Solid Dispersions of Benidipine Hydrochloride. II. Investigation of the Interactions among Drug, Polymer and Solvent in Preparations

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The solubilization mechanism of benidipine hydrochloride in two kinds of organic solvent systems has been investigated: one in an organic solution of Eudragit® E-100 (OSE), and the other in binary solvent mixtures (BSM) of alcohol–cosolvent. In the OSE, the organic solubility of the drug was increased in proportion to the polymer concentration. Fourier transform infrared spectroscopy clearly demonstrated the existence of hydrogen bonds between dimethylamino groups of the polymer and piperidine NH^+ of the drug. The ultraviolet absorption maximum of the drug in the 350 nm region blue-shifted in dichloromethane or chloroform with the polymer, whereas this shift was not found in ethanol or acetonitrile with the polymer. In the BSM, the logarithmic maximum solubility of the drug in ethanol–cosolvent mixtures was linearly related to the π^* (dipolarity–polarizability) value of the cosolvent. The initial slope of the drug solubility curve in alcohol–dichloromethane mixtures was in good correlation with the α (hydrogen-bond donor acidity) value of alcohol. Therefore, it was understood that the solubilization of benidipine hydrochloride in the OSE resulted from the drug–polymer complexation with the intermolecular hydrogen bonding and dipolar interactions, and the solubilization effect in the BSM arose from the enhancement of the proton donor ability of alcohol molecules by the dipolar interactions with the cosolvent.

Key words benidipine hydrochloride; solubilization; intermolecular interaction; hydrogen bonding; dipolar interaction

In deviations from regular solutions due to the self-association of a solute or solvent, solvation of the solute by the solvent molecules, or complexation of two or more solute species, a qualitative and quantitative understanding of the nature and strength of intermolecular interactions is obviously important to the pharmaceutical sciences.

Many approaches have been developed for separating the contributions of hydrogen-bond donor (HBD) acidity, hydrogen-bond acceptor (HBA) basicity and dipolarity to the overall solvent strength. In chromatography, Snyder's solvent triangle approach has been used very widely,^{1,2)} defining χ_d (HBD), χ_e (HBA) and χ_n (dipolarity). These parameters represent the fraction of the polarity index, P' , contributed by interactions associated with dioxane, ethanol and nitromethane, respectively. As another approach, the solvatochromic parameters α (HBD), β (HBA) and π^* (dipolarity–polarizability) have been also reported by Kamlet *et al.*,³⁾ in conjunction with linear solvation energy relationships (LSER). These parameters have been measured for hundreds of liquids. Various linear combinations of these three parameters have been used to describe a wide variety of important solution processes.⁴⁾

Intermolecular complexing ability and its effect on the solubility of pharmaceuticals have prompted many investigations into its usefulness by ultraviolet (UV) or infrared (IR) spectroscopy, nuclear magnetic resonance and thermodynamic analysis.^{5–7)} When describing complex formation, hydrogen bonding is often invoked as one of the intermolecular forces. It is not strong, but plays an important role in determining the property of a drug in which it occurs. Actually, in the solid state, hydrogen bonding interactions of drug–polymer may help account for the formation of amorphous solid dispersions.^{8,9)}

Benidipine hydrochloride, a calcium-antagonist, is a slightly soluble compound in a weak acid, so that its

bioavailability is likely to be influenced by the gastric acidity of patients. The drug is also poorly soluble in commonly used organic solvents.¹⁰⁾ The authors have been developing a preparation of solid dispersions of benidipine hydrochloride with a water-insoluble polymer (Eudragit® E-100) or water-soluble polymer (polyvinylpyrrolidone or hydroxypropylmethylcellulose) by the solvent removal process.¹¹⁾ This process was based on an improved organic solubility of the drug in two kinds of solvent systems: dichloromethane with Eudragit® E-100 and ethanol–dichloromethane mixtures.

In this paper, complex formation between benidipine hydrochloride and Eudragit® E-100 was examined in thermodynamic analysis and spectroscopy. The interactions of both alcohol–cosolvent and drug–alcohol in alcohol–cosolvent mixtures were investigated by the solvatochromic parameters with the solubility data. Good solvent groups for dissolving the drug were also clarified from the Snyder's solvent triangle.

