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INFLUENCE OF PHYSICOCHEMICAL INTERACTIONS ON THE PROPERTIES OF SUPPOSITORIES. III. RHEOLOGICAL BEHAVIOUR OF FATTY SUPPOSITORY BASES AND ITS EFFECT ON SPREADING IN RATS

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ABSTRACT

The viscosity and other rheological properties of the molten base at rectal temperature can markedly affect the rate of release and absorption of drugs from fatty suppositories. The rheograms of pure mono-acid triglycerides, their mixtures and triglyceride suppository bases were determined at various temperatures using a rotational rheometer. Completely molten systems gave Newtonian behaviour, while incompletely molten mixtures, containing a suspension of higher melting triglyceride, exhibited plastic behaviour with thixotropy which reverted to Newtonian behaviour on

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removal, dissolution or melting of the higher melting component. The plastic yield values ($\nmid$ 67 Nm^{-2}) were less than the reported rectal pressure ($\nmid$ 300 Nm^{-2}), suggesting that they exert little effect on spreading in the rectum.

INTRODUCTION

The first paper in this series lists the factors that affect the release of drugs from suppositories.[1] In the present paper we describe rheological studies of triglycerides and their mixtures and the effect of viscosity changes on the spreading of suppositories in the rat rectum.

The viscosity of the molten base at body temperature can have a marked effect on the release of a drug. Baichwal and Lohit[2] reported that release diminished in proportion to the logarithm of viscosity. On the other hand, Neuwald and Ackad[3] could find no difference in the release of sodium salicylate from microenemas of varying viscosity. Rutten-Kingma[4] noted that an increased viscosity leads to a decreased release of sodium chloride.

The effect of viscosity of suppository bases can be complicated by rheological factors such as plastic flow, pseudoplasticity (decreasing viscosity with increasing shear stress) and thixotropy. For example Moës[5,6] determined rheograms of pure suppository bases and of suppositories containing paracetamol, and often observed plastic behaviour. In some cases slight thixotropy was noticed. As a consequence, a complete profile of shear rate vs.

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shear stress of the base is required to predict the spreading within the rectum.

MATERIALS AND METHODS

The materials, their purity, the preparation of binary mixtures, melting point determinations and the procedure for differential thermal analysis(DTA) have been described in a previous paper.[1] Rheological measurements were carried out using a variable stress cone and plate rheometer (Deer Rheometers Ltd.) with a variable-temperature thermal jacket. Samples, stored for one week after preparation, were placed on the plate, the cone assembly was then lowered to a pre-set distance from the plate and the torsional force (shear stress) was plotted against the angular velocity (rate of shear) at each of various temperatures. On increasing the temperature from one run to another, expansion caused the gap between the cone and the plate to decrease. Consequently, the cone portion of the rheometer had to be re-set at each new temperature. After running samples at high torsional forces, time-dependent behaviour, e.g. thixotropy or rheopexy, were tested by reducing the high torsional force to the force initially applied. Any divergence between the initial and final angular velocities at this same torsional force (between "run up" and "run down") indicated either thixotropy or rheopexy of the sample.

The procedure used for the preparation of the suppositories was similar to that previously described for the preparation of

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binary mixtures of triglycerides and drugs, except that Oil Blue dye (Colour Number N 61555, Sigma Chemical Company product number 08376) was substituted for the drug. The molten dye + triglyceride mixture was then sucked into a 1 ml insulin syringe to the 0.2 ml mark. The syringe was then placed in an ice bath for five minutes, stored at 4°C for one week and then the luer end of the syringe was removed to enable the suppository to be inserted directly from the syringe into the rat's rectum. Female Wistar rats of mass 180 to 320 g were used to study the ingression of suppositories containing the dye into the rectum and to devise the most efficient method of rectal sealing.

