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Skin Permeation of Lidocaine from Crystal Suspended Oily Formulations

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ABSTRACT In vitro permeation of lidocaine (lidocaine base, LID) through excised rat skin was investigated using several LID-suspended oily formulations. The first skin permeation of LID from an LID-suspended oily solution such as liquid paraffin (LP), isopropyl myristate (IPM), polyoxyethylene (2) oleylether (BO-2), and diethyl sebacate (DES) was evaluated and compared with that from polyethylene glycol 400 (PEG400) solution, a hydrophilic base. The obtained permeation rate of LID, J_{app}, from PEG400, LP, IPM, BO-2, and DES was in the order of DES>BO-2=IPM>LP>PEG400, and increased with LID solubility in the oily solvents, although LID crystals were dispersed in all solvents. Subsequently, oily formulations that consisted of different ratios of the first oily solvent (IPM, BO-2, or DES) (each 0–20%), the second oily solvent (LP) and an oily mixture of microcrystalline wax/white petrolatum/paraffin (1/5/4) were evaluated. BO-2 groups at a concentration of 5% and 10% had the highest J_{app} among the oily formulations, although a higher BO-2 resulted in lower skin permeation. In addition, pretreatment with BO-2 increased the skin permeation of LID. These results suggest that the penetration enhancing effect by the system may be related to the skin penetration of BO-2 itself. Finally, mathematical analysis was done to evaluate the effect of BO-2, and it was shown that BO-2 improved the LID solubility in stratum corneum lipids to efficiently enhance the LID permeation through skin.

KEYWORDS Lidocaine, Skin permeation, Oily solvent, Oily formulation, Solubility

INTRODUCTION

Lidocaine (lidocaine base, LID) has been widely used in skin permeation studies as a typical lipophilic drug (MW=234.3, log P=2.56) (Sintov & Shapiro, 2004; Welin-Berger et al., 2002). Moreover, many clinical investigations using the drug have been performed for local anesthesia to evade needle pain (Cordoni & Cordoni, 2001), post-herpetic neuralgia (Campbell et al., 2002), and laser treatment (Bryan & Alster, 2002). It is

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necessary, however, to maintain a high LID concentration around free nerve endings in the skin in order to achieve an anesthetic effect by topical delivery of LID. Several physical skin permeation-enhancement techniques, such as iontophoresis and ultrasound treatments, have been investigated to increase skin permeation (Katz et al., 2004). Unfortunately, satisfactory anesthetic effects have not yet been obtained by topical application of LID. Nevertheless, LID patches (Penless® and Lidoderm®) and EMLA® cream using the eutectic compound of LID with prilocaine (Welin-Berger et al., 2002) are on the market, and they moderately affect the above-mentioned pain.

Cheng et al. (1994) evaluated skin permeation of LID from pressure sensitive adhesive (PSA) tapes made of styrene-isoprene-styrene block copolymer by considering the lipophilicity of LID in the PSA matrices, and found that the apparent skin permeation rate increased with the LID concentration in the matrices up to 40% LID, although the saturated concentration was about 20%. These results can be explained by an increase in the LID solubility in the matrices by penetration of endogenous lipids from the stratum corneum to the PSA matrices. Thus, attention must be paid to the effect of skin lipids on the increase/decrease in thermodynamic activity of LID in the topical formulation. Of interest is the increase in the solubility of LID by skin lipids.

Many oily solvents and formulations have been evaluated for their effect on the increase in skin permeation of lipophilic compounds. For example, aliphatic esters such as isopropyl myristate (IPM) were found to increase the lipid fluidity by lipid extraction from the stratum corneum (Leopold & Lippold, 1995). Polyoxyethylene alkyl ethers also increase the skin permeation of compounds by affecting the stratum corneum (Hofland et al., 1994). These oily solvents may also increase solubility of lipophilic permeants in the skin barrier as well as in the formulations. Park et al. (2000) reported that the effect of polyoxyethylene alkyl ethers on skin permeation was different from the effect of the lipophilic enhancers. They suggested that different hydrophilic-lipophilic balance (HLB) might be closely related to the physical interaction between the permeants and enhancers.

We therefore used oily solvents and formulations with different solubilizing capacities against LID and evaluated the effect of the compounds on the in vitro permeation of LID through excised rat skin. The obtained results were discussed from a thermodynamic point of view of LID.

MATERIALS AND METHODS

Materials

Lidocaine base was purchased from Delta Synthetic Co., Ltd. (Taipei, Taiwan). Polyethylene glycol 400 (PEG400) (NOF Corporation, Tokyo, Japan) was used as a control hydrophilic solvent for the skin permeation study using an LID-suspended oily solution. Liquid paraffin (LP) (Shima Trading Co., Ltd., Tokyo), IPM (Nippon Fine Chemical Co., Ltd., Osaka, Japan), polyoxyethylene (2) oleylether (BO-2) (Nikko Chemicals Co., Ltd., Tokyo), and diethyl sebacate (DES) (Hokoku Corporation, Osaka) were used as oily solvents. Microcrystalline wax (Nikko Rika Corporation, Tokyo), white petrolatum (Nikko Rika Corporation), and paraffin (Nippon Seiro Co., Ltd., Tokyo) were used as oily formulation bases.

Preparation of LID-Suspended Solution and Determination of LID Solubility

An adequate amount of LID was mixed with each solvent and dissolved at 80°C. LID solubility in each solvent was determined by high performance liquid chromatography (HPLC) after 2 days of storage at 30°C. The assay samples were diluted with acetonitrile or tetrahydrofuran.

Preparation of Oily Formulations for Each Oily Solvent

Oily formulations containing 5%–60% LID were prepared as follows: 10%–65% melting mixture of microcrystalline wax/white petrolatum/paraffin (1/5/4, w/w), 30%, 25%, 20%, or 10% LP, 0%, 5%, 10%, or 20% other solvents (IPM, BO-2, or DES), and LID were mixed at 80°C. Total solvent concentration in the formulation was adjusted to 30%. The final oily formulations were obtained by cooling at −5°C for 5 min.

TABLE 1 Compositions of Oily Formulations

	LP system	IPM containing system	BO-2-containing system	DES-containing system
Lidocaine	5–60 (w/w)	5–60 (w/w)	5–60 (w/w)	5–60 (w/w)
Microcrystalline wax/white petrolatum/paraffin (1/5/4, w/w)	10–65	10–65	10–65	10–65
LP	30	25, 20, 10	25, 20, 10	25, 20, 10
IPM		5, 10, 20		
BO-2			5, 10, 20	
DES				5, 10, 20

LID crystals in the formulations were confirmed using a microscope after 1 day of storage at 30°C. Table 1 shows the composition of these oily formulations of LID.

Preparation of Rat Abdominal Skin Samples

Male Sprague Dawley rats (IGS) weighing 200–300 g, supplied by Charles River Japan (Yokohama, Japan), were used in all animal experiments. The intact skin sample was excised from the abdomen after the hair was carefully clipped with hair clippers. The subcutaneous fat was removed and the samples were soaked in physiological saline before the excised skin was mounted on the diffusion cell.

In Vitro Skin Permeation of LID from LID-Suspended Solutions

The skin permeation of LID from each saturated solution was measured using a 2-chamber side-by-side glass diffusion cell (effective diffusional area: 0.95 cm^2, donor and receiver cell volume: 3 mL). The intact skin sample was placed between donor and receiver cells. The receiver cell, defined as the side facing the dermis, was filled with pH 7.4 phosphate buffer, whereas the donor cell, defined as the side facing the stratum corneum, was filled with each solution containing LID crystals. Each solution was stirred with a magnetic stirrer bar and kept at 30°C by water circulation in the chamber jacket. Aliquots (1.0 mL) were withdrawn from the receiver solution every 2 h for a total of 10 h and the same volume of fresh buffer was added to keep the volume constant. LID concentrations in the receiver solution were determined by HPLC. The apparent steady-state permeation rate (J_{app}) and the apparent diffusion coefficient (D_{app}) in the skin barrier were calculated by the least-squares method using the solver-function of Microsoft® Excel 2000.

In Vitro Skin Permeation of LID from Oily Formulations

Skin permeation of LID from oily formulations was measured using Franz type diffusion cell (effective diffusional area: 3.14 cm^2, receiver volume: 17 mL). The intact skin sample was placed on the receiver cell with the stratum corneum facing upwards. The oily formulation (50 mg) was applied on the stratum corneum surface, the donor chamber was clamped in place, and then pH 7.4 phosphate buffer was added to the receiver cell. The receiver cell was stirred with a magnetic stirrer bar and kept at 37°C in order to hold the temperature at 30°C on the stratum corneum surface. Aliquots (1.0 mL) were withdrawn from the receiver solution every 2 h for a total of 10 h and the same volume of fresh buffer was added to keep the volume constant. LID concentrations in the receiver solution were determined by HPLC. The apparent steady-state permeation rate (J_{app}) and the apparent diffusion coefficient (D_{app}) were calculated by the least-squares method as explained above.

BO-2 or DES Pretreatment Studies

The pretreatment effects of BO-2- or DES-containing formulations on the stratum corneum on the skin permeation of LID were measured using the Franz type diffusion cell as mentioned above. The intact skin sample was placed on the cell, and 100 mg BO-2- or DES-containing formulations without LID were applied on the stratum corneum surface and the donor chambers were clamped in place. Table 2 shows the

TABLE 2 **Compositions of BO-2- and DES-Containing Formulations for the Pretreatment Study**

	BO-2-containing system	DES-containing system
Lidocaine	0 (w/w)	0 (w/w)
Microcrystalline wax/white petrolatum/ paraffin (1/5/4, w/w)	70	70
LP	25, 20, 10	25, 20, 10
BO-2	5, 10, 20	
DES		5, 10, 20

composition of BO-2- and DES-containing formulations. Phosphate buffered solution (pH 7.4) was added to the receiver cell. The receiver cell was stirred with a magnetic stirrer bar and kept at 37°C. After 14 h pretreatment, the applied formulation was taken off and the pretreated skin was placed on a separate diffusion cell. An LP formulation containing 30% LID (total 100 mg) was applied on the skin surface and the donor chambers were clamped in place, whereas phosphate buffered solution (pH 7.4) was added to the receiver cell. Aliquots (1.0 mL) were withdrawn from the receiver every 2 h for a total of 10 h and the same volume of fresh buffer was added.

HPLC Analysis of LID

LID was determined by HPLC, which consisted of a pump (LC-9A, Shimadzu, Kyoto, Japan), an ultraviolet detector (SPD-6AV, Shimadzu), a packed column (CAPCELL PAK® C18 UG120, 5 μm, 4.6 mm × 250 mm, Shiseido, Tokyo, Japan) and an integrator (C-R4A, Shimadzu). The mobile phase was distilled water/acetonitrile (60/40, v/v) with 5 mmol/L sodium 1-decansulfonate, adjusted to pH 2.2 by phosphoric acid. The flow rate was 1.0 mL/min. Detection was done by UV absorbance at 220 nm and propyl *p*-hydroxybenzoate was used as an internal standard in acetonitrile.

RESULTS AND DISCUSSION

In Vitro Skin Permeation of LID from LID-Suspended Solutions

Figure 1 shows skin permeation profiles of LID from the LID-suspended solutions. LID permeations from LP, IPM, BO-2, and DES were higher than that from PEG400. The rank was in the order of DES > BO-2 = IPM > LP > PEG400.

Generally, steady state permeation rates of a drug through skin from the drug-suspended vehicles, J_{app}, must be determined by the Higuchi's equation (Higuchi, 1962). The application of this equation is limited to the cases in which the vehicle has no effect on the skin barrier function. PEG400 does sometimes directly affect the stratum corneum because of its hydrophilicity, when applied as a vehicle. Therefore, the effect of the oily solvents on the skin barrier function against the LID permeation was evaluated by this equation as a ratio against the mean value for PEG400. According to Higuchi's equation, J_{app} becomes:

$$J_{app} = K_{app} C_v D_{app} / L = a_v D_{app} / \gamma_s L \qquad (1)$$

where C_v is concentration of dissolved LID in each solvent, a_v is the thermodynamic activity of the drug in the solution where $a_v = \gamma_v C_v$ (γ_v is defined as the activity coefficient of LID in the vehicle), D_{app} and γ_s are the apparent diffusion coefficient and the activity coefficient of LID in the skin barrier, K_{app} is the apparent partition coefficient of LID where $K_{app} = \gamma_v / \gamma_s$, and L is the thickness of the skin barrier.

Table 3 summarizes solubility, J_{app} and γ_s of LID for each solvent. J_{app} was not well correlated with the LID solubility in the vehicle, although the solubility was in the order of DES > BO-2 > IPM > PEG400 > LP. However, J_{app} increased because of a decrease in γ_s in contrast to the solubility. Moreover, the γ_s for the oily solvents decreased compared with PEG400. A good

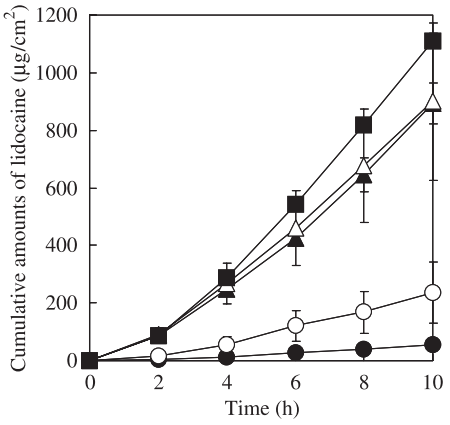

FIGURE 1 **Time Course of the Cumulative Amount of LID That Permeated from LID-Suspended Solutions Through Excised Rat Skin. Symbols: PEG400 (Closed Circle), LP (Open Circle), IPM (Closed Triangle), BO-2 (Open Triangle), and DES (Closed Square). Each Data Point is Presented as the Mean ± S.D. (n = 3).**

TABLE 3 LID Solubility and Calculated Permeation Parameters of LID-Saturated Solvents

Solvent	Solubility* (mg/g)	J_{app}* (μg/h/cm^2)	Relative J_{app}	${\gamma_s}^*_7$ (mL/mg)	Relative γ_s
PEG400	209.1±6.06	7.25±1.32	1.00	0.490±0.0742	1.00
LP	92.4±5.54	27.7±12.2	3.82	0.165±0.0525	0.336
IPM	330.8±2.51	93.9±7.71	12.9	0.0832±0.0109	0.170
BO-2	527.6±1.48	103.9±33.2	14.3	0.0699±0.0296	0.143
DES	639.0±3.12	137.3±6.77	18.9	0.0328±0.000648	0.0670

*Data are presented as the mean±S.D. (n=3).

correlation was obtained between J_{app} and γ_s for the oily solvents (Fig. 2). The decrease in the activity coefficient can be evaluated as an increase in the solubilizing capacity of LID. Thus, LP, IPM, BO-2, and DES penetrated into the skin barrier and increased the LID solubility in the stratum corneum lipids, even though the stratum corneum is the primary barrier to the skin permeation of LID. These results indicated that the solubilizing capacity of LID in the stratum corneum lipids was in the order of DES>BO-2>IPM>LP.

In Vitro Skin Permeation of LID from Oily Formulations

Since the permeation rate of LID, J_{app}, depended on the activity coefficient in the skin barrier, the following experiments were performed by considering the LID solubility across the skin barrier, not in the formulations. Several oily formulations containing the above-mentioned oily solvents (LP, IPM, BO-2, and DES) were evaluated. The amount of oily solvents was fixed to 30% in the formulations. Figures 3–5 show the relationship between LID concentration in the vehicle and the permeation rate of LID for the IPM-, BO-2-, and DES-containing systems, respectively. The LP system was used as a control. The observed LID solubility was dependent on the applied vehicle, as shown in Table 3. The solubility increased with an increase in the solvent ratio in the oily formulations (open symbols in Figs. 3–5 show no LID crystal in the vehicles, whereas closed symbols show the existence of LID crystal). Interestingly, the highest solubility of LID was observed for the BO-2-containing system among the systems evaluated in the present study, although DES showed the highest solubility among the oily solvents (Table 3).

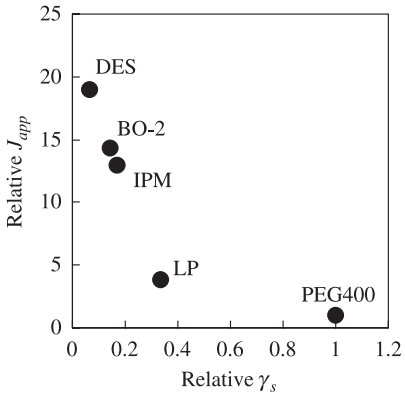

FIGURE 2 Relationship Between the Relative Permeation Rate of LID for LID-Suspended Solutions, J_{app}, and the Relative Activity Coefficient of LID in Skin, γ_s. Relative Permeation Rate of LID from Each Oily Solvent was Obtained by Dividing by the Skin Permeation Rate from PEG400. Each Data Point is the Mean Ratio Against that of PEG400.

The observed J_{app} of LID increased with an increase in LID concentration in the formulations to reach the maximum flux. The results are very similar to those determined by Cheng et al. (1994). They measured skin permeation of LID from PSA matrices of styrene-isoprene-styrene block copolymer and found that the permeation rate was increased by penetration of the skin lipid to the PSA matrices. It is still unclear, however, whether the increase of LID solubility was a result of the formulations or the skin barrier. In the present study, a similar increment of LID solubility was obtained in the formulations or in the skin barrier, and this is probably related to the increase in the skin permeation of LID from these oily formulations. The increasing ratios of LID solubility and J_{app} were closely related to the kind of oily formulations topically applied. A BO-2-containing system showed a high skin permeation as well as high solubility of LID among oily formulations used in this experiment.

The effect of the oily formulations on the skin barrier function against the LID permeation was evaluated by Eq. 1 in the same way as in the previous study using LID-suspended solutions. Figure 6 shows the relationship between the solvent concentration

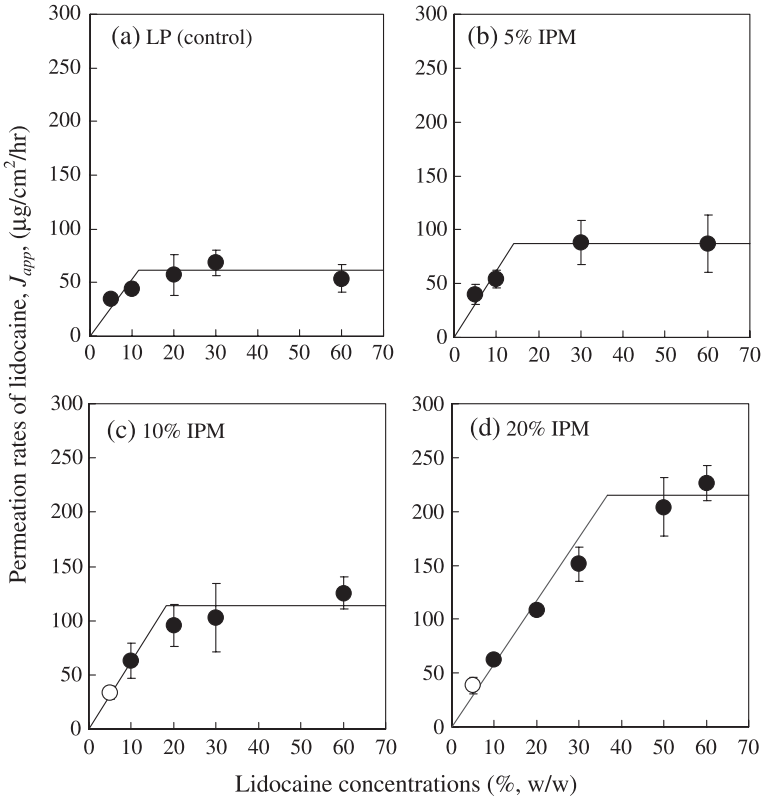

FIGURE 3 **Relationship Between Concentration and Skin Permeation Rate of LID, J_{app}, for IPM-Containing Oily Systems. Open and Closed Symbols Indicate LID-Unsaturated and Saturated Oily Formulations, Respectively. Each Data Point is Presented as the Mean ± S.D. (n=3).**

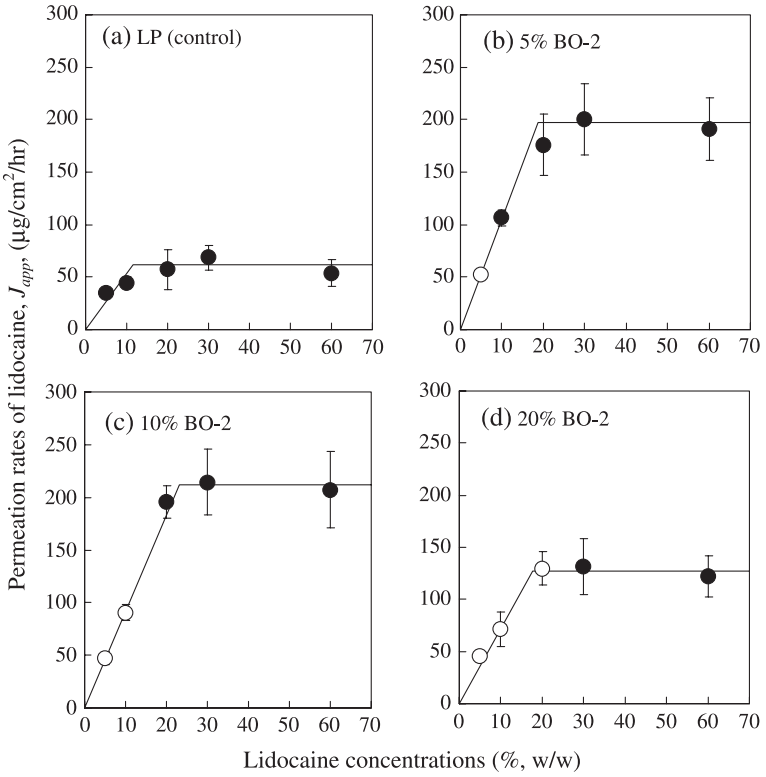

FIGURE 4 **Relationship Between Concentration and Skin Permeation Rate of LID, J_{app}, for BO-2-Containing Oily Systems. Open and Closed Symbols Indicate LID-Unsaturated and Saturated Oily Formulations, Respectively. Each Data Point is Presented as the Mean ± S.D. (n=3).**

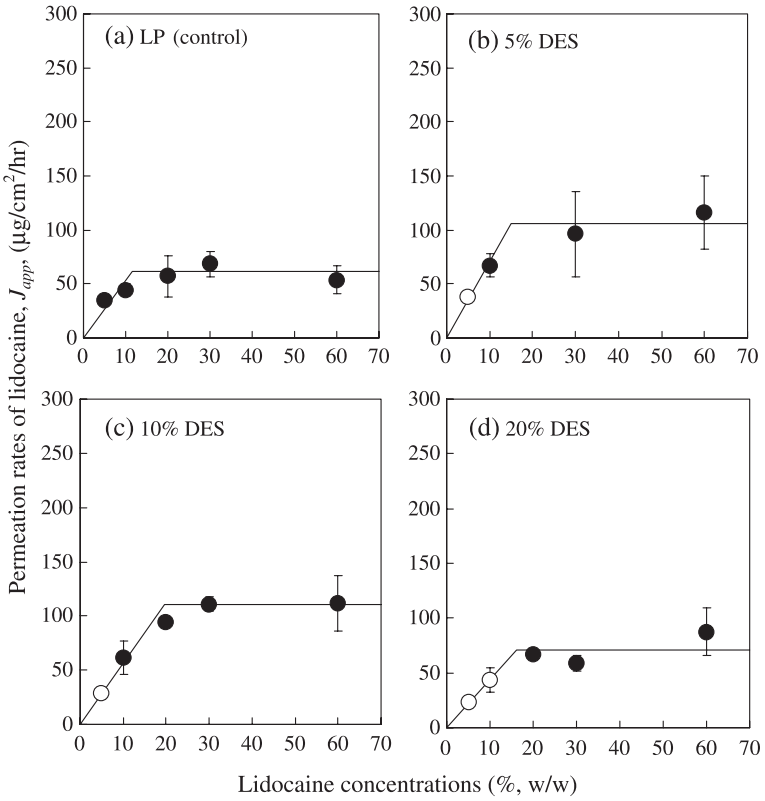

FIGURE 5 **Relationship Between Concentration and Skin Permeation Rate of LID, J_{app}, for DES-Containing Oily Systems. Open and Closed Symbols Indicate LID-Unsaturated and Saturated Oily Formulations, Respectively. Each Data Point is Presented as the Mean ± S.D. (n=3).**

and C_v (a) and J_{app} (b). C_v in all formulations used in this experiment was higher than that in the control vehicle, LP (Fig. 6a). However, different patterns were observed depending on the oily solvents (IPM-, BO-2-, and DES-containing systems). The C_v in the IPM-containing system was increased with an increase in the oily solvent, whereas C_v in the BO-2- and DES-containing systems increased to 10% then decreased to 20%. Similar profiles were observed for J_{app} vs. the solvent concentration as shown in Fig. 6b. We emphasize that a higher skin permeation of LID was observed from oily vehicles showing a higher solubility of the drug, in spite of the same thermodynamic activity of LID in the vehicles.

Table 4 shows two kinds of activity coefficients, γ_v and γ_s, which were calculated as a ratio against the mean value for LP by Eq. 1. The relative γ_s of IPM-, BO-2-, and DES-containing systems was low as compared with LP. These results suggest that these oily solvents increase the LID solubility in the stratum

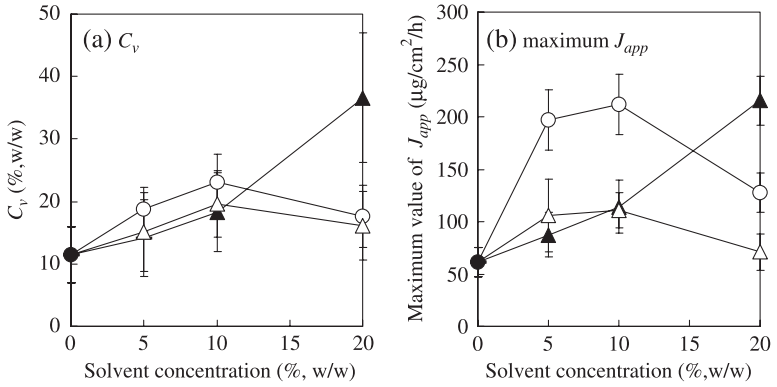

FIGURE 6 **Relationships Between C_v (a) and J_{app} (b) of LID and Solvent Concentration in Each Oily Formulation. Symbols: LP (Closed Circle), IPM (Closed Triangle), BO-2 (Open Circle) and DES (Open Triangle). Each Data Point is Presented as the Mean ± S.D. (n=6–9).**

TABLE 4 Calculated Relative Permeation Parameters in Oily Formulations Through Excised Rat Skin

	LP system	IPM-containing system			BO-2-containing system			DES-containing system		
	Solvent concentration	Solvent concentration			Solvent concentration			Solvent concentration		
	30%	5%	10%	20%	5%	10%	20%	5%	10%	20%
D_{app}	1.00	1.01	1.37	1.36	0.736	0.949	0.662	1.43	1.37	1.17
J_{app}	1.00	1.43	1.87	3.52	3.22	3.46	2.09	1.74	1.82	1.16
γ_v	1.00	0.831	0.612	0.296	0.559	0.454	0.615	0.772	0.549	0.691
γ_s	1.00	0.710	0.734	0.386	0.229	0.274	0.317	0.821	0.754	1.01

Data are calculated as the ratio against the mean value for the LP system.

corneum lipids. Leopold and Maibach (1999) have previously reported that the anesthetic effect of a topically applied compound was affected by its solubility in the stratum corneum lipids. The γ_s value for the BO-2-containing system was lower than that for the IPM- and DES-containing systems. In other words, LID solubility was increased by addition of BO-2, much more than that for IPM and DES. This is the reason why BO-2 showed a higher skin permeation effect than IPM and DES. Since BO-2 is a surfactant, it may affect the ordered structure of the stratum corneum. Therefore, BO-2 can be used as an effective penetration enhancer as well as a solubilizer against LID in the oily formulations.

On the other hand, γ_s did not increase with 20% BO-2 or DES, although the thermodynamic activity of LID in the vehicles was also high, suggesting that migration of oily solvents may take place through the skin barrier. As a result, the solubility parameter of the oily solvents was determined using cohesive energy density and molar volume (Grulke, 1999). The obtained values were 17.5, 18.8, and 27.6 $(J/cm^3)^{1/2}$ for IPM, BO-2, and DES, respectively. The solubility parameter of the skin barrier was found to be about 20 $(J/cm^3)^{1/2}$ (Liron & Cohen, 1984). Thus, IPM and BO-2 may more easily permeate through the stratum corneum from the oily formulations than DES. In addition, these oily solvents have a high solubilizing capacity compared with LP, as shown in Table 3. High affinity of these solvents to LID may decrease the distribution and penetration of LID into the stratum corneum.

Effect of BO-2 or DES Pretreatment on the Skin Permeation of LID from Oily Formulations

Next, a pretreatment experiment using the BO-2- and DES-containing systems was performed to evaluate the effect of LID in the oily formulations on the skin permeation of LID. Oily formulations containing 5%, 10%, or 20% BO-2 or DES without

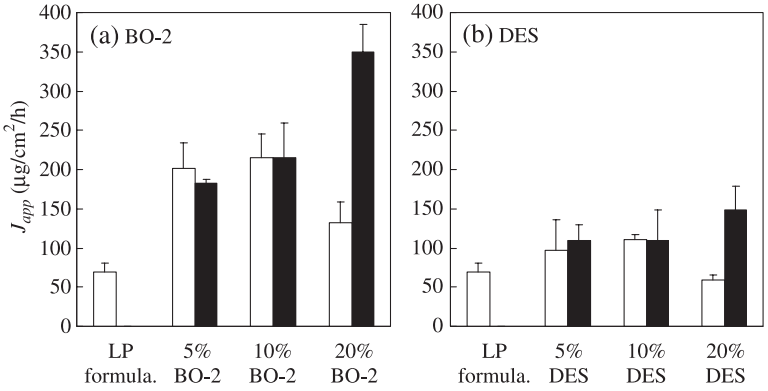

FIGURE 7 Effect of Pretreatment of BO-2- (a) and DES-Containing System (b) on the Skin Permeation Rate of LID, J_{app}. Open and Closed Columns Indicate Without and With the Pretreatment. Each Data Point is Presented as the Mean ± S.D. (n=3).

LID were prepared (Table 2), and the stratum corneum side was pretreated with the formulations for 14 h. The LP formulation containing 30% LID was then applied on the pretreated skin to determine the skin permeation rate of LID, J_{app}. Figure 7 shows the results obtained after pretreatment with the BO-2- or DES-containing systems as well as direct treatment data (without pretreatment).

The J_{app} for the pretreatment groups increased with an increase in the solvent concentration. Pretreatment with the oily formulation containing 20% solvent markedly improved the skin permeation rate of LID. These results indicate that the suspended LID may inhibit migration and diffusion of BO-2 and DES into the skin. In the present study using LID-suspended solutions, the J_{app} of LID correlated with the γ_s. Thus, these oily solvents had a solubilizing capacity of LID in the skin barrier. In other words, effective penetration of BO-2 or DES into the skin barrier must be acquired from the high J_{app} of LID. The penetration properties of BO-2 and DES may be lower than those of IPM, considering their different lipophilicity or solubility parameters. These solubility parameters indicate that DES does not easily penetrate the skin barrier compared with BO-2 and IPM. In order to explain the different effects between BO-2 and DES, the affinity of the oily solvents to LID was used. The solubility parameter of LID was determined to be 20.7 $(J/cm^3)^{1/2}$ (Grulke, 1999). Therefore, BO-2 has a better affinity to LID than DES, although the penetration property of BO-2 is better than DES. Since BO-2 has a strong affinity for LID, the penetration of BO-2 into the skin barrier was inhibited and LID activity in the oily formulation was decreased.

In conclusion, LID solubility in the oily formulations was increased, although the LID crystal was still dispersed. A high skin permeation of LID was observed when BO-2 was contained in the oily formulations as an oily solvent. A suitable concentration of BO-2 was also found for the high permeability of LID, suggesting that a higher solubilizing capacity of the formulations is not directly related to higher skin permeation. This is probably due to a lowered activity of LID by excess addition of the solubilizer. In other words, a relatively hydrophilic solvent did not provide a great enough solubilizing capacity against the LID crystals, whereas a relatively lipophilic oily solvent may penetrate the skin. Thus an excess amount of a lipophilic oily solvent must be added in the formulations to solubilize LID and improve the skin permeation of LID. Oily solvents solubilizing LID have a great effect on the solubility in the skin barrier as well as in topical formulations. Therefore, close attention must be paid to the skin permeation and drug activity in formulations. Selection of a solubilizer is very important in making a strong transdermal formulation.

CONCLUSIONS

Skin permeation of LID from crystals suspended in oily formulations increased with an increase in the LID concentration. The maximum activity was obtained at a high LID concentration. From an equation for the steady-state permeation rate, each oily solvent had different effects on the LID solubility in the skin barrier. BO-2 had the highest LID skin permeation rate, because it improved the LID solubility in the stratum corneum lipids.

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