FA 2.2.1-32-367

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
faculty for foreign citizens' education
Department of Industrial Technology of Drugs

QUALIFICATION WORK

on the topic: **"DEVELOPMENT OF THE COMPOSITION OF CAPSULES WITH DRY CRANBERRY EXTRACT"**

Prepared by: Higher education student of the group (Phm 18 (4,10d)-03 English) specialties 226 Pharmacy, industrial pharmacy of the educational program Pharmacy
Youness SADIK
Supervisor: Head of the Department of Industrial Technology of Drugs, professor,
Olena RUBAN
Reviewer: Head of the Department of Drug Tecnology, professor,
Liliia VYSHNEVSKA

Kharkiv – 2023

ANNOTATION

Qualification work contains 44 pages, 6 tables, 8 figures, a list of references of 41 titles.

To develop the composition of hard capsules for the treatment of cystitis, active pharmaceutical ingredients of natural origin were selected - dry cranberry extract and dry St. John's wort extract. Based on a set of studies selected: filler - microcrystalline cellulose, moisture regulator - Syloid 244FP, lubricant - Compritol 888 ATO. The technology of obtaining hard gelatin capsules has been developed.

Key words: capsules, cystitis, composition, technology.

АНОТАЦІЯ

Кваліфікаційна робота містить 44 сторінки, 6 таблиць, 8 рисунків, список літератури з 41 найменувань.

Для розробки складу твердих капсул для терапії циститу були обрані активні фармацевтичні інгредієнти природного походження – сухий екстракт журавлини та сухий екстракт звіробою. На підставі комплексу досліджень підібрано: наповнювач – мікрокристалічну целюлозу, вологорегулятор – Syloid 244FP, лубрикант – Compritol 888 ATO. Розроблено технологію одержання твердих желатинових капсул.

Ключові слова: капсули, цистит, склад, технологія.

CONTENTS

INTRODUCTION 5

SECTION 1 CYSTITIS: ETIOLOGY, PATHOGENESIS AND MODERN ASPECTS OF TREATMENT 8

1.1 Cystitis: etiology and pathogenesis 8

1.2 Modern tactics of cystitis treatment 11

Conclusions 16

EXPERIMENTAL PART

SECTION 2 RESEARCH OBJECTS AND METHODS 17

2.1 Rationale for selecting API in hard capsules 17

2.2 Characterization of the research objects 19

2.3 Characterization of research methods 20

Conclusions 24

SECTION 3 SUBSTANTIATION OF THE COMPOSITION OF HARD CAPSULES FOR THE TREATMENT OF CYSTITIS 25

3.1 Analysis of medicines for the treatment of cystitis available on the Ukrainian pharmaceutical market 25

3.2 Study of physicochemical and pharmacotechnological properties of APIs 29

3.3. Experimental substantiation of the choice of excipients in the composition of the encapsulation mass 32

3.4 Selecting the optimal humidifier 33

3.5. Selecting the optimal lubricant concentration 34

3.6. Substantiation of the technology for obtaining hard capsules 35

Conclusions 39

GENERAL CONCLUSIONS 40

LIST OF REFERENCES 41

APPENDIXES 45

LIST OF CONDITIONAL ABBREVIATIONS

API - active pharmaceutical ingredient

SPU – State Pharmacopoeia of Ukraine

DF - dosage form

BAR - biologically active substance

UTIs - urinary tract infections

MD – Medicinal drug

MPM – Medicinal plant material

INTRODUCTION

The relevance of the research problem. According to epidemiological studies, the most common localization of all urinary tract infections is the bladder. According to scientific sources, 25% of women have had cystitis in their lifetime. In addition, cystitis is characterized by a high rate of recurrence, observed in 30-40% of patients, which occurs within 4 months after the disease [11, 14]. In men, cystitis is 50 times less common and more often occurs in old age. In children, it occurs at any age, in girls 3 times more often than in boys, mainly from 4 to 12 years. The long course and high rate of cystitis recurrence causes impaired urodynamics and functional activity of the kidneys, which can eventually become chronic [12].

The cause of this disease is infection with pathogenic microorganisms, so the main method of treatment is antibiotic therapy [11, 19].

In addition to antibiotics, herbal medicines are widely used, as they increase the effectiveness of complex treatment and do not have acute side effects and can be taken for a long time. This is especially true in the treatment of chronic kidney disease, which requires constant medication to prevent relapses [10].

Given that the number of herbal medicines used to treat inflammatory diseases of the urinary system is limited on the Ukrainian pharmaceutical market [6, 13], it is advisable to develop them to replenish the Ukrainian market with effective and harmless products.

Purpose and objectives of the work. The purpose of the qualification work is to substantiate the composition of hard capsules for the treatment of cystitis based on components of plant origin.

Achieving this goal required solving the following research tasks:

- summarize the literature on the classification, etiology and pathogenesis of cystitis;
- to consider modern tactics of cystitis treatment;
- describe medicinal plants and their pharmacological effects;

- justify the choice of active pharmaceutical ingredients in the composition of hard capsules;
- select modern excipients and their concentration in the mass for encapsulation;
- to develop a technology for manufacturing hard capsules for use in urological practice.

Object of study - hard capsules; APIs: dry extracts of cranberry and hypericum; fillers - microcrystalline cellulose, GaleniQ and Tabletosa-80; moisture regulators - Syloid 244FP, Aerosil and Neusilin UFL 2; and lubricant - Compritol.

The subject of the study is the selection of APIs and modern excipients in the composition of a solid dosage form for the treatment of cystitis; conducting a set of physicochemical and pharmacotechnological studies to develop solid capsules.

Research methods. The following research methods were used in the course of the master's thesis:

- organoleptic:
  - appearance;
- physical and chemical:
  - moisture absorption capacity;
- technological:
  - homogeneity of the mass;
  - fluidity;
  - the angle of the natural slope;
  - bulk density and density after shrinkage;
- math:
  - statistical processing of the results.

Approval of research results and publication. Fragments of the master's thesis are covered in the publication:

Sadik Y., Ruban O. A. Research of pharmaco-technological properties of cranberry dry extract. *Problems and Achievements of Modern Biotechnology: Materials of the III International Scientific and Practical Internet Conference*, Kharkiv, 24 March 2023. Kharkiv: NUPh, 2023. P. 93–94.

Scope and structure of the work. The qualification work is set out on 44

pages and consists of an introduction, main body, general conclusions and a list of references. The bibliography includes 41 sources of literature. The work is illustrated with 6 tables and 8 figures.

SECTION 1
CYSTITIS: ETIOLOGY, PATHOGENESIS AND MODERN ASPECTS OF TREATMENT

1.1 Cystitis: etiology and pathogenesis

Cystitis is an acute or chronic inflammatory process in the bladder mucosa. Sometimes the entire bladder wall is involved in the pathological process. Cystitis is the most common urological disease that causes patients to visit emergency and urgent care doctors, therapists, urologists, gynecologists, and sometimes surgeons. Women are most often affected, which is due to the anatomical, morphological, and hormonal characteristics of their bodies [18].

Cystitis are classified into uncomplicated, complicated, and sepsis depending on clinical symptoms, laboratory data, and microbiological findings [21, 27]. The classification of cystitis is shown in Table 1.1.

Table 1.1

Classification of cystitis

By pathogenetic principle:	● primary; ● secondary, which occurs as a complication of pre-existing diseases or abnormalities of the bladder and genitals.
By etiology:	● infectious (nonspecific, specific); ● chemical; ● radiation; ● medication; ● thermal.
In progress:	● acute cystitis; ● chronic cystitis (latent, recurrent), which is most often secondary.

Depending on the extent of the inflammatory process:	● diffuse (total); ● fire; ● cervical (trigonitis) - if only the bladder neck is involved in the process.
Depending on the nature and depth of pathomorphological changes:	● catarrhal, follicular, hemorrhagic, ulcerative, necrotic; ● encrusting, polypoid, cystic, ulcerative, interstitial [42].

Cystitis is considered to be the cause of cystitis [31]:

- violation of personal hygiene rules;

- general and local hypothermia (pelvic and bladder areas);

- drinking low-quality water;

- unhealthy diet: frequent consumption of spicy foods and carbonated drinks;

- instrumental examination of the urinary tract;

- genital and extragenital (non-sexual) infections (sore throat, flu, acute respiratory viral infection, rhinitis, caries);

- diabetes mellitus;

- psycho-emotional stress;

- mechanical cystitis; mechanical cystitis occurs as a result of damage to the mucous membranes of the ureters, bladder and urethra by sharp salt crystals and calculi (stones); in case of mechanical damage, blood may appear in the urine (hemorrhagic cystitis, cystitis with blood);

- inadequate treatment (without urine culture for flora and determination of bacterial sensitivity to antibiotics);

- early discontinuation of antibiotics prior to treatment of infectious cystitis and the development of addictive bacteria as a result;

- repeated self-infection (for example, with other strains - varieties - of E. coli) or from a sexual partner;

- insufficiency (weakness) of the pelvic floor (perineum) muscles;

- physical activity associated with tension and strain of the perineal muscles (carrying a child in your arms, daily imperceptible tension - straining - when lifting and carrying bags, strollers, buckets, etc.)

- radiation cystitis; radiation cystitis (radiation) can occur after radiotherapy (radiation) to treat a malignant neoplasm of the bladder or pelvis.

There are several ways of bladder infection. For example, infections that cause cystitis can be transmitted through the following routes [18, 34]:

hematogenous; the pathogen enters the lesion with the bloodstream; this mechanism is more common in generalized septic processes and massive bacterial invasion of the body;

- lymphogenic; infection occurs by the introduction of infection from the pelvic organs with the flow of lymph; as a rule, it occurs with pre-existing inflammatory processes in the pelvis;

- ascending and descending; in the 1st case, the pathogen enters the focus of the disease from an existing inflamed area of the urethra, in the 2nd case - from the kidneys and ureters;

- contact; infectious cystitis of a contact nature occurs as a result of sweating of media containing pathogenic microflora from adjacent organs in the bladder.

