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INFLUENCE OF PHYSICOCHEMICAL INTERACTIONS ON THE PROPERTIES OF SUPPOSITORIES. II. INTERACTIONS BETWEEN THE CONSTITUENTS OF FATTY SUPPOSITORY BASES AND KETOPROFEN OR METRONIDAZOLE.

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ABSTRACT

The rate at which drugs are released from suppositories and absorbed by the rectal mucosa tends to decrease with increasing solubility of drug in the base or increasing strength of interaction between them. The solubility of ketoprofen or metronidazole in various molten mono-acid triglyceride constituents of fatty suppositories was determined at various temperatures and extrapolated to 37°C and to 100°C. With increasing acyl chain length of the triglyceride solvent the solubility of both drugs tended to decrease and the enthalpy and entropy of solution, determined by van't Hoff or Hildebrand plots, tended to become increasingly positive. The solubility data did not accord with regular solution theory, indicating that specific solute-solvent interactions are important in the solutions. The R_f values of

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the drugs were determined on triglyceride-impregnated layers of silica gel using water: methanol: glacial acetic acid (10:10:1 v/v) as the moving phase. For ketoprofen the rank order of the R_f values was the inverse of that of the solubility values, but metronidazole gave a poor rank order correlation between partition chromatography and solubility. Therapeutic concentration of the drugs (3.4% w/w ketoprofen or 23.4% w/w metronidazole) had small effects on the phase diagrams of binary mixtures of the triglycerides, the eutectic temperatures being lowered by less than 1°C and the eutectic composition of the lower melting triglyceride being increased by about 10% w/w. The implications of these data to drug release are discussed.

INTRODUCTION

The previous paper in this series [1] considered the interactions occurring between the triglyceride constituents of fatty suppository bases. In the present paper we shall consider the interactions occurring between drugs and the individual triglyceride suppository constituents (or excipients). Metronidazole and ketoprofen were the drugs chosen, mainly on account of their contrasting properties. Metronidazole has an aqueous solubility of approximately 1% (w/w), a low solubility in triglycerides and is present in fatty suppositories as a suspension consisting of about 25% w/w of metronidazole in the base. Ketoprofen, on the other hand, is practically insoluble in water even at 80°C, is quite soluble in triglycerides and is present in suppositories as a solid solution (i.e. a molecular dispersion) consisting of approximately 3% (w/w) of ketoprofen in the triglyceride base.

The release of a drug from a molten suppository base is dependent upon a number of factors which have been listed in a previous paper.[1] The rate at which the active substances are released from the suppository and absorbed by the rectal mucous membrane is directly linked to the solubility of the active substance in the excipient. Active substances which are highly

soluble in the excipient usually diffuse out of the excipient much less rapidly than do those which are sparingly soluble in the excipient. Hence solutes which are highly soluble in the excipient are relatively poorly absorbed, an observation which has been widely reported.[2-12]

Solubility parameters have been much used for predicting the solubility and partitioning behaviour of many compounds including drugs and have been reviewed by Barton.[13] The application of solubility parameters for predicting the solubility of metronidazole and ketoprofen in triglycerides is tested in the present work.

The use of quantitative structure activity relationships (QSAR) and chromatographic techniques in predicting partitioning behaviour, free energies of mixing, group contributions to interactions, R_m values, ionisation constants and trends in homologous series have been received by Tomlinson.[14] However, such work has concentrated on homologous series of drug molecules themselves and no work has been reported using homologous series of excipients, such as triglycerides. In principle, the group contributions of alkyl side chain to the interaction with the drug could be determined from the R_f values of the drugs with various stationary phases. If various drugs were chromatographed, those showing lower R_f values would be expected to interact more strongly with the triglyceride suppository bases. Since an increased interaction will reduce the release of the drug from the suppository mass, it may be preferable to avoid incorporating such drugs into such suppository bases. The present work tests this hypothesis by comparing the interactions of metronidazole and ketoprofen with various triglycerides.

The incorporation of drugs into suppository bases commonly affects the melting point of the base, often leading to a dramatic lowering of the melting point of the suppository. This effect may be compensated for by altering the proportions of the triglycerides in the excipient. For this purpose knowledge of the influence of the therapeutic proportion of drug on the phase diagrams is most useful.

The classical U-tube and open-tube methods of determining melting point are not equivalent.[1,15] The effect of suspended drug in the suppository may also contribute to the inequality of the values obtained from either test.

