Application of an Oily Gel Formed by Hydrogenated Soybean Phospholipids as a Percutaneous Absorption-Type Ointment Base[1)]

Takeshi HENMI, Makiko FUJII,* Keiko KIKUCHI, Naoko YAMANOBE, and Mitsuo MATSUMOTO

Showa College of Pharmaceutical Sciences, Machida, Tokyo 194, Japan.
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We investigated the possibility of developing an oily gel formed by hydrogenated soybean phospholipids (HSL) as a percutaneous absorption-type ointment base. Liquid paraffin (LP) was used as the oil, and indomethacin (IM), ketoprofen (KP), flurbiprofen (FP) and ibuprofen (IP) were used as model drugs. IM did not dissolve in LP, but solubilized when heated with HSL at a concentration of about 1% with 15% HSL at 95°C. IM gel was thus prepared as follows: IM and HSL were mixed, added into LP, capped tightly, heated in a water bath and cooled. The consistency of the gel increased with increasing IM concentration, indicating some kind of interaction between IM and HSL. The release of IM from the IM gel was faster than that from a preparation in which IM was mixed in gel at room temperature (Gel + IM). The release rate of IM from IM gel was proportional to IM concentrations up to 1%, but became constant above that. Permeation of IM through hairless rat abdominal skin from IM gel was higher than that from the Gel + IM. The permeation rate was proportional to IM concentrations in the range of 0.1 to 0.5% in 15% HSL gel. KP and FP also solubilized in gel when subjected to the same procedure as IM, and their release and permeation increased when they were formulated as gels. However, no evident improvement of permeation was observed in the case of IP, which had high LP solubility. It was suggested that HSL showed no enhancing effect, but solubilized IM, KP or FP, leading to high permeation from the gel. After 3 months' storage, the permeation rate did not change for 0.5% IM in 15% HSL gel, but decreased for 1% IM in 15% HSL gel. This indicates that in the case of 1% IM in 15% HSL gel, IM is in a supersaturated state immediately after preparation and then recrystallizes with time.

Keywords oily gel; indomethacin; hairless rat skin permeation; hydrogenated soybean phospholipid; liquid paraffin; nonsteroidal anti-inflammatory drug

In the development of a percutaneous absorption-type pharmaceutical ointment, the selection of vehicle composition is important, since properties of the vehicle lead to changes in solubility, diffusion and partition to skin of the drug and influence the permeability of a drug.[2-4)] Vehicles used in commercial percutaneous absorption-type preparations are of an aqueous base, composed of aqueous polymers and hydrophilic solvents such as ethanol or propylene glycol. However, it has been reported that these ingredients sometimes irritate the skin. On the other hand, oily bases such as white petrolatum or plastibase are not useful because they result in low solubility and low permeability of the drugs.[5,6)] Recently, several reports have demonstrated good permeation of drugs using lipophilic vehicles,[7-9)] but these have been few and far between.

We have reported that hydrogenated soybean phospholipids (HSL) changed hydrocarbon oils or higher fatty acid esters into a gel (oily gel).[10-12)] This oily gel has a relatively high flowing temperature, approximately 60 °C, and has appropriate consistency, which could be controlled by the HSL concentration in the gel.[10)] Moreover, the consistency and flowing temperature did not change during storage at room temperature. Furthermore, drugs such as salicylic acid, aminobenzoic acid or prednisolone, which are insoluble in liquid paraffin (LP), dissolved in the oily gel, and the release of prednisolone from an oily gel was faster than from a conventional oily base.[10,11)]

Thus, we examined the usefulness of an oily gel as a vehicle for percutaneous absorption dosage forms. Several oils can be utilized to make the gel, but LP was chosen because of its wide use as a raw material of the oil phase in pharmaceuticals. Nonsteroidal anti-inflammatory drugs which have often been used as percutaneous absorption-type pharmaceutical ointments and have been confirmed to undergo passive partition from an aqueous solution to the stratum without the use of an enhancer[13)] were used as model drugs.

Experimental

Materials HSL (Nikko Chemicals, Lecinol S-10) contained more than 80% phospholipids, about 25% phosphatidylcholine and the iodine value was under 10. LP was supplied by Nikko Chemicals Co., Ltd. (P-70). Indomethacin (IM), ketoprofen (KP) and ibuprofen (IP), which are of JP grade, and flurbiprofen (FP) were obtained from Nippon Bulk Yakuhin. Other reagents used were of analytical grade.

Preparation of Oily Gel IM gel: IM and HSL, whose water content was controlled to 0.7—0.9%, were added to LP in a flask, capped tightly, then heated at 95 °C in a water bath with stirring until a homogeneous solution was obtained. The solution was packed into metal ointment tubes and cooled to 20 °C in water for 30 min. Then they were maintained at 40 °C in an air incubator for 3 d, followed by storage at room temperature.[11)]

Gel + IM: IM was mixed at room temperature with an ointment spatula in HSL 15% oily gel which was previously prepared without IM.

Suspension: IM and HSL were added to LP in a flask and shaken in a water incubator at 37 °C.

Gels with the other drugs were prepared using the same procedures as above.

Physical Properties Solubility at 95 °C: A fixed amount of drug (0.1% intervals) was added in LP, with or without HSL, and heated at 95 °C. The drug concentration at which drug particles could not be detected by the naked eye was determined as its solubility at 95 °C.

Solubility at 37 °C: An excess amount of drug was suspended in LP and incubated at 37 °C overnight. After centrifugation, the supernatant was extracted by a pH 7.1 phosphate buffer solution (PBS). The resulting concentration in PBS was determined by high-performance liquid chromatography (HPLC), and its solubility in LP was calculated taking

into account the partition coefficient. Solubility in the gel at 37 °C was not determined, because the soluble and insoluble versions of the drug could not be separated in gel.

Infrared (IR) Spectra: IR spectra from 4000 to 400 cm^{-1} were obtained using the Fourier transform-infrared spectrophotometer (FT/IR 8000, Jasco). Samples were held between KBr plates (sample thickness: 0.1 mm). IM in chloroform and in LP were also measured as controls in liquid and crystalline states, respectively.

Consistency: Consistency was shown using load weights to spread 0.40 g of gel to a 0.50 mm thickness using a pressure tension meter (Tensipresser®, Taketomo Electric, Inc.).[10] The consistency of white petrolatum was about 1.5 kg by this method.

Release Studies Release of a drug from a gel was measured in a Franz-type diffusion cell apparatus. The effective area available for release was 1.1 cm^2. The receptor compartment was filled with 15 ml of pH 7.1 isotonic PBS, kept at 37 °C, and mixed with a star-head magnet at 600 rpm. Approximately 0.1 g of oily gel was spread on a membrane filter (cellulose nitrate, pore size 0.45 μm, Advantec Toyo), which was then mounted on the cell. At appropriate times, 200 μl samples were withdrawn from the receptor. The same volume of buffer solution from the same stock was added to the receptor compartment to keep the volume constant. All studies were done at least 3 times.

Permeation Studies Skin permeation was measured in the same cell apparatus as that for the release test. A piece of suitably sized abdominal skin from hairless male rats (5—6 weeks old, Saitama Laboratory Animals, Japan) was excised immediately before the skin permeation experiments. Approximately 0.1 g of oily gel was spread on the cornual layer side of the excised skin, and was mounted on the cell. In the case of suspension, a piece of skin was mounted on the cell and approximately 0.1 g of suspension was poured onto it. Each experiment was carried out for 10 h using the same procedure as that of the release test.

Analysis of Drug Concentration Drug concentrations were determined using HPLC. The analytical system consisted of a pump (LC 6A, Shimadzu), A UV detector (SPD 6A, Shimadzu) operated at 264 nm and an integrator (CPR 4A Shimadzu). The sample from the receptor was directly injected by filling it with either 10 or 30 μl loop injection volume. The column (150 mm × 4.6 mm i.d.) packed with Zorbax BP-ODS (7 μm particle size) was eluted at an ambient temperature with a mobile phase consisting of 0.1% phosphoric acid solution–methanol, (25 : 75) in the cases of IM, FP and IP, and (30 : 70) in the case of KP, at a flow rate of 1 ml/min.

Results and Discussion

Physical Properties Table I shows the solubilities of IM in various concentrations of HSL at 95 °C. IM is insoluble in LP, but soluble in LP with HSL by heating at 95 °C. IM solubility increased in proportion to the concentration of HSL. When this solution was cooled to 20 °C, a transparent yellow gel was obtained. The solubility at lower than 60 °C could not be determined because it changed into a gel in which soluble and insoluble IM could not be separated.

Table II shows the solubilities of drugs under various conditions. The solubilities at 37 °C in LP varied from 0.001% (IM) to 3.5% (IP). Solubilities of KP and FP also increased with the addition of HSL, but not to as great an extent.

Figure 1 shows the IR spectra of various preparations containing 1% IM. There were no differences observed between IM gel and the oily gel without IM, except for some IM peaks such as 1685 and 1320 cm^{-1}. IM in chloroform showed IM carboxyl peaks at 1685 and 1320 cm^{-1}, whereas IM in LP showed peaks at 1690 and 1306 cm^{-1}. The spectrum of IM gel is similar to that of IM in chloroform, while the spectrum of Gel+IM is similar to that of IM in LP. This indicates that IM exists in IM gel in the dissolved state but exists in Gel+IM in the crystalline state.

Other drugs showed no evident change, similar to the case of IM, because the peaks which represented changes in the solution and crystal overlapped with HSL or LP.

The effect of IM on the consistency of the gel is shown in Fig. 2. When the IM concentration has not reached

TABLE I. Effect of HSL on Solubilities of IM in LP

	Concentration of HSL in LP (w/w%)			
	0	10	15	20
Solubility at 95 °C	<0.05	1.2	1.8	2.7

TABLE II. Solubilities of Drugs in LP under Various Conditions

Drug	Solubility (w/w%)		
	in LP		in LP+15%HSL
	37 °C	95 °C	95 °C
IM	0.001	<0.05	1.8
KP	0.02	0.7	2.0
FP	0.15	1.2	3.0
IP	3.52	>10.0	>10.0

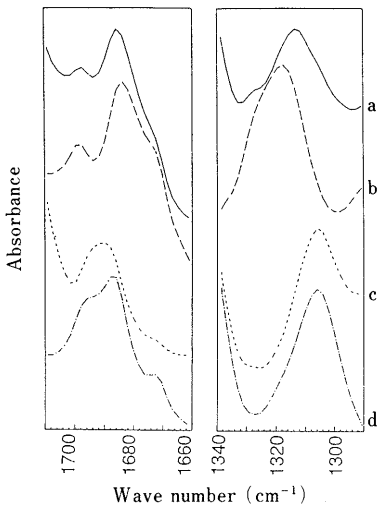

Fig. 1. IR Spectra of Various Preparations Containing 1% IM
a, IM gel (HSL 15%); b, chloroform; c, gel (HSL 15%)+IM; d, LP.

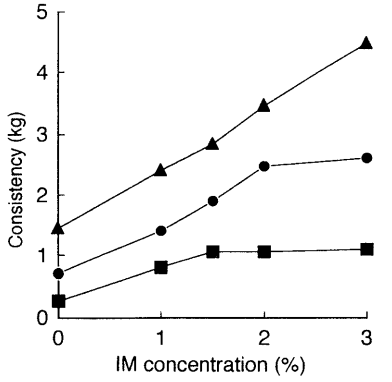

Fig. 2. Influence of IM Concentration on the Consistencies of Oily Gel
HSL concentrations in oily gels are 10% (■), 15% (●) and 20% (▲).

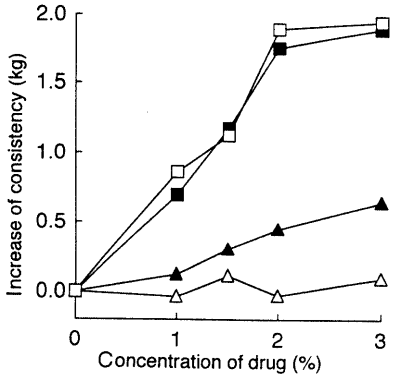

Fig. 3. Influence of Drug Concentration on the Consistencies of Gels Containing 15% HSL

■, IM; □, KP; ▲, FP; △, IP. The increase in consistency was calculated by differences between gels with and without the drug.

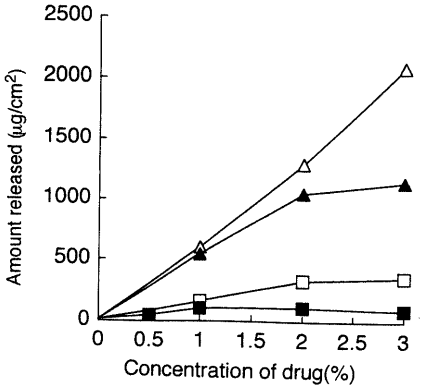

Fig. 5. Effect of Drug Concentration on Cumulative Amount of Drug Released within 6 h from Oily Gel Containing 15% HSL

■, IM; □, KP; ▲, FP; △, IP.

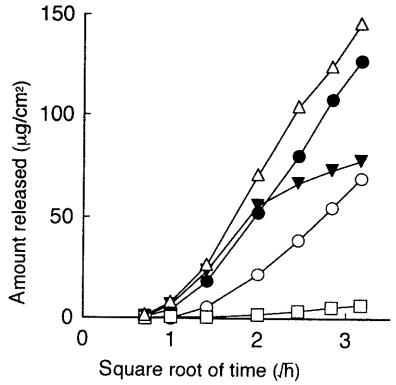

Fig. 4. Release Profiles of IM from IM Gels Containing 15% HSL

IM gel containing 2% IM (▼); 1.5% IM (△); 1%IM (●); 0.5%IM (○); Gel+1%IM (□).

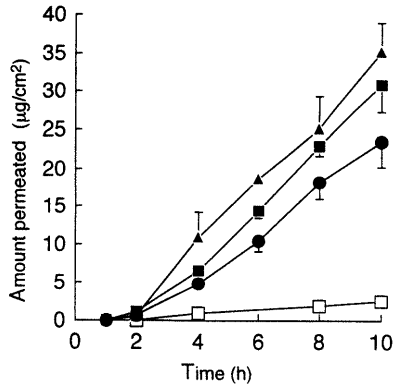

Fig. 6. Permeation Profiles of IM through Excised Hairless Rat Abdominal Skin from Various Preparations Containing 1% IM

IM gel containing HSL 15% (●); 20% (▲); 30% (■); Gel+IM (□). Each value represents the mean±S.D. ($n=3$—4).

saturation, the consistency of the gel in various concentrations of HSL increased in proportion to the concentration of IM, but above saturation, the consistency showed no additional increase. Figure 3 shows the effect of drug concentration on the consistency of 15% HSL gel. The effect of KP on the consistency is almost the same as that of IM, while FP showed a slight effect. IP, which dissolved more than 3.5% without HSL, had no effect on the consistency. On the other hand, the flowing temperature showed no change even with the addition of drugs; this temperature was approximately 60 °C.

We found that the solid dispersion of IM, KP and FP can be prepared using phosphatidylcholine (PC), which is one of the principal components of HSL, as a carrier. In this solid dispersion, they interact weakly with PC, and exist in an amorphous state.[14] In addition, the solid dispersion could be prepared not at room temperature, but by heating at near 100 °C.[15] In the oily gel, it was considered that they had some interaction with HSL and dissolved in gel, leading to an increase in consistency. In the case of IP, IP dissolved in LP and had little interaction with HSL.

Release Studies The amounts of IM released from Gel+IM and from IM gel in which the HSL concentration was 15% are shown in Fig. 4. A linear relationship was observed between the amount of IM released and the square root of time, except for the IM gel containing 2% IM. The release from Gel+IM was slow because IM exists in a crystalline state. In the case of IM gels, the release of IM was faster than from Gel+IM. In the case of a solution-type ointment, the release rate was proportional to the drug concentration.[16] The release rate from 1% IM gel was about 2-fold that from 0.5% IM gel, but that from 1.5% IM gel was almost the same as from 1% IM gel. This indicates that IM solubility in gel was not as high as 1.5% at room temperature. The 2% IM gel did not show a linear relationship. The reason for this was not clear, but some changes occurred during the test, and Higuchi's theory[16] failed in this case.

When HSL concentration was changed to 20%, the rate of IM release was almost the same as that for 15%. In the case of 30% HSL, however, the release rate was about half that from 15% HSL gel. The consistency of 30% HSL gel was extremely high, thus the diffusion in the gel might have been suppressed.

Figure 5 shows the cumulative amount of drug released within 6 h from HSL 15% gel containing various concentrations of a drug. The amount released was proportional to concentrations up to 1% in gel in the case of IM. In the case of KP and FP, they were proportional up to 2%, and in the case of IP, up to 8% (5.4 mg/cm² within 6 h). This indicated that the solubilities of these

drugs in gel may be at around these concentrations.

Permeation Studies The permeation of IM through hairless rat abdominal skin from various formulations containing 1% of IM was determined (Fig. 6). When the suspension of IM and HSL in LP was applied, permeation of IM through the skin was low and could not be determined within 10 h. With Gel+IM, the permeated amount at 10 h was only 2 $\mu g/cm^2$. On the other hand, permeation from IM gels was good, over 10-fold that of Gel+IM. It is well known that the permeation of a drug is influenced by the concentration of drug in the vehicle; permeation is less with suspended systems in which the drug is present in an crystalline state than in systems wherein the drug is completely dissolved.[5,6] In a suspension and Gel+IM, only a little IM dissolved and almost all of it exists in a crystalline state. Moreover, the dissolution rate of IM into LP or gel might be extremely low. Thus, the permeation of IM from a suspension and from Gel+IM was low, and that from an IM gel in which IM was dissolved was high. Since the amount of permeated IM was linear with time from 4 to 10 h, the slope of this line was considered to be the permeation rate.

The permeation of IM from IM gel with HSL concentrations varying from 15—30% is compared. IM permeability from IM gel with 20% HSL was higher than that from IM gel with 15% HSL. However, there was no difference in the permeation rate between 20 and 30% HSL.

Figure 7 shows the permeation profiles of IM from an IM gel with 15% HSL and various concentrations of IM. The permeation rate increased in proportion to IM concentrations ranging from 0.1 to 0.5%. In contrast, the permeation rate from an IM gel containing IM concentrations above 0.5% did not show a proportional increase.

In the case of 0.5% IM gel, the effect of HSL concentration on the permeation rate was different from that in the case of 1% IM gel; permeation rates were 3.0, 3.2 and 2.3 $\mu g/cm^2/h$ for an IM gel containing 15%, 20% and 30% HSL, respectively. There was no difference in the permeation rate between 15% and 20% HSL when the IM concentration in gel was 0.5%, but a difference was observed when the IM concentration was 1%. Skin permeation enhancement of several drugs by HSL,[17] egg yolk lecithin[18] and PC[19] was reported. However, these findings suggested that HSL had no enhancing effect on the skin; instead, the solubilizing effect of HSL affected the permeation rate. IM solubility might be higher in the case of 30% HSL, in comparison to 15% or 20% HSL gel, but diffusion in the gel might be suppressed.

The permeation of other drugs was also investigated with HSL 15% gel. Since other drugs showed good correlation between the amount permeated and time, permeation rates were compared. Figure 8 shows the relationship between permeation rate and drug concentration in a gel. the permeation rates of KP, FP and IP were larger than that of IM, because of the inherent drug character.[20] The permeation rate was proportional to drug concentration in gels containing up to 2%, 1.5% and 5% of KP, FP and IP, respectively. It is considered that the solubility of a drug in an oily gel affects the relationship.

Maximum permeation rates from the gel and the suspension were compared (Fig. 9). IM showed no permeation from the suspension. KP and FP were permeated from the suspension, but the permeation rates from the gels were about 3-fold those from the suspension. IP, which has a high solubility, showed almost the same permeation rate from gel and suspension.

Effect of Storage on IM Gel The consistency and flowing temperature of the oily gel itself did not change upon storage for 4 months.[11] IM gel was stored at room temperature to evaluate its stability as a dosage form. IM gel also showed no change in consistency and flowing

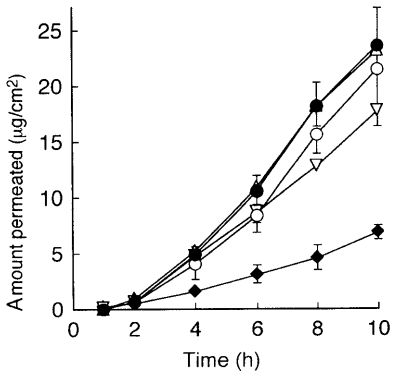

Fig. 7. Permeation Profiles of IM through Excised Hairless Rat Abdominal Skin from IM Gel Containing 15% HSL

IM concentrations in IM gels are 1.5% (△); 1% (●); 0.5% (○); 0.3% (▽); and 0.1% (◆). Each value represents the mean ± S.D. (n=3—4).

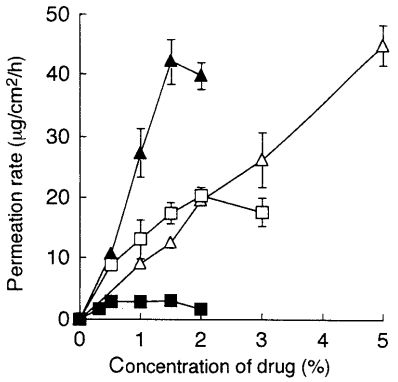

Fig. 8. Effect of Concentration of Drug on the Permeation Rate through Excised Hairless Rat Skin from Oily Gel Containing 15% HSL

■, IM; □, KP; ▲, FP; △, IP. Each value represents the mean ± S.D. (n=3—4).

