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Medicament release from fatty suppository bases

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The consistency in terms of viscosity index and the rheology of mixtures of cacao butter with different fats was examined with a Stormer viscometer. Most bases showed shear rate thickening at low stresses and marked fall in consistency between 35°–40°. The drug release from them was related inversely to the consistency of the bases.

Earlier work on the fatty suppository bases has been mainly qualitative, including studies on melting points (Melangeau, 1948), viscosity (Zampfira Csath-Stincel, 1966), softening and liquefaction ranges (Setnikar and Fantelli, 1962, 1963) and rheological changes in mixtures of cacao butter with added water soluble substances (Tufegdzic and Lj Parezanovic-Dordevic, 1961).

Cacao butter possesses non-Newtonian flow characteristics (Sterling & Wuhrman, 1960). Describing the consistency of its mixtures with other fats in terms of a single physical property such as melting point or viscosity, therefore appears inadequate. We have tried to measure the consistency of such mixtures and have examined changes in their consistency with temperature.

Reports on the release of medicaments from fatty suppository bases and their *in vitro* disintegration are few. Plaxo (1967) has suggested dialysis through cellophane membrane and subsequent measurement of extinction. Medicament release has also been estimated microbiologically (Ghafoor & Huych, 1962; Blissitt, Tinker & Husa, 1961). We have estimated medicament release from the bases using an apparatus affording simulated body conditions.

EXPERIMENTAL

Materials. Cacao butter (B.D.H.), beeswax (B.P.), spermaceti (B.P.C.) and kokum butter (I.P.).

Preparation of mixtures of fats as bases. Cacao butter was gently melted on a water-bath below its critical temperature of 36°, since above that temperature the stability of the fat is affected (Sterling & Wuhrmann, 1960). The melted fat was added slowly with constant stirring to other previously melted fats. The mixtures were warmed sufficiently to effect a thorough mixing and then chilled immediately to avoid separation of the constituents. They were stored in a refrigerator for 24 h at 5° and then allowed to attain room temperature (28–30°) slowly. The mixtures did not show any separation of the constituents when kept for 12 to 16 weeks at room temperature.

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The mixtures prepared contained (i) 5, 10, 25, 35 and 50% kokum fat, (ii) 1, 2, 3, 4 and 5% beeswax, and (iii) 2, 4, 6, 8 and 10% spermaceti, in cacao butter.

Rheological study. A Searle type rotational viscometer, commercially available as the Stormer viscometer, involving the use of a cup and rotor was used because of the facility of measuring the rate of shear against varying shear stresses. The cup was filled with the sample and allowed to attain the required temperature with the aid of a heater and a thermostat. Ten min were generally allowed for equilibration. The level of the sample in the cup was maintained just enough to keep the rotor completely immersed and also to prevent the formation of a vortex during rotation. After temperature equilibration, loads from 40 to 400 *g* (shear stress) were applied and the number of revolutions of the rotor were noted to give the shear rate, once while increasing the order of weights and again while decreasing their order, with a view to studying any time dependant flow characteristics like thixotropy. Readings were recorded at 35°, 37°, 40°, 45° and 50°. Except for cacao butter-beeswax mixtures, no appreciable (±0·5 s/100 rev) differences in the readings were observed at different loads. Hence the mean of the two readings was taken as the final reading. The results were plotted to obtain flow curves as shown in Fig. 1.

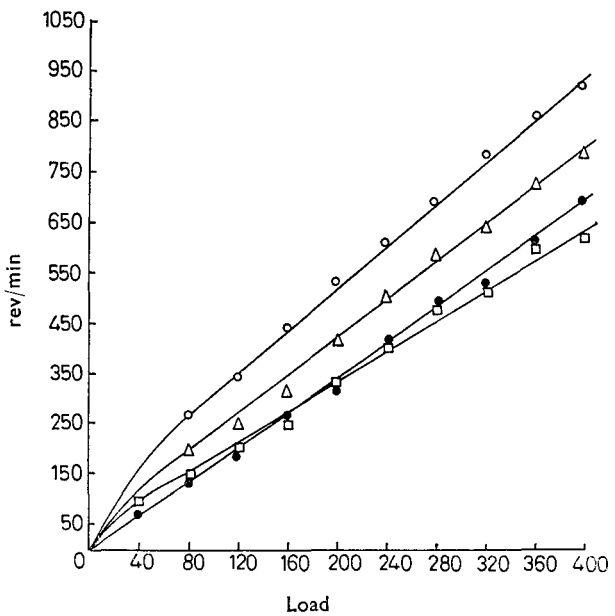

FIG. 1. Rheograms (at 37°). —□—□—, Pure cacao butter; —●—●—, cacao butter + spermaceti 10%; —○—○—, cacao butter + kokum fat 25%; —△—△—, cacao butter + beeswax 1%.

Preparation of suppositories

Salicylic acid (freely soluble in fat), boric acid (less soluble in fat), and copper sulphate (water soluble) were used.

The suppository bases were melted with the minimum amount of heat and part was used to prepare a fine paste of the ground medicament (2 grains/suppository) which was then stirred thoroughly into the bulk of the base. When cloudiness developed the base was poured into chilled moulds. No attempt was made to deter-

mine the particle size or the degree of uniformity of distribution of the medicament. After initial cooling the suppositories were trimmed, kept for 24 h at 5° and then allowed to attain room temperature (28–30°) slowly.

Medicament release from suppositories

The medicament release from the bases was examined using an apparatus in which normal saline at a rate of 100 drops/min was allowed to flow onto the suppository supported on a cotton plug in a glass funnel, mounted on a hot-water jacket. Care was taken to keep the suppository completely immersed in normal saline. Temperature was controlled thermostatically at 37 ± 0·5°. The amount of mediment released from each suppository was determined by analysing aliquot samples of saline collected at regular intervals over 1 h.

The medicaments were estimated spectrophotometrically using a Beckmann spectrophotometer Model DB. Salicylic acid was estimated by colour development with ferric nitrate and measuring the extinction at 525 nm (Stemler, Cosmides & Miya, 1956). Copper sulphate was estimated by the diethyl dithiocarbamate method measuring the extinctions at 425 nm (Callan & Henderson, 1929; Haddock & Evers, 1932). Estimation or boric acid was by using carmine solution for colour development and measuring the extinction at 585 nm (Hatcher & Wilcox, 1950).

RESULTS

Rheology. Rheograms showing shear rate (rev/min) against shear stress (load g) were plotted for all the samples as shown in Fig. 1. The viscosity indices of the bases were determined using the power law equation originally proposed by Ostwald (1926),

$$T = K\, r^n$$

where T = shear stress; r = shear rate; n = flow index; and K = viscosity index (Rogers & Sabin, 1911). These values as determined from the graphs are recorded

Table 1. *Viscosity indices of bases at different temperatures.* (The main base was cacao butter. The values in parentheses are those obtained by arithmetic interpolation)

	Viscosity index at		
Base	35°	37°	40°
Pure cacao butter	72·4	51·3 (52·2)	22·4
Added fat			
Cacao + % kokum butter			
5	113·5	70·1 (78·0)	24·0
10	134·9	82·1 (92·8)	18·2
25	—	102·3	18·2
35	—	—	35·3
50	—	—	—
Cacao + % spermaceti			
2	25·7	24·5 (23·9)	20·9
4	35·1	30·1 (28·5)	19·5
6	43·2	34·6 (34·5)	20·9
8	50·7	38·9 (39·0)	20·9
10	57·9	44·6 (44·0)	20·7
Cacao + % beeswax			
1	95·5	59·5 (66·0)	19·5
2	139·6	91·2 (92·4)	20·9
3	171·8	113·2 (114·0)	24·8
4	298·5	160·3 (186·0)	18·2
5	—	—	16·9

in Table 1. The viscosity indices were plotted against temperature to study the changes in consistency of the different bases with temperature (Fig. 2).

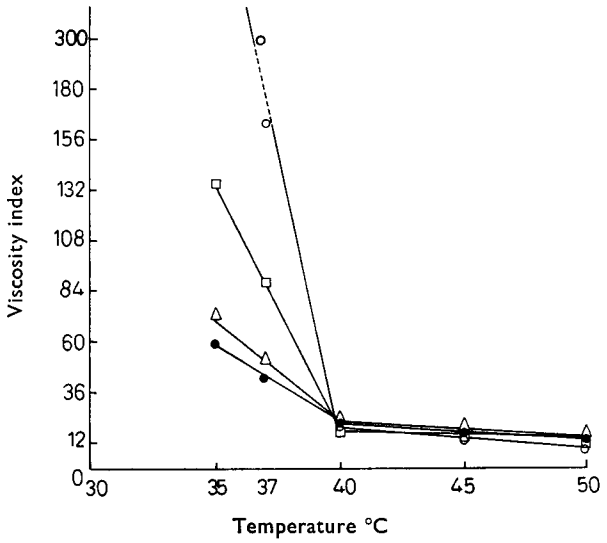

FIG. 2. Effect of temperature on cacao butter and its mixtures. —△—△—, Pure cacao butter; —○—○—, cacao butter + beeswax 4%; —□—□—, Cacao butter + kokum fat 10%; —●—●—, cacao butter + spermaceti 10%.

The rheograms of nearly all bases exhibited slight shear rate thickening. Only mixtures of cacao butter–beeswax showed thixotropy, but this was neither confirmed nor investigated further, because of the operational limitations of the viscometer.

All the bases except those containing 35 and 50% kokum fat in cacao butter and the base with 5% beeswax showed a sharp fall in their consistency, i.e. viscosity index values in the temperature range of 35 to 40°.

Medicament release. To understand the relative drug releasing efficiency of the bases the total amount of medicament released during 1 h was plotted against the viscosity index values at 37° of the bases (Fig. 3). Almost all the graphs were rapidly falling curves.

To examine the pattern of medicament release, the quantity released in an aliquot sample was plotted against the time at which the sample was collected. All the graphs obtained were smooth curves. The rate of drug release was rapid in the first 10 min but fell as the time increased up to 50 min (Fig. 4).

The slopes of the straight lines (fitted for values, between 10–50 min) with the time axis expressed as the tangent of the angle made with the axis have been used to indicate the amount of the drug released per unit time. The slopes were obtained by plotting concentration of medicament against time and were found to fit in accordance with the χ^2 test. In Table 2 the different samples tested and the amount of medicament released is given in terms of the tangent.

When the values for drug release in unit time were plotted against the logarithms of viscosity indices at 37° (calculated as well as verified by experiment, Table 1) of the respective bases, the relation was linear and fitted in accordance with the χ^2 test.

Estimation of medicament release from pure cacao butter suppositories for com-

parative purposes could not be made as it was not possible to obtain suppositories with this base alone at the ambient temperature of 28° to 31°.

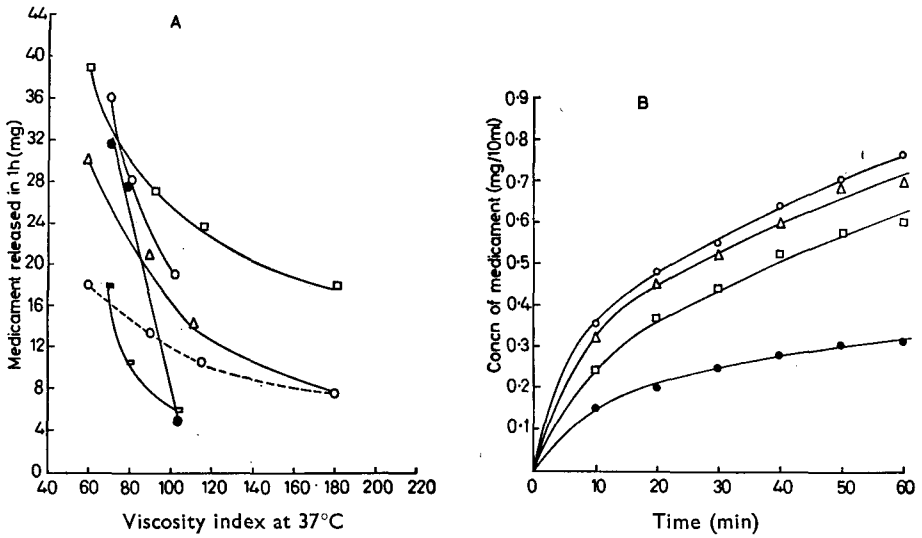

FIG. 3A. Plots showing the total medicament release in 1 h from different bases at 37°. —□—□—, Salicylic acid from cacao butter + beeswax (1, 2, 3 and 4%); —○—○—, salicylic acid from cacao butter + kokum fat (5, 10 and 25%); —△—△—, copper sulphate from cacao butter + beeswax (1, 2, 3 and 4%); —●—●—, copper sulphate from cacao butter + kokum fat (5, 10 and 25%); —·—·—, boric acid from cacao butter + kokum fat (5, 10 and 25%); ..○..○.., Boric acid from cacao butter + beeswax (1, 2, 3 and 4%).

B. Plots showing drug release pattern. —○—○—, Copper sulphate in cacao butter + kokum fat 10%; —△—△—, salicylic acid in cacao butter + kokum fat 10%; —□—□—, salicylic acid in cacao butter + beeswax 3%; —●—●—, copper sulphate in cacao butter + beeswax 3%.

Table 2. *Relative efficiency of medicament release in unit time from various bases, evaluated in terms of the tangent of the angle made by the slope of the straight lines with the* x *axis (tan θ), higher values indicating greater release.*

Medicament	Base	With % of wax or fat added to cacao butter	Tan θ
Salicylic acid	+Beeswax	1	0·9325
	,,	2	0·6745
	,,	3	0·6249
	,,	4	0·5317
	+Kokum fat	5	0·8089
	,,	10	0·5543
	,,	25	0·2679
Boric acid	+Beeswax	1	0·4663
	,,	2	0·3640
	,,	3	0·1405
	,,	4	0·1051
	+Kokum fat	5	0·7536
	,,	10	0·6009
	,,	25	0·3640
Copper sulphate	+Beeswax	1	0·7536
	,,	2	0·4663
	,,	3	0·2126
	,,	4	0·1405
	+Kokum fat	5	0·6249
	,,	10	0·5319
	,,	25	0·1510

DISCUSSION

The sharp fall in the viscosity index values of the mixtures of fats in the temperature range of 35° to 40° indicated a transition in their consistency and hence these bases could be expected either to melt or soften around body temperature. This was further confirmed by determining the viscosity indices at 37° experimentally.

The viscosity index of the base containing 5% beeswax and 35% kokum fat at 37° did show a comparatively low value at 40°, and it is possible that it may be useful for drugs which lower the m.p. of the base. Further increase in the percentage of kokum fat did not seem to be advantageous. With the preparation containing spermaceti (2–10%) there was a sharp fall in the viscosity index values in the temperature range of 35° to 40°, and below those for pure cacao butter, so such a combination would not offer a suitable preparation.

The extent of change in the viscosity index value is related to the amount of added fat. The mixtures of cacao butter with beeswax up to 5% show comparatively greater effects on the viscosity index values than the other bases under investigation.

The rapidly falling curves in Fig. 3A suggest that the total amount of medicament released varied inversely with the consistency of the base which in turn increased with the amount of fat added.

The release of drug from the bases was linear after an initial period. That the magnitude of release of the medicament depended at least to some extent on the consistency of the base, in which it was incorporated is further substantiated by the linear relation of the plots of logs of viscosity indices of the bases at 37° against values for the release of drug in unit time.

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