents have revealed that the interaction occurs predominantly by electrostatic interaction, including hydrogen bonding and dipolar interactions. Other studies on interactions in aqueous solution found evidence for strong electrostatic interactions between acidic drugs and EUD-E in ion exchange experiments. 1H-NMR studies using high-resolution magic-angle spinning, nuclear Overhauser effect spectroscopy, diffusion, and relaxation time measurements successfully identified the interaction site and strength in aqueous solution. Hydrophobic and ionic interactions occurred between drugs and EUD-E. The conformation of EUD-E, which was affected by the ionic strength and pH of the aqueous media, also influenced the interaction. The knowledge discussed in this review will be helpful in designing solid dispersion formulations with EUD-E, which will efficiently enhance drug concentration and subsequent absorption into the body.

Key words  solubility; supersaturated solution; solid dispersion; ionic interaction; hydrophobic interaction; polymer conformation

1. Introduction
Most current drug candidates are poorly water-soluble. 1) Technologies to enhance drug concentration in water are desired in order to achieve adequate plasma concentrations of the drug after absorption into the body. Several techniques to enhance drug absorption and bioavailability from solid dosage forms have been developed, including polymorph, 2) co-crystal/salt, 3) cyclodextrin inclusion complex, 4) and nanoparticles. 5) Solid dispersion is also a promising technology for improving drug concentration in water. 6) Many pharmaceutical companies regard solid dispersion as a practical technique. Several dozen products using solid dispersion techniques are now commercially available. 7) As poorly water-soluble drug candidates become more common, the use of solid dispersion will increase.

Amorphous drugs have higher Gibbs free energy than crystalline drugs. Thus, amorphous drugs exhibit greater solubility than crystalline drugs. 8) When dispersed in water, amorphous drugs rapidly dissolve and reach high concentrations. However, the use of amorphous drugs without excipients in a solid formulation is difficult because amorphous drugs crystallize easily during preparation and storage. Furthermore, high drug concentrations exhibited after amorphous drugs disperse in water are temporary; the concentration readily decreases to crystalline solubility over time because of rapid drug recrystallization. 9) To prevent this, solid dispersions in which drug molecules are dispersed in a water-soluble polymer matrix in the amorphous state have been used. 10) Amorphous drugs in solid dispersions are stabilized by homogeneous mixing with a polymer. 11) This effect allows for the production of practical solid formulations which are highly stable even under stressed conditions such as heat and humidity. Furthermore, after dispersion into water, drug recrystallization can be inhibited by a dissolved polymer. 12) This contributes to the maintenance of high drug concentrations for an extended duration, as well as the enhanced absorption of poorly water-soluble drugs.

Various water-soluble polymers have been used for solid dispersion formulations such as vinyl, cellulose, polyethylene glycol, and methacrylate derivatives. 13) The Eudragit® series, supplied by Evonik Degussa Co., Ltd., Germany, are copolymers derived from esters of acrylic and methacrylic acid. Eudragit® has been widely used for various purposes such as moisture protection, taste/smell masking, and immediate/sustained/time-controlled release. This breadth of effects of Eudragit® is possible because its characteristics and functions can be controlled depending on its substituents. 14) Eudragit® E (EUD-E) is supplied under the product names Eudragit® E 100 (granule) or Eudragit® E PO (powder). EUD-E is an...
a aminoalkyl methacrylate copolymer composed of dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate at a ratio of 2:1:1 (Fig. 1). The monomers are randomly distributed along the alkyl chain, and the average molar mass is approx. 47000 g/mol. EUD-E is cationic because of its amino group, and is soluble in acidic conditions. EUD-E has been used as an enteric coating film for both moisture protection and taste-masking. EUD-E is also available as a solid dispersion carrier.

