Influence of Solid Fat Index in Triglyceride Suppository Bases on Drug Release

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In order to elucidate the factors affecting drug release characteristics from triglyceride suppositories, we have measured the solid fat index (SFI) of triglyceride suppository bases by the differential scanning calorimetry method. When Witepsol H15, widely used for suppository bases, was stored at 30 °C for 2 weeks, an increase in the SFI value of Witepsol H15 occurred, resulting in decreases in the release rate of morphine hydrochloride from stored suppositories. However, the degree of increase in SFI of stored Witepsol H15 was found to be different among some lots. To further investigate the relation between SFI and drug release rate in triglyceride bases, mixed bases of Witepsol H15 and Witepsol E85, which have various SFI values, were prepared. The addition of Witepsol E85 to Witepsol H15 resulted in an increase in SFI of the Witepsol H15–Witepsol E85 (H15–E85) mixed base. The increase of SFI brought about changes in some physicochemical properties of the H15–E85 mixed base such as increases in the melting point and the apparent viscosity. The release profiles of brilliant blue as a model drug from the H15–E85 mixed base could be expressed by Jander's equation. The logarithms of the release rate constants of brilliant blue from the H15–E85 mixed base, as well as those of morphine hydrochloride from stored Witepsol H15, were found to have a linear relation with SFI. These results indicate that SFI, which is considered to directly represent the melting state of suppository bases, is closely correlated with the drug release rate from triglyceride suppository bases.

Keywords solid fat index; triglyceride suppository base; polymorphic transition; Jander's equation; morphine hydrochloride

Triglyceride suppository bases have been widely used for the rectal administration of many drugs.[1–3] However, it has also been well known that many pharmaceutical properties of triglyceride suppositories tend to change during storage because of their polymorphisms.[4–6] Previously, we have reported that the release of morphine hydrochloride from Witepsol H15 used as a triglyceride suppository base changed during storage and that the degree of change in the release rates was different among some lots of Witepsol H15.[7]

In this study, we have measured the solid fat index (SFI), a parameter mainly used in food chemistry, by the differential scanning calorimetry (DSC) method.[8,9] SFI is a parameter directly indicating the melting state of fats and oils. We have applied this parameter to triglyceride suppository bases in order to clarify the influence of SFI in triglyceride suppository bases on the pharmaceutical properties of suppositories. The relation of SFI to the physicochemical properties and drug release characteristics in suppository bases was investigated.

Experimental

Materials Witepsol H15 and Witepsol E85 (hüls A.G.) were obtained from Mitsuba Trading Co., Ltd. Morphine hydrochloride (Dainippon Pharmaceutical Co., Ltd.) was purchased from Nihon Shoji Co., Ltd. Brilliant blue was purchased from San-ei Chemical Ind., Ltd.

Preparation of Suppository Suppositories were prepared using the fusion method. Morphine hydrochloride or brilliant blue was mixed with a melted base and dispersed homogeneously. When a mixture of Witepsol H15 and Witepsol E85 was used as the suppository base, Witepsol E85 was mixed well with Witepsol H15 at 60 °C before brilliant blue was added. It was then poured into plastic molds and allowed to cool at room temperature. Prepared samples were stored at 4 °C until use.

Release Tests The drug release test from the suppository (1.2 g) was performed by a rotating dialysis cell method using a PTSW type cell (Pharma Test, Germany).[10,11] The dissolution phase was 900 ml of 20 mM phosphate buffered saline (pH 7.4) and 5 ml of phosphate buffered saline was placed in the release cell. The cell was rotated at 25 rpm and the dissolution phase was maintained at 37 °C. Durapore HVLP, 0.45 μm (Millipore Ltd.), was used as a membrane. An aliquot (3 ml) of the dissolution phase was removed at appropriate intervals and the volume of the removed sample was replaced. The concentrations of morphine and brilliant blue were assayed spectrophotometrically at 240 and 630 nm, respectively.

Determination of Melting Point The melting point of each base was measured according to the second method of the Japan Pharmacopoeia XII melting point guidelines.

Measurement of Viscosity The apparent viscosity of each base was measured with a cone and plate viscometer (visconic model E, Tokyo Keiki Co., Ltd.) at 37 °C. The quantity of each sample was 1.0 g and the shear rate was 192 s^{-1}.

