Drug Development and Industrial Pharmacy, 2011; 37(8): 917–925

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.550299

informa
healthcare

RESEARCH ARTICLE

Formulation study of topically applied O/W lotion containing vitamin D3 derivative, focusing on skin permeability of the drug

Shin-ichi Harada[1], Eijiro Horisawa[1], Satoshi Kano[1], and Kenji Sugibayashi[2]

[1]*Kyoto R&D Center Drug Development Laboratories, Maruho Co., Ltd., Kyoto, Japan, and* [2]*Faculty of Pharmaceutical Sciences, Josai University, Saitama, Japan*

Abstract

Permeation of 22-oxacalcitriol-1α, 25-dihydroxyvitamin D_3 (OCT) through excited hairless mouse skin was determined after application of OCT as solutions and O/W lotions consisted of different polarities of solvents: medium-chain fatty acid triglyceride (MCT), myristate isopropyl (IPM), 1,3-butylene glycol (1,3-BG), and propylene glycol (PG). OCT concentration in skin was also followed after applying these formulations. A two-layer diffusion model was composed to analyze dermatopharmacokinetic profiles of OCT for each vehicle. In the OCT solutions, skin permeation profile of OCT differed depending on solvent polarity. The O/W lotion with a high MCT content led to a low amount of OCT in skin. On the other hand, the O/W lotion with a high 1,3-BG content led to a high amount of OCT in skin. This dermatopharmacokinetic analysis indicated that addition of MCT to the formulation decreases the skin/vehicle partition coefficient of OCT and increases the diffusion coefficient of OCT in skin. However, the opposite effects on these two parameters were found in the case of 1,3-BG. Thus, skin permeability of OCT differed depending on the solvents used in the formulation. These results indicate that skin permeability of OCT is influenced by the physicochemical properties (i.e. polarity) of OCT, solvent, and skin. Our findings on the solvent effects of the skin permeability of OCT are thus useful for designing topical drug formulation, especially in aiming for bioequivalent dosage formulas.

Keywords: Topical formulation, O/W lotion, skin permeation, partition, diffusion, solvent polarity

Introduction

OCT ointment containing an activated vitamin D_3 derivative (22-oxacalcitriol-1α, 25-dihydroxyvitamin D_3, hereinafter referred to as OCT) is widely used in medical institutions as a therapeutic agent for psoriasis vulgaris, ichthyosis, and palmoplantar keratosis. As it was formulated with white petrolatum as an oily-base component, good protection and coverage of the skin surface were observed with the ointment. However, the adhesive skin sensation related to the oily base makes the ointment difficult to apply to the scalp, a common site of psoriasis, necessitating a change in formulation. We therefore surveyed the required dosage forms and pharmaceutical characteristics of topical formulations suitable for psoriasis on the scalp used at medical institutions. Based on the results of this surveillance, we have planned to develop O/W emulsion-type lotion with easy application on to the scalp and coverage and humectant effects.

Drug delivery and control of absorption have been considered as one of the critical factors in designing of topical skin formulations because topically skin applied drugs (clinical efficacies) are easily affected by dosage formula and vehicles[1,2]. For example, ointment vehicles exhibit strong drug permeation and skin hydration by suppressing water volatilization from the skin surface due to their occlusive properties, whereas creams and lotions exhibit less drug permeation than ointments because of their low skin coverage effects following water volatilization after application[3,4]. Several studies have reported that even formulations containing the same drug at the

Address for Correspondence: Shin-ichi Harada, Kyoto R&D Center Drug Discovery Research Laboratories, Maruho Co., Ltd., 92 Awata-Cho, Chudoji, Shimogyo-ku, Kyoto, 600-8815, Japan. Tel.: +81-(0)75-325-3250; Fax: +81-(0)75-325-3471. E-mail: harada_cdg@mii.maruho.co.jp

(Received 20 July 2010; revised 12 December 2010; accepted 19 December 2010)

same concentration exhibit different drug delivery rates through skin depending on the physicochemical characteristics of the vehicle used[5] and that formulations containing the same ingredients exhibit different drug delivery rates through skin depending on the droplet size of emulsion[6]. Moreover, different pharmaceutical effects were observed between generic and advanced formulations[7,8] containing a variety of drugs such as steroids[9–11], antibiotics[12], and salicylate[13].

On the other hand, several reports concerning pharmaceutical technologies for designing topical formulations have also been published. For example, Ostrenga et al.[14–16] suggest that in designing topical formulations, vehicle composition and drug solubility in vehicle are important and that *in vitro* drug release tests are helpful in estimating the effects of dosage formulas. Hadgraft[17] reported that ingredients in formulations have two effects on skin permeation: one is to change the lamellar structure of intercellular lipids in the stratum corneum, while the other is modification of solubility parameters of the lipids. In addition, Kumar et al.[18] insisted that solubility parameters of drug and vehicle are important in designing topical formulations and that drug retention in skin after administration is more critical than the drug permeability through skin. Moreover, new topical drug delivery carriers and formulations mainly aiming for enhancement of drug skin permeation have been reported[19–22]. These studies provide important suggestions to consider in devising technologies for designing topical formulations. However, few studies have referred to vehicles used in practical formulations and practical methods to obtain equivalence of skin permeability among different dosage formulas.

Accordingly, for designing OCT lotion (O/W-type lotion) bioequivalent to OCT ointment, we focused on the vehicle effects on OCT permeability through skin. We hypothesized that OCT permeability through skin is strongly affected by vehicle (solvent) polarity, which alters the polarity of the stratum corneum and/or characteristics of the route of permeation. In order to investigate the hypothesis, we selected solvents having different polarities and evaluated their effect on skin permeability of OCT. In this process, there are two parameters to evaluate: thermodynamic activity coefficient and partition coefficient. The former parameter is suitable for solvent effect in vehicle. However, when solvents affect on skin, the change of thermodynamic activity coefficient in skin is also necessary to estimate. On the other hand, the latter parameter (partition coefficient) makes it possible to evaluate solvent effects in vehicle and skin concomitantly because it is indicated as [thermodynamic activity coefficients in vehicle/thermodynamic activity coefficients in skin]. Therefore, in this study, we analyzed partition coefficient to evaluate the solvent effect on skin permeability of OCT.