MATERIALS AND METHODS

The materials, their sources, the methods of purity determination and the purities are described in the first paper[1] in this series.

Binary mixtures of triglycerides and the drugs were prepared as follows. The weighed constituents in a glass test tube were rapidly heated to 76°C and maintained at this temperature with shaking for 10 mins; this provided sufficient time for all the ketoprofen to dissolve and for the metronidazole to form a saturated solution in the triglycerides. The mixtures were then rapidly cooled to 0°C and maintained at this temperature, still shaking for 5 mins. The mixtures were stored at room temperature. After 7 days 6 mg samples were removed, cooled to 0°C and analysed[1] by differential thermal analysis (DTA) and by hot stage microscopy (HSM). Melting points were also determined by the U-tube method[16-18] and by the open-tube method.[16,17] The suppository disintegration test of the British Pharmacopoeia[19] was employed.

Thin layer chromatographic plates were prepared as follows. Merck TLC plates 20 x 20 cm, precoated with silica gel 60F 254 to a thickness of 0.25 mm were immersed in toluene solutions of each of the following triglyceride materials: Witepsol E75, Witepsol W35, Suppocire A, tricaprin, trilaurin, trimyristin, tripalmitin, tristearin. The concentration of the triglycerides in the solutions were 5%, 10% and 30% w/v. Owing to the insolubility of tristearin in toluene, analogous coatings were obtained from chloroform solutions. After the plates had been thoroughly soaked they were removed from the solution and allowed to evaporate to dryness in air in the horizontal position to avoid a triglyceride gradient on the plate. Small samples of

the triglyceride-coated silica gel were then removed and further dried under vacuum. The proportion by weight of the triglyceride in the coating was determined by analysis of the carbon and hydrogen content of these weighed samples using Belcher and Ingrams Elemental Analyser. 50 µg of ketoprofen in diethyl ether or 50 µg of metronidazole in glacial acetic acid were spotted onto coated, dried TLC plates. The chromatograms were developed with the solvent mixture: glacial acetic acid, water, methanol (1:5:5 v/v), a system which eluted the drugs but not the triglycerides. The spots were visualised under u.v. light and their R_f values measured.

The solubility of the drug in the triglyceride was determined at a number of different temperatures. The temperature was measured at which each of the various mole fractions of the drug just became soluble in each triglyceride; in practice the temperature was recorded at which the last crystal disappeared. The triglyceride (10 g) was placed in a large boiling tube surrounded by a paraffin bath which was heated electrically. Magnetic followers in the paraffin bath and boiling tube enabled both liquids to be stored to maintain thermal equilibrium. Nitrogen gas was passed very slowly over the liquid to prevent oxidation while heating. Under these conditions evaporation of the solvent was negligible. An appropriate mass of drug (1-5% w/w) expressed as the mole fraction was added to the triglyceride. While heating at a constant rate of about 0.5 to 1.0°C per minute the temperature was noted at which the last crystal of solute just dissolved in the molten solvent. This temperature was within about 1°C of the true equilibrium solubility temperature for the entire contents of the tube on account of the following observations: (a) the temperature was increased very slowly, (b) agitation was very rapid, (c) the temperatures were reproducible within 0.5 to 1.0°C, (d) linear van't Hoff (or Hildebrand) plots of ln solubility against 1/T (or ln T) were obtained with correlation coefficients invariably better than (±) 0.9987 and usually better than (±) 0.9995 as shown in Tables 2 and 3. The

procedure was repeated for at least five different mole fractions of the drug.

RESULTS AND DISCUSSION

The solubility of the drug in the base can determine the mechanism of release and is therefore an important quantity. The rate determining step for drug release from suppositories containing the drug suspended as particles is generally the sedimentation of the suspended drug to the interface, whereas that from supposition containing the drug in solution is the diffusion of the drug from the suppository to the interface.[6,20] Consequently, the solubility of ketoprofen or metronidazole in the triglyceride bases was determined at various temperatures. The standard temperature chosen to define the standard state for comparison of the solubilities of the drugs in the lower triglycerides (tricaprin and trilaurin) was taken as 37°C (310.15 K) corresponding to body temperature. For the higher triglycerides (trimyristin, tripalmitin and tristearin) the standard state temperature was taken to be 100°C (373.15 K). The reason for the choice of these two standard temperatures is as follows. For the two lower triglycerides the experimentally determined points lie close to 37°C and extrapolation to this temperature will be more accurate than extrapolation to 100°C. The converse is true for the higher triglycerides.

