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Effect of Formulation on the Rheology of Theophylline Compound Suspensions in Gelucires

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Abstract

The theophylline derivatives, etofylline, diprophylline and proxyphylline, which exhibit increasing aqueous solubitity, were used to prepare suspensions in seven saturated polyglycolysed glycerides (Gelucires) characterized by their rising hydrophilic-lipophilic balance (HLB). Drug concentration was set at 25% w/w and the production temperature was set at the Gelucire melting point plus 30°C in order to obtain suitable suspensions. Various formulation factors were studied.

Ostwald flow indices revealed that the suspensions had a thixotropic shear-thinning behaviour and a relative viscosity which increased as drug aqueous solubility rose and Gelucire HLB decreased. These rheological properties could be explained by the chemical composition of Gelucires and drugs used.

A microstructure was proposed for the liquid suspension such that colloidal particles and aggregates formed in these suspensions directly influenced the observed rheological properties. Observation of solidified suspensions by scanning electron microscopy confirmed this hypothesis. Moreover, a correlation between the relative viscosity of drug suspensions on the one hand and drug concentration, drug solubility and Gelucire HLB on the other allowed for the calculation of the required concentration of each theophylline derivative in each Gelucire to obtain a given viscosity.

Saturated polyglycolysed glycerides (Gelucires) are defined as mixtures of glyceryl monoesters, diesters and triesters, and of polyethyleneglycol monoesters and diesters. These amphiphilic waxes can be used in drug formulation to fill hard gelatin capsules. Thus, monolithic extended-release capsules can be prepared (Ratsimbazafy & Brossard 1991). These excipients can also be used to prepare multiple-unit capsules containing minitablets (Ratsimbazafy et al 1996) or spheroids made by extrusion (Bidah et al 1992; Edimo et al 1993) or by prilling (Bruguera et al 1990). In the latter case, the melted mixture is divided into small droplets before congealing. This particular technique requires that a previous rheological study be undertaken to assess the feasibility of microbead formation and to correctly identify formulation parameters. Gelucires have the advantage of possessing diverse melting points and hydrophilicities (HLB). The purpose of the present work is to investigate the association of these amphiphilic waxes formulated in beads with three theophylline derivatives of different aqueous solubilities: etofylline, diprophylline and proxyphylline.

Whereas Sutananta et al (1995) found a Newtonian behaviour for the Gelucires that they used, Bourret et al (1994) previously showed that the rheological behaviour of pure Gelucires was weakly shear thickening and that this behaviour became more evident when the temperature and the lipophilicity increased. The effect of four formulation factors are now being investigated on drug suspensions in Gelucires: temperature of water-bath, concentration of drug, solubility of drug and type of Gelucires.

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Materials and Methods

Materials

The drugs used in this study were etofylline (Sigma Chemical Co., St. Louis, MO), diprophylline (Cooperation Pharmaceutique Française, Melun, France) and proxyphylline (Sigma Chemical Co., St. Louis, MO), whose water solubilities at 25°C are 0·049, 0·140 and 0·601 g cm^{-3} respectively.

Seven Gelucires (Gattefossé, St. Priest, France) of increasing HLB were selected, designated by their respective melting point/hydrophile-lipophile balance identified (MP/HLB): 50/02, 46/07, 48/09, 53/10, 42/12, 50/13 and 44/14. They covered the entire range of HLB from 2 to 14 and had melting points over 40°C in order to maintain the matrix so as not to melt in the gastrointestinal tract.

Methods

Median volume particle size d (0·5) and dispersion index [d (0·9) – d (0·1)]/d (0·5) of the drugs, determined with a laser particle sizer (Mastersizer X, Malvern, Orsay, France), were respectively: etofylline 31 μm, 3·1; diprophylline 6 μm, 3·3; proxyphylline 8 μm, 2·7.

The influence of water-bath temperature (60–90°C) and of suspension concentration (10–30% w/w) was first of all studied with diprophylline and Gelucire 50/02 in order to fix these two parameters. Then, all the suspensions were prepared at the corresponding wax mp +30°C and at a drug concentration of 25% w/w with the different drugs and Gelucires.

The theophylline derivatives were progressively dispersed in the melted Gelucires, by agitation for 15 min with a rotary stirrer (Rayneri, Montreuil, France) fitted with a defloculating blade.

Rheological behaviour and apparent viscosity determinations were carried out at the manufacturing temperature using a

coaxial cylinder viscosimeter (Rheomat 15T, Contraves, Zürich, Switzerland) fitted with thermostated measuring systems MS-A or MS-B. Fifteen shear rates were sequentially applied on the same sample for 15 s in duration. The shear rates varied respectively from 11 to 702 s^{-1} and from 3 to 196 s^{-1}. Apparent viscosities were determined from the down-curve of the rheograms. These latter were fitted to the Ostwald relationship, also termed the power law (Chevalier 1994):

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

where γ is the shear rate applied to the sample, expressed in s^{-1}, τ is the shear stress expressed in pascal and k and n are constants characterizing the rheological behaviour (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, statistically either greater or smaller than unity, pinpoints respectively shear thickening or shear thinning. This index was determined by linear regression with the logarithmic form of equation 1 (Bourret et al 1994). A linearity statistical test allowed for the calculation of the deviations of the regression and to show the model validity.

The suspensions were studied using a field emission scanning electron microscope (S 4000 Hitachi, Tokyo, Japan). Samples were subjected to a slight metallization with gold-palladium to a thickness of 1–1·5 nm.

Results and Discussion

Influence of temperature

In the case of diprophylline suspension at 25% w/w in Gelucire 50/02, increase of the water-bath temperature resulted in a logical decrease in apparent viscosity (Table 1). An Arrhenius-type relationship could be applied in this case as was previously done for pure Gelucires (Bourret et al 1994). To ensure that suspensions were sufficiently fluid and to preserve Gelucire stability, the water-bath temperature was fixed at 80°C for Gelucire 50/02 (mp + 30°C for all Gelucires).

Influence of drug concentration

At all diprophylline concentrations in Gelucire 50/02, flow curves (Fig. 1) and flow indexes (Table 2) indicate shear thinning behaviour of the suspensions. The high correlation coefficient r^2 of the regression lines show that the use of the Ostwald model is well founded, where in the worst case, 97·6% of the shear stress variations can be explained by variations in shear rate.

The very strong increase in apparent viscosity in relation to the drug concentration reveals the formation of weak aggregates of growing size which are destroyed by shear, confirmed by the simultaneous increase of shear thinning. In fact, this suspension, which is prepared with a freely water soluble drug in a Gelucire of very low HLB, is not expected to have great stability, which explains the destruction of the aggregates under the influence of shear.

Table 1. Influence of temperature on apparent viscosity of 25% diprophylline suspension in Gelucire 50/02 (shear rate 196 s^{-1}).

Temperature (°C)	Apparent viscosity η_{196} (mPa s)
60	193
70	170
80	159
90	149

Table 2. Influence of diprophylline suspension concentration in Gelucire 50/02 on apparent viscosity at shear rate 196 s^{-1}, and on flow index.

Drug concn (%)	η_{196} (mPa s)	Flow index	Correlation coefficient r^2
10·0	37·2	0·78 ± 0·03	0·995
17·5	69·1	0·43 ± 0·03	0·984
20·0	85·6	0·37 ± 0·03	0·979
22·5	123·0	0·33 ± 0·03	0·976
25·0	159·0	0·28 ± 0·02	0·980
27·5	176·0	0·28 ± 0·02	0·987
30·0	200·0	0·24 ± 0·02	0·982

Flow index is given together with the 95% confidence interval. Correlation coefficient is fitted according to Equation 1.

Since the object was to produce small, easily administered beadlets of matrix-dispersed drug for subsequent filling into hard gelatin capsules, maximum drug concentration in the waxes was desirable. In order not to exceed an apparent viscosity (η_{app}), at a shear rate of 196 s^{-1}, of about 200 mPa s (maximal limit compatible with bead manufacturing process), optimum drug concentration was settled at 25% w/w for all of the subsequent formulae.

Influence of drug aqueous solubility

The flow curves $\tau = f(\gamma)$ of the suspensions in the different Gelucires (at 25% w/w drug concentration and at mp + 30°C) show a shear thinning behaviour (Fig. 2). The down-curves of rheograms reveal a slight hysteresis with the more aqueous soluble derivatives of theophylline for Gelucires of high HLB.

The rheological behaviour of Gelucires changed with the incorporation of the theophylline derivatives: pure Gelucires were slightly shear thickening whereas drug suspensions had a thixotropic shear thinning behaviour. Suppository bases of fatty substances with HLB values very close to that of the low HLB Gelucires, which have been used to prepare semi-solid matrix capsules (Naidoo 1989), have previously been shown to exhibit such a change in the rheological behaviour after drug incorporation (Margarit et al 1992).

Regression fitting of the logarithmic form of equation 1 (Fig. 3) points out the linear decrease of apparent viscosity under the influence of shear. Apparent and relative viscosities progressively decrease from the most aqueous soluble derivative, proxyphylline, to the least aqueous soluble derivative, etofylline (Table 3).

The shear thinning behaviour is confirmed by the flow index values. The results in Table 4 express very clearly the increasing shear thinning behaviour of the formulations from etofylline to proxyphylline, that is to say increasing with drug aqueous solubility.

Rheological properties of suspensions are related to the shape and size of the particles making up the dispersed phase. Shear thinning behaviour renders particle orientation in the flow direction as well as aggregate frailty to shear (Zangger 1969). The scanning electron micrograph of proxyphylline in Gelucire 50/02 (Fig. 4a) shows oblong particles. This shape is roughly compatible with the shear thinning behaviour of the

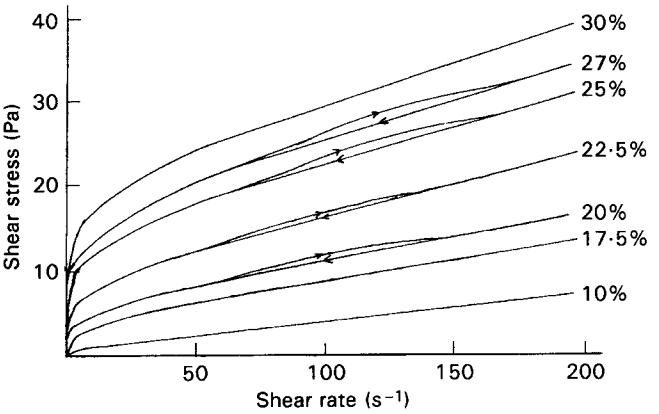

FIG. 1. Flow curves of various concentrations of diprophylline suspended in Gelucire 50/02.

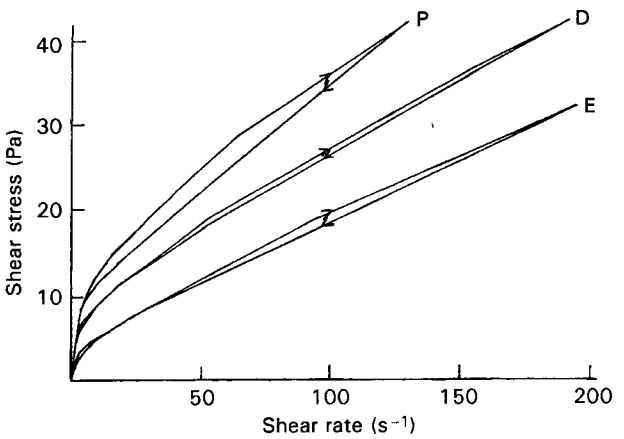

FIG. 2. Flow curves of proxyphylline (P), diprophylline (D) and etofylline (E) suspended in Gelucire 50/13.

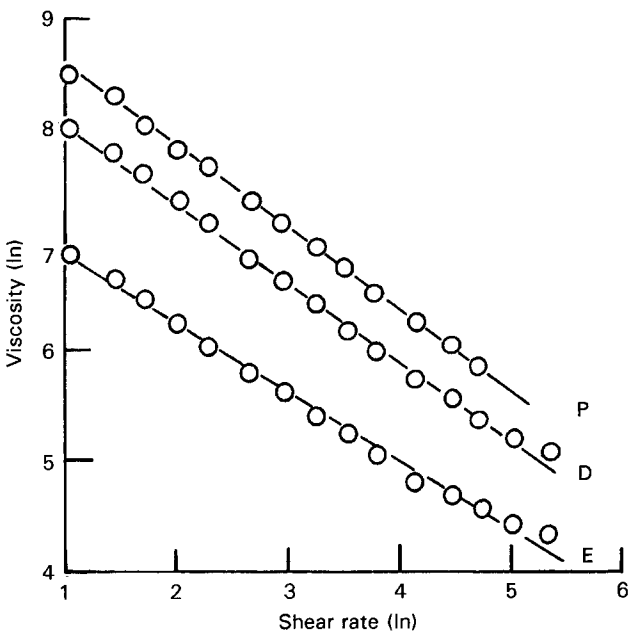

FIG. 3. Apparent viscosity vs shear rate of proxyphylline (P), diprophylline (D) and etofylline (E) suspended in Gelucire 50/02.

Table 3. Apparent (η_{app}) and relative (η_r) viscosities at shear rate $\gamma = 111\ s^{-1}$ of the different suspensions.

Gelucire	η_o (mPa s)	Etofylline		Diprophylline		Proxyphylline	
		η_{app} (mPa s)	η_r	η_{app} (mPa s)	η_r	η_{app} (mPa s)	η_r
50/02	14·6	94·6	6·48	217	14·90	352	24·10
46/07	19·8	114·0	5·76	162	8·18	284	14·30
48/09	23·0	132·0	5·73	157	6·83	244	10·60
53/10	33·3	157·0	4·71	195	5·86	348	10·40
42/12	44·4	206·0	4·64	265	5·97	350	7·88
50/13	47·6	183·0	3·84	257	5·40	337	7·08
44/14	46·6	221·0	4·74	233	5·00	341	7·33

η_o = apparent viscosity of pure Gelucire.

Table 4. Flow index of 25% w/w theophylline derivatives suspended in 5 Gelucires.

Gelucire	Etofylline	Diprophylline	Proxyphylline
50/02	0·36 ± 0·03	0·28 ± 0·02	0·26 ± 0·01
46/07	0·42 ± 0·04	0·36 ± 0·04	0·37 ± 0·05
48/09	0·43 ± 0·04	0·40 ± 0·03	0·34 ± 0·04
53/10	0·47 ± 0·04	0·44 ± 0·04	0·36 ± 0·04
50/13	0·55 ± 0·05	0·43 ± 0·04	0·40 ± 0·05

Values are expressed together with their 95% confidence limits.

suspension since this shape is more conducive to orientation in the direction of flow. Proxyphylline suspensions have the largest apparent and relative viscosities regardless of the Gelucire used in the formula. The particles probably form slightly cohesive and pseudo-stable aggregates which are easily destroyed by applying shear. This is expressed in the shear thinning behaviour becoming more marked from etofylline to proxyphylline. This aggregate destruction is confirmed by the thixotropic specificity which appears for proxyphylline in most Gelucires.

Influence of Gelucire HLB

Flow curves $\tau = f(\gamma)$ of the suspensions in all Gelucires show a shear thinning behaviour. Shear stress values increase with Gelucire HLB (Fig. 5).

The hysteresis area previously indicated appears with Gelucires having a high HLB. Flow index values (Table 4) illustrate that, for a particular drug, shear thinning decreases when the hydrophilic specificity of Gelucire increases.

Apparent viscosity of suspensions follows the same evolution as the shear stress. The influence of drug aqueous solubility is very strong for Gelucire 50/02 which gives very high viscosities with low values of the flow index for diprophylline and proxyphylline. Shear thinning is very strong in the case of both of these derivatives because oblong particles (Fig. 4a) easily orientate in the direction of the flow.

Relative viscosity shows an inverse relationship to apparent viscosity. It decreases with the HLB value of Gelucires all the more quickly as drug aqueous solubility increases. The diminution is very evident for proxyphylline and diprophylline while scarcely marked for etofylline. Since apparent viscosity of pure Gelucires increases with HLB (Table 3), this observation suggests that the amphiphilic specificity of Gelucire plays a more important role when the drug is more aqueous

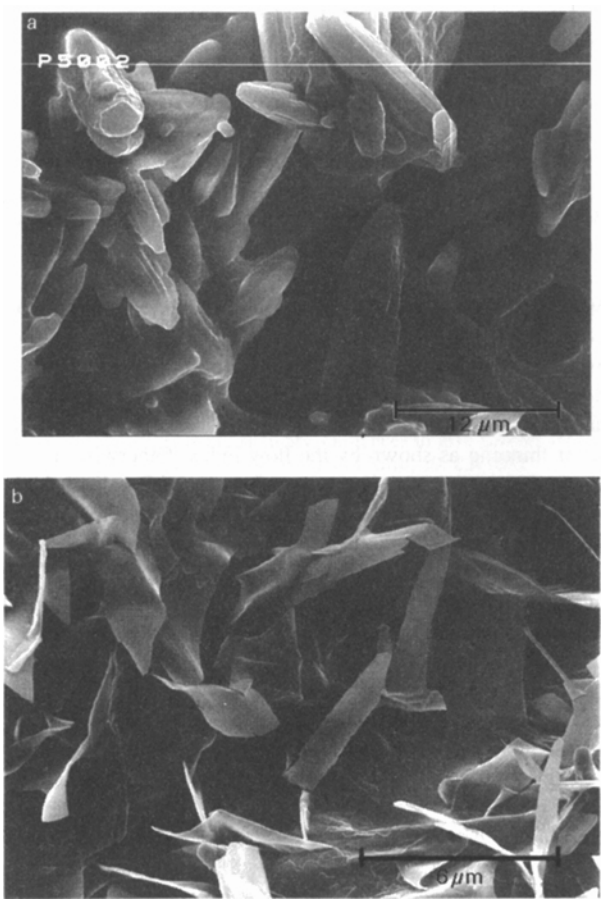

FIG. 4. Electron scanning micrographs of solidified suspensions of proxyphylline in Gelucire 50/02 (a) and Gelucire 50/13 (b).

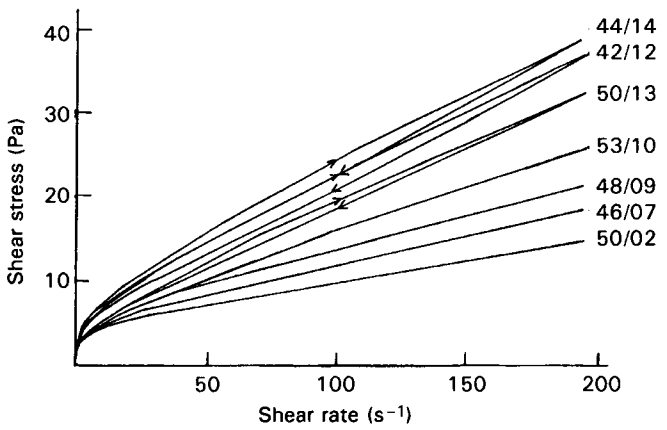

FIG. 5. Flow curves of etofylline suspended in the various Gelucires.

soluble. Although etofylline shows shear-thinning behaviour similar to that of diprophylline and proxyphylline, it does not reveal an actual influence of HLB.

The viscosity of a dispersed system depends on the viscosity of the exterior medium and on the fraction of the suspension volume occupied by the dispersed particles (Quivoron 1972). In the present case, the relative viscosity increase, in direct accord with the HLB of the Gelucires, shows that the suspension is little influenced by the amphiphilic specificity of Gelucire if the drug is slightly water soluble. In this case, the contribution of the dispersed phase to the increase of the suspension viscosity is negligible when drug aqueous solubility is low as, for example, with etofylline. Its rheological behaviour is essentially linked to the hydrodynamic properties of the continuous phase.

For the more water soluble diprophylline and proxyphylline, relative viscosity falls strongly from Gelucire 46/07 while apparent viscosity increases moderately. One may postulate that the 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 Gelucire 50/13 (Fig. 4b) shows a ribbon-like structure. Similarly to Gelucire 50/02, this structure explains shear thinning by progressive orientation of these linear particles according to the flow. However, particle entanglement offers a stronger resistance to the flow (as shown by apparent viscosity) and it lowers shear thinning as shown by the flow index. Otherwise, Fig. 4 shows that particle size is smaller when the HLB value is high. As a result, 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 parallel to the increase of drug aqueous solubility, the hydrophilicity of the dispersing phase rises, the affinity between drug and Gelucire favours its dispersion and minimizes aggregate formation, which explains the shear-thinning attenuation. The hydrophilic specificity of Gelucire slightly stabilizes the resulting suspension.

Correlation between relative viscosity and formulation factors

The simultaneous influence of the different parameters was studied by multiple linear regression at the given temperature of mp + 30°C (Table 5). Among the 16 possible models tested with the arithmetic and logarithmic values, the best one selected on the basis of higher correlation coefficient was the following:

$$\ln \eta_r = 0{\cdot}118\, X_1 + 0{\cdot}279 \ln X_2 - 0{\cdot}466 \ln X_3 + 0{\cdot}497 \quad (2)$$

where X_1, X_2, X_3 and η_r are respectively drug concentration, drug aqueous solubility, Gelucire HLB and predicted relative viscosity.

The coefficient signs match the way the parameters vary. The correlation coefficient being equal to 0·973, 94·7% of the viscosity fluctuations are explained by the model. Its validity is demonstrated by the close proximity of the 30 experimental points evaluated in this study to the calculated theoretical line (Fig. 6). Linear regression between calculated and experimental values of viscosity gives a slope of 0·998 and the significant degree of the linearity test is much inferior to 1%. This model allows calculation of the required concentration of each theophylline derivative, in each Gelucire, to obtain a suspension with a given viscosity. Thus, to obtain a diprophylline suspension in Gelucire 46/07 with an apparent viscosity of 200 mPa s at shear rate 111 s^{-1} (10·10 relative viscosity), equation 2 calculates that a diprophylline concentration of 27·7% is required. After preparation of this suspension, experimental apparent viscosity was 198 mPa s, which validates the model.

Conclusions

During drug dispersion in amphiphilic Gelucires, particle formation and the degree of aggregate cohesion reveal the affinity of the dispersing phase towards the dispersed drug. For a given Gelucire, when drug aqueous solubility increases, the theophylline derivative has less affinity for the dispersing phase: the lipophilic specificity prevails. Larger colloidal particles are formed which explain the increase of apparent and relative viscosities as drug aqueous solubility increases from etofylline to proxyphylline. Simultaneously, any formed aggregates are less stable as HLB decreases. By increasing the hydrophilicity of Gelucire, the affinity between the two phases improves, hence a lessening of both aggregate formation and shear-thinning specifity.

The results show that the dispersing phase having the lowest HLB gives the most stable dispersion with the least aqueous soluble drug. A previous report on drug release (Mouricout et al 1990) indicated that the slowest drug release is obtained with Gelucires of low HLB. It is therefore possible to conclude that drug availability from pharmaceutical dosage forms is closely linked to the stability of the formed colloidal particles. An analysis of the partial correlation coefficients may reveal the

Table 5. Correlation between formulation factors and relative viscosity (shear rate 111 s^{-1}) calculated according to Equation 2.

Gelucire	Drug	Drug concn	Drug solubility	Gelucire HLB	Relative viscosity	
		X_1 (%)	X_2 (g cm^{-3})	X_3	Experimental (ln)	Calculated (ln)
50/02	Etofylline	25·0	0·049	2	2·290	1·869
	Diprophylline	10·0	0·140	2	0·808	0·829
	Diprophylline	17·5	0·140	2	1·696	1·765
	Diprophylline	20·0	0·140	2	1·992	2·011
	Diprophylline	22·5	0·140	2	2·287	2·380
	Diprophylline	25·0	0·140	2	2·583	2·701
	Diprophylline	27·5	0·140	2	2·879	2·809
	Diprophylline	30·0	0·140	2	3·175	2·955
	Proxyphylline	25·0	0·601	2	2·990	3·182
46/07	Etofylline	25·0	0·049	7	1·706	1·751
	Diprophylline	25·0	0·140	7	2·000	2·102
	Proxyphylline	25·0	0·601	7	2·407	2·660
48/09	Etofylline	25·0	0·049	9	1·589	1·746
	Diprophylline	25·0	0·140	9	1·883	1·921
	Proxyphylline	25·0	0·601	9	2·290	2·361
53/10	Etofylline	25·0	0·049	10	1·540	1·550
	Diprophylline	25·0	0·140	10	1·833	1·768
	Proxyphylline	25·0	0·601	10	2·240	2·342
42/12	Etofylline	25·0	0·049	12	1·455	1·535
	Diprophylline	25·0	0·140	12	1·749	1·787
	Proxyphylline	13·2	0·601	12	0·755	0·793
	Proxyphylline	25·0	0·601	12	2·156	2·064
50/13	Etofylline	25·0	0·049	13	1·418	1·345
	Diprophylline	25·0	0·140	13	1·703	1·686
	Proxyphylline	15·3	0·601	13	0·965	0·770
	Proxyphylline	25·0	0·601	13	2·110	1·957
44/14	Etofylline	25·0	0·049	14	1·376	1·556
	Diprophylline	25·0	0·140	14	1·669	1·609
	Proxyphylline	18·1	0·601	14	1·261	1·141
	Proxyphylline	25·0	0·601	14	2·075	1·992

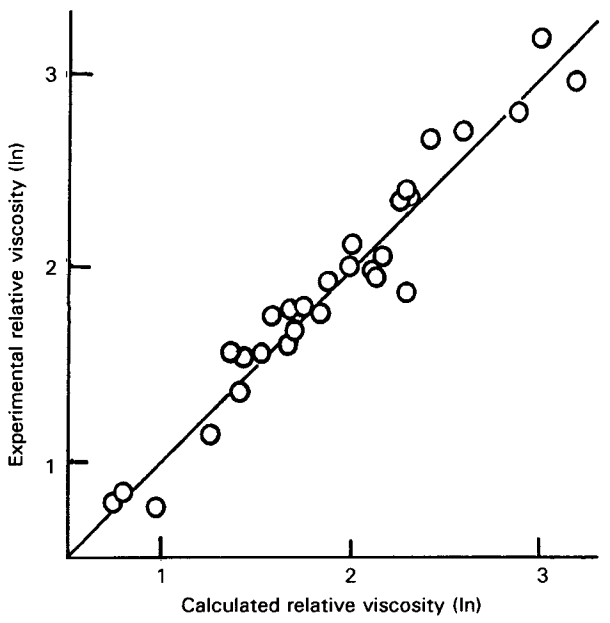

FIG. 6. Correlation between experimental and calculated (according to Eqn 2) relative viscosities expressed in logarithms.

relative importance between Gelucire HLB and drug aqueous solubility.

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