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Use of Silicone Membrane Permeation to Assess Thermodynamic Activities of Ionic Liquids and Their Component Cation and Anion

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Ionic liquid (IL) was prepared by mixing lidocaine and ibuprofen as a cation and anion, respectively, at various ratios. We determined the permeation of both compounds from the IL through a silicone membrane selected as a model biological membrane, and mathematically analyzed the permeation data from the viewpoint of the thermodynamic activities of lidocaine, ibuprofen, and the IL. As a result, IL and ibuprofen diffusely permeated through the membrane in the case of applying IL preparations with a molar fraction of ibuprofen of 0.5 or higher. The IL was thought to separate into lidocaine and ibuprofen in the receiver. On the other hand, when applying IL preparations with a molar fraction of lidocaine of 0.5 or higher, IL and lidocaine permeated. The permeation rate of IL itself was maximized when the applied IL was prepared using equimolar amounts of lidocaine and ibuprofen, and it decreased when the fraction of lidocaine or ibuprofen increased by more than 0.5. Their membrane permeation rates increased with an increase in their activity, and no more increase was found when the drugs were saturated in the IL. These membrane permeation profiles reflected well the mathematically calculated ones according to the concept of activity.

Key words ionic liquid; membrane permeation; permeation rate; activity; anion compound; cation compound

Introduction

It has been several decades since topical dermatological formulations and transdermal delivery systems (TDSs) with the skin as the application site occupied the third administration method after oral preparations and injections. Many studies on the mechanism of percutaneous absorption[1–4] and many formulations on the skin[5–8] have been examined during these decades. Recently, in the field of pharmaceutics, the method of adding a counterion to an active drug to make ionic liquids (ILs) has received considerable attention to stably permeate the drug through several biological membranes such as the skin, to prevent drug inactivation at the absorption site, and to improve the poor dissolution of drugs.[9–12]

ILs compose only anionic and cationic substances and form salts with a melting point of less than 100 °C.[13–16] Thus, the application of IL may improve the skin permeation of drugs with physicochemical properties that have been considered unsuitable for TDSs.[17] If the development of TDSs containing more drugs can be further promoted by ILs, not only may it be possible to meet diverse unmet medical needs, but it will also contribute to improving the QOL of patients. Another feature of ILs is the possibility of direct application to the biological membrane without using a solvent or a vehicle because it is liquid itself. Common TDSs require a solvent or vehicle in addition to therapeutic drugs. Some solvents and vehicles may cause skin irritation. Thus, ILs have the great merit of being formulated without using a solvent or vehicle.

On the other hand, the skin permeation from IL preparations must be considered as the sum of those of the IL itself and the anions or cations dissolved in the IL. However, little is known on the effects of the physicochemical properties of ILs themselves on the permeation of the component anions and cations of the IL through biological membranes. Therefore, clarifying their effects on the permeation of anion and cation components through the skin can reveal the permeation profiles that might not be explained by simple dissolution-diffusion theory, which can lead to the design TDSs containing ILs as well.

In the present study, lidocaine and ibuprofen were selected as a monovalent cationic and anionic substance, respectively, to prepare IL preparations consisting of both substances, and their permeation profiles were determined through a silicone membrane,[3,18,19] which is commonly used as a skin model together with three-dimensional (3D) cultured human skin models[20] and Strat-M®.[21,22] Thermodynamic activities theory was used analysis drug permeation through the membrane.[23–27] The skin permeation of lidocaine and ibuprofen was analyzed from the viewpoint of thermodynamic activities of the IL itself and its components (lidocaine, ibuprofen). Figure 1 shows the structural formulas of the ILs prepared in this study. Table 1 shows the molecular weight (*M.W.*), pK_a, and logarithmic *n*-octanol/water partition coefficient ($\log K_{ow}$) of lidocaine and ibuprofen. The reasons why a silicone membrane was selected instead of real skin were: (1) much lower variation in permeation through the silicone membrane than that through real skin, (2) need for a detailed and accurate evaluation to clarify the physicochemical properties of IL on the membrane permeation, and (3) recommendation from the standpoint of alternative animal experiments.[19]

Theoretical

The skin (or silicone membrane) permeation profile of chemical substances can be explained by the dissolution-diffusion theory,[23] and its steady-state flux, dQ/dt, can be explained generally by the thermodynamic activity of chemical substances in the vehicle, A_v, as shown in Eq. 1.[24]

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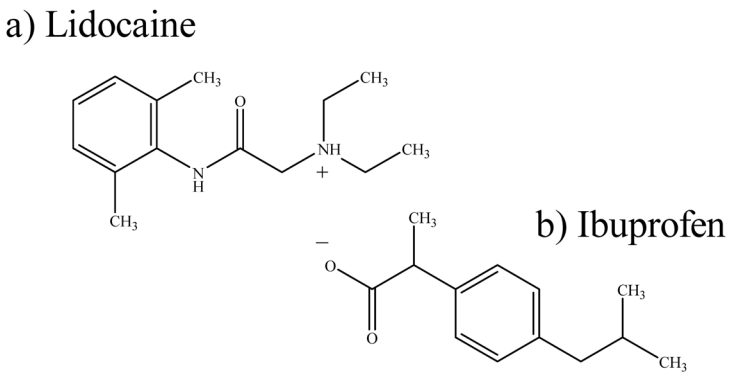

Fig. 1. Ionic Liquid (IL) Structure Composed of Lidocaine (a) and Ibuprofen (b)

Table 1. Physicochemical Parameters of IL and Its Components, Lidocaine and Ibuprofen

	Lidocaine	Ibuprofen	IL
M.W.	234.3	206.8	441.1
pK_a	7.86	7.86	—
Log K_{ow} *a)*	2.37 *b)*	3.94 *b)*	
Melting point or glass transition temp. (°C)	66–68	74–75	Less than −28.8

a) K_{ow} is the partition coefficient between *n*-octanol and water. *b*) These values were from our previously determined data.[18]

$$\frac{dQ}{dt} = \frac{A_v D_m}{\gamma_m L_m} \quad (1)$$

where D_m is the diffusion coefficient of the penetrant in the membrane, γ_m is the activity coefficient of the penetrant in the membrane, and L_m is the membrane thickness. When a certain aqueous vehicle is used, a chemical substance (solute) distributes from the aqueous vehicle to the membrane to diffuse/permeate through the membrane. The permeability of chemical substances through the membrane from an aqueous vehicle is determined by A_v, as shown in Eq. 1. In other words, the skin permeation rate of chemical substances, dQ/dt, is proportional to the thermodynamic activity of the compound in the vehicle, A_v. Equation 1 is more useful compared with the Fick's 1st law of diffusion when the membrane permeation rates are compared from several donor solutions.[28]

When applying IL preparations to the membrane, the permeated substances become IL as well as its components. Then, the permeation rate of lidocaine or ibuprofen through the membrane is represented in the following Eq. 2.

$$\frac{dQ}{dt_{tot}} = \frac{dQ}{dt_{IL}} + \frac{dQ}{dt_{sol}} \quad (2)$$

where dQ/dt_{tot}, dQ/dt_{IL}, and dQ/dt_{sol} are the total membrane permeation rate of lidocaine or ibuprofen, that for only IL, and that for only lidocaine or ibuprofen dissolving in IL preparations, respectively, after application of IL preparations. Equation 2 can be applied both for lidocaine or ibuprofen in the case of IL preparation application.

Furthermore, the first term on the right side in Eq. 2, dQ/dt_{IL}, becomes a product of the concentration ratio of IL in the preparations, $C_{IL}/C_{IL} + C_{sol}$, and the membrane permeation rate of IL when applied saturated IL, $dQ/dt_{IL(A_v = 1)}$, as shown in the following Eq. 3, where C_{IL} and C_{sol} are the concentration (mol/L) of IL and the component (lidocaine or ibuprofen), respectively. Thermodynamic activity of neat IL can be assumed to be unity.[28] In addition, the second term on the right-hand side, dQ/dt_{sol}, becomes a product of the concentration ratio, C_{sol}/C_{max}, of lidocaine or ibuprofen dissolved in IL, C_{sol}, against the solubility of the component in the aqueous vehicle, C_{max}, and the membrane permeation rate when applied as saturated lidocaine or ibuprofen in IL, $dQ/dt_{sol(A_v = 1)}$, as shown in the following Eq. 4. Again, thermodynamic activity of lidocaine or ibuprofen in their suspended solution can be assumed to be unity.[28]

$$\frac{dQ}{dt_{IL}} = \frac{C_{IL}}{C_{IL} + C_{sol}} \cdot \frac{dQ}{dt_{IL(A_v = 1)}} \quad (3)$$

$$\frac{dQ}{dt_{sol}} = \frac{C_{sol}}{C_{max}} \cdot \frac{dQ}{dt_{sol(A_v = 1)}} \quad (4)$$

Experimental

Materials and Methods Lidocaine and ibuprofen were used as a model base and acid, respectively (both are not salt form, see Fig. 1). These were purchased from Tokyo Kasei Co., Ltd. (Tokyo, Japan). The special grade methanol used to form the IL was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Silicone membrane (thickness: 75 μm) was provided by LINTEC Corporation (Tokyo, Japan). Other reagents and solvents were of LC or special grade and used without purification.

IL Preparations IL preparations were obtained by dissolving various ratios of lidocaine/ibuprofen mixtures with a stepwise molar fraction of 0.1 each (0.1/0.9 to 0.9/0.1) in methanol and completely removing methanol at reduced pressure using an evaporator. Table 2 shows the molar fraction in IL, lidocaine, and ibuprofen at and after IL preparation. The preparation numbers were named #0 to 10 as shown in Table 2 based on the molar fraction of lidocaine or ibuprofen in the lidocaine/ibuprofen mixture at preparation. Because #0 was ibuprofen only and #10 was lidocaine only, they were not IL preparations. Because the IL preparation #5 was prepared using equimolar amounts of lidocaine and ibuprofen, it was 100% IL without free lidocaine or ibuprofen.

Preparation of Lidocaine- or Ibuprofen-Suspended Aqueous Solution About three times higher amounts of lidocaine or ibuprofen compared with their solubility in water were added to purified water and stirred at 37 °C for 24 h to obtain lidocaine- or ibuprofen-suspended aqueous solutions. The observed permeation rate of lidocaine or ibuprofen

Table 2. Molar Fraction of Lidocaine (LID) and Ibuprofen (IBU) at and after IL Preparation

Preparation #		0	1	2	3	4	5	6	7	8	9	10
At preparation	LID/IBU ratio	0/1.0	0.1/0.9	0.2/0.8	0.3/0.7	0.4/0.6	0.5/0.5	0.6/0.4	0.7/0.3	0.8/0.2	0.9/0.1	1.0/0
After preparation	LID/IBU as IL	0/0	0.1/0.1	0.2/0.2	0.3/0.3	0.4/0.4	0.5/0.5	0.4/0.4	0.3/0.3	0.2/0.2	0.1/0.1	0/0
	Dissolved LID/IBU in IL	0/0	0/0.26	0/0.52	0/0.4	0/0.2	0/0	0.2/0	0.4/0	0.38/0	0.19/0	0/0
	Suspended LID/IBU in IL	0/1.0	0/0.54[a)]	0/0.08[a)]	0/0	0/0	0/0	0/0	0/0	0.22[b)]/0	0.61[b)]/0	1.0/0

Numbers *x*/*y* in any column "at preparation" mean the mixing molar ratio of LID/IBU at preparation, and those "after preparation" mean the corresponding number of moles of LID/IBU as IL and the dissolved and suspended LID/IBU in IL preparations. The number of moles for *x* is the same to that for *y* in IL, because the equal moles of LID and IBU make the IL. The sum of 3 rows of *x* and *y* in any column "after preparation" equals to the *x* and *y* "at preparation." *a*) IBU-suspended IL was obtained in #1 and 2. *b*) LID-suspended IL was obtained in #8 and 9.

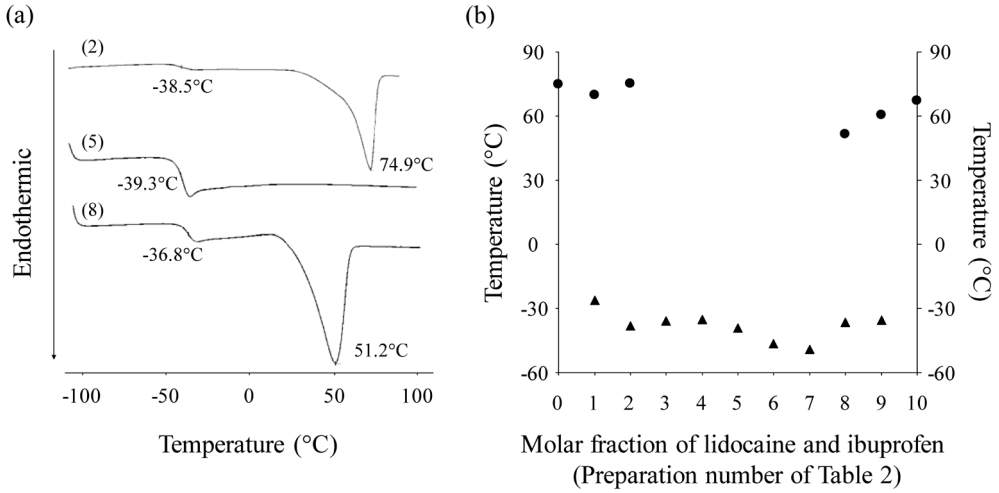

Fig. 2. DSC Thermograms of IL Preparation #2, 5 and 8 (a) and Endothermic Peak Temperatures of Each IL Preparation (b)

Symbols: endothermic peak 1 (peak temperature; ●), endothermic peak 2 (midpoint temperature; ▲).

through the silicone membrane from this suspended solution was introduced to $dQ/dt_{sol(A_v=1)}$ shown in Eq. 4. hermodynamic activity of chemicals in different solvents must be the same when the chemicals are suspended in the solvents.[28)]

Determination of Differential Scanning Calorimeter (DSC) in IL Preparations A DSC (DSC-60plus) with a cooling system (TAC-60L) (both from Shimadzu Corporation, Kyoto, Japan) was used to examine the melting point of IL preparations used in this experiment. The measurements were performed using the following conditions: temperature range from −100 to 100 °C, heating rate at 10 °C/min, in an atmosphere of N_2 gas at a flow rate of 50 mL/min, sample amount about 10 mg, and an aluminum seal cell for the sample cell.

