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Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellulose and hydroxypropylmethylcellulose

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Abstract

The purpose of this study is to investigate the release mechanism of poorly water-soluble drug from the extended release solid dispersion systems with water-insoluble ethylcellulose (EC) and water-soluble hydroxypropylmethylcellulose (HPMC) (1:1). Indomethacin (IND) was used as a model of poorly water-soluble drug. Two kinds of solid dispersions were prepared by the solvent evaporation methods, which consist of the same formulation but exhibit different physical performance. It appeared that the dissolution behavior of IND depended on the structures of EC–HPMC matrices, which were governed by the preparation method. In addition, the dissolution behavior showed pH dependency that the dissolution rate of IND was slower in acidic medium than that in neutral medium. The experimental results revealed that the hydrophobic interaction between IND and EC occurred under lower pH and strongly delayed the dissolution rate of IND. The relationship between this hydrophobic interaction and the dissolution rate of IND was also proposed.

Keywords: Indomethacin; Ethylcellulose; Hydroxypropylmethylcellulose; Solid dispersion formulation; Dissolution mechanism

1. Introduction

Recent technological innovation of combinatorial chemistry and high-throughput screening can effectively discover the seeds of new drugs, which presents good pharmacological activities. However, since many seeds of new drugs discovered by those techniques are poorly water-soluble, it is often difficult to adopt them as a candidate of new drug. To improve such poor solubility issues, solid dispersion techniques are widely applied to increase the apparent solubility or enhance the oral bioavailability of poorly water-soluble compounds (Chiou and Riegelman, 1971; Sekiguchi and Obi, 1961). However, despite many papers, which sug-

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gested that the release mechanisms of drugs from a variety of solid dispersions depend on the physical properties of carriers as well as drug substances, preparation methods and so on, basic principles of their dissolution mechanisms have not been understood sufficiently (Serajuddin, 1997, 1999; Tantishaiyakul et al., 1996; Craig, 2001).

From quality control point of view, the release profiles of the extended release formulation must be controlled under the strict specifications as many guidances in US, Japan and Europe stated (Drug Approval and Licensing Procedures in Japan, 2001; Guidance for Industry, Extended Release Oral Dosage Forms, 1997; Note for Guidance on Quality of Modified Release Products, 1999). Thus, it is important to grasp the release mechanisms of the extended release formulation for the stable manufacturing with consistent qualities when the extended release formulation is developed as possible commercial product.

In the present study, solid dispersions of IND with the water-insoluble EC and water-soluble HPMC (1:1) matrices were prepared as the model formulation having functions of both the extended release and the solid dispersion properties. Solvent evaporation methods (Chiou and Riegelman, 1969; Simonelli et al., 1969), in which ethanol to dissolve IND as well as EC and to suspend HPMC, and a mixed solution of ethanol and methylene chloride (1:1, v/v) to dissolve all three components before the evaporation, were applied to prepare the model solid dispersions. The influence of this formulation factor on the physical structures of solid dispersion granules and the dissolution mechanism was examined.

As reported by Ozeki et al. (1994, 1995), behavior of water-soluble polymers during dissolution has a key factor in mechanism of drug release from solid dispersions prepared with water-insoluble and water-soluble polymers. Model solid dispersions prepared in this study contain water-insoluble EC and water-soluble HPMC as carrier polymers. It was expected that water-insoluble polymer, EC, kept its three-dimensional structure during the dissolution while the water-soluble polymer, HPMC, gelated in the EC matrices, or dissolved and diffused quickly into dissolution medium. Therefore, the HPMC behavior was investigated by gel-permeation chromatography system with refractive index detector to elucidate a role of HPMC on IND release mechanism.

Furthermore, since IND is an acidic compound whose ionic dissociation state is changeable around its pK_a, 4.5, dissolution tests were conducted with neutral to acid pH. Especially, the mechanism of pH dependent dissolution rate was studied in consideration of interaction between drug and carrier polymer occurring in lower pH region where the solubility of IND was extremely low.

