ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Experimental Research on the Development of Extemporaneous Ointment for the Treatment of Proctologic Diseases

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Abstract

Hemorrhoids are the most common proctological diseases affecting an average of 12 people out of 100. Hemorrhoid affects more than 10 % of the adult population of the planet, and the proportion of the total number of proctological diseases is 40 %. Hemorrhoid is the most common reason to see a proctologist. Therefore, the problem of choosing the tactics of treatment of this category of patients remains relevant. If constipation is called "intellectual disease", then hemorrhoid is called "royal disease". Men and women suffer from this disease equally. In women, exacerbation of hemorrhoid often occurs during pregnancy, usually in the last trimester. Sooner or later, enlargement of the hemorrhoid appears in most people. The objective of this work is the development of extemporaneous ointment for the treatment of proctologic diseases. To achieve this goal the following tasks were solved: the literature on the current state of such diseases as hemorrhoids has been analyzed and summarized; the range of medicines used to treat hemorrhoids has been analyzed. As a result the composition of the combined ointment for the treatment of hemorrhoid has been substantiated and its technology has been developed, the stability and microbiological purity of the created extemporaneous combined ointment has been studied.

Keywords: *Hemorrhoids, Treatment, Extemporaneous ointment, Development, Experimental research.*

Introduction

Hemorrhoids are delicate but very common problem in both men and women. Most often, people over 45 years old are affected by this disease, but today this diagnosis is also made to younger people [1, 3]. Hemorrhoid is a disease associated with thrombosis, inflammation, pathological expansion and tortuosity of hemorrhoidal veins that form nodes around the rectum. Hemorrhoids do not only cause discomfort, they are dangerous with numerous complications in the form of iron deficiency anemia, thrombosis and infringement of hemorrhoids. Hemorrhoids develop due to the increased flow of arterial blood and the decrease in its outflow through the veins, which leads to stagnation.

In this case, the vascular formations of the final part of the rectum, called cavernous bodies or caverns, overflow with blood, increase in size and deform, forming hemorrhoidal nodes. A prolonged overflow of cavernous corpuscles with blood, in its turn, causes the expansion and thinning of the walls of the veins, which are therefore easily injured [4]. Hemorrhoidal nodes are attached to the walls of the anal canal by connecting and muscle fibers. If this situation is violated due to excessive straining, the nodes slide down along with the mucous membrane. Following this is the restructuring and impaired blood supply, which causes the hemorrhoids to increase in size and bulge out. Hemorrhoid is caused by stagnation of the blood in the veins of the lower intestines. This is a "professional" disease of everyone who spends a lot of time in a sitting position, for example, drivers and office workers who do not get up from the wheel and computer for hours [5, 6].

Frequent constipation, pregnancy and childbirth also contribute to the development of hemorrhoid-in short, all conditions that provoke a noticeable increase in intra-abdominal pressure. Both overweight people and those who are often forced to lift weights (movers, athletes) are at risk. This disease

has a wide symptomatology, and its manifestations may vary in different people. Hemorrhoid develops gradually, over the course of several years, so sometimes it is difficult to notice its early signs. Proctologists distinguish four stages of hemorrhoid: enlargement of hemorrhoid nodes; prolapse of hemorrhoids during bowel movements or weight lifting; loss of nodes even at low tension and persistent hemorrhoid prolapse [7, 9]. Medicine distinguishes three forms of hemorrhoid: internal, external and combined.

In the early stages of the disease, combinations of analgesic, anti-inflammatory, thrombolytic, hemostatic and phlebotonic agents are used for the treatment [10]. Conservative treatment of hemorrhoid is based on a combination of systemic and topical medicines. Phlebotonic medicines, micronized diosmin with a fraction of hesperidin in particular, occupy a leading position at the basis of systemic therapy.

To eliminate thrombosis of hemorrhoidal nodes, pentoxifylline, acetylsalicylic acid and, of course, combined phlebotonic medicines are also taken as systemic medicines. Benzopyron medicines also improve blood flow in the hemorrhoid [11, 13]. The use of local medicines helps to reduce pain and inflammatory syndromes, enhances the effect of systemic analgesic and phlebotonic medicines, which reduces the rehabilitation time.

