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Influence of Fatty Acid Composition on the Properties and Polymorphic Transition of Fatty Suppository Bases^{1,2)}

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In order to investigate the reasons for the variation in the properties or the polymorphic transition behavior of semisynthetic fatty suppository bases, fatty acid composition, melting point, I_R value and the transition rate were measured for many kinds of commercial brands and batches. Then, the mutual relations of the above characteristics were examined. It was found that $I_{R\max}$, the I_R value of the most stable crystal form, was correlated with both the melting point and the content of higher fatty acids such as stearic acid and/or palmitic acid. However, the transition rate did not show any special relation with $I_{R\max}$, but was well correlated with the contents of lower fatty acids, such as caprylic acid and/or capric acid. These tendencies were also confirmed by the results of a fractionation experiment on Witepsol H-15, performed to investigate the above phenomena in more detail. In this experiment, it was observed that the X-ray diffraction pattern and I_R value of the physical mixture prepared from the fractionated samples coincided with those of the intact Witepsol H-15 in the cases of both stable and unstable crystal forms. These results suggest that the vehicle is constituted of many kinds of unit crystal cells differing in fatty acid composition, crystalline mode and physical properties. Thus, it was considered that the observed change of X-ray diffraction accompanying the A-to-B transition was mainly due to the higher melting point unit cells and that the transition acceleration was due to the lower melting ones.

Keywords—semisynthetic fatty suppository base; transition rate; polymorphism; melting point; fatty acid composition; unit cell

Previously, we showed that the polymorphism of semisynthetic fatty vehicles affected various pharmaceutical properties of the suppository,³⁾ and that the transition rate could be evaluated quantitatively by using the I_R values calculated from the X-ray diffraction pattern of the vehicle.⁴⁾ This method seems to have many advantages for the study of fatty suppositories: 1) many kinds of commercial vehicles have a common X-ray diffraction pattern for both unstable and stable crystal forms (denoted as A- and B-form, respectively), so the method is applicable to most commercial vehicles; 2) the difference of I_R values between A-form and B-form was large, so the A-to-B transition process was revealed more easily than by other conventional indexes such as melting point or softening time; 3) the presence of other materials, active ingredients and/or additives, did not interfere very much with the I_R measurement, so their influence on the transition could be conveniently examined; 4) the measurement was easy and the inherent errors were rather small; *etc.* Thus, this value is a practical and useful index for the evaluation of the physical stability of a suppository.

In our recent examination, however, it has also been found that the I_R values and their changes during storage differ not only among different commercial brands but also among different batches even if they are of the same brand. As these variations were presumed to affect the properties and the physical stability of suppositories it seemed necessary to investigate them in detail in order to develop more effective suppository pharmaceuticals and to maintain a constant quality level of products.

Thus, in this work, we measured the polymorphic transition rate, the maximum value of I_R ($I_{R\max}$), fatty acid composition, melting point and other properties of various commercially available vehicles. These measurements were also performed for the fractionated fats of

Witepsol H-15 separated from acetone solution. The mutual relations of the above characteristics were examined, and the possible nature of unit crystal cells composing the vehicle is discussed.

Experimental

Materials——Nine brands of semisynthetic fatty suppository bases were used for this examination, and several batches were examined for three brands to study the inter-batch variability. All of these vehicles were obtained from commercial sources and used as received. Witepsol H-15 used for the fractionation experiments was purchased from Dynamit Nobel.

Analysis of Fatty Acid Composition——1) Preparation of Methyl Esters: About 0.5 g of vehicle was subject to saponification according to the J.P. method (J.P.X, General Tests, Fats and Fatty Oils, Saponification value), and fatty acids produced were collected and converted to methyl esters by the use of diazomethane.

2) Gas-Liquid Chromatography (GLC): A Shimadzu model GC-4BM gas chromatograph equipped with FID was employed for analysis of the constituent fatty acids. Glass tubing (1.1 m×3 mm i.d.) packed with 10% 1,4-butanediol succinate polyester on Chromosorb W (60–80 mesh) was used for the analysis of fatty acid methyl esters. The column temperature range was 130–210 °C (programmed at 8 °C/min) and nitrogen was used as the carrier gas (50 ml/min).

3) Identification and Calculation: Identification of fatty acids was done by injecting authentic samples of methyl esters as standards. The content of each was determined by direct comparison of the peak area with that of the authentic sample. Fatty acid composition was expressed conveniently in terms of the percent content of each fatty acid relative to the total contents of fatty acids detectable.

Storage Experiments——Vehicles were completely melted and molded into a cylindrical shape weighing about 2.3 g at room temperature. These samples were placed in a refrigerator overnight and then stored in a water bath controlled at the desired temperature within $\pm 0.1^\circ\text{C}$.

