[Chem. Pharm. Bull.]
30(8)2941—2950(1982)

Influence of the Liquid Phase Coexisting in Fatty Suppository Bases on the Polymorphic Transition Rate¹⁾

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(Received January 13, 1982)

The influence of the liquid phase on the A-to-B transition of semisynthetic fatty suppository vehicles during storage was investigated. The addition of a liquid having a high affinity, such as isopropyl myristate, fatty oil, lauryl alcohol, *etc.*, remarkably accelerated the transition, whereas that of a low affinity liquid had little effect. The transition rate evaluated from the time course of transition degree (k_T) increased linearly with the weight fraction ratio of liquid phase (f_L) to solid phase ($1-f_L$).

The case where liquid phase was produced only from molten vehicle containing no liquid additive was also examined. The relation between k_T and $f_L/(1-f_L)$ was investigated 1) for the transition of Witepsol H-15 in the temperature range from 26 to 32°C, and 2) for several commercial vehicles at 30°C. Linear relations also appeared to hold for both cases. Here, the weight fraction of liquid phase at a given temperature was determined by means of differential scanning calorimetry (DSC).

The activation energy of transition (E^*) was compared in the presence and absence of liquid additives. E^* values of Witepsol H-15 containing 10 and 25% fatty oil were about 40 kcal, less than one-half of that of Witepsol H-15 not containing any liquid additives. The transition mechanism was considered to involve dissolution of the solid A-form in the intervening liquid phase followed by crystallization as solid B-form.

Keywords—semisynthetic fatty suppository base; polymorphic transition; transition rate; transition mechanism; liquid additives; X-ray diffraction

It is well known that some pharmaceutical properties of fatty suppositories, such as melting point, softening time, drug release, and even drug bioavailability, tend to change during storage.²⁾ These phenomena have been considered in connection with the polymorphism of suppository base.^{2a,3)}

Previously we investigated this transition in commercially available vehicles by means of the X-ray diffraction method.⁴⁾ It was shown that the degree of the transition from the unstable A-form to the more stable B-form could be evaluated in terms of I_R which was defined as the relative value of the diffraction intensities of the characteristic peaks of each crystal. The transition rates were greatly dependent on the storage temperature, on the commercial brand and on the drug mixed with the vehicles. Moreover, we recently found that the transition behavior sometimes differed in different lots even if they were of the same brand. These results suggest that some difference of constituents in vehicles may cause the differences of physical stability of fatty suppositories.

One of the important factors contributing to these phenomena may be the quantitative solid and liquid balance of the vehicle (SLB). Imamura *et al.* stated that the polymorphism of hardened coconut oil proceeded faster in the fraction rich in liquid oil phase,⁵⁾ and Asada *et al.* also showed that the α -to- β transition of pure tristearin was accelerated by the coexistence of organic solvents.⁶⁾

Therefore, the SLB of suppositories was also expected to play an important role in relation to the pharmaceutical properties and stability. Thus, we investigated the effects of liquid coexisting in the vehicles on the characteristics of suppositories using Witepsol H-15, E-75 and other semisynthetic fatty vehicles.

Experimental

Materials—Witepsol H-15 and Witepsol E-75^{7a)} mainly used in this study were of the quality listed in Table I. Other commercial vehicles such as Witepsol W-35,^{7a)} Suppocire AM, AS₂,^{7b)} S. B-H^{7c)} and Isocacabutter MO-5^{7d)} were also used for comparison. Liquid additives used were isopropyl myristate (IPM), a medium chain (C₆–C₁₂) triglyceride commercially named Miglyol 812 (MIG), lauryl alcohol (LA), heavy liquid paraffin (LP), squalane (SQ), propylene glycol (PG), polyethylene glycol 400 (PEG 400), and distilled water. These compounds (other than water) were obtained from commercial sources⁸⁾ and used without further purification.

