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Oil-in-water emulsion lotion providing controlled release using 2-methacryloyloxyethyl phosphorylcholine n-butyl methacrylate copolymer as emulsifier

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ABSTRACT

Lotion is a useful vehicle for active ingredients used to treat skin disease because it can be applied to the scalp, can cover large areas of skin, and it is easy to spread due to low viscosity. An emulsion lotion (EL) containing 2-methacryloyloxyethyl phosphorylcholine n-butyl methacrylate copolymer (PMB) as an emulsifier that provides controlled-release was developed. Diphenhydramine (DPH) was used as a model drug. Formulation with 5% DPH, 5% soybean oil, and 4% PMB in water was emulsified using a high-pressure homogenizer. Polysorbate 80 (TO) was used instead of PMB for comparison. They were applied *in vitro* to Yucatan micropig intact or stripped skin at a practical dose (2 µL/cm^2). For stripped skin, penetration of DPH from 4% PMB EL was slower than that from 1% TO EL; results for intact skin were similar. The same phenomenon was observed with application to rabbit skin *in vivo*. When 4% PMB EL dried on the skin, it made a thin film matrix incorporating the oil phase, which controlled the release of DPH. The release rate could be controlled by the ratio of oil phase to PMB. The EL with PMB shows promise as a vehicle for long-acting treatment of skin diseases.

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1. Introduction

Skin is an attractive site for systemic drug delivery, and many new vehicles have been developed that promote good skin permeation [1]. In addition, topical delivery of drugs for skin diseases is effective with few systemic side effects. The choice of vehicle is made based on the type of skin condition. Ointments, creams, and lotions are common dosage forms. Lotion is especially convenient for use on the scalp (or other site with hair) or to cover large areas because it has low viscosity and is easy to spread. However, lotion does possess some disadvantages: drugs with low water solubility require solubilizing agents and procedures; the formulation of lotion is affected by the vaporization of some ingredients after application to skin that leaves drug and additives on the skin surface, which can cause irritation; and the amount of drug per unit area is relatively small and the duration of effectiveness is short when applied on damaged skin because lotion does not provide controlled release as an ointment does [10]. Thus, a new vehicle consisting of an oil-in-water (o/w) emulsion lotion (EL),

which can accommodate poorly water-soluble drugs in the oil phase and provides controlled release, was developed.

Polymers are often employed to control drug release, with carboxyvinyl polymer and hydroxypropylmethyl cellulose commonly used for this purpose. However, these polymers do not have solubilizing or emulsifying properties. Therefore, a polymer is needed with solubilizing or emulsifying properties that can provide controlled release. The PMB, 2-methacryloyloxyethyl phosphorylcholine (MPC) n-butyl methacrylate (BMA) copolymer, possesses both hydrophilic and hydrophobic characteristics. The MPC also has excellent biocompatibility [12] and is used for contact lens [3]. Since the MPC unit is extremely hydrophilic, the copolymer with the MPC unit can be dissolved in water. Some drugs can be solubilized by PMB [4,8,5]. The PMB also is used in cosmetics to moisturize skin [6]. Since the molecular weight of PMB is as high as 600,000, it may remain on the skin surface and so is likely to be safer than conventional surfactant which sometimes irritates skin. We previously reported that skin penetration of 2-ethylhexyl methoxycinnnamate, which is a UV absorber, was inhibited when PMB was used as an emulsifier [2]. Thus, PMB was tested as an emulsifier for the EL that provides sustained drug release. Diphenhydramine (DPH), which is a widely used antihistamine for allergy relief, is a liquid insoluble in water, and capable of rapidly penetrating skin [9], was used as the model

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drug in this study. EL containing DPH and PMB was prepared, and penetration of DPH into skin was determined through in vitro and in vivo experiments. In addition, the mechanism of sustained release of DPH from EL was studied.

2. Materials and methods

2.1. Materials

DPH (JP grade) was obtained from Nippon Bulk Yakuhin (Osaka). PMB (Lipidure-PMB®; MPC: BMA=8:2) was supplied by NOF Co., Ltd (Tokyo) as a 5% solution. Polyoxyethylene (20) sorbitan mono-oleate (TO) was a gift from Nikko Chemicals Co., Ltd (Tokyo). Soybean oil (SO, reagent grade) was purchased from Wako Pure Chemical Industries (Osaka). Other reagents were of analytical grade.