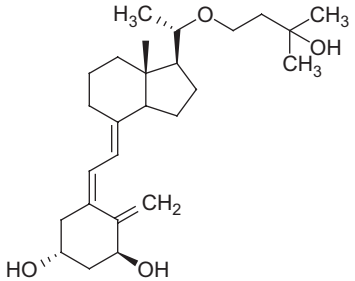
Methods

Materials

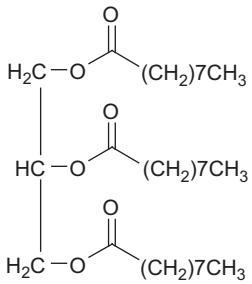
OCT and the ointment containing 0.0025% OCT (hereinafter referred to as OCT ointment) were obtained from Chugai Pharmaceutical Co. (Tokyo, Japan). Other ingredients used as solvents or vehicles were purchased from each manufacturer as official specification products (JP14, JPE2003, JSFAvol.7). All other regents were of analytical grade and used without further purifications.

Solubility parameters of drug, solvents, and skin

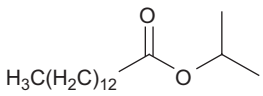
Chemical structure of OCT and solvents are shown in Figure 1. Based on these structures, solubility parameters



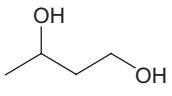
OCT (M.W.418.62)



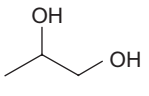
MCT (M.W.560.51)



IPM (M.W. 270.46)



1, 3-BG (M.W. 90.12)



PG (M.W. 76.09)

Figure 1. Chemical structures and molecular weight (MW) of 22-oxacalcitriol-1α, 25-dihydroxyvitamin D_3 (OCT) and solvents. Medium-chain fatty acid triglyceride (MCT) is the triglyceride of straight-chain fatty acid; $CH_3(CH_2)_nCOOH$ (n = 4–10). In this study, we assumed that the repeat number of polyethylene (n) is 7 for calculating the MW.

of OCT and solvents were calculated by Fedors method[23]. Solubility parameter of skin (animal stratum corneum) was quoted from the literature[24].

Experimental methods of evaluated samples

Manufacture of OCT solutions

The OCT solutions containing 0.0025% OCT (hereinafter referred to as OCT solutions) were prepared using the following procedure. To 50 g of each solvent (medium-chain fatty acid triglyceride [MCT], myristate isopropyl [IPM], 1,3-butylen glycol [1,3-BG], or propylene glycol [PG]) in a glass beaker, 2.5 mg of OCT was added as a 100 μL ethanol solution. To these solutions, each solvent was added to adjust the total weight to 100 g.

Manufacture of OCT (O/W) lotions

According to the formulations indicated in Tables 1 and 2, the lotion containing 0.0025% OCT (hereinafter referred to as OCT lotions or O/W lotions) were prepared using the following procedure. Oil phase (MCT and emulsifier) and water phase (all other ingredients without OCT) were dissolved at 85°C. OCT as an ethanol solution and the water phase were added to the oil phase, agitated at 6000 rpm about 2 min, and then cooled to room temperature.

In vivo hairless mouse skin permeation test

Animal experiments and their protocols are obeyed to the "General Considerations for Animal Experiments" and were approved by the Ethics Committee for Treatment of Laboratory Animals at Maruho Co., Ltd. Hairless mice (Hos: HR-1, 7 weeks old, weighing 25–35 g) were supplied by Japan SLC (Tokyo, Japan). After sweeping the dorsal region in mice with warm water, 20 mg of sample for evaluation was applied on the skin surface within a plastic framework (1.6 × 2.5 cm:4 cm^2). At settled time (during 1 to 24 h) after application, residual samples on the skin surface were wiped off four times with cotton dipped in

Table 1. Formulations and amounts of OCT in skin after application of OCT ointment and OCT lotions containing MCT.

Ingredients	OCT ointment	Rp.1[b]	Rp.2[b]	Rp.3[b]
Drug (OCT)	0.0025	0.0025	0.0025	0.0025
Dehydrated ethanol	q.s.	q.s.	q.s.	q.s.
White petrolatum	q.s.	—	—	—
MCT	q.s.	1	5	20
Emulsifier	—	1	1	1
Diisopropanolamine	—	1.16	1.16	1.16
1,3-BG	—	10	10	10
Carboxyvinyl polymer	—	0.2	0.2	0.2
Stabilizer etc.	—	q.s.	q.s.	q.s.
Total	100	100	100	100
OCT amount in skin[a] (% of dose)				
1 h	13.7 ± 3.3	7.4 ± 1.4	6.6 ± 2.0	2.8 ± 0.5
4 h	10.2 ± 2.2	6.6 ± 0.6	3.6 ± 0.2	1.2 ± 0.5

OCT, 22-oxacalcitriol-1α, 25-dihydroxyvitamin D_3; MCT, medium-chain fatty acid triglyceride; 1,3-BG, 1,3-butylene glycol.
[a]OCT amount in skin represents the mean ± S.D (n = 3).
[b]Rp means formulation recipe of OCT lotion.

Table 2. Formulations and amounts of OCT in skin after application of OCT ointment and OCT lotions containing 1,3-BG.

