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RHEOLOGICAL STUDY OF RECTAL FORMULATIONS OF SODIUM VALPROATE

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ABSTRACT

The importance of the spreading capacity of the suppository base in the rectal ampulla makes it important to determine dynamic viscosity of lipophilic excipients and to characterize the changes in their rheological properties caused by the addition of other components. We evaluated the influence of colloidal silica (Aerosil R 972), Span 80 and sodium valproate on the excipients Witepsol H-15 and Suppocire AS_2. Subsequent analyses in rabbits established the correlation between viscosity of the suppository mass after melting and the release and absorption of drugs administered rectally. The results show that excipients with initially dilating flow subsequently showed plastic flow characteristics, with marked thixotropy and increased viscosity which delayed release and absorption.

INTRODUCTION

The viscosity of a suppository excipient upon melting or dissolving in the rectal ampulla is one of the factors involved in the release and absorption of the drug, and is affected by active substances or technological coadjuvants added to prevent sedimentation of the drug within the molten base, or to improve

TABLE 1

Composition of the Suppositories

Composition	Formulations (g/100 suppositories)					
	I	II	III	IV	V	VI
Sodium valproate	15.0	15.0	15.0	15.0	15.0	15.0
Witepsol H-15	73.37	69.19	56.64	--	--	--
Suppocire AS_2	--	--	--	74.22	69.95	57.14
Aerosil R 972 (5%)	--	4.18	--	--	4.27	--
Span 80 (20%)	--	--	16.73	--	--	17.08

the softness of the suppository itself[1]. Technical motives and availability factors make studies of the dynamic viscosity of suppositories important in the preformulation phase of development. We therefore evaluated the influence of colloidad silica, Span 80 and sodium valproate on the rheological properties of the lipophilic excipients Witepsol H-15 and Suppocire AS_2.

MATERIALS AND METHODS

Rheological studies were carried out for the fatty bases Witepsol H-15 (Dynamit Nobel, Troisdorf-Oberlar, FRG) and Suppocire AS_2 (Gattefosse, Barcelona, Spain), b) combinations of both these with 5% (w/w) Aerosil R 972 (Degussa, Frankfurt, FRG) and 20% (w/w) Span 80 (Atlas Chemical, Barcelona), and c) formulations I and VI (Table 1) of suppositories made by adding 150 mg sodium valproate (L. Labaz, Madrid, Spain) to the vehicles described under a) and b).

The tests were performed according to the following protocol: 130 g of sample was melted in a 150 ml flask and allowed to resolidify at room temperature. The sample was then placed in an

TABLE 2

Viscosity of the Excipients and Formulations of Suppositories Containing Sodium Valproate.

	EXCIPIENTS						FORMULATIONS					
r.p.m.	W	W+A	W+S	SUP.	SUP+A	SUP+S	F-I	F-II	F-III	F-IV	F-V	F-VI
0.3	--	2166.70	--	--	666.70	--	13.00M*	163.33M	20.67M	14.00M	190.00M	83.33M
0.6	--	500.00	--	--	1250.00	--	11.50M	145.00M	15.00M	14.00M	143.33M	63.33M
1.5	--	1233.34	20.00	--	1066.66	13.33	5.60M	90.00M	10.13M	10.13M	119.33M	33.33M
3	16.67	833.33	30.00	13.33	816.67	30.00	3.60M	53.00M	6.20M	6.87M	87.33M	20.33M
6	25.00	600.00	40.00	26.67	558.33	38.33	2.07M	34.00M	4.10M	4.50M	54.67M	13.17M
12	30.00	500.00	42.50	30.00	420.83	41.67	1.29M	20.08M	2.48M	2.83M	31.83M	8.92M
30	32.67	398.33	47.33	30.66	363.33	47.00	0.55M	10.53M	1.52M	1.71M	15.67M	4.77M
60	37.83	335.83	49.67	36.83	281.67	49.83	0.40M	6.30M	1.05M	1.15M	9.55M	3.13M
30	32.00	386.67	47.33	30.67	321.67	46.67	0.53M	9.87M	1.46M	1.69M	14.93M	4.63M
12	30.00	437.50	42.50	30.00	354.17	41.67	8.80M	17.92M	2.30M	2.90M	29.25M	8.75M
6	25.00	525.00	38.33	26.67	450.00	36.67	1.12M	26.67M	3.30M	4.43M	52.17M	14.00M
3	16.67	700.00	30.00	13.33	583.33	30.00	1.60M	44.33M	5.07M	6.73M	86.00M	23.00M
1.5	--	1000.00	20.00	--	800.00	6.67	2.50M	69.33M	7.73M	9.07M	127.33M	40.00M
0.6	--	1750.00	--	--	1250.00	--	5.25M	130.00M	14.00M	13.67M	176.67M	83.33M
0.3	--	2166.70	--	--	666.70	--	7.00M	233.33M	21.33M	15.33M	236.67M	143.33M