In acute thrombosis of hemorrhoid, combined topical medicines are most often used to relieve inflammation, and with hemorrhoidal bleeding, and ointments are among the most effective [14]. The objective of our work is to analyze the modern range of medicines for the treatment of hemorrhoids at the pharmaceutical market, as well as the development of the composition and technology of a combined extemporaneous ointment for local treatment of hemorrhoids.

Materials and Methods

It is known that in the process of developing the composition and technology of a new medicine it is important to study the degree of release of medicinal substances. Evaluation of the release of medicinal substances from the ointment based on the ability of the base to release medicinal substances. Methods for determining medicinal substances release from ointment bases have been sufficiently described in the literature. All methods are divided into: *in vitro*, based on physical, chemical and microbiological studies and biological methods *in vivo*, which are carried out on living organisms. In the development of ointment technology, the *in vitro* method of agar plates was used to evaluate active components release from the medicine.

The agar gel was prepared with 2 % concentration in a glass beaker and with a tightly closed lid. Crushed agar was poured over with purified water and left for 30 minutes to swell. After swelling, the agar was heated to boiling, brought to the desired weight and to a frothy gel, 5 % Ehrlich reagent was added. Ehrlich reagent composition: para-dimethyl aminobenzaldehyde 0.5, concentrated hydrochloric acid and ethyl alcohol 95 % 15 mL each, n-butanol 90 mL. Samples of ointments were placed in the wells of two Petri dishes with agar. The plates were placed in a thermostat with a temperature of 37 °C.

Lidocaine hydrochloride was released and diffused into an agar gel to form the azo dye reaction and to form a colored zone. After 1, 2, 3 hours the diameter of the painted areas was measured. Statistical processing of these results was performed. The pharmacotherapy degree of grinding and polymorphism of active components is the most significant. Grinding active components is the simplest but at the same time one of the most important technological operations.

The dispersion of active components affects not only the flow ability of powdered materials, bulk, homogeneity of mixing, metering accuracy. It is particularly important to note that the particle size depends on the rate and completeness of absorption of the medicinal substance, as well as its concentration in liquids, mainly in the blood. The effect of the degree of grinding on the absorption process is particularly pronounced in ointments prepared on the same base, but with the use of fractions of medicinal substances the size of which is significantly different.

Thus, medicinal substances in the medicine should have the optimum degree of grinding, on which its bioavailability depends. The size of the particles of methyluracil was studied before and after grinding.

The researches were carried out by microscopy using the method of State Pharmacopoeia of Ukraine, under the microscope of the firm KRŰSS (Germany, magnification X 150). For microbiological purity studies, thioglycolic medium, Saburo liquid medium as well as Chistovich medium, blood agar based on nutrient agar, Endo medium were used.

Prior to the studies, studies were conducted to match the growth characteristics of the nutrient media. Petri dishes of the same diameter mounted on a horizontal surface were filled with 10 mL of meat-peptone agar. After the gel's solidifying, metal cylinders with an outside diameter of 8 mm were placed on its surface and filled with a 15 mL agar layer, which is pre-introduced with a suspension of microorganism strains. After the agar's solidifying, the cylinders were carefully removed and 0.3 of the test sample of the ointment placed in the wells formed. The cups were placed in a thermostat and kept at 37 °C for 24 hours; the diameter of retention zones of microorganisms was measured.

Results and Discussion

The analysis of the assortment of medicines for the local treatment of hemorrhoid showed that medicines existing on the pharmaceutical market are produced mainly in the form of rectal suppositories, ointments and gels. Medicines for systemic use exist in the form of tablets, capsules and solutions for injections. Escin, hydrosmin, hesperidin and other substances both of natural and synthetic origin are used as active substances in the composition of systemic medicines (Table 1).

Table 1: The assortment of medicines for the systemic treatment of hemorrhoid

The name of the medicine	Medicinal form	Active ingredients	Producer
Cycle 3 Fort	capsules	uscus aculeatus, hesperidin methyl chalcone, ascorbic acid	France
Detralex	tablets	diosmine, hesperidin	France
Escin	tablets	alpha escin	Ukraine
Esculus compositum	oral drops	acidum benzoicum, aesculus hippocastanum, apis mellifica, arnica montana, etc.	Germany
Flebodia	tablets	diosmine	France
Normoven	tablets	diosmine, hesperidin	Ukraine
Troxevasin	capsules	troxerutin	Bulgaria
Venosmill	capsules	hydrosmine	Spain
Venosmin	tablets	diosmine, hesperidin	Ukraine
Vikasol	solution for injections	menadione sodium bisulfite	Ukraine

In the composition of medicines for external use, xeroform, heparin, streptokinase, local anesthetics, phenylephrine hydrochloride, glucocorticoids and others are the most common (Table 2).

