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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF FAST-DISSOLVING TABLETS WITH NIMESULIDE»**

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ANNOTATION

In this work the physical, chemical and technological properties of mannitol, nimesulide were studied. Fast-dissolving tablets tablets have a greater advantage among other dosage forms due to ease of use, speed of onset of action, and minimal side effects. After conducted research, we can conclude that the disintegrant Ludiflash is suitable for the composition of fast-dissolving tablets with Nimesulide.

The work consists of the following parts: introduction, literature review, choice of research methods, experimental part, general conclusions, list of used literature sources, total volume of 46 pages, contains 25 tables, 1 figures, 36 references.

Key words: nimesulide, mannitol, sodium croscarmylose, magnesium stearate, fast-dissolving tablets.

АНОТАЦІЯ

У роботі досліджено фізико-хімічні та технологічні властивості маніту, німесуліду. Таблетки швидкорозчинні Таблетки мають більшу перевагу серед інших лікарських форм за рахунок зручності застосування, швидкості початку дії та мінімуму побічних ефектів. Після проведених досліджень можна зробити висновок, що дезінтегрант Лудіфлеш підходить до складу швидкорозчинних таблеток з німесулідом.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних літературних джерел, загальний обсяг 46 сторінок, містить 25 таблиць, 1 рисункf, 36 посилань.

Ключові слова: німесулід, маніт, натрію кроскармілоза, магнію стеарат, швидкорозчинні таблетки.

CONTENT

LIST OF ABBREVIATIONS

API - active pharmaceutical ingredient

BAS – biologically active substance

COX - cyclooxygenase

EU - European Union;

GMP - good manufacturing practice

LBP - low back pain

NSAID - non-steroidal anti-inflammatory drug

ODT – orally desintegrated tablets

Ph.Eur. - European Pharmacopoeia

SPhU - State Pharmacopoeia of Ukraine

WHO - World Health Organization

INTRODUCTION

The relevance of the topic

The development of fast-dissolving tablets has gained significant attention in the field of pharmaceutical research and development. Fast-dissolving tablets offer numerous advantages over conventional oral dosage forms, including ease of administration, enhanced patient compliance, and rapid onset of action. In this context, the present study focuses on the development of the composition and technology of fast-dissolving tablets with nimesulide.

Nimesulide, a non-steroidal anti-inflammatory drug (NSAID), possesses potent analgesic and anti-inflammatory properties. It is widely used for the treatment of various acute and chronic pain conditions. However, the oral delivery of nimesulide in conventional tablet forms often poses challenges, particularly for patients with swallowing difficulties or those who prefer alternative dosage forms.

Fast-dissolving tablets provide a promising solution to overcome these limitations by rapidly disintegrating or dissolving in the oral cavity, thereby facilitating ease of administration and ensuring convenient drug delivery. The formulation and technology employed in the development of fast-dissolving tablets play a crucial role in achieving the desired characteristics, including rapid disintegration, adequate mechanical strength, and effective drug release.

The aim of this study is to explore and develop an optimized composition and technology for fast-dissolving tablets with nimesulide, thereby providing a novel dosage form that combines the therapeutic benefits of nimesulide with the advantages of fast dissolution and ease of administration. The development of such tablets holds great potential for improving patient compliance and enhancing therapeutic outcomes.

By examining the formulation aspects, manufacturing techniques, and physicochemical properties of these fast-dissolving tablets, we aim to optimize their performance and ensure their suitability for practical use. Furthermore,

comprehensive characterization and evaluation will be conducted to assess the relevant parameters.

The development of fast-dissolving tablets with nimesulide represents a significant advancement in pharmaceutical technology. This study aims to contribute to the existing knowledge by providing insights into the formulation and technology required for the successful development of these innovative dosage forms. The findings of this research have the potential to positively impact patient care and provide a convenient and effective option for the administration of nimesulide.

The purpose of the study

The development of the composition and technology of fast-dissolving tablets with nimesulide

Research tasks are

1. To study the technological parameters of nimesulide and auxiliary substances.

2. To develop the composition and technology of fast-dissolving tablets with nimesulide.

3. To investigate the technological parameters fast-dissolving tablets with nimesulide.

The object of research

Nimesulide, auxiliary substances, fast-dissolving tablets.

The subject of the study

The process of development of technology of fast-dissolving tablets.

Research methods

Methods of technological research according to the methods of the State Pharmacopoeia of Ukraine were used.

Practical significance of the obtained results

The results of the study can be used in the development of fast-dissolving tablets at the pharmaceutical plants.

Elements of scientific research

The process of tabletting of fast-dissolving tablets with nimesulide and additional substances were studied.

Structure and scope of qualification work

Qualification work consists of the following parts: introduction, literature review, choice of research methods, experimental part, general conclusions, list of used literature sources, total volume of 46 pages, contains 25 tables, 1 figure, 36 references.

CHAPTER 1

CURRENT STATE OF THE TECHNOLOGY OF FAST-DISSOLVING TABLETS

1.1 Statistics of diseases

The oral route of drug administration is considered one of the most widely accepted due to its convenience and ease of use. But due to the size of capsules and tablets, not every person manages to swallow the medicinal form, which leads to some inconveniences in use, especially for the elderly and children. Also, it is not excluded that the percentage of the population suffers from diseases of the pharynx and esophagus, which makes it impossible to take tablet medicinal forms [1, 2].

Approximately 22 million people worldwide suffer from dysphagia. Among the diseases of the elderly, stroke and dementia reflect high rates of dysphagia. Any disturbance in the swallowing process can be defined as dysphagia [3]. Individuals with anatomic or physiologic deficits in the mouth, pharynx, larynx, and esophagus may exhibit signs and symptoms of dysphagia. In addition, dysphagia contributes to various negative health conditions; especially, an increased risk of malnutrition [4]. The consequences of untreated or inadequate treatment can be serious, including dehydration, malnutrition, airway obstruction by solid food, airway aspiration of liquids and semi-solid food, which can cause aspiration pneumonia, or pneumonitis [5].

Fast-dissolving tablets are a good alternative for the treatment of people with both diseases and for convenience when it is not possible to ask for medicine with water.

Nimesulide is a drug from the group of NSAIDs, which has an anti-inflammatory, analgesic, antipyretic effect. The very creation of the drug "Nimesulide ODT" will allow to quickly realize its pharmacological properties, regardless of the difficulties listed above, which may be with the patient [6].

1.2. Market analysis of NSAIDs and nimesulide in the composition of fast-dissolving tablets

Nonsteroidal anti-inflammatory drugs occupy leading positions in Ukraine among the population's use in the fight against pain and inflammation of varying intensity. Rheumatic diseases, muscle pain, sprains are problems with which people turn to doctors and pharmacists [7].

Thanks to the wide assortment of NSAIDs, it is possible to choose the drug that will have the maximum effect and cause minimal side effects.

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) effective in the treatment of a number of diseases accompanied by inflammation and pain, including acute pain in primary dysmenorrhea [8]. It is available on the market since 1985. Preparations containing nimesulide are sold in a number of countries of the European Union, including Bulgaria, Cyprus, the Czech Republic, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Poland, Portugal, Romania, Slovakia and Slovenia. Nimesulide is the only representative of the sulfanilamide class among NSAIDs. According to the degree of selectivity in relation to cyclooxygenase (COX) isoforms, nimesulide belongs to drugs that inhibit mainly COX-2, the activity of which in relation to COX-2 is 5-50 times surpasses activity against COX-1 [9, 10]. In in vivo experiments, when using nimesulide in a therapeutic dose (100 mg 2 times a day), a significant decrease in the level of prostaglandin concentration was demonstrated E2 (PGE2) in blood plasma. Assessment of COX-1 induced activity showed that nimesulide does not affect platelet aggregation [11].

In clinical practice, nimesulide has been shown to be effective in several models of acute pain, in particular, in acute low back pain (LBP). In one of the studies, it was confirmed that nimesulide is a more effective and well-tolerated drug in general medical practice for acute pain at a dosage of 100 mg 2 times a day for 10 days compared to ibuprofen, which was used at 600 mg 3 times a day for 10 days [12, 13, 14].