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

Determination of I_R Values——From the diffraction intensities at $20.7^\circ (I_{20.7})$, $21.1^\circ (I_{21.1})$ and $30.0^\circ (I_{30.0})$ Bragg's angle (2θ), I_R values were calculated according to the following equation.⁴⁾

$$I_R = I_B / I_A$$

$$I_B = I_{21.1} - I_{30.0}$$

Estimation of the Transition Rate——The half-transition time, $t_{1/2}$, was estimated as reported previously;⁴⁾ namely, the maximal I_R value ($I_{R \max}$) and the minimal value ($I_{R \min}$) were read from the profile of the I_R versus the storage time, and $t_{1/2}$ was regarded as the time required for the I_R value to reach $(I_{R \max} + I_{R \min})/2$ from $I_{R \min}$.

Saponification Value——This value was measured according to the method described in J.P. X (General test, Fats and Fatty oils).

Melting Point——1) Differential Thermal Analysis (DTA): Measurement conditions were as follows: apparatus, Shimadzu model DT 20 B thermal analyzer; heating speed, $2^\circ\text{C}/\text{min}$; reference, α -alumina; range, $\pm 100 \mu\text{V}$. The accuracy of temperature measurement was checked by measuring the melting points of methyl stearate (39.2°C) and methyl arachidate (46.4°C).

2) Open Capillary Method: The value was obtained according to the method in JP X (General tests, Melting point, Method 2).

Differential Scanning Calorimetric Measurement (DSC)——Measurement conditions were as follows: apparatus, Shimadzu model SC 20 differential scanning calorimeter; heating speed, $2.5^\circ\text{C}/\text{min}$ from 5 to 45°C ; reference, α -alumina; range, $\pm 5 \text{ mcal/s}$.

Fractionation of Witepsol H-15——Portions of Witepsol H-15 (200 g each) were dissolved in one liter of acetone. The solution was allowed to stand overnight at 20°C . The crystallized and precipitated materials was separated by filtration *in vacuo* (F_1). Then, the mother liquor was again allowed to stand for three hours at 10°C , and the second fraction (F_2) was separated in the same way. The same treatment was repeated at 5°C , and the third fraction (F_3) was obtained. Finally, the solvent was evaporated from the remaining mother liquor *in vacuo* and residue obtained was designated as F_4 .

Preparation of Physical Mixture——The above fractions were powdered in a cool place and blended in a desired ratio, then 20 g portions of the mixture were stirred vigorously in 100 ml of cooled 50 % aqueous methanol in a homomixer for a few minutes. Next, the solvent was rapidly removed by filtration *in*

vacuo. The mixed samples thus prepared were immediately subjected to X-ray diffraction measurement.

Results and Discussion

The Relations of $I_{R\max}$ with Melting Point and Fatty Acid Composition

As previously described, when suppositories of fatty vehicles are stored at high temperature, the I_R values of vehicles commonly decrease a little at first, then increase *via* the minimum value ($I_{R\min}$) and finally reach a constant maximum value ($I_{R\max}$). The vehicle showing $I_{R\max}$ is regarded as having attained the most stable B-form crystal. Most vehicles showed similar $I_{R\min}$ values near 0.8, but the $I_{R\max}$ values differed considerably in each kind of vehicle.

Table I shows the values of $I_{R\max}$ and the fatty acid compositions of twenty-one commercially available vehicles of various brands or batches. Almost all of the fatty acids were saturated and ranged from caprylic acid (C_8) to stearic acid (C_{18}). The main constituent was lauric acid (C_{12}) in all vehicles (38.5–54.1%). It was observed that $I_{R\max}$ took considerably different values, ranging from 1.19 (brand B, lot j) to 1.84 (brand F, lot r). The results for brands A, B and C showed that the variance among batches was rather smaller than that among brands, but it was larger than we had expected.

Figure 1 shows the relations between the values of $I_{R\max}$ and the melting point measured by DTA [Fig. 1(A)] and by the open capillary method [Fig. 1(B)]. Significant positive correlations were found in both cases, and the greater the $I_{R\max}$, the higher the melting point. The correlation was found to be better in Fig. 1(A) than Fig. 1(B) (the correlation coefficient of former, $r=0.904$; the latter, $r=0.705$). It had been confirmed that the I_R values of the all vehicles used had attained $I_{R\max}$. Therefore, the better linearity of the former than

TABLE I. $I_{R\max}$ Values and Fatty Acid Compositions of Various commercially Available Semisynthetic Fatty Vehicles

Vehicle		$I_{R\max}$	Fatty acid composition (%)					
Brand	Lot		C_8	C_{10}	C_{12}	C_{14}	C_{16}	C_{18}
A	a	1.50	1.6	0.8	44.8	18.9	14.7	19.3
	b	1.37	0.8	0.2	49.4	19.2	13.1	17.2
	c	1.47	0.8	1.0	38.5	21.0	16.6	22.1
	d	1.31	1.4	0.9	47.0	18.6	14.4	17.6
	e	1.45	0.4	1.1	43.5	18.3	15.4	21.3
	f	1.57	0.7	1.3	45.7	18.1	14.4	19.7
	g	1.64	0.9	1.2	42.5	18.2	16.2	21.0
	h	1.57	0.5	0.8	45.2	18.2	16.0	19.3
B	i	1.22	0.5	0.6	52.9	20.7	11.6	13.6
	j	1.19	1.2	0.6	54.1	21.2	11.1	11.8
	k	1.26	0.7	0.2	52.0	20.7	11.6	13.4
	l	1.51	0.2	1.0	48.1	18.5	16.9	15.3
C	m	1.78	0.9	1.6	43.3	17.5	15.7	21.0
	n	1.59	0.8	0.7	45.9	18.4	15.8	18.4
	o	1.74	0.9	0.6	44.3	18.2	17.4	18.5
D	p	1.55	1.9	1.4	48.4	18.6	12.1	17.6
E	q	1.80	3.9	3.3	43.8	15.4	11.2	22.4
F	r	1.84	3.7	3.1	43.5	15.0	11.3	24.4
G	s	1.63	4.2	3.1	41.8	14.6	12.1	24.2
H	t	1.69	2.4	1.7	47.8	17.0	15.7	21.0
I	u	1.41	0.4	0.1	49.0	22.9	9.2	18.0

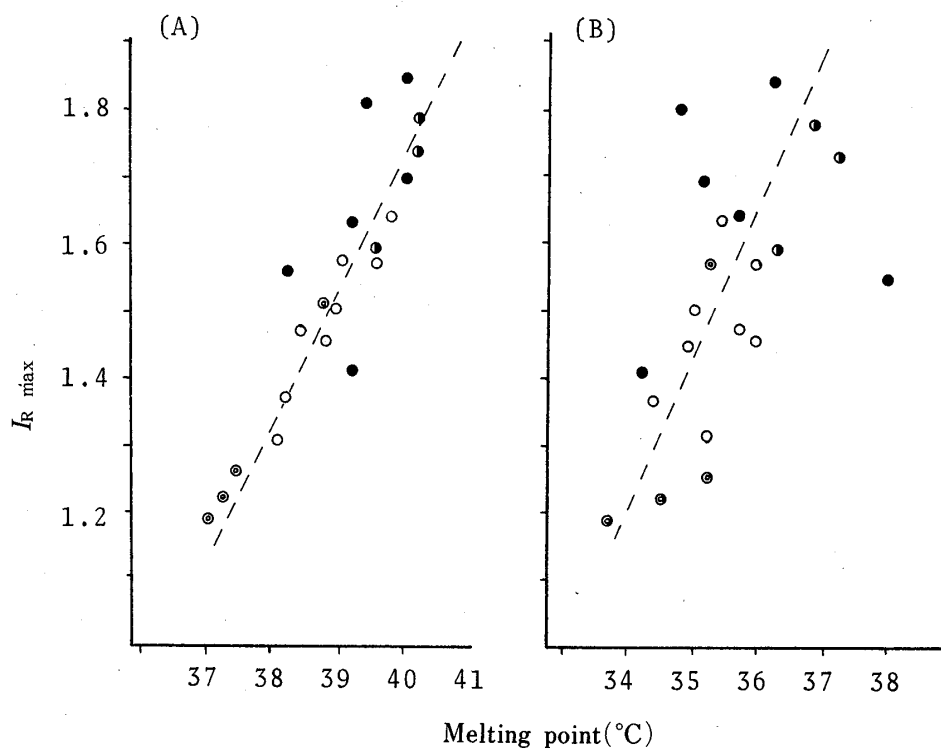


Fig. 1. Relations between $I_{R \max}$ Value and Melting Point of Vehicle

○, brand A; ⊙, brand B; ◌, brand C; ●, other brands.

(A) Melting points were measured by DTA method.

(B) Melting points were measured by the open capillary method.

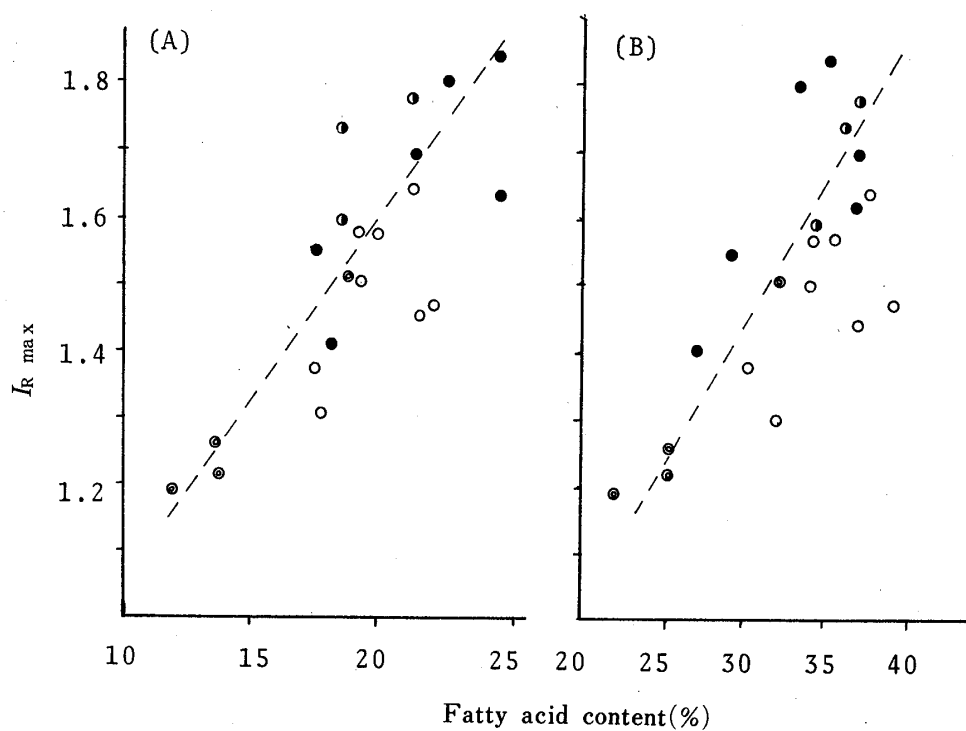


Fig. 2. Relations between $I_{R \max}$ Value and Longer Chain Fatty Acid Composition of Vehicle

For symbols, see the caption of Fig. 1.

(A) Plotted against C_{18} content.

(B) Plotted against the sum of C_{16} and C_{18} content.

the latter is reasonable, because the former was measured without any pretreatment of the vehicles, and consequently the vehicle was in B-form at the time of the measurement. On the other hand, in the latter case, the vehicle was melted and packed into the capillary, so a considerable part of B-form might have changed to A-form during this process, and thus the melting point obtained would reflect that of the A-form crystals. Thus, the melting point found by the DTA method corresponds to that of the stable B-form, and consequently shows a better linear relation with $I_{R\max}$.

Figure 2 shows the relation between the $I_{R\max}$ values and the contents of longer-chain fatty acids in the vehicle used. All the $I_{R\max}$ values were plotted against the contents of C_{18} [Fig. 2(A)] and $(C_{16}+C_{18})$ [Fig. 2(B)]. A positive correlation, though moderate in degree, was obtained in each case (former, $r=0.785$; latter, $r=0.748$).

These relationships in Figs. 1 and 2 suggest that the melting point and fatty acid composition of a vehicle can be roughly estimated from the $I_{R\max}$ value. The results are in accord with the generally known fact that the melting point increases with increasing higher fatty acid content.

The Relation between Transition Rate and Fatty Acid Composition

It was shown in our previous paper that the transition rate was different in different brands of vehicles.¹⁾ Such variation was also found in batches of the same brands, though its extent was comparatively small. Figure 3 (A) shows the relation between $I_{R\max}$ and the transition rate at 30°C in terms of the reciprocal of half-transition time ($t_{1/2}^{-1}$) of some vehicles. No clear relation is apparent. However a plot of $t_{1/2}^{-1}$ against the sum of contents of caprylic acid and capric acid (C_8+C_{10}) showed a nearly linear relation [Fig. 3(B)].

Previously, we showed that the transition was accelerated by the presence of liquid phase.¹⁾ In view of the fact pure triglycerides composed of C_8 or C_{10} are generally liquid at room temperature, the tendency shown in Fig. 3(B) seems reasonable. In fact, commercial vehicles are generally composed of many kinds of triglyceride molecules and the arrangements of the three fatty acids in a triglyceride may be rather random, so it cannot be directly concluded that the liquid phase increases with the fraction ratio of shorter chain fatty acids. However, it seems probable that vehicles rich in C_8 or C_{10} tend to contain more liquid phase at higher temperature. The following experiment was performed to check this.

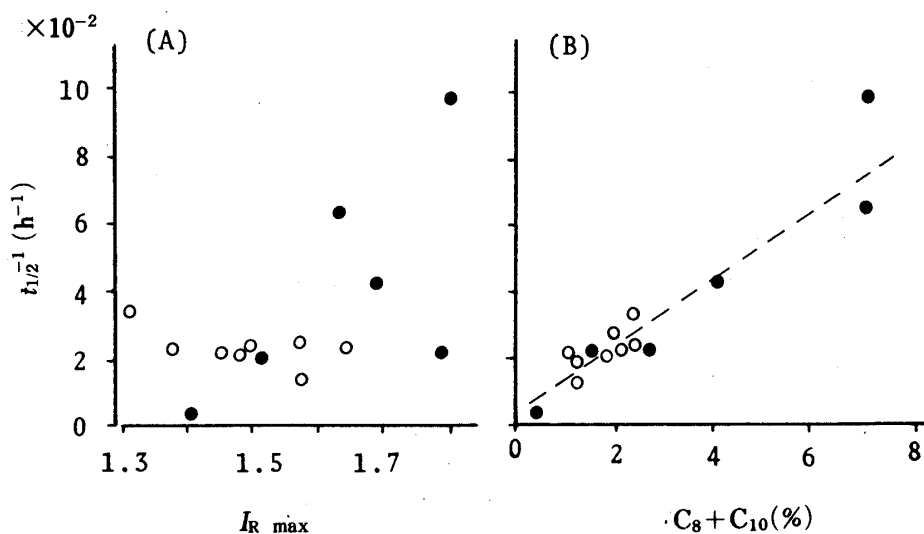


Fig. 3. Relations between Transition Rate at 30°C and Fatty Acid Composition of Vehicle

○, brand A; ●, other brands.

(A) Plotted against $I_{R\max}$ value.

(B) Plotted against the sum of C_8 and C_{10} content.

TABLE II. Comparisons of Yields and Properties of Fractionated Fats and W_{int}

	Yield (%)	Melting point (°C)	Saponification value	Fatty acid composition (%)					
				C_6, C_8	C_{10}	C_{12}	C_{14}	C_{16}	C_{18}
F_1	17.0	45.6 ^{a)}	220.1	Trace	0.5	31.6	18.5	23.5	25.9
F_2	28.5	42.4 ^{a)}	230.9	Trace	0.6	37.9	20.1	21.0	20.4
F_3	34.2	34.6 ^{a)}	256.7	0.4	1.0	51.3	18.5	15.3	13.5
F_4	19.4	31.6 ^{a)}	234.2	1.2	2.6	63.2	15.7	9.1	7.0
W_{int}	—	38.8 ^{b)}	237.0	0.2	1.0	48.1	18.6	16.9	15.3

a) The sample was measured immediately after being fractionated.

b) B-Form was measured.

Fractionation of Witepsol H-15 and the Characteristics of Each Fraction

Witepsol H-15 was used as a representative commercial vehicle, and fractionation was performed by recrystallization from acetone solution. In Table II, the yield, melting point, saponification value and fatty acid composition of each fraction are listed together with those of the B-form of the intact Witepsol H-15 (hereafter denoted as W_{int}). It was found that the fraction that crystallized earlier from acetone contained higher chain fatty acids such as C_{16} and C_{18} . This tendency was also apparent in the saponification values; that is, the order of saponification values was $F_3 > W_{int} > F_2 > F_1$, and this is consistent with the order of C_{18} contents. However, F_4 showed a lower value than expected. This might be caused by some unknown materials coexisting in the fraction, because F_4 was not prepared by crystallization but by evaporation of the solvent from the residual solution.

The crystals of F_1 and F_2 were seen to be needles by microscopic observation, and F_3 was mostly needles, but included leaflets and a little apparently amorphous material. F_4 was rich in amorphous material and liquid fat immediately after preparation, but it partially changed to leaflets after being allowed to stand for more than a week at room temperature.

The X-ray diffraction patterns of the fractions immediately after fractionation are shown in Fig. 4(A). However, after they had been melted and resolidified by rapid cooling, the diffraction patterns changed to those shown in Fig. 4(B). In Fig. 4(A), the X-ray diffraction patterns of all four fractions are clearly different from each other. Among them, F_1 , F_2 and F_3 could be regarded as the patterns of the most stable crystalline state. It is generally considered that the more stable crystal form is produced by slow recrystallization from a good solvent. In fact, these patterns did not change during storage under various conditions. However, the pattern of F_4 changed during storage at room temperature, as will be mentioned later.

On comparing these patterns with that of the B-form of W_{int} , it was noticed that the diffraction lines characterizing each fraction all coincided with characteristic diffraction peaks of the B-form pattern. Thus, the physical mixture was prepared by mixing F_1 , F_2 , F_3 and F_4 at weight ratios equal to the yield (%) values, and immediately subjected to X-ray diffraction measurement. This X-ray diffraction pattern was almost exactly the same as the B-form pattern of W_{int} , as shown in Fig. 5(A). Moreover, the calculated I_R value was also nearly the same as the observed value (I_R value of physical mixture, 1.48; W_{int} , 1.51). The I_R values were in the order $F_1(2.42) > F_2(2.03) > W_{int}(1.51) > F_3(0.72)$ (F_4 was excluded because of the absence of clear diffraction lines). This sequence is the same as that of the contents of C_{16} and C_{18} and that of melting point, as shown in Table II.

In Fig. 4(B), F_1 and F_2 showed the typical A-form pattern, having two characteristic lines of 4.27 Å and 3.83 Å; F_3 was similar to the A-form but had two small additional peaks of 4.11 Å and 4.43 Å; F_4 did not show any clear diffraction peak. The pattern of the physical mixture prepared in the same as described in the case of the B-form was A-form [Fig. 5(B)], and the I_R value was similar to that of A-form of W_{int} (physical mixture, 0.79; W_{int} , 0.82).

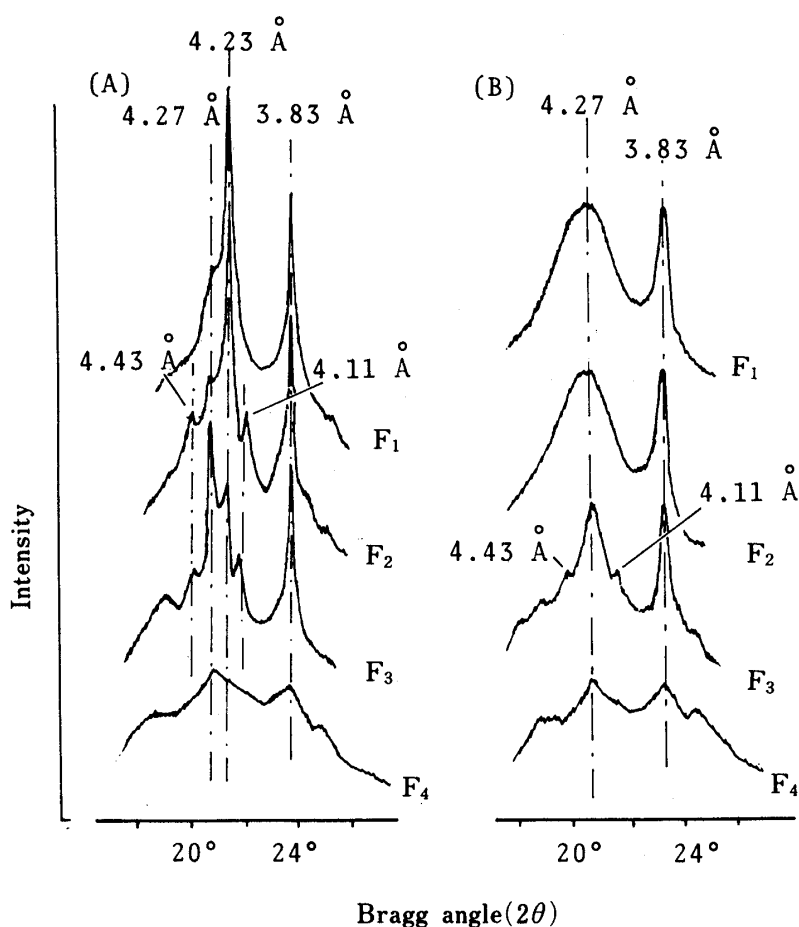


Fig. 4. Comparison of X-Ray Diffraction Patterns of Fractionated Fats

(A) The patterns immediately after fractionation from acetone solution.
 (B) The patterns after melting of the fractions followed by resolidification by rapid cooling.

When these fractions of unstable forms of F_1 , F_2 and F_3 were stored at higher temperature, they were transformed again to stable patterns like those shown in Fig. 4(A), but F_4 remained unchanged. In Table III, the times required for the transition from the unstable form of each fraction to the stable one during storage at 30 and 40°C are compared.

At 30°C, W_{int} , F_2 and F_3 took four days, seven days and two days, respectively, to transform from the unstable form to the stable form. F_4 was almost liquefied and could not be evaluated. On the other hand, F_1 did not show any change for more than a month. However, when this fraction was stored at 40°C, it rapidly transformed to stable form in two days; the other fractions melted or considerably softened.

Figure 6 illustrates the DSC patterns of the unstable form of the fractions and of W_{int} . Each of them shows a broad endothermic curve. From this thermogram, it was found that, at 30°C, F_1 did not melt at all, F_2 , F_3 and W_{int} melted partially and F_4 almost liquefied. The value of solid fat index (SFI) at 30°C, estimated as described previously,¹⁾ was in the order $F_4 < F_3 < W_{int} < F_2 < F_1$. This sequence is compatible with that of the transition speed. F_1 was partially liquefied at 40°C, at which temperature the transition was accelerated. These findings are in accord with the fact described in the previous paper that the presence of some liquid phase is necessary for the A-to-B transition of a vehicle.¹⁾

Attempts to Explain the Transition Behavior from Unit Cell Levels

The agreement between the X-ray diffraction patterns of the physical mixtures of fractions and those of W_{int} for both A- and B-form might suggest that the fatty vehicle, composed

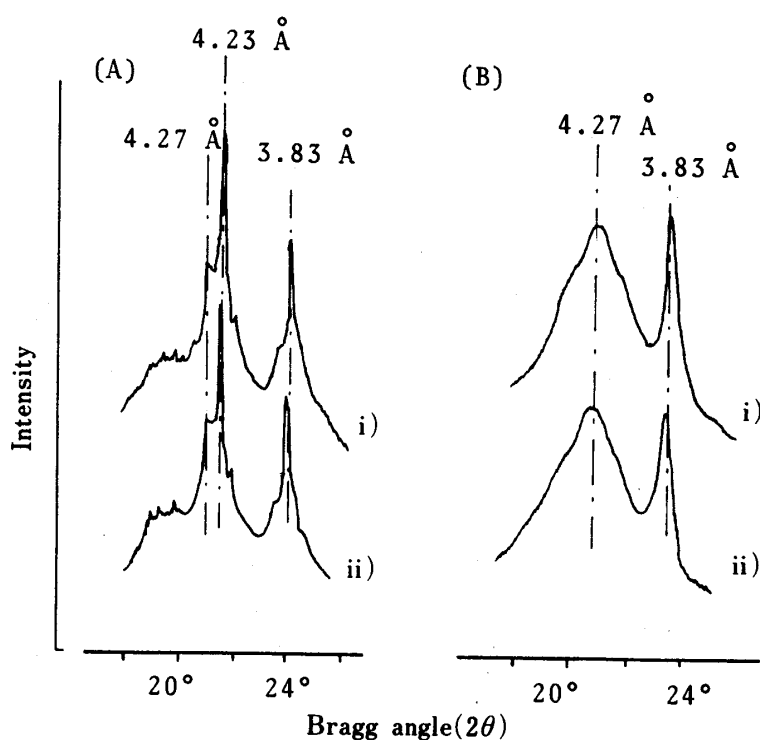


Fig. 5. Comparison of X-Ray Diffraction Patterns of Rhysical Mixture and A- and B-Form of Witepsol H-15

- (A) i) B-form of W_{int} , ii) physical mixture of fractions immediately after separation from acetone solution.
 (B) i) A-form of W_{int} , ii) physical mixture after melting of the fractions followed by resolidification by rapid cooling.

TABLE III. Time Required for the Transition fo Each Fraction during Storage

Storage temperature (°C)	F ₁	F ₂	F ₃	F ₄	W_{int}
30	> 30 d	7 d	2 d	— ^{a)}	4 d
40	2 d	— ^{a)}	— ^{a)}	— ^{a)}	— ^{a)}

a) Could not be estimated because of melting or softening.

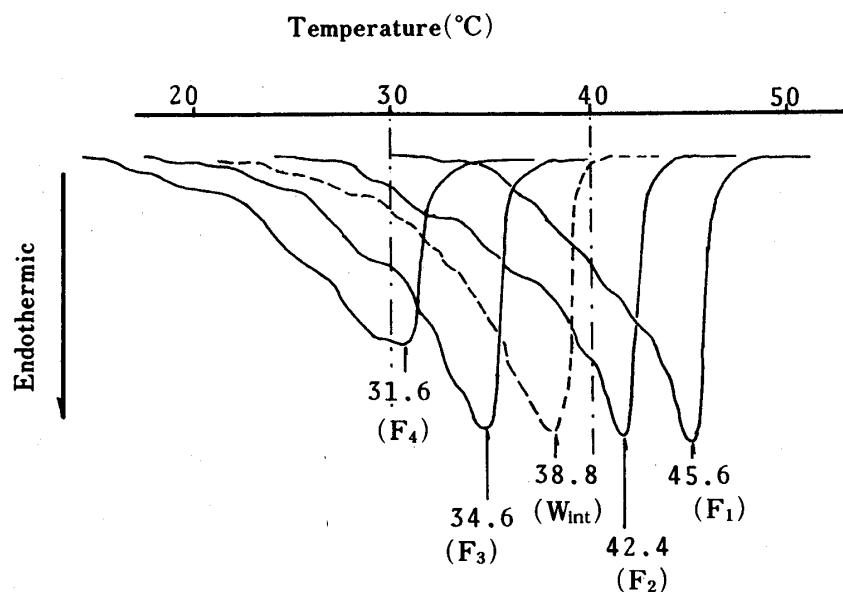


Fig. 6. Comparisons of the DSC Patterns of Unstable Crystal Forms

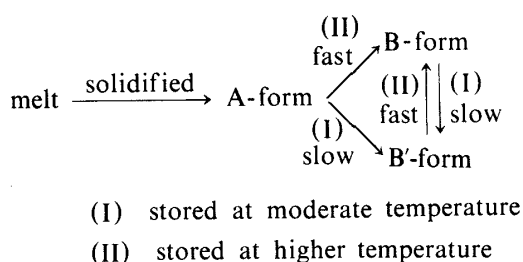


Chart 1. The Possible Mutual Relations of A-, B- and B'-Form

of many kinds of triglycerides, is not homogeneous at the molecular level (*i.e.* a complex mixture such as a solid solution or molecular composite), but is a eutectic mixture aggregated with large number of very fine crystal species. We use the term unit cell for this species according to Imamura *et al.*⁵⁾ Each unit cell is presumed to be composed of chemically similar triglycerides. Our proposal is basically in agreement with the concept of Guillot and Lombard.⁶⁾ Thus, the transition should occur essentially at the level of the individual unit cell, and be detected only at the overall level by X-ray diffraction.⁷⁾ This also suggests that the physical properties of a vehicle might be understood as the sum of those of the unit cells to some extent, though interactions among unit cells should also be present.

In the manufacturing process of suppositories, when the melt of the vehicle is cooled, the higher melting point material (probably rich in the triglycerides of higher fatty acids) should crystallize first, then the lower melting point materials may crystallize successively. Thus, the vehicle obtained by cooling in an ordinary manufacturing process can be considered as an assemblage of many kinds of unit cells of triglycerides. This view is supported by the following observations.

Sometimes a different X-ray diffraction pattern resembling B-form in appearance and having the same I_R value can be observed. This has two characteristic peaks of 4.60 Å and 3.75 Å in addition to the characteristic peaks of B-form, and was often observed for vehicles stored at moderate temperature for a long period. Hereafter, we denote this form as B'-form. The B'-form of Witepsol H-15 from the same batch as used in Figs. 4 and 5 is shown in Fig. 7a). It is known that: (1) B'-form changes to B-form in a very short time, with the disappearance of the 4.60 Å and 3.75 Å diffraction lines, when stored at a temperature such as 30 °C; (2) B-form does not change to B'-form easily, but sometimes does so after prolonged storage at a moderate temperature such as 20–25°C. Thus the possible relationships of A-, B- and B'-form are presumed to be as shown in Chart 1.

When each fractionated sample prepared in the preceding section was allowed to stand at moderate temperature, F₁, F₂, and F₃ did not show any change in the X-ray diffraction pattern, but F₄ changed from the broad pattern (Fig. 4) to a more distinct pattern and attained the stable form in ten days or so [Fig. 7c]. A physical mixture was prepared from F₁, F₂, F₃ and the stable F₄, and compared with the B'-form of W_{int} (Fig. 7). It is clear that

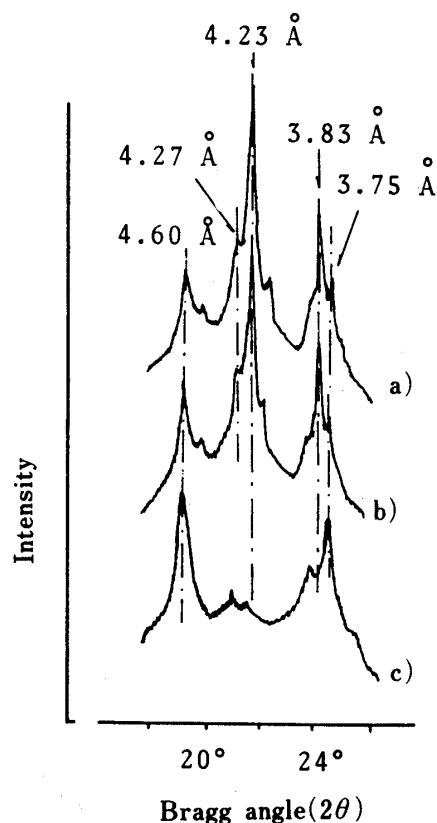


Fig. 7. Comparison of X-Ray Diffraction Patterns

- a) B'-Form of Witepsol H-15.
- b) Physical mixture prepared from the stable forms of fractions.
- c) Stable form of F₄.

the patterns are almost the same. As was already indicated in Fig. 5(A), the B-form could be "synthesized" from F_1 , F_2 , F_3 and the unstable F_4 . Thus, the difference between the B'- and B-form might be attributable to a difference in the crystalline state of a large number of unit cells of F_4 , which is rich in low melting point triglycerides.

In our experience, the form of the vehicle, B-form or B'-form, does not greatly affect most of the pharmaceutical properties of the suppository, such as the release rate of active ingredient, softening time, disintegration time, and melting point, as long as the I_R value is the same. This is easily explained as follows: the unit cells of low melting point, which cause the difference between B- and B'-form, usually melt completely at below body temperature even if they take the most stable form, so when the properties of the suppository are evaluated at near body temperature, both forms might exhibit almost the same physical properties because the low melting point fractions of both B- and B'-form would be liquefied to almost the same extent at this temperature.

Thus, the main properties of the suppository are primarily decided by the melting behavior of the unit cells of higher melting point. These unit cells are probably rich in triglycerides of longer chain fatty acids and take larger $I_{R\max}$ values, as can be seen from Fig. 1, 2 and Table II. Thus, $I_{R\max}$ may correlate with many properties of the suppository. However, the unit cells of lower melting points must influence the physical stability of vehicles, because the polymorphic transition was accelerated, as is evident from Fig. 3 and Table III. Therefore, it should be possible to obtain further useful information on the physical stability of the vehicles by more detailed investigation on the unit cells of lower melting point.

References and Notes

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