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Solid Dispersions of Benidipine Hydrochloride. I. Preparations Using Different Solvent Systems and Dissolution Properties

Hideshi SUZUKI,* Norifumi MIYAMOTO, Tomoaki MASADA, Eiji HAYAKAWA, and Kunio ITO

Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411, Japan. Received July 3, 1995; accepted October 16, 1995

The solid dispersion technique has been widely utilized to improve the dissolution profile and oral bioavailability of water insoluble drugs. Benidipine hydrochloride, a calcium-antagonist, is a slightly soluble compound in a weak acid, so that its bioavailability is liable to be influenced by the gastric acidity of patients. In the preparation of solid dispersions by the solvent removal process, organic solvents are used as agents to intimately mix a drug or drugs and carrier molecules. Benidipine hydrochloride is also poorly soluble in commonly used organic solvents. The application of the solvent removal process for preparing solid dispersions of the drug makes it necessary to enhance the organic solubility of the drug. Two kinds of solvent systems have been investigated: one in an organic solution of Eudragit® E-100 (OSE) and the other in binary solvent mixtures (BSM). In the OSE, the presence of Eudragit® E-100 in dichloromethane resulted in an appreciable increase in drug solubility. However, in ethanol, this solubilization effect of the polymer was completely inhibited. In the BSM, enhanced solubility of the drug was obtained in ethanol–dichloromethane mixtures. Further, the addition of polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC) to this system did not deposit the dissolved drug. In these two solvent systems, solubilization of benidipine hydrochloride was presumed to be caused by intermolecular interactions. It enabled the preparation of solid dispersions of benidipine hydrochloride with Eudragit® E-100, PVP or HPMC. Especially, when dispersed in PVP or HPMC, the dissolution rate of the drug improved remarkably in a weak acid (pH 6.0).

Key words benidipine hydrochloride; solid dispersion; dissolution rate; Eudragit® E-100; binary solvent mixture

Solid dispersions possess tremendous potential for improving the dissolution rate and bioavailability of drugs whose absorption is limited by solubility. This technique has therefore been studied extensively,[1,2] and in general there are two methods of preparing solid dispersions, namely, by either fusion or solvent processes. However, it is occasionally difficult to apply these methods to some drugs because of the following problems: thermal instability and immiscibility[3] in the fusion method; and solvent volume and solvent removal[4] in the solvent method.

Benidipine hydrochloride, a dihydropyridine calcium-antagonist, is used (Fig. 1) as an antihypertensive drug similar to the structurally related compounds, nifedipine and nicardipine.[5] The therapeutic effect of the drug slowly develops and is extremely long-lasting, which is useful for improving the compliance of patients. However, the solubility of benidipine hydrochloride is dependent on pH variations (pK_a 7.34): the solubilities of the drug in pH 4.0 and 7.0 are 2.2 mg/ml and 3.2 μg/ml, respectively.[6] It is well known that the acidity of the gastric fluid affects the bioavailability of some drugs administered orally whose dosage forms show pH-dependent drug release.[7,8] It was thought that the solid dispersion method would be a good technique for obtaining good bioavailability of benidipine hydrochloride in patients having low gastric acidity. However, the drug is poorly soluble in commonly used organic solvents such as ethanol, dichloromethane, acetone, *etc.*, and undergoes decomposition at or near its melting point.[6] These properties of the drug result in disadvantages in the preparation of solid dispersions.

Deviations from regular solutions are caused by solvation, association or complexation, which is commonly encountered in the pharmaceutical sciences. There have been several reports dealing with investigations of drug solubility and solvent composition. Many of the observations to date indicate that the solubility of many drugs is enhanced in binary systems: by the addition of adjuvants[9,10] and the use of solvent–cosolvent mixtures.[11,12]

The aim of this study was to improve the poor organic solubility of benidipine hydrochloride using two kinds of solvent systems: an organic solution of Eudragit® E-100 and binary solvent mixtures, for preparing solid dispersions by the solvent removal process. We also aimed to characterize the dissolution profile of the drug from solid dispersions with Eudragit® E-100, polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC). Furthermore, the influence of an anionic surfactant to the drug release from solid dispersions was also studied.

Experimental

Materials Benidipine hydrochloride (Kyowa Hakko Kogyo Co., Ltd., Japan) sieved through 48 mesh (297 μm) was used. The molecular weight was 542.03. The acrylic polymers used were methylmethacrylate butylmethacrylate dimethylaminoethylmethacrylate, methacrylic acid methylmethacrylate and ethylacrylate methylmethacrylate chlorotrimethylammoniumethylmethacrylate copolymers (Eudragit® E-100, S-100 and RL-PM, respectively, Röhm Pharma GmbH, Germany). Eudragit® E-100 and S-100 were soluble up to pH 5 and above pH 7, respectively. The swelling and permeability of Eudragit® RL-PM was independent of the pH conditions. Polyethylene glycol (PEG 6000, Wako

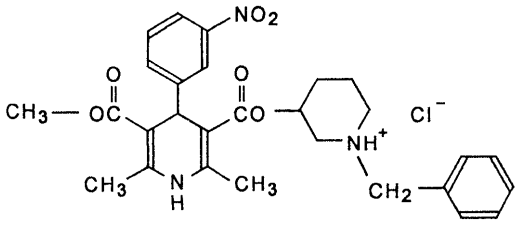

Fig. 1. Chemical Structure of Benidipine Hydrochloride

* To whom correspondence should be addressed.