TABLE I. Properties and Fatty Acid Compositions Witepsol H-15 and E-75 used in the Experiment

Vehicle	Properties ^{a)}				Fatty acid (%) ^{b)}				
	A.V	S.V	I.V	OH.V	C ₁₀	C ₁₂	C ₁₄	C ₁₆	C ₁₈
Witepsol H-15	0.06	237	0.8	12.1	1.2	48.1	18.5	16.9	15.3
Witepsol E-75	0.91	230	0.3	14.7	0.8	36.4	14.1	25.5	23.2

a) A.V; acid value, S.V; saponification value, I.V; iodine value, OH.V; hydroxyl value.

b) Measured by GLC. Others were none or trace.

Preparation of Mixed Vehicle—A suitable amount of liquid component was added to the molten vehicle under vigorous stirring in a homomixer. The mixture was cooled at room temperature with continuous stirring and poured into the metallic mold, where it became viscous by partial solidification. It was allowed to stand for two hours at room temperature to solidify, then was stored in a refrigerator. The mixed vehicle suppository thus obtained weighed about 2.4 g and had a cylindrical shape.

Storage Conditions—The mixed vehicles which had been stored in the refrigerator overnight after preparation were regarded as initial samples. Storage experiments were carried out in a water bath maintained at a desired temperature within $\pm 0.1^\circ\text{C}$.

Evaluation of Transition Degree—The degree of the A-to-B transition of vehicles was evaluated in terms of the I_R value presented in a previous paper,^{4b)} which was defined by eq. (1), and calculated from the X-ray diffraction pattern. In eq. (1), $I_{21.1}$, $I_{20.7}$ and $I_{30.0}$ mean the diffraction intensities at Bragg's angle (2θ) values of 21.1° , 20.7° and 30.0° , respectively.

$$I_R = \frac{I_{21.1} - I_{30.0}}{I_{20.7} - I_{30.0}} \quad (1)$$

X-ray diffraction measurement conditions were as follows: apparatus, Geigerflex 2013 (Rigaku Denki Co., Ltd.); radiation, Ni-filtered Cu- K_α ($\lambda = 1.54 \text{ \AA}$); voltage/current, 40 kV/35 mA; divergence/receiving/scattering slit, $0.5^\circ/0.3 \text{ mm}/0.5^\circ$; scanning speed, $2^\circ/\text{min}$.

Measurement of Amount of Liquid Phase—The solid fat index (SFI) of the vehicle was measured by differential scanning calorimetry (DSC) according to Maruyama *et al.*⁹⁾ The weight fraction ratio of the liquid phase of the vehicle was regarded as $(100 - \text{SFI})$. Measurement conditions were as follows: apparatus, Shimadzu SC 20 differential scanning calorimeter; heating speed, $2.5^\circ\text{C}/\text{min}$ from 5°C to 45°C ; reference, α -alumina; range, $\pm 5 \text{ mcal/s}$. The accuracy of the temperature was checked by measuring the melting points of methyl stearate (39.2°C) and methyl arrachidate (46.4°C).

Solubility of Vehicle in the Liquid Component—The solubility measurement was conveniently carried out by visual observation. The vehicles were weighed accurately in test tubes to obtain a series of weights in steps of about 5 mg, and 5 ml portions of liquid were added thereto. Then, after being sealed, all the test tubes were shaken in the water bath adjusted to 24°C for 24 h. The solubility was determined as the maximum concentration which did not show any turbidity on visual observation.

Measurement of Wetting Spreadability—The molten vehicle was spread on a flat clean glass plate and then cooled to room temperature. Thus, a smooth solid surface was formed. About $100 \mu\text{l}$ of liquid was carefully put on the surface as a droplet by use of a syringe. This droplet was allowed to stand for one hour at room temperature, and then the diameter of the spread droplet (d) was measured under a microscope. The volume of the droplet (V) could be calculated from the weight of the droplet and the specific gravity of the liquid. The spreadability was expressed as d/V .

