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Comparison of physical properties and drug-releasing characteristics of white petrolatums

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White petrolatums of Japanese Pharmacopoeia grade and Sun white® marketed as a cosmetic were characterized by measuring their physical properties and drug-releasing characteristics. White petrolatums of Japanese Pharmacopoeia grade available commercially in Japan were Perfecta, White 1S, Ultima, Snow, Snow V and Regent (Propeto®). Penetrating stress, shear stress and spreading properties were measured as physical properties of the white petrolatums. The physical properties of white petrolatums varied, and Regent was the softest and the most spreadable ointment base. *In vitro* release test was performed using flow-through Franz diffusion cells. Fluorescein isothiocyanate and tetracycline hydrochloride were used as drug models. Their release characteristics varied among the tested white petrolatums, and Regent had the best release properties. Among the white petrolatums, with the exception of Regent, the release properties should depend on the distribution of drugs between white petrolatum and the receiver solution. Considerations of usability and characteristics of the principal agent are needed when choosing white petrolatums.

1. Introduction

Almost all drugs can be mixed with white petrolatum without incompatibility, so white petrolatum is widely used as an ointment base and a cosmetic vehicle. Moreover, white petrolatum is often applied to the skin upon burning, inflammation and injury because it can prevent contact with air and the transpiration of moisture. White petrolatum is made by purification after a compound of hydrocarbons obtained from oil is bleached. Natural petrolatum consists mainly of isoparaffins (branched-chain paraffins) and alicyclic hydrocarbons (cycloparaffins or naphthenes). It also contains saturated n-paraffins and small amounts of unsaturated compounds such as olefins and aromatic hydrocarbons (Dooms-Goossens and Degreef 1983). From our previous investigation (Ogita et al. 2007), it became clear that white petrolatum manufactured in the United States is repackaged into smaller sizes and sold as Japanese Pharmacopoeia (JP) grade in Japan. There are six main brands of white petrolatum (JP) distributed commercially in Japan, namely, Perfecta, White 1S, Ultima, Snow, Snow V and Regent (Propeto). Perfecta and White 1S are manufactured by Sonneborn Co. and Ultima, Snow, Snow V and Regent are manufactured by Penreco Co.

White petrolatum is often used as an ointment base in medical institutions. The dilution or mixing of corticosteroid ointments is a common practice in Japan because of the expected improvement of compliance and reduction in the adverse effects of the corticosteroid (Kizu et al. 2004; Ohtani et al. 2002a,b). However, the preparative procedure and the choice of materials for hospital preparations have been empirically determined, even if the preparation has been conducted by pharmacists (Kizu et al. 2004). Therefore, the selection of white petrolatums might vary among medical institutions.

In this study, we tried to characterize the six brands of white petrolatum (JP) and Sun white marketed as cosmetics by measuring physical properties and drug-releasing characteristics to provide useful information that could facilitate choosing the appropriate white petrolatums for hospital preparations.

2. Investigations, results and discussion

2.1. Physical properties of white petrolatums

Figures 1 and 2 show the result of the penetrating stress and the shear stress in white petrolatums. Ultima exhibited the highest value and Regent exhibited the lowest value for both the penetrating stress and the shear stress. Regent exhibited approximately one-quarter of the value of penetrating stress and approximately one-half of the value of shear stress compared with those of Ultima. Fig. 3 shows the yield points calculated from the diameter of sample-time plots in the spread-meter test. The lowest value was also exhibited by Regent. The yield point of Regent was 450 dyne/cm^2 and this result corresponded to that in the report of Fukami et al. (2006). Regent exhibited approximately one-third of the value of yield point compared with that of Ultima. Regent is used for not only dermatological treatment but also ophthalmic treatment and classified as a comparatively soft ointment base from the determined yield point (Ishizaki et al. 1984; Yasuno et al. 1996). In this study, it was confirmed