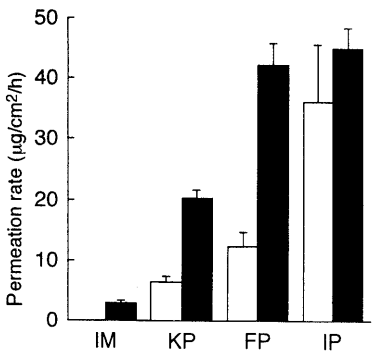

Fig. 9. Comparison of Maximum Permeation Rate from Oily Gel Containing 15% HSL and from Suspension

■, oily gel; □, suspension. Each value represents the mean ± S.D. (n=3—4).

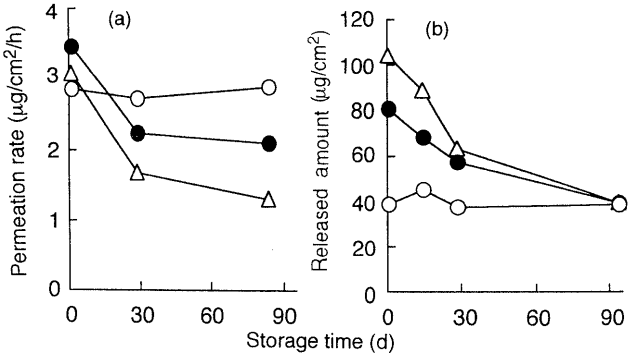

Fig. 10. Effect of Storage Time on the Permeation and Release Rate of IM from IM Gel Containing 15% HSL

(a) skin permeation rate, (b) amount released within 6 h. IM concentrations in IM gels are 1.5% (△); 1% (●); and 0.5% (○). Each point represents the mean of 2—3 experiments.

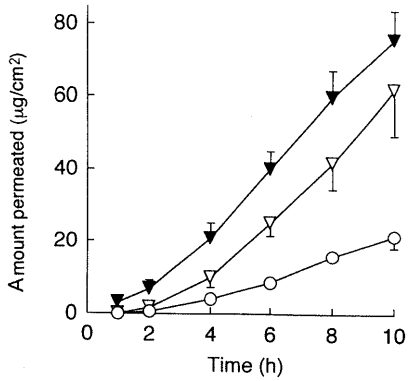

Fig. 11. Comparison of IM Permeation from Oily Gel and Commercial Hydrogel-Type Ointment

○, 0.5% IM gel with 15% HSL; ▽, 3% menthol added to 0.5% IM gel with 15% HSL; ▼, commercial hydrogel-type ointment which contained 0.75% IM and 3% menthol. Each value represents the mean ± S.D. ($n=3$—4).

temperature.

The time course of the permeation rate of various concentrations of IM in 15% HSL gel was determined (Fig. 10a). Permeation rates were almost the same for all three IM concentrations immediately after preparation. The permeation rate of the 0.5% IM gel did not change during the 3-month period, but those of the 1% and 1.5% IM gels decreased to about half.

The release results agreed well with those from permeation studies: with the IM gel containing 0.5% IM, the amount released within 6 h did not change; however, the release amount decreased with 1.0% and 1.5% IM (Fig. 10b). This might indicate that IM was supersaturated in the gel immediately after preparation, because it dissolved at 95 °C and recrystallized with time. Therefore, the most stable preparation is 0.5% IM with 15% HSL.

Conclusions

IM, KP and FP, which had low solubilities in LP, could be solubilized with HSL at 95 °C. Permeation rates which were low from the LP suspension were improved by using this oily gel. In contrast, IP which dissolved in LP and permeated from the suspension did not change in permeation rate when it was formulated in the gel. In view of the relationship between drug concentration and maximum permeation rate, improvement of skin permeation might be dependent on the solubilizing effect of HSL. The permeation rate decreased with time when the IM concentration was high, because recrystallization was considered to have occurred. Therefore, the drug concentration must be determined taking this factor into consideration.

The permeation rate from a commercial hydrogel-type ointment (Vantelin®; IM 0.75%, menthol 3%) was about 2-fold that from oily gel (Fig. 11). However, when 3% menthol, which is a skin-permeation enhancer, was added to IM 0.5% and HSL 15% gel, the lag time was longer than that of the commercial ointment, but the permeation rate increased to approximately the same as that of the commercial ointment.

Therefore, this oily gel may be applicable for use as a percutaneous absorption-type pharmaceutical ointment base.

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