Experimental

Materials Benidipine hydrochloride (Kyowa Hakko Kogyo Co., Ltd., Japan) sieved through 48 mesh (297 μm) was used. Methylmethacrylate butylmethacrylate dimethylaminoethylmethacrylate copolymer (Eudragit® E-100) was obtained from Röhm Pharma GmbH, Germany. The mean molecular weight was 150000. All solvents used in this work were of the best commercially available grades.

Drug Solubility Studies (a) In Pure Organic Solvents: Excess amounts of benidipine hydrochloride were added to thirty-five kinds of organic solvents (5 ml). After shaking for 12 h at 25 °C, samples were withdrawn, filtered (0.5 μm), diluted and analyzed at 237 nm by HPLC.¹¹⁾ Dibutyl ether, diisopropyl ether, *p*-xylene, toluene, chlorobenzene, bromobenzene, diethyl ether, isoamyl alcohol, anisole, 2-propanol, 1-butanol, 1-propanol, tetrahydrofuran, dichloromethane, chloroform, ethanol, butyronitrile, 2-butanone, cyclohexanone, benzonitrile, acetophenone, 1,4-dioxane, pyridine, acetonitrile, methoxyethanol, nitromethane, benzyl alcohol, γ -butyrolactone, aniline, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, dimethyl sulfoxide, trifluoroethanol and hexafluoroisopropanol were used as organic

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solvents.

(b) In an Organic Solution of Eudragit® E-100: Benidipine hydrochloride (200 mg) was added to organic solvents (5 ml) containing various concentrations of Eudragit® E-100. After shaking for 12 h at 5 and 25 °C, samples were analyzed as above. Acetone, dichloromethane and chloroform were used as organic solvents.

(c) In Binary Solvent Mixtures: Different concentrations ranging from 0 to 100% v/v of the cosolvent, viz., tetrahydrofuran, acetone, 2-butanone, cyclohexanone, acetonitrile, nitromethane, benzonitrile, dichloromethane, chloroform and chlorobenzene, in ethanol were prepared. Similarly, different concentrations of dichloromethane in alcohols, viz., methanol, ethanol and 2-propanol, were also prepared. Excess amounts of benidipine hydrochloride were added to both ethanol-cosolvent and alcohol-dichloromethane combinations (5 ml). After shaking for 12 h at 25 °C, samples were analyzed as above.

UV Absorption Spectra The UV absorption spectra of benidipine hydrochloride were determined after dissolving the drug in organic solvents with or without Eudragit® E-100 (U-3200, Hitachi Seisakusho Co., Ltd., Japan). The final concentrations of the drug and the polymer were 3×10^{-5} and 1×10^{-7} M, respectively. Ethanol, acetonitrile, dichloromethane and chloroform were used as organic solvents.

Fourier Transform IR (FT-IR) Spectra The FT-IR spectra of benidipine hydrochloride, Eudragit® E-100 and drug-Eudragit® E-100 dispersions (1:0.5–1:3 weight ratio of drug:polymer) prepared by the solvent removal process¹¹ were measured by an FT-IR spectrometer (1725X, Perkin-Elmer) using the KBr disk technique.

Results and Discussion

Drug Solubility in Pure Organic Solvents Benidipine hydrochloride is a poorly soluble compound in commonly used organic solvents, e.g., ethanol, dichloromethane.¹⁰ The solubility of benidipine hydrochloride in thirty-five kinds of organic solvents was determined in order to clarify good solvent groups for dissolving the drug using Snyder's solvent characterization parameters: P' , χ_d , χ_e and χ_n .²⁾ Figure 1 shows the relationship between Snyder's polarity index (P') value of the individual solvents and the logarithmic solubility of the drug. The P' value is a measure of the strength of a solvent or its ability to dissolve or to interact with various polar test solutes. As the P' value of the solvent increased, the logarithmic solubility of the drug

Fig. 1. Plot of the Logarithmic Solubility of Benidipine Hydrochloride in Individual Solvents at 25 °C as a Function of Snyder's Polarity Index (P')