De Filippis et al. in 1991 used EUD-E as a solid dispersion carrier of indomethacin. The solid dispersion of indomethacin/EUD-E was prepared by a solvent evaporation technique. Powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) experiments showed that up to 50% of the indomethacin was dispersed in an amorphous state in an EUD-E matrix. Furthermore, rapid dissolution and a high drug concentration of indomethacin in pH 1.2 solution was demonstrated. In the 1990s and the early 2000s, several articles reported the preparation and characterization of drug/EUD-E solid dispersions. After the late 2000s, the number of articles has increased greatly, to more than 100 papers (Fig. 2). The application of EUD-E as a solid dispersion carrier has gained increased attention for several reasons. First, studies of solid dispersions have intensified recently in response to increased attention for several reasons. First, studies of solid dispersions have intensify recently in response to increased numbers of poorly water-soluble drug candidates. Secondly, hot-melt extrusion has become a practical technique for the preparation of solid dispersions. EUD-E has a low glass transition temperature \(T_g\) of approximately 45–50°C, and is suitable as a solid dispersion carrier for the hot-melt extrusion process. Thirdly, properties of EUD-E as an excellent solid dispersion carrier have been recognized among academic and industrial researchers. Solid dispersions containing EUD-E stabilize drugs in the amorphous state despite low \(T_g\). In addition, high drug concentrations in solution are maintained for an extended duration after aqueous dispersion of the solid dispersion. These characteristics of EUD-E as a solid dispersion carrier are attributed to strong interactions between drugs and EUD-E, both in the solid dispersion and in the aqueous dispersion. To date, many studies examining interactions in solid dispersions have been performed mainly by thermal analysis (DSC, dynamic mechanical thermal analysis) and spectroscopic analyses (IR, Raman, and solid-state NMR). In a study by Chokshi et al., a single \(T_g\) was observed in the DSC curves of solid dispersions with weight ratios of indomethacin/EUD-E of 3:7, 5:5, and 7:3, demonstrating high miscibility. Furthermore, the experimental \(T_g\) showed positive deviation from the theoretical \(T_g\) derived from the Gordon–Taylor equation, suggesting a strong intermolecular interaction. A recent excellent article by Lubach and Hau investigated solid dispersions of indomethacin and EUD-E by multiple solid-state NMR techniques, including \(^{13}\)C and \(^{15}\)N spectroscopies and \(^1\)H relaxation times. An ionic interaction between the carboxylic acid group of indomethacin and amino groups of EUD-E, and the molecular dispersibility of indomethacin in the EUD-E matrix were clearly shown. Other studies evaluated ternary solid dispersions composed of drug/EUD-E/polymer to enhance the stability of amorphous drugs in solid dispersions and in a control drug dissolution. The complex interactions of drug/EUD-E, drug/polymer, and EUD-E/polymer in ternary solid dispersion were characterized by thermal and spectroscopic analyses.

While many studies have focused on drug–EUD-E interactions in solid dispersions, studies evaluating interactions in solution are limited. However, understanding these interactions in solution is equally important in designing a good solid dispersion. Intermolecular interactions between drug and polymer in a solvent can be maintained after solvent evaporation. Thus, understanding of drug–EUD-E interactions in an organic solvent can be informative when solid dispersions are prepared by solvent techniques such as spray-drying. Furthermore, interactions in an aqueous solution can significantly influence the dissolution rate, maximum concentration, maintenance time of high concentration, permeation through the intestinal wall, and the bioavailability of the drug. In this review, we summarize reports focused on interactions between drugs and EUD-E in solution.