Table 2: The assortment of medicines for the local treatment of hemorrhoid

The name of the medicine	Medicinal form	Active ingredients	Producer
Aekol	oily solution	retinol acetate, alpha-tocopherol acetate, menadione, beta-carotene	Ukraine
Anuzol	rectal suppositories	xeroform, belladonna extract, zinc sulfate	Ukraine
Biostrepta	rectal suppositories	streptokinase, streptodornase	Poland
Distreptase	rectal suppositories	streptokinase, streptodornase	Poland
Doloproct	cream, rectal suppositories	fluocortolone pivalate, lidocaine hydrochloride	Italy
Escin	gel	diethylamine salicylate, heparin sodium	Ukraine
Hesup	rectal suppositories	hamamelis virginiana, lamium album, plantago major, potentilla anserina	Germany
Procto-Glyvenol	rectal suppositories, cream	tribenoside, lidocaine hydrochloride	France
Relief	rectal suppositories, ointment	phenylephrine hydrochloride	Italy
Relief Advance	rectal suppositories, ointment	benzocaine	Italy
Relief Pro	rectal suppositories, cream	fluocortolone pivalate, lidocaine hydrochloride	Italy

Relief Ultra	rectal suppositories	hydrocortisone acetate, zinc sulfate monohydrate	Italy
Troxevasin	gel	troxerutin	Bulgaria

As for the range of medicines of extemporaneous preparation, it is significantly narrower and is represented mainly by rectal suppositories of anti-inflammatory and analgesic action. Extemporaneous ointments for local treatment of hemorrhoid are practically absent, because in extemporaneous compounding, Vaseline is mainly used as an ointment base, which is unacceptable for this pathology. That is why one of our tasks is to create an extemporaneous ointment for the treatment of proctologic diseases. Methyluracil and lidocaine hydrochloride were used as active ingredients of the developed ointment.

Dioxomethyltetrahydropyrimidine, (trade name "Methyluracil"), is a white crystalline powder, odorless, slightly soluble in water and alcohol, practically insoluble in ether and chloroform. It has anabolic and anti-catabolic effects, accelerates the process of cellular regeneration, heals wounds, stimulates cellular and humoral immunity, increases the body's resistance to infections, has an anti-inflammatory effect, and increases the body's resistance to blood loss and oxygen deficiency. A characteristic specific property of methyluracil is a stimulating effect on erythro- and especially leukopoiesis. Lidocaine hydrochloride is a white or almost white crystalline powder, poorly soluble in water. Used in the form of hydrochloric acid, readily soluble in water.

It has a local anesthetic effect. The mechanism of the local anesthetic effect is to stabilize the neuronal membrane, reducing its permeability to sodium ions, which prevents the emergence of action potential and impulses, is effective for all types of local anesthesia. Expands blood vessels, does not irritate tissues. When applied topically to intact skin, a therapeutic effect arises that is sufficient to relieve pain without developing a systemic effect. The combination of these medicinal substances in the composition of the ointment on the emulsion base will provide its long-lasting different-sided pharmacological effect.

The Lanette emulsion base was chosen as the ointment base because it promotes the penetration of the active substances into the deeper layers of the skin and mucous membranes. In addition, the ointments based on these bases are characterized by low viscosity, reduce the dryness of the skin, and increase its softness and elasticity.

The Lanette base includes: cetyl stearyl alcohol, vaseline and vaseline oil. It promotes the penetration of nutrients into the deeper layers of the skin, is easily applied to the skin and mucous membranes, and is easily removed from them. In order to determine the degree of release of lidocaine hydrochloride from the ointment base, we prepared model samples of ointments on the vaseline-lanoline and emulsion bases (Table 3).

Table 3: Diffusion of lidocaine hydrochloride from ointments

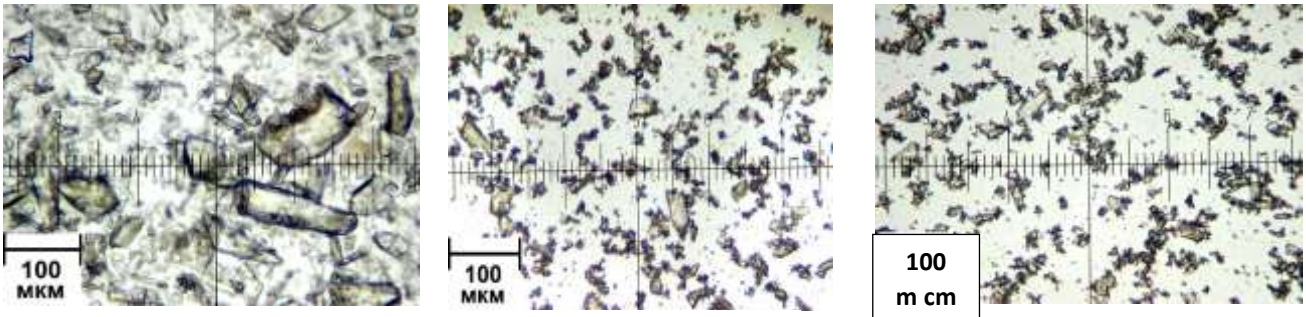
Ointment	Diameter of painted zones, mm		
	1 hour	2 hours	3 hours
Vaseline-lanoline base	6.21 ± 0.07	8.25 ± 0.13	10.45 ± 0.11
Lanette emulsion base	12.13 ± 0.12	16.82 ± 0.14	21.65 ± 0.27

Our studies have shown that lidocaine hydrochloride is released from the ointment on the Lanette emulsion base about 2 times faster than from the ointment on the vaseline-lanoline base. Thus, all further studies were conducted with the use of the ointment samples on the Lanette emulsion base. In order to develop a rational technology of extemporaneous ointment, we conducted a study of the solubility of the active substances of the medicine (Table 4).

Table 4: Solubility of ointment's active substances

Substance	Solubility		
	Water	Base	Fatty oil
Methyl uracil	1:1000-10000	1:>10000	1:>10000
Lidocaine hydrochloride	1:1	1:>10000	1:1-10

According to the results of the researches it was concluded that the ointment contains active substances with different physical and chemical properties, which in turn requires the preparation of different types of ointments: suspension (methyluracil is poorly soluble in water, insoluble in the base) and emulsion (lidocaine hydrochloride is easily soluble in water, practically insoluble in the base). In order to study the grinding time of methyluracil for the preparation of high-quality suspension ointment, we conducted a study of the particle size of methyluracil before and after grinding (Fig. 1).



without grinding after 3 min of grinding after 5 min of grinding

Figure 1: The particle size of methyl uracil before and after grinding

The average particle size of methyluracil was: without grinding -100-150 microns, after 1 minute of grinding -20-50 microns, after 3 minutes of grinding -20-30 microns, after 5 minutes of grinding-10-30 microns. As a result of the studies, it was found out that 3 minutes of grinding of methyluracil is sufficient. Grinding improves both physical and chemical characteristics of the substance; the particles become uniform in size and shape. The preparation of the combined ointment begins with the preparation of the suspension ointment. Methyluracil is placed in a mortar, dispersed first in the dry state and then with half of its weight with the melted base. A part of the base is added; the mass is mixed and placed on the edge of the mortar. The emulsion ointment is prepared: lidocaine hydrochloride is placed in a mortar; purified water is added to dissolve it. Then the rest of the base is added and mixed. The ointment-suspension and ointment-emulsion are mixed to homogeneity. The results of the study on the microbiological purity of samples of extemporaneous combined ointment prepared by the above technology are shown in Table 5.

Table 5: The results of the study on the microbiological purity

The name of the sample	The number of colonies forming units by the decadal logarithm of the degree of growth during cultivation on solid nutrient media			
	Method of deep sowing in 1 g of the ointment		Method of surface sowing in 1 g of the ointment	
	Nutrient agar	Saburo medium	Nutrient agar	Saburo medium
Created extemporaneous ointment	3.9 ±1.2	X	3.4 ± 0.5	X

Note: X – no growth of fungi

Conclusions

- The modern range of medicines for the treatment of hemorrhoids at the pharmaceutical market has been analyzed. It was shown that extemporaneous ointments for local treatment of hemorrhoids are practically absent.
- Composition and technology of a new combined extemporaneous ointment for local treatment of hemorrhoidal diseases have been developed.

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