Ingredients	OCT ointment	Rp.4[b, c]	Rp.5[b]	Rp.6[b]	Rp.7[b]
Drug (OCT)	0.0025	0.0025	0.0025	0.0025	0.0025
Dehydrated ethanol	q.s.	q.s.	q.s.	q.s.	q.s.
White petrolatum	q.s.	—	—	—	—
MCT	q.s.	1	1	5	5
Emulsifier	—	1	1	0.2	0.2
Diisopropanolamine	—	1.16	1.16	1.16	1.16
1,3-BG	—	10	45	10	20
Carboxyvinyl polymer	—	0.2	0.2	0.2	0.2
Stabilizer etc.	—	q.s.	q.s.	q.s.	q.s.
Total	100	100	100	100	100
OCT amount in skin[a] (% of dose)					
1 h	13.7 ± 3.3	7.4 ± 1.4	2.6 ± 0.6	8.6 ± 2.3	5.4 ± 1.2
4 h	10.2 ± 2.2	6.6 ± 0.6	10.3 ± 1.8	7.4 ± 1.4	10.4 ± 2.9

OCT, 22-oxacalcitriol-1α, 25-dihydroxyvitamin D_3; MCT, medium-chain fatty acid triglyceride; 1,3-BG, 1,3-butylene glycol.
[a]OCT amount in skin represents the mean ± SD (n = 3).
[b]Rp means formulation recipe of OCT lotion.
[c]Rp.4 is the same formulation as Rp.1 in Table 1.

70% ethanol solution. The skin with sample applied was then excised under ether anesthesia.

To the excised skin, 3 mL of methanol and 100 µL of internal standard (*p*-hydroxyl butyl benzoate ethanol solution; 3 µg/mL) were added, and the mixture was then immediately homogenized and centrifuged (3000 *g* for 5 min at room temperature) to recover the supernatant. The extraction procedure was performed twice with 3 mL of methanol. Total supernatant was evaporated under a nitrogen steam at 40°C. To the residue, 4 mL of diethyl ether and 1 mL of distilled water were added, and the sample was mixed and centrifuged (under the same conditions as above) to recover the organic phase. The extraction procedure was performed twice with 4 mL of diethyl ether. The total organic phase was evaporated under a nitrogen steam at 40°C. The extract was dissolved with 0.2 mL of ethanol and analyzed by reverse-phase high-performance liquid chromatography (HPLC) (Waters alliance 2695/2487; UV 265 nm with C18 analytical column; InertsilODS-3V) to measure the amount of OCT in skin. A mixed solution of 50 mM ammonium acetate: acetonitrile (60:40) was used as a mobile phase, with a flow rate of 1 mL/min (25°C).

To the cotton used for wiping, 10 mL of ethanol and 100 µL of internal standard (*p*-hydroxyl butyl benzoate ethanol solution; 10 µg/mL) were added, then heated in an 80°C water bath for 5 min, and centrifuged (3000 *g* for 5 min at room temperature) to recover the liquid phase. The extraction procedure was performed twice with 10 mL of ethanol. Total liquid phase was evaporated under a nitrogen steam at 40°C. The extract was dissolved with 0.2 mL of ethanol and analyzed by reverse-phase HPLC (under the same conditions as described above) to measure the residual amount of OCT (residual amount of OCT on the skin surface).

The apparent amount of OCT absorbed was calculated as: administered amount of OCT – residual OCT amount. The amount of OCT in skin (%), residual amount of OCT (%), and apparent amount of OCT absorbed (%) are represented as percentages of OCT dose.

Dermatopharmacokinetic parameters using a two-layered diffusion model

A two-layered (vehicle-skin) diffusion model was designed to analyze permeation profiles of OCT through hairless mouse skin for each vehicle[25]. Figure 2 illustrates the typical concentration-distance profiles in vehicle and skin. Drug concentration in the vehicle ($C_{vehicle}$) at position (x) and time (t) can be expressed by Fick's second law as follows:

$$\frac{\partial C_{vehicle}}{\partial t} = D_{vehicle}\frac{\partial^2 C_{vehicle}}{\partial x^2} \quad (1)$$

where $D_{vehicle}$ is the effective diffusion coefficient of OCT in the vehicle.

In the same fashion, drug concentration in the skin (C_{skin}) at position (x) and time (t) can be expressed as follows:

$$\frac{\partial C_{skin}}{\partial t} = D_{skin}\frac{\partial^2 C_{skin}}{\partial x^2} \quad (2)$$

where D_{skin} is the effective diffusion coefficient of OCT in the skin.

Initial and boundary conditions are as follows:

Initial conditions:

$$t=0 \quad -L_{vehicle} < x < 0 \quad C_{vehicle} = C_0$$

$$0 < x < L_{skin}\ C_{skin} = 0 \quad (3)$$

Boundary conditions:

$$t>0 \quad x=-L_{vehicle} \quad C_{vehicle} = C_{vehicle,i+1}$$

$$x=0 \quad C_{skin} = K_{skin/vehicle}\cdot C_{vehicle}$$

$$D_{vehicle}\frac{dC_{vehicle}}{dx} = D_{skin}\frac{dC_{skin}}{dx}$$

$$x = L_{skin}\ \ C_{skin} = 0 \quad (4)$$

where $L_{vehicle}$ and L_{skin} are the thicknesses of vehicle and skin, respectively. $K_{skin/vehicle}$ is the partition coefficient of drug from donor vehicle to skin. $C_{vehicle}$ and C_{skin} at position (x) and time (t) are calculated using Eq. 1 and Eq. 2, the initial conditions (Eq. 3), and the boundary conditions (Eq. 4).

Eqs. 1 or 2 can be changed to the following Eqs. 5 or 6 by means of differential methods:

$$\frac{dC_{i,j}}{dt} = \frac{1}{\Delta t}\left(C_{i,j+1} - C_{i,j}\right) \quad (5)$$

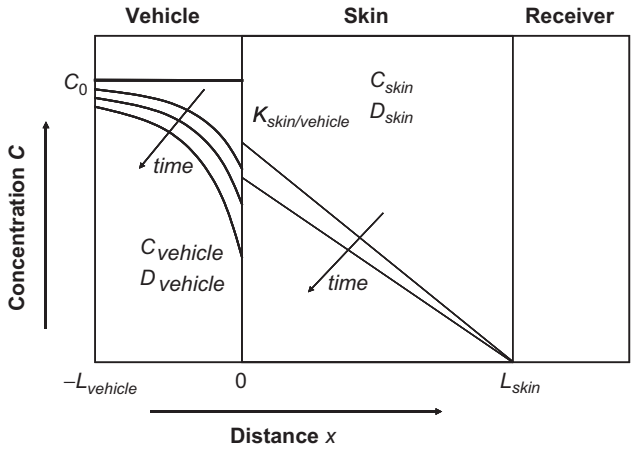


Figure 2. A two-layered diffusion model; Diffusion and partition profile in vehicle/skin. C_0 is the initial drug concentration in vehicle. $C_{vehicle}$ and C_{skin} are the drug concentrations in vehicle and skin, respectively. $D_{vehicle}$ and D_{skin} are the effective diffusion coefficients of the drug in vehicle and skin, respectively. $L_{vehicle}$ and L_{skin} are the thicknesses of vehicle and skin, respectively. $K_{skin/vehicle}$ is the partition coefficient from vehicle to skin.

$$\frac{d^2C_{i,j}}{dx^2} = \frac{1}{\Delta x^2}\left(C_{i-1,j} - 2C_{i,j} + C_{i+1,j}\right) \quad (6)$$

where $C_{i,j}$ is the drug concentration at the i-th position and j-th time in vehicle or skin. Δx is $x_{i+1} - x_i$ and Δt is $t_{j+1} - t_j$. By substitution of Eqs. 5 and 6 into Eqs. 1 or 2, the following equations are obtained.

$$C_{\text{vehicle},i,j+1} = rD_{\text{vehicle}}C_{\text{vehicle},i-1,j} + \left(1-2rD_{\text{vehicle}}\right)C_{\text{vehicle},i,j} + rD_{\text{vehicle}}C_{\text{vehicle},i+1,j} \quad (7)$$

$$C_{\text{skin},i,j+1} = rD_{\text{skin}}C_{\text{skin},i-1,j} + \left(1-2rD_{\text{skin}}\right)C_{\text{skin},i,j} + rD_{\text{skin}}C_{\text{skin},i+1,j} \quad (8)$$

where r is $\Delta t/\Delta x^2$.

Calculations were performed using Microsoft® Excel. In the calculations, the number of divisions of vehicle and skin was set at 10. The mean drug concentrations in vehicle and skin were calculated by averaging drug concentration at each position (x) and time (t). Δt was set to be less than 0.5 for $D_{\text{skin}}\cdot\Delta t/\Delta x^2$. The effective diffusion coefficients (D_{vehicle} and D_{skin}) and partition coefficient ($K_{\text{skin/vehicle}}$) were obtained by fitting the observed data using the nonlinear least-squares method.

Results

OCT skin permeation profile with ointment

Figure 3A and 3B show the OCT skin permeation profile after application of OCT ointment to hairless mouse calculated by a two-layered diffusion model. Figure 3A indicates the profile analyzed from five sampling points (1, 2, 4, 8, 24 h) and Figure 3B from two sampling points (1, 4 h). These data indicate that two simulation curves well fitted and the calculated parameters (D_{skin} and $K_{\text{skin/vehicle}}$) were almost coincident in both sampling methods. Therefore, we assumed that the method by two sampling points (1, 4 h) is sufficient to evaluate the effect on skin permeation profile of OCT instead of using five sampling points (1, 2, 4, 8, 24 h).

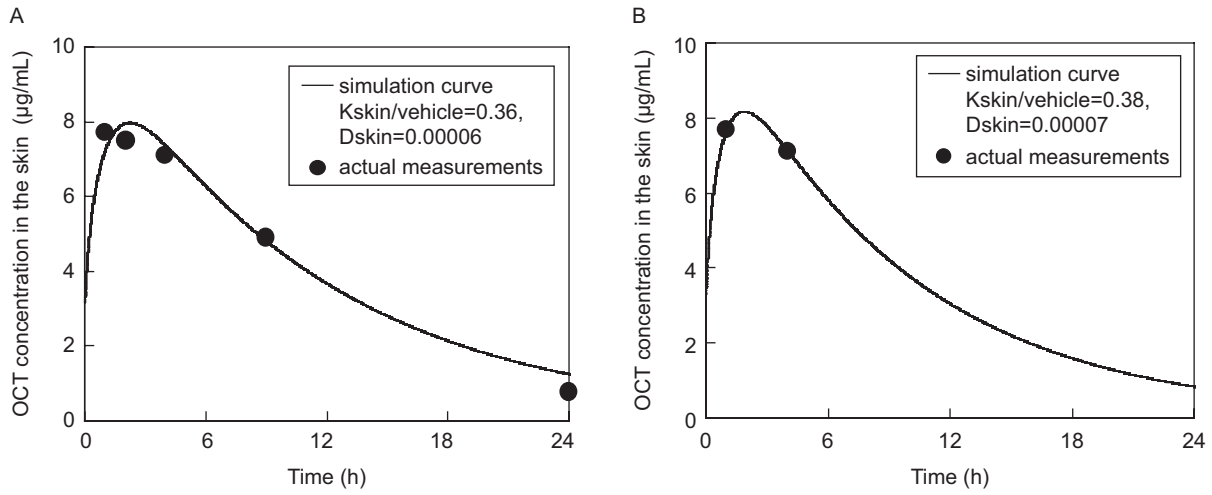


Figure 3. *In vivo* hairless mouse skin permeation profile of OCT (simulation curves) after application of OCT ointment. (A) Permeation profile analyzed by five sampling points. (B) Permeation profile analyzed by two sampling points. Lines show the theoretical curves evaluated by a two-layered diffusion model. Each value represents the mean (n=3).