1, dibutyl ether; 2, diisopropyl ether; 3, *p*-xylene; 4, toluene; 5, chlorobenzene; 6, bromobenzene; 7, diethyl ether; 8, isoamyl alcohol; 9, anisole; 10, 2-propanol; 11, 1-butanol; 12, 1-propanol; 13, tetrahydrofuran; 14, dichloromethane; 15, chloroform; 16, ethanol; 17, butyronitrile; 18, 2-butanone; 19, cyclohexanone; 20, benzonitrile; 21, acetophenone; 22, 1,4-dioxane; 23, pyridine; 24, acetonitrile; 25, methoxyethanol; 26, nitromethane; 27, benzyl alcohol; 28, γ -butyrolactone; 29, aniline; 30, *N,N*-dimethylformamide; 31, *N,N*-dimethylacetamide; 32, *N*-methyl-2-pyrrolidone; 33, dimethylsulfoxide; 34, trifluoroethanol; 35, hexafluoroisopropanol.

exhibited an approximately linear increase.

In general, the dispersion or London (induced dipole-induced dipole) interactions, which can be considered to arise from fluctuating dipoles in each atom, predominate over all other interactions in organic solvents, whether polar or not. However, it is well known that the existence of specific interactions, except for dispersion forces, results in the deviations from regular solutions: the orientation or Keesom (dipole-dipole) forces occurring between molecules which have permanent dipole moments; the induction or Debye (dipole-induced dipole) forces occurring between molecules with permanent dipole moments and neighboring molecules with an induced non-uniform charge; and hydrogen bonding association, etc. The P' value was approximately corrected for the dispersion interactions using an *n*-alkane.¹⁾ It was therefore considered that the contribution of interactions other than the dispersion energies would be important to dissolving benidipine hydrochloride in organic solvents.

It was useful (but not precise) to consider the Snyder's selectivity parameters, χ_d , χ_e and χ_n , as reflecting the relative ability of the solvent to function, respectively, as HBD or a proton donor, HBA or a proton acceptor and dipolarity. These parameters can be plotted on a triangular diagram, and liquids with the same chemical functional group tend to appear in the same region of the triangle.²⁾ Figure 2 shows the solubility of benidipine hydrochloride in the individual solvents by the selectivity triangle. Two regions, A and B, appeared to reflect the dissolution of significant amounts of the drug. As a solvent of more than 100 mg/ml of solubility, the A region included pyridine, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidone and dimethyl sulfoxide; the B region included benzyl alcohol, trifluoroethanol and hexafluoroisopropanol. Particularly, fluoroalkanol in the B region exhibited more than 500 mg/ml of solubility.

Fig. 2. Triangular Selectivity Parameter Diagram for the Solubility of Benidipine Hydrochloride in Individual Solvents at 25 °C

Δ , < 10 mg/ml; $\circ$, 10–100 mg/ml; $\bullet$, 100–500 mg/ml; $\bullet$, 500 mg/ml <. 1, dibutyl ether; 2, diisopropyl ether; 3, *p*-xylene; 4, toluene; 5, chlorobenzene; 6, bromobenzene; 7, diethyl ether; 8, isoamyl alcohol; 9, anisole; 10, 2-propanol; 11, 1-butanol; 12, 1-propanol; 13, tetrahydrofuran; 14, dichloromethane; 15, chloroform; 16, ethanol; 17, butyronitrile; 18, 2-butanone; 19, cyclohexanone; 20, benzonitrile; 21, acetophenone; 22, 1,4-dioxane; 23, pyridine; 24, acetonitrile; 25, methoxyethanol; 26, nitromethane; 27, benzyl alcohol; 28, γ -butyrolactone; 29, aniline; 30, *N,N*-dimethylformamide; 31, *N,N*-dimethylacetamide; 32, *N*-methyl-2-pyrrolidone; 33, dimethylsulfoxide; 34, trifluoroethanol; 35, hexafluoroisopropanol.