Results and Discussion

I. Effect of Liquid Additives on the Transition Rate

Fig. 1 shows the change of I_R values of Witepsol E-75 containing 20 w/w% of various liquid components at 24°C. All of these liquids may be used for suppository preparation in order to adjust the melting point, to improve the properties for ease of manufacture, to control the release rate of active ingredient or to modify other properties. It was clear that the transition was affected by different kinds of liquid to various extents, that is, it was accelerated by IPM, LA, MIG and LP, whereas PG, PEG and water had almost no effect.

It was noted in the cases of IPM, MIG and LA that I_R decreased at the initial stage to the minimum ($I_{R\ min}$) and then increased to the maximum ($I_{R\ max}$), and all of these $I_{R\ max}$ values were close to that of Witepsol E-75 B-form which can be obtained by storage at room temperature for a long time. So, it could be expected that I_R might reach $I_{R\ max}$ also in the case of other liquid additives if the observation were continued for a longer period.

When a suppository base is stored at somewhat higher temperature, liquid phase originating in the molten vehicle may complicate the effect of liquid additives. Therefore, in this experiment, we chose Witepsol E-75 as a representative commercial base and 24°C as the storage temperature, because this vehicle has a high melting point among commercial vehicles, and is known to have a very small liquid fraction at temperature below 26°C from DSC measurement.

The influence of the weight fraction of the added liquid on the transition behavior was investigated for IPM, MIG and LP. The I_R changes of Witepsol E-75 containing these liquids at 24°C are shown in Fig. 2.

Fig. 1. The Changes of I_R Values of Witepsol E-75 containing 20 w/w % of Various Additives during Storage at 24°C

○, IPM; ●, LA; ◆, MIG; △, LP; □, SQ; ■, PG; ▲, PEG 400; ◇, Water; ●, Witepsol E-75 alone.
—; is the linear approximation from the I_R change near $I_{R\ mid}$.

Fig. 2. Effects of Concentration of Liquid Additives on the I_R Change during Storage at 24°C

(A) MIG, (B) IPM, (C) LP; ○, 25%; ●, 20%; △, 15%; ▲, 10%; ◇, 7.5%; ◆, 5%.

It is clear that the greater the amount of liquid added, the faster the transition. Under these storage conditions, the weight fraction of liquid phase of mixed vehicle (f_L) could be considered to be approximately equal to the weight fraction of the liquid added, because, as

shown in Table II, the vehicle cannot dissolve to a large extent in any liquid component at 24°C. This was confirmed by Suzuki *et al.* who showed by means of nuclear magnetic resonance (NMR), DSC and dilatometry that the liquid fraction of the mixed fat of hardened beef tallow and soybean oil was nearly equal to the amount of soybean oil.¹⁰⁾

Previously, we showed that I_R values increased linearly with the weight fraction of B-form in the vehicles,^{4b)} so the degree of transition, T_D , could be calculated from eq. (2),

$$T_D = (I_R - I_{R \min}) / (I_{R \max} - I_{R \min}) \quad (2)$$

The transition rates is:

$$\frac{dT_D}{dt} = \frac{dI_R}{dt} \left(\frac{1}{I_{R \max} - I_{R \min}} \right) \quad (3)$$

Fig. 3. Relationships between Transition Rate and SLB of Mixed Vehicles during Storage at 24°C

◇, IPM/Witepsol E-75; ○, MIG/Witepsol E-75;
●, MIG/Witepsol H-15; △, LP/Witepsol E-75.

As the extent of acceleration seemed to reflect some physicochemical interaction between the liquid additives and vehicle, the solubility of the solid in the liquid and the wetting spreadability of the liquid on the vehicle surface were measured and compared with k_T calculated from Fig. 1 (Table II). It was considered that the former might represent the mutual affinity

As shown in Fig. 1 or 2, I_R displayed rather complicated patterns and dI_R/dt could not be determined simply. However, over a rather wide range of I_R , especially centering around the midpoint of I_R , $I_{R \text{ mid}} [=1/2 (I_{R \max} + I_{R \min})]$, they seemed to increase linearly with time. Thus we approximated this region as linear, and calculated the transition rate parameter k_T (h^{-1}) as follows:

$$k_T = k_I / (I_{R \max} - I_{R \min}) \quad (4)$$

where k_I is the slope of the linear portion in the I_R -time plot. Thus, k_T values were calculated from Fig. 2 and are plotted against $f_L/(1-f_L)$ in Fig. 3.