Cystitis pathogens:

- sexually transmitted bacterial infections - ureaplasma, mycoplasma, chlamydia, trichomonas, gonococcus - cause specific cystitis;

- saprophytic bacteria (nonspecific microflora) - staphylococcus, proteus, Klebsiella, Escherichia coli, enterobacter, yeast fungi - are found in the urinary tract of healthy girls and women, but with a decrease in immunity can cause an inflammatory process; in 85% of cases of acute and 60% of chronic recurrent (reoccurring) cystitis, E. coli is detected;

- viral infection; herpes virus types 1 and 2, cytomegalovirus can cause persistent, difficult to treat viral cystitis;

- Sometimes the cause of long-term untreated cystitis in women and children is worm infestation.

1.2. Modern tactics of cystitis treatment

Treatment of cystitis includes a diet (exclusion of fried, spicy, spicy foods from the diet), plenty of drinking and good hygiene.

Cystitis is a urinary tract infection (UTI) that affects the bladder, causing inflammation and discomfort. The main approaches in the treatment of cystitis include:

- Antibiotics: The most common treatment for cystitis is a course of antibiotics. The choice of antibiotic will depend on the severity of the infection, the patient's age, and any underlying health conditions. The duration of treatment can vary from a few days to several weeks.
- Pain relief: Over-the-counter pain medications such as ibuprofen or acetaminophen can be used to relieve the pain and discomfort associated with cystitis.
- Increased fluid intake: Drinking plenty of water can help flush bacteria out of the urinary tract, reducing the severity of symptoms and speeding up recovery.
- Cranberry juice: Some studies suggest that drinking cranberry juice or taking cranberry supplements may help prevent or reduce the severity of UTIs, including cystitis.
- Avoiding irritants: Certain foods and drinks, such as spicy foods, caffeine, and alcohol, can irritate the bladder and worsen symptoms. Avoiding these irritants can help reduce discomfort and promote healing.

While antibiotics are an effective treatment for cystitis, there are some negative aspects associated with their use. These include:

- Antibiotic resistance: Overuse of antibiotics can lead to the development of antibiotic-resistant bacteria, which can make future infections more difficult to treat.
- Side effects: Antibiotics can cause side effects such as nausea, vomiting, diarrhea, and allergic reactions. These side effects can be mild or severe and may require additional medical treatment.
- Destruction of healthy bacteria: Antibiotics not only kill the bacteria causing the infection, but they also kill the healthy bacteria in the gut and urinary tract. This can lead to digestive issues and a weakened immune system, increasing the risk of future infections.
- Recurrent infections: Antibiotics can sometimes suppress symptoms of cystitis without completely clearing the infection, leading to recurrent infections that may require additional rounds of antibiotics.

Pharmacotherapy solves several problems: eradication of infection, prevention of complications, and relief of symptoms (pain and dysuria). Antibiotic therapy is prescribed orally, empirically, to prevent ascending pyelonephritis. However, it is important to prevent the emergence of antimicrobial resistance, and therefore the antibiotic should affect gram-negative aerobic infection, in particular *E. Coli* [23, 35].

In the treatment of acute uncomplicated cystitis in non-pregnant women, the first-line drugs include nitrofurantoin or cotrimoxazole or phosphomycin. Fluoroquinolones are used as second-line drugs: ciprofloxacin or levofloxacin [11, 19].

Non-steroidal anti-inflammatory drugs (ketorolac, sodium diclofenac) are used as analgesic therapy, and drotaverine is used as antispasmodic therapy [6, 13].

With timely treatment of cystitis, the prognosis is favorable.

Treatment of cystitis includes a course of antibiotic therapy with correction of the immune status, if necessary, a course of physiotherapy procedures, laser therapy. Antispasmodics, analgesics, and cholinolytics are used [22,39].

Given the problem of antibiotic resistance progression, the use of herbal medicine is of great importance in the treatment of urinary tract infections [4, 10, 20, 32].

It is known that herbal medicine helps to reduce bacterial adhesion to the mucous membrane (diuretic effect), reduces inflammation, heartburn and pain during urination (anti-inflammatory effect), and eliminates bladder spasm (antispasmodic effect) [20, 24, 26, 28]. Plants used in urology are listed in Table 3.2.

Table 1.2

Pharmacological effect of plants used in urology

Action.	**Medicinal plant**
1	2
Antibacterial, antimicrobial, antiviral and disinfectant	Preparations of birch, lingonberry, bearberry, juniper, fir, hypericum, peppermint, cranberry, oregano, common hop, linden, etc.
Anti-allergic	Preparations of nettle, burdock, plantain, licorice, horsetail, common hops, three-leaved turnip, etc.
Antihypoxic	Preparations of birch, sweet clover, calendula, nettle, corn, linden, lemon balm, kidney tea, wolfberry, violet, three-leaved string, etc.
Immunotropic	Preparations of nettle, lemon balm, lemon balm, three-leaved string, violet, birch, burdock, yarrow, echinacea purpurea, etc.
Antihypertensive	Preparations of marsh cinquefoil, hawthorn, Baikal

	helmetwort, etc.
Anti-inflammatory and reparative	Preparations of medicinal sage, common hops, marsh cinquefoil, yarrow, fir, peppermint, calendula officinalis, wild carrot, chamomile, oregano, nettle, etc.
Diuretic	Preparations of birch, lingonberry, blue cornflower, bird's foot, hypericum, juniper, kidney tea, wild carrot, field broom, oregano, bearberry, strawberry, etc. Horsetail and knotweed preparations containing silicon compounds enhance uric acid excretion from the body
Antispasmodic and analgesic	Preparations of peppermint, caraway seeds, fennel, dill, common hops, yarrow, wild carrot, oregano, calendula officinalis, chamomile, etc.
Litholytic	Preparations of cowberry, strawberry, scrofula, wild carrot, dioecious nettle, kidney tea, field broom, bearberry, three-leaved string, etc. Oxalatolytic effect is provided by preparations of black elderberry, birch, lingonberry, gentian, cranberry, lemon balm, peppermint, kidney tea, parsley, bearberry, sage, rosehip, etc.; phosphatolytic effect is provided by preparations of elecampane, snake oil, burdock, dyeing mary, juniper, etc.
Nephroprotective	Preparations of black currant, strawberry, blueberry, raspberry, dioecious nettle, primrose, etc.

Thus, herbal medicine is an alternative method of treating cystitis, as medicinal plants have a complex effect on the main mechanisms of cystitis development. They demonstrate good clinical efficacy and can be prescribed in the complex therapy of acute cystitis or to prevent relapses.

CONCLUSIONS

1. Cystitis is one of the most common infectious diseases in the world, which not only reduces the patient's standard of living but also requires significant financial costs, which indicates the urgency of this problem.

2. Modern methods of cystitis treatment are presented. It is indicated that frequent use of antibacterial agents can cause significant damage to the body, which is the cause of the development of antibiotic resistance, so the use of drugs of natural origin is relevant.

EXPERIMENTAL PART
SECTION 2
OBJECTS AND METHODS OF RESEARCH

2.1 Rationale for selecting APIs in hard capsules

Cystitis is a common disease and occurs mainly in women. The disease recurs in 50% of women within a year. Treatment of lower urinary tract infections, in particular cystitis, remains an urgent problem today [12, 18]. The high prevalence of the disease, the formation of resistant strains of etiologic microorganisms, changes in the microbiota, and a limited arsenal of antimicrobial measures lead to annual changes in recommendations for the rational treatment of cystitis [30, 33]. The latest recommendations of the European Association of Urology significantly limit the use of antibiotics, as traditional courses of antibacterial therapy do not always have the expected effect. From this point of view, it is interesting to use complex therapy of cystitis, where herbal medicines are used together with short courses of antibiotics, which significantly increases the effectiveness of treatment and reduces the number of recurrences of bladder infection during the year [4, 10, 37].

Therefore, it is promising to develop a new drug with a wide range of pharmacological effects based on components of natural origin for the treatment of cystitis, where dry extracts of cranberry and hypericum are proposed as APIs. Solid capsules were proposed as the optimal dosage form that would provide ease of use, masking of taste, odor, and stability of composition and content [25,40,41].

Cranberries in cystitis have a wide range of pharmacological effects on the urinary system due to the presence of the following active ingredients in the chemical composition of berries [2-3, 16]:

- *Organic acids*, especially benzoic *acid*, have antibacterial properties. Chemical compounds prevent bacteria from forming inflammatory foci on the inner lining of the bladder;

- *Triterpenoids* (oleanolic and ursolic acids) have anti-inflammatory effect. Regular use of cranberry juice helps to reduce the number of infectious foci, prevents pathogens from moving along the pathways to the kidneys;
- *Pectins* cleanse the organs of the urinary system from toxic waste products. These polysaccharides are involved in the elimination of toxins and harmful mineral salts from the body;
- *Tannins* prevent pathogenic bacteria from entering the cells. These compounds are able to prolong the effect of antibacterial drugs;
- *Flavonoids* affect small and large blood vessels, increasing their elasticity and permeability. Eating cranberries helps to normalize blood circulation in the pelvic organs, ensures delivery of nutrients and biologically active substances to the affected tissues.

The presence of the trace element potassium in the chemical composition of the berry is important. An increase in its content in the body leads to more frequent and normalized urination. This helps to flush out viruses and pathogenic fungi from the bladder and urogenital canal. Such sanitation can significantly speed up recovery and prevent exacerbation of chronic cystitis [29, 35].

A promising source of herbal medicines is hypericum, which is widely used both in Ukraine and abroad. hypericum, which is a natural antibiotic in its own right, is used as a first aid at the first signs of cystitis, in acute and chronic clinics of the disease, only after completion of antibiotic therapy, and as a preventive treatment [6].

It is known that hypericum has a complex chemical composition, represented by flavonoids (rutin, hyperoside), anthracene derivatives (hypericin, pseudohypericin), floroglucins (hyperforin), tannins, essential oil and other biologically active compounds, which provide antimicrobial, diuretic, anti-inflammatory and analgesic effects [10, 15].

The combination of effects on the body of a complex of biologically active components of plants is manifested in cystitis:

- tonic and vasodilating effect, preventing the development of venous stasis (blood stasis) in the pelvic area, which often becomes a provocative factor in the development of inflammatory reactions in the bladder walls.
- normalizes blood circulation in the affected tissues, stabilizes the functions of the vascular system, relieves spasms of blood vessels.
- provides sufficient diuresis to flush out pathogenic flora.
- stimulates immune phagocytosis (immune defense of the body).
- ensures rapid elimination of the infection focus, has an antibacterial effect due to the substance hypericin. That is why the plant has the potential to treat infectious diseases of the genitourinary sphere.