In some scientific works, it was shown that nimesulide can suppress the mechanisms that determine the progression of articular cartilage degeneration, which is the basis of the development of osteoarthritis [15]. There are also reports about the ability of nimesulide to increase the synthesis of cartilage matrix components and inhibit chondrocyte apoptosis, which can also have a beneficial effect on the condition of the cartilage tissue of patients with osteoarthritis. [16, 17]

On the Ukrainian pharmaceutical market, preparations with nimesulide are presented in various forms of release.

Table 1.1

Preparations with nimesulide are presented in various forms

Name	Producer	Customer
Affida Fort, sachet	Fine Foods and Pharmaceuticals N.T.M. S.P.A., Italy	Delta Medical Promotions AG, Switzerland
Nimesulide, tablets	Private joint-stock company "Lekhim - Kharkiv", Ukraine	Private joint-stock company "Lekhim - Kharkiv", Ukraine
Nise, pills	Dr Reddy's Laboratories Ltd, Manufacturing Site - II, India Dr. Reddy's Laboratories Limited, India	Dr. Reddy's Laboratories Limited, India
Nimelgan, tablets	"ASTRAPHARM" LLC, Ukraine	"ASTRAPHARM" LLC, Ukraine
Nimesulide, tablets	JSC "Lubnyfarm", Ukraine	JSC "Lubnyfarm", Ukraine
Nimedar, tablets	PrJSC "Pharmaceutical	PrJSC "Pharmaceutical

	firm "Darnytsia", Ukraine	firm "Darnytsia", Ukraine
Nimesulide - Fitopharm, tablets	PRIVATE LIMITED LIABILITY COMPANY "FITOFARM", Ukraine	PRIVATE LIMITED LIABILITY COMPANY "FITOFARM", Ukraine
Nimesil, Sashe	Laboratorios Menarini S.A. (production "in bulk", primary and secondary packaging, control and release of series), Spain Fine Foods and Pharmaceuticals N.T.M. SPA. (production "in bulk", primary and secondary packaging, control and release of series), Italy	Laboratorios Menarini S.A. Italy
Remesulide, tablets	PJSC Farmak, Ukraine	PJSC Farmak, Ukraine
Nimid forte, tablets	Kusum Healthcare Pvt Ltd, India	Kusum Healthcare Pvt Ltd, India

Having analyzed the modern market of NSAIDs, over the past 5 years in Ukraine no form of ODT with Nimesulide was found.

In some cases, on the background of taking NSAIDs, serious specific side effects may occur, the risk of developing of which increases significantly depending on the duration of use of the drugs. Among these complications, the most well-known is NSAID gastropathy, a pathology of the upper parts of the gastrointestinal tract, associated with the systemic effect of NSAIDs and characterized by the development of erosions, ulcers and dangerous complications of gastrointestinal bleeding (GI) and perforation. The risk of this pathology in

patients who regularly take nonsteroidal anti-inflammatory drugs increases in comparison with the general population by more than 4 times (approximately 0.5-1.0 cases per 100 patients per year). Patients who regularly take non-steroidal anti-inflammatory drugs die from such complications 2-3 times more often than people who do not take NSAIDs.

Dyspepsia is the most frequent complication from the gastrointestinal tract that occurs against the background of taking NSAIDs. Various unpleasant symptoms - gastralgia, a feeling of heaviness and burning in the epigastrium, nausea, occur in 20-30% of patients who regularly use these drugs. Fortunately, this pathology is not associated with dangerous consequences, but it significantly affects the quality of life, leads to tangible material losses (related to the need to take drugs to stop dyspepsia) and is a frequent reason (~ 10%) for stopping therapy [18].

It is important to emphasize that the undesirable effects of NSAIDs are serious, but it is quite possible to solve them. The fact is that the vast majority of dangerous complications occur in patients with risk factors. For NSAID gastropathy, this is advanced age (over 65 years old), an ulcer history and concomitant use of drugs that affect blood coagulation (most often - low doses of aspirin). For cardiovascular disasters - the presence of uncompensated hypertension, heart failure, ischemic heart disease, as well as diseases and pathological conditions accompanied by an increased risk of vascular thrombosis [19].

Careful accounting of risk factors and rational use of adequate preventive methods allow to minimize the risk of developing complications. And nimesulide in this regard is safer than many other representatives of the group of NSAIDs. Thus, the Irish researcher Bradbury F. estimated the frequency of complications from the gastrointestinal tract when using diclofenac (n = 3553), nimesulide (n = 3807) and ibuprofen (n = 1470) in real clinical practice. Most patients (77.8%) received NSAIDs for no more than 14 days. It turned out that the total frequency of gastrointestinal complications when using nimesulide did not differ from that when

using ibuprofen (8.1 and 8.6%), but was significantly less compared to diclofenac (2.1%; $p < 0.05$).

According to the research plan, nimesulide in a dose of 200 mg was prescribed to 20 patients, immediately before that they underwent a course of anti-ulcer treatment for ulcers or multiple (more than 10) erosions of the stomach and / or duodenum, which occurred when using other NSAIDs. The control group consisted of 20 patients, matched by age, sex and diagnosis of the main disease, who were prescribed diclofenac in rectal suppositories after elimination of NSAID gastropathy. Recurrence of erosive-ulcerative lesions during 2 months of observation was noted in only 1 (5.6%) patient who received nimesulide, and in 33.3% of patients treated with diclofenac ($p < 0.05$).

Thus, nimesulide is a drug with a very favorable combination of powerful analgesic, anti-inflammatory action and good tolerability. Clinical studies and extensive experience of using this drug in real clinical practice show that the risk of developing side effects with long-term use of nimesulide is generally lower than with the use of traditional (non-selective) NSAIDs. Therefore, nimesulide is the drug of choice for the treatment of CB associated with damage to the joints and spine. The most important factor that determines the expediency of using generic nimesulide (such as the well-proven Nize® in our country) is financial availability, which is of fundamental importance for the long-term use of NSAIDs in socially disadvantaged groups of patients with chronic rheumatic diseases. [20]

1.3. The current state of technology for the production of fast-dissolving tablets

Orodispersible tablets are gaining more and more popularity in the pharmaceutical market. Due to the ease of administration, they can be recommended to the elderly, with diseases and difficulty swallowing, which is often found in pediatrics and gastroenterology [21].

In the production of the dosage form, two technologies are used: lyophilization and direct pressing.

Lyophilization allows you to achieve a very fast disintegration time, allows you to create an easily soluble amorphous porous structure in the form of a tablet due to the sublimation of water from the polymer matrix. The active drug is dissolved or dispersed in an aqueous solution of the carrier polymer. The obtained oral lyophilisates have instant disintegration and are well absorbed. But limiting factors, such as the fragility of the resulting tablet, the impossibility of providing a high dosage of the active substance, do not give the desired result [22].

The direct pressing method has a number of advantages. It allows you to achieve high labor productivity, significantly reduce the time of the technological cycle due to the cancellation of a number of operations and stages, exclude the use of several items of equipment, reduce production areas, reduce energy and labor costs, significantly reducing the cost of tablets. Direct pressing makes it possible to obtain tablets from moist, thermolabile and incompatible substances. However, a small number of tablet names are obtained by this method. This is explained by the fact that most medicinal substances do not have properties that ensure their direct pressing. These properties include: isodiametric shape of crystals, good fluidity and compressibility, low adhesiveness to the press tool [17].

ODT tablets are a good alternative to liquid medicinal forms (syrup, infusion, drops), and in some cases can replace them. There are also a number of reasons for which we can evaluate this type of dosage form.

- ODTs do not require water to swallow, which makes it much easier for people who travel, workers who have long meetings or conferences, patients with nausea and vomiting, who are on a limited amount of water intake to take the medicine [25].

- are suitable for use in pediatric practice due to taste masking. In this way, it is possible to facilitate the reception of "bitter pills".

- Patients who have diseases that make swallowing impossible or difficult (heart attack, stroke, radiation therapy of the head and neck, neurological disorders, etc.).

- are suitable for immediate relief of a cough attack or allergic manifestations.

Due to the fact that ODTs are able to quickly start the action of the active pharmaceutical ingredients, as they begin to be absorbed in the oral cavity, this makes it possible to improve bioavailability, reduce dosage and side effects.

The development of ODT tablets expands the range of drugs and has a positive impact on the state of the pharmaceutical business.

There are different types of fast-dissolving tablets [26].

The first type is exactly ODT tablets, which do not have a shell, they are placed in the oral cavity, where they quickly disperse before swallowing. This type of tablets is defined in the SPhU as those that must disintegrate within 3 minutes. The composition of these tablets ensures a slow release and local effect of active substances or substances that are absorbed in certain areas of the mouth.

Requirements for orodispersible tablets:

- Must be pleasant to the taste;

- To be strong, in order to withstand mechanical loads in the process of packaging, transportation, opening the package before use;

- Insensitive to temperature and humidity; Tablets in most cases can be fragile and hygroscopic, therefore special packaging is used for stable and safe storage and opening before use;

- The packaging should be easily peeled off to prevent damage to the tablets. To obtain ODT tablets, disintegrants or substances with high water solubility are used [27].

There are many technologies for preparing fast-dissolving tablets. These include: lyophilization, direct pressing, molding, spray drying, extrusion, sublimation, shell coating, nanonization, and others. Each type of tablet prepared

by one or another method differs in mechanical strength, taste, speed of disintegration, stability, bioavailability, speed of dissolution in saliva [28].

To obtain tablets by lyophilization, the active substance is dissolved in an aqueous solution, and then poured into the wells of the blister pack by weight. They are then passed through liquid nitrogen for freezing, after which they are placed in a refrigerator for continued sublimation. After sublimation, blisters are dried and covered with foil, packaged. The sublimation method improves the bioavailability of the drug [29].

Initially, this technology was used to obtain ODT with water-soluble excipients, but the tablets themselves were glassy, very fragile and crumbled under stress. To prevent this, it was proposed to introduce cryoprotectants, such as mannitol, into the tablets. Thanks to their properties, cryoprotectants form crystals during lyophilization, induce the formation of a crystalline structure, which gives the ODT tablet rigidity and strength [32]

In general, ODT tablets may contain flavorings, preservatives, dyes, suspending substances, which significantly improve the taste of this product.

Tablets obtained by molding are designed to improve the absorption of active ingredients through the oral cavity. Thanks to this type of technology, the tablet acquires porosity, which accelerates disintegration. For the forming method, the mixture is pre-moistened with a water-alcohol solution followed by pressing at low pressures. The solvent is removed by drying [20].

It is also possible to pre-mix the mixture with agar during heating, and then pour this mixture into the wells of the blister, but this method requires additional taste adjustment.

Direct pressing is the most common and simplest method, as it uses conventional equipment, traditional production steps and excipients. In this way, it is possible to maintain high doses of active ingredients. This method uses a combination of disintegrants, water-soluble fillers and effervescent agents to obtain ODT tablets [18].

The composition of such a tablet includes superdisintegrants (1-15% of the total mass), binders (5-10%), antistatic agents (0-10%), fillers (0-85%). Excipients are divided into water-soluble (sugars, binders, surfactants, flavorings), water-insoluble (microcrystalline cellulose, hydrogen phosphate), disintegrants (polyvinylpyrrolidone, starch).

Ludiflash is one of the promising auxiliary substances of modern technology. Due to its properties, it is used as a filler, disintegrant and binder, gives tablets hardness and low fragility. This significantly reduces storage costs and analytical work, accelerates product development and process validation [16].

Thanks to this, it is possible to choose any method of technology for creating fast-dissolving tablets.

In pharmaceutical technology, the extrusion method is also used, which consists in mixing medicinal and auxiliary substances, moistening them with a solvent containing water-soluble polyethylene glycol with methanol, obtaining cylindrical granules and drying them, followed by the formation of tablets [4].

Melt granulation is carried out by agglomeration of pharmaceutical powders by adding binding auxiliary substances in the form of a molten liquid or a solid substance that melts during heating. For this method, high-speed mixers are used, in which the temperature of the product rises above the melting point of the binding component.

The method of nanonization involves the reduction of drug particles to nanosize. Methods of obtaining nanocrystals:

- Nanodeposition;
- High pressure homogenization;
- Moderate grinding.

Nanocrystals of active substances are placed on separate stabilizers to prevent agglomeration, thanks to which this technology can be used for hydrophobic medicinal substances, as well as for a wide range of doses [8].

For the formation of fast-dissolving tablets, shells are used that dissolve quickly and contain water-soluble polymers (polysaccharide pullulan, hydroxypropylmethylcellulose, polyvinylpyrrolidone, etc.)

CONCLUSION

1. Through the study of the literature, we determined that fast-dissolving tablets are becoming more and more popular among the public and pharmaceutical manufacturers. People of different ages and with various deviations with swallowing need to use this dosage form.

2. Pharmaceutical manufacturers use the methods of direct pressing, wet granulation, lyophilization for the preparation of orodispersible tablets and take into account the properties of the main and active substances for the choice of technology.

3. The modern market of NSAIDs includes preparations with Nimesulide in the form of tablets, granules, ointments, which significantly improves treatment.

4. On the basis of the study of drugs with nimesulide registered in Ukraine over the past 5 years, no specific form of ODT was found, which confirms the relevance of these studies.

5. Among other representatives of NSAIDs - Nimesulide is safer to use, has a less pronounced side effect in the form of gastric ulcer.

CHAPTER 2
OBJECTS AND RESEARCH METHODS

2.1 Choice of general research methodology

Nimesulide, a nonsteroidal anti-inflammatory drug, offers several therapeutic benefits but has limited oral bioavailability due to its poor aqueous solubility. Fast dissolving tablets, designed to rapidly disintegrate and release the drug, have gained significant attention as a patient-friendly dosage form. This review highlights the importance of selecting an appropriate research methodology to optimize the formulation and technology of fast dissolving tablets with nimesulide.

In General there could be the stages as follows:

- Overview of Fast Dissolving Tablets
- Significance of Nimesulide as an Active Pharmaceutical Ingredient
- Relevance of Fast Dissolving Tablets with Nimesulide
- Formulation Design
- Characterization of Excipients
- Tablet Preparation Techniques
- Evaluation of Tablet Properties

Formulation Design

- Literature Review
- Consideration of Excipients
- Disintegration Time and Mechanical Strength
- Drug Release Profile

Characterization of Excipients

- Physicochemical Properties of Excipients
- Compatibility Studies

- Excipient Selection Criteria

Tablet Preparation Techniques
- Direct Compression Method
- Blending Techniques
- Compression Forces

Evaluation of Tablet Properties
- Weight Variation
- Thickness
- Hardness
- Friability
- Disintegration Time
- Drug Content Uniformity
- Dissolution Testing

The introduction provides an overview of fast dissolving tablets, highlights the significance of nimesulide as an active pharmaceutical ingredient, and emphasizes the relevance of developing fast dissolving tablets with nimesulide.

The research methodology selection section discusses various aspects of the chosen research methodology, including formulation design, characterization of excipients, tablet preparation techniques, and evaluation of tablet properties.

The formulation design section explores the importance of conducting a literature review, considering excipients, and optimizing disintegration time, mechanical strength, and drug release profile.

The characterization of excipients section focuses on the evaluation of physicochemical properties, compatibility studies, and criteria for selecting suitable excipients.

The tablet preparation techniques section discusses the direct compression method, blending techniques, and the role of compression forces in achieving the desired tablet characteristics.

The evaluation of tablet properties section covers various quality attributes such as weight variation, thickness, hardness, friability, disintegration time, drug content uniformity, and dissolution testing.

Further research is needed to explore additional formulation strategies, such as the incorporation of novel excipients or the use of advanced manufacturing techniques like hot melt extrusion or spray drying. Additionally, studies on the stability of the formulated tablets under various storage conditions will provide valuable insights into their shelf-life and potential for commercialization.

Characterization of Excipients

Characterizing the excipients used in the formulation is crucial to ensure their compatibility and functionality. Physicochemical properties of excipients such as particle size, density, solubility, and hygroscopicity should be evaluated. Compatibility studies between nimesulide and excipients should be conducted to identify any potential interactions that may affect the stability and efficacy of the formulation. The selection of excipients should be based on their safety, compatibility, functionality, and ability to enhance the desired properties of fast dissolving tablets.

Tablet Preparation Techniques

Several tablet preparation techniques can be employed in the development of fast dissolving tablets with nimesulide. Direct compression method, which involves the simple blending of active pharmaceutical ingredients and excipients, is commonly used due to its simplicity and cost-effectiveness. Other techniques such as wet granulation or freeze-drying may be explored depending on the specific requirements of the formulation. The compression forces applied during tablet manufacturing should be optimized to achieve the desired hardness and disintegration properties.

Evaluation of Tablet Properties

Various parameters should be evaluated to assess the quality and performance of the formulated fast dissolving tablets. These include weight variation, thickness, hardness, friability, disintegration time, drug content uniformity, and dissolution testing. Weight variation and thickness measurements ensure the uniformity of tablet size, while hardness and friability tests assess their mechanical strength and robustness. Disintegration time, a critical parameter for fast dissolving tablets, should be evaluated to ensure rapid disintegration and dissolution of the tablet. Drug content uniformity analysis is essential to ensure consistent dosage delivery, while dissolution testing provides information on drug release kinetics.

In conclusion, the development of fast dissolving tablets with nimesulide requires a well-defined research methodology encompassing formulation design, excipient characterization, tablet preparation techniques, and comprehensive evaluation of tablet properties. By selecting appropriate excipients, optimizing the tablet formulation, and employing suitable manufacturing techniques, it is possible to develop fast dissolving tablets with enhanced hepatoprotective effects. The choice of research methodology plays a vital role in achieving the desired formulation characteristics and ensuring the quality, efficacy, and patient acceptability of the final product.

Further research should focus on optimizing the formulation parameters, exploring novel excipients, and conducting comprehensive stability studies to assess the long-term storage and performance of the developed tablets. Additionally, clinical studies are necessary to evaluate the therapeutic efficacy and safety profile of the formulated tablets. By continuing to refine the composition and technology of fast dissolving tablets with nimesulide, researchers can contribute to the advancement of hepatoprotective therapies and provide patients with a convenient and effective treatment option.

The purpose of the study

The development of the composition and technology of fast-dissolving tablets with nimesulide

Research tasks are

1. To study the technological parameters of nimesulide and auxiliary substances.

2. To develop the composition and technology of fast-dissolving tablets with nimesulide.

3. To investigate the technological parameters fast-dissolving tablets with nimesulide.

2.2. Objects of research

The main object of research are Nimesulide, auxiliary substances, fast-dissolving tablets.

Nimesulide is a light yellow granular powder with an orange smell, after partial dissolution the color of the suspension is white or light yellow.

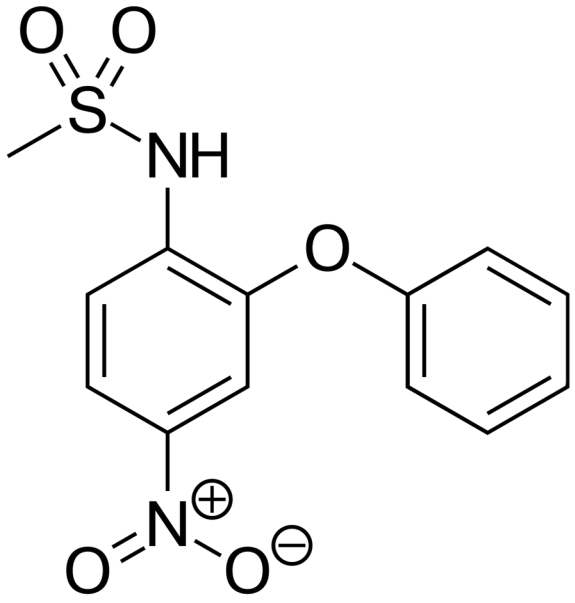

Fig. 2.1 Nonsteroidal anti-inflammatory drug

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits potent analgesic, anti-inflammatory, and antipyretic properties. It belongs to the class of selective cyclooxygenase-2 (COX-2) inhibitors and is widely used for the management of pain and inflammation associated with various conditions, including musculoskeletal disorders, rheumatoid arthritis, and osteoarthritis.

Chemically, nimesulide is a sulfonanilide derivative with a molecular weight of approximately 308.33 g/mol. It is a yellow crystalline powder that is sparingly soluble in water but highly soluble in organic solvents. Nimesulide's chemical structure consists of a sulfonamide group attached to an aromatic ring, which confers its pharmacological activity.

Nimesulide acts primarily by inhibiting the synthesis of prostaglandins, which are inflammatory mediators involved in pain and inflammation pathways. By selectively inhibiting COX-2 enzyme activity, nimesulide suppresses the production of prostaglandins responsible for pain perception and inflammation, while sparing the constitutive COX-1 enzyme involved in maintaining normal physiological functions.

The pharmacokinetic profile of nimesulide is characterized by its rapid absorption after oral administration, with peak plasma concentrations reached within 1-2 hours. It undergoes extensive hepatic metabolism, primarily via cytochrome P450 enzymes, leading to the formation of several metabolites. The majority of the metabolites are conjugated and subsequently eliminated through urine and feces.

Nimesulide's therapeutic efficacy and safety profile have been well-documented through clinical studies and extensive clinical experience. It offers effective relief from pain and inflammation, and its selective COX-2 inhibition is associated with a reduced risk of gastrointestinal adverse effects compared to non-selective NSAIDs. However, as with any medication, caution should be exercised, and it should be used at the lowest effective dose and for the shortest duration possible to minimize potential side effects.

Nimesulide is a valuable NSAID that demonstrates potent anti-inflammatory and analgesic properties. Its selective COX-2 inhibition and favorable safety profile make it a suitable choice for the management of various painful and inflammatory conditions. However, further research and clinical studies are warranted to explore its full therapeutic potential and optimize its use in patient care.

Croscarmellose sodium, also known as sodium croscarmellose or croscarmellose, is a commonly used pharmaceutical excipient with excellent disintegrating properties. It is a cross-linked polymer derived from cellulose, specifically carboxymethyl cellulose.

Chemically, croscarmellose sodium is a sodium salt of a cross-linked carboxymethyl cellulose. It is a white to off-white, odorless, and tasteless powder that is highly hygroscopic. Due to its cross-linked structure, croscarmellose sodium exhibits the ability to rapidly absorb water and swell upon contact, leading to the rapid disintegration and dissolution of tablets or capsules.

One of the primary functions of croscarmellose sodium in pharmaceutical formulations is to promote disintegration. When incorporated into solid dosage forms, such as tablets, it absorbs water from the surrounding environment or gastric fluids, causing the tablet to rapidly disintegrate into smaller particles. This property is crucial for the effective release and absorption of active pharmaceutical ingredients (APIs) in the gastrointestinal tract.

Croscarmellose sodium is widely used in the formulation of fast-dissolving tablets, orally disintegrating tablets, and other immediate-release dosage forms. Its ability to enhance dissolution and improve drug release makes it suitable for drugs with low solubility or those that require rapid onset of action. It is compatible with a variety of APIs and can be used in both hydrophilic and hydrophobic drug formulations.

The disintegration mechanism of croscarmellose sodium involves the swelling of the polymer upon contact with fluids, which creates internal pressure within the tablet and leads to its rapid breakup. This allows the drug particles to be

readily available for dissolution and absorption, promoting bioavailability and therapeutic efficacy.

Croscarmellose sodium is generally recognized as safe (GRAS) by regulatory authorities and has a long history of safe use in pharmaceutical formulations. It is considered inert and does not interact significantly with drug substances or other excipients. It is also compatible with various processing methods, including direct compression and wet granulation.

Croscarmellose sodium is a widely utilized pharmaceutical excipient that enhances the disintegration and dissolution properties of solid dosage forms. Its ability to promote rapid tablet disintegration and release of active ingredients makes it a valuable ingredient in the development of fast-dissolving tablets and other immediate-release formulations.

Mannitol is a naturally occurring sugar alcohol commonly used as an excipient in the pharmaceutical industry. It is a white, crystalline powder with a sweet taste and odorless characteristic. Mannitol is derived from mannose, a monosaccharide, and it is found in various plants, algae, and fungi.

Chemically, mannitol is classified as a polyol, a sugar alcohol that contains multiple hydroxyl groups. Its molecular formula is C6H14O6, and its molecular weight is 182.17 g/mol. Mannitol has a unique property of being highly soluble in water, making it suitable for various pharmaceutical applications.

In the pharmaceutical industry, mannitol serves multiple purposes. It is primarily used as a bulking agent, filler, and diluent in solid dosage forms, such as tablets and capsules. Mannitol's low hygroscopicity allows it to maintain stability and prevent moisture absorption, ensuring the integrity and shelf-life of the formulated products.

One of the notable characteristics of mannitol is its ability to provide tablet hardness and strength. It possesses good compressibility properties, making it suitable for direct compression or as a component in wet granulation processes. Mannitol can be mixed with active pharmaceutical ingredients (APIs) and other

excipients to create a uniform blend, facilitating the formation of tablets with desired hardness and disintegration properties.

Mannitol is also recognized for its taste-masking properties. Its sweet taste helps mask the bitterness or unpleasant flavors of certain drugs, thereby improving patient acceptance and compliance. This feature is particularly useful in the formulation of orally disintegrating tablets, chewable tablets, and lozenges.

Furthermore, mannitol exhibits a cooling effect when dissolved in water or saliva, making it a common ingredient in products like chewing gums, breath mints, and oral care preparations. Its cooling sensation provides a refreshing experience and contributes to a perceived sense of freshness and cleanliness.

From a safety perspective, mannitol is considered generally recognized as safe (GRAS) by regulatory authorities and has a long history of use in pharmaceutical and food applications. It is well-tolerated by most individuals, with minimal adverse effects reported. However, individuals with specific medical conditions, such as diabetes or kidney dysfunction, should consult their healthcare provider before consuming mannitol-containing products.

In summary, mannitol is a versatile excipient widely employed in the pharmaceutical industry. Its role as a bulking agent, tablet binder, taste-masker, and cooling agent makes it valuable in the formulation of various solid dosage forms. Mannitol's favorable properties, such as low hygroscopicity, high solubility, and sweet taste, contribute to its widespread use in the development of high-quality pharmaceutical products.

Magnesium stearate is a white, fine powder that is widely used in the pharmaceutical industry as an excipient or an inactive ingredient in the formulation of various medications. It is a magnesium salt of stearic acid, a saturated fatty acid.

Chemically, magnesium stearate is represented by the molecular formula (C18H35O2)2Mg. It consists of long-chain fatty acids attached to a central magnesium ion. The compound has a melting point of approximately 120-130°C and is insoluble in water but soluble in organic solvents.

One of the primary functions of magnesium stearate in pharmaceutical formulations is as a lubricant and a flow agent. It possesses excellent lubricating properties, which help reduce friction between the particles of the active pharmaceutical ingredient (API) and other excipients during the manufacturing process. This facilitates the uniform mixing of ingredients, prevents sticking to equipment, and aids in the efficient tablet compression or capsule filling processes.

Additionally, magnesium stearate acts as a glidant, improving the flow characteristics of powders. It helps enhance the powder's ability to flow freely through the processing equipment, ensuring uniformity in dosage and preventing the formation of lumps or clumps. This is particularly important in the manufacturing of tablets and capsules, where consistent flow properties are necessary for proper dosage and content uniformity.

Another advantage of magnesium stearate is its hydrophobic nature. It forms a thin, hydrophobic film on the surface of particles, which provides a barrier against moisture absorption and enhances the stability of the formulated product. This moisture-repelling property helps protect the integrity and shelf-life of medications by preventing the degradation or deterioration of active ingredients.

Magnesium stearate is generally regarded as safe for consumption in pharmaceutical products and is widely used in the industry. It has a long history of use and has been thoroughly evaluated for its safety profile. It is considered inert and has low toxicity levels, posing no significant risk to human health when used as directed.

However, it is worth noting that in rare cases, some individuals may be sensitive or allergic to magnesium stearate. If any adverse reactions occur, such as skin irritation or gastrointestinal discomfort, it is recommended to seek medical advice.

Magnesium stearate is a commonly used excipient in the pharmaceutical industry due to its lubricating, flow-enhancing, and moisture-repelling properties. Its presence in formulations aids in the manufacturing process by improving tablet and capsule production efficiency and ensuring content uniformity. Magnesium

stearate has a well-established safety profile and contributes to the overall quality and stability of pharmaceutical products.

2.3 Research methods

The following research methods were used during the experimental studies: microscopy methods, studies of fractional composition, bulk density, friability, fluidity.

CHAPTER 3

DEVELOPMENT TECHNOLOGIES OF TABLETS AND THEIR RESEARCH

3.1. Study of physical, chemical and technological properties

Determination of fractional composition

Based on the State Pharmacopoea of Ukraine method to determine the fractional composition, we took sieves with sizes of 0.355; 0.25; 0.18; 0.09. Mannitol and nimesulide were taken for analysis.

20 g of each substance was measured separately on electronic scales. Next, it was poured onto the top layer of the sieve, closed with a lid and slowly shaken for 5 minutes so that the particles were separated by size. The powder from each sieve was poured onto a scale and weighed.

The data are presented in tables 3.1 and 3.2

Table 3.1

Fractional composition of mannitol

Sieve size	Fraction, g	Percentage, %
<0.355 mm	3.135 g	15.67%
0.25mm - 0.355mm	2.925 g	14.62%
0.18 mm - 0.25 mm	5.660 g	28.3%
0.09mm - 0.18mm	6.445 g	32.22%
>0.09 mm	1.355 g	6.77%

Table 3.2

Fractional composition of nimesulide

Sieve size	Fraction, g	Percentage, %
<0.355 mm	6.535 g	32.67%
0.25mm - 0.355mm	5.3 g	26.5%
0.18 mm - 0.25 mm	5.075 g	25.37%
0.09mm - 0.18mm	0.975 g	4.87%
>0.09 mm	0.09 g	0.45%

The main part of mannitol is particles with a size of 0.09 mm - 0.18 mm, which will in the future have a positive effect on the formation of a homogeneous mass of the tablet and will hold its shape well.

Nimesulide is a powder that has quite large particles <0.355 mm in size, which will make it difficult to form a homogeneous mass.

Determination of bulk density

The bulk density is determined by mannitol and nimesulide. According to t the State Pharmacopoea of Ukraine method for determining the bulk density, 50 g of the substance was weighed on an electronic scale and poured into a measuring cylinder. We fixed the cylinder on the device, set the necessary parameters, and we are monitoring what the volume of powder will be at 10, 500 and 1250 blows. Next, the density of the substance was determined using the formula.

$$\rho = \frac{m}{V}$$

m - is the mass of the investigated substance, g;

V - is the received volume, ml.

The results are presented in Tables 3.3 and 3.4

Manit sample is 50 ml - 32.045 g

Table 3.3

Determination of the bulk density of mannitol

V, volume	ρ, density
V10 = 46 ml	ρ1 = 0.6966 g/ml
V500 = 42 ml	ρ2 = 0.7630 g/ml
V1250 = 41 ml	ρ3 = 0.7816 g/ml

Nimesulide sample is 50 ml - 20.645 g

Table 3.4

Determination of the bulk density of nimesulide

V, volume	ρ, density
V10 = 46 ml	ρ1 = 0.4488 g/ml
V500 = 39 ml	ρ2 = 0.529 g/ml
V1250 = 38 ml	ρ3 = 0.5433 g/ml

Determination of fluidity

Mannitol was checked for fluidity. Based on the State Pharmacopoea of Ukraine method, 20 g of mannitol was weighed into a measuring cylinder and poured into the funnel with the valve closed. The device was turned on with the toggle switch, at the same time the stopwatch was turned on and opened the shutter, watching the powder flow from the funnel into the receiving cup. This experiment is carried out 3 times.

Using the same method, we checked the flowability of nimesulide. The results are shown in the table.

Table 3.5

Determination of fluidity of mannitol and nimesulide

Ingredient	1	2	3	Average
Manit	1.77 sec	2.31 sec	2.15 sec	9.61 g/ sec
Nimesulide	8.7 sec	9.1 sec	8.9 sec	2.24 g/ sec

3.2. Development of tablet composition and technology

New methods and technologies for improving tablets are increasingly appearing at the pharmaceutical enterprise. ODTs were not an exception. But the requirements for orodispersible tablets remain unchanged:

Should quickly dissolve or disintegrate in the oral cavity in no more than 30 seconds. They must be compatible with other auxiliary substances both in terms of taste and physical and chemical parameters. After oral administration, they should not remain in the oral cavity or remain in a minimal amount.

In order to remain in the form of tablets, they must withstand environmental conditions such as moisture and temperature. According to the cost of production, tablets should be budget-friendly, because the market price depends on the cost of production.

Due to the preliminary research of the substances that will be included in the composition of our tablets, 8 variants of the composition of the tablets were created.

Nimesulide is an active substance, so it should be taken 0.100 g for the production of 1 fast-dissolving tablet according to European standards.

It is better to take croscarmylose sodium and magnesium stearate from Vava Sol. Excipients are more refined and of higher quality. With the help of pharmacy scales, weigh nimesulide into 50 tablets of 5 grams, pour into a mortar.

Then we weigh the mannitol. 0.296 g per 1 tablet, which is 14.8 g per 50 tablets. We add the disintegrant croscarmylose sodium in the amount of 0.5 g. We also add magnesium stearate 0.004 - 0.2 g per 50 tablets. Pour into a mortar and mix.

Table 3.6

Formulation number 1

F1	For 1 tablet	For 50 tablets
Nimesulide	0.100 g	5 years
Manit	0.286 g	14.3 g
Sodium croscarmylose	0.010 g	0.5 g
Magnesium stearate	0.004 g	0.2 g
Total:	0.4 g	20 years

We press the tablet with the help of a press tool. Pour the mass of one tablet into the funnel. The press tool was set at a diameter of 11 mm. The tablet turned out to be fragile.

For this composition of tablets, we determine the friability.

Abrasion is determined on a friabilator545-R-AK-8.

We determine the total weight of all the tablets until they are crushed. Then we place the tablets in the drum, close the lid and turn on the device for 5 minutes.

After that, pour the tablets on a sieve and carefully shake off the dust that has formed on top with a brush. Next, we determine the mass of tablets after grinding. The difference in the weight of the tablets is converted into a percentage. For fast-dissolving tablets, the rub should not exceed 1%.

The first composition of the tablets had 1.7% friability.

Next, the solubility of the tablets was determined. For this, we take 2 glasses with water t=37 ºC. Place one tablet in each glass. We measure for 30 seconds (standard).

Result were disintegration time: 5 minutes, complete disintegration time – 20 minutes.

The fluidity of F1 was determined. T1 = 13.07 sec; t2 = 9.96 sec; t3 = 13.37 sec

X=1.65 g/sec

In the next Formulation No. 2, instead of croscarmylose sodium, we add starch gluconate. The production technology remains the same.

Table 3.7

Formulation number 2

F2	For 1 tablet	For 50 tablets
Nimesulide	0.100 g	5 g
Manit	0.286 g	14.3 g
Starch gluconate	0.010 g	0.5 g
Magnesium stearate	0.004 g	0.2 g
Total:	0.4 g	20 g

For the obtained composition, we define the same parameters as for the first one.

Abrasion was 1.7%. Disintegration time: 3 minutes - swelling time, 7 minutes 30 seconds - complete disintegration time.

Fluidity of Formulation 2

t1 = 10.06 sec; t2 = 10.59 sec; t3 = 10.35 sec

X = 1.94 g / sec

By the conducted experiments, we determined that the Formulation number 2, in which the disintegrant is starch gluconate, has a faster disintegration time than the first composition with the disintegrant sodium croscarmylose. But neither the first nor the second composition satisfies the rate of disintegration of tablets.

Therefore, it was decided to increase the amount of disintegrant to accelerate the disintegration of the tablet.

Thus, formulation 1.1 has the following components as shown in table 3.8.

Table 3.8

Formulation number 1.1

F 1.1	For 1 tablet	For 50 tablets
Nimesulide	0.100 g	5 g
Manit	0.276 g	13.8 g
Sodium croscarmylose	0.020 g	1 g
Magnesium stearate	0.004 g	0.2 g
Total:	0.4 g	20 g

The technology remains unchanged. The resulting tablets are strong. Next, we check desintegration time and friability.

Abrasion of the Formulation 1.1 – 1.8%.

Disintegration time: 2 minutes - swelling time, 5 minutes - complete disintegration time.

Fluidity of composition 1.1

t1 = 12.34 sec; t2 = 10.66 sec; t3 = 10.62 sec

X = 1.78 g/sec

Then we improved the Composition to make Formulation number 2.1, which had the following ingredients as mentioned in table 3.9.

Table 3.9

Formulation number 2.1

F 2.1	For 1 tablet	For 50 tablets
Nimesulide	0.100 g	5 g
Manit	0.276 g	13.8 g
Starch gluconate	0.020 g	1 g
Magnesium stearate	0.004 g	0.2 g
Total:	0.4 g	20 g

The technology remains unchanged. The resulting tablets are strong. Next, we check desintegration and friability.

Abrasion of the Formulation number 2.1 - was 2.2%.

Disintegration time: 1 minute - swelling time, 3 minutes 20 seconds - complete disintegration time.

Fluidity of Formulation number 2.1:

t1 = 10.92 sec; t2 = 10.02 sec; t3 = 13.77 sec

X = 1.73 g / sec

Due to the increase in the number of disintegrants, formulation 1.1 and formulation 2.1 reduced the time of disintegration of tablets, but do not meet the requirements of fast-dissolving tablets. Also, in the composition of starch gluconate, the abradability increased, which also does not meet the requirements.

In order to increase the rate of tablet disintegration, we decided to increase the content of disintegrants and compare the results.

So, composition 1.2 looked like in table 3.10.

Table 3.10

Formulation number 1.2

F 1.2	For 1 tablet	For 50 tablets
Nimesulide	0.100 g	5 g
Manit	0.266 g	13.8 g
Sodium croscarmylose	0.030 g	1.5 g
Magnesium stearate	0.004 g	0.2 g
Total:	0.4 g	20 g

The technology remains unchanged. The resulting tablets are strong. Next, we check desintegration and friability.

Abrasion of the composition is 1.2 – 2%.

Disintegration time: 1 minute 20 seconds - swelling time, 4 minutes - complete disintegration time.

Fluidity of Formulation 1.2

t1 = 8.59 sec; t2 = 8.89 sec; t3 = 12.22 sec

X = 2.02 g / sec

Formulation 2.2 had the following content of ingredients (table 3.11).

Table 3.11

Formulation number 2.2

F 2.2	For 1 tablet	For 50 tablets
Nimesulide	0.100 g	5 g
Manit	0.266 g	13.8 g
Starch gluconate	0.030 g	1.5 g
Magnesium stearate	0.004 g	0.2 g
Total:	0.4 g	20 g

The technology remains unchanged. The resulting tablets are strong. Next, we check desintegration and friability.