2. Drug–EUD-E Interaction in Organic Solvent

In pioneering works by Suzuki et al. in 1996, the solubility of benidipine hydrochloride (BH) in a solvent containing EUD-E was examined. BH is poorly soluble in commonly used organic solvents, such as acetone, ethanol, and dichloromethane. The solubility of BH in acetone and dichloromethane was evaluated in the presence of various polymers. EUD-E markedly enhanced BH solubility compared with other polymers such as Eudragit® S 100, which contains a free carboxylic acid group, Eudragit® RL PM, which contains a quaternary ammonium group, and polyvinylpyrrolidone (PVP), which contains a tertiary amide group. The enhancement of BH solubility in solvent was attributed to strong interactions in the EUD-E structure. Thus, EUD-E, a weak base, aided the solubilization of BH, a weak acid, by intermolecular interactions. The effect of organic solvents in forming the interaction between BH and EUD-E was examined. Acetone, dichloro-
methane, and chloroform containing EUD-E maintained a high BH concentration, whereas the effect of EUD-E became lower in acetonitrile, and was completely inhibited in ethanol. Based on hydrogen bonding capability and the magnitude of dipole moments of these solvents, the interaction between BH and EUD-E did not occur predominantly by hydrophobic interaction but by electrostatic interactions, including hydrogen bonds and dipolar interactions.39) UV absorption spectroscopy was used to confirm electrostatic interactions in each solvent. The maximum wavelength of BH in the 350 nm region showed approx. 5 nm blueshift in dichloromethane and chloroform in the presence of EUD-E. Meanwhile, EUD-E did not result in a blueshift of the BH peak in either ethanol or acetonitrile. Figure 3 summarizes the effects of each solvent on BH-EUD-E interactions, and on the solubilization of BH by EUD-E. Thermodynamic parameters for the solubility of BH in dichloromethane with EUD-E were determined. A solubility plot of BH against the EUD-E concentration in dichloromethane demonstrated a linear concentration-dependent increase in solubility. Changes in Gibbs free energy (ΔG) and enthalpy (ΔH) determined by the analysis of the plot were negative, demonstrating the spontaneity and exothermic nature of the solubilization of BH with EUD-E. ΔH gradually decreased with increased EUD-E concentration, indicating that the interaction was progressively increased by the addition of EUD-E. The ΔH values (not more than approximately 13 kJ/mol) implied weak hydrogen bonding between BH and EUD-E.

3. Ionic Interaction of Drug and EUD-E in Aqueous Solution

Researchers in Argentina conducted a series of studies focused on an ionic interaction between acidic drugs and basic EUD-E, regarding EUD-E as a polyelectrolyte (PE).40–44) Quinteros et al. investigated complexes of seven acidic drugs (benzoic acid (BA), diclofenac (DF), furosemide, indomethacin, mesalamine, saccharin, and salicylic acid (SA)) with EUD-E.40) The drug50–EUD-E solid complex was prepared by solvent evaporation, controlling the amount of drug in order to neutralize 50% of the EUD-E amino groups. The drug50Cl50–EUD-E solid complex was obtained by neutralizing the remaining amino groups of EUD-E with 1.0 N HCl following drug addition. Each of the seven drugs in each complex were present in the amorphous state. Only two drug50–EUD-E complexes, those using BA and mesalamine, resulted in clear solutions when 50mg of each complex was suspended in 5 mL water. Dispersion of all the drug50Cl50–EUD-E complexes into water resulted in clear solutions. Distribution of a drug in aqueous dispersions using a DF50Cl50–EUD-E complex was calculated as a model case. The concentrations of free DF, ionized DF, and DF–EUD-E ion complex were 1.31, 0.80 and 97.37%, respectively. Thus, nearly all DF were present with EUD-E in the form of ion pairs. The effect of NaCl addition on the ionic equilibria of aqueous dispersions of complexes was investigated using titration. pH changes by ion-exchange between EUD-E and NaCl were negligibly small, as shown in the Cl50–EUD-E complex. In contrast, pH clearly increased with the percentage of NaCl relative to moles of drug in the drug50Cl50–EUD-E complexes. The pH change in complexes containing the relatively strong acid, SA, was smaller than that in complexes using the relatively weak acid, DF. Both SA and DF contain a carboxylic acid group. The ionic exchange between RCOO⁻ of the drug and Cl⁻ explained the observed pH shift. The main contribution to drug–EUD-E interactions arose from electrostatic attractions.