2.2. Preparation of lotion

DPH itself or DPH mixed with SO was used as oil phase, and a PMB solution of the appropriate concentration was added to the oil phase. Pre-emulsification was performed using a mixer (Quick Homomixer LR-1 Mizuho, Osaka) at 3000 rpm for 2 min. The mixture was then introduced into a high-pressure homogenizer (Microfluidizer®, Mizuho) and passed through 10 times at a pressure of 10,000 psi. The standard formulation consisted of 5% DPH, 5% SO, 4% PMB, and water (PMB4% EL). For preparation of PMB8% EL, a commercial PMB solution was lyophilized and the PMB powder was dissolved in water at an appropriate concentration. TO was used as emulsifier instead of PMB for comparison.

An EL consisting of 10% DPH, 10% SO, and 2% TO was prepared using the procedure described above, followed by mixing at the same volume of 8% PMB solution (TO1%+PMB4% EL). The standard formulation prepared pre-emulsification was used as comparison (PMB4%-pre EL).

The mean diameter of droplets in the prepared EL was measured by dynamic light scattering (DLS, ELS-800, Otsuka Electric, Osaka) at a dilution of 200. The mean diameter was calculated using cumulant method. Each sample was measured doublicated and at least 3 samples were used.

Particle shape was observed with transmission electron microscopy (TEM) (JEM1200EX, Jeol, Tokyo) at 80 kV with negative staining by phosphotungstic acid. It was done in Hanaichi Ultra-Structure Research Institute (Okazaki, Japan).

2.3. In vitro skin permeation study

The skin permeation study was performed under two conditions, infinite dose conditions (infinite dose) and the practical small amount application recommended in OECD guideline 428 (practical dose).

Yucatan micropig (YMP) skin sets frozen at $-80\,°C$ were purchased from Charles River Japan, Inc. (Kanagawa, Japan). Skin was thawed at 20–25 °C for approximately 30 min, followed by removal of the adhering fat layer using scissors and a grater, and cut into appropriate sizes (intact skin). YMP intact skin has the stratum corneum (SC) consists of about 20-layer, a part of SC was removed from intact skin with adhesive tape (Scotch®313, 3 M, Tokyo) 15 times (stripped skin) to make a model of damaged skin. Skin penetration was measured in a modified Franz diffusion cell apparatus [effective area, 1.1 cm^2; receptor, 16 mL isotonic phosphate buffered solution (pH 7.1) maintained at 37 °C mixed with a star-head magnet at 600 rpm].

For the infinite dose condition, skin was mounted directly on the cell, a 2.0-mL aliquot of EL was poured into the donor phase, and the donor phase was occluded. At predetermined times, 200-μL aliquots were withdrawn from the receptor compartment. The same volume of fresh solution was added to the receptor compartment after withdrawal to maintain constant volume. At 27 h after application, skin was removed from the cell, washed with purified water, gently dried, and used for further testing.

For the practical dose, EL was spread on the skin at 2 μL/cm^2, and the skin was mounted on the cell. The donor phase was not occluded. At 4, 14, and 24 h after application, 200-μL aliquots were withdrawn from the receptor compartment and skin was removed from the cell and used for further tests without washing to determine the mass balance of DPH.

After the skin permeation study, skin was stripped 10 times (intact skin) or 5 times (stripped skin) with adhesive tape (Scotch CC1820-Bx-J, 3 M) to determine the amount of DPH near the surface of skin, followed by soaking in methanol. The skin was then separated into the epidermis and dermis by the heat separation method [7]. Methanol was added to each part, and the epidermis and dermis were homogenized and centrifuged at 3000 rpm for 5 min, and the supernatant filtered with a membrane filter (0.45 μm for epidermis and 0.20 μm for dermis). The DPH concentration in the solutions obtained was determined using HPLC.

2.4. In vivo skin permeation study

Rabbits (Japanese white, males, body weight ca. 3 kg) were used for the in vivo skin permeation study. The hair of the back was removed using an electric hair clipper followed by depilatory cream the day before application. The EL was spread at 2 μL/cm^2. After 4-h application, SC was stripped 5 times with adhesive tape, followed by sacrifice of the rabbit and isolation of the skin. The skin was separated into the epidermis and dermis using the heat separation method. The remaining process followed was the same as that of the in vitro study. This study was approved by the Ethics Committee of Showa Pharmaceutical University.

2.5. In vitro release test

Two types of release tests were arranged for the infinite and practical dose. For the infinite dose study, DPH release was determined by dialysis using a cellulose dialysis tube and JP XV dissolution test apparatus (Toyama Sangyo, Osaka). One mL of EL and 10 mL of water were placed in a rotation basket covered with a dialysis membrane filter (#36, Wako Pure Chemical). The release test was done at a rotation speed of 100 rpm, dissolution medium of 900 mL at pH 7 phosphate buffer solution. At predetermined time intervals, 5 mL of medium were removed and fresh medium was added. DPH concentration was determined by absorbance at 218 nm.

For the practical dose, release from dried EL was determined using a glass plate and oil clear paper. The EL was applied to the glass plate at 20 μL/10 cm^2 followed by drying placed in room at 25 °C for 2 h. A piece of oil clear paper (Gatsby, Mandom, Osaka) was placed on the glass plate for adsorbed oil. The amount of oil released at 0 h was calculated from the weight difference of the paper before and after oil absorption. Then, the glass plate was placed upside down on the oil clear paper for 1 or 2 h, and the test paper was changed. Amounts of DPH released at 0, 1, 2, and 4 h after drying were determined. DPH absorbed to the paper was extracted with methanol and absorbed amount was determined using HPLC.

2.6. Analytical method

DPH concentrations were determined by an HPLC instrument (Shimadzu, Kyoto) equipped with a spectrophotometric detector (SPD-6A). The DPH were eluted from the column

(Wakosil, 150 × 4.8 mm, Wako Pure Chemicals Industry, Osaka) at ambient temperature with a mobile phase of 0.1% phosphoric acid solution-methanol (55:45), at flow rate of 1 mL/min. DPH was detected at 230 nm. The retention time of DPH was about 9 min and no interference peak of skin component was observed.

2.7. Statistical analysis

The amount of DPH on or permeated into the skin was determined for at least 3 experiments and the data subjected to analysis of variance (ANOVA) followed by Dunnett's test using TO1% EL as a control. A value of $P < 0.05$ was considered significant.

3. Results and discussion

3.1. Characterization of emulsions

Various formulations of ELs were prepared and oil droplet size in ELs determined by DLS is shown in Table 1. When only DPH was

Table 1
Oil droplet size in emulsions as measured by DLS.

	Formulation (%)			Droplet size (nm)	
	DPH	SO	Emulsifier	1 Day	1 Month
PMB4% without SO	5	0	4	1473 ± 381	C
PMB1% EL	5	5	1	183 ± 8	191 ± 13
PMB4% EL	5	5	4	250 ± 29	254 ± 9
TO1% EL	5	5	1	124 ± 31	119 ± 14

C; Creaming was observed.

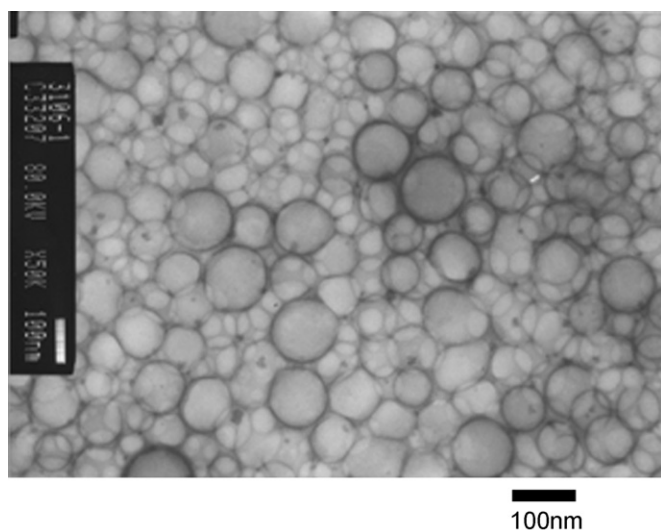**Fig. 1.** TEM photograph of PMB 4% EL with negative staining by phosphotungstic acid. Bar in the photograph shows 100 nm.

used as the oil phase, oil droplet size was greater than 500 nm one day after preparation, and creaming occurred within a month, even if the PMB concentration was 4% and the Microfluidizer was used. Thus, SO (a lipophilic oil) was added to the oil phase. The DPH was mixed with SO (oil phase) then the PMB solution (water phase) was added. Pre-emulsified EL was not stable and phase separation occurred. A stable emulsion was obtained using the Microfluidizer. The size of oil droplet measured by DLS was *ca.* 200 nm for PMB ELs. PMB is a polymer, there was a possibility that PMB trap oil in its polymer chain and so called emulsion was not formed. Thus, TEM images of PMB4% EL was observed (Fig. 1). The image shows relatively uniform spheres, which size were slightly smaller than those obtained by DLS measurement (100–200 nm). It indicates that PMB is not a so called "surfactant," a stable EL was obtained with a high shear rate emulsifying.

The EL using the nonionic surfactant TO also was prepared as a control, which was stable when prepared by the same method as PMB ELs, and the droplet sizes were smaller than those of PMB ELs.

3.2. Skin permeation in vitro

3.2.1. Infinite dose

The cumulative permeation of DPH from 2 mL TO1%, PMB1%, and PMB4% ELs through YMP intact skin was determined. The steady-state flux and lag time, which were calculated from the linear section of time-cumulative amount plots, and skin concentrations are shown in Table 2. No significant difference in flux or lag time was found among the formulations. Amounts of DPH in skin after application of PMB4% EL tended to be less than those of other formulations, and concentration in SC was significantly lower than that of TO1% EL.

The amount of DPH in the EL was 100 mg; the total amount of DPH that penetrated and permeated the skin was *ca.* 1 mg for all formulation. Thus, the amount of DPH was adequate and infinite conditions are maintained to 27 h after application. In contrast, the partition coefficient of DPH between SO and water (P) was high (log $P = 4.6$), so that the amount of DPH in the water phase of the donor EL was only about 50 μg. Thus, DPH in the oil phase should be released into the water phase as the DPH in the water phase decreases due to penetration of DPH into the skin. DPH release from the oil phase appeared to be sustained for PMB4% EL. Release of DPH was determined by dialysis. Release of DPH from PMB4% EL was 25% at 1 h and 77% at 6 h, which was less than that from TO1% EL (71% at 1 h and 90% at 2 h). However, the flux of DPH through skin is not as great as release from the oil phase; thus, the difference in formulation does not affect skin permeation.

3.2.2. Practical dose

In practical use, the amount of emulsion applied onto the skin is small. Thus, the water in the EL evaporates, which changes the condition of the emulsion, disrupts its structure, can result in inversion from o/w to w/o or make a thin film consisting of non-vaporized materials, drug, oil, or surfactant. When EL was applied

Table 2
Skin permeation parameters after application of 2 mL/cm^2 of various formulations to intact skin.

	Flux (μg/cm^2/h)	Lag time (h)	SC (μg/cm^2)	Epidermis (μg/cm^2)	Dermis (μg/cm^2)	Receptor (μg)
TO1%EL	17.8 ± 3.3	5.4 ± 2.1	31.0 ± 5.9	67.7 ± 5.8	556 ± 13	381 ± 42
PMB1%EL	16.8 ± 5.5	6.4 ± 4.1	29.4 ± 10.8	70.2 ± 7.9	605 ± 54	331 ± 58
PMB4%EL	16.5 ± 1.8	7.5 ± 1.1	13.5 ± 4.3[a]	54.3 ± 2.0	489 ± 23	320 ± 18

All formulations contain 5% DPH and 5% SO.
Each value represents the mean ± S.D. of three experiments.

  [a] Significantly different ($p < 0.05$) from TO1%.

on intact skin and stripped skin, the amount of DPH in SC near the surface, in the epidermis, in the dermis, and in the receptor phase was determined at 4, 14, and 24 h after application.

Fig. 2 shows the distribution of DPH in the skin and receptor phase. For intact skin (solid lines), the DPH in SC decreased with time, but about one-half of the DPH applied remained near the skin surface after 24 h application. The DPH levels in the epidermis and dermis were almost constant, *ca.* 10–20% of the dose within 24 h. The DPH in the receptor phase increased with time, but less than 20% of the applied DPH permeated within 24 h. Some points were significantly different for formulations (in SC and dermis at 4 h after application of PMB4% EL and in the receptor phase at 24 h after application), but formulation had little effect on the skin distribution of DPH. This suggests that the rate-limiting step of DPH skin permeation is related to the skin barrier, not the formulation of the EL.

