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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION OF COMBINATION TABLETS FOR DEMENTIA TREATMENT»**

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ANNOTATION

The pharmaceutical development of a combination form of memantine and donepezil for the treatment of cognitive disorders, which will improve patient compliance, is a topical area of research. Investigation of the technological properties of the active pharmaceutical ingredients: memantine hydrochloride and donepezil hydrochloride was in the framework of the development of a fixed dose combination. The qualification work provides theoretical and experimental justifications for the development of composition of tablets.

The work consists of the parts: introduction, literature review, choice of research methods, experimental part, conclusions, list of used literature sources, total volume of work 40 pages, contains 5 tables, 5 figures, 36 literature sources.

Key words: memantine hydrochloride, donepezil hydrochloride, Alzheimer's disease, tablets, granules, composition.

АНОТАЦІЯ

Актуальним напрямком досліджень є фармацевтична розробка комбінованої форми мемантину та донепезилу для лікування когнітивних розладів, яка покращить комплаєнс пацієнта. Дослідження технологічних властивостей діючих фармацевтичних речовин: мемантину гідрохлориду та донепезилу гідрохлориду проводилося в рамках розробки комбінації фіксованих доз. У кваліфікаційній роботі наведені теоретичні та експериментальні обґрунтування розробки складу таблеток.

Робота складається з наступних частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних джерел літератури, загальний обсяг роботи 40 сторінки, містить 5 таблиць, 5 рисунків, 36 джерел літератури.

Ключові слова: мемантину гідрохлорид, донепезилу гідрохлорид, хвороба Альцгеймера, таблетки, гранули, склад.

CONTENTS

LIST OF ABBREVIATIONS

AD	–	Alzheimer’s disease
API	–	active pharmaceutical ingredients
AUC	–	Area Under Curve
C max	–	maximum observed concentration of medicine
CNS	–	central nervous system
DSM-5	–	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ER	–	Extended-Release
FDA	–	Food and Drug Administration
IR	–	Immediate-Release
LOD	–	granule loss on drying test
MCC		microcrystalline cellulose
mg	–	milligram
NMDA- receptor	–	(N-Methyl-D-Aspartate)-receptor
RH	–	relative humidity
PVP	–	polyvinylpyrrolidone
sec	–	seconds
SPhU	–	State Pharmacopeia of Ukraine
T max	–	observed mean time to maximum concentration of medicine
WHO	–	World Health Organization

INTRODUCTION

The relevance of the topic. Nowadays, over 55 million people worldwide suffer from dementia, more than 60% of whom live in low- and middle-income countries. Each year, approximately 10 million new cases occur.

Dementia is considered presently the seventh leading cause of death and one of the leading causes of disability and dependency among the world's seniors [1, 2].

According to the WHO, dementia is a syndrome in which there is a progressive deterioration in cognitive function beyond what might be expected from normal aging. This deterioration can include impaired judgment, memory loss, and difficulty with language, communication, and daily activities. Each type of dementia has its own etiology. Alzheimer's disease is the most common type of dementia and is caused by the accumulation of amyloid plaques and neurofibrillary tangles. Most commonly used treatments for dementia include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which can improve memory and thinking by increasing levels of a neurotransmitter called acetylcholine in the brain, and memantine, which works by blocking the action of a neurotransmitter called glutamate in the brain and can help to slow down the progression of symptoms in people with moderate to severe dementia.

Currently, pharmaceutical companies in Ukraine do not produce combination tablets with donepezil and memantine. But combination of donepezil and memantine in the hard dosage form has certain advantages. The addition of memantine to donepezil is associated with a favorable risk / benefit ratio in the treatment of patients with moderate to severe Alzheimer's disease and provides additional benefits for patients, caregivers and society at large.

The purpose and research tasks. The aim of our researches was a composition development of tablets with memantine hydrochloride and donepezil hydrochloride.

It was necessary deciding the tasks for achievement of the purpose:

– to analyze the modern state of problem of the dementia treatment and combination tablets creation;

– to conduct research on the study of physical and chemical and pharmacotechnological properties of memantine hydrochloride and donepezil hydrochloride;

– to conduct the scientifically-grounded search of excipients for creation of tablets;

– to define the rational type of packing and condition of storage of tablets of memantine and donepezil.

Research objects are memantine hydrochloride and donepezil hydrochloride, granules and tablets on its basis.

The article of research is composition and technology of production of medicinal preparation as compressed tablets, on the basis of memantine and donepezil.

Research methods. For the decision of tasks the methods of researches from SPhU were used for estimation: physical, chemical properties of memantine hydrochloride and donepezil hydrochloride, granules, them technological properties (flowability, bulk volume, angle of repose); in accordance to requirements of SPhU (tablets middle mass and homogeneity of mass) and prepared tablets parameters of quality, hardness, appearance. Experimental data were carried out with methods of mathematical statistics.

Practical recommendations. On the basis of the carried out complex of researches of crystallography, physical and chemical, pharmaco-technological properties of memantine hydrochloride and donepezil hydrochloride developed and offered for manufacture medicinal preparation of memantine and donepezil in form of tablets, for treatment of Alzheimer's diseases.

The approbation of research results and publications – participation in the XXIX International Scientifical and Practical Conference of Young Scientists and Students “Topical issues of new medicines development”, April 19-21, 2023 with abstract writing and the presentation.

Structure of work. Qualification master degree work consists from introduction, three chapters, general conclusions, list of the references (36 sources) and appendix. The content of work is presented on 40 pages of basic text and contains 5 tables and 5 pictures.

CHAPTER 1.
THE CURRENT STATE OF THE PROBLEM OF THE DEMENTIA TREATMENT AND COMBINATION TABLETS CREATION

1.1. Medicines for the dementia treatment

Dementia is a contition that describes a group of symptoms including memory loss, difficulties with thinking, problem-solving or language formation, and often changes in mood or behavioural conduct. More than 100 type of dementia exist. The most common are Alzheimer’s disease and vascular dementia [3, 4].

Clinical and pathological features distinguishing the diverse causes of dementia. Dementia's etiologies include both progressive, irreversible causes and reversible causes that can be resolved with the treatment of the underlying disease processes.

Most of dementia causes are progressive where only 9–11 % of dementias being of the reversible type [3]. Causes of reversible type of dementia are mainly drug and alcohol toxicity, depression, nutritional deficiencies, metabolic diseases, normal pressure hydrocephalus, central nervous system infections, intracranial tumors, and others [4, 5, 6].

Causes of irreversible type of dementia are classified into groupings resulting in a complete understanding of the risk factors and underlying pathologies as the table 1.1 shows [7].

There are genetic and nongenetic risk factors of dementia. Age is designated as the only universally, nongenetic accepted risk. The prevalence of dementia doubles every five years from age 65 onwards [8]. It has been observed that with approximately 50 % of the population over the age of 82 years having some form of dementia [9]. The brain's capacity for auto-repair declines, but varies greatly from one person to another as a person gets older. Furthermore, aging increases the prospect of additional risk factors associated with dementia, mainly diabetes and

cardiovascular disease [10, 11].

Table 1.1

Type of dementia, diagnoses associated with dementia and common early symptoms

Type of dementia	Common early symptoms
Alzheimer's disease	Difficulty remembering, depression, impaired judgment, confusion, behavior changes, difficulty with word finding
Vascular dementia	Impaired judgment and ability to plan, location in the brain determines how individual's thinking and physical function is affected
Dementia with Lewy bodies	Memory loss, sleep disturbances, visual hallucinations, muscle rigidity, and Parkinsonian movement features
Frontotemporal dementia	Behavior and personality changes, difficulty with language
Chronic traumatic encephalopathy	Decreased attention, memory deficits, disorientation, and behavioral changes
Huntington's disease	Decline in thinking and reasoning skills, mood changes
Wernicke-Korsakoff syndrome	Severe memory loss with intact social and other thinking skills

Some disorders that cause dementia can run in families. Doctors often suspect an inherited cause if someone younger than 50 has symptoms of dementia [12].

Approved pharmacologic treatments for dementia in warld [12, 13]:

A. Acetylcholinesterase inhibitors

– Donepezil (Tablet or orally disintegrating tablet, Transdermal patch) used in all stages of dementia [13].

