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department of Technologies of Pharmaceutical Preparations

QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF TABLETS WITH TURMERIC ROOT POWDER AND BLACK PEPPER EXTRACT»**

Prepared by: higher education graduate of group (Фм19(4,10д.)англ-02)
specialty 226 Pharmacy, industrial pharmacy
educational program Pharmacy
Soukaina ICAME
Supervisor: associate professor of higher education institution of department of Technologies of Pharmaceutical Preparations, PhD, associate professor Antonina SICHKAR
Reviewer: associate professor of higher education institution of department of Drugs Technology, PhD, associate professor Marina BURYAK

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ANNOTATION

A high dose tablet composition of the turmeric root powder and a low dose of a black pepper extract was developed and evaluated using silicified microcrystalline cellulose PROSOLV SMCC® 50 and sodium starch glycolate EXPLOTAB® in a wet granulation process. The properties of tablets compositions containing different concentrations of povidone were compared. The resulting final blend was compressed into capsule-shaped, biconvex tablets and tablets were film coated.

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 46 pages, contains 4 tables, 17 figures, 37 literature sources.

Key words: tablets, turmeric root powder, black pepper extract, composition, wet granulation.

АНОТАЦІЯ

Розроблений і проаналізований склад таблеток з високою дозою порошку кореня куркуми і низькою дозою екстракту чорного перцю з використанням силіфікованої мікрокристалічної целюлози PROSOLV SMCC® 50 і натрій крохмаль гліколяту EXPLOTAB® у процесі вологої грануляції. Порівнювали властивості таблеток, до складу яких входила різна концентрація повідону. Суміш речовин розробленого складу пресували в таблетки капсульної двоопуклої форми і покривали таблетки плівковою оболонкою.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних джерел літератури, загальний обсяг роботи 46 сторінок, містить 4 таблиці, 17 рисунків, 37 джерел літератури.

Ключові слова: таблетки, порошок кореня куркуми, екстракт чорного перцю, склад, волога грануляція.

CONTENTS

LIST OF ABBREVIATIONS

API	–	active pharmaceutical ingredients
EU	–	The European Union
FDA	–	U.S. Food and Drug Administration
IUPAC	–	International Union of Pure and Applied Chemistry
mg	–	milligram
LOD	–	loss-on-drying test
NSAIDs	–	non-steroidal anti-inflammatory drugs
OA	–	osteoarthritis
OSD	–	oral solid dose
Ph.Eur	–	The European Pharmacopoeia
RH	–	relative humidity
sec	–	seconds
SPU	–	State Pharmacopeia of Ukraine
WHO	–	World Health Organization

INTRODUCTION

The relevance of the topic. Phytomedicines have long-standing utility toward treating many different diseases. It is estimated that about two-thirds of population depend on traditional herbal-derived medicine for primary medical needs worldwide.

Over the thirty years, the industrial manufacture of herbal-derived medicines has grown considerably. Despite of its importance in the pharmaceutical market, several herbal medicines are sold only in the form of hard gelatine capsules [1]. It depends on the excipients; although capsules as a dosage form have been around for many years, when choosing a dosage form, patients still prefer tablets as a more familiar dosage form. Tablets are more stable than capsules among solid dosage forms. The one tablet can include a higher dose of the substance than one capsule because the active ingredients are compressed with excipients in tablets. Another advantage of tablets is this solid medicinal form can be divided in two parts for obtaining a smaller dose.

Osteoarthritis is form of arthritis, which affects millions of people in the world. OA is a degenerative joint condition characterized by progressive limited joint function, joint inflammation leading to pain, and loss of social activity. Synthetic medicines are ineffective for patients in many cases of such disease, and are usually associated with gastrointestinal side effects (for example non-steroidal anti-inflammatory medicines).

