Skin Permeation Enhancement of Tegafur by Ethanol/Panasate 800 or Ethanol/Water Binary Vehicle and Combined Effect of Fatty Acids and Fatty Alcohols

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Abstract □ The effects of vehicle and enhancer on the skin permeation of tegafur across excised hairless mouse skin were investigated. Ethanol, water, panasate 800 (tricaprylin), and their mixtures were used as vehicles, and then a series of fatty acids or fatty alcohols was employed as representative enhancers. The skin permeability of tegafur was dramatically increased by the combination of ethanol and panasate 800, whereas the combination of ethanol and water resulted in only a little increase. The greatest permeation ratio (56.8% of dose at 12 h) was obtained with the ethanol/panasate 800 (40/60) binary vehicle. Furthermore, the skin permeability of tegafur could be enhanced by the addition of fatty acids or fatty alcohols to ethanol/panasate 800 (40/60) and ethanol/water (60/40) binary vehicles. The infinite dose studies suggested that panasate 800 decreased the lag time by increasing the diffusion of tegafur, and ethanol increased the permeation rate by increasing the partition of tegafur into skin. The effects of fatty acids or fatty alcohols added to ethanol as a single vehicle were dramatic, but did not appear in the case of panasate 800 as a single vehicle. In conclusion, panasate 800 was an excellent hydrophobic vehicle in that it minimized time lag and promoted tegafur permeability combined with ethanol. This improvement was further promoted when enhancers were added.

Many investigators have examined the possibility of the transdermal delivery of drugs, but a major difficulty is the impermeability of the stratum corneum. Especially, hydrophilic drugs can not penetrate through a dense and hydrophobic stratum corneum barrier at a rate sufficiently high to achieve therapeutic efficacy. The feasibility of skin permeation of a drug may depend on judicious solvent selection to enhance the transdermal delivery. However, most of the studies on vehicles for skin permeation of drugs have focused on hydrophilic vehicles, such as propylene glycol, ethanol, water, or their mixture,[1,2] and the number of reports on hydrophobic vehicles are limited.[3,4]

We have already reported on the skin permeation of ketoprofen [logarithm of the *n*-octanol–water partition coefficient (log *P*) = 2.9[5]) from various vehicles, such as triglycerides, medium-chain hydrocarbons as a hydrophobic vehicle, and short-chain alcohols as a hydrophilic vehicle.[6] The results showed that ethanol had a long lag time (8.1 h) and a permeation of 13% of the dose by 24 h and that panasate 800 (caprylic triglyceride) had the shorter lag time (0.9 h). Panasate 800 is a neutral oil that is not miscible with water and is stable on oxidation when compared with natural vegetable oils. It has been also suggested that ethanol/panasate 800 (40/60) mutual enhancement of skin permeation might form the basis for novel system designs.

In the present study, tegafur [1-(tetrahydro-2-furanyl)-5-fluorouracil] was chosen as a model hydrophilic drug (log *P* = −0.48[7]). Such a low lipophilicity may be a predominant factor for the poor skin permeability of the drug. Tegafur, a masked form of 5-fluorouracil, has been used for treatment of carcinoma of the breast and gastrointestinal tract.[8] However, the dosage for daily oral administration of tegafur is often limited due to its side effects.[9,10] The dose-limiting factor in tegafur administration is gastrointestinal toxicity that causes side effects such as diarrhea, nausea, and vomiting.[11–13] The high initial plasma concentration of the drug after its oral administration appears to be responsible for the side effects. The development of a transdermal delivery system involving tegafur may be advantageous for long-term maintenance chemotherapy and decrease of these side effects. Ethanol/panasate 800 binary vehicles mixed in various volume fractions were studied as enhancers for tegafur permeation across excised hairless mouse skin. Ethanol/water binary vehicles (hydrophilic) were also examined for comparison with ethanol/panasate 800 binary vehicles (hydrophobic). In addition, several kinds of fatty acids or fatty alcohols[14–22] were used as permeation enhancers because the choice of them was considered to be essential for the reduction of a skin barrier function.

Experimental Section

Materials and Formulations—Tegafur was obtained from Taiho Pharmaceutical Company (Tokushima, Japan). Fatty acids (saturated C6–C18, oleic acid and linoleic acid) and fatty alcohols (saturated C8-OH–C18-OH) were purchased from Nacalai Tesque Company (Kyoto, Japan). Panasate 800 as tricaprylin was kindly supplied by Nihon Yushi Company (Tokyo, Japan). All other chemicals were of reagent grade. Ethanol/panasate 800 hydrophobic binary vehicles were prepared by mixing ethanol and panasate 800, which are completely miscible, in various volume proportions. In finite dose experiments, test preparations (10 g) were prepared by dissolving tegafur (50 mg) in the binary vehicles and divided for charging (0.5 mL) to each diffusion cell. Fatty acids or fatty alcohols were added to the ethanol/panasate 800 (40/60) or ethanol/water (60/40) binary vehicle containing tegafur at 37 °C. The C14–C18 acids could not be used in the ethanol/water (60/40) binary vehicle because of these solubility limitations. The percentage of fatty acids or fatty alcohols added to the vehicles was 4% (w/w). In infinite dose experiments, test preparations (10 g) were prepared by suspending tegafur (1 g) in each ethanol/panasate 800 binary vehicle at 37 °C.

In Vitro Permeation Studies—The abdominal skin of hairless female mice was obtained from 8–9 weeks old, 27–33 g animals. The animals were sacrificed by cervical dislocation just before an in vitro skin permeation experiment. The full-thickness abdominal skin sections were excised with surgical scissors. Adhering subcutaneous fat on the side was carefully removed from the under side of the skin. The skin samples obtained by this procedure were uniform, and no further treatment was needed to clean them. We used vertically assembled LOVEDAY type diffusion cells[23] with an effective diffusional area of ~0.785 cm^2 and downstream volume of 5 mL. Each cell was individually calibrated with respect to its receiver volume and diffusional surface area. The receiver compartment was mixed continuously with a Teflon-coated magnetic bar (3 × 3 mm, Central Scientific Comm., Tokyo, Japan) driven by a 150 rpm constant-speed motor (magnetic stirrer, RC-2, Tokyo Rikakikai Company, Tokyo, Japan). The excised skin was immediately laid on the diffusion cell, epidermal side up, and the receiver compartment was filled with 5 mL

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of 50 mM phosphate buffer saline (PBS; pH 7.4) that was maintained at 37 °C. The cell was equilibrated for 30 min in a water bath maintained by immersion of a thermostatic pump at 37 °C, and then the donor compartment was charged with 0.5 mL of drug preparation at 37 °C and capped. Aliquots (0.5 mL) were withdrawn from the receiver compartment periodically and replaced with 0.5 mL of PBS maintained at 37 °C. The experiments were performed for 12 h at 37 °C. The first sample needed no concentration correction in calculating the cumulative amount of tegafur permeated. However, the cumulative amount in the subsequent samples was calculated by correcting the amount of drug removed at each sample point.

Determination of Solubility at 37 °C—Excess amounts (1.5–6.0 g) of tegafur and vehicles (30 mL) were placed in a screw-cap centrifugation glass tube, which was capped and shaken at 50 °C for 2 h to ensure saturation. The tube contents were incubated for 7 days at 37 °C. An aliquot of the vehicle (1 mL) was removed periodically from the tube and filtered through Millipore filters (cellulose acetate, 0.2 μm, Tosoh Company, Tokyo, Japan), and then 0.7 mL of the filtrate was immediately diluted with ethanol (10–100 mL). The concentration of tegafur was measured by HPLC. The solubility equilibrium of tegafur in ethanol/panasate 800 or ethanol/water binary vehicles was attained within 3–5 days in all cases. The solubilities at 7 days of incubation in ethanol/panasate and ethanol/water vehicles are shown in Table I.

HPLC Analysis—All tegafur concentrations were determined by HPLC. The samples were filtered by Millipore filters, and injected into the HPLC with or without dilution. The HPLC consisted of a solvent pump (LC-9A, Shimadzu Company, Kyoto, Japan), a column (Shimpack CLS-ODS, 0.6 × 15 cm, Shimadzu Company, Kyoto, Japan), a UV detector (280 nm, SPD-6A, Shimadzu Company, Kyoto, Japan), and an integrator (area mode, C-R6A, Shimadzu Company, Kyoto, Japan). The mobile phase was made up of 10 mM phosphate buffer (pH 7.0):acetonitrile (83:17, v/v). The flow rate and column temperature were 1.5 mL/min and 40 °C, respectively. The retention time of tegafur was 3.8 min when 10 μg/mL of tegafur was applied. In this assay method, the calibration curve of tegafur was linear in the range of 0.1 to 100 μg/mL, and the linear regression analysis of data gave a value of r that was consistently >0.999. The CVs calculated from the peak area during the experimental period were <5%.

Calculation of Permeation Parameters—For each diffusion cell, the cumulative amount of tegafur penetrated per unit area was plotted against time, and from the slope of the linear portion of such plots, tegafur steady-state flux was calculated. The comparison of results in infinite dose experiments was done by calculating the permeation characteristics, steady-state flux, and permeability coefficient with the following equations:

$$LT = L^2/6D \quad (1)$$

$$J_{ss} = DC_0K/L = K_pC_0 \quad (2)$$

In eqs 1 and 2, LT is the lag time, L is the membrane thickness, D is the diffusion coefficient (cm^2/h), J_{ss} is the steady-state flux [($\mu g/cm^2$)/h], C_0 is the concentration at time 0, K is the partition coefficient of the drug between the vehicle and the skin, and K_p is the permeability coefficient (cm/h). In determining the above parameters, L was set at 0.041 cm, a value presumably representative of the thickness of hairless mouse skin.[24] Four experiments per group were performed.

Table I—Solubility of Tegafur in Ethanol/Panasate 800 and Ethanol/Water Binary Vehicles at 37 °C[a]

Ethanol/Panasate 800		Ethanol/Water	
Ratio (v/v)	Solubility, mg/mL	Ratio (v/v)	Solubility, mg/mL
100/0	21.3 (0.2)	100/0	21.3 (0.2)
80/20	23.7 (0.1)	80/20	48.7 (0.2)
60/40	23.9 (0.1)	60/40	64.3 (0.2)
40/60	20.4 (0.2)	40/60	55.2 (0.2)
20/80	14.3 (0.2)	20/80	36.5 (0.1)
0/100	2.7 (0.1)	0/100	25.3 (0.2)

[a] Each value represents the mean (SD) of three experiments.

All data were expressed as mean with SD in parentheses. Statistical analysis was performed with the t test for significant differences.

Results and Discussion

Skin Permeability of Tegafur from Ethanol/Panasate 800 Binary Vehicles—Figure 1 represents the permeation profiles of tegafur across the hairless mouse skin with (a) ethanol/panasate 800 or (b) ethanol/water binary vehicles containing 0.5% (w/w) tegafur. The corresponding values of lag time, steady-state flux, and permeation percentage by 12 h for each donor composition are listed in Table II.

The skin permeability of tegafur was remarkably enhanced by ethanol/panasate 800 binary vehicles. The greatest enhancing effect was observed in the ethanol/panasate 800 (40/60) vehicle. The values of permeation percentage by 12 h and steady-state flux were 56.8% of dose and 179.9 ($\mu g/cm^2$)/h, respectively. We also achieved a value of 2.2 h for lag time, and this value was much smaller than 8.1 h that was obtained with ethanol only. It is interesting that a greater enhancing effect could be observed by combining a hydrophilic vehicle (ethanol) and hydrophobic vehicle (panasate 800), compared with single vehicles.

On the other hand, ethanol/water binary vehicles were quite ineffective in the enhancement of skin permeability of tegafur. As illustrated in Figure 1b, the maximum permeation percentage at 12 h with the ethanol/water (60/40) binary vehicle was quite small (2.5% of dose).

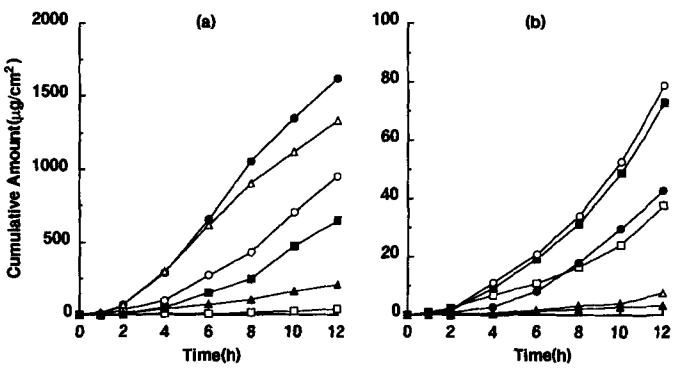

Figure 1—Permeation profiles of tegafur across excised hairless mouse skin from (a) ethanol/panasate 800 and (b) ethanol/water binary vehicles. Key: (□) 100/0; (■) 80/20; (○) 60/40; (●) 40/60; (△) 20/80; (▲) 0/100. Each value is the mean of four experiments.

Table II—Permeation Parameters of Tegafur from Ethanol/Panasate 800 or Ethanol/Water Binary Vehicles[a]

Vehicle	Ratio (v/v)	Lag Time, h	Flux, ($\mu g/cm^2$)/h	Permeation Percent (% of dose at 12 h)
Ethanol/panasate 800	100/0	8.1 (0.3)	11.2 (2.0)	1.3 (0.5)
	80/20	3.7 (0.3)	68.5 (14.0)[b]	22.7 (3.0)[b]
	60/40	3.1 (0.4)	99.2 (25.2)[b]	33.1 (8.5)[b]
	40/60	2.2 (0.7)	179.9 (29.0)[b]	56.8 (5.4)[b]
	20/80	1.6 (0.7)	137.9 (10.0)[b]	46.5 (4.9)[b]
	0/100	2.0 (0.2)	19.8 (0.9)	7.3 (0.3)
Ethanol/water	100/0	8.1 (0.3)	11.2 (2.0)	1.3 (0.5)
	80/20	5.8 (0.6)	14.3 (1.4)[c]	2.4 (0.4)[c]
	60/40	6.3 (0.5)	14.6 (0.6)[c]	2.5 (0.3)[c]
	40/60	7.8 (0.6)	12.6 (1.4)	1.3 (0.3)
	20/80	9.3 (1.1)	7.7 (0.6)	0.2 (0.1)
	0/100	8.8 (0.3)	2.6 (0.3)	0.1 (0.0)

[a] Each value represents the mean (SD) of four experiments. [b] Significantly different than ethanol or panasate 800 single vehicle ($p < 0.05$). [c] Significantly different than ethanol or water single vehicle ($p < 0.05$).

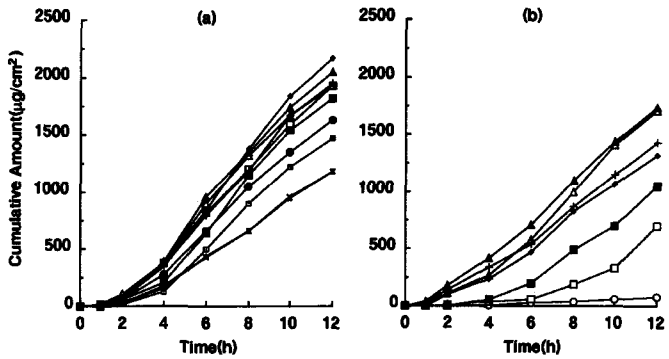

Figure 2—Permeation profiles of tegafur across excised hairless mouse skin from (a) ethanol/panasate 800 (40/60) and (b) ethanol/water (60/40) binary vehicle containing various fatty acids. Key: containing no fatty acids: (●) ethanol/panasate 800 (40/60); (○) ethanol/water (60/40); containing fatty acids: (□) C6; (■) C8; (△) C10; (▲) C12; (⊡) C14; (△) C16; (×) C18; (◆) C18:1Δ9; (+) C18:2Δ9.12. Each value is the mean of four experiments.

Addition Effect of Fatty Acids—From the above skin permeation profiles, the two best vehicle combinations, the ethanol/panasate 800 (40/60) and ethanol/water (60/40) systems, were chosen. We tried to improve the efficiency by addition of saturated fatty acids (C6–C18) and unsaturated fatty acids (oleic and linoleic acids) to the above two binary vehicles: the results are summarized in Figure 2 and Table III. The large majority of fatty acids increased the skin permeation flux of tegafur in the ethanol/panasate 800 (40/60) binary vehicle. The skin permeability of tegafur decreased in the following order: oleic acid > C12 > linoleic acid > C10 > C8 > C6 > no fatty acid > C14 > C16 > C18. The permeation percentage of tegafur across the hairless mouse skin by 12 h using C12 and oleic acid were 71.4 and 75.6% of dose, respectively.

All fatty acids dramatically increased the skin permeation flux of tegafur in the ethanol/water (60/40) binary vehicle. The skin permeability of tegafur decreased in the following order: C12 > C10 > linoleic acid > oleic acid > C8 > C6 > no fatty acid. In spite of the notable increase of skin permeability of tegafur, the maximum permeation percentage by 12 h with C12 was 54.7% of dose. This value is almost the same as 56.8% of dose obtained with the ethanol/panasate 800 (40/60) binary vehicle containing no fatty acid.

Addition Effect of Fatty Alcohols—All fatty alcohols, except the C18-OH, slightly increased the skin permeability of tegafur in the ethanol/panasate 800 (40/60) binary vehicle (Figure 3 and Table IV). The same degree of permeation percentage of tegafur at 12 h (64.1–67.9% of dose) was obtained in all cases, and no significant difference between them was observed.

On the other hand, all fatty alcohols significantly enhanced the skin permeation flux of tegafur with an ethanol/water (60/40) binary vehicle. The skin permeation flux of tegafur increased with an increase in alkyl chain length, reached a maximum permeation in C12-OH, and then decreased with further alkyl chain length increases. The skin permeability of tegafur followed the following order: C12-OH > C10-OH > C9-OH > C8-OH > C14-OH > C16-OH > C18-OH > no fatty alcohol. The addition of three fatty alcohols (C12-OH, C10-OH, and C9-OH) showed the greatest permeation percentage of tegafur at 12 h in the ethanol/water (60/40) binary vehicle. These values obtained (61.3–70.3% of dose) were almost the same as those obtained with the ethanol/panasate 800 (40/60) binary vehicle containing a wide range of fatty alcohols (C8-OH–C16-OH, 63.4–67.9% of dose).

It has been reported that the increase of skin permeability in the presence of fatty alcohols with increasing chain length may reflect an interaction of fatty alcohol with the matrix lipids of the stratum corneum because the distribution of fatty alcohols from aqueous vehicles to the skin increases with the increase in carbon number.[25] Chien and co-workers reported that as the alkyl chain length in the alkanols and alkanoic acids increases, the transdermal permeation rate of indomethacin increases initially, reaches a maximum rate, and then drops as the number of methylene groups in the alkyl chain is greater than six to eight.[26] Furthermore, it has been suggested that because the melting point of C14-OH is above the temperature of the skin, its mobility into skin is low and then the enhancing effect of C14-OH will be small.[21] Our results in the ethanol/water (60/40) binary vehicle containing fatty alcohols agree well with the above reports. However, in the case of the ethanol/panasate 800 (40/60) binary vehicle, the enhancing effect obtained in C14-OH or C16-OH was almost the same as the results in other fatty alcohols (C8-OH–C12-OH). When the ethanol/panasate 800 (40/60) lipophilic binary vehicle distributes to the skin and the lipophilic environment is formed, the mobility of C14-OH in the skin may be increased due to its lipophilic property. However,

Table III—Permeation Parameters of Tegafur from Ethanol/Panasate 800 or Ethanol/Water Binary Vehicles containing Various Fatty Acids[a]