– Rivastigmine (Capsule, Immediate-release tablet or oral solution) used in Mild to moderate dementia.
– Galantamine (Extended-release capsule, Tablet or oral solution) used in Mild to moderate dementia [13, 15].

B. N-Methyl-D-Aspartic acid receptor antagonist

– Memantine (Extended-release capsule, Tablet or oral solution) used in moderate to severe dementia [13, 15].

C. Combination drugs

– Memantine and donepezil (Capsule or tablets) used in moderate to severe dementia. Target dose 10 mg donepezil and 28 mg memantine extended-release once in the evening. For patients with renal problems: maximal dose is 10 mg donepezil with 14 mg memantine extended once daily [14, 15].

There are some advantages of using memantine in combination with donepezil. Based on several studies it has been proved that combining memantine with donepezil has major positive effects on the cognitive and neuropsychotic symptoms of dementia along the improvement of daily activities execution [16–24]. Economically, memantine plus donepezil are more cost-effective than donepezil because memantine may slow the progression of AD meaning less expanses on drugs.

Currently there are only few countries manufacturing memantine and donepezil in combination tablets as more studies are showing their potent effect if administered in combination. The leading country in this manufacturing is India with several brands in market including “ARIZEX”, “DONPEZ-M-5” [20, 21].

The manufacture of combination memantine plus donepezil tablets is flourishing as more countries are developing it and more researches are being done to increase the tablets quality(disintegration, solubility, flowability and other) [25, 26].

Memantine is an antagonist of the NMDA-receptor subtype of glutamate receptor. Medicine is used to slow the neurotoxicity thought to be involved in Alzheimer disease and other neurodegenerative diseases. It blocks the NMDA-

receptor subtype of glutamate receptors preventing glutamine receptors over-activation while allowing the normal activity. Its blocking effects antagonize an overactive glutaminergic system in the CNS which is thought to be involved in the neurotoxicity seen in Alzheimer disease. This activity reviews indications, the uses, contraindications and side effects of memantine and highlights a role of the interprofessional team in a management of patients with dementia [1–3].

Pharmacologic Class of Memantine is NMDA-receptor antagonist. FDA indication [4] is treatment of moderate to severe Alzheimer dementia. Other Uses of this medicine (non-FDA approved) are

– Mild cognitive impairment;
– Mild to moderate Alzheimer dementia;
– Mild to moderate vascular dementia;
– Psychiatric disorders;
– Chronic pain;
– Diagnosis of Alzheimer Disease.

The DSM-5 criteria for diagnosis for memantine use include the following characteristics:

– evidence of significant cognitive decline from a previous level of performance in such cognitive domains (executive function, learning, complex attention, and memory, perceptual-motor, language, or social cognition);
– cognitive deficits do not occur only in the context of delirium;
– cognitive deficits interfere with independence in everyday activities;
– another mental disorder does not better explain cognitive deficits;
– the onset is the gradual progression and insidious of impairment in at least two cognitive domains: evidence of a causative Alzheimer disease genetic mutation from genetic testing or family history; and also all three of the following: clear evidence of the decline in learning and memory and more other domains; steadily gradual decline in cognition, progressive, without extended plateaus; and no evidence of mixed etiology due to other cerebrovascular disease or neurodegenerative disorders.

Alzheimer disease is the neurodegenerative disorder which characterized by the presence of extracellular amyloid-beta protein an intracellular neurofibrillary tangle composed of hyperphosphorylated protein in the brain. There is the impaired cortical cholinergic function and a decrease in acetylcholine synthesis in patients with Alzheimer dementia. So cholinesterase inhibitors (like donepezil, galantamine, rivastigmine) in dementia provide symptomatic relief by inhibiting cholinesterase at increasing cholinergic transmission and synaptic cleft. However, the mechanism of memantine action is distinct from those of cholinergic agents and is proposed to be neuroprotective. Glutamate is the major excitatory neurotransmitter in the brain. One of receptors activated by glutamate is the NMDA-receptor which is essential for process like memory and learning. Excessive activation of NMDA-receptor has been shown to be associated with neuronal loss or damage contributing to the various chronic and acute neurological disorders including dementia. However physiological activity of NMDA-receptor is also needed for normal neuronal function. Any agents that block all activity of NMDA-receptor will have unacceptable clinical side effects. Memantine, through its action as the low-affinity, uncompetitive, open-channel blocker (uncompetitive antagonist of extrasynaptic NMDAR), preferentially enters the channel of receptor-associated ion when it is excessively open, and hence, it does not interfere with the normal synaptic transmission. By doing so, it protects against further damage or prevents from death of neuronal cell induced by excitotoxicity. Therefore, memantine is used in combination with acetylcholinesterase inhibitors for the Alzheimer dementia treatment [3].

According to the mechanism of action memantine is the uncompetitive antagonist of the NMDA subtype of receptors of glutamate in the CNS. Alzheimer disease is believed to be caused by overstimulation of glutamate (the primary excitatory amino acid in the CNS) resulting in excitotoxicity and neuronal degeneration. The NMDA receptor is the voltage-gated cation channel that in a physiologic unstimulated state is blocked by magnesium ions. Stimulated magnesium is displaced allowing calcium influx and activation. There is

pathologic overstimulation of the receptor causing it to be in a chronically active state in Alzheimer disease. Memantine also helps to counteract an excessive stimulation [1].

Memantine exhibits antagonist activity at the nicotinic acetylcholine and serotonergic type 3 (5-HT3) receptors. It has no activity at the gamma-aminobutyric acid (GABA), benzodiazepine, histamine, dopamine, adrenergic, or glycine receptors or for voltage-dependent calcium, potassium, or sodium channels [1].

As for administration of memantine the starting dosage is 5 mg once daily, target dosage is 20 mg once daily. Dosage increased by 5 mg daily in weekly intervals as tolerated. Titration schedule is week 1 (5 mg daily), week 2 (10 mg daily or 5 mg twice daily), week 3 (15 mg daily or 5 mg one time and 10 mg one time daily), week 4: 20 mg daily or 10 mg twice daily. Switching from Immediate-Release (IR) to Extended-Release (ER): start ER day after the last dosage of IR; IR 10 mg twice daily should be switched to ER 28 mg daily. Single memantone dose missed do not double up on next dose; if several dosages are missed, resume at a lower of medicine dose and titrate as tolerated.

In the presence renal impairment: a target dose of 5 mg twice daily is recommended in patients with renal severe impairment. Creatinine clearance of 5 to 29 ml per minutes is based on the Cockroft-Gault equation. At hepatic impairment: severe use with caution, mild to moderate no dosage adjustment necessary. At pregnancy: FDA category B (animal reproduction studies have shown adverse events, no evidence of risk in studies); patient must use with caution. Effectiveness and safety have not been established for pediatric use.

Main adverse effects are dizziness, headache, confusion, diarrhea, and constipation [25].

Generic dosage forms of memantine as hydrochloride are 24-hour oral extended-release capsules with 7 mg, 14 mg, 21 mg and 28 mg [3, 10, 20], oral solution 2 mg/mL, (360 ml), oral tablet with 5 mg, 10 mg of API. Extended-release capsules may be entire contents of capsule sprinkled on food and swallowed

immediately or swallowed whole. Oral solution must not be mixed with any other liquid; must be administered with provided dosing device supplied with the device consisting of a syringe adaptor cap, or other needed supplies; must be slowly squirt into the corner of the mouth. Time to peak concentrations is three to seven hours for oral immediate-release, nine to 12 hours for oral extended-release. Absorption is 100 % in oral administration with 100 % bioavailability.

The storage condition memantine hydrochloride is room temperature between 20 °C to 25 °C.

Donepezil is the piperidine derivative acetylcholinesterase inhibitor which used to treat the cognitive and behavioral effects of Alzheimer's disease and is used to manage other types of dementia.

Donepezil was first approved in 1996 by the FDA, and its extended-release form was approved in combination with memantine in 2014 to manage severe and moderate forms of Alzheimer's dementia. A donepezil transdermal delivery system was approved by the FDA in 2022 for the treatment of Alzheimer's dementia. Donepezil is effective in managing the symptoms of its associated dementia, though it does not alter the progression of Alzheimer's disease [18].

Donepezil as hydrochloride, administered via transdermal delivery system or orally, is indicated for the treatment of the Alzheimer's type dementia. It is also available as extended-release capsules in combination with memantine produced in other contries for the treatment of moderate-to-severe of the Alzheimer's type dementia in patients previously stabilized on 10 mg of donepezil once daily.