Pure Chemical Industries Co., Ltd., Japan), HPMC (TC-5E, Shin-Etsu Chemical Industries Co., Ltd., Japan), PVP (K-30, BASF, Germany), polyvinylacetal diethylaminoacetate (AEA®, Sankyo Co., Ltd., Japan) and sodium dodecyl sulfate (SDS, Nikko Chemicals Co., Ltd., Japan) were used. AEA® was soluble up to pH 5.8. The molecular weight of SDS was 288.38. All other chemicals were of reagent grade.

Drug Solubilization Studies (a) In an Organic Solution of Polymer: Excess amounts of benidipine hydrochloride were added to organic solutions (5 ml) containing Eudragit® E-100, Eudragit® S-100, Eudragit®RL-PM, AEA® or PVP (4% w/v), and samples were shaken for 6 h at 25 °C. Acetone and dichloromethane were used as organic solvents. Benidipine hydrochloride (200 mg) was also introduced into organic solutions (5 ml) containing Eudragit® E-100 (4% w/v), and samples were shaken for 10, 60, 180 and 360 min at 25 °C. Acetone, dichloromethane, chloroform, acetonitrile and ethanol were used as organic solvents. After shaking, samples were withdrawn, filtered (0.5 μm), diluted and analyzed by HPLC.

(b) In Binary Solvent Mixtures: Different concentrations ranging from 0 to 100% v/v of the cosolvent, *viz.*, ethanol, acetonitrile and 1,4-dioxane, in water, were prepared. Different concentrations of the cosolvent, *viz.*, acetone, acetonitrile and dichloromethane, in ethanol, were also prepared. Excess amounts of benidipine hydrochloride were added to both water–cosolvent and ethanol–cosolvent combinations (5 ml). After shaking for 12 h at 25 °C, samples were analyzed as above.

Drug Solubility Assay Aliquots obtained by filtration were appropriately diluted with methanol and assayed at 237 nm by HPLC. The chromatograph operating conditions were as follows: C18 reversed-phase column (YMC-Pack ODS-A); 0.05 M phosphate buffer (pH 3.0): methanol : tetrahydrofuran (65 : 27 : 8) eluant; flow rate of 1 ml/min; benzoin as an internal standard; 237 nm detector (Shimazu Seisakusho Co., Ltd., Japan).

Preparation of Solid Dispersions and Solid Dispersion Granules (a) Solid Dispersions-1: Eudragit® E-100 (0.5—3 g) or Eudragit® E-100 : PEG (0.5 g : 1 g) was dissolved in 20 ml of dichloromethane, and then benidipine hydrochloride (1 g) was added to this solution.

(b) Solid Dispersions-2: Benidipine hydrochloride (1 g) was dissolved in 20 ml of ethanol : dichloromethane (1 : 9 or 5 : 5), and then PVP or HPMC (3 g) was added to this solution.

(c) Solid Dispersion Granules: Benidipine hydrochloride (10 g) and the polymer (PVP or HPMC, 30 g) were dissolved in 150 ml of ethanol : dichloromethane (3 : 7), and then lactose (160 g) was added to this solution.

Solid dispersions and solid dispersion granules were prepared by the solvent removal process; that is, by drying for 2 d at 35 °C under reduced pressure and then sieving through 48 mesh (297 μm) and 32 mesh (500 μm), respectively. Products were assayed for their drug content before use by HPLC at 237 nm.

Differential Scanning Calorimetry (DSC) DSC analyses were carried out on samples of 5 to 10 mg on a DSC 10 (Seiko Denshi Kogyo Co., Ltd., Japan). Samples were heated at a rate of 10 °C/min from 30 to 250 °C in the nitrogen.

Dissolution Studies Dissolution tests according to JP XII (paddle method, 100 rpm) were carried out at 37 °C. A weighed quantity of solid dispersions or solid dispersion granules containing 20 mg of benidipine hydrochloride was placed in 900 ml of distilled water, 0.1 M hydrochloric solution (pH 1.2) or McIlvaine buffer (pH 4.0, 6.0). Samples were filtered (0.2 μm) and assayed at 237 nm by HPLC. Dissolution studies of solid dispersion granules were also performed in media with SDS (3×10^{-4}—0.2% w/v).

Results and Discussion

Preparation of Solid Dispersions with Eudragit® E-100 Using Interactions between Drug and Polymer (a) Improvement of Drug Solubility in Organic Solution of Eudragit® E-100: Benidipine hydrochloride is poorly soluble in commonly used organic solvents, *e.g.*, ethanol, dichloromethane, acetone,[6] so attempts have been made to improve the organic solubility of the drug by using interactions with a polymer. In this study, Eudragit® E-100, Eudragit® S-100, Eudragit® RL-PM, AEA® and PVP were used as polymers. They have different functional groups: tertiary amine groups of Eudragit® E-100, free carboxyl groups of Eudragit® S-100, quaternary ammonium groups of Eudragit® RL-PM, tertiary amine groups of AEA® and tertiary amide groups of PVP are based on dimethylaminoethylmethacrylate, methacrylic acid, chlorotrimethylammoniumethylmethacrylate, dimethylaminoacetic acid and a pyrrolidone moiety, respectively.