Thus, the combination of dry extracts will provide anti-inflammatory effects and also increase diuresis: the amount of urine produced in a certain period of time. This is very important because cystitis pathogens must be "flushed out" of the bladder. In addition, the pain syndrome will decrease, which will help to achieve relaxation of the smooth muscles of the bladder and urethra [36,38].

A wide range of pharmacological effects of the selected cranberry and hypericum extracts indicates the possibility of creating a competitive Ukrainian drug.

2.2. Characteristics of the research objects

The properties of the dry extracts and excipients are listed below.

Active pharmaceutical ingredients

- **Cranberry extract -** hygroscopic powder of purple color. It has a tart, refreshing taste with a pleasant delicate aroma. It is well soluble in water and in 20% ethanol.

  Chemical composition: organic acids (2-3.84%): benzoic, citric, malic, quinic; essential oil, including linalool, n-propanol, *isobutanol*, n-butanol;

triterpenoids: ursolic, oleanolic acids; vitamins: ascorbic acid, riboflavin, carotene; hydroxycinnamic acids; tannins (0.1-4.9%), flavonoids: quercetin, rutin, hesperidin; anthocyanins; macro- and microelements: I, Cu, Mn, Mo, Fe.

- **Hypericum extract -** The powder is light brown in color. It has a bitter taste and grassy aroma, insoluble in water.

Chemical composition: anthraquinones: emodin, etc.; condensed anthracene derivatives: hypericin (0.1-0.4%), pseudohypericin; flavonoids (2-5%): rutin, hyperoside, quercitrin; anthocyanins - 5.7% and leukoanthocyanidins; catechins; coumarins; phenolic carboxylic acids; xanthones; tannins 2.8-12.38%. There is also essential oil - up to 1.25%; saponins; vitamins: C, E, PP, carotenoids; steroids; alkaloids.

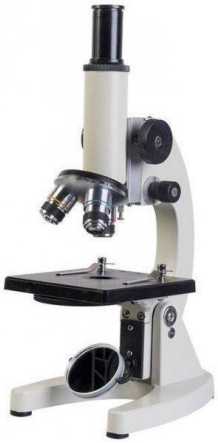
2.3 Characterization of research methods

A set of modern studies was used to create the solid dosage form, which are presented in Table 2.2 [7].

Table 2.2

General characteristics of research methods

Title.	Characteristics
1	2
Microscopic studies	Visual analysis of the powder was performed. The image from the slide was displayed on a computer monitor using a Krüss MBL 2100

	microscope (Germany) with an eyepiece micrometer at 40x magnification.
Weight loss during drying 	1.0 g (exact weight) of the sample was dried at a temperature between 100 °C and 105 °C to a constant weight. The loss in weight during drying was referred to the initial weight and expressed as a percentage.
The angle of the natural slope	The angle between the face of the dry powder cone and the horizontal plane. This characteristic was determined using the goniometer of the same device. The final conclusions on the flowability and angle of natural slope were based on five repeated measurements.
Moisture absorption	The study was conducted at a relative humidity of 75%. During the 6 hours of the experiment, the change in the weight of the powder in the laboratory exciter was recorded.

	A relative humidity of 75% was created using a saturated sodium chloride solution.
Determination of fluidity 	Flowability characterizes the ability of dry extracts to pour out of a funnel in a vertical position under the influence of their own weight. The flowability of dry extracts was determined using a VP12A vibration device. Weights of dry extracts weighing 100.0 g, weighed to an accuracy of ±0.01 g, were placed in a funnel. The flap was opened and the time of the extract flowing out of the funnel was observed. The accuracy of the flow time was calculated in seconds and tenths of a second, referred to 100.0 g of sample.
Bulk volume and density before and after shrinkage	A dry cylinder was filled with 100.0 g of the test sample without compaction. The cylinder was fixed on a stand and the bulk volume before shrinkage V_0 was recorded. We performed 10, 500, and 1250 bounces of the cylinder and recorded the volumes V_{50} , V_{500} , V_{1250} to the nearest digit. The bulk density before shrinkage of the test specimen was

	determined by the formula m/V_0 and expressed in g/ml. The bulk density after shrinkage is determined by the formula m/V_{1250} , g/ml
Carr's index	It is used to characterize the degree of compressibility of a powder. Calculated by the formula: $C = \frac{V_0 - V_{1250}}{V_0} * 100\%$ The higher the Carr's index, the lower the fluidity of the powder
Gaussner coefficient	Calculated by the formula: $HR=V /V_{01250(2500)}$

CONCLUSIONS

1. A combination of dry extracts of cranberry and hypericum in the composition of hard capsules has been substantiated, which will provide a wide range of pharmacological effects in the treatment of cystitis.

2. The characteristics and chemical composition of dry extracts of cranberry and hypericum are presented.

3. The article describes modern physicochemical and pharmacotechnological studies that allowed to choose the optimal composition of the solid dosage form.

SECTION 3
SUBSTANTIATION OF THE COMPOSITION OF HARD CAPSULES FOR THE TREATMENT OF CYSTITIS

3.1. Analysis of medicines for the treatment of cystitis available on the Ukrainian pharmaceutical market

To determine the necessity and feasibility of developing new drugs for the treatment of cystitis, we first studied the Ukrainian market for this category of drugs. The analysis was based on the State Register of Medicines of Ukraine and the electronic reference book "Compendium" [6, 13].

The analysis showed that medicines of natural and synthetic origin are used to treat cystitis, as shown in Table 3.1.

Table 3.1

Medicines used to treat cystitis

№	Name of the drug	Pharmaceutical form	Active ingredient and dose	Manufacturer
1	**2**	**3**	**4**	**5**
1	Trinefron-Zdorovye	capsules, drops	goldenseal herb 18 mg; rosemary leaves, 18 mg; lovage medicinal root 18 mg;	FC Zdorovye LLC, Ukraine
2	Uronephron	tablets, drops, gel	188 mg of dry extract from 9 plants: onion peel, birch hanging leaves, wheatgrass creeping rhizome, parsley curly root, hay seed, scrofula grass, horsetail stem, knotweed grass, lovage root	Farmak JSC, Ukraine
3	Urolesan	capsules, drops	wild carrot fruit (1:1) - 1.84 mg, hop cones (1:1) - 6.33 mg, oregano herb (1:1) - 1.46 mg; peppermint oil - 7.46 mg; fir oil - 25.50 mg;	Galichpharm PJSC, Ukraine
4	Kanefron H	dragees, drops	goldenrod herb 0.6 g lovage root 0.6 g rosemary leaves 0.6 g;	Bionorica CE, Germany
5	Cystone	Tablets	Didymocarpus stem leaves - 65 mg, saxifrage roots - 49 mg, marshmallow roots - 16 mg, filmy twitch rhizomes - 16 mg, rough strawflower seeds - 16 mg, aerial part of onosma bracteata - 16 mg,	Himalaya Drag Company, India

			vernonia ash - 16 mg; powders: silicon lime - 16 mg; purified mineral resin - 13 mg.	
6	Nolicin	pills	Norfloxacin 400mg	KRKA, Slovenia
7	Monural	granules for oral solution.	Phosphomycin 3.0	Zambon Switzerland Ltd.
8	Palin	capsules	Pipemic acid 200 mg	Lek, Slovenia
9	Norfloxacin	Tablets	Norfloxacin 400 mg	FC Zdorovye LLC, Ukraine
10	Furadonin	Tablets	Nitrofurantoin 50 mg, 100 mg	"Borisov Plant of Medical Preparations, Belarus
11	Furagin	Tablets	Furazidine 50 mg	PJSC "KMP", Ukraine
12	Furamag	capsules	Furagin soluble 25 mg	JSC "Olinpharm", Latvia
13	Nitroxoline	Tablets	Nitroxoline 50 mg	PJSC "Kyiv Vitamin Plant", Ukraine
14	Urosept	Suppositories	Pipemic acid 200 mg	PJSC "Lekhim-Kharkiv", Ukraine
15	Hexicon	vaginal suppositories	Chlorhexidine bigluconate 0.5 mg	Nizhpharm JSC, Russian Federation.
16	Betadine	vaginal suppositories	Povidone-iodine 200 mg	EGIS Pharmaceutical Plant, Hungary
17	McMorrow	Vaginal capsules	Nifurtel 500 mg, nystatin 200 000 IU	Doppel, Italy
18	Methyluracil	Rectal suppositories	6-methyluracil 0.5 g	PJSC "Lekhim-Kharkiv", Ukraine
19	Cystoral	granules for oral solution.	Phosphomycin 3 g	LLC FC Zdorovye. Ukraine
20	Phytolysin	paste	wheatgrass rhizomes - 12.5 g, onion husks - 5 g, birch leaves - 10 g, fenugreek seeds - 15 g, parsley roots - 17.5 g, goldenrod herb - 5 g, horsetail herb - 10 g, lovage roots - 10 g, bird's foot herb - 15 g	Herbapol, Poland
21	Urokran	pills	cranberry large-fruited fresh fruit dry extract 500 mg; blueberry fresh fruit dry extract 7.5 mg; bearberry leaves	Pharma, Australia

			dry extract 93.02 mg; corn stalks dry extract 62.5 mg; parsley leaves powder 100 mg;	

The analysis by dosage form revealed that tablets accounted for 20%, capsules - 20%, drops - 15%, suppositories - 15%, granules - 10%, gel - 5%, vaginal tablets - 5%, paste - 5%, and dragees - 5% (Fig. 3.1).

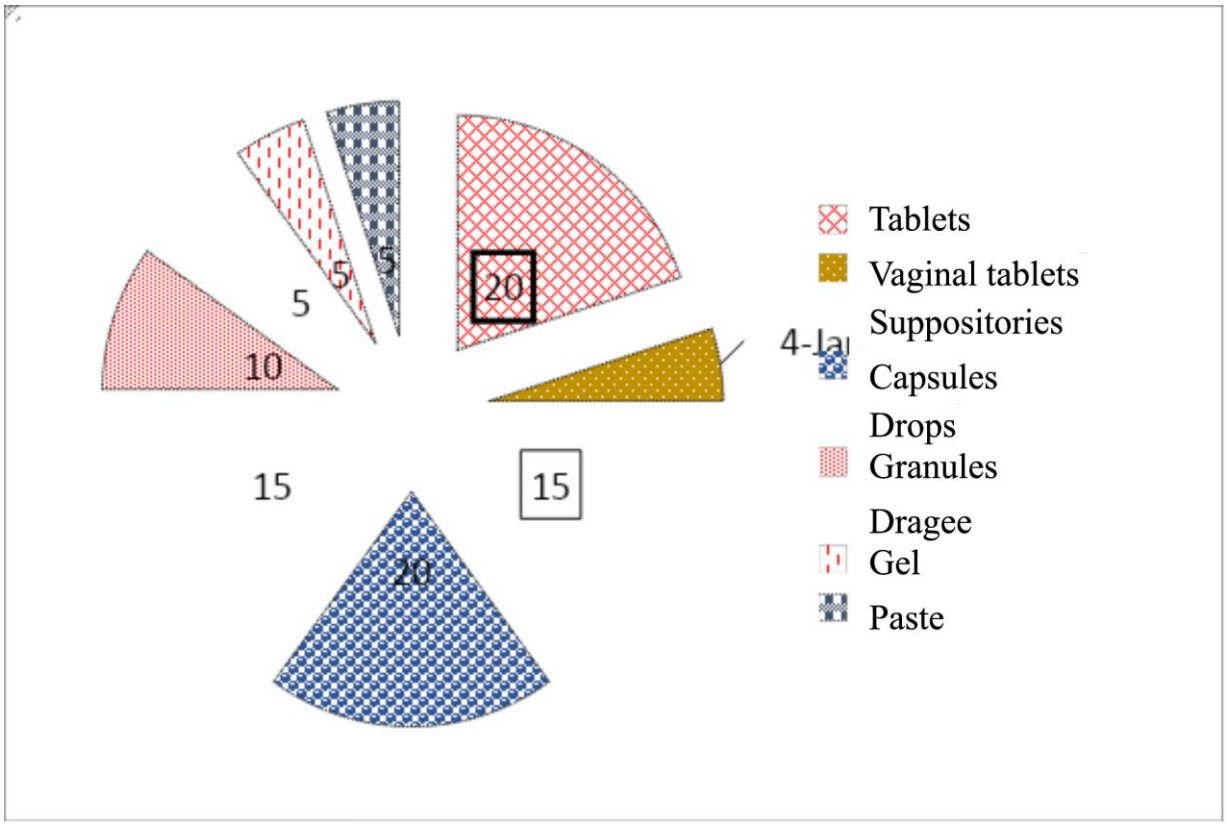


Fig. 3.1. Division of drugs by dosage form

It was also found that the Ukrainian market is dominated by foreign-made drugs, which is 53.5%, and Ukrainian drugs - 46.5%.

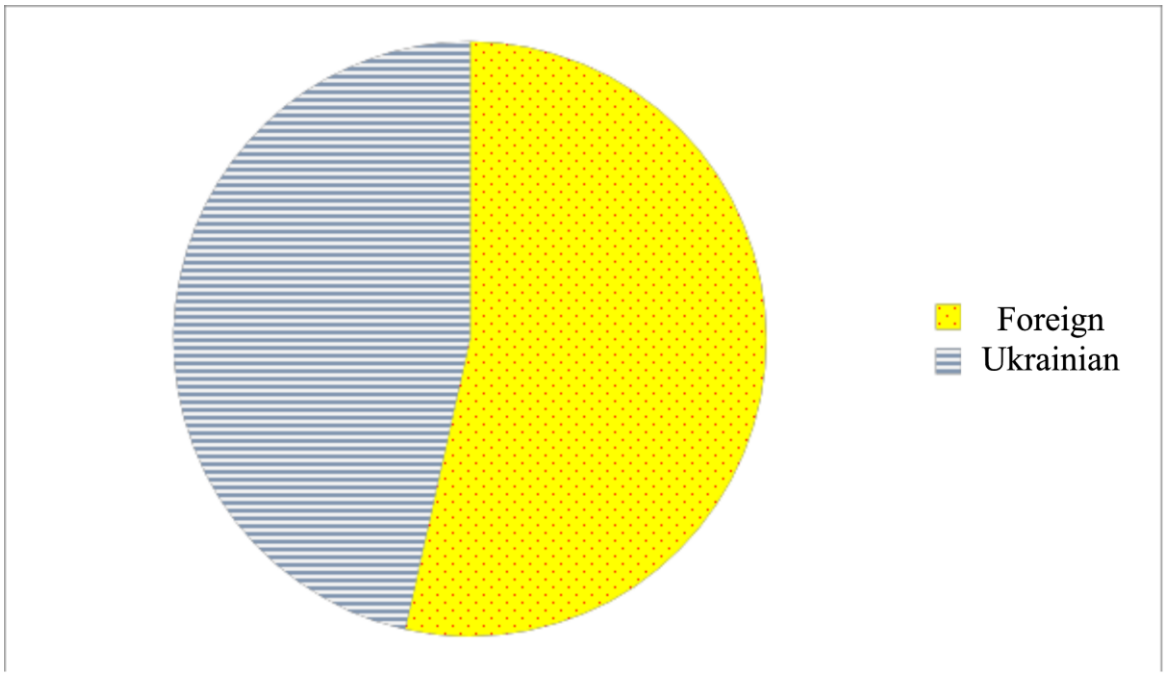


Fig. 3.2 Ratio of foreing and Ukrainian drugs.

The analysis of medicinal products by origin showed that the Ukrainian market is dominated by synthetic products, which account for 65%, and natural products only 35% (Fig. 3.3).

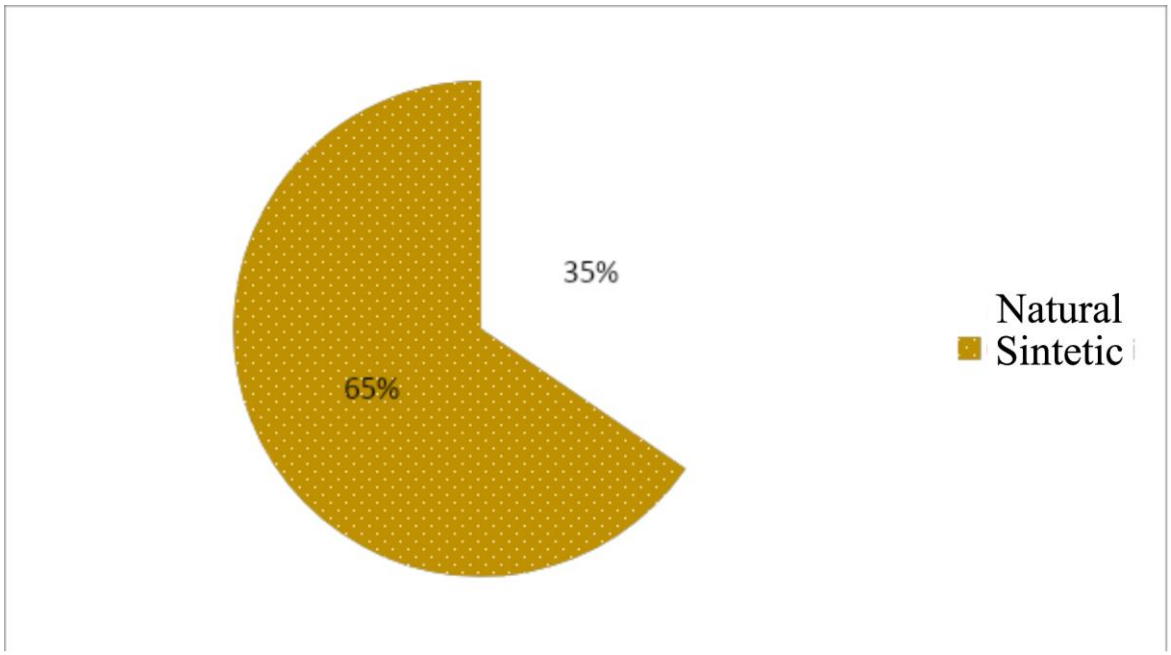


Fig. 3.3 Ratio of natural and synthetic medicines

Thus, the analysis of the pharmaceutical market of Ukraine indicates the feasibility of developing Ukrainian products based on components of natural origin.

3.2. Study of physicochemical and pharmacotechnological properties of APIs

The development of a rational composition of hard capsules always begins with the study of the properties of the starting drug substances, which largely determine the rational method of technology and the choice of the range and amount of modern excipients [1].

To select rational technological methods and modes of obtaining hard capsules, we studied the crystallographic characteristics of dry cranberry and hypericum extracts.

Microscopic analysis of the proposed APIs was performed by light microscopy using a visual substance analysis system. Images were displayed on a computer monitor from the microscope. The results of microphotography of the powder particles of the extracts are shown in Fig. 3.4.

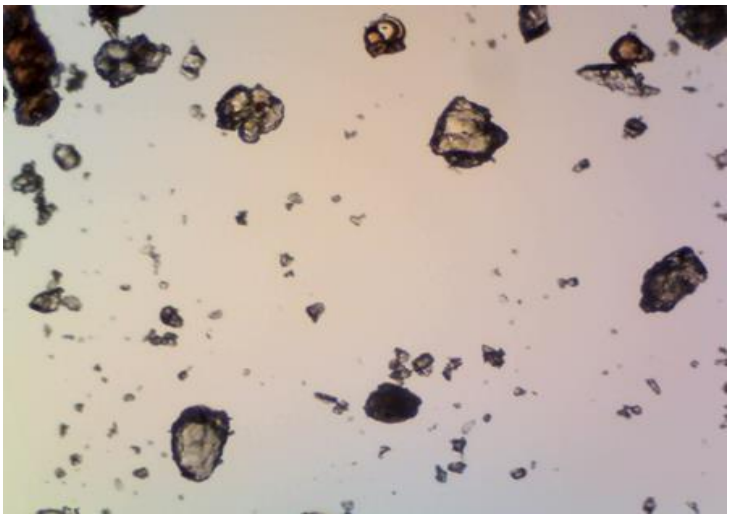


Fig. 3.4. Results of microphotography of cranberry extract powder particles.