Guzman et al. studied the interaction between phosphate groups of drugs and amino groups of EUD-E using dexamethasone phosphate (DP) as a model drug.41) The amorphous DP50Cl50–EUD-E complex was prepared by a process similar to those described above. Titration with NaCl was performed on aqueous dispersions of the DP50Cl50–EUD-E complex compared with BA50Cl50–EUD-E and DF50Cl50–EUD-E complexes. BA and DF contain a carboxylic acid group. All aqueous dispersions of these complexes showed pH increases in response to NaCl addition, suggesting an ionic exchange between the ionized drug and Cl⁻. The required amount of NaCl to achieve a pH plateau was more than four times larger in aqueous dispersions of the DP50Cl50–EUD-E complex compared to NaCl required in the BA50Cl50–EUD-E and DF50Cl50–EUD-E complexes. These results indicated that the interaction between DP and EUD-E was stronger than that observed with the two drugs containing carboxylic acid groups. This could be due to different interaction properties. The phosphate group in DP was able to interact with more than one protonated amino group in EUD-E, whereas carboxylic acid groups in BA and DF could only interact with one protonated amino group. In this report, drug release from the aqueous dispersion of the DP50Cl50–EUD-E complex was also examined. A Franz cell, where a semipermeable acetate cellulose membrane is placed between donor and receptor compartments, was used to differentiate free drug and complexed drug with EUD-E. When the receptor compartment was filled with water, DP by itself could rapidly diffuse. In contrast, diffusion of DP from the aqueous dispersion of the DP50Cl50–EUD-E complex was significantly suppressed. The release of ionized DP was prevented by electrostatic interaction with EUD-E; the main release occurred through the diffusion of free DP. When the receptor compartment solution was replaced with NaCl solution, DP diffusion was greatly enhanced. Diffusion of Na⁺...
and Cl\(^-\) from receptor to donor compartments produced a larger amount of free DP and its salt, formed by ionic exchange, each of which were able to diffuse. Figure 4 shows comparative experiments between the drug release behavior from aqueous dispersions of DP\(_{38}\)Cl\(_{25}\)–EUD-E and BA\(_{50}\)Cl\(_{25}\)–EUD-E complexes when the NaCl concentration in the donor compartment was increased. The DP release rate was quite low and remained constant regardless of NaCl concentration. In contrast, the BA release rate was quite high and gradually increased in response to increased NaCl concentration. The stronger interaction between the phosphate groups of drugs and EUD-E delayed drug release from the complex, whereas the release of drugs with a carboxylic acid group was faster from the complex due to its weaker interaction with EUD-E.