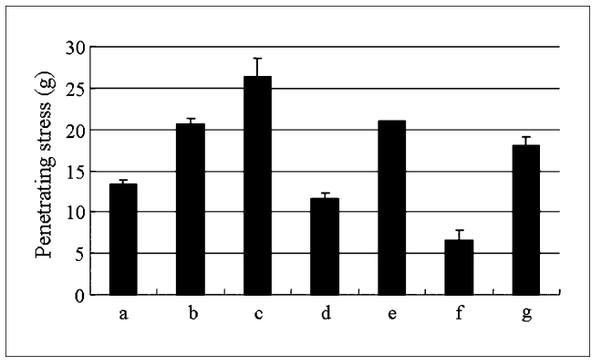


Fig. 1: Penetrating stress of white petrolatums a: Perfecta, b: White 1S, c: Ultima, d: Snow, e: Snow V, f: Regent, g: Sun white. Each value represents the mean ± S.D. (n = 3)

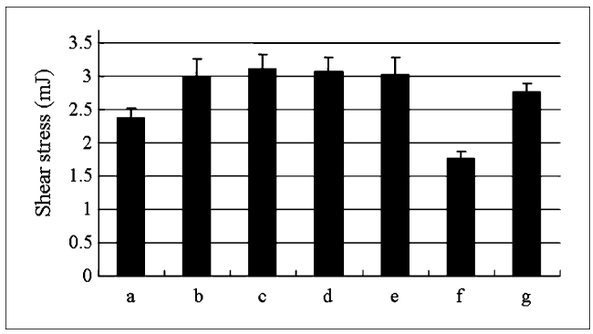


Fig. 2: Shear stress of white petrolatums a: Perfecta, b: White 1S, c: Ultima, d: Snow, e: Snow V, f: Regent, g: Sun white. Each value represents the mean ± S.D. (n = 3)

that Regent was the softest and most spreadable ointment base among the tested white petrolatums. Although Sun white was the only cosmetic among the tested white petrolatums, its physical properties were similar to those of Perfecta or White 1S and there were no distinct properties. The correlation between physical properties is shown in Table 1. A rather strong correlation was observed between physical properties. The yield point suggests consistency among the ointments because a strong correlation was observed between the penetrating stress and the yield point. From the results, the physical properties of white petrolatums were shown to vary, and it is suggested that the usability in terms of application to the skin differs among the white petrolatums.

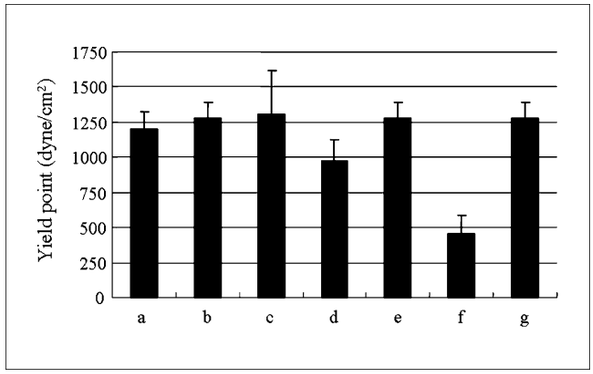


Fig. 3: Yield point of white petrolatums. a: Perfecta, b: White 1S, c: Ultima, d: Snow, e: Snow V, f: Regent, g: Sun white. Each value represents the mean ± S.D. (n = 3)

Table 1: Determination coefficients (R^2) on simple regression analysis for physical properties of white petrolatums

	X1	X2	X3
X1	1.0000	0.5979	0.7031
X2		1.0000	0.6191
X3			1.0000

X1: Penetrating stress (g)
X2: Shear stress (mJ)
X3: Yield point (dyne/cm^2)