W=Witepsol H-15, SUP.=Suppocire AS_2, A=Aerosil R 972, S=Span 80, (*)M=1000, Viscosity (mPa.s).

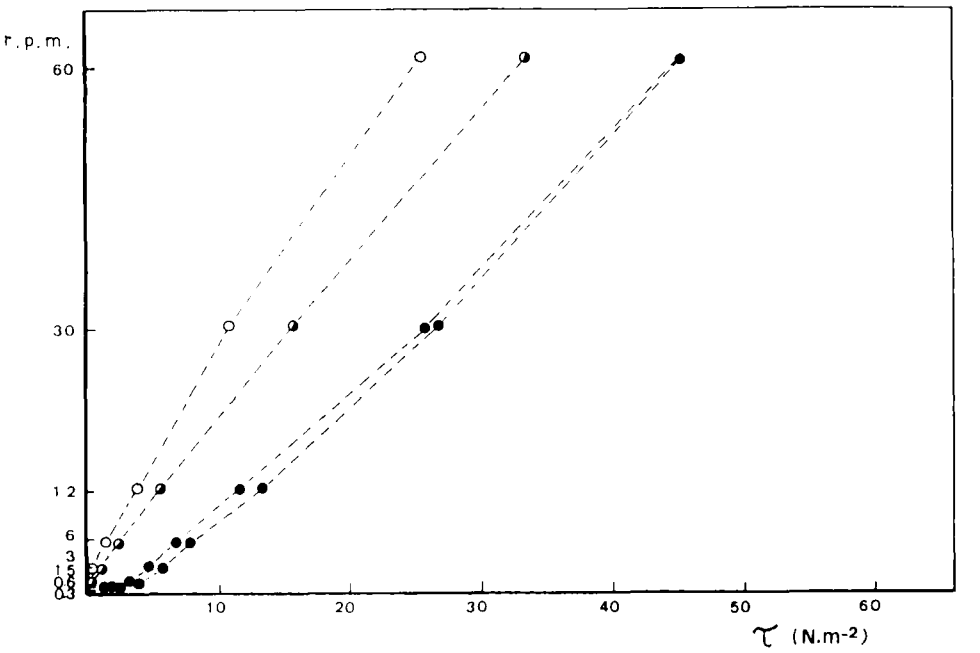

FIGURE 1

Rheograms of excipients Witepsol H-15 (○), Witepsol H-15 + Aerosil R 972 (●) and Witepsol + Span 80 (◑).

oven at 39°C for 24 h. The flask containing the molten mass was then set in a thermostated water bath (39°C) for 30 min, and immediately thereafter placed in a Synchro-Lectric LVT rotary viscosimeter[2] (Brookfield, Stoughton, Mass., USA).

RESULTS AND DISCUSSION

Table 2 presents the means of three viscosity determinations in all samples. The rheograms (Figures 1-5) of shearing force τ ($N \cdot m^{-2}$) and shearing rate (rpm) illustrate the rheological behavior. Samples consisting of Witepsol H-15 and Suppocire AS_2

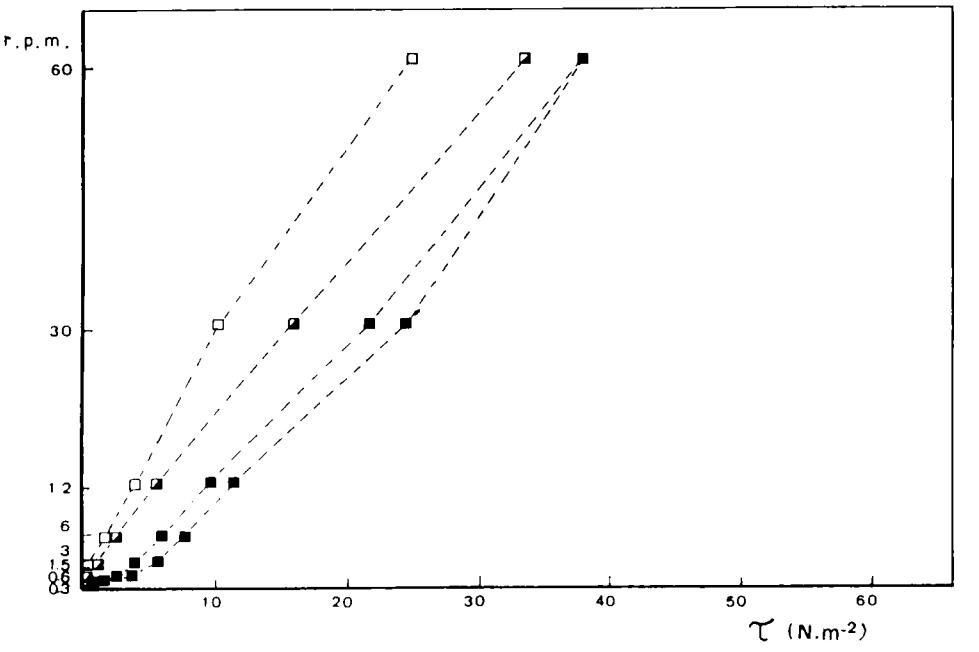

FIGURE 2

Rheograms of excipients Suppocire AS_2 (□), Suppocire AS_2 + Aerosil R 972 (■) and Suppocire AS_2 + Span 80 (◪).

(Figs. 1 and 2) showed dilating flow characteristics, in agreement with the results obtained by Möes[3,4]. The addition of the tensioactive Span 80 to these semisynthetic glycerides modified their rheological behavior, slightly increasing viscosity, but not affecting the flow characteristics.

The addition of colloidal silica (Aerosil) as a viscosity-enhancing agent led to gelling of the fatty bases and changes in their rheological properties. Doucet et al.[5,6], in their studies of the influence of a series of concentrations of colloidal silica on the rheological properties of semisynthetic glycerides, noted that at low concentrations the mixtures behaved like pseudoplastic

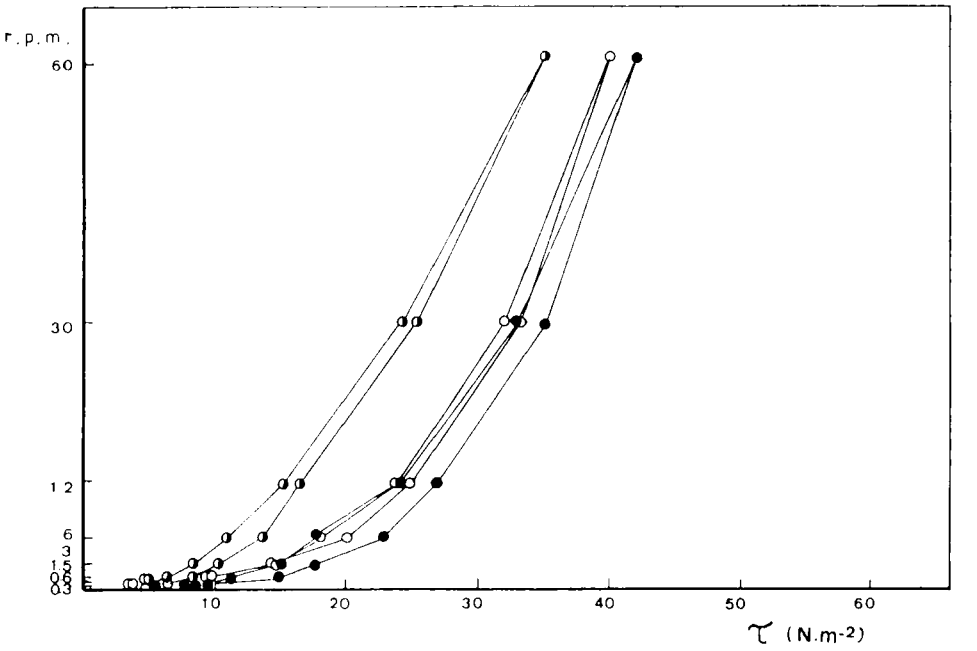

FIGURE 3

Rheograms of formulations containing Witepsol H-15. Formula I (O), Formula II (●) and Formula III (O).

fluids, while concentrations of 4% produced a flow threshold, with thixothropic plastic fluid behavior. Our findings were similar, with 5% Aerosil yielding a slight flow threshold and a thixotropic hysteresis loop, which was more pronounced in samples containing Suppocire AS_2.

The addition of sodium valproate to the fatty bases increased viscosity notably, making it necessary to change the spindle of the viscosimeter. The bases Witepsol H-15 and Suppocire AS_2, which acted initially as dilating fluids, also modified the rheological properties of the base in formulas I and IV, with the appearance of thixotropic plastic fluid properties (Figs. 3 and

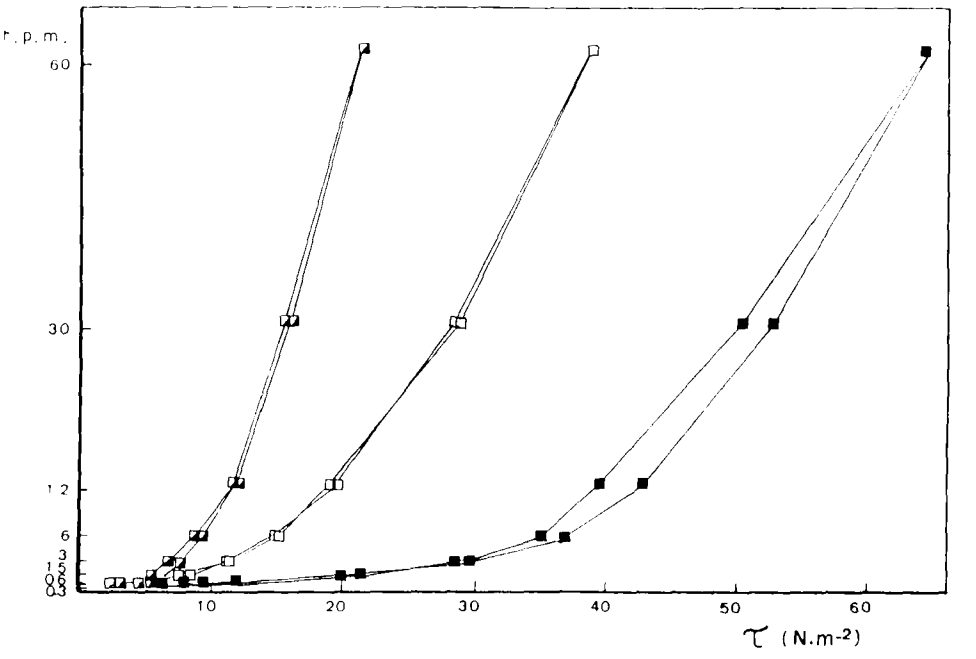

FIGURE 4

Rheograms of the formulas containing Suppocire AS_2 . Formula IV (□), Formula V (■) and Formula VI (◪).

4). Span 80 and sodium valproate (formulas III and VI) gave similar results, with a more pronounced hysteresis loop in preparations containing Witepsol H-15 (formula III).

The influence of the drug on fatty bases containing Aerosil (formulas II and V) was patent as a marked rise in viscosity and yield value (flow threshold, τ_c), especially in samples prepared with Suppocire AS_2 (formula V). Hence sodium valproate increased the viscosity of the Witepsol H-15-Span 80 and Suppocire AS_2-Aerosil combinations.

Formula I, which contained Witepsol H-15 and sodium valproate, exhibited different rheological properties from the

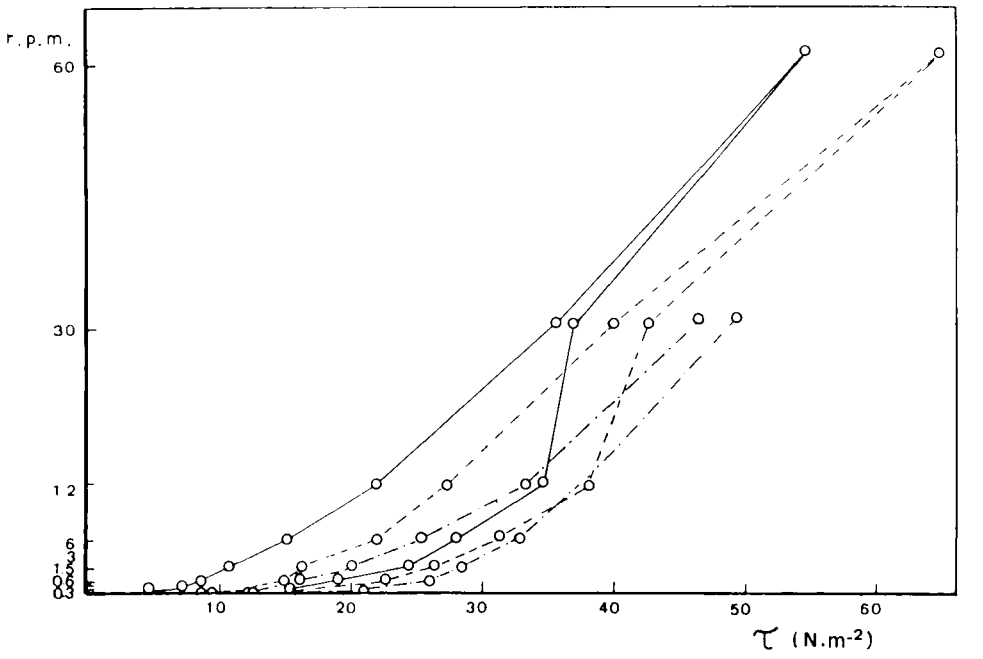

FIGURE 5

Rheograms of formulas tested at different intervals after preparation. Freshly prepared (——), prepared 24 h earlier (– – –) and prepared 48 h earlier (–·–·–).

rest of the samples tested. Figure 5 shows the results when the formula was freshly prepared, and 24 and 48 h after preparation. Viscosity, together with the flow threshold, rose steadily with time, making it necessary to change the spindle. The rheological characteristics of this formula stabilized after one week.

Not only did the viscosity of the excipient increase steadily for the first three days after melting, but by the end of two weeks, small crystals had formed. Since separation was evident within three days when the drug was present, this formula seemed to accelerate crystal formation, possibly accounting for the

TABLE 3

Correlation between Rheological Parameters, Pharmaceutical Availability and Biopharmaceutical Parameters.

		"in vitro" parameters			"in vivo" parameters		
FORMULA	$\eta_{\tau c}$	% D(1h)	$t_{50\%}$	K	$(AUC)_5$	$F_{rel}\%$	$(FD\%)_{0.5}$
I	13.00M	91.607	13.223	0.0386	304.42	129.09	98.21
II	163.33M	41.403	102.400	0.0049	355.08	171.70	62.64
III	20.67M	74.372	35.074	0.0281	242.33	105.88	94.82
IV	14.00M	88.085	15.219	0.0271	243.28	106.48	103.03
V	190.00M	28.907	81.717	0.0101	396.25	167.68	74.14
VI	83.33M	72.277	30.403	0.0156	306.64	139.06	89.49

			Theoretical lineal equation	$r_{exptl.}$
"in vitro"	$\eta_{\tau c}$	%D(1h)	$y = 91.23 - 3.1128\times10^{-4}\ x$	-0.9702
	$\eta_{\tau c}$	$t_{50\%}$	$y = 11.78 + 4.2815\times10^{-4}\ x$	0.9176
	$\eta_{\tau c}$	K	$y = 0.032 - 1.4516\times10^{-7}\ x$	-0.9073
"in vivo"	$\eta_{\tau c}$	$(AUC)_5$	$y = 251.39 + 7.0133\times10^{-4}\ x$	0.9134
	$\eta_{\tau c}$	$F_{rel}\%$	$y = 109.24 + 3.3948\times10^{-4}\ x$	0.9384
	$\eta_{\tau c}$	$(FD\%)_{0,5}$	$y = 101.72 - 1.8173\times10^{-4}\ x$	-0.9267

$r_{theor.}$: $(p = 0.01) = 0.9172$; $(p = 0.05) = 0.8114$; $(p = 0.10) = 0.7293$

$\eta_{\tau c}$: Viscosity at the yield value; %D(1h): Percentage of the dose in the diffusion medium during the first hour; $t_{50\%}$: Release-diffusion half-life; $(AUC)_5$: Area under the plasma concentration/time curve at a total time of 5 h; $F_{rel}\%$: Relative bioavailability; $(FD\%)_{0.5}$: Fraction of dose absorbed after 30 min.

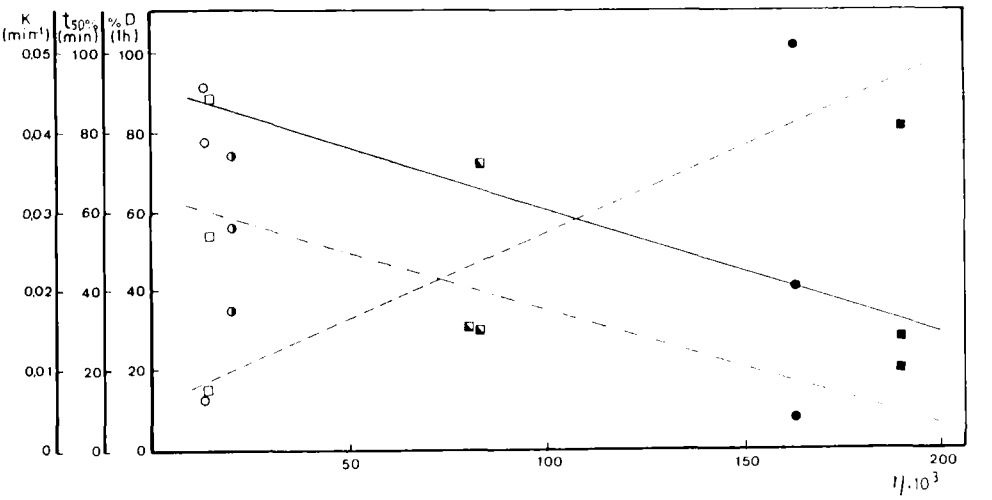

FIGURE 6

Correlation between kinetic parameters of release-diffusion and viscosity at the yield value (η_{τ_c}) of the molten excipients. Viscosity/%D (1 h) (——), viscosity/$t_{50\%}$ (min) (– – –) and viscosity/K (min^{-1}) (–·–·–).

increase in viscosity within this time. The active substance suspended in the molten excipient might have provided nuclei for the crystallization of higher melting point glycerides, thus accelerating separation.

The rheograms of three consecutive assays showed a large spur in the ascending portion of the curve, ie at intermediate values of shearing rate and force, apparent viscosity was considerably increased. Maximum values for viscosity were obtained at 55 and 65 $N \cdot m^{-2}$ in assays 1 (freshly prepared) and 2 (24 h) respectively, while in assay 3 (48 h), viscosity was too high to measure with a no. 2 spindle, and a no. 3 was used. The rheogram however showed no such spur, indicating that the behavior of this formula was somewhat similar to that in the other formulations.

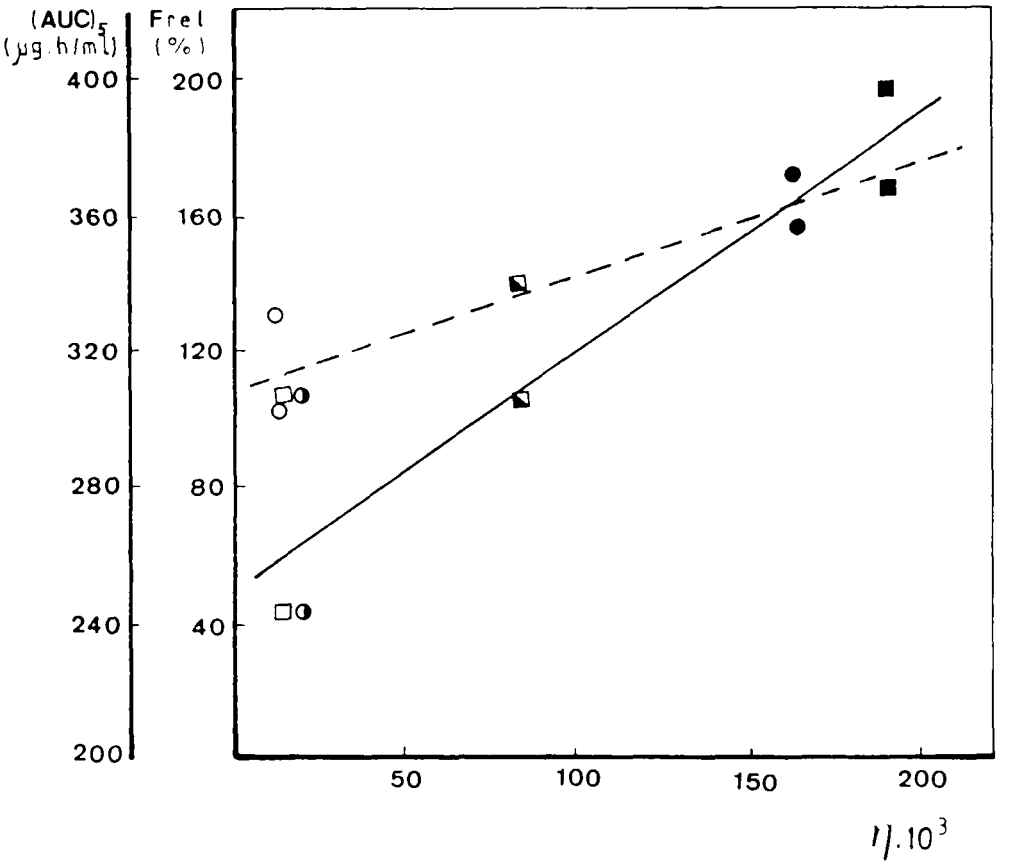

FIGURE 7

Correlation between pharmacokinetic parameters and viscosity at the yield value ($\eta_{\tau c}$) of the molten excipients. Viscosity/$(AUC)_5$ (——) and viscosity / relative bioavailability (– – –).

As certain parameters in pharmaceutical technology may serve to predict the behavior of a given formulation, we analyzed the possible correlation between viscosity ($\eta_{\tau c}$)of the suppository mass after melting and pharmaceutical availability in vitro, and between viscosity and biopharmaceutical parameters in vivo, based on earlier publications[7,8]. Table 3 shows the parameters used in correlation analyses of each parameter. Linear regression

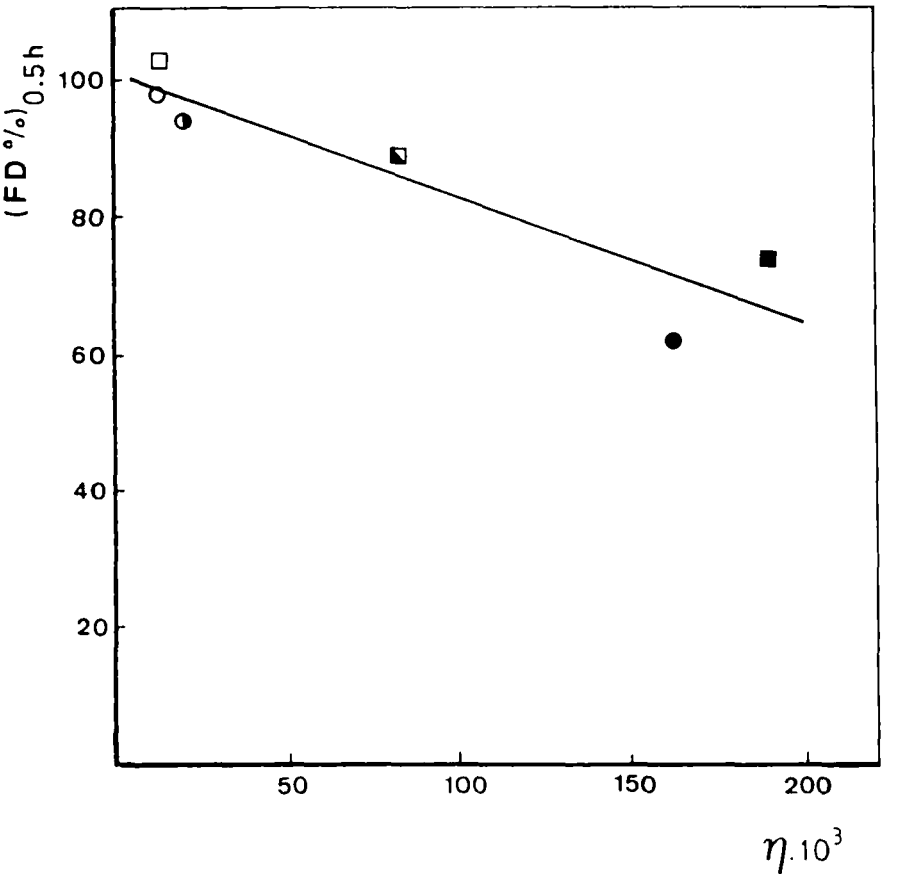

FIGURE 8

Correlation between viscosity at the yield value (η_{tc}) of the molten excipients and the percentage of the dose absorbed (FD%) after 30 min.

analysis yielded a correlation coefficient greater than 0.9. Viscocity was inversely related with percentage of the dose dissolved and the release-diffusion rate constant, and was directly related with the time required for release of 50% of the dose (Fig. 6). A direct relationship was also evident between viscosity and the amount of dose absorbed, and viscosity and AUC_5 (Fig. 7), whereas viscosity was inversely related with $FD\%_{0.5}$ (Fig. 8).

These findings were unsurprising, given that the drug was in suspension, and had to settle at the lipid/aqueous interface in order to be dissolved and diffused or absorbed. If sedimentation is delayed due to increased viscosity, release and absorption are more gradual and prolonged. Higher viscosity also reduces exposure of the suppository mass to the aqueous medium, significantly reducing the effective surface for drug transfer and absorption. However, other factors such as the location of the suppository mass in the rectum and the presence of tensioactive substances may be responsible for the low correlation between the parameters analyzed.

In the present data, a p value of 0.05 or less was considered significant.

CONCLUSIONS

The drug used influenced the rheological characteristics of the lipophilic excipients by changing the flow model from dilating, as reported by Möes and described in the present paper, to plastic, with high thixotropy and viscosity. This latter effect was especially notable in suppositories containing the coadjuvant Aerosil R 972, whereas Span 80 had a less marked effect on flow characteristics.

Only suppositories containing Witepsol H-15 showed altered rheological behavior of the drug as a function of time, leading to increased viscosity and a higher flow threshold.

The rheological characteristics of lipophilic excipients were modified by the presence of coadjuvants used in the formulations. Plastic flow patterns without thixotropy appeared with the use of Span 80, while Aerosil R 972 caused plastic flow with thixotropy. Upon establishing the correlation between viscosity ($\eta_{\tau c}$) of the molten excipients and kinetic parameters of release-diffusion, increased viscosity was found to reduce the rate of release-diffusion, and hence the percentage of the dose diffused (inverse correlation), and to increase the mean time of diffusion (direct correlation).

With regard to pharmacokinetic parameters, there was a parallel increase in the rate of absorption and time of action of the drug in the organism, which may have been due to the choice of the rectum as the site of absorption determinations, thus obviating the influence of first pass hepatic metabolism. Another observation was the inverse relation between viscosity and the percentage of dose absorbed after 30 min, owing possibly to the delayed settling of the drug on the lipid/aqueous interface in the rectum before release-diffusion.

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REFERENCES

(1) M.M. Pruvost, Sci. Techn. Pharm., 4, 101 (1975).

(2) J.H. Wood, G. Catacalos and S.V. Leiberman, J. Pharm. Sci., 52, 296 (1963).

(3) A. Möes, J. Pharm. Belg., 29, 113 (1974).

(4) A. Möes, J. Pharm. Belg., 31, 355 (1876).

(5) J.J. Tukker, W.T.P.M. van Vught and C.J. De Blaey, Acta Pharm. Techn., 29, 187 (1983).

(6) J. Doucet, C.L. Taborin and M. Rollet, Ann. Pharm. Franc., 33, 253 (1975).

(7) M.V. Margarit, I.C. Rodríguez and A. Cerezo, An. Real Acad. Farm., 55, 485 (1989).

(8) M.V. Margarit, I.C. Rodríguez and A. Cerezo, Pharm. Pharmacol., (In press).