Quite good linearity was obtained in all three cases. Here, $(1-f_L)$ is the weight fraction of solid vehicle, so that $f_L/(1-f_L)$ means the weight ratio of liquid phase to solid phase. This is considered to be an index of SLB.

TABLE II. Comparison of k_T and Interaction Properties of Liquid Additives and Witepsol E-75

Liquid additives	Solubility (mg/ml)	Wetting ^{a)} spreadability d/V (cm^{-2})	k_T ^{b)} ($\times 10^2 \text{ h}^{-1}$)
IPM	35	38.6	20.32
MIG	18	25.5	3.12
LA	11	17.9	4.17
PG	<0.5	10.5	≈ 0
PEG 400	<0.5	10.6	≈ 0
SQ	7	27.9	0.28
LP	17	22.1	0.46
Water	<0.5	5.6	≈ 0

a) Each value is the mean of three measurements.

b) Calculated from the data shown in Fig. 1.

between the liquid and vehicles and the latter might correlate with the contact area of both phases in the mixed vehicles. Contact angle (θ) which is often used to estimate the affinity of two phases at the solid-liquid interface, can be calculated from d and V according to the following equation, if θ is smaller than 90° ; $(d/2)^3/V = 24 \sin^3\theta/\pi(2 - 3\cos\theta + \cos^3\theta)$.¹¹⁾ However, some of the liquids used gave θ values over 90° , so we conveniently estimated the spreadability in terms of the d/V value instead of θ .

From the data in Table II, it is apparent that IPM, which has the highest solubility and spreadability, shows the fastest transition rate. PEG, PG and water, having low solubility and poor wettability, hardly accelerated the transition. MIG, LA, LP and SQ, having medium acceleration capacity, also showed medium solubility and wettability even though the order of relative values of the properties did not completely coincide. Thus, in spite of some conflict we can conclude that the affinity or wetting spreadability is an important factor for the transition, in general.

The influence of MIG on the transition of Witepsol H-15 was also examined and the results are shown in Fig. 3 together with those for Witepsol E-75. A linear relation was also found in this case, but the slopes K (shown in Table III) differed considerably.

II. The Influence of Liquid Phase Originating from the Molten Vehicle

In the work described above, SLB of the vehicle was altered by adding liquid components and the solid vehicle was considered to remain in the solid phase throughout the storage period, because the temperature was comparatively low. But, even in the case where no liquid component is added, when the storage temperature is raised, some fraction of the solid vehicle will melt and liquid phase will be produced.

Previously we performed storage test on commercial suppository bases and measured the transition rates. These were strongly dependent on the storage temperature.^{4b)} This phenomenon was also presumed to have some relation to the liquid phase produced by melting of the vehicle. The extent of liquid phase coexisting in the fatty vehicles can be evaluated in terms of SFI (solid fat index), which is the weight fraction of solid fat in the vehicle, and has generally been used as an important parameter for the quality evaluation of fatty materials. This value is measured by dilatometry according to the official method,¹²⁾ but recently, other methods using NMR,¹³⁾ DSC^{9,10,14)} or an electronic density meter¹⁵⁾ were proposed as more convenient methods. Thus, we adopted the DSC method to evaluate the fraction ratio of liquid originating from molten vehicle.

Fig. 4(A) shows two DSC patterns of Witepsol H-15 as an example of commercial vehicles. One is the pattern immediately after solidification of the melt and the other is that after storage of the vehicle at ambient temperature for a year. The crystal forms of the former and the latter were identified as A- and B-form, respectively, by X-ray diffraction.

Both of them displayed a broad endothermic peak in the range from 25°C to 37°C or to 40°C . The SFI values were calculated at each temperature and are plotted in Fig. 4(B). It was found that both A- and B-form had very large SFI below 25°C , but SFI gradually decreased with temperature. In the case of

Fig. 4. DSC and SFI Curves of A- and B-Form of Witepsol H-15

(A) DSC curve; a) A-form, b) B-form.
(B) SFI curve; (○) A-form, (●) B-form.

freshly prepared sample, the solid had completely melted at over 37°C, while in the case of aged sample it had done so at over 40°C. In this melting range, the B-form usually had larger SFI than the A-form.

Fig. 4 also suggested that SFI would not be constant but would change accompanying polymorphic transition even if the storage temperature remained constant. Namely, with increase of B-form during storage, SFI values were presumed to become higher. Thus, in these cases, f_L could not be regarded as a constant and this might cause some difficulties in examining the relation between f_L and transition rate, as described previously. However, it was presumed that the transition rate might depend on the f_L values of the A-form at least qualitatively.

Thus, k_T vs. $f_L/(1-f_L)$ was plotted for the transition of Witepsol H-15 at various temperatures (Fig. 5). Here, k_T values were calculated from data taken from the previous paper,^{4b)} and f_L values at each temperature were read from the SFI curve of the A-form in Fig. 4 (B). Good linearity was obtained in the range of storage temperature from 26 to 32°C. The slope K was calculated and is also listed in Table III.

A similar relation may be valid in various kinds of vehicles. Thus, the k_T values of six commercial vehicles (calculated using data taken from the previous paper)^{4b)} were also plotted against $f_L/(1-f_L)$ of the A-form of each vehicle. Here, the f_L values were estimated from the SFI curves shown in Fig. 6 at the storage temperature (30°C).

In this case, the linearity was not as good as previously obtained. This may be due to invalidity of the estimation of f_L , some difference of purities or other physical characteristics or other unknown reasons. In any event, the results shown in Figs. 5 and 6 suggest that the transition rate can be predicted for various kinds of vehicles from the SFI values at given temperatures.

As the chemical composition of MIG seemed to have considerable similarity to that of the molten vehicles, the vehicles containing MIG were expected to show behavior similar to that of the vehicles without added liquid. However, when the K value of Witepsol H-15 was compared with that of Witepsol H-15/MIG system, the former was about three or four times greater. Thus, the following experiment was performed.

Fig. 5. The Relationship between Transition Rate and SLB of Witepsol H-15 at Various Storage Temperature

A; 26°C, B; 27°C, C; 28°C, D; 29°C, E; 30°C
F; 32°C.

Fig. 6. SFI Curves and the Relationship between Transition Rate and SLB of Various Semisynthetic Vehicles during Storage at 30°C

(A) SFI curve, (B) k_T vs. SLB plot; ○, Witepsol H-15;
●, Witepsol W-35; ▲, Suppocire AM; △, Suppocire AS₂;
□, S.B.-H; ◇, Isocacaobutter MO-5.

III. Difference of the Temperature Dependency of the Transition Rate

To examine the difference of transition mechanism between the two cases cited above and to determine the contribution of temperature to the transition rate in each case, storage experiments using Witepsol H-15 containing 10 and 25% MIG were carried out at 20, 22 and

24°C. In this temperature range, the solid phase of the vehicle scarcely melted, so the liquid fraction f_L was considered to be constant irrespective of temperature. The I_R curves obtained are shown in Fig. 7. It was found that the transition was affected by SLB and temperature. The k_T values were plotted according to Arrhenius' equation (Fig. 8). Linear relations were obtained in both cases, and the activation energies calculated from the slopes were 40.2 and 39.6 kcal for MIG contents of 10% and 25%, respectively. These values are very similar, so it is likely that the temperature dependencies in this case were almost the same and were hardly affected by SLB.

In Fig. 8, k_T of Witexsol H-15 alone at storage temperatures in the range from 26 to 32°C are also plotted for comparison. The activation energy in this case was about 113 kcal, two or three times greater than in the above cases. This may be because f_L in the former case did not change with temperature whereas f_L in the latter case increased with temperature, so that the temperature dependency in the latter case was larger than in the former case.

Fig. 7. The Changes in I_R Values of Witexsol H-15 containing 10 and 25 w/w % MIG during Storage at 20, 22 and 24°C

●, 10%, 20°C; ■, 10%, 22°C; ▲, 10%, 24°C;
○, 25%, 20°C; □, 25%, 22°C; △, 25%, 24°C.

Fig. 8. Arrhenius Plots of k_T of the Mixed Vehicles of Witexsol H-15 and MIG

▲, MIG 10%; △, MIG 25%; ○, Witexsol H-15 alone.

IV. The Function of the Liquid Phase

The mechanism of acceleration of the liquid phase can be considered in two ways from a microlevel viewpoint; 1) liquid additive was mixed completely with solid vehicle to produce something like a solid solution, and the acceleration was the result of interaction between the components at the molecular level; 2) liquid additive was dispersed in the solid vehicle as small liquid particles and the transition occurred at these phase levels.

Considering that the solubilities of solid phase in liquid phase were not large (Table II), the latter case seems more reasonable. Indeed, we found many liquid particles dispersed in the mixed vehicles upon microscopic observation.

If the latter hypothesis is correct, three mechanisms can be considered as follows. Case A): The transition occurred only at the liquid-solid interface. In this case, the portion of A-form not in contact with the liquid phase would not undergo transition at all or only to a very small degree. Consequently, $I_{R \max}$ should depend on f_L . Then, the value of T_D should change as shown in Fig. 9(a) when f_L is assumed to take a value of α , β or γ ($\alpha > \beta > \gamma$). However as shown in Fig. 2, $I_{R \max}$ showed almost the same value irrespective of f_L , so this scheme can be rejected. Case B): The liquid phase penetrates into the solid phase, and the transition is stimulated by the liquid and occurs at the interface between the solid A-form and the penetrated liquid phase. In this case, the transition described in Case A) may proceed rapidly at the initial state and then slow transition may follow, accompanying penetration of the liquid phase. Thus, T_D patterns should be as shown in Fig. 9(b). Case C): The solid phase dissolves

Fig. 9. The Possible Transition Patterns of Vehicle with Liquid Phase

- (a) Transition occurs only at the liquid-solid interface.
 (b) Transition occurs at the liquid-solid interface, and thereafter the liquid penetrates into the vehicle.
 (c) Transition occurs after dissolution of liquid phase.
 α , β and γ are values of f_L ($\alpha > \beta > \gamma$).

Chart 1

to the liquid phase to form a saturated solution, then recrystallizes as the B-form from the liquid phase. The solute removed by crystallization is replaced by A-form crystal. In this case, T_D might change in a zero order manner in analogy with the decomposition behavior of drugs in saturated solution.¹⁶⁾ The transformed product should be proportional to the amount of liquid phase, as shown in Fig. 9(c). The existence of a linear portion of rather wide range in the I_R curve (Fig. 1, 2) and the

dependency of the transition rate on f_L suggest that Case C) is applicable, and thus the transition mechanism is suggested to be as shown in Chart 1. In this case, the vehicles were considered to exist in three form, *i.e.*, as A- and B-form in the solid state and as solute in the liquid phase. When the weight fractions are denoted as f_A , f_B and f_s respectively, then:

$$f_A + f_B + f_s + f_L = 1 \quad (5)$$

the rate of increase of f_B can be described by eq. (6):

$$\frac{df_B}{dt} = k_c \cdot f_s + k_s \cdot f_A \quad (6)$$

where k_c is the rate constant of crystallization of B-form, and k_s is that of the A-to-B transition without intervening liquid phase. This can be neglected because I_R scarcely changed in the absence of liquid additives, as shown in Fig. 1. As the liquid phase may be saturated with vehicle throughout the transition process,

$$f_s = C_s \cdot f_L \quad (7)$$

where C_s is the solubility of vehicle in the liquid additive. Therefore, from eqs. (6) and (7):

$$\frac{df_B}{dt} = k_c \cdot C_s \cdot f_L + k_s \cdot f_A \approx k_c \cdot C_s \cdot f_L \quad (8)$$

T_D can be defined as $f_B/(f_A + f_B)$ and can be approximately described by eq. (9), because in the case of this experiment the solubility of the vehicle in the liquid phase was not high, as shown

in Table II, and f_s was negligible compared with f_L .

$$T_D = \frac{f_B}{f_A + f_B} = \frac{f_B}{1 - f_L - f_s} \doteq \frac{f_B}{1 - f_L} \quad (9)$$

Consequently,

$$\frac{dT_D}{dt} = \frac{1}{1 - f_L} \cdot \frac{df_B}{dt} = \frac{f_L}{1 - f_L} \cdot (k_c \cdot C_s) \quad (10)$$

dT_D/dt can be regarded as approximately equal to k_T , so eq. (10) can be rewritten finally as follows:

$$k_T = k_c \cdot C_s \cdot \frac{f_L}{1 - f_L} \quad (11)$$

Thus, we can account for the linear relationship between k_T and $f_L/(1 - f_L)$.

As f_s in the liquid phase was considered to be constant, df_s/dt should be equal to $-df_A/dt$. This means that the dissolution rate of A-form in the liquid is equal to crystallization rate to B-form from the liquid phase. However, the mechanism of transition is probably more complicated than shown in Chart 1. Indeed, the A-form may be crystallized from the liquid phase or the B-form also may dissolve in the liquid phase. However, the dissolution or crystallization rate can be considered as the summation of many rate processes and estimated grossly.

The slope K in Fig. 3 was considered to be the product of k_c and C_s , so that k_c was calculated by using the solubility in Table II. The results are listed in Table III. k_c values differed with the kinds of additives, as was expected from the cases of IPM, MIG and LP with Witpsol E-75. These phenomena were considered to reflect some differences of physicochemical interaction between solute and solvent. For instance, the k_c value decreased with increase of the viscosity of added liquid (IPM 5cp, MIG 28cp, LP 162cp at 24°C). This may reflect the mobility of the solute in the liquid phase, and may be related to the rates of migration and rearrangement of triglyceride molecules to a more stable lattice at the interface.

TABLE III. List of K and k_c Values of Various Vehicles containing Liquid Phase

Liquid phase	Solid phase	K (h^{-1}) ^{a)}	k_c ^{b)} ($\times 10^3$ mg/ml·h)
IPM	Witpsol E-75	0.606 ($r=0.992$)	17.3
MIG	Witpsol H-15	0.059 ($r=0.983$)	3.3
	Witpsol E-75	0.129 ($r=0.989$)	7.2
LP	Witpsol E-75	0.021 ($r=0.969$)	3.5
Witpsol H-15 (melted)	Witpsol H-15 (unmelted)	0.185 ($r=0.983$)	—

a) Calculated from the data shown in Fig. 3 and Fig. 5 by means of the least-squares method.

b) Regarded as K/C_s .

k_c values also differed between Witpsol H-15 and E-75, even if the same MIG was used as the liquid additive. This may be caused by the physicochemical differences of vehicles, *i.e.* fatty acid composition, purity, additives, *etc.* Further work is necessary to clarify the importance of these factors in more detail.

In the case without any liquid additive, the mechanism might be fundamentally analogous with that in the presence of liquid. When the vehicle is stored at a fairly high room temperature, a part of the crystals having lower melting point might melt and constitute a liquid phase. The unmelted solid fraction might dissolve in this liquid phase, then the transition could proceed in the same way as in the case where liquid additive is present. However, the amount

of the liquid phase increases with temperature, so the dependency of the transition rate on the temperature should be greater than that of the vehicle containing added liquid.

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