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QUALIFICATION WORK

on the topic «**RESEARCH ON THE DEVELOPMENT OF HYDROCORTISONE GEL TECHNOLOGY FOR VETERINARY USE**»

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ANNOTATION

The structural and mechanical parameters of the developed gel with hydrocortisone for use in veterinary medicine were studied. To install a rational gelling agent, we have prepared the following model samples. The concentration of hydrocortisone (1%) was selected on the basis of analysis of literature sources and propylene glycol (8%) on the basis of studies. With the help of pharmacotechnological and rheological studies it was established that the use of aristoflex as a gelling agent in the development of a topical veterinary drug with hydrocortisone will ensure the availability of appropriate extrusion properties (namely, easy and uniform application to the skin).

The work is set out on 53 pages, includes 4 tables, 12 figures, 50 references and 2 appendices.

Key words: gel, gelling agent, aristoflex, technology, rheology, veterinary medicine

АНОТАЦІЯ

Досліджено структурно-механічні показники розробленого гелю з гідрокортизоном для застосування у ветеринарії. Для встановлення раціонального гелеутворювача нами були приготовані наступні модельні зразки. Концентрацію гідрокортизону (1 %) обрано на підставі аналізу літературних джерел та пропіленгліколю (8 %) на підставі проведених досліджень. Модельні зразки готували загально прописаної у ДФУ технології приготування гелівЗа допомогою фармакотехнологічних і реологічних досліджень встановлено, що використання аристофлексу як гелеутворювача при розробці ветеринарного препарату місцевої дії з гідрокортизоном забезпечить наявність відповідних екструзійних властивостей (а саме легке і ріномірне нанесення шкіру тварини, зручність у застосуванні).

Робота викладена на 53 сторінках, включає 4 таблиць, 12 рисунки, 50 джерел літератури та 2 додатки.

Ключові слова: гель, гелеутворювач, аристофлекс, технологія, реологія, ветеринарія

CONTENT

LIST OF SYMBOLS

AD – atopic dermatitis

APhI – active pharmaceutical ingredient

SPhU – State Pharmacopoeia of Ukraine

EPh– European Pharmacopoeia

MS – mechanical stability

INTRODUCTION

Actuality of theme. One of the most common diseases among animals is atopic dermatitis. According to statistics, compared to previous years, the number of animals affected by this pathology is rapidly increasing. According to experts, modern environmental conditions that provoke the susceptibility of animals to allergens are to blame. [27].

Allergic diseases are common in dogs and cats. Improper feeding, untimely treatments against ectoparasites, the environment - all these factors can cause an acute reaction of the body's immune system. Pediatrician Clemens von Pirke introduced the term "allergy" in 1906. According to his observations, a number of symptoms in his patients could be caused by certain substances, such as dust, pollen from flowers, eating certain foods.

Atopic dermatitis – common disease of cats and dogs, described as genetically caused itchy inflammation of the skin associated with the formation of IgE antibodies, usually directed against environmental allergens or airborne allergens. According to international statistics, 3 to 30 % of dogs worldwide have atopic dermatitis т [25, 48].

Many factors contribute to the appearance of atopic dermatitis in animals. These can be adverse climatic conditions, and chronic diseases, and heredity, and various allergens (pollen, dust mites, flea products, etc.). And, of course, the microclimatic habitat of the pet. Dermatitis caused by parasites is manifested in animals that are not well cared for by their owners. It is very important to timely treat fleas and ticks, because up to 80% of animals suffer from flea dermatitis, which is a reaction to insect bites [26].

Atopic dermatitis affects young animals aged 1 to 5 years, but can be diagnosed earlier. The first symptoms of dermatitis appear at the age of six months, when the allergen is introduced into the body and causes the immune system to produce neutralizing antibodies, then the pathology recurs throughout life.

Atopic dermatitis has a pronounced clinical picture. The symptoms include the main and additional signs. The main symptoms are [40]:

1. Severe itching of the skin, which gives the animal great discomfort.
2. Damage to the skin, scratches, abrasions (especially in the face and paws), which appear due to the fact that the animal is constantly itching and tearing the claws of the skin.
3. The infection which has got to wounds provokes emergence of furuncles, hyperpigmentation, abscesses.
4. Hair loss, alopecia.
5. Characteristic smell from the ears, reminiscent of yeast dough.

Additional signs of atopic dermatitis include: excessive dryness of the skin; immediate reaction to the allergen; external form of allergic otitis; superficial manifestations of staphylococcal infection.

Symptomatic treatment is carried out at the initial stage of immunotherapy, but may be prescribed after: if the effect is short-lived or not fully manifested. Drugs of different groups for the treatment of atopic dermatitis, as well as special shampoos for skin care are prescribed by a veterinarian, self-medication is dangerous to the health of the dog and can only worsen the situation [31].

Be sure to prescribe corticosteroids. They have a powerful and rapid effect, reduce the activity of a number of inflammatory factors. These drugs are hormonal, their action is aimed at eliminating itching, allergic edema, redness [26].

Prednisolone, methylprednisolone, dexamethasone and hydrocortisone are the most commonly prescribed.

That is why it is important to create new veterinary drugs with hydrocortisone for local therapy of atopic dermatitis.

The aim of the study. Development of extemporaneous gel with hydrocortisone for local treatment of atopic dermatitis.

Objectives of the study:

– to analyze the literature on the clinical picture, pathogenesis and pharmacotherapy of atopic dermatitis in animals;

– to analyze the current state of veterinary drugs in the pharmaceutical market of Ukraine on the range for local therapy of atopic dermatitis;

– to develop the composition of the gel with hydrocortisone for the treatment of selected pathology;

– to develop rational gel technology.

Subject of study. Structural and mechanical studies on the development of the composition and technology of hydrocortisone gel for the treatment of atopic dermatitis in animals.

Objects of research. Hydrocortisone, propylene glycol, Aristoflex gelling agent, purified water.

Research methods. Organoleptic, structural and mechanical.

The practical significance of the results obtained. The composition of the gel with hydrocortisone for the local treatment of atopic dermatitis in animals is substantiated.

Elements of scientific research. For the first time, the composition and hydrocortisone gel technology for the local treatment of atopic dermatitis in animals were developed and proposed.

Structure and scope of qualification work. Qualification work consists of an introduction, literature review (section 1), experimental part (sections 2 and 3), general conclusions, list of used literature sources, appendices. The work is presented on 53 pages, includes 4 tables, 12 figures, 50 sources of literature.

CHAPTER I.

ETIOLOGY, PATHOGENESIS AND CLINICAL FEATURES OF ATOPIC DERMATITIS IN ANIMALS

1.1. Etiology and pathogenesis of atopic dermatitis in animals

Atopic dermatitis (atopy, atopic diseases) is a genetically predisposed to the appearance of immunoglobulin E after contact with surrounding allergens, which leads to a characteristic inflammatory itchy dermatosis.

The pathogenesis of atopic dermatitis is complex and new concepts of the etiology of the disease still appear. It is currently believed that contact of the allergen with the epidermis leads to its absorption by Largengans cells and subsequent presentation of the allergen to T lymphocytes**.** (fig. 1.1).

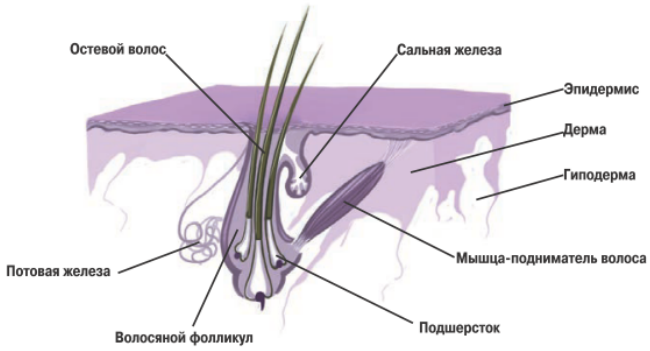


Fig 1.1. Histological section of the skin

Established in humans and presumed in animals, there is a violation of the degree of relationship between T1-helper cells (which contribute to delayed hypersensitivity, macrophage activation, products opsonizing and fixing complement antibodies and antibody-dependent cells that mediate cytotoxicity) and T2 helper mast cells and eosinophils, reduce the production of immunoglobulin G1, but stimulate the synthesis of immunoglobulin E and

immunoglobulin A). Increased T2 helper cells lead to excessive production of immunoglobulin E cells. In addition, there are other changes in cell-mediated immunity.

These cellular disorders, together with the release of other mediators of inflammation from mast cells and basophils due to the connection of the allergen with antigen-specific immunoglobulin E, leads to a cascade of release of substances of inflammation and itching [39, 43].

Defects of the epidermal barrier

The stratum corneum consists of exfoliated corneocytes surrounded by intercellular lipids, which probably play the role of a normal skin barrier and provide a protective function of the skin. There is much evidence of skin barrier dysfunction in people with atopy. In particular, recent studies have found a mutation in the loss of phliaggreen function in 25% of atopic patients, especially in early onset, with high levels of immunoglobulin E and in severe cases.

There is some evidence that atopic animals may have defects in fatty acid metabolism in the skin. Another study showed that the length and thickness of lipid deposits in the stratum corneum were lower in the skin of atopic animals without clinical manifestations of the disease, compared with healthy animals. In addition, it was found that intercellular lipid plates have many structural defects in the stratum corneum in animals with atopic dermatitis. Thus, there is evidence of a defect in the epidermal skin barrier in atopic animals [30].

The role of staphylococci in the pathogenesis or persistence of lesions

Staphylococcal skin infections are a common occurrence. Studies have shown that the corneocytes of atopic animals have increased adhesion to Staphylococcus intermedius and the skin of atopic animals with symptoms of the disease has an increased number of these microorganisms. Some studies suggest that inflammation of the skin allows staphylococcal antigens to penetrate the skin.

In addition, serum levels of antistaphylococcal immunoglobulin E were higher in animals with recurrent superficial pyoderma secondary to atopic dermatitis. Therefore, it is possible that there was an immediate type of hypersensitivity reaction to staphylococcal antigens, which may have contributed to the inflammatory process.

Staphylococcal toxins can also contribute to the inflammatory process to the same extent as allergens. There is some evidence that dogs with atopic dermatitis have impaired cell-mediated immune effects that may possibly contribute to the development of infection. A recent study found that S. intermedius produces a superantigen that induces T cell proliferation and inflammation in humans with atopic dermatitis and in rodents in the experiment. [34].

The role of Malassezia in the pathogenesis or persistence of lesions

The main feature of secondary malassezia dermatitis is itching, which may be expressed in some animals. The number of these microorganisms on the skin surface of atopic animals is higher than or equal to their number in healthy animals. Animals with atopic dermatitis have higher serum levels of immunoglobulin E against Malassezia antigens than non-atopic animals or animals with malassezia dermatitis, but without atopic dermatitis. Specific intradermal tests, T-cell proliferation and passive transfer test for hypersensitivity to Malassezia have also been demonstrated.

Therefore, an immediate type of hypersensitivity reaction to this microorganism is possible, leading to inflammation. In addition, fungi also contain or secrete various substances that can cause a complementary cascade and cause an inflammatory reaction [31, 39].

Borderline phenomenon

Itching threshold. According to this concept, a certain level of stimuli that cause itching can be tolerated without clinical symptoms. However, if there is an increase in stimuli from one or more sources, such as bacteria, fungi or ectoparasites, the threshold will be exceeded and itching will occur. (fig. 1.2).

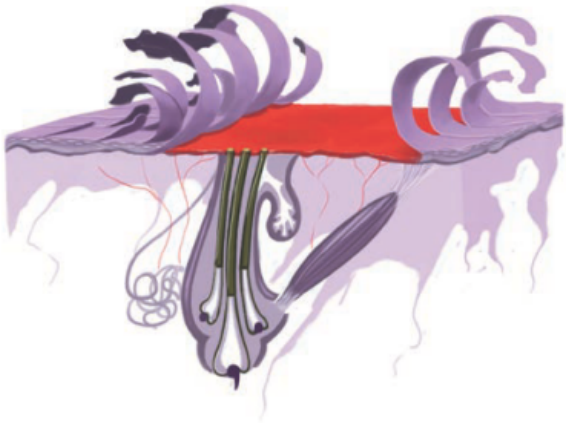


Fig. 1.2. Schematic representation of lesions caused by combing the skin

Threshold of clinical symptoms of atopic dermatitis. According to this concept, a certain amount of allergenic stress can be tolerated. However, if the allergen load increases, the threshold may be exceeded and a clinically severe disease develops. An example is an animal that is hypersensitive to house dust mites but does not itch during the winter, in addition it is hypersensitive to plant pollen, which will exceed the threshold and lead to clinically severe disease during the year when the air is high in plant pollen. Concomitant presence of food hypersensitivity or parasitic hypersensitivity are other examples of situations where the sensitivity threshold may be exceeded [32, 47].

1.2. Clinical features of atopic dermatitis in animals

The clinical manifestations of atopic dermatitis in animals vary widely, and there are no physical or anamnestic findings that can accurately diagnose the disease. The true incidence of atopic dermatitis in animals is unknown and probably varies in different geographical regions and populations within these regions.

In one survey, the incidence of 53 private physicians in the United States was 8.7%. Most often, clinical symptoms of atopic dermatitis are first detected in

animals from 1 year to 3 years of age. However, the disease occurs in very young (approximately 12 weeks of age) and very old (approximately 16 years of age) animals. Breed susceptibility to atopic dermatitis will vary depending on the local gene pool, but in the United States, the United Kingdom and other European countries, certain breeds have an increased risk of disease [36].

If hypersensitivity develops to plant pollen, clinical symptoms are more likely to be seasonal (eg summer and / or autumn, depending on the type of pollen). However, many animals show perennial disease as a reaction to indoor allergens, including house dust mites. In addition, there are animals with perennial disease, the condition of which deteriorates during certain seasons.

An example is a dog with an allergy to house dust mites, which develops severe clinical symptoms during the pollen season. It is noted that the deterioration of the dog's condition can occur during late autumn and early winter, when intensive use of air heating systems, leading to increased circulation of dust and mold. Enhanced air or central heating can also dry out skin and hair. The degree of itching can vary from very mild to intense, and itching can be generalized, or, more often, localized [28, 35].

If the itching is localized, it may be specific to one or more of the following areas: ears, skin around the eyes, snout, ventral neck, elbows, armpits, groin, torso, paws (especially the interdigital and skin under the tail) (see Fig.1.3. and 1.4.).

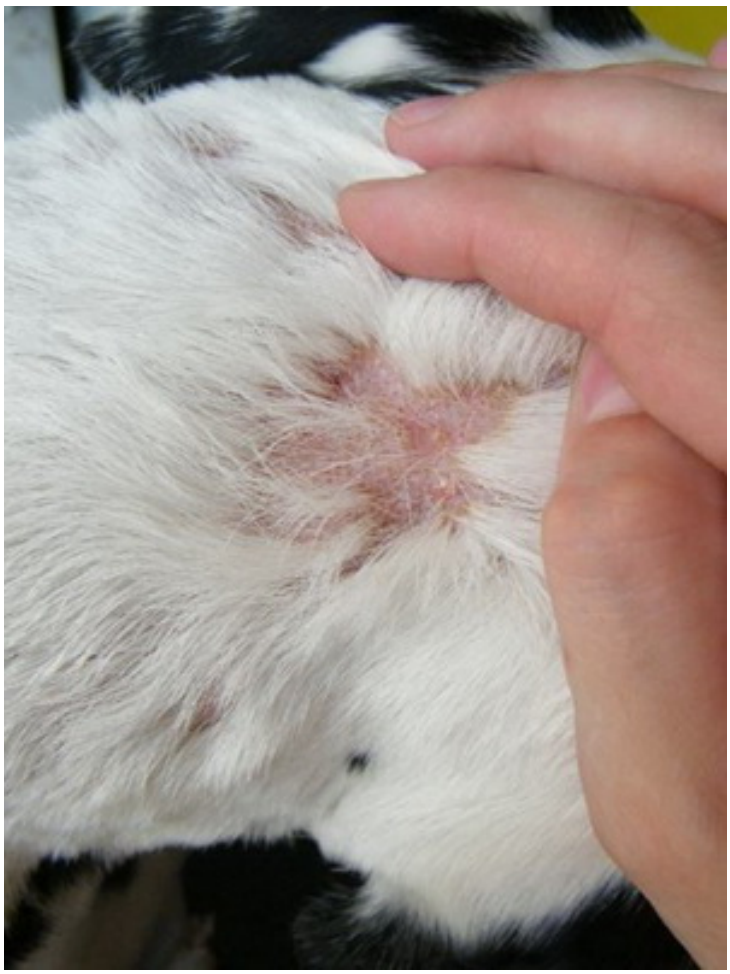


Fig 1.3. An example of atopic local dermatitis on the skin of a cat

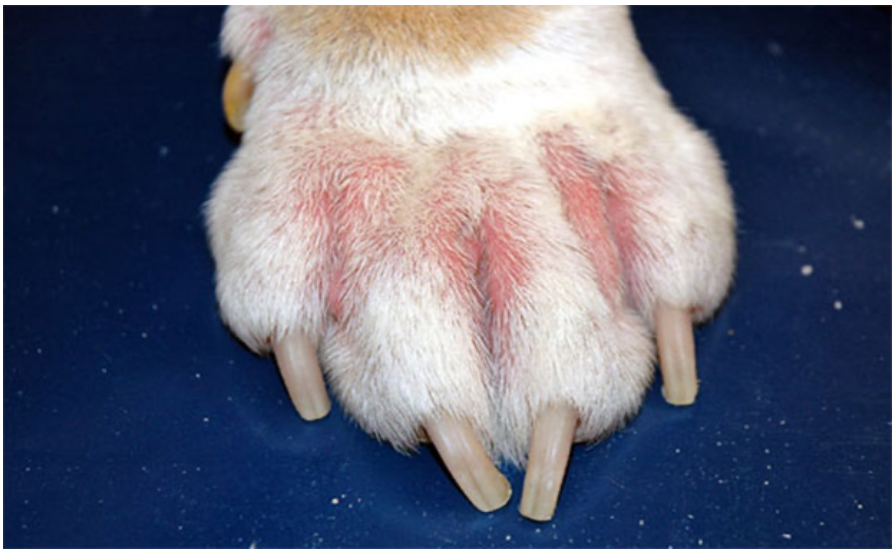


Fig 1.4. An example of atopic local dermatitis on a dog's paw

Primary lesions. Some animals with atopic dermatitis will not have primary lesions and will only itch. Erythema, when present, is the primary lesion and may

be generalized or specific to one or more of the following areas: ears (especially ventral and concave part of the auricle), periocular area, muzzle, ventral neck, anterior elbow area, axillary area , groin, torso, paws (especially the interdigital) and the skin under the tail. In most cases, erythema will be diffuse rather than macular-popular, although it is often complicated by self-injury and excoriation [33].

Secondary changes, complications and additional features.

- ***Hyperpigmentation.*** It can be observed anywhere where there is inflammation or irritation of the skin. Focal areas are often observed in areas of disappearance of staphylococcal lesions.
- ***Lichenification.*** This is a thickening of the skin with the formation of a large number of folds. It can develop in any place where there is chronic inflammation or skin irritation. Constant licking of animals can significantly contribute to its development. It is most common in the ears (especially on the concave part of the ear and in the vertical canal), periocular area, ventral neck (especially in cocker spaniels and springer spaniels), axillary cavities, folds of the torso, lips and tail.
- ***Seborrhea.*** It can be generalized and often contribute to the appearance of a pronounced odor from the animal. It can be localized, in which case the ears, ventral neck (especially in cocker spaniels and springer spaniels), interdigital, axillary and groin are often affected.
- ***Peeling.*** Increased peeling can occur both due to accelerated recovery of the epidermis and due to dyskeratosis.
- ***Alopecia.*** Inflammation of the skin can sometimes lead to hair synchronization in the telogen phase, leading to both sparse hair and complete hair loss. More often, focal areas of alopecia can occur in areas of skin with secondary staphylococcal infection or due to combing, biting or licking the skin.

- ***Alopecia and peeling of the edges of the auricles.*** In some cases, alopecia and peeling will affect the edges of the auricles and the animal will exhibit an auricular pedal reflex, mimicking the defeat of the sarcoptosis mite. This finding can be found in dogs of any breed, but is most common in German Shepherds, Cocker Spaniels and Springer Spaniels.
- ***Perianal dermatitis.*** It is often misdiagnosed as intestinal parasitism or inflammation of the paraanal glands. Lesions occur in the skin under the tail, as well as in the skin of the perianal area. Erythema may be the only finding in some cases, in other cases the skin of the perianal area becomes very hyperplastic. Animals will rub the rectal area against the floor in an attempt to eliminate the itching.
- ***Obsessive compulsive behavior.*** Some animals become abscessively compulsive towards the area of minimal erythema and will lick, bite and scratch certain areas of the skin continuously, until excoriation and bleeding [38].