Dry cranberry extract is a polydisperse powder with particles of irregular anisodiameter shape in the form of spheres, prisms and their fragments. The main fraction is from 10 to 110 microns.

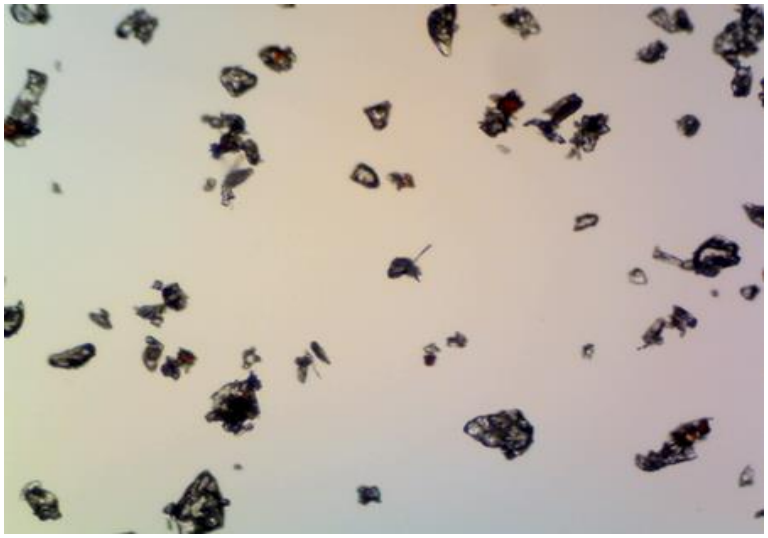


Fig. 3.5 Results of microphotography of hypericum powder particles.

The dry extract of hypericum (Fig. 3.5) also has anisodiametric particles in the form of shapeless fragments with linear dimensions from 20 to 90 microns, which are capable of agglomeration.

The next stage of research is to study the pharmacotechnological properties of dry cranberry and Hypericumhn's wort extracts. The results are shown in Table 3.2.

Table 3.2

Pharmacotechnological properties of APIs

Parameters.	**Units of measurement**	**Meaning. dry cranberry extract**	**Meaning. hypericum dry extract**
Fluidity	s/ 100g	96,0±2,4	75,20±1,60
The angle of the natural slope	hail	39±1,02	45±1,08
Bulk density	g/ml	0,48±0,01	0,65±0,06
Density after shrinkage	g/ml	0,66±0,01	0,84±0,04
Moisture content	%	3,18±0,15	3,6±0,1
Carr's index	%	27	23
Gaussner coefficient	-	1,38	1,29

The analysis of the pharmacotechnological properties of the studied dry extracts showed that the dry extract of hypericum has an acceptable fluidity, which is confirmed by the calculated Gausner's index of 1.29 and Carr's index of 23, respectively. Cranberry dry extract has unsatisfactory fluidity. The calculated Gausner's coefficient is 1.38, and the Carr's coefficient is 27. The bulk density and density after shrinkage have a significant difference in values, which indicates the ability of powders to clump, which is undesirable in the technological process, as it can lead to heterogeneity of API dosage.

Thus, our studies on the crystallographic, pharmacotechnological properties of dry cranberry and hypericum extracts indicate that the investigated substances have a polydisperse system with anisodiameter particles, which has an unsatisfactory effect on their flowability and allows us to predict the introduction of excipients from the group of fillers and lubricants in the development of a solid dosage form in the form of capsules.

3.3. Experimental substantiation of the choice of auxiliary substances in the composition of the encapsulation mass

Capsules have a number of advantages over other solid dosage forms, so the selection and selection of excipients that would give capsule masses and finished capsules appropriate physicochemical and pharmacotechnological properties is the main task of modern pharmaceutical technology [5, 25].

Therefore, the next stage of our research was to select the optimal filler. We prepared experimental compositions of masses for encapsulation, where we used the following excipients: MCC 102, GaleniQ and Tabletosa-80 at a concentration of 40%. The fluidity of the model samples was investigated. The results are shown in Fig. 3.6.

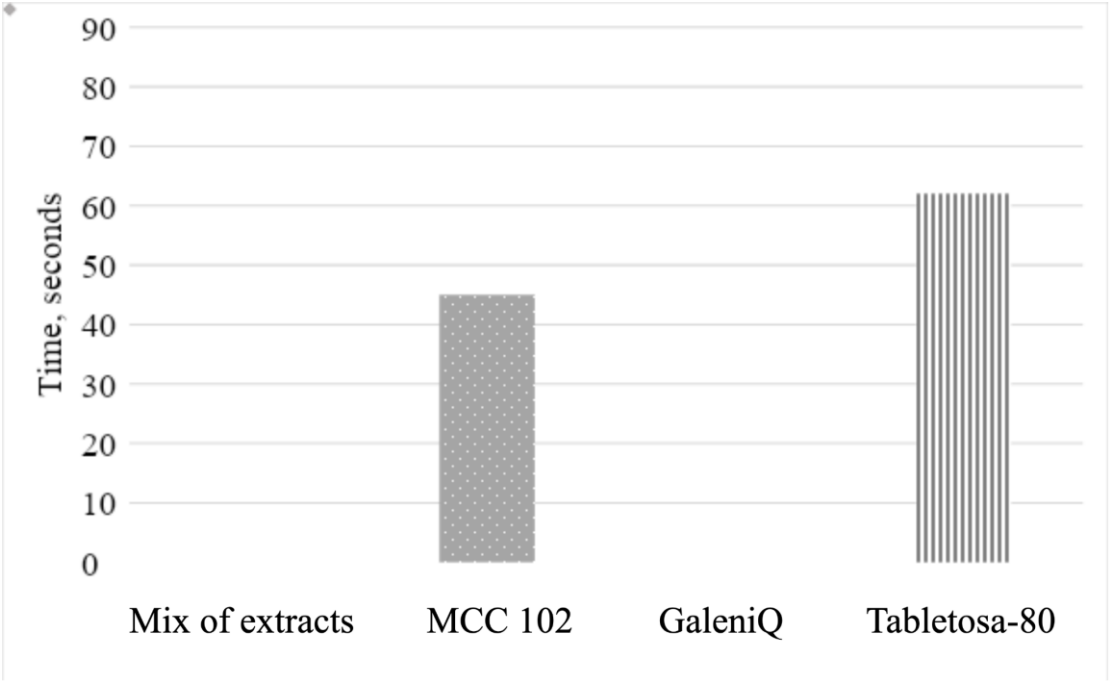


Fig. 3.6. Fluidity of a mixture of dry extracts with different fillers

The results show that the introduction of excipients significantly improves the flowability index. When introducing the filler microcrystalline cellulose, the mass flowed the fastest (45 s/100g), so it was selected for further research.

3.4. Choosing the optimal humidity controller

Plant extracts are hygroscopic substances, and their high moisture absorption affects many technological characteristics of mixtures, including flowability [1]. Therefore, the next step in our work was to select a rational moisture regulator. We investigated the effect of moisture regulators that are most commonly used in the production of solid dosage forms, namely: Syloid 244FP, Aerosil and Neusilin UFL 2 at a concentration of 2%. The moisture absorption of the mixture was studied at a relative humidity of 75%. The results are shown in Fig. 3.7.

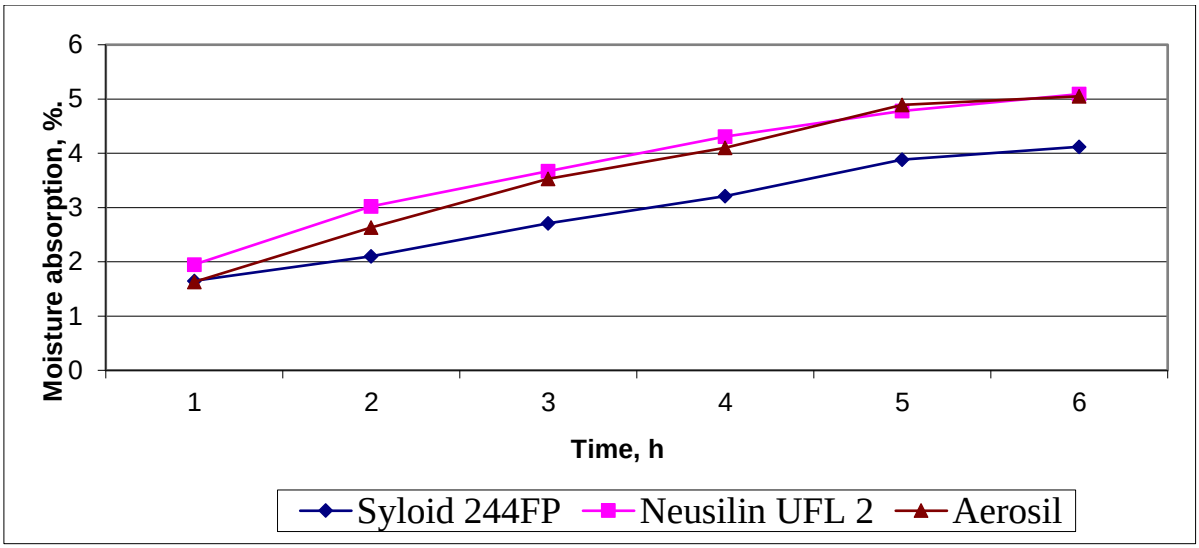


Fig. 3.7. Moisture absorption of the mixture at 75% relative humidity.

As can be seen from the results, the investigated substances have different moisture absorption capacities. It should be noted that the moisture absorption of the mixture with Aerosil and Neusilin UFL 2, after 6 hours of testing, was almost at the same level and amounted to 5.05 and 5.09%. The lowest moisture absorption was observed with Syloid 244FP, which amounted to 4.12%. Thus, based on the

research, Syloid 244FP was chosen as the optimal moisture regulator for the production of hard capsules.

3.5. Selecting the optimal lubricant concentration

In solid dosage forms (tablets and capsules), along with such excipients as fillers, disintegrants (baking powder), lubricants play a significant role, despite the fact that in formulations, as a rule, lubricants are used in small amounts of 1-3% by weight, in combination with other excipients and depending on the production technology, they significantly affect a number of pharmacopoeial characteristics of the dosage form.