For the thermodynamic analysis of the solubility data, the standard state of unit activity of the solute is the pure supercooled liquid at the appropriate defined temperature (310.15 K or 373.15 K) and the temperature dependence of the solubility was expressed according to two alternative methods, A and B. In each method the standard Gibbs free energy change, ΔG^{θ}, was calculated from the solubility, x_2^{θ}, at the standard temperature, T, by means of the equation

$$\Delta G^{\theta} = -RT \ln x_2^{\theta} \qquad \text{Eq. 1}$$

Method A assumed that the difference in heat capacity, ΔC_p between the solid and the supercooled liquid was negligible, or in other words that the temperature dependence of the solubility x_2, obeyed the van't Hoff isochore equation

$$-\left(\frac{\partial[\Delta G/RT]}{\partial T}\right)_p = \left(\frac{\partial \ln x_2}{T}\right)_p = \frac{\Delta H^{\ominus}}{RT^2} \qquad \text{Eq. 2}$$

where x_2 is the solubility at any temperature, T, R is the gas constant, 8.3144 J K^{-1} mol^{-1} and $\Delta H^{\ominus}$ is the standard enthalpy of solution. Integrating, assuming that $\Delta H^{\ominus}$ is independent of temperature, affords

$$\ln x_2 = -\frac{\Delta H^{\ominus}}{R} \cdot \frac{1}{T} + C_A \qquad \text{Eq. 3}$$

where C_A is a constant. In method A $\ln x_2$ was plotted against $1/T$, $\Delta H^{\ominus}$ was calculated from the gradient, $x_2^{\ominus}$ was obtained by interpolation (or expolation) at the standard temperature and $\Delta G^{\ominus}$ was calculated using Eq. 1. Since

$$\Delta G^{\ominus} = \Delta H^{\ominus} - T\Delta S^{\ominus} \qquad \text{Eq. 4}$$

the standard entropy of solution, $\Delta S^{\ominus}$, was given by the intercept, C_A.

Method B assumed that ΔC_p at the melting point was equal to ΔS at the melting point or in other words that the temperature dependence of the solubility x_2 obeyed the Hildebrand entropy equation

$$\Delta S^{\ominus} = R\left(\frac{\partial \ln x_2}{\partial \ln T}\right)_p \qquad \text{Eq. 5}$$

where $\Delta S^{\ominus}$ is the standard entropy of solution. Thus, ln x was plotted against ln T, $\Delta S^{\ominus}$ was calculated from the gradient, $x_2^{\ominus}$ was obtained by interpolation (or extrapolation) at the standard temperature, $\Delta G^{\ominus}$ was calculated using Eq. 1 and $\Delta H^{\ominus}$ from Eq. 4.

Table 1 presents the standard solubilities of the drugs, $x_2^{\ominus}$, from each method. There is a general trend of decreasing

TABLE I

Solubilities of Ketoprofen and Metronidazole in Mono-acid Triglycerides at Standard Temperatures

Triglyceride	Standard Temp °C	x_2^{Θ} Ketoprofen		x_2^{Θ} Metronidazole	
		Method A	Method B	Method A	Method B
Tricaprin	37	0.04237	0.04506	0.004184	0.004248
Trilaurin	37	0.02589	0.02710	0.003383	0.003485
Tricaprin*	100	0.5037	0.5502	0.02582	0.02728
Trilaurin*	100	0.7010	0.7451	0.02655	0.02903
Trimyristin	100	0.6638	0.7079	0.02382	0.02403
Tripalmitin	100	0.6527	0.6749	0.02364	0.02395
Tristearin	100	0.6113	0.6270	0.02033	0.02076

* The extrapolated values of mole fraction solubility, x_2^{Θ} are probably less accurate owing to the long extrapolation required.

solubility of each drug upon ascending the homologous series of the triglyceride solvents. The exceptional position of tricaprin could be due to an inaccurate value at 100°C resulting from the large extrapolation. Thus, (with the exception of tricaprin) the standard free energy of solution for both drugs becomes more positive as the homologous series of triglycerides is ascended.

The thermodynamic quantities of solution for ketoprofen (table II) or for metronidazole (table III) determined by the two methods, A and B, show similar trends but differ in absolute values. This is ascribed to the different assumptions inherent in Eq. 2 and 3.