DSC Analysis DSC thermograms were obtained using a Rigaku Thermoflex TAS200 system. The milled samples were weighted in aluminum pans and heated at 2 °C/min. For measurement of SFI at 37 °C, the samples were heated at 2 °C/min until they reached 37 °C, and were then maintained at that temperature for 5 min and heated at 2 °C/min again. From the area under the peaks before 37 °C (S_1) and the area after 37 °C (S_2), SFI was calculated as:

$$\mathrm{SFI}(\%) = 100S_2/(S_1 + S_2)$$

Results and Discussion

Effect of Storage on Release Rate of Morphine Hydrochloride from Witepsol H15 Suppositories We have previously reported that the release rate of morphine hydrochloride from Witepsol H15 suppositories changed during storage.[7] Figure 1 shows the release profiles for the Witepsol H15 suppositories before and after storage. Before storage, the suppositories exhibited almost the same release profiles among the different lots, A—D, whereas the release rates of morphine hydrochloride from these suppository bases stored at 30 °C for 2 weeks were slower than those before storage. In addition, the degree of reduction in the release rates were different among lots A—D. A slight decrease in the release rate with the base of lot A, for example, was observed, whereas the release rate with the base of lot D significantly decreased. These

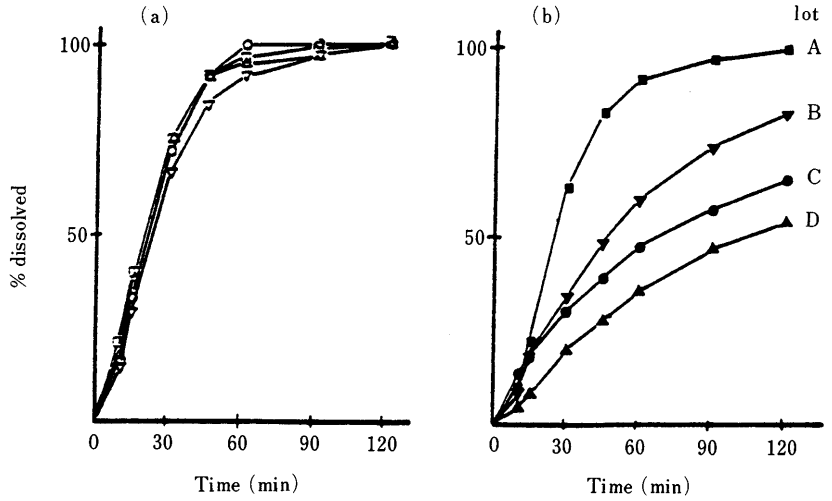

Fig. 1. Release Profiles of Morphine Hydrochloride from Witepsol H15 Suppositories
(a) before storage, (b) stored at 30°C for 2 weeks. Each point represents the mean of 3 experiments.

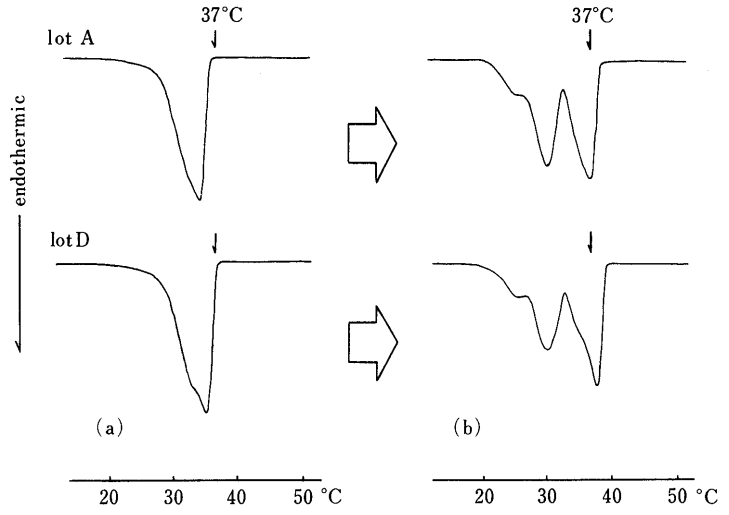

Fig. 2. DSC Thermograms of Witepsol H15 Bases
(a) before storage, (b) stored at 30°C for 2 weeks. Lot A and lot D represent the lot number of the Witepsol H15 base shown in Fig. 1.

differences in release rates among the different lots were remarkably greater than the deviations of the release rates within the same lot. Increases in the melting point and apparent viscosity at 37 °C of these bases were also observed during storage (data not shown).

Effect of Storage on DSC Thermograms and the SFI of Witepsol H15 Bases Figure 2 shows DSC thermograms of the Witepsol H15 bases of lots A and D before and after storage at 30 °C for 2 weeks. The separation of one endothermic peak into two peaks was observed in both bases of lot A and D, but the peak temperatures were different. One peak at 34.8 °C separated into two peaks at 30.0 °C and 37.0 °C for the base of lot A, whereas a peak at 35.5 °C separated into 30.2 °C and 37.9 °C for the base of lot D. Complete melting at 37 °C was observed in both bases of lots A and D before storage. In contrast, neither of the bases stored at 30 °C for 2 weeks melted completely at 37 °C. Therefore, the melting state at 37 °C of both the stored bases seemed to be attributed to the endothermic peaks on the side of the higher temperature.

To quantitatively represent the differences in endothermic peaks of these bases, we measured and calculated the SFI of these Witepsol H15 bases at 37 °C. As a result, the SFI values were 1.2, 3.9, 5.0, and 8.4% for lots A, B, C, and D respectively. The SFI values of these bases were found to coincide in order with the release rates of morphine hydrochloride from stored Witepsol H15 suppositories as shown in Fig. 1.

It is known that the fatty acid composition of various commercially available semisynthetic fatty vehicles, such as Witepsol H15, differed considerably among different lots, even if they were of the same brand, and the polymorphic transition of fatty suppository bases was correlated with the content of higher fatty acids.[5] We also observed considerable differences in fatty acid composition among lots A—D, and such differences seemed to be related to differences in the endothermic peaks in Fig. 2. However, no evident correlation between the fatty acid composition of Witepsol H15 and the release rate of morphine hydrochloride from stored Witepsol H15

suppositories was found.

Preparation of Mixed Bases of Witepsol H15 and Witepsol E85 We prepared mixed bases of Witepsol H15 and Witepsol E85 as model bases which have various SFI values. Although both Witepsol H15 and Witepsol E85 are mainly composed of triglyceride, Witepsol E85 is a base which has a relatively high melting point (42.0—44.0 °C) compared with Witepsol H15, whose melting point is 33.5—35.5 °C. Figure 3 shows DSC thermograms of Witepsol H15–Witepsol E85 (H15–E85) mixed bases. When Witepsol H15 was mixed with Witepsol E85, the endothermic peak derived from Witepsol H15 was shifted to higher temperatures. The shift of the endothermic peak to a higher temperature resulted in an increase in SFI of the H15–E85 mixed base. As shown in Fig. 4, the SFI of the H15–E85 mixed bases increased linearly with Witepsol E85 content in the mixed bases above about 13% of Witepsol E85 content. Therefore, the H15–E85 mixed bases would melt completely at 37 °C up to about 13% of Witepsol E85 content.

Some physicochemical properties of the H15–E85 mixed base, such as the melting point and the apparent viscosity, were found to be affected by the SFI. The melting points of the mixed base were represented as a function of SFI in Fig. 5A. A linear relation was observed between the melting point and SFI, indicating that an increase in SFI brought about an increase in the melting point of the mixed base. A similar relation was shown between the logarithm of the apparent viscosity η and SFI (Fig. 5B).

Release of Brilliant Blue from Mixed Bases Figure 6 shows the release profiles of brilliant blue from the H15–E85 mixed bases, which have various values of SFI at 37 °C. An increase of Witepsol E85 content in the mixed base reduced the release rate of brilliant blue from the mixed base. In other words, a slower drug release rate was obtained with a higher SFI value. A similar relation was observed regarding the release rates of morphine hydrochloride from stored Witepsol H15 suppositories (see

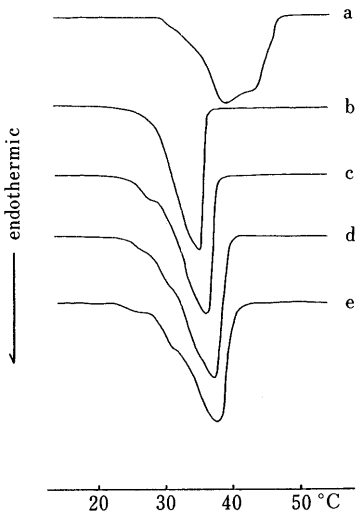

Fig. 3. DSC Thermograms of Mixed Bases of Witepsol E85 and Witepsol H15

(a) Witepsol E85, (b) Witepsol H15, (c) E85 20%, (d) E85 30%, (e) E85 40% in weight ratio.

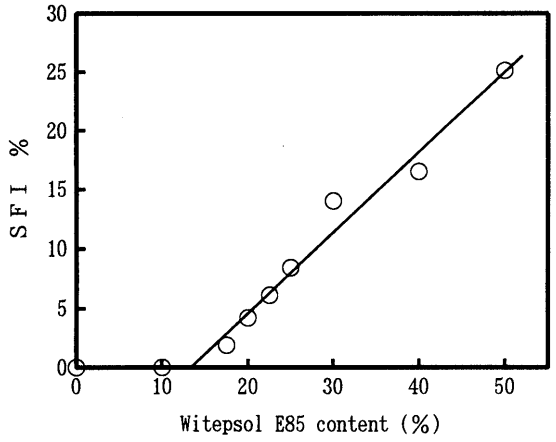

Fig. 4. SFI of the H15–E85 Mixed Base as a Function of the Content of Witepsol E85

Each point represents the mean of 3 experiments. The solid line represents the least-squares linear regression line of the data points above 13% of Witepsol E85 content.

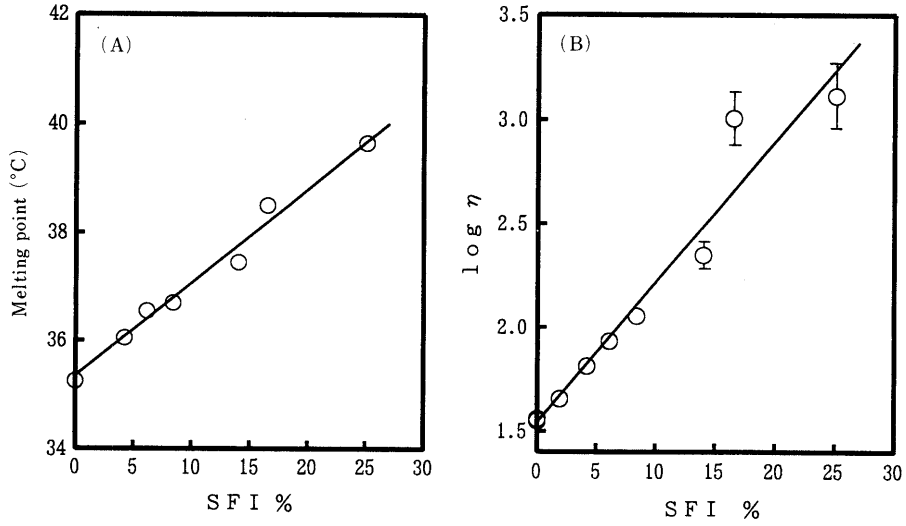

Fig. 5. Melting Point (A) and Logarithm of Apparent Viscosity (B) of the H15–E85 Mixed Base as a Function of SFI

Each point represents the mean of 5 experiments. The standard error was smaller than the size of the symbols when error bars are not shown. Solid lines represent least-squares linear regression lines of the data points.

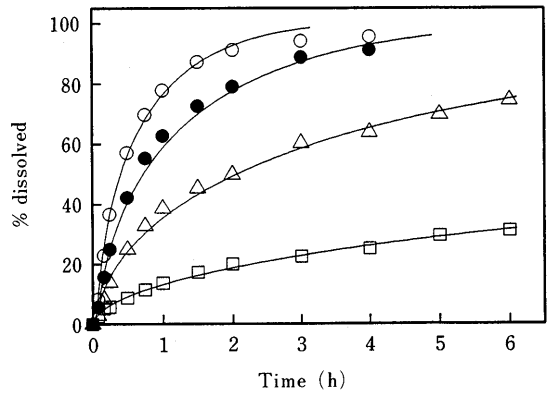

Fig. 6. Release Profiles of Brilliant Blue from the H15–E85 Mixed Bases

Witepsol E85 content: ○, 20%; ●, 22.5%; △, 25%; □, 30%. Each point represents the mean of 5 experiments. The standard error was smaller than the size of the symbols. Theoretical curves (solid lines) are calculated by Jander's equation (see Results and Discussion).

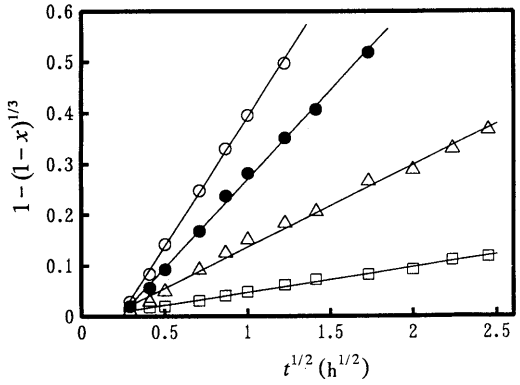

Fig. 7. Jander's Plot of Brilliant Blue Release Rate

Witepsol E85 content: ○, 20%; ●, 22.5%; △, 25%; □, 30%. Solid lines represent least-squares linear regression lines of the data points.

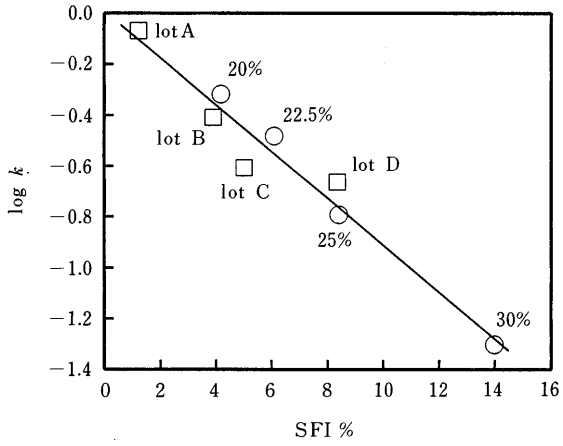

Fig. 8. Relationship between the Logarithm of Jander's Rate Constant k and SFI

○, H15–E85 mixed base; □, Witepsol H15 stored at 30 °C for 2 weeks. Lots A—D represent the lot number of Witepsol H15 base shown in Fig. 1. The solid line represents the least-squares linear regression line of the data points.

Fig. 1).

Akiyama *et al.*[12] have reported that the drug release rate from a micromatrix could be expressed by Jander's equation which considers the change in the interfacial areas where the actual release of a solid drug occurs. Since the suppository base with a certain SFI value is considered to be a kind of matrix, we tried to apply Jander's equation to the release data of brilliant blue from the H15–E85 mixed bases.

Jander's equation is expressed as:

$$1-(1-x)^{1/3}=kt^{1/2}(k=k'/r)$$

where x is the fraction of drug released at time t, k and k' are the rate constants and r is the radius of the matrix. As shown in Fig. 7, when the release data of brilliant blue from the H15–E85 mixed bases were plotted according to Jander's equation, linear relations with $1-(1-x)^{1/3}$ and square root of time were obtained. The lag time observed in Fig. 7 is probably due to the poor wettability of the base surface. The solid curves in Fig. 6 show a percentage of dissolved brilliant blue calculated from Jander's equation using the release rate constant k determined from the slopes of the straight lines in Fig. 7, and an appropriate lag time as a function of time. When up to 80% of brilliant blue was dissolved, the theoretical curves were in good agreement with the experimental values, as shown in Fig. 6.

Judging from a good fit with Jander's equation, it is considered that the release from the suppository base with various SFI values is a diffusion controlled process within the base as a matrix.

Relation between Release Rate Constant and SFI As shown in Fig. 7, the H15–E85 mixed base with a higher SFI value resulting from a higher content of Witepsol E85 tended to release brilliant blue more slowly than those with a lower SFI value. Since a similar relation was observed in the case of the release of morphine hydrochloride from stored Witepsol H15 suppositories, the logarithm of the release rate constant ($\log k$) obtained in Fig. 7 was plotted as a function of SFI in combination with the case of the release rate constant of morphine hydrochloride from stored Witepsol H15 suppository bases (Fig. 8). As shown in Fig. 8, a linear relation was obtained between the $\log k$ and SFI, indicating that the release rate constants were dependent on SFI in spite of the difference of the crystal forms of triglyceride bases.

From Jander's equation, the rate constant k involves the reciprocal of radius of a matrix, $1/r$, which is proportional to the specific surface area of a matrix. The suppository bases, which melt and spread to a certain extent at 37 °C, would have various specific surface areas according to their SFI values. Therefore, a decrease in k with an increase in SFI is considered to be due to the decrease in specific surface area of the suppository base at 37 °C. That is, SFI may be correlated with the drug release rate through regulation of the melting and spreading state of the suppository base.

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