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PHYSICO-CHEMICAL AND PHARMACO-TECHNOLOGICAL RESEARCH AT A SUBSTANTIATION OF RATIONAL COMPOSITION AND TECHNOLOGY OF SUPPOSITORIES «INDOXAM»

©V. Zaychenko, O. Ruban, Yu. Maslii, N. Gerbina

Розробка нових високоефективних лікарських засобів у формі ректальних супозиторіїв для лікування захворювань передміхурової залози не втрачає своєї актуальності і сьогодні, оскільки чисельність хворих з даними патологіями зростає з кожним роком. Дані захворювання негативно впливають на фізичне, психологічне здоров'я та якість життя чоловіків взагалі.

Важливим питанням при обґрунтуванні складу та розробці технології виробництва супозиторіїв є дослідження їх фізико-хімічних та фармако-технологічних властивостей, які безпосередньо впливають на їх споживацькі якості та режим ведення технологічного процесу.

***Метою** роботи стало вивчення фізико-хімічних і фармако-технологічних властивостей комбінованих ректальних супозиторіїв «Індоксам» для вибору раціональних умов ведення технологічного процесу.*

***Матеріали та методи.** При обґрунтуванні складу та технології комбінованих ректальних супозиторіїв «Індоксам» використовували сучасні фізико-хімічні (термічний аналіз, метод ротаційної віскозиметрії) та фармако-технологічні (розпадання супозиторіїв, стійкість до руйнування) дослідження згідно вимог ДФУ.*

***Результати**. Для вибору оптимального співвідношення поліетиленоксидів у складі супозиторної основи вивчено стійкість супозиторіїв до руйнування та час розпадання зразків, виготовлених з різною кількістю ПЕО-1500 і ПЕО-400. Для визначення оптимальної технології виготовлення препарату проведено дослідження температури розкладання АФІ, що дозволило визначити температурні режими приготування супозиторіїв і введення діючих речовин в основу без небезпеки руйнування структури субстанцій та зміни їх фармакологічної дії. Оскільки під впливом механічної, теплової та інших дій супозиторії зазнають декілька видів деструкції, також досліджено їх реологічні характеристики.*

***Висновки**. Результати фармако-технологічних досліджень дозволили обґрунтувати оптимальне співвідношення поліетиленоксидів у супозиторній основі. Проведений термогравіметричний аналіз АФІ та супозиторіїв «Індоксам» встановив термостабільність субстанцій і відсутність хімічної взаємодії між компонентами у складі ректального лікарського засобу. За реологічними характеристиками визначено тиксотропність системи та оптимальну температуру розливання супозиторної маси*

***Ключові слова**: ректальні супозиторії «Індоксам», індол-3-карбінол, мелоксикам, фізико-хімічні та фармако-технологічні дослідження, склад, технологія*

1. Introduction

According to statistics, benign prostatic diseases (BPD) are one of the most common urological diseases in men, due to their significant prevalence, with a negative impact on the quality of life and reproductive capacity of the patient [1].

In the course of marketing analysis of drugs for the treatment of BPD, a limited range of domestic medicinal products in the form of suppositories with significant clinical advantages over other forms of drugs was established [2, 3]. Therefore, a new combined drug in the form of rectal suppositories under the conditional name "Indoxam" is being developed at the Department of Industrial technology of drugs of NUPh, which includes as an APIs an indole-3-carbinol and meloxicam, as a base – an alloy of polyethylene oxides 1500 and 400, as a surfactant – Montanox 80 [4].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

It is known that great importance in the design of technology of any dosage form is the study of their properties in accordance with the methods of SPHU. Physico-chemical and pharmaco-technological parameters of suppositories directly affect their consumer qualities (appearance, resistance to destruction, etc.) and the mode of technological process (temperature of manufacturing and pouring of the suppository mass) [5].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

In the last decade, scientists and technologists continue to research on the development and improvement of the composition and technology of drugs in the form of suppositories. Among the scholarly works closely related to the direction of research, the work of domestic and foreign developers [5-7] occupy an important place.

4. The field of research considering the general problem, which is described in the article

The analysis of the range of drugs for the treatment of BPD has shown that the pharmaceutical market has a relatively small proportion of domestic combined medicinal products that contain plant material, therefore its expansion due to domestic herbal medicines is relevant for pharmaceutical science and practice [8]. In European countries, more than 70 % of patients with BPD prefer to have herbal preparations based on extracts of Palbal fruit Sabal, African plum corms, nettle root,

pumpkin seeds, and others [2, 8]. At the same time, according to numerous studies, the positive effect of BAS of broccoli cabbage on the prostate tissue, which is represented by a number of indole compounds that exhibit antioxidant, anti-enzyme and hormone-like effects, has been established [9, 10]. With diseases of the prostate, meloxicam has an analgesic effect by blocking prostaglandin synthesis, improves microcirculation in the blood vessels, reduces inflammatory processes, which facilitates the condition of patients with acute and chronic forms [11]. Therefore, the promising direction in the treatment of BPD is the development of rectal suppositories with a combination of indole-3-carbinol and meloxicam, which can simultaneously affect the various pathogenesis of these diseases and have a polyvalent pharmacological effect on the patient's body. One of the stages of pharmaceutical development of the drug is the study of its physico-chemical and pharmaco-technological properties [12].

5. Formulation of goals (tasks) of article

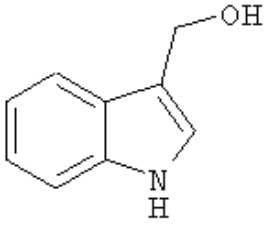
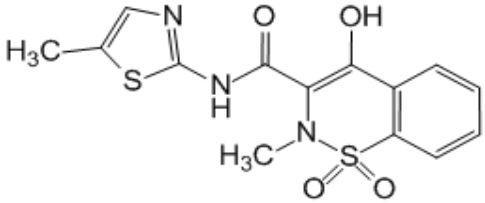
Therefore, the purpose of the work was to study the physicochemical and pharmaco-technological properties of combined rectal suppositories with indole-3-carbinol and meloxicam to select a rational composition and optimal conditions for conducting the technological process.

6. Presentation of the main research material (methods and objects) with the justification of the results

The objects of our work were APIs – indole-3-carbinol and meloxicam, polyethylene oxide base and the complete composition of the developed preparation under the conventional name "Indoxam" (Table 1).

Table 1

Characteristics of APIs

Indole-3-carbinol	 C_9H_9NO M. м 147,18	By appearance it is a powder from white to yellow and light brown color, partially soluble in cold water.
Meloxicam	 $C_{14}H_{13}N_3O_4S_2$ M. м. 351,4	By appearance it is a powder of light yellow color, insoluble in water, well soluble in acids, alkalis and ethanol

The composition of rectal suppositories under the conventional name "Indoxam" for the treatment of BPD, g:

Indole-3-carbinol– 0.2000
Meloxicam– 0.0075
Montanox 80– 0.0900
PEO-1500 : PEO-400 (95 : 5)– to 3.0 g

The research of physico-chemical and pharmaco-technological studies was carried out in accordance with the requirements of the SPHU 2nd ed., vol. 1 [13].

The stability of the suppositories to the destruction was carried out in accordance with the SPHU 2nd ed., vol. 1, p. 1.4 [13] with the help of the device SBT by firm Erweka (Germany).

The disintegration of suppositories was carried out in accordance with the SPHU 2nd ed., vol. 1, p. 2.9.2 [13] using the "PTS 3E device for determining the decomposition of the Pharma Test suppositories" (Germany).

Thermogravimetric analysis was performed according to the SPHU 2nd ed., vol. 1, p. 2.2.34 [13] on the derivative digitizer Q-1500-D of the system "F. Paulik, J. Paulik, L. Erdey "of the Hungarian firm" IOM "with a platinum-platinum-based thermocouple that allows measurement of temperature (T), mass change (TG), rate of change of mass (DTG) and change of thermal effects (DTA) of the investigated sample depending on time. The studies were carried out in the temperature range from 22 °C to 500 °C in air when samples were heated in ceramic crucibles. Thermograms were shot in the following mode: the weight of the API was 100 mg, the rate of increase in temperature was 2.5 ^{o}C/min. The standard was roasted aluminum oxide.

Structural-mechanical (rheological) properties of the suppository base and samples of suppositories were studied using a rotating viscometer "Reotest-2" (Germany) with coaxial cylinders. Measurements were carried out in a wide range of temperatures, which were recorded by a laboratory thermometer with a sensitivity of 0.2 °C. Thermostating of samples was carried out using the ultra-thermostat TC-16A.

It is known that suppositories are a solid dosage form with certain physico-chemical properties, which depend on the ratio of shape-generating and non-aqueous solvents to their composition. This, in turn, affects the consumer properties of suppositories. Therefore, in this

case, it is important to determine the index of their resistance to destruction, which contributes to the fact that the suppositories did not change their shape in the manufacture, storage, transportation and provided convenience of use for the patient. It is known that an acceptable empirical lower limit of resistance to fracture for rectal suppositories is 1.5–1.6 kg [14]. On the other hand, the time of dissolution or decomposition, which ensures the speed of onset of the therapeutic effect of the drug, is no less important as a quality indicator for hydrophilic base suppositories.

Therefore, to select the optimal polyethylene oxide ratio in the base, we have prepared samples of suppositories with different amounts of PEO-1500 and PEO-400 – (100:0), (95:5), (90:10), (80:20), and the stability of the suppositories to destruction and the time of decomposition have been studied.

On the basis of the obtained data, the curves of the dependence of the suppositories on the destruction and decay time from different ratios of polyethylene oxides were constructed. The results are presented in Fig. 1, 2.

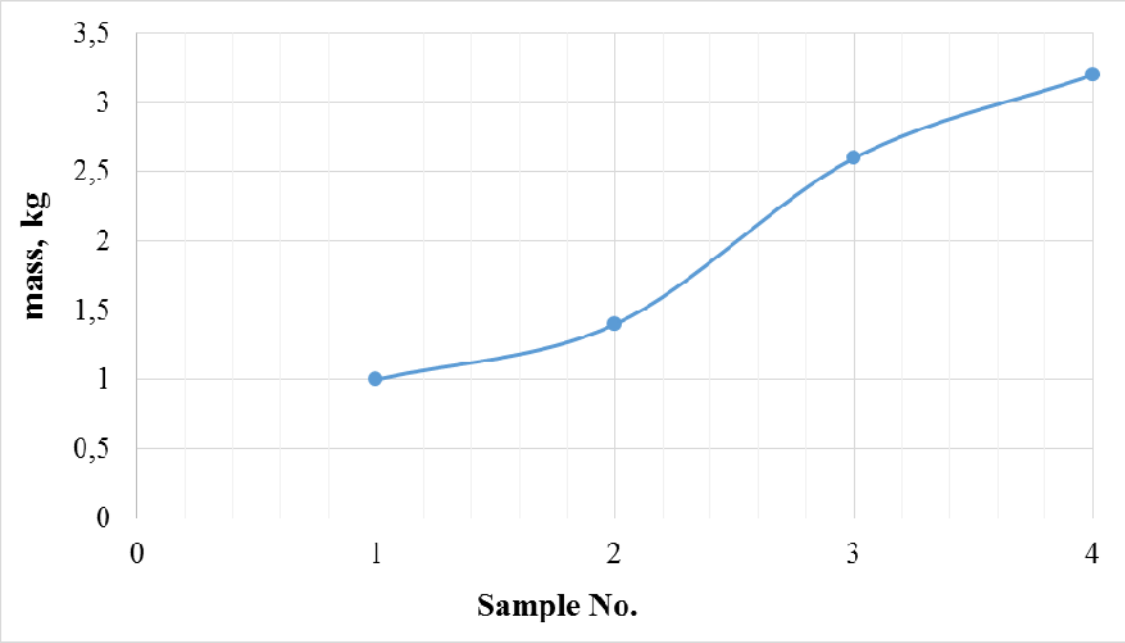


Fig. 1. Dependence of resistance to the destruction of suppositories from the ratio PEO-1500 and PEO-400: No. 1 – 80:20; No. 2 – 90:10; No. 3 – 95:5; No. 4 – 100:0

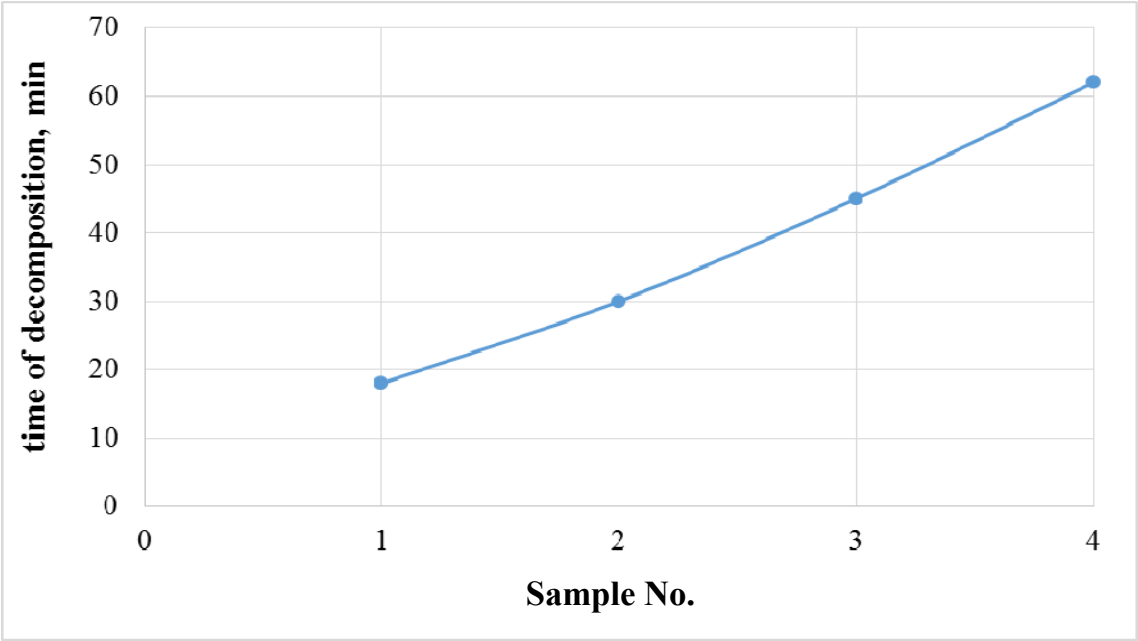


Fig. 2. Dependence of the time of decomposition of suppositories from the ratio PEO-1500 and PEO-400: No. 1 – 80:20; No. 2 – 90:10; No. 3 – 95:5; No. 4 – 100:0

From the above results it can be seen that the stability of the suppositories to destruction and the time of disintegration increases with the increase of the concentration of shape-generating PEO-1500. However, it should be noted that samples made in the ratio of 90:10 and 80:20 correspond to the requirements of the SPHU in the disintegration time, but do not provide the necessary mechanical stability of the suppositories, which can negatively affect their consumer properties. The investigated samples №3 and №4 are more stable – the index was more than 1.5 kg. However, the time of decomposition of sample number 4 exceeded the permissible standards in accordance with the state control system.

Thus, on the basis of the conducted research it can be concluded that the optimal ratio PEO-1500 and PEO-400 is 95:5, which simultaneously provides sufficient hardness of suppositories, and on the other hand, their rapid disintegration and the onset of the pharmacological effect.

To determine the optimal technology of manufacturing the drug, we conducted a study of the decomposition temperature of the API and the total composition of the "Indoxam" suppositories. These data will allow us to determine the temperature modes of cooking suppositories and the introduction of active substances into the basis without the danger of destruction of the structure of substances and changes in their pharmacological effect. The study was conducted using thermogravimetric analysis [5, 13]. Thermograms of substances indole-3-carbinol and meloxicam are presented in Fig. 3.

As can be seen from the results (Fig. 3, *a*), at a temperature of 95 °C, the indole-3-carbinol melting occurs without loss in mass. In the temperature range of 110–233 °C, the mass loss was 11.5 % of the weight gain, with a maximum decomposition rate at 152 °C, which is most likely accompanied by boiling. When the substance is burned to 500 ^{o}C, splitting takes place in 2 stages – at temperatures of 343 ^{o}C and 365 ^{o}C, above 365 ^{o}C, the combustion process is observed.

In the study of meloxicam (Fig. 3, *b*), it was found that the substance is stable to 257 °C, mass loss does not occur. At this temperature there is a process of melting of matter, the maximum rate of splitting – 260 ^{o}C. At a temperature of 278 °C, the combustion process is observed, and within the range 315–393 ^{o}C it is boiling. Up to 315 ^{o}C the mass loss was 57 %, and with an increase in temperature to 460 ^{o}C – 72 %, and the process of mass release stops.

The conducted studies of thermal API behavior suggest that the thermal transformation of the indole-3-carbinol begins with 95 ^{o}C, and meloxicam – from 257 ^{o}C. This indicates the thermal stability of these substances when they introduced into the supportive basis.

Thermogram of suppositories composition (Fig. 3, *c*) showed the complete identity of the thermal effects of the individual active pharmaceutical ingredients included in their composition, indicating no chemical interaction between components in the rectal medicinal product.

The suppositories belong to complex structured systems, which at certain temperatures are characterized by specific rheological properties (structural viscosity, type of flow, thixotropy, etc.). The study of structural and mechanical properties is important for optimizing the technological process of producing this dosage form, since under the influence of mechanical, thermal and other suppository actions, several types of destruction are subjected to destruction, which may lead to changes in their initial rheological parameters.

The research of rheological characteristics of the developed suppositories was carried out on a rotating viscometer "Reotest-2" with coaxial cylinders. The rheological behavior of the systems was determined in the temperature range from 45 °C to 60 °C, in which the suppository base and the suppository mass were in a fluid state. The results are presented in Fig. 4.

The results of rheological studies (Fig. 4) showed that when the temperature ranged from 45 °C to 55 °C, the value of structural viscosity of the suppository mass decreased by almost 9 times, and the polyethylene oxide base was more than 12 times higher. In this range, the temperature of the system is converted to a liquid misty gel. Further increase of temperature from 55 °C to 60 °C leads to the complete destruction of the structure.

Thus, when comparing the structural viscosity of the suppository mass and the polyethylene oxide base, it was found that the introduction of the suppositories of the API and the Montanox 80 emulator leads to a slight decrease in rheological indexes.

The consistency properties of the suppository masses directly affect the technological parameters of the process of manufacturing rectal suppositories. Therefore, the next stage of our research was the determination of the flow type and the presence of thixotropic properties of the suppository mass. The dependence of the shear stress (τ_r) on the shear rate gradient (D_r) was determined and rheograms were constructed. The research results are presented in Fig. 5.

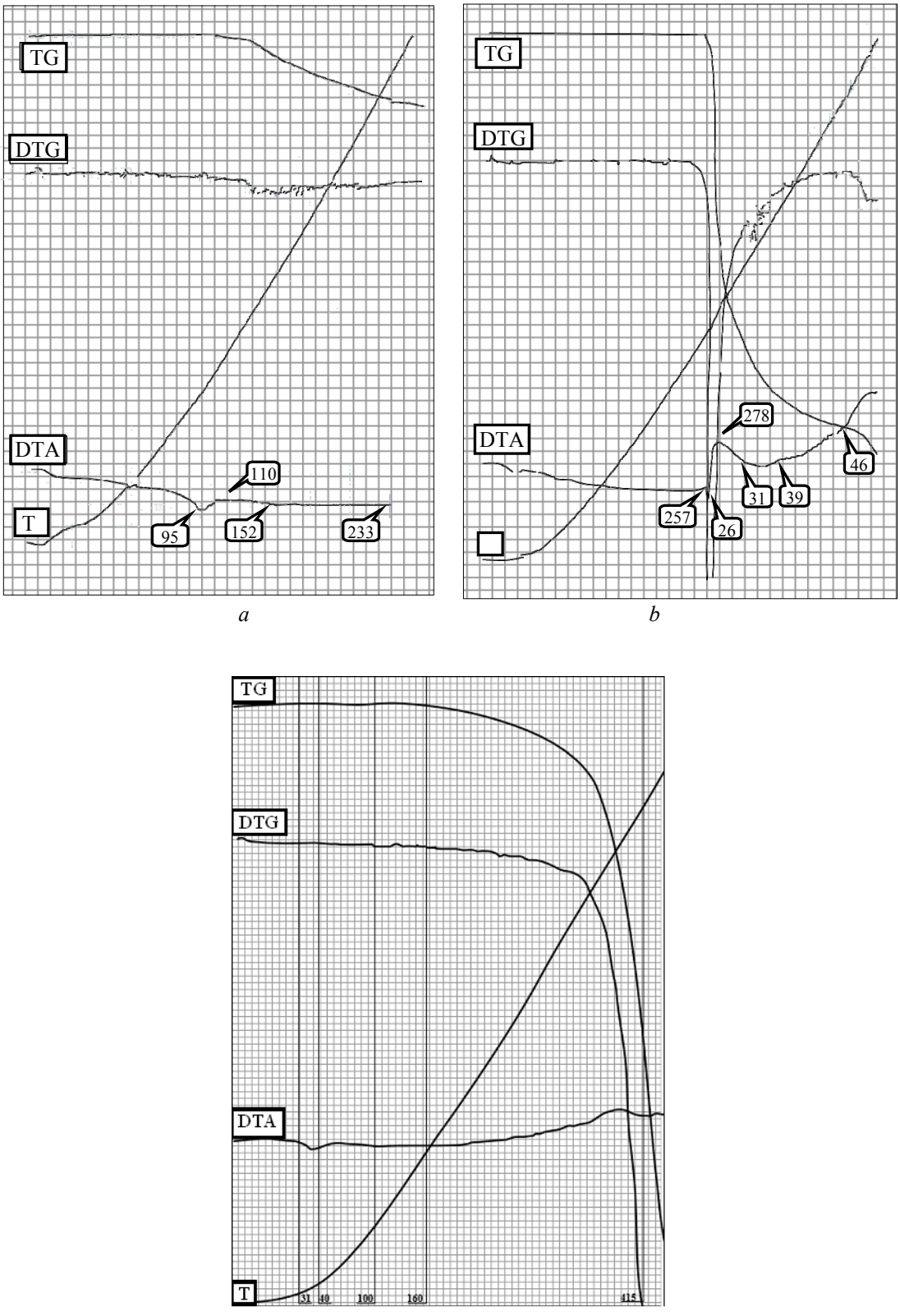


Fig. 3. Thermogram: *a* – indole-3-carbinol substance; *b* – meloxicam substance; *c* – suppositories under the conditional name "Indoxam"

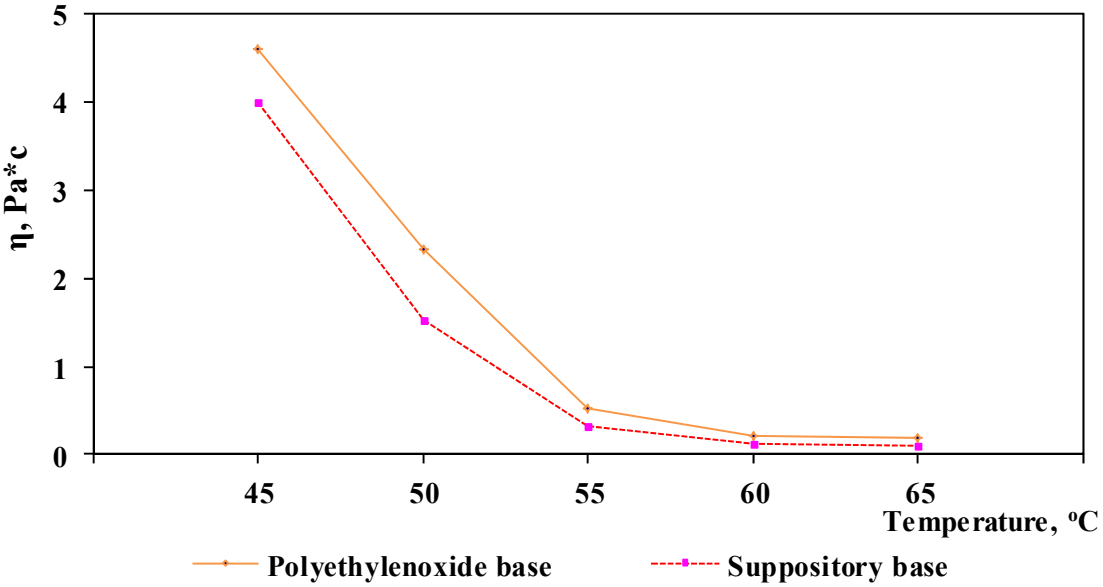


Fig. 4. The dependence of the structural viscosity of the polyethylene oxide base and the suppository mass on temperature at a gradient of shear rate of 27 s^{-1}

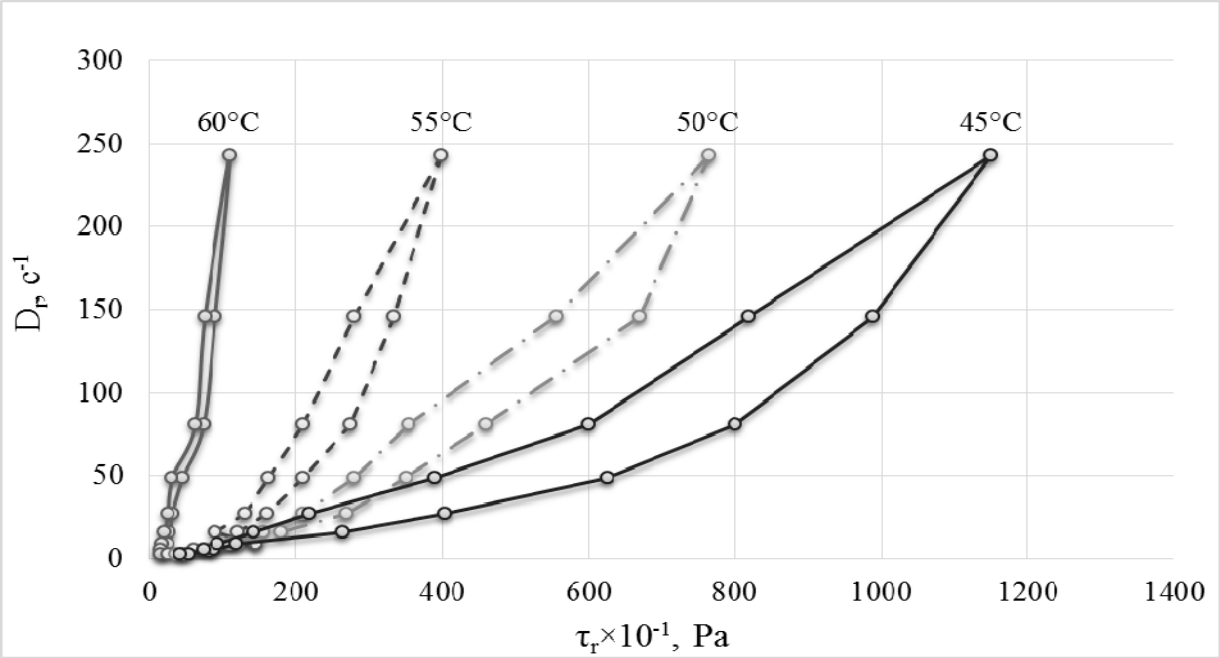


Fig. 5. Rheograms of the flow of combined suppositories at different temperatures

The results of studies (Fig. 5) indicate the non-Newtonian type of the flow of the suppository system. On rheograms, ascending and downward curves form hysteresis loops, the presence and area of which testify to the thixotropy of the sample. At a temperature of 60 °C, the suppository mass has a very low viscosity, which will accelerate the sedimentation of API particles during the production of suppositories. At a temperature of 45 °C, a mass with very high values of structural viscosity is formed, as indicated by a large area of the hysteresis loop, and this can lead to some difficulties in dosing. The temperature range of 50–55 °C is the most optimal, since at these temperatures the system is in the form of a sol-gel having the optimal fluidity and will ensure the production of a homogeneous suppository mass, its passage through the pipeline and the dosage in the primary packaging.

7. Conclusions from the conducted research and prospects for further development of this field

Based on the physico-chemical and pharmaco-technological investigations of the properties of combined rectal suppositories with indole-3-carbinol and meloxicam, a quantitative correlation of polyethylene oxide base and optimal conditions for conducting the technological process of their production is established.

1. Expansion of the pharmaceutical market at the expense of domestic herbal remedies, in particular for the treatment of diseases of the prostate gland, is relevant for domestic pharmaceutical science and practice.

2. Based on the pharmaco-technological studies, the optimal correlation of the polyethylene oxide base in suppositories, namely, PEO-1500 : PEO-400 – 95:5, was substantiated.

3. Thermogravimetric analysis shows the thermal stability of the investigated APIs at the temperature limits of the melting of the suppository bases and the absence of chemical interaction between the components in the rectal drug.

4. The rheological properties of developed suppositories were investigated and their non-Newtonian type of flow and thixotropy were established. The optimum temperature range of suppository pouring was determined – 50–55 °C, which allowed to obtain a high quality homogeneity of the preparation.

5. The prospect of further work is the development of a rational technology for the manufacture of suppositories under the conventional name "Indoxam" and its testing in industrial conditions.

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Volodymyr Zaychenko, Postgraduate Student, Department of Industrial Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: schweppes159753@gmail.com

Olena Ruban, Doctor of Pharmacy, Professor, Head of Department, Department of Industrial Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: ruban_elen@ukr.net

Yuliia Maslii, PhD, Associate Professor, Department of Industrial Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: julia.masliy@gmail.com

Natalia Gerbina, PhD, Associate Professor, Department of Industrial Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: n.a.gerbina@gmail.com