# Novel silicones for transdermal therapeutic systems: 1. Synthesis of 1-methyl-4-pyridinio-terminated polydimethylsiloxane and evaluation as a transdermal penetration enhancer

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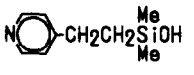
α-(2-(4-Pyridyl)ethyl)-polydimethylsiloxane (Py-PDMS) was prepared according to the anionic ring opening polymerization of hexamethylcyclotrisiloxane ($D_3$) initiated with sodium 2-(4-pyridyl)ethyl-dimethylsilanolate, which were derived from the reaction of 2-(4-pyridyl)ethyl-dimethylsilanol with sodium hydride. The average degree of polymerization of Py-PDMS was controlled in the range between 3 and 34 by changing the ratio of $D_3$ and the initiator. Furthermore, the preparation of α-(2-(1-methyl-4-pyridinio)ethyl)-polydimethylsiloxane (MePy-PDMS) was carried out by the reaction of Py-PDMS with methyl iodide. In order to evaluate the activity of MePy-PDMS as a transdermal penetration enhancer, the permeability of indomethacin through rabbit abdominal skin with and without MePy-PDMS was measured by *in vitro* experiment. MePy-PDMS showed effective enhancing activity for drug penetration through the skin. It was also revealed that the enhancing activity was due to an increase of the partition coefficient of the drug into the stratum corneum, from the determination of kinetic parameters in the drug permeation.

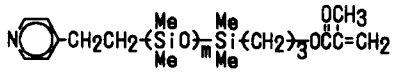
**(Keywords: polydimethylsiloxane; transdermal penetration; indomethacin)**

## INTRODUCTION

In a previous paper[1] we reported the preparation of 2-(4-pyridyl)ethyldimethylsilanol (**1**) and α-(2-(4-pyridyl)ethyl)-ω-(3-methacryloxypropyl)-polydimethylsiloxane (**2**), which was obtained by the non-equilibrium polymerization of hexamethylcyclotrisiloxane ($D_3$) by using **1** as the initiator.



**1**



**2**

Also, **2** acted as a so-called 'macromonomer' and was copolymerized with vinyl monomers to produce polydimethylsiloxane (PDMS) grafted copolymers containing a pyridyl group at the side chain ends. PDMS has been known to possess unique properties, e.g. very high chain flexibility, very low glass transition temperature, hydrophobicity, thermal stability and high gas permeability. In addition, owing to its good biocompatibility and physiological inertness[2,3], PDMS can be chemically or physically modified for practical applications, such as implants[4] or pressure sensitive adhesives[5,6] in the biomedical or pharmaceutical fields. The pyridyl group is one of the polar substituents and also possesses some functional properties, which can be quaternized with alkyl halide or make a complex with a metal. Therefore, such a combination of a functional pyridyl group and a PDMS chain can be expected to bring about unique functional properties.

We have also investigated a novel type of polymeric transdermal penetration enhancer which itself permeated the skin only with difficulty[7,8]. The polymeric enhancer was prepared by radical polymerization of a cationic surfactant monomer, *p*-vinylbenzyldimethylalkylammonium chloride containing a long alkyl group. Furthermore, it was revealed that both the cationic surfactant monomer and polymer showed the enhancing activity of 5-fluorouracil (5-FU) penetration through the skin by the interaction with the lipid and protein in the stratum corneum, but the polymer scarcely penetrated any deeper than the stratum corneum[7].

From these points of view, pyridinio-terminated PDMS, which can be derived from pyridyl-terminated PDMS reacted with an alkyl halide, is expected to act as a cationic surfactant polymer and one of the polymeric transdermal penetration enhancers. In this paper, we describe a study for the preparation of pyridinio-terminated PDMS and an evaluation for the enhancing activity of drug penetration through the skin by means of *in vitro* experiments.