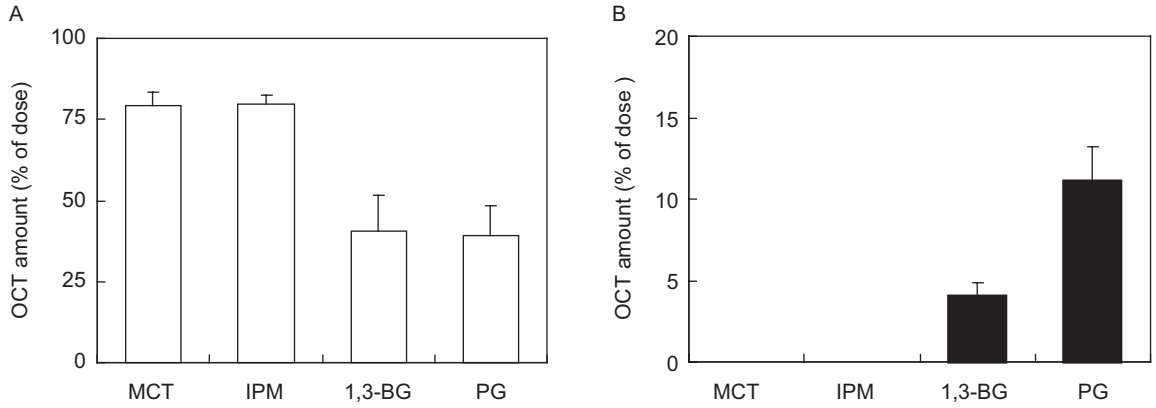


Figure 4. *In vivo* hairless mouse skin permeation profile of OCT after application of various OCT solutions. (A) Apparent amount of OCT absorption at 4 h after application. (B) Amount of OCT in skin at 4 h after application. Each value represents the mean ± SD (n=3).

OCT skin permeation with solutions

Figure 4 shows the permeation characteristics of OCT through excised hairless mouse skin after application of various OCT solutions. In OCT solutions prepared with MCT and IPM as solvents for OCT, the apparent amounts of OCT absorbed were relatively high (about 80% of dose 4 h after application) compared to ones with 1,3-BG and PG, although OCT was not detected in the skin. As the maximum amount of OCT in skin, about 3–6% of dose, was found at 30 min after application (data not shown). These findings suggest that most OCT is immediately absorbed into skin and rapidly eliminated from skin with application of the lipophilic OCT solvents (MCT, IPM) to skin.

In OCT solutions prepared with 1,3-BG and PG as solvents for OCT, on the other hand, the apparent amounts of OCT absorbed were relatively low (about 40–50% of dose 4 h after application) compared to ones with MCT and IPM, although about 5–12% for the amount of OCT was detected in skin. These findings suggest that the apparent amounts of OCT absorbed are lower than those with MCT and IPM because OCT tends to remain in skin when hydrophilic OCT solvents (1,3-BG, PG) are applied to skin.

OCT skin permeation with O/W lotions containing MCT

Table 1 shows the amounts of OCT in skin 1 and 4 h after application of similar O/W lotions containing 1%, 5%, or 20% MCT. The results with OCT ointment are also shown for comparison. As shown in Table 1, the rank order of OCT amount in skin was Rp.1 > Rp.2 > Rp.3 (Rp means formulation recipe). Thus, with increase in the MCT amount in the formulation, OCT amount in skin decreased. The simulation curves and dermatopharmacokinetic parameters obtained with a two-layered diffusion model are represented in Figure 5. As shown in this figure, with increase in the MCT amount in the formulation (from 1% to 20%), $K_{skin/vehicle}$ decreased, D_{skin} increased, and AUC decreased.

OCT skin permeation with O/W lotions containing 1,3-BG

Table 2 shows the amounts of OCT in skin 1 and 4 h after application of similar O/W lotions containing 10% or 45% of 1,3-BG and 10% or 20% of 1,3-BG. The results with OCT ointment are shown for comparison. As shown in the table, the rank order of the OCT amount in skin was Rp.4 > Rp.5 and Rp.6 > Rp.7 at 1 h and Rp.4 < Rp.5 and Rp.6 < Rp.7 at 4 h after application. Thus, with increase in the

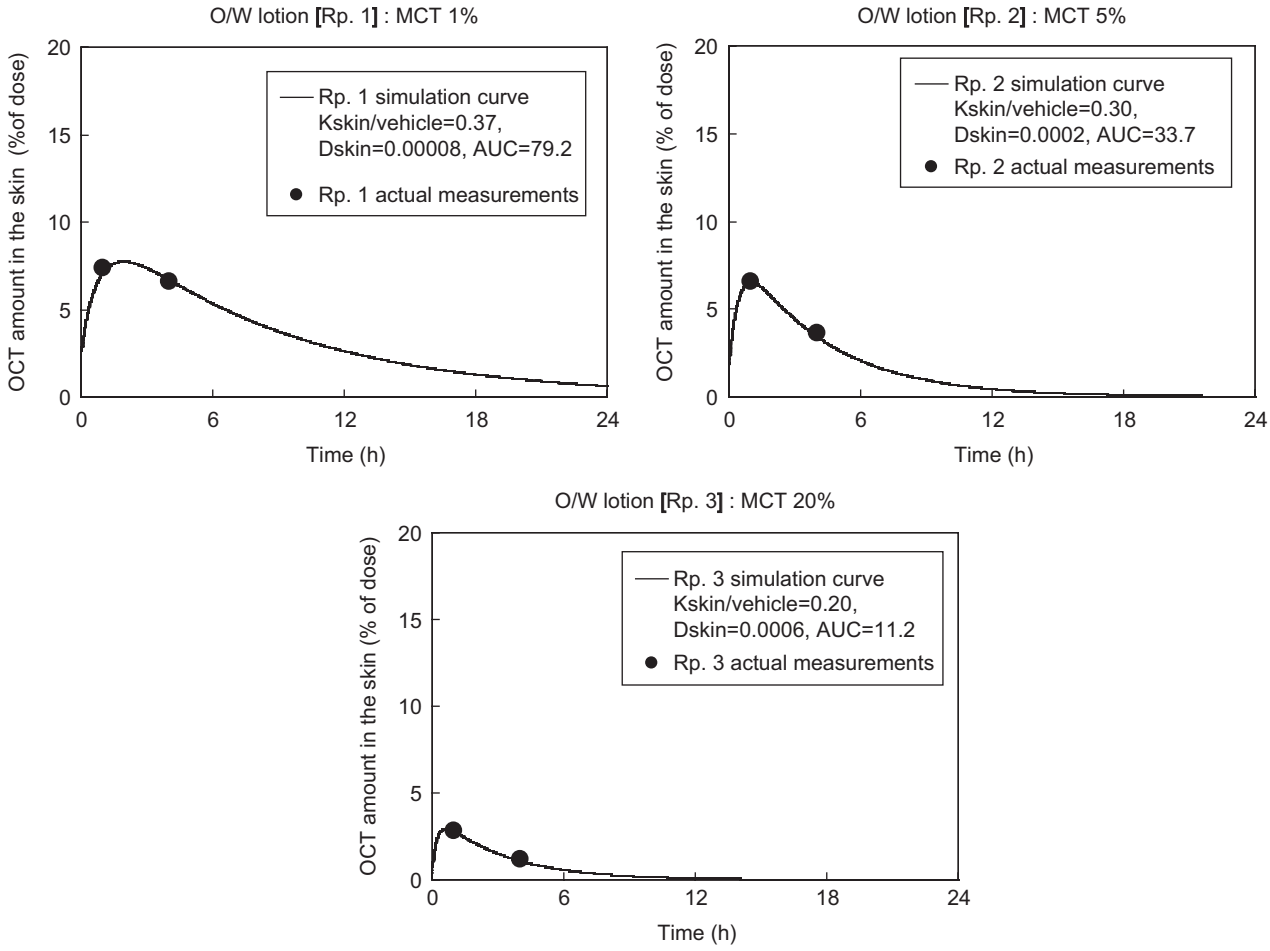


Figure 5. Simulation curves and dermatopharmacokinetic parameters of O/W lotions [Rp.1–Rp.3]. Lines show the theoretical curves evaluated by a two-layered diffusion model. Each value represents the mean ($n = 3$).

amount of 1,3-BG in the formulation, the OCT amount in skin decreased 1 h and increased 4 h after application. The simulation curves and dermatopharmacokinetic parameters obtained with a two-layered diffusion model are represented in Figure 6, suggesting that $K_{skin/vehicle}$ increased, D_{skin} decreased, and AUC increased with increase in amount of 1,3-BG in the formulation.

Discussion

Drug-metabolic effects must be considered for accurate evaluation of skin permeation of OCT, as OCT is converted to several metabolites in the epidermis and dermis[26]. However, the main barrier to skin permeation of OCT is the most outer layer of skin, stratum corneum[26], which has less drug metabolic functions. Therefore, to clarify the effect of vehicle (solvent), it is sufficient to evaluate the OCT permeability in the stratum corneum that the applied vehicles come into contact directly. Based on these assumptions, we focused on the OCT skin permeation without measuring metabolic effects of OCT in this study.

Effects of solvent on OCT skin permeation

It is known that increase in the solvent amount in the formulation (vehicle) leads to decrease in the tendency for drug to escape from vehicle[27]. If this escape-tendency is applicable in all cases, the amount of OCT in skin should always decrease when the amounts of solvents (MCT and 1,3-BG) increase in vehicle. However, as shown in Tables 1 and 2, the results were inconsistent with this theory. Namely, the relationship between the amount of solvent in the formulation and amount of OCT in skin differs depending on kinds of OCT solvents used. In addition, as all ingredients contained in the formulations can be distributed within the stratum corneum[28], design of topical formulation of OCT should be performed based on the idea that solvents can penetrate to stratum corneum.

On the basis of the results in Figure 5, increase in $K_{skin/vehicle}$ and decrease in D_{skin} were observed with a low content of MCT in vehicle, which lead to increase in the OCT amount in skin. On the other hand, decrease in $K_{skin/vehicle}$ and increase in D_{skin} were observed with a high content of MCT in vehicle, which lead to decrease in the OCT amount in skin. In the same way, on the basis of the results in Figure 6, the opposite effects on these two parameters ($K_{skin/vehicle}$ and D_{skin}) were noted with 1,3-BG in vehicle: a low content of 1,3-BG lead to decrease in the OCT amount in skin, while a high content of 1,3-BG lead to increase in the OCT amount in skin. Based on these considerations, it is speculated that the differences in OCT skin permeation with MCT and 1,3-BG are attributable to the opposite effects of these solvents on the OCT partition ($K_{skin/vehicle}$) and OCT diffusion (D_{skin}).