Vehicle	Fatty Acid	Lag Time, h	Flux, (μg/cm²)/h	Permeation Percent (% of dose at 12 h)
Ethanol/panasate 800 (40/60)	No fatty acid	2.2 (0.7)	179.9 (29.0)	56.8 (5.4)
	Caproic acid(C6)	2.4 (0.6)	207.8 (30.4)	66.0 (4.1)[b]
	Caprylic acid(C8)	2.4 (0.2)	215.8 (32.1)	66.5 (3.6)[b]
	Capric acid(C10)	2.3 (1.1)	228.2 (31.8)	67.3 (6.3)[b]
	Lauric acid(C12)	2.1 (0.3)	233.3 (23.2)	71.4 (8.8)[b]
	Myristic acid(C14)	3.3 (0.1)	199.5 (9.8)	51.4 (4.9)
	Palmitic acid(C16)	2.8 (0.3)	129.6 (14.9)	41.2 (3.3)
	Stearic acid(C18)	2.9 (1.2)	129.0 (28.7)	41.0 (11.1)
	Oleic acid(C18:1Δ9)	2.1 (0.3)	245.4 (36.1)	75.6 (10.0)[b]
	Linoleic acid(C18:2Δ9,12)	2.4 (0.3)	217.3 (40.7)	67.9 (6.6)[b]
Ethanol/water (60/40)	No fatty acid	6.3 (0.5)	14.6 (0.6)	2.5 (0.3)
	Caproic acid(C6)	3.9 (0.2)	46.2 (6.9)	21.9 (7.8)[c]
	Caprylic acid(C8)	3.6 (0.7)	100.3 (10.6)	32.9 (10.5)[c]
	Capric acid(C10)	2.6 (0.7)	172.8 (18.1)	53.6 (11.5)[c]
	Lauric acid(C12)	2.1 (0.7)	165.8 (18.1)	54.7 (7.4)[c]
	Oleic acid(C18:1Δ9)	2.4 (0.5)	128.4 (23.5)	41.6 (9.3)[c]
	Linoleic acid(C18:2Δ9,12)	2.2 (0.9)	130.4 (12.3)	45.0 (15.9)[c]

[a] Each value represents the mean (SD) of four experiments. [b] Significantly different than ethanol/panasate 800 (40/60) vehicle containing no fatty acid ($p < 0.05$). [c] Significantly different than ethanol/water (60/40) vehicle containing no fatty acid ($p < 0.05$).

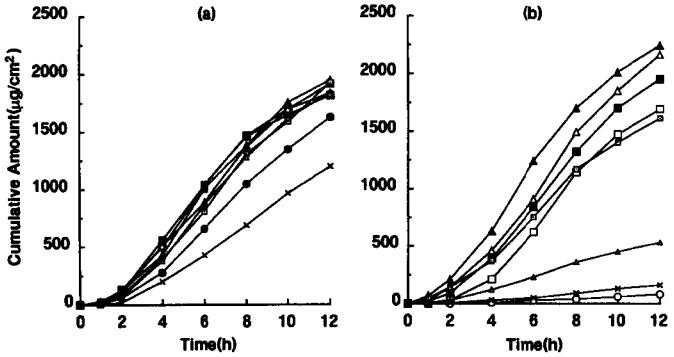

Figure 3—Permeation profiles of tegafur across excised hairless mouse skin from (a) ethanol/panasate 800 (40/60) and (b) ethanol/water (60/40) binary vehicle containing various fatty alcohols. Key: containing no fatty alcohols: (●) ethanol/panasate 800 (40/60); (○) ethanol/water (60/40); containing fatty alcohols: (□) C8; (■) C9; (△) C10; (▲) C12; (⊡) C14; (△) C16; (×) C18. Each value is the mean of four experiments.

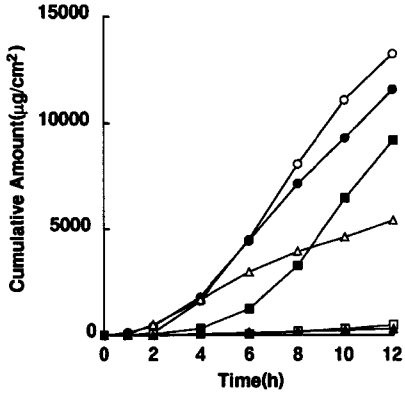

Figure 4—Permeation profiles of tegafur across excised hairless mouse skin from ethanol/panasate 800 binary vehicles containing suspended tegafur. Key: (□) 100/0; (■) 80/20; (○) 60/40; (●) 40/60; (△) 20/80; (▲) 0/100. Each value is the mean of four experiments.

further study is necessary to elucidate the difference behavior of the ethanol/panasate 800 (40/60) binary vehicle.

Enhancing Mechanism of Ethanol/Panasate 800 Binary Vehicles on the Skin Permeation of Tegafur—To evaluate the enhancing mechanism of ethanol/panasate 800 binary vehicles on the skin permeation of tegafur, we were interested in studying the different behavior of each vehicle (ethanol or panasate 800). The infinite dose studies (Figure 4) provided some insight into these observations. The permeation parameters determined in the infinite dose experiments for ethanol/panasate 800 binary vehicles are listed in Table V. In the combination of ethanol and panasate 800, the diffusion coefficient of tegafur increases as the volume fraction of panasate 800 increases, and the partition coefficient increases as the volume fraction of ethanol in the vehicle increases. It has been reported that ethanol increased the skin permeability of a drug by increasing the drug solubility in the skin.[1] This report[1] agrees well with the results in this experiment. Therefore, we suggest that panasate 800 is useful for decreasing the lag time by increasing the diffusivity of tegafur in the skin and ethanol is useful for increasing the permeation rate by increasing the partition of tegafur into the skin. Also, the skin permeation mechanism of the ethanol/panasate 800 binary vehicle is due to the cooperative and mutual enhancing effect between ethanol and panasate 800.

Enhancing Mechanism of Ethanol and Panasate 800 Vehicles Containing Fatty Acids and Fatty Alcohols as Enhancers on Skin Permeation of Tegafur—Figure 5 shows the skin permeation profiles of tegafur from (a) ethanol or (b) panasate 800 vehicles containing C12 or C12-OH as an enhancer. Ethanol vehicle in the presence of C12 or C12-OH enhanced the skin permeation of tegafur remarkably compared with ethanol only, and the lag time decreased from 8.1 h for ethanol to 5.6 and 7.1 h, respectively, for ethanol vehicles containing enhancers C12 and C12-OH. In the combination of panasate 800 and enhancers, no differences were observed in relation to flux and lag time for tegafur permeation. Francoeur and co-workers[27] reported that oleic acid is capable of selectively perturbing the lipids of the stratum corneum, resulting in a net increase of piroxicam flux. The effect is most likely specific for *cis*-unsaturated or short-chain ($C \leq 12$) free fatty acid. The extent of the effect of oleic acid on lipid perturbation and flux is quantitatively related to the amount of free fatty acid incorporated by the stratum corneum bilayer or to the shift in the endogenous lipid transition temperatures. Accordingly, it is supposed that the amounts of enhancers (fatty acids or fatty alcohols) distributed from the vehicles to the skin may be different between the vehicles and much higher for ethanol than for panasate 800. Also, the drug distribution to the skin may be governed by the thermody-

Table IV—Permeation Parameters of Tegafur from Ethanol/Panasate 800 or Ethanol/Water Binary Vehicles containing Various Fatty Alcohols[a]

Vehicle	Fatty Alcohol	Lag Time, h	Flux, (μg/cm²)/h	Permeation Percent (% of dose at 12 h)
Ethanol/panasate 800 (40/60)	No fatty alcohol	2.2 (0.7)	179.9 (29.0)	56.8 (5.4)
	Octyl alcohol(C8)	1.6 (0.7)	227.0 (16.1)	66.9 (4.2)[b]
	Nonyl alcohol(C9)	1.3 (0.5)	212.1 (33.8)	63.4 (5.8)
	Decyl alcohol(C10)	1.6 (0.6)	211.2 (25.5)	64.1 (4.6)
	Lauryl alcohol(C12)	1.7 (0.4)	217.3 (10.0)	67.9 (2.0)[b]
	Myristyl alcohol(C14)	2.0 (0.4)	203.5 (27.2)	67.2 (6.4)[b]
	Cetyl alcohol(C16)	2.0 (0.6)	207.2 (12.3)	64.7 (3.3)[b]
	Stearyl alcohol(C18)	2.6 (0.1)	128.7 (8.9)	39.0 (4.6)
Ethanol/water (60/40)	No fatty alcohol	6.3 (0.5)	14.0 (0.6)	2.5 (0.3)
	Octyl alcohol(C8)	2.8 (1.0)	192.9 (31.5)	53.1 (12.4)[c]
	Nonyl alcohol(C9)	2.4 (0.9)	211.0 (25.8)	61.3 (3.6)[c]
	Decyl alcohol(C10)	2.0 (0.7)	213.8 (24.9)	67.8 (3.5)[c]
	Lauryl alcohol(C12)	1.5 (0.5)	226.4 (26.1)	70.3 (5.8)[c]
	Myristyl alcohol(C14)	1.8 (0.5)	157.6 (16.3)	50.6 (4.1)[c]
	Cetyl alcohol(C16)	1.6 (0.4)	49.6 (8.0)	16.6 (3.3)[c]
	Stearyl alcohol(C18)	2.7 (0.2)	15.8 (0.6)	16.6 (1.6)[c]

[a] Each value represents the mean (SD) of four experiments. [b] Significantly different than ethanol/panasate 800 (40/60) vehicle containing no fatty alcohol ($p < 0.05$). [c] Significantly different than ethanol/water (60/40) vehicle containing no fatty alcohol ($p < 0.05$).

Table V—Permeation Parameters of Tegafur from Ethanol/Panasate 800 Binary Vehicles in Infinite Dose Experiments[a]

Ethanol/Panasate 800 Ratio	J_{ss}, (μg/cm^2)/h	LT, h	K_p ($\times 10^3$), cm/h	D ($\times 10^5$), cm^2/h	K, K_p L/D
100/0	164.3 (42.9)	8.3 (0.7)	7.7 (1.9)	3.4 (0.3)	9.3 (2.6)
80/20	1356.1 (80.6)	5.3 (0.3)	57.3 (3.1)	5.3 (0.3)[b]	44.3 (1.6)[c]
60/40	1540.8 (107.4)	3.0 (0.1)	64.5 (4.3)	9.2 (0.3)[b]	28.7 (1.6)[c]
40/60	1326.2 (133.9)	2.6 (0.3)	65.0 (6.3)	10.9 (1.0)[b]	24.4 (4.1)[c]
20/80	535.6 (27.6)	1.1 (0.3)	37.5 (2.0)	28.7 (7.2)[b]	5.4 (1.8)[c]
0/100	24.8 (0.5)	1.7 (0.8)	9.2 (0.1)	17.0 (0.8)	2.2 (0.1)

[a] Each value represents the mean (SD) of four experiments. [b] Significantly different than ethanol single vehicle ($p < 0.05$). [c] Significantly different than panasate 800 single vehicle ($p < 0.05$).

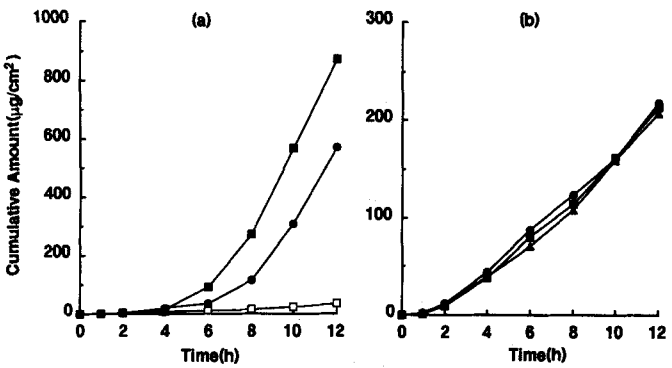

Figure 5—Permeation profiles of tegafur across excised hairless mouse skin from (**a**) ethanol or (**b**) panasate 800 containing lauric acid or lauryl alcohol. Key: containing no enhancers: (□) ethanol; (▲) panasate 800; containing enhancers: (■) lauric acid; (●) lauryl alcohol. Each value is the mean of four experiments.

namic activity of enhancers in the applied vehicle. The notable enhancement effect caused by combinations of the ethanol/water (60/40) binary vehicle and fatty acids or fatty alcohols could be explained by the above considerations, which are supported by our previous experimental results[6] that the amount of uptake of ketoprofen to the skin increased with ethanol as a vehicle.

Conclusions

The skin permeation of tegafur was remarkably enhanced by combinations of ethanol and panasate 800 vehicles, and the effects appeared to be due to increasing the partition of tegafur into the skin by ethanol and increasing the diffusivity of tegafur in the skin by panasate 800. Furthermore, the skin permeability of tegafur was enhanced by adding fatty acids or fatty alcohols. The effects of fatty acids or fatty alcohols added to ethanol appeared dramatic, but were not significant in the case of panasate 800. Panasate 800, a hydrophobic vehicle, was useful for decreasing the lag time and for increasing the flux in combination with ethanol as a hydrophilic vehicle. Therefore, the ethanol/panasate 800 (40/60) binary system could be a useful vehicle for the development of a transdermal delivery system involving tegafur as a hydrophilic drug.

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