Curcuma longa L. or turmeric and Piper nigrum L. or Black pepper can be called promising sources for obtaining herbal-derived preparations for the treatment of osteoarthritis (OA). The bioactive compounds of Curcuma longa L. such as curcumin exert chondroprotective activity against osteoarthritis. Curcumin is effective as ibuprofen for the treatment of pain in knee osteoarthritis. Plant Black pepper and its extract possesses diverse biological activities including anti-inflammatory properties. The active component in black pepper, such as piperine, has the anti-inflammatory activity in human OA chondrocytes. Also, the

combining black pepper extract with piperine and turmeric root powder with curcumin in enhances curcumin absorption. The turmeric root powder may be more beneficial than the curcumin extract: only very small amounts of curcumin are absorbed into the bloodstream. The turmeric root powder stays in the digestive tract longer than subctance curcumin, releasing this active ingredient along with other beneficial substances [26].

A high dose of the turmeric root powder is needed for oral dosage forms; therefore, special excipients and technology are required to create tablets with this extract.

The purpose and research tasks. This study was aimed to demonstrate the possibility of composition and technology development with a turmeric root powder and a black pepper extract. The research tasks that we decide to achieve the purpose:

- to analyze the current state of problem of OA treatment with phitopreparations, of drugs technology with plant extracts, with a high dose of the powder and a small dose of the extract;

- to conduct studies of physical, chemical, and different special technological properties of a turmeric root powder and a black pepper extract;

- to conduct the grounded selection of suitable components for developing coated tablets composition;

- to develop technology of coated tablets with a turmeric root powder and a black pepper extract

- to establish a type of pack, define shelf-life and storage conditions of tablets with the turmeric root powder and the black pepper extract.

Research objects are the turmeric root powder and the black pepper extract and tablets with such conponents.

The article of presented research in qualification work is the rational composition and technology of tablets with the turmeric root powder and the black pepper extract.

Research methods. The methods of researches from Ph.Eur were used for determining such properties of active ingredients as physical, chemical, their technological properties among which angle of repose of powders, bulk volume, compressibility of the turmeric root powder and the black pepper extract and tablets mass on their basis; on the recommendations of Ph.Eur (homogeneity of mass) and parameters of prepared tablets quality, such as disintegration, appearance, friability, resistance to crushing. Experimental data for the development of tablets with the turmeric root powder and the black pepper extract were carried out with mathematical statistics methods.

The approbation of qualifying work results and scientific publications — author's participation in the 5th International scientific and practical conference “European congress of scientific achievements”, Barcelona, 20−22 May 2024. with writing abstract [13].

Structure of work. Qualification work consists from introduction, three chapters, general conclusions, list of the references (37 sources) and appendix. The content of work is presented on 46 pages of basic text and contains 4 tables and 17 pictures.

CHAPTER 1.
CURRENT STATE OF PROBLEM OF OBTAINING PHYTOPREPARATIONS FOR THE TREATMENT OF OSTEOARTHRITIS (REVIEW OF LITERATURE)

1.1. Curcuma longa and Black pepper as the most promising medicinal herbs

Poor diet, physical inactivity, and obesity are now known to be associated with multiple comorbidities, including diabetes, cardiovascular disease, and chronic musculoskeletal conditions, including osteoarthritis (OA) [28, 29].

OA is the frequent musculoskeletal illness. OA brings suffering to patients in the form of functional decline. With this disease, patients experience reduced life quality. Clinically, the condition is characterized by tenderness, joints pain, crepitus, stiffness and limitation of movement with occasional effusion and different degrees of inflammation locally.

The pain in OA is frequently activity related; pain becomes a frequent property in the disease later [29].

Constant pain in OA is not only attributable to changes in the structure of the joint that affected, but also the result of interactions between change in the structure, in the processing mechanisms of a peripheral and central pain in the joint.

Also, pain does not apply the only one aftermath of OA suffering patients. Pain is associated with physical movements, with function triggering pain, also pain causes limit in physical function in turn.

Sensation of buckling or instability, joint stiffness in the morning is frequent; a palpable and audible «cracking» or «crunching» during a joint passive or active movement are prevalent in later OA stages especially.