Membrane Permeation Experiments The silicone membrane was cut slightly larger than the effective diffusional area of the horizontal two-chamber diffusion cell.[29)] No pretreatment such as hydration was done to the membrane. The cut silicone membrane was set in the 2-chamber diffusion cell. Phosphate-buffered saline (PBS; pH 7.4) (approx. 3 mL) was placed on the receiver side, whereas 3.0 mL of various IL preparation or lidocaine- or ibuprofen-suspended aqueous solution was applied on the donor side to start the permeation experiment. During the experiment, warm water was circulated outside the duplicated cells to keep the applied IL preparation, receiver solution, and silicone membrane at 37 °C. The applied donor and receiver solutions were stirred with a magnetic stirrer during the permeation experiments. The receiver solution (2.0 mL) was periodically collected to keep the sink condition of the receiver solution, and the same amount of PBS was returned. The lidocaine or ibuprofen concentration of the obtained sample solution was measured using HPLC.

Determination Methods of Lidocaine and Ibuprofen Lidocaine and ibuprofen concentrations in the collected samples were measured using the absolute calibration curve method. The following HPLC system was used: a system controller, an auto injector (SIL-20A), a pump (LC-10AD VP), a UV detector (SPD20-AV), a column oven (CTO-10A VP), and an analysis software (Lab Solution). All above were from Shimadzu Corporation. The column was TSKgel ODS-80Ts QA (TOSOH, Tokyo, Japan) kept at 40 °C. The mobile phase was acetonitrile : 10 mM sodium dodecyl sulfate (1 : 1) with a flow rate of 1.0 mL/min. The injection volume was 10 μL, and the UV wavelength was set to 249 and 262 nm for lidocaine and ibuprofen, respectively.

Calculation of Steady-State Flux through the Silicone Membrane The silicone membrane permeation rate of lidocaine and ibuprofen from IL preparations showed a steady-state flux, $flux_{ss}$, after a short lag time period. In this study, $flux_{ss}$ was calculated from the slope of cumulative permeation through the membrane from 1 to 8 h.

Results

A viscous liquid was obtained immediately after methanol was evaporated at reduced pressure in all IL preparations (#1–9, Table 2). The numbers (*x*/*y*) in "At preparation" in Table 2, mean the molar fraction of lidocaine/ibuprofen mixed at preparation. No change was observed in IL preparations #3–7 when left overnight at room temperature, whereas solids were

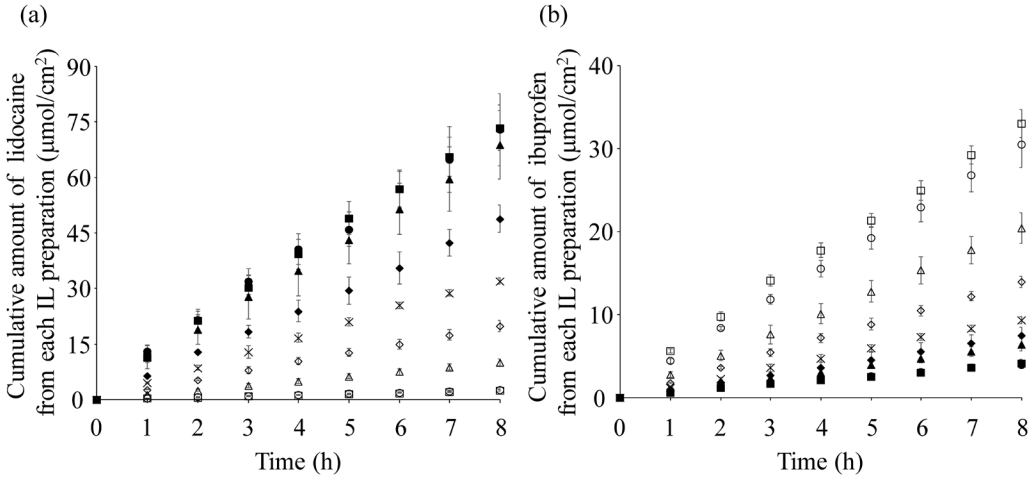

Fig. 3. Time Course of Changes in the Cumulative Amounts of Lidocaine (a) and Ibuprofen (b) That Permeated through the Silicone Membrane from Different IL Preparations

Symbols: preparation #1 (○), #2 (□), #3 (△), #4 (◇), #5 (×), #6 (◆), #7 (▲), #8 (■), #9 (●). Each data point represents the mean ± standard deviation (S.D.) ($n = 3$).

precipitated in IL preparations #1 and 2 and #8 and 9 when left in the same way.