4. Direct Observation of Drug–EUD-E Interactions in Aqueous Solutions by NMR Spectroscopy

Recently, \(^1\)H-NMR spectroscopy was used to observe interactions between drugs and EUD-E in solution.\(^{35,49}\) Our group has investigated drug–EUD-E interactions in detail using various \(^1\)H-NMR techniques.\(^{33,49}\) Kojima \textit{et al.} prepared a solid dispersion of mefenamic acid (MFA) and EUD-E at a weight ratio of 24:76 by cryogenic cogrinding.\(^{33}\) The MFA/EUD-E solution was obtained by dispersing the solid dispersion into 0.1 M acetate buffer at pH 5.5. The concentration of MFA in the MFA/EUD-E was almost equal to the dosed concentration (500 µg/mL), and more than 200-fold higher compared with that of unprocessed MFA (2.2 µg/mL). In a rat oral absorption study, the absorption of MFA was significantly enhanced in the MFA/EUD-E solution. Figure 5 shows \(^1\)H-NMR spectra of MFA dissolved in \(d\)-chloroform, as well as EUD-E and MFA/EUD-E solid dispersions dissolved in \(d\)-acetate buffer at pH 5.5. The peaks of MFA in the MFA/EUD-E solution were clearly observed at a lower magnetic field but were significantly broadened compared with the MFA peaks in \(d\)-chloroform. This peak broadening of MFA could be due to mobility suppression by the interaction with EUD-E. The peaks of EUD-E were also different in the presence or absence of MFA, presumably due to intermolecular interaction. The mobility of MFA and EUD-E in each solution was evaluated by \(^1\)H-spin-lattice relaxation time (\(T_1\)) measurement. Each \(^1\)H peak of MFA in \(d\)-chloroform showed different \(T_1\) values across a range of 1.7–3.3 s. In contrast, the \(^1\)H peaks of EUD-E in \(d\)-acetate buffer showed similar \(T_1\) values, ranging from 0.8–1.0 s. This single \(T_1\) value was due to the low mobility of polymeric EUD-E, with a large molecular weight of approx. 47000. The \(T_1\) values of individual EUD-E protons were approximately equal as a result of spin diffusion arising from \(^1\)H–\(^1\)H homonuclear dipolar coupling. In the MFA/EUD-E solution, the \(^1\)H peaks of both MFA and EUD-E had a single \(T_1\) value of 1.0–1.2 s due to spin diffusion. Thus, magnification transfer by cross relaxation could occur between MFA and EUD-E protons. These results suggested that MFA behaved as a component of the EUD-E polymer by forming an intermolecular interaction. A difference in nuclear Overhauser effect (NOE) experiment was performed to determine the intermolecular interaction site. The H3 proton of MFA was selectively irradiated by changing an attenuator that limits power output. Homogeneous negative NOE was shown throughout the spectrum, and the absolute intensity of MFA and EUD-E peaks increased simultaneously, depending on the increase in irradiation power. This difference in NOE experiment supported the observed interaction between MFA and EUD-E, although information on the specific interaction site was not obtained.

The high-resolution magic-angle spinning (HR-MAS) technique was applied to determine the interaction sites in the MFA–EUD-E solution.\(^{49}\) In HR-MAS experiments, viscous solutions and gels were placed into a glass rotor and spun at a rate of several kHz at a magic-angle of 54.74° with respect to the direction of the magnetic field. According to MAS, a highly-resolved spectrum was obtained by averaging out anisotropic interactions, such as chemical shift anisotropy and internuclear dipolar couplings. MFA peaks in the spectrum of
MFA/EUD-E solution at the MAS rate of 2.7 kHz were considerably narrower than those under a static (non-MAS) condition, due to the suppression of dipolar couplings. The highly resolved peaks of MFA in HR-MAS spectra allowed for peak assignment, which was difficult to accomplish under the static condition because of broadened and overlapping peaks. A two-dimensional (2D) $^1$H/$^1$H nuclear Overhauser effect spectroscopy (NOESY) experiment under MAS conditions was carried out to directly observe the intermolecular interaction between MFA and EUD-E (Fig. 6). Due to the MAS-induced reduction of dipolar coupling, NOE correlations between MFA and EUD-E were clearly detected in the 2D spectrum. The $–$C–CH$_3$– peak of EUD-E at 0.82 ppm had a cross peak with the aromatic peaks of MFA. Cross peaks were also observed between protons next to the $–$N–CH$_3$– group in a side chain of EUD-E at 2.86 ppm and aromatic protons of MFA. In contrast, the $–$O–CH– peak in another side chain showed only weak cross peaks with the peaks of MFA. It was difficult to determine the precise interaction site from the 2D spectrum. Thus, the relative intensities of each of the cross peaks in the spectrum sliced at the $–$C–CH$_3$– and $–$N–CH$_3$– peaks were compared against 1D $^1$H-NMR spectrum ($t_2$ projection in Fig. 6a). The relative intensity of the H3 peak against the H4–H6 and H4’–H6’ peaks was similar or slightly lower in the 1D NOESY spectrum sliced at the $–$C–CH$_3$– peak compared to the 1D $^1$H-NMR spectrum (Fig. 6b). This suggested that hydrophobic interactions between two aromatic groups of MFA and the $–$C–CH$_3$– group in EUD-E occurred. In contrast, relative intensity was higher in the 1D NOESY spectrum sliced at the $–$N–CH$_3$– peak than in the 1D $^1$H-NMR spectrum. It follows that the protons in the $–$N–CH$_3$– group in the side chain of EUD-E were close to H3 near the carboxylic acid group of MFA. This suggested an ionic interaction between the carboxylic acid group of MFA and amino groups of EUD-E. As shown in Fig. 6c, both hydrophobic and ionic interactions occurred between MFA and EUD-E, which resulted in high concentrations of MFA and also stabilized the solution, preventing the recrystallization of MFA.

5. Aqueous Solubility Enhancement by Drug–EUD-E Interaction Investigated by Diffusion NMR

Saal et al. reported on solubility enhancement of poorly water-soluble, acidic, basic, and chemically diverse drugs in aqueous EUD-E solutions. The equilibrium solubility of seven acidic drugs, bezafibrate ($pK_a$ 3.2), furosemide ($pK_a$ 3.5), indomethacin ($pK_a$ 4.5), mefenamic acid ($pK_a$ 4.2), piroxicam ($pK_a$ 2.3), tolbutamide ($pK_a$ 5.1), and warfarin ($pK_a$ 5.0) in solution with different EUD-E concentrations (0.1%–5% w/w) at pH 6.0 were evaluated. No polymorphic change occurred in solution, as confirmed by PXRD measurement. The solubility of bezafibrate, indomethacin, piroxicam, and warfarin increased with increasing EUD-E concentration, with a maximum solubility observed at 2% EUD-E. The solubility decreased at EUD-E concentrations above 2%, then reached a plateau. In the cases of furosemide and mefenamic acid, solubility increased with EUD-E concentration up to 5%. Tolbutamide reached a plateau at 2% EUD-E. As shown above, the effect of EUD-E concentration on drug solubility enhancement varied by drug. In addition to ionic interactions, other possible interactions such as an interaction between the methyl amino group of EUD-E and aromatic groups of a drug, or hydrophobic interactions could occur. The molecular structures of drugs examined are quite diverse, and the interaction mode and strength differs depending on drug species. Further, the effect of interaction with drugs on EUD-E conformation should be considered, although a certain conformation of EUD-E could be theoretically suitable for drug solubilization. The authors noted that no simple relationship between solubility enhancement and EUD-E concentration would be due to these complex molecular interactions. The drug diffusion coefficient in both the presence and absence of EUD-E was determined by diffusion $^1$H-NMR spectroscopy to investigate the strength of the drug–EUD-E interaction. The diffusion coefficient of drugs in 0.5% EUD-E solution substantially
The solubility enhancement of six basic drugs, carvedilol (pKₐ 8.1), cinnarizine (pKₐ 7.8), mefloquine (pKₐ 9.2), pimozide (pKₐ 8.6), tamoxifen (pKₐ 9.7), and terfenadine (pKₐ 9.1), in the presence of EUD-E were also examined. EUD-E may seem less promising for the solubility enhancement of basic drugs, since both basic drugs and EUD-E (pKₐ = 8.4) have a positive charge at around pH <8. However, the equilibrium solubility of basic drugs greatly increased with increasing EUD-E concentration. No general solubilization effect with EUD-E concentration was found for basic drugs as well as for acidic drugs. The solubility enhancement of carvedilol, cinnarizine, and tamoxifen reached a plateau at 2% EUD-E. EUD-E concentration-dependent increases in drug solubility were observed for mefloquine, pimozide, and tamoxifen. The solubility enhancement of basic drugs was attributed to hydrophobic interactions between aromatic systems of the drugs and hydrophobic side chains of EUD-E. The diffusion coefficients of drugs, determined by diffusion ¹H-NMR spectroscopy, were reduced in EUD-E solutions compared with D₂O (Table 1). Interestingly, the diffusion coefficient of EUD-E was greater in the presence of basic drugs, which was not observed with acidic drugs. The addition of a positively charged drug induced a conformational change in EUD-E. Added positive charges weakened electrostatic interactions and promoted shrinkage of EUD-E chains and the formation of spherical globules. Thus, the EUD-E diffused faster in the presence of basic drugs than in D₂O. The authors mentioned that hydrophobic interactions may play an important role beyond the obvious electrostatic interactions.