Off-label uses include the management of vascular dementia, Lewy body dementia, and Parkinson's disease-associated dementia, amongst others.

Donepezil improves cognitive and behavioral symptoms and signs of Alzheimer's disease, which may include confusion, apathy, aggression, and psychosis by inhibiting the acetylcholinesterase enzyme.

The commonly accepted cholinergic hypothesis proposes that a portion of a behavioral and cognitive decline associated with Alzheimer's are the result of decreased cholinergic transmission in the CNS. Donepezil reversibly and

selectively inhibits an acetylcholinesterase enzyme, which normally breaks down acetylcholine. The main pharmacological action of this medicine is believed to occur as the result of enhancing cholinergic transmission, the enzyme inhibition, which relieves the Alzheimer's dementia symptoms. Other mechanisms of action of this medicine are possible, including the regulation of amyloid proteins and the opposition of glutamate-induced excitatory transmission via downregulation of NMDA receptors, which have demonstrated significant effects on the Alzheimer's disease process. Other possible targets for the drug may also include the inhibition various signaling inflammatory pathways, exerting neuroprotective effects [22–25].

Donepezil is slowly absorbed after oral administration via the gastrointestinal tract. The C_{max} of 5 mg donepezil tablets is estimated to be 8.34 ng/ml. Tmax is 3–4 hours with a bioavailability of 100% and steady-state concentrations are attained within 15–21 days of administration. The AUC of 5 mg donepezil tablets has been determined to be 221.90–225.36 ng.hr/ml. This medicine is largely distributed in the extravascular compartments. It crosses the blood-brain barrier and cerebrospinal fluid concentrations have been measured at 15.7% at the above doses.

1.2. Combination tablets technologies

Currently there are different technologies of combination tablets may be used. One example is the development of tablets in NPhaU with quercetin and voglibose [31]. At the stage of developing the composition and technology of combination tablets, attention was paid to the choice of disintegrant and lubricant. The addition of excipients that have the property of disintegration makes it possible to reduce the tablets side effects, as well as increase the medicines bioavailability. Disintegrants should have low gel formation, low solubility, good hydration, satisfactory forming properties and flowability, according to the requirements of good manufacturing practice. Sodium starch glycolate may be

used for tablets produced by direct pressing. In this case, the medicine disintegration occurs due to the rapid water absorption. This leads to a significant increase in the volume of tablets and parts of tablets, and causes uniform and rapid disintegration. Another excipient for rapid disintegration is crospovidone, which not soluble in water and used in the concentration of 2–5 % in the technology of tablets by direct pressing. Crospovidone has a hydration capacity and a rapid high capillary action with little tendency to gel formation. In this stydy, model samples of tablets with a concentration of 2–5 % of sodium starch glycolate or crospovidone were obtained to determine a type and concentration of disintegrant. This study was carried out according to the requirements of the SPhU, 2 edition. The authors identified, that both excipients have high rates of disintegration. But sodium starch glycolate at a concentration of 3 % has the minimum time of disintegration. Also the type of lubricant and its concentration in the tablets were determined.

Neusilin, Aerosil, and magnesium stearate have recently been widely used as glidants, lubricants and antiadhesives. Neusilin, Aerosil are moisture regulators at the same time, that is important when creating tablets with solid dispersions (quercetin was in the form of the solid dispersion in this sudy).

The effect of magnesium stearate and aerosil on tabletting mass parameters was investigated as neuselin is part of the solid dispersion. The flowability indicators with the magnesium stearate addition and Aerosil addition was almost the same. At the same time Aerosil, with a contentration of 1 % of the whole mass for tabletting, approaches the calculated indicator. Also, the disintegration time of the obtained model tablet samples was determined. According to the results, it was established that the aerosil addition does not increase the disintegration time of the developed samples. When obtaining tablet samples, sticking to punches was observed when using magnesium stearate. In the case of Aerosil use as an antiadherent, in concentrations of 0.5 % and 1.0 %, sticking to punche and the appearance of external defects of tablets do not occur. To ensure the minimum time of disintegration and an optimal speed, it was advisable to add to the tablets

composition the combination of sodium starch glycolate (3 %) and Aerosil (1 %). In this study the rational composition of tablets was established: active substancies voglibose and quercetin solid dispersion, excipients sodium starch glycolate, and Aerosil. To develop the technology of combination tablets, the vibration compaction coefficient was studied. Such coefficient was determined based on the values of a bulk density; the higher it was, the lower the flowability of the sample under that study. The vibration compaction coefficient also characterized the homogeneity of the size and shape of the particles, the deformation degree, and cohesive properties. The angle of repose and collapse angle were determined to establish the class of flowability, which is the universal school of the flowability assessment (Carr method) applicable to any flowable materials. Taking into account the angle of repose and the angle of collapse, the obtained mass of the quercetin solid dispersion (at the temperature 45–50 °C), has a value of 94 points. In this case, the mass can be attributed to the I class of flowability, which does not require additional excipients and additional equipment. Taking into account the multicomponent composition of the tabletting mixture, the compression pressure was 170 MPa. The developed composition and technology in that study was: active ingredient voglibose — 0.2 mg; quercetin — 50 mg; PEO-6000 — 100 mg; MCC — 25.2 mg; neuselin— 26.1 mg; sodium starch glycolate — 6.1 mg; aerosil — 2.1 mg; total: 210.0 mg [32].

Also currently bilayer tablets are drug delivery systems where combination of two medicines in a single unit having different release profiles can be delivered. Bilayer tablets can deliver two incompatible drugs in a single formulation, may prolong the medicines action and improve patient compliance. Bilayer tablets consist from one layer of active ingredient for immediate release and a second layer for delayed release of medicines, either as a second dose or in an extended release fashion. Bilayer tablets have helpful advancing technologies to overcome disadvantages of single-layered tablets. However, as it is known bilayer tablet technology is resource-intensive. A thorough selection of manufacturing conditions and excipients for each technical stage is also required. Patients with high blood

pressure and Alzheimer's disease often have difficulty or are unable to regulate their symptoms and bad condition with just a single medication. The majority of hypertension patients and with Alzheimer's disease will need to take two or more medicines in order to meet treatment goals. Combinations of medicines from various categories have been found to be more effective than either medicine alone in treating in people with hypertension and with Alzheimer's disease whose blood pressure and good condition of body cannot be maintained satisfactorily with monotherapy. Combining two medications with mutually beneficial mechanisms of action may result in much greater blood pressure lowering efficacy and Alzheimer's disease treatment than any of these components alone.

Thus, currently there are several technologies for obtaining combination tablets with two active substances [33].

Conclusions to chapter 1

1. Treatment of dementia is currently an important problem in modern medicine. Memantine and donepezil combination may be used to treat dementia (mental changes and memory loss) associated with moderate or severe Alzheimer's disease. Donepezil and memantine can not cure Alzheimer's disease, however, this combination improve thinking ability, behavior, or functional ability.

2. According to the results of physicochemical and technological studies, the composition and rational technology of combination tablets of donepezil and memantine may be established.

CHAPTER 2
THE JUSTIFICATION OF THE RESEARCHES GENERAL CONCEPT. OBJECTS AND METHODS OF RESEARCHES

2.1 Methodological approaches to the development of the composition and technology of tablets with memantine and donepezil

In this chapter 2 objects and methods of researches, most full reflective essence and character of the conducted work, are presented in decision of this problem of development of tablets of memantine and donepezil. Materials are expounded in obedience to the sequence of the conducted scientific researches.

2.2. Specification of memantine and donepezil and excipients as research objects

Description of Memantine hydrochloride: chemical name is 1-amino-3,5-dimethyladamantane hydrochloride, is a white to off white crystalline solid powder, not hygroscopic (Hetero Drags Limited (India)).

Synonym: 3-5-dimethyltricyclo [3.3.1.13,7]decan-1-amine hydrochloride; 3,5-dimethyl1-adamantanamine hydrochloride; 1-amino-3,5- dimethyladamantane (fig. 2.1)

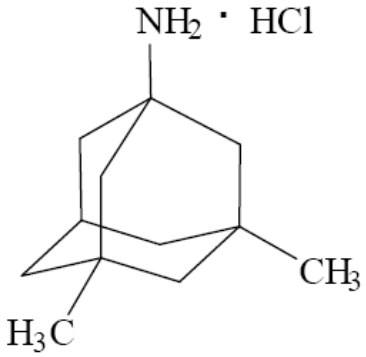

Fig. 2.1. Memantine hydrochloride chemical structure

Molecular formula of Memantine hydrochloride: C12H21N•HCl. Molecular weight: 215.76 g/mol. Melting Point: 258 °C, 295 °C (varying reports). This

product is soluble in water (1 mg/ml), yielding a clear, colorless solution, soluble in dimethyl Sulfoxide (DMSO) (43 mg/ml at 25 °C), and ethanol (43 mg/ml at 25 °C), soluble in ethanol and methanol, practically insoluble in acetone and in ethyl acetate.

Memantine hydrochloride is the first drug to be approved by US FDA, manufactured as Torrent Pharmaceuticals Ltd [33].

This product must be store at room temperature.

Memantine hydrochloride has a non-chiral molecular structure. Polymorphism has been observed for this product. The manufacturing process consistently produces the same crystalline form of memantine hydrochloride, form I. The crystalline form does not change upon storage.

Donepezil chemical name chemical name (IUPAC) is 2-[(1-benzyl-4-piperidyl)methyl]- 5,6-dimethoxy2,3-dihydroinden-1-one hydrochloride monohydrate. Description of donepezile hydrochloride or 1H-Inden-1-one, 2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-, hydrochloride (fig. 2.2): empirical formula (Hill Notation): $C_{24}H_{29}NO_3 \cdot HCl$, molecular weight: 415.95.

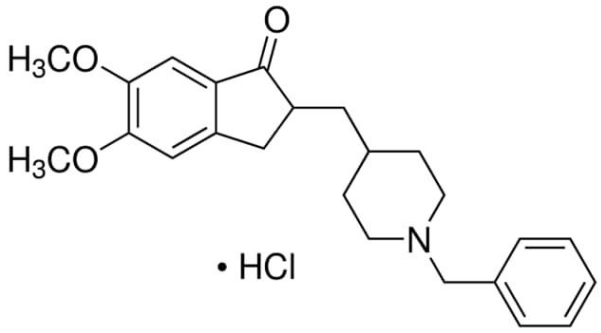

Fig. 2.2. Donepezile hydrochloride chemical structure

Donepezil hydrochloride is a reversible inhibitor of acetylcholinesterase. It produces its therapeutic effects by increasing the concentration of acetylcholine and enhancing the cholinergic function in the brain. Active substance is used for the treatment of mild-to-moderate dementia associated with Alzheimer's disease. Melting point is 220–222 °C. The aqueous solubility of donepezil hydrochloride is

more 20 mg/ml. Therefore, it is considered to be a highly water-soluble active pharmaceutical ingredient.

Excipients used in the formulation of tablets were all compendial, well-known and widely used for this dosage form. The excipients used include: microcrystalline cellulose (filler), colloidal anhydrous silica (glidant), croscarmellose sodium (disintegrant) and magnesium stearate (lubricant).

Microcrystalline cellulose (MCC) is a pure partially depolymerized cellulose synthesized from α-cellulose precursor (type Iβ), obtained as a pulp from fibrous plant material, with mineral acids using hydrochloric acid to reduce the degree of polymerization. The moisture content of MCC influences compaction properties, tensile strength, and viscoelastic properties. Moisture within the pores of MCC may act as an internal lubricant, reduce frictional forces, and facilitate slippage and plastic flow within the individual microcrystals. The lubricating properties of water may also reduce tablet density variation by providing a better transmission of the compression force through the compact and by decreasing the adhesion of the tablet to the die wall. Compressibility of MCC depends on moisture content, which means that when MCC having different moisture content is compressed with the same pressure, it may not result in the same compact porosity. It is very well known that compaction pressure required to produce certain porosity (or solid fraction) decreases with increasing moisture content. Sun reported that below 3% water content, the compaction properties of MCC were insensitive to variation of moisture. However up to an optimum level, an increase of moisture will increase the tablet strength of most excipients. This can be explained by the fact that molecular binding in water vapor layers reduces interparticular surface distances, hence increasing intermolecular attraction forces [34].

MCC is one of the types of filler which is water insoluble having swelling tendencies and excellent water imbibing or wicking action. Other filler examples with the same property are calcium pectinate and sodium alginate. This property makes MCC as also an excipient of choice for wet granulation. Both Avicel PH 101 and Avicel PH 102 can be used advantageously as fillers in wet granulation in

a concentration of 5.15%. When used as filler in wet granulation method, the wicking action of MCC promotes rapid wetting of the powder mix. Another advantage offfered by using MCC as wet granulation filler is the ability to retain water, which makes the wet mass less sensitive to overwetting due to an excess of granulating fluid. The milling of the wet mass will be much easier due to less clogging of the screen; hence it will produce a more uniform granules. Drying process also will be more homogeneous, and the case of hardening can be reduced. Case hardening is a phenomenon which is observed in incompletely dried granules. This case happened when the granules are dried at a high temperature, from which the inside part of the granules remains wet, while the surface seems dried. The granules are often hard and resist disintegration. When coming to compaction process, the compression forces will break the granules and deform plastically to form soft tablets due to the moisture coming out of the incompletely dried granules. The use of Avicel PH 101 or Avicel PH 302 as filler in wet granulation promotes rapid wetting as a result of the wicking action of MCC. They reduce sensitivity of the wet mass to overwetting and increase the drying process speed. Since there is fewer excess of granulating fluid, screen blockages and case hardenings can be reduced. Homogeneous and uniform granule when MCC is used as wet granulation filler will reduce dye migration. When MCC is employed, faster disintegration from granules and tablets will be obtained.

MCC has benefits in wet granulation. Basically, using MCC in wet granulation included wetting MCC with water followed by drying and compression. The process resulted in lower hardness tablets than that with dry compression. The wet granulation reduces the density of agglomerated particles thereby decreasing their internal surface area. In contrast, it can also cause adhesion between particle agglomerates, reducing external surface area resulting in less particle interlocking and hydrogen bonding. In general, using Avicel PH-101 or Avicel PH-102 in wet granulation formulations with concentration between 5 and 20% offers the following benefits:

– Rapid adsorption of water by MCC and distribution through the mixture;

– Decrease of sensitivity to water content, wet screening, and localized overwetting due to the large surface area of MCC, hence high adsorptive capacity;

– Increased drying efficiency;

– Decreased color mottling;

– Better drug content uniformity;

– Higher tablet hardness at the same compression force with less friability.

Croscarmellose Sodium is a cross-linked carboxymethylcellulose, for use as a superdisintegrant in pharmaceutical formulations. Unlike conventional disintegrants, croscarmellose sodium can be utilized in low concentrations and still impart exceptional disintegrating properties to the final dosage forms. Benefits of croscarmellose sodium are faster disintegration due to large particle size, does not contain peroxides – for better API stability, fast water absorption, flexible in use and good tablet dissolution for a wide variety of applications.

Polyvinylpyrrolidone (fig. 2.3) is a powder that Synonyms are PVP, Polyvidone, Povidone, Polyvinylpyrrolidone.

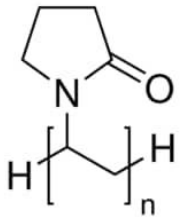

Fig. 2.3. Polyvinylpyrrolidone chemical structure

Polyvinylpyrrolidone or povidone is a hygroscopic, amorphous, synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups. As a binder, PVP is used in the concentration range of 0.5%–5% w/w. Different degrees of polymerization of PVP resulted in polymers of various molecular weights. It is generally characterized by its viscosity in aqueous solution relative to that of water and expressed as a *K* value in the range of 10–120. Povidones with *K*-values ≤ 30 are manufactured by spray drying as spheres, whereas povidones with higher *K*-values are manufactured by drum drying as plates. Wet granulation with povidone

K25/30/90 generally gives harder granules with better flow properties than with other binders with lower friability and higher binding strength. Moreover, povidone also promotes the dissolution of APIs [35].

Colloidal silicon dioxide (Aerosil® Pharma) has been used as a pharmaceutical adjuvant. Classified as a nanomaterial with an average particle size around 30 to 40 nm, it is an amorphous solid consisting of highly pure silicon dioxide. The mode of action enhances powder flow over the pure excipient (glidant application). The type and concentration of colloidal silicon dioxide depends on the physical properties of the powder, i.e., composition, particle shape and size, and the processing equipment [36].

2.3. Methods of researches

2.3.1 Formulation of tablets

The tablets formulation consisting of memantine and donepezil and all other ingredients was prepared through wet granulation, and the granules were subsequently dried in the oven at 40 ^{o}C for 8 h. These were then directly compressed into round, beconvex tablets with a tablet press, filling an average weight of 200 mg. Obtained tablets were approximately 7,0 ± 0,2 mm in diameter and 3,1 ± 0,3 mm in height.

2.3.2 Evaluation of granules (pre-compression parameters)

The granules consisting of memantine hydrochloride and donepezil hydrochloride and excipients were evaluated using flow properties, determined with angle of repose and compressibility parameters, as well as tapped and bulk density [29, 30].

2.3.3 Evaluation of memantine and donepezil tablets (post-compression parameters)

2.3.3.1 The thickness and weight variation of tablets.

A total of 20 tablets per formula were measured for thickness testing, using a Vernier Caliper. Also, 20 tablets were individually weighed using an electronic

balance, and the values obtained were compared to the average tablet weight, and the results presented as mean ± standard deviation (SD).

2.3.3.2 Hardness.

This test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing. The hardness of 10 tablets with memantine and donepezil for each formula was determined using the tablet hardness tester instrument, and the results presented as mean ± SD.

2.3.3.3 Friability

Twenty tablets with memantine and donepezil from each formula were accurately weighed and placed in tablet friability tester, which rotated at 25 rpm for 4min. These were subsequently brushed and reweighed, and then the percent of weight loss was calculated using the formula:

% friability = ([initial weight – final weight]/initial weight) × 100.

2.3.3.4 Disintegration time

The disintegration time analysis of tablets with memantine and donepezil was conducted according to the State Pharmacopoeia of Ukraine (SPhU), using a disintegration tester instrument containing the water medium maintained at 37°C ± 0.5°C.

2.3.3.5 Stability test

Stability studies of tablets with memantine and donepezil were conducted at 40 oC with relative humidity (RH) 75%, and also at room temperature (25 oC) with 75% RH for 30 days.

2.3.3.6 Statistical analysis

The experimental data, including in vitro study and physical stability presented as mean of samples ± SD, were statistically analyzed using one-way analysis of variance method.

Conclusions to chapter 2

1. Methodological approaches to the development of tablets based on memantine and donepezil are proposed.

2. The characteristics of memantine and donepezil and excipients that were used in the development of tablets are given.

3. The methods of pharmaco-technological researches necessary for development of composition tablets with memantine and donepezil are defined.

CHAPTER 3.
EXPERIMENTAL PART.
EVALUATION STUDIES OF PHARMACO-TECHNOLOGICAL PROPERTIES OF GRANULES AND TABLETS CONTAINING MEMANTINE AND DONEPEZIL

3.1 Study of physical-chemical and technological properties of memantine hydrochloride and donepezil hydrochloride

The crystallography structure of powdery materials, including medicinal matters, determines their pharmaco-technological characteristics**:** by volume properties, flowability, compressibility and other [29, 31]. Crystallography researches of powders allow forecasting the rational choice of technological methods at development of technology tableted medicinal preparations.

All of powdery matters consist of the polydisperse systems, having various forms and sizes of crystalline particles.

For the choice of optimum technological parameters and modes of receipt of tablets we studied microscope descriptions and pharmaco-technological properties of powder memantine hydrochloride and donepezil hydrochloride.

Most full the real structure of medicinal powder can be passed a microscopic method. Study of form and sizes of particles, and also the middle size of their dominant factions was carried out on the microscope of MBI-15 at an increase in 75-340 times.

The memantine hydrochloride particles appears smooth and crystalline with an average particle length of 100 μm and width of 10 μm (fig. 3.1).

The micrographs obtained for the substance donepezil hydrochloride showed tile shaped crystals of uniform size and low thickness. The crystals of donepezil hydrochloride have a rough surface, that stipulates enhanceable force of friction between particles (fig. 3.2). The donepezil hydrochloride particles have an average length of 140 μm, width of 120 and thickness of 5 μm.

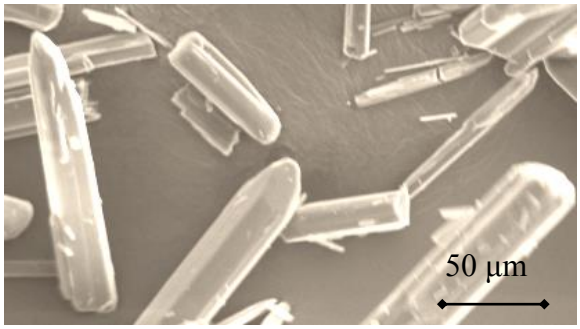

Fig. 3.1 Memantine hydrochloride particles

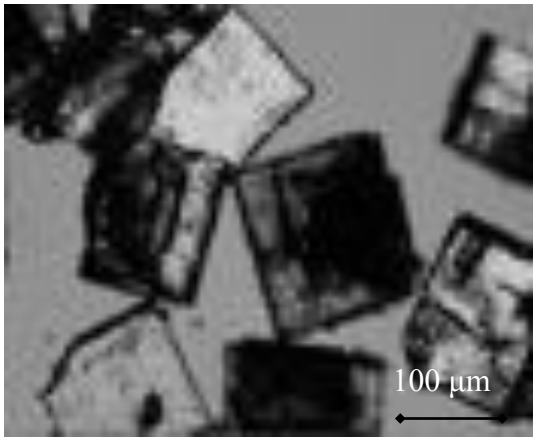

Fig. 3.2 Donepezile hydrochloride particles

Microscope observations have demonstrated that due to the compound surface of particles and constant particles cohesion the active substances has insufficient pharmaco-technological characteristic, namely flowability.

For the choice of optimum technological parameters and modes of tablets obtaining we studied also pharmaco-technological properties of memantine hydrochloride and donepezil hydrochloride (tabl. 3.1).

The analysis of pharmaco-technological properties of the test substance (table 3.1.) shawed that memantine hydrochloride and donepezil hydrochloride has not sufficient values of flowability (115±4,5 sec/100 g of sample and 93 ± 3,5 sec/100 g of sample), about what the angle of repose and fine-dispersed particles of powder testifies also. Compressibility of substances also not quite satisfactory (11 ± 0,5) and (9 ± 0,5) N.

The results of pharmacotechnological researches have shown that memantine hydrochloride and donepezil hydrochloride with poor flowability have large bulk volume. That is predetermined application of special excipients.

Table 3.1

Pharmaco-technological and physical-chemical properties of memantine hydrochloride and donepezil hydrochloride

Investigated characteristics of substance	Measure	Values for memantine hydrochloride	Values for donepezil hydrochloride
1. Bulk volume (100 g of sample)	ml	185,2 ± 0,09	197,1 ± 0,09
2. Bulk density before/after compaction (m/V1250)	g/ml	0,54 ± 0,05 /0,65±0,02	0,51 ± 0,05 /0,67±0,02
3. Flowability	sec/100 g of sample or (g/sec)	115 ± 4,5 (0,87 ± 0,05)	93 ± 3,5 (1,07 ± 0,05)
4. Angle of repose	degree	52 ± 2,0	59 ± 2,0
5. Compressibility	N	11 ± 0,5	9 ± 0,5
6. Ejection force	MPa	43,0 ± 0,4	41,0 ± 0,4
7. Specific humidity	%	4,0 ± 0,3	2,5 ± 0,3

Note: In the table mean values are presented from five measurings.

It predetermined the application of excipients for improvement technological properties of substance when formulating of tablet mass.

Pharmaceutical substances of memantine hydrochloride and donepezil hydrochloride salt have unsatisfactory technological properties, which can complicate the processes of die filling and dosing of pharmaceutical substances during tableting.

Wet granulation is preferred in this case as it can help to improve the flowability and compressibility of the powders, resulting in more uniform and consistent tablets.

3.2 The evaluation of granules

The manufacturing process of combination tablets consists of five main steps: (1) mixing, (2) blending (3) compression, (4) film coating and (5) packaging. The process of combination tablets is considered to be a standard manufacturing process. The manufacturing process of combination tablets has been adequately described and the critical steps have been identified. Adequate flow-charts were provided and the different steps of the manufacturing process of combination tablets are described, together with equipment type and operating parameters. The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in-process testing as well as the results of finished product (combination tablets) testing.

The objective was to develop a combination tablet formulation containing memantine hydrochloride and donepezil hydrochloride. The manufacturing process retained after different trial formulations was a method by direct compression. The active pharmaceutical ingredient memantine hydrochloride is classified as a highly soluble drug substance. In addition, parameters such as water content, and particle size of the active pharmaceutical ingredient were studied and controlled during the pharmaceutical development. In order to improve disintegration time, the developed formulae were further optimized for the composition. Satisfactory dissolution and stability at 40 °C and 75 % RH were achieved with the final formulation of combination tablets. The chosen excipients are widely used for this immediate-release dosage form as combination tablets, and they are microcrystalline cellulose as filler, croscarmellose sodium as disintegrant, PVP as binder, magnesium stearate as lubricant. All the excipients are of compendial grade. There are no compatibility concerns with the proposed excipients in these

tablets, as is demonstrated in long-term and accelerated testing and supporting compatibility screening studies of binary mixtures.

The excipients used are memantine and donepezile tablets are standard pharmacopoeial excipients for solid oral dosage forms. Such materials comply with Ph.Eur. requirements. Stability studies of memantine and donepezile tablets have been performed and confirm the appropriateness of the packaging.

The manufacture of memantine and donepezile tablets can be summarised in the following main steps: blending and sifting of the ingredients (active substances and excipients), mixing, then compression, coating of the tablets and packaging. Appropriate in-process controls such as assay, uniformity of weight, hardness have been applied during the manufacture of the combination tablets. A process validation protocol at pilot scale has been provided as well as validation results on three pilot batches for the 10 mg tablets. Results showed that the combination tablets could be manufactured reproducibly according to the agreed finished product specification. Tablets were made in five formulas namely F1, F2, F3, F4 and F5. The five formulas had different ratios of PVP as the binding agents of 200 mg tablet (Table 3.2).

Table 3.2

Tablets formula of memantine and donepezil

Materials	Formula (%)				
	1	2	3	4	5
Memantine 20 mg and donepezil 10 mg	15	15	15	15	15
Croscarmellose sodium	1.5	1.5	1.5	1.5	1.5
PVP	1.5	1.6	2	2.7	5
Magnesium stearate	1	1	1	1	1
Colloidal silicon dioxide	2	2	2	2	2
MCC ad to	100	100	100	100	100

Tablets Production

All materials were prepared and weighed. The memantine and donepezil was put into the container, MCC, croscarmellose sodium were added and stirred resulting in a homogeneous mixture. The PVP solution was prepared by dissolving it in the water before mixing. PVP solutions were added slowly and stirred to be homogeneous and mass was wet enough could be formed into granules.

The granules was sieved using a 12-mesh sieve and then put into an oven at 40 ° C for ± 8 hours. The granules were then sieved back with an 18-mesh sieve. The magnesium stearate and colloidal silicon dioxide were added and mixed homogeneously. The granule evaluation was then conducted. The granules were prepared and put into the hopper. The tablet weight and hardness were set. The upper punch was set if the tablet weight was less than 200 mg. The engine ran until all granules transform into tablets.

The evaluation of granules included the flow time, the angle of repose, the compressibility, the granule size distribution and the loss on drying.

The purpose of the granule evaluation is to examine the quality of granules in each formula concerning the excellent granule requirements meeting the requirements for the compression process to tablets.

The granule loss on drying (LOD) test aims to investigate how many volatile materials include water in the drying process and to determine the moisture of the granules. The results (table 3.3) showed that the sample F1 resulting a greater LOD value than F2, while F5 had the biggest LOD value. This is due to the amount of solvent in each formula (table 3.3).

The LOD values in F2, F3 and F4 were not significantly different since the PVP concentration was not as large as F1. The results of the LOD value test of granules in all formulas meet the requirements of 3-5 %. The LOD value of the granules may affect the nature of the tablet produced. It is concerned that the large LOD value may contribute to the attachment of granules on the punch at the time of printing which in turn can affect the weight and size of the tablet produced. The

results of the granule flow time test of the five formulas met the requirements of the flow time.

Table 3.3

The results of the granule of memantine and donepezil evaluation

Formula	Flowability (g/sec)	Angle of Repose	Compres-sibility or Carr`s index (%)	LOD (%)	Granule size (μm)
F1	3,21 ± 0,15	43º	2,7 ± 0,25	3,27 ± 0,23	798
F2	3,76 ± 0,65	35º	2,8 ± 0,32	3,28 ± 0,15	813
F3	5,51 ± 0,35	29º	2,6 ± 0,08	3,45 ± 0,27	817
F4	5,74 ± 0,15	31º	2,6 ± 0,21	3,70 ± 0,15	826
F5	6,09 ± 0,12	27º	2,5 ± 0,12	4,38 ± 0,45	859

The inappropriate amount of the binder will reduce the bonding between the granules particles (cohesive force), consequently the particle size is not good enough and the granules are difficult to flow. The results showed that F5 has the best flow properties, indicating that the binder is the best to obtain the optimal granule cohesive force so that the granules can flow smoothly. Flow time is also affected by the moisture of the granules.

The repose of the angle test aimed to examine the flow properties of the granules when subjected to the tableting process. The angle of repose is the fixed angle between the cone-shaped particles and the horizontal plane. The results presented that the angle of repose in the five formulas were different.

The difference may be affected by the cohesiveness of the granules caused by the binder. The shape, size and moisture of the granules influence the magnitude of the repose angle. The value of repose angle ranges from 25^{o} to 45^{o}.

The five formulas met the requirements of the repose angle. The measurement of the granular particle size distribution to determine the granule size and depth was necessary because it can affect the mixing process. Based on the

results of the study, the granules left in the 18-24 sieve was the heaviest. A relatively small size granule has smaller internal porosity contributing to the greater cohesion force and causes the granules to pass the mesh size of the larger sieve hardly. The larger particles of granules tend to separate from the smaller particles and move downward while small particles will rise.

The larger PVP concentration in the binder can lead to an increase in the sensitivity of PVP as a binder. The size of the granules that generally falls on the 12-20 sieve is 840-1680 μm.

The large granule size will decrease the granule mass density. Smaller granules can form a more compact mass than larger granules. The result of the granular compressibility index test after the determination on 100 ml granule for F1 to F5 satisfied the requirement of good flow property category, the compressibility ≤ 20%. The granular density influences the compressibility of the granules leading to the decreased internal porosity of the granules to increase the hardness of the tablets produced. Thus, the cohesive forces between the granules and the decreased porosity of the granules increased the compressibility values in F5.

3.3 Researches of quality parameters of the obtained tablets

The tablets evaluation included the organoleptic, uniformity size, weight uniformity, tablet fragility and tablet hardness tests.

The purpose of the tablet evaluation is to examine the quality of tablets in each formula concerning the requirements of good tablets. The tablet evaluation includes colour, shape, taste, weight uniformity, uniformity size, tablet hardness and tablet fragility.

Details of tablet evaluation results can be seen in Table 3.4.

The obtained tablets of all formulas were white, round and spicy-sweet. The round shape is adjusted to the availability of the punch for a tablet weight of 0.2 g.

Tablets shape generally are round but it can also be oval or other shapes. In the pharmaceutical industry, tablet shape is used as a product.

Table 3.4

The tablets test results

Evaluation	F1	F2	F3	F4	F5
Organoleptic:					
a. Shape	round, beconvex	round, beconvex	round, beconvex	round, beconvex	round, beconvex
b. Smell	Specific	Specific	Specific	Specific	Specific
c. Color	White	White	White	White	White
Thick (mm)	3.1 ± 0,3	3.1 ± 0,2	3.1 ± 0,3	3.1 ± 0,2	3.1 ± 0,3
Diameter (mm)	7.0	7.0	7.0	7.0	7.0
Weigh (g)	0,208 ± 0,005	0,205 ± 0,005	0,206 ± 0,004	0,208 ± 0,003	0,207 ± 0,006
Friability (%)	0.74 ± 0,01	0.77 ± 0,01	0.67 ± 0,01	0.63 ± 0,01	0.47 ± 0,01
Hardness (N)	60 ± 1	61 ± 1	69 ± 1	75 ± 1	83 ± 1

The tablet weight uniformity test was performed by testing the weights of 20 tablets per formula. The results of the test for F1 to F5 fulfilled the requirement as no two tablets having a weight deviation of 5% from the mean tablet weight and no one tablet having weight deviation of 10% from the average weight.

The tablet size uniformity test was performed by measuring the diameter and thickness of the tablet. There was no difference in diameter and thickness of the tablets as they were determined by the size of the punch. If there was a difference in thickness of the tablet, it might be due to the moisture of granules causing a granule attached to the punch.

However, there were differences in the thickness of the tablets due to the rise and fall of punch in the die hole. This study used a single punch tablet machine

with only a pair of punch. The downward movement of the bottom punch along with the up movement of punch to a certain distance during the process of filling the die hole resulted in the granule down due to the gravitational effect. The distance between the punch can be different, therefore there was a thickness difference in the tablets produced yet it was not significant.

The results (table 3.4) reported that all formulas had different hardness values; F1-F4 have lower hardness. The characteristic of PVP is that the higher concentration dissolved in water, the stronger the liquid bridge formed; so that the drying process of the solid bridge formation is also stronger resulting in reduced granular porosity increasing the greater granule density and the tablet hardness. When it is exposed to the pressure on the machine, the tablet becomes moist and the bond strength between granular particles is decreased resulting in reduced tablet hardness [31].

The tablets fragility test was performed to determine the tablet physical stability from mechanical shock effects during the manufacturing, packing and transportation process. The results of tablet fragility test obtained from F1 to F5 fulfilled the requirement that was below 0.8% due to the character of the binder components. The properties of gelatine that can absorb water into its bonds, result in a more spherical and homogeneous granule and increase the cohesion force between granular particles leading to increase tablet hardness and decrease the tablet fragility value.

The PVP characteristic is that the higher the concentration dissolved in water, the stronger the liquid bridge is formed; thus, the process of drying solid bridge formation is also stronger which in turn reduce the granular porosity and increase the granule density leading to increase the tablet hardness and reduce the tablet fragility.

Therefore, tablet hardness decreases, and tablet fragility increases.

Research on physical-chemical stability of medicinal preparation in form of tablets, containing Memantine and donepezil, in air-tight were carried out.

The tablets, containing Memantine and donepezil, were stable during three months.

The 3-5 % solutions of polyvinylpyrrolidone were utillized for the study of concentration influence of binders on granulates pharmaco-technological properties and tablets quality parameters.

As the slide information indicates technological characteristics of granules, obtained with 5 % solution of polyvinylpyrrolidone, were the best.

Croscarmellose sodium was added for providing optimum tablets disintegration. Disintegration time of tablets with 2 % croscarmellose sodium was 10 min.

Colloidal silicon dioxide was added in the tablets composition in an amount 2 % as a glidant besides a lubricant 1% magnesium stearate.

Thus, the next composition of tablets was offered on the basis of researches (table 3.5).

Table 3.5

The tablets composition

Components	mg	(%)
Memantine hydrochloride	20	10
Donepezil hydrochloride	10	5
MCC	151	75.5
Croscarmellose sodium	3	1.5
PVP	10	5
Colloidal silicon dioxide	4	2
Magnesium stearate	2	1
Total	200	100

Conclusions to chapter 3

1. The composition of tablets containing memantine and donepezil have been developed as a result of experimental researches.

2. Excipients influence is estimated on the technological characteristics of granules and parameters of quality of the ready tablets with memantine and donepezil.

3. This drug development approach using two substances can be a platform for formulating tablets products with small doses.

GENERAL CONCLUSIONS

1. Monotherapy is ineffective in many cases of treatment, and many individuals will develop severe side effects at larger doses of a single drug. In this broad population of patients, fixed-dose combination medicines are an appropriate and beneficial therapeutic option. Combination tablets present an ideal chance for producers to differentiate themselves from competitors, increase the efficacy of product, and safeguard against counterfeit items. Significant advancements in a manufacture of tablets have been made recently. This has resulted in the improvement of physicochemical qualities of tablets.

2. As a result of analysis of data of literature as evaluated by the modern state of production and application of medicinal preparations in the form of tablets the necessity of creation of preparation for the treatment of cognitive disorders is grounded in the form of compressed tablets .

3. The complex of theoretical and experimental researches is conducted on development of composition of medicine in form of tablets on the basis of memantine hydrochloride and donepezil hydrochloride.

4. Physical and chemical and pharmaco-technological properties of powder of memantine hydrochloride and donepezil hydrochloride, allowing to ground composition of tablets on its basis, are studied.

5. Research on physical-chemical stability of medicinal preparation in form of tablets, containing memantine and donepezil, were carried out.

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APPENDIX

ANNEX A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ДИПЛОМ

II СТУПЕНЯ

нагороджується

Guerbi Amel

у секційному засіданні студентського наукового товариства кафедри технологій фармацевтичних препаратів

XXIX Міжнародна науково-практична конференція молодих вчених та студентів

«Актуальні питання створення нових лікарських засобів»

В.о. ректора
Національного фармацевтичного університету

Алла КОТВІЦЬКА

19-21 квітня 2023 р.
м. Харків

ANNEX B

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

СЕРТИФІКАТ УЧАСНИКА

Цим засвідчується, що

Guerbi A., Kryklyva I.O.
Scientific supervisor: Sichkar A.A.

брав(ла) участь у роботі
XXIX Міжнародної науково-практичної конференції молодих вчених та студентів
«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»

В.о. ректора
Національного фармацевтичного
університету

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Національний фармацевтичний університет
№02010936

Алла КОТВІЦЬКА

19-21 квітня 2023 р, м. Харків

ANNEX C

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ`Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

МАТЕРІАЛИ
XXIX МІЖНАРОДНОЇ НАУКОВО-ПРАКТИЧНОЇ
КОНФЕРЕНЦІЇ МОЛОДИХ ВЧЕНИХ ТА СТУДЕНТІВ

19-21 квітня 2023 року
м. Харків

Харків
НФаУ
2023

been proved. Literature data suggest a scientific and practical importance of the study of medicinal raw material for creating new medicines.

The conducted analysis of the current state of production of solid dosage forms in the form of capsules.

As active substances, a mixture of medicinal herbal raw materials is proposed, which is characterized by stimulation of bile secretion, anti-inflammatory action, relieving spasm of the sphincters of the biliary tract, and changing the composition of bile. The physicochemical and technological parameters of this mixture were studied.

The expediency of use is substantiated and the number of excipients in the composition of the proposed preparation, such as potato starch and calcium stearate, is experimentally confirmed. Was studied influence of excipients on technological figures of obtained granules. It was established that the best moisturizer for mixture, that encapsulated, is 5% potato starch.

Moisture research showed high hygroscopic of obtained granulate allows to make a conclusion about advisability of creation of a dosage form as capsules.

Conclusions. Development of composition of the capsules for the treatment of the biliary excretory system diseases was conducted.

DEVELOPMENT OF THE COMPOSITION OF COMBINATION TABLETS FOR DEMENTIA TREATMENT

Guerbi A., Kryklyva I.O.
Scientific supervisor: Sichkar A.A.
National University of Pharmacy, Kharkiv, Ukraine
antoneo@ukr.net

Introduction. According to the World Health Organization (WHO), dementia is a syndrome in which there is a progressive deterioration in cognitive function beyond what might be expected from normal aging. This deterioration can include impaired judgment, memory loss, and difficulty with communication, language, and daily activities. Each type of dementia has its own etiology. Alzheimer's disease is the most common type of dementia and is caused by the accumulation of amyloid plaques and neurofibrillary tangles in most commonly used treatments for dementia include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which can improve memory and thinking by increasing levels of a neurotransmitter called acetylcholine in the brain, and memantine, which works by blocking the action of a neurotransmitter called glutamate in the brain and can help to slow down the progression of symptoms in people with moderate to severe dementia.

Aim. Currently, pharmaceutical companies in Ukraine do not produce combination tablets with memantine and donepezil. But such combination has certain advantages. The addition of memantine to donepezil is associated with a favorable risk/benefit ratio in the treatment of patients with moderate to severe Alzheimer's disease and provides additional benefits for patients, caregivers and society at large. The aim of our researches was to study technological characteristics of these active pharmaceutical ingredients, choose excipients for the creation of tablets with memantine hydrochloride and donepezil hydrochloride.

Materials and methods. All excipients in the composition were standard excipients of pharmaceutical quality. We used generally accepted research methods according to the State Pharmacopoeia of Ukraine.

Results and discussion. A targeted search for acceptable compositions allowed us to determine the list of auxiliary components necessary for the creation of tablets with memantine hydrochloride and donepezil hydrochloride. As a result of research, the composition of tablets was developed, including filler-binder, desintegrant and lubricant.

Conclusions. The results of the research have been showed that excipients for tablets with memantine hydrochloride and donepezil hydrochloride were selected correctly, since the technological and physical and chemical parameters of obtained tablets were within the limits of optimal values.

BIOLOGICALLY ACTIVE SUBSTANCES OF BLACK POPLAR (POPULUS NIGRA L.) AS A PROMISING COMPONENT OF MEDICINES

Poliakov D.I.
Scientific supervisor: Vyshnevska L.I.
National University of Pharmacy, Kharkiv, Ukraine
poliakov.d@i.ua

Introduction. The growing demand for new biologically active substances (BAS) derived from natural sources has significantly intensified research efforts aimed at discovering and studying potential medicinal plants. Black poplar (Populus nigra L.), a widespread deciduous tree from the Salicaceae family, has great potential to meet demand. The current research is aimed at studying the potential of black poplar (Populus nigra L.) for the development of new medicinal products (MPs), taking into account its phytochemical composition and traditional use in medicine. Thus, the historical use of Populus nigra L. in medicine, the latest scientific data on the BAS isolated from this raw material and their therapeutic use indicate the relevance of conducting more extensive research, studying the mechanisms of action and further clinical use of new drugs.

Aim. The aim of the study is to identify various BAS presented in black poplar and to evaluate their pharmacological properties. Along with this, the study aims to determine the main mechanism of action of the identified components of Populus nigra L., to study the possibilities of their therapeutic use and clinical benefits, and to assess their safety.

Materials and methods. The study has a comprehensive approach, using in vitro and in vivo experiments to identify the therapeutic potential of black poplar. The research methodology includes: a comprehensive literature review on the traditional use of Populus nigra L., pharmacological properties and bioactive components; extraction of individual parts of Populus nigra L., in particular, the buds, using various solvents such as ethanol, methanol, water and others; phytochemical analysis using liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance spectroscopy (NMR); evaluation of antioxidant, anti-inflammatory, analgesic, antimicrobial and antitumor properties of extracts using cellular assays, enzyme inhibition assays and in vivo models, evaluation of the toxicity of extracts and compositions obtained from Populus nigra L., in accordance with the standard recommendations, which may not be limited to the above methods.

Results and discussion. The study of Populus nigra L., which have been conducted previously, revealed the presence of bioactive substances in black poplar extracts, including flavonoids, phenolic acids, terpenoids, etc. The experiments have shown that these components have significant antioxidant, anti-inflammatory, analgesic, antimicrobial, antitumor and other properties. The research results also showed the effectiveness of the extracts in mitigating oxidative stress and

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Technologies of Pharmaceutical Preparations

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Technologies of
Pharmaceutical
Preparations

_____
Oleksandr KUKHTENKO
"__" __of_____ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Amel GUERBI

1. Topic of qualification work: «Development of the composition of combination tablets for dementia treatment», supervisor of qualification work: Antonina SICHKAR, PhD, assoc. prof.

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

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

3. Outgoing data for qualification work: to evaluate of pharmaco-technological properties of granules and tablets containing memantine hydrochloride and donepezil hydrochloride, to develop of the composition of combination tablets

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

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

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Antonina SICHKAR, professor of higher education institution of department Technologies of Pharmaceutical Preparations	20.05.2022	20.05.2022
2	Antonina SICHKAR, professor of higher education institution of department Technologies of Pharmaceutical Preparations	21.01.2023	21.01.2023
3	Antonina SICHKAR, professor of higher education institution of department Technologies of Pharmaceutical Preparations	18.02.2023	18.02.2023

7. Date of issue of the assignment: «_ _ ___» _____ 2023.

CALENDAR PLAN

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

An applicant of higher education _____ Amel GUERBI

Supervisor of qualification work _____ Antonina SICHKAR

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**				
Гербі Амель	Розробка складу комбінованих таблеток для лікування деменції	Development of the composition of combination tablets for dementia treatment	доцент Січкар А.А.	професор Бобрицька Л.О.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 114406 від «31 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Гербі Амель, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Розробка складу комбінованих таблеток для лікування деменції / Development of the composition of combination tablets for dementia treatment», 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**

1%

31%

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

Amel GUERBI

on the topic: «Development of the composition of combination tablets for dementia treatment»

Relevance of the topic. Taking into account the current state of medicines of domestic production for the treatment of dementia, development and introduction into the manufacture of a medicine on the basis of memantine and donepezil in the form of tablets is relevant.

Practical value of conclusions, recommendations and their validity is the possibility of using the results of research for the further introduction into the industrial production of composition for obtaining tablets based on memantine hydrochloride and donepezil hydrochloride.

Assessment of work. According to the form and content of the qualification work of the student corresponds to the current requirements, is an independent study, in which the student showed knowledge about a particular subject of his research, the ability to receive information using modern scientific methods, the ability to comprehend the information received and submit it in an acceptable form.

General conclusion and recommendations on admission to defend. In general, the qualification work on the topic «Development of the composition of combination tablets for dementia treatment» deserves a positive assessment, and its author Amel GUERBI — admission to the defense of the qualification work.

Scientific supervisor _____ Antonina SICHKAR

«__» of April 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

Amel GUERBI

on the topic: «Development of the composition of combination tablets for dementia treatment»

Relevance of the topic. Given the current state of production of drugs in tablets form, advantages of combination memantine with donepezil, the development of a new drug based on memantine and donepezil is relevant.

Theoretical level of work. The student of higher education independently conducted an analysis of the current state of tablets manufacture, carried out the granules analysis, developed the composition of tablets combination memantine with donepezil based on the results of physico-chemical and technological studies.

Author's suggestions on the research topic. The author developed suggestions for solving the problem of obtaining tablets with memantine hydrochloride and donepezil hydrochloride.

Practical value of conclusions, recommendations and their validity is the possibility of using the research results for the further introduction into the industrial production of technology of tablets with memantine and donepezil.

Disadvantages of work. Minor, namely, disproportionate placement of material, presented in separate sections, were revealed. However, these disadvantages are not important and should not affect the overall assessment of work.

General conclusion and assessment of the work. The qualification work is executed on an urgent topic, because it covers the issues of developing the composition of the new tablets with memantine and donepezil. The work as a whole meets the requirements of the qualification level and deserves an excellent assessment.

Reviewer _____ prof. Larysa BOBRYTSKA

«___» of _April___ 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. Ніколайчук 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 комбінованих таблеток для лікування деменції»

здобувачки вищої освіти випускного курсу Фм18(5,0д)англ-06 групи НФаУ 2023 року випуску _____ Амель ГЕРБІ _____
(ім'я, прізвище)

Науковий (-ві) керівник (-ки)_к.фарм.н., доц. Антоніна СІЧКАР_____
Рецензент_____д.фарм.н., проф. Лариса БОБРИЦЬКА _____

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувачки вищої освіти _5_ курсу Фм18(5,0д)англ-06 групи_____Амель ГЕРБІ_____
(ім'я, прізвище)

на тему:__«Розробка складу комбінованих таблеток для лікування деменції»_____

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 Гербі Амель до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка складу комбінованих таблеток для лікування деменції».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувачка вищої освіти Гербі Амель виконала кваліфікаційну роботу на високому рівні, з логічним викладенням матеріалу та обговоренням, оформлення роботи відповідає вимогам НФаУ до випускних кваліфікаційних робіт та може бути рекомендована до захисту у Екзаменаційній комісії НФаУ.

Керівник кваліфікаційної роботи

_____ Антоніна СІЧКАР

«___» _____ 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувачка вищої освіти Гербі Амель 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

_____ / Oleg SHPYCHAK /