Solvents of less than 100 mg/ml of solubility in the A region were tetrahydrofuran (No. 13) and methoxyethanol (No. 25); dipole moments of these solvents are lower than those of the other solvents in the same region.¹²⁾

Since Snyder' parameters are defined by using various polar test solutes, the triangular diagram should not allow very strong discrimination between solvents of different dipolarities.²⁾ This restriction was confirmed in that not only tetrahydrofuran but dioxane (No. 22), which has a fairly low dipole moment, was close to *N,N*-dimethylformamide (No. 30) and dimethyl sulfoxide (No. 33) in Fig. 2. In comparison with the χ_e and χ_d values of aliphatic alcohols (*e.g.*, ethanol, No. 16), the A and B regions showed moderate χ_e and high χ_d values, respectively. These results implied that both the aprotic solvents, with high dipole moment and moderate proton acceptor ability, and the protic solvents, with high proton donor ability, led to a marked increase in drug solubility.

Mechanism of Drug Solubilization in Organic Solution of Eudragit® E-100 (a) Thermodynamic Analysis: In the preceding paper,¹¹⁾ it was proven possible to prepare solid dispersions of benidipine hydrochloride with Eudragit® E-100 by the solvent removal process, since the poor organic solubility of the drug was greatly improved by the formation of drug-polymer complexes. This solubilization effect of the polymer was kept in acetone, dichloromethane and chloroform, whereas it was somewhat depressed in acetonitrile and was completely inhibited in ethanol.

The effect of Eudragit® E-100 on the drug solubilization in acetone, dichloromethane and chloroform was evaluated as shown in Fig. 3. The plots of drug solubility against the polymer concentrations at 25 °C gave linear relationships in all solvents, with approximately similar positive slopes. Furthermore, in dichloromethane, the straight line obtained at 5 °C qualitatively paralleled that at 25 °C. These findings suggested that the mechanism of drug solubilization by drug-polymer complexation was essentially the same for the different solvents and temperatures.

Table 1 presents the different thermodynamic parameters associated with the solubility of benidipine hydro-

Fig. 3. Relationship between Solubility of Benidipine Hydrochloride and Molarity of Eudragit® E-100 in Organic Solvents

○, in dichloromethane at 5 °C; ●, in dichloromethane at 25 °C; ▲, in acetone at 25 °C; ■, in chloroform at 25 °C.

chloride in dichloromethane with Eudragit® E-100. An indication of the type of reaction occurring between solute and solvent may be obtained from the values of the free energy change ΔF that was calculated according to the following relationship¹³⁾:

$$\Delta F = -2.303RT \log \frac{S_s}{S_o} \quad (1)$$

where S_s and S_o are the molar solubilities of the drug in dichloromethane with the polymer and in dichloromethane, respectively. At a constant temperature (T), the free energy change will be determined by the enthalpy change ΔH (bonding strength) and the entropy change ΔS (disordering or bond breaking), the equilibrium considered to be between the same standard states.

$$\Delta F = \Delta H - T\Delta S \quad (2)$$

ΔH can be determined using an integrated form of the van't Hoff equation¹³⁾:

$$\Delta H = 2.303 \log \frac{(S_s/S_o)_2}{(S_s/S_o)_1} \times \frac{RT_2T_1}{T_2 - T_1} \quad (3)$$

The data in Table 1 provide further information regarding the enhanced solubility of benidipine hydrochloride in organic solutions of Eudragit® E-100. ΔS values were negative, revealing the possibility of an increased ordering of the species by complexation. Both ΔF and ΔH values were negative, indicating the spontaneity and exothermic nature of the drug solubilization process based on complexation with the polymer. Furthermore, the ΔH values decreased with an increase in the polymer concentrations, demonstrating that the drug-polymer complexation became progressively favorable with the addition of the polymer. The ΔH values (not more than about 13 kJ/mol) implied weak hydrogen bonds in the drug-polymer interactions.¹⁴⁾

(b) UV Absorption Spectroscopy: The UV absorption spectra of benidipine hydrochloride were determined in the various organic solvents with or without Eudragit® E-100 (Table 2). The maximum wavelength ($\lambda_{1\max}$) in the 250 nm region was scarcely affected by the addition of the polymer. On the other hand, the maximum wavelength ($\lambda_{2\max}$) in the 350 nm region blue-shifted by about 5 nm in dichloromethane or chloroform with the polymer. The position of $\lambda_{2\max}$ was presumed to be due to the $\pi \rightarrow \pi^*$ transition (K-band) of 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid dimethyl ester for the following reasons¹⁵⁾: the K-band of $\text{HO-CO-C}(\text{CH}_3)=\text{C}(\text{CH}_3)\text{-NR}_2$ is calculated at about 340 nm, and the intensity of

