einem Widerstand von 18 MegOhm · cm, HNO_3 65% p. a. und H_2SO_4 95 bis 97% p. a. Merck, H_2O_2 30% p. a. Baker sowie Einzelelementstandards von Na, Cu, Mg, Zn, B, Sr der Firma Merck. Die Standards werden auf folgende Endkonzentrationen in mg/l und einen Gehalt von 1% HNO_3 verdünnt: Na 20,00; Mg 5,00; Cu und Zn 2,00; B 1,50; Sr 0,10.

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Influence of coupling medium on *in vitro* sonophoresis of clobetasol 17-propionate

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Sonophoresis (phonophoresis), defined as the movement of drug molecules contained in a coupling medium through the skin under the influence of ultrasound, has been studied for clinical uses and is known to increase skin permeation of corticosteroids [1]. Clobetasol 17-propionate (CP; $C_{25}H_{32}ClFO_5$) is currently considered to be the most potent corticosteroid. However, the transmission of ultrasound through commercial CP cream (Dermovate®) is very low [2]. Hence, an optimal selection of the ultrasound coupling medium (vehicle) to achieve desired drug delivery characteristics is needed in broadening the range of applying sonophoresis. The frequency of ultrasound used for sonophoresis typically ranges from 20 kHz to 10 MHz [3]. Low frequency ultrasound enhances the percutaneous absorption of drugs more effectively than therapeutic ultrasound. The low frequency ultrasound can also induce acoustic cavitation which causes several biological effects [4]. Accordingly, low frequency ultrasound (20 kHz) was used in this study to enhance the *in vitro* permeation of CP through hairless mouse skin.

The Fig. shows the *in vitro* CP permeation through hairless mouse skin with or without 4 h continuous ultrasound at an intensity of 0.2 W/cm^2. The results show that the ultrasound effectively increased the permeation of CP for all the vehicles examined. The various enhancement ratios (E.R.) after ultrasound application (Table) suggests that the coupling medium in the donor greatly influenced the effect of sonophoresis. Results from the experiment of passive CP permeation revealed that both the flux and solubility of CP in vehicles increased in the order of pH 7.4 buffer < propylene glycol (PG)/pH 7.4 buffer < ethanol (EtOH)/pH 7.4 buffer. This indicates that a greater extent of solubilization resulted in a significantly greater flux. However, the calculation of permeability coefficients (P.C.) (Table), shows an exactly opposite trend. This decrease of P.C. reflects that the media of 20% PG and 20% EtOH were less polar and more attractive environments for lipophilic drugs, resulting in lower skin P.C.

The sonophoretic enhancements of CP in various media are also shown in the Table. Despite the fluxes of CP were independent of medium compositions, higher sonophoretic enhancements of CP in pH 7.4 buffer and PG/pH 7.4 buffer were observed, which can be partially explained by the fact that the amounts of CP in the skin were significantly increased by sonophoresis (Table). This result is in good agreement with the previous result that the transdermal sonophoretic enhancement of corticosterone is greatly reduced after incorporation of EtOH in pH 7.4 phosphate buffer [5]. The enhancement ratio of CP in PG/pH 7.4 buffer was slightly lower than that in pH 7.4 buffer, which may be due to the influence of viscosity. The viscosity of PG was 51.2 cps measured by a cone and plate viscometer in our laboratory which was higher than the viscosity of water (1.0019 cps) mentioned in the literature [6]. Previous literature indicates that a low or therapeutic frequency of ultrasound is relatively ineffective in enhancing molecular transport when applied with a

Table: *In vitro* permeation profiles of clobetasol 17-propionate from various coupling medium with 0.2 W/cm^2 ultrasound application for 4 h

		Solubility (μg/ml)	CP in skin at 8 h (μg/g)	Flux (μg/cm^2/h)	P.C. × 10^3 [d] (cm/h)	E.R.[e]
pH 7.4 buffer	without US[c]	1.22 ± 0.43	269.90 ± 40.92	0.15 ± 0.04	122.95 ± 32.98	–
	with US		498.72 ± 92.35	1.02 ± 0.31	836.07 ± 256.80	6.80
PG/buffer[a]	without US	9.74 ± 1.05	581.21 ± 146.98	0.20 ± 0.05	20.53 ± 12.64	–
(2 : 8)	with US		1124.47 ± 144.97	1.18 ± 0.49	121.15 ± 53.61	5.90
EtOH/buffer[b]	without US	29.17 ± 5.92	335.07 ± 83.37	0.48 ± 0.07	16.46 ± 2.40	–
(2 : 8)	with US		498.85 ± 110.71	1.00 ± 0.15	34.28 ± 5.14	2.08

[a] PG, propylene glycol; [b] EtOH; [c] US, ultrasound; [d] P.C., permeability coefficient = flux/solubility; [e] E.R., enhancement ratio = flux with US/flux without US. Each value represents the mean ± S.D. (n = 5 for solubility; n = 3 for in vitro permeation experiment).

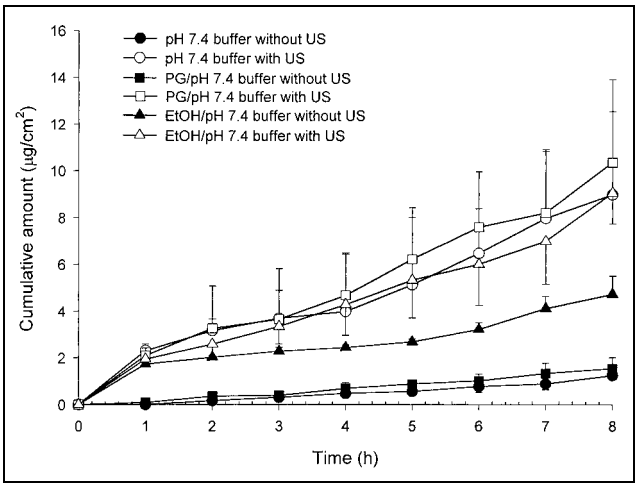

Fig.: Cumulative amount-time profiles of clobetasol 17-propionater across hairless mouse skin from various coupling medium with or without 0.2 W/cm^2 intensity ultrasound application for 4 h. Each value represents the mean and SD (n = 3)

highly viscous coupling medium [7]. This effect may result in the lower permeation enhancement for PG/pH 7.4 buffer relative to pH 7.4 buffer during sonophoresis in the present study. The results were also consistent with a previous study, where the vehicle viscosity greatly influenced the permeability of CP [8].

Experimental

1. Materials

Clobetasol 17-propionate (CP) was obtained from Sigma Chemical Co. (USA). Propylene glycol (PG) was supplied by Nihon Shiyasku Ind. Co. (Japan). All other chemicals and solvents were of analytical grade.

2. In vitro permeation study

Excised female hairless mouse skin was used as the skin barrier. The flux of CP was determined using a modified Franz diffusion cell. A 2 ml solution of coupling medium containing 0.05% (w/v) CP was used as the donor vehicle. The details of the *in vitro* permeation experiment are described in an earlier report [8].

3. Application of low frequency ultrasound

Ultrasound was applied with a sonicator (VCX 600, Sonics and Materials Inc., USA) with a transducer with radiating diameter of 13 mm. The frequency was 20 kHz, and the estimated skin intensity was 0.2 W/cm^2. The mode of continuous ultrasound application was used in this study. The ultrasound transducer was located approximately 0.5 cm from the surface of the skin.

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