2. Materials and methods

2.1. Materials

Indomethacin (IND, γ-crystals) was purchased from ICN Biomedicals, Inc. (OH, USA). Hydroxypropylmethylcellulose (HPMC, TC-5EW) was purchased from Shinetsu Chemical Industry Company, Ltd. (Tokyo, Japan). Ethylcellulose (EC, ETHOCEL STD 10FP) was purchased from DOW Chemical Industries, Ltd. (MI, USA). All other chemicals were of analytical grade, and the water used was filtered through a Mill-Q Water Purification System prior to use.

2.2. Preparation of the solid dispersions, physical mixture and amorphous IND

2.2.1. Solid dispersion by Suspending Method

Solid dispersions consisting of IND, EC and HPMC (1:1:1, w/w) were prepared as follows. IND of 1 g was dissolved in ethanol of 100 mL followed by dissolving EC of 1 g in the solution. Then, HPMC of 1 g was suspended in the solution. The solvents were evaporated under the reduced pressure using rotary evaporator at 35 °C. Solid dispersions obtained were dried for 12 h under vacuum, milled and sieved (150–355 μm). After being dried in a desiccator, the solid dispersions were used for the following studies.

2.2.2. Solid dispersion by Dissolving Method

To the HPMC suspended solution described in Section 2.2.1, methylene chloride of 100 mL was added to dissolve HPMC before the evaporation of the solvent. All other procedures were the same as Section 2.2.1.

2.2.3. Preparation of physical mixture

1:1:1 (w/w) physical mixture of IND, EC and HPMC was prepared by thorough mixing in polyethylene bag.

2.2.4. Preparation of amorphous IND

Amorphous IND was prepared by melting IND drug substance at 165 °C and quench cooling in liquid nitrogen. This amorphous material was used for analysis immediately after preparation.

2.3. X-ray powder diffraction (XRD)

Powder X-ray diffraction was performed using a Philips MPD1880 X-ray Powder Diffraction system (Philips, Netherlands). The radiation was generated by Cu Kα at 40 kV and 30 mA. The instruments was operated in the continuous scan mode with the scanning speed at 2°/min.

2.4. FTIR analysis

FTIR spectra were recorded with a HORIBA FT-720 spectrometer (HORIBA, Kyoto, Japan). Samples were scanned by the ATR method at resolution of 2 cm^{-1} for 50 scans.

2.5. Dissolution studies

A JP XIV type 2 apparatus (rotating paddle method, Model NTR-6100A, Toyama-sangyo, Osaka, Japan) was utilized to obtain all dissolution profiles of solid dispersions. The dissolution tests were carried out at 37 ± 0.5 °C at a rotation speed of 50 rpm with 90 mg of solid dispersions (30 mg as IND). The concentrations of IND were measured by using UV spectrometer at 265 nm (model UV-1600, Shimadzu, Kyoto, Japan) with automatic sampling system. A 10 μm filter (full flow filters, Varian, Palo Alto, USA) was attached to the sampling probe. Diluted McIlvaine buffers were used as mediums of pH 3.5–6.5, and USP phosphate buffer was used for medium of pH 7.2. Concentrations of HPMC were measured by gel-permeation chromatography (Asahipak GS-220HQ, Shodex, Tokyo, Japan) with refractive index detector (model RI-71, Shodex), in which dissolution medium was used as mobile phase with flow rate at 1.0 mL/min and solvent for standard solution. HPLC analysis (model 515 pump and model 717 plus auto sampler, Waters, Milford, USA) was performed with 100 μL injection volume under ambient temperature including column and detection temperatures.

2.6. Observation of the surface of solid dispersions

Photographs of solid dispersions before and after dissolution test were taken using JSM-840 scanning electron microscope (JEOL, Tokyo, Japan). Granules of solid dispersions were taken out from dissolution medium at 7 h from the start of dissolution test with pH 7.2 medium, dried thoroughly, and used as sample after dissolution test.

2.7. Determination of the interaction between IND and intact EC

IND was dissolved in ethanol and diluted with appropriate buffers to the concentration of 2 μg/mL, which is less than saturated solubility. This solution was used as IND reference solution. Separately, 10 mg of intact EC was suspended in 100 mL of the IND reference solution. This suspended solution was shaken for 30 min with a frequency of 1 time per second and a stroke length of about 10 cm. This solution was then filtrated with membrane filter with 0.45 μm pore size (Chromatodisk 25P, GL Science, Tokyo, Japan) and the filtrate was used as sample solution. UV absorbances at 265 nm of reference and sample solutions were determined by UV spectrometer (model UV-2400PC, Shimadzu, Kyoto, Japan). The difference of the UV absorbances between reference and sample solutions was determined as amount of adsorbed IND onto EC. EC phase/buffer solution phase partition coefficient of IND ($P_{EC/buffer}$) was determined by using the following equation:

$$P_{EC/buffer} = \frac{\text{absorbance of reference solution} - \text{absorbance of sample solution}}{\text{absorbance of sample solution}} \quad (1)$$

3. Result and discussion

3.1. Physicochemical property and structure of solid dispersions

3.1.1. Powder X-ray diffraction studies

XRD patterns for IND drug substance (γ-form crystal), solid dispersions, and the corresponding physical mixture are shown in Fig. 1. Sharp and intense crys-

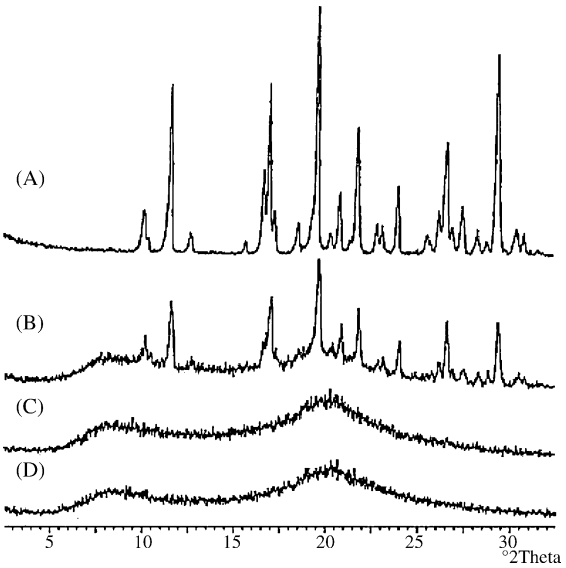

Fig. 1. Powder X-ray diffraction patterns of (A) IND; (B) physical mixture; (C) solid dispersion obtained by Suspending Method; (D) solid dispersion obtained by Dissolving Method.

talline peaks due to IND were observed in the diffraction spectra of IND drug substance as well as physical mixture. On the other hand, solid dispersions prepared by Suspending Method and Dissolving Method showed no diffraction peaks, suggesting that IND was in amorphous state.

3.1.2. IR spectrum

To elucidate molecular level dispersion condition of IND in EC/HPMC solid dispersions, FTIR spectra were obtained. Acid carbonyl group of IND γ-form crystal has been reported to have an intermolecular hydrogen bond to form cyclic dimers, corresponding to characteristic peak at 1717 cm^{-1} (Taylor and Zografi, 1997). Amorphous IND has also been reported to have a peak at 1710 cm^{-1} indicating that the acid carbonyl is similarly hydrogen bonded as cyclic dimers even in amorphous phase. Table 1 shows peak positions for the acid carbonyl region of IND drug substance (γ-form crystal), amorphous IND and IND in solid dispersions. The peaks of acid carbonyl appeared at 1711 and 1705 cm^{-1} for IND γ-form crystal and amorphous IND were confirmed to coincide with values of literatures. However, the peak of acid carbonyl of IND in solid dispersion by Suspending Method and Dissolving Method shifted

Table 1
IR peak positions for acid carbonyl streching vibration of IND

Compound	Wavenumbers (cm^{-1})	
γ-Form crystal of IND	–	1711
Amorphous form of IND	s*	1705
IND in solid dispersions by Suspending Method	1729	–
IND in solid dispersions by Dissolving Method	1733	–

s*: shoulder peak was observed.