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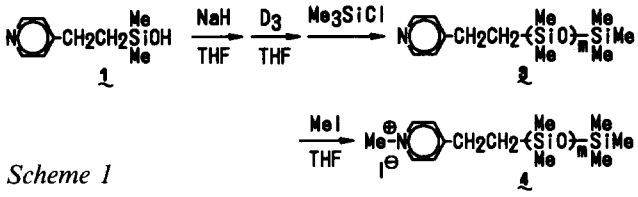
## EXPERIMENTAL

### *Materials*

Hexamethylcyclotrisiloxane ($D_3$) and trimethylchlorosilane were purchased from Chisso Corporation and used without further purification. Tetrahydrofuran (THF) was twice distilled over calcium hydride and sodium, respectively, to remove the small amount of water. 2-(4-Pyridyl)ethyldimethylsilanol, **1**, was synthesized via metallation of 4-methylpyridine with phenyllithium followed by treating with chloromethyldimethylsilane and the conversion of the hydrosilyl group into a hydroxysilyl group. The detailed procedure was described in our previous paper[1]. Indomethacin (IND) was obtained from Sigma and used as received.

### *Preparation of α-(2-(4-pyridyl)ethyl)-polydimethylsiloxane (Py-PDMS, 3)*

Py-PDMS was prepared by the non-equilibrium polymerization of $D_3$ initiated with sodium 2-(4-pyridyl)-ethyldimethylsilanolate followed by terminating the reaction with trimethylchlorosilane. The synthesis reaction is shown in *Scheme 1*.



*Scheme 1*

A typical procedure is as follows. Sodium hydride (60% dispersion in mineral oil, 0.433 g, 10.8 mmol) was washed with hexane, and suspended in 20 ml of dry THF under an argon atmosphere. To this mixture a solution containing **1** (1.10 g, 6.07 mmol) dissolved in 10 ml of dry THF was added at r.t. After stirring for 2 h, $D_3$ (4.05 g, 18.2 mmol) dissolved in 20 ml of dry THF was added, and the solution was stirred for 12 h at r.t. Then, trimethylchlorosilane (1.54 ml, 12.2 mmol) was added to halt the anionic polymerization and block the polymer end with a trimethylsilyl group. The mixture was evaporated and filtered off to remove sodium chloride. The filtrate was purified by silica gel column chromatography to produce 3.80 g of Py-PDMS as a transparent viscous oil. The average degree of polymerization, $\bar{m}$, was determined by $^1$H n.m.r. spectroscopy to be about 9.5 (theory: 10.0). $\bar{m}$ could be controlled in the range 3 to 30 by adjusting the ratio of $D_3$ and **1** in the reaction (*Scheme 1*).

I.r. (KBr, cm$^{-1}$): 3100, 3050, 2980, 2950, 1600 (-Py), 1560, 1500, 1420, 1315, 1260 (Si–C), 1220, 1175, 1100–1000 (SiOSi), 840, 800. $^1$H n.m.r. $\delta$ ($CDCl_3$, ppm): 0.10 (s, 6$\bar{m}$H), 0.90 (m, 2H), 2.68 (m, 2H), 7.15 (dd, 2H), 8.48 (dd, 2H).

### *Preparation of α-(2-(1-methyl-4-pyridinio)ethyl)-polydimethylsiloxane (MePy-PDMS, 4)*

Py-PDMS thus obtained was reacted with an excess amount of methyl iodide to produce MePy-PDMS, as shown in *Scheme 1*. The following describes a typical procedure.

A solution of Py-PDMS ($\bar{m}$ = 9.5, 0.46 g) and methyl iodide (0.08 g) in 10 ml of dry THF was prepared under an argon atmosphere, and it was stirred at 50°C for 4 h. The reaction mixture was evaporated and heated at 60°C *in vacuo* for 2 h to remove the solvent and the excess methyl iodide. MePy-PDMS (0.45 g) was obtained as a brown viscous liquid. The average degree of polymerization, $\bar{m}$, was 9.5, which was unchanged as compared with $m$ of the starting Py-PDMS.

I.r. (KBr, cm$^{-1}$): 3080, 2990, 2950, 1740, 1650 (-Py), 1580, 1520, 1480, 1420, 1330, 1260 (Si–C), 1180, 1100–1000 (SiOSi), 840, 800. $^1$H n.m.r. $\delta$ ($CDCl_3$, ppm): 0.10 (s, 6$\bar{m}$H), 0.90 (m, 2H), 2.70 (m, 2H), 5.02 (m, 3H), 6.98 (dd, 2H), 7.65 (dd, 2H).

### *Characterizations*

$^1$H n.m.r. spectra were measured by using a Bruker AM-400 (400 MHz) FT-NMR spectrometer using $CDCl_3$ as the solvent, and the chemical shifts were obtained relative to tetramethylsilane. I.r. spectra were recorded on a Jasco A-202 diffraction grating i.r. spectrometer. The number-average and weight-average molecular weights ($\bar{M}_n$ and $\bar{M}_w$) were determined with a Tosoh HLC-802A gel permeation chromatograph, equipped with four columns of TSK gels G5000H$_6$, G4000H$_6$, G3000H$_6$ and G2000H$_6$. THF was used as the solvent, and standard polystyrenes were used for calibrating molecular weight.

### *Drug penetration through the skin*

The abdomen of a rabbit (Japanese White, male, 2.5–2.7 kg) was carefully shaved, under sodium pentobarbital anaesthesia. The blood was gradually withdrawn from the femoral artery and the rabbit was completely exsanguinated. The abdominal skin was excised and mounted between two half cells of a two-chamber diffusion cell, with a cross-section[7,8] of 0.95 cm$^2$. An ethanolic aqueous solution (50 wt%, 2 ml) of IND (2 w/v%, suspended) and the penetration enhancer (2 w/v%, completely dissolved) were poured into the donor compartment. A phosphate buffer solution (2 ml) adjusted to pH = 7.4 was poured into the receiver compartment. Then, the diffusion cell was immersed in a water bath maintained at 37°C. The solutions in both donor and receiver compartments were mechanically stirred. Portions (50 μl) of the solution were withdrawn from the receiver compartment at 2 h intervals up to 12 h.

High performance liquid chromatography (h.p.l.c.) (pump, CCPE; detector, UV-8 model 2; column, TSK gel ODS-80TM, Tosoh Corporation) was used to measure the amount of IND permeated. The mobile phase was a mixture of acetonitrile and 45 mM $KH_2PO_4$ aqueous solution adjusted to pH = 3.00 with phosphoric acid (6/4 by weight), of which the flow rate was 1.0 ml min$^{-1}$. The sample solution was diluted with the mobile phase and injected into the h.p.l.c. system. The amount of IND was determined by calculating the integrated area monitored at 240 nm.

### *Determination of solubility of IND*

IND was suspended in 50% EtOH aqueous solution containing the polymer (2% w/v), and the mixture was stirred for one day at 37°C. A part of this suspension was taken, and the concentration of soluble IND was measured by h.p.l.c. after the insoluble IND had been filtered off.

## RESULTS AND DISCUSSION

### *Preparation of Py-PDMS and MePy-PDMS*

In general, silanols react with a base, e.g. alkyllithium, to produce silanolate anions which act as the initiator of

**Table 1** Results of preparation of Py-PDMS (**3**) and MePy-PDMS (**4**)

| Sample no. | $D_3/1^a$ (mole ratio) | $\bar{m}$ of $3^b$ Theory | Obs. | $M_n{}^c$ of **4** | $M_w/M_n{}^c$ of **4** |
|---|---|---|---|---|---|
| P-1 | 1.0 | 4.0 | 3.2 | –[d] | –[d] |
| P-2 | 1.5 | 5.5 | 5.1 | 460 | 1.14 |
| P-3 | 3.0 | 10.0 | 9.5 | 1000 | 1.15 |
| P-4 | 5.0 | 16.0 | 15.0 | 1400 | 1.18 |
| P-5 | 7.0 | 21.0 | 19.8 | 2200 | 1.25 |
| P-6 | 10.0 | 31.0 | 34.0 | 3000 | 1.07 |

[a]Molar ratio of hexamethylcyclotrisiloxane ($D_3$) and 2-(4-pyridyl)ether-dimethylsilanol (**1**) in the polymerization
[b]The theoretical value of the average degree of polymerization $\bar{m}$ was calculated from the equation, $\bar{m} = 3[D_3]/[1] + 1$, and the observed value of $\bar{m}$ was determined on the basis of the $^1$H n.m.r. spectrum
[c]Determined by g.p.c.
[d]Insoluble in THF used as g.p.c. eluent

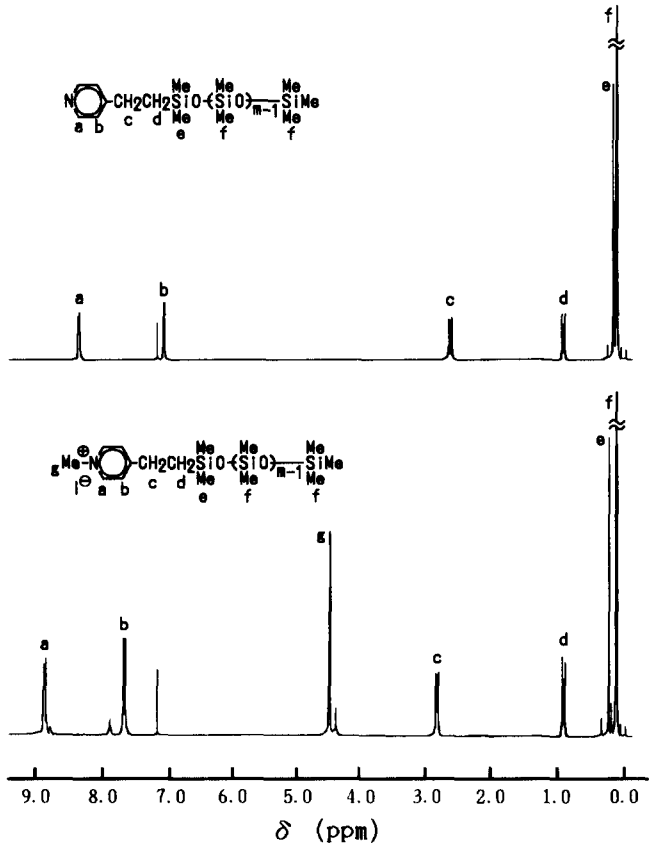



**Figure 1** 400 MHz $^1$H n.m.r. spectra of Py-PDMS and MePy-PDMS

non-equilibrium polymerization of siloxane using $D_3$. However, when **1** reacted with n-butyllithium at 0°C, the product did not initiate the polymerization. This may be due to a side reaction between the base and the pyridine ring of **1**. Therefore, in this case, sodium hydride (NaH) was used as the base to produce sodium 2-(4-pyridyl)-ethyldimethylsilanolate[1]. The obtained silanolate anion initiated the ring-opening polymerization of $D_3$ to produce Py-PDMS, **3**, followed by treating with trimethylchlorosilane. Then, MePy-PDMS, **4**, was prepared with good yield by the reaction of **3** with methyl iodide as described in the experimental section.

The results for the preparation of **3** and **4** are summarized in *Table 1*. The average degree of polymerization, $\bar{m}$, of these PDMSs could be easily controlled by changing the ratio of $D_3$ to **1**. Furthermore, the observed $\bar{m}$ of **3** agreed with the theoretical value, and the polydispersity ($\bar{M}_w/\bar{M}_n$) of **4** was in the range of 1.07–1.25. *Figure 1* shows typical $^1$H n.m.r. spectra of **3** and **4**. The proton signals were assigned as shown in the figure. Proton signals on the pyridyl group of **3** (a and b) shifted to the lower magnetic field by reaction with methyl iodide. The values of $\bar{m}$ of **3** and **4** were determined from the ratio of the peak intensity of the methyl protons in the PDMS unit (f, 0.10 ppm) and that of the methylene protons next to the pyridyl group (c, 2.68–2.70 ppm).

*Skin penetration experiment*

*Figure 2* shows the permeation profiles of IND through the skin with MePy-PDMSs as penetration enhancers, as compared with that without enhancer. Only MePy-PDMS of $\bar{m} = 34$ (P-6) was not completely dissolved in the donor solution; therefore, this penetration experiment could not be carried out for P-6. Other MePy-PDMSs showed the effective enhancing activity of the drug penetration through the skin.

The skin consists structurally of three layers, i.e. epidermis, dermis and subcutaneous tissue. The stratum corneum exists at the outer layer of the epidermis and functions as a barrier to environmental insult[9]. In order to clarify the enhancing mechanism of MePy-PDMS, the kinetic parameters in the IND permeation were determined. In the drug penetration through the skin, the permeation rate $dQ/dt$ at the steady state can be

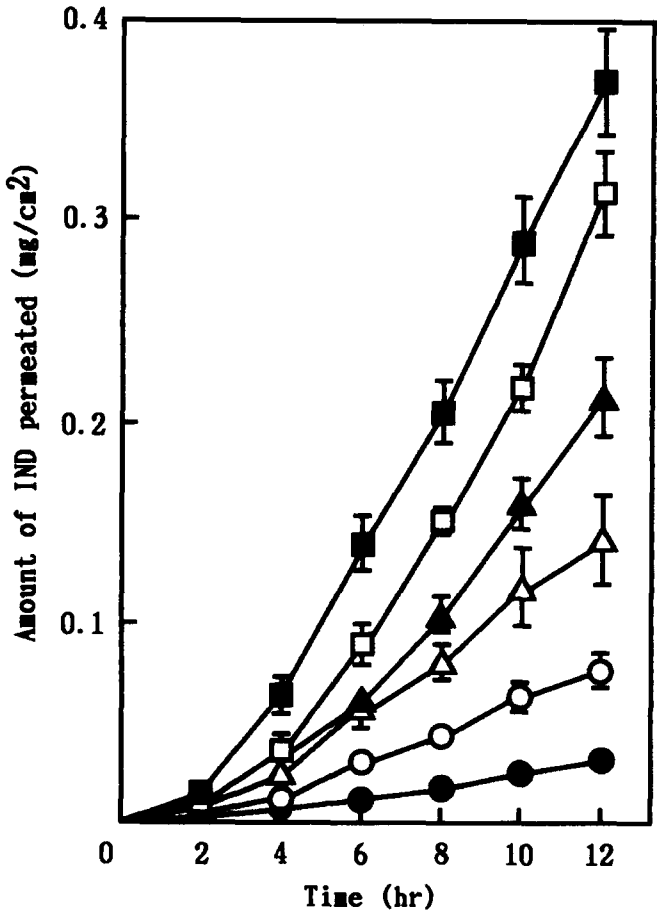



**Figure 2** Permeation profiles of IND through rabbit abdominal skin using MePy-PDMSs as penetration enhancers. ●; control (without enhancer); ○, P-1; △, P-2; ▲, P-3; □, P-4; ■, P-5

**Table 2** Effect of addition of the polymers on IND permeation through the skin and the solubility of IND in the donor solution

| Sample no. | Permeation coefficient, $P^a$ ($\times 10^{-6}$ cm s$^{-1}$) | Lag time, $\tau^a$ (h) | Diffusion coefficient, $D^b$ ($\times 10^{-11}$ cm$^2$ s$^{-1}$) | Partition coefficient, $K^c$ | Solubility, $C_v{}^d$ (mg ml$^{-1}$) |
|---|---|---|---|---|---|
| P-1 | 0.69 | 1.80 | 2.57 | 27.0 | 3.36 |
| P-2 | 1.02 | 2.10 | 2.20 | 46.3 | 3.89 |
| P-3 | 2.09 | 3.75 | 1.23 | 169.3 | 3.41 |
| P-4 | 2.88 | 3.24 | 1.42 | 202.3 | 3.44 |
| P-5 | 3.55 | 2.48 | 1.87 | 190.2 | 3.01 |
| Control[e] | 0.22 | 2.30 | 2.01 | 11.0 | 4.06 |

[a]Calculated graphically from *Figure 2*
[b]Calculated by lag time method
[c]Determined by the value of $P$ and $D$
[d]In 50% ethanolic aqueous solution containing 2% of penetration enhancer
[e]Without enhancer

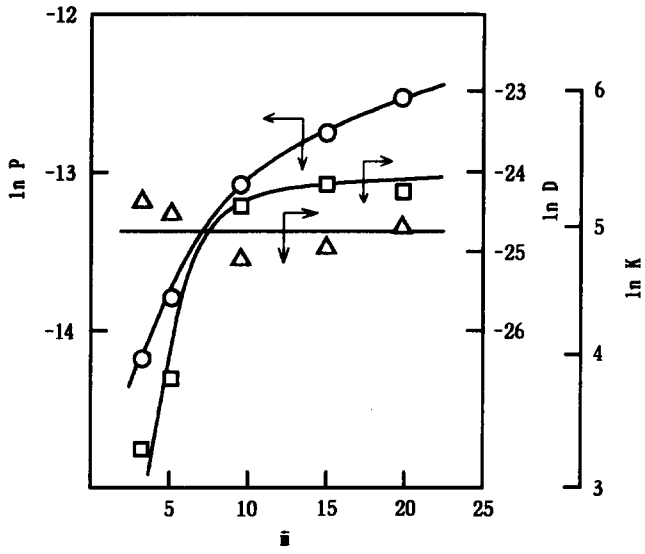



**Figure 3** Effect of the average degree of polymerization, $\bar{m}$, of MePy-PDMS on the permeation coefficient, $P$ (○), the diffusion coefficient, $D$ (△), and the partition coefficient, $K$ (□) in the penetration of IND through the skin

represented by Fick's law[10]:

$$\frac{dQ}{dt} = \frac{KC_vDA}{L} \tag{1}$$

where $K$ is a partition coefficient between the vehicle and the skin barrier, $C_v$ is the concentration of the drug in the donor phase, $D$ is a diffusion coefficient in the barrier, $A$ is the effective area of the drug permeation and $L$ is the thickness of the barrier. Equation (1) contracts on the sink condition, where $C_v$ is constant in the course of the diffusion experiment and the concentration of drug in the receiver phase is zero at any time. In equation (1), $P$ ($=KD/L$) is the so-called permeation coefficient. The values of $P$ for IND with and without penetration enhancer were calculated on the basis of the data in *Figure 2* and listed in *Table 2*. In this diffusion experiment, IND was saturated in the donor phase, and therefore, $C_v$ for IND remained constant. In fact, the values of $C_v$ for IND measured in every donor solution were almost equal, as shown in *Table 2*. Thus, the permeability coefficients clearly established the efficiency of MePy-PDMS as a penetration enhancer.

Furthermore, taking the time to reach the steady state into consideration, the amount of the drug permeated can be represented by equation (2)[11]:

$$Q = \frac{KC_vDA}{L}\left(t - \frac{L^2}{6D}\right) - \frac{2KC_vLA}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2} \times \exp\left(-\frac{Dn^2\pi^2t}{L^2}\right) \tag{2}$$

where the symbols are the same as in equation (1). In equation (2), the lag time $\tau$ ($=L^2/6D$) is estimated by extrapolation of the $Q$ *versus* $t$ plot to the time axis. The experimental values of $\tau$ were determined from *Figure 2* and $D$ values were calculated from $\tau$ and $P$ values, as indicated in *Table 2*. For the calculations of $D$, the thickness of the barrier was set at 10 $\mu$m, the average thickness of the stratum corneum. In addition, the partition coefficient $K$ ($=PL/D$) of each case was calculated from $D$ and $P$ and also listed in *Table 2*.

As indicated in *Figure 2* and *Table 2*, the enhancing activity of the series of MePy-PDMS depended on $\bar{m}$. This tendency is revealed more clearly in *Figure 3*, which represents the effect of $\bar{m}$ on $P$, $D$ and $K$ of IND permeated through the skin. The permeation coefficients and the partition coefficients proportionally increased with increases of $\bar{m}$ (up to 20), i.e. molecular weight. On the other hand, the diffusion coefficients remained constant over the range $1-3 \times 10^{-11}$ cm$^2$ s$^{-1}$. Therefore, the diffusivity of IND in the skin barrier remained unchanged in both cases with and without the penetration enhancers. However, the values of $K$ using P-4 and P-5 as enhancer were about 20 times as much as that for the control. From these results, the enhancing activity of MePy-PDMS in the IND penetration through the skin was clearly due to the significant increase of $K$ for the drug into the stratum corneum.

In our previous study, we investigated the effect of the cationic surfactant polymer, benzalkonium chloride-type polymer, on 5-FU penetration through the skin[7]. In that case, the enhancing activity increased with decreasing molecular weight in the range between 3000 and 15 000, because the mobility of enhancer decreased with an increase in the molecular weight of the surfactant polymer. Furthermore, in our other papers[12,13], the novel pyrrolidone derivatives and three kinds of compounds containing a phosphoryl group were prepared and the effect of chemical structure of these compounds on the transdermal penetration of IND was investigated. According to these results, the penetration enhancing

effect closely correlated with the physicochemical property, namely, lipophilicity of the enhancers.

Consequently, the enhancing activity of MePy-PDMS would be due to its physicochemical nature, namely, both molecular weight and lipophilicity. Such a high enhancing activity of MePy-PDMS, P-4 or P-5, was found to be due to the function of the stratum corneum in causing an increase of the partition coefficient of IND. It was considered that the suitable balance of hydrophilic and hydrophobic groups, i.e. the pyridinium group and polysiloxane chain, played a more dominant role rather than the molecular weight.

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