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The study of the physicochemical properties of rectal cream samples with the carrot extract and rutin

The modern arsenal of drugs aimed at eliminating pathological processes of the anorectal zone, as a rule, consists of suppositories and soft drugs. When using suppositories, hemorrhoidal nodes may be injured, uneven distribution of the drug along the walls of the anal canal may be observed. In addition, with external and combined hemorrhoids, there is a need to apply the drug not only to the walls of the anal canal, but also to the perianal skin. Therefore, preference is given to the use of soft drugs since the process of their introduction is as easy as possible. Today, the pharmaceutical market of Ukraine has a wide range of products for the treatment of diseases of the anorectal zone, but the constant increase in the number of patients indicates that this problem has not been solved. Therefore, the study on the creation of a new rectal soft medicine that will have a complex effect on pathological processes and expand the range of domestic drugs for use in proctology is relevant.

Aim. To substantiate the type of base for a soft rectal medicine by studying the organoleptic and physicochemical properties of the experimental samples.

Materials and methods. The study objects were samples of a soft dosage form of various compositions and the reference drug "Procto-Glivenol Cream" (VAMPHARMA S.R.L., Italy). Samples on different carrier bases were examined by their organoleptic and textural properties; their colloidal and thermal stability, viscosity and pH were studied.

Results and discussion. It has been found that the use of a sample on a gel base with Aristoflex does not ensure the presence of an optimal adhesive layer between the mucous membrane of the anorectal zone and the dispersion medium of the drug. The proxanol-188 sample does not have satisfactory thermal and colloidal stability indicators. The use of an emulsion base provides the necessary ability to spread over the surface, adhesion and cohesion.

Conclusions. Therefore, for further research, it is advisable to use a sample of the rectal cream, which is an emulsion system.

Keywords: *thick carrot extract; rutin; technology; excipients; proctological diseases*

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Дослідження фізико-хімічних властивостей зразків крему ректального з екстрактом моркви посівної та рутином

Сучасний арсенал лікарських препаратів, спрямованих на усунення патологічних процесів аноректальної зони, як правило, складається із супозиторіїв та м'яких лікарських засобів. За використання супозиторіїв може відбуватися травмування гемороїдальних вузлів, нерівномірний розподіл препарату по стінках анального каналу. До того ж, за зовнішнього і комбінованого геморою виникає необхідність нанесення лікарського засобу не тільки на стінки анального каналу, але й на перианальну шкіру. Тому віддають перевагу застосуванню м'яких лікарських засобів, адже процес їх введення максимально полегшений. На сьогодні на фармацевтичному ринку України наявний широкий спектр засобів для лікування захворювань аноректальної зони, але постійне зростання кількості хворих свідчить про невирішеність цієї проблеми. Тому актуальними є дослідження зі створення нового ректального м'якого лікарського засобу, що матиме комплексний вплив на патологічні процеси та розширить спектр вітчизняних препаратів для застосування у проктології.

Метою роботи було обґрунтування типу основи м'якого ректального лікарського засобу шляхом дослідження органолептичних та фізико-хімічних властивостей дослідних зразків.

Матеріали та методи. Об'єктами дослідження стали зразки м'якої лікарської форми різного складу та препарат порівняння «Прокто-глівенол крем» (ВАМФАРМА С.Р.Л., Італія). Досліджено зразки на різних основах-носіях за органолептичними, текстурними властивостями, вивчено їхню колоїдну та термічну стабільність, в'язкість та рН.

Результати та їх обговорення. З'ясовано, що використання зразка на гелевій основі з аристофлексом не забезпечує наявності оптимального адгезійного шару між слизовою оболонкою аноректальної зони та дисперсійним середовищем лікарського препарату. Зразок на основі проксанолу-188 не має задовільних показників термічної та колоїдної стабільності. Використання емульсійної основи забезпечує необхідну здатність до розподілу поверхню, адгезію та коагезію.

Висновок. Отже, для подальших досліджень доцільно використовувати зразок крему ректального, що становить собою емульсійну систему.

Ключові слова: *екстракт моркви посівної густий; рутин; технологія; допоміжні речовини; проктологічні захворювання*

Introduction. The development of new highly effective drugs for the treatment of proctological diseases remains an important problem of modern medicine due to the prevalence of these diseases and the limitation of domestic drugs that would have high bioavailability, act on the affected target tissues of the rectum, providing a complex effect on the pathological process [1]. In addition, based on the studies of the domestic pharmaceutical market conducted, it has been found that, despite the constant development of the proctological drug market, its structure remains to be import-dependent [2]. An important place is occupied by rectal ointments containing natural active pharmaceutical ingredients with a wide spectrum of biological activity [3].

