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Research paper

Rheological behavior of drug suspensions in Gelucire® mixtures and proxyphylline release from matrix hard gelatin capsules

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Abstract

Mixtures of Gelucires® 50/02 and 50/13 showing different hydrophilic-lipophilic balances (HLB) and of proxyphylline were used to prepare suspensions at a concentration of 25% and to manufacture extended release hard gelatin capsules by cooling. The rheological behaviors of Gelucire® mixtures with and without drug were determined by adjustment of the rheograms to the Ostwald power-law and by statistical assessment of the flow index. Pure Gelucire® mixtures were very slightly shear thickening whereas proxyphylline suspensions had a thixotropic shear thinning behavior. These rheological behaviors can be explained by the chemical composition and by the ratio of the two Gelucires® used. Extended release of proxyphylline was obtained with all these mixtures. Drug release increased with Gelucire® mixture HLB owing to higher erosion. A viscosity-release relationship was found and allowed, with these two Gelucires® of extreme HLB and viscosities, to define the formulations which will give an optimal drug release, by the determination of their suspension viscosity. Modeling of dissolution kinetics has generally shown the predominance of surface erosion of the plugs relative to drug diffusion inside the matrix. This was confirmed by the better linearization of percentage released, according to Hixson–Crowell as compared with Higuchi.

Keywords: Gelucire®; Hydrophilic-lipophilic balance; Rheology; Lipidic matrix; Hard gelatin capsules; Extended release; Surface erosion

1. Introduction

Gelucire® lipid matrix capsules are new dosage forms which can modulate drug release in relation to the melting point (MP) and the hydrophilic-lipophilic balance (HLB) of the saturated polyglycolysed glycerides used (Gelucire® MP/HLB) [1]. Sometimes, mixtures of Gelucires® must be employed to modulate drug release [2–6]. As capsules are generally filled with drug suspensions, it seems interesting to study the rheology of Gelucire® mixtures before and after associating them with drugs. Moreover, a previous paper [7] showed the existence of a correlation between the relative viscosity of the drug suspension and the release from capsules, with different Gelucires® used alone. Such a relationship could be of great interest in the case of mixtures of Gelucires® 50/02 and 50/13 of extreme HLB and viscosities [8], to preselect the formulations of potential optimal release kinetics by measuring their suspension viscosity. Other authors mentioned likewise a correlation between drug release from matrices and the viscosity of theophylline suspensions in polyethylene glycols (PEG) [9] or of hydrophilic polymer solutions [10–17]. Only one work has used this form of relationship to optimize drug release so far [11].

Therefore, the aim of this work was firstly to study the rheology of Gelucire® 50/02 and 50/13 mixtures without and with a freely hydrosoluble drug, proxyphylline. Then, drug release from capsules was investigated and a correlation between the relative viscosity of drug suspensions and drug release searched for, to ease optimization of the release. Finally, the release mechanisms of proxyphylline were also investigated in terms of Fickian diffusion and surface erosion.

2. Materials and methods

2.1. Materials

Proxyphylline (Sigma Chemical Co., St Louis, MO) was the drug used in this study. Its particles were rectangular (4×30 μm) as observed by optical microscopy and its

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aqueous solubility at 25°C was 0.601 g/cm^3. Proxyphylline was insoluble in the different melts at the utilized temperature of 80°C.

Gelucires® 50/02 and 50/13 (Gattefossé, Saint-Priest, France) were chosen as matrix materials. By mixing, they are allowed to cover a large range of HLB from 2–13 and had melting points over 40°C in order to give subsequently real matrices which would not melt in the gastrointestinal tract. Gelucires® are mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of polyethylene glycols with fatty acids. Gelucire® 50/02 (hydrogenated palm/palm kernel oil PEG-6 esters) contained little polyethylene glycols whereas Gelucire® 50/13 (hydrogenated palm oil PEG-32 esters) included PEG esters with a high degree of condensation. HLB of Gelucire® mixtures were determined by the HLB additivity rule and were set at the following values: 2, 3, 6, 9, and 13 (Table 1).

2.2. Preparation and rheology of Gelucire® mixtures and of drug suspensions

As previously described [18], in order to obtain suitable suspensions, Gelucires® or Gelucire® mixtures were melted at 80°C with a water bath (Salvis, Luzern, Switzerland) and stirred for 15 min with a rotary stirrer (Rayneri, Montreuil, France) fitted with a defloculating blade. Proxyphylline suspensions were prepared at the concentration of 25% w/w, by dispersing the drug progressively in Gelucires® or mixtures of Gelucires®, and by stirring mixtures in the same conditions.

Rheological behavior and apparent viscosity determinations were performed at 80°C using a coaxial cylinder viscosimeter (Rheomat® 15T, Contraves, Zürich, Switzerland) [18]. Rheograms were fitted to the Ostwald relationship:

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

where τ is the shear stress, γ is the shear rate, k is the consistency index and n is the flow index. $n = 1$ if the flow is Newtonian. $n > 1$ or $n < 1$ indicates respectively shear thickening or shear thinning. This index was determined by linear regression with the logarithmic form of Eq. (1) [8]:

$$\ln \tau = \ln k + n \ln \gamma \quad (2)$$

Table 1
Dissolution efficiency (DE), apparent η_{app} and relative η_r viscosities at shear rate $\gamma = 84.5\ s^{-1}$ of the different formulations (η_o pure Gelucire® mixture viscosity)

Gelucires® (%)		HLB	η_o (mPa.s)	η_{app} (mPa.s)	η_r	DE (%)
50/02	50/13					
100	–	2	14.7	430	29.3	13.9
90.9	9.1	3	16.7	296	17.7	26.0
63.6	36.4	6	22.6	298	13.2	46.6
36.4	63.6	9	30.9	348	11.3	66.1
–	100	13	47.5	410	8.6	77.0

The deviations of the regression were calculated by a linearity statistical test and allowed to highlight the model validity. The residual variations unexplained by the linear model were used as an estimate of experimental error and allowed the assessment of the 0.95 confidence limits of the flow index.

2.3. Preparation and evaluation of capsules

00-size capsules were filled with proxyphylline suspensions using a syringe in such a way as to contain 200 mg of drug. Capsule cooling was carried out at room temperature.

Disintegration testing was operated with a USP Erweka® ZT 3 Tester (Euraf, Colombes, France). The medium for the test was distilled water at 37°C. Six capsules were tested without disks and mean disintegration times were calculated.

Drug release measurement was performed at 37°C in a USP rotating paddle apparatus (Dissolutest®, Prolabo, Paris, France) as previously described [19]. Released proxyphylline was measured by UV spectrophotometry at 273 nm (Uvikon® 930, Kontron Instruments, Milano, Italy). The results are the average of six trials. The reference optimal kinetics was the following: drug release of 16 ± 2% at time $t = 1$ h, 43 ± 5% at $t = 4$ h and 73 ± 8% at $t = 8$ h [20]. It corresponded to a dissolution efficiency (DE) [21] at time $t = 8$ h of 42 ± 5%.

Drug release mechanism was investigated in comparison with modelings according to the equations of Higuchi (Eq. (3)), Hixson–Crowell (Eq. (4)) and Kopcha (Eq. (5)) [1,22]:

$$Q = at^{1/2} + b \quad (3)$$

$$100^{1/3} - (100 - Q)^{1/3} = ct + d \quad (4)$$

$$M = At^{1/2} + Bt \quad (5)$$

where Q (≤90%) and M (≤70%) are the percentage of drug released at time t and a, b, c, and d are regression constants. A is a diffusional term and B an erosional term [4]. The Kopcha model is an application to erodible matrices of the initial equation of Ritger and Peppas [23] which was first used in the case of swelling matrices.

3. Results and discussion

3.1. Rheological behavior of Gelucire® mixtures

Fig. 1 presents the rheograms of pure Gelucires® (HLB 2 and 13) and of Gelucire® mixtures (HLB 3, 6 and 9). The linearity test of the logarithmic form of the Ostwald equation is always highly significant of good fitting. The correlation coefficient, r^2, is always equal to 0.999.

The flow indexes n (Table 2) are scarcely greater than 1 and do not directly allow a conclusion on flow behavior. A Student's t-test is used to compare these values with the theoretical unity value. The difference is always significant

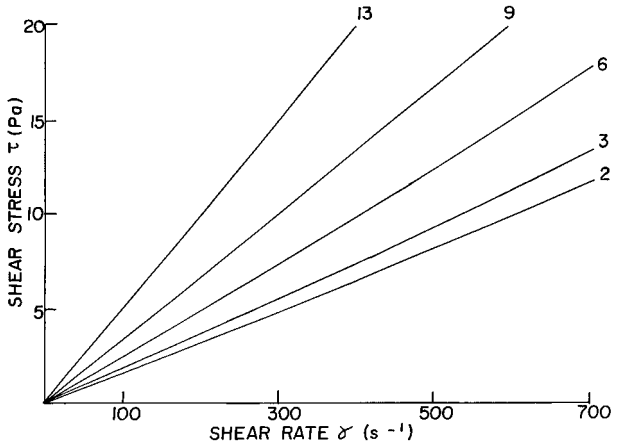

Fig. 1. Influence of HLB on the rheological behavior of mixtures of Gelucires® 50/02 and 50/13.

for a non-Newtonian flow because the significant probability level is always less than 0.05. However shear thickening is very weak and it decreases as the HLB of Gelucire® mixture increases. The 0.95 confidence limits of the flow indexes furthermore illustrate the very weak divergence to unity, specially for mixtures of HLB 9 and 13.

Such very slight shear thickening behavior had also been particularly observed for suppository bases [24,25] and for Gelucires® [8] or polyol behenates [26] of various melting points and HLB, that is to say for mixtures of fatty acid esters of glycerol or of PEG. Shear thickening was very slight for high HLB mixtures and it is not surprising that other works only showed a Newtonian behavior for Gelucire® 50/13 [27] or for the wax-based vehicles which they used to fill hard gelatin capsules [28–30].

The slight shear thickening decreased when Gelucire® mixture HLB rose. It accounted for a reorganization of the particles under the shear which became more difficult when the PEG amount increased with the hydrophilicity of Gelucire® mixture.

Apparent viscosity η_0 (Table 1) rose with Gelucire® mixture HLB according to the steric hindrance of PEG chains in high HLB mixtures. The chain lengthening induced an increase of the friction forces and then a resistance to flow. Apparent viscosity increase followed Eq. (6):

$$\ln \eta_0 = 0.106\ \mathrm{HLB} + 2.486 \quad (6)$$

Table 2
Flow indexes and confidence intervals of the different formulations with mixtures of Gelucires® 50/02 and 50/13

HLB	Pure Gelucire® mixtures	Proxyphylline suspensions
2	1.05 ± 0.01	0.23 ± 0.02
3	1.05 ± 0.01	0.26 ± 0.03
6	1.03 ± 0.01	0.34 ± 0.04
9	1.01 ± 0.01	0.34 ± 0.04
13	1.007 ± 0.004	0.38 ± 0.05

where η_0 is apparent viscosity at shear rate $\gamma = 84.5\ s^{-1}$. The linear fit is widely significant with $P < 10^{-3}$.

3.2. Rheological behavior of proxyphylline suspensions

The flow curves of the suspensions in the Gelucire® mixtures showed a shear thinning behavior (Fig. 2). The down-curves of rheograms revealed a slight hysteresis. The shear thinning behavior was confirmed by the flow index values (Table 2). Such a shear shinning behavior was also found for drug suspensions in suppository excipients [24] or waxes designed to fill hard gelatin capsules [18,26,30,31]. Except for one case [30], a weak thixotropy was always observed.

Shear thinning behavior results from particle orientation in the flow direction as well as from aggregate frailty to the shear. Observation by scanning electron microscopy of solidified suspensions of proxyphylline in HLB 2 Gelucire® had previously shown oblong particles [18]. This shape is conducive to orientation in the direction of flow. The particles form slightly cohesive and pseudo-stable aggregates which are easily destroyed by applying shear. This aggregate destruction is confirmed by their thixotropic specificity. Proxyphylline in Gelucire® of HLB 13 had previously shown a ribbon-like structure [18]. Similarly to Gelucire® of HLB 2, this structure explains shear thinning by progressive orientation of linear particles according to flow.

Moreover, particle size decreases with HLB and the number of particles rises [18]. This highlights the decrease of relative viscosity and the increment of medium resistance to flow as it is reflected by apparent viscosity, except for Gelucire® 50/02. This phenomenon could be explained by the increase of drug affinity for the waxy material as Gelucire® mixture hydrophilicity was increasing.

3.3. Release of proxyphylline from capsules

As shown earlier with capsules [2] or tablets [6], drug release increased when Gelucire® mixture HLB rose (Table 1; Fig. 3). Except for HLB 13, real matrices were obtained and could be recovered after the dissolution test, more or less eroded from HLB 9 to 2. The release of HLB 6 formulation was optimal.

During the disintegration test, after dissolution of the gelatin capsule, plugs of HLB 2 remained intact with no signs of disintegration after 8 h and the medium was limpid. With HLB 3 mixture, the liquid was turbid and the plugs were slightly eroded after 8 h. In the case of HLB 6 and 9 mixtures, plugs were nearly entirely eroded at time 8 h. Concerning HLB 13, disintegration time was 3.25 h.

3.4. Viscosity-release relationship

A correlation between relative viscosity of the drug suspensions and capsule dissolution efficiency was found following Eq. 7 with a correlation coefficient $r = 0.989$:

$$\ln \mathrm{DE} = -1.495 \ln \eta_r + 7.662 \quad (7)$$

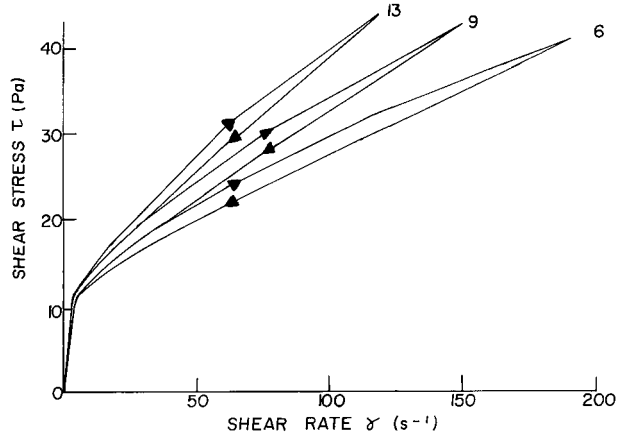

Fig. 2. Influence of HLB on the rheological behavior of proxyphylline in mixtures of Gelucires® 50/02 and 50/13.

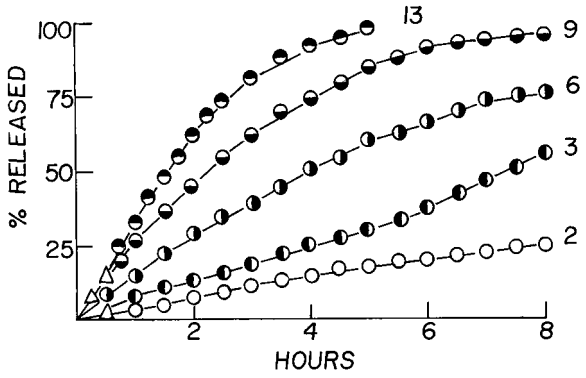

Fig. 3. Influence of HLB on proxyphylline release from capsules containing mixtures of Gelucires® 50/02 and 50/13.

Drug release decreased as relative viscosity of suspensions increased. Other authors mentioned likewise a correlation between drug release from matrices and the viscosity of theophylline suspensions in polyethylene glycols [9] or of hydrophilic polymer solutions [12–17].

Relative viscosity of suspensions allowed one to predict drug release from the capsules: for optimal dissolution efficiencies DE = 42 ± 5%, Eq. 7 gave relative viscosities $\eta_r = 13.9 \pm 1.1$. There was a correlation (Eq. 8) between relative viscosity and Gelucire® mixture HLB, which was obtained with a correlation coefficient $r = 0.978$:

$$\ln \eta_r = -0.594 \ln \text{HLB} + 3.673 \quad (8)$$

Hence optimal HLB could be calculated: HLB = 5.8 ± 0.8. Consequently, optimal formulations must include 34.6 ± 7.2% of Gelucire® 50/13 in the Gelucire® mixtures. With the viscosity-release relationship, all the formulations giving an optimal drug release could be determined by simple measurement of suspension viscosity.

3.5. Drug release mechanism

Table 3 shows the results obtained for the different mixtures of Gelucires® concerning the release modeling. The Kopcha model [4] 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 [20]. Except for HLB 6, the diffusion/erosion ratios *A/B* are <1 and express the predominance of surface erosion relative to drug diffusion inside the matrices. Generally, *A/B* ratios decrease when HLB of Gelucire® mixture increases, that is to say when high proportions of hydrodispersible Gelucire® 50/13 that are present in the mixture entail a growing matrix erosion. Two abnormalities have however been noticed: first, the case of Gelucire® 50/02 used alone, for which the dissolution percentage at time 8 h is low. Secondly, HLB 3 mixture that presents an abnormal ratio $A/B = 0$, implying a non-existent diffusion. In the case of Gelucire® 50/02, the erosion term *B* is greater than the diffusional term *A* although it seems there is no erosion during the dissolution test. However, these two parameters

Table 3
Influence of HLB on the modelling of proxyphylline release from capsules containing mixtures of Gelucires® 50/02 and 50/13

Model	Parameters	HLB				
		2	3	6	9	13
Kopcha	r^2	0.996	0.994	0.998	0.998	0.998
	A	2.24	–	10.44	11.87	4.75
	B	2.44	6.97	6.99	13.97	27.68
	A/B	0.92	0	1.49	0.85	0.17
Higuchi	r^2	0.996	0.940	0.996	0.998	0.980
	a	11.51	23.80	34.08	45.67	55.66
	b	−7.90	−19.01	−18.00	−17.92	−19.80
Hixson Crowell	r^2	0.991	0.970	0.996	1.000	1.000
	c	0.053	0.131	0.225	0.428	0.014
	d	0.018	−0.056	0.050	0.014	−0.098

Table 4
Influence of HLB of Gelucire® 50/02 and 50/13 mixtures on the evolution versus time of the Kopcha model parameters

HLB	$t \leq$ (h)	A	B	A/B	Point number	% Released
2	4	0.31	4.02	0.00	8	15
	5	0.47	3.48	0.14	10	18
	6	1.25	2.99	0.42	12	20
	7	1.76	2.70	0.65	14	23
	8	2.24	2.44	0.92	16	25
3	4	3.00	4.65	0.64	8	25
	5	2.69	4.87	0.55	10	31
	6	2.05	5.30	0.39	12	38
	7	0.57	6.12	0.09	14	47
	8	−1.02[a]	6.97	0.00	16	56
6	4	6.44	9.54	0.68	8	51
	4.5	7.11	9.07	0.78	9	55
	5	7.61	8.73	0.87	10	60
	5.5	8.70	8.00	1.09	11	63
	6	9.65	7.50	1.29	12	66
	6.5	10.44	6.99	1.49	13	70
9	2.5	9.38	16.21	0.58	7	55
	3.5	11.87	13.97	0.85	9	70
13	1.25	2.41	30.10	0.08	7	55
	2.25	4.75	27.68	0.17	9	68

[a] Non-significant.

are the lowest obtained among all the formulations. For HLB 3 mixture, the corresponding dissolution profile actually shows that during the last 4 h there was an increased drug release subsequent to a predominant matrix erosion. These phenomena are shown up by the observation of the evolution versus time of the parameters A and B (Table 4). In the case of a low HLB (HLB 3), a diffusional phenomenon is mainly predictable because erosion is initially negligible. Nevertheless, the diffusional term A is lower than the erosion term B. However, A decreases correctly in the course of time as erosion appears. In the case of high HLB (HLB 13), the erosion term B is logically much superior to the diffusional term A. For intermediate HLB (HLB 6 and 9), diffusion term A increases with time while erosion term B decreases. For these formulations containing 36–64% of hydrodispersible Gelucire® 50/13, erosion can take place earlier than in mixtures of low HLB (HLB 2 and 3): erosion term B decreases versus time because the plug size decreases while the erosion surface is decreasing as well. The diffusion term A increases versus time because diffusion though the hydrated eroded layer or the layer in process of erosion is easier. There is accelerated diffusion though a layer in process of erosion.

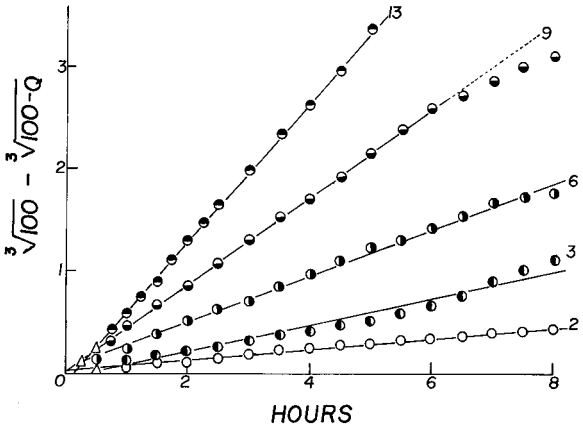

Fig. 4. Hixson–Crowell modeling of proxyphylline release from capsules containing mixtures of Gelucires® 50/02 and 50/13.

With the exception of Gelucire® 50/02 for which diffusion prevails [4,5,20,27,32], the predominance of surface erosion relative to drug diffusion inside the matrices (Table 3) is also confirmed by the better linearization of percent released according to Hixson–Crowell (Fig. 4) if compared with Higuchi's, except for HLB 2 formulation. HLB 6 mixture is as well as described by the two plottings, due to its higher erosion.

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