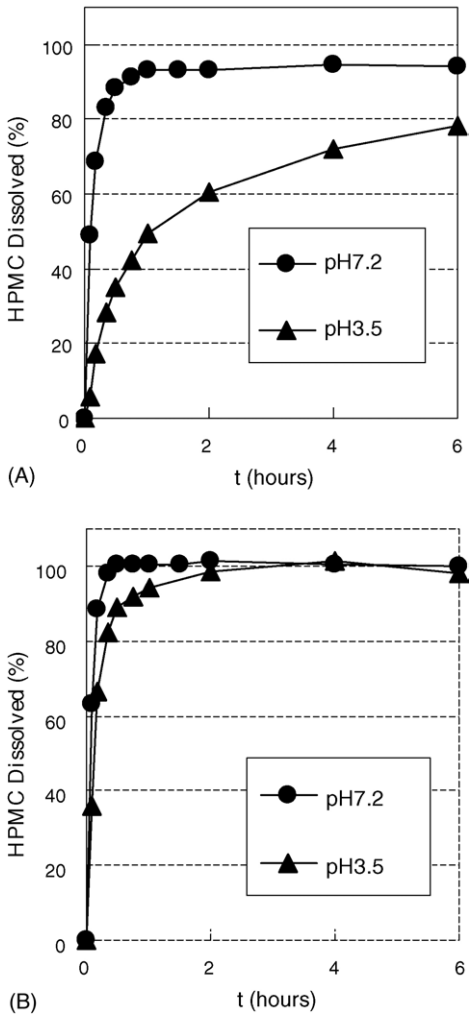

Fig. 2. Release of HPMC from solid dispersions by Suspending Method (A) and Dissolving Method (B), medium pH: pH 7.2 (●); pH 3.5 (▲).

toward high wavenumbers at 1729 and 1733 cm^{-1}, respectively. These shifts of approximately 20 cm^{-1} suggest that intermolecular hydrogen bonds between IND molecules were destroyed and IND interacted with polymers of cellulose derivatives by hydrogen bondings (Nakai et al., 1978). Therefore, molecular level dispersion of IND in HPMC/EC matrices as solid dispersion state was confirmed by IR spectrum as well.

3.1.3. Release behavior of HPMC

To evaluate an influence of water-soluble carrier behavior on IND release profile, dissolution of HPMC from solid dispersions was investigated. Fig. 2 shows the dissolution profiles of HPMC in the medium of pH 7.2 and 3.5 buffers. Solid dispersions by Dissolving Method showed quick HPMC releases in both pH 3.5 and 7.2 buffers. HPMC release of solid dispersion by Suspending Method was also rapid in pH 7.2 buffer, although it exhibited slower dissolution in pH 3.5. However, the HPMC release reached approximately 80% at 6 h and showed continuous dissolution afterwards up to approximately 90% (data not shown). Therefore, it was confirmed at this point that water-soluble carrier, HPMC, was not retained in water-insoluble EC matrices during the dissolution at pH 3.5–7.2 but was dissolved and released from water-insoluble carrier matrices.

3.1.4. Internal structures of solid dispersions

As described in Section 3.1.3, HPMC completely released from solid dispersion granules prepared by both Suspending and Dissolving Methods in medium of pH 7.2 buffer. This indicates that the granules manufactured by both methods consisted of only water-insoluble EC matrices after dissolution test. As shown in Fig. 3A and B, formations of pores with diameter of few tens of micrometer were seen for granules of solid dispersion by Suspending Method after dissolution. Therefore, in the core of solid dispersion granules prepared by Suspending Method, HPMC should exist