To improve the flowability of the capsule mass, a modern excipient Compritol 888 ATO was added to the composition of the capsule mass in a concentration of 0.5 to 3. By chemical structure, it is an ester of glycerol and fatty acids of vegetable origin. It is an inert chemical compound that is approved for use in the pharmaceutical industry [17]. The results of the study are presented in Fig. 3.8.

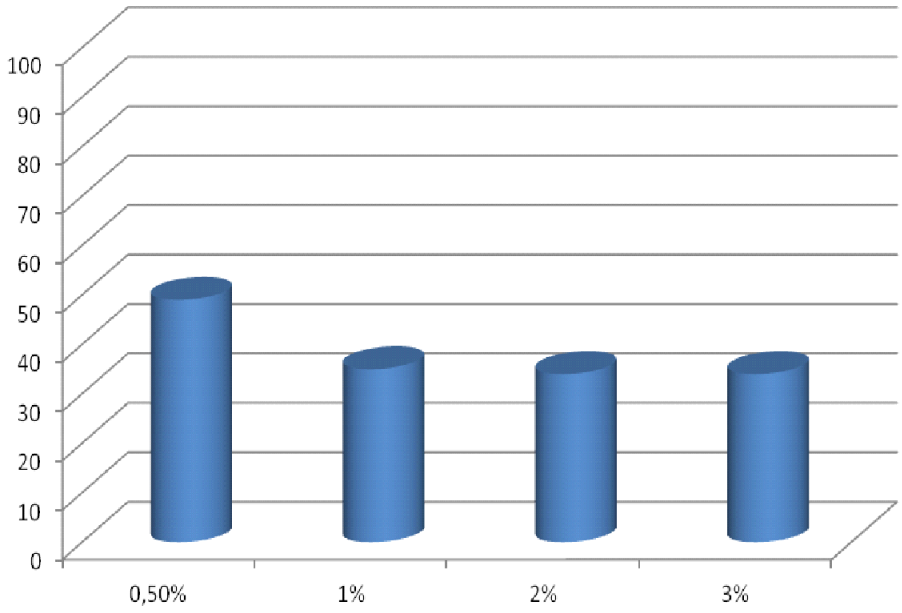


Fig. 3.8. Dependence of fluidity on Compritol concentration

Studies have shown that the optimal concentration of this lubricant is 1%. Further increasing the concentration of Compritol to 2 and 3% does not increase the fluidity index.

Thus, based on the conducted set of studies, the following composition of hard capsules for the treatment of cystitis was proposed:

Composition per capsule:	g	%
Dry cranberry extract	0,1000	29
Hypericum dry extract	0,1000	29
MCC 102	0,1395	39
Syloid 244FP	0,007	2,00
Compritol	0,0035	1,00
Total	0,35	100

3.6. Substantiation of the technology for obtaining hard capsules

The main operations that ensure uniformity and accuracy in the manufacture of solid dosage forms are mixing and dosing. The principles underlying these operations determine the requirements for the physicochemical and technological properties of medicinal and excipients, the need to process them for a dosage form, or the need to optimize certain physicochemical properties of the medicinal product.

Based on the study of the physicochemical and pharmacotechnological properties of the selected dry extracts, the effect of excipients on the quality parameters of solid capsules, and the study of the process parameters, we have developed a technology for obtaining solid capsules, which consists of the following stages:

- Stage 1: Preparation of raw materials.

- ❖ Stage 2: Obtaining the mass for encapsulation.
- ❖ Stage 3: Encapsulation.
- ❖ Stage 4. Packing capsules in blisters.
- ❖ Stage 5. Packing blisters into packs.
- ❖ Stage 6. Packing the packs in boxes.

A detailed description of the technological stages is given in Table 3.3.

Table 3.3

Description of the technological stages

No. of stage	Stage name	Characteristics of the stage
1	**2**	**3**
Stage 1.	**Preparation of raw materials**	First, all the raw materials were pre-weighed on a balance: dry cranberry extract, dry hypericum extract, microcrystalline cellulose, Syloid 244FP, Compritol. After that, the weighed components were sieved on a vibrating sieve.
Stage 2.	**Preparation of mass for encapsulation**	The active pharmaceutical ingredients and excipients from step 1 are loaded into the mixer and mixed until a homogeneous mass is obtained. The quality of mixing is visually checked.
Stage 3.	**Filling capsules**	The capsule machines are used to fill solid capsules with the mass for encapsulation, after which the average weight of the capsule is controlled.
Stage 4.	**Packing capsules**	Capsules were packaged on an automatic

	in blisters.	machine in 10 capsules in contour packaging made of polyvinyl chloride film and printed aluminum lacquered foil.
Stage 5.	**Packing blisters into packs**	The blister, along with the instructions for use, was placed in a cardboard package for consumer packaging.
Stage 6.	**Packing packs in boxes.**	The finished product was sent to the warehouse for group packaging.

The technological scheme for the production of hard capsules is shown in Fig. 3.9.

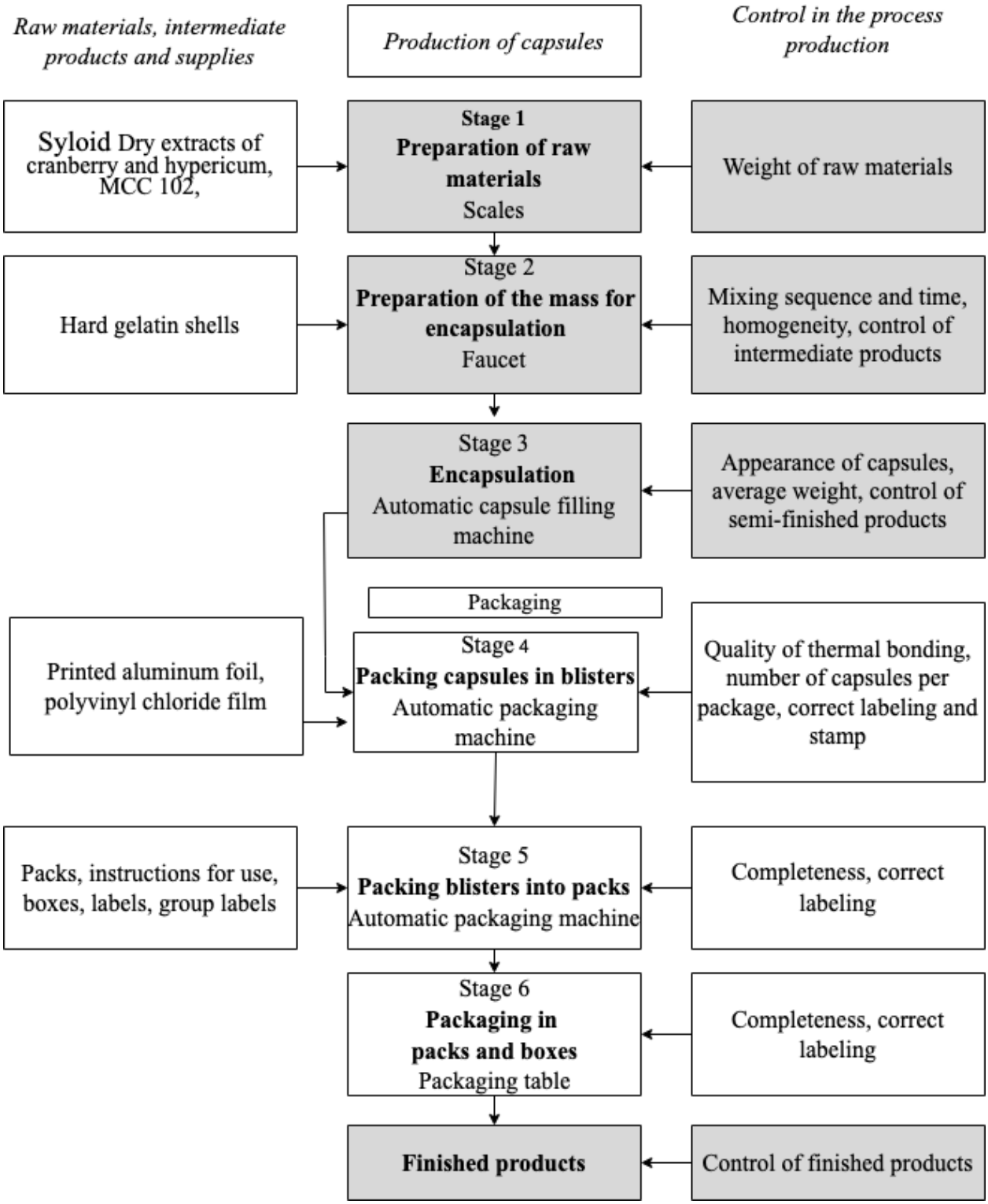


Figure 3.9. Flow chart of capsule production

CONCLUSIONS

1. The microscopic analysis of dry cranberry and hypericum extracts was carried out and their technological properties were studied, on the basis of which the need to introduce excipients into the composition of the encapsulation mass was established.

2. The influence of modern fillers: MCC No. 102, GaleniQ, and Tabletosa-80 on the fluidity of model mixtures, and a rational filler, MCC No. 102, was selected.

3. The effect of various moisture regulators on the moisture-absorbing activity of dry extracts was studied and the optimal moisture regulator, Syloid 244FP, was selected.

4. On the basis of a set of studies, the rational composition of solid capsules for the treatment of cystitis was selected and a rational technology for their manufacture was presented.

GENERAL CONCLUSIONS

1. Cystitis is the most common manifestation of urinary tract infections, which causes great harm to children and adults, worsens the quality of life, namely limits activity, makes it impossible to attend classes or work, which indicates the urgency of this problem.

2. Market research of the Ukrainian market has established the superiority of foreign products of synthetic origin, which confirms the feasibility of developing new Ukrainian herbal medicines

3. A solid dosage form with dry extracts of cranberry and hypericum was developed for the treatment of cystitis based on technological, physicochemical studies.

4. The choice of auxiliary substances in the composition of the encapsulation mass is substantiated, namely: filler - MCC No. 102, moisture regulator - Syloid 244FP, lubricant - Compritol 888 ATO.

