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Rheology of polyol behenates and drug release from matrix monolithic capsules

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Abstract

Three polyol behenates with similar melting points (MP) and different hydrophilic–lipophilic balances (HLB) were studied (MP/HLB: 70/02, 63/05 and 57/13). After melting at MP + 30°C, the rheological behaviour of behenates was determined by adjustment of the rheograms to the Ostwald power-law and by statistical assessment of the flow index. Behenates showed slight shear thickening. This shear thickening increased when HLB of behenates decreased. This behaviour accounted for a reorganization of the particles under the shear, which became easier when the proportion of the polyethylene glycol chains in the wax decreased. Proxyphylline was used to prepare suspensions at a concentration of 25% in the melted behenates, and to manufacture monolithic capsules by cooling. The suspensions had a shear-thinning behaviour with or without thixotropy. Colloidal particles and aggregates formed in these suspensions directly influenced the rheological properties, as observation of solidified suspensions by scanning electron microscopy confirmed. Extended release of proxyphylline was obtained with the three waxes. Behenates 63/05 and 70/02 gave inert matrices and released drug very slowly. Hydrodispersible behenate 57/13 swelled and made up a kind of hydrophilic matrix that released proxyphylline more quickly, due to slight erosion. In the three cases, the release mechanism was basically diffusional in nature.

Keywords: Polyol behenates; Rheology; Lipidic matrix; Monolithic capsules; Diffusion

1. Introduction

Behenic acid is a saturated fatty acid containing 22 carbon atoms. It is also called docosanoïc acid and was used by Otsuka and Matsuda (1995) to prepare matrix tablets.

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Three esters of behenic acid and of polyhydric alcohols (polyols) are also employed to manufacture extended release solid dosage forms. These are, respectively, glyceryl behenate, a mixture of polyethylene glycol (PEG) 400 behenate and of glyceryl butyrate, and PEG 1000 behenate. These waxes are characterized by their melting points (MP) and their hydrophilic–lipophilic balance (HLB) values. As for saturated polyglycolysed glycerides, also called Gelucires (Ratsimbazafy and Brossard, 1991), behenates can be described by their MP/HLB ratios, i.e. 70/02, 63/05 and 57/13, indicating the increasing hydrophilicity, respectively, for glyceryl behenate (Compritol 888), PEG behenate and glyceryl butyrate mixture (Compritol HD5), and PEG behenate (Compricoat).

Physico-chemical properties of behenates have already been described (Yolou et al., 1992; Kaloustian et al., 1995). A few publications have compared these three behenates, either in matrix tablets (Pelletier et al., 1992; Joachim et al., 1994) or in matrix granules (Ausseur et al., 1998). Extended release of theophylline was achieved in both cases, although results were different concerning the influence of behenate hydrophilicity, owing to the very distinct dissolution surface areas of tablets and granules. Consequently, work is required to compare these three materials.

Among the three products, behenate 70/02 is the most often used in extended release products. It was first used in experimental monolithic capsules and matrix granules by Massin et al. (1982), then by Abdallah (1992). Several works dealt with matrix tablets (Abdallah, 1992; Perez et al., 1993; Meshali et al., 1995; El-Sayed et al., 1996) and extended release spheres (Thomsen et al., 1994; Joachim et al., 1996).

The purpose of the present work was to compare the three behenates formulated in monolithic hard gelatin capsules with proxyphylline as a model drug. A special interest will be on the mechanism of drug release. As capsules are filled with proxyphylline suspensions in melted behenates, the rheological behaviour of behenates with or without drug in suspension has also been studied.

2. Materials and methods

2.1. Materials

Proxyphylline (Sigma Chemical, St Louis, MO) was the drug used in this study. Its particles were rectangular (4×30 μm) and its aqueous solubility at 25°C was 0.601 g/cm^3.

Three polyol behenates (Gattefossé, Saint-Priest, France) were chosen as matrix materials of different melting points and hydrophilic–lipophilic balances (MP/HLB): Compritol 888 (glyceryl behenate, 70/02), Compritol HD5 (mixture of PEG 400 behenate and of glyceryl butyrate, 63/05) and Compricoat (PEG 1000 behenate, 57/13), formerly named Lubrifiant WL 3284.

2.2. Rheological measurements

As for the Gelucires (Ratsimbazafy et al., 1997), all waxes were melted using a water bath (Salvis, Luzern, Switzerland) at temperatures of MP + 30°C, and drug suspensions were prepared at a concentration of 25% w/w. Proxyphylline was progressively dispersed in the melted behenates by agitation for 15 min with a rotary stirrer (Rayneri, Montreuil, France) fitted with a deflocculating blade.

Rheological behaviour and apparent viscosity determinations were carried out at the manufacturing temperature using a coaxial cylinder viscosimeter (Rheomat 15T; Contraves, Zürich, Switzerland) as previously described (Ratsimbazafy et al., 1997).

Rheograms were fitted to the Ostwald relationship, also termed the power law:

$$\tau = k\gamma^n \quad (1)$$

where γ is the shear rate, τ is the shear stress, k is the consistency index and n is the flow index. The flow index is equal to unity if the flow is Newtonian. A value either greater or smaller than unity indicates, respectively, shear thickening or shear thinning. This index was determined by linear regression with the logarithmic form of Eq. (1) (Bourret et al., 1994). A statistical test for linearity allowed the calculation of the deviations

of the regression and showed the validity of the model. The divergence from Newtonian flow was tested statistically by comparison with the unity value of the linear regression coefficient n.

2.3. Preparation and evaluation of capsules

Capsules, size 00, were filled with a syringe and contained 200 mg of drug. Capsule cooling was performed at room temperature. The solidified suspensions were studied using a field emission scanning electron microscope (S 4000 Hitachi; Tokyo, Japan). Samples were coated with gold–palladium to a thickness of 1–1.5 nm.

Disintegration testing was performed using an Erweka ZT 3 Tester (Euraf, Colombes, France). A 800 ml volume of distilled water at 37°C was the medium for the test. Six capsules were tested without disks and mean disintegration times were determined.

Drug release measurements were carried out in a USP rotating paddle apparatus (Dissolutest; Prolabo, Paris, France) with 1000 cm^3 of distilled water at 37°C and a rotation speed of 100 rpm. Released proxyphylline was measured by UV spectrophotometry at 273 nm. The results were the average of six trials. Dissolution efficiencies (DE) were determined by counting squares with a Hewlett-Packard computer 9825 B. DE is defined as the area beneath the release curve, up to time $t = 8$ h, expressed as a percentage of area of the rectangle described by 100% release in 8 h.

Erosion of capsules was measured by the loss of weight after an 8-h stay in the dissolution apparatus under the previously described conditions, and a 12-h stay at 30°C in an oven. The amount of drug released was taken into account (Brossard et al., 1983).

The release mechanism was investigated by comparing it with models derived according to the equations of Higuchi (Eq. (2)), Hixson–Crowell (Eq. (3)), Kopcha (Eq. (4)) and Ritger–Peppas (Eq. (5)) (Brossard and Wouessidjewe, 1990; Ratsimbazafy and Brossard, 1991):

$$Q = at^{1/2} + b \quad (2)$$

$$100^{1/3} - (100 - Q)^{1/3} = ct + d \quad (3)$$

$$M = At^{1/2} + Bt \quad (4)$$

$$M = Kt^{n} \quad (5)$$

where Q ($\leq 90\%$) and M ($\leq 70\%$) are the percentages of drug released at time t. A is a diffusional term and B an erosional term (Kopcha et al., 1991), n is the diffusion exponent indicative of the release mechanism (Ritger and Peppas, 1987), and a, b, c, d and K are regression constants.

3. Results and discussion

3.1. Rheological behaviour

3.1.1. Pure behenates

Figs. 1 and 2 show the flow and viscosity curves of pure behenates. Whatever the shear rate, shear stress and apparent viscosity increase with HLB. To determine rheological behaviour, a linear model adjustment according to $\ln \tau = \ln k + n \ln \gamma$ was investigated. The linearity test was always highly significant of a good fitting. In all the fittings which gave rise to the flow index estimate, the correlation coefficient, r^2, which indicated the proportion of the shear stress explained by the shear rate, was always equal to 0.999.

Regression coefficient values, n, which give the flow indexes (Table 1), are scarcely greater than 1 and do not directly allow a conclusion on flow behaviour. The comparison of these values with the theoretical value of 1 by a Student's t-test shows that the difference between experimental values n and 1 is always significant for non-Newtonian flow because the significant probability level is always less than 0.05. However, shear thickening is very weak and the influence of the HLB on the flow indices is not clear. To corroborate these results, the residual variations unexplained by the linear model were used as an estimate of the experimental error. This allowed the assessment of the 0.95 confidence limits of regression coefficients. These intervals illustrate the divergence from unity.

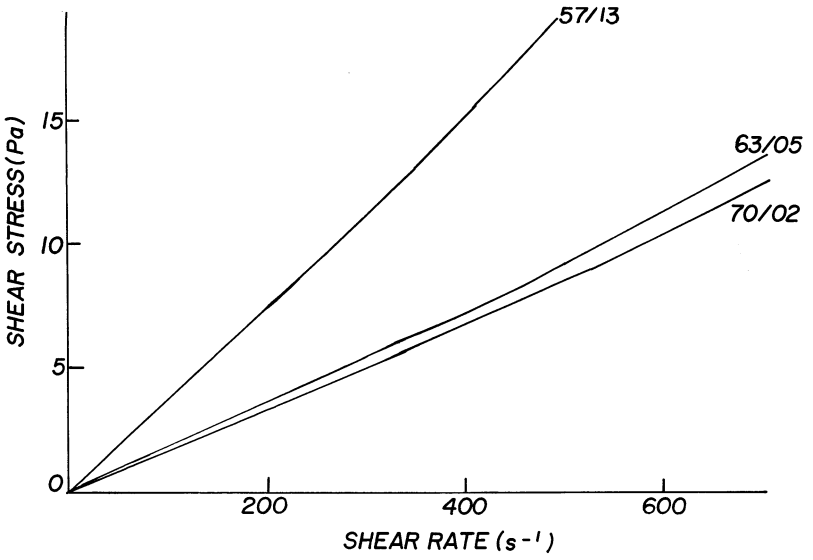


Fig. 1. Rheograms of melted pure polyol behenates.

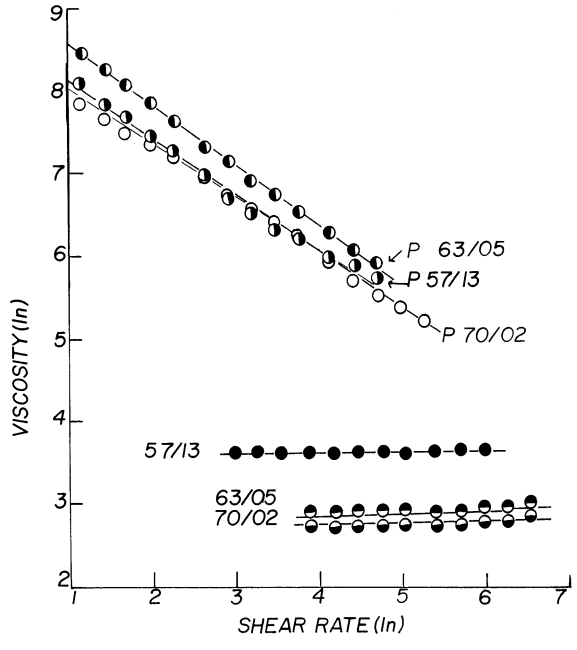


Fig. 2. Apparent viscosity vs shear rate of pure polyol behenates and proxyphylline suspensions (P).

Such slight shear thickening behaviour had also been particularly observed by Fabregas (1991) and Margarit et al. (1992) for suppository bases and by Bourret et al. (1994) for Gelucires. On the other hand, Sutananta et al. (1995) only found a Newtonian behaviour for Gelucires. Hawley et al. (1992) and Shah et al. (1996) also described such a Newtonian behaviour for the wax-based vehicules they used to fill hard gelatin capsules.

Table 1
Flow indexes of the melted pure polyol behenates and of the proxyphylline suspensions ($n \pm 95\%$ confidence interval, $P < 0.05$)

Behenates	Pure	Suspensions
70/02	1.04 ± 0.01	0.35 ± 0.01
63/05	1.04 ± 0.01	0.27 ± 0.01
57/13	1.01 ± 0.01	0.34 ± 0.04

The slight shear thickening of behenates, depending on the HLB value, allows us to link their flow patterns to their composition. Behenates of low HLB contain little or no PEG, whereas behenates of high HLB include only PEG esters (Yolou et al., 1992). The slight shear thickening observed in the rising part of the rheogram, depending on the initial structure, usually stems from molecular reorganization; in media where particles in suspension are free of strong bonds,

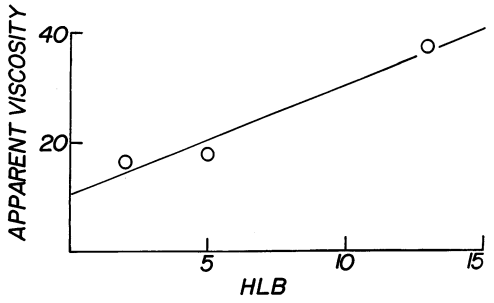


Fig. 3. Influence of polyol behenate HLB on apparent viscosity at shear rate $\gamma = 84.5\ s^{-1}$.

there would be local rearrangement of particles, due to the shear effect, which would show through a slight increase in viscosity (Bourret et al., 1994). Our observations may effectively account for such a reorganization; a structural rearrangement is possible when the degree of PEG condensation is low but becomes difficult when the polyethylene chain is extended. When the shear rate returns to zero, the initial structure of the system is restored.

Apparent viscosity of melted behenates increases with the HLB value (Fig. 3 and Table 2), following Eq. (6):

$$\eta_o = 2.040\text{HLB} + 10.102 \quad (6)$$

where η_o is apparent viscosity at shear rate $\gamma = 84.5\ s^{-1}$ and HLB is the hydrophilic–lipophilic balance of the behenate. The increase of the shear stress and that of the apparent viscosity with the hydrophilic specificity may also be explained by the behenate composition. With steric hindrance of PEG chains in the high HLB behenate, the chain lengthening induces an increase of the frictional forces and then a resistance to flow.

Table 2
Apparent (η_{app}) and relative (η_r) viscosities at shear rate $\gamma = 84.5\ s^{-1}$ of the proxyphylline suspensions in polyol behenates

Behenates	η_o (mPa s)	$\eta_{app}\nearrow$ (mPa s)	$\eta_{app}\searrow$ (mPa S)	η_r
70/02	16.0	328	314	19.6
63/05	17.8	438	438	24.6
57/13	37.3	381	357	9.57

3.1.2. Proxyphylline suspensions

The rheograms of the suspensions in the three behenates show shear thinning behaviour (Fig. 4). The down-curves of rheograms reveal a slight hysteresis for behenates 70/02 and 57/13. The rheological behaviour of behenates changed with the incorporation of proxyphylline: pure waxes showed slight shear thickening but drug suspensions had thixotropic, shear thinning behaviour. Suppository excipients and polyglycolysed glycerides have previously been shown to exhibit such a change in the rheological behaviour after drug incorporation (Margarit et al., 1992; Ratsimbazafy et al., 1997). Baykara and Yüksel (1992) also found such thixotropic shear shinning behaviour for suspensions of oxprenolol in a mixture of arachis oil and beeswax destined to fill hard gelatin capsules.

The viscosity curves of proxyphylline suspensions (Fig. 2) indicate the linear decrease of apparent viscosity under the influence of shear. The shear thinning behaviour is confirmed by the flow index values (Table 1).

Rheological properties of suspensions are related to the shape and size of the particles making up the dispersed phase. Shear thinning behaviour results from particle orientation in the flow direction as well as from aggregate breaking under shear. The scanning electron micrograph of proxyphylline in behenate 70/02 (Fig. 5a) shows oblong particles. This shape is compatible with the shear thinning behaviour of the suspension since this shape is more conducive to orientation in the direction of flow. The particles probably form slightly cohesive and pseudo-stable aggregates which are easily destroyed by applying shear. This aggregate destruction is confirmed by the thixotropic specificity which appears with behenates 70/02 and 57/13, as shown by the values of apparent viscosities obtained with up- and down-curves of rheograms (Table 2).

Although apparent viscosity of pure behenates increases with HLB, apparent and relative viscosities of proxyphylline suspensions do not reveal actual influence of HLB. As concerns behenates 70/02 and 57/13, relative viscosity falls strongly while apparent viscosity increases moderately.

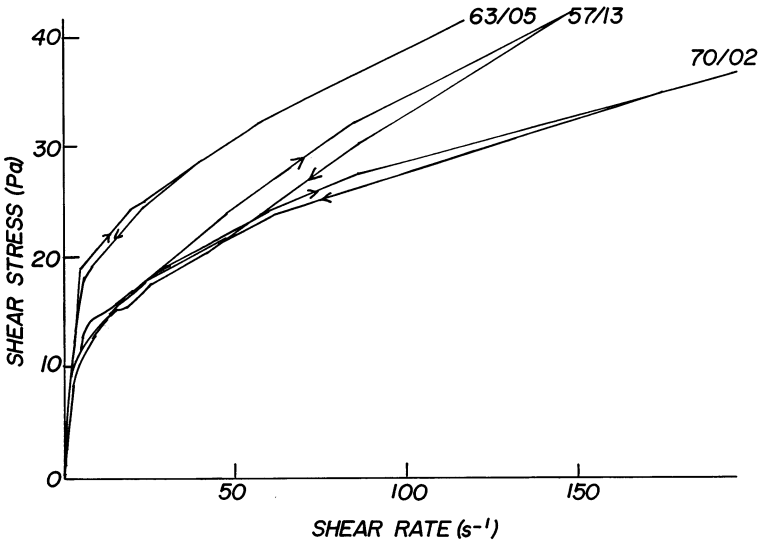


Fig. 4. Rheograms of proxyphylline suspensions in melted polyol behenates.

One may postulate that particle size decreases with HLB and that the number of particles rises, hence the increment of medium resistance to flow reflected by apparent viscosity. Proxyphylline in behenate 57/13 (Fig. 5c) shows a ribbon-like structure. As with behenate 70/02, this structure explains shear thinning by progressive orientation of these linear particles under flow conditions. However, in the case of behenate 57/13, particle entanglement offers a stronger resistance to the flow, as shown by the apparent viscosity. Otherwise, Fig. 5 illustrates that particle size is smallest when the HLB value is high. Concerning behenate 63/05, an intermediate appearance was observed (Fig. 5b): massive shapes were obtained and gave the largest values of apparent and relative viscosities.

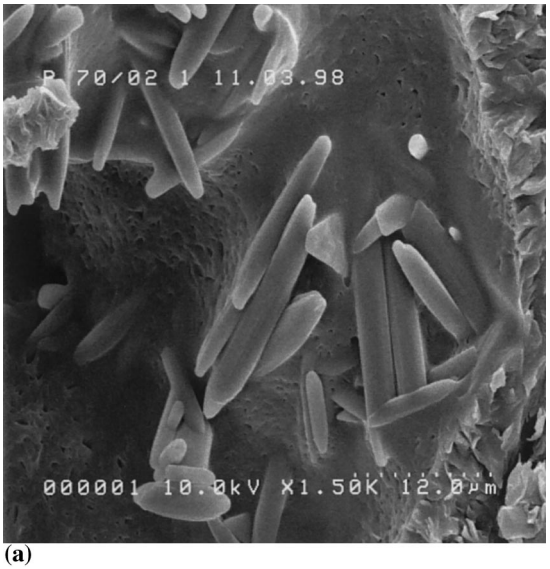
Consequently, shape and size of particles observed in electron microscopy corroborate measurements of apparent and relative viscosities, and they confirm the hypothesis expressed on the microstructure of suspensions. Thus, if the hydrophilicity of the dispersing phase rises, the affinity between drug and behenate favours its dispersion and minimizes aggregate formation, which explains the shear-thinning attenuation. The hydrophilic specificity of behenate slightly stabilizes the resulting suspension.

3.2. Drug release

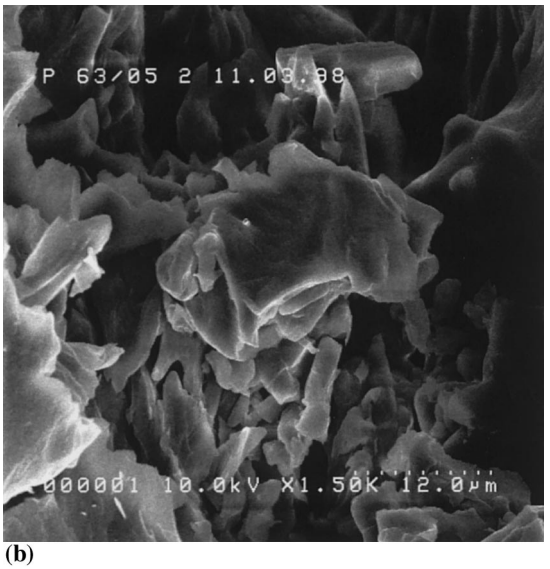
3.2.1. Dissolution profiles

Fig. 6 and Table 3 show the proxyphylline release from capsules containing the three behenates. Extended release was obtained with the three waxes. Behenates 63/05 and 70/02 released proxyphylline very slowly, due to their low HLB, and remained unaltered with a very weak erosion. Drug release could be increased by replacing a part of behenates with a more hydrophilic glyceride as Gelucire 50/13, as it has been done previously to improve proxyphylline (Brossard et al., 1994) or a basic drug (Mouricout et al., 1990) release from Gelucire 50/02. Behenate 57/13 released drug more quickly, due to its high HLB entailing a greater erosion of capsule content. Simultaneously, the matrix swelled and its size became twofold at $t = 8$ h.

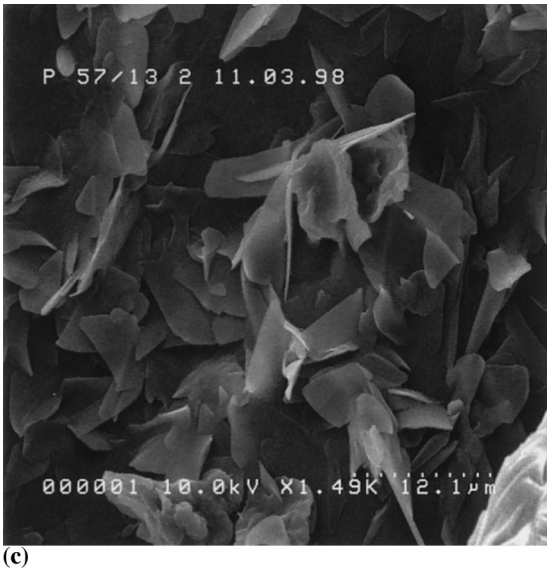
During the disintegration test, after dissolution of the gelatin capsule, plugs of behenates 70/02 and 63/05 remained intact with no signs of disintegration after 8 h. The medium with behenate 70/02 was limpid and turbid in the case of behenate 63/05. The same results were obtained with tablets of behenate 70/02 by Meshali et al. (1995) and El-Sayed et al. (1996). As concerns behenate 57/13, after initial swelling, a strong erosion inter-



(a)



(b)



(c)

Fig. 5. Electron scanning micrographs of solidified suspensions of proxyphylline in behenates 70/02 (a), 63/05 (b) and 57/13 (c).

vened and less than half a plug was recovered from each capsule. As behenate 57/13 is dispersible in water, the medium was limpid and foaming was extensive.

A linear correlation was found (Fig. 7) between capsule dissolution efficiency, DE, and relative viscosity, η_r, of the proxyphylline suspensions in melted behenates, following Eq. (7):

$$DE = -2.22\eta_r + 62.44 \quad (7)$$

Drug release decreased as the relative viscosity of the suspensions increased. The decrease of release may be suggested by a hindered diffusion of proxyphylline in the matrices when, respectively, behenates 57/13, 70/02 and 63/05 are used, due to their increasing relative viscosity (Table 2). Other authors have mentioned a correlation between drug release from matrices and the viscosity of theophylline suspensions in polyethylene glycols

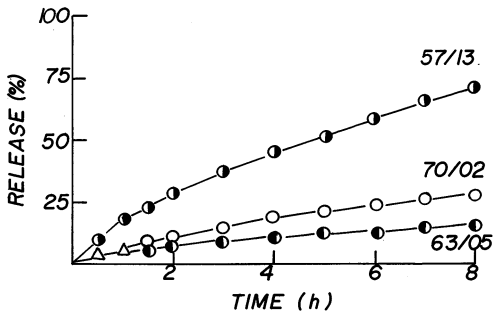


Fig. 6. Release profiles of proxyphylline from monolithic capsules containing polyol behenates.

Table 3
Dissolution and erosion characteristics of proxyphylline–behenate capsules at time $t = 8$ h

Characteristics	Behenates		
	70/02	63/05	57/13
Dissolution efficiency (%)	16.2	9.64	42.1
Erosion (%)	3.5	2.5	23
Aspect	Unaltered	Unaltered	Swelling ($\times 2$)

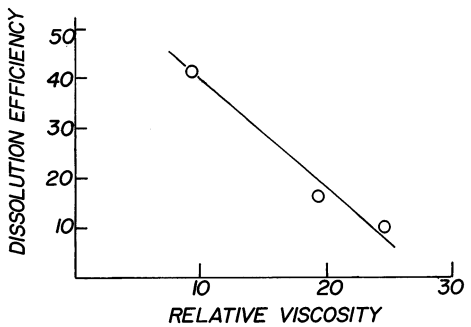


Fig. 7. Influence of relative viscosity of proxyphylline suspensions on dissolution efficiency.

(Gaudy et al., 1989) or of hydrophilic polymer solutions (Bonferoni et al., 1992; Wan et al., 1992).

3.2.2. Release mechanism

Table 4 presents the results obtained for the three behenates concerning the release modelling. Kopcha et al. (1991) monitored the diffusion to erosion ratio A/B. When $A/B = 1$, the release mechanism included diffusion and erosion equally. If $A/B > 1$, diffusion prevailed and if $A/B < 1$, erosion predominated (Ratsimbazafy et al., 1996). The diffusion/erosion ratios A/B express the predominance of drug diffusion inside the matrices relative to surface erosion, as highlighted by the low erosion ratios (Table 3) for behenates 70/02 and 63/05. This is also confirmed by the better linearity of percent released according to Higuchi (Fig. 8) as compared with Hixson–Crowell, except for behenate 57/13. Drug release from the latter was as well as described by the plottings of Higuchi and of Hixson–Crowell, due to its higher erosion ratio. The same A/B ratio was obtained by El-Sayed et al. (1996) with matrix tablets made of behenate 70/02. Moreover, with this wax, all authors have found a diffusion controlled release of drug from matrix tablets following Higuchi kinetics (Perez et al., 1993; Meshali et al., 1995; El-Sayed et al., 1996) or from hot-melt coating spheres (Joachim et al., 1996). However, Abdallah (1992) showed zero-order kinetics for ibuprofen released from behenate 70/02 monolithic capsules.

n values of Ritger and Peppas (1987) were greater than the theoretical diffusion value of 0.43 for cylinders having an aspect ratio close to 2 (Ratsimbazafy et al., 1996). These n values also expressed the coexistence of the two mechanisms, mainly diffusion, sometimes surface erosion, particularly in the case of behenate 57/13. These results were confirmed with behenate 70/02 by other workers, although lower values (Meshali et al., 1995; El-Sayed et al., 1996) or higher values of n (Abdallah, 1992) have been obtained.

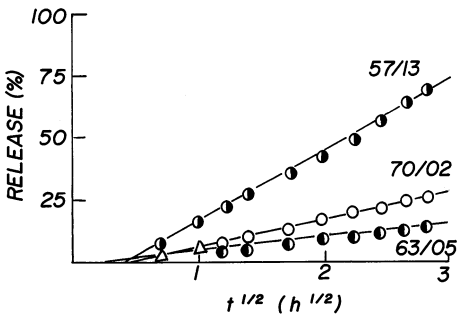


Fig. 8. Square root of time dependence of proxyphylline release from polyol behenate capsules.

Table 4
Modelling of proxyphylline release from polyol behenate capsules

Model	Parameters	Behenates		
		70/02	63/05	57/13
Higuchi	r	0.999	0.999	0.998
	a	11.22	5.60	28.57
	b	−4.57	−0.82	−11.61
Hixson–Crowell	r	0.990	0.989	0.999
	c	0.053	0.025	0.181
	d	0.068	0.055	0.102
Kopcha	r	0.999	0.999	0.999
	A	5.71	4.62	14.2
	B	1.47	0.26	3.92
	A/B	3.88	17.8	3.61
Ritger–Peppas	r	0.998	0.997	0.997
	K	6.53	4.68	16.8
	n	0.71	0.57	0.71

4. Conclusions

The rheological behaviour or melted behenates changed with the incorporation of proxyphylline. Pure behenates showed slight shear thickening, whereas proxyphylline suspensions had a shear thinning behaviour with or without thixotropy. These rheological behaviours could be explained by the chemical composition of the behenates used.

Extended release matrix capsules of 25% proxyphylline can be directly prepared with behenate 57/13. The very slow release obtained with behenates 70/02 and 63/05 could be improved by mixture with a more hydrophilic glyceride as Gelucire 50/13.

Solidified suspensions examined by scanning electron microscopy showed that an increase in size of particles increases suspension relative viscosity and decreases drug release rate.

The release mechanism was basically diffusion in nature, but erosion interfered slightly with hydrodispersible behenate 57/13. This wax showed a different behaviour, releasing drug more quickly from a hydrophilic matrix characterized by significant swelling and weak erosion.

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