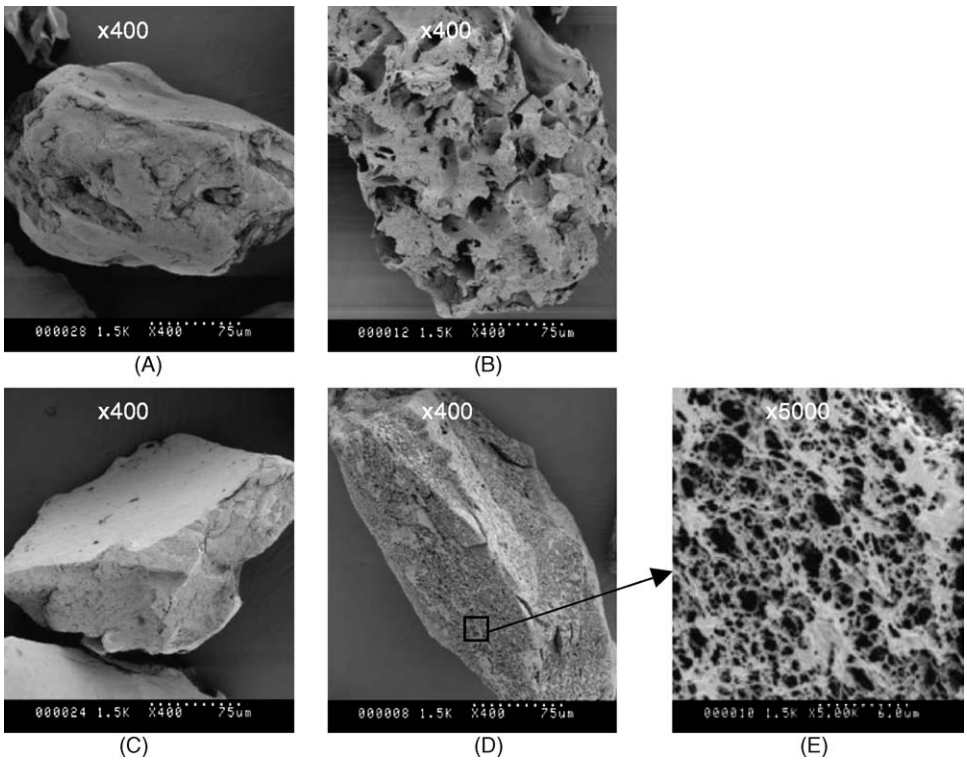

Fig. 3. SEM photographs of solid dispersions by Suspending Method: before dissolution ×400 (A) and after dissolution ×400 (B), by Dissolving Method: before dissolution ×400 (C), after dissolution ×400 (D) and ×5000 (E).

in the pores as mass with few tens of micrometer diameters. On the other hand, as shown in Fig. 3C–E, granules of solid dispersion by Dissolving Method after dissolution had mesh-like structures, indicating that HPMC dispersed finely and uniformly in EC matrices as microparticles with submicron to micron diameters. Consequently, these photographs suggest that homogenious or heterogenious conditions during the preparation of solid dispersions dominated structures of HPMC/EC matrices.

3.2. Dissolution mechanism of the solid dispersion by Suspending Method

3.2.1. Dissolution in sink condition

Fig. 4A shows release profile of IND from solid dispersion by Suspending Method in sink condition (pH 7.2 buffer). Obviously, the profile could be divided into two parts before and after 1 h from start of dissolution. If this profile was re-plotted with square root time ($h^{1/2}$) against the fraction of drug released, the release profile of latter stage well fitted to a straight line with r^2 of 0.99. This indicated that a certain amount of IND was released from the EC matrices by the diffusion, expressed by Higuchi equation (Higuchi, 1961):

$$m = kt^{1/2} \quad (2)$$

where m is cumulative amounts of drug released at time t and k is the dissolution rate constant. Moreover, as shown in Fig. 4B, the first stage profile up to 1 h, which the fraction of diffusion release was separated from, was well superimposed on release profile of HPMC obtained by HPLC analysis. This indicates that simultaneous release of IND and HPMC occurred in the first stage of dissolution. Thus, it was considered that IND release from solid dispersion by Suspending Method in sink condition consisted of two mechanisms (i) the release accompanied with HPMC occurring in the early stage and (ii) the diffusion release from EC matrices occurring throughout dissolution.

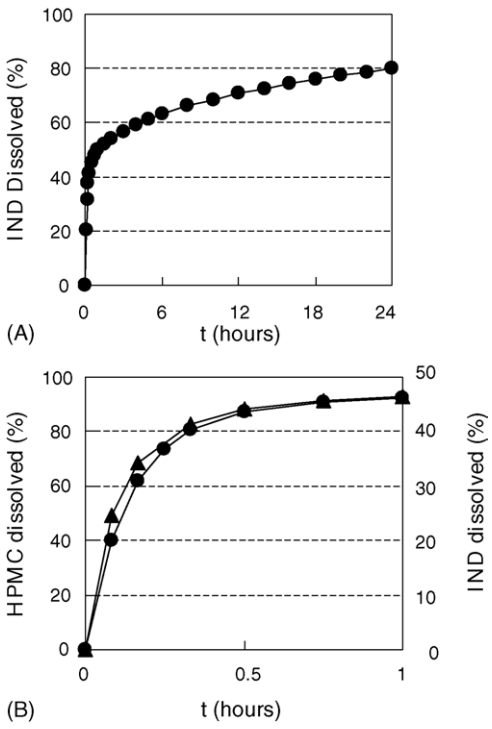

Fig. 4. Release profile of IND from solid dispersion by Suspending Method in sink condition (pH 7.2) (A), HPMC release profile and corrected IND release profile by eliminating the fraction of diffusion release (●) IND and (▲) HPMC (B).

3.2.2. pH-dissolution profile

Fig. 5 shows dissolution profiles of IND from solid dispersion by Suspending Method under various mediums of pH 3.5–7.2. As pH of dissolution medium was lowered, dissolution rates markedly decreased. Furthermore, separation of two stages of dissolution profiles became uncertain. At the lowest pH condition of

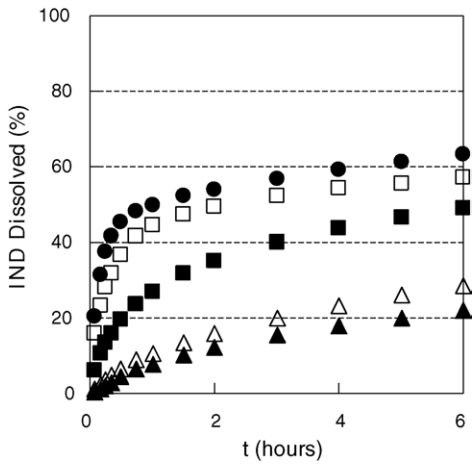

Fig. 5. Release profiles of IND from solid dispersion by Suspending Method in various pHs: pH 7.2 (●); pH 6.5 (□); pH 5.5 (■); pH 4.5 (△); pH 3.5(▲).

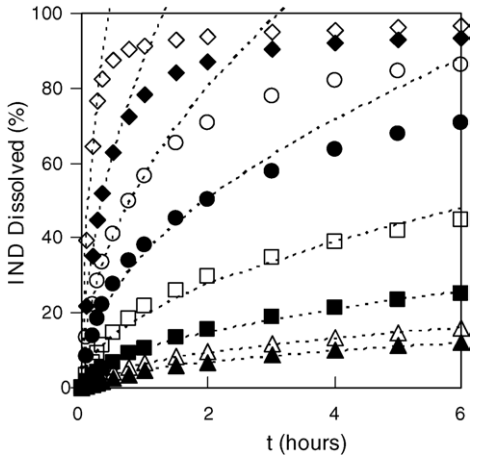

Fig. 6. Measured and simulated release profiles of IND from solid dispersion by Dissolving Method in various pHs, measured: pH 7.2 (◊); pH 6.5 (♦); pH 6.0 (○); pH 5.5 (●); pH 5.0 (□); pH 4.5 (■); pH 4.0 (△); pH 3.5 (▲), simulated (- - -).

3.5, IND dissolution rate was only 20% at 6 h, although 80% of HPMC dissolution was achieved in 6 h even in pH 3.5 buffers mentioned in Section 3.1.3. This could be explained by the fact that another mechanism would be working in low pH medium. Detail discussion will be mentioned in later section.

3.3. Dissolution mechanism of solid dispersion by Dissolving Method

3.3.1. pH-dissolution profile

In Fig. 6, dissolution profile of IND from solid dispersion by Dissolving Method in sink condition (pH 7.2) is shown with open diamond symbols. The release of IND completed rapidly without phase separation that was observed in solid dispersion by Suspending Method.

On the other hand, as shown in Fig. 6, dissolution rates of this solid dispersion were much delayed with lowering pH of dissolution medium. However, in this case, dissolution rates up to 60% for all pH mediums were well fitted to the Higuchi equation (r^2: 0.97–0.99). Simulation curves of dissolution profiles calculated using these obtained k values also support this release mechanism (see Fig. 6). Therefore, it was concluded that the apparent dissolution of solid dispersion by Dissolving Method could be characterized as diffusional mechanism in all pHs applied.

As shown in Fig. 2, a rapid HPMC release was observed from solid dispersion by Dissolving Method as was the case in IND release in pH 7.2. However, no similarity of release profile in pH 7.2 between IND and HPMC was observed. Therefore, it was considered that HPMC behavior did not have any direct impact on the IND release in the case of solid dispersion by Dissolving Method.

3.4. Hydrophobic interaction between EC and IND

Since IND is an acidic compound whose ionic dissociation state is changeable with pH, hydrophobicity of IND may change with pH, especially near the pH of its pK_a (4.5). This may result in change of interaction between EC and IND with pH of dissolution medium. Therefore, interaction between EC and IND in buffers of various pHs was determined as partition coefficient of IND (EC phase/buffer solution phase). As shown in Table 2, the partition coefficient of IND increased with lowering buffer pH. Taking into account of the fact that pK_a of IND was 4.5, it was considered that undissociated molecules of IND adsorbed onto EC molecules by increased hydrophobic interaction. This hydrophobic interaction could explain well the delay of IND release in acid pH region. Fig. 7 shows the relationship between dissolution rate constants (k) of solid dispersion by Dissolving Method and partition coefficients. From these results, it appeared that hydrophobic interaction between IND and EC was a key function of diffusion process in solid dispersion by Dissolving Method.

As for solid dispersion by Suspending Method, it was observed that IND released together with HPMC release in sink condition in early stage of dissolution.

Table 2
Partition coefficient of IND in EC phase/buffer solution phase

pH	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.2
Patition coefficient	1.064	0.559	0.387	0.183	0.100	0.081	0.012	0.006

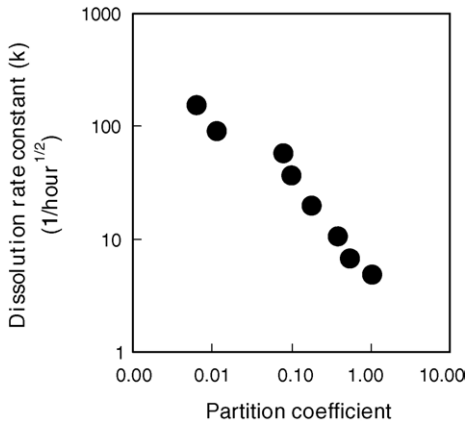

Fig. 7. Relationship between partition coefficient and dissolution rate constant (k).

However, in the medium of pH3.5, even though HPMC release reached up to 80% in 6 h, released IND was only 20%. This result also can be explained by the hydrophobic interaction of EC and IND, that is, in acid region, when HPMC was released from solid dispersion granules, IND was not released out to bulk dissolution medium with HPMC, but was adsorbed onto EC matrices. Then, IND gradually came out into the bulk dissolution medium.

4. Conclusion

Dissolution mechanism of IND from solid dispersions with water-soluble HPMC and water-insoluble EC was investigated. The dissolution mechanism was affected by internal structures of solid dispersions governed by the preparation methods and medium pH. If solid dispersion contained finely and uniformly dispersed HPMC in its internal structure, release of IND followed a diffusional mechanism whose dissolution rate constants (k) depended on medium pH. However, if solid dispersion contained mass of HPMC with few tens of micrometer diameters in its internal structure, IND release mechanism could be divided into two phase under sink condition – release together with HPMC erosion and diffusion from insoluble EC matrices. For both solid dispersions, it was implied that the hydrophobic interaction between IND and EC occurred under lower pH region and strongly delayed dissolution of IND.

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