The applicability of regular solution theory,[21] Small's group contribution method[22] and Hoy's[23] concept of chamelionic character, to the solubility data was tested. Solubility parameters were calculated (table IV) using the data from Hoy[23] and Ahmad and Yaseen.[24] The smaller the numerical difference between the solubility parameters of the ketoprofen monomer and that of each triglyceride the greater the standard solubility, x_2^{θ}, of the drug in the triglyceride at 37°C. This is also valid at 100°C, with the notable exception of tricaprin, which, although it has the smallest difference between its solubility parameter and that of ketoprofen, gives the lowest solubility at 100°C. The anomalous behaviour of tricaprin at 100°C can be attributed to the following limitations: (a) the extrapolation previously mentioned; (b) the proportional error in the calculation of the solubility parameter, which may be significant owing to the ability of the polar functional groups, carbonyl and carboxyl, to form hydrogen bonds[13,22,25] either with other solute molecules or with solvent molecules; the solute-solute interaction is sterically more favourable on account of the hydrocarbon chains; (c) breakdown of the geometric mean rule which strictly applied to molecules capable of interacting solely by London dispersion forces; (d) breakdown of the assumption that the entropy of mixing is ideal owing to differences in size of the solute and solvent molecules and to specific orientation effects.

TABLE II

Thermodynamic Parameters of Ketoprofen in Triglyceride Solvents

Solvent	Stand. Temp. °C	Method A				Method B			
		Correlation Coeff.	$\Delta H^{\ominus}$ kJ mol^{-1}	$\Delta G^{\ominus}$ kJ mol^{-1}	$\Delta S^{\ominus}$ J K^{-1} mol^{-1}	Correlation Coeff.	$\Delta H^{\ominus}$ kJ mol^{-1}	$\Delta G^{\ominus}$ kJ mol^{-1}	$\Delta S^{\ominus}$ J K^{-1} mol^{-1}
Tricaprin	37.0	-0.9963	37.7	8.15	95.2	0.9970	42.9	7.99	112.4
Trilaurin	37.0	-0.9934	49.8	9.92	128.6	0.9956	55.4	9.30	148.8
Tricaprin	100.0	-0.9963	37.7	2.13	95.3	0.9970	43.8	1.85	112.4
Trilaurin	100.0	-0.9934	49.8	1.10	130.6	0.9956	56.4	0.913	148.8
Trimyristin	100.0	-0.9985	49.5	1.27	129.1	0.9989	55.1	1.07	144.9
Tripalmitin	100.0	-0.9996	51.4	1.32	134.3	0.9996	56.1	1.22	147.0
Tristearin	100.0	-0.9997	57.0	1.53	148.8	0.9998	61.6	1.45	161.1

TABLE III
Thermodynamic Parameters of Metronidazole in Triglyceride Solvents

Solvent	Stand. Temp. °C	Method A				Method B			
		Correlation Coeff.	ΔH^{θ} kJ mol^{-1}	ΔG^{θ} kJ mol^{-1}	ΔS^{θ} J K^{-1} mol^{-1}	Correlation Coeff.	ΔH^{θ} kJ mol^{-1}	ΔG^{θ} kJ mol^{-1}	ΔS^{θ} J K^{-1} mol^{-1}
Tricaprin	37.0	-0.9981	27.8	14.1	44.1	0.9987	40.1	14.1	83.9
Trilaurin	37.0	-0.9961	31.5	14.7	54.2	0.9966	43.8	14.6	94.0
Tricaprin	100.0	-0.9981	27.8	11.3	44.1	0.9987	42.5	11.2	83.9
Trilaurin	100.0	-0.9961	31.5	11.3	54.2	0.9966	46.1	11.0	94.0
Trimyristin	100.0	-0.9916	31.2	11.6	52.6	0.9922	44.3	11.6	87.6
Tripalmitin	100.0	-0.9967	39.6	11.6	75.0	0.9962	53.3	11.6	111.9
Tristearin	100.0	-0.9964	36.0	12.1	64.2	0.9968	48.8	12.0	98.5

TABLE IV

Solubility Parameter values (δ) of Various Triglycerides, Ketoprofen and Metronidazole.

Compound	Solubility Parameter $\partial/cal^{\frac{1}{2}}\ cm^{-3/2}$
Tricaprin	9.12
Trilaurin	9.06
Trimyristin	9.02
Tripalmitin	8.99
Tristearin	8.97
Ketoprofen (monomer)	12.66
Ketoprofen (dimer)	8.95
Metronidazole (monomer)	11.58
Metronidazole (dimer)	8.19

If the metronidazole data (table I) is treated in a manner similar to that of ketoprofen, the rank order of ascending solubilities at 37°C is: tristearin < tripalmitin < trimyristin trilaurin < tricaprin. This is the order of decreasing molecular weights. However, at 100°C metronidazole is more soluble in trilaurin than in tricaprin. This anomoly at 100°C can be attributed to the limitations (a) - (d) stated above for ketoprofen, particularly those arising from the presence of the polar, hydrogen-bonding functional groups, hydroxyl, tertiary amino and nitro groups.

Values of the solubility parameter obtained for the drug monomers indicate that metronidazole should be more soluble than metronidazole in the triglycerides. That this is not the case casts doubt on the validity of the calculated solubility para-

meters of the drugs. This re-enforces the explanations for the non-regular behaviour of the solubility of each drug in the triglycerides listed above under limitations (a) - (d).

If dimerisation of the drugs is assumed, the solubility parameters take very similar values to those of the triglycerides (table IV). Similar values of solubility parameters should, if regular solution theory were applicable, give rise to almost ideal solutions. However, the experimental mole fraction solubilities of ketoprofen or metronidazole in the triglycerides (table 1) are considerably lower than the ideal mole fraction solubilities (nearer to 1.0 at 100°C in table V) as might be expected. The ideal solubilities were calculated from the enthalpy of fusion corrected for heat capacity differences.[26] Thus, predictions of solubility and partitioning behaviour based on δ values cannot be made for drugs in lipid systems, such as triglycerides, because of the breakdown of regular and ideal solution theory.

Extrapolation of the solubility data to 37°C predicts that ketoprofen should form a supersaturated solution which should slowly precipitate crystals of ketoprofen upon storage, as in fact observed. The incorporation of therapeutic proportions of either metronidazole (23.4% w/w) or ketoprofen (3.4 w/w) caused a change in the phase diagrams of the binary mixtures of tricaprin/trilaurin and tricaprin/trimyristin. The effect was most marked near the eutectic point, both the eutectic composition and temperature being changed, as sumarised in table VI. The relatively small effects of the drugs on the phase diagrams are attributed to the low solubilities of the drugs in the triglycerides.

The effects of the incorporation of drugs on the U-tube and open-tube melting points and on the B.P. disintegration test of proposed new suppository formulations were studied and the results are summarised in tables VIIa and b and VIIIa and b. Agreement between the U-tube and open-tube melting points in tables VIIIa and VIIIb is poor. This probably arises from differences in the design of the tests. The open-tube measurement is much more dependent on the rheology, such as the shearing properties and viscosity of

TABLE V

Ideal Mole Fraction Solubilities, x_2^{θ} (ideal), and Ideal Thermodynamic Quantities for Metronidazole and Ketoprofen in Triglyceride Solvents at the Standard State Temperatures.

Drug	Standard Temp °C	x_2^{θ} (ideal)	ΔH^{θ}(ideal k J mol^{-1}	ΔG^{θ}(ideal) k J mol^{-1}	ΔS^{θ}(ideal)$_{-1}$ J K^{-1} mol^{-1}
Metronidazole	37.0	0.0832	16.8	6.41	33.4
Metronidazole	100.0	0.3179	22.9	3.56	51.9
Ketoprofen	37.0	0.1106	29.7	5.68	77.6
Ketoprofen	100.0	1.0000	41.3	0.00	110.7

The ideal mole fraction solubility was calculated from the entropy of fusion corrected for heat capacity differences using the procedure of James and Roberts[26]. The enthalpies of fusion (= ideal enthalpies of solution) determined by DSC in kJ mol^{-1} are: ketoprofen at 96°C (m.p.) and at 100°C, 41.326; at 37°C, 29.735: metronidazole at 160°C (m.p.), 28.405; at 100°C, 22.926; at 37°C, 16.761. The ideal free energies and entropies of fusion were calculated by means of Eq. 1 and 3, respectively.

TABLE VI

Influence of Therapeutic Proportions of Ketoprofen or Metronidazole on the Eutectic Compositions and Eutectic Temperatures of Binary Mixtures of Triglycerides

	Binary Triglyceride Mixture		
	Without drug	With 23.4% w/w Metronidazole	With 3.47% w/w Ketoprofen
Eutectic composition (% w/w)	60% tricaprin 40% trilaurin	70% tricaprin 30% trilaurin	70% tricaprin 30% trilaurin
Eutectic temperature	32.6 °C	33.3 °C	32.3 °C
Eutectic composition (% w/w)	80% tricaprin 20% trimyristin	90% tricaprin 10% trimyristin	90% tricaprin 10% trimyristin
Eutectic temperature	35.6 °C	35.0 °C	35.0 °C

TABLE VIIa

Composition of Mixtures of Triglycerides and Drugs Chosen for Empirical Testing. The Coding Described is used in Table VIIIa

Code	Proportions (% w/w) of the excipient components	Drug present in 100 mg of suppository formulation
α	100% tricaprin	
αm	100% tricaprin	23.4 mg metronidazole
αk	100% tricaprin	3.4 mg ketoprofen
βm	90% tricaprin/10% trilaurin	23.4 mg metronidazole
βk	90% tricaprin/10% trilaurin	3.4 mg ketoprofen
γ	60% tricaprin/40% trilaurin	
γm	60% tricaprin/40% trilaurin	23.4 mg metronidazole
γk	60% tricaprin/40% trilaurin	3.4 mg ketoprofen
δm	50% tricaprin/50% trilaurin	23.4 mg metronidazole
δk	50% tricaprin/50% trilaurin	3.4 mg ketoprofen
ε	40% tricaprin/60% trilaurin	
εm	40% tricaprin/60% trilaurin	23.4 mg metronidazole
εk	40% tricaprin/60% trilaurin	3.4 mg ketroprofen
ζ	85% tricaprin/15% trimyristin	
ζm	85% tricaprin/15% trimyristin	23.4 mg metronidazole
ζk	85% tricaprin/15% trimyristin	3.4 mg ketoprofen
η	75% tricaprin/25% trimyristin	
θ	90% tricaprin/10% tripalmitin	
θm	90% tricaprin/10% tripalmitin	23.4 mg metronidazole
θk	90% tricaprin/10% tripalmitin	3.4 mg ketoproten

TABLE VIIb

Composition of Mixtures of Triglycerides and Drugs Chosen for Empirical Testing. The Coding Described is used in Table VIIIb

Code	Proportions (% w/w) of the excipient components	Drug present in 100 mg of suppository formulation
ι	70% tricaprin/30% tripalmitin	
ιm	70% tricaprin/30% tripalmitin	23.4 mg metronidazole
ιk	70% tricaprin/30% tripalmitin	3.4 mg ketoprofen
κ	90% tricaprin/10% tristearin	
κm	90% tricaprin/10% tristearin	23.4 mg metronidazole
κk	90% tricaprin/10% tristearin	3.4 mg ketoprofen
λ	80% tricaprin/20% tri stearin	
λm	80% tricaprin/20% tristearin	23.4 mg metronidazole
λk	80% tricaprin/20% tristearin	3.4 mg ketoprofen
μ	Witepsol E75	
μm	Witepsol E75	23.4 mg metronidazole
μk	Witepsol E75	3.4 mg ketoprofen
Ψ	Witepsol W35	
Ψm	Witepsol W35	23.4 mg metronidazole
Ψk	Witepsol W35	3.4 mg ketoprofen
ξ	Suppocire A	
ξm	Suppocire A	23.4 mg metronidazole
ξk	Suppocire A	3.4 mg ketoprofen
oF	May and Baker suppository of metronidazole freshly prepared	
oA	May and Baker suppository of metronidazole aged	

TABLE VIIIa

Results of the Empirical Tests on the Formulations Listed in Table VIIa

Code composition	BP Disintegration test	'U' tube melting point °C	Open tube melting point °C
α	Pass	31.6	31.1
αm	Pass	30.4	31.1
αk	Pass	31.3	30.8
βm	Pass	30.8	31.0
βk	Pass	29.9	29.7
γ	Pass	37.6	35.9
γm	Pass	36.9	38.1
γk	Pass	37.3	36.8
δm	Pass	37.0	38.2
δk	Pass	36.2	37.6
ε	Fail	38.4	39.0
εm	Fail	38.4	40.0
εk	Fail	37.6	33.9
ζ	Pass	40.6	38.3
ζm	Pass	40.0	39.7
ζk	Pass	39.3	35.5
η	Fail	44.6	39.8
Θ	Pass	45.6	31.4
Θ m	Pass	39.6	41.3
Θk	Pass	42.6	31.4

the system, than is the U-tube method.[15] For mixtures containing metronidazole the open-tube melting point is generally less than the U-tube value, the exceptions being δk, εk, Ψk. The rank order of melting points for mixtures containing metronidazole is generally U-tube < open-tube, the exceptions being ζm, lm, μm, ξm, oF. The reversal of rank order is attributed to the follow-

TABLE VIIIb

Results of the Empirical Tests on the Formulations Listed in Table VIIb

Code Composition	BP Disintegration test	'U' tube melting point °C	Open tube melting point °C
ι	Fail	55.3	47.0
῾m	Fail	55.1	52.9
ιk	Fail	55.8	46.6
κ	Pass	35.4	32.0
κm	Pass	36.4	40.3
κk	Pass	32.2	30.9
λ	Fail	61.4	52.4
λm	Fail	57.4	58.2
λk	Fail	60.6	51.9
μ	Pass	38.0	37.4
μm	Pass	38.4	37.9
μk	Pass	37.4	36.7
ψ	Pass	37.0	35.3
ψm	Pass	35.6	35.4
ψk	Pass	34.6	35.1
ξ	Pass	35.8	34.9
ξm	Pass	35.8	35.6
ξk	Pass	35.4	33.9
oF	Pass	35.4	35.2
oA	Pass	37.4	not applic.

ing effects: (a) Suppositories containing metronidazole have a high proportion of the drug in the form of suspended matter. Thus the apparent viscosity and shear stress will be higher than in suppositories containing ketoprofen or in drug-free base. The open-tube method is more sensitive to these effects and will

therefore give a higher melting point value for metronidazole suppositories than for ketoprofen suppositories or for the drug-free base. (b) The first sign of movement of suppositories containing metronidazole in the U-tube method is attributed to the filtration of the molten triglyceride base through the more rigid drug particles and is less dependent on the overall shear of the suppository. Consequently, a lower U-tube temperature is obtained.

For studying the effects of ageing on the melting point of a triglyceride suppository, it is recommended that the U-tube method be used, because a sample is taken directly from the solid suppository using a trochar, a procedure which does not affect the polymorphic content of the suppository. On the other hand, in the open-tube method the aged suppository has first to be melted; capillary tubes are then dipped into the molten fat and the samples are stabilised at $0^{o}C$ for 24 hours. Upon melting, all previous thermal history of the suppository is erased and the melting point determined is that of suppositories which are always only 24 hours old. The open-tube method is, however, more suitable for the quality control of triglyceride ingredients prior to suppository manufacture, than for tests in which the effects of ageing are important, as for example in hospitals.

The drugs ketoprofen and metronidazole were chromatographed using reverse phase TLC plates coated with various triglycerides. The R_f values obtained could then be related to the relative interactions of each drug with each triglyceride. Table IX summarised the results for a 13% w/w coating of triglyceride on silica. More concentrated coatings gave reduced sensitivity which was attributed to the adherence of separate silica particles leading to a reduction in specific surface area. Thus a less concentrated coating (13% w/w) gives more accurate R_f values as there is a greater surface area for partitioning. The rank order in ascending values of R_f for ketoprofen is: tricaprin < trimyristin < Witepsol E75 < trilaurin < tripalmitin < tristearin < Suppocire A < Witepsol W 35. The R_f values are a function of partitioning of ketoprofen into the triglycerides under the chromatographic con-

TABLE IX

R_f Values of Ketoprofen and Metronidazole on TLC Plates coated with a Pure Triglyceride

Coating % w/w triglyceride	R_f value of ketoprofen	R_f value of metronidazole
None	0.95	0.92
13% tricaprin	0.31	0.53
18% tricaprin	0.36	0.69
39% tricaprin	0.62	0.75
13% trilaurin	0.42	0.31
18% trilaurin	0.51	0.50
38% trilaurin	0.56	0.60
13% trimyristin	0.32	0.42
18% trimyristin	0.50	0.73
13% tripalmitin	0.48	0.45
13% tristearin	0.53	0.52
18% tristearin	0.54	0.63
13% Witepsol W35	0.59	0.48
13% Witepsol E75	0.40	0.57
13% Suppocire A	0.57	0.79

ditions and, on thermodynamic grounds, should be inversely related to the solubility of ketoprofen in the triglycerides. This prediction was tested at 22°C at which the solubility of ketoprofen was evaluated by extrapolating the plots by methods A and B and taking the arithmetic mean of the two ln x_s values at 22°C. The rank order of the mean extrapolated values of the solubility of ketoprofen in the triglycerides at 22°C is: tricaprin < trimyristin < trilaurin < tripalmitin < tristearin. The R_f values show a perfect inverse rank order correlation with the solubilities, as predicted thermodynamically, despite (a) the long extrapolation in the case of trimyristin, tripalmitin and

tristearin, and (b) the fact that the values obtained refer to the drug's solubility in the supercooled liquid triglyceride and not necessarily to the concentrated solutions of the drug and triglyceride created on the plate by the developing solvent.

When the solubility and R_f values are compared for metronidazole the rank order correlation is poor. This lack of correlation may result from the following effects: (a) Metronidazole is much less soluble than ketoprofen in the triglycerides by a factor of approximately 30 and may therefore be less sensitive to changes in the nature of the triglyceride coating in the stationary phase. This is reflected in the much higher R_f values for metronidazole than for ketoprofen. (b) Under the acidic chromatographic conditions metronidazole may be partially ionised owing to its amphoteric nature, whereas most of the ketoprofen will remain unionised. This may further reduce the sensitivity of the chromatography of metronidazole to changes in the stationary phase and also reduces the extent of partitioning into the triglycerides which results in the much higher R_f values for metronidazole than for ketoprofen.

Under the chromatographic conditions employed, a comparison of the R_f values for metronidazole cannot be used to predict the relative interactions or affinities occurring in suppository formulations for the reasons stated above.

The next paper in this series considers the rheological properties of the triglycerides, of the proposed new suppository formulations and of some commercial suppository bases. The relationships between the rheological properties of the suppository bases and spreading in the rectum are also investigated.

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REFERENCES

1. Liversidge, G.G., Grant, D.J.W. and Padfield, J.M., Int. J. Pharmaceut. 7, 211 (1981).

2. Armstrong, N.A. and James, K.C., Int. J. Pharmaceut. 6,185 (1980).

3. Moolenaar, F. and Schoonen, A.J.M., Pharm. Int., July, 146 (1980).

4. Grzesiczak, A., Ludwicki, H. and Oetrowska, E., Acta. Polon. Pharm. 37 (3), 343 (1980).

5. Pasich, J., Galoch, B. and Kustra, K. Pharmazie 34 (H7), 413 (1979).

6. Schoonen, A.J.M., Moolenaar, F. and Huzinga, T., Int. J. Pharmaceut. 4 (2), 141 (1979).

7. Cassahoursat, L., Palancade, P. and Bildet, J., Sci. Tech. Pharm. 7(5), 223 (1978).

8. Möes, A., Labo. Pharm. Problem. Tech., (260), 1027 (1976).

9. Voigt, T. and Falk, C., Pharmazie, 23, 709 (1968).

10. Kerckhoffs, H.P.M. and Huzinga, T., Pharm. Weekblad 102, 1183 (1967).

11. Lowenthal, W. and Borzelleca, J.F., J. Pharm. Sci. 54 (12), 1790 (1965).

12. Neuwald, V.F. and Kunze, F., Arzneim.-Forsch. 14, 1162 (1964).

13. Barton, A.F.M., Chem. Rev. 75(6), 731 (1975).

14. Tombinson, E., J. Chromatog. 113, 1 (1975).

15. Hannewijk, J., Haighton, A.J. and Hendrikse, P.W. "The Analysis and Characteristics of Oils, Fats and Fat Products", Bockenoogen, H.A., ed., Wiley Interscience, New York, N.Y. Vol. I, 1964, 119-182.

16. D.G.F. Einheitsmethoden C-IV 3^e (1952).

17. D.G.F. Einheitsmethoden C-IV 3^e (1957).

18. A.O.C.S. Committee on Analysis of Commercial Fats and Oils. Ind. Engng. Chem. 18, 1346 (1926).

19. British Pharmacopeia, Pub. H.M. Stationery Office, London, A132(1980).

20. Schoonen, A.J.M., Moolenaar, F., Reuvers, K.A. and Huzinga, T. Int. J. Pharmaceut., 7 (1), 29 (1980).

21. Hildebrand, J.H., Prausnitz, J.M. and Scott, R.L. "Regular and Related Solutions", 1970, Van Nostrand, New York, N.Y.

22. Small, P.A., J. Appl. Chem. 3, 71 (1953).

23. Hoy, K.L., J. Paint. Technol. 42, 76 (1970).

24. Ahmad, H. and Yaseen, M., J. Oil Col. Chem. Assoc. 60, 99 (1977).

25. Burell, H. "Polymer Handbook" 2nd Edn. 1975, Interscience, New York, N.Y.

26. James, K.C. and Roberts, M., J. Pharm. Pharmacol. 20, 709 (1968).