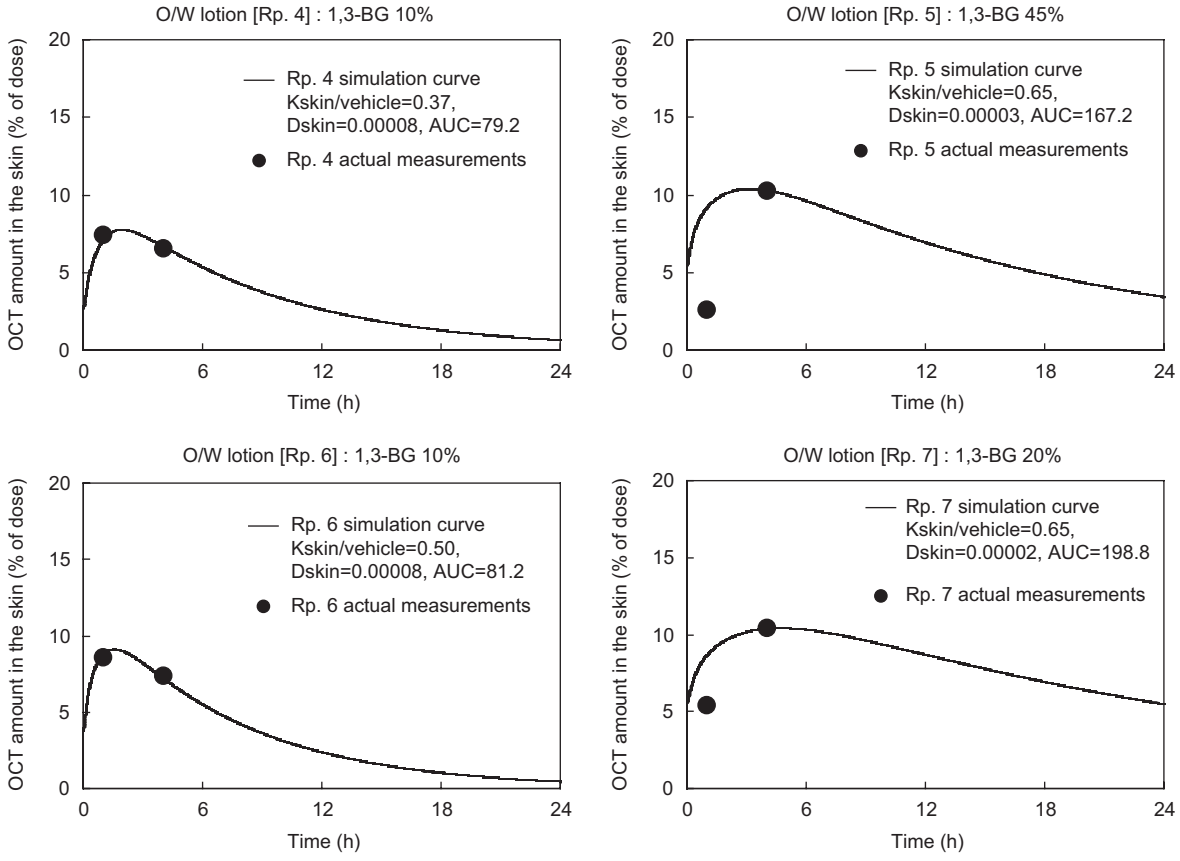


Figure 6. Simulation curves and dermatopharmacokinetic parameters of O/W lotions [Rp.4–Rp.7]. Lines show the theoretical curves evaluated by a two-layered diffusion model. Each value represents the mean ($n=3$). Rp.4 is the same formulation as Rp.1.

Effects of polarity between vehicle (solvent), OCT, and skin on OCT skin permeation

As described in the section of Effects of Solvent on OCT Skin Permeation, we hypothesized that vehicle (drug-solvent) could penetrate the stratum corneum after application of topical formulations. In this case, interaction between solvent and stratum corneum (skin) causes change in the partition ($K_{skin/vehicle}$) and diffusion (D_{skin}) of OCT. Table 3 shows solubility parameters of OCT, solvents, and skin as indicators of lipophilic and hydrophilic balance (polarity). We consider that these parameters can be used to propose the reasons of different OCT skin permeation by solvents.

Concerning the OCT partition ($K_{skin/vehicle}$), the rank order of solubility parameters in Table 3 (1,3-BG > OCT > skin > MCT) is important to be considered. While affinity between vehicle and OCT increase (escape tendency between vehicle and OCT decrease) with an increase in the MCT amount in vehicle, the polarity of skin is shifted to that of MCT, causing decrease in affinity between skin and OCT. Therefore it is speculated that the ratio change of the OCT concentration in skin becomes smaller than that in vehicle. In the similar way, while affinity between vehicle and OCT increase (escape tendency between vehicle and OCT decrease) with an increase in the 1,3-BG amount in vehicle, the polarity of skin is shifted to that of 1,3-BG, causing increase in affinity between skin and OCT. Thus, the ratio change of the OCT concentration in skin would become larger than that in vehicle.

Regarding OCT diffusion (D_{skin}), as the same reason indicated above, the decrease in affinity between skin (stratum corneum) and OCT with an increase in the MCT concentration in vehicle could be related to the decrease in OCT retention in skin. On the other hand, the increase in affinity between skin and OCT with an increase in the 1,3-BG amount in vehicle could be related to improvement of OCT retention in skin.

Usage of solvent polarity in design of topical formulations

Many authors report that solvents have an effect on drug skin permeation by altering drug partition ($K_{skin/vehicle}$), diffusion (D_{skin}), and solubility parameters[18,29,30]. Therefore, it is important in designing topical formulations to investigate the effects of solvents on the drug permeation profile. In particular, for designing transdermal bioequivalent formulations for different types of topical dosage forms, selection of two types of solvents having opposite solubility parameters to those of drug and skin is useful for controlling and optimizing drug skin permeability. Using the findings in the present study, we obtained O/W-type lotion (OCT lotion) with OCT permeation profile almost equivalent to that of OCT ointment by controlling OCT permeability with different polarities of solvents, MCT, and 1,3-BG (data not shown).

Table 3. Solubility parameters of OCT, solvents, and skin.

Drug, solvents, and skin	Solubility parameters $(cal/cm^3)^{1/2}$
Drug (OCT)	12.5
Medium-chain fatty acid triglyceride (MCT)[a]	9.2
Myristate Isopropyl (IPM)	8.5
1,3-butylene glycol (1,3-BG)	14.8
Propylene glycol (PG)	15.9
Skin	9.7–10

OCT, 22-oxacalcitriol-1α, 25-dihydroxyvitamin D_3.
[a]MCT is the triglyceride of straight-chain fatty acid; $CH_3(CH_2)_nCOOH$ (n = 4–10). In this study, we assumed that the repeat number of polyethylene (n) is 7 for calculating the solubility parameter.

Conclusion

In order to control skin permeability from topical dosage forms, we examined the permeation profile of OCT from solutions and O/W-type lotions prepared using solvents with reciprocal solubility parameters (polarity) to that of OCT and skin. The obtained results suggested that MCT and 1,3-BG have different effects on the OCT partition from vehicle to skin and OCT diffusion in skin, due to alterations of stratum corneum polarity. Selection of two types of solvents having opposite polarities to those of drug and skin could be useful for efficiently optimizing the drug permeation from topical formulations.

Acknowlegements

The authors are very grateful to Drs. H. Todo and N. Hada at the Faculty of Pharmaceutical Sciences, Josai University for their useful advice. We also thank K. Tujimura, T. Paku, Y. Ueda, S. Nomura, and J. Takahara of Maruho Co., Ltd., Kyoto R&D Center for their assistance with practical experiments.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Polano MK, Bonsel J, van der Meer BJ. (1950). The relation between the effect of topical irritants and the ointment bases in which they are applied to the skin. Dermatologica, 101:69–79.
2. Hadgraft J. (1989). Formulation of anti-inflammatory agents. In: Hensby C, Lowe NJ (eds.), Nonsteroidal anti-inflammatory drugs. Pharmacol. Skin. Basel, Karger, 2, 21–43.
3. Pershing LK, Silver BS, Krueger GG, Shah VP, Skelley JP. (1992). Feasibility of measuring the bioavailability of topical betamethasone dipropionate in commercial formulations using drug content in skin and a skin blanching bioassay. Pharm Res, 9:45–51.
4. Christian STT, Smith EW. (2002). Ointment, cream, and lotion as topical drug delivery system. In: Robert L, Bronaugh HI (eds.), Topical absorption of dermatological products. Fragrance Journal, Tokyo.

5. Smith EW, Meyer E, Haigh JM. (1990). Blanching activities of betamethasone formulations. The effect of dosage form on topical drug availability. Arzneimittelforschung, 40:618–621.
6. Haigh JM, Smith EW, Meyer E, Fassihi R. (1992). Influence of the oil phase dispersion in a cream base on the in vivo release of betamethasone 17-valerate. S.T.P. Pharma Sciences, 2:259–264.
7. Richard B, Stoughton MD. (1987). Are generic formulations equivalent to trade name topical glucocorticoids? Arch Dermatol, 123:1312–1314.
8. Stoughton RB, Wullich K. (1989). The same glucocorticoid in brand-name products. Does increasing the concentration result in greater topical biologic activity? Arch Dermatol, 125:1509–1511.
9. Somerma S. (1980). The chamber vasoconstrictor assay. I. Comparison with occluded and unoccluded tests using four corticosteroids. Clin Exp Dermatol, 5:191–196.
10. Smith EW, Meyer E, Haigh JM, Maibach HI. (1991). The human skin blanching assay for comparing topical corticosteroid availability. J Dermatol Treat, 2:69–72.
11. Gao HY, Li Wan Po A. (1994). Topical formulations of fluocinolone acetonide. Are creams, gels and ointments bioequivalent and does dilution affect activity? Eur J Clin Pharmacol, 46:71–75.
12. Trottet L, Owen H, Holme P, Heylings J, Collin IP, Breen AP et al. (2005). Are all aciclovir cream formulations bioequivalent? Int J Pharm, 304:63–71.
13. Tsai J, Chuang S, Hsu M, Sheu H. (1999). Distribution of salicylic acid in human stratum corneum following topical application in vivo: a comparison of six different formulations. Int J Pharm, 188: 145–153.
14. Ostrenga J, Steinmetz C, Poulsen B. (1971a). Significance of vehicle composition. I. Relationship between topical vehicle composition, skin penetrability, and clinical efficacy. J Pharm Sci, 60:1175–1179.
15. Ostrenga J, Steinmetz C, Poulsen B, Yett S. (1971b). Significance of vehicle composition. II. Prediction of optimal vehicle composition. J Pharm Sci, 60:1180–1183.
16. Ostrenga J, Steinmetz C, Poulsen B, Yett S. (1971c). Significance of vehicle composition. II. Prediction of optimal vehicle composition. J Pharm Sci, 60:1180–1183.
17. Hadgraft J. (1999). Passive enhancement strategies in topical and transdermal drug delivery. Int J Pharm, 184:1–6.
18. Kumar S, Malick AW, Meltzer NM, Mouskountakis JD, Behl CR. (1992). Studies of *in vitro* skin permeation and retention of a leukotriene antagonist from topical vehicles with a hairless guinea pig model. J Pharm Sci, 81:631–634.
19. Adnan A., Zeenat IK, Aqil M, Farhan JA, Roop KK, Sushama T. (2009). Microemulsions as a surrogate carrier for dermal drug delivery. Drug Dev Ind Pharm, 35:525–547.
20. Rachna P, Sneh A, Roop KK, Amit KD, Veena K. (2009). Studies on in vitro and in vivo transdermal flux enhancement of methotrexate by a combinational approach in comparison to oral delivery. Drug Dev Ind Pharm, 35:1281–1292.
21. Karimunnisa SS, Bothiraja C, Atmaram PP. (2010). Studies on nonionic surfactant bilayer vesicles of ciclopirox olamine. Drug Dev Ind Pharm, 36:946–953.
22. Marchiori ML, Lubini G, Dalla Nora G, Friedrich RB, Fontana MC, Ourique AF et al. (2010). Hydrogel containing dexamethasone-loaded nanocapsules for cutaneous administration: preparation, characterization, and *in vitro* drug release study. Drug Dev Ind Pharm, 36:962–971.
23. Yamamoto H. (2007). Application handbook of solubility parameters. Jouhoukikou, Tokyo.
24. Liron Z, Cohen S. (1984). Percutaneous absorption of alkanoic acids II: Application of regular solution theory. J Pharm Sci, 73:538–542.
25. Hada N, Hasegawa T, Takahashi H, Ishibashi T, Sugibayashi K. (2005). Cultured skin loaded with tetracycline HCl and chloramphenicol as dermal delivery system: mathematical evaluation of the cultured skin containing antibiotics. J Control Release, 108:341–350.
26. Yamaguchi K, Mitsui T, Yamamoto T, Shiokawa R, Nomiyama Y, Ohishi N et al. (2006). Analysis of *in vitro* skin permeation of 22-oxacalcitriol having a complicated metabolic pathway. Pharm Res, 23:680–688.
27. Higuchi T. (1960). Physical chemical analysis of percutaneous absorption process from creams and ointment. J Soc Cosm Chem, 11:85–97.
28. Smith EW, Christian STT, Tassopoulos A, Maibach HI. (2002). Skin applied base ~comprehensive approach~. In: Robert L, Bronaugh HI. (eds.), Topical absorption of dermatological products. Fragrance Journal, Tokyo.
29. Hadgraft J. (2001). Modulation of the barrier function of the skin. Skin Pharmacol Appl Skin Physiol, 14 Suppl 1:72–81.
30. Dias M, Hadgraft J, Lane ME. (2007). Influence of membrane-solvent-solute interactions on solute permeation in model membranes. Int J Pharm, 336:108–114.