

UDC 615.454

DOI: 10.15587/2519-4852.2023.286315

## STUDY OF FACTORS AFFECTING SOME PROPERTIES OF HYDROPHILIC SUPPOSITORY BASES

Olena Bezugla, Yuriy Stolper, Nikolay Lyapunov, Igor Zinchenko, Oleksii Liapunov

**The aim.** To study the effect of the composition of hydrophilic suppository bases on the physicochemical and osmotic properties of suppositories made from them.

**Materials and methods.** The bases were studied with varying compositions of excipients. The microstructure of the bases was evaluated, and the disintegration time and resistance to rupture of suppositories made from them were determined. The kinetics of water absorption and solvent release were studied by dialysis. The content of propylene glycol (PG) and macrogol 400 (M400) in the receptor medium was determined by gas chromatography. The melted bases were studied by rotational viscometry. The electron paramagnetic resonance spectra of spin probes in hydrophilic solvents and bases were obtained; the type of spectrum, isotropic constant ( $A_N$ ), rotational correlation times ( $\tau$ ), and anisotropy parameter ( $\epsilon$ ) were determined.

**Results.** The disintegration times and resistance to rupture of suppositories were determined depending on such factors as the content and grade of poloxamers, the ratio between high molecular weight macrogols and the mixed solvent PG-M400 (60:40 % m/m), the ratio of nonionic surfactant and cetostearyl alcohol (CSA) and their total content, water and hard fat content. The introduction of solid fat and a mixture of surfactants and CSA provides the uniform structure of the bases. The mass ratio between surfactants and CSA and their total content are important factors that provide acceptable resistance to rupture and disintegration times for suppositories and reduce water absorption and solvent release. As the temperature decreases from 45 °C to 20 °C, the bases transform from Newtonian liquids to solids. At that time, the microviscosity of the environment of the spin probes increased by about 5 times, but the parameters of their rotational diffusion in solid bases and the mixed solvent PG-M400 are comparable. This indicates the dissolved state of the spin probes in the bases and the absence of the formation of mixed associates from molecules of surfactant and CSA.

**Conclusions.** By varying the composition of excipients, the properties of hydrophilic suppository bases can be controlled, significantly reducing their osmotic properties. The active substances in these bases may be in a dissolved state due to the high content of non-aqueous solvents

**Keywords:** suppository, base, solvent, excipient, resistance to rupture, disintegration time, release, water absorption

### How to cite:

Bezugla, O., Stolper, Y., Lyapunov, N., Zinchenko, I., Liapunov, O. (2023). Study of factors affecting some properties of hydrophilic suppository bases. ScienceRise: Pharmaceutical Science, 5 (45), 4–15. doi: <http://doi.org/10.15587/2519-4852.2023.286315>

© The Author(s) 2023

This is an open access article under the Creative Commons CC BY license

## 1. Introduction

Suppositories are a promising dosage form for use in proctology, gynaecology, urology and other areas of medicine [1]. Medicinal products in the form of suppositories have a local or systemic effect [2, 3]. The physicochemical, biopharmaceutical and therapeutic properties of medicinal products in this dosage form depend on the composition of the active ingredients and the type and composition of the suppository bases, which can be divided into two large groups – lipophilic and hydrophilic [4]. The most widely used are lipophilic suppositories with bases containing hard fat of various brands [1, 5].

Manufacturers offer a wide range of lipophilic suppository bases [5], which differ in the composition of fatty acid glycerides, solidification and melting points, hydroxyl values, resistance to rupture of suppositories made from them, as well as additives of hydrophilic and lipophilic surfactants [6]. During the pharmaceutical development of medicinal products, it is necessary to substantiate the choice

of a suitable lipophilic suppository base, taking into account the nature and content of the active substance, as well as the route of administration [3, 7]. For example, hard fat with low hydroxyl values, such as Witepsol® H 35 («IOI Oleo»), is used for suppositories containing non-steroidal anti-inflammatory drugs to prevent the formation of ester impurities. The suppository base Ovucire® 3460 («Gattefosse») contains hard fat, ricinoleate and macrogol 20 cetostearyl ester; it is characterised by high hardness and increased spreadability in the molten state and is recommended for pessaries. The suppository base Suppocire® AGP («Gattefosse») contains hard fat, glyceryl monostearate and PEG-75 stearate; this base is recommended for suppositories with hydrophilic active substances and plant extracts.

Despite the wide range of suppository bases, scientific publications contain the results of studies on the development of new bases or the use of new excipients for such bases. Some scientific papers deal with the effect of surfactants with different hydrophilic-lipophilic balances

on the physicochemical properties of lipophilic suppositories and the *in vitro* release of some active substances from them, e.g., meloxicam [6], paracetamol [7], dehydroepiandrosterone [8].

In general, hydrophilic suppository bases contain high-molecular-weight macrogols as forming agents [9, 10], which have a dehydrating and irritating effect on mucous membranes [10]. Suppositories with such bases often cause diarrhoea when administered rectally and may cause irritation and pain when administered vaginally. Due to these side effects, the use of suppositories based on macrogols is limited. Scientific research on polyethylene oxide bases is devoted to the choice of the mass ratio of macrogols with different molecular weights [7], the addition of hydrophilic polymers to the bases, in particular, carboxymethyl cellulose and polyvinylpyrrolidone [11], hydroxypropylmethylcellulose [12], poloxamers 407 and 188 [12, 13], xanthan gum [14]. Polymers improve or prolong the release of active substances such as metronidazole [11], ondansetron [12], carbamazepine [13], metoclopramide [14]. In general, the *in vitro* release of active substances from hydrophilic bases is faster and more complete than from lipophilic bases; in particular, this has been shown for indomethacin [15] and ibuprofen [16].

One of the new directions is the creation of liquid bases that transform into a gel with increasing temperature after rectal administration [17]. The development of the liquid mucoadhesive formulation with ondansetron and the study of its characteristics, such as gelation temperature, mucoadhesive and rheological properties, and *in vitro* release parameters, are presented in the paper [18]. The bases for the so-called «liquid suppositories» were developed using hydroxypropylmethylcellulose and poloxamers.

Poloxamers are promising excipients that can be used as forming agents and mucoadhesive agents in the composition of suppositories with hydrophilic bases [19]. The use of poloxamers makes it possible to include macrogol 400 (M400) and propylene glycol (PG) in the composition of hydrophilic bases [20]. The combination of hydrophilic forming agents with low molecular weight hydrophilic solvents is rational [21]. Due to their high molecular weight, the forming agents (poloxamers and macrogols) do not penetrate biomembranes but cause nonspecific dehydration of the biological object along with exudate absorption, resulting in local irritation. In the presence of low molecular weight hydrophilic solvents in the suppository base, diffusion processes should be different *in vivo* [21]. Glycols should penetrate rapidly into tissues, resulting in an osmotic equilibrium between the biological object and the base, which should prevent dehydration of the biological object. In addition, the osmotic properties of the suppository base could probably be reduced by the addition of a complex emulsifier containing surfactant and cetostearyl alcohol (CSA), as has been shown for semi-solid preparations [22].

**The aim.** To study the effect of the composition of hydrophilic suppository bases on the physicochemical and osmotic properties of suppositories made from them.

## 2. Planning (methodology) of the research

It was planned to introduce a mixed solvent PG – M400 (60:40 % m/m) into the composition of hydrophilic suppository bases, which could provide a preferential release of PG [23] and replace some or all of the high-molecular-weight macrogols with a suitable poloxamer [9]. It was also planned to introduce a complex emulsifier containing macrogol 20 cetostearyl ether (M20CSE) and CSA into the composition of the bases [9]. This planning was based on the results of previous studies on semi-solid preparations [22].

It was necessary to study the resistance to rupture of suppositories on hydrophilic bases, disintegration time and the kinetic of water absorption depending on the following factors:

- the ratio between the content of the mixed non-aqueous solvent and the total content of high-molecular-weight macrogols;
- the ratio between M20CSE and CSA at a certain total content;
- total content of M20CSE and CSA at a certain ratio;
- water content;
- grade of poloxamers at their certain content;
- content of hard fat, which is a dispersed phase of hydrophilic bases.

The suppository base containing 80 % M1500 and 20 % M400 (hereinafter referred to as the PEO base) was used as the comparator (reference base) [10].

It was planned to identify the factors affecting the microstructure of hydrophilic bases by means of optical microscopy [24].

Since, in the case of semi-solid preparations, the water absorption and solvent release were significantly dependent on the presence of surfactants and CSA [22], it was planned to carry out the same studies with two hydrophilic suppository bases, one containing M20CSE and CSA, and the other without these excipients.

Finally, it was planned to study the hydrophilic base containing non-aqueous solvents, M20CSE and CSA, by rotational viscometry [24] and spin probe method [25, 26], depending on the temperature. Two probes were selected for the study, one based on the fatty acid simulating a w/o emulsifier and the other simulating a hydrophilic substance soluble in hydrophilic solvents. The parameters of the EPR spectra of these spin probes could be used to provide an idea of the possible formation of M20CSE and CSA associates, as well as the state of the hydrophilic substance in the bases depending on temperature. Of scientific interest was the comparison of the parameters of rotational diffusion of the probes and the physicochemical properties of the suppository base (flow behaviour, viscosity, consistency).

## 3. Materials and methods

In the experiments, excipients produced by «BASF» were used: macrogol 1500 (Pluracare® E 1500 Flakes – M1500); macrogol 4000 (Pluracare® E 4000 Flakes – M4000); macrogol 20 cetostearyl ether (Kolliphor® CS 20 – M20CSE); cetostearyl alcohol (Kolliphor® CSA 50 – CSA); poloxamer 188 (Kolliphor® P 188 –

P188); poloxamer 338 (Kolliphor® P 338 – P338); poloxamer 237 (Kolliphor® P 237 – P237); poloxamer 407 (Kolliphor® P 407 – P407); propylene glycol (Kollisol® PG – PG); macrogol 400 (Kollisol® PEG 400 – M400). In addition, hard fat Suppocire® NA 15 («Gattefossé SAS») (hereinafter referred to as hard fat) and purified water (hereinafter referred to as water) were used. All substances were of pharmaceutical grade and met the requirements of the relevant monographs of European Pharmacopoeia [9].

The mass ratio was 6:4 for PG and M400 and 3:1 for M1500 and M4000.

The compositions of the studied bases are given in Tables 1–6.

The total content of the mixed solvent PG – M400 varied from 15.0 % to 45.0 %, and the total content of M1500 and M4000 varied from 70.0 % to 40.0 %. The content of other components was constant (Table 1).

The mass ratio between M20CSE and CSA (with their total content of 1.0 %) varied from 1.0:0 to 0:1.0 (Table 2), and the total content of M20CSE and CSA (with their mass ratio of 3:7) was varied from 0.5 % to 4.0 % (Table 3).

The content of hard fat was changed from 1.0 % to 7.0 % (Table 4), and the water content was varied from 0.5 % to 6.0 % (Table 5).

In addition, P338 or P237 or P407 were used in the bases instead of P188 (Table 5).

A series of suppository bases containing only P188 as a forming agent was studied. The content of P188 and the total content of the mixed solvent PG – M400 were varied in these bases (Table 6).

The suppository mass was obtained by melting the mixture of all components at 65–70 °C with stirring, then degassing the melted base and cooling it to ~50 °C. The melted suppository mass was dosed at 3.0 g into disposable suppository moulds made of laminated PVC film, and the suppositories were then cooled at ~12 °C.

The water content was determined in each component, and the amount of water to be added to the melted suppository mass was calculated. The water content was determined by the semi-micro method (2.5.12) [9, 24] using 870 KF Titrino titrator (Metrohm AG; software Firmware 58700025).

The determination of resistance to rupture was performed using an SBT apparatus («Erweka») according to the monograph 2.9.24 of State Pharmacopoeia

of Ukraine [25]. Measurements were performed at 25 °C, and the average value of 10 measurements was calculated.

Table 1

Compositions of suppository bases with different content of mixed non-aqueous solvents and different total content of high-molecular-weight macrogols

Components	Content (% m/m) in suppository bases:						
	No. 1. 1	No. 1. 2	No. 1. 3	No. 1. 4	No. 1. 5	No. 1. 6	No. 1. 7
M20CSE	0.3	0.3	0.3	0.3	0.3	0.3	0.3
CSA	0.7	0.7	0.7	0.7	0.7	0.7	0.7
PG	9.0	12.0	15.0	18.0	21.0	24.0	27.0
M400	6.0	8.0	10.0	12.0	14.0	16.0	18.0
P188	10.0	10.0	10.0	10.0	10.0	10.0	10.0
M1500	52.5	48.75	45.0	42.25	37.5	33.75	30.0
M4000	17.5	16.25	15.0	13.75	12.5	11.25	10.0
Hard fat	4.0	4.0	4.0	4.0	4.0	4.0	4.0

Table 2

Compositions of suppository bases containing M20CSE and CSA at different mass ratios

Components	Content (% m/m) in suppository bases:				
	No. 2. 1	No. 2. 2	No. 2. 3	No. 2. 4	No. 2. 5
M20CSE	1.0	0.7	0.5	0.3	0
CSA	0	0.3	0.5	0.7	1.0
PG	15.0	15.0	15.0	15.0	15.0
M400	10.0	10.0	10.0	10.0	10.0
P188	10.0	10.0	10.0	10.0	10.0
M1500	45.0	45.0	45.0	45.0	45.0
M4000	15.0	15.0	15.0	15.0	15.0
Hard fat	4.0	4.0	4.0	4.0	4.0

Table 3

Compositions of suppository bases with different total contents of M20CSE and CSA

Components	Content (% m/m) in suppository bases:							
	No. 3. 1	No. 3. 2	No. 3. 3	No. 3. 4	No. 3. 5	No. 3. 6	No. 3. 7	No. 3. 8
M20CSE	0	0.15	0.30	0.45	0.60	0.75	0.90	1.20
CSA	0	0.35	0.70	1.05	1.40	1.75	2.10	2.80
PG	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
M400	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
P188	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
M1500	45.5	45.38	45.0	44.63	44.25	43.88	43.50	42.75
M4000	15.589	15.12	15.0	14.87	14.75	14.62	14.50	14.25
Hard fat	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0

Table 4

Compositions of suppository bases with different content of hard fat

Components	Content (% m/m) in suppository bases:						
	No. 4. 1	No. 4. 2	No. 4. 3	No. 4. 4	No. 4. 5	No. 4. 6	No. 4. 7
M20CSE	0.3	0.3	0.3	0.3	0.3	0.3	0.3
CSA	0.7	0.7	0.7	0.7	0.7	0.7	0.7
PG	15.0	15.0	15.0	15.0	15.0	15.0	15.0
M400	10.0	10.0	10.0	10.0	10.0	10.0	10.0
P188	10.0	10.0	10.0	10.0	10.0	10.0	10.0
M1500	47.25	46.50	45.75	45.0	44.25	43.50	42.75
M4000	15.75	15.50	15.25	15.0	14.75	14.50	14.25
Hard fat	1.0	2.0	3.0	4.0	5.0	6.0	7.0

Table 5  
Compositions of suppository bases with different water content

Compo- nents	Content (% m/m) in suppository bases:					
	No. 5. 1	No. 5. 2	No. 5. 3	No. 5. 4	No. 5. 5	No. 5. 6
M20CSE	0.3					
CSA	0.7					
PG	15.0					
M400	10.0					
P188	10.0					
M1500	45.0					
M4000	15.0					
Hard fat	4.0					
Base	99.5	99.0	98.0	97.0	96.0	95.0
Water	0.5	1.0	2.0	3.0	4.0	5.0

Table 6  
Compositions of suppository bases with different content of P188 and total content of mixed solvent *PG – M400*

Compo- nents	Content (% m/m) in suppository bases:					
	No. 6. 1	No. 6. 2	No. 6. 3	No. 6. 4	No. 6. 5	No. 6. 6
M20CSE	0.30	0.30	0.30	0.30	0.30	0.30
CSA	0.70	0.70	0.70	0.70	0.70	0.70
P188	37.0	40.0	45.0	50.0	55.0	60.0
PG	37.2	35.4	32.4	29.4	26.4	23.4
M400	24.8	23.6	21.6	19.6	17.6	15.6

The disintegration tests (2.9.2) [9, 24] were performed using PTS 3E apparatus («Pharma Test Apparatebau AG»).

Rheograms (plots of the shear stress ( $\tau_r$ ) vs the shear rate ( $D_r$ )) were obtained at certain temperatures by rotational viscometry (2.2.10) [9, 24] using a rotating viscometer «Rheolab QC» with coaxial cylinders CC-27 (for non-Newtonian liquids) and DG42 (for Newtonian liquids) («Anton Paar GmbH»; software RHEOPLUS, 2.66 version). Rheograms were used to characterise the flow behaviour as well as to determine the yield stress ( $\tau_0$ ) and the apparent viscosity or the dynamic viscosity ( $\eta$ ).

The microstructure of the bases was examined by optical microscopy (2.9.37) [9, 24] using a microscope MBL-2100 with an eyepiece micrometer («A. Krüss Optronic»).

The experiments in regard to the *in vitro* release of *PG* or *M400* from suppository bases were performed using vertical diffusion cells and cellulose membranes (GOST 7730-89); the membranes were pre-soaked in the receptor medium (water R) for 24 hours. The tests were performed at 37 °C. The donor chamber contained 3.0 g of the melted suppository base; the membrane contact area was 7.065 cm<sup>2</sup>; the medium in the receptor chamber was stirred by a magnetic stirrer with a mixing rate of 600 rpm. Samples (1.0 ml) were collected from the receptor chamber at 0.5, 1, 2, 3, 4, 5, and 6 h after application of the tested system and the volume withdrawn was replaced with

stock receptor medium (water R). The concentrations of *PG* or *M400* in receptor medium at different sampling times were measured, and the amount of *PG* or *M400* (mg) released at a given time per unit area (cm<sup>2</sup>) was calculated for each sample. The results were assessed according to the requirements of EMA draft guidelines [26], USP General Chapter <1724> [27] and using accepted approaches [28, 29].

Quantitative determination of *PG* and *M400* in the receptor medium was performed according to the validated procedures [22, 30] by gas chromatography (2.2.28) [9, 24] using GC-2014 gas chromatograph with FID detector and AOC-5000 autosampler («Shimadzu»; software: GC solution version 2.30.00).

Water absorption by the bases was studied by dialysis using vertical diffusion cells and cellulose membranes (GOST 7730-89), which were pre-soaked in the water R for 24 h. The chamber containing 3.0 g of sample was weighed at regular intervals, and the conditional mass of absorbed water was calculated from the change in the weight of the chamber contents. The tests were carried out at 37 °C.

Electron paramagnetic resonance (EPR) spectroscopy was used for the research [31, 32]. The following spin probes were used:

- (1): 4-Palmitamido-2,2,6,6-tetramethylpiperidine-1-oxyl;  $M_r$  409.67; CAS: [22977-65-7];
- (2) 4-Hydroxy TEMPO (TEMPOL);  $C_9H_{18}NO_2$ ;  $M_r$  172.24; CAS: [2226-96-2].

Probe 1 simulated a w/o emulsifier, and probe 2 simulated a hydrophilic active substance.

Each of the spin probes was added into the mixed solvent *PG – M400* (60:40 % m/m) and suppository base at the concentration of 10<sup>-4</sup> mol/l. EPR spectra were obtained using an «EPR Spectrometer CMS8400» («Adani», software EPRCMD) at 20 °C, 25 °C and 45 °C.

Using the EPR spectra, which were triplets, the height of the low-field, central and high-field peaks ( $h_{+1}$ ,  $h_0$  та  $h_{-1}$ , respectively), as well as the width ( $G_s$ ) of the low-field component ( $\Delta H_{+1}$ ) and central component ( $\Delta H_0$ ), were determined. Rotational correlation times of spin probes ( $\tau_{-1}$ ,  $\tau_{+1}$ ) and anisotropy parameter ( $\varepsilon$ ) were calculated by the following equations [31, 32]:

$$\tau_{-1} = \left( \sqrt{\frac{h_0}{h_{-1}}} - 1 \right) \cdot \Delta H_0 / 3.6 \cdot 10^9; \quad (1)$$

$$\tau_{+1} = \left( \sqrt{\frac{h_{+1}}{h_{-1}}} - 1 \right) \cdot \Delta H_{+1} \cdot 6.65 \cdot 10^{-10}; \quad (2)$$

$$\varepsilon = \frac{\sqrt{h_0 / h_{+1}} - 1}{\sqrt{h_0 / h_{-1}} - 1}. \quad (3)$$

The rotational correlation time of the spin probe ( $\tau$ ) is directly proportional to the effective radius of the molecule ( $R$ ) and to the microviscosity of its local surround-



ing ( $\eta$ ) and inversely proportional to the absolute temperature ( $T$ ) [32]:

$$\tau = (4 \cdot \pi \cdot R^3 \cdot \eta) / 3 \cdot k \cdot T. \quad (4)$$

The hyperfine splitting constant ( $A_N$ ) was determined as the distance ( $mT$ ) between the central and high-field components by the EPR spectra, which were triplets; the  $A_N$  characterises the micropolarity of the environment in the vicinity of the nitroxyl radical [32].

A circulating thermostat, «Julabo F12-ED» («Julabo Labortechnik GmbH»), was used to maintain a necessary temperature.

#### 4. Research results

*Resistance to rupture of suppositories and disintegration test.*

When the concentration of the mixed non-aqueous solvent was increased from 15 % to 40 % and the total content of M1500 and M4000 was reduced from 70 % to 45 % (Table 1), the resistance to rupture of the suppositories decreased from 4.9 kg to 0.8 kg (Fig. 1, *a*), and the disintegration time decreased from 55 min to 30 min (Fig. 1, *b*).

Taking into consideration the dependence of the studied characteristics on the content of the mixed non-aqueous solvent, it can be concluded that its concentration of about 25 % was optimal since, at this content of the mixed solvent, the suppositories were quite hard (breaking occurred at mass of 3.3 kg), and the time of their disintegration was about 40 minutes (Fig. 1).

The resistance to rupture of suppositories was maximal at the mass ratio between M20CSE and CSA of 3:7 (Table 2) (Fig. 2, *a*). As the amount of CSA in the emulsifier mixture increased from 30 % to 70 %, the disintegration time of the suppositories decreased (Fig. 2, *b*).

The resistance to rupture of suppositories was maximal at the content of the mixture of emulsifiers of 1.0 % and 1.5 %; the mass required to break the suppository was 3.3 kg (Fig. 3, *a*); the disintegration times were 40 min and 45 min and increased sharply to 220 min

with a further increase in the content of mixture of emulsifiers to 2.5 % (Fig. 3, *b*). The disintegration of suppositories containing 0.5 % to 2.0 % of mixture of M20CSE and CSA occurred as described in points (*a*) or (*b*) of the pharmacopoeial monograph 2.9.2, and the disintegration of suppositories containing more than 2.0 % of these emulsifiers occurred as described in point (*c*) [9, 24].

Hard fat was the dispersed phase of the suppository mass. The resistance to rupture of suppositories was maximal at the hard fat content of 4.0 % (Fig. 4, *a*). As the hard fat content was increased to 4.0 %, the disintegration time decreased and then did not change with the further increase in the hard fat content to 7.0 % and was approximately 30 min (Fig. 4, *b*).

Hard fat and emulsifiers, when used together in certain concentrations, provided a homogeneous structure of the bases (Fig. 5), preventing uneven crystallisation of poloxamers and high-molecular-weight macrogols.

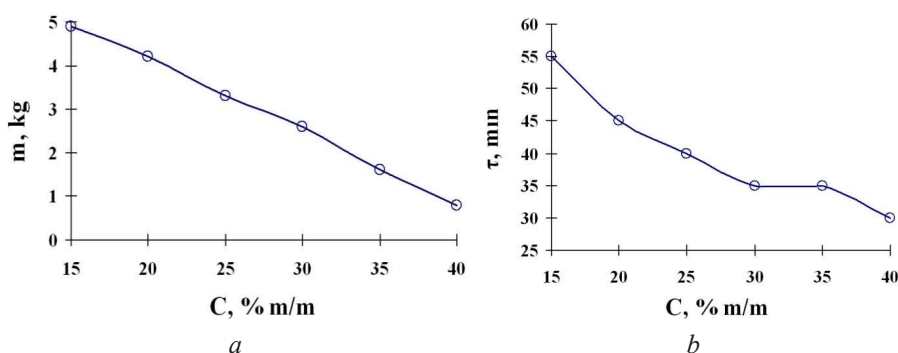


Fig. 1. Characteristics of suppositories depending on content (*C*) of mixed solvent (Table 1): *a* – resistance to rupture; *b* – disintegration time

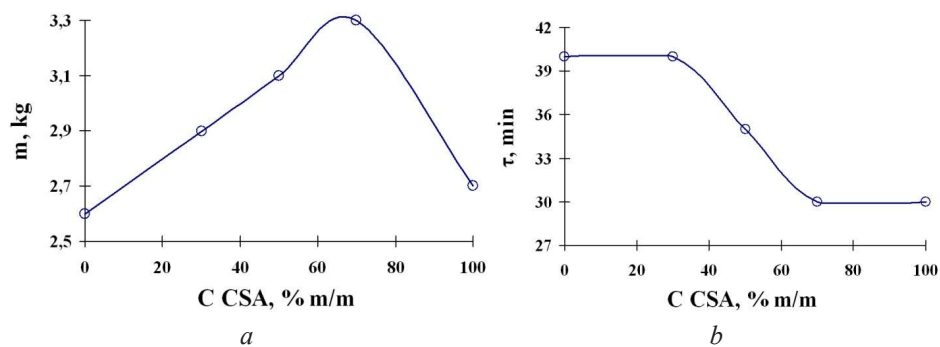


Fig. 2. Characteristics of suppositories depending on CSA content (*C*) in the mixture of M20CSE and CSA at their total content 1.0 % (Table 2): *a* – resistance to rupture; *b* – disintegration time

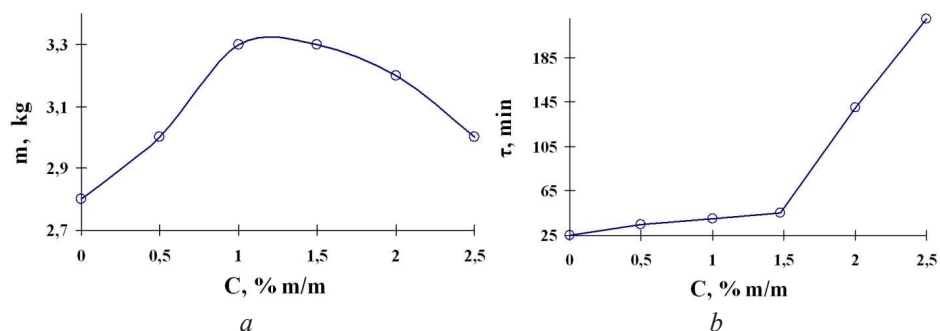


Fig. 3. Characteristics of suppositories depending on total content (*C*) of M20CSE and CSA at their ratio 3:7 (Table 2): *a* – resistance to rupture; *b* – disintegration time

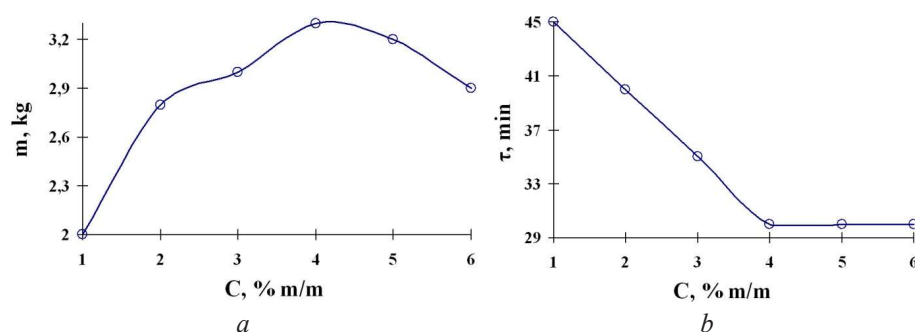


Fig. 4. Characteristics of suppositories depending on hard fat content ( $C$ ) (Table 4):  
 $a$  – resistance to rupture;  $b$  – disintegration time

Suppository base No. 3.1 contained 4.0 % hard fat and did not contain M20CSE and CSA (Table 3). When 2.5 % of the mixture of M20CSE and CSA was added to the suppository base in their mass ratio of 3:7, the microstructure of the base changed and became homogeneous (suppository base No. 3.6) (Fig. 5). Suppository base No. 4.1 contained only 1.0 % hard fat and 1.0 % emulsifiers; as the content of solid fat was increased to 4.0 %, the microstruc-

ture of the base changed: the forming agents crystallised in the form of small particles, and the base became more homogeneous (suppository base No. 4.4) (Fig. 5).

The resistance to rupture of suppositories depended on the grade of poloxamer in their composition, being minimal in the case of poloxamer 407 and maximal in the case of poloxamer 237 (Fig. 7,  $a$ ). On the contrary, the disintegration time was maximal when poloxamer 407 was used and minimal when poloxamer 237 was used (Fig. 7,  $b$ ).

In the case of suppository bases with poloxamer 188 as the main forming agent (Table 6), with an increase in its content from 37.0 % to 60.0 % and, accordingly, a decrease in the content of the mixed solvent, both the resistance to rupture of suppositories (Fig. 8,  $a$ ) and the disintegration times (Fig. 8,  $b$ ) increased.

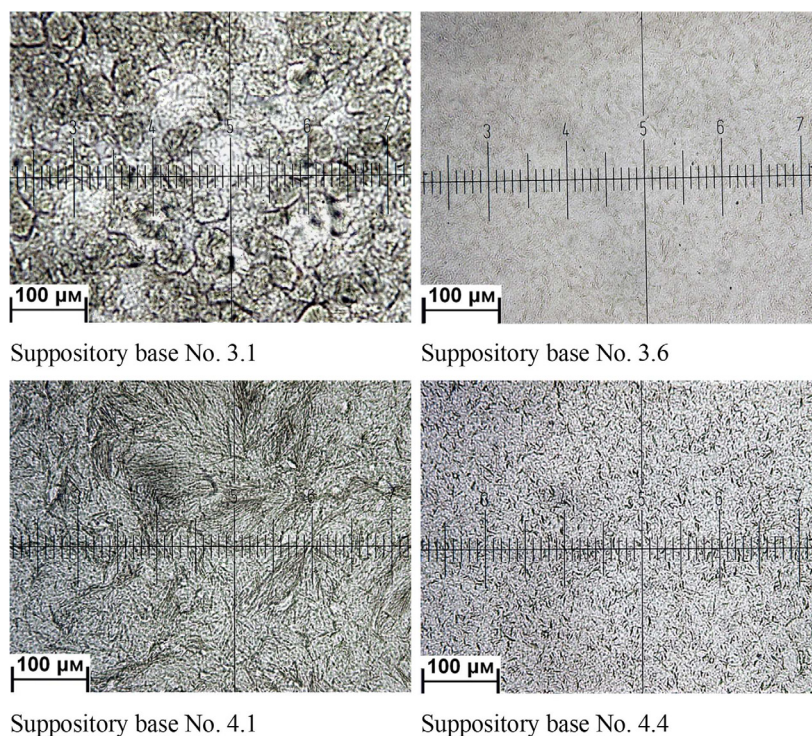


Fig. 5. Micrographs of the suppository bases (Table 3, 4) at  $\times 150$

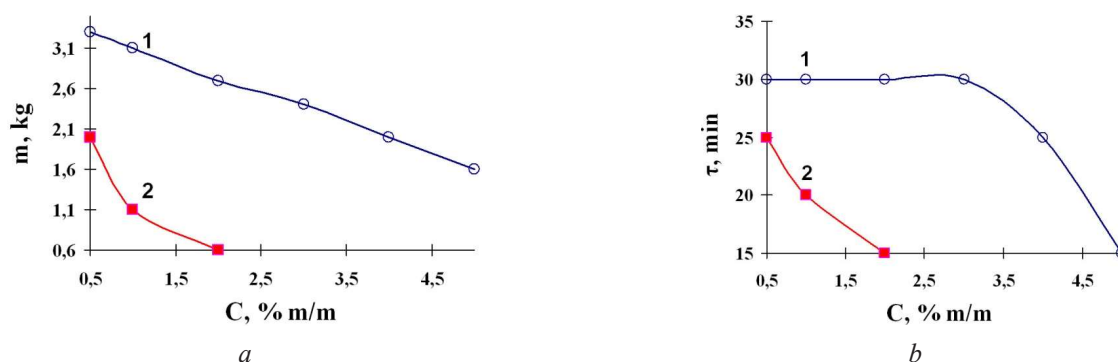


Fig. 6. Characteristics of suppositories depending on water content ( $C$ ):  $a$  – resistance to rupture;  $b$  – disintegration time for:  
 1 – bases with different water content (Table 5); 2 – PEO base with added water

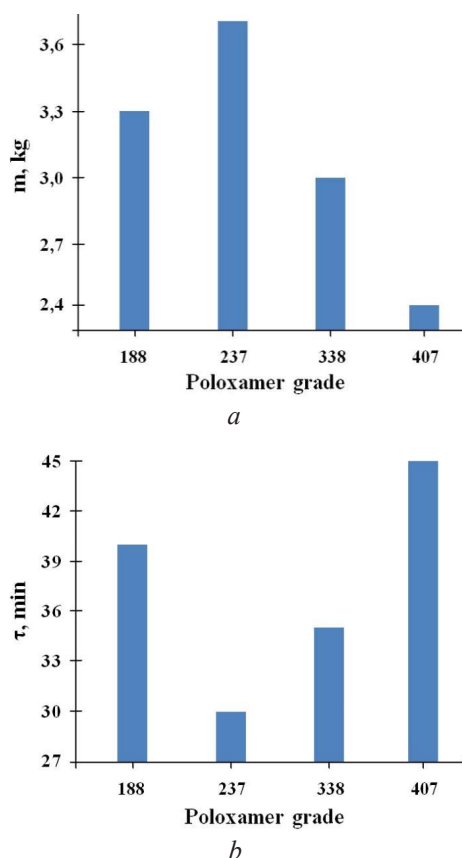


Fig. 7. Characteristics of suppositories depending on poloxamer grade (Table 5):

$a$  – resistance to rupture;  $b$  – disintegration time

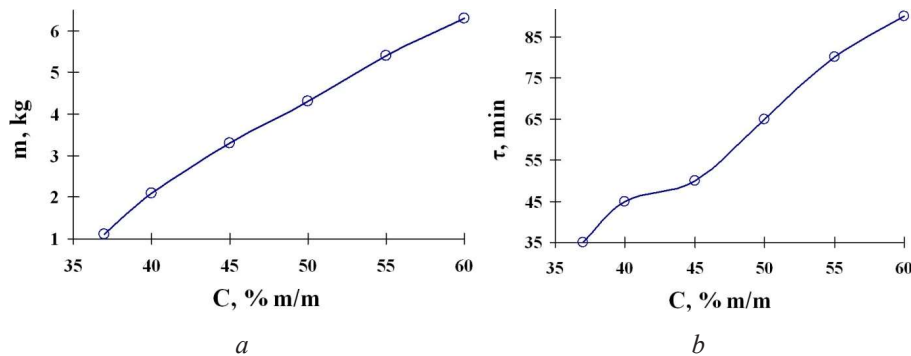


Fig. 8. Characteristics of suppositories depending on content ( $C$ ) of poloxamer 188 (Table 6):  $a$  – resistance to rupture;  $b$  – disintegration time

#### Study of osmotic properties of suppository bases.

In addition to pharmaceutical technical tests, it was important to study the influence of pharmaceutical factors on the osmotic activity of hydrophilic suppository bases, in particular, on their water absorption as a characteristic of the potential dehydrating effect of bases on mucous membranes.

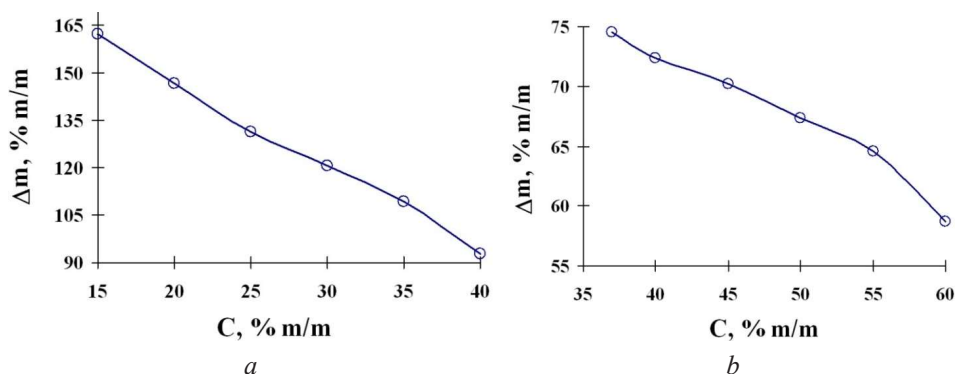


Fig. 9. Change in mass ( $\Delta m$ ) of chambers containing suppository bases after 3 hours of the experiment depending on:  $a$  – the content ( $C$ ) of mixed non-aqueous solvent (Table 1);  $b$  – the content ( $C$ ) of poloxamer 188 (Table 6)

The results of the study of the osmotic activity of suppository bases are shown in Fig. 9, 10.

As the concentration of the mixed non-aqueous solvent was increased from 15 % to 40 % and the total content of M1500 and M4000 was reduced from 70 % to 45 % (Table 1), the conditional mass of absorbed water decreased from 162.2 % to 92.7 %, i.e., by 1.75 times (Fig. 9,  $a$ ). The weight of the chamber with the PEO base increased by 220.1 % after 3 hours of experiment, which was significantly higher compared to hydrophilic bases, the composition of which is given in Table 1 (Fig. 9). An increase in the content of high-molecular-weight macrogols led to more intense water absorption (Fig. 9,  $a$ ), and an increase in the content of the more hydrophobic poloxamer 188, on the contrary, contributed to a decrease in the mass of absorbed water (Fig. 9,  $b$ ). An increase in the mass fraction of CSA in the emulsifier mixture resulted in a 1.43-fold decrease in the water absorption by suppository bases (Fig. 10,  $a$ ). With an increase in the total concentration of emulsifiers, the water absorption by suppository bases decreased from 190.2 % (no emulsifiers) to 73.7 % (2.5 % emulsifiers) and became 3 times lower compared to the PEO base (Fig. 10,  $b$ ).

The osmotic activity of the suppository bases is also manifested by the diffusion of *PG* and *M400* into the chamber with water. Two suppository bases were selected to study this process. One of them contained 50.0 % P188, 30.0 % *PG* and 20.0 % *M400* (base No. 1), and the other contained 0.45 % M20CSE, 1.05 % CSA, 48.5 % P188, 30.0 % *PG* and 20.0 % *M400* (base No. 2). That is, the bases differed in the presence of emulsifiers.

The graphs in Fig. 11 and the values of the correlation coefficients in Table 7 indicate that the dependence of the amount of *PG* or *M400* released per unit membrane area on the square root of time was linear in all runs of the *in vitro* release experiment. The values of the coefficients of determination were higher than the acceptance criterion ( $>0.90$ ) [28, 29].



The introduction of 0.45 % M20CE and 1.05 % CSA into the hydrophilic suppository base resulted in a significant decrease in the *in vitro* release of *PG* and *M400*. The average release rate (*R*) for *PG* and *M400* decreased by 70.8 % and 79.2 %, respectively; the cumulative content (*A*) after 6 hours – by 61.1 % and 76.5 %, the content of *PG* and *M400* in the dialysate (*C*) – by 61.0 % and 76.4 %, and the released amount – by 61.1 % and 76.5 %. During 6 hours of experiment,

the mass of the chamber with the base without emulsifiers increased by 269.6 %, and the mass of the chamber with the base containing 1.5 % emulsifiers increased by 87.7 %, which is 3.07 times less (Fig. 12). The presence of emulsifiers M20CE and CSA in the hydrophilic suppository base led to a decrease in its osmotic activity, which was manifested by a decrease in both the mass of absorbed water and the parameters of *in vitro* release of hydrophilic solvents.

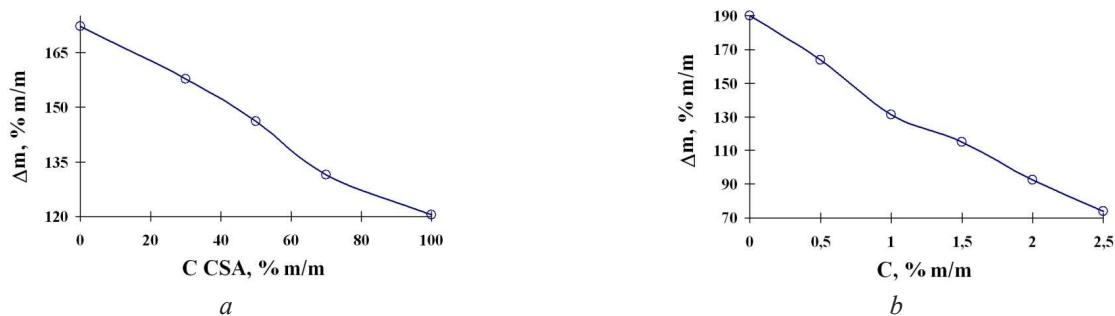


Fig. 10. Change in mass ( $\Delta m$ ) of chambers containing suppository bases after 3 hours of the experiment depending on: *a* – the content (*C*) of CSA in the mixture of M20CSE and CSA (Table 2); *b* – as well as the total content of M20CSE and CSA (Table 3)

Table 7

Parameters of *in vitro* release for *PG* and *M400* (see Fig. 11)

Parameter	<i>PG</i>		<i>M400</i>	
	Base No. 1	Base No. 2	Base No. 1	Base No. 2
Release rate, mg/cm <sup>2</sup> /h <sup>-1/2</sup>	51.41±11.90 SD: 4.07	15.00±1.73 SD: 0.59	32.18±4.03 SD: 1.38	6.68±1.58 SD: 0.54
Cumulative amount ( <i>A</i> ) (at the time point 6 h), mg/cm <sup>2</sup>	113.10±10.17 SD: 3.48	44.04±6.70 SD: 2.29	55.76±1.09 SD: 0.37	13.13±2.79 SD: 0.96
Content ( <i>C</i> ) in the receptor medium (at the time point 6 h), mg/ml	13.32±1.20 SD: 0.41	5.19±0.79 SD: 0.27	6.57±0.13 SD: 0.04	1.55±0.33 SD: 0.11
Correlation coefficient <i>r</i>	0.98465	0.99615	0.99541	0.98393
Coefficient of determination <i>R</i> <sup>2</sup>	0.9695	0.9923	0.9908	0.9681
Released amount (at the time point 6 h), %	88.78±7.99 SD: 2.73	34.57±5.26 SD: 1.80	65.65±1.28 SD: 0.44	15.46±3.29 SD: 1.13

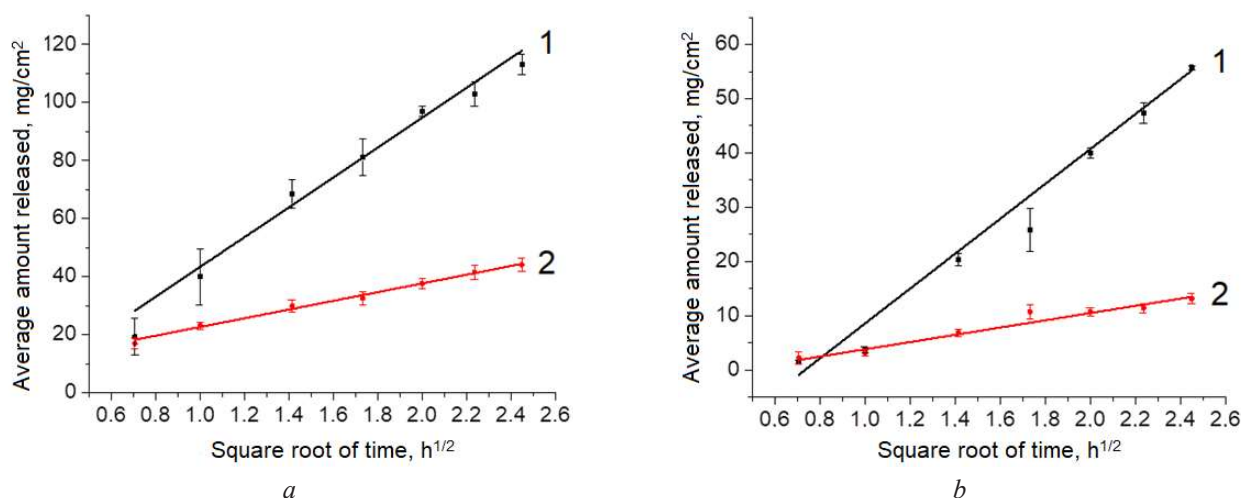


Fig. 11. Release rate plots for: *a* – *PG*; *b* – *M400* in the case of their release from: 1 – base without emulsifiers, 2 – base containing 1.5 % M20CSE and CSA (3:7)



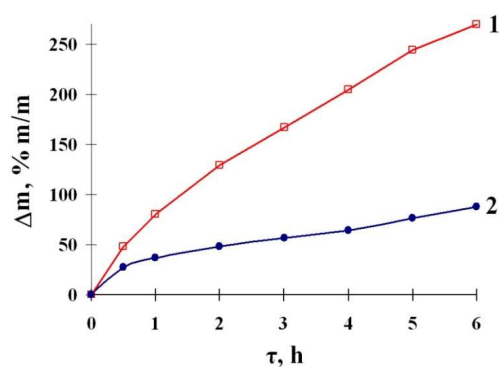


Fig. 12. Kinetics of change in chamber mass with hydrophilic suppository bases No. 1 (1) and No. 2 (2)

*Study of suppository bases by rotational viscometry and spin probes method.*

Base No. 2, containing 50 % hydrophilic non-aqueous solvents and 1.5 % M20CSE and CSA (3:7), was studied by rotational viscometry and spin probe method at different temperatures.

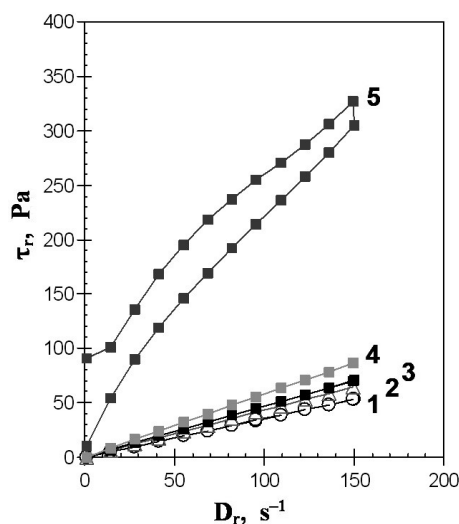


Fig. 13. Rheograms of the base No. 2 at temperature: 1 – 50 °C, 2 – 45 °C, 3 – 41 °C, 4 – 39 °C, 5 – 37 °C

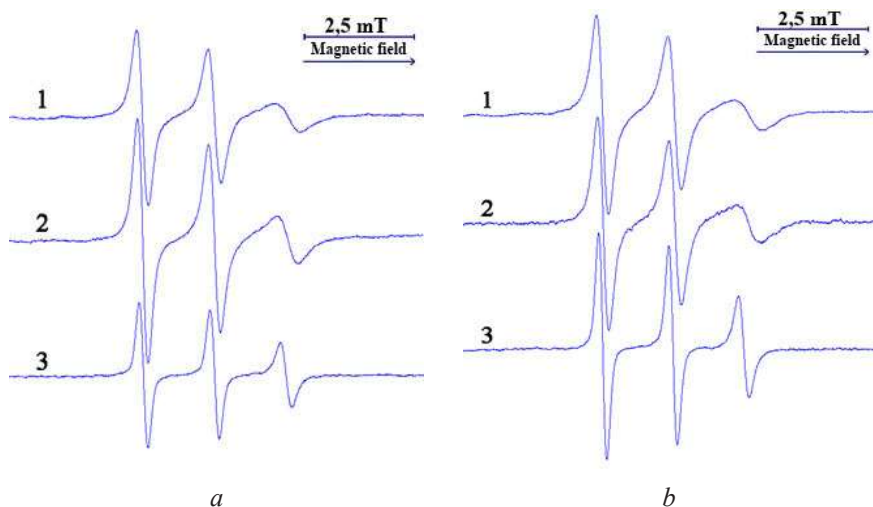


Fig. 14. EPR spectra of probe 1: a – in the mixed solvent PG – M400 (6:4); b – in the hydrophilic base No. 2 at temperature: 1 – 20 °C, 2 – 25 °C, 3 – 45 °C

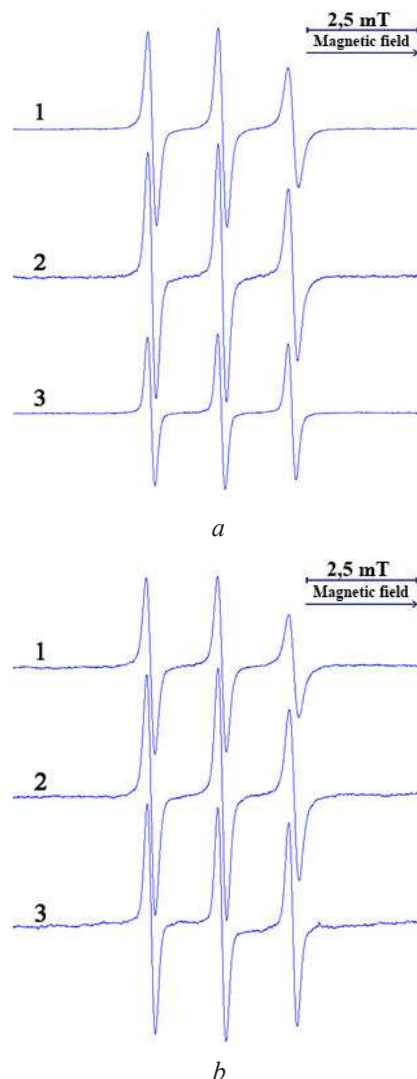


Fig. 15. EPR spectra of probe 2: a – in the mixed solvent PG – M400 (6:4); b – in the hydrophilic base No. 2 at temperature: 1 – 20 °C, 2 – 25 °C, 3 – 45 °C

As can be seen from the rheograms in Fig. 13, the hydrophilic suppository base No. 2 in the melted state was a Newtonian fluid. The dynamic viscosity increased with decreasing temperature and was 354 mPa·s at 50 °C, 431 mPa·s at 45 °C, 470 mPa·s at 41 °C, and 578 mPa·s at 39 °C. At 37 °C, a sol→gel transition occurred; the base became a non-Newtonian fluid with a yield stress ( $\tau_0$ ) of 90.8 Pa, an apparent viscosity of 7.0 Pa·s (at  $D_r = 14.55$  s<sup>-1</sup>), and thixotropic properties (Fig. 13). With further cooling, the values of the rheological parameters of the system increased, and the hydrophilic base became solid.

At 45 °C, the dynamic viscosity of the mixed solvent PG – M400 (6:4) was 19.4 mPa·s, and it was 22.2 times lower than the dynamic

viscosity of the melted base (Table 8). At the same time, the spin probes No. 1 and No. 2 dissolved in the mixed solvent and in the hydrophilic base had the EPR spectra with the same shape (Fig. 14, 15), almost identical rotational correlation times ( $\tau_{-1}$ ,  $\tau_{+1}$ ), anisotropy parameters ( $\epsilon$ ), and isotropic constants ( $A_N$ ) (Table 8). This indicates that the probe molecules were dissolved in the mixed solvent *PG* – *M400* and that neither emulsifiers nor poloxamer 188 had any effect on the parameters of the EPR spectra of these probes.

Table 8

Parameters of EPR spectra of the spin probes in mixed solvent *PG* – *M400* and in suppository base No. 2, as well as dynamic viscosity ( $\eta$ ) of liquid systems at different temperatures ( $t$ )

Object	$t$ , °C	Probe	$A_N$ , mT	$\tau_{-1}$ , ns	$\tau_{+1}$ , ns	$\epsilon$	$\eta$ , mPa·s
<i>PG</i> – <i>M400</i> (6:4)	20	No. 1	1.68	0.92	2.62	–0.11	66.8
	25		1.67	0.76	2.06	–0.13	50.4
	45		1.63	0.24	0.66	–0.14	19.4
Base No. 2	20	No. 1	1.68	1.01	2.92	–0.10	Solid
	25		1.67	0.84	2.28	–0.12	Solid
	45		1.62	0.22	0.63	–0.16	431
<i>PG</i> – <i>M400</i> (6:4)	20	No. 2	1.62	0.16	0.37	0.05	66.8
	25		1.62	0.12	0.25	0.11	50.4
	45		1.61	0.03	0.05	0.30	19.4
Base No. 2	20	No. 2	1.62	0.17	0.40	0.01	Solid
	25		1.62	0.12	0.24	0.11	Solid
	45		1.60	0.04	0.08	0.12	431

As the temperature decreased to 25 °C and then to 20 °C, the rotational correlation times of ( $\tau_{-1}$ ,  $\tau_{+1}$ ) of the spin probes in the mixed solvent *PG* – *M400* increased, indicating an increase in the microviscosity of the environment surrounding their molecules. The hydrophilic base No. 2 became a solid at these temperatures, but the parameters of the EPR spectra of the spin probes did not correspond to their localisation in a solid but to their localisation in the mixed solvent *PG* – *M400* (Fig. 14, 15). This means that, due to the high concentration of the mixed solvent, the dispersion medium of the solid suppository is a liquid in which the active substances can be dissolved.

When emulsifiers and poloxamer 188 were added to the non-aqueous solvent *PG* – *M400*, the shape and parameters of the EPR spectra of spin probe 1 based on palmitic acid remained almost unchanged (Fig. 14). That is, according to the EPR spectra of spin probe 1, it can be concluded that neither associates of poloxamer 188 nor mixed aggregates of M20CE and CSA molecules were formed in a non-aqueous hydrophilic environment. These substances crystallised in the hydrophilic mixed solvent upon cooling and did not affect the EPR spectra of spin probe 1 (Fig. 14).

## 5. Discussion of research results

According to the data of scientific literature, suppositories with water-soluble PEO bases provide a rapid and complete release of active substances [15, 16]. How-

ever, high-molecular-weight polyethene oxides (macrogols) are commonly used as foaming agents in PEO bases, which have a strong dehydrating effect on the mucous membranes causing certain side effects. A very limited amount of solvents can be added to PEO bases, in particular, macrogol 400 and water. These factors limit the use of PEO-based suppositories.

The studied multicomponent hydrophilic bases additionally contain poloxamers, o/w and w/o emulsifiers, hard fat, and hydrophilic non-aqueous solvents (*PG* and *M400*) in relatively high concentrations (Tables 1–4, 6). Moreover, in contrast to PEO bases, these multicomponent bases can contain up to 4.0 % water (Table 5, Fig. 6), which expands the possibilities for the incorporation of water-soluble active substances into these suppository bases.

The properties of the developed hydrophilic bases can be controlled by changing various pharmaceutical factors. In particular, the resistance of suppositories to rupture and the time of their disintegration depended on such factors as the ratio between the content of the mixed non-aqueous solvent and the total content of high-molecular-weight macrogols (Fig. 1), the mass ratio of o/w and w/o emulsifiers and their total content (Fig. 2, 3), the grade and content of poloxamers (Fig. 6, 7) as well as the content of hard fat (Fig. 4). When emulsifiers were used together with hard fat, the microstructure of suppository bases changed and became more homogeneous (Fig. 5). Bases with an emulsifier content of more than 1.5 % may be promising for the development of prolonged-release suppository formulations due to their long disintegration time (Fig. 3, b).

The factors contributing to a significant decrease in the mass of water absorbed by multicomponent bases compared to PEO bases are as follows:

- partial or complete substitution of high-molecular-weight macrogols with poloxamer 188 (Fig. 9, 12),
- an increase in the content of hydrophilic non-aqueous solvents and a decrease in the content of high-molecular-weight macrogols (Fig. 9, a),
- an increase in the content of poloxamer 188 (Fig. 9, b),
- an increase in the total content of emulsifiers and an increase in the CSA fraction in the mixture of emulsifiers (Fig. 10).

Reducing the mass of absorbed water and the possibility of introducing a sufficiently large amount of low-molecular-weight solvents *PG* and *M400* released from the bases (Fig. 11, Table 7) should eliminate the side effects [21, 23] associated with PEO bases due to their dehydrating effect on the mucous membranes. It is important to note the difference in water absorption when using different forming agents. While an increase in the content of high-molecular-weight macrogols promoted intensive water absorption (Fig. 9, a), then an increase in the content of the more hydrophobic poloxamer 188 led to a decrease in the mass of absorbed water (Fig. 9, b).

It should be noted that the addition of 1.5 % emulsifiers (M20CE and CSA in a mass ratio of 3:7) to the hydrophilic suppository base resulted in a significant decrease in the release parameters of *PG* and *M400* (Fig. 11, Table 7).

Using the spin probe method, it was shown that hydrophilic non-aqueous solvents were the dispersion medium in the developed multicomponent suppository bases (Fig. 14, 15, Table 8), which could contribute to increasing the therapeutic efficacy of medicinal products in the form of suppositories. It was shown that in a non-aqueous hydrophilic medium, there was no formation of poloxamer 188 associates as well as mixed aggregates from molecules of emulsifiers (M20CE and CSA) (Fig. 14, Table 8). These substances crystallised in the hydrophilic mixed solvent upon cooling and had some influence on the properties of the suppository bases.

According to the research results, by varying the composition of the excipients, it is possible to control the properties of multicomponent hydrophilic suppository bases, which have advantages over PEO bases.

**Study limitations.** This article presents the results of studies of suppository bases without considering the possible influence of active substances on the characteristics studied.

**Prospects for further research.** In the future, the release of hydrophilic and lipophilic drugs from the de-

veloped suppository bases should be studied depending on various pharmaceutical factors.

## 6. Conclusions

By varying the composition of excipients, the properties of hydrophilic suppository bases can be controlled, significantly reducing their osmotic properties. The active substances in these bases may be in a dissolved state due to the high content of non-aqueous solvents.

## Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

## Financing

The study was performed without financial support.

## Data availability

Data will be made available on reasonable request.

## References

1. Buckingham, R. (Ed.) (2020). Martindale: The Complete Drug Reference. London: Pharmaceutical Press, 4912.
2. Ul Haq, M. M., Ur Razzak, M. M., Uddin, M. A., Ahmed, N., Shahidulla, S. M. (2021). Rectal Drug Delivery System: An Overview. *Clinical Pharmacology and Biopharmaceutics*, 10 (5), 219.
3. Hua, S. (2019). Physiological and Pharmaceutical Considerations for Rectal Drug Formulations. *Frontiers in Pharmacology*, 10. doi: <https://doi.org/10.3389/fphar.2019.01196>
4. Melnyk, G., Yarnykh, T., Herasymova, I. (2020). Analytical Review of the Modern Range of Suppository Bases. *Systematic Reviews in Pharmacy*, 11 (4), 503–508. doi: <https://doi.org/10.31838/srp.2020.4.76>
5. Sheskey, P. J., Hancock, B. C., Moss, G. P., Goldfarb, D. J. (Ed.) (2020). Handbook of Pharmaceutical Excipients. London: Pharm. Press, 1296.
6. Szulc-Musiol, B., Bulas, L., Dolinska, B. (2019). Effect of Selected Surfactants on Kinetics of Meloxicam Release from Rectal Suppositories. *Indian Journal of Pharmaceutical Sciences*, 81 (6), 1115–1121. doi: <https://doi.org/10.36468/pharmaceutical-sciences.610>
7. Ilomuanya, M. O., Ifudu, Ndu. D., Odulaja, J., Igwilo, C. (2012). Assessment of the effect of base type and surfactant on the release properties and kinetics of paracetamol suppositories. *Journal of Chemical and Pharmaceutical Research*, 4 (6), 3280–3286.
8. Kasperek, R., Galczyński, K., Nalesniak, M., Iwaniak, K., Poleszak, E. (2014). Influence of the dissolution medium on the release of dehydroepiandrosterone from lipophilic suppositories. *Current Issues in Pharmacy and Medical Sciences*, 27 (1), 46–50. doi: <https://doi.org/10.2478/cipms-2014-0012>
9. The European Pharmacopoeia (2022). EDQM. Strasbourg: Council of Europe. Available at: <http://pheur.edqm.eu/subhome/11-0>
10. Hanning, S. M., Matiz, S., Krasser, K., Orlu, M., Dodoo, C., Gaisford, S., Tuleu, C. (2020). Characterisation of rectal amoxicillin (RAMOX) for the treatment of pneumonia in children. *Drug Delivery and Translational Research*, 11 (3), 944–955. doi: <https://doi.org/10.1007/s13346-020-00804-6>
11. Akhtar, M., Akhtar, N., Ahmad, M., Arif, A. S., Shah, P. A. (2000). Drug release from PEG suppository bases and from their combination with polymers. *Journal of Faculty of Pharmacy of Istanbul University*, 33, 7–16.
12. Zawar, L. R., Bhandari, G. S. (2012). Formulation and Evaluation of Sustained Release Ondansetron Poloxamer Based Solid Suppositories. *Journal of Applied Pharmaceutical Science*, 2 (7), 186–190. doi: <https://doi.org/10.7324/japs.2012.2729>
13. Havaladar, V. D., Yadav, A. V., Dias, R. J., Mali, K. K., Survase, A. B., Ghorpade, V. S., Salunkhe, N. H. (2017). Screening of Suppository bases for Rectal delivery of Carbamazepine. *Research Journal of Pharmacy and Technology*, 10 (8), 2697–2703. doi: <https://doi.org/10.5958/0974-360x.2017.00479.6>
14. Ali, M. M., Mashrai A., Al-dholimi, N. (2018). Sustained Release Suppositories of Metoclopramide HCl: Formulation and In vitro Evaluation. *Journal of Chemical and Pharmaceutical Research*, 10 (1), 169–175.
15. Mori, K., Hori, S., Kawata, T., Kogure, S., Matsumoto, K., Hasegawa, T., Akimoto, M. (2017). The in Vitro Release of Indomethacin from Suppositories: Effects of Bases and Comparison of Different Dissolution Methods. *Chemical and Pharmaceutical Bulletin*, 65 (7), 674–677. doi: <https://doi.org/10.1248/cpb.c16-00794>
16. El Majri, M. A., El Baseir, M. M. (2016). Formulation and evaluation of ibuprofen suppositories. *International Research Journal of Pharmacy*, 7 (6), 87–90. doi: <https://doi.org/10.7897/2230-8407.07670>
17. Bialik, M., Kuras, M., Sobczak, M., Oledzka, E. (2021). Achievements in Thermosensitive Gelling Systems for Rectal Administration. *International Journal of Molecular Sciences*, 22 (11), 5500. doi: <https://doi.org/10.3390/ijms22115500>

18. Ban, E., Kim, C.-K. (2013). Design and evaluation of ondansetron liquid suppository for the treatment of emesis. *Archives of Pharmacol Research*, 36 (5), 586–592. doi: <https://doi.org/10.1007/s12272-013-0049-y>
19. Bodratti, A., Alexandridis, P. (2018). Formulation of Poloxamers for Drug Delivery. *Journal of Functional Biomaterials*, 9 (1), 11. doi: <https://doi.org/10.3390/jfb9010011>
20. Liapunov, N. A., Bezuglaia, E. P., Fadeikina, A. G., Lysokobylka, A. A., Stolper, Iu. M. (1999). Sozdanie miagkikh lekarstvennykh sredstv na razlichnykh osnovakh. *Soobshchenie 1. Issledovanie reologicheskikh svoistv mazi na vodorastvorimykh osnovakh*. *Farmakom*, 6, 10–16.
21. Bezugla, O. P., Lyapunov, M. O., Zinchenko, I. O., Lisokobilka, O. A., Liapunova, A. M. (2022). Modeling of processes of solvent diffusion from ointment bases using in vitro experiments. *Functional materials*, 29 (4), 553–558. doi: <https://doi.org/10.15407/fm29.04.553>
22. Lyapunov, N., Bezuglaya, E., Liapunova, A., Zinchenko, I., Liapunov, O., Lysokobylka, O., Stolper, Y. (2022). Effect of the composition of emulsifiers and the dispersion medium on the properties of bases for semi-solid preparations. *ScienceRise: Pharmaceutical Science*, 5 (39), 29–45. doi: <https://doi.org/10.15587/2519-4852.2022.266001>
23. Bezuglaya, E., Krasnopyorova, A., Liapunova, A., Zinchenko, I., Lyapunov, N., Sytnik, O. (2023). Influence of physico-chemical properties and structure of mixed solvents propylene glycol – macrogol 400 on their in vitro release. *ScienceRise: Pharmaceutical Science*, 1 (41), 4–13. doi: <https://doi.org/10.15587/2519-4852.2023.274468>
24. Derzhavna Farmakopeia Ukrainy. Druhe vydannia. Vol. 1 (2015). Kharkiv: Derzhavne pidpriemstvo «Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 1128.
25. Derzhavna Farmakopeia Ukrainy. Pershe vydannia. Dopovnennia 1 (2004). Kharkiv: Derzhavne pidpriemstvo «Nauko-vo-ekspertnyi farmakopeinyi tsentr», 520.
26. Draft guideline on quality and equivalence of topical products (2018). CHMP/QWP/708282/2018. Available at: [www.ema.europa.eu/en/quality-equivalence-topical-products](http://www.ema.europa.eu/en/quality-equivalence-topical-products)
27. The United States Pharmacopoeia, 41 – NF 36 (2018). The United States Pharmacopoeial Convention. Rockville. Available at: <https://www.worldcat.org/title/united-states-pharmacopoeia-2018-usp-41-the-national-formulary-nf-36/oclc/1013752699>
28. Ilić, T., Pantelić, I., Savić, S. (2021). The Implications of Regulatory Framework for Topical Semisolid Drug Products: From Critical Quality and Performance Attributes towards Establishing Bioequivalence. *Pharmaceutics*, 13 (5), 710. doi: <https://doi.org/10.3390/pharmaceutics13050710>
29. Tiffner, K. I., Kanfer, I., Augustin, T., Raml, R., Raney, S. G., Sinner, F. (2018). A comprehensive approach to qualify and validate the essential parameters of an in vitro release test (IVRT) method for acyclovir cream, 5%. *International Journal of Pharmaceutics*, 535 (1-2), 217–227. doi: <https://doi.org/10.1016/j.ijpharm.2017.09.049>
30. Bezuglaya, E., Zinchenko, I., Lyapunov, N., Vlasenko, H., Musatov, V. (2021). Substantiation of an approach to determination of ketoprofen macrogol 400 esters. *ScienceRise: Pharmaceutical Science*, 3 (31), 51–63. doi: <http://doi.org/10.15587/2519-4852.2021.235980>
31. Kuznetsov, A. N. (1976). *Metod spinovogo zonda (Osnovy i primeneniye)*. Moscow: Nauka, 210.
32. Likhtenshtein, G. I. (1974). *Metod spinovykh zondov v molekuliarnoi biologii*. Moscow: Nauka, 256.

*Received date 17.08.2023*

*Accepted date 22.09.2023*

*Published date 31.10.2023*

**Olena Bezugla\***, PhD, Senior Researcher, Head of Laboratory, Laboratory of Technology and Analysis of Medicinal Products, State Scientific Institution «Institute for Single Crystals» of National Academy of Sciences of Ukraine, Nauky ave. 60, Kharkiv, Ukraine, 61072

**Yurij Stolper**, PhD, Senior Researcher, Laboratory of Technology and Analysis of Medicinal Products, State Scientific Institution «Institute for Single Crystals» of National Academy of Sciences of Ukraine, Nauky ave. 60, Kharkiv, Ukraine, 61072

**Nikolay Lyapunov**, Doctor of Pharmaceutical Sciences, Professor, Leading Researcher, Laboratory of Technology and Analysis of Medicinal Products, State Scientific Institution «Institute for Single Crystals» of National Academy of Sciences of Ukraine, Nauky ave. 60, Kharkiv, Ukraine, 61072

**Igor Zinchenko**, PhD, Researcher, Laboratory of Technology and Analysis of Medicinal Products, State Scientific Institution «Institute for Single Crystals» of National Academy of Sciences of Ukraine, Nauky ave. 60, Kharkiv, Ukraine, 61072

**Oleksii Liapunov**, PhD, Researcher, Laboratory of Technology and Analysis of Medicinal Products, State Scientific Institution «Institute for Single Crystals» of National Academy of Sciences of Ukraine, Nauky ave. 60, Kharkiv, Ukraine, 61072

*\*Corresponding author: Olena Bezugla, e-mail: [bezugla.op@gmail.com](mailto:bezugla.op@gmail.com)*