### 6. Interaction between Drug and Modified EUD-E in Aqueous Solution

Drug/EUD-E binary solid dispersions may not work efficiently to enhance in vivo drug absorption since basic EUD-E is soluble below pH 5.0 but not practically soluble at a neutral pH. Yoshida et al. reported a strong anti-reprecipitation effect of EUD-E/HCl (named E-SD) under a neutral condition. E-SD was prepared by spray-drying or freeze-drying a dissolved solution of EUD-E and HCl. Tacrolimus was used as a model of a poorly water-soluble drug, which is commercially available (Prograf®) as a solid dispersion formulation with hydroxypropyl methylcellulose (HPMC). The solid dispersion with E-SD prepared by solvent evaporation successfully achieved higher concentrations of tacrolimus than that with HPMC in the Japanese Pharmacopeia second (JP2) solution at pH 6.8. Moreover, in vivo oral absorption experiments using a rat in an in situ closed loop method showed higher absorption in the solid dispersion with E-SD than with ingredients in a Prograf® capsule. The correlation between in vitro drug concentration and in vivo drug absorption was consistently observed. In a dog oral administration study, solid dispersions with E-SD loaded in HPMC capsules showed higher absorption than Prograf® capsules. These results indicated the potential of E-SD as a solid dispersion carrier, which effectively enhances drug absorption as well as drug concentration. The authors investigated an underlying mechanism of drug concentration enhancement by E-SD. Ionic strength and pH were evaluated in a reprecipitation study using the co-solvent ASP2151 over 12h was observed at an ionic strength of 0.1 to 1.0M. The reprecipitation inhibition effect was weak in the pH range of 2.0–5.0, while E-SD showed strong reprecipitation inhibition within a neutral pH range of 6.0–7.0. The presence of basic drugs enhanced the inhibitory effects of E-SD on drug reprecipitation.
The surface activity of EUD-E was also affected by pH and ionic strength. It was hypothesized that the surfactant function of E-SD, which resulted in the formation of a micelle-like structure, was related to reprecipitation inhibition. Fluorescence measurement using pyrene as a probe confirmed that E-SD formed micelle-like structures. Dynamic light scattering was applied to solutions with different E-SD concentrations and at different pH and ionic strengths. In solutions with low E-SD concentrations (i.e., 10 µg/mL), no structures were present in the JP2 solution. In contrast, E-SD formed nano-sized particulates in JP2 solution at E-SD concentrations greater than 100 µg/mL. The sizes of E-SD particles were quite different in tested solutions where E-SD concentration was fixed at 1000 µg/mL. The particle sizes were within diameters of 10–20 nm in JP2 solution and 0.1 M NaCl solution. In contrast, particles greater than 100 nm in diameter were formed in water and JP 1st (JP1) solution at pH 1.2. From these results, the authors illustrated changes in E-SD conformation at different pH and ionic strengths (Fig. 8). In solutions at low pH and low ionic strength, such as water and the JP1 solution, the amino group in E-SD was protonated, and hydrophobic interactions were weak. Hence, the surfaces of E-SD micelle-like structures were in a swollen state. Water had ready access to ASP2151, resulting in faster aggregation and precipitation of ASP2151. In contrast, in a solution with high pH and high ionic strength, such as JP2 solution and 0.1 M NaCl solution, the interaction between E-SD and ASP2151 was strong due to reduced electrostatic repulsion of the amino group as well as increased hydrophobic interaction by the salting-out effect. The authors concluded that the mechanism of drug concentration enhancement by E-SD was derived from its surfactant property, allowing it to form polymeric micelle-like structures.

We developed a ternary solid dispersion composed of drug/EUD-E/saccharin (SAC). SAC is an acidic additive (pKₐ approx. 2) used as an artificial sweetener. The ternary solid dispersion was prepared by a single process wherein a ternary physical mixture was cryogenically coground. In the dissolution test in JP2 solution at pH 6.8, the ternary solid dispersion of drug/EUD-E/SAC allowed for remarkable dissolution of the drug compared with physical mixtures of drug/EUD-E binary solid dispersions and SAC. An ionic interaction formed between the amino groups of EUD-E and the amide groups of SAC in the ternary solid dispersion, allowing for rapid dissolution of EUD-E, even at neutral pH. Drug dissolution was enhanced by accompaniment with the increased EUD-E dissolution. A drug/EUD-E/SAC ternary solution was obtained by dispersing the ternary solid dispersion into water, and the subsequent molecular state was evaluated by ¹H-NMR spectroscopy (Fig. 9). A neutral drug,
phenytoin (PHT), was used as a model of poorly water-soluble drugs. In the EUD-E/SAC binary solution, the $^1$H peak of the –N–CH– group in EUD-E was shifted downfield compared to that in the EUD-E solution. In addition, the aromatic peaks of SAC were broadened and shifted upfield in the EUD-E/SAC binary solution compared with the SAC solution alone. This was due to ionic interactions between the amino groups of EUD-E and amide groups of SAC. In the PHT/EUD-E/SAC ternary solution, the peaks of PHT were significantly broader than those in PHT solution alone. The peaks of the –C–CH– group in EUD-E presented with a different shape than those in EUD-E and EUD-E/SAC solutions. A hydrophobic interaction between aromatic systems of PHT and hydrophobic side chains of EUD-E could suppress the mobility of PHT. It should be mentioned that the ionic interaction between EUD-E and SAC was maintained, even in the presence of hydrophobic interactions between PHT and EUD-E. The $^1$H relaxation time ($T_1$) and spin–spin relaxation time ($T_2$) were determined in order to precisely evaluate the molecular mobility of each component. Calculated $T_1/T_2$ values were used as an index that correlates with molecular mobility; a high $T_1/T_2$ value indicates low molecular mobility. The $T_1/T_2$ value of PHT in the ternary solution, at 440, was considerably higher than in PHT solution at 14. SAC also exhibited a higher value in ternary solution, at 25, than in SAC solution at 2.4. Thus, both PHT and SAC mobility were suppressed in ternary solutions. Comparing the $T_1/T_2$ values, the mobility suppression of PHT was much stronger than that of SAC. Based on these results, poorly water-soluble PHT should be strongly embedded in the micelle-like structure of EUD-E via hydrophobic interactions. In addition, a portion of SAC should interact with EUD-E by ionic interaction, although most of the SAC was freely dissolved, presumably due to its relatively high water-solubility and weaker interaction with EUD-E. The SAC peaks in the spectrum could reflect an average of free water-solubility and weaker interaction with EUD-E. The 1H peaks of the –C–CH– groups have been gradually clarified by recent studies. Not only ionic interactions but also hydrophobic interactions potentially affect intermolecular interactions. For example, intermolecular interactions are sensitive to EUD-E conformation, which varies depending on many factors such as interaction with drugs and/or additives, ionic strength, and pH. The application of additional analytical techniques will be helpful to further investigate intermolecular interactions. As shown in this review, the NMR technique will be one of the most powerful tools to investigate the precise interaction site and strength. Other advanced analytical tools, including X-ray techniques and microscopy, will help to monitor changes in EUD-E conformation. Computer simulations will also play an important role in explaining experimental results. The relationship between drug state in solution and drug absorption in vitro should also be clarified. Most studies have demonstrated drug absorption enhancement using EUD-E, reflecting a high drug concentration in vitro. However, recent studies showed delayed and lower drug absorption in vitro, in spite of a high concentration in EUD-E solution. Variable molecular states and interactions resulting from solution conditions in the gastrointestinal tract should also be studied. Thus, further investigations to understand drug–EUD-E interactions in solution are required in order to design solid dispersions with EUD-E, which efficiently improves the absorption of poorly water-soluble drugs.

**Conflict of Interest** The authors declare no conflict of interest.

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