5. The technology for the production of hard capsules for the treatment of cystitis in industrial conditions is described.

LIST OF REFERENCES

1. Аль-Товайти Мурад, Е. А. Рубан, С. А. Малиновская Выбор вспомогательных веществ при разработке капсул с сухим экстрактом шишек хмеля. Зб. Наук. Праць співроб. НМАПО ім. П.Л. Шупика. 2015. 24 (5). С. 158-162.

2. Безшейко В. Г. Клюква может предотвратить развитие инфекций мочевыводящих путей. Український медичний часопис. 2012. № 2. С. 10–11.

3. Быков А. Т., Бова С. И., Шамко И. А. Натуральная медицина: уропротекторная роль клюквы. Медицинский журнал. 2012. № 3 (41). С. 4–7.

4. Гарник Т. П. Сучасні технології виробництва фітозасобів та перспективи фітотерапії. Фітотерапія часопис. 2008. № 1. С. 59–63.

5. Дем’яненко Д. В. Технологічні властивості наповнювачів для капсул із фреоновими екстрактами суцвіть липи. Вісн. фармації. 2012. № 2. С. 17–20.

6. Державний реєстр лікарських засобів України [Електронний ресурс] : Інформаційний фон. – Режим доступу : http://www.drlz.kiev.ua/.

7. Державна Фармакопея України : в 3 т. / Державне підприємство "Український науковий фармакопейний центр якості лікарських засобів". 2-е вид. Харків: Державне підприємство "Український науковий фармакопейний центр якості лікарських засобів", 2015. Т. 1. 1128 с.

8. Допоміжні речовини у виробництві ліків : навч. посіб. для студентів вищ. фармац. навч. закл. / О. А. Рубан та ін. ; за ред. І. М. Перцева. Харків: Золоті сторінки, 2016. 720 с.

9. Іванов Д. Д. Інфекції сечових шляхів у жінок та сучасна антибіотикотерапія. Почки. 2012. № 10. С. 33–42.

10. Іванов Д. Д. Інфекції сечових шляхів: діагностика. Почки. 2013. № 3. С. 11–20.

11. Компендіум online. URL : https://compendium.com.ua/uk/.

12. Кругляк Л. Г. Камни в почках, нефрит, цистит. М. : ИГ «Весь», 2012; 144 с.

13. Медведь В. И., Исламова Е. В., Кирильчук М. Е. Экстракт ягод клюквы в профилактике и лечении инфекций мочевыводящих путей у беременных. Здоровье женщины. 2015. № 1 (97). С. 36–40.

14. Могилюк В. Лубриканты для твердых лекарственных форм: Compritol® 888 ATO и Precirol® ATO 5. Фармацевтическая отрасль. 2010. № 6. – С. 60-63.

15. Пасєчніков С. П. Цистит: етіопатогенез, класифікація, клінічна картина, діагностика, лікування. Український медичний часопис. 2016. № 4 (114). С. 17–21.

16. Рослини з протимікробними властивостями / Н. Є. Стадницька, О. З. Комаровська-Порохнявець, Х. Я. Кіщак та ін. Хімія, технологія речовин та їх застосування. 2011. № 700. С. 111–116.

17. Скворцов В. В., Тумаренко А. В., Скворцова Е. М., Элленбергер Н. А. Нефротический синдром: диагностика и лечение. Клиническая нефрология. 2013. №1. С. 73–75.

18. Стратегія лікування неускладнених інфекцій нижніх сечовивідних шляхів / В. М. Григоренко, О. В. Ромащенко, В. В. Білоголовська та ін. Новости медицины и фармации в Украине. № 11 (585). 2016. С. 9–14.

19. Сучасна фітотерапія : навч. посіб. / С. В. Гарна, І. М. Владимирова, Н. Б. Бурд та ін. Харків : Друкарня Мадрид, 2016. 580 с.

20. Сучасний стан створення, виробництва і контролю якості капсул / М. Б. Чубка, та ін. Фармацевтичний часопис. 2012. № 2. С. 165-168.

21. Товчига О. В., Штыголь С. Ю. Влияние лекарственных растений на выделительную функцию почек. Экспериментальная и клиническая фармакология. 2009. Т. 72, № 3. С. 50-59.

22. Цистит / У. А. Халилова, и др. Медицинская сестра. 2018. № 20 (6). С. 6–11.

23. Яцюк К. М. Федоровська М. І. Аналіз вітчизняного ринку фітозасобів для лікування та профілактики інфекцій сечовидільної системи. Одеський медичний журнал. 2016. № 3. С. 18–22.

24. Яцюк К. М., Ковальська Н. П., Федоровська М. І. Журавлина болотна (Oxycoccus palustris Pers.) як джерело для одержання лікарських засобів. Фітотерапія часопис. 2015. № 2. С. 26–28.

25. Afshar K., Fleischmann N., Schmiemann G. Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA) - a double-blind, randomized, controlled comparative effectiveness trial. BMC Complement Altern Med. 2018 Jul 3. №18(1). P. 203.

26. Bonkat G., Bartoletti R.R., Bruyère F., et al. EAU Guidelines: Urological Infections. Available from: https://uroweb.org/guideline/urological-infections/#3.

27. Butterweck V., Khan Saeed R. Herbal medicines in the management of urolithiasis: alternative or complementary? Planta Med. 2009. Vol. 75. P. 1095–1103.

28. Chughtai B., Thomas D., Howell A. Variability of commercial cranberry dietary supplements for the prevention of uropathogenic bacterial adhesion. Am J. Obstet. Gynecol. 2016 Jul;215(1). P.122-123.

29. Ivanov D.D., Ivanova T.P., Fedorenko O.G., Kushnirenko S.V. Options of modern anti-relapse therapy for urinary tract infections in children. CRUTIL trial. Počki. 2019. №8(2). P. 80-89.

30. Yatsyuk K. M., Fedorovska M. I., Antymis O.V. Study of anti-inflammatory effect of concentrated juice and granules from Vaccinium oxycoccos fruits on the model of bacterial cystitis in rats. EUREKA: Health Sciences. 2020. № 6. Vol. P. 88–94.

31. Karuna B. Taste masking to improve compliance / B. Karuna, G. Savita, S. Sushma // Internat. Research J. Of Pharm. and Applied Science. – 2013. – № 3. – P. 224–237.

32. A review: taste masking techniques in pharmaceuticals / S. B. Ahire, V. H. Bankar, P. D. Gayakwad, S. P. Pawar // Pharma Science Monitoran International J. of Pharm. Sciences. – 2012. – № l-3 (3). – P. 68–82.

33. Saddiqe, Z., Naeem, I., & Maimoona, A. (2010). A review of the antibacterial activity of Hypericum perforatum L. Journal of ethnopharmacology, 131(3), 511-521.

34. Saddiqe, Z., Naeem, I., Maimoona, A. A review of the antibacterial activity of Hypericum perforatum L. Journal of ethnopharmacology, 2010, 131.3: 511-521.

35. Nahrstedt, A., Butterweck, V. Biologically active and other chemical constituents of the herb of Hypericum perforatum L. Pharmacopsychiatry, 1997, 30.S 2: 129-134.

36. Khalil, R. R., Mohammed, E. T., Mustafa, Y. F. . Various promising biological effects of cranberry extract: A review. Clinical Schizophrenia & Related Psychoses, 2021.

37. Côté, J., Caillet, S., Doyon, G., Dussault, D., Sylvain, J. F., & Lacroix, M. (2011). Antimicrobial effect of cranberry juice and extracts. Food Control, 22(8), 1413-1418.

38. Gbingie, Oghenekome A., et al. Cranberry extract for symptoms of acute, uncomplicated urinary tract infection: a systematic review. Antibiotics, 2020, 10.1: 12.

39. Tempera, G., et al. Inhibitory activity of cranberry extract on the bacterial adhesiveness in the urine of women: an ex-vivo study. International journal of immunopathology and pharmacology, 2010, 23.2: 611-618.

40. Srividya, B.; Reddy, C. S. Capsules And It'S Technology: An Overview. International Journal of Pharmaceutical Drug Analysis, 2014, 2.9: 727-33.

41. Agrosi, M., et al. Oral bioavailability of active principles from herbal products in humans. A study on Hypericum perforatum extracts using the soft gelatin capsule technology. Phytomedicine, 2000, 7.6: 455-462.

APPENDIXES

Appendix A

III Міжнародна науково-практична інтернет-конференція

ПРОБЛЕМИ ТА ДОСЯГНЕННЯ СУЧАСНОЇ БІОТЕХНОЛОГІЇ

24 березня 2023 р.
м. Харків, Україна

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
КАФЕДРА БІОТЕХНОЛОГІЇ

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
DEPARTMENT OF BIOTECHNOLOGY

ПРОБЛЕМИ ТА ДОСЯГНЕННЯ СУЧАСНОЇ БІОТЕХНОЛОГІЇ

PROBLEMS AND ACHIEVEMENTS OF MODERN BIOTECHNOLOGY

Матеріали
ІІІ міжнародної науково-практичної
Інтернет-конференції

Materials
of the III International Scientific and Practical
Internet Conference

ХАРКІВ
KHARKIV
2023

at a dose of 80 mg/kg. All animals were on a standard diet. The duration of the experiment was 28 days. Histological preparations were made from pancreas according to the standard method.

A decrease in the number of CT was found in the pancreas of rats treated with L-tryptophan. This was evidenced by a probably smaller relative area of CT by 38% and a smaller stromal-parenchymal index by 42% compared to the control. The width of interlobular and interacinus CT layers in experimental animals was probably smaller by 33 and 12%, respectively, compared to controls. The stroma is the most important component of the histo-hematic barrier, and reducing its number and layer thickness improves the transport of oxygen to the parenchymal elements of the gland, improves the conditions for metabolic processes, and increases the penetration of hormones into the blood.

That is, L-tryptophan and preparations based on it can be used in the prevention and correction of existing fibrotic changes in the pancreas tissue.

Research of pharmaco-technological properties of cranberry dry extract

Youness Sadik, Ruban O.

Department of Industrial Technology of Drugs of the National University of Pharmacy, Kharkiv, Ukraine

ruban_elen@ukr.net

Cystitis is an acute or chronic inflammatory process in the bladder mucosa. Sometimes the entire wall of the bladder is involved in the pathological process. The most common treatment for cystitis is antibiotic therapy. But an alternative method of treating cystitis is phytotherapy, since medicinal plants have a complex effect on the main mechanisms for the development of cystitis. They demonstrate good clinical efficacy, can be prescribed in the complex therapy of acute cystitis or to prevent relapses.

Therefore, it was decided to develop hard capsules for the treatment of cystitis based on components of plant origin, namely with dry cranberry extract.

At the first stage of developing the composition of hard capsules, the properties of the initial medicinal substances are studied, which determine the rational method of technology and the choice of the range and quantity of excipients. The pharmacotechnological properties of cranberry dry extract were studied. An analysis of the pharmacotechnological properties of the studied dry extract showed that the cranberry dry extract has unsatisfactory fluidity. The calculated Gausner coefficient is 1.38 and the Carr coefficient is 27. Bulk density and density after shrinkage have a significant difference in values, which indicates the ability to clumping, which is undesirable in the technological process, since it can lead to inhomogeneous dosage of the active pharmaceutical ingredient. Microscopic examination of dry cranberry extract showed that it is a polydisperse powder with particles of irregular anisodiametric shape in the form of spheres, prisms and their fragments. The main fraction is from 10 to 110 microns.

The conducted studies on the study of crystallographic, pharmacotechnological properties of dry cranberry extract indicate that the studied substance is a polydisperse system with anisodiometric particles, which unsatisfactorily affects flowability and makes it possible to predict the introduction of excipients from the group of fillers and lubricants when developing a solid dosage form in the form of capsules.

The relevance of the development of herbal collection of antidepressant action

Zamkovaja A.V., Borysiuk I.Yu., Karim Yassim

Department of drug technology Odessa State Medical University, Odessa, Ukraine

zamkovaya@gmail.com

According to the WHO, as well as based on the publications presented on the website of the electronic database of medical and biological publications «PubMed», there is an increase in the prevalence of diseases of the population suffering from mental disorders of various degrees. Medicines of various pharmacological groups are currently used to correct depressive disorders. Among such drugs, benzodiazepines,

Ф А 2.2.1-32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Industrial Technology of Drugs
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of the
Department
of Industrial Technology
of Drugs

_____

Olena RUBAN
"_15_" __of May__ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Youness SADIK

1. Topic of qualification work: «Development of the composition of capsules with dry cranberry extract», supervisor of qualification work: Olena RUBAN, head of the Department of Industrial Technology of Drugs, professor.

approved by order of NUPh from "6th" of February_2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: April 2023.

3. Outgoing data for qualification work: tablets, rhodiola, quercetin, psycho-emotional stress, technology.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): literature review, objects and methods, experimental part, references _____

5. List of graphic material (with exact indication of the required drawings):

tables – 6, pictures – 8

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Olena RUBAN, head of the Department of Industrial Technology of Drugs, professor	17.05.2022	17.05.2022
2	Olena RUBAN, head of the Department of Industrial Technology of Drugs, professor	12.12.22 - 21.01.2023	12.12.22 - 21.01.2023
3	Olena RUBAN, head of the Department of Industrial Technology of Drugs, professor	16.02.2023	16.02.2023

7. Date of issue of the assignment: «15» __ May _____ 2022.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Literature review	September	**Done**
2.	Experiment planning	October	**Done**
3.	Experiment execution	November-February	**Done**
4.	Processing of results	March- April	**Done**
5.	Submission to EC	April	**Done**

An applicant of higher education _____ Youness SADIK

Supervisor of qualification work _____ Olena RUBAN

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі заводської технології ліків**				
Садік Юнесс	Розробка складу капсул з сухим екстрактом клюкви	Development of the composition of capsules with dry cranberry extract.	проф. Рубан О.А.	проф. Вишневська Л.І.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 112734 від «29 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Садік Юнесс, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Розробка складу капсул з сухим екстрактом клюкви / Development of the composition of capsules with dry cranberry extract», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,

професор **Інна ВЛАДИМИРОВА**

8%

30%

Ф А2.2.1-32-353

REVIEW

for qualification work of the master`s level of higher education, specialty

226 Pharmacy, industrial pharmacy

Youness Sadik

on the topic: «Development of the composition of capsules with dry Cranberry extract»

Relevance of the topic. Cystitis is one of the most urgent problems of modern medicine. 25% of women develop cystitis during their lifetime. This disease is characterized by frequent relapses, complications, and a decrease in the quality of life. Cystitis leads to functional disorders of the kidneys and urodynamics. It is also known that capsules are one of the most popular dosage forms. They have many advantages over other oral solid dosage forms, such as: better bioavailability and good consumer properties. Therefore, the creation of a new drug in the form of capsules with cranberry dry extract is an urgent task of pharmaceutical technology.

Practical value of conclusions, recommendations and their validity. Youness Sadik considered the main etiopathogenetic aspects of cystitis, modern approaches to its treatment, theoretically substantiated the use of active pharmaceutical ingredients - cranberry dry extract and hypericum dry extract. Based on the analysis of the results of the studies, the author made conclusions on the assessment of the pharmacotechnological properties of the studied extracts, the substantiation of the composition of excipients. An industrial technology has been developed for obtaining capsules with dry extracts for the treatment of cystitis.

Assessment of work. Qualifying work is done at a high level.

General conclusion and recommendations on admission to defend. The qualifying work meets all the requirements for qualifying papers and can be

submitted for defense to the Examination Board of the National University of Pharmacy.

Supervisor of qualification work _____ Olena RUBAN

"08" April 2023 p.

Ф А2.2.1-32-356

REVIEW

for qualification work of the master`s level of higher educftion, specialty

226 Pharmacy, industrial pharmacy

Youness Sadik

on the topic: «Development of the composition of capsules with dry cranberry extract»

Relevance of the topic. According to medical statistics, cystitis is a very common disease of the urinary system, especially among the female population. For the treatment of cystitis, preparations containing synthetic antimicrobial active pharmaceutical ingredients and antibiotics are widely used. These drugs often have a wide range of side effects, and long-term use of antibiotics can lead to antibiotic resistance. According to the literature, it is known that plant extracts have a wide range of pharmacological activity, can be used for a long time, and do not adversely affect the human body. In this regard, the development of new drugs that contain active pharmaceutical ingredients of plant origin is relevant.

Theoretical level of work. The literature review presents the etiology and pathogenesis of cystitis, the main directions of its treatment. On the basis of literature data, the author justified the use of two plant extracts - cranberry and helichrysum as part of capsules for the treatment of this disease. The expediency of creating such a dosage form as capsules is substantiated. The necessity of using excipients with different pharmacotechnological properties in the composition of the preparation has been proved.

The author's suggestions on the topic of research. Based on the results of the studies, the choice of filler, moisture regulator and lubricant in the composition of the capsules is substantiated. It has been proven that the introduction of Compritol 888 into capsules significantly improves flowability. It has been determined that such moisture regulators as Syloid 244FP, Aerosil and Neusilin UFL 2

significantly reduce the hygroscopicity of the mass for encapsulation. Moisture absorption is most effectively reduced by Syloid 244FP. MCC 102 was introduced into the capsules as a filler.

Practical value of conclusions, recommendations and their validity. Scientific provisions, conclusions and recommendations formulated in the work are based on experimental data. The reliability of the results is beyond doubt.

Disadvantages of work. In the work there are unsuccessful expressions, and grammatical errors.

General conclusion and evaluation of the work. The qualification work of Youness Sadik in terms of the volume and results of research meets all the requirements that apply to qualifying works and can be submitted for defense to the Examination Board of the National Pharmaceutical University.

Reviewer _____prof. Liliia VYSHNEVSKA

"15" April 2023 p.

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'ЯУКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 9

« 21 » квітня 2023 року

м. Харків

засідання кафедри

заводської технології ліків

ПРИСУТНІ: проф. Рубан О.А., проф. Бобрицька Л.О., проф. Гриценко В.І., доц. Хохлова Л.М., доц. Сліпченко Г.Д., доц. Ковалевська І.В., доц. Криклива І.О, ас. Пономаренко Т.О.

ПОРЯДОК ДЕННИЙ:

1. Обговорення кваліфікаційних робіт щодо їх представлення до захисту в Екзаменаційній комісії НФаУ.

СЛУХАЛИ: здобувача вищої освіти5 курсу групи Фм18(4,10)англ-3 Юнесса САДІКА про представлення до захисту в Екзаменаційній комісії НФаУ кваліфікаційної роботи на тему: «Розробка складу капсул з сухим екстрактом журавлини». (Керівник: д.фарм.н., професор Олена РУБАН).

В обговоренні кваліфікаційної роботи брали участь проф. Бобрицька Л.О., доц. Хохлова Л.М., доц. СліпченкоГ.Д.

УХВАЛИЛИ: рекомендувати до захисту в Екзаменаційній комісії НФаУ кваліфікаційну роботу здобувача вищої освіти факультету з підготовки іноземних громадян групи Фм18(4,10д)англ-3 Юнесса САДІКА на тему: «Розробка складу капсул з сухим екстрактом журавлини».

Голова
Завідувачка кафедри ЗТЛ **Олена РУБАН**

Секретар **Тетяна ПОНОМАРЕНКО**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ

ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Юнесса САДІКА до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я

спеціальністю226 Фармація, промислова фармація

освітньою програмою Фармація

на тему: «Розробка складу капсул з сухим екстрактом журавлини».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ /Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Юнесс САДІК у процесі роботи розглянув сучасні підходи до лікування циститу, провів аналіз асортименту засобів для терапії даного захворювання та обґрунтував доцільність створення нового лікарського засобу у формі капсул для лікування циститу. Автором обґрунтовано оптимальний склад і розроблено технологію одержання лікарського засобу. Юнесс САДІК допускається до захисту даної кваліфікаційної роботи у Екзаменаційній комісії Національного фармацевтичного університету.

Керівник кваліфікаційної роботи

_____ Олена РУБАН

«08» квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри

заводської технології ліків

_____ Олена РУБАН

« 21» квітня 2023 року

Qualification work was defended

of в Examination commission on

« __ » _____2023 г.

With the grade_____

Head of the State Examination commission,

DPharm Sc. Professor

_____ / Oleg SHPYCHAK /