Abrasion of the formulation 2.2 - was 2.2%. Disintegration time: 2 minutes 10 seconds – swelling time, 6 minutes – complete disintegration time. Fluidity of formulation 2.2

t1 = 13.39 sec; t2 = 9.54 sec; t3 = 10.26 sec

X = 1.81 g / sec

With a change in the amount of disintegrant in the composition, the time of disintegration decreases, but the percentage of erasure of the tablet increases. The parameters of the study do not meet the requirements of fast-dissolving tablets.

Also, due to the fact that nimesulide is a poorly flowing substance, it will be impractical to use the direct pressing method. Therefore, the direct pressing technology was changed to wet granulation based on the best formulation 1.2 and 2.2

For wet granulation, two solutions with a concentration of crospovidone 2.5% and 5% were made.

The technology was as follows. Wetting agent (crospovidone solution 2.5% or 5%) was added to the mortar with the tested composition and mix thoroughly.

Pour on paper and dry. After that, rub the mixture through a sieve.

We determine the bulk density of tablet compositions after granulation.

Formulation 1.2 with 2.5% crospovidone solution.

Table 3.12

Bulk density of Formulation 1.2 granulated with 2.5% crospovidone solution (17.595 g)

Volume, ml	ρ, density
V10 = 42 ml	ρ1 = 0.419 g/ml
V500 = 38 ml	ρ2 = 0.463 g/ml
V1250 = 38 ml	ρ3 = 0.463 g/ml

Formulation 1.2 with 5% crospovidone solution.

Table 3.13

Bulk density. Formulation 1.2 granulated with 5% crospovidone solution (19.160 g)

V, volume	ρ, density
V10 = 46 ml	ρ1 = 0.416 g/ml
V500 = 42 ml	ρ2 = 0.456 g/ml
V1250 = 41 ml	ρ3 = 0.467 g/ml

Formulation 2.2 with 2.5% crospovidone solution.

Table 3.14

Bulk density. Formulation 2.2 with 2.5% crospovidone solution (16,780g)

V, volume	ρ, density
V10 = 36 ml	ρ1 = 0.466 g/ml
V500 = 32 ml	ρ2 = 0.524 g/ml
V1250 = 31 ml	ρ3 = 0.541 g/ml

Formulation 2.2 with 5% crospovidone solution

Table 3.15

Bulk density. Formulation 2.2 granulated with 5% crospovidone solution (17,310g)

V, volume	ρ, density
V10 = 36 ml	ρ1 = 0.481 g/ml
V500 = 35 ml	ρ2 = 0.494 g/ml
V1250 = 33 ml	ρ3 = 0.524 g/ml

Due to the previously carried out wet granulation, the bulk density was improved in all formulations.

We determine the fluidity of tablet compositions. The technology remains unchanged.

Table 3.16

Fluidity of Formulation 1.2 granulated with 2.5% crospovidone solution and 5% crospovidone solution

Formulation	t1	t2	t3	Average
1.2 – 2.5% m=17,610 g	3.04 sec	2.93 sec	2.98 sec	5.909 g/sec
1.2 – 5% m=19,180g	3.22 sec	3.26 sec	3.25 sec	5.920 g/sec
2.2 – 2.5% m=16.805g	2.58 sec	2.60 sec	2.34 sec	6.695 g/sec

By pre-wet granulation, the fluidity of the powders became greater.

After the research, we press the tablet with the help of a press tool. Pour the mass of one tablet into the funnel. The press tool was set at a diameter of 11 mm. The tablet came out strong.

We check the friability of new batches of tablets.

Table 3.17

Abrasion

Formulation 1.2 – 2.5%	1.3%
Formulation 1.2 – 5%	1.6%
Formulation 2.2 - 2.5%	5.5%
Formulation 2.2 – 5%	2.05%

So, taking into account all previous experiments, we can conclude that no composition is suitable for creating fast-dissolving tablets. Therefore, the disintegrant Ludyflash was introduced into the composition of the tablets.

First, we determine the fractional composition of ludiflash. The detection technology remains unchanged.

Table 3.19

Fractional composition of ludiflesh

Sieve size	Fraction? g	Percentage, %
<0.355 mm	1.4 g	7.025%
0.25mm - 0.355mm	0.920 g	4.6%
0.18 mm - 0.25 mm	2,820 g	14.1%
0.09mm - 0.18mm	11,270 g	56.35%
>0.09 mm	2,250 g	11.25%

The main part of ludiflesh consists of particles with a size of 0.09 mm - 0.18 mm, which in the future will have a positive effect on the formation of a homogeneous mass of the tablet and will hold its shape well.

Determination of the bulk density of ludiflash. The detection technology remains unchanged.

Ludiflash up to the mark of 50 ml - 25.290 g

Table 3.20

Ludiflash bulk density

V, volume	ρ, density
V 10 = 45 ml	ρ1 = 0.562 g/ml
V 500 = 40 ml	ρ2 = 0.632 g/ml
V 1250 = 39 ml	ρ3 = 0.648 g/ml

Determination of fluidity of ludiflash. The technology remains unchanged.

t1 = 8.18 sec; t2 = 9.81 sec; t3 = 7.89 sec

X = 2.32 g/sec

According to research results, Ludiflash disintegrant is suitable for forming fast-dissolving tablets.

We carry out wet granulation with a new disintegrant. The technology remains as before. We determine the bulk density of the composition with Ludiflash:

Table 3.21

Bulk density of Formulation 3 with 2.5% crospovidone solution (16.830g)

V, volume	ρ, density
V10 = 43 ml	ρ1 = 0.391 g/ml
V500 = 39 ml	ρ2 = 0.432g/ml
V1250 = 39 ml	ρ3 = 0.432 g/ml

Table 3.22

Bulk density of Formulation 3 with 5% crospovidone solution (16.680 g)

V, volume	ρ, density
V10 = 39 ml	ρ1 = 0.428 g/ml
V500 = 36 ml	ρ2 = 0.463g/ml
V1250 = 36 ml	ρ3 = 0.463 g/ml

Determination of the fluidity of the composition of tablets with Ludiflash.

Table 3.23

Fluidity of the formulations

Formulation 3 – 2.5%	t1=2.36c	t2=3.06c	t3=2.83c	X=6.125 g/s
Formulation 3 - 5%	t1=3.22c	t2=3.26c	t3=3.25c	X=5.920 g/s

We form tablets with Ludiflash. The technology remains unchanged.

We determined the friability of tablets.

Table 3.24

Friability of tablets

Formulation 3 – 2.5%	0.8%
Formulation 3 - 5%	0.9%

Table 3.25

Disintegration of tablets

Formulation	Disintegration time	Time of complete Disintegration
Formulation 3 – 2.5%	5 sec	12 sec
Formulation 3 - 5%	7 sec	14 sec

According to the results of research, the composition of tablets with ludiflash with a concentration of 2.5% is the most appropriate to use for creating fast-dissolving tablets.

CONCLUSION

1. To create fast-dissolving tablets with Nimesulide, it is advisable to use the method of wet granulation.

2. Fast-dissolving tablets tablets have a greater advantage among other dosage forms due to ease of use, speed of onset of action, and minimal side effects.

3. Thanks to the conducted research, we can conclude that the disintegrant Ludiflash is suitable for the composition of fast-dissolving tablets with Nimesulide.

4. This composition of tablets disintegrates in 12 seconds, which satisfies the needs.

5. The wet granulation method is a good alternative for creating fast-dissolving tablets, thanks to the simple technology and can compete with more expensive methods.

GENERAL CONCLUSION

1. Through the study of the literature, we determined that fast-dissolving tablets are becoming more and more popular among the public and pharmaceutical manufacturers. People of different ages and with various deviations with swallowing need to use this dosage form.

2. Pharmaceutical manufacturers use the methods of direct pressing, wet granulation, lyophilization for the preparation of orodispersible tablets and take into account the properties of the main and active substances for the choice of technology.

3. The modern market of NSAIDs includes preparations with Nimesulide in the form of tablets, granules, ointments, which significantly improves treatment.

4. On the basis of the study of drugs with nimesulide registered in Ukraine over the past 5 years, no specific form of fast-dissolving was found, which confirms the relevance of these studies.

5. Among other representatives of NSAIDs - Nimesulide is safer to use, has a less pronounced side effect in the form of gastric ulcer.

6. To create fast-dissolving tablets with Nimesulide, it is advisable to use the method of wet granulation.

7. Fast-dissolving tablets have a greater advantage among other dosage forms due to ease of use, speed of onset of action, and minimal side effects.

8. Thanks to the conducted research, we can conclude that the disintegrant Ludiflash is suitable for the composition of fast-dissolving tablets with Nimesulide.

9. This composition of tablets disintegrates in 12 seconds, which satisfies the needs.

10. The wet granulation method is a good alternative for creating fast-dissolving tablets, due to the simple technology and can compete with more expensive methods.

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Ф А 2.2.1-32-366

National University of Pharmacy

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

APPROVED
The Head of Department
Technology of pharmaceutical preparations

_____
Oleksandr KUKHTENKO

"___" _____

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Yasser EZAARAOUI

1. Topic of qualification work: «Development of the composition and technology of fast-dissolving tablets with nimesulide», supervisor of qualification work: Dmytro Soldatov, PhD, assoc. prof.,

approved by order of NUPh from "06" of February 2023 № 35

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

3. Outgoing data for qualification work: To develop the composition and technology of fast-dissolving tablets with nimesulide

4. Contents of the settlement and explanatory note (list of questions that need to be developed): introduction, literature review, objects and methods of research, experimental part, conclusions, list of used sources

5. List of graphic material (with exact indication of the required drawings):
tables – 15, pictures - 1

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Dmytro SOLDATOV, PhD, assoc. prof. of higher education institution of department Technology of pharmaceutical preparations		
2	Dmytro SOLDATOV, PhD, assoc. prof. of higher education institution of department Technology of pharmaceutical preparations		
3	Dmytro SOLDATOV, PhD, assoc. prof. of higher education institution of department Technology of pharmaceutical preparations		

7. Date of issue of the assignment: __“_____”_____

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Preparation of literature review	May-September 2022	**done**
2	Experiment planning	October-December 2022	**done**
3	Conducting an experiment	January-March 2023	**done**
4	Registration of results	April 2023	**done**
5	Submission to the examination commission	May 2023	**done**

An applicant of higher education _____ Yasser EZAARAOUI

Supervisor of qualification work _____ Dmytro SOLDATOV

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 113733 від « 21 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Езаарауі Яссер, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Розробка складу та технології швидкорозчинних таблеток з німесулідом / Development of the composition and technology of fast-dissolving tablets with nimesulide», 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**

2%

31%

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 технологій фармацевтичних препаратів**				
Езаарауі Яссер	Розробка складу та технології швидкорозчинних таблеток з німесулідом	Development of the composition and technology of fast-dissolving tablets with nimesulide	доцент Солдатов Д.П.	доцент Ковальов В.В.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

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

Yasser EZAARAOUI

on the topic: **«Development of the composition and technology of fast-dissolving tablets with nimesulide»**

Relevance of the topic. The development of fast-dissolving tablets with nimesulide addresses the need for a convenient and easily administered dosage form, particularly for patients who have difficulty swallowing or prefer not to take tablets with water. The optimized formulation and technology of these tablets can enhance the bioavailability of nimesulide, leading to improved therapeutic efficacy and more predictable pharmacological effects, thereby offering a promising alternative for efficient drug delivery.

Practical value of conclusions, recommendations and their validity. The developed composition and technology of fast-dissolving tablets with nimesulide can be implemented in pharmaceutical companies in drugs development reseaches. Conclusions and recommendations in the work are scientifically justified and reliable.

Assessment of work. The author while working learned to use the data of scientific literature, to search for the necessary information, proved to be a talented experimenter, able to draw sound conclusions from the results.

General conclusion and recommendations on admission to defend. In general, the qualification work of the applicant deserves high marks, meets the requirements and can be submitted for official defense to the examination commission of the National University of Pharmacy.

Scientific supervisor _____ Dmytro SOLDATOV

«___» _____ 2023

Ф А 2.2.1-32-356

REVIEW

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

Yasser EZAARAOUI

on the topic: **«Development of the composition and technology of fast-dissolving tablets with nimesulide»**

Relevance of the topic. The development of fast-dissolving tablets with nimesulide is highly relevant due to the growing demand for convenient and patient-friendly dosage forms. Fast-dissolving tablets offer an attractive solution for individuals who have difficulty swallowing traditional tablets or require immediate drug action.

Theoretical level of work. The work was performed at a high level using modern research methods according to the State Pharmacopoeia of Ukraine

Author's suggestions on the research topic. The studies are devoted to the determination of technological indicators of substances and auxiliary substances, and the substantiation of the technology of fast-dissolving tablets with nimesulide. The author suggests using the disintegrant Ludiflash is suitable for the composition of fast-dissolving tablets with Nimesulide.

Practical value of conclusions, recommendations and their validity. The research results can be used in the development of the technology of fast-dissolving tablets with nimesulide in industrial conditions.

Disadvantages of work. According to the text of the work there are some typographical errors, bad expressions. However, this does not reduce the value of the work and does not call into question the results obtained.

General conclusion and assessment of the work. The qualification work of the applicant deserves high marks, meets the requirements and can be submitted for official defense to the examination commission of the National University of Pharmacy.

Reviewer _____ assoc. prof. Volodymyr KOVALOV

«__» _____ 2023

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Витяг з протоколу
засідання кафедри технологій фармацевтичних препаратів НФаУ
№ 10 від 24 квітня 2023 року

Голова: завідувач кафедри, доктор фарм. наук, проф. Кухтенко О. С.

Секретар: к. фарм. н., доц. Січкар А. А.

ПРИСУТНІ: зав. каф., проф. Кухтенко О. С., доц. Безрукавий Є. А., доц. Кутова О. В., доц. Ляпунова О. О., доц. Манський О. А., доц. Ніколай-чук Н. О., доц. Сайко І. В., доц. Січкар А. А., доц. Солдатов Д. П., доц. Трутаєв С. І.

ПОРЯДОК ДЕННИЙ:
1. Про представлення до захисту в Екзаменаційну комісію кваліфікаційних робіт здобувачів вищої освіти випускного курсу НФаУ 2023 року випуску

СЛУХАЛИ: Про представлення до захисту в Екзаменаційній комісії кваліфікаційної роботи на тему: «Розробка складу та технології швидкорозчинних таблеток з німесулідом»

здобувача вищої освіти випускного курсу Фм18(5,0д)англ-02 групи НФаУ 2023 року випуску Яссер ЕЗААРАУІ
(ім'я, прізвище)

Науковий (-ві) керівник (-ки) к.фарм.н., доц. Дмитро СОЛДАТОВ
Рецензент к.фарм.н., доц. Володимир КОВАЛЬОВ

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувача вищої освіти 5 курсу Фм18(5,0д)англ-02 групи Яссер ЕЗААРАУІ
(ім'я, прізвище)
на тему: «Розробка складу та технології швидкорозчинних таблеток з німесулідом»

Голова
завідувач кафедри,
доктор фарм. наук, проф. _____ Олександр КУХТЕНКО
(підпис)

Секретар
к. фарм. н., доцент _____ Антоніна СІЧКАР
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Яссер ЕЗААРАУІ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка складу та технології швидкорозчинних таблеток з німесулідом».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Яссер ЕЗААРАУІ виконав кваліфікаційну роботу на високому рівні, з логічним викладенням матеріалу та обговоренням, оформлення роботи відповідає вимогам НФаУ до випускних кваліфікаційних робіт та робота може бути рекомендована до захисту в ЕК НФаУ.

Керівник кваліфікаційної роботи

_____ Дмитро СОЛДАТОВ

«___» _____ 2023 р.

Висновок кафедри про кваліфікаційну роботу

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

Завідувач кафедри
технологій фармацевтичних препаратів

_____ Олександр КУХТЕНКО

«___» _____ 2023 року

Qualification work was defended

of Examination commission on

« ____ » _____ 2023

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /