Design of Novel Controlled-Release Suppositories Containing Polyglycerol Ester of Fatty Acid

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A novel controlled release suppository consisting of Witepsol H15 as a triglyceride base and polyglycerol ester of fatty acid (PGEF) has been designed and developed. The addition of PGEF to Witepsol H15 resulted in an increase in the solid fat index (SFI), which is correlated with melting point and apparent viscosity, of the Witepsol H15-PGEF (H15-PGEF) mixed base in a similar manner to the case of Witepsol H15-Witepsol E85 (H15-E85) mixed base. In the *in vitro* release tests, the release rate of Brilliant Blue from the H15-PGEF mixed base was reduced with increase of PGEF content, indicating that the drug release rate from the H15-PGEF mixed base depended on SFI. The change in the drug release rate from the H15-PGEF mixed base with temperature in release tests ranging from 36 °C to 39 °C was small, whereas the release rate in the H15-E85 mixed base changed significantly with temperature. These changes in drug release rate with temperature in the H15-E85 and H15-PGEF mixed bases were found to be attributable to the variation of SFI of both the mixed bases. In addition, the change in SFI during storage at 30 °C in the H15-PGEF mixed base was relatively small as compared with that of the H15-E85 mixed base. From these results, the H15-PGEF mixed base is expected to be useful for stable controlled release suppositories.

Keywords controlled-release suppository; polyglycerol ester of fatty acid (PGEF); solid fat index (SFI); Jander's equation; polymorphic transition; differential scanning calorimetry (DSC)

The rectal route of administration is of interest because it avoids hepatic first-pass elimination and because of the constancy of the rectal environment with respect to pH, composition, volume and viscosity of fluid.[1-5] However when a drug has a relatively short elimination half-life, it is impossible to maintain the therapeutic plasma concentration without frequent dosing. Recently, several investigations have been reported on the preparation of controlled-release suppositories with various additives.[6-9] Controlled-release suppositories are preferred over conventional suppositories because they reduce the frequency of drug administration and maintain an effective concentration without transient undesirable high concentration. We have previously reported that solid fat index (SFI) was closely correlated with drug release rate from triglyceride suppository bases.[10] In other words, it is possible to obtain controlled release of drug from a suppository by regulating the SFI value of the suppository base.

In the present study, a novel controlled-release suppository containing polyglycerol ester of fatty acid (PGEF), which is used in food and has recently been reported to be available as a micromatrix base,[11,12] has been designed and developed. The drug release characteristics of the novel suppository base containing PGEF were investigated. The polymorphic transition of the suppository base during storage was also examined.

Experimental

Materials Witepsol H15 and Witepsol E85 (hüls A.G.) were obtained from Mitsuba Trading Co., Ltd. Hexaglycerol pentastearate (Hg5S), used as PGEF, was obtained from Nikko Chemicals Co., Ltd. Brilliant Blue was purchased from San-ei Chemical Ind., Ltd.

Preparation of Suppository Suppositories were prepared using the fusion method. Brilliant Blue was mixed with a melted base and dispersed homogeneously. When a mixture of Witepsol H15 and Hg5S (or Witepsol E85) was used as the suppository base, Hg5S (or Witepsol E85) was mixed well with Witepsol H15 at 60 °C before adding Brilliant Blue. 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 release test was carried out by a rotating cell method described in our previous paper.[10] The dissolution phase (900 ml) was 20 mM phosphate-buffered saline (pH 7.4), whitch was maintained at 37 °C. A 1.2 g suppository containing 2% w/w of Brilliant Blue (24 mg) was put into a PTSW-type cell with 5 ml of the dissolution fluid. The cell was rotated at 25 rpm and the concentration of Brilliant Blue was assayed spectrophotometrically at 630 nm. The percentages of dissolved Brilliant Blue were reproducible within ±3%.

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

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

Differential Scanning Calorimetry (DSC) Analysis DSC thermograms were obtained using a Rigaku Thermoflex TAS200 system. The milled sample was weighed in an aluminum pan and heated at 2 °C/min. Measurement and calculation of solid fat index (SFI) were performed as previously described.[10] Briefly, SFI was calculated as

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

where S_1 is the area under the peaks before 37 °C and S_2 is that after 37 °C. More than 3 measurements were performed in order to obtain reproducible SFI values (±0.4%).

Results and Discussion

Preparation of Mixed Base of Witepsol H15 and Hg5S

Figure 1 shows DSC thermograms of Witepsol H15, Hg5S, and their mixtures. The endothermic peaks of Witepsol H15 and Hg5S appeared at 34.5 °C and 52.8 °C, respectively. When Witepsol H15 was mixed with Hg5S, a shoulder at the higher temperature side of the main endothermic peak derived from Witepsol H15 was observed and this shoulder peak increased with increase of Hg5S content in the H15-Hg5S mixed base.

The increase of the shoulder peak at the higher temperature side caused an increase of SFI value of the H15-Hg5S mixed base. Figure 2 shows the SFI value of

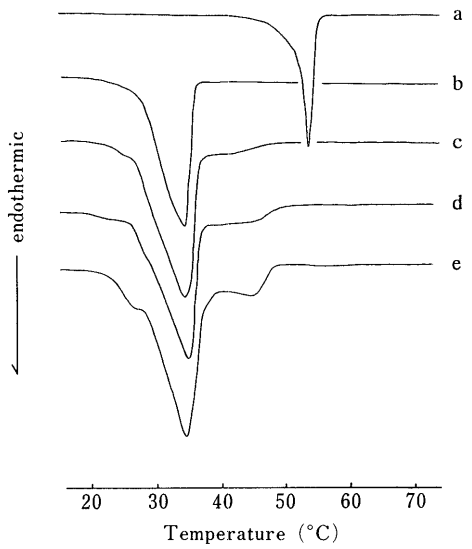

Fig. 1. DSC Thermograms of Mixed Bases of Hg5S and Witepsol H15

a, Hg5S; b, Witepsol H15; c, Hg5S 15%; d, Hg5S 20%; e, Hg5S 30% weight ratio.

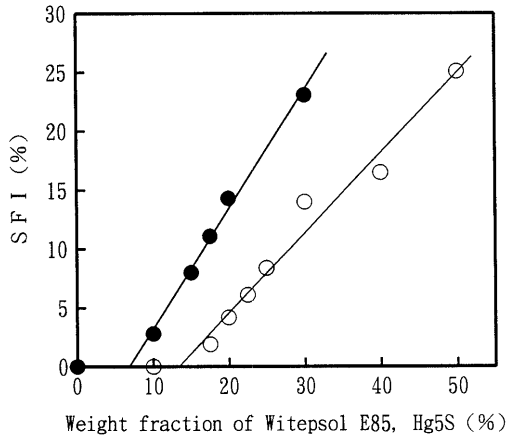

Fig. 2. SFI of Mixed Bases as a Function of the Weight Fraction of Witepsol E85 or Hg5S

○, H15-E85 mixed base; ●, H15-Hg5S mixed base.

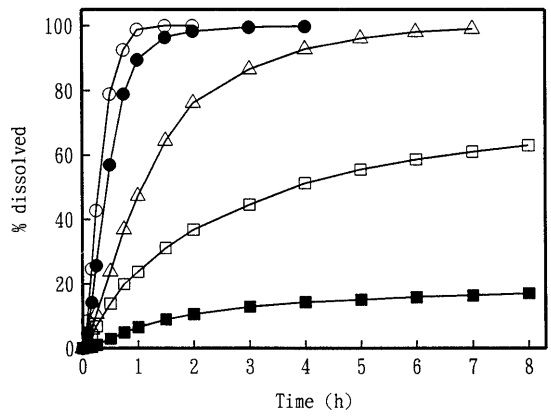

Fig. 3. Release Profiles of Brilliant Blue from H15-E85 Mixed Bases

Hg5S content: ○, 0%; ●, 10%; △, 15%; □, 20%; ■, 30% weight ratio. Each point represents the mean of 5 experiments.

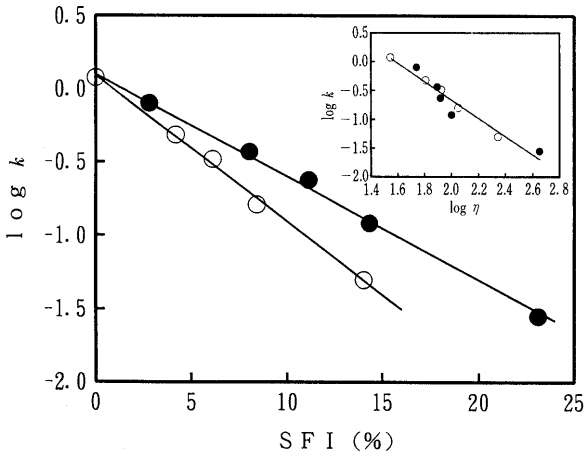

Fig. 4. Logarithm of Jander's Rate Constant k (log k) as a Function of SFI

(○), H15-E85 mixed base; (●), H15-Hg5S mixed base. The inset shows the relation of log k of the mixed bases with log η, whitch represents the logalithm of apparent viscosity of the mixed base at 37 °C. Solid lines represent least-squares linear regression lines of the data points.

the H15-Hg5S mixed base (closed circles) as a function of Hg5S content. SFI value in the H15-E85 mixed base (open circles) is also shown in Fig. 2 as a function of Witepsol E85 content. The SFI value of the H15-Hg5S mixed bases increased above about 7% Hg5S content, whereas in the H15-E85 mixed bases the threshold value was about 13% Witepsol E85 content.[10] That is, the same SFI value could be obtained with a smaller amount of additive (Hg5S) in the H15-Hg5S mixed base as compared with the addition of Witepsol E85 in the H15-E85 mixed base. Melting point and apparent viscosity increased with an increase in SFI of the H15-Hg5S mixed base, as previously observed in the H15-E85 mixed base.[10]

Release of Brilliant Blue from Mixed Base Figure 3 shows the release profiles of Brilliant Blue from H15-Hg5S mixed bases with various values of SFI at 37 °C. The release rate from the H15-Hg5S mixed base decreased with an increase in the weight fraction of Hg5S in the mixed base. Previously, we have found that the drug release rate from the triglyceride suppository base could be expressed by Jander's equation.[10] PGEFs are widely used as surfactants having a wide range of hydrophile-lipophile balance (HLB) values. Hg5S with an HLB value of 3.5 is considerably hydrophobic and is used as an oily base. We attempted, therefore, to apply Jander's equation to the release data from the H15-Hg5S mixed base.

Jander's equation is expressed as:

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

Here, x is the fraction of drug released at time t, k and k' are the rate constants and r is a radius of matrix base. When the release data in Fig. 3 were plotted according to Jander's equation, a linear relation of $1-(1-x)^{1/3}$ with the square root of time was observed (data not shown). Akiyama *et al.*[12] have shown that the drug release from PGEF-based microspheres could be expressed by Jander's equation, indicating a diffusion-controlled process within the microsphere matrix. In our case of release from suppository bases, the good fit with Jander's equation may suggest that the drug release from the suppository bases is also a diffusion-controlled process within the matrix composed of suppository base.

Relation between Release Rate Constant and SFI In

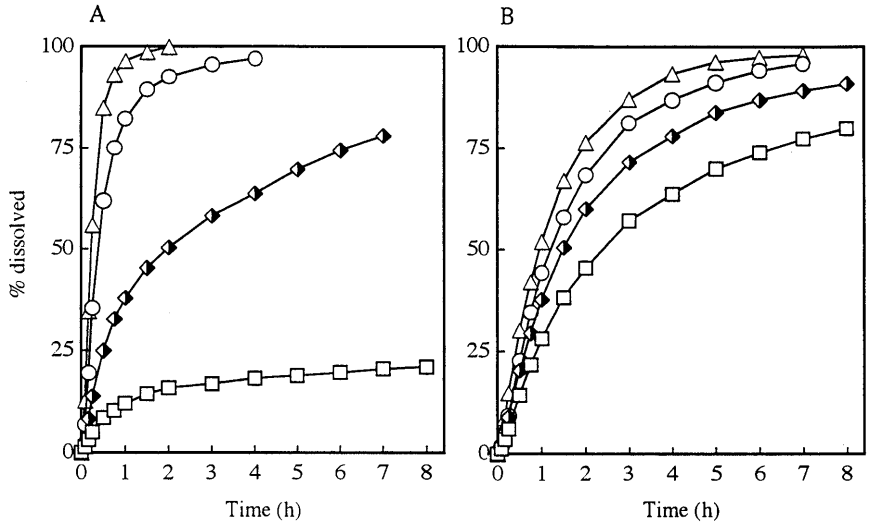

Fig. 5. Release Profiles of Brilliant Blue from Mixed Bases at Various Temperatures