The following method was developed to test the spreading of suppositories in rats. Rats were deprived of food for 24 hrs prior to the experiment but water was provided ad libitum. The method took advantage of the fact that rats defaecate when frightened. The rat was removed from its cage and held by its tail such that its rear legs were held clear of the bench. Either after five minutes or after defaecation was complete, whichever was later, an outer cover of a plastic syringe was gently inserted into the rat's rectum. The presence of any faecal pellets was detected by a sharp increase in the resistance to insertion. The plastic cover was then removed and the rat held until the pellet was expelled. The plastic cover was again inserted and the process repeated until no further pellets were encountered.

After the initial purging described above the rat was replaced in its cage, removed after one hour and the whole process

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listed above was repeated as a final purging. The suppository was then inserted into the rectum followed by sealing of the rectum with cyanoacrylate ester adhesive (Loctite Super Glue 3). The rat was then placed in a cage with food and sacrificed after the allotted time by humane asphixiation. The dead animal was dissected and the distance of ingression of the suppository containing the dye was neasured from the external anal sphincter.

RESULTS AND DISCUSSION

The viscosity of the base is one of the most important parameters governing the release of a drug from a suppository. A base of low viscosity should spread further up the rectum giving an increased surface area for diffusion and absorption. In drug-suspension suppositories a base of lower viscosity should give rise to a higher rate of sedimentation of the drug, and if the drug is readily soluble in water, this effect will increase the dissolution rate. When the suppository spreads, its bulk thickness is reduced, thereby further increasing the rate of sedimentation of the drug from the base.

The viscous behaviour exhibited by triglycerides and binary mixtures of triglycerides can be classified as either Newtonian or non-Newtonian. Newtonian behaviour is indicated when a plot of angular velocity (shear rate) vs. torsional farce (shear stress) gives a straight line through the origin (Figure 1, line A). The slope of the line is taken as the simple viscosity, η_s. Non-Newtonian behaviour encountered in binary mixtures is illustrated

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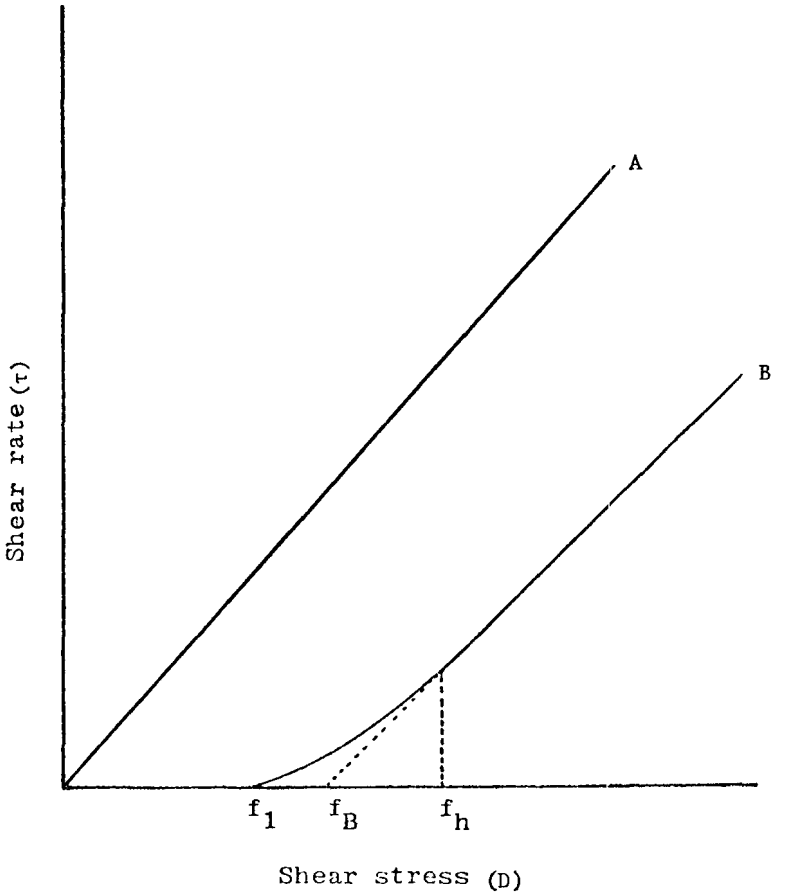

FIGURE 1

Relationship between shear rate, τ, and shear stress, D, for materials that exhibit Newtonian flow (line A) and plastic flow (line B)

in Figure 1, line B. This type of behaviour is classified as non-Newtonian plastic behaviour. In some cases slight thixotropy is also observed. Non-Newtonian plastic behaviour can be treated in a number of ways: Two plastic viscosity values are used in this paper, namely apparent viscosity, η_a, and Bingham plastic viscosity, η_{pl}. Apparent viscosity, η_a, is obtained by treating the data, used to plot line B in Figure 1, to a linear regression

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analysis, the slope corresponding to the apparent viscosity, η_a. The Bingham plastic viscosity, η_{pl}, is obtained by treating the mixtures as Bingham bodies. Figure 1 line B shows a plastic system, where f_1 corresponds to the static yield value (i.e. lowest shear stress at which flow can occur), f_B corresponds to the Bingham yield value (determined by extrapolation of the linear portion of the cure to the shear stress axis) and f_h corresponds to the shear stress beyond which the flow curve becomes linear. For Bingham bodies the plastic viscosity, η_{pl}, is given by

$$\eta_{pl} = \frac{D - f_B}{\tau}$$

where D represents the shear stress and τ the shear rate. Rearrangement gives

$$\tau\eta_{pl} = D - f_B$$

Thus, a plot of shear rate against corrected shear stress $(D - f_B)$ over the linear portion of the curve will give a straight line whose slope corresponds to the plastic viscosity, η_{pl}. Since this plastic viscosity will only manifest itself above a given shear stress, f_h, the value of the plastic viscosity must be quoted with reference to a minimum value of shear stress.

The pure monoacid triglycerides, tricaprin, trilaurin, trimyristin, tripalmitin and tristearin, all show Newtonian behaviour with a simple viscosity, η_s, and no time-dependent effects. Figure 2 shows that η_s decreases with increasing temperature, but becomes less sensitive to temperature variations

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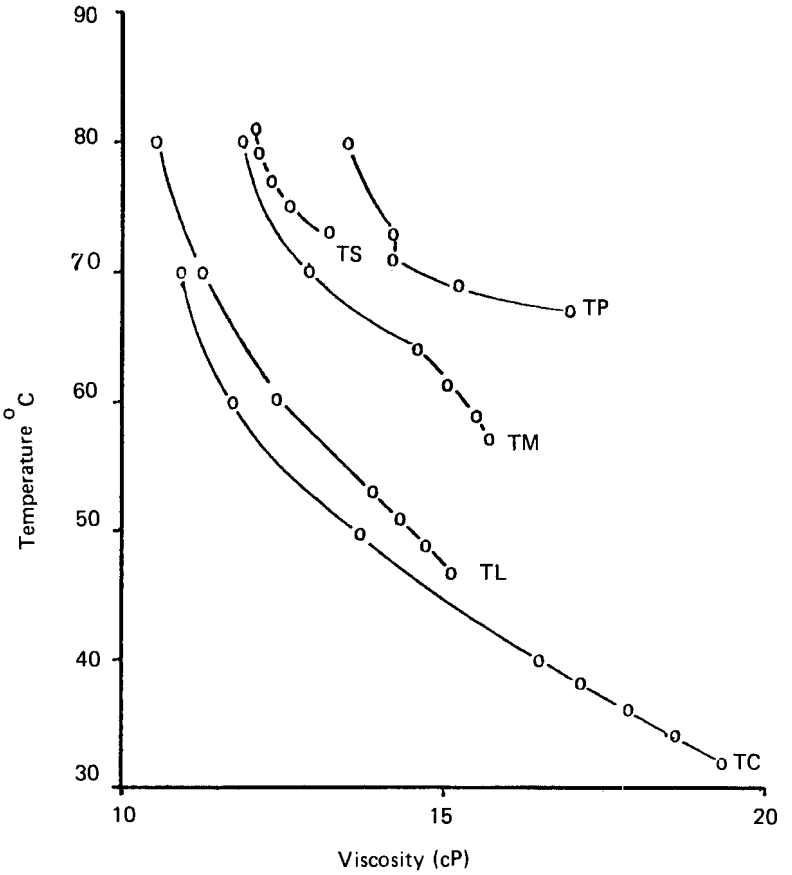

FIGURE 2

Variation of viscosity with temperature for:
tricaprin (TC), trilaurin (TL), trimyristin (TM), tripalmitin (TP), and tristearin (TS)
1 cP = 1 $mN.m^{-2}.s$ = 1 mPa.s

at higher temperatures. On ascending the homologous series of monoacid triglycerides, there is a general trend of increased η_s at a given temperature. However, tripalmitin was the exception to this rule and Figure 2 also reveals a discrete discontinuity in the curve of tripalmitin at 71°C to 73°C. A similar, though less pronounced, discontinuity was detected in

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the curve for trimyristin at 64°C. These effects may be attributed to small quantities of impurities in the sample. Joglekar and Watson[7,8] found that the presence of small quantities of impurities in tristearin had a large effect on the viscosity, although it did not alter significantly those properties which represent classical criteria of purity, e.g. density and refractive index.

The variation with temperature of the viscosity of the following binary mixtures is illustrated in Figure 3: 60% w/w tricaprin + 40% w/w trilaurin (tc_1); 40% w/w tricaprin + 60% w/w trilaurin (tc_2); 75% w/w tricaprin + 25% w/w trimyristin (tc_3); 90% w/w tricaprin + 10% w/w tripalmitin (tc_4); 92% w/w tricaprin + 8% w/w tristearin (tc_5). In Figure 3 the continuous line corresponds to points that exhibited Newtonian simple viscosities, η_s, and the dotted line corresponds to points that exhibited non-Newtonian behaviour from which apparent viscosities, η_a, were calculated. It can be seen that at high temperatures, such as 80°C, the viscosities of the mixtures tend to converge. At 80°C the rank order of increasing η_s is: $tc_4 < tc_1 < tc_5 < tc_3 < tc_2$. At 43°C the rank order of increasing viscosity is $tc_1 < tc_2 < tc_3 < tc_4 < tc_5$, although at this temperature tc_3, tc_4 and tc_5 are exhibiting η_a and the significance of the rank order is somewhat doubtful.

Figure 3 shows that Newtonian (η_s) behaviour is exhibited by tc_1 over the entire range. Comparison with the phase diagram[1],

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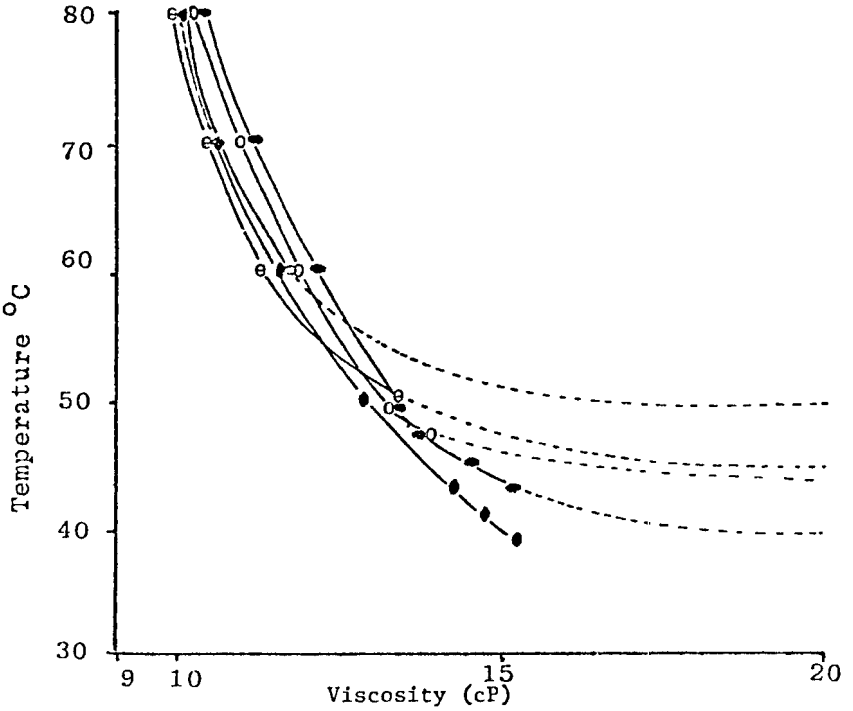

FIGURE 3

Variation of viscosity with temperature for binary mixtures of:

60% w/w tricaprin + 40% w/w trilaurin (●)
40% w/w tricaprin + 60% w/w trilaurin (◆)
75% w/w tricaprin + 25% w/w trimyristin (○)
90% w/w tricaprin + 10% w/w tripalmitin (θ)
92% w/w tricaprin + 8% w/w tristearin (⊂)

----- = extrapolation to a point exhibiting non-Newtonian behaviour.

$1\ cP = 1\ mN.m^{-2}.s = 1\ mPa.s$

Figure 4, shows that tc_1 corresponds to the eutectic composition. Since complete melting of the mixture occurs at the eutectic temperature, no suspended particles of excess triglyceride are present in tc_1 above this temperature. For tc_2 Newtonian (η_s)

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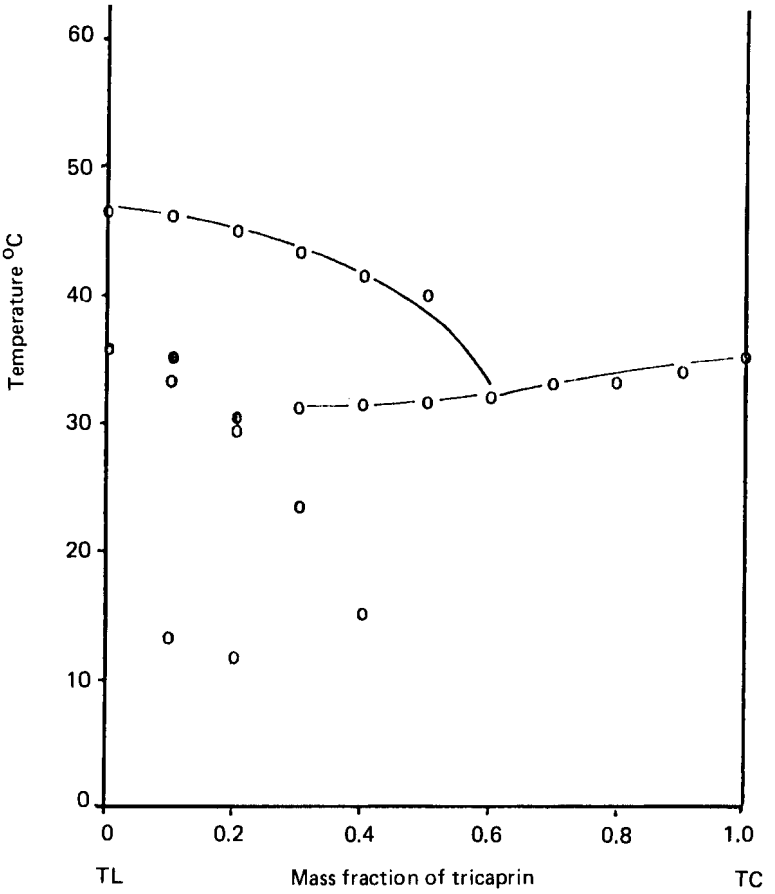

FIGURE 4

Phase diagram of binary mixtures of tricaprin (TC) and trilaurin (TL) determined by DTA

O = endotherm ● = exotherm

behaviour is exhibited at 43°C, and, for the composition under consideration (40% w/w tricaprin/60% w/w trilaurin), reference to the phase diagram (Figure 4) shows that this temperature corresponds quite closely to the melting point of the higher melting triglyceride, trilaurin, which is in excess. Thus, non-Newtonian

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behaviour is exhibited when the higher melting component, trilaurin, is present as a solid suspended in the binary liquid mixture. When, at a higher temperature, the excess solid has melted (or dissolved), rheological behaviour becomes Newtonian (η_s). Analogous behaviour is exhibited by tc_3, tc_4 and tc_5. These observations indicate that any mixture of triglycerides will behave in a Newtonian (η_s) manner provided all the components are in the liquid state.

Figure 5 shows the temperature dependence of viscosity of three commercial suppository bases. The continuous line corresponds to points that exhibited Newtonian simple viscosities (η_s) and the dotted line to points that exhibited non-Newtonian behaviour from which the apparent viscosities, η_a, were calculated. For Witepsol E75 Newtonian (η_s) behaviour is exhibited at or above 42°C, which exceeds the DTA melting point[1] at 40.4°C. This indicates that Newtonian (η_s) flow is given only at temperatures above the melting point of the higher melting component of this commercial base. Similar behaviour is exhibited by Witepsol W35 and Suppocire A. Thus, the generalisation at the end of the last paragraph for binary mixtures of mono-acid triglycerides also applies to the complex mixtures of triglycerides that constitute commercial suppository bases. Any suspended triglyceride material evidently give non-Newtonian behaviour.

Mixtures that exhibited non-Newtonian plastic flow at given temperatures are listed in Table 1 together with the η_{pl}, f_B, f_h

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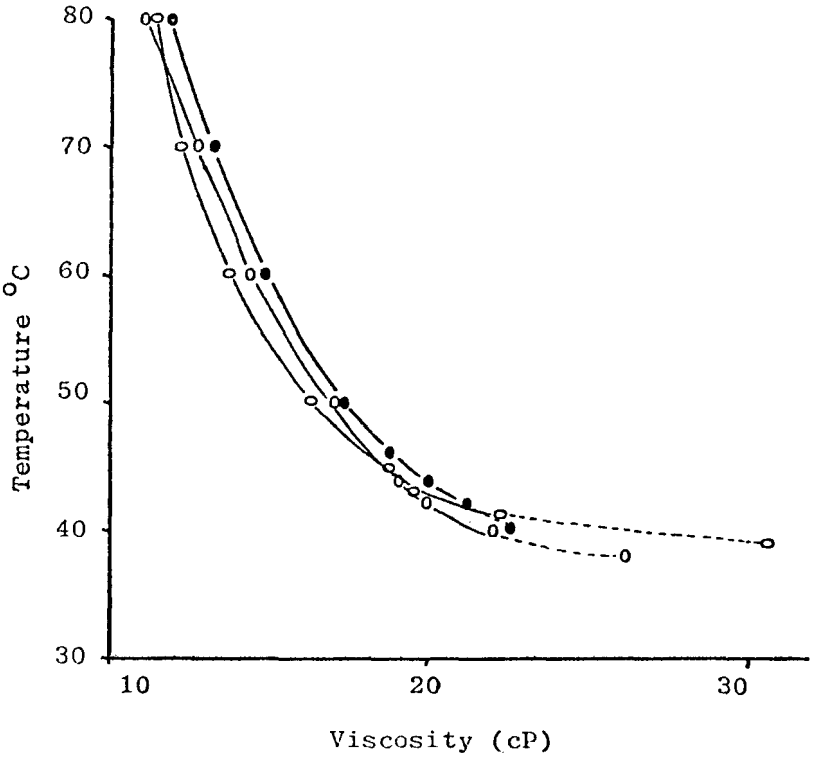

FIGURE 5

Variation of viscosity with temperature of the commercial suppository bases Witepsol E75 (●), Witepsol W35 (o) and Suppocire A (0)

------ = extrapolation to a point that is exhibiting non-Newtonian behaviour

$$1\ cP = 1\ mN.m^{-2}.s = 1\ mPa.s$$

and f_1 values and the correlation coefficient of the linear D vs. τ plot. The data in Table 1 show that a linear plot corresponding to a finite plastic viscosity (η_{pl}) is given by each mixture above a yield value (f_h) of 66.99 N $m.^{-2}$ Since the pressure in the rectum[9-12] is normally 300 N $m,^{-2}$ the melted mass exhibits plastic flow (η_{pl}) in the rectum. Although thixotropy further

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TABLE 1

Plastic viscosities of triglycerides from plots of shear stress (τ) vs. shear rate (D) using the Bingham yield value correction.

Sample Coding (see text)	Temperature ^{o}C	Correlation Coefficient	Slope* η_{pl}/cP	Bingham Yield Value f_B/N m^{-2}	Static Yield Value f_1/N m^{-2}	Yield at which η_{pl} becomes linear f_h/N m^{-2}
Suppocire A	38	0.9998	52.82	1.776	1.776	1.776
Witepsol E75	40	0.9993	46.02	1.180	1.180	1.180
Witepsol W35	39	1.0000	54.43	7.548	2.664	19.98
tc_2 see p. 8	41	0.9993	43.60	14.92	7.459	31.97
tc_3 see p. 8	43	0.9998	43.07	14.39	6.926	35.96
tc_3 see p. 8	45	1.0000	33.35	1.181	1.181	1.181
tc_4 see p. 11	37	0.9983	44.66	50.77	8.462	57.12
tc_4 see p. 11	39	0.9997	59.96	23.27	3.526	47.95
tc_4 see p. 11	41	0.9994	49.06	20.45	3.526	35.96
tc_4 see p. 11	43	1.0000	40.71	12.69	3.526	31.73
tc_5 see p. 11	38	0.9996	62.17	37.37	11.28	66.99
tc_5 see p. 11	40	0.9993	58.35	33.85	9.872	57.12
tc_5 see p. 11	42	1.0000	52.11	30.32	7.757	57.82
tc_5 see p. 11	50	0.9995	39.77	17.63	7.052	33.85

*1 cP = 1 mN.m^{-2} s = 1 mPa.s

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complicates predictions of the rheological behaviour of the base in the rectum, this effect is only slight in the present system and would not be expected to exert a significant effect on the rheology in the rectum. It is therefore possible to make valid predictions of the viscosity of a plastic base in the rectum.

Plastic behaviour and thixotropy have also been found by Moës[5,6] and by Moës and Jaminet[13] in commercial triglyceride bases examined at temperatures below their clear point, which is the temperature above which all the solid triglyceride components have melted or dissolved.

Rutten-Kingma et al.[14], found that a decrease in the viscosity caused an increase in spreading in the gut. Suspended particles are dragged along with the suppository base, provided that the density of the particles is not too high. Variables, such as particle size and concentration, are seen to have little effect on the spreading behaviour of the suppositories. This was confirmed by Schoonen et al.[15] Thus the viscosity of the base is of prime importance in determining spreading. With this in mind, suppositories of varying viscosity and composition, and containing a dye, were inserted into rat recta. The measured distance of ingression of the dye up the gastrointestinal tract is shown in Table 2. The spread of the molten mass of the suppository was found to be inhibited by the lowest faecal pellet in the tract. This is illustrated by Table 2 columns 2-5 which relate to the methods of purging. With no purging at all, suppositories spread only as far as the first faecal pellet. Using only the initial

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TABLE 2

The ingression of suppositories containing dye from the rectum into the gastro-inestinal tract of rats determined by using various methods of purging.

Formulation of 200 mg suppository (see below)	Distance of ingression/cm			
	No purging	One purging	Two purgings with a 10 min interval	Two purgings with a 120 min interval
tc_{1D}	3.3	6.1	11.4	13.1
tc_{2D}	3.1	4.2	5.6	7.2
tc_{3D}	4.4	7.6	8.2	10.0
tc_{4D}	2.8	2.8	10.0	12.2
tc_{5D}	3.6	4.9	9.8	12.5

Formulation	Dye mg	Tricaprin mg	Other triglyceride
tc_{1D}	20.0	108.0	72.0 mg of trilaurin
tc_{2D}	20.0	72.0	108.0 mg of trilaurin
tc_{3D}	20.0	135.0	45.0 mg of trimyristin
tc_{4D}	20.0	162.0	18.0 mg of tripalmitin
tc_{5D}	20.0	165.6	14.4 mg of tristearin

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purging, the ingression of the suppository is still limited by the lowest faecal pellet. However, when the rat is subjected to both the initial and final purging, no faecal pellets were encountered upon spreading by the suppository mass. Thus, the spreading should now be related to the physico-chemical properties, such as the viscosity of the base.

For rats that have been subject to both the initial and final purging, Table 2 shows that the initial spreading is very rapid (e.g. tc_{1D} which corresponds to formulation tc_1 with dye added, spreads 11.4 cm in 10 min), followed by a much slower rate of spreading (corresponding to a further 1.7 cm in the subsequent 110 min). This spreading behaviour can be explained by considering the rectum to be initially distended by a solid suppository of volume 0.2 cm^3. This causes a relatively large rectal pressure in the area of the suppository so that, during melting, the suppository is squeezed out along the gastro-intestinal (g.i.) tract until the mass has melted completely. Following this rapid process, subsequent spreading is governed by the normal pressure in the g.i. tract, such as that caused by peristalsis. The extent of initial spreading will, of course, be determined by the viscosity as well as by the distension of the rectum.

The spreading of the molten suppository mass will occur in both directions along the g.i. tract. Thus an efficient but non-irritant method of rectal sealing must be used to prevent expulsion of the suppository material by the rat. The various methods used for sealing the rat's rectum can only be performed

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on rats that have been anaesthetised or restrained in some way. All these methods alter the g.i. tract movement and some procedures e.g. anaesthesia, also alter the rectal temperature. Cyanaocrylate ester glue was placed over the rectum after insertion of the suppository. This procedure was very effective and had the following advantages: (a) it produced a strong seal with no leaking, as indicated by no loss of dye; (b) it was not distressing to the rat. Unfortunately, the seal is permanent, so the animal must be sacrificed after such a procedure.

If the viscosity of a base is the determining factor in the spreading of a suppository, a decreased viscosity should lead to increased spreading. The rank order correlation between the spreading of suppository (Table 1: $tc_1 > tc_4 > tc_5 > tc_3 > tc_2$) and the viscosities (Figure 3, Table 1: $tc_5 > tc_3 > tc_4 > tc_2 > tc_1$) should show an inverse relationship, but a poor rank order correlation, τ, was obtained. Using Kendall's method of rank correlation[21] $\tau = -0.2$ with a statistical significance of less than 0.5 (having made a correction for continuity in the statistical significance). If a similar comparison is made after 120 min (rank order of spreading $tc_1 > tc_5 > tc_4 > tc_3 > tc_2$), a better correlation $\tau = -0.6$, is obtained with a significance of approximately 0.1, though a perfect rank order correlation, $\tau = -1.0$, is not observed. This indicates that additional factors may govern the spread of the molten suppository mass in the rectum, for example, movement by peristalsis or movement arising from the variable posture of the rat. The interfacial tension could also affect the spreading

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but may be of minor or negligible significance in view of the fact that the normal g.i. tract pressure is about 300 $Nm.^{-2}$ Initial spreading correlates with viscosity with less statistical significance than spreading after a longer period of time, for the reasons outlined in the previous paragraph.

The previous paper[22] in this series considered the interactions between the constituents of fatty bases and the drugs, ketoprofen and metronidazole, while the next paper will assess the influence of the rheological and spreading data on the *in vivo* release of the drugs from suppositories.

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