Table 1. Effect of Chemical Structure of Polymers on the Solubility of Benidipine Hydrochloride at 25 °C.

Solvent	Polymer (Characteristic functional group)	Solubility of drug (mg/ml)
Acetone	Without polymer	1.5
	Eudragit® E-100 (tertiary amine)	57.0
	AEA® (tertiary amine)	14.4
	Eudragit® S-100 (free carboxylic acid)	2.5
	Eudragit® RL-PM (quaternary ammonium)	3.4
Dichloromethane	Without polymer	8.7
	PVP (tertiary amide)	12.2

Concentration of polymer in solvent = 40 mg/ml.

Table 1 shows the solubility of benidipine hydrochloride in organic solutions of the different polymers (4% w/v). In the organic solution of Eudragit® E-100 or AEA®, there was an apparent increase in drug solubility. Particularly, Eudragit® E-100 brought about a marked improvement in the poor organic solubility of the drug. On the other hand, with the other polymers, such enhanced solubility was not recognized. This phenomenon would thus be attributed to the existence of tertiary amine groups in the polymers. The highest drug solubility in Eudragit® E-100 solution is most likely to depend on the larger quantities of tertiary amine groups of the polymer compared with AEA®. In some Eudragit® or PVP solid dispersions, the formation of drug–polymer complexes, such as a weak acid and a weak base salt, has been reported: ibuprofen, being a weak acid, acts on Eudragit® E-100[13] and PVP[14]; and dipyridamole and furosemide, being a weak base, have an effect on Eudragit® S-100[15] and Eudragit® RL-PM,[16] respectively. A reasonable explanation for the solubilizing action on benidipine hydrochloride in Eudragit® E-100 solution may be due to the intermolecular interactions between the drug as a weak acid and the polymer as a weak base. Although the exact mechanism of nonsolubilization of the drug in PVP solution is unknown, it is possible that PVP could have weaker basicity than Eudragit® E-100.

Since the enhanced organic solubility of benidipine hydrochloride was observed in Eudragit® E-100 solution, the effect of organic solvents in forming the drug–polymer interactions has been investigated (Table 2). When the drug was added to five kinds of organic solvents with Eudragit® E-100 (4% w/v), all solvents completely dissolved the drug in 10 min of shaking time. Acetone, dichloromethane and chloroform helped to maintain the polymer effect on the drug solubilization after 6 h, whereas acetonitrile and ethanol lowered the drug concentration with the elapse of time. Especially, more

Table 2. Effect of Organic Solutions of Eudragit® E-100 on the Solubilization of Benidipine Hydrochloride at 25 °C

Solvent	Concentration of drug (mg/ml)			
	10 min[a]	60 min	180 min	360 min
Acetone	40.2	—	40.6	40.8
Dichloromethane	39.8	—	40.6	39.5
Chloroform	40.7	—	39.5	40.4
Acetonitrile	40.3	40.3	26.4	27.3 (4.5)[b]
Ethanol	40.2	24.1	13.3	13.3 (8.1)

Concentration of polymer in solvent = 40 mg/ml. *a*) Shaking time after adding drug (200 mg) to solvent with polymer (5 ml). *b*) In solvent without polymer.

rapid precipitation of the drug was observed in ethanol than in acetonitrile. Furthermore, after 3 h, the drug concentration in ethanol with Eudragit® E-100 was similar to that in ethanol without the polymer, indicating the solubilization effect of the polymer was almost completely inhibited.

Solvent effects on complex formation with specific types of intermolecular forces, *i.e.*, hydrophobic interactions and electrostatic interactions, are varied and complicated. In general, it can be anticipated that if the hydrophobic effect makes a major contribution to the stability of a complex in water, the incorporation of an organic solvent into the medium will decrease the complex stability. On the other hand, if the interest is in a complex (in a non-hydroxylic solvent) whose stability is derived largely from intermolecular hydrogen bonding, then the incorporation of water or an alcohol will reduce the complex stability due to competition by the hydroxylic solvent. It is seen that the chemical behavior of the incorporated solvent is compatible with the complex type.[17]

The ability of hydrogen bonding and the magnitude of dipole moment of the solvents used conformed with the following order[18]: ethanol > acetone > acetonitrile, chloroform, dichloromethane; and acetonitrile > acetone > ethanol > dichloromethane > chloroform, respectively. From the results of the formation of a drug–polymer complex depressed not by chloroform and dichloromethane but by ethanol and acetonitrile, it appeared reasonable to consider that the intermolecular forces between benidipine hydrochloride and Eudragit® E-100 were not hydrophobic but electrostatic interactions, including hydrogen bonds and dipolar interactions. Especially, the complete inhibition of the solubilization effect of the polymer in ethanol suggested that a major contribution to the stability of a drug–polymer complex would be derived from the intermolecular hydrogen bonding. In this case, ethanol might compete with the drug for tertiary amine groups of the polymer to destroy the hydrogen bonds. Concerning the stability of the drug–polymer complex in acetone, a possible explanation is that acetone has a different hydrogen bonding ability from ethanol and a lower dipole moment than acetonitrile.

(b) Thermal Analysis and Drug Dissolution Profiles for Eudragit® E-100 Solid Dispersions: The poor organic solubility of benidipine hydrochloride was improved by interactions with Eudragit® E-100, which made possible the preparation of solid dispersions of drug–Eudragit® E-100 by the solvent removal process. However, this polymer is soluble up to pH 5, while above this pH value it is capable of swelling and permeable to water. Further, since the solubility of benidipine hydrochloride decreases drastically at above pH 4, the dissolution rate of the drug from Eudragit® E-100 dispersions at pH 6.0 was hardly expected to increase markedly. Therefore, we also examined whether the addition of PEG, a water-soluble polymer, in this system helped to enhance the dissolution rate of the drug at pH 6.0. In dichloromethane with Eudragit® E-100, the existence of PEG did not depress the drug solubilization.

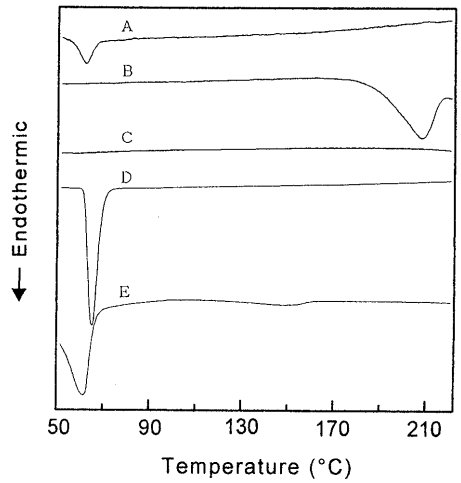

Fig. 2. The DSC Thermograms of Benidipine Hydrochloride Solid Dispersions with Eudragit® E-100

A, Eudragit® E-100; B, benidipine hydrochloride; C, drug : Eudragit® E-100 = 1 : 0.5; D, PEG 6000; E, drug : Eudragit® E-100 : PEG 6000 = 1 : 0.5 : 1.

In order to obtain further evidence of the possible interactions of benidipine hydrochloride with Eudragit® E-100, DSC studies were performed on the drug, Eudragit® E-100, drug–Eudragit® E-100 dispersions and drug–Eudragit® E-100–PEG dispersions (Fig. 2). Eudragit® E-100 showed a glass transition peak at 62.1 °C, while the melting peaks of benidipine hydrochloride and PEG were at 204.9 and 64.4 °C, respectively. The DSC thermograms of solid dispersions denoted the disappearance of the endothermic melting peaks of the drug (Fig. 2C, E), whereas a broadened melting peak of PEG was observed (Fig. 2E). In view of these results, it followed that the intermolecular interactions of drug–Eudragit® E-100 were maintained during the solvent removal process, so that the recrystallization of the drug was inhibited in Eudragit® E-100 matrix, even at a lower content of this polymer. The intermolecular interactions between the drug and Eudragit® E-100 in the liquid state would be consistent with those in the solid state.[19] With regard to the broadened melting peak of PEG, it can be presumed that PEG was precipitated prior to the coprecipitation of the drug with Eudragit® E-100 during the solvent evaporation because of the different solubility of the polymers.

The release of benidipine hydrochloride from solid dispersions containing different weight fractions of Eudragit® E-100 was evaluated in the media at pH 1.2 and 6.0 (Fig. 3). For the drug–Eudragit® E-100–PEG dispersions, the dissolution test was carried out at pH 6.0.

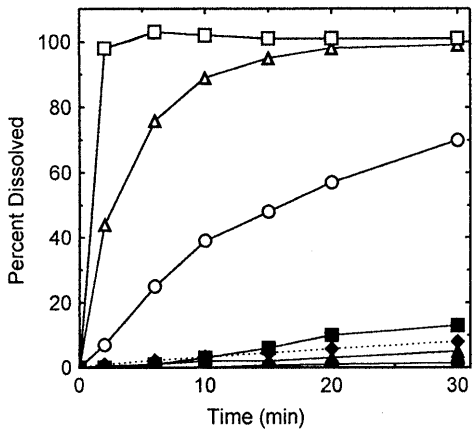

Fig. 3. Dissolution Profiles of Benidipine Hydrochloride Solid Dispersions with Eudragit® E-100

○, ●, benidipine hydrochloride; △, ▲, drug : Eudragit® E-100 = 1 : 0.5; □, ■, drug : Eudragit® E-100 = 1 : 3; ◆, drug : Eudragit® E-100 : PEG6000 = 1 : 0.5 : 1. Open symbols: in 0.1 M hydrochloric solution (pH 1.2); closed symbols: in McIlvaine buffer (pH 6.0).