A, H15-E85 mixed base containing 25% Witepsol E85; B, H15-Hg5S mixed base containing 17.5% Hg5S. Temperature in release test: □, 36 °C; ◇, 37 °C; ○, 38 °C; △, 39 °C. Each point represents the mean of 5 experiments.

the previous paper, we showed that the logarithm of the release rate constant k ($\log k$) obtained by Jander's equation for the H15-E85 mixed base had a linear relation with SFI.[10] Figure 4 shows that $\log k$ exhibited a similar relation with SFI for the H15-Hg5S mixed base (data for H15-E85 mixed base are also shown). The linear relations between $\log k$ and SFI were considered to indicate that an increase in SFI of both the mixed bases brought about a reduction of the drug release from the mixed bases. As can be seen in Fig. 4, the slope of the $\log k$ – SFI line for the H15-Hg5S mixed base exhibited a positive deviation from that for the H15-E85 mixed base. However, $\log k$ had the same relation with the apparent viscosity η in both mixed bases, as shown in the inset of Fig. 4. Two reasons can be considered for this discrepancy. The first is the difference in wettability of both the mixed bases, which affects the diffusion rate within the bases. This, however, seems unlikely because Hg5S is a hydrophobic PGEF having a low wettability close to that of triglyceride suppository bases. The second is some uncertainty in the equivalency of SFI values measured by the DSC method. The part of the endothermic peak causing the increase in SFI of the H15-Hg5S mixed base was relatively broad as compared with that of the H15-E85 mixed base. This difference may mean that the SFI values of the H15-Hg5S mixed base and the H15-E85 mixed base are not precisely equivalent. Measurements of SFI of both the mixed bases by other methods such as NMR and dilatometry will be necessary to test this hypothesis.

Effect of Temperature on Drug Release Rate from Mixed Base In general, drug release from a suppository is significantly affected by the temperature because of the change in the melting state of the suppository base.[13] However, a sharp change in the drug release is undesirable for controlled-release suppositories. Thus, we have examined the effect of temperature on the drug release from the mixed base suppository in release tests *in vitro*.

Figure 5A shows the release profiles of Brilliant Blue from the H15-E85 mixed base when the temperature in release tests was varied from 36 °C to 39 °C. A remarkable change in the drug release rate with temperature was observed in the H15-E85 mixed base. On the other hand, the change in the drug release rate from the H15-Hg5S mixed base was relatively small, as shown in Fig. 5B. SFI values for both the mixed bases at temperatures ranging from 36 °C to 39 °C were also measured (Table I). SFI value for the H15-E85 mixed base was found to decrease sharply with increase of temperature, whereas a small decrease in SFI values with temperature was observed in the case of H15-Hg5S mixed base. These results suggest that the drug release rate was closely correlated with SFI in the mixed base, not only when the amount of additives such as Witepsol E85 and Hg5S in the mixed base was increased, but also when the temperature in the release test was changed. Figure 6 shows the relation between the logarithm of the release rate constant k ($\log k$) obtained by applying Jander's equation to the release data in Fig. 5 and SFI in both the H15-E85 mixed base (open circles) and H15-Hg5S mixed base (closed circles). The $\log k$ values estimated from the SFI values in Table I using the linear relation between $\log k$ and SFI in Fig. 4 (indicated by broken lines in Fig. 6) were in good agreement with the experimental ones, except for the H15-E85 mixed base at 36 °C (SFI = 19.7%). The discrepancy can be explained by assuming a constant value of k above a threshold SFI value, 15—20% in this case. Decrease in k is considered to be proportional to decrease in the specific surface area of the suppository, which is brought about by an increase in SFI.[10] Therefore, an increase in SFI would result in a constancy of k that can be determined by the minimum specific surface area when no change in the form of the

Table I. SFI Values of Mixed Bases at Various Temperatures

	Temperature			
	36 °C	37 °C	38 °C	39 °C
H15-E85	19.7	8.4	4.5	0.6
H15-Hg5S	14.8	11.1	10.6	9.7

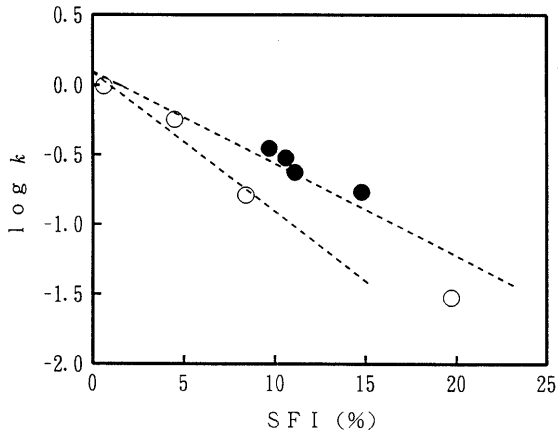

Fig. 6. Logarithm of Jander's Rate Constant k as a Function of SFI at Different Temperatures in Mixed Bases

○, H15-E85 mixed base containing 25% Witepsol E85; ●, H15-Hg5S mixed base containing 17.5% Hg5S. Rate constant k were evaluated from the release data shown in Fig. 5. Broken lines are the least-squares linear regression lines shown in Fig. 4 (see Results and Discussion).

TABLE II. SFI Values of Mixed Bases Stored at 30 °C

	Storage time (weeks)			
	0	7	14	28
H15-E85	8.4	32.0	31.7	32.5
H15-Hg5S	11.1	13.0	13.9	13.7

suppository occurs during the release test.

Effect of Storage on Polymorphic Transition of the Mixed Base Polymorphic transition during storage is well known to bring about changes in many pharmaceutical properties of triglyceride suppository bases.[14-16] We have found that the release rate of morphine hydrochloride from Witepsol H15 suppository considerably decreased during storage at 30 °C for 2 weeks because of the polymorphic transition of Witepsol H15.[10] In the cases of the H15-E85 and H15-Hg5S mixed bases, we observed reductions of the drug release from the mixed bases during storage at 30 °C for 2 weeks. The release rate of Brilliant Blue from the H15-E85 mixed base significantly decreased during storage, whereas the stored H15-Hg5S mixed base exhibited a small decrease of the release rate.

Table II shows the changes in SFI of both the H15-E85 and H15-Hg5S mixed bases during storage at 30 °C for up to 4 weeks. The SFI of the H15-E85 mixed base stored at 30 °C increased significantly, whereas a small increase of SFI in the H15-Hg5S mixed base was observed up to 2 weeks. However, no further appreciable change in SFI of either of the mixed bases was observed beyond 2 weeks, indicating that both the H15-E85 and H15-Hg5S mixed bases were entirely transformed to their stable forms in 2 weeks.

DSC thermograms of the H15-E85 and H15-Hg5S mixed bases stored at 30 °C for 2 weeks are shown in Fig. 7A and 7B. In the H15-E85 mixed base containing 25% Witepsol E85, the endothermic peak at around 37 °C observed before storage separated into two peaks at 28.6 °C and 39.5 °C after storage, which seemed to bring

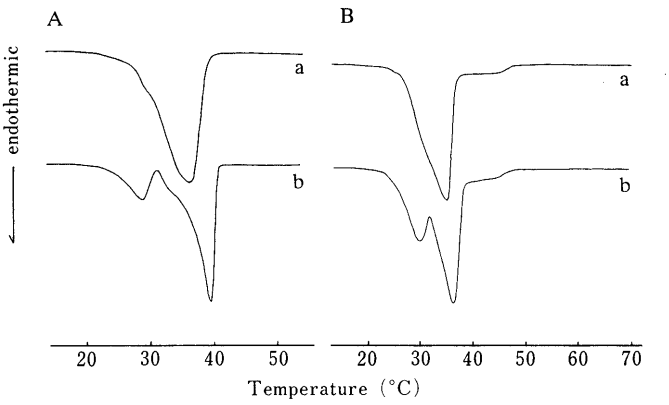

Fig. 7. DSC Thermograms of Mixed Bases

a, before storage; b, after storage at 30°C for 2 weeks. A, H15-E85 mixed base containing 25% Witepsol E85; B, H15-Hg5S mixed base containing 17.5% Hg5S.

about a large increase of SFI. The H15-Hg5S mixed base containing 17.5% Hg5S also showed polymorphism during storage. Two endothermic peaks at 30.0 °C and 36.2 °C separated from the main peak derived from Witepsol H15, however, were considered to cause only a slight increase of SFI, while the shoulder peak at the higher temperature side of the main peak did not change at all.

Based on these investigations of polymorphic transitions of the mixed bases, we would expect that the H15-Hg5S mixed base would provide relatively stable drug release during storage as compared with the H15-E85 mixed base, in accordance with the experimental observations. This may be related to the fact that PGEF does not show polymorphism, like triglyceride.[11]

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