Medicinal tactics intended for the treatment of proctological diseases consist in the use of the systemic therapy together with the surgical and local treatment. The local therapy involves the use of drugs in various dosage forms containing analgesic, antiseptic, anti-inflammatory, hemostatic and capillary-stabilizing active pharmaceutical ingredients (API). An important place is occupied by rectal ointments containing natural active pharmaceutical ingredients with a wide spectrum of biological activity [3].

The extract of carrot and rutin were chosen as active pharmaceutical ingredients in the composition of the drug under development. The pharmacological studies have demonstrated a moderate anti-inflammatory, anti-exudative, membrane-protective and antioxidant activity of the carrot extract. It has been found that it has moderate antimicrobial properties and inhibits the growth of *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Candida albicans* [4]. Rutin reduces the permeability and fragility of capillaries, strengthens the cell wall, reduces the aggregation of platelets, has the anti-inflammatory effect (including inhibition of the hyaluronidase activity), antioxidant properties, participates in redox processes. In addition, rutin is characterized by such effects as a decrease in the exudation of the liquid part of the blood plasma and the diapedesis of blood cells through the vascular wall. Rutin leads to a decrease in swelling, pain syndromes and trophic disorders [5].

It is also important to rationally choose excipients in the composition of the drug, which will ensure the achievement of the necessary biopharmaceutical indicators and the possibility of creating an optimal adhesive layer between the mucous membrane of the anorectal zone and the dispersion medium of the drug used [6].

The use of bases with hydrophobic excipients is a widespread modern technological practice, but along with the positive aspects, hydrophobic bases have a significant drawback in the form of an unsatisfactory release of APIs with diphilic properties [7].

Therefore, the aim of the work was to substantiate the type of base for a soft rectal medicine by studying the organoleptic and physicochemical properties of the experimental samples.

Materials and methods. The study objects were samples of a soft dosage form of various compositions (Table 1) and the reference drug "Procto-Glivenol Cream"

(VAMPHARMA S.R.L., Italy) containing tribenoside and lidocaine hydrochloride as APIs (sample No. 4). Samples were prepared in laboratory conditions according to the traditional technology [8]. A thick extract of carrot root (FECR) was obtained at the Department of Chemistry of Natural Compounds of the National University of Pharmacy of the Ministry of Health of Ukraine under the supervision of professor Kislychenko V. S. and professor Zhuravel I. O. [9]. The amount of rutin and FECR in the dosage form was proven by the previous pharmacological studies [10].

Samples prepared on different carrier bases were assessed by their organoleptic and textural properties; their colloidal and thermal stability, viscosity and pH were studied. The textural properties were studied by the method of direct extrusion (imitation of the force required to extrude the sample by the consumer) and the method of reverse extrusion characterizing the product viscosity. The research was carried out on a TA.XT Plus texture analyzer (Stable Micro Systems Ltd., Surrey, Great Britain). Reverse extrusion tests were performed using an A/BE equipment. Approximately 50 ml of the sample was placed in a standard 100 ml sample container, avoiding the appearance of air and ensuring the formation of a smooth surface. The disk (40 mm diameter), which was placed above the surface of the sample at the beginning of the test, was compressed, resulting in the extrusion of the product upwards between the walls of the container and the edges of the disk. The following study parameters were selected: movement speed – 2 mm/s, distance (insertion depth) – 10 mm [11].

Parameters, such as strength (maximum compressive force), consistency (cohesive and adhesive ability), were determined from the resulting force-time graph. During the movement of the piston with the disk down direction, the positive part of the reverse extrusion graph is created: the maximum compression force required for deformation shows the strength of the sample, and the area of the graph above zero shows its cohesion. The higher the value, the more viscous the consistency

Table 1

The sample composition of a soft medicine (%)

The name of the substance	Sample number		
	No.1	No.2	No.3
FECR	5.0	5.0	5.0
Rutin	2.0	2.0	2.0
Aristoflex	1.5		–
Nipagin	0.0015	0.0015	0.0015
Nipazole	0.005	0.005	0.005
Glycerin	–	10.0	–
Cytostearyl alcohol	–	8.3	–
Stearic acid		4.0	
Liquid paraffin	–	6.0	–
Vegetable		15.0	
Proxanol 188	–		17.0
Purified water	till 100	till 100	till 100

of the sample. After the disk returns to its original position, its upward movement creates the negative part of the graph: the area below zero gives an idea of the adhesion and resistance of the sample when it is removed from the disk (minimum pulling force). The higher the value, the more energy is needed to break the contact of the sample with the surface of the disc and, accordingly, the better the adhesive ability of the samples [12, 13].

The colloidal stability was determined by centrifugation for 5 min at 5000 rpm and 10000 rpm. The thermostability was determined under the conditions of a thermostat at a temperature of 40.0 ± 1 °C for 7 days and by freezing the weight of the sample in a test tube to -20.0 ± 1 °C and the subsequent gradual thawing at room temperature [14, 15]. The pH of the model samples was measured by the potentiometric method in 10 % aqueous extraction from the samples on an Ezodo PL-700PV pH meter (Poland). The rheological studies were carried out on a V2R 3000 viscometer (Spain) in the range of shifting rates of 300 s^{-1} , 700 s^{-1} , 1000 s^{-1} at temperatures of 20 ± 1 °C and 37 ± 1 °C [16].

Results and discussion. According to the data presented in Table 2, it can be concluded that all samples were homogeneous, without signs of stratification, samples No. 1-3 had a specific sweet vegetable smell, sample No. 4 had a characteristic smell of AFI (Table 2).

The value of the hydrogen indicator of sample No. 1 was close to neutral, the pH of the other samples was within the physiological pH value of the anorectal zone (7.3-7.8).

The study of colloidal stability showed that at 5000 rpm all samples were stable. When the speed increased to

10000 rpm, delamination was observed in sample No.3. While determining the thermal stability, the samples showed no signs of delamination when frozen. When heated, sample No.3 lost the signs of a homogeneous structure.

Further, textural characteristics were determined (Fig.). As it can be seen from Figure, samples No. 2-4 had high strength indicators, unlike sample No.1 (153.62 g). Samples No. 2 and 3 showed almost the same values of strength and cohesiveness. Sample No. 1 had a small area under the curve for the first negative peak – 26.08 g.sec, indicating a small degree of its adhesiveness and a possible loss of thixotropic properties during the technological processing and use. The high values of the viscosity index for samples No.2 and 4 (29.98 g.sec and 26.58 g.sec, respectively) allow us to conclude about their better fluidity at room and physiological temperatures in the anorectal zone. Samples No.2 and 3 had elasticity values (the first significant peak at the first compression) approaching the reference sample. The strength of these samples bonding increased with increasing adhesion.

Therefore, samples No.2-4 are able to stick to the mucous membrane, which can prolong the time of staying of the drug at the site of application.

When developing a rectal medicinal product, the cohesiveness of its components should be taken into account. The degree of a soft medicine spreading is inversely proportional to its cohesion. Cohesive forces reduce the fluidity of the system and, thus, the ability to spread over the affected surface. Thus, according to the results of the extrusion test, sample No.1 containing

Table 2

The results of determination of organoleptic and physicochemical parameters

Sample No.	Appearance	pH	Stability	
			thermal, +40 °C/ -20 °C	colloidal
1	A homogeneous transparent mass of a yellow color	6.42 ± 0.23	+/+	+
2	A homogeneous yellow-white mass	7.33 ± 0.56	+/+	+
3	A homogeneous mass of a yellow color	7.65 ± 0.48	-/+	-
4	A homogeneous white mass	7.62 ± 0.64	+/+	+

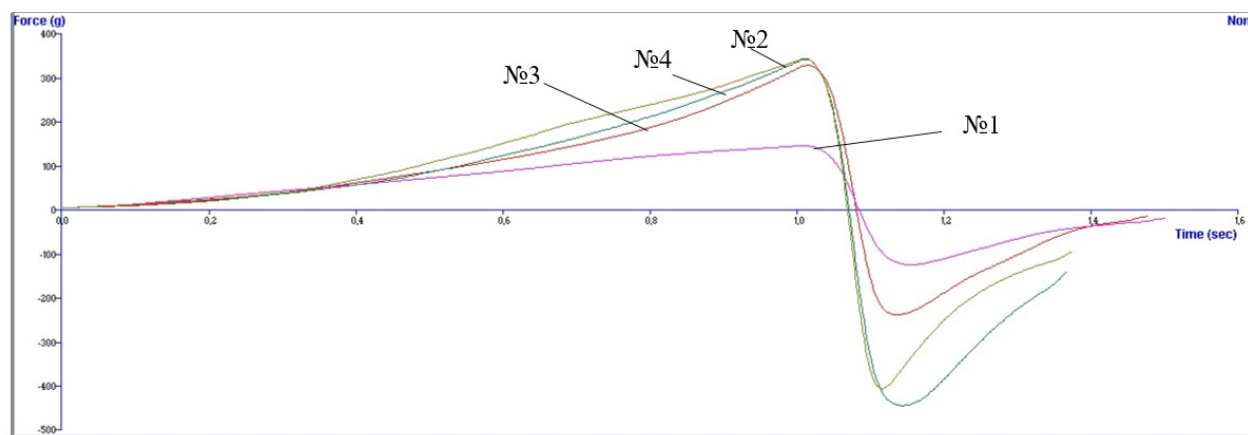


Fig. The extrusion test results

Table 3

Viscosity parameters of the samples

Sample No.	Shifting rate					
	300 s ⁻¹		700 s ⁻¹		1100 s ⁻¹	
	Viscosity, (mPa·s), 25 °C	Viscosity, (mPa·s), 37 °C	Viscosity, (mPa·s)	Viscosity, (mPa·s), 37 °C	Viscosity, (mPa·s), 25 °C	Viscosity, (mPa·s), 37 °C
1	1622 ± 13	1423 ± 14	1096 ± 56	984 ± 25	877 ± 19	644 ± 29
2	2071 ± 89	1853 ± 32	1364 ± 88	1236 ± 25	798 ± 26	782 ± 5
3	1907 ± 43	754 ± 13	1257 ± 26	528 ± 42	741 ± 21	471 ± 8
4	2749 ± 63	2272 ± 51	1295 ± 137	1148 ± 10	914 ± 44	858 ± 13

Aristoflex as a gelling agent has reduced cohesive properties, while the emulsion-based sample No.2 shows satisfactory spreading, adhesion, cohesion and elasticity indicators, which are as close as possible to the reference drug.

The next stage was the viscosity determination of the test samples. As you know, viscosity is not a constant value and depends on such factors as temperature and the shifting rate. Therefore, the study was conducted at temperatures corresponding to the surface of the rectal zone and room temperature with a range of shifting rates from 300 s⁻¹ to 1100 s⁻¹. The values of viscosity and shifting rate determined are presented in Table 3.

As it can be seen from Table, the temperature and the shifting rate significantly affect the viscosity of the samples. At a shifting rate of 300 s⁻¹ and 700 s⁻¹ at 37 °C for samples No. 1 and 4, the viscosity is reduced by almost half. The indicator of samples No.2 and 3 decreases by 30 % - 35 %, approximately 1.45 times under the same conditions. At a shifting rate of 1100 s⁻¹ with an increase in temperature, the viscosity in sample No.1 decreases by approximately 1.5 times, and for No.2, No.3, and No.4, it changes to indicators that will ensure a satisfactory ability to be distributed and retained on the affected surface.

Conclusions and prospects for further research.

According to the organoleptic tests results, it has been determined that all samples are a homogeneous mass

with their characteristic color and smell. Using the potentiometric method it has been found that the pH of samples No.2 and 3 corresponds to the physiological pH value of the anorectal zone (7.3-7.8).

The results of determination of colloidal and thermal stability allow us to conclude that sample No.1, 2 and 4 have no signs of delamination after exposure to mechanical forces and temperature.

Based on the determination of textural properties, it has been found that the use of a sample on a gel base with Aristoflex does not ensure the presence of an optimal adhesive layer between the mucous membrane of the anorectal zone and the dispersion medium of the drug used. The emulsion-based sample shows satisfactory textural parameters, which are as close as possible to the reference drug.

The viscosity study of rectal drug samples in the range of shifting rates of 300 s⁻¹, 700 s⁻¹, 1000 s⁻¹ at temperatures of 20 ± 1 °C and 37 ± 1 °C has shown that the parameters of sample No.2 are close to the reference drug; it will provide a satisfactory ability to be distributed and retained on the affected surface.

For further research on the development of the composition and technology of a soft medicine for the treatment of proctological diseases, it is proposed to use an emulsion-based sample.

Conflict of interests: authors have no conflict of interests to declare.

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