OA is a degenerative illness which belongs to chronic; this illness is experienced by the elderly in many cases. OA is as a result of an association

between the bone remodeling, inflammatory of joint fluid, and the degradation of cartilage. Different factors can affect this illness such as overweight, trauma, elderly, strenuous physical activity, and many other things.

OA may be caused by capsular contractures, muscle spasm, pain, effusion, or weakness, intra-articular loose bodies, different mechanical constraints and joint deformity / misalignment [28].

OA causes changes in mobility and function. Functional disability is a second problem of OA. Functional disability is linked to articular limitation, crepitus, and stiffness frequently.

Patients with OA experience difficulties with personal care, physical limitations, and problems with their household and work ability frequently.

Worldwide OA is the common musculoskeletal illness and also an escalating public health concern. It is known that in people prior to 40 years, the AO incidence is lower and is secondary, due to trauma most frequently.

The prevalence increases in people between age from 40 to 60, and there is a linear increase in later ages in the prevalence.

OA of the knee is the common form of such disease as arthritis.

Worldwide illness estimates show that in people 18% of women and 9.6% of men of 60 years and certainly older have symptomatic OA probably.

Global OA prevalence increased more than 113% between 1990 (247.51 million) and 2019 (527.81 million) and onwards, with the most cases appearing in China, India and the United States, according to data published in «Arthritis and Rheumatology».

Results from a systematic annual review presented information about knee desease prevalences that ranged, for example, from 6.3 % in Greece to 68.4 % in the United Kingdom; in hand from 2% in Greece to 77.1% in Israel, in hip from 0.9 % in Greece to 23% in Croatia. In the Instituto Nacional Dr. Ricardo Jorge (in Portugal), in a report on the prevalent chronic illness, studied that 24 % of the participants suffering from different form of rheumatic disease.

Despite advances in understanding of the physiopathology of OA, which is considered a major cause of morbidity and disability worldwide, no treatment has yet proven effective in the prevention, cure, or slowing of its progression. Paracetamol and NSAIDs are endorsed to treat arthritis, such as osteoarthritis, but emerging evidence has challenged this recommendation and revealed the potential for adverse events. Long-term use of pharmacological agents, such as NSAIDs, has potential adverse effects that can lead to serious consequences, including gastrointestinal bleeding and adverse cardiac effects [27].

Following consideration of the potential side effects of NSAIDs and the long duration of treatment, one may prefer the use of less toxic compounds with a good safety profile. Medicines based on medicinal plant raw materials can be an alternative [16]. Curcuma longa L. or turmeric and Black pepper (Piper nigrum L.) can be called promising sources for obtaining phytopreparations for the treatment of OA [5, 10, 36].

No significant toxicity was noted either acute or chronic administration of turmeric extracts at standard doses. Curcumin is a substance with an excellent profile of safety. It has potential to treat different inflammatory diseases [6, 14].

Turmeric (botanical name Curcuma longa) is a flowering plant in the ginger family Zingiberaceae (Fig. 1.1).

Fig. 1.1. Curcuma longa L. or turmeric, botanical view (source: Wikipedia).

This is a perennial herbaceous plant. It grows in India and China and is widely cultivated in these same countries. The height of the C. longa is approximately 1 m and their leaves appear like lance structures with yellow flower prickles that ripen in its fleshy rhizome or in its underground stem. The source of turmeric medicinal powder is the orange pulp enclosed inside the rhizome (Fig. 1.2).

Fig. 1.2. Rhizomes of Curcuma longa (source: Wikipedia).

Its large leaves, oblong or elliptical, lanceolate, alternate arranged in two rows. Stem bracts are present at the top of the inflorescence, on that stem bracts no flowers occur. Its flowers are sterile. The plant propagates by spontaneous cuttings of rhizomes [4].

Curcumin is the main active ingredient in turmeric, which is classified as a curcuminoid. It gives yellow color to turmeric powder. Curcumin constitutes up to 3.14%. Also, turmeric rhizomes contain quinoids, alpha and gamma altones, campesterol, which has anti-inflammatory properties, monoterpenes, essential oils, organic acids such as caffeic and coumaric acid, etc. [6, 35].

