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The Influence of Drugs on the Physical Stability of Fatty Suppositories[1)]

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To examine the influence of drugs on the physicochemical stability of semisynthetic fatty suppositories, model suppositories containing various kinds of drugs were prepared with Witepsol H-15 and storage experiments were performed.

It was shown that the stability of pharmaceutical properties was largely dependent on the solubility of drugs in the fatty vehicle (S_o). That is, the rate of polymorphic transition of the vehicle measured by X-ray diffraction was accelerated by lipid-soluble drugs but was not much affected by lipid-insoluble drugs. The melting points measured by DTA generally decreased with increasing S_o, but they all increased by about 2 or 3°C during storage. The softening time decreased with increasing S_o. The release properties measured at 37°C were dependent on the solubility of the drugs in the dissolution fluid (S_w) initially but became dependent on S_o during storage. This phenomenon is discussed on the basis of the transportion mechanism of drugs in the lipid phase.

Keywords——suppository; stability; polymorphism; semisynthetic fatty suppository base; X-ray diffraction; transition rate; drug release; softening time; melting point

Previously, we showed that the crystal forms of semisynthetic fatty suppository bases gradually transformed from an unstable A-form to a more stable B-form during storage, and that this transition was generally accompanined by changes of the pharmaceutical properties, such as an increase of melting point, prolongation of softening time, depression of drug release and so on.[2)] The kinetic analysis of the transition showed that this process was so greatly affected by storage temperature that the activation energy was as large as about 100 kcal.[1)] Additionally, suppositories usually contain drugs with various physicochemical properties at various concentrations as required clinically. Since any sort of drug must interact to some degree with the vehicle, it seems necessary to clarify the influence of drugs on the pharmaceutical properties of suppositories. They may affect not only the initial pharmaceutical properties but also the physical stability during storage.

So far, many researchers have investigated these subjects,[3)] but they mostly used only one or two drugs and have not yet attempted to examine the relation between stability and a series of physicochemical properties of drugs.

In this paper, in order to obtain fundamental information useful for formulation study or quality control, storage experiments were performed using Witepsol H-15 suppositories containing drugs of various physicochemical properties. The melting point, polymorphic transition, drug release, etc. were measured, and the correlation between these pharmaceutical properties and the hydrophilicity and/or lipophilicity of drugs was investigated.

Experimental

Materials——Witepsol H-15[4)] was used as a representative semisynthetic fatty vehicle. Its physicochemical properties are as follows: acid value, 0.06; iodine value, 0.8; hydroxyl value, 12.1; saponification value, 237.0; fatty acid composition measured by GLC, 1.2% $C_{10:0}$, 48.1% $C_{12:0}$, 18.5% $C_{14:0}$, 16.9% $C_{16:0}$, 15.3% $C_{18:0}$, and others, none or trace. The model drugs used were as follows, and all met the requirements of JP IX: acetaminophen (AAP), aminophylline (APH), aminopyrine (APY), aspirin (ASP), benzoic acid (BA), ethenzamide (ETZ), indomethacin (IM), salicylic acid (SA) and sodium salicylate (SA-Na). They

were powdered in a mortar and the particle sizes were adjusted to the range of 53 μm to 105 μm by passing the powder through the JP standard sieves before use.

Preparation of Suppositories——A 10.0 g portion of drug was homogeneously mixed with 150 g of molten vehicle at 35°C, and the mixture was poured into metallic molds. It was allowed to stand for 2 h at room temperature (22—24°C) to solidify. The suppositories thus obtained weighed about 2.4 g, and the drug amount was 150 mg per suppository (6.25 w/w%). The placebo suppositories used as a reference consisted of vehicle alone, and were prepared in the same way.

Storage Conditions—— The suppositories which had been stored in a refrigerator overnight after preparation were regarded as initial samples. Storage experiments were carried out in a water bath controlled at the desired temperature within ±0.1°C.

X-Ray Diffraction——Measurement conditions were as follows: apparatus, Geigerflex 2013 (Rigaku Denki); radiation, Ni-filtered Cu-K_α (λ=1.54 Å); voltage/current, 40 kV/35 mA; divergence/receiving/scattering slit, 0.5°/0.3 mm/0.5°; scanning speed, 2°/min.

Melting Point——Differential thermal analysis was used. Measurement conditions were as follows: apparatus, Shimadzu DT 20B thermal analyzer; heating speed, 2°C/min; reference, α-alumina; range, ±100 μV. Accuracy of the temperature was checked by measuring the melting points of methyl stearate (39.2°C) and methyl arrachidate (46.4°C).

Drug Release Measurement——The dialysis method was used as described previously.[2] 500 ml of the 2nd fluid of the disintegration test (JP IX, phosphate buffer, pH 7.5) was used as the dissolution fluid. The test temperature was 37.0±0.1°C. The amount of drug released was assayed by spectrophotometry.

Solubility of Drug in the Vehicle (S_0)——A 3 g sample of drug was added to 20 ml of molten Witepsol H-15 at 37°C. The mixture was shaken for 24 h in the controlled water bath at 37°C, then filtered. A part of the filtrate was weighed accurately and diluted with ethanol. The assay was carried out by double beam spectrophotometry.

Solubility of Drug in the Dissolution Fluid (S_W)——An excess of drug was added to 10 ml of the dissolution fluid. The mixture was shaken for 24 h in the controlled water bath at 37°C, then filtered. The filtrate was diluted adequately with the dissolution fluid and assayed by spectrophotometry. In the case of ASP, to avoid hydrolysis during this procedure, the shaking time was shortened to 5 h. It had previously been confirmed that the equilibrium state was attained in 2 or 3 h, and that degradation was almost negligible in this period.

Softening Time—— Krowczynski's method[5] was used at 37.0±0.1°.

Results and Discussion

I. Measurement of the Degree of Polymorphic Transition in the Presence of the Drug

We showed in our previous paper that the degree of polymorphic transition of semisynthetic vehicle could be estimated by means of X-ray diffraction measurement, and that I_R values [defined as the relative intensity of characteristic diffraction peaks of unstable A-form (4.27 Å) and stable B-form (4.23 Å)] were useful for this purpose. Namely,

$$\begin{aligned} I_R &= I_B/I_A \\ I_B &= I_{21.1} - I_{blank} \\ I_A &= I_{20.7} - I_{blank} \end{aligned} \qquad (1)$$

where $I_{20.7}$ and $I_{21.1}$ mean the diffraction intensities at Bragg's angle (2θ) of 20.7° and 21.1°, respectively. I_{blank} is the background intensity; the intensity at 30.0° was used in the case of measurement of the vehicle alone.

However, in the case of suppositories containing drug, the diffraction patterns usually become rather complicated as a result of diffraction due to the drugs. Thus, before beginning this series of experiments, we confirmed the applicability of Eq. (1) for all model suppositories used in this paper. Fig. 1 shows the X-ray diffraction patterns of SA suppository as a representative example.

It is clear that the diffraction patterns of both initial and aged samples of SA suppository are almost coincident with that of the physical mixture. Similar results were obtained with all other drug suppositories used in this experiment. It was thus presumed that the drugs are all dispersed homogeneously as solid particles in the solid vehicle, and that essentially no special complexes between vehicles and drugs are formed during the preparation or storage time. Then, to check the applicability of I_R measurement, physical mixtures of higher drug

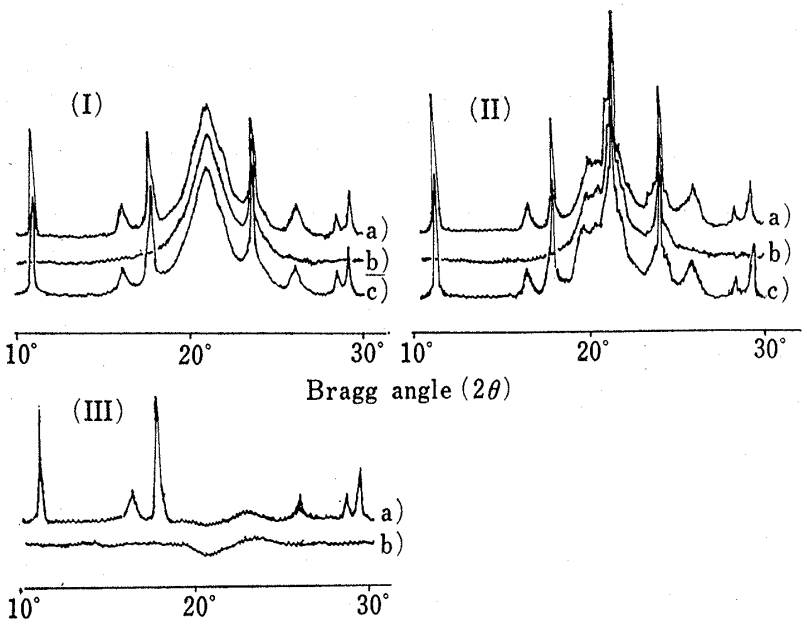

Fig. 1. Comparison of the X-Ray Diffraction Patterns of SA Suppository and Physical Mixture

(I) Freshly prepared sample; a) SA suppository, b) vehicle (Witepsol H-15), c) physical mixture produced with b) and SA at the same ratio as a). (II) Aged sample; a) SA suppository, b) vehicle, c) physical mixture. (III) SA; a) diluted with amorphous cornstarch powder at the same concentration as SA suppository, b) amorphous cornstarch powder.

TABLE I. I_R Values[a] of Physical Mixtures of Drugs and the A– or B–Form of Witepsol H-15 at Two Drug Concentrations

Drug	A-form		B-form	
	6.25%	15%	6.25%	15%
Acetaminophen	0.86±0.01	0.84±0.01	1.46±0.01	1.39±0.02
Aminophylline	0.87±0.02	0.86±0.01	1.49±0.02	1.47±0.01
Aminopyrine	0.86±0.01	—[b]	1.47±0.02	—[b]
Aspirin	0.85±0.02	0.87±0.01	1.47±0.03	1.38±0.01
Benzoic acid	0.86±0.01	0.88±0.02	1.50±0.02	1.50±0.01
Ethenzamide	0.87±0.01	0.85±0.02	1.46±0.02	1.48±0.02
Indomethacin	0.87±0.01	0.85±0.02	1.48±0.02	1.53±0.02
Salicylic acid	0.87±0.01	0.86±0.02	1.49±0.02	1.50±0.03
Sodium salicylate	0.87±0.01	0.87±0.02	1.46±0.01	1.49±0.01
Vehicle alone[c]	0.85±0.02		1.49±0.02	

a) Each value represents the mean ± S.D of five determinations.
b) Determinations were impossible because a diffraction peak due to the drug itself interfered.
c) Witepsol H-15.

concentration, 15%, were prepared with A- or B-form Witepsol H-15, and were subjected to X-ray diffraction measurement. The I_R values of the physical mixtures of 6.25% and 15% are listed in Table I. The values of I_{30} were used as I_{blank} for all suppositories except in the case of BA, for which I_{29} was used because of the presence of a small diffraction peak near 30° (2θ).

As shown in Table I, when the drug content was 6.25%, the mean I_R values for A-form were from 0.85 to 0.87 and those for B-form were from 1.46 to 1.50. These values are almost the same as the vehicle values. Thus, it seemed that drugs had hardly any influence on the measurement of I_R values at this concentration. However, when the concentration was raised to 15%, it was impossible to assess I_R values of APY because of the large variances of measure-

ment for both A- and B-form. This is because APY has a X-ray diffraction peak near 20.5° (2θ), and this peak interferes with the measurement seriously when the drug content is high. Besides APY, the I_R values of B-form of AAP and ASP suppositories were reduced somewhat, but those of the other six drugs were almost the same as the vehicle values.

Thus, it is difficult to assess the degree of transition in terms of I_R values for some drugs at higher concentration, but even if drugs have diffraction peaks near 20.7° or 21.1°, this method might be applicable to most drugs at concentrations below 6% or so.

The influence of drugs on the polymorphism of vehicles was therefore examined in the region of concentration where the drugs had hardly any effect on the I_R measurement.

II. The Rate of Transition of the Vehicle in the Presence of Drugs

The variations of I_R values during storage at 30.0°C are shown in Fig. 2 for nine model suppositories and the vehicle. It was found that they all fell to a minimum (I_{Rmin}) in the early period, subsequently increased to a maximum (I_{Rmax}) and then remained constant. For all suppositories, the values of I_{Rmin} and I_{Rmax} were in the range from 0.78 to 0.83 and from 1.45 to 1.49, respectively, and were close to those of the vehicle itself. Thus, it was considered that the A- and B-crystal forms of the vehicle were not affected by addition of the drug. However, as regards the rates of transition, there seemed to be some differences among drugs. Namely, in the case of BA, SA and APY, the rates were faster than that of the vehicle, while in the cases of SA–Na, APH and AAP, they were almost the same or slightly lower.

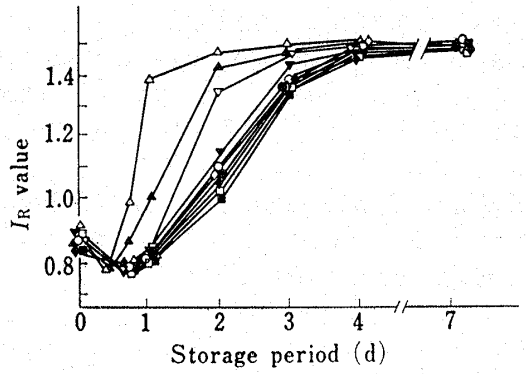

Fig. 2. Changes of I_R Value of Suppositories Containing Various Drugs during Storage at 30°C

△, BA; ▲, SA; ▽, APY; ▼, ASP; ○, vehicle alone; ●, IM; ◇, ETZ; ◆, SA–Na; □, AAP; ■, APH.

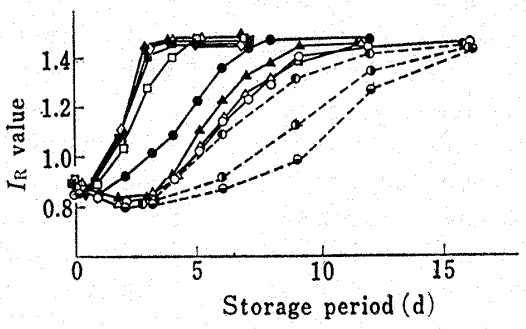

Fig. 3. Change of I_R Values of BA and SA–Na Suppositories of Various C_D Values during Storage at 28°C

—○— Vehicle, —△— BA, 0.25%,
—▲— BA, 0.5%, —●— BA, 1.0%,
—□— BA, 3.0%, —■— BA, 5.0%,
—◇— BA, 10%, —◆— BA, 20%,
—◐— SA–Na, 5.0%, —◑— SA–Na, 10%,
—◒— SA–Na, 20%.

Fig. 3 showed the concentration dependencies of the change of I_R value at 28.0°C for BA and SA–Na. These drugs were selected because they showed typical fast and slow transition rates, respectively. Here ,the storage temperature was lowered from 30.0 to 28.0°C, because the transition proceeds more slowly at 28.0°C and it should be possible to distinguish the difference of transition more distinctly than at 30.0°C. In the case of BA, the transition was accelerated with increasing concentration of drugs (C_D) in the region of less than 5%, but it hardly changed when C_D was over 5%. On the other hand, the transition of SA–Na suppository was delayed with increasing C_D to some extent.

The opposite effects on the rate of transition may reflect some difference of physicochemical interaction between the drugs and the vehicle. Thus, we performed differential thermal analysis at the same time and measured the melting point as described previously[2] (Fig. 4). The melting point of both suppositories increased by about 2°C during storage, irrespective of C_D. However, in the case of BA, it decreased with C_D in the region below 5%, and became

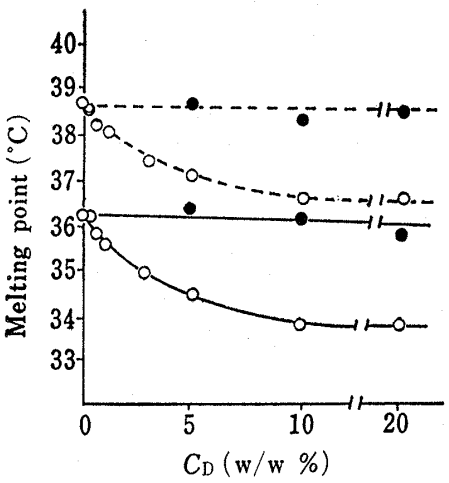

Fig. 4. Changes of the Melting Point of BA and SA–Na Suppositories *vs.* C_D

○, BA suppository; ●, SA–Na suppository; ——, freshly prepared; – – –, aged at 30°C for two weeks.

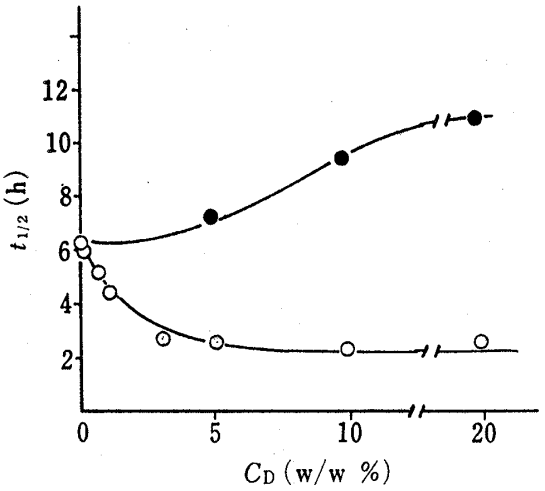

Fig. 5. The Changes of $t_{1/2}$ of BA and SA–Na Suppositories *vs.* C_D

○, BA suppository; ●, SA–Na suppository.

almost constant above 10%, whereas SA–Na suppositories showed almost the same melting point as the vehicle in both initial and aged samples.

Here, as a rate parameter, the half-transition time ($t_{1/2}$) was calculated as described previously[1] from the data in Fig. 3; the results are plotted against C_D in Fig. 5.

A comparison of Fig. 4 and Fig. 5 shows that, in the case of BA, the C_D ranges where $t_{1/2}$ and the melting point change coincide well. This phenomenon indicates that there is a relation ship between the rate of transition and the melting point. However, in the case of SA–Na suppositories, the correspondence was poor.

When a substance containing a minor amount of impurity melts, it is well known that eq. (2) describes the relation between the molar fraction of impurity (N) and the degree of melting point decrease (ΔT),[6] if the solid solution is not formed in the solid phase.

$$N = A(\Delta T) \tag{2}$$

where A is a constant related to the fusion of the pure substance. If the vehicle can be regarded as a pure substance (in practice, it is not pure but a mixture of many kinds of triglycerides), the equation may be applicable to the melting behavior of the suppository. Here, it should be pointed out that the drugs do not dissolve in the solid phase but dissolve in the molten liquid phase.

The curves of the initial and aged samples of BA suppository (Fig. 4) show almost linear decrease of melting point in the lower C_D range, and the slopes are almost the same in both samples. Therefore, Eq. (2) can be applied to the linear region of the curves. The flat region may indicate that the drug was present in excess of its solubility in the liquefied vehicle. It should be possible to calculate the solubilities of drugs in the vehicles from the ΔT values by means of Eq. (2), but the results are not very precise because a small difference of temperature (within 0.1 or 0.2°C) could not be clearly distinguished by DTA. Moreover, we regarded the temperature corresponding to the maximum on the DTA curve as the melting point, but this may not always be the temperature at which the solid is completely liquefied. As shown in Table II, the melting points of suppositories were all lower than that of the vehicle (that is $\Delta T > 0$°C) with the exception of AAP in the initial state. But, in this case, such a slight difference as 0.2°C can be ascribed to experimental error and may be regarded as effectively equal to 0°C. Therefore ΔT should be regarded as reflecting the solubility only qualitatively.

The solubilities of drugs in the liquefied vehicle at 37°C (S_0) were measured. The values of S_0 are listed in Table II with ΔT for the initial and aged suppositories. For the purpose of

discussion, we adopted S_0 as an index of the affinity between drugs and vehicle.

Fig. 6 shows the relationship between $t_{1/2}$ and S_0 for the drugs. It was found that $t_{1/2}$ decreased with increasing S_0. In the case where S_0 is more than about 4 mg/g, the transition was accelerated by the drugs, where S_0 is about 4 mg/g, it was almost the same as that of the vehicle, and where S_0 is particularly low, such as for AAP, APH and SA–Na, it was delayed slightly.

Goto *et al.* stated that the α-to-β transition of tristearin was remarkably accelerated in the presence of organic solvents or liquid oils having high affinity for tristearin.[7] These results are in accord with ours. As Witepsol H-15 is composed of many kinds of triglycerides, the vehicle is partly liquefied at the storage temperature, 30°C, so that solid and liquid phases coexist in it. Consequently, if the added drug is lipophilic, its melting point is lowered, and the fraction of liquid phase becomes greater than that of the vehicle.

Table II. ΔT Values[a] of Suppositories and the Solubilities of Drugs

Drug	ΔT_{in}[b] (°C)	ΔT_{ag}[c] (°C)	S_o (mg/g)	S_w (mg/ml)
Acetaminophen	0	0	0.5	17.5
Aminophylline	−0.2	0.2	0.5	53.6
Aminopyrine	1.2	1.2	26.1	41.5
Aspirin	0.2	0.4	4.8	19.0
Benzoic acid	1.4	1.8	59.4	14.9
Ethenzamide	0.2	0.2	4.1	1.3
Indomethacin	0	0.2	3.9	2.6
Salicylic acid	1.4	1.6	34.2	13.4
Sodium salicylate	0.2	0	0.6	114.8

a) ΔT = the melting point of vehicle alone − the melting point of suppository.
b) ΔT_{in} means ΔT of the freshly prepared sample.
c) ΔT_{ag} means ΔT of the aged sample for two weeks at 30°C.

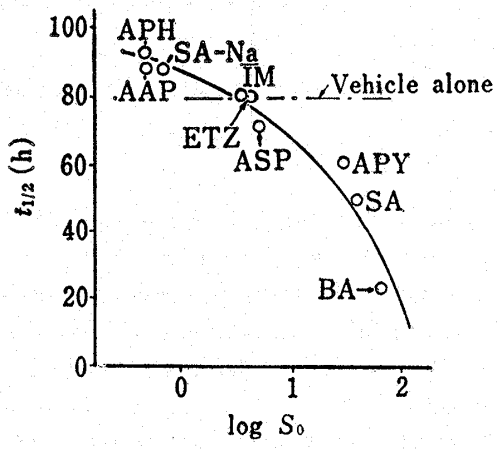

Fig. 6. Relation between $t_{1/2}$ of 6.25% Suppositories and S_0 of Various Drugs

They also stated that the transition proceeded faster at the liquid–solid interface.[7] The delay of transition by the addition of a poorly lipophilic drug may also be explained from their viewpoint. That is, the presence of an insoluble drug should tend to reduce the area of the liquid–solid interface of fat because of the interference of drug particles there. This

Table III. Changes of the Melting Point and Softening Time of Suppositories during Storage at 30°C

Drug	Melting point[a] (°C)			Softening time[a]		
	initial	3 d	14 d	initial	3 d	14 d
Acetaminophen	36.2	38.4	38.8	16′45″	41′10″	40′40″
Aminophylline	36.4	38.2	38.6	18′05″	41′20″	42′05″
Aminopyrine	35.0	37.6	37.6	15′20″	29′05″	28′50″
Aspirin	36.0	38.2	38.4	16′10″	34′45″	33′20″
Benzoic acid	34.8	36.8	37.0	10′55″	16′05″	16′20″
Ethenzamide	36.2	38.0	38.6	16′20″	37′40″	38′05″
Indomethacin	36.2	38.4	38.6	17′40″	39′25″	40′30″
Salicylic acid	34.8	37.0	37.2	12′05″	20′05″	18′10″
Sodium salicylate	36.0	38.6	38.8	16′20″	40′35″	41′05″
Vehicle alone[b]	36.2	38.4	38.8	14′30″	38′20″	39′55″

a) Each value represents the mean of three determinations.
b) Witepsol H-15.

phenomenon is interesting, and of practical significance. We intend to carry out further investigations.

III. The Influence of Drugs on Melting Point and Softening Time

The values of melting point and softening time of the suppositories during storage at 30°C are given in Table III. The freshly prepared samples exhibited various melting points from 34.8 to 36.4°C, but all melting points showed an increase of about 2 or 3°C within three days, and subsequently remained constant.

The softening times seeme to be shorter than that of the vehicle when the drugs are soluble in the vehicle and longer when the drugs are insoluble. The reason for the latter phenomenon is presumably the increase of rigidity caused by addition of an insoluble solid drug. The softening times increased at the initial period of storage and subsequently became almost constant in the same manner as the melting point.

For convenience in evaluating the influence of drugs on the stability of softening time, the relative softening time, R_{ST}, was defined according to Eq. (3) and calculated for each suppository.

$$\begin{aligned} ST &= \text{Softening time of the aged sample} \\ &\quad - \text{Softening time of the initial sample} \\ R_{st} &= ST_{sup}/ST_{ve} \end{aligned} \tag{3}$$

where ST_{sup} and ST_{ve} mean the ST of suppository containing a drug and that of vehicle, respectively. When the values of R_{st} are smaller than 1, the drugs are regarded as having some ability to depress the prolongation of softening time, but when they are larger than 1, they are regarded as promoting the prolongation. The R_{st} values of model suppositories aged for two weeks at 30°C are plotted against S_0 in Fig. 7. Under these storage conditions, the crystal forms of these suppositories all changed to B-form, as shown in Fig. 2. The R_{st} values generally decreased as S_0 increased. This tendency should reflect the extents of liquefied fraction. That is, the higher the S_0 values of drugs, the lower the melting point of the suppositories; consequently, the liquefied fraction increases and the suppositories become softer with increasing S_0 at the measurement temperature, 37°C.

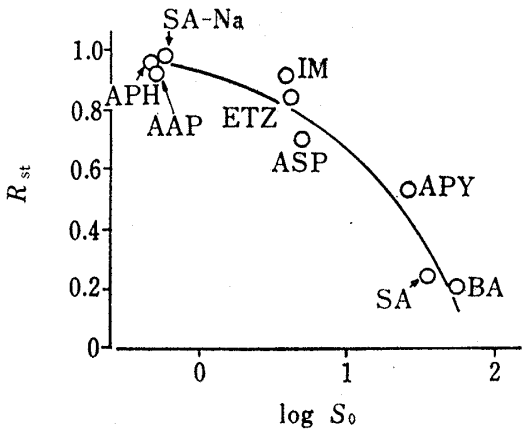

Fig. 7. Relation between R_{st} of Various Suppositories and the Solubility of the Drugs in the Vehicle

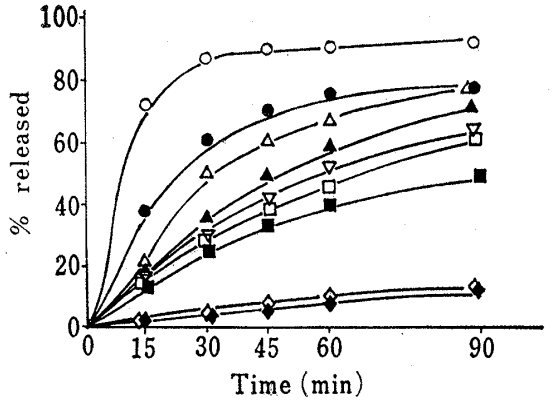

Fig. 8. The Release Curve of Drugs from Freshly Prepared Suppositories at 37°C

(○) SA-Na, (●) APH, (△) BA, (▲) AAP, (▽) SA, (□) APY, (■) ASP, (◇) ETZ, (◆) IM.

IV. The Influence on the Release of Drug from Suppositories

Fig. 8 shows the release of drugs as a function of time from freshly prepared suppositories. To calculate the release rate parameters from these curves, pseudo-first order plots or plots according to Higuchi's equation were tried,[8] but they deviated from linearity in some cases.

Thus, for convenience we adopted the released % after 90 minutes (R_{90}) as a rate parameter, as in a previous paper.[2] We tried to plot values of R_{90} against S_0, but there appeared to be no relation. However, plots against the solubility in the dissolution fluid (S_w, listed in Table II) showed a correlation between S_W and R_{90} (Fig. 9).

The values of R_{90} decreased for all suppositories during storage at 30°C as shown in Table IV. The bulk of the change in release behavior was completed within three days, as was the case with other physical properties such as melting point, softening time and I_R. Therefore, this phenomenon is also attributable to the polymorphism of the vehicle. The value of R_{90} of the suppositories stored for two weeks at 30°C was plotted against log S_0 (Fig. 10). It was shown that R_{90} increased with S_0, but there was no correlation with S_W.

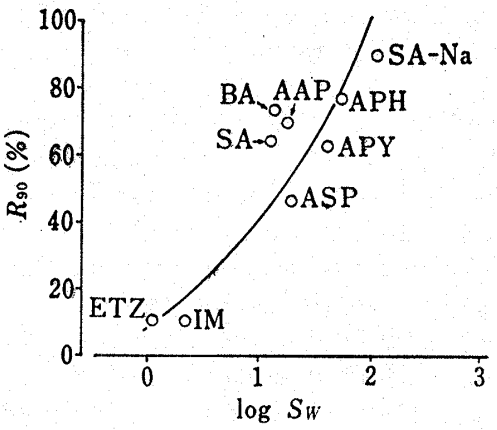

Fig. 9. Relation between R_{90} of Freshly Prepared Suppositories and the Solubility of Drugs in the Dissolution Fluid

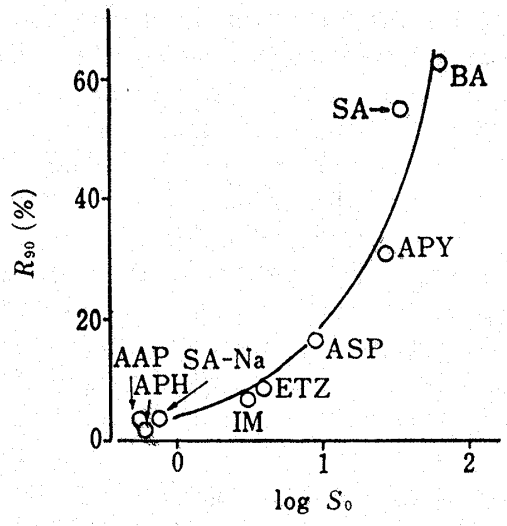

Fig. 10. Relation between R_{90} of Aged Suppositories and the Solubility of Drugs in the Vehicle

TABLE IV. Changes of the Drug Release Properties of Suppositories during Storage at 30°C

Drug	R_{90}[a] (%)		
	initial	3 d	14 d
Acetaminophen	70.8	2.6	3.5
Aminophylline	77.3	3.1	3.8
Aminopyrine	61.5	30.1	31.1
Aspirin	47.8	15.0	14.6
Benzoic acid	75.2	62.0	63.2
Ethenzamide	12.8	8.6	8.8
Indomethacin	12.4	6.4	6.8
Salicylic acid	63.2	56.4	54.8
Sodium salicylate	91.8	4.1	3.6

a) Each value represents the mean of three determinations.

Many studies have been reported on the mechanism of drug release from fatty suppositories.[9] According to them, a lipid-soluble drug dissolves in the vehicle first and passes through the lipid–water interface by diffusion (case A). However, a lipid-insoluble drug has to be carried to the lipid–water interface by some mechanical transportion process, such as sedimentation. There, the particles are wetted by the water phase and released from the vehicle into the dissolution fluid (case B).

In our experiments, the mechanisms of transportion of the drug to the lipid–water interface

may differ from drug by drug because they have different S_0 values. For instance, in the case of small S_0 (SA–Na, APH and AAP), the process should follow "case B." But, on the other hand, in the case of larger S_0 (BA, SA and APY), it should follow not only "case B," but also "case A," because the drug partly dissolves in the liquefied vehicle. Whether it follows "case A" or "case B," the results should depend largely on the rheological characteristics of the liquefied vehicle, because both Fick's diffusion coefficient (case A) and Stokes' sedimentation rate (case B) are functions of the viscosity of the medium.

In our dissolution test using a cellulose tube, the influence of spreading of the molten vehicle in the tube due to the hydrostatic pressure of the dissolution fluid should also be considered. The spreading presumably accelerates transport of the drug particles to the interface because the distance of the interface is reduced by spreading. The spreading mechanism is not simple to analyze, but it also depends on the viscosity, as does sedimentation.

Thus, the findings that the values of R_{90} of initial samples are related to S_W (Fig. 9) but not S_0, and that those of aged samples have a similar relation with S_0 (Fig. 10), but not with S_W, can be explained as follows.

At the test temperature, 37°C, the suppositories of low melting point A-crystal form are easily liquefied, irrespective of the kind of drug contained. Consequently, the vehicle become less viscous and the drugs can be transported so easily to the interface that the rates of transportion do not differ much. After the drugs reach the interface, the dissolution of the drugs into the aqueous phase becomes the rate-limiting process and depends on the solubility of the drugs in the dissolution fluid. Thus, R_{90} increases with S_W for the freshly prepared samples. However, the suppositories of higher melting point B-crystal form are not always liquefied easily in a test at 37°C. As the result, the medium is generally more viscous than those of the initial samples. In such a case, the transport of the drugs to the lipid-water interface may become the rate-limiting process.

As described in our earlier paper,[2] the release behavior was significantly affected by the test temperature (T_t). The relations between T_t and the melting range of suppository (M_R) could be classified into three main cases. (1) T_t is rather lower than M_R, so that the drugs can hardly be transported to the interface through the solid vehicle. (2) T_t is nearly coincident with M_R, so that the release tends to change greatly with even a little variation of T_t. (3) T_t is rather higher than M_R, so that the vehicles readily liquefy and the drug is easily transported to the interface; thus, release occurs more easily than in the former two cases and is not so much affected by the variation of T_t.

Thus, in case (3), R_{90} should have a good correlation with S_W, but in case (2), it should have a good correlation with S_0, in contrast. The change of release dependency from on S_W in the initial sample to on S_0 in the aged sample probably reflects the change in the relation of T_t and M_R from case (3) to case (2) due to the A-to-B transition of the vehicle.

In order to ensure good and equivalent bioavailabilities at any time the vehicles should liquefy readily even after completing the A-to-B transition. Thus, the selection of vehicles of low melting point is desirable, though in such cases, there may be some difficulties in practical use because the suppository easily softents at higher room temperature or in the hand of the patient. Therefore, it is necessary in formulation studies to achieve a balance between these two opposite requirements.

References and Notes

1) This paper forms Part III of "Studies on the Stability of Suppositories." The preceding paper, Part II; H. Yoshino, M. Kobayashi, and M. Samejima, *Chem. Pharm. Bull.*, **29**, 2661 (1981).
2) H. Yoshino, M. Kobayashi, and M. Samejima, *Yakuzaigaku*, **41**, 102 (1981).
3) G. Regdon, G. Mezey, and K. Sztankovanszky, *Pharmazie*, **28**, 461 (1973); *idem*, *ibid.*, **28**, 405 (1973); A. Moës and F. Jaminet, *Pharm. Acta Helv.*, **51**, 119 (1976); C.J.de Blaey and J.J. Rutten-Kingma, *ibid.*, **51**, 186 (1976); *idem*, *ibid.*, **52**, 11 (1977); K. Yonezawa, I. Yamaguchi, K. Saito, Y. Kanakubo,

and M. Nakamura, *Yakuzaigaku*, **40**, 188 (1980).
4) Produced by Dynamit Nobel Chemicals, Witlen, West Germany.
5) B.R. Guillot and A.P. Lombard, "The Suppository," Maloin S.A, Paris, 1973, p. 119.
6) T. Takeuchi, "Kiso-Bunsekikagaku Koza," Vol. 28, Kyoritsu-shuppan Co., Ltd., Tokyo 1967, p. 73.
7) M. Goto and E. Asada, *Yukagaku*, **21**, 257 (1972).
8) A. Akazawa, N. Watanabe, Y. Yasuda, Y. Fukunaga, S. Shimizu, K. Yano, K. Furukawa, and C. Konda, *Yakuzaigaku*, **34**, 47 (1974); S. Muranishi, Y. Okubo, and H. Sezaki, *ibid.*, **39**, 1 (1979).
9) A.J.M. Schoonen, F. Moolenaar, C. Haverschmidt, and T. Huizinga, *Pharm. Weekbl.*, **111**, 585 (1976); *idem*, *Int. J. Pharm.*, **4**, 141 (1979); J.J. Rutten-Kingma, C.J.de Blaey, and J. Polderman, *ibid.*, 3, 179 (1979); *idem*, *ibid.*, 3, 39 (1979).