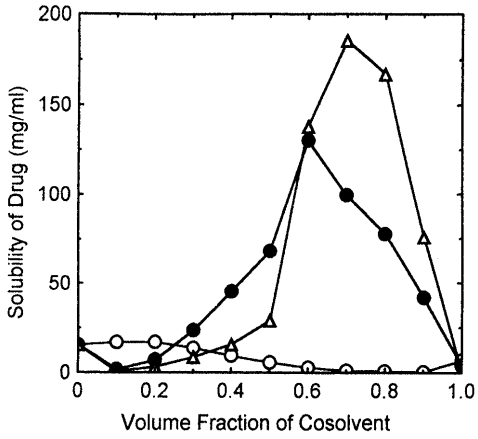

Fig. 4. Solubility of Benidipine Hydrochloride in Water–Cosolvent Mixtures at 25 °C *versus* Volume Fraction of Cosolvent

○, water–ethanol; ●, water–acetonitrile; △, water–dioxane.

At pH 1.2, it was evident that the dissolution rate of the drug was enhanced as the proportion of Eudragit® E-100 content increased in solid dispersions. On the other hand, at pH 6.0, this favorable effect on drug release was only slightly observed, and the addition of PEG in Eudragit® E-100 dispersions did not help to improve the drug release. In fact, the dissolution rate of the drug from Eudragit® E-100–PEG dispersions was almost the same as that from Eudragit® E-100 dispersions without PEG.

Eudragit® E-100 dispersions increased the dissolution rate of benidipine hydrochloride very slightly at pH 6.0. Similar observations were noted by Kislalioglu *et al.* for ibuprofen solid dispersions prepared with Eudragit® polymers.[13] They described that qualitative wetting tests demonstrated instantaneous wetting of the coprecipitates of drug–Eudragit® polymers. A reasonable mechanism of the drug release would depend on the penetration of the dissolution medium into the polymeric matrix and subsequent diffusion of the drug through the matrix. The diffusional process with the drug–polymer system may be the main release factor. Interestingly, the higher Eudragit® E-100 content resulted in a somewhat higher amount of drug released at pH 6.0. This finding was an anomalous behavior, although it is consistent with the results reported by Filippis *et al.*, who studied the solid dispersions of indomethacin with Eudragit® E-100.[20] The exact mechanism involved in such behavior at pH 6.0 is not apparent to us. The PEG included in the solid dispersions had no effect on the drug release at pH 6.0, which has a connection with the results of DSC studies. It can be assumed that the drug was barely present in the PEG matrix, and hence the solid dispersions might consist of the two phases of drug–Eudragit® E-100 complexes and PEG.

Preparation of Solid Dispersions with PVP or HPMC Using Interactions between Drug and Solvents (a) Improvement of Drug Solubility in Binary Solvent Mixtures: Binary mixtures of miscible solvents may provide a valuable means for investigating and assessing some interactions. Röthlisberger *et al.* have reported that binary mixtures of water and aprotic or protic solvents showed the form of a viscosity maximum based on intermolecular interactions.[21] Also, the formation of hydrogen bonding in binary mixtures of alcohol and aprotic or nonpolar solvents has been examined by Inlow *et al.*[22] Since in the majority of binary solvent mixtures, intermolecular interactions result in deviations from ideality, we have investigated the solubility of benidipine hydrochloride in water–cosolvent or ethanol–cosolvent mixtures as a function of the volume fraction of a cosolvent. Acetonitrile, dioxane or ethanol in water–cosolvent mixtures, and acetone, acetonitrile or dichloromethane in ethanol–cosolvent mixtures were used as a cosolvent.

The solubility behavior of benidipine hydrochloride in water–cosolvent mixtures is depicted in Fig. 4. When acetonitrile or dioxane was used as a cosolvent, drug solubility was greatly increased, and parabolic relationships were observed with a peak solubility at 0.6—0.7 volume fraction of a cosolvent. On the other hand, when ethanol was used as a cosolvent, increased solubility of the drug was also noted at an early shaking time, whereas the dissolved drug suddenly began to deposit after that. Ultimately, improved solubility of the drug was not observed in various proportions of water and ethanol.

The parabolic solubility relationships of caffeine in both water–dioxane[11] and water–ethanol[12] mixtures have been explained by the result of self-association of the solute as the polarity changed. Conceivably, benidipine hydrochloride is not the planar molecules that probably undergo hydrophobic stacking interactions in water, as does caffeine. Therefore, it is possible that the maximum solubility in water–acetonitrile or dioxane mixtures and the initial increased solubility in water–ethanol mixtures are due to the formation of solvated or hydrated states of benidipine hydrochloride resulting from the changes produced by cosolvents in the structure of water. Similar solubility curves between acetonitrile and dioxane suggested that a specific interaction of dioxane–drug did not occur, in which *e.g.*, the two oxygens of dioxane are involved, permitting simultaneous interaction with water as well as the drug. With regard to the peculiar behavior

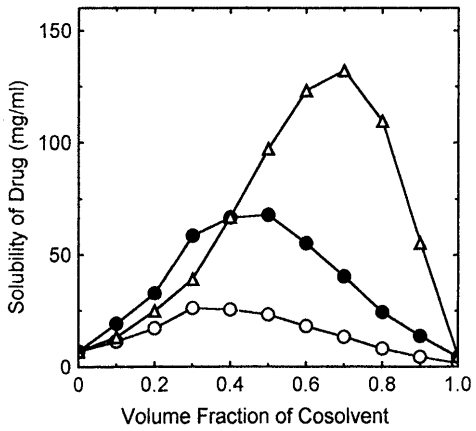

Fig. 5. Solubility of Benidipine Hydrochloride in Ethanol–Cosolvent Mixtures at 25 °C *versus* Volume Fraction of Cosolvent

○, ethanol–acetone; ●, ethanol–acetonitrile; △, ethanol–dichloromethane.

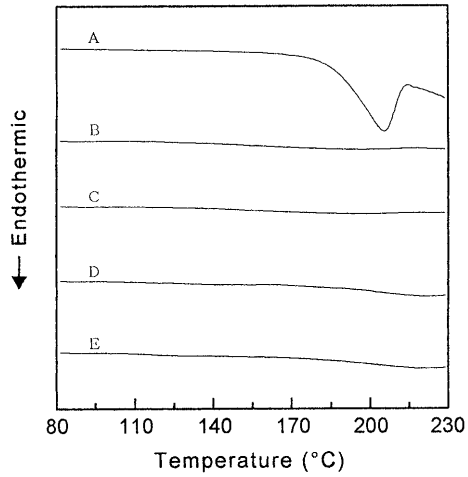

Fig. 6. The DSC Thermograms of Benidipine Hydrochloride Solid Dispersions with PVP or HPMC (Drug : Polymer = 1 : 3)

A, benidipine hydrochloride; B, C, PVP; D, E, HPMC. B, D, coprecipitated from ethanol : dichloromethane = 1 : 9; C, E, coprecipitated from ethanol : dichloromethane = 5:5.

of the drug solubility in water–ethanol mixtures, this may be because the extent of differences between water–drug and protic solvent–drug interactions is not the same as that of differences between water–drug and aprotic solvent–drug interactions.[23]

The ethanol–cosolvent mixtures also showed distinct parabolic relationships (Fig. 5). Higher solubility of the drug was found when dichloromethane was used as a cosolvent, followed by acetonitrile, then acetone. Moreover, it was interesting to note that ethanol–dichloromethane mixtures exhibited a peak solubility at 0.7 volume fraction of dichloromethane, while a peak solubility in ethanol–acetone or acetonitrile mixtures was observed at a 0.3—0.5 volume fraction of a cosolvent.

As hydrogen bonding ability increased (acetone > acetonitrile > dichloromethane), the maximum solubility of the drug decreased. Actually, any hydrogen bonded adduct of ethanol–dichloromethane must be of negligible stability in comparison to the stability of self-associated ethanol molecules. It seemed reasonable to assume that in ethanol–dichloromethane mixtures, dichloromethane might cleave a self-association of ethanol molecules by intermolecular forces, except for the hydrogen bonding, and then the heightened solvation of ethanol molecules would lead to the increase in drug solubility. This assumption conformed to the results reported by Taeye and Zeegers-Huyskens,[24] who studied the hydrogen bonds between caffeine and proton donor solvents in 1,2-dichloroethane so as to avoid a self-association of proton donor solvents. Considering that the dipole moment of acetonitrile is larger than that of acetone, the dipolar interactions probably operate to hinder the self-association of ethanol molecules without blocking the hydrogen bonding ability. In the following experiments, the binary mixtures of ethanol and dichloromethane were used because they are general solvents used in the preparation of solid dispersions.[25]

(b) Thermal Analysis and Drug Dissolution Profiles for PVP or HPMC Dispersions: As the poor organic solubility of benidipine hydrochloride was improved in the binary mixtures of ethanol and dichloromethane, there has been an attempt to prepare solid dispersions with a water-soluble polymer. However, there was a fear of recrystallization of the drug during the solvent evaporation, so we used PVP and HPMC as water-soluble polymers; both have been reported to inhibit the recrystallization of some drugs from the solution.[26,27] When PVP or HPMC was added to ethanol–dichloromethane mixtures from 0.5 to 0.9 volume fractions of dichloromethane in which benidipine hydrochloride was previously dissolved, there was no precipitation of the drug in these solutions. This indicated that these water-soluble polymers did not depress the drug solubilization in the binary solvent mixtures. Therefore, it was possible to prepare drug–PVP or drug–HPMC dispersions by the solvent removal process.

With the intention of investigating the effect of the solvent:cosolvent ratio during solvent evaporation, drug–PVP or drug–HPMC dispersions (1 : 3 weight ratio of drug : polymer) were prepared in a 1 : 9 or 5 : 5 ratio of ethanol:dichloromethane. The DSC thermograms of the drug and solid dispersions are shown in Fig. 6. As dichloromethane is more liable to evaporate than ethanol, the 1 : 9 ratio of ethanol : dichloromethane will be changed to 5 : 5 during the solvent removal process. Therefore, the 1 : 9 ratio of ethanol:dichloromethane will pass through the 3 : 7 ratio shown to provide the maximum solubility of the drug, which may be subject to the inhibitory effect of the polymer on drug recrystallization. On the other hand, it is expected that the decrease in drug solubility, that is, recrystallization of the drug, will occur rapidly in the 5 : 5 ratio of ethanol : dichloromethane. Nevertheless, all thermograms of the solid dispersions exhibited no melting peak of the drug. It was indicated that the presence of the polymer would result in the inhibition of drug recrystallization, even in the 5 : 5 ratio of ethanol : dichloromethane. The drug lost its crystal structure in a PVP or HPMC matrix, so that the dissolution rate of the drug from these solid dispersions will be considerably greater than the crystal drug.

The dissolution profiles of benidipine hydrochloride solid dispersions with PVP or HPMC prepared in a 1 : 9 or 5 : 5 ratio of ethanol:dichloromethane are illustrated in

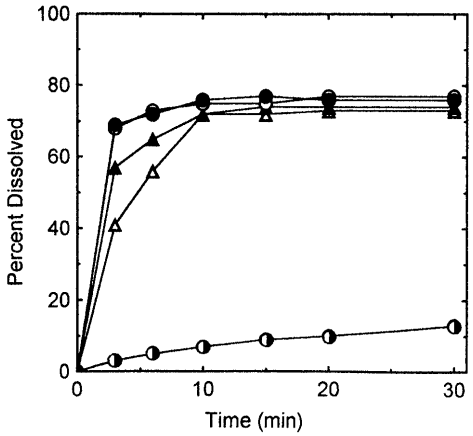

Fig. 7. Dissolution Profiles of Benidipine Hydrochloride Solid Dispersions with PVP or HPMC (Drug : Polymer = 1 : 3) in Water

◑, benidipine hydrochloride; ○, ●, PVP; △, ▲, HPMC. Open symbols: coprecipitated from ethanol : dichloromethane = 1 : 9; closed symbols: coprecipitated from ethanol : dichloromethane = 5 : 5.

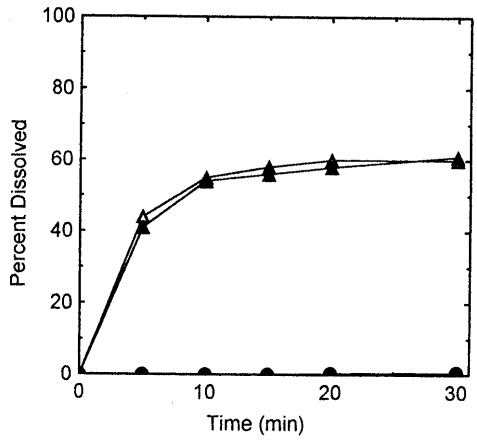

Fig. 8. Dissolution Profiles of Benidipine Hydrochloride Solid Dispersion Granules (Drug : PVP or HPMC : Lactose = 1 : 3 : 16) in McIlvaine Buffer (pH 6.0)

●, benidipine hydrochloride; △, PVP granules; ▲, HPMC granules.

Fig. 7. As expected, the dissolution rate of the drug from all solid dispersions was markedly improved in distilled water. Consequently, the effect of the solvent : cosolvent ratio on the drug release was not evident. The small difference in dissolution rates between PVP and HPMC dispersions would be due to the variant wettability and solubility of the polymers. What factors might contribute to the inhibitory effects of PVP and HPMC on the drug recrystallization during the solvent evaporation? First, it is possible that the polymer was able to complex specifically with the drug in the liquid state, causing a change in the types and distribution of molecular motions. It has been shown that PVP in solution can form molecular complexes with furosemide through an intermolecular hydrogen bond.[19] However, PVP did not induce the solubilization of benidipine hydrochloride in Table 1. It is also possible that the polymer accumulated in a higher concentration at the particle surfaces of the drug, where it might be in a better position to inhibit nucleation and growth initiated in these area. The recrystallization of sulfathiazole[28] and nifedipine[27] in solution was remarkably inhibited by PVP and HPMC, respectively. In this case, an absorption of polymers on the surface of drug nuclei was a main factor affecting the crystal growth of the drug. Also, it is possible that the larger molecular size of the polymer relative to the drug promotes a tendency to accumulate at the interface or to act as a very efficient steric barrier for nucleation and growth. Since the recrystallization of benidipine hydrochloride was inhibited even in a 5 : 5 ratio of ethanol : dichloromethane with PVP or HPMC, it was thought that the ethanol : dichloromethane ratio appropriate to preparing solid dispersions was 3 : 7 considering of the solubility of both drug and polymer.

Drug Dissolution Profiles for Solid Dispersion Granules in Media with or without Anionic Surfactant (a) Without Anionic Surfactant: Solid dispersion granules were composed of benidipine hydrochloride and two components : PVP or HPMC and lactose (1 : 3 : 16 weight ratio of drug : polymer : lactose). As a solvent, the 3 : 7 ratio of ethanol : dichloromethane was used. Figure 8 shows the dissolution profiles of the drug from the solid dispersion granules at pH 6.0. As expected, the solvent removal process did not give rise to drug recrystallization, which led to a great increase of the drug dissolution rate at pH 6.0. These solid dispersion granules will thus provide a good bioavailability of the drug, even for patients with low acidity of the gastric fluid. Although the solubilization of benidipine hydrochloride in the binary solvent mixtures permitted the preparation of solid dispersions with PVP or HPMC, it should be noted that the crystallization of amorphous drug in the polymer matrix at high relative humidity is liable to cause a decrease in not only the dissolution rate but also the bioavailability.[29] Sugimoto *et al.* have revealed that the preparation of fine granules using HPMC would provide a useful approach to good stability and bioavailability of nifedipine because the stability of an amorphous drug in the fine granules using HPMC was obtained on the grounds that the hygroscopicity of HPMC was lower than that of PVP.[25]

Table 3. Effect of SDS on the Dissolution Properties of Benidipine Hydrochloride from Solid Dispersion Granules

Surfactant	Polymer	Percent dissolved			
		pH 4.0		pH 6.0	
		5 min	30 min	5 min	30 min
Without SDS	PVP	98.4	102.2	44.0	58.5
	HPMC	99.0	99.7	41.0	60.5
With SDS	PVP	45.6	52.1	8.4	12.8
(2×10^{-3} % (w/v))	HPMC	49.0	56.9	16.3	14.0

In McIlvaine buffer (pH 4.0, 6.0).

(b) With Anionic Surfactant: SDS, an anionic surfactant, is finding increasingly widespread applications in pharmaceutical formation as a solubilizer and cosolubilizer. SDS is known to act as a fully dissociated electrolyte at low concentrations; nevertheless, SDS has also been shown to participate in several interactions with a substance of the opposite charge.[30,31] The effect of an anionic surfactant on the dissolution properties of benidipine hydrochloride from solid dispersion granules was investigated in media at pH 4.0 and 6.0, as shown in Table 3. These dissolution media contained 2×10^{-3} %

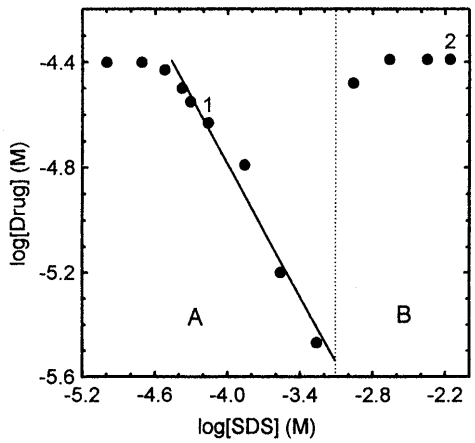

Fig. 9. Plot of the Logarithmic Concentration of Benidipine Hydrochloride Released from HPMC Dispersions at 30 min against the Logarithmic Concentration of SDS in McIlvaine Buffer (pH 4.0)

A, region of complex formation; B, region of complex solubilization in excess SDS. 1 and 2, correspond to 2×10^{-3} and 0.2% w/v of SDS, respectively. Slope = −0.871; intercept = −8.273; correlation coefficient = 0.987.

w/v of SDS, that is, about a 1 : 1 weight ratio of drug : SDS, which is quite low compared to the SDS critical micelle concentration (CMC) in water of approximately 0.2% w/v.[32] In both dissolution media at pH 4.0 and 6.0, the presence of SDS significantly decreased the amount of the dissolved drug. Daly *et al.* observed that SDS could retard the release of a cationic drug from HPMC matrix tablets.[33] This effect was attributed to the binding of the surfactant to the polymer, thereby causing an increase in gel viscosity. However, small differences in the release of benidipine hydrochloride were detected not only in the dispersion granules of PVP and HPMC, but also in the dissolution times of 5 and 30 min. These results indicated that the depressed dissolution properties of the drug arose from interactions between the drug and SDS.

Further investigations were carried out at pH 4.0, varying the SDS concentrations and using HPMC dispersion granules. The plot of the logarithmic concentration of benidipine hydrochloride at 30 min against a logarithmic concentration of SDS is given in Fig. 9. The interaction between the drug and SDS was characterized by two separate regions. Region A was described as the start of complex formation and the separation of an insoluble phase. The drug concentration can be represented by a differential line. Especially, the part in which the drug concentration decreased remarkably produced a straight line with a slope of approximately one. It would be reasonable to assume that a 1 : 1 complex was formed between the drug and the surfactant. This was expected since both compounds provide monovalent ions. Region B was regarded as the micellar solubilization of the complex. The complex formed would be hydrophobic in nature and could be considered an oily solubilizate in the micelles. Also, the CMC of SDS would be lowered by the presence of the drug cation and by the complex formation. These findings are similar to the results reported by Mukhayer *et al.*, who described a typical conductivity curve for the titration of SDS against a solution of a phosphonium compound.[34] Since the complex precipitated readily at low concentrations of SDS, it should be noted that if a dosage form including a slight amount of SDS is simultaneously administered with these solid dispersion granules, the bioavailability of benidipine hydrochloride may be influenced.

In conclusion, the solubilization of benidipine hydrochloride in an organic solution of Eudragit E-100 or binary solvent mixtures made it possible to prepare solid dispersions. In a weak acid (pH 6.0), the dissolution rate of the drug dispersed in Eudragit E-100 was not markedly increased, whereas when dispersed in PVP or HPMC, a great improvement in the dissolution rate was obtained. The process of elucidating the mechanism of interactions, *i.e.*, drug–polymer, solvent–cosolvent, *etc.*, on the drug solubilization in these systems is now being undertaken.

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