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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION OF ORODISPERSIBLE ANTIEMETIC TABLETS»**

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ANNOTATION

The qualification work contains 40 pages, 5 tables, 3 figures, and a list of 30 references.

The necessity of development of ODT tablets for nausea suppression with synthetic API has been established. Physicochemical and technological studies of the properties of ondacetron allowed to select the composition of excipients and determine the method of obtaining a solid dosage form, which resulted in the production of high-quality tablets that meet the requirements of the SPhU.

Keywords: tablets, ondasetron hydrochloride, excipients, composition, technology.

АНОТАЦІЯ

Кваліфікаційна робота містить 40 сторінок, 5 таблиць, 3 рисунків, список літератури з 30 найменувань.

Встановлено необхідність розробки ODT таблеток для пригнічення нудоти з синтетичним АФІ. Фізико-хімічні та технологічні дослідження властивостей ондасетрону гідрохлориду дозволили підібрати склад допоміжних речовин та визначити спосіб одержання твердої лікарської форми, у результаті чого одержані таблетки відповідають вимогам ДФУ.

Ключові слова: таблетки, ондасетрону гідрохлорид, допоміжні речовини, склад, технологія.

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INTRODUCTION

The relevance of the research problem. The issue of nausea and vomiting is highly relevant in medical practice due to their frequent occurrence across a wide range of pathological conditions, including gastritis, poisoning, and various infectious disorders. These symptoms are not only common but also often emerge as unintended side effects of numerous therapeutic treatments, such as chemotherapy, radiation therapy, and post-operative care. The presence of nausea and vomiting can significantly impair the overall health of a patient, exacerbating the burden of the underlying disease. Furthermore, they are associated with a host of secondary complications that can complicate patient recovery and prolong hospital stays. These complications include severe exhaustion, dehydration, and dangerous electrolyte imbalances, which, in turn, can affect the patient's overall prognosis. The impact of nausea and vomiting extends beyond physical discomfort, drastically reducing a patient's quality of life and complicating the management of chronic diseases[8, 22].

In response to these challenges, antiemetics have become a crucial part of clinical care. These drugs, designed to prevent or alleviate nausea and vomiting, are essential in managing various medical conditions. For instance, in patients undergoing chemotherapy, the use of antiemetics can help prevent treatment-induced nausea and vomiting, thus improving the ability to continue with essential cancer treatments. However, despite their widespread use, there remain significant concerns regarding the safety and efficacy of currently available antiemetics. Many of the drugs used today come with side effects, which can sometimes outweigh their benefits, further complicating the treatment process. The range of adverse effects varies across different antiemetics and can include sedation, constipation, dizziness, and, in some cases, more severe complications such as cardiovascular events or drug interactions[5, 12].

Therefore, there is an urgent need to further investigate and develop more effective and safer antiemetic treatments. Research should focus on discovering

novel antiemetic agents with minimal side effects, especially those that can target specific pathways involved in nausea and vomiting. Moreover, improving therapeutic strategies for managing these symptoms - such as personalized medicine or combination therapies - could significantly enhance patient outcomes. Given the increasing number of patients undergoing treatments like chemotherapy, radiation, and surgery, advancing the science of antiemetics is critical for improving patient care and ensuring better clinical results.

The aim and objectives of the study. Development of composition and technology of antiemetic tablets.

According to the goal, the following tasks had to be solved:

- analyze the literature on antiemetic agents;
- conduct comprehensive physicochemical and technological studies to create the optimal composition of the solid dosage form;
- develop and substantiate the technology for producing tablets.

Object of study - tablets; API - ondacetron hydrochloride; excipients: F - MELT® type M, sodium stearyl fumarate.

The subject of the study is to conduct physicochemical and technological tests of APIs, tablet mass and tablets; selection of excipients and determination of their concentration in order to develop the composition and technology of solid dosage form (SDF) for nausea suppression.

Research methods. The following test methods were used in the qualification work [6]:

- organoleptic (appearance);
- physical and chemical (moisture content, geometric size of tablets);
- technological (optical microscopy, sieve analysis, flowability, angle of natural slope; bulk density and density after shrinkage; resistance to crushing, disintegration);
- mathematical (statistical processing of results).

Approval of research results and publication. The results of the research were discussed at: IV International Scientific and Practical Conference (October 25, 2024, Kharkiv).

Publication:

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Scope and structure of the work. The qualification work consists of 40 pages, an introduction, three chapters, conclusions, and a list of references containing 30 items. The work is illustrated with 5 tables and 3 figures.

CHAPTER 1
CURRENT STATE OF THE PROBLEM OF NAUSEA TREATMENT

1.1 Pathomechanism, causes and treatment of nausea

Many physiological or pathological factors can cause the typical symptoms of nausea and vomiting. Vomiting is the quick expulsion of stomach contents via the mouth due to violent spasms of the abdominal and chest muscles, whereas nausea is an unpleasant, painless, subjective sense of wanting to throw up. The passage of stomach contents into the oral cavity without the reflexes and effort associated with vomiting is known as regurgitation[1, 30].

Physiological or pathological stimuli that stimulate the chemoreceptor trigger zone at the bottom of the IV ventricle or the vomiting center in the medulla oblongata cause nausea and vomiting. Since these regions receive input from a variety of bodily receptors, including chemoreceptors, they are essential for managing nausea and vomiting.

The vomiting center is located in the medulla oblongata and consists of several subcenters that control different aspects of vomiting. These sub-centers include [17, 28]:

1. Chemoreceptor trigger zone (CTZ): Located at the bottom of ventricle IV, the CTZ responds to various chemical stimuli such as toxins, drugs, and metabolites.
2. The vomiting trigger region (VTR): Located in the medulla oblongata, the VTR receives information from the CTZ and other receptors and initiates the gag reflex.
3. The region of the vomiting executive center (VIC): Located in the medulla oblongata, the VIC controls the muscle spasms necessary for vomiting.

Receptors involved in the pathomechanism of nausea and vomiting include:

1. Chemoreceptors: Respond to chemical stimuli such as toxins, drugs, and metabolites.
2. Mechanoreceptors: Respond to mechanical stimuli such as stretching of the stomach or intestines.
3. Baroreceptors: Respond to changes in pressure in the chest and abdomen.
4. Sensory receptors: Respond to smells, tastes, and visual stimuli.

Physiologic and pathologic disorders are among the many causes of nausea and vomiting. These include gastrointestinal (GI) and peritoneal diseases, biliary tract diseases, liver diseases, pancreatic diseases, endocrine diseases, urinary system diseases, mental illness, labyrinthine diseases, central nervous system (CNS) diseases, medications and toxins, and other diseases and physiological causes.

The effects of drugs including digoxin, cytostatics (e.g., dacarbazine, cisplatin), opioids, antibiotics, and anticoagulants, as well as toxins that can result from alcohol misuse, fungus poisons, insect poisons, and plant poisons, can induce nausea and vomiting.

Nausea and vomiting can also be symptoms of central nervous system (CNS) disorders. Nausea and vomiting are common side effects of migraines. These symptoms can also be brought on by CNS tumors and neoplasms, including medullary thyroid cancer and brain tumors. Nausea and vomiting may also be brought on by meningitis, encephalitis, brain pseudotumor, cerebrovascular events (stroke, transient ischemic attack), and intracranial bleeding (hemorrhagic stroke, subdural hematoma).

Nausea and vomiting can also be symptoms of mental disorders such bulimia, anorexia, and depression. One of these illnesses' prevalent symptoms is psychogenic vomiting [9, 20].

Nausea and vomiting can be caused by labyrinth diseases, including inner ear tumors, motion sickness, Meniere's disease, and inflammation (vestibular neuritis, labyrinthitis).

Moreover, peritoneal and gastrointestinal disorders are frequent causes of nausea and vomiting. These symptoms can be brought on by Crohn's disease, acute dilatation of the large intestine, gastroparesis, gastric and duodenal ulcers, appendicitis, small bowel blockage, food poisoning, food hypersensitivity, infectious gastroenterocolitis, and Crohn's disease.

Nausea and vomiting can also be symptoms of biliary system conditions such cholecystitis and biliary colic.

Nausea and vomiting can also be symptoms of liver illnesses such cirrhosis, hepatitis, and liver failure [4, 28].

These symptoms can also be brought on by pancreatic diseases such acute pancreatitis and pancreatic tumors.

Nausea and vomiting can also accompany endocrine gland diseases, including diabetic ketoacidosis, adrenal crisis (acute adrenal cortex failure), thyrotoxic crisis, hyperparathyroidism, and hypoparathyroidism.

These symptoms can also be brought on by conditions affecting the urinary system, such as pyelonephritis, renal colic, and uremia [3, 24].

Nausea and vomiting may also be associated with various conditions, including myocardial infarction, heart failure, hypotension, superior vena cava syndrome, hypervitaminosis A or D, extended fasting, acute intermittent porphyria, postoperative nausea and vomiting, and radiation treatment.

Pregnancy and sensitivities to taste, smell, and visual stimuli are among the physiological reasons of nausea and vomiting. Stimuli that impact the senses can induce nausea and vomiting.

Vomiting and nausea can be categorized according to their duration [1, 14, 23]:

- Acute nausea and vomiting (1-2 days): Most often caused by infectious diseases, drugs, exogenous (alcohol, mushrooms) or endogenous toxins (uremia, diabetic ketoacidosis).
- Chronic nausea and vomiting (>7 days): A symptom of chronic illnesses, including mental illness.

Different pharmacological approaches are used for effective treatment of nausea and vomiting, based on blocking various receptors involved in the pathophysiological mechanisms of these phenomena. The main classes of antiemetics include:

- Serotonin antagonists: Block the 5-HT3 serotonin receptors in the central nervous system and intestines, which prevents activation of the vomiting center and reduces intestinal motility. Examples: ondansetron, granisetron.
- Dopamine antagonists: Block dopamine D2 receptors in the central nervous system and intestines, which reduces stimulation of the vomiting center and improves intestinal motility. Examples: metoclopramide, prochlorperazine.

- Corticosteroids: The mechanism of action is not fully understood, possibly related to anti-inflammatory effects and modulation of the immune system. Examples: dexamethasone.
- Neurokinin receptor antagonists: Block the NK1 neurokinin receptors in the central nervous system, which prevents the activation of the vomiting center. Examples: aprepitant.

The best course of therapy is determined by the etiology of nausea and vomiting, the intensity of symptoms, the existence of comorbidities, and the patient's tolerance to medications. Each of these pharmacological groups has pros and cons. Ondansetron was selected as the active component of the medication being developed for additional study due to the intricacy of the symptoms and potential side effects.

1.2 Biopharmaceutical aspects of the development of orally disintegrating tablets

The term "orally disintegrating tablets" refers to oral disintegrating tablets (ODTs), which are fast-release dosage forms of the active substance (AS) that dissolve and release the AS in the oral cavity in a matter of seconds (typically up to a minute) and do not require chewing or washing down with water [30].

ODTs were initially created in the late 1970s as a substitute for conventional tablets, capsules, and syrups in the treatment of juvenile and geriatric patients who have trouble swallowing for whatever cause.

Nonetheless, there has been a steady rise in interest in the utilization of suitable dosage forms, alternate routes of administration, and drug delivery technologies in recent decades. The growth of the list of medications in the biggest and most developed pharmaceutical marketplaces worldwide serves as evidence of this (USA, Europe, Japan).

In the past, topical therapy was the primary use of pharmacological dosage forms with oral release. Chewable tablets and washing solutions have been utilized to treat gums and periodontal pockets, while oral disintegrating lozenges, sprays, and tablets have been widely used to treat oral and throat illnesses locally [25].

Oral dose forms, which release oral fluids and are then absorbed by oral tissues, have gained popularity as a way to administer systemic medications in recent years. There are several reasons for this, ranging from logical pharmacology to marketing benefits.

Sublingual usage of nitroglycerin, nifedipine, buprenorphine, essential oils, and validol to generate a quick therapeutic impact is a well-known example of the potential for drug adsorption in the oral cavity with a resorptive effect.

Absorption determines a drug's capacity to pass through the oral mucosa. The passage of a material from the site of absorption to the fluid of the human body's internal environment is ensured by a series of processes known as absorption. Numerous factors, such as the physicochemical and biological characteristics of the substances and the blood flow rate at the site of absorption, influence the site of absorption, which in turn defines the idiosyncrasies of the absorption processes and the related elimination [2, 18].

The skin and gastrointestinal tract's epithelium and the oral mucosa's epithelial layer, where absorption takes place, are somewhat same. It is made up of populations of cells that are continually growing as a result of cell division in the basal layer. In contrast to the skin, the oral mucosa's epidermis is thinner than the dermal epidermis, has a thickness of 100–600 microns, and is not penetrated by sweat ducts, sebaceous glands, or hair follicles. The mouth mucosa has a far lower resistance than the skin.

Because of the mouth cavity's mucous membrane's robust blood supply, items taken via it swiftly reach the right atrium via the superior vena and internal jugular vein.

Saliva, which is constantly present in the oral cavity, plays an important role in the adsorption of ODTs by the mucous membrane. Due to the presence of saliva, ODTs are able to be destroyed without additional mechanical action (chewing). Saliva is produced by three pairs of large salivary glands (parotid, submandibular and hyoid) and small glands of the oral mucosa. The physiological role of saliva is to moisturize and process food. Drug substances in contact with saliva undergo moderate fermentation, slightly acidic or slightly alkaline action, which starts the digestive process. pH of saliva varies between 5.8-7.8. If saliva is produced in small quantities, it has a slightly acidic reaction, if saliva is actively secreted (a person can produce up to 750-1000 ml of saliva

per day), its reaction is slightly alkaline. It should be noted that saliva pH, salivary gland secretion productivity, and age-related changes in oral tissues have a significant impact on the bioavailability of DS [11].

However, the use of oral tissues for medication administration has some drawbacks. These tissues have restricted absorption capacity or are unable to absorb all chemicals. This is mostly because of the drug's and the delivery system's biological and physicochemical characteristics. The potential for drug delivery to the systemic circulation through the oral tissues is first evaluated using characteristics like dose, molecular weight, water and saliva solubility, degree of ionization (at pH 6.8), ability to diffuse through the epithelium (log P), and ability to dissolve in blood.

Another potential limiting factor for medication absorption is the 100 cm2 region of the oral mucosa. In contrast, the gastrointestinal tract's interior surface has a total size of around 300 m^2. The short half-life of the medication material is a drawback of adopting rapid release delivery methods through the oral mucosa. Furthermore, repeated usage may cause mucous membrane irritation [10, 29].

Nevertheless, the oral cavity often does not fully absorb the ODT active component. Salivary reflexes carry a portion of the API dosage to the lower GI tract.

The esophagus, which is coated with tissues that have a poor capacity for absorption, is where medications reach the stomach. Numerous factors affect how long a medication remains in the stomach (in a normal condition) and how long it takes for some compounds to be absorbed. These variables include the drug's rate of release from tablets or granules, the way it is administered, the type of food and liquids, the amount of time that passes between meals and when the drug is administered, the digestive enzymes and motility of the stomach, and the acidity of the surrounding environment (pH about 1-3). Adsorption in the following sections of the gastrointestinal system is impacted by these parameters, which also affect the variability of drug absorption in the stomach or the variability of drug transit time through the stomach [5, 16].

The medication enters the portal circulation and the liver after going via the stomach and/or intestinal wall. Liver enzymes have the ability to significantly alter some pharmaceutical compounds ("first pass effect"). To get a therapeutic effect, the dosage of some medications should be significantly larger when taken orally than when

given intravenously, and this is due to this factor rather than inadequate absorption. The rate of hepatic blood flow determines how strong the main passage impact is. ACE inhibitors, nitrates, lipophilic β, -adrenergic blockers, calcium antagonists, and others are among the medications with a high level of presystemic metabolism.

The gut is the second most crucial organ for drug metabolism, behind the liver. The gut walls are where metabolic processes take place. It is important to recognize the cytochrome P459 (CYP) superfamily of enzymes that are involved in drug metabolism. Half as much of this hemoprotein's primary isoform is present in the small intestine as in the liver. The interaction between the intestinal microflora's enzymes and its mucous membrane is the most intricate and poorly understood of all the bodily systems that metabolize medicines.

Both the quantity of bacteria and their strains and the shape of the epithelial tissue vary between the various sections of the digestive system. The mucosal layer is home to some microbial strains. A pharmacological substance passes through three barriers in the intestine: the membrane of the epithelial cell facing the intestinal lumen arrives first, followed by the membrane of the same cell facing the capillaries, and lastly the capillary's basement membrane [5, 12].

Because it is primarily dependent on biological factors, the process of drug absorption from the small intestine varies widely. These factors include the presence of other substances, the peculiarities of drug interaction with food, the destruction of the substance by gastrointestinal juice, and impaired absorption due to increased intestinal peristalsis.

Therefore, the bioavailability (BA) and variability of the BA of pharmaceuticals and medical goods are influenced by presystemic metabolism (the metabolism of a pharmacological material prior to its entry into the systemic circulation) as well as other variables [8, 15].

Presystemic drug metabolism and gastrointestinal side effects can be avoided in a number of ways. Some techniques include altering the dosage schedule, such as raising the drug's single dosage and decreasing the time between doses. Prodrugs, such as ACE inhibitors (enalapril, perindopril, ramipril, trandolapril, and cilazopril), are

made using other techniques. These prodrugs go through presystemic metabolism and are transformed into active ingredients that have a therapeutic effect.

To circumvent presystemic metabolism and biotransformation in the gastrointestinal tract, in addition to the previously stated techniques, other routes of drug administration, PT, and suitable drug delivery systems, such as ODT, can be employed [2].

ODTs designed for systemic use have an advantage over conventional tablets and capsules in that a portion of the drug dose is absorbed by the oral mucosa, avoiding the lower gastrointestinal tract and all of its associated side effects, such as the impact of the drug's initial passage through the liver and intestinal wall metabolism. Therefore, in comparison to conventional tablets and capsules, a lesser dosage of API can be needed to provide a similar therapeutic effect with ODT.

The overall quantity of inactive metabolites is also decreased at the same time, which might improve the benefit/risk ratio by lowering the frequency and severity of API metabolite-related side effects in comparison to an equivalent therapeutic effect. After API is absorbed by the oral tissues and enters the systemic bloodstream, the pace at which the therapeutic impact begins is equivalent to that of intravenous and inhalation methods of administration, but it is much faster than that of conventional oral medications [5, 26].

The following may be the benefits of ODTs over conventional oral medications as they are not made to administer medications through the oral mucosa. ODTs remove pain and trouble swallowing when the medication travels down the throat (capsules, for example, can stick to the esophageal wall). The medication passes through the stomach more quickly and with less variation thanks to its formulation. While the transit duration of conventional oral medications is determined by their geometric size, disintegration time, and stomach dissolution, this is accomplished by the drug's quick breakdown at the start of the gastrointestinal system and the passing of the gastric sphincter (Pylorus) [9, 25].

As a result, ODT may have a more predictable and quicker therapeutic impact than standard medications. Because of their higher bioavailability, ODTs containing

APIs that are able to be adsorbed in the oral cavity can have an equal therapeutic effect at lower dosages.

The frequency and severity of adverse effects may be decreased by lowering the dosage and, thus, by lowering inactive metabolites. Significant benefits over counterparts made in conventional dosage forms can be obtained when employing oral disintegrating tablets.

CONCLUSIONS TO SECTION 1

1. Orally disintegrating tablets are now one of the most promising dosage forms, according to the study of literature data. This is because, in comparison to conventional tablets and capsules, ODT requires a lower quantity of active ingredients to have a comparable therapeutic effect. When compared to intravenous and inhalation methods of administration, the pace at which the therapeutic effect begins to take effect after the medication has been absorbed by the oral tissues and entered the systemic circulation is significantly higher than for conventional oral dose forms.

2. According to the pharmaceutical market study, the nausea suppressant industry is still relatively untapped and has great potential for the creation of new medications. The usage of ondasetron hydrochloride as an active component is recommended, according to research on the variety of antiemetic medications.

CHAPTER 2
OBJECTS AND METHODS OF RESEARCH

Because the direct pressing method is more affordable than the wet granulation process, it is increasingly being used in technical methods for the production of solid dosage forms [5]. Modern drug tableting technology, such as direct pressing, offers several benefits over other tableting techniques, including fewer technological operations, high labor productivity, negating the effects of moisture on unstable drug substances, minimizing microbial contamination, saving production space, equipment, and energy costs, and employing fewer people [8, 10].

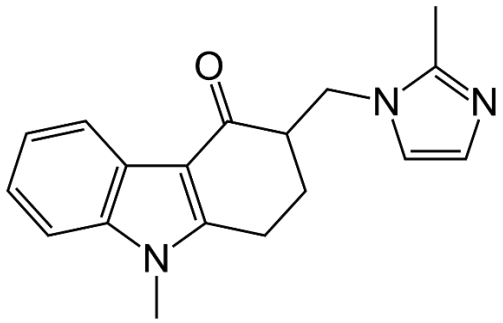
This technique has gained importance recently, despite the fact that the majority of therapeutic chemicals are not suited for direct pressing at the necessary concentrations and have technical characteristics that need to be optimized. Binders are used to pre-granulate hard-to-press substances so that direct tableting may be done. Furthermore, direct pressing makes use of excipients [1, 3, 6, 11].

High-quality mixing of dry medicinal and excipients, lowering the tendency of substances to stratify, and increasing the fluidity of non-granular powders can all help to ensure the most popular technological technique, which involves adding excipients to improve the technological properties of a powdered substance (direct pressing) [1, 8, 16]. The best excipient compositions must be chosen for low dosages of a drug substance in order to counteract the adverse effects of the substance's attributes. These compositions must have enough technical, structural, and mechanical qualities. Finding ways to enhance the qualities of tablets with trace levels of excipients is essential for high dosages of a active component.

Therefore, one of the key requirements for generating tableted medications with optimum therapeutic action at lowest dosages and side effects is a scientifically sound selection of excipients in each situation [2, 13, 15].

2.1. Characteristics of the research objects

Ondansetron hydrochloride (*(RS)-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4(9H)-one (as monohydrochloride dihydrate)).* By its physical properties, ondasetron hydrochloride is a white or off-white powder, soluble in water and saline.



Sodium stearyl fumarate (Sodium Stearyl Fumarate, sodium stearyl fumarate CAS 4070-80-8) is an excipient, a highly effective modern lubricant.

It is a substitute for the traditional lubricant made of magnesium stearate. It is the chosen auxiliary material in high-speed direct press technology because of its greater melting point.

A white powder with an average particle size of around 15 nm, sodium stearyl fumarate is comparatively inert, improving formulation stability.

It is compatible with all known active substances, unlike magnesium stearate. More hydrophilic than magnesium stearate, sodium stearyl fumarate speeds up the rate of pill dissolving and disintegration. It has high strength, doesn't taste metallic, has less compaction force, wears down equipment, requires less ejection force, and is less susceptible to longer mixing times.

F - Melt® type F1. It is a ready-to-use system for tablets that disintegrate in the oral cavity. Properties of F-Melt® Type F1: Spherical particles with excellent flowability, compressibility and disintegration.

This system's enormous porosity, good fluidity, quick disintegration in a little amount of liquid, and pleasing flavor are all the result of carefully chosen components, initial particle size, and a meticulously regulated spray drying process. This is because

ODT (Oral Disintegration Tablets), a novel pharmaceutical form that has found usage in the pharmaceutical sector, are directly pressed using F-Melt® type F1.

Composition F - Melt® type F1 :

Amylopectin;

Corn starch;

Microcrystalline cellulose;

Magnesium carbonate;

Calcium carbonate.

The Ludiflash warehouse is a complex for direct pressing:

D-Mannitol

Cropovidone

Polyvinyl acetate

Providone

Direct pressing of the tablet mass follows a straightforward mixing process with lubricants and active components.

As an ester of glycerol and vegetable-derived fatty acids, Precirol® ATO 5 (S&D Chemical Ltd., UK) is a safe, tasteless, inert chemical substance that is authorized for use in pharmaceutical and cosmetic applications.

2.2. Research methods

The technological properties of powdered medicinal substances depend on their physical and chemical properties.

*The fractional (*particle size distribution*) composition* has an effect on a powder's fluidity, which in turn affects the tablet machines' regular functioning, the stability of the weight of the tablets produced, the precision of the medicinal substance's dose, and the tablets' quality attributes (appearance, disintegration, strength, etc.).

Sifting 100.0 g of the material under test through a series of sieves is the method used for this analysis (mesh diameters of 2.0, 1.0, 0.5, 0.25, and 0.1 mm). The mass of each fraction and its % content are then calculated when the material is placed on the biggest (upper) sieve and the complete set of sieves is shaken for five minutes, either manually or using a vibrating machine.

The mass of a loosely packed powdered substance per unit volume is known as *its bulk (volumetric) density*. The size, shape, density, and moisture content of powder particles (granules) all affect bulk density. The volume of the matrix channel may be predicted using the bulk density value. Using the device model 545P-AK-3 , the bulk density of the powder is calculated.

Pour 5.0 g of powder into the measuring cylinder after weighing it to the closest 0.001 g. After marking the scale, use a screw to set the oscillation amplitude (35–40 mm) and a lock nut to secure the setting. Using a transformer, the oscillation frequency is adjusted between 100 and 120 rpm based on the counter. After that, use a toggle switch to turn the gadget on and keep an eye on the cylinder's powder level. The machine shuts off after the powder level stabilizes, which normally takes ten minutes.

Bulk density is calculated by the formula:

$$\rho_н = \frac{m}{V} = \frac{5 \times 10^3}{V},$$

where $\rho_н$ is the bulk density, kg/m^3 ;

m - weight of bulk material, kg;

V is the volume of powder in the cylinder after compaction, m^3 .

Relative density is the ratio of bulk density to true density:

$$\tau_л = \frac{\rho_н}{\rho} \cdot 100,$$

where $\rho_н$ is the bulk density, kg/m^3 ;

ρ - true density (specific gravity), kg/m^3.

Porosity is the volume of free space (voids) between powder particles.

Porosity is determined based on the values of bulk density and true density:

$$П = \left(1 - \frac{\rho_н}{\rho}\right) \cdot 100 \text{ или } П = 100 - \tau,$$

where, $\rho_н$ is the bulk density kg/m^3;

ρ - true density (specific gravity), kg/m^3;

τ - relative density.

The ability of the powder to seal under pressure depends on these bulk characteristics.

Pressing ratio is the ratio of the height of the powder in the matrix (H_1) to the height of the resulting tablet (H_2).

A matrix is used to carry out the determination. Powder is poured into the matrix channel while 1200 kg/cm^2 of pressing pressure is used. The height is measured when the resultant tablet is punched out.

The shape of the particles and their capacity to move and deform under pressure affect how well powdered medications compress. One crucial process variable is the compression ratio; the larger the ratio, the longer the compression time. Additionally, pushing the tablet out of the die channel's depths takes additional work.

The three most crucial process characteristics in tableting are slip, pressability, and fluidity, which enable the tablet to be pushed out of the die with ease.

The ability of a powdered solution to "flow" or pour out of a funnel container due to its own gravity and guarantee even filling of the die channel is known as *flowability*. Poorly flowing material in the funnel adheres to its walls, breaking the flow's rhythm as it enters the die. As a result, the pills' stated weight and density change. The VP-12A vibrating instrument for bulk material characterization is used to measure the fluidity.

By firmly attaching the conical funnel to an electromagnetic device that runs off the AC mains, the gadget allows the funnel to vibrate. The gadget and stopwatch are turned on, and a 50.0 g sample of powder (granules) with an accuracy of ~0.01 g is poured into the funnel with the flap closed. Open the flap and note how long it takes for material to flow out of the funnel after 20 seconds of shaking, which is required to get consistent results. The outflow time has an accuracy of up to 0.2 seconds.

Pressability is the ability of powder particles to cling together under pressure, meaning that they may create a stable, powerful compression when subjected to mechanical connections, mutual attraction, and adhesion as well as electromagnetic forces (molecular, adsorption, and electrical).

The strength of a model tablet following the release of pressure is a measure of pressability. The strength of the tablet increases with the powder's pressability. When pushed out of the die, a tablet with poor pressability is brittle and may even collapse entirely.

A weight of around 0.3 or 0.5 g is forced into the matrix using punches that have a diameter of 9 mm and approximately 11 mm on a hydraulic press at a pressure of 120 MPa in order to determine the compressibility of a powder (granulate). A balance is used to weigh the resultant tablet, a micrometer is used to measure its height, and the following formula is used to get the pressing coefficient (Kpres, g/mm):

$$K_{press} = \frac{m}{H},$$

where: m - weight of the tablet, g;

H is the height of the tablet, mm.

The force to push the tablets out of the die. A force must be exerted to overcome the friction and adhesion between the tablet's side and the die wall in order to push a pressed tablet out of the die. The addition of antifriction chemicals is predicted based on the amount of ejection force. A 0.3 or 0.5 g powder sample is compressed using a hydraulic press at a pressure of 120 MPa into dies that have a diameter of 9 or 11 mm, respectively, in order to measure the ejection force. The lower punch ejects the pushed tablet. The press manometer records the ejection force.

Dosage uniformity. The quantitative amount of the active ingredient in the tablets serves as the foundation for dosage consistency checks. Ten pills are administered for the analysis, and the API is ascertained using the QCM. A API of 85 to 115 percent of the average content should be present in tablets containing less than 2 milligrams of the active ingredient or less than 2 percent of the tablet's weight.

Mass homogeneity for a unit of dosed drug. After 20 pills are weighed individually, the average weight is determined. If there are no more than two tablets that differ from the average weight by the amount indicated in Table 2.1, the medication passes the test.

Table 2.1

Permissible deviations in the average weight of tablets

Average weight	Permissible deviations,%.
80 milligrams and less	10
more than 80 milligrams but less than 250 milligrams	7,5
250 milligrams and more	5

CONCLUSIONS TO SECTION 2

1. The active ingredient ondasetron hydrochloride and excipients that satisfy regulatory document standards and are authorized for pharmaceutical use were utilized as research items while creating the solid dosage form in the form of ODT.

2. It was determined that it was possible to undertake research to create the composition, technology, quality evaluation, and stability of the dosage form containing ondasetron hydrochloride utilizing contemporary research methodologies, namely physicochemical and technical methods of analysis.

CHAPTER 3

DEVELOPMENT OF COMPOSITION AND TECHNOLOGY OF ORALLY DISINTEGRATING ONDASETRON HYDROCHLORIDE TABLETS

When put on the tongue, ODT pills, a solid dose form, dissolve quickly (often in a matter of seconds). ODT is a unique dose form created especially for elderly patients, youngsters, newborns, patients with swallowing issues, and patients who have water intake limits before to or following surgery. It is a handy dose form that may be taken anywhere, at any time, and without the need for water.

Studying the physicochemical and technical characteristics of the therapeutic ingredient, using excipients in a scientific manner, and utilizing contemporary pharmaceutical technology are all prerequisites for developing solid dosage forms [19].

3.1 Study of the physicochemical and technological properties of ondasetron hydrochloride

Studying the active substance's physicochemical and technical characteristics was the initial step in our project. Microscopic investigations were conducted using a 50x magnification laboratory microscope and SkopeTek picture processing software.

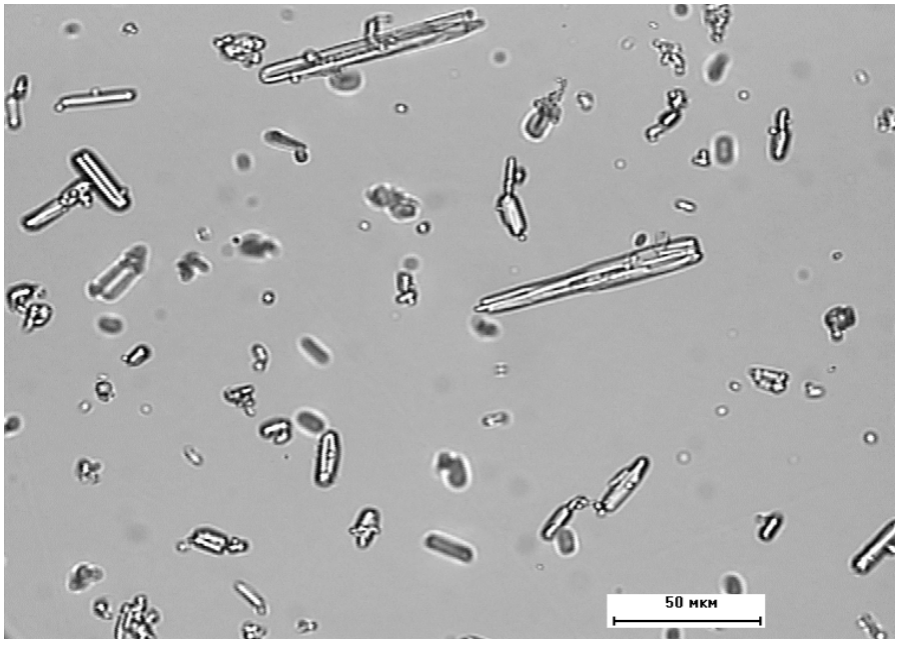


Figure 3.1. Substance of ondasetron hydrochloride

Figure 3.1 illustrates that ondasetron hydrochloride powder is a finely distributed monosystem that resembles stick-shaped crystals and has a particle size of up to around 10 microns. A large specific surface area of the powder and the adhesive force between the particles may be indicated by the form factor, which ranges from 0.04 to 0.2.

The following variables affect the process of generating a medication of appropriate quality: compaction, density, bulk volume, and fluidity. Poorly flowing material in the funnel adheres to its walls, breaking the flow's rhythm into the matrix. As a result, the pills' stated weight and density change.

The size, shape, density, and moisture content of powder particles (granules) all affect bulk density. The volume of the matrix channel may be predicted using the bulk density value. The fluidity, and therefore the stability of tablet weight, the precision of medication dosing, and the qualitative attributes of tablets (appearance, disintegration, strength, etc.) are all impacted by the fractional (particle size distribution) composition [24].

Table 3.1

Technological parameters of ondasetron hydrochloride substance

Technological characteristics	Indicators
Fluidity, g/s	1,22 ± 0,01
Density, g/cm^3	1,17 ± 0,02
Porosity, %.	67,70 ± 0,80
Pressibility, H	79,57 ± 2,68
Angle of natural slope, deg.	51° ± 2
Residual moisture, %.	1,07 ± 0,02
Relative density, %.	28,53 ± 1,15
Bulk density -to seal - after compaction, g/cm^3	 0,26 ± 0,01 0,40 ± 0,05
Hausner index	1,57
Determination of particle size distribution up to 10 microns, %.	93,3 ± 1,40

Note P<95, n=3

A vibrating funnel was used to test the fluidity of ondasetron hydrochloride powder while also determining the angle of natural slope.

According to the table's data, ondacetron hydrochloride needs excipients to be added since it lacks the technical criteria needed for direct pressing at the therapeutic concentrations needed. Ondacetron hydrochloride is classified as a very heavy powder with limited fluidity. The powder is a finely distributed monosystem that resembles stick crystals and has a primary particle fraction size of up to 10 μm (6.20 ± 0.15 μm).

3.2. Selection of excipients

Predicting the likelihood of making tablets via direct compression was made achievable by a high enough compression ratio. The direct pressing method of producing tablets guarantees the stability of the active ingredients, a positive economic impact, environmentally friendly production practices, and increased bioavailability of pharmaceutical ingredients.

It is advisable to incorporate highly effective modern excipients in the drug composition that would contribute to the production of strong tablets on the one hand, and meet the requirements for tablet disintegration on the other, even though the active substance of tablets has acceptable technological characteristics that were developed to ensure their production in industrial conditions by direct pressing in full compliance with the requirements for the dosage form.

One unique feature of an orally disintegrating medicinal composition is that it may be taken without chewing or water. In the mouth, it breaks down rapidly into its component pieces, ideally in less than three minutes and even more ideally in less than a minute [20,21,23].

Generally speaking, the methods previously discussed share the usage of a disintegrating agent as Ac Disol®, Explotab® (carboxymethyl starch), and Kollidon® CL (cross-linked polyvinylpyrrolidone) (cross-linked sodium carboxymethyl cellulose).

A direct-press filler should be employed in conjunction with such a disintegrating agent, which is required for the composition of tablets that dissolve in the oral cavity [30].

The manufacturing of such tablets presents challenges, including the difficulty of obtaining tablets with constant, repeatable physical features that meet the demands of typical tablet handling. However, the often utilized mixes produce tablets that are extremely hard, making them totally inappropriate for the oral cavity's quick breakdown. Therefore, choosing excipients that permit quick breakdown, have a neutral taste, and have a tolerable texture is essential to producing tablets of the right quality [22, 29, 30].

The main technological characteristics of the excipients used are presented in Table 3.2.

Table 3.2

Technological characteristics of excipients

Indicator	F - MELT®	Ludiflash
Moisture content, %.	1,7	0,8
Bulk density to the crumbling, g/ml after tamping, g/ml	 0,47 0,55	 0,46 0,56
Particle size of the main fraction, μm	130	180
The angle of the natural of the natural slope, ^{0}	33,9	36,5
The Hausner coefficient	1,20	1,30
Pressibility, H	60	70

Note P<95, n=3

The agglomerated particles that make up Ludiflash® are white in color and just 192 microns in size. With a Hausner value of 1.30 and a natural slope angle of 36.5°, the fluidity is deemed good.

F-MELT is a white or slightly yellowish powder with spherical particles that are around 120 microns in size, which is comparable to the size of the active ingredient's particles. High fluidity is indicated by the lower density and angle of natural slope, which are 1.20 and 33.9, respectively. The compressibility values of 60 and 70 N, respectively, are high for both samples. Therefore, we have selected F-MELT type M,

which is specifically meant for pharmaceutical goods, and Ludiflash as complex fillers in order to create the composition and technology of tablets dissolving in the oral cavity.

Next, we looked into the masses' technological traits for tableting (Table 3.3). We created model formulations with ondasetron hydrochloride and an excipient in the ratios of 1:10, 1:15, and 1:20 in order to support the rational composition of ondasetron hydrochloride tablets that dissolve in the oral cavity. Each tablet contains 8 milligrams of ondasetron hydrochloride, and the tablets were compounded on a laboratory press using a working part of the press tool that had a diameter of 6 mm (for formulations weighing 100 milligrams), 7 mm (for formulations weighing 150 milligrams), and 8 mm (for formulations weighing 200 milligrams).

Table 3.3

Technological characteristics of tablet samples

№	Composition		Tablet weight characteristics			
			Fluidity, g/s	The angle of the natural slope, ^{0}	Bulk density, g/ml	
					ρ_0	ρ_{1250}
1	Ondasetron hydrochloride F - MELT ®	0,008 г 0,09 г	5,52 ± 0,72	37,0 ± 2,0	0,44 ± 0,02	0,56 ± 0,01
2	Ondasetron hydrochloride F - MELT ®	0,008 г 0,14 г	6,23 ± 0,78	35,4 ± 2,1	0,45 ± 0,03	0,58 ± 0,03
3	Ondasetron hydrochloride F - MELT ®	0,008 г 0,19 г	7,12 ± 0,63	33,4± 1,0	0,62 ± 00,1	0,62 ± 0,02
4	Ondasetron hydrochloride Ludiflash ®	0,008 г 0,09 г	5,97 ± 0,34	32,0± 1,2	0,17 ± 0,03	0,56± 0,01
5	Ondasetron hydrochloride Ludiflash ®	0,008 г 0,14 г	5,80 ± 0,35	32,0 ± 2,0	0,55 ± 0,04	0,63 ± 0,03
6	Ondasetron hydrochloride Ludiflash ®	0,008 г 0,19 г	6,80 ± 0,35	32,0 ± 2,0	0,52 ± 0,02	0,63 ± 0,02

The data in the table shows that, except for samples 1 and 2, every composition had a slope angle less than 35^0. The samples had the greatest fluidity indices. №3 and №6. We may thus conclude from the examination of the results that the addition of supplementary compounds greatly enhanced the technical indicators, particularly fluidity.

We were particularly concerned with the disintegration of the resultant tablets because of the high pressing ratio of ondasetron hydrochloride. A crucial step in guaranteeing the drug's high bioavailability and effectiveness is the solid form's breakdown upon coming into contact with water or gastric juice. We investigated how excipients affected the breakdown of tablets. Table 3.4 displays the findings of the investigation into how the composition of excipients affects tablet disintegration.

Table 3.4

Quality parameters of samples of ondasetron hydrochloride tablets

№	Composition		Characteristics of tablets		
			Durability, H	Erasability, %	Disintegration, s
1	Ondasetron hydrochloride F - MELT ®	0,008 г 0,09 г	47,13 ± 1,34	1,14	56
2	Ondasetron hydrochloride F - MELT ®	0,008 г 0,14 г	48,90 ± 1,68	0,86	41
3	Ondasetron hydrochloride F - MELT ®	0,008 г 0,19 г	50,33 ± 2,26	0,56	32
4	Ondasetron hydrochloride Ludiflash ®	0,008 г 0,09 г	32,91 ± 2,67	1,20	40
5	Ondasetron hydrochloride Ludiflash ®	0,008 г 0,14 г	35,22 ± 2,39	1,32	34
6	Ondasetron hydrochloride Ludiflash ®	0,008 г 0,19 г	35,23 ± 2,39	1,33	34

Only samples №2 and №3's mechanical strength satisfied the State Pharmacopoeia's standards, although the tablets derived from the tested samples had exceptional disintegration results. Based on the strength and abrasion indicators, we decided to conduct additional research using formulation № 3, which uses substance F-MELT® Type M (Fuji Chemical Industry Co., Ltd., Japan) as the excipient. This formulation has the following benefits: it can be used for direct pressing (high fluidity, low or no clumping), and it can be used to create tablets that dissolve in the mouth.

We added sodium stearyl fumarate (PRUV), precerol, and magnesium stearate to tablet mass № 3's composition to increase the tablet's fluidity and mechanical strength. Table 3.5 displays the research data.

Table 3.5

Performance of ondasetron hydrochloride tablet samples depending on the type of lubricant

Lubricant	Characteristics of the weight		Characteristics of tablets		
	Fluidity, g/s	The angle of the slope, ^{0}	Strength, N	Erasability, %	Disintegration, s
Magnesium stearate	10,27± 0,25	28,4 ±1,0	80,33 ± 2,26	0,8	76
Precerol	8,16 ± 0,11	27,2 ±1,0	82,50 ± 2,34	0,5	67
PRUV®	10,18 ± 0,25	26,7 ±1,0	64,67 ± 3,26	0,3	52

Note P<95, n=3

With almost little increase in the tablets' disintegration time, the results show that the addition of this class of chemicals greatly enhanced the strength properties.

The plate-shaped particles in magnesium stearate act as a sort of cementing agent, increasing the tablet's mechanical strength, but doing so severely shortens its disintegration time of more than a minute.

Because of its composition, PRUV® (sodium stearyl fumarate) increases the tablet's strength while essentially preventing it from disintegrating more quickly. Additionally, it is a material that enhances organoleptic properties. The use of PRUV®

(sodium stearyl fumarate) in the technology of ondasetron hydrochloride tablets dissolving in the oral cavity seems promising due to the aforementioned characteristics.

The composition of tablets containing ondasetron hydrochloride that dissolve in the oral cavity was suggested based on the findings of the analysis:

Composition	***g***
Ondasetron hydrochloride	0,008
F - MELT® type M	0,190
Sodium stearyl fumarate	0,002
Weight of the tablet	*0,2*

3.3 Technology of ondasetron hydrochloride tablets

Fig. 3.2 illustrates how ondasetron hydrochloride tablets are made using direct pressing.

Stage 1: Preparation of raw materials

Raw ingredients that are not need to be packaged are carried in closed containers in accordance with GMP regulations. The scales, collectors, vibrating screen, reactor, and meter utilized in stage 1 are all inspected.

The serviceability and cleanliness of the sieves and collectors used at this stage of manufacturing must be examined before beginning to sift the raw materials.

Ondasetron hydrochloride, sodium stearyl fumarate, and F-MELT® type M are the raw components that are weighed in quantities on scales.

After being weighed, ondasetron hydrochloride is moved to stage 2 from the warehouse. A vibrating sieve with a mesh size of 0.20±0.030 is used to screen the weighted raw materials (sodium stearyl fumarate and F-MELT® M) that were received from the warehouse.

Install the vibrating sieve in the receiver using a rubber belt before doing any work on it. A frequency of 2500 rpm should be set.

When the vibrating screen is connected to the mains, it ought to function without making any unnecessary noise. Remove the belt and load the raw material after ensuring the vibrating screen is in excellent operating order. For ten minutes, turn it on.

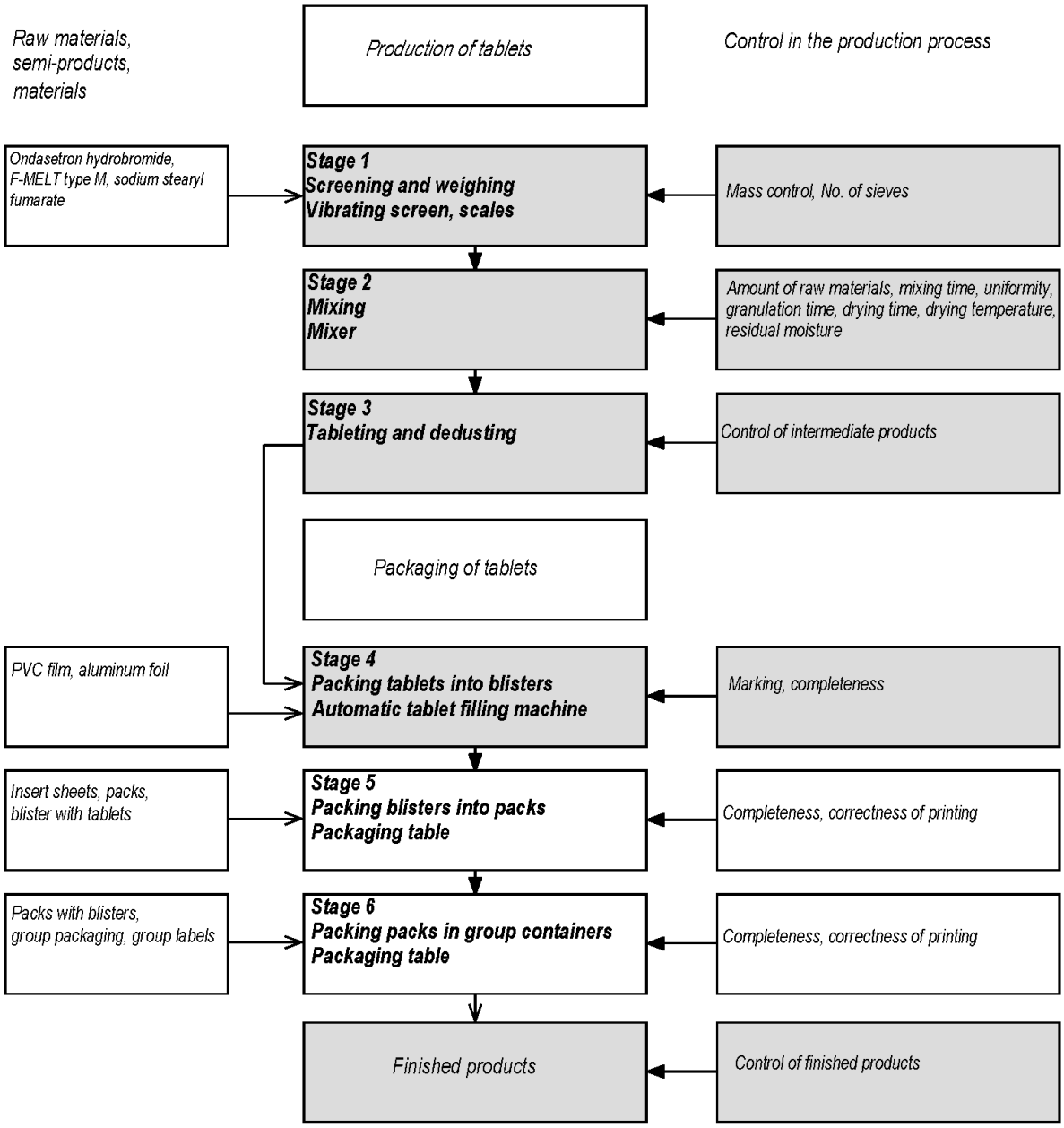


Fig. 3.2. Flow diagram of ondasetron hydrochloride tablets production

Manual labor is used for loading and unloading. When the job is over, the sieve is taken out, the vibrating screen is unplugged from the power source, and the number of revolutions is lowered to zero. Visual inspection is used for sifting quality control. On the operating sheet, the operator writes the date, the batch number of the raw materials, and the quantity of weighted components to be sieved.

Sodium fumarate stearyl and F - MELT® type M, pre-sieved, are collected in a container and transferred to stage 2 "Mixing".

Stage 2. Mixing.

The mixer is used to mix the components. Before using the mixer, make sure it is clean.

The mixer was manually filled with the following raw materials: sodium stearyl fumarate, ondasetron hydrochloride, and F-MELT® type M. Shut the container's lid. On the control panel, select the preferred mixing mode. Three minutes are needed for mixing. In the mixer, stir the bulk until it is dispersed uniformly.

A label bearing the date, batch number, equipment number where the operation is performed, operator name, and signature is affixed to the container once the resultant mass has been emptied. The mixture in the container is then moved to "Tableting" step three.

Stage 3: Tableting and dedusting.

Verify the tablet press's operational readiness. For the production of tablets with a specific diameter, the press tool is examined and, if required, installed. At the reject valve and deduster's output, pre-weighed containers with lids are placed to collect rejected, conditioned, and subpar tablets.

The settings are established by manually loading a tiny amount of tablet mass onto the rotor feeder tray. There is regulation of the pushing force. Individual tablet weight variations of up to 7.5% of the mean tablet weight are permitted.

Three tablet press rotations in automated mode yield the tablets after the settings have been specified. Verify the tablet's geometric measurements. Modify the tablet press settings if required.

The tablet press hopper is filled with the tablet mass. Make sure the tablet press is operational. A press tool is inspected and, if necessary, installed to create tablets with a particular diameter. Pre-weighed containers with lids are positioned near the reject valve and deduster's output to collect conditioned, substandard, and rejected tablets. .

A little amount of tablet mass is manually placed into the rotor feeder tray in order to establish the parameters. The pushing force may be controlled. Weight variations of up to ±7.5 percent of the mean tablet weight are allowed for each

individual tablet. A batch of the medication is tableted using a tablet press that is programmed to produce 1300 tablets per minute.

The machine operator controls tablet appearance and geometry factors during the tableting process, while the QC laboratory controls pharmaceutical and technological parameters.

The resultant conditioned tablets are put into a collecting system after automatically passing through a dedusting equipment.

To monitor the quality of the semi-product, or bulk tablets, a sample of dedusted conditioned tablets is obtained at the conclusion of tableting. This is done based on the following indicators: appearance, identity, disintegration, average weight, and quantification.

Each collection is sealed with a cover after sampling.

The bulk pills move on to the "Packaging, Labeling and Packaging" phase when the SQC issues a favorable ruling.

The tablets are disposed of in line with the Authorized Person's directive in the event that the SQC issues a negative ruling.

Stage 4: "Packing Tablets in Blisters"

The packing process begins by activating the control system of the blister packing machine. This advanced system is designed to automate the entire process, ensuring both speed and precision. The roller carriage of the machine is loaded with a roll of PVC film, which will form the base of the blister packs, and aluminum foil, which will serve as the sealing layer. As the aluminum foil roll is installed, the accuracy of the foil labeling or printing is checked to confirm that all markings, including batch numbers and expiration dates, are correct and legible. This step is crucial for traceability and regulatory compliance, as it ensures that the correct product information is displayed on each blister pack.

The automatic packing machine's settings are then adjusted to accommodate the specific product being packed. These adjustments include calibrating the machine to achieve the required level of tightness for the blister packs, ensuring that each tablet is securely sealed within the blister. Once the sealing process is confirmed, the batch

number and expiration date printed on the supplied empty blisters are checked again to ensure the details are accurate.

Ondansetron hydrochloride tablets, which have passed the quality control and quality assurance (QCQA) checks in Stage 3 ("Production of Ondansetron Hydrochloride Tablets"), are manually transferred from the collector to the loading hopper of the blister packing machine. After the hopper is filled with the required number of tablets, it is securely covered to prevent contamination during the packing process.

The blister packing machine is highly efficient, with the capacity to package up to 180 blisters of ondansetron hydrochloride tablets per minute. The machine's infrared controller automatically regulates the filling of the blister cavities to ensure uniform distribution of tablets. This step is essential for maintaining product consistency and quality. After the blisters are filled, they are carefully transferred from the clean zone, where the packing process takes place, to the regulated zone via a belt conveyor system. The controlled movement of the blisters through these zones ensures that the integrity of the product is maintained and that environmental standards are adhered to throughout the packaging process.

Stage 5 and Stage 6: "Packing Blisters into Packs" and "Packing Packs into Group Containers"

In Stage 5, the blister packs containing the ondansetron hydrochloride tablets are manually arranged into boxes and packs on the GF 22 packing table. This step involves organizing the blister packs into their final consumer-ready presentation, ensuring that each box or pack contains the correct number of blisters. The quality assurance team is involved in this stage to conduct further inspections, checking the accuracy and integrity of the packaging, including labels, seals, and batch information. This ensures that the products meet all regulatory requirements and maintain high-quality standards before they reach the end user.

Following this, the packed boxes or packs are transferred to the completed goods quarantine storage facility. This storage area serves as a temporary holding space where the final products are stored until they undergo further inspection. A representative from the QCQA team performs a random sampling of several finished products to assess

whether they meet the required standards outlined in the International Acceptance Criteria (IAC) for finished goods. This step is critical to ensure that the packaged ondansetron hydrochloride tablets are safe for distribution and use.

Once the final products pass this rigorous quality control check and receive a positive result, they are transferred to the completed products warehouse, where they are ready for shipment to distribution channels. In contrast, if the random sampling reveals any discrepancies or failures in quality control, the affected batches are held for further investigation and, if necessary, discarded in accordance with the Authorized Person’s directive. This ensures that only products meeting the highest standards of quality are released for distribution.

CONCLUSIONS TO SECTION 3

1. Ondasetron hydrochloride was the subject of technological and physicochemical investigations.

2. It was discovered that the material has a comparatively high powder compressibility and low fluidity properties.

3. A logical tablet composition was chosen and a technical plan for tablet manufacture was put forth based on the analysis of the technological characteristics of the tableting mixture.

GENERAL CONCLUSIONS

1. According to recent findings in the literature review, oral disintegrating tablets (ODTs) have emerged as one of the most promising and innovative dosage forms in pharmaceutical development. Unlike traditional tablets and capsules, ODTs are designed to rapidly dissolve or disintegrate in the mouth, facilitating quicker absorption of the active ingredient. This formulation approach offers the advantage of requiring a lower quantity of active pharmaceutical ingredients to achieve the same therapeutic effect as conventional dosage forms. ODTs provide significant benefits in terms of convenience, particularly for patients with difficulties swallowing pills, as well as enhanced patient compliance. Moreover, the speed at which the therapeutic effects of ODTs are observed is comparable to that of more invasive drug administration methods such as intravenous injections or inhalation therapies. After the active ingredient is absorbed by the mucosal tissues of the mouth, it swiftly enters systemic circulation, leading to rapid onset of action. This characteristic makes ODTs a highly effective and efficient option for treating conditions that require fast relief, including nausea and vomiting.

2. According to a comprehensive analysis of the pharmaceutical market, the antiemetic drug sector remains far from being fully saturated, presenting substantial opportunities for the development of new and improved medications. Despite the availability of several antiemetic drugs currently in use, there is still a significant demand for innovative formulations that are more effective, have fewer side effects, and can be tailored to specific patient needs. Research on the variety of antiemetic medications has highlighted the potential benefits of utilizing ondansetron hydrochloride as an active pharmaceutical ingredient (API). Ondansetron is a well-established antiemetic, commonly used to prevent nausea and vomiting associated with chemotherapy, radiotherapy, and post-operative recovery. Its inclusion in new formulations could offer substantial therapeutic advantages, making it an attractive candidate for further research and development. Additionally, the growing interest in targeted therapies and personalized medicine further

underscores the need for novel antiemetic solutions that can better address the unique needs of individual patients.

3. The selection of excipients and the design of research methodologies are crucial steps in the development of pharmaceutical formulations, and they are primarily determined by the physicochemical properties of the active substance involved. Excipients, which are inert substances used in drug formulations, must be chosen carefully to complement the API's characteristics, such as solubility, stability, and bioavailability. The choice of excipients not only impacts the efficiency of drug delivery but also affects the overall quality, safety, and performance of the final product. Furthermore, the research techniques employed during the development process are selected based on the specific properties of the active substance, ensuring that the most suitable and effective methods are used for formulation optimization. This personalized approach to formulation development helps maximize the therapeutic potential of the drug while minimizing any adverse effects or complications.

4. Ondansetron hydrochloride, a widely used antiemetic, has been the subject of extensive technical and physicochemical investigations to better understand its behavior and optimize its formulation. Studies have revealed that ondansetron hydrochloride possesses relatively high powder compressibility, which indicates its ability to form solid tablets under pressure. However, the material also exhibits low fluidity, meaning it does not flow easily, which can pose challenges during the tableting process. To overcome this, a logical and efficient tablet composition was selected based on a detailed analysis of the technological characteristics of the tableting mixture. This involved identifying the ideal excipients and formulation techniques that would enhance the material's flow properties and compressibility. Additionally, a comprehensive technical plan for the manufacturing of ondansetron hydrochloride tablets was proposed, ensuring that the final product would meet the necessary quality standards. This technological approach is crucial for ensuring the tablet's consistent quality, efficacy, and patient acceptability.

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APPLICATION

Application A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
КАФЕДРА ПРОМИСЛОВОЇ ТЕХНОЛОГІЇ ЛІКІВ ТА КОСМЕТИЧНИХ ЗАСОБІВ
КАФЕДРА АПТЕЧНОЇ ТЕХНОЛОГІЇ ЛІКІВ

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
DEPARTMENT OF INDUSTRIAL TECHNOLOGY OF MEDICINES AND COSMETICS
DEPARTMENT OF DRUG TECHNOLOGY

Матеріали
IV міжнародної науково-практичної конференції
Proceedings of the IV International Scientific and Practical Conference

ФУНДАМЕНТАЛЬНІ ТА ПРИКЛАДНІ ДОСЛІДЖЕННЯ У ГАЛУЗІ ФАРМАЦЕВТИЧНОЇ ТЕХНОЛОГІЇ

FUNDAMENTAL AND APPLIED RESEARCH IN THE FIELD OF PHARMACEUTICAL TECHNOLOGY

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Kharkiv, Ukraine

DEVELOPMENT OF THE COMPOSITION OF ORODISPERSIBLE ANTIEMETIC TABLETS

Puliaiev D.S., Azeba Ali
National University of Pharmacy, Kharkiv, Ukraine

Introduction. Orodispersible tablets (ODTs) have gained significant attention in recent years due to their convenience and ease of administration, particularly for patients with swallowing difficulties, such as children, the elderly, and those suffering from dysphagia. The rapid disintegration of these tablets in the mouth without the need for water provides a solution for individuals in various clinical scenarios, including chemotherapy, post-operative recovery, and gastrointestinal disorders that are often accompanied by nausea and vomiting. Antiemetic drugs, when delivered in the form of ODTs, offer the advantage of faster absorption and onset of action, which is crucial for managing sudden episodes of nausea and vomiting. This study aims to develop an effective orodispersible antiemetic tablet formulation that improves patient compliance while ensuring therapeutic efficacy.

ODTs are particularly useful in situations where immediate relief is required, such as during chemotherapy-induced nausea or in cases of motion sickness. Traditional antiemetic formulations may not always be suitable, as they can take longer to act, or may be difficult for patients to ingest. Developing a stable and efficient ODT formulation addresses these challenges by focusing on rapid drug release, pleasant taste, and overall patient comfort.

The aim of the study. This research aims to develop a well-balanced composition for orodispersible antiemetic tablets that meet pharmaceutical quality standards, including rapid disintegration, optimal bioavailability, and sufficient stability over time. The study also aims to explore the impact of various excipients on the tablet's properties, such as its mouthfeel, disintegration time, and release profile. Additionally, the research seeks to optimize the concentration and type of superdisintegrants used, to achieve the fastest possible disintegration time without compromising the physical integrity of the tablet.

Moreover, this research will evaluate the compatibility of the active antiemetic ingredient with different excipients to ensure that the therapeutic effectiveness is maintained during the shelf life of the product. The final objective is to develop a patient-friendly dosage form that combines fast action with a pleasant taste profile, making it suitable for a wide range of patient populations.

Methods of research. Initial formulation trials were conducted using various superdisintegrants such as croscarmellose sodium, sodium starch glycolate, and crospovidone, which were evaluated for their efficiency in reducing disintegration time. Sweeteners, flavoring agents, and fillers like mannitol and microcrystalline cellulose were incorporated to enhance the sensory attributes of the tablets. Disintegration time was measured using standard pharmacopoeial methods, and the dissolution profile of the active antiemetic ingredient was determined using in vitro techniques. The research also evaluated the mechanical strength of the tablets to ensure they withstand transportation and handling.

Main results. The research resulted in the identification of an optimized formulation that successfully reduced the disintegration time of the orodispersible tablets. Among the tested superdisintegrants, crospovidone yielded the most effective results, ensuring both fast disintegration and a smooth mouthfeel.

Conclusions. The development of an orodispersible antiemetic tablet has proven to be successful, offering a dosage form that not only meets pharmaceutical standards but also meets the needs of patients. The optimized formulation should provide rapid absorption, rapid onset of action and improved patient tolerance, making it a highly effective treatment for nausea and vomiting. The pleasant taste and ease of use further enhance the practical benefits of this product, especially for patients who have difficulty with traditional tablet forms. In addition, further optimization of the tablet formulation may be aimed at incorporating natural excipients or alternative antiemetic compounds to improve the versatility and safety profile of the product. With the ongoing development of pharmaceutical technologies, the potential of orodispersible tablets to address unmet medical needs remains enormous, especially in patient-centered drug delivery systems.

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of industrial technology of drugs and cosmetics

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The head of department
industrial technology of drugs and cosmetics

_____
Olena RUBAN_____
"02" September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Azeba Ali

1. Topic of qualification work: «Development of the composition of orodispersible anitemetic tablets», supervisor of qualification work: Denys Puliaiev, PhD, assoc. prof.,

approved by order of NUPh from "06" of February 2024 № 34

2. Deadline for submission of qualification work by the applicant for higher education: October 2024.

3. Outgoing data for qualification work: solid dosage form, active ingredient: ondasetron hydrochloride.

4. Contents of the settlement and explanatory note: literature review on the topic, objects and methods of research, experimental part, conclusions.

5. The work should contain tables, graphs, figures in a volume sufficient to cover the topic.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Denys PULIAIEV, associate professor of higher education institution of department of pharmaceutical preparations technologies	02.09.2024	02.09.2024
2	Denys PULIAIEV, associate professor of higher education institution of department of pharmaceutical preparations technologies	02.09.2024	02.09.2024
3	Denys PULIAIEV, associate professor of higher education institution of department of pharmaceutical preparations technologies	02.09.2024	02.09.2024

7. Date of issue of the assignment: «02» September 2024.

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	The study of literary sources in the main directions of the development of drugs for the treatment of nausea. Writing a literature review.	July 2024	**done**
2	Definition of objects and methods of research. Formation of the second chapter.	August 2024	**done**
3	Study of physico-chemical and pharmaco-technological properties of research objects.	September 2024	**done**
4	Substantiation of the composition and technology of tablets with ondasetron hydrochloride for the treatment of nausea. Formation of chapter 3.	October 2024	**done**

An applicant of higher education _____ Azeba Ali

Supervisor of qualification work _____ Denys Puliaiev

ВИТЯГ З НАКАЗУ № 34
По Національному фармацевтичному університету
від 06 лютого 2024 року

1. Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу 2 циклу Фм20*(4,10д) 2024-2025 навчального року, ступінь вищої освіти «магістр», галузь знань 22 Охорона здоров'я, спеціальність 226 – Фармація, промислова фармація, освітньо-професійна програма – Фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців). Мова навчання англійська.

№ з/п	Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі промислової технології ліків та косметичних засобів**					
14.	Азеба Алі	Розробка складу таблеток антиеметичної дії, що диспергуються в ротовій порожнині	Development of the composition of orodispersible antiemetic tablets	доц. Пуляєв Д.С.	доц. Ковальов В.В.

Ректор

Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«15» листопада 2024 р. № 329600244

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Азеба Алі, Фм20*(4,10д)-англ-02, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Розробка складу таблеток антиеметичної дії, що диспергуються в ротовій порожнині / Development of the composition of orodispersible antiemetic tablets», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

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

Azeba Ali

on the topic: **«Development of the composition of orodispersible antiemetic tablets»**

Relevance of the topic. The problem of creating solid dosage forms of combined action with the substantiation of the composition, the rational choice of excipients and the optimal technology is quite relevant and opens up new opportunities in the complex therapy of nausea.

Practical value of conclusions, recommendations and their validity. The analysis of literature sources on rational pharmacotherapy of nausea, considering their etiology and pathogenesis, was carried out, the range of drugs for the treatment of these pathologies available on the pharmaceutical market of Ukraine was studied, and the relevance of developing a new drug in the form of tablets with ondasetron hydrochloride was proved. A technology for the manufacture of ODT is proposed, according to which a technological scheme for its production is drawn up.

Assessment of work. The results of the experiments were statistically processed and presented in the work in the form of tables and graphs. The conclusions are the logical conclusion of theoretical and experimental studies.

General conclusion and recommendations on admission to defend. The master's work of Azeba Ali meets all the requirements for qualification work and can be submitted for defense at the State Examination Commission of the National University of Pharmacy.

Scientific supervisor Denys PULIAIEV

«03» of October 2024

Ф А 2.2.1-32-356

REVIEW

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

Azeba Ali

on the topic: **«Development of the composition of orodispersible antiemetic tablets»**

Relevance of the topic. One of the urgent problems of our time is the increase in the growth of nausea. The range of medicines for the treatment of these pathologies of Ukrainian production is limited, most of the drugs have a unidirectional effect. Therefore, the development of domestic complex preparations of antiemetic action is an urgent task.

Theoretical level of work. Based on the literature data, the author substantiates the need to create antiemetic tablets. Azeba Ali conducted a search for the most appropriate active substances and auxiliary components.

Author's suggestions on the research topic. As active ingredients, the author proposed ondasetron hydrochloride. The expediency of using and experimentally confirmed number of excipients in the composition of the proposed preparation is substantiated.

Practical value of conclusions, recommendations and their validity. In the course of the work, the rational composition of the ODT was substantiated. The technology of tablets has been developed, according to which a technological scheme has been drawn up.

General conclusion and assessment of the work. The conclusions formulated in the work are based on experimental data and follow logically from the results obtained. The qualification work of Azeba Ali meets all the requirements for qualification works and can be submitted for defense at the State Examination Commission of the National University of Pharmacy.

Reviewer _____associate professor Volodymyr KOVALOV

«14» of October 2024

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Витяг з протоколу
засідання кафедри промислової технології ліків та косметичних засобів НФаУ
№ 4 від 22 листопада 2024 року

Голова: завідувач кафедри, доктор фарм. наук, проф. Рубан О.А.

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

ПРИСУТНІ: зав. каф., проф. Рубан О.А., проф. Ковалевська І.В., проф. Бобрицька Л.О., проф. Гриценко В.І., проф. Сліпченко Г.Д., проф. Кухтенко О. С., доц. Безрукавий Є. А., доц. Кутова О. В., доц. Манський О. А., доц. Ніколайчук Н. О., доц. Пуляєв Д.С., доц. Січкар А. А., доц. Солдатов Д. П., доц. Трутаєв С. І., ас. Пономаренко Т.О.

ПОРЯДОК ДЕННИЙ:

1. Про представлення до захисту в Екзаменаційну комісію кваліфікаційних робіт здобувачів вищої освіти випускного курсу НФаУ 2024 року випуску

СЛУХАЛИ: про представлення до захисту в Екзаменаційній комісії кваліфікаційної роботи на тему: «Розробка складу таблеток антиеметичної дії, що диспергуються в ротовій порожнині»

здобувача вищої освіти випускного курсу group Фм20*(4,10) англ-02 групи НФаУ 2024 року випуску Азеба Алі
(ім'я, прізвище)

Науковий (-ві) керівник (-ки) к.фарм.н., доц. Денис ПУЛЯЄВ

Рецензент к.фарм.н., доц. Володимир КОВАЛЬОВ

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувача вищої освіти групи Фм20*(4,10) англ-02 Азеба Алі
(ім'я, прізвище)

на тему: «Розробка складу таблеток антиеметичної дії, що диспергуються в ротовій порожнині»

Голова
завідувач кафедри,
доктор фарм. наук, проф. _____ Олена РУБАН
(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 Азеба Алі до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка складу таблеток антиеметичної дії, що диспергуються в ротовій порожнині».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Азеба Алі виконав на кафедрі промислової технології ліків та косметичних засобів НФаУ кваліфікаційну роботу, яка присвячена створенню складу таблеток антиеметичної дії.

В процесі роботи Азеба Алі дослідив загальні напрями етіопатогенезу та терапії станів, що супроводжуються нудотою, обґрунтував доцільність створення та застосування таблеток із ондасетроном гідрохлорідом. Автором було обґрунтовано оптимальний склад таблеток та розроблено промислову технологію їх отримання.

У цілому подана до захисту кваліфікаційна робота Азеба Алі на тему «Розробка складу таблеток антиеметичної дії, що диспергуються в ротовій порожнині» відповідає вимогам, що висуваються до кваліфікаційних робіт, оцінюється позитивно і може бути рекомендована для захисту в Екзаменаційну комісію НФаУ.

Керівник кваліфікаційної роботи Денис ПУЛЯЄВ

«03» жовтня 2024 р.

Висновок кафедри про кваліфікаційну роботу

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

Завідувач кафедри
промислової технології ліків
та косметичних засобів Олена РУБАН

«22» листопада 2024 р.

Qualification work was defended

of Examination commission on

« ____ » _____2024

With the grade _____

Head of the State Examination commission,

D.Pharm.Sc., Professor

_____ / Oleh SHPYCHAK /