1.3. Modern therapy of atopic dermatitis in animals

Treatment of atopic dermatitis of animals is always lifelong, the disease can not be cured, have to take some life measures to correct it and the favorable existence of animals with allergens.

First you need to rule out the primary possible pathologies - flea allergic dermatitis. Constant treatment of the cat, regardless of the season, as well as the treatment of the house and objects of content (litter, couches, houses) of the animal can give good results.

The second stage, the exception of food allergies (food intolerance / food allergy), monitoring the reaction to the elimination diet, which should be provided for a minimum of four weeks, and in some cases for twelve weeks [37].

It is recommended to start with the detection and, if possible, avoid contact with the allergen. It is impossible to avoid contact with the allergen, but changing

the habitat of the animal can significantly reduce the number of cases of allergies, it helps with meson manifestation, such as the flowering of certain plants.

At year-round manifestation of itching preventive, hygienic bathing of animals with soft shampoos is used, for achievement not only mechanical washing away of an allergen from skin, but also additional moistening, strengthening of a lipid barrier of skin.

In periods of exacerbation of bacterial / fungal infections, systemic drugs should be used: antibiotics and antifungals. In case the bacterial infection is under control and the itching is still present connect medical medications such as antihistamines and glucocorticoids.

The effectiveness of the first 20%, in the acute period of the disease itching is not controlled, corticosteroids are the most effective drugs, but have a number of side effects, so it should be prescribed in acute, severe cases [46].

Topical application of ointments, gels, sprays is recommended to control local manifestations - it is rare due to the difficulties that arise when trying to wash the animal.

Preparations contain ceramides, essential fatty acids - useful for cats with atopy, completely safe, spray-shaped, easy to apply to large areas and even the whole body. Due to the elasticity of the skin and the connection of the horny scales of the skin complicate the penetration of the allergen through the skin barrier [49].

At round-season manifestation of an allergy detection of an allergen will not help in treatment, except for an allergen of specific immunological therapy (ASIT). The effectiveness of treatment is 50%, the animals respond positively to this method. This method is not standardized and not certified in Ukraine. To date, this method is the safest for animals.

There is no universal scheme for the treatment of atopic dermatitis in cats, it is necessary to take into account the severity of the clinical manifestations of itching, the presence and frequency of exacerbations, side effects of various drugs. Bacterial / fungal infection should always be kept under control, animals should receive quality insect treatments, moisturize and restore the skin barrier [50].

To moisturize and restore the skin barrier, it is possible to use safe drugs and feeds containing essential polyunsaturated fatty acids. Omega-3-6 polyunsaturated fatty acids (PUFAs) have a specific effect on metabolism. They are included in many dietary supplements, high quality feed.

The use of antihistamines to control pruritus remains controversial, because only 15-30% of patients with atopy to a greater or lesser extent respond positively to treatment with these drugs.

Analysis of the medical and veterinary literature on atopic dermatitis shows that this pathology has been described for a long time and is always difficult to treat. Existing treatment recommendations are based on a global approach – ***complex therapy*** [41, 44] (fig. 1.5).

Fig. 1.5. The main areas of treatment

1. ***Getting rid of the allergen.*** This approach is, of course, ideal, but, unfortunately, it is difficult to implement in practice. Allergens can be identified by history (seasonality, region), by provocation and by allergy tests. You can reduce the impact of animal allergens in the environment, through hygienic measures such as mechanical vacuuming, the use of acaricides and denaturing drugs. Careful periodic treatment of residential premises benzyl benzoate leads to negative test results for ticks and improves the clinical condition of atopy-suffering animals.

Air conditioning and dehumidification will also reduce allergenic stress on animals.

2. ***Specific immunotherapy.*** If you have managed to accurately identify the allergen or allergens, and the owner wants to try to cure his pet, then one of the best ways is desensitization - specific immunotherapy. Specific immunotherapy is based on administering to the animal an allergen extract in increasing doses. This method is usually called desensitization or hyposensitization, but it is better to call it specific immunotherapy. Several hypotheses have been proposed to explain the mechanism of desensitization. The most popular theory in the last 40 years suggests that the introduction of small amounts of specific allergens induces an immune response that provides the synthesis of lgG or “blocking” antibodies.

3. ***Corticosteroids.*** After oral or topical administration, corticosteroids are very rapidly absorbed and distributed to all tissues of the body. Resorption of injectable forms of corticosteroids depends on the presence of ether in their composition: by the criterion they are divided into fast-acting and long-acting drugs. They are excreted by the kidneys and liver. The rate of elimination of corticosteroids from the body depends on the degree of their substitution. Corticosteroids are fixed on cortisol receptors and act as natural hormones. Glucocorticosteroids are active at the level of cell nuclei by stimulating or slowing the expression of various genes. They are particularly inhibitory of cytokine synthesis and release. In the skin, their main targets are keratinoids and Langerhans cells. These drugs are most commonly used in the last 30 years to treat atopic dermatitis in animals, and veterinarians are aware of their effectiveness. Their oral and topical application are part of the treatment regimens of the disease.

4. ***Cyclosporine.*** Recently, cyclosporine has become a favorite tool of dermatologists (and veterinarians), but its use is controversial. There is no need for a long search for this drug (previously it was used to prevent tissue rejection during organ transplantation). Cyclosporine belongs to the group of calcineurin inhibitors. After absorption, it acts mainly on T-helpers, although it is clear that such activity

does not affect T-suppressors. Cyclosporine affects mast cells, eosinophils and Langerhans cells, reducing their antigen-presenting function.

5. ***Antimicrobials: antibiotics and antifungal drugs.*** Secondary bacterial infections are often reported in animals suffering from atopic dermatitis. They are the basis of superficial and deep pyoderma, which must be further treated. Therefore, antibiotic therapy in this pathology is used as one of the most urgent measures. Usually drugs prefer a small spectrum of action. They are prescribed in fairly high doses (pre-determined body weight of the animal) and for a long time.

6. ***Antihistamines.*** These drugs block histamine receptors (not histamine release). There are two types of histamine receptors: H1 and H2. H1 is responsible, among other things, for itching and dilation of blood vessels. H2-receptor blockers are used mainly in diseases of the gastrointestinal tract - they do not relieve itching. The advantages of such drugs are fatigue, which can be used for prophylactic purposes. This sometimes reduces the cost of treatment because it helps reduce the dose of corticosteroids.

7. ***Local funds.*** Local remedies are widely used in medical dermatology, they have good prospects for the treatment of animals. Over the last 10 years, the forms of pharmacological drugs have changed significantly. Aerosols, preparations for point drawing, shampoos appeared. This pharmacological form is currently most commonly used in veterinary dermatology. The gel-aqueous solution, which is made more or less dense as a result of the addition of viscosity enhancers, is quickly absorbed and is therefore very convenient for treating areas of skin accessible to animals for licking..

1.4. Glucocorticosteroids: mechanisms of action and indications for use in veterinary medicine

The development of drugs containing corticosteroids is one of the breakthroughs in pharmacology of the last century, comparable in importance except that with the advent of antibiotics. In 1950, a group of researchers led by F.

Hench was awarded the Nobel Prize in Medicine and Physiology for the discovery of glucocorticoid hormones and the creation of glucocorticoids on this basis.

And today, despite the great achievements of pharmacology, drugs of this group continue to be the strongest anti-inflammatory drugs. The appointment of corticosteroids (in nephrology for systemic use, prednisolone or methylprednisolone is preferred) is an integral part of the pathogenetic therapy of all kidney diseases that develop by autoimmune mechanisms. This includes [42]:

- all forms of acute and subacute GN, as well as some forms of TIN in dogs and cats;
- most CKD (both acute and primary-chronic) in cats in the non-azotemic stage of their course, accompanied by isolated proteinuria or proteinuria and nephritic (inflammatory) urine sediment;
- high activity of CKD in dogs (many times less common than in cats), as well as CKD in this species in the period of exacerbation (relapse), when there is reason to believe that the pathogenesis of the disease again involved autoimmune mechanisms.

Regardless of the nosological form of the disease, which led to the development of chronic renal failure and the appearance of hyperphosphatemia (including compensated) and hyperparathyroidism, often develop in parallel with azotemia, the final stages of the renal continuum and CKD are contraindications. This is due to the fact that persistent renal dysfunction in this case is associated primarily with the processes of destruction in the renal parenchyma (atrophy, dystrophy, sclerosis, etc.), and autoimmune inflammatory processes are either long overdue or weak expressed and places of application of ACS simply do not exist [26].

It should also be borne in mind that the greater the decrease in glomerular filtration rate (GFR) (and at the time of azotemia, it is reduced, usually more than 75% of normal), the higher the nephrotoxic properties of corticosteroids. Renal insufficiency of III-IV degree according to the IRIS2 classification is a contraindication to the use of corticosteroids (exceptions are only cases where

there are vital indications for their use, such as acute allergic reactions). It is all the more unacceptable to use any dose of corticosteroids in animals with azotemia to "treat" the chronic nephropathies themselves.

In diseases of the lower urinary tract (urocystitis, urethritis) rationally short-term (1-3 days) appointment of corticosteroids as part of complex therapy to reduce edema and redness of the mucous membranes of the lower urinary tract.

Catheterization of the bladder in acute urinary retention is also an indication for local (as part of ointments and liniments) and systemic use of products containing steroid hormones (especially in cats and dogs). This is due to the fact that mechanical injury to the delicate mucous membrane of the urethra usually leads to its edema and, as a consequence, to an even greater narrowing of the urethral lumen [35].

Mechanism of action and pharmacological effects of corticosteroids

Pharmacodynamic effects of corticosteroids are realized due to their anti-inflammatory (including antiexudative and antiproliferative effects), immunosuppressive and antiallergic action. These drugs also actively affect various metabolic processes in the body.

The most important pharmacological effect of corticosteroids in terms of pathogenesis of nephropathy is, in particular, suppression of edema and proliferation of resident glomerular cells (resulting in partial or complete obliteration of vessels of the primary microcapillary network of kidneys), reduced infiltration of renal parenchyma hence, and irreversible processes of sclerosis in the renal parenchyma).

The mechanism of action of corticosteroids is complex, diverse and to date not fully understood. Since the 70's of XX century in science the theory of two-stage action of GKS prevails [49].

At intravenous administration to the patient of large doses (ie At introduction directly into a blood-groove of a large number of molecules) in some seconds the so-called direct anti-inflammatory effect of GKS develops. It is realized due to the interaction of ACS molecules with glucocorticoid receptors

(GCR3) located on cell and subcellular membranes (mitochondria and lysosomes), as well as in the cytoplasm4. The penetration of GCC molecules into cells occurs both passively, by diffusion, and actively, as part of complexes with carrier proteins. Also, due to the high lipophilicity of steroids, they are able to "dissolve" in cell membranes.

All these processes cause changes in the physical properties of membranes, especially fluidity and permeability, increase their resistance, as well as the cell as a whole, to various factors and cause antiexudative and antiproliferative effects of corticosteroids. In addition, the anti-inflammatory effect of corticosteroids is associated with their ability to reduce the permeability of the vascular wall, in particular capillaries, and have a vasoconstrictive effect in the site of inflammation.

Indirect or molecular anti-inflammatory and immunosuppressive action of glucocorticoids (with the introduction of both large and medium and small doses) is realized by [38]:

1) influence on the expression of a number of genes (at the transcriptional and posttranscriptional levels), which is carried out as a result of the influence of the activated hormone-receptor complex on the components of the cell nucleus;

2) suppressing the production of many inflammatory mediators and reducing the sensitivity of these mediators to cells involved in inflammatory and autoimmune reactions;

3) inhibition of prostaglandin synthesis at the level of arachidonic acid and anti-inflammatory cytokines.

These changes appear within 30 minutes or more (and in some cases several hours or even days) after the introduction of corticosteroids. The severity and predominance of anti-inflammatory and immunosuppressive effects in gene-mediated action directly depends not only on the dose of the drug, but also on the duration of therapy. At the same time, the method of introduction (giving) does not matter much.

Hormone therapy for nephropathies that occur by autoimmune mechanisms is a means of pathogenetic therapy, because [43]:

1) significantly reduces the intensity of autoimmune processes in the glomeruli and tubulointerstitia due to direct and indirect anti-inflammatory and immunosuppressive effects;

2) reduces the severity of the response of cells of fenestrated endothelium to damage, in particular: reduces their release of vasoconstrictive substances (endothelin-1 (Et-1), thromboxane A2 (TxA2), prostaglandin H2 (PgH2), ATII, isoprostane, acid), inhibits the synthesis and expression of procoagulant factors (thrombin, plasminogen activator inhibitor, von Willebrand factor) and inhibits the response to anti-inflammatory cytokines;

3) reduces the rate and intensity of peri and intraglomerular and peritubular infiltration of inflammatory cells;

4) reduces the porosity of the primary microcapillary network of the kidneys, including due to vasoconstriction in the site of inflammation;

5) inhibits the activity of the complement system, and hence the formation of the CEC, an integral part of which is C3;

6) slows down the intensity of the processes that eventually lead to nephrosclerosis (and hence the progressive reduction of GFR) due to the impact on the production of connective tissue growth factors (including by inhibiting hyaluronidase activity) and reducing the sensitivity of glomerular cells , mesangial matrix) and tubulointerstitium.

Conclusions to the chapter1

1. The etiology, pathogenesis and clinical features of atopic dermatitis in animals are considered.
2. The analysis of literature sources is carried out and the modern data concerning modern therapy of atopic dermatitis at animals are generalized.
3. Glucocorticosteroids, their mechanism of action and indications for use in veterinary medicine are considered.

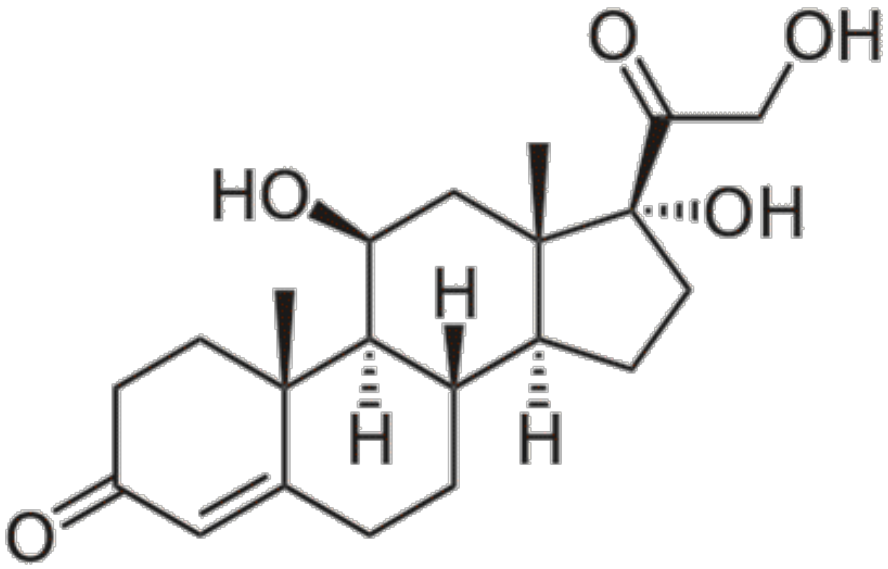
CHAPTER II

OBJECTS AND METHODS OF RESEARCH

2.1 Objects of research

Hydrocortisone

($C_{21}H_{30}O_5$)

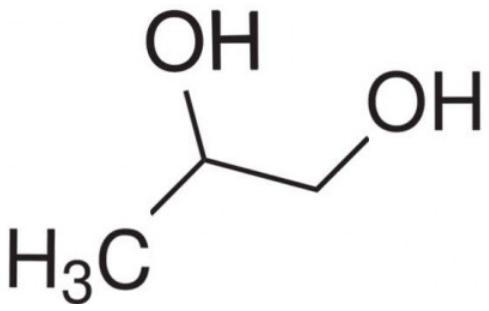


Hydrocortisone - white or almost white powder without odor, bitter taste. Solubility (mg / ml) at 25 ° C: water 0.28; ethanol 15.0; methanol 6.2; acetone 9.3; chloroform 1.6; propylene glycol 12.7; ether - about 0.35. Soluble in concentrated sulfuric acid with the formation of a fluorescent solution of intense green color. Molecular Weight 362.47.

Pharmacological action - anti-inflammatory, anti-allergic, immunosuppressive, antipruritic, antishock, antiexudative, glucocorticoida [5].

Propylene Glycol

(C3H8O2**)**



It is a colorless transparent viscous liquid with a slightly sweet taste, which is obtained chemically from refined products. Is an effective moisturizing and moisture-retaining substance. It is widely used to dissolve flavors, preservatives, pigments, natural oils and many other substances. The ability of propylene glycol to help penetrate substances is so good that propylene glycol formulations are not recommended for patients with eczema, as it can promote the penetration of other irritants into the skin. Although propylene glycol itself is not a carcinogenic or irritating component, even with prolonged use in concentrated form.

Purified water **(ДФУ 2.0, том 2, С. 129)**

Clear colorless liquid without taste and smell. Purified water can be obtained from drinking water by distillation (distilled water), ion exchange, reverse osmosis or electrodialysis. Purified water is used to make a list of liquid drugs and is the basis from which to prepare water for injection.

Aristoflex AVC

Copolymer of acrylamidomethylpropanesulfonic acid and vinylpyrrolidone. Is a neutralized crosslinked copolymer of acrylamidopropylpropanoic sulfonic acid and vinylpyrrolidone. Emulsions with Aristoflex AVC have good rheological and sensory properties, can be manufactured at low pH values (from 4) and remain stable even without additional introduction of emulsifiers. The polymer is pre-neutralized, so no neutralization step is required.

Sepimax Zen

Snow. High-tech thickener to create transparent gel structures. Resistant to electrolytes. Suitable for moisturizing gels and serums, and for thickening detergents. Before use, it is recommended to dilute in a small amount of warm water - this will avoid the formation of lumps and get a more uniform texture.

Carbopol Ultrez 21

White hygroscopic powder weakly acidic reaction, swells in water and other polar solvents after dispersion and forms stable gels when neutralized with alkaline solutions.

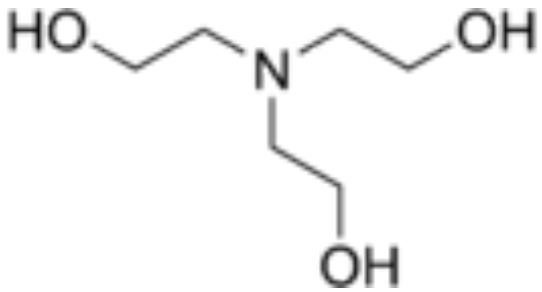
Soluble in water. Neutralization is required. To neutralize and preserve, add up to 1% alkaline solution dropwise to form a gel. As an alkaline solution, it is best to take triethanolamine, or 18% sodium hydroxide solution (NaOH), a solution of borax in glycerin or, in the worst case, a solution of baking soda. However, when using soda, the gel comes out with bubbles

Carbopol is a high molecular weight carboxyvinyl polymer. Carbopol is widely used in the cosmetic and pharmaceutical industries, used in eye drops, toothpastes, baby gels for gums, in natural cosmetics. Carbopol contains ionized areas that retain water around the molecule due to electrostatic forces.

Carbopol is sensitive to pH in the formula. To prepare the gel, carbopol must be completely dissolved in water. When the pH increases to 7 (range 5-8) carbopol gives the structure of the gel. Neutralization is usually performed with inorganic bases (NaOH, KOH) or amines (triethanolamine).

Triethanolamineн

(HO-CH2CH2) 3N



Colorless liquid, miscible with water in all respects, weak base. It is used together with carbopol as a neutralizer.

2.2 Research methods

Description. Controlled the appearance and organoleptic properties of gel samples - color, odor. The studied samples of gel bases, the developed drug was controlled for the presence of a rancid odor, as well as the presence of physical instability (aggregation of particles, coagulation, coalescence, delamination) [5].

Definition of homogeneity. The determination was carried out according to the method described in the SFU I ed., Art. 511. Take five samples of each sample of 20-30 mg each, place two samples on a glass slide, cover with a second glass slide and press firmly to form spots with a diameter of about 2 cm [15].

The obtained samples were examined with the naked eye (at a distance of about 30 cm from the eyes). The sample was considered homogeneous if in all four samples no visible particles, foreign inclusions and signs of physical instability were detected. If one of the samples did not pass the test, the determination was performed on an additional eight samples, and all eight samples had to pass the test [28].

Determination and control of the appearance of samples and organoleptic properties were performed by visual and organoleptic methods in accordance with modern requirements of the SPU (1st ed., 2.2.3). Control of organoleptic properties of gel samples was performed on the following indicators: appearance, color, odor, consistency [5].

Determination of thermal stability. The determination was performed according to modern methods, which are presented in the National Standard of Ukraine "Cosmetic creams. General technical conditions: DSTU 4765: 2007.

A tube of 8.0 ± 2.0 g of test samples was placed in a thermostat with a temperature of (40 ± 2) ° C was left for 1 week, then placed in a refrigerator with the appropriate temperature (10 ± 2) ° C for 1 week, then kept for 3 days at room temperature (15-25º C). The stability of the studied gel samples was determined visually - in the absence of delamination [5].

Determination of colloidal stability.

The tubes were filled with test samples of 2/3 volume (approximately 9.0 g) of the test samples (so that the weights of the test tubes with the drug did not differ by more than 0.02 g), and weighed to the nearest 0.01 g The tubes were then placed in a water bath at the desired temperature (42.5 ± 2.5) ° C for 20 min, then wiped dry on the outside and placed in centrifuge wells. Centrifuged for 5 min at 6000 rpm [17]. The stability of the studied gel samples was determined visually - in the absence of delamination.

Determination of solubility. According to SPU 1.2, Art. 36 [5].

Determination of pH value. The pH level of the studied samples was determined potentiometrically (HFC I ed., 2.2.3). For samples with electrically conductive medium - emulsions o / v pH determination was performed on a universal ionometer EV-74 directly on the samples themselves - by the express method (pH meter is designed for analysis of solutions of weak ionic strength, as well as soft dosage forms). The electrodes of the calibrated potentiometer were immersed in a beaker and the pH was determined. The test was performed 5-6 times with new portions of the studied samples [5].

Determination of rheological properties. Rheological properties of the samples were determined using a rotary viscometer Brookfield HB DV (USA), spindle SC4 - 21.

The samples were thermostated using a tratermostat. A portion of the gel of about 17.0 (± 0.5) g was placed in the container of the outer stationary cylinder. The required test temperature was set with the help of a thermostat, then the necessary test conditions were set with the help of software (shear rate gradient, number of test points on the sample flow curve and measurement duration at each point of the curve). The device allows you to measure the shear stress in the range of 0.5 - 3.0 · 104 PA, shear rate from 0.1 to 4000 s -1, viscosity - 1 - 109 MPa · s.

Calculation of mechanical stability of gel samples. For a more complete study of gel samples, the indicators of their mechanical stability (MS) were calculated. It is known that the optimal value of MS is 1. The value of MS is defined as the ratio of the value of the tensile strength of the structure to failure ($\tau 1$) to the value of the tensile strength after failure (τ_2) [5].

$$\mathrm{MS} = \frac{\tau_1}{\tau_2}, \text{ (2. 1)}$$

To study the extrusion properties according to the indicators of rheological studies, the coefficients of dynamic dilution (Kd) were calculated for the drug during the shelf life according to the formula (2.2).

$$Kd = \frac{(\eta_{18,6} - \eta_{93,0}) \times 100\%}{\eta_{18,6}}, \text{ (2. 2)}$$

where $\eta_{18,6}$ – viscosity of the gel at shear rate 18,6 s^{-1},

$\eta_{93,0}$ - viscosity of the gel at shear rate 93,0 s^{-1} .

CHAPTER III

JUSTIFICATION OF THE COMPOSITION AND DEVELOPMENT OF GEL TECHNOLOGY FOR THE TREATMENT OF ATOPIC DERMATITIS IN ANIMALS

3.1. Analysis of the range of drugs for the treatment of atopic dermatitis in the pharmaceutical market of Ukraine

In small animals (cats and dogs), pathologies such as hypersensitivity to flea bites and atopic dermatitis have become one of the most common reasons for consulting a veterinary dermatologist. Cases of spontaneous healing in these diseases are almost not observed. Long-term therapy is usually needed to help control the disease and keep the patient in a satisfactory condition. The most effective drugs in the treatment of allergic diseases are glucocorticoids [40]. The analysis of the market of veterinary drugs for the treatment of allergic diseases shows that currently the range is represented by only 11 drugs (Table 3.1). Due to the catastrophic shortage of drugs, humane drugs (suprastin, tavegil, etc.) are often prescribed in a reduced dose by a veterinarian.

Table 3.1

Range of veterinary drugs for the treatment of atopic dermatitis in animals

№	The name of the drug	Composition	Release form	Producer
1	2	3	4	5
1.	**Апоквель**	oklacitinib maleate (in terms of oklacitinib) 3.6 mg; 5.4 mg and 16 mg, respectively	16 mg 20 tablets 5.4 mg 100 tablets	Zoetis USA
2.	**Аллергостоп для собак**	triamcinolone - 0.1%, vit. B2 - 0.4%, vit. B6 - 0.2%, vit. PP - 0.02%, methionine - 0.1%	suspension, 15 ml	Ukraine

Continuation of the table. 3.1.

1	2	3	4	5
3.	**Аллергостоп для кішок**	triamcinolone - 0.1%, vitamin B2 - 0.4%, vitamin B6 - 0.2%, vitamin PP - 0.02%, methionine - 0.1%	suspension, 10 ml	Ukraine
4.	**Аллергостоп для кішок і собак**	triamcinolone - 0.05%, chloramphenicol - 0.5%, metronidazole - 1%, lidocaine hydrochloride - 5.0%, calendula extract - 0.4%	spray, 30 ml	Ukraine
5.	**Ветадекс**	dexamethasone sodium phosphate - 2.64 mg (equivalent to 2 mg dexamethasone)	розчин для ін'екій, 50 мл	Ukraine
6.	**Дексавет**	1 ml of solution contains: dexamethasone sodium phosphate - 0,0027 g	solution for injection, 50 ml	Brovapharma Ukraine
7.	**Декса-кел**	dexamethasone phosphate eq. 2 mg dexamethasone	solution for injection, 50 ml	Kela, Belgium
8.	**Екзекан**	dexamethasone 1 mg, nicotinamide (vitamin PP) 10 mg, pyridoxine hydrochloride (vitamin B6) 50 mg, methionine 300 mg	sugar cubes 16 pcs	Ceva Sante Animale France
9.	**Дексаметазон**	1 ml of the drug contains: dexamethasone disodium phosphate - 2 mg.	solution for injection, 100 ml	Alfasan, Netherlands
10.	**Санодерм**	betamethasone dipropionate, clotrimazole, gentamicin sulfate	ointment, 15 g	Arterium, Ukraine
11.	**Тріосан**	1 g of cream contains active substances: dexamethasone - 0.64 mg, ciprofloxacin hydrochloride - 10 mg, clotrimazole - 10 mg.	cream, 20 g	Ukraine

Table 3.1 shows that 10 drugs as an active ingredient contain glucocorticoids (triamcinolone - 3 drugs, dexamethasone - 6 drugs, betamethasone - 1 drug) and 1 drug as an active ingredient contains oklacitinib - a specific inhibitor of Janus kinase (Fig. 3.1.) [1, 4, 7].

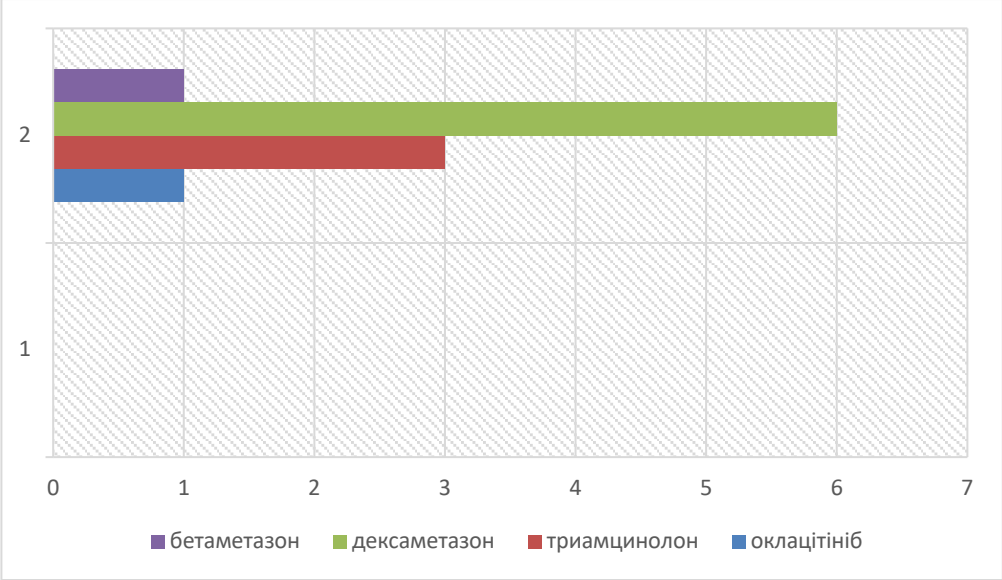


Fig. 3.1. Active ingredients in veterinary drugs for the treatment of atopic dermatitis in animals

In general, medicines present on the Ukrainian veterinary pharmaceutical market are presented in the form of tablets, creams, ointments, suspensions, solutions for injections, sugar cubes (Fig. 3.2).

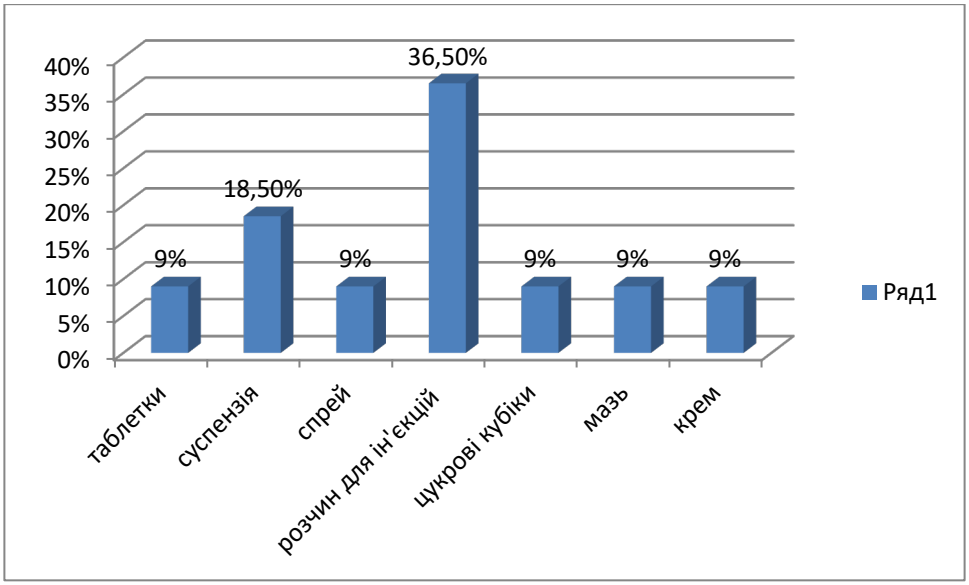


Fig. 3.2. The range of drugs for the treatment of atopic dermatitis by dosage form

As can be seen from the data in the table (given in Table 3.1.), The range of these veterinary drugs is small, which necessitates the development of a new

veterinary drug for the treatment of atopic dermatitis in domestic animals. At present, the market is represented by veterinary drugs of both domestic and foreign production in approximately equal percentages (Fig. 3.3.) [7, 18, 20].

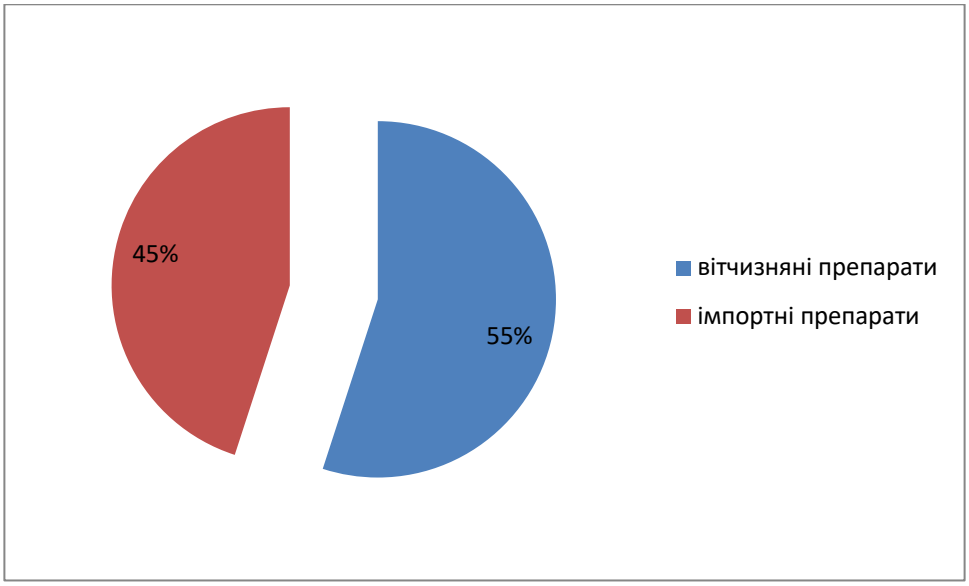


Fig. 3.3. The range of drugs for the treatment of atopic dermatitis by manufacturers

3.2 Justification of the gel composition

The composition of the veterinary drug should be determined by scientific and experimental studies on the choice of active pharmaceutical ingredients (APIs), excipients, and their required concentration, respectively. It should be noted that the high therapeutic activity of the veterinary drug can be achieved only with the right combination of active ingredients and base [10, 17].

Based on the literature search for local therapy of atopic dermatitis in animals, we chose a mild dosage form in the form of a gel. When developing a mild veterinary medicinal product, it is necessary to pay attention to the type of carrier used, nature and physicochemical properties of active pharmaceutical ingredients, excipients (solvents, moisturizing components, etc.), take into account the influence of pH, temperature and other factors. on structural-mechanical, technological properties of the developed gel basis. These factors contribute to the

release and absorption of active pharmaceutical ingredients from the mild dosage form [24].

Thus, a properly selected mild dosage form with appropriate active ingredients, such as a carrier base and excipients will have the necessary powerful therapeutic activity.

Dosage form in the form of a gel in veterinary medicine

Gel is an ointment in which gel-forming agents of natural and synthetic origin are used to obtain the base, which has an elastic-plastic consistency and is able to retain its shape. Intended for external use. It is used to treat skin diseases and for resorptive action. Unlike ointments, various gelling agents are the formative substance in the gel. Compared to ointments, gels are a very promising dosage form, as they have a pH close to the pH of the skin, are quickly made, do not clog skin pores, quickly and evenly distributed on its surface, they can include hydrophilic drugs, you can make suspension gels [6, 22].

Currently, in order to introduce into pharmaceutical practice soft dosage forms based on gel is actively studying the properties of gel polymers (Russian - Arespol, Mars; Belgian - Ultrez 10; German - Carbopol 940, Carbopol 941, Carbopol 2020 and Carbopol 2001) and etc.

Advantages of gels:

- they have a prolonged effect on the background of rapid absorption;
- easily gets on clothes without leaving traces.

Based on the literature review, it is important to choose the right base when developing a new topical drug in the form of a gel. The first and important indicator in the development of topical drugs is the compliance of the pH of the drug to the pH of animal skin, it has a great influence on the release of active pharmaceutical ingredients from the base and prevent irritant reactions [8, 15].

It is known that the normal skin pH of dogs is 5-7.5, in cats - 3-6, and in humans the rate varies from 3.5 to 4.5 [29]. Accordingly, the pH of the developed

gel should be in the range from 5.0 to 5.5. In view of this, we have chosen the following substances as gelling agents: Aristoflex AVC, Sepimax and Carbopol brand Ultrez 21. These gelling agents work in our chosen pH mode.

Aristoflex AVC – is a neutralized crosslinked copolymer of acrylamidopropylpropanoic sulfonic acid and vinylpyrrolidone. Gels with Aristoflex AVC have good rheological and sensory properties, can be manufactured at low pH values (from 4) and remain stable even without the additional introduction of emulsifiers.

Properties and benefits of Aristoflex® AVC:

- gives the skin a fresh effect, makes it silky and soft;
- in combination with plant extracts used in the recipe helps to effectively cleanse the skin;
- has a mild lifting effect;
- has an active effect on the intensity and duration of exposure to the skin of biologically active substances;
- used in drugs used in the treatment of demodicosis and blepharitis;
- is resistant to ultraviolet radiation;
- is a stabilizing component with the introduction of sunscreens and various components with a bleaching effect.

SepiMAX ZEN – high-tech thickener to create transparent gel structures. Resistant to electrolytes. Suitable for moisturizing gels and serums, and for thickening detergents. Before use, it is recommended to dilute in a small amount of warm water - this will avoid the formation of lumps and get a more uniform texture. Emulsifies a small amount of oils. The viscosity of SepimaX (SepiMAX ZEN) is stable in a wide pH range from 2 to 8.

Carbomer Carbopol Ultrez 21 – in pharmacology carbopol plays the role of gelling agent. It is the basis for gels and creams-gels: without it they would flow like water. It is he who gives them the comfortable structure that we like so much in gels.

Carbopol gives stable formulations: the gel with carbopol does not flake off, does not dry out, does not clump, does not change color. Easy to use: soluble in water, easily mixed with any active ingredients.

Advantages of carbopol:

- high viscosity of gels at low concentrations of polymer;
- hermal and microbiological resistance;
- stability and chemical stability during storage;
- compatibility with many active substances;
- the ability to obtain gels with a wide pH range from 4 to 10;
- the ease of controlling the viscosity properties of the obtained gels;
- ability to stabilize emulsions;
- hypoallergenicity;
- ease of application and removal from the skin surface;
- high absorption of active and medicinal substances.

Recommendations for use: the percentage of introduction of 0.1-1.5. Dilute with water, mix, wait 1-2 hours until the lumps swell, mix well again, neutralize with alkali (you can add a few drops of borax solution in glycerin). The gel will remain thick at a pH of 5.5 to 8. If you add alkaline or acidic ingredients, the pH will change and the gel may turn into water. The addition of oils can lead to clouding of the gel [9, 16].

Selection of active pharmaceutical ingredients

The composition of a veterinary medicinal product for the topical treatment of atopic dermatitis should include an active pharmaceutical ingredient that has targeted anti-inflammatory, antimicrobial and reparative effects. And also had the appropriate properties to improve the condition of animal skin.

Corticosteroid hormones (glucocorticoids) are one of the most powerful antiallergic drugs. They are effective in treating almost all types of allergic reactions. The reason is in their structural similarity to some adrenal hormones. The mechanism of their antiallergic action is very diverse: they reduce the

permeability of capillaries, inhibit the inflammatory reaction and the growth of connective tissue, have the effect of replacement therapy in adrenal insufficiency. It has been established that glucocorticoids affect the development of any stage of allergic reactions, but most of all - the pathophysiological stage. At the same time, their anti-inflammatory effect is manifested as much as possible [19].

As veterinary practice shows, most often atopic dermatitis in animals manifests itself in the form of a rash (in the ears, muzzle, paws, etc.), which in turn is accompanied by itching. First of all, prescribe a single injection of glucocorticoids, or short-term therapy (2-3 days). An appropriate dose of glucocorticoids is required to obtain a rapid effect, and the form of the drug should be convenient to use.

Hydrocortisone - a hormone secreted by the adrenal cortex - glucocorticoid. Pharmacological action of hydrocortisone - anti-inflammatory, antiallergic, immunosuppressive, antipruritic, antishock, antiexudative, glucocorticoid. When applied to the skin: inflammatory and allergic skin diseases of non-microbial etiology, including eczema, dermatitis (allergic, atopic, bullous herpetiform, exfoliative, seborrheic, contact); itchy dermatoses, photodermatoses, anogenital itching, insect bites, pemphigus, erythroderma, psoriasis [19].

Given the above, the gel for the treatment of atopic dermatitis in animals as API was chosen glucocorticoid - hydrocortisone.

The choice of excipients in the gel

Propylene glycol is a polyhydric alcohol obtained by hydrolysis of propylene oxide. Its widespread use in the pharmaceutical industry is due:

1. Proven safety for the human body. It is non-toxic by inhalation of its vapors, dermal application, entry into the gastrointestinal tract, as well as intravenous or intramuscular injection.

2. Ability to dissolve both hydrophilic and hydrophobic chemical compounds. Due to this, it became possible to mix previously incompatible

substances in one solution, thus creating new multicomponent drugs. Therefore, propylene glycol is used as a solvent and filler in medicines.

3. Weak bactericidal action. This property is used in the production of aerosols and liquids for disinfection of air and surfaces in hospitals and homes, restaurants and vehicles. In addition, propylene glycol is used as a stabilizer in many drug solutions for intravenous or intramuscular administration.

4. Participation in the construction of the lipid membrane of all human cells and the ability to transport large molecules of hydrophobic and hydrophilic drugs into the cell. Therefore, it is used as a carrier in medicines, especially in the form of ointments for external application.

5. The ability to absorb and retain moisture, reduce the severity of edema and the ability to soften the surface layer of the epidermis. Many moisturizing massage creams contain propylene glycol. In combination with its bactericidal properties, it has found application in the creation of multicomponent ointments designed to treat and accelerate the healing of wounds, calluses, trophic ulcers and fistulas on the skin and mucous membranes [12, 13, 21].

The choice of the optimal amount of propylene glycol in the gel base is based on the study of the osmotic activity of the samples. Its concentration in 8% is defined as optimum.

To establish a rational gelling agent, we have prepared the following model samples. The concentration of hydrocortisone (1%) was selected on the basis of analysis of literature sources and propylene glycol (8%) on the basis of research. Model samples were prepared by the technology of gel preparation generally prescribed in the SPU (shown in Table 3.2.).

Table 3.2.

Samples of gels with hydrocortisone were studied

№	APIs / excipients	Samples		
		№1	№2	№3

1.	Carbopol Ultrez 21	1,5	-	-
2.	Trometamol	1,5	-	-
3.	Sepimax	-	1,5	-
4.	Aristoflex			1,5
5.	Hydrocortisone	1,0	1,0	1,0
6.	Propylene glycol	10,0	10,0	10,0
7.	Purified water	Up to 100,0		

The results of the obtained data are presented in table 3. 3:

Table 3.3.

The results of studies of samples of gels with hydrocortisone

№	Indicators	Sample number		
		№1	№2	№3
1.	Appearance	Gel transparent white color	Gel transparent white color	Gel transparent white color
2.	pH of 0 % solution	7,6±0,2	7,5±0,3	5,5±0,2
3.	Structural viscosity, η (MPa · s)	6800	1900	3700
4.	Colloidal stability (at 6000 rpm)	-	-	+
5.	Mechanical			

	stability (MS)	1,63	1,55	1,33

According to experimental data, we excluded from further studies samples №№ 1, 2. In the studied samples under the influence of a complex of active substances, the gel structure was destroyed.

Thus, for further research we selected sample № 3 based on Aristoflex at a concentration of 1.5%, which had satisfactory consumer, physicochemical and structural-mechanical properties, respectively.

The next stage of our research was to study the effect of selected substances on the rheoparameters of the gel system with aristoflex:

- sample № 1 – gel base;
- sample № 2 – gel base + hydrocortisone
- sample № 3 – gel base + hydrocortisone + propylene glycol;
- sample № 4 – gel base + propylene glycol + hydrocortisone.

The obtained rheograms (Fig. 3.4) show that with the introduction of active (hydrocortisone) and auxiliary (polyethylene glycol) substances, the type of flow did not change and was characterized as plastic [32].

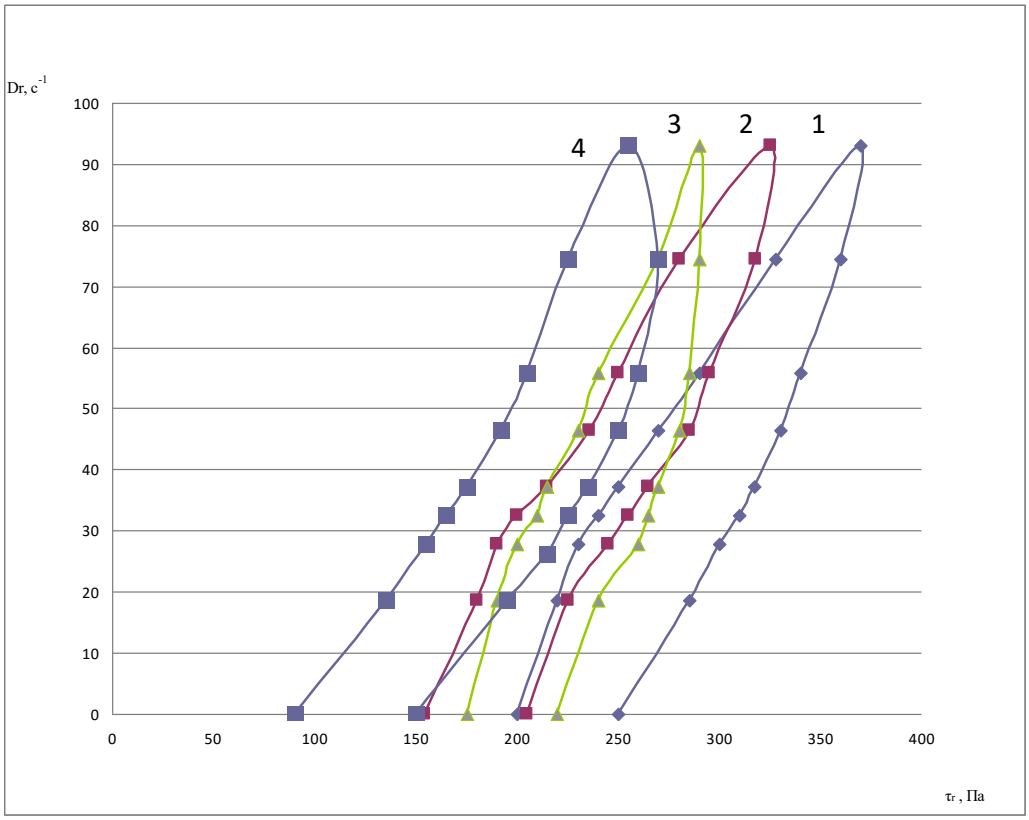


Fig 3. 4. Rheograms of gels: 1 - gel base; 2 - gel base + hydrocortisone; 3 - gel base + hydrocortisone + propylene glycol; 4 - gel base + propylene glycol + hydrocortisone

The results of our research show that the structural viscosity was restored when the shear stress was reduced. The "ascending" curves of the hysteresis loops indicated a decrease in structural viscosity after the destruction of the structure of hydrocortisone gels, and the "descending" curves reflected the optimal state of equilibrium in which the systems were after the destruction. It is noted that the addition of hydrocortisone reduced the rheoparameters, and also proved that the technology of introduction of sample № 3 is rational: first hydrocortisone, then propylene glycol. It is his system that is more structured, which is primarily due to the addition of glucocorticosteroids.

These data are confirmed in digital format and are given in table. 3. 4:

Table 3. 4

The results of studies of the selected gel with hydrocortisone

Sample number	Components	η, mPa · s	MS
№ 1	gel base + hydrocortisone + propylene glycol	13100	1,16
№ 2	gel base + propylene glycol + hydrocortisone	10500	1,23

From the data presented in the table it can be concluded that the two samples have satisfactory performance for a stable gel system. However, for further research, we selected sample № 1, which has higher viscosity and better values of mechanical stability (MS), namely 13100 and 1.16, respectively.

When studying the dependence of structural viscosity on the shear rate gradient, it is seen that the structural viscosity of the studied gel samples gradually

decreased with increasing shear rate gradient (Fig. 3.5).

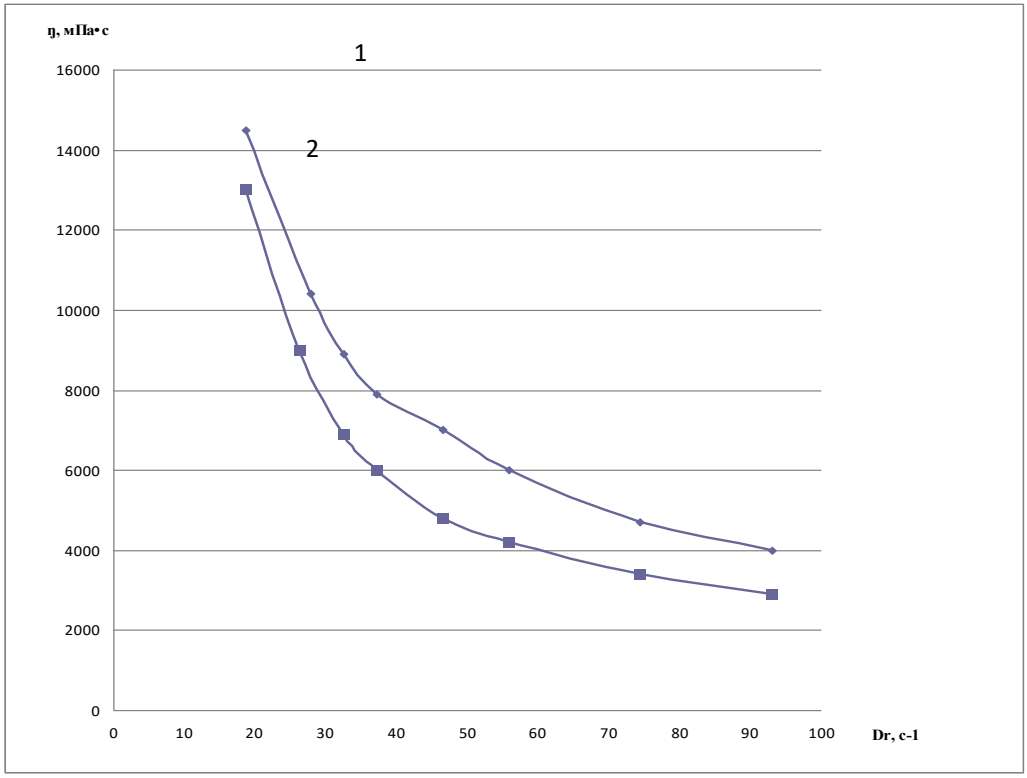


Fig. 3. 5. Dependence of structural viscosity of hydrocortisone gels on shear rate: sample № 1, sample № 2.

This dependence is also characteristic of systems that have a plastic type of flow and characterizes the studied samples of gels as structured dispersed systems in which the addition of active and excipients does not interact with the developed gel base, and involves uniform and gradual application to the skin.

Thus, we can conclude that the use of aristoflex as a gelling agent in the development of a veterinary drug of local action will ensure the availability of appropriate extrusion properties (namely, easy and even application of animal skin, ease of use).

3.3. Development of hydrocortisone gel technology

According to the current requirements of the SPU, the technology of soft dosage forms should consist of preparation of the base and the introduction of active pharmaceutical ingredients [11, 14].

A typical technological process of obtaining a gel consists of:

– stages of ancillary work;

– stages of the main technological process;

– stages of packaging, labeling and shipment to the warehouse of finished products [23].

The optimal amounts of solvents required for each technological stage were calculated taking into account the solubility of the gel components, the sequence and stages of mixing of the components, temperature and other parameters and their impact on the quality of the drug [11].

Stage 1. Weighing of components.

Raw materials for gel preparation after passing the input control are weighed using BP-1 and BP-5:

Aristoflex	1,5
Hydrocortisone	1,0
Propylene glycol	10,0
Purified water	up to 100,0

Stage 2. Preparation of gel base.

Pre-calculated amount of purified water is measured with a measuring cylinder and placed in a glass container № 1. Weigh the required amount of Aristoflex on the scales and add to the water.

Then stir vigorously with a glass rod for 5 minutes at room temperature to obtain a homogeneous transparent gel-like mass (Fig. 3.6.).

Fig. 3.6. Gel base with aristoflex

Stage 3. Obtaining and homogenizing gel

Hydrocortisone is injected into the container № 2 with a pre-prepared gel base according to Deryagin's rule (by suspension type). Then weigh the propylene glycol. Stir thoroughly for 10 minutes to obtain a homogeneous mass.

After homogenization, we take a control sample and analyze the intermediate product - the finished gel - a homogeneous mass of semi-white odorless (Fig. 3.7.).

Fig. 3.7. Ready gel with hydrocortisone

Conclusions to the chapter 3

1. The analysis of the current state of the market of veterinary drugs used for atopic dermatitis in animals. The urgency of creating a complex action gel for the local treatment of atopic dermatitis has been proved.

2. The optimal composition of the gel with hydrocortisone was chosen.

3. The technology of gel with hydrocortisone is developed.

CONCLUSIONS

1. The current state of treatment of atopic dermatitis in animals has been studied. Literature data on clinical manifestations and pathogenesis of atopic dermatitis are summarized.
2. The state of the pharmaceutical market of Ukraine in relation to veterinary drugs used in the treatment of atopic dermatitis has been studied. The expediency of creating a new drug in the form of a gel for the local treatment of atopic dermatitis in animals has been proven.
3. The composition and technology of the gel for the local therapy of atopic dermatitis in animals with glucocorticosteroid - hydrocortisone have been developed.

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APPENDIX

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of technology of drugs

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
f technology of drugs

_____

Tetyana YARNYKH
"24" May 2021

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Sadiq HAJAR

1. Topic of qualification work: «Research on the development of hydrocortisone gel technology for veterinary use», supervisor of qualification work: Viktoriia PUL-LUZAN, PhD, assoc. prof.,

approved by order of NUPh from "17th" of February 2022 № 76

2. Deadline for submission of qualification work by the applicant for higher education: april 2022.

3. Outgoing data for qualification work: The purpose of the study is to develop an extemporaneous gel with hydrocortisone for local treatment of atopic dermatitis in accordance with structural and mechanical studies.

4. Contents of the settlement and explanatory note (list of questions that need to be developed):

• analyze the literature on the definition, classification, etiology, epidemiology, pathogenesis, clinical picture and diagnosis of atopic dermatitis in animals, the main aspects of systemic and local therapy of atopic dermatitis in animals, and study the range of veterinary drugs in the pharmaceutical market of Ukraine for symptomatic treatment of atopic dermatitis in animals;
• substantiate the feasibility of creating a new gel with hydrocortisone atopic dermatitis in animals;
• theoretically substantiate the composition (choice of API and excipients) of the gel for the complex treatment of atopic dermatitis in animals;
• to establish a rational concentration of hydrocortisone and choose the optimal gelling agent to create a new stable gel for the treatment of atopic dermatitis in animals.

5. List of graphic material (with exact indication of the required drawings):
tables – 4, pictures – 12

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Viktoriia PUL-LUZAN, assoc. professor of higher education institution of department of technology of drugs	10.06.2021	10.06.2021
2	Viktoriia PUL-LUZAN, assoc. professor of higher education institution of department of technology of drugs	21.10.2021	21.10.2021
3	Viktoriia PUL-LUZAN, assoc. professor of higher education institution of department of technology of drugs	15.12.2021	15.12.2021

7. Date of issue of the assignment: «24» May 2021.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Choice of theme	June 2021 year	**done**
2	Analysis of literature sources	October 2021 year	**done**
3	Conducting experimental research	November 2021 year	**done**
4	Registration of work	December 2021 year	**done**
5	Providing finished work to the commission	March 2022 year	**done**

An applicant of higher education _____ Sadiq HAJAR

Supervisor of qualification work _____ Viktoriia PUL-LUZAN

ВИТЯГ З НАКАЗУ № 76

По Національному фармацевтичному університету
від 17 лютого 2022 року

1. нижченаведеним студентам 5-го курсу 2021-2022 навчального року, навчання за освітньо-кваліфікаційним рівнем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація освітня програма – фармація, денна форма навчання (термін навчання 4 роки 10 місяців), які навчаються за контрактом, затвердити теми магістерських робіт:

№ з/п	Прізвище студента	Тема магістерської роботи	Посада, прізвище та ініціали керівника	Рецензент магістерської роботи
по кафедрі технології ліків				
1.	Садік Хаджар	Дослідження з розробки технології гелю з гідрокортизоном для застосування у ветеринарії Research on the development of hydrocortisone gel technology for veterinary use	доц. Пуль-Лузан В.В.	доц. Ковалевська І.В.

Підстава: подання декана, згода ректора.

Ректор

Вірно. Секретар

УКРАЇНА Національний фармацевтичний університет Факультет з підготовки іноземних громадян №02010936 місто Харків

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Sadiq HAJAR

on the topic: «Research on the development of hydrocortisone gel technology for veterinary use»

Relevance of the topic. One of the most common diseases among animals is atopic dermatitis. According to statistics, compared to previous years, the number of animals affected by this pathology is rapidly increasing. According to experts, modern environmental conditions that provoke the susceptibility of animals to allergens are to blame for all this. The purpose of this study is to develop the optimal technology for creating a gel with hydrocortisone for the treatment of atopic dermatitis in animals.

Practical value of conclusions, recommendations and their validity. The practical value of the work is based on theoretical and experimental substantiation of the composition and technology of hydrocortisone gel for the treatment of atopic dermatitis in animals. With the help of structural and mechanical studies, the optimal gelling agent - aristoflex was selected to create a stable gel.

Assessment of work. Qualification work in terms of theoretical and practical research fully meets the requirements for qualification work.

General conclusion and recommendations on admission to defend. The qualification work of Sadiq HAJAR can be submitted for defense to the Examination Commission of the National University of Pharmacy for the award of the educational qualification level of master

Scientific supervisor _____ Viktoriia PUL-LUZAN

«15th» of April 2022

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Sadiq HAJAR

on the topic: «Research on the development of hydrocortisone gel technology for veterinary use»

Relevance of the topic. Treatment of atopic dermatitis of animals is always lifelong, the disease can not be cured, have to take some life measures to correct it and the favorable existence of animals with allergens. Topical application of ointments, gels, sprays is recommended to control local manifestations. With this in mind, the Department of Drug Technology is developing a gel with hydrocortisone for the treatment of atopic dermatitis in animals.

Theoretical level of work. The paper analyzes the literature on atopic dermatitis in animals, the main aspects of systemic and local therapy of atopic dermatitis in animals, studied the range of veterinary drugs in the pharmaceutical market of Ukraine for local treatment of atopic dermatitis in animals; the expediency of creating a new tool in the form of a gel with hydrocortisone for local therapy of atopic dermatitis in animals is substantiated.

Author's suggestions on the research topic. The author theoretically substantiates the composition and technology of hydrocortisone gel for the treatment of atopic dermatitis in animals; research on structural and mechanical parameters of the investigated solution was carried out.

Practical value of conclusions, recommendations and their validity. On the basis of organoleptic, structural-mechanical, pharmacotechnological researches carried out by the author the structure and rational technology of preparation of gel with hydrocortisone for treatment of atopic dermatitis at animals in the conditions of drugstores are proved.

Disadvantages of work. According to the text of the work there are spelling and grammatical errors.

General conclusion and assessment of the work. The qualification work of Sadiq HAJAR can be submitted for defense to the Examination Commission of the National University of Pharmacy for the award of a master's degree.

Reviewer _____ assoc. prof. Inna KOVALEVSKA

«22nd» of April 2022

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 10
«28» квітня 2022 року
м. Харків

засідання кафедри
технології ліків

Голова: завідувачка кафедри, доктор фарм. наук, професор Тетяна ЯРНИХ
Секретар: канд. фарм. наук, доцент Володимир КОВАЛЬОВ

ПРИСУТНІ: професор Олександр КОТЕНКО, професор Юлія ЛЕВАЧКОВА, доцент Марина БУРЯК, доцент Оксана Данькевич, доцент Ганна ЮР'ЄВА, доцент Вікторія ПУЛЬ-ЛУЗАН, асистент Світлана ОЛІЙНИК

ПОРЯДОК ДЕННИЙ

1. **Про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт другого (магістерського) рівня вищої освіти**

СЛУХАЛИ:
Здобувача вищої освіти 5 курсу групи Фс17(5.0д)-03 спеціальності 226 Фармація, промислова фармація Садік ХАДЖАР з доповіддю на тему Дослідження з розробки технології гелю з гідрокортизоном для застосування у ветеринарії» (науковий керівник: доцент Вікторія ПУЛЬ-ЛУЗАН).
УХВАЛИЛИ:
Рекомендувати до захисту кваліфікаційну роботу.

Голова засідання **Тетяна ЯРНИХ**

Секретар **Володимир КОВАЛЬОВ**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Садік Хаджар до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Дослідження з розробки технології гелю з гідрокортизоном для застосування у ветеринарії».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Садік Хаджар представила кваліфікаційну роботу, яка за об'ємом теоретичних і практичних досліджень повністю відповідає вимогам до оформлення кваліфікаційних робіт.

Керівник кваліфікаційної роботи

_____ Вікторія ПУЛЬ-ЛУЗАН

«15» квітня 2022 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Садік ХАДЖАР допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
технології ліків

_____ Тетяна ЯРНИХ

«28» квітня 2022 року

Qualification work was defended

of Examination commission on

« ___ » _____ 2022

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /