1. Introduction

One of the most common diseases in the adult population is proctological, including haemorrhoids. The frequency of its occurrence in the structure of coloproctological diseases ranges from 34% to 41% [1]. Almost every second patient with haemorrhoids consults a doctor because of pain in the anus caused by acute thrombosis of external hemorrhoidal nodes [2].

Pharmacotherapy of haemorrhoids is primarily aimed at eliminating the symptoms characteristic of the acute course of this disease: bleeding, discomfort, itching, pain and burning in the anus. Complex treatment consists of topical and systemic therapy [3]. Topical agents play an important role in treating acute and chronic haemorrhoids. Preparations in the form of ointments, emulsions and rectal suppositories are widely available on the pharmaceutical market [4, 5]. Such drugs often contain analgesic, anti-inflammatory, thrombolytic and hemostatic agents and enzymes. However, in the pathogenesis of haemorrhoids, the vascular theory prevails. Therefore, the basis of systemic pharmacotherapy consists of drugs that improve microcirculation in the system of hemorrhoidal vessels [6, 7]. For this reason, phlebo- and lymphotropic drugs are widely and effectively used to treat acute haemorrhoids. These include troxerutin, diosmin, tribenoside, escin, detralex, endothelon, and venophlebin, which, among other active pharmaceutical ingredients, contain biologically active substances of flavonoid nature [8, 9].

Flavonoids are one of the most diverse and widespread groups of phenolic compounds. More than 8,000 flavonoids are known today. They are widely distributed in the plant world and are characterised by an exceptional diversity of species. In the therapy of proctological diseases, this group of compounds is mainly used as P vitamins and capillary-strengthening agents. Rutin is one of the most well-known and well-studied flavonoids with high...
phlebotropic activity. It was first isolated from Ruta (Ruta graveolens) and later found in many other plants. It, like other flavonoids, increases the elasticity of blood vessels, has antitumor and anti-radiation effects, is non-toxic, does not cause side effects, and is also one of the most powerful antioxidant agents and is known as vitamin P. According to the literature, more than 130 medicinal products contain rutin in their composition. Preparations based on it have been used for treating chronic venous insufficiency, lymphedema, and haemorrhoids for several decades. Rutin, along with its capillary protective effect, has anti-inflammatory, antioxidant and anti-mutagenic properties. It enhances the vasoconstrictive effect of adrenaline and norepinephrine on the venous wall, increases venous tone, reduces venous and lymphatic stasis, prevents the formation of sclerotic plaques, improves the elasticity of venous and lymphatic vessels, and has an antiplatelet effect [10].

The criterion for assessing the degree of influence of individual or sum pharmaceutical factors on the drug’s therapeutic activity is the drug’s testomological availability, which is inherent in herbal drugs [11].

Medicinal plant raw materials play a significant role in health care today, and the specific weight of herbal preparations in the arsenal of medicines is very large. Scientific research in the field of creating medicines with plant substances is constantly being conducted. Special attention is drawn to already-known, widely used plants [12].

The common garden carrot (D. c. subsp. sativus) is a two-year herbaceous plant of the Apioaceae family, grown throughout Ukraine as a vegetable and fodder crop [13, 14].

Carrot roots are used not only as a food product but also as a valuable therapeutic agent. As a source of carotene, raw carrots or fresh carrot juice are prescribed to patients with hypo- and avitaminosis A, pregnant and lactating women, people whose profession involves eye strain, myocardial infarction, with conjunctivitis, keratitis, blepharitis, hemeralopia and retinal fatigue; as a mild laxative is used for chronic constipation and haemorrhoids; as a diuretic – in kidney diseases [15–17].

For the local treatment of proctological diseases, preparations in gels, ointments and creams are widely used, which are highly bioavailable and convenient to use [18].

Thus, the aim of the research was to study the influence of the composition of excipients on the biopharmaceutical parameters and pharmacological activity of a soft medicine for the treatment of haemorrhoids.

2. Planning (methodology) of research

The study of a complex rectal remedy based on plant components has a significant number of critical stages. Therefore, in our work, we focused on the study of pharmacological, biopharmaceutical and technological parameters and determining the relationship between them. Pharmacological, technological and analytical research methods were used to directly or indirectly analyse the strength and completeness of the drug. Thus, in this work, we combined the study of the specificity of the drug’s pharmacological action, the analysis of the structural and mechanical properties of the drug, and the study of the release profile of active pharmaceutical ingredients.

3. Material and methods

Rutin (rutoside trihydrate, manufactured by Sichuan Seli Pharmaceutical Co., Ltd., China) and carrot extract were used as APIs. Carrot seed root thick extract was obtained by Professor Zhuravel Iryna O. at the NUPh at the Department of Chemistry of Natural Compounds and Nutriciology under Professor Kyslychenko Viktoriaia S. The extract was obtained by the fractional maceration method. As an extractant, 80 % ethanol was chosen, the degree of grinding of raw materials is 2–3 mm, and the ratio of raw materials to extractant is 1:5. Crushed raw materials were poured with 1/3 of the calculated volume of the extractant and insisted in a water bath at a temperature of 60–65 °C for 2 hours, the hood was drained, and the extraction was repeated two more times. After combining the extracts obtained was filtered and concentrated in a rotary evaporator.

The quantitative content of polyphenolic compounds in terms of gallic acid (15.28±0.61 %), hydroxycinnamic acids in terms of chlorogenic acid (7.30±0.29 %), flavonoids in terms of luteolin (1.93±0.09 %), substances of a steroid nature (0.57±0.03 %) were determined by the spectrophotometric method in the extract.

The production of samples of soft medicine, the composition of which is given in Table 1, was carried out in laboratory conditions. Emulgel samples were obtained at the following stages: preparation of raw materials, preparation of API concentrate and preservatives, preparation of the base, and preparation of emulgel.

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Carrot extract</th>
<th>Rutin</th>
<th>Aristofflex</th>
<th>Nipagin</th>
<th>Nipazolo</th>
<th>Tween 80</th>
<th>Glycerol</th>
<th>Carbopol</th>
<th>Ethanol</th>
<th>Cetostearyl alcohol</th>
<th>Stearic acid</th>
<th>PEO-400</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>2</td>
<td>1.5</td>
<td>0.0015</td>
<td>0.005</td>
<td>0.05</td>
<td>0.4</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>2</td>
<td>0.0015</td>
<td>0.0015</td>
<td>0.005</td>
<td>0.05</td>
<td>0.4</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>2</td>
<td>0.0015</td>
<td>0.0015</td>
<td>0.005</td>
<td>0.05</td>
<td>0.4</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
<td>0.0015</td>
<td>0.0015</td>
<td>0.005</td>
<td>0.05</td>
<td>0.4</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>4.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

3. 1. Quantitative determination of active substances by spectrophotometric method

Since the dosage form is planned to be administered rectally, a buffer solution with a pH of 6.8, corresponding to the rectal mucosa’s pH, was chosen as the dissolution medium.
To prepare a solution of a standard sample of rutin, 0.05 g of rutin was placed in a volumetric flask with a capacity of 50 ml, 35 ml of 96 % ethyl alcohol was added, stirred until dissolved, brought up to the mark with the same solvent and thoroughly mixed again (solution A of a standard sample of rutin). 1 ml of solution A was placed in a volumetric flask with a capacity of 100 ml, brought up to the mark with a phosphate buffer solution with a pH of 6.8 and thoroughly mixed. The absorption spectrum of the obtained solution from 220 to 400 nm was recorded on an Evolution 60 S spectrophotometer in cuvettes with a layer thickness of 10 mm; a phosphate buffer solution with a pH of 6.8 was used as a control solution.

3. 2. The release profile of active pharmaceutical ingredients

The release of rutin was studied by the method of equilibrium dialysis through a semipermeable membrane. The dialyser is a device consisting of a dialysis chamber and an internal container. The bottom is a semipermeable membrane («Cuprophan»: thickness=11.5±0.5 μm; molecular weight cutoff=20 kDa, type=150 pm; area =2000 mm²).

The optical density of the obtained solutions was determined on a spectrophotometer at a wavelength of 352 nm in a cuvette with a layer thickness of 1 cm. A phosphate buffer solution with a pH of 6.8 was used as a control solution.

The concentration of the obtained solutions as a result of dialysis (g/ml) was determined according to the graduated graph or calculated using the data of the optical densities of the standard solutions obtained during the construction of the graduated graph

\[
\frac{A}{A_n} = \frac{C}{C_n},
\]

where of

\[
C = \frac{A \cdot C_n \cdot b}{A_n},
\]

where in \(A\) – optical density of the investigated solution; 
\(A_n\) – optical density of the standard solution; 
\(C_n\) – concentration of standard solution g/ml; 
\(b\) – the dilution factor.

When calculating the total amount of rutin that went into the solution, the amount contained in the samples taken earlier was considered:

\[
X_{n+1} = C_n \cdot V_p + \frac{X_n - 1}{V_p} \cdot V_a,
\]

where in \(X_0\) – the total amount of the substance that went into the solution in \(n\) hours of the experiment; 
\(C\) – the concentration of the substance in the dialysate after \(n\) hours of the experiment, g/ml;  
\(V_p\) – the total volume of the solution in the dialysis chamber, ml;  
\(X_{n+1}\) – the total amount of the substance that went into the solution in \(n+1\) hours of the experiment;  
\(V_a\) – the volume of the aliquot selected for analysis, ml.

3. 3. Research of technological parameters

Rheological studies were performed on a rotary viscometer MYR-3000 with coaxial cylinders. Organoleptic indicators, colloid stability, and pH were determined according to the methods of the State Pharmacopoeia of Ukraine, II edition [19, 20]

3. 4. Research of the pharmacological activity of active pharmaceutical ingredients

The study was performed on outbred sexually mature rats kept in the vivarium of the Educational and Scientific Training Center for Medical and Biological Research of the National University of Pharmacy. The animals were kept in a separate room with controlled microclimate parameters: air temperature 18–22 °C, relative humidity 50–65 %, light mode «12 hours day/night», in plastic cages with individual ventilation [21]. Sterilisation of the laboratory room with the help of a UV lamp was carried out daily. The animals had free access to water (pre-settled tap water from drinking fountains). Granulated balanced feed (TU.U15.7-2123600159-001:2007) was used for animal feeding. Animal care was carried out following standard operating procedures of the Educational and Scientific Training Center for Medical and Biological Research of the National University of Pharmacy. All stages of the research were conducted following Directive 2010/63/EU of the European Parliament and the Council of the EU dated September 22, 2010 «On the protection of animals used for scientific purposes» (Protocol of the Bioethics Commission No. 2021).

Before the experiment, the animals were acclimatised for 7 days. During the acclimatisation period, each animal was examined daily (behaviour and general physical condition were evaluated), and animals were observed for possible causes of morbidity or mortality.

The wound-healing activity of the new objects was studied on the model of a full-layered incision wound. The study was conducted on 24 rats weighing 200–240 g, aged 3–3.5 months.

Plane wounds were reproduced on a pre-depilated area of skin in anaesthetised animals (thiopental, 40 mg/kg); for this, the skin was excised using surgical scissors, tweezers and a stencil. As part of the humane treatment of animals, in our experiment, stencil wounds were made with a size of 1×1 cm² (100 mm²).

The skin and tools were treated with a 96 % solution of ethyl alcohol. After surgical intervention, the wound was treated with a 3 % hydrogen peroxide solution. On the second day after modelling stencil wounds, the animals were randomised into groups according to the wound area size, and treatment began. 4 groups of animals were used: positive control (PC), comparative drug «Hemorol» (RZ), a sample of a medicinal product
Animals were observed until complete scarring of the wound. After reaching a steady temperature of 37.7–38.0 °C, the damaged area was treated with a sample of the medicinal product (erect cinquefoil rhizomes, cytisus grass, deadly nightshade grass, chamomile flowers, horse chestnut bark, benzocaine, common yarrow grass) [22]. The reference sample (suppository mass melted in a water bath at 37.7–38.0 °C) was applied to the damaged area.

The main indicators of verification of the expressiveness of the wound-healing effect of the drugs were changes in the area of the wound (S, mm²), the rate of healing and the percentage of rats with healed wounds in comparison with the control group. The effectiveness of the drugs was studied dynamically – on 1, 4, 7, 10 and every subsequent day of treatment until complete healing. Animals were observed until complete scarring of the wounds. The nature of wound healing was assessed by the presence of oedema and hyperemia in dynamics. The area was measured according to the method of Popova LN, applying transparent stencilled millimetre paper to the wound and calculating the wound area (in mm²). The quantitative percentage of animals with complete epithelisation of the wound on the current measurement day was calculated.

### 3.5. Statistical processing of results

The results were expressed as arithmetic mean (M) and standard error of the mean (SEM). Comparisons between the studied groups were performed using non-parametric methods of analysis (Mann-Whitney U-test) and alternative methods (Fisher’s angular transformation φ). The probability of differences was determined at the significance level of P<0.05. Statistical processing was carried out using the basic package of MS Excel 2007 and IBM SPSS Statistics 22.

### 4. Results

All samples were checked for organoleptic indicators, colloidal stability (time – 5 min, rpm – 1000⁻¹), and pH value immediately after production and on the 7th and 21st day of storage (Table 2).

As can be seen from the data given in Table 2, all samples were stable during 21 days of storage; in sample No. 3, the degree of density increased as the temperature increased.

According to the data of rheological studies (Fig. 1, 2), which were carried out at room temperature (19±1 °C) and the temperature of the physiological environment (37±1 °C), it was established that all systems are thixotropic, but the recovery time of the systems is different, which is related to the physical and chemical properties of the auxiliary substances that form the basis of the samples. Samples No. 1, 2 and No. 4 had almost the same rheological behaviour at different temperature regimes. The structural and mechanical parameters of sample No. 3 differed greatly depending on the temperature, which is explained by the presence of proxanol-188 in the composition of its base.

### Table 2

<table>
<thead>
<tr>
<th>Sample</th>
<th>External appearance</th>
<th>pH</th>
<th>Colloidal and thermal stability (37±1 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Transparent light brown mass with a specific smell, with satisfactory mucoadhesive characteristics</td>
<td>7.8±0.3</td>
<td>Stable</td>
</tr>
<tr>
<td>2</td>
<td>Thick opaque light brown mass with a specific smell, sticky, with satisfactory mucoadhesive characteristics</td>
<td>7.6±0.2</td>
<td>Stable</td>
</tr>
<tr>
<td>3</td>
<td>Liquid at room temperature brown mass with a specific smell</td>
<td>7.6±0.2</td>
<td>Stable</td>
</tr>
<tr>
<td>4</td>
<td>Thick opaque light brown mass with a specific smell, sticky, with satisfactory mucoadhesive characteristics</td>
<td>7.7±0.1</td>
<td>Stable</td>
</tr>
</tbody>
</table>

In order to establish the kinetics of the release of flavonoids from the samples of the medicinal product for the treatment of haemorrhoids, at the first stage of the work, the method of determining the number of flavonoids in terms of rutin was tested in pH conditions close to physiological ones (Fig. 3).

As can be seen from the data (Fig. 3), the absorption spectrum of a solution of rutin in a phosphate buffer solution with a pH of 6.8 has a complex character. In the region of 250–270 nm, there is an integrated absorption band, which has a broad maximum at 255–257 nm and a plateau at 261–265 nm. It can be assumed that it corresponds to the sum of absorptions of several bands of aromatic radicals of rutin.

The maximum at 256 nm is broad and convenient but cannot be recommended for quantitative determination, as it is located in an insufficiently specific region and may be superimposed by the residual absorption of the base components of the soft dosage form.

At the limit of absorption of ultraviolet and visible light in the spectrum of rutin, there is another, the slightly less intense but wide and sloping band with a maximum of 352 nm. In this area, the vast majority of substances that are included in the bases of soft medicines are no longer absorbed and will not interfere with the determination of rutin. Therefore, we had chosen the maximum at 352 nm as the analytical absorption band when quantifying the concentration of rutin in the dialysates obtained during the study of the bioavailability of API in the composition of the new dosage form.
The next stage was the determination of the subordination of light absorption of solutions of the investigated substance to the Bouguer-Lambert-Beer law, which is the main condition for using the method of absorption spectroscopy. On the basis of the conducted data, a linear dependence was established on the entire area of the investigated concentrations from $0.4 \cdot 10^{-3}$ to $4.0 \cdot 10^{-3}$ %.

We studied the absorption spectra of the dialysates obtained after 4 hours of the experiment in order to check whether the base components of the drug samples and the thick extract of carrot roots do not interfere with the determination of rutin in dialysates with pH 6.8 by the absorption spectrophotometry method at a wavelength of 352 nm (Fig. 4).
Dialysates of samples 1, 2, and 4 were diluted at 1:10; the dialysate spectrum of sample 3 is presented without dilution. For comparison, Fig. 2 also shows the spectrum of a solution of rutin in a phosphate buffer solution with a pH of 6.8.

Analysis of the spectra in Fig. 2 shows that in the aromatic region, the spectra of samples 1 and 4 practically do not differ from the spectra of rutin. The spectrum of sample 2 gives a bathochromic shift of the absorption band. Thus, its maximum is located at 268 nm. The absorption band in visible light is best expressed in the dialysate spectrum of sample 4; it practically repeats the band in the rutin’s spectrum. Absorption bands on the spectra of other samples become inclined and less pronounced, apparently due to the flavonoid components of the thick extract of carrot roots. Since the absorption band in the spectrum of rutin with a maximum at 352 nm is characteristic of substances of a flavonoid nature, we can talk about the determination of the number of flavonoids in the dialysates in terms of rutin.

Thus, the performed spectral analysis of dialysate solutions of experimental samples of a soft medicinal product indicates the possibility of quantitative determination of the number of flavonoids in dialysates in terms of rutin. The obtained results are presented in Table 3 and Fig. 5.

According to the results of the research, graphs of the dependence of the number of flavonoids that passed into the solution at the time of the experiment were drawn (Fig. 5), which characterise the dynamics of the process.

Analysis of the data obtained from the study of the release of flavonoids in terms of rutin from experimental samples into phosphate buffer solution by dialysis through a semipermeable membrane shows that the most effective release is provided by the excipients used in the preparation of sample 4. This sample showed an effective uniform dynamic release during 3 hours, with practical access to the plateau during the fourth hour.

Table 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C \times 10^{-3}$, g/ml</td>
<td>$\lambda \times 10^{-3}$, g</td>
<td>$C \times 10^{-3}$, g</td>
<td>$\lambda \times 10^{-3}$, g</td>
</tr>
<tr>
<td>1</td>
<td>0.0738</td>
<td>3.690</td>
<td>0.00504</td>
<td>0.2518</td>
</tr>
<tr>
<td>2</td>
<td>0.0752</td>
<td>4.129</td>
<td>0.00597</td>
<td>0.3236</td>
</tr>
<tr>
<td>3</td>
<td>0.0779</td>
<td>4.308</td>
<td>0.02046</td>
<td>1.0553</td>
</tr>
<tr>
<td>4</td>
<td>0.0873</td>
<td>4.798</td>
<td>0.000734</td>
<td>4.472</td>
</tr>
</tbody>
</table>

So, on the basis of the conducted biopharmaceutical, and physico-chemical studies, No. 4 was chosen as the priority sample.

When conducting a pharmacological study of samples made on the basis of No. 4, a day after the reproduction of stencil wounds, the animals were randomised into groups according to the minimisation of the area of the wound defect, which was within 98–112 mm² of individual values. The wound healing process is always accompanied by a natural inflammatory reaction (hyperemia and oedema), which is normally observed for several days. Hyperemia and oedema were observed in all animals in the experimental groups. Macroscopic signs of inflammation gradually decreased over time, and further epithelisation of the wound was observed. Visual signs of joining the infectious process were not observed in any operated animal. Complete healing of stencil wounds in all animals in the positive control group was observed on the 20th day of the study.

In animals treated with experimental samples, the severity of clinical signs of the inflammatory process was less, and the time required for complete healing was significantly reduced. A significant decrease in the area of the wound surface was observed already on the
fourth day of the study in each of the studied groups, a decrease in hyperemia and oedema was noted, and no active discharge of exudate was observed. The animals were active and had a satisfactory appetite. The analysis of planimetric parameters (Table 4) showed that on the 4th day of treatment, the wound area decreased by 21.46% in the group of animals treated with the «Hemorol» suppository mass, and by 18.53% in the group treated with carrot extract cream, in the group where cream with carrot extract and rutin was used – by 23.93% (Table 1). In all studied groups, the area of the wound was probably smaller than the similar indicator in the positive control group.

On the seventh day of observation, the expressiveness of reparation increased, which was evidenced by a decrease in the area of the wound surface in the comparison drug group by 32.75%, in the TZ group by 30.03%, and in the TZ+R group by 38.67% (Table 1). The average values of the wound surface in the indicated groups were statistically lower than the similar indicator in the PC group (p<0.05), the average value was only 18.61% on the seventh-day scarring.

On the tenth day of the study, the tendency to increase the speed of healing was maintained in the studied groups, and the average area of the wound was significantly smaller than in the PC group (p<0.05). At the same time, against the background of the use of the reference agent, healing was 40.86% of the initial area, and under the conditions of using the test samples, it was 42.01% and 51.03% in the TZ and TZ+R groups, respectively (Table 4). A similar picture with gradual epithelisation of the wounds in the experimental groups, which took place much faster than in the PC group, was also observed during the following days of the experiment.

The first animals with complete epithelisation of the wound were observed on the 13th day, in the group where cream with carrot extract and rutin was used; the number of animals with a completely healed wound probably exceeded those in all other groups of animals (p<0.05), which indicates higher speed reparations in this group. On the 14th day of the study, the number of animals with a repaired wound probably exceeded the similar indicator in the PC and RZ groups. Achieving complete epithelisation in 100% of animals also occurred in the TZ+R group faster than in the others, namely on the 17th day of the study. There are in the background of the application (Table 4). Complete epithelisation in all animals in the RZ and TZ groups was noted on the 18th day.

Table 4

<table>
<thead>
<tr>
<th>The day of the experiment</th>
<th>Indicators</th>
<th>Positive control</th>
<th>Suppositories «Hemorol»</th>
<th>TZ</th>
<th>TZ+R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day (source data)</td>
<td>S, mm²</td>
<td>105.667±2.108</td>
<td>104.833±1.740</td>
<td>104.333±1.430</td>
<td>105.167±1.641</td>
</tr>
<tr>
<td>4th day</td>
<td>S, mm²</td>
<td>93.833±1.887</td>
<td>82.333±1.764</td>
<td>85.000±2.098*</td>
<td>80.000±2.556*</td>
</tr>
<tr>
<td>7th day</td>
<td>S, mm²</td>
<td>86.000±1.949</td>
<td>70.500±1.708</td>
<td>73.000±2.989*</td>
<td>64.500±3.775*</td>
</tr>
<tr>
<td>10th day</td>
<td>S, mm²</td>
<td>78.167±2.414</td>
<td>62.000±2.633</td>
<td>60.500±4.217*</td>
<td>51.500±5.156*</td>
</tr>
<tr>
<td>11th day</td>
<td>S, mm²</td>
<td>68.500±3.713</td>
<td>51.667±2.275</td>
<td>47.167±4.468*</td>
<td>39.833±5.498*</td>
</tr>
<tr>
<td>12th day</td>
<td>S, mm²</td>
<td>60.833±4.498</td>
<td>39.833±3.250</td>
<td>34.667±5.031*</td>
<td>27.333±7.868*</td>
</tr>
<tr>
<td>13th day</td>
<td>S, mm²</td>
<td>53.167±4.331</td>
<td>27.167±3.535</td>
<td>22.333±5.743*</td>
<td>15.667±6.702*</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>2/6***</td>
<td>2/6***</td>
</tr>
<tr>
<td>14th day</td>
<td>S, mm²</td>
<td>44.667±4.372</td>
<td>16.667±4.224</td>
<td>11.833±5.244*</td>
<td>9.000±4.719*</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>0/6</td>
<td>0/6</td>
<td>1/6</td>
<td>3/6***</td>
<td>3/6***</td>
</tr>
<tr>
<td>15th day</td>
<td>S, mm²</td>
<td>35.167±3.410</td>
<td>6.667±4.349</td>
<td>6.000±4.590*</td>
<td>3.667±2.940*</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>0/6</td>
<td>2/6*</td>
<td>4/6*</td>
<td>4/6*</td>
<td>4/6*</td>
</tr>
<tr>
<td>16th day</td>
<td>S, mm²</td>
<td>24.000±2.898</td>
<td>3.333±3.333</td>
<td>2.000±2.000*</td>
<td>1.000±1.000*</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>0/6</td>
<td>5/6*</td>
<td>5/6*</td>
<td>5/6*</td>
<td>5/6*</td>
</tr>
<tr>
<td>17th day</td>
<td>S, mm²</td>
<td>12.333±3.263</td>
<td>1.333±1.333</td>
<td>0.333±0.333*</td>
<td>0.000±0.000*</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>0/6</td>
<td>5/6*</td>
<td>5/6*</td>
<td>6/6*</td>
<td>6/6*</td>
</tr>
<tr>
<td>18th day</td>
<td>S, mm²</td>
<td>4.667±1.856</td>
<td>0.000±0.000</td>
<td>0.000±0.000*</td>
<td>–</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>2/6</td>
<td>6/6*</td>
<td>6/6*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>19th day</td>
<td>S, mm²</td>
<td>0.667±0.667</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>n animals with scars</td>
<td>5/6</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>20th day</td>
<td>S, mm²</td>
<td>0.000±0.000</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>n animals with scars</td>
<td>6/6</td>
<td>–</td>
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</tr>
</tbody>
</table>

Note: * – differences are probable relative to the group of positive control PC (p<0.05); * – differences are probable relative to the group of the comparison drug RZ (p<0.05); # – differences are likely relative to the group of the test sample of the TZ (p<0.05).
5. Discussion
The disadvantage of research is the implementation of pharmacological studies on animals.
Availability of alternative methods. In recent years, several alternative methods have emerged that do not require the use of animals, such as in vitro studies, computer simulations, and human-based studies. These methods are often more reliable, cost-effective, and ethical than animal studies.

The advantage of this study is the development of a medicinal product for the treatment of hemmorhoids with a thick carrot extract. The study of carrot (Daucus carota L. var. sativus) and the development of an antimicrobial agent with it was carried out by Prof. Zhuravel I., prof. Kyslychenko A., Horiacha L. But there were no studies on the development of a drug for the treatment of hemmorhoids and establishing its specific activity [14, 23].

The obtained results are the basis for further research on the development of a rectal medicine for the treatment of hemmorhoids with a thick carrot extract.

Research limitations. The term drug release refers to the processes by which drug molecules are transferred from their initial position in a drug delivery system to the outer surface and, in turn, as solutes, into the release medium. It is (or it can be) a complex phenomenon, which depending on the delivery system, can comprise one or (usually) more of the following processes: drug diffusion, drug dissolution, and/or drug partitioning, as well as osmosis, swelling, erosion, disintegration, and/or degradation of the delivery system.

Prospects for further research. The obtained research results are the basis for further pharmaceutical development of a mild medicinal product with thick carrot extract and rutin.

6. Conclusion
The physicochemical and biopharmaceutical parameters of samples of the drug for the treatment of haemorrhoids with various excipients were studied. According to the results of rheological studies, it was established that all samples are thixotropic, but samples No. 3 and No. 4 have satisfactory structural and mechanical indicators.

The absorption spectrum of a solution of rutin in a phosphate buffer solution with a pH of 6.8, which corresponds to the pH of the rectal mucosa, was studied. It was established that in the range from 220 to 400 nm in the absorption spectrum of rutin, there is a wide, sufficiently intense inclined absorption band with a maximum of 352 nm, which can be used as an analytical absorption band to determine the concentration of rutin solutions.

The analysis of the data obtained as a result of the study of the release of rutin from samples with different compositions into a phosphate buffer solution by dialysis through a semipermeable membrane shows that the most effective release is provided by the excipients used in the preparation of sample 4.

To sum up, the obtained data of positive dynamics of planimetric indicators on the model of stencil wounds in rats demonstrated the presence of wound healing effect in both the studied samples and the reference agent. However, the use of sample No. 4 in the treatment of a stencil wound promotes faster healing, which in clinical use can contribute to reducing the risk of infection, the spread of infection, and reducing the area of the wound defect.

Taking into account the above, sample No. 4 was selected for further research on the development of the composition of the drug for the treatment of proctological diseases.

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.

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Data availability
Data will be made available on reasonable request.

References

Fig. 5. Graph of the dependence of the number of flavonoids transferred to the dialysate in terms of rutin on the dialysis time
Values on the Rheological, Textural and Release Properties of Carbomer Polacril® 40P-Based Dental Gel Formulation with Plant-De-