Phytochemical components of C. longa include other curcuminoids, such as bisdemethoxycurcumin and demethoxycurcumin. Turmerone, germacrone, atlantone, and zingiberene found among essential oils [4].

Thus, the anti-inflammatory and antioxidant activity of C. longa has been proven in some studies, and scientists are trying to use C. longa as a component of anti-tumor therapy or for the treatment of arthritis.

However, it has been observed that curcumin has poor bioavailability and needs the help of a synergist. It turned out that black pepper can be used as a synergist. It contains piperine, an active substance that increases the absorption of curcumin in the body. Turmeric with black pepper improves overall health and helps the body fight inflammation and infections.

Piper nigrum L. (Black pepper) is called the king of spices in India [5]. The name of this plant comes from the Sanskrit word «Pipali». P. nigrum is an endemic species from India.

Today it grows on almost all continents, Africa, Asia, South America in countries with tropical climates such as Cambodia, Sri Lanka, Vietnam, Thailand, China, Indonesia, India, Madagascar, Brazil [5].

P. nigrum L. is the perennial climbing plant, species of the genus Pepper (Piper) of the Pepper family (Piperaceae) (Fig. 1.3). It is a vine that requires support to grow. This could be a tree or a pole. The plant grows up to 15 m or more height.

Fig. 1.3. Black pepper (Piper nigrum L.), botanical view (source: Wikipedia).

The plant has 10-20 adventitious roots that form at the base of the stem. The type of branching is dimorphic. Fruiting branches are formed in the axils of the leaves. The plant also has aerial roots that form at the nodes of the stem. The plant clings to the support with these roots.

The leaves are simple, ovate, leathery, alternate, 2-5 cm long and 12-20 cm wide. The flowers are small, gray-yellow or white. They are collected in loose inflorescences 7-10 cm long. The fruits are round, single-seeded drupes 3-5 mm in diameter. The green fruit turns red when ripe and turns black when dry. Inflorescences 80-140 mm long contain 20-30 drupes. Plants bloom in May-July during the southeast monsoon 2-3 years after planting. After the peduncle appears, flowers appear 10-15 days later. They bloom for 6-10 days. The inflorescence is naked. The flowers of the cultivated species are monoecious. The flowers are self-pollinating. The matured fruits are spherical in shape (~ 5 mm diameter). The harvested fruits are sun-dried for further use. P. nigrum bears fruit 2 times a year for 25-30 years [5].

A typical photograph of stages of fruit development, fresh fruits and dried seeds of P. nigrum are presented in Fig. 1.4.

a b c

Fig. 1.4. Stages of fruit development (a), fresh fruits (b) and dried seeds (c) of P. nigrum [5].

Black pepper is rich in vitamins and minerals. It contains B vitamins, vitamins C, K, potassium, calcium, magnesium, phosphorus, iron, manganese,

copper, zinc. But besides this, black pepper contains many active biochemical compounds. The phytochemical composition of pepper is represented by resins (1-2%), fatty oils (6-12%), starch, flavonoids such as catechin, quercetin and myricetin, carotenoids such as lutein and β-carotene. The hot substance in pepper, the alkaloid piperine (5-9%), occupies a special place. The positive effects of this alkaloid are reflected in the ability to protect healthy cells from destruction and increase the absorption of nutrients [5].

The smell of pepper is due to the presence of essential oil (up to 2.5%), which includes the monoterpenes dipentene, phellandrene and the sesquiterpene caryophyllene. Oleoresin contained in black pepper is used as a food additive in industrial food production.

P. nigrum has found wide application not only as a food product, but also in medicine, veterinary medicine, and perfumery. It is used as an insecticide in the fields. For medicinal purposes, it is most widely used in India. Therefore, most literature sources refer specifically to this country.

In folk medicine it is used as a remedy for diarrhea. The sun-dried fruits of black pepper are used in medicine as a digestive aid, for the treatment of diseases of the ENT organs, and for menstrual disorders.

Antimicrobial and antiviral, analgesic, anti-inflammatory, antioxidant, antidiabetic, and anticancer effects of biologically active compounds in black pepper were also discovered. The experiment showed the hypolipidemic activity of pepper. Numerous studies have shown the strong antioxidant properties of black pepper. Antioxidants are substances that can protect cells from damage by free radicals. The formation of free radicals is provoked by smoking, neglect of healthy eating rules, exposure to active sun, and exposure to harmful substances. The antioxidant effect was confirmed using reactive oxygen and nitrogen species.

Using breast, prostate and intestinal cells, the anti-cancer activity of pharmaceutical preparations of pepper was shown.

1.2 The Moroccan pharmaceutical industry

The pharmaceutical industry is the second largest chemical industry in Morocco after phosphate production and ranks second in Africa as a whole [3].

Morocco is an example of stability in the region, with an economy valued at $314 billion in 2021 and an average annual pharmaceutical market growth rate of more than 4%. The national pharmaceutical industry is one of the highest value-added sectors in the country, thanks to continuous investments in technological innovation, quality and training. It also carries out a large-scale social mission: the creation of effective and high-quality medicines available to the general public.

There are 11,000 pharmacies in Morocco. The annual turnover is more than 15 billion dirhams. About 450 million boxes of medicine are produced annually and Dh497 is spent per resident.

SANOFI MAROC, MAPHAR, COOPER MAROC, LAPROPHAN and SOTHEMA are the main companies in the sector.

The Moroccan pharmaceutical industry represents a growth pole thanks to the technologies it has acquired, its know-how recognized by international bodies, and the results it achieves both in terms of production volumes and the quality of medicines. It should be noted that the WHO has classified Morocco's pharmaceutical industry as a European zone due to the quality of its products. It covers most of the domestic demand, i.e. almost 70%. Morocco exports up to 8% of its production to African countries, but also to Europe.

This industry has great potential for development. The production of medicines and the production of medical devices is expanding.

The pharmaceutical market in Morocco has experienced significant growth in recent years, driven by increasing government investment in healthcare infrastructure. The Pharmaceuticals market in Morocco is expected to achieve revenue of US$ 643.10 m in 2024 [24].

In 2022, a program contract was signed for the pharmaceutical sector for 2022–2027, which aims to create 16,000 jobs.

But despite the government's best efforts to expand the pharmaceutical sector, Morocco's ability to provide essential medicines and quality, affordable health care needs further development. As a result, the demand for generic and over-the-counter drugs is increasing as cheaper and more accessible options, limiting citizens' out-of-pocket spending on medications. Thus, the long-term outlook for pharmaceutical spending will be boosted by improved coverage through uniform pricing, an improved regulatory framework, and resulting improved health care services. This will put Morocco on the path to increasing its potential as a regional centre for the production of medicinal products [19].

1.3 Tablet formulations incorporating herbal powders and dry extracts

Oral solid dose (OSD) forms are typically preferred by patients due to their efficiency, cost-effectiveness, shelf stability, and ease of administration.

The wet granulation, dry granulation and direct compression are the most well-known tablet manufacturing technologies [2].

Granulation serves as the basis for the production of solid dosage forms. Granulation is a process by which small particles agglomerate to form granules. These granules serve as the basis for various forms, such as tablets, capsules or granules themselves.

The main purposes of granulation in pharmaceutical production are:

- improved flow and uniformity by converting fine powders into granules. This ensures consistent and uniform dosing of substances;
- improved dispersion and dissolution. Granules have higher dispersibility and dissolution rate than powders. This promotes optimal absorption of drugs in the body;
- reduced Dust: Granules reduce the risk of airborne particles, providing a safer work environment and minimizing product loss.

The wet granulation involves adding a liquid binder to a powder mixture, followed by mixing to form granules. The method is suitable for compounds that are sensitive to moisture and require quick drying.

The dry granulation. Unlike wet granulation, dry granulation does not require the use of liquid binders. Instead, the powder mixture is compacted and then broken down into granules. This approach is ideal for moisture-sensitive or chemically unstable compounds.

The direct compression involves compressing a powder mixture directly into tablets without the need for granulation. However, it may not be suitable for all formulations and may require additional processing steps for some drug substances.

The physical and chemical stability of active pharmaceutical ingredients (APIs) influences the choice of granulation method and overall production. The main equipment is granulators, fluidized bed dryers, various grinders, mixers.

The granular tablet manufacturing process involves weighing, crushing and mixing APIs with powdered excipients; preparing a binder solution; mixing this solution with powders; granule formation; drying wet granules; mixing dry granules with disintegrators; pressing granules into tablets [12, 33].

The process of producing tablets using the dry granulation method is somewhat different. It consists of pressing powder mixtures into large pieces, then crushing them into granules and pressing. The method is used when the excipients have sufficient inherent binding properties.

Direct compression is the most efficient and least complex method of producing tablets, since the process involves a minimum of steps. It avoids the problems of dry and wet granulation, but the selection of the correct tablet manufacturing process is influenced by the properties of the APIs; particle size of ingredients; availability of necessary technological equipment; also the cost of production [32].

Thus, the wet granulation method was used to obtain tablets based on Lannea microcarpa Engl. et K. Krause (Anacardiaceae) extracts for arterial hypertension therapy [9].

Tablets based on neem leaf extract were obtained using the wet granulation method followed by the application of a moisture-resistant film coating [8].

1.0% magnesium stearate without PVP binder was added to the tablet mass to prepare tablets based on extract of Lippia origanoides [23].

In review [20], four formulation strategies that have been employed to tackle hygroscopicity issues in oral solid dosage forms of pharmaceuticals/nutraceuticals were discussed. The four strategies are (1) film coating, (2) encapsulation by spray drying or coacervation, (3) co-processing with excipients, and (4) crystal engineering by co-crystallization.

Ruban E.A. et al. developed the technology of tablets with dry extract of zingiber officinale [30]. Tablets are obtained by direct compression.

Shulga L. et al. studied the choice of excipients as a rationale for the composition of tablets with dry extract of Sanguisorba officinalis [31]. It was shown that among fillers based on microcrystalline cellulose, Prosolv 90 showed the best results; among fillers based on sugars, masses with sugar Perlitol 500 DC, Compri and Tablettoza 80 showed equally good results.

Zhumashova G. T., Sakipova Z. B. substantiated the optimal tableting method using wet granulation, which makes it possible to obtain tablets of the proper pharmacopoeial quality and the following composition: soft rhubarb root extract, magnesium hydroxycarbonate, croscarmellose sodium, microcrystalline cellulose 102, Plasdone S-630, magnesium aluminum metasilicate, calcium stearate [37].

Thus, we see that an individual approach is necessary in each specific case for the development of herbal extract tablet technology.

Conclusions to chapter 1

1. Herbal-derived products have long-standing utility toward treating many diseases. Its antioxidant, anti-inflammatory and chondroprotective properties, Curcuma longa or turmeric can contribute to health. The bioactive compounds of Curcuma longa such as curcumin exert chondroprotective and analgesic effects against OA. Black pepper possesses different biological activities including anti-inflammatory properties in human OA chondrocytes. The combining black pepper extract with turmeric root powder enhances curcumin absorption.
2. The Moroccan pharmaceutical industry constitutes the large chemical industry in Morocco, and new effective medicines are needed for its further development.
3. An individual approach is necessary in each specific case for the development of tablets with substances from plant raw material.

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 the turmeric root powder and the black pepper extract. Excipients in tablets

According to the high dose of the turmeric root powder which was 750 mg its difficult to obtain tablets by direct compression. Further experiments obtaining of tablets by wet granulation process have provided medicine in solid form with good parameters of the quality. Granulation of the powder blend for equable distribution of particles in each granule is one of solutions of segregation problems used for low dose unit dosage forms. And the dose of 5mg black pepper extract is a very low. When mixing low dose substances with other powders, trituration must be mixed first.