Table 1. Thermodynamic Parameters for the Solubility of Benidipine Hydrochloride in Dichloromethane with Eudragit® E-100

Concentration of polymer ($\times 10^{-5}$ M)	ΔF (kJ·mol ⁻¹)		ΔH (kJ·mol ⁻¹)	ΔS (J·mol ⁻¹ ·K ⁻¹)
	5 °C	25 °C		25 °C
2.0	-1.614	-1.278	-6.281	-16.79
4.0	-2.493	-2.030	-8.926	-23.14
6.0	-3.158	-2.660	-10.084	-24.91
8.0	-3.607	-3.041	-11.463	-28.26

Table 2. Wavelengths ($\lambda_{\max}$) and ϵ Values of UV Absorption Spectra of Benidipine Hydrochloride in Organic Solvents with or without Eudragit® E-100

Solvent	$\lambda_{1\max}$ (nm)	ϵ	$\lambda_{2\max}$ (nm)	ϵ
Ethanol ^{a)}	237	(27767)	358	(6903)
Ethanol/polymer ^{b)}	237	(27740)	357	(6693)
Acetonitrile	237	(26407)	349	(6437)
Acetonitrile/polymer	235	(27163)	348	(6353)
Dichloromethane	237	(25867)	348	(6670)
Dichloromethane/polymer	236	(26197)	343	(6447)
Chloroform	—	—	348	(6247)
Chloroform/polymer	—	—	344	(6377)

Concentrations of drug and polymer in solvent = 3×10^{-5} and 1×10^{-7} M, respectively. a) In solvent without polymer. b) In solvent with polymer. —: Not available.

this band will decrease ($\epsilon < 10^4$) by steric hindrance in a cyclic system. Polar solvents generally (but not always) red-shift the K-band, so that the position of $\lambda_{2\max}$ would change to a longer wavelength in ethanol.

Beten *et al.*¹⁶⁾ have reported that the hypsochromic shifts by about 6 nm were caused by hydrogen bonds between dipyridamole and Eudragit® S. The existence of Eudragit® E-100 did not lead to a blue shift of the $\lambda_{2\max}$ position of benidipine hydrochloride in either ethanol or acetonitrile; it was thought that the electrostatic interactions, including dipolar interactions and hydrogen bonds, would operate as intermolecular forces of drug–polymer. Furthermore, considering that the polymer's solubilization effect was completely inhibited in ethanol,¹¹⁾ the hydrogen bonding is likely to contribute predominantly to the drug–polymer complexation.

(c) FT-IR Absorption Spectroscopy: To characterize the drug–polymer interactions in the solid state, FT-IR absorption spectra were obtained for the solid dispersions of benidipine hydrochloride with Eudragit® E-100 as prepared in the previous paper,¹¹⁾ as shown in Fig. 4. Benidipine hydrochloride and Eudragit® E-100 showed a piperidine NH^+ band at 2528 cm^{-1} (Fig. 4B) and dimethylamino bands at 2823 and 2772 cm^{-1} (Fig. 4A), respectively. The solid dispersions (1:0.5 weight ratio of drug:polymer) exhibited that the piperidine NH^+ band of the drug was broadened, weakened and split, and the dimethylamino bands of the polymer were shifted to lower frequencies (Fig. 4C). In addition, with increasing the polymer proportion in the solid dispersions (Fig. 4D, E), the piperidine NH^+ bond of the drug became broadened and weakened, whereas the dimethylamino bands of the polymer reverted to the frequencies and intensities shown in Fig. 4A.

These characteristic changes were attributed to the fact that the piperidine NH^+ group of benidipine hydrochloride bound with the dimethylamino group of Eudragit® E-100 via forming stable complexes with the hydrogen bonding. It is thus inferred that the drug and the polymer interact with the hydrogen bonding as a proton donor and a proton acceptor, respectively. Hence, a proton donor solvent such as ethanol should compete with the drug for the polymer. Also, the dipole–dipole (or ion–dipole) forces of $\text{R}_3\text{NH}^+ \cdots \text{NR}_3$ probably participated in the hydrogen

Fig. 4. FT-IR Spectra of Benidipine Hydrochloride Solid Dispersions with Eudragit® E-100

A, Eudragit® E-100; B, benidipine hydrochloride; C, drug:polymer = 1:0.5; D, drug:polymer = 1:1; E, drug:polymer = 1:3. 1, attributable to dimethylamino groups of Eudragit® E-100; 2, attributable to the piperidine NH^+ stretch of benidipine hydrochloride.

bonding formation of drug–polymer, which might be disturbed by a dipolar solvent such as acetonitrile. These findings were consistent with the high solubility of drug in the aprotic solvents with high dipole moment and moderate proton acceptor ability, as shown in Fig. 2 (A region).

Mechanism of Drug Solubilization in Binary Solvent Mixtures (a) Ethanol–Cosolvent Systems: The authors have presented the preparation of solid dispersions of benidipine hydrochloride with a water-soluble polymer (polyvinylpyrrolidone or hydroxypropylmethylcellulose) based on the drug solubilization in ethanol–dichloromethane mixtures.¹¹⁾ In that case, there was no precipitation of the drug when the water-soluble polymer was added into binary solvent mixtures with the drug previously dissolved, and the solvent removal process was carried out under reduced pressure.

The solubility of benidipine hydrochloride was investigated in various binary mixtures of ethanol and cosolvent at 25°C , in order to understand both the solvent–cosolvent and drug–solvent interactions in drug solubilization. As can be seen in Fig. 5, the solubility of the drug was greatly improved when nitromethane or benzonitrile, with poor proton acceptor ability, as well as dichloromethane, was used as a cosolvent. Especially, the highest solubility of the drug was obtained in ethanol–benzonitrile mixtures. On the other hand, in the case of tetrahydrofuran, with moderate proton acceptor ability, as a cosolvent, increased solubility of the drug was not recognized. These data indicated that a cosolvent able to form hydrogen bonding as a proton acceptor would reduce

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

A (cosolvent): ○, acetone; ●, benzonitrile; △, nitromethane; ▲, cyclohexanone; □, dichloromethane. B (cosolvent): ○, tetrahydrofuran; ●, 2-butanone; △, acetone; ▲, chloroform; □, chlorobenzene.

the proton donor ability of ethanol, which did not result in the enhanced solubility of the drug.

In this investigation, cosolvents with greater dipole moment had a tendency to increase the solubility of benidipine hydrochloride in the binary solvent mixtures. However, this relationship was not exactly proportional, *e.g.*, the dipole moments of benzonitrile, dichloromethane and acetonitrile are 13.51, 5.17 and 11.48 $\times 10^{-30}$ Cm, respectively.¹²⁾ When hydrogen bonding association is excluded, the solvent-solvent interaction is always made up of dipolar and dispersion interactions. Meyer *et al.*^{17,18)} revealed that induction was more important than orientation regarding dipolar interactions in polar organic solvents. The ethanol-cosolvent interactions would not only be related to the permanent dipole moment of the cosolvent, but dependent to some extent on the induced dipole caused by the polarizability of ethanol molecules.

The solvatochromic parameters α (HBD), β (HBA) and π^* (dipolarity-polarizability)³⁾ are widely used by physical organic chemists to rationalize, correlate and predict the effect of a solvent on chemical reactions. The π^* scale is correlates quite well with the other empirical polarity scale widely used,¹⁹⁾ and rather insensitive to dispersion interactions.²⁰⁾ In addition, a very good correlation between the π^* parameters and a simple function of the relative permittivity (ϵ_r) and the refractive index (n), $(\epsilon_r - 1)(n^2 - 1)/(2\epsilon_r + 1)(2n^2 + 1)$, has been reported by

Fig. 6. Relationship between the Logarithmic Maximum Solubility of Benidipine Hydrochloride in Ethanol-Cosolvent Mixtures at 25 °C and the Solvatochromic Parameter (π^*) of the Cosolvent

1, tetrahydrofuran; 2, acetone; 3, 2-butanone; 4, cyclohexanone; 5, acetonitrile; 6, nitromethane; 7, benzonitrile; 8, dichloromethane; 9, chloroform; 10, chlorobenzene.

Bekárek.²¹⁾ The values of ϵ_r and n depend on solvent polarity and polarizability, respectively. Therefore, the π^* scale may be a better measure of dipolar interactions, including both orientation and induction forces.

The plot of the logarithmic maximum solubility of benidipine hydrochloride in binary solvent mixtures against the π^* value of the cosolvent is given in Fig. 6. Except for the ethanol-chloroform mixtures, the logarithmic maximum solubility of the drug in this system was found to be linearly related to the π^* value of the cosolvent (correlation coefficient = 0.969). These results indicated that dipolar interactions with orientation and induction forces between ethanol and cosolvent might cleave the self-association of ethanol molecules, and the proton donor ability of ethanol molecules would be enhanced. The drug solubility in ethanol-chloroform mixtures was higher than that predicted by the π^* value of chloroform. This was presumed to be due to the proton donating nature of chloroform, which led to a considerably stronger hydrogen bonding than the haloethanes.^{22,23)} Thus, the formation of hydrogen bonds between ethanol and chloroform could result in enhancing the proton donor ability of ethanol molecules.

(b) Alcohol-Dichloromethane Systems: The solubility of benidipine hydrochloride in different binary solvent mixtures of alcohol (methanol, ethanol or 2-propanol) and dichloromethane at 25 °C was determined so as to evaluate the importance of the proton donor ability of alcohol (Fig. 7A). The solubility curves of the drug had similar shapes, but a large difference in the maximum solubility of the drug was observed: the ratio of maximum solubility was approximately 11, 4 and 1 when methanol, ethanol and 2-propanol were used. Furthermore, it was interesting to note that a linear relationship existed between the solvatochromic parameter α value of the alcohol and the initial slope of the drug solubility curve (Fig. 7B).

The α values are intended to represent the HBD strengths of the neat, strongly self-associated solvents, so that it is possible that R-OH monomers might show markedly different orderings of HBD strengths.²⁴⁾

Fig. 7. Solubility of Benidipine Hydrochloride in Alcohol-Dichloromethane Mixtures at 25°C versus Molarity of Alcohol (A), and Relationship between the Initial Slope of Solubility Curve and the Solvatochromic Parameter (α) of Alcohol (B)

○, methanol; ●, ethanol; △, 2-propanol. A: the final point in each case represents the solubility in pure alcohol.

However, it is apparent that the aliphatic alcohols show decreasing HBD acidity with the increasing electron donating ability of R in R-OH. It is reasonable to think that the increase in drug solubility in alcohol-dichloromethane mixtures will depend on the proton donor ability of alcohol molecules that cleaved self-association by dipolar interactions with dichloromethane. Since ethanol red-shifted the position of λ_2 max, which was likely due to the K-band of α,β -unsaturated carboxylic acid methyl ester in UV absorption spectroscopy (Table 2), it was assumed that alcohol molecules dissociated by dichloromethane could act as a high proton donor solvent primarily to the carbonyl groups of the drug. These results were compatible with the high solubility of the drug obtained in protic solvents with high proton donor ability, as shown in Fig. 2 (B region).

In conclusion, the solubilization of benidipine hydrochloride in both dichloromethane with Eudragit® E-100 and binary mixtures of ethanol-dichloromethane was understood to involve the following mechanism: in the former system, it involves drug-polymer complexation with intermolecular hydrogen bonding and dipolar interactions (Fig. 8A), and in the latter system, it involves the enhancement of the proton donor ability of ethanol molecules that cleaved self-association by the dipolar

Fig. 8. Schematic Presentation of the Solubilization Mechanism of Benidipine Hydrochloride (BH)

A, complexation between BH and Eudragit® E-100 in dichloromethane; B, enhancement of ethanol solvation to BH in ethanol-dichloromethane mixtures. *, in the case of using ethanol or acetonitrile instead of dichloromethane as a solvent.

interactions with dichloromethane (Fig. 8B).

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