ORIGINAL ARTICLE

Rheological Behavior of Sodium Valproate Suppositories

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Background: Because the valproic derivates are frequently used in the treatment of epilepsy, bipolar disorders, major depression cases, migraines and other neurological disorders at children, the rectal administration is a real advantage.
Aim: In this study we aimed to assess the influence of the formulation on the rheological characteristics of lipophilic suppository bases Suppocire NAI, Witepsol W_{35}, Massa $Estarinum_{299}$, $Lipex_{403}$, containing Cetyl alcohol and Solutol HS_{15}, respectively.
Methods: Spreadability was determined by the Pozo Ojeda-Sune Arbussa method. Half a gram suppository was placed on the bottom plaque of the extensiometer, and the upper plaque was added over it. After equal intervals of time (1 minute) different weights (2, 5, 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 350, 400, 500 g) were placed. Following each weight addition, the diameters of the obtained circles were measured, and the corresponding area was calculated. The viscosity was determined using the Brookfield (DV-II +Pro) rotational viscosimeter. The measurements were performed at 37±0.5°C and 5, 10, 20, 50, 100, 50, 20, 10, 5 rpm.
Results: The experimental results demonstrated that sodium valproate as active substance induces an increase in viscosity and consequently a decrease in the spreading capacity of the lipophilic suppository bases used. $Lipex_{403}$ (a base consisting in fatty acids) manifests the lowest viscosity compared to the bases consisting in mixtures of glycerides (Suppocire NAI, Witepsol W_{35}, Massa $Estarinum_{299}$). Solutol HS_{15} as emulsifier determines a higher decrease in viscosities and a better spreading capacity than Cetyl alcohol. Sodium valproate suppositories obtained with $Lipex_{403}$ as excipient base show plastic flow characteristics without thixotropy.
Conclusions: The experimental results demonstrated that sodium valproate as active substance induces an increase in viscosity and consequently a decrease in the spreading capacity of the lipophilic suppository bases used. Solutol HS_{15} determines a higher decrease in viscosities and a better spreading capacity than Cetyl alcohol.

Keywords: suppositories, rheology, viscosity, extensometry, sodium valproate

Introduction

Valproic derivates (valproic acid, sodium valproate) are used as anticonvulsants, in the treatment of epilepsy, bipolar disorder, major depression, migraine headaches and others neurological disorders [1]. Considering that these substances are frequently prescribed in children, rectal administration represents a real advantage, if the oral administration is not possible [2].

In the case of lipophilic suppositories, it is known that the rate and the intensity of the action is influenced by the size of the rectal area covered with the melted mixture of the active substances dissolved or dispersed in the lipophilic base of the suppository. The ability of the melted suppository to spread on the mucosa depends on several important properties: the softening time and the melting temperature; the viscosity of the mixture and its capacity to stretch under pressure; the presence of other additives, especially surfactants [3,4].

The objective of our studies consists in developing a formulation of sodium valproate suppositories for pediatric use. In this preliminary study we aimed to assess the influence of formulation (active substance, emulsifier type) on some rheological characteristics (viscosity and spreading capacity) of some fatty suppositories bases (Suppocire NAI, Witepsol W35, Massa Estarinum299, Lipex403) with improved bioavailability by adding emulsifiers (Cetyi alcohol, Solutol HS15).

Material and methods

Analyzed suppositories:

- Materials: sodium valproate – Sigma-Aldrich, India; Solutol HS_{15} – BASF, Germany; Cetyl alcohol – Huls AG, Trisdorf Germany; Massa $Estarinum_{299}$ (Adeps $solidus_3$) – Huls AG, Trisdorf Germany; Witepsol W_{35} (Adeps solidus50) – Huls AG, Trisdorf Germany; Suppocire NAI – Gattefossé, France; Lipex403 – Stéarinerie Dubois, France.
- Suppositories obtained: by fusion method [3], according to Table I.

Determination of spreading capacity:

- Device: Pozo Ojeda-Sune Arbussa extensometer.
- Measurement principle: determination of the increase in the area of a fixed quantity of product compressed between two parallel planes under the effect of the pressure exerted by different weights in ascending order during a fixed period of time (1 min for each weight used).
- Experimental conditions: measurements were carried out at 37±0.5° C, with a 0.5 g suppository sample. The

Table I. Composition of the analyzed suppositories

Formulations 1–4					Formulations 5-8			
Active substance: Sodium valproate		Emulsifier: 5% Cetyl alcohol		Lipophilic base: As necessary to 2.000 g/supp:	Emulsifier: 3% Solutol HS 15		Active substance: Sodium valproate	
F1		L1		Suppocire NAI		L5		F_5
F2		L2		Witepsol W 35		L6		F_6
F3	0.2305g/supp	L3	0.1000 g/supp	Massa Estarinum 299	0.0600 g/supp	L7	0.2305g/supp	F_7
F4		L4		Lipex 403		L8		F_8

L= excipient base + emulsifier; F = excipient base + emulsifier + active substance

weight of the upper plate was 54,17 g and the weights used were 2, 5, 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 350, 400, 500 g.

Viscosity measurement:

- Device: Brookfield (DV-II + Pro) rotational viscosimeter.
- Measurement principle: assessment of the torque needed to overcome the resistance to rotation generated by a disk immersed in the sample.
- Experimental conditions: viscosity measurements were carried out under laminar flow conditions. The sample was placed in a standard container which was slowly heated to the temperature of 37±0.5°C. For the rheological behavior determination, the measurements were made according to a fixed cycle of increasing-decreasing shear rate (5, 10, 20, 50, 100, 50, 20, 10, 5 rpm). In order to determine the dynamic viscosity the measurements were made directly at 100 rpm.

Results

Analyzed suppositories (Table I):

Spreading capacity:

Experimental determination consisted in measuring the diameters (mm) of the spread surfaces under increasing weights (g), at 37 °C. For a more suggestive representation, the applied weights were transformed in force and the diameters of the spread surfaces were expressed in terms of area (Table II).

Viscosity and rheological properties:

Experimental determination consisted in measuring the viscosity at 37 °C. Incremental shear rates were followed by the same but decremental shear rates (Table III).

In another experiment (37 °C, 100 rpm), the following dynamic viscosities were determined: F_1- 47.23; F_2-59.13; F_3-53.90; F_4-25.80 mPa s.

Discussions

Rheological properties of the suppositories (extensibility, viscosity) are determined by the nature of the excipients, the amount of active substances or the type of their dispersion and by other additives, especially emulsifiers [5]. The importance of the spreading capacity of the suppository after the rectal administration makes it important to determine the rheological behavior and to characterize the changes in their rheological properties caused by the addition of other components [2].

Extensibility expresses the capacity of spreading on a surface, and it is inversely proportional to viscosity and

Table II. Extensiometrically calculated parameters

f	Force (N) / Spreading surface (mm²)														
	0.55	0.58	0.62	0.72	0.82	0.92	1.02	1.51	2.00	2.49	2.98	3.47	3.96	4.45	5.43
F1	63.6	63.6	63.6	63.6	63.6	63.6	63.6	95.0	176.6	201.0	226.9	254.4	254.4	254.4	254.4
L1	78.5	95.0	113.0	153.9	176.6	226.9	283.4	346.2	380.0	380.0	415.3	415.3	415.3	452.3	530.8
F2	63.6	63.6	63.6	63.6	63.6	63.6	63.6	63.6	63.6	78.5	113.0	132.7	176.6	176.6	201.0
L2	63.6	63.6	63.6	63.6	78.5	113.0	132.7	153.9	201.0	254.4	283.4	283.4	283.4	314.1	314.1
F3	63.6	63.6	63.6	63.6	78.5	95.0	95.0	153.9	176.6	201.0	226.9	283.4	346.2	346.2	380.0
L3	78.5	78.5	95.0	113.0	201.0	226.9	226.9	226.9	254.4	254.4	254.4	254.4	283.4	314.1	346.2
F4	63.6	63.6	63.6	63.6	63.6	78.5	113.0	176.6	226.9	226.9	226.9	254.4	283.4	314.1	314.1
L4	78.5	95.0	153.9	201.0	380.0	415.3	572.4	660.3	706.7	754.6	804.0	804.0	804.0	855.1	907.7
F5	63.6	63.6	78.5	95.0	113.0	132.7	153.9	176.6	201.0	226.9	254.4	283.4	314.1	380.0	415.3
L5	78.5	113.0	113.0	176.6	201.0	254.4	314.1	380.0	415.3	415.3	452.3	452.3	490.7	530.8	572.4
F6	63.6	63.6	63.6	78.5	95.0	113.0	153.9	176.6	201.0	226.9	254.4	254.4	283.4	314.1	346.2
L6	63.6	63.6	78.5	95.0	113.0	132.7	176.6	201.0	226.9	283.4	314.1	346.2	346.2	380.0	415.3
F7	63.6	78.5	95.0	113.0	176.6	226.9	254.4	314.1	346.2	380.0	415.3	490.7	530.8	530.8	572.4
L7	78.5	95.0	132.7	153.9	254.4	346.2	415.3	490.7	530.8	572.4	615.6	660.3	706.7	804.0	855.1
F8	63.6	95.0	132.7	153.9	201.0	226.9	254.4	283.4	314.1	314.1	346.2	380.0	415.3	415.3	452.3
L8	78.5	113.0	176.6	226.9	415.3	452.3	615.6	706.7	754.6	754.6	804.0	855.1	907.7	907.7	961.9

f = formula; results represent the average of 3 determinations

Table III. Viscosities determined at different shear rates

f	rpm / Viscosity (mPa s) ± SD								
	5	10	20	50	100	50	20	10	5
F1	44.07±0.07	28.21±0.34	20.22±0.50	10.17±0.30	6.40±0.15	12.43±0.41	21.01±0.21	27.50±0.44	42.47±0.43
L1	34.16±0.23	21.82±0.19	18.21±0.21	9.96±0.29	5.50±0.25	10.15±0.25	18.16±0.18	27.06±0.17	32.41±0.53
F2	34.09±0.13	27.53±0.31	18.68±0.25	9.75±0.17	5.09±0.09	9.64±0.17	18.03±0.10	27.09±0.14	35.05±0.06
L2	31.3±0.45	22.61±0.14	14.33±0.37	9.64±0.17	4.75±0.28	9.19±0.11	14.50±0.39	23.03±0.13	30.93±0.12
F3	28.69±0.29	17.21±0.31	10.41±0.37	9.58±0.25	2.85±0.11	9.33±0.08	10.09±0.13	16.65±0.47	20.93±0.16
L3	11.20±0.18	8.87±0.15	4.49±0.14	3.82±0.17	2.24±0.11	4.27±0.09	4.52±0.16	8.42±0.16	12.16±0.14
F4	21.82±0.47	15.74±0.65	9.20±0.22	4.78±0.24	2.06±0.09	4.68±0.27	9.37±0.25	14.75±0.29	21.04±0.18
L4	19.07±0.71	9.64±0.21	6.66±0.39	4.07±0.20	1.93±0.09	5.04±0.19	8.90±0.14	11.13±0.21	18.89±0.33
F5	31.04±0.46	22.27±0.67	15.28±0.48	7.09±0.29	4.05±0.28	11.05±0.31	16.11±0.27	18.04±0.37	36.05±0.39
L5	27.37±0.83	21.49±0.58	13.78±0.75	6.41±0.53	3.03±0.51	10.07±0.34	14.59±0.65	17.29±0.35	31.22±0.78
F6	26.45±0.52	16.88±0.19	11.93±0.16	4.08±0.25	3.22±0.22	3.64±0.38	11.25±0.59	16.06±0.18	32.90±0.25
L6	25.92±0.51	16.01±0.23	11.05±0.38	3.46±0.49	2.92±0.25	3.06±0.20	10.57±0.46	15.75±0.38	30.49±0.48
F7	12.49±0.49	8.57±0.55	7.38±0.46	5.61±0.44	1.75±0.24	6.99±0.45	8.01±0.77	8.93±0.22	11.89±0.16
L7	10.95±0.15	7.86±0.36	4.32±0.33	3.62±0.38	1.46±0.22	4.02±0.41	4.06±0.29	8.05±0.38	10.85±0.44
F8	13.66±0.34	7.01±0.65	3.58±0.55	2.05±0.47	1.20±0.22	1.83±0.28	3.26±0.24	7.75±0.23	15.50±0.48
L8	12.82±0.61	6.41±0.60	2.79±0.45	1.96±0.18	1.10±0.25	1.26±0.26	2.90±0.28	7.02±0.56	14.80±0.44

f = formula; results represent the average of 3 determinations; SD = standard deviation (%)

melting point. Viscosity represents a property which characterizes fluid forms. It is considered a transfer of momentum between molecules that are moving in parallel layers without crossing from one layer to another, but with similar processes leading to the formation of unstable molecular association. The structural recovery capacity after mechanical destruction is expressed by the thixotropy [6,7].

In this study we evaluated the influence of certain emulsifier agents (cetyl alcohol, Solutol HS_{15}) and that of the sodium valproate as active substance on the rheological behavior of Suppocire NAI, Witepsol W_{35}, Massa $Estarinum_{299}$, $Lipex_{403}$ used as lipophilic excipients (according to Table I) at 37 °C.

By comparison, we can observe that in all cases (F_1-F_8) sodium valproate determines an increase in viscosity (Figure 1) and consequently a decrease in spreading capacity (Figure 2) of the suppository bases (L_1–L_8, lipophilic excipients containing emulsifier, without active substance).

Also in all cases, Solutol HS_{15} (polyethylene glycol 660 12-hydroxystearate) as emulsifier determines a lower viscosity than cetyl alcohol (palmityl alcohol, 1-hexadecanol) as emulsifier. This behavior may be due to the high melting point of the cetyl alcohol (45–49 °C), while Solutol HS15 (which has a paste consistency at room temperature) becomes liquid at ≈30 °C.

The majority of these formulations show characteristics of plastic flow, which occurs after melting at 37 °C and manifests by the reduction of viscosity while the shear rate increases. Considering the chemical composition of the used lipophilic excipients, it results that $Lipex_{403}$ (a base consisting in fatty acids) manifests the lowest viscosity compared to the bases consisting in mixtures of glycerides (Suppocire NAI, Witepsol W_{35}, Massa $Estarinum_{299}$). In all cases, the viscosity decreases even more if Solutol HS_{15} is used as emulsifier instead of cetyl alcohol. The viscosity curves for the sodium valproate suppositories in Lipex403 using cetyl alcohol (F_4) and Solutol HS_{15} as emulsifier (F_8) are comparatively illustrated in Figure 3.

Moreover, the absence of thixotropy is advantageous, considering that a marked thixotropy can delay the release of the active substance and consequently its absorption [2].

Conclusions

Sodium valproate as an active substance determines an increase in viscosity and consequently a decrease in spreading capacity of the lipophilic suppository bases that contain

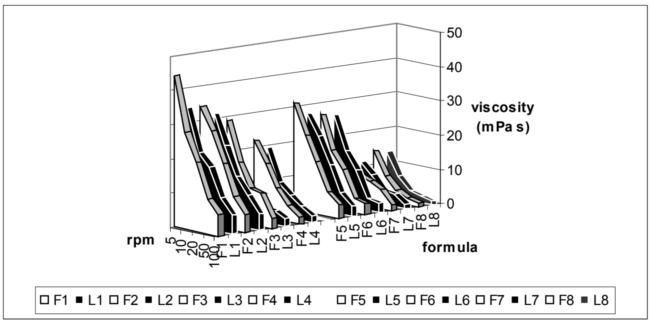

Fig. 1. Comparative viscosities

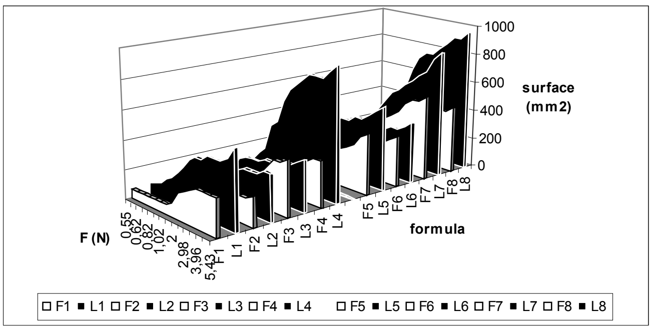

Fig. 2. Comparative spreading surfaces

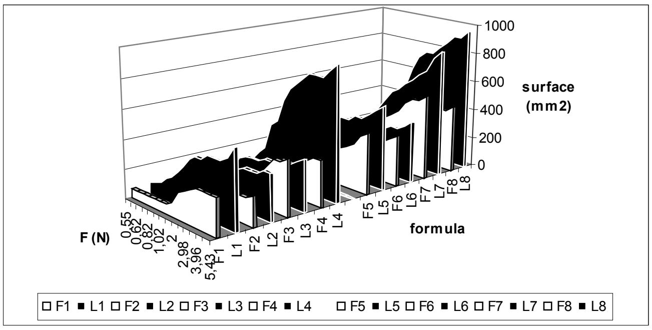

Fig. 3. Viscosities of sodium valproate suppositories with Lipex 403, under increasing-decreasing shear rate (F4-cetyl alcohol, F8-Solutol HS 15 as emulsifiers)

emulsifiers. The nature of the emulsifier agent also influences the rheological properties of the suppositories. Thus, Solutol HS_{15} determines a higher decrease in viscosities and a better spreading capacity than Cetyl alcohol.

The viscosity of a 2 g suppository containing 0.2305 g sodium valproate and 3% Solutol HS_{15} depends on the base excipient. The viscosities of these suppositories at 37 °C and 100 rpm (Brookfield DV-II+PRO) are the following: 47.23 (Suppocire NAI); 59.13 (Witepsol W_{35}); 53.90 (Massa $Estarinum_{299}$); 25.80 ($Lipex_{403}$) mPa s.

Sodium valproate suppositories obtained with $Lipex_{403}$ as excipient base show plastic flow characteristics without thixotropy. This behavior is considered to favor the release of the active substance after administration.

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