2.2. Release properties

The cumulative amount released-time profiles after the application of FITC ointments are shown in Fig. 4. Regent showed higher values than the other white petrolatums. Table 2 shows release parameters of FITC from ointments. The amount of FITC released from Regent ointment for 1 h was significantly higher than those with the other white petrolatums and the value for Regent was approximately six times higher than that for White 1S. Release rate was calculated from the slope of the linear portion of cumulative amount released-time$^{1/2}$ plot for a zero-order model. The highest release rate was also observed for Regent. The level of FITC release for 1 h might depend on FITC release from the surface of ointments. Hence, the level of FITC released for 1 h should depend on the distribution of FITC from ointment to the receiver solution. The release rate should depend on FITC release from a rather deep portion of ointments. The cumulative amount released-time profiles after the application of TCH ointments are shown in Fig. 5. Regent showed higher values than other white petrolatums. Table 2 shows release parameters of TCH from ointments. TCH released from Regent ointment for 1 h was significantly higher than those from other white petrolatums. The highest release rate was observed for White 1S. Fig. 6 shows the correlation between drug released for 1 h and the release rate. Since a strong correlation was observed, the amount released from both the surface and deep portions of ointments might depend on the distribution of drugs between ointment and the receiver solution. The correlations between physical properties and the release parameters are shown in Table 3. Although strong correlations were observed for FITC ointment, they were not observed for TCH ointment. Hence, it was considered that physical properties were not major factors

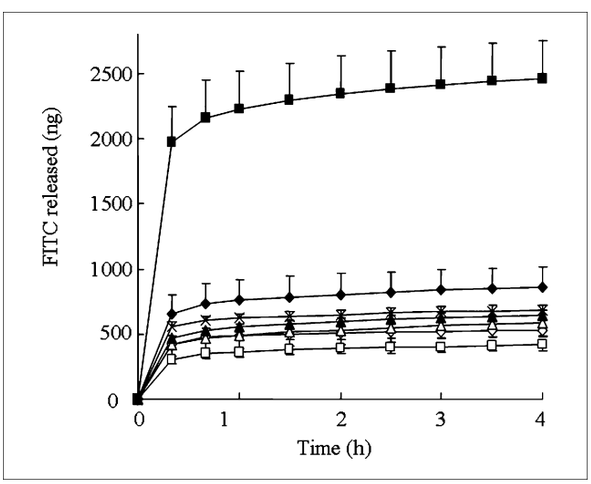


Fig. 4: Release profiles of FITC from 0.1% (w/w) FITC ointments. ◊ Perfecta. □ White 1S. △ Ultima. × Snow. ♦ Snow V. ■ Regent. ▲ Sun white. Each point represents the mean ± S.E. (n = 3)

Table 2: Release parameters of FITC and TCH from ointments

	FITC		TCH	
White petrolatum	FITC released for 1 h* (ng)	Release rate (ng/min$^{1/2}$)	TCH released for 1 h* (μg)	Release rate (μg/min$^{1/2}$)
Perfecta	488.4 ± 75.8**	7.97	28.4 ± 2.2**	0.97
White 1S	364.0 ± 69.7**	8.77	43.7 ± 5.3***	1.63
Ultima	491.9 ± 176.2**	14.31	31.3 ± 9.8**	0.80
Snow	620.2 ± 60.6**	10.21	27.0 ± 4.4**	0.66
Snow V	759.2 ± 275.0**	17.45	26.8 ± 4.2**	1.06
Regent	2228.1 ± 502.6	40.11	51.4 ± 1.9	1.60
Sun white	551.5 ± 43.5**	15.02	24.8 ± 3.3**	1.02

*: Each value represents the mean ± S.D. (n = 3)
**: $p < 0.005$ *versus* Regent
***: $p < 0.005$ *versus* Snow, Snow V and Sun white

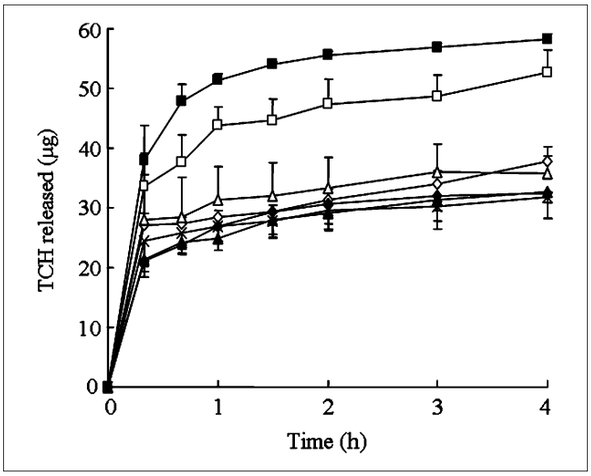


Fig. 5: Release profiles of TCH from 3% (w/w) TCH ointments. ◊ Perfecta. □ White 1S. △ Ultima. × Snow. ♦ Snow V. ■ Regent. ▲ Sun white. Each point represents the mean ± S.E. (n = 3)

in determining the release properties of drug models from white petrolatum ointments. Among the white petrolatums, with the exception of Regent, a relatively high value of FITC release for 1 h was observed for Snow V, and a relatively low value of FITC release for 1 h was observed for White 1S. On the other hand, a relatively high value of TCH release for 1 h was observed for White 1S, and a relatively low value of TCH release for 1 h was observed for Snow V. The partition coefficient (P) is an important parameter determining percutaneous absorption (Lien et al. 1971; Czerwinski et al. 2006; Nicoli et al. 2008). Furthermore, the P value of drug models has a major role in the distribution from ointment to receiver solution. Since the P values of FITC and TCH were 0.96 and −1.11, respectively, FITC is a relatively lipophilic material and TCH is a relatively hydrophilic material. Hence, FITC with its lipophilic character should have affinity for White 1S and TCH with its hydrophilic character should have affinity for Snow V, and thus the release parameters are low for these ointments. From the results, Regent shows the highest drug release. Among the white petrolatums, with the exception of Regent, release should depend on the distribution of drugs between white petrolatum and the receiver solution.

Table 3: Determination coefficients (R^2) on simple regression analysis for characteristics of white petrolatums

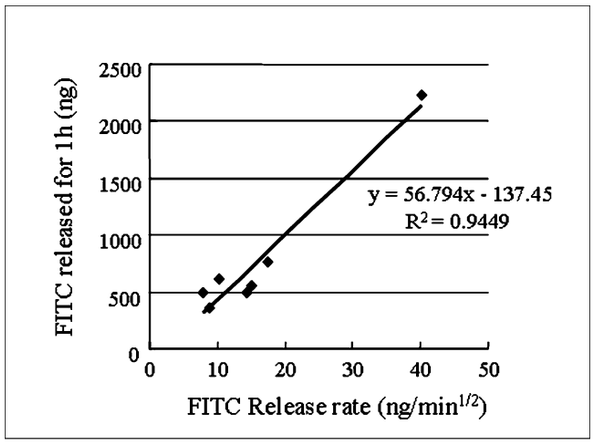
	Y1	Y2	Y3	Y4
X1	0.8668	0.699	0.4478	0.152

X1: Yield point (dyne/cm^2)
Y1: FITC released for 1 h (ng)
Y2: FITC release rate (ng/min$^{1/2}$)
Y3: TCH released for 1 h (μg)
Y4: TCH release rate (μg/min$^{1/2}$)

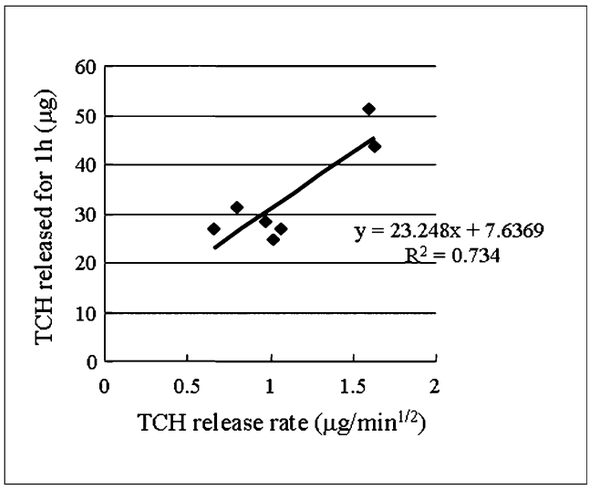
3. Experimental

3.1. Materials

Perfecta (Kozakai Pharmaceutical Co., Ltd., Tokyo, Japan), White 1S (Tsukishima Pharmaceutical Co., Ltd., Tokyo, Japan), Ultima (Kozakai



(A)



(B)

Fig. 6: Correlations between release parameters of FITC ointment (A) and TCH ointment (B)

Pharmaceutical Co., Ltd., Tokyo, Japan), Snow (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan), Snow V (Sioe Pharmaceutical Co., Ltd., Osaka, Japan) and Regent (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) were used as white petrolatums (JP). Sun white marketed as a cosmetic was purchased from Nikko Rica Corporation (Tokyo, Japan). Fluorescein isothiocyanate (FITC) was purchased from Sigma-Aldrich Co. (Tokyo, Japan). Tetracycline hydrochloride (TCH) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemicals were obtained commercially as the purest grade available.

3.2. Measurement of physical properties

Penetrating stress, shear stress and spreading properties were measured as physical properties of white petrolatums. Penetrating stress was measured using a FUDOH rheometer (RT-3005D, Rheotech Co., Ltd., Tokyo, Japan) and an electronic recorder (R-61AC, Rikadenki Co., Ltd., Tokyo, Japan). An attached adaptor (No. 7) was installed in the FUDOH rheometer, and the penetrating stress when the adaptor was penetrated into white petrolatum at a speed of 30 cm/min was measured. An attached adaptor (No. 36) was used for the measurement of shear stress. White petrolatum was applied to the adaptor (No. 36) at a thickness of 2 mm, and a flat plate (2.6 g, 2.5 cm × 2.5 cm) was placed on to the white petrolatum. The stress when pulling the flat plate along the surface of the ointment at a speed of 6 cm/min was measured with a FUDOH rheometer. The shear stress was calculated using the following equation:

$$\text{Shear stress (mJ)} = \text{stress(g)} \times \text{movement distance(mm)}. \quad (1)$$

Spreading was measured using a spread-meter (Imoto Machinery Co., Ltd., Kyoto, Japan) (Fukami et al. 2006). White petrolatum (0.5 cm^3) was applied to the spread-meter, and the diameter of samples (D) was measured by visual observation for 210 s. The diameter at 210 s (D_∞, cm) was used to calculate the yield point (S_0, dyne/cm^2). The yield point (S_0) was calculated using the equation of Ichikawa (Ichikawa 1977):

$$S_0(\text{dyne/cm}^2) = 48\,PVG/\pi^2\,{D_\infty}^5, \quad (2)$$

where G is acceleration due to gravity (980 cm/s^2), P is weight of a glass plate (g) and V is volume of samples (cm^3).

3.3. Release test

3.3.1. Preparation of ointment

FITC and TCH were used for *in vitro* release test as drug models. FITC or TCH was ground using a pestle in a mortar with a small amount of ethanol. After the ethanol was evaporated, white petrolatum was added and mixed with the drug models. For the release test, 0.1% (w/w) FITC ointment and 3% (w/w) TCH ointment were prepared.

3.3.2. In vitro release test

In vitro release test was performed using flow-through Franz diffusion cells (Funke et al. 2002). A membrane filter (polycarbonate, pore diameter: 0.8 μm) was mounted on the flow-through Franz diffusion cells. The exposed area was 0.785 cm^2 and the test ointments (0.3 g) were applied onto the membrane filter. Phosphate buffer (pH 7.4) was used as a receiver solution, and magnetically stirred and maintained at 37 ± 1 °C. The receiver solution was pumped through the diffusion cell by a Micro tube pump MP-3 (Tokyo Rikakikai, Tokyo) at a flow rate of approximately 1.5 mL/min for 0.1% (w/w) FITC ointment, and the spilled solution was collected in a glass flask. For 3% (w/w) TCH ointment, receiver solution of approximately 2 mL was pumped at each sampling point and the spilled solution was collected in a glass flask. The concentration of the drug models in the collected solution was determined by spectrofluorometry. The detection wavelength was 495 nm for excitation and 520 nm for emission for FITC, and 390 nm for excitation and 520 nm for emission for TCH.

3.4. Determination of partition coefficient

The partition coefficients of FITC and TCH were determined using n-octanol and phosphate buffer (pH 7.4). FITC and TCH were dissolved in phosphate buffer (10 ng/mL for FITC, 50 μg/mL for TCH) and allowed to partition into equal volumes of n-octanol. The system was equilibrated in a shaker bath maintained at 37 °C for 6 h. After 6 h, the aqueous phase was separated and the concentration of the drug models in the aqueous phase was determined by spectrofluorometry. The detection wavelengths were the same as those for the release test. The partition coefficient (P) was calculated using the following equation:

$$\text{P} = \log\left(\text{C}_{\text{initial}} - \text{C}_{\text{aqueous}}\right)/\text{C}_{\text{aqueous}}, \quad (3)$$

where $C_{initial}$ is the initial concentration of the drug models in the aqueous phase and $C_{aqueous}$ is the concentration of the drug models in the aqueous phase after equilibration.

3.5. Statistical evaluation

Statistical analysis was performed using ANOVA with post hoc Bonferroni-Dunn correction. The level of significance was set as $p < 0.005$.

Considerations of usability and the P value of a principal agent are needed when choosing an appropriate white petrolatum for hospital preparations.

References

Czerwinski SE, Skvorak JP, Maxwell DM, Lenz DE, Baskin SI (2006) Effect of octanol:water partition coefficients of organophosphorus compounds on biodistribution and percutaneous toxicity. J Biochem Mol Toxicol 20: 241–246.

Dooms-Goossens A, Degreef H (1983) Contact allergy to petrolatums (I). Sensitizing capacity of different brands of yellow and white petrolatums. Contact Dermatitis 9: 175–185.

Fukami T, Yamamoto Y, Nakamura Y, Kamano M, Umeda Y, Makimura M, Furuishi T, Suzuki T, Tomono K (2006) Quality testing of steroidal ointment mixed with white petrolatum: rheological properties and stability testing. Jpn J Pharm Health Care Sci 32: 964–969.

Funke AP, Gunther C, Muller RH, Lipp R (2002) *In-vitro* release and transdermal fluxes of a highly lipophilic drug and of enhancers from matrix TDS. J Control Release 82: 63–70.

Ichikawa I (1977) Easy sciences for paper, ink, print. Insatsu Choyokai Foundation, Tokyo, p. 133–135.

Ishizaki S, Fujimaru T, Takano M (1984) Pharmaceutical evaluation on spreading property of marketed corticosteroid ointment and cream. JJSHP 20: 955–958.

Kizu J, Ichihara W, Tomonaga E, Abe J, Watanabe T, Inoue T, Hori S (2004) Survey of mixing commercially available corticosteroid ointments with other ointments and the anti-inflammatory activity of the admixtures. Yakugaku Zasshi 124: 93–97.

Lien E, Koda RT, Tong GL (1971) Physicochemical properties, bioavailability of drugs: buccal and percutaneous absorption. Drug Intell Clin Pharm 5: 38–41.

Nicoli S, Zani F, Bilzi S, Bettini R, Santi P (2008) Association of nicotinamide with parabens: effect on solubility, partition and transdermal permeation. Eur J Pharm Biopharm 69: 613–621.

Ogita Y, Takahashi Y, Honda T, Kikkawa Y, Machida Y, Sudo H (2007) Comparison of quality characteristics of white petrolatums. Jpn J Pharm Health Care Sci 33: 613–618.

Ohtani M, Yamada N, Takayama K, Kotaki H, Etoh T, Kariya S, Uchino K, Iga T (2002a) Effect of admixture of commercially available corticosteroid ointments and/or creams on vasoconstrictor activity. Yakugaku Zasshi 122: 107–112.

Ohtani M, Kotaki H, Kariya S, Uchino K, Iga T (2002b) Evaluation of the permeability of corticosteroid in hairless mouse and hairless micropig skin from admixture of commercially available corticosteroid ointments and/or creams. Yakugaku Zasshi 122: 589–594.

Yasuno N, Tsuchiya M, Kizu J, Uzu S, Hasegawa Y, Ono H, Okuda O, Tejima Y (1996) Preparation and clinical application of 2% ethenzamide oral ointment. Jpn J Hosp Pharm 22: 556–563.