Figures 2a and b illustrate the DSC results of IL preparations. Two kinds of endothermic peaks were observed in the preparations #2, 5 and 8 as shown in Fig. 2a. The peaks 1 and 2 show the melting point (●) and glass transition temperature (▲), respectively, in Fig. 2b. The melting points corresponded to those for suspended ibuprofen and lidocaine in IL preparations #1 and 2 and #8 and 9, respectively (see Table 1). The melting point for ibuprofen was almost the same at about 70 °C even when the lidocaine concentration increased (#0→1→2). On the other hand, when the ibuprofen concentration increased (#10→9→8), the melting point of lidocaine clearly decreased from 66–68 to 51.9 °C. In addition, endothermic peak 2 was the glass transition temperature of IL (A rather big variation was observed in the DSC measurement below 0 °C).

Using IL preparation #2 or 8 having a precipitation for ibuprofen or lidocaine, respectively, the solids precipitated were filtered using a filter with a pore size of 0.25 μm and determined the lidocaine or ibuprofen solubility, respectively, in the neat IL. As a result, ibuprofen in the same molar amount as lidocaine, and lidocaine in the same molar amount as ibuprofen contributed to the IL formation in the IL preparation (the same molar amount of lidocaine and ibuprofen formed IL). Moreover, it was considered that ibuprofen or lidocaine, which did not become IL and did not precipitate, in preparation #2 or 8, respectively, were dissolved in IL. Ibuprofen or lidocaine dissolved in IL was determined as 0.52 ± 0.01 or 0.38 ± 0.02 parts (mean ± standard deviation (S.D.), $n = 3$) in 0.2 parts of IL, respectively (see #8 and 2 in Table 2). That is, 2.6 parts of ibuprofen or 1.9 parts of lidocaine were dissolved in 1.0 part of IL.

The numbers (x/y) in "After preparation" in Table 2, mean the molar fraction of lidocaine/ibuprofen. The "LID/IBU as IL" corresponds the value of lidocaine and ibuprofen in IL, and the "Dissolved LID/IBU" or "Suspended LID/IBU in IL" represents the values of dissolved or suspended lidocaine and ibuprofen in IL. When comparing each value in the three columns for lidocaine and ibuprofen, the ratio of these drugs was realized as "IL: the dissolved drugs: the suspended drugs in IL." The sum of these three corresponds to the mole ratio shown in "At preparation" both for lidocaine and ibuprofen. For example, regarding preparation #2, lidocaine and ibuprofen were mixed at a molar fraction of 0.2/0.8, so that the obtaining IL was 0.2 and the other was 0.6 among the ibuprofen amount of 0.8. In addition, 0.52 was dissolved in IL and 0.08 was present as a solid (not dissolved) among the non-IL ibuprofen amount of 0.6. That is, the ibuprofen (0.8) became "the IL : dissolved ibuprofen : suspended ibuprofen" = 0.2 : 0.52 : 0.08. Further, regarding preparation #4 in which lidocaine and ibuprofen were mixed at a molar fraction of 0.4/0.6, ibuprofen (0.6) became "the IL : dissolved ibuprofen : suspended ibuprofen" = 0.4 : 0.2 : 0. That is, all of the non-IL ibuprofen was dissolved in IL.

Figures 3a and b show the silicone membrane permeabilities of lidocaine and ibuprofen from IL preparations #1–9 with various fractions of lidocaine/ibuprofen. The permeation rate of lidocaine and ibuprofen through the silicone membrane increased depending on the respective molar fractions. However, they became almost constant when they were suspended in the IL preparations (A_v for lidocaine and ibuprofen is 1.0).

Figures 4a and b show the silicone membrane permeation rates of lidocaine and ibuprofen (● and ▲), respectively, from IL preparations #1–9. The relationship between the membrane permeation rate and the molar fraction of lidocaine (or preparation #) was a sigmoid curve, whereas that between the permeation rate and the molar fraction of ibuprofen (or preparation #) was an inversed sigmoid curve. That is, the membrane permeation rate of lidocaine increased as the molar fraction of lidocaine increased, and that was almost constant above the saturated solubility of lidocaine (A_v is 1.0). The ibuprofen results were similar.

Figures 4a and b also show theoretical membrane permeation rates of lidocaine and ibuprofen (calculated from Eqs. 2, 3 and 4) from IL preparations #1–9 derived according to the concept of thermodynamic activities of each penetrant in the donor solution. $dQ/dt_{IL(A_v = 1)}$ used in the calculation of the theoretical permeation rate of lidocaine and ibuprofen (Eqs. 3, 4) was the membrane permeation rate when the IL activity was 1.0 (lidocaine and ibuprofen permeation rates from IL preparation #5 were 3.99 ± 0.06 and 1.18 ± 0.05 μmol/cm^2/h, respec-

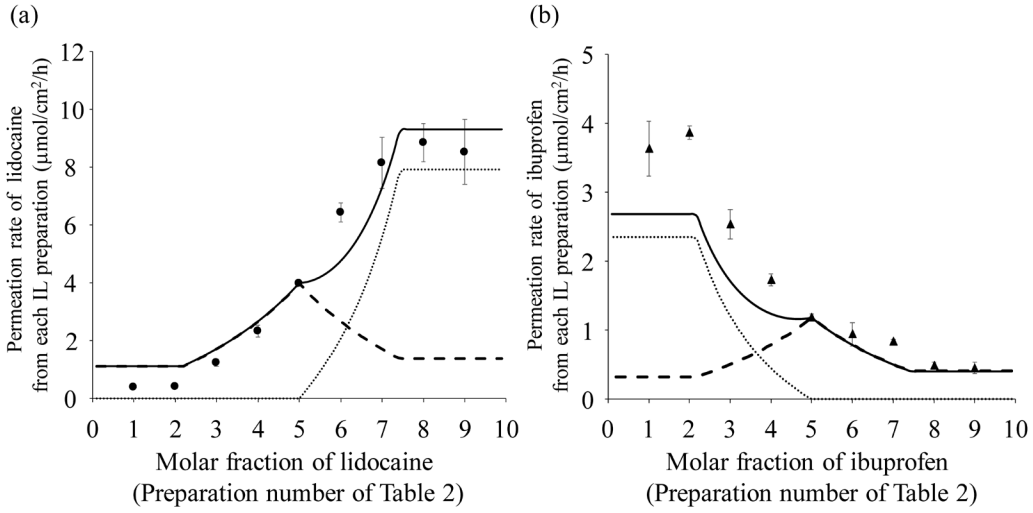

Fig. 4. Relationship between Theoretical and Observed Permeation Rates of Lidocaine (a) and Ibuprofen (b) through the Silicone Membrane from Different IL Preparations

Symbols: observed permeation rate of lidocaine (●) and ibuprofen (▲), theoretical total permeation rate (—), theoretical IL permeation rate (---), and theoretical lidocaine or ibuprofen permeation rate (····). Each data point represents the mean ± S.D. ($n = 3$).

tively. mean ± S.D., $n = 3$). The $dQ/dt_{sol(A_v = 1)}$ was the membrane permeation rate of lidocaine or ibuprofen when their activity in water was 1.0 (lidocaine and ibuprofen permeation rates from the suspended aqueous solution were 7.92 ± 0.39 and $2.35 \pm 0.20\,\mu$mol/cm^2/h, respectively. mean ± S.D., $n = 3$).

First, the membrane permeation rate of IL calculated in Eq. 3 (broken line in Fig. 4a) is explained. The theoretical membrane permeation rate of IL itself was fastest from the IL preparation #5 (A_v of IL is 1.0). As the IL molar fraction departed from 0.5 (#5 to 1 and #5 to 9), the IL flux became slower with an inverted V-shape for the membrane permeation rate of IL against the molar fraction of lidocaine (or ibuprofen). In addition, the theoretical membrane permeation rate of lidocaine dissolved in IL (Eq. 4) began to permeate through the silicone membrane when the molar fraction of lidocaine becomes higher than 0.5, and became constant when it attained the saturated solubility of lidocaine (A_v of lidocaine is 1.0, #8 and 9) (dotted line in Fig. 4a). The sum of both (Eq. 2, solid line in Fig. 4a) agreed well with the observed value (● in Fig. 4a).

The behavior of each theoretical formula for ibuprofen permeation from IL preparations was almost the same to that for lidocaine permeation from IL preparations, as shown in Fig. 4b. On the other hand, the observed value of the ibuprofen permeation rate from IL preparations (▲ in Fig. 4a) was in good agreement with the theoretical value (Eq. 2), which was derived according to the concept of activity when the molar ratio of ibuprofen was 0.5 or less (IL preparations #5–9). However, the theoretical membrane permeation rate was lower than the observed value when the ibuprofen molar fraction was high (IL preparations #1–2).

Discussion

Lidocaine and ibuprofen are a monovalent cation and anion, respectively; therefore, they form an IL at a molar ratio of 1 : 1. In other words, IL preparation #5 contained only IL, and the other IL preparations (#1–4, 6–9) dissolved or suspended lidocaine or ibuprofen in IL (Table 2). As a result of DSC measurement (Fig. 2), the melting points caused by lidocaine or ibuprofen were observed in IL preparations #1 and 2 and 8 and 9, respectively, whereas no melting point was detected in IL preparations #3–7. In the IL preparations #3–7 where the melting point was not detected, lidocaine or ibuprofen must be dissolved in IL. Moreover, the IL preparations #1, 2, 8, and 9 and those #3–7 were conformed to be suspended solution and clear solution, respectively, by visual confirmation. In addition, the drug crystals were not disappeared in the IL preparations containing drug crystals, and no drug crystal precipitation was observed in the IL preparations without the crystal in the donor cell during 8 h-membrane permeation experiments. The solubilities of ibuprofen or lidocaine in IL preparations #2 and 8 were determined to be 0.52 ± 0.01 or 0.38 ± 0.02 parts (mean ± S.D.) in 0.2 parts of IL, respectively. That is, 1.9 parts of lidocaine or 2.6 parts of ibuprofen were dissolved in 1.0 part of IL. These saturated solubilities agreed well with the DSC results.

Several papers have been published on the solubilizing ability of IL of poorly soluble substances.[30,31] de Azevedo *et al.*[31] prepared an IL using [1-ethyl-3-methylimidazolium chloride] as a cation and [CH_3COO] or [BF_4] as an anion to evaluate the solubility of a poorly soluble third component. They found that the solubility of the component was highest with IL with [CH_3COO], which is related to the hydrogen bond among the IL. The present lidocaine-ibuprofen IL may increase the solubility of lidocaine or ibuprofen.

The silicone membrane permeability of lidocaine from each IL preparation increased as the molar fraction of lidocaine increased (IL preparations #1 to 9) and became a certain value when it was more than a saturated lidocaine (A_v is 1.0 in IL preparations #8–9) (Fig. 3a). Because the membrane permeation rate of lidocaine from IL preparations #1–5 was only due to the IL amount in the preparations, the IL preparations #5 with the highest IL amount showed the maximum value. On the other hand, the permeation rates of lidocaine from the IL preparations #6–9 with a molar fraction of lidocaine of more than 0.5 were from the permeation of IL itself as well as lidocaine dissolved in IL. Therefore, the amount of membrane permeation from IL preparations #6–9 was higher than that

of IL preparation #5. This phenomenon was the same in the membrane permeation of ibuprofen.

The membrane permeation rates of lidocaine from the IL preparations #1–5 with molar fractions of lidocaine below 0.5 or and those of ibuprofen from the IL preparations #5–9 with molar fractions of ibuprofen below 0.5 come only from IL permeation through the silicone membrane as described above. If IL diffuses and permeates through the silicone membrane as it is, the membrane permeation rates of lidocaine from IL preparations #1–5 must be the same as those of ibuprofen from IL preparations #5–9. However, these two did not match (Fig. 4). The present IL preparations become lidocaine and ibuprofen immediately touching with water. Thus, most IL became these drugs in the receiver solution after the permeation of IL through the silicone membrane. This decomposition may be observed even in the silicone membrane near the receiver cell.

The relationship was in good agreement between the observed silicone membrane permeation rate of lidocaine from each IL preparation and the theoretical value (Eq. 2) derived according to the concept of thermodynamic activity (Fig. 4a). The relationship was almost the same between the observed and theoretical (Eq. 2) membrane permeation rates of ibuprofen from each IL preparation in cases that the molar fraction of ibuprofen was less than 0.5 (Fig. 4b). Some deviation was found between the observed and theoretical permeation rates of ibuprofen in IL preparations #1–4 with a molar fraction of ibuprofen higher than 0.5.

The membrane permeation rates of lidocaine and ibuprofen mostly depended on the thermodynamic activities of IL itself and those of a component in the IL preparations. It was possible to predict the membrane permeation rate of IL itself or components dissolved in IL by using Eqs. 3 and 4. On the other hand, the membrane permeation rate of ibuprofen from IL preparations #1 and 2 with a molar fraction higher than 0.5 (Fig. 4b) was slightly different between the observed and theoretical values. The possible reasons for this deviation are as follows:

I. In the present study, we hypothesized that a monovalent cation lidocaine and a monovalent anion ibuprofen form a 1 : 1 ratio of IL. It was assumed that all became IL when prepared using the same amounts of molecules of lidocaine and ibuprofen. However, IL preparation #5 may contain components other than IL. This may be a reason for the slight difference between the observed and theoretical values.

