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Effect of liposomes and niosomes on skin permeation of enoxacin

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Abstract

The skin permeation and partitioning of a fluorinated quinolone antibacterial agent, enoxacin, in liposomes and niosomes, after topical application, were elucidated in the present study. In vitro percutaneous absorption experiments were performed on nude mouse skin with Franz diffusion cells. The influence of vesicles on the physicochemical property and stability of the formulations were measured. The enhanced delivery across the skin of liposome and niosome encapsulated enoxacin had been observed after selecting the appropriate formulations. The optimized formulations could also reserve a large amount of enoxacin in the skin. A significant relationship between skin permeation and the cumulative amount of enoxacin in the skin was observed. Both permeation enhancer effect and direct vesicle fusion with stratum corneum may contribute to the permeation of enoxacin across skin. Formulation with niosomes demonstrated a higher stability after 48 h incubation compared to liposomes. The inclusion of cholesterol improved the stability of enoxacin liposomes according to the results from encapsulation and turbidity. However, adding negative charges reduced the stability of niosomes. The ability of liposomes and niosomes to modulate drug delivery without significant toxicity makes the two vesicles useful to formulate topical enoxacin.

Keywords: Enoxacin; Liposomes; Niosomes; Skin permeatiom

1. Introduction

Liposomes, prepared from a variety of natural and synthetic phospholipids, are being considered as drug-carrying structures or vesicles. They may serve as a solubilization matrix, as local depot for sustained release of dermally active compounds, as permeation enhancers, or as a rate-limiting membrane barrier for the modulation of systemic absorption of drugs via the skin (Schreier and Bouwstra, 1994). Niosomes, non-ionic surfactant vesicles, are now widely studied as an alternative to liposomes. These vesicles appear to be similar

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in terms of their physical properties to liposomes, being prepared in the same way and, under a variety of conditions, forming unilamellar or multilamellar structures (Yoshioka et al., 1994). Niosomes alleviate the disadvantages associated with liposomes such as chemical instability, variable purity of phospholipids and high cost (Vora et al., 1998).

Enoxacin is a fluoquinolone antibiotic structurally related to nalidixic acid. It has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria (Zinner, 1989). Drug interactions and adverse drug effects after oral administration have limited its use (Sorgel et al., 1989). The plasma half-life of enoxacin is 3–6 h, suggesting frequent dosing is needed. Since enoxacin is effective for topical skin and soft tissue infections (Henwood and Monk, 1988). Accordingly the transdermal drug delivery system may be suitable for enoxacin to reduce the adverse effects caused by oral administration and to prolong the therapeutic duration (Fang et al., 1998).

The purpose of the current study was to investigate the feasibility of liposomes and niosomes to formulate the transdermal administration of enoxacin. Formulations composed of different percentages of lipids and surfactant compositions, charge on bilayers and cholesterol (CH) have been tested to optimize the skin permeation of enoxacin. The stability of vesicles characterized by drug encapsulation and turbidity was also measured. The possible mechanisms for skin permeation of liposomes and niosomes was elucidated with the results of a series of skin permeation experiments.

Table 1
Constituents of the enoxacin liposomes and niosomes[a]

No.	Code	Composition
1	DMPC	DMPC
2	DMPC/CH	DMPC:CH = 7:3 (molar ratio)
3	Soybean PC	Soybean PC:CH = 9:1 (weight ratio)
4	Egg PC	Egg PC:CH = 9:1 (weight ratio)
5	Span40	Span40:CH = 1:1 (molar ratio)
6	Span60	Spana60:CH = 1:1 (molar ratio)
7	Span60/DCP	Span60:CH:DCP = 4.5:4.5:1 (molar ratio)

[a] The total lipid concentration was adjusted to 15.6 mM.

2. Materials and methods

2.1. Materials

Enoxacin, dimyristoyl-L-α-phosphatidylcholine (DMPC), soybean phosphatidylcholine (Soybean PC; 99%), egg phosphatidylcholine (Egg PC; 99%), cholesterol (CH) and dicetyl phosphate (DCP) were obtained from Sigma Chemical Co. (USA). Sorbitan monopalmitate (Span40) and sorbitan monostearate (Span60) were supplied by Wako Chemical Co. (Japan). All other chemicals and solvents were of analytical grade.

2.2. Preparation of liposomes and niosomes

Liposomes and niosomes were prepared by a combination of ethanol injection and freeze-drying techniques modified from the methods of Lin et al. (1996). Enoxacin was directly added to an ethanol solution containing lipids and surfactants. The solution was then rapidly injected into a fivefold greater volume of magnetically stirred citrate–phosphate buffer (pH 5). Ethanol in the dispersion was then removed by a rotary vacuum evaporator (Eyela Co., Japan). The final dispersion was frozen in a dry ice-acetone bath and dried in a freeze-dryer (Labconco Co., USA) under 10 microHg vacuum at −50°C for 24 h. The lyophilized liposome or niosome powders were reconstituted and diluted with deionized bi-distilled water. A small volume of suspension was pipetted and into sample vials and re-loaded into the freeze-dryer if necessary. The total lipid concentration was adjusted to 15.6 mM. Seven liposome and niosome formulations used in this study are listed in Table 1.

2.3. Determination of enoxacin encapsulation percentage

The method for determining encapsulation percentages of enoxacin was developed previously

(Fang et al., 1997; Lin et al., 1996). Briefly, the enoxacin-containing vesicles were separated from the unencapsulated drug by filtering the dispersion under vacuum through a 0.05 mm filter (Millipore Co., USA); these vesicles were then washed with buffer to completely remove the free drug. The amount of entrapped enoxacin was determined by lysis of the vesicles with absolute ethanol. The vesicle dispersion was mixed with an equal volume of ethanol to give a clear solution. The amount of enoxacin was measured by a HPLC method as described previously (Fang et al., 1997). The percentage of drug encapsulated was calculated from the ratio of the enoxacin in the vesicles to the total amount of enoxacin in the aqueous suspension.

2.4. Turbidity measurement

Liposomes and niosomes were diluted with bidistilled water to give a total lipid concentration of 0.312 mM. After rapid mixing by sonication for 5min, the turbidity was measured as the absorbance at 400 nm with an ultraviolet–visible diode array spectrophotometer (WPA Co., UK) (Ishida et al., 1991).

2.5. Stability of vesicle dispersion

A stability test of the liposome or niosome dispersions was conducted by incubating the hydrolyzed vesicles with bidistilled water at 25°C. Samples were withdrawn after 48 h. Encapsulation efficiency and turbidity of these dispersions were then determined as described above.

2.6. Separation of unencapsulated enoxacin

The skin permeation experiment with enoxacin from liposomes and niosomes was performed after removing the unencapsulated drug. The liposome dispersion was centrifuged at 100 000 rpm, and 4°C for 20 min in order to separate the incorporated enoxacin from free enoxacin molecules. The vesicles and supernatant were then separated and the vesicles were reconstituted in buffer at pH 5 to obtain an enoxacin concentration of approximately 0.1% (w/v) before application to the skin.

2.7. In vitro permeation experiments

The permeation of enoxacin from liposomes and niosomes was determined by using a Franz vertical diffusion cell. The nude mouse skin (6 weeks old) was mounted on the receptor compartment with the stratum corneum (SC) side facing upward into the donor compartment. The donor compartment was filled with 2 ml liposome or niosome formulation with 0.1% (w/v) enoxacin. A 10 ml aliquot of citrate–phosphate buffer (pH 7.4) was used as receptor medium. The available diffusion area of the cell was 0.785 cm^2. The receptor compartment was maintained at 37°C, with magnetic stirring at 600 rpm. At appropriate intervals, 200 μl aliquots of receptor medium were withdrawn and immediately replaced with an equal volume of fresh receptor solution. The samples from the receptor medium were analyzed by HPLC.

3. Results and discussion

3.1. Characterization of enoxacin liposomes and niosomes

The encapsulation and turbidity of the formulations of enoxacin liposomes and niosomes are listed in Table 2. DMPC liposomes with a 15.6 mM lipid concentration showed a high ratio of encapsulation of enoxacin ($83.32 \pm 0.58\%$). In our previous study, the DMPC liposomes with a 3.9 mM lipid concentration showed a lower enoxacin encapsulation ($61.55 \pm 6.79\%$) (Fang et al., 1997). This suggested that the increase in the amount of phospholipid led to an increase in drug encapsulation. The incorporation of CH to the DMPC liposomes (DMPC/CH liposomes) caused a reduction in the encapsulation efficiency of enoxacin (DMPC vs. DMPC/CH = 83.32 ± 0.58 vs. 67.78 ± 13.71). Since CH might lower the partitioning of drug molecules to the bilayer membrane, the degree of encapsulation would decrease (Handa et al., 1987). The specific turbidity, the indicator of vesicle size (Fang et al., 1997; Goormaghtigh and Scarborough, 1986), increased dramatically from 0.362 ± 0.122 to 0.831 ± 0.019

Table 2
Encapsulation and turbidity of enoxacin liposomes and niosomes[a]

Formulations	Encapsulation (%)		Turbidity at 400 nm	
	Initial	After 48 h	Initial	After 48 h
DMPC	83.32 ± 0.58	34.48 ± 12.11	0.362 ± 0.122	0.153 ± 0.087
DMPC/CH	67.78 ± 13.71	45.04 ± 13.43	0.831 ± 0.019	1.010 ± 0.080
Soybean PC	48.30 ± 1.43	31.17 ± 9.98	0.672 ± 0.076	0.438 ± 0.176
Egg PC	50.51 ± 11.42	35.42 ± 6.61	0.772 ± 0.162	0.742 ± 0.013
Span40	75.42 ± 9.98	65.62 ± 3.44	0.798 ± 0.031	0.627 ± 0.031
Span60	71.10 ± 12.80	57.71 ± 5.59	0.189 ± 0.074	0.142 ± 0.030
Span60/DCP	69.27 ± 15.72	41.42 ± 6.64	0.553 ± 0.055	0.280 ± 0.098

[a] Each value represents the mean ± SD (n = 3).

after adding CH (Table 2). This result might be explained in terms of the DMPC content. The addition of CH to liposomes reduced the DMPC content from 100% (DMPC liposomes) to 70% (DMPC/CH liposomes), inducing more aggregation because PC-enriched liposomes have difficulty aggregating due to the repulsive hydration force between bilayers (Hazemoto et al., 1993).

PC with saturated long alkyl chains provided rigid bilayers with low permeability for encapsulated molecules (Talsma and Crommelin, 1993). The PC extracted from biological sources, such as soybean oil (Soybean PC liposomes) and egg yolk (Egg PC), was composed of a mixture of saturated and unsaturated fatty acids. Hence, the enoxacin encapsulation of Soybean PC and Egg PC liposomes was lower, as compared to DMPC liposomes.

No significant differences (48.30 ± 1.43 vs. 50.51 ± 11.42 vs. 83.32 ± 0.58 for soybean PC, Egg PC and DMPC, respectively) were found between the encapsulation of Span40 and Span60 niosomes (t-test, $P > 0.05$), whereas the turbidity of Span40 was much higher (t-test, $P < 0.05$) than that of Span60 niosomes (Table 2). The relationship observed between niosome size and sorbitan monoester hydrophobicity has been attributed to the decrease in surface energy with increasing hydrophobicity (Yoshioka et al., 1994), resulting in the smaller vesicles. DCP was added to give a net negative charge to the niosomes (Span60/DCP niosomes). The drug encapsulation did not change significantly after incorporation of DCP, but the turbidity evaluation of Span60/DCP niosomes showed a higher value compared to the uncharged ones. The presence of an anionic surfactant such as DCP, that shows a high degree of hydrophilicity, led to vesicles becoming larger than those without DCP (Carafa et al., 1998).

3.2. Stability of enoxacin liposomes and niosomes

The encapsulated drug tends to leak out from the bilayer structure during storage. A significant loss in enoxacin encapsulation of DMPC liposomes was noted after incubation in suspension form for 48 h (Table 2). Encapsulation loss was always associated with an increase in vesicle size and turbidity value, which is a thermodynamically more stable status as observed in enoxacin liposomes stored in lyophilized form (Fang et al., 1997). However, the data in Table 2 indicates the turbidity of DMPC liposomes is significantly reduced from 0.362 ± 0.122 to 0.153 ± 0.083 (t-test, $P < 0.05$) after 48 h incubation in suspension form. It might correlate with the hydrolysis of liposomes after reconstitution with water, resulting in a decrease in the number of liposomes per unit volume and hence the degree of turbidity (Vemuri et al., 1990; Virtanen et al., 1995).

Phospholipid loss, in the presence of water, from the liposome bilayers leads to the formation of pores and leakage. After incorporation of CH, leakage of enoxacin is significantly reduced. The turbidity of DMPC/CH liposomes did not change

even after 48 h incubation (t-test, $P > 0.05$). Inclusion of CH in liposomes improved the fluidity of the bilayer membrane and reduced the permeability of drugs through the membrane (Vemuri et al., 1990; Virtanen et al., 1995). This effect lessened the leakage of the entrapped drug from the liposomes and resulted in a higher stability of the formulation. Similarly, there was no significant difference among the leakage percentages of enoxacin from three liposome formulations with CH (DMPC/CH liposomes, 33.55% loss; Soybean PC liposomes, 35.47% loss; Egg PC liposomes, 29.88% loss) after 48 h incubation. However, the turbidity of the Soybean PC liposomes was significantly decreased after incubation. A higher susceptibility to lipid peroxidation for unsaturated fatty acid molecules as compared to saturated molecules was reported (Piraube et al., 1988; Vemuri and Rhodes, 1995). The content of PC with unsaturated fatty acids in Soybean PC was higher than Egg PC (Vemuri and Rhodes, 1995), which might contribute to the weaker stability of Soybean PC liposomes than DMPC/CH, as well as Egg PC liposomes.

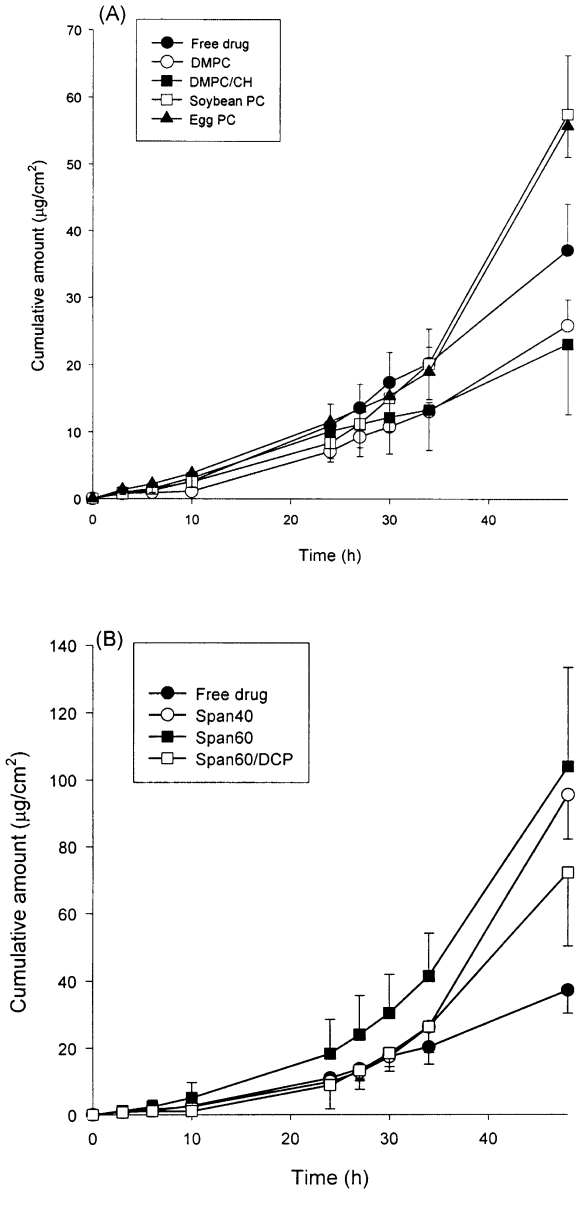

Fig. 1. In vitro cumulative amount–time profiles of enoxacin permeated across nude mouse skin from liposomes (A) and niosomes (B). All data represent four experiments (mean ± SD).

Both Span40 and Span60 niosomes showed good stability according to encapsulation and turbidity after 48 h incubation (Table 2). The problems of phospholipid hydrolysis and fatty acid peroxidation in liposomes were not observed for non-ionic surfactants. The presence of ionic surfactants in the formulation is generally used to stabilize niosomes by means of an increase of their zeta potential and optimized ion–dipole interaction. However, the incoporation of negatively charged DCP did not yield stable vesicles and thus reduced the stability of niosomes during storage in this present study. This phenomenon might be due to an induced repulsion within the double layers which ccurred when there was a large amount of DCP in the niosomes (Carafa et al., 1998).

3.3. Skin permeation of enoxacin liposomes and niosomes

Fig. 1 shows the cumulative amount–time profiles of free and liposome- or niosome-encapsulated enoxacin across nude mouse skin. The curves were suitable to fit by a first-order equation. DMPC liposomes reduced the enoxacin permeation (t-test, $P < 0.05$) based on the total amount of enoxacin permeated during the 48 h in vitro permeation experiment (Table 3). DMPC

Table 3
Total amount of enoxacin permeated from liposomes and niosomes (μg/cm^2) across intact nude mouse skin during 48 h[a]

Formulations	Total amount permeated during 48 h (μg/cm^2)[b]
Free drug	31.50 ± 5.88
DMPC	20.56 ± 2.94
DMPC/CH	19.21 ± 10.88
Soybean PC	44.97 ± 8.25
Egg PC	41.35 ± 5.32
Span40	70.89 ± 8.26
Span60	85.79 ± 19.20
Span60/DCP	57.00 ± 19.44

[a] The data was calculated by the trapezoidal method from the area under curve (AUC) of flux–time profiles.
[b] Each value represents the mean ± SD ($n = 4$).

also did not increase the enoxacin amount retained in skin after 48 h application (Fig. 2). The presence or absence of CH in the lipid bilayers did not reveal any significant differences (t-test, $P > 0.05$) in transdermal delivery and residual enoxacin in the skin. The amount of enoxacin permeated was significantly increased in Soybean PC or Egg PC liposomes compared to that in the free form or in DMPC liposomes, indicating the lipid composition of liposomes influenced the transdermal activity of entrapped enoxacin. These two formulations also allowed a high accumulation of enoxacin in skin. Both Soybean PC and Egg PC contain phosphatidylcholine, phosphatidylethanolamine, phosphatidylionsitol and unsaturated fatty acid. The presence of unsaturated fatty acids in the phospholipids may be responsible for the enhancer effect. Lecithin has a high affinity for SC. The packing nature of unsaturated fatty acids changed the fluidity of SC lipid structure and facilitated the skin permeation of drugs (Valenta et al., 2000; Valjakka-Koskela et al., 1998).

The transdermal permeation and skin partitioning of enoxacin from Span40 and Span60 niosomes were similar (t-test, $P > 0.05$), but much higher than that from the free form and from liposomes (Fig. 2 and Table 3). Surfactant in formulation always acts as a permeation enhancer (Sarpotdar and Zatz, 1986; Vora et al., 1998),

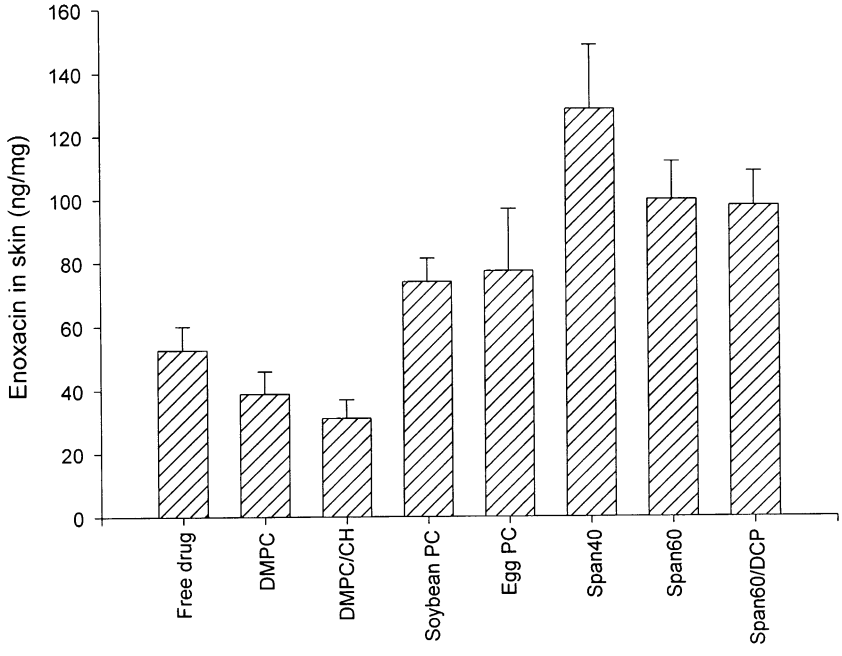

Fig. 2. Enoxacin amount in nude mouse skin from liposomes and niosomes after 48 h in vitro topical application. All data represent four experiments (mean ± SD).

which might partly contribute to the enhancement of enoxacin permeation from niosomes. Another explanation was that niosomes fused at the interface of the SC, and the high local drug concentration in the bilayers generated a high thermodynamic activity of enoxacin in the upper part of the SC (Schreier and Bouwstra, 1994). The plausibilities of these mechanisms will be discussed in the following section. DCP reduced the permeation of enoxacin across the skin without affecting enoxacin partitioning into the SC. Since the adsorption of liposomes or niosomes onto the skin is due to physical or electrostatic forces (Vulta et al., 1996), it was expected that the charged niosomes might alter this interaction. Lower enoxacin skin permeation of negatively charged niosomes could be attributed to a repulsion within the skin surface in physiological conditions.

The correlation coefficient between the skin permeation and skin tissue uptake of enoxacin from all formulations tested was calculated. There was a significant correlation (correlation coefficient, $r = 0.905$) between the total enoxacin permeated during 48 h and the total amount accumulated in the skin tissue. A better correlation ($r = 0.982$) was observed between the skin permeation and the cumulative amount in the skin from liposome formulations . Previous studies have documented that the amount of some drugs in the skin reservoir after a single topical dose demonstrated a strong association with the total permeated drug amount (Kurosaki et al., 1991; Rougier et al., 1983). Therefore, the measurement of the skin reservoir of enoxacin may predict the permeation of enoxacin across skin especially for liposomes.

3.4. Permeation of enoxacin liposomes and niosomes across various types of skin

Two types of interaction between the skin and vesicles may induce the enhancing effect on transdermal drug delivery: (1) adsorption and fusion of drug loaded vesicles onto the surface of the skin leads to a high thermodynamic activity gradient of the drug–SC interface; (2) the effect of vesicles on SC may cause changes in drug permeation kinetics due to an impaired barrier function of the SC for the drug (Schreier and Bouwstra, 1994; Touitou et al., 1994). In order to explore the mechanisms of enoxacin vesicles across the skin, Soybean PC liposomes and Span60 niosomes were selected as model vesicles to investigate the possible reasons for enoxacin permeation enhancement. Pretreatment of skin with phospholipid and non-ionic surfactant was performed to clarify whether phospholipid or surfactant affected the structure of skin. The nude mouse skin was pretreated by Soybean PC or Span60 at the same concentration in vesicles in pH 5 buffer for 12 h, then 0.1% enoxacin free drug (pH 5 buffer) was applied to the skin for 48 h in in vitro permeation experiments. Fig. 3 shows that the enoxacin permeation across Soybean PC-treated and Span60-treated skin was significantly higher (t-test, $P < 0.05$) than that across non-treated skin. The total enoxacin amount permeated across Soybean PC-treated skin is higher (t-test, $P < 0.05$) than that across intact skin (Table 4). A further increase after pretreatment by phospholipid was observed in enoxacin deposition into nude mouse skin (Table 5). Surfactant-treated formulations were superior to phospholipid-treated and non-treated formulations in facilitating the permeation of enoxacin, as well as the drug deposition on the skin. These results indicated that Soybean PC and Span60 can serve as permeation enhancers for enoxacin delivery via the skin.

The permeation of enoxacin across SC-stripped skin was measured using Soybean PC liposomes and Span60 niosomes to clarify the degree of the vesicle contribution to permeation across the SC. The total enoxacin amount permeated across the stripped skin was much higher (t-test, $P < 0.05$) than that across intact skin in the free drug form (Fig. 4 and Table 4), implicating the barrier function of SC for the skin permeation of the drug. Enoxacin in liposomes and niosomes also permeated more rapidly across the stripped skin than across the intact skin. However, the enhancement ratio (ER = total amount permeated $_{\text{stripped skin}}$/total amount permeated $_{\text{intact skin}}$) of liposomes (ER = 5.53) and niosomes (ER = 2.37) were smaller as compared with that of the free drug form (ER = 7.48). The action of liposomes and

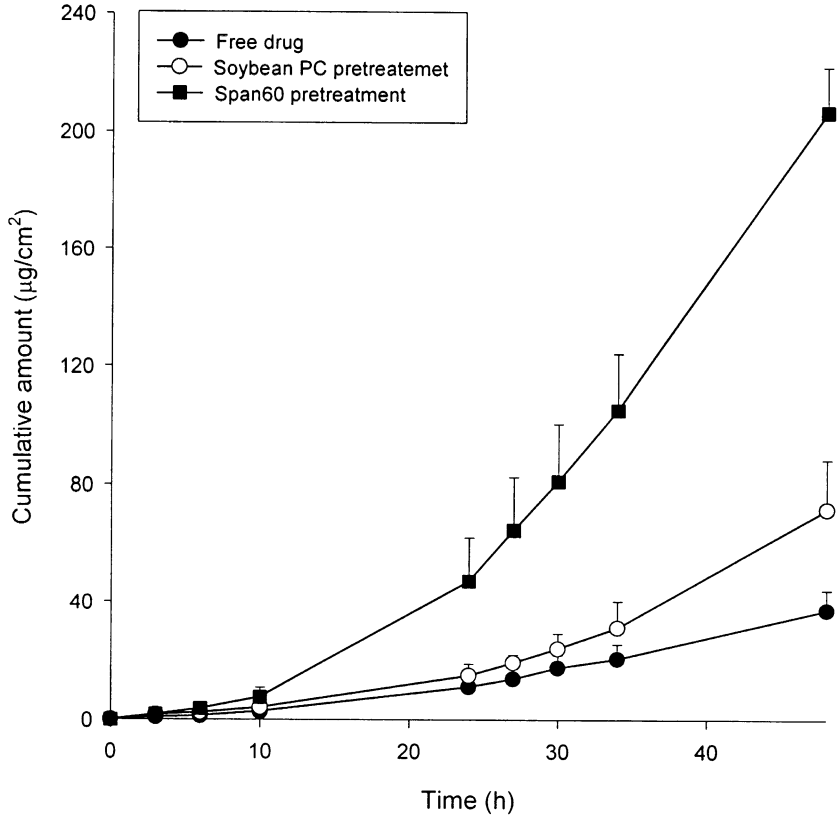

Fig. 3. In vitro cumulative amount–time profiles of enoxacin permeated across soybean PC or Span60 pretreated-nude mouse skin. All data represent four experiments (mean ± SD).

Table 4
Total amount of enoxacin permeated from liposomes and niosomes (μg/cm^2) across various types of skin during 48 h[a]

Formulations	Free drug	Soybean PC	Span60
Across intact skin	31.50 ± 5.88[b]	44.97 ± 8.25	85.79 ± 19.20
Across pretreated skin	–	59.28 ± 9.44	178.40 ± 19.69
Across stripped skin	235.47 ± 14.14	248.86 ± 27.99	203.29 ± 60.53
Direct addition (physical mixture)	–	32.73 ± 9.05	40.34 ± 6.49

[a] The data was calculated by the trapezoidal method from the area under curve (AUC) of flux–time profiles.
[b] Each value represents the mean ± SD ($n = 4$).

niosomes as permeation enhancers might predominantly be on the intercellular lipids of SC, raising the fluidity and weakness of the SC (Valjakka-Koskela et al., 1998; Vora et al., 1998; Yokomizo, 1996). Additionally, the enhancement ratio after strippings was lower for niosomes than for liposomes. This result might suggest a weaker SC barrier effect when niosomes were applied. The direct permeation of the vesicles into the viable epidermis and dermis was largely restricted, probably due to the delayed release of drug from the vesicles or to the decreased diffusion of vesicles in hydrated tissues (Ogiso et al., 1996). Additionally, the result suggests that liposomes and niosomes

largely contribute to the rapid permeation of enoxacin across the SC which may be due to the higher diffusion of vesicles with drug in the SC. As shown in Table 5, no significant difference in drug partitioning (t-test, $P > 0.05$) was observed, when comparing intact skin to stripped skin for all the formulations tested. This finding reflected the fact that deeper layers of skin are important reservoirs for enoxacin permeation via the skin.

Enoxacin was formulated as suspensions containing the same amounts of Soybean liposomes and Span60 niosomes, without any further preparation procedure. This physical mixture, by directly adding all the components in the donor, was used to study the effect of liposome or nio-

Table 5
Skin residual of enoxacin permeated from liposomes and niosomes (ng/mg) in various types of skin during 48 h[a]

Formulations	Free drug	Soybean PC	Span60
Across intact skin	38.84 ± 7.07	74.06 ± 7.35	100.11 ± 11.91
Across pretreated skin	–	135.54 ± 26.33	177.07 ± 35.73
Across stripped skin	51.66 ± 13.94	75.81 ± 4.12	105.00 ± 26.24
Direct addition (physical mixture)	–	87.68 ± 13.62	109.00 ± 20.11

[a] Each value represents the mean ± SD ($n = 4$).

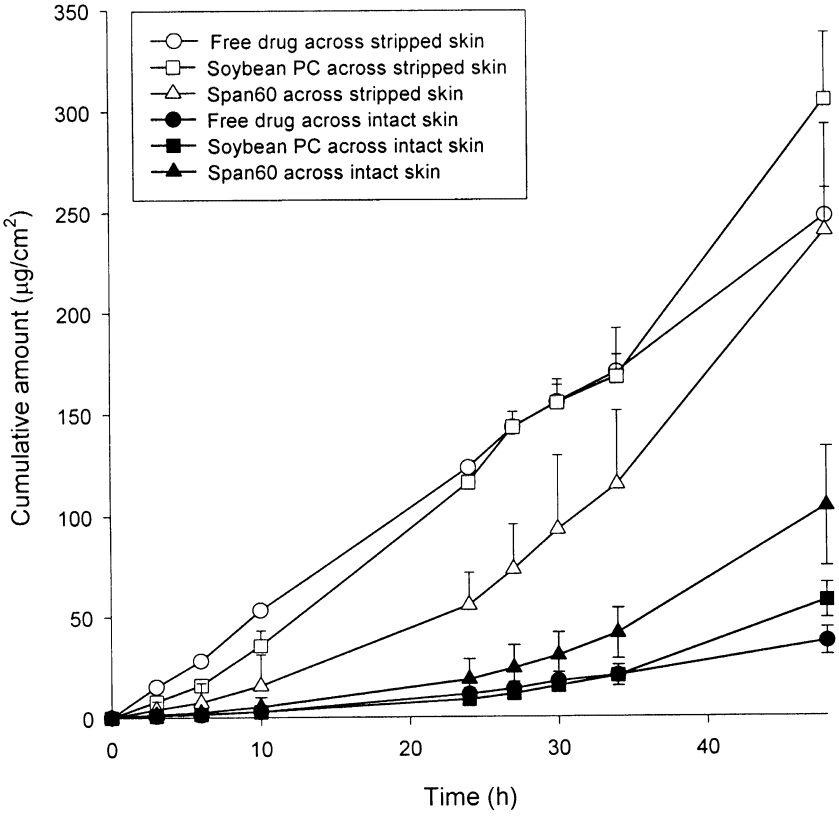

Fig. 4. In vitro cumulative amount-time profiles of enoxacin permeated across intact and stratum corneum-stripped skin from Soybean PC liposomes and Span60 niosomes. All data represent four experiments (mean ± SD).

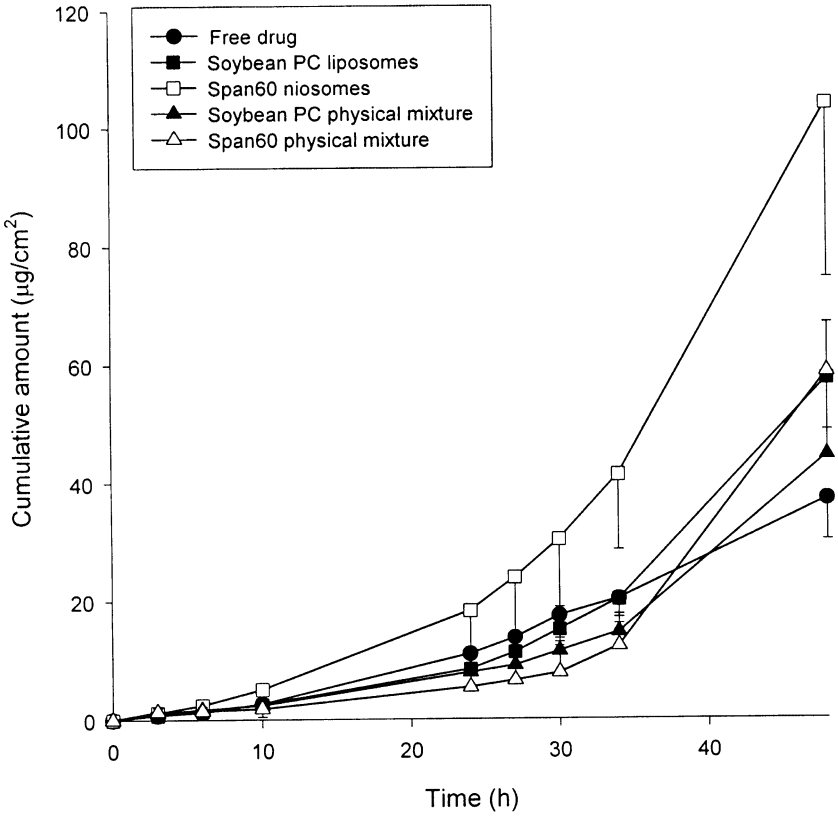

Fig. 5. In vitro cumulative amount-time profiles of enoxacin permeated across nude mouse skin from vesicles or physical mixtures. All data represent four experiments (mean ± SD).

some vesicles on the permeation of enoxacin. Fig. 5 and Table 4 clearly demonstrated that the Span60 physical mixture had a signicantly lower (t-test, $P < 0.05$) permeation than Span60 niosomes. The permeation of enoxacin in the Soybean PC physical mixture was also lower than that in liposomes, but this was insignificant (t-test, $P > 0.05$). Therefore the permeation of enoxacin from the formulations containing the physical mixtures cannot reach to the extent from liposomes and niosomes. It is suggested that factors other than the permeation enhancer effect of phospholipids or surfactants in the vesicles are involved in the enhancement of enoxacin permeation across skin. For Soybean PC liposomes and Span60 niosomes, less than 35% of the drug was released during 48 h (Table 2). Hence a higher amount of total drug may be delivered across the skin, directly via vesicles, relative to simple aqueous solutions. It has been demonstrated recently that liposomally encapsulated enoxacin was intercalated within the bilayer structure of the lipids (Fang et al., 1997). Experimental data and theoretical analysis support the concept that the direct transfer of drug from liposome to skin occurs only when the drug is intercalated within the bilayers (Weiner et al., 1989). Phospholipids are known to have a high affinity for biological membranes. It is shown that mixing of liposomes with the skin lipids in the intercellular layers could be one mechanism contributing to the enhancement of drug permeation of the skin to lipid vesicles (Ogiso et al., 1997; Weiner et al., 1989). The same phenomenon is observed in niosomes (Schreier and Bouwstra, 1994). Accordingly the use of liposomes and niosomes disrupt the mem-

brane properties of SC as well as directly fusing into the upper layer of skin, thereby enhancing the skin permeation of enoxacin.

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