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INFLUENCE OF PHYSICOCHEMICAL INTERACTIONS ON THE PROPERTIES OF SUPPOSITORIES I. INTERACTIONS BETWEEN THE CONSTITUENTS OF FATTY SUPPOSITORY BASES

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SUMMARY

Using differential thermal analysis (DTA) the increase in melting point on storage of fatty suppository bases was found to be closely associated with the conversion of the α- and β'-polymorphs of the constituent bases to the more stable β-polymorph. The rate of this process was found to decrease with increasing chain length. The phase diagrams of binary mixtures of tricaprin, trilaurin, trimyristin, tripalmitin and tristearin showed eutectic or monotectic behaviour. For each $\cdot CH_2-CH_2\cdot$ increment in side-chain length by which the two triglycerides differ, the eutectic composition was reduced by about 20% (w/w) with respect to the higher melting component. The lower the chain length (and melting point) of the glycerides in the binary mixtures, the closer the agreement in melting point determined by U-tube, open tube or DTA methods. The thermal data enabled the following binary mixtures of pure triglycerides to be proposed as suppository bases: 2–8% (w/w) tristearin in tricaprin; 3–10% (w/w) tripalmitin in tricaprin; 10–25% (w/w) trimyristin in tricaprin; 55–65% (w/w) trilaurin in tricaprin; 40% (w/w) trilaurin in tricaprin.

INTRODUCTION

The release of a drug from a fatty suppository is influenced by the following factors: (a) size of the drug particles (Rutten-Kingma et al., 1979a and b; Schoonen et al., 1976; Kerckhoffs and Huizinga, 1967); (b) solubility of the drug in water and in lipid (Schoonen et al., 1976; Kakemi et al., 1965); (c) compatibility between the drug and the

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base (Taylor, 1978): (d) spreading of the base in situ (Rutten-Kingma et al., 1979a); (e) liquefaction time of the suppository (Setniker and Fantelli, 1962); (f) melting point of the suppository (Jones et al., 1977); (g) viscosity of the molten mass (Baichwal and Lohit, 1970; Bhavnagri and Speiser, 1976; Gattfossé, 1979); and (h) age of the suppository (Jones et al., 1977). In this paper we examine the factors which affect the melting characteristics of fatty suppositories.

Commercial fatty suppository bases consist of complex mixtures of triglycerides, as exemplified by Table 1. In order to study the physicochemical interactions within fatty suppositories, it is desirable initially to simplify such complex systems. If one considers the constituents of the fatty base represented in Table 1, each of the 11 fatty acids can esterify any of the 3 hydroxyl groups of glycerol. As a result, the number of structural isomers formed from esterification is in excess of 726. Moreover, each triglyceride species is able to exist in alpha (α), beta (β) or beta-prime (β') polymorphic forms giving a possible number of 2178 polymorphs; these can form mix-crystals, i.e. solid solutions (Ravich and Volnova, 1942; Bailey, 1950; Rossell, 1967; Hannewijk et al., 1964), thus further increasing the number of possible transitions and melting points encountered on warming. The observed properties are a complex summation of these effects. To simplify the system binary mixtures of pure monoacid triglycerides were studied in this work, and blends are proposed which are capable of giving the melting characteristics required of a suppository base. The base should: (a) pass the pharmacopoeial disintegration test; (b) melt at or slightly below 37°C; (c) contract on cooling in the mould; (d) be physically stable during ageing, particularly with regard to melting; (e) be chemically stable; and (f) be non-toxic. Since monoacid triglycerides certainly fulfill requirements (e) and (f), their blends will also do so. Thus, interest here is focussed on requirements (a), (b), (c) and (d).

The effect of storage on suppositories is well documented (e.g. Jones et al., 1977). Ageing causes an elevation of melting point which decreases the release rate of the drug

TABLE 1

SIDE-CHAIN FATTY ACID CONSTITUENTS OF TRIGLYCERIDES PRESENT IN SUPPOCIRE A (GATTEFOSSÉ, 1979)

Acid side-chain	% (w/w)
Caproic (C_6)	traces
Caprylic (C_8)	3
Capric (C_{10})	4
Lauric (C_{12})	45
Myristic (C_{14})	14
Pentadecanoic (C_{15})	traces
Palmitic (C_{16})	11
Margaric (C_{17})	traces
Stearic (C_{18})	21
Unsaturated (C_{18})	traces
Arachidic (C_{20})	traces
Total	98 + traces

(Möes, 1975) and therefore affects drug bioavailability. A mechanism for the elevation of melting point during ageing is proposed in this report. Spontaneous polymorphic transitions encountered in monoacid triglycerides are always monotropic (Hannewijk et al., 1964; Perron, 1973) from the less stable polymorph to the more stable, the least stable form being α, the form of intermediate stability being β' and the most stable form being β. It was therefore necessary to consider carefully these polymorphic changes.

To determine the most suitable compositions for suppository bases from the point of view of melting and polymorphic change, complete phase diagrams of binary mixtures of the monoacid triglycerides were derived. Heating methods, particularly differential thermal analysis (DTA), were used because these present a number of advantages over the cooling curve and thaw–melt methods. The cooling curve method is time consuming, large amounts of sample are required and transitions, which are shown by changes of slope, can be missed. The thaw–melt method relies on subjective observations and is not very reproducible (Guillory et al., 1969).

MATERIALS AND METHODS

The commercial suppository bases were purchased from the following companies: Witepsol W35 and Witepsol E75 from Dynamit-Nobel; Suppocire A from Gattefossé. The following triglycerides were gifts from Dynamit-Nobel: tricaprin (glyceryl tri-*n*-decanoate, Dynasan 110); trilaurin (glyceryl tri-*n*-dodecanoate, Dynasan 112); trimyristin (glyceryl tri-*n*-tetradecanoate, Dynasan 114); tripalmitin (glyceryl tri-*n*-hexadecanoate, Dynasan 116); and tristearin (glyceryl tri-*n*-octadecanoate, Dynasan 118). By means of thin-layer chromatography (Storry and Tuckley, 1969) each triglyceride was found to contain less than 1% of monoglycerides or diglycerides.

Mixtures of pure triglycerides were prepared as follows. The weighed consituents, in a glass test tube, were rapidly heated to 76°C and maintained at this temperature with shaking for 10 min. The mixtures were then cooled rapidly to 0°C and maintained at this temperature, still shaking for 5 min. The mixtures were stored at room temperature. After suitable periods of time 6-mg samples were removed and cooled to 0°C and analyzed by differential thermal analysis (DTA) and by hot stage microscopy (HSM). Comminution and grinding were not carried out in order to avoid the introduction of additional energy.

Differential thermal analysis (DTA) was carried out in a Stanton Redcroft model 671 Thermal Analyzer coupled to a two-channel potentiometric recorder (Servoscribe 2S Smiths Industries). Unless otherwise stated the sample size was 6 mg and the heating rate was 2°C per min. The reasons for this choice are given in the next section. Alumina was used as the reference material and static air as the gas phase. The instrument was calibrated using benzoic acid, thermochemical grade (B.D.H. Chemicals). For each DTA peak (first-order or enthalpic transition), tangents at the steepest slope of the curve were drawn on each side of the summit. The temperature corresponding to the point of intersection of the tangents was taken to be the temperature of the transition.

Hot stage microscopy (HSM). A fraction of 1 mg of sample was placed between a microscope slide and a cover slip and the temperature was increased at a rate of 1–5°C per min. Most of the work was carried out using a Kofler hot stage microscope fitted with polarizers. A Stanton-Redcroft (TLHS) instrument was used to confirm the data.

The U-tube melting point was determined by the German standard method DGF (1952, 1957) and AOCS (1926).

The open tube melting point was determined by the German standard method DGF (1952, 1957).

The disintegration test employed was that of the British Pharmacopoeia (1973).

RESULTS AND DISCUSSION

A number of workers (Bailey et al., 1945; Chapman, 1962; Clarkson and Malkin, 1948; Filer et al., 1946; Grüntzic, 1939; Hoerr, 1960; Lutton, 1945, 1950; Malkin, 1954; Quimby, 1950; Weygand and Grüntzic, 1932) have published conflicting data on the transitions and melting points of the triglycerides. This is a result of: (a) the complex polymorphism of these substances; (b) differences of sample purity; and (c) differences between the methods used to characterize the transitions. Before commencing stability or storage tests, it is necessary to erase the previous thermal history of the sample by melting followed by cooling. Storage times were measured from this zero point. This procedure was carried out immediately before thermal analysis of unstored samples. The heating rate can profoundly affect the subsequent behaviour of a triglyceride (e.g. tristearin) under DTA (Fig. 1). At certain heating rates, whole transitions become obscured and the eventual melting point can vary by up to 13°C. Since the maximum number of transitions was given by a heating rate of 2°C per min, this condition was applied in all subsequent work.

Sample size can also have a small but significant effect on the DTA curves (Table 2) because of the finite thermal conductivity of the sample. As the mass of the sample is increased, the recorded melting point is also increased and some transitions can be obscured. Since the maximum number of transitions was given for a sample mass of 6 mg, this condition was applied in all subsequent work; lower masses gave reduced sensitivity.

The DTA curves of the commercial suppository bases were more complicated than those of the pure triglycerides owing to the variety of glycerides which the former contained (e.g. Table 1). Furthermore, HSM of the commercial bases showed that they melted over a considerable temperature range for the same reason. The melting point of each commercial base was therefore taken to be: (a) the temperature at the last peak maximum under DTA; and (b) the melting point of the highest melting component under HSM. These two temperatures agreed to within 1°C and are presented in Table 3 and Fig. 2. At any given storage temperature the melting point of each base increases with time of storage. During storage at room temperature (22°C) the melting point increases greatly within the first day and thereafter slowly increases asymptotically towards the maximum final value. With increasing temperature of storage the time required for the melting point of each base to reach the maximum value is reduced, a phenomenon which is expected from consideration of chemical kinetics. If the samples are stored above the melting point, the resolidified base has a very low melting point, which is due to insufficiency of time for stabilization of the crystal form.

The DTA transitions for each of the pure triglycerides studied were identified as shown in Fig. 1, by comparison with Chapman's (1962) appraisal of the results of his group and those of other workers. The relative amount of each polymorph, α, β and β'

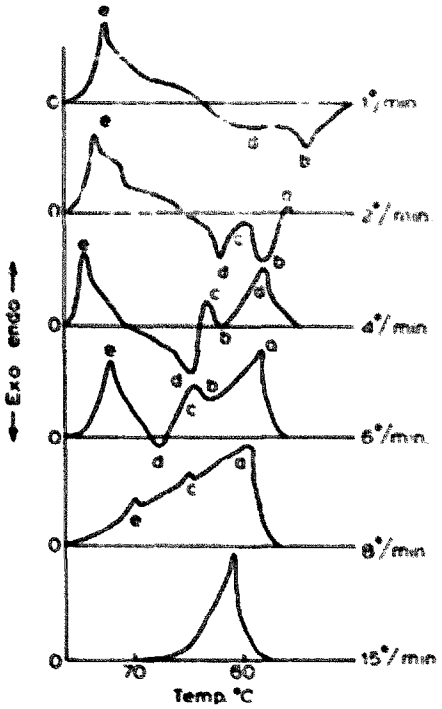

Fig. 1. The effect of heating rate on the DTA curve of tristearin (6 mg). The assignment of the peaks is as follows: a, melting of α-polymorph; b, crystallization of β′-polymorph; c, melting of β′-polymorph; d, crystallization of β-polymorph; e, melting of β-polymorph.

was determined by the measurement of peak areas, corresponding to the melting of each polymorph assuming that the amount of polymorph present is proportional to the peak area. Storage of each pure triglyceride at any given temperature affects the DTA transitions as follows: (a) the final melting point of the highest melting polymorph, β, is increased; (Table 4); and (b) the less stable, lower melting polymorphs, α and β′, are converted to the more stable, higher melting polymorph, β (e.g. Fig. 3). It is highly probable

TABLE 2

EFFECT OF SAMPLE WEIGHT ON THE DTA TRANSITIONS OF TRICAPRIN

Sample weight (mg)	Exothermic peak maximum temperature (°C)	Exothermic peak maximum temperature (°C)	Endothermic peak maximum temperature (°C)
2	9.0	23.1	32.7
4	9.0	23.1	33.3
6	9.2	23.2	34.7
8	10.3	absent	35.2
10	10.3	absent	35.8

TABLE 3

EFFECTS OF TIME AND TEMPERATURE OF STORAGE ON THE MELTING POINTS OF COMMERCIAL TRIGLYCERIDE BASES DETERMINED BY DIFFERENTIAL THERMAL ANALYSIS

Storage time (days)	Storage temp. (°C)	Witepsol E75 m.p. (°C)	Witepsol W35 m.p (°C)	Suppocire A m.p. (°C)
1	3	39	38	37
1	22	39	38	37
1	30	39	38	37
1	37	39	36	37
1	40	37	36	32
1	50	36	36	32
7	3	39	38	37
7	22	40	39	37
7	30	40	39	37
7	37	40	40	37
7	40	38	36	32
7	50	36	36	37
33	3	40	39	37
33	22	41	40	38
33	30	41	41	40
33	37	41	41	40
33	40	38	36	32
33	50	36	36	32
70	3	40	39	38
70	22	41	41	40
70	30	41	41	40
70	37	41	41	40
70	40	38	36	32
70	50	36	36	32

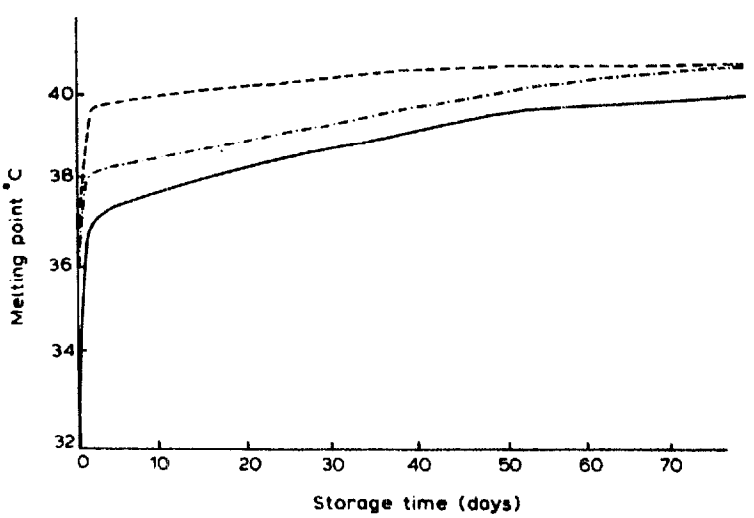

Fig. 2. The effect of storage time at 22°C on the DTA melting point of the following commercial suppository bases: Suppocire A, ———; Witepsol E75, - - - - - -; and Witepsol W35, · – · – ·.

TABLE 4

THE EFFECT OF STORAGE TIME AT 22°C ON THE DTA MELTING POINT OF PURE TRIGLYCERIDES

Melting point	Initially (°C)	After 26 weeks (°C)	After 52 weeks (°C)
Tristearin	73.3	74.0	74.4
Tripalmitin	65.0	65.6	66.3
Trimyristin	58.6	59.0	59.0
Trilaurin	45 4	46.2	46.4
Tricaprin	34.4	35.4	35.4

that the change in the polymorphic content towards the more stable β takes place among all the triglycerides present in commercial suppository bases and explains the observed increase in the softening and melting points on storage. The rate of change of the less stable α and β′ polymorphs to the more stable β polymorph increased with decreasing chain length of the fatty acid side-chains of the triglycerides, i.e. tristearin << tripalmitin < trimyristin < trilaurin < tricaprin. A possible explanation is that the shorter the side-chain, the greater the molecular mobility or ability of the molecules to reorientate from the less stable to the more stable polymorph. In other words, the shorter the side-chain, the less energy is required to twist within the solid matrix, with a consequently lower activation energy and higher entropy of activation or probability of reaction.

Unfortunately no pure triglyceride has the melting characteristics required of a suppository base. For example, the melting point of pure tricaprin becomes stabilized at

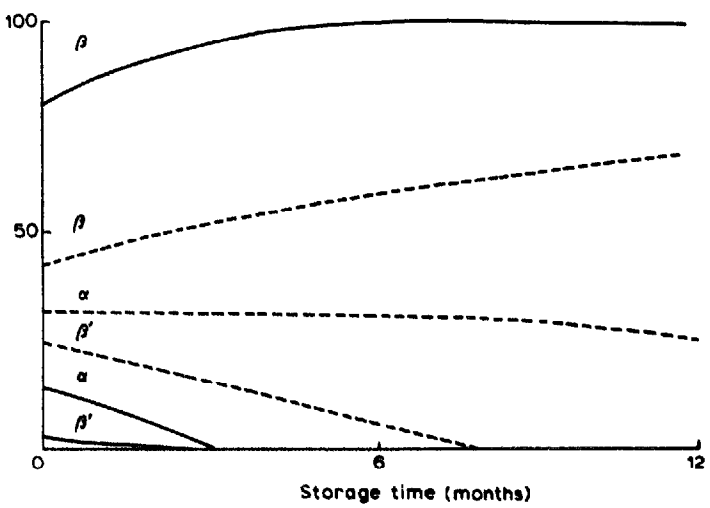

Fig. 3. The effect of storage time at 22°C on the polymorphic content of tricaprin (———) and tristearin (- - - - -).

35.4°C as shown in Table 4, the presence of a drug often lowers the melting point by 1.4°C to 34°C, making tricaprin unacceptable as a base. (The influence of drugs will be considered in the next paper in this series.) The alteration in the melting point of the binary mixture resulting from the incorporation of a drug can, however, be compensated by a small change in composition of the binary mixture. For this reason the phase diagrams of binary mixtures of triglycerides were determined, e.g. Fig. 4. The binary triglyceride mixtures which melted at or near 37°C were part of eutectic or monotectic phase diagrams which usually contained no area corresponding to the depression of the freezing point of tricaprin by any of the higher melting triglycerides. This indicates that the lower melting triglyceride in the mixtures melts completely at or just below the melting point of the pure substance. The molten lower melting triglyceride either: (a) dissolved at the same temperature as the higher melting triglyceride in an amount limited by the eutectic composition (e.g. tricaprin at 35°C dissolves up to 43% trilaurin in Fig. 4); or (b) did not dissolve any of the higher melting triglyceride (e.g. tristearin or tripalmitin in Fig. 4) unless the temperature was raised above the melting point of the lower triglyceride (e.g. tricaprin in Fig. 4). Thus, case (a) corresponds to a eutectic system with one arm missing whereas case (b) corresponds to a monotectic system. Table 5 summarizes data for the phase equilibrium diagrams of the binary triglyceride mixtures studied. For each $\cdot CH_2-CH_2\cdot$ increment in side-chain length by which the two triglycerides differ, the eutectic composition is reduced by about 20 mole% with respect to the higher melting component. Monotectic systems are given when the acyl chain lengths of the two triglycerides

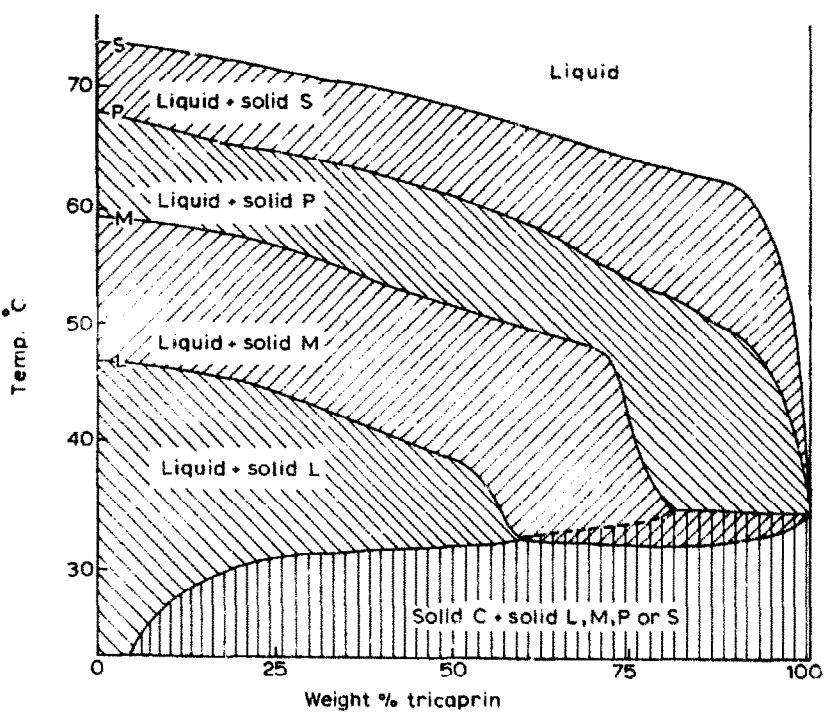

Fig. 4. Phase equilibrium diagram of binary mixtures of tricaprin (C) with trilaurin (L), trimyristin (M), tripalmitin (P) or tristearin (S).

TABLE 5

SUMMARY OF THE PHASE EQUILIBRIUM DIAGRAMS OBTAINED FOR MIXTURES OF MONO-ACID TRIGLYCERIDES USING DTA

triglyceride pure m.p.	tricaprin 36°C	trilaurin 48°C	trimyristin 57°C	tripalmitin 68°C	tristearin 74°C
tricaprin (C) m.p.		E (30%L) 33°C	E (10%M) 36°C	M (0%P) 35°C	M (0%S) 35°C
trilaurin (L) m.p.			E (30%M) 45°C	E (20%P) 47°C	M (0%S) 47°C
trimyristin (M) m.p.				E (40%P) 55°C	E (30%S) 59°C
tripalmitin (P) m.p.					E (40%S) 61°C

E = eutectic (composition in % (w/w) shown in brackets, m.p. underneath). M = monotectic (higher melting component shown in brackets, m.p. underneath).

differ by $(CH_2)_6$ or $(CH_2)_8$. The results of Rossell (1967) and Hannewijk et al. (1964) for binary mixtures of trilaurin with tripalmitin or trilaurin with tristearin or tripalmitin with tristearin accord qualitatively with those of the present work.

The eutectic phase diagram of freshly prepared binary mixtures of tripalmitin and tristearin (Fig. 5) was unlike those of the other binary mixtures, since it consisted of areas representing the depression of the freezing point of each component by the presence of the other. The liquidus and solidus curves did, however, coincide at compositions within

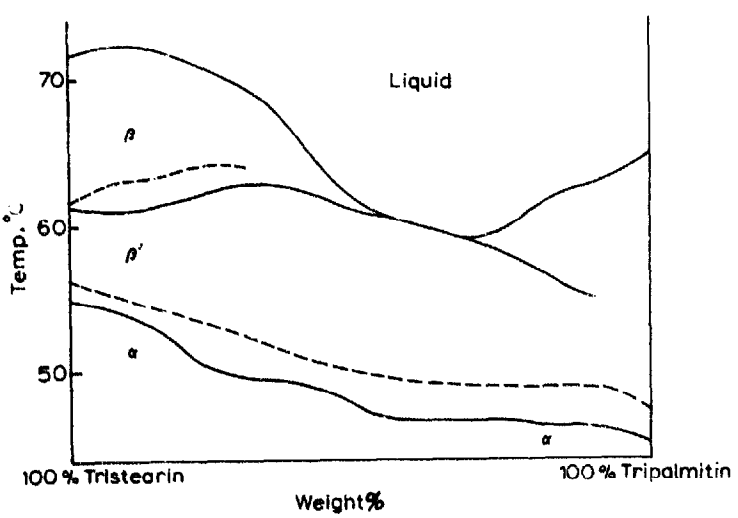

Fig. 5. Phase equilibrium diagram of freshly prepared binary mixtures of tripalmitin (P) and tristearin (S). ———, melting endotherm; - - - - -, crystallization exotherm.

±10% of the eutectic composition. On increasing the temperature compositions rich in tristearin underwent the transitions typical of tristearin itself (Fig. 1 at 2°C per min).

The DTA melting behaviour of binary mixtures of tripalmitin and tristearin are particularly influenced by ageing of the mixtures (cf. Figs. 5 and 6). The number of discernible transitions has been reduced on ageing and the eventual melting point has risen. Ageing produces similar effects on the DTA transitions of other binary triglyceride mixtures, and, significantly, on those of the pure triglycerides. Thus, by analogy with the behaviour of the pure triglycerides, storage increases the proportion of the stable β-polymorph and thereby increases the melting point of the binary mixtures.

Certain binary triglyceride mixtures, possessing melting points close to 37°C, were selected from the DTA data after presentation in the form of phase equilibrium diagrams (e.g. Fig. 4, Table 5). These selected mixtures were subjected to the disintegration test of the British Pharmacopoeia (1973) and to the U-tube and open tube methods of determining melting points. A batch of suppositories must pass these or similar standard quality-control tests before it can be classed as satisfactory. Comparison of the melting points of the selected compositions determined by the various methods (Table 6) show poor agreement although in this table they all passed the B.P. disintegration test. The alarming disagreement between the methods in the case of tricaprin–tripalmitin and tricaprin–tristearin mixtures can be accounted for by the steep melting point–composition curves for the higher melting component in the mixtures shown on the right of Fig. 4. The bulk of the material (tricaprin) melts at a lower temperature, leaving the excess higher triglyceride in suspension and it is the melting point of the latter that is determined at this higher temperature. With one exception the melting points are in the rank order: open tube < U-tube < DTA. The U-tube value is close to the mean value for the 3 methods. The open tube method gives a result which is a function of the rheology of the system as well as melting.

From the phase equilibrium diagrams and melting data, the following binary mixtures

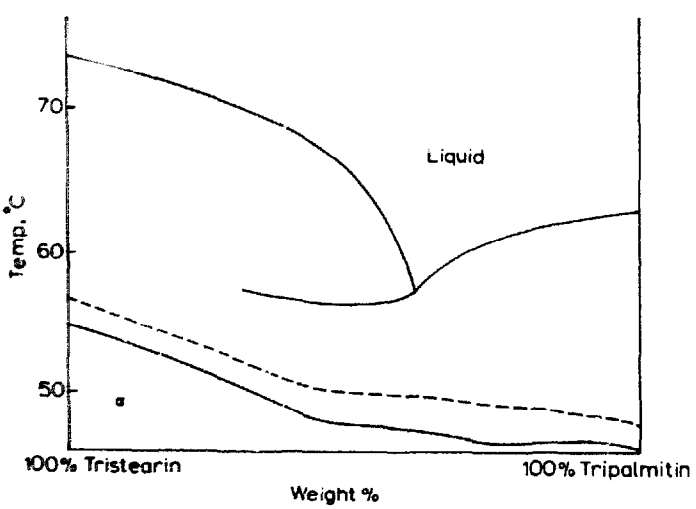

Fig. 6. Phase equilibrium diagram of aged binary mixtures of tripalmitin (P) and tristearin (S). ———, melting endotherm; - - - - -, crystallisation exotherm.

TABLE 6

COMPARISON OF THE MELTING POINTS OF BINARY TRIGLYCERIDE MIXTURES AND OF COMMERCIAL SUPPOSITORY BASES DETERMINED BY THE U-TUBE, OPEN TUBE AND DTA METHODS

Composition	Melting point (°C)				
	U-tube	Open-tube	DTA	Mean value	Standard deviation
92% tricaprin : 8% tristearin	35.4	32.0	59.1	42.2	14.8
90% tricaprin : 10% tripalmitin	45.6	31.4	51.3	42.8	10.2
75% tricaprin : 25% trimyristin	44.6	39.8	46.2	43.5	3.3
60% tricaprin : 40% trilaurin	37.6	35.8	34.0	35.8	1.8
40% tricaprin : 60% trilaurin	38.4	36.8	41.0	38.7	2.1
Witepsol E75	38.0	37.4	40.4	38.6	1.6
Witepsol W35	37.0	35.3	38.6	37.0	1.7
Suppocire A	35.8	34.9	37.2	36.0	1.2

of triglycerides are proposed for suppository bases: 2–8% (w/w) tristearin in tricaprin; 3–10% (w/w) tripalmitin in tricaprin; 10–25% (w/w) trimyristin in tricaprin; 55–65% (w/w) trilaurin in tricaprin; and 40% (w/w) trilaurin in tricaprin. These ranges of compositions afford the latitude required for the incorporation of drugs. The precise composition must be determined in the presence of the appropriate concentrations of the drugs. Since the shorter chain length (i.e. lower melting) triglycerides have shorter stabilization times (Fig. 3) and afford more reproducible melting of binary mixtures (Table 6) than do the longer chain length (i.e. higher melting) triglycerides, formulations consisting of the former are preferable. Studies of the rate of drug release and drug bioavailability from these formulations will form the basis of the next paper in this series.

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