II. In the permeation of IL itself from IL preparation #5, permeation depended on the concentration gradient of IL in the membrane. IL became lidocaine and ibuprofen molecules in the receiver after permeation. Therefore, lidocaine and ibuprofen concentrations in the receiver were higher than the donor, so that their membrane permeation may occur from the receiver to donor side.

III. The permeation rate of ibuprofen from IL preparations #1–4 at a higher molar fraction of ibuprofen than 0.5 was the sum of the permeation rates of IL itself and ibuprofen dissolved in IL. The permeation rate of ibuprofen from IL preparations #6–9 with ibuprofen molar fractions lower than 0.5 agreed with the theoretical value (Fig. 4b). On the other hand, the permeation rates of ibuprofen from IL preparations #1 and 2 were higher than the theoretical values. This was the reason for the different permeabilities of ibuprofen dissolved in IL from the theoretical value. When the drug-suspended solution is applied to the membrane, in general, the drug activity (A_v) in the formulation and the membrane thickness (L_m) in Eq. 2 are invariable parameters. On the other hand, the activity coefficient (γ_m) in the silicone membrane and the diffusion coefficient (D_m) of the penetrant may change due to its diffusion through the membrane. For example, a skin-penetration enhancer affects by changing the γ_m and D_s (diffusion coefficient in skin). When the IL permeates through the silicone membrane, γ_m and D_m may be changed. However, the observed permeation rates of lidocaine agreed with the theoretical values. The solubility of lidocaine in IL (1.9 parts of lidocaine/1.0 part of IL) was lower than that of ibuprofen in IL (2.6 parts of ibuprofen /1.0 part of IL). The contribution of γ_m to the membrane permeation became higher with a higher solubility in IL (ibuprofen had about 1.4 times higher solubility than lidocaine in IL). Therefore, the theoretical membrane permeation rates of lidocaine almost coincided with the observed values, whereas the theoretical membrane permeation rate of ibuprofen was slightly different from the observed value.

IV. Solvent drag may affect the membrane permeation.[32] Solvent drag is the term used to describe solute migration secondary to solvent flow. In the present study, as shown in Eq. 4, the theoretical membrane permeation rate of lidocaine or ibuprofen from the drug-suspended IL preparations where A_v of lidocaine or ibuprofen in the formulations was 1.0 was determined using the membrane permeation of lidocaine or ibuprofen from aqueous suspension. Because water is almost insoluble in the silicone membrane, the solvent drag effect can be ignored when water was applied as the solvent. On the other hand, the solvent drag effect may be involved in the membrane permeation when applied IL, which is much more lipophilic than water. The effect of solvent drag on the membrane permeation rate of ibuprofen may be higher than that of lidocaine, because ibuprofen is more soluble in IL than lidocaine. This may be another reason why the observed membrane permeation of ibuprofen was higher than the theoretical one.

V. The total membrane permeation rate, dQ/dt_{tot}, is obtained as the sum of Eqs. 3 and 4, as shown in Eq. 2. Permeation rate data of lidocaine or ibuprofen through silicone membrane from their aqueous suspension were substituted into $dQ/dt_{sol(A_v = 1)}$, to obtain (expected) theoretical values in this study. Since this theoretical one was just the experimental data, the expected value for dQ/dt_{tot} as not always match the observed permeation rate. We had considered using lidocaine- or ibuprofen-suspended IL. However, we thought that the permeation rate may be the sum of the permeation rate of LID or IBU suspended and dissolved in IL. Thus, we had finally decided to use an aqueous suspension according to an important paper[23] that the membrane permeation of chemicals from their suspensions are the same independent of the kind of solvents. Generally, water is hardly permeable, but IL is permeable through the silicone membrane, so the activity coefficient of lidocaine and/or ibuprofen in the silicone membrane changes due to IL penetration. As a result, the predicted dQ/dt_{tot} can be lower than the measured one.

However, these are possible reasons. The membrane permeability of lidocaine and ibuprofen from the present IL preparations could be predicted more accurately by collecting lidocaine and ibuprofen permeabilities from IL preparations with lidocaine + other cations and ibuprofen + other anions, respectively.

Conclusion

Various ILs consisting of different ratios of lidocaine and ibuprofen were prepared, and the permeation of both components through the silicone membrane was investigated. It was found from the experiment that IL and lidocaine or ibuprofen dissolved in IL permeated the membrane. It was also found that their permeation rates were explained well by theoretical values calculated based on their thermodynamic activities. The present study can be applied to predict drug permeability through the membrane when the third drug is contained in IL preparations. It is important to examine the membrane permeabilities using other ILs. Because this phenomenon for IL permeation through silicone membrane can also be applied to skin permeation, however, ILs will be a good candidate for use for TDSs.

Conflict of Interest The authors declare no conflict of interest.

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