For stripped skin (dashed lines), DPH in SC decreased immediately, with only 20% remaining at 4 h after application and almost none at 14 h. The DPH in the epidermis reached a peak at 4 h and then decreased at 24 h. The amount of DPH in the dermis

and receptor phase tended to be high after application of TO1% and PMB1% ELs. In contrast, after application of PMB4% EL, the DPH in the SC was significantly greater, but in the dermis it was significantly less than after application of TO1% EL. In the epidermis, no significant difference among formulations was found, although the DPH level tended to be low after application of PMB4% EL.

The permeation of DPH through stripped skin was faster than that through intact skin, because the thickness of SC, main barrier of skin permeation was decreased. Ohtani et al. [10] reported that the difference in skin permeation between intact and stripped skin was greater for a lotion than for a cream or ointment. However, after application of PMB4% EL to stripped skin, the distribution of DPH was similar to that of intact skin, which suggests that the release of DPH was controlled by the vehicle for PMB4% EL.

3.3. Skin permeation in vivo

An *in vitro* skin permeation study showed increased skin concentration of the drug due to lack of clearance by blood flow [11].
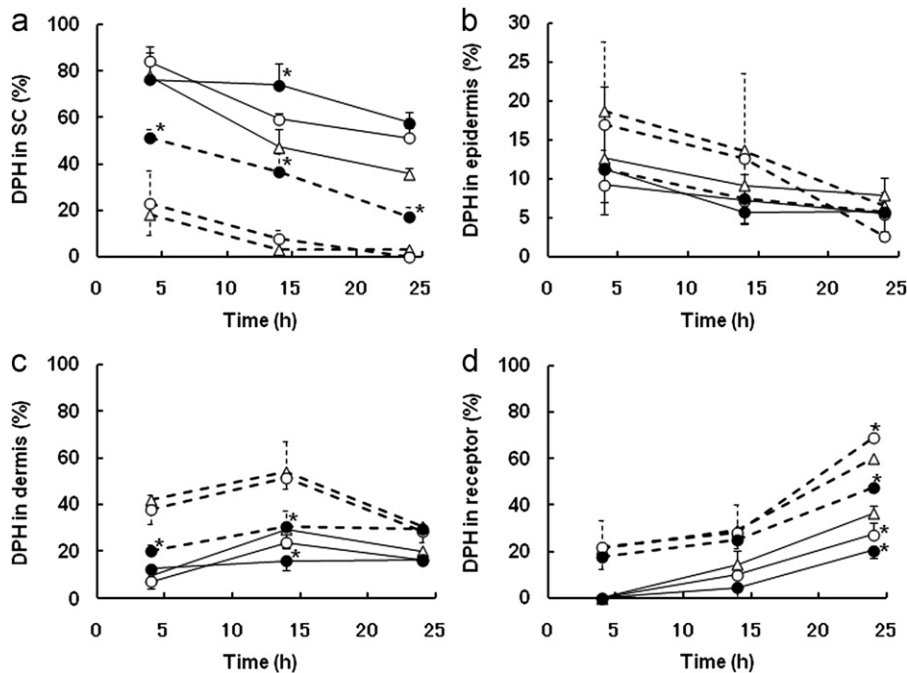

Fig. 2. Skin distribution of DPH after application of 2 μL/cm^2 EL to YMP skin *in vitro*. (a) Stratum corneum near the surface of skin; (b) Epidermis; (c) Dermis; (d) Receptor Solid line, intact skin; dashed line, stripped skin. △, TO1% EL; ○, PMB1% EL; ●, PMB4% EL. Each point represents the mean ± SD of three experiments. *Significantly difference *versus* TO 1% EL applied the skin with the same condition.
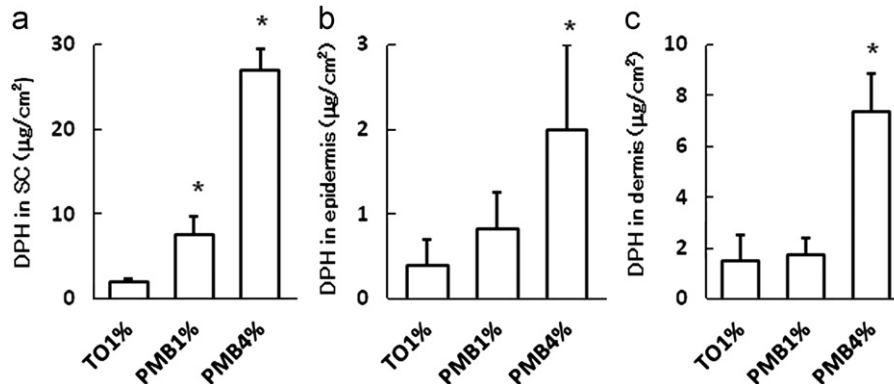

Fig. 3. Skin distribution of DPH at 4 h after application of 2 μL/cm^2 EL to rabbit skin *in vivo*: (a) Stratum corneum; (b) Epidermis; (c) Dermis. Each point represents the mean ± SD of three experiments. *Significantly difference *versus* TO 1% EL.

Thus, EL was applied to rabbit skin *in vivo* with practical dose. Fig. 3 shows the amount of DPH in skin per unit area at 4 h after application of EL. Only 5% of the applied dose remained on or in the skin after application of TO1% EL. Rabbit skin resistance is less than that of human skin [13], DPH permeated the skin rapidly and almost all of the DPH was cleared by the bloodstream. Amounts of DPH in the SC, epidermis, and dermis after application of PMB4% EL were significantly greater than those after application of TO1% EL, which suggests that DPH permeation was controlled by DPH release from the vehicle when PMB4% EL was used.

3.4. Condition of EL after drying

Significant differences among formulations were observed after application of practical usage condition. Under practical usage conditions, only nonvolatile ingredients remained on the skin surface because of evaporation of water from the EL. Usually, an o/w emulsion converts into a w/o emulsion during drying because of water evaporation increasing the relative oil concentration. Thus, the weight of oil absorbed onto the paper was measured after drying EL on a glass plate (Fig. 4). An application of 20 μL EL contained 1 mg of DPH, 1 mg of SO, and 0.2 or 0.8 mg surfactant or polymer. For TO1% EL, the amount of oil absorbed was high as 70%. For PMB1% EL, the amount of absorbed oil was less than that of TO1% EL, and for PMB4% EL, only a very small amount of nonvolatile ingredients was absorbed onto the paper. These results indicate that PMB prevents absorption of the oil phase onto the test paper.

Since PMB is a polymer, it has the ability to form films that can prevent oil absorption onto the paper. Thus, two types of emulsions were prepared for comparison. One used TO as an emulsifier, adding PMB after preparation of the emulsion (TO1%+PMB4% EL). The other was pre-emulsified PMB4% only, without using a high-pressure emulsifying procedure with the Microfluidizer (PMB4%-pre EL). For TO1%+PMB4% EL, the amount of absorbed oil was similar to that of TO1% EL. Oil absorption was prevented for PMB4%-pre EL even though the effect was low, which indicates emulsification with PMB is necessary to prevent oil absorption onto the paper. A stable emulsion also is important. It appears as if PMB is adsorbed on the surface of the oil phase, and this condition is maintained after water evaporation.

3.5. Release of DPH

The features of dried PMB4% EL were different from those of other ELs. DPH release profiles from dried emulsions were compared (Fig. 5). The release of DPH after 2-h drying (time 0 h
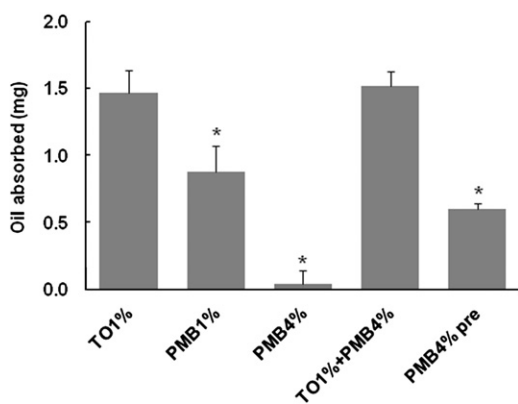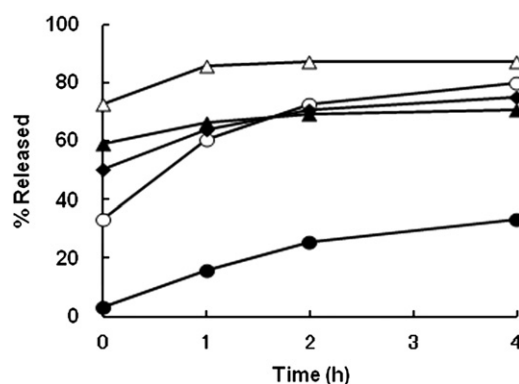

Fig. 5. Release profiles of DPH from various formulations. Twenty μL EL was spread over 10 cm² on the glass plate, followed by drying for 2 h, when the release test was initiated: △, TO1% EL; ○, PMB1% EL; ●, PMB4% EL; ▲, TO1%+ PMB4% EL; ◆, PMB4% -pre EL. Each point represents the mean of at least three experiments.
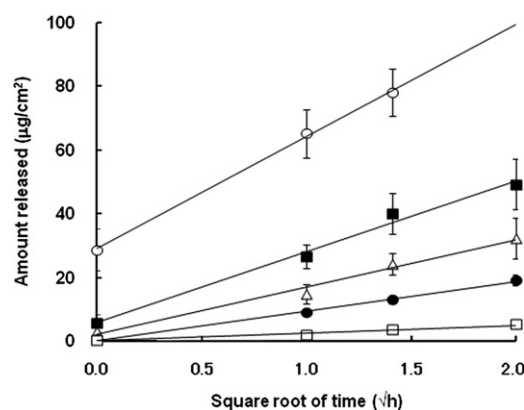
Fig. 6. Higuchi's plots of DPH release from the EL using various concentrations of PMB: ○,1%; ■, 2%; △, 3%; ●, 4%; □, 8%, Each point represents the mean ± SD of at least three experiments.

in the graph) was high for TO1% EL (70%), TO1%+PMB4% EL (60%), and PMB4%-pre EL (50%), and low for PMB4% EL (3%). These percentages were similar to the amount of oil absorbed to the paper, which indicates that DPH is released with SO.

The release profiles of DPH from PMB4% EL seem to obey Higuchi's equation (*i.e.*, a linear plot is obtained from a plot of released amount as a function of the square root of time). Fig. 6 shows the Higuchi plots of DPH release from ELs with various concentrations of PMB. In all cases, the plots show good linearity. For PMB1% EL, a burst of DPH release occurred at time 0. But when the concentration of PMB was greater than 2%, only a small amount of DPH was released at time 0. The slope of the approximation lines decreased with increasing PMB concentration in the EL, therefore, it was defined as the apparent release rate (k). The concentrations of SO and DPH varied from 1% to 15% and 3–8%, respectively. The release profiles were a Higuchi type in all cases, and k increased with increasing SO and DPH concentrations.

Table 3 summarizes the results of release tests. For experiments involving a high oil phase (DPH+SO) to PMB ratio (> 5), a burst was observed at time 0 h. The amount of DPH released (Q) at time t could then be described as:

$$Q = k\sqrt{t} + Q_0 \qquad (1)$$

where Q_0 is released amount at time 0 h. Investigation of the effect of formulation on k revealed that the ratio of the amount of the oil phase (SO+DPH) at time 0 h (M_{oil}) to the amount of PMB

Fig. 4. The amount of oil phase absorbed onto the paper after 2 h drying the ELs. 20 μL EL was spread over 10 cm² on the glass plate. The column and bar show the mean ± SD of at least 3 experiments. *Significantly difference *versus* TO 1% EL.

Table 3
The amount of ingredients after drying and apparent release rate obtained from Higuchi's plots.

	Formulation (%)			Applied amount (μg/cm^2)			Released amount at 0 h (μg/cm^2)		Residual amount at 0 h(μg/cm^2)[a]			M_{oil}/M_{PMB}[b]	k (μg/cm^2/$\sqrt{}$h)[c]	R^2[d]
	PMB	SO	DPH	PMB	SO	DPH	SO[e]	DPH[f]	PMB	SO	DPH			
Standard	4	5	5	80	100	100	3	0.3	80	97	100	2.46	9.2	0.996
PMB														
1%	1	5	5	20	100	100	54	29.0	20	75	71	7.28	35.3	0.999
2%	2	5	5	40	100	100	15	5.8	40	91	94	4.62	22.3	0.989
3%	3	5	5	60	100	100	5	2.3	60	97	98	3.25	14.8	0.984
8%	8	5	5	160	100	100	14	0.0	160	86	100	1.16	2.5	0.974
SO														
1%	4	1	5	80	20	100	11	2.4	80	11	98	1.36	7.7	0.999
3%	4	3	5	80	60	100	0	0.1	80	60	100	2.00	8.1	0.992
10%	4	10	5	80	200	100	5	0.5	80	196	100	3.70	16.2	0.982
15%	4	15	5	80	300	100	27	1.7	80	275	98	4.66	24.9	0.996
DPH														
3%	4	5	3	80	100	60	13	0.9	80	88	59	1.83	8.0	0.999
8%	4	5	8	80	100	160	19	1.6	80	83	158	3.02	17.5	0.999

[a] Calculated from applied amount and released amount.
[b] Calculated from residual amount of each ingredient; (DPH+SO)/PMB.
[c] Apparent release rate calculated from slope of Higuchi's plots of release study.
[d] Square of correlation coefficient of Higuchi's plot regression.
[e] Oil phase weight absorbed to paper.
[f] Y-intercept of Higuchi's plot of DPH release.
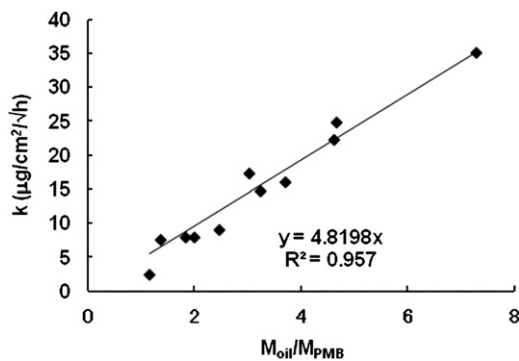
Fig. 7. The relation between the ratio of oil phase/PMB in the formulation and apparent release rate.

Fig. 8. Speculation of EL condition after application of the practical dose to the skin.

(M_{PMB}) showed good correlation (Fig. 7):

$$k = 4.8M_{oil}/M_{PMB} \qquad (2)$$

For a homogeneous matrix, apparent release rate is expressed as

$$k = 2C_0(D/\pi)^{0.5} \qquad (3)$$

where C_0 is DPH concentration in dried ELs and D is the diffusion constant in the matrix. In this case, C_0 is expressed as
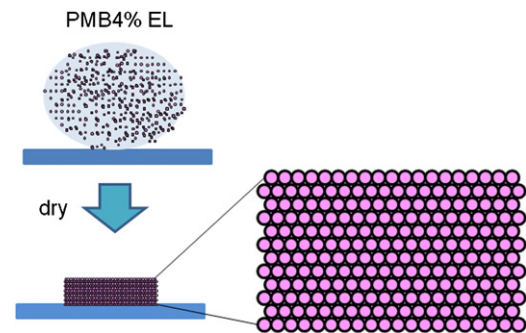
$$C_0 = M_{DPH}/M_{total} \qquad (4)$$

where M_{DPH} and M_{total} is residual amount of DPH and EL (SO+DPH+PMB) at time 0 h, respectively. From Eqs. (2), (3), and (4), D can be described as:

$$4.8M_{oil}/M_{PMB} = 2M_{DPH}/M_{total}(D/\pi)^{0.5}$$
$$(D/\pi)^{0.5} = 2.4(M_{oil}/M_{PMB})(M_{total}/M_{DPH})$$
$$= 2.4(M_{total}/M_{PMB})(M_{oil}/M_{DPH})$$

This shows that $D^{0.5}$ is correlated with the reciprocal of PMB concentration in residual EL and DPH concentrations in the oil phase.

A proposed mechanism is shown in Fig. 8. In the EL, the oil phase is covered with PMB, which acts like a nanocapsule. When the emulsion is applied on skin and dried, the emulsion is not converted into a w/o emulsion, but becomes a thin film of polymer containing the oil phase. The film is homogeneous from a macro view, so the release of DPH occurs in a controlled matrix-type diffusion. The dried EL consisted of two different phases. The DPH existed in the oil phase, and diffusion through the PMB layer was rate limiting; thus, the concentration of PMB in the matrix affected D.

4. Conclusions

An emulsion lotion with controlled release function was prepared. When a PMB EL was applied to skin with practical dose, a thin film formed after evaporation of water without phase conversion of the emulsion. The release pattern of DPH was of a matrix type and could be controlled by the ratio of the oil phase to PMB. The penetration of DPH into skin could be controlled even if the skin barrier function was compromised.

A PMB EL can function as a controlled release formulation for application to the scalp or large areas of skin.

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