2.1.1 Active substancies of developed tablets

The first object of our research was the turmeric root powder. Dried and ground turmeric root was used as the turmeric root powder with curcumin content 3–4% (India) (Fig. 2.1). The turmeric root powder is a bright yellow-colored spice made from the dried and ground roots of the turmeric plant, scientifically known as Curcuma longa. Turmeric root powder contains about 60–70% carbohydrates, 1–6% curcuminoids, 3–7 % minerals, 6–8 % protein, 6–13 % water, 5–10 % fat, 3–7% essential oils and 2–7% fiber [15, 17, 18, 22]. The curcumin chemical structure is shown in Fig. 2.2.

Fig. 2.1 The turmeric root powder

The yellow color of turmeric is due to curcumin. The IUPAC (International Union of Pure and Applied Chemistry) name of curcumin is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, chemical gross formula $C_{21}H_{20}O_6$, molecular weight of 368.38.

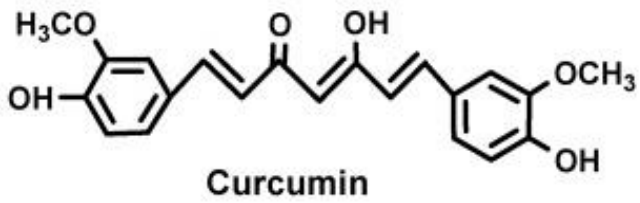

Fig. 2.2 Structure chemical formula of curcumin

The Black pepper dry extract, standardized to contain ≥ 95 % piperine (Ukraine) was used as second active ingredient (Fig. 2.3).

Fig. 2.3 The Black pepper dry extract

The molecular formula of piperine is $C_{17}H_{19}NO_3$ and its chemical structure is shown in Fig. 2.4. Average mass is 285.338 Da. The IUPAC name of piperine is (2E,4E)-5-(1,3-Benzodioxol-5-yl)-1-(1-piperidinyl)-2,4-pentadien-1-on/

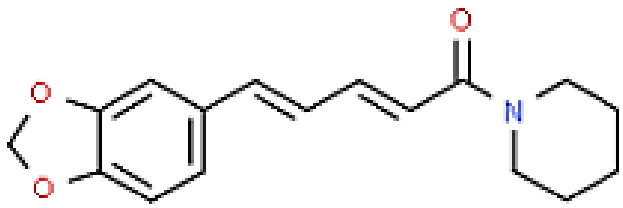

Fig. 2.4 Chemical formula of piperine

Piperine is found naturally in plant Piper nigrum L belonging to the Piperaceae family, commonly known as black pepper.

2.1.1 Excipients in the research and development of tablets with the turmeric root powder and the black pepper extract

Sodium Starch Glycolate EXPLOTAB® (from JRS Pharma) is a disintegrant which belong to the group of superdisintegrants. Tht excipient EXPLOTAB® made from potato starch by carboxymethylation and crosslinking and corresponds to the chemical name, Sodium carboxymethyl starch. Its chemical structure is shown in Fig. 2.5. This highly pure excipient demonstrates strong swelling properties upon contact with water and media of stomach and offers excellent formulations and benefits to the pharmaceutical industry. Sodium Starch Glycolate retains its spheroid structure to promote good flowability, contains little ethanol or sodium chloride, and has high brightness [11].

Chemical modification of potato starch is achieved through controlled cross-linking of the starch polymer backbone, which is followed by the introduction of carboxymethyl sodium groups (on C_2 of the glucose molecule). These changes in potato starch increase the hydrophilicity of sodium starch glycolate, and reduce its water solubility and gelling tendency, giving rise to the functionality of EXPLOTAB® as a tablet superdisintegrant. Empirical formula is $(C_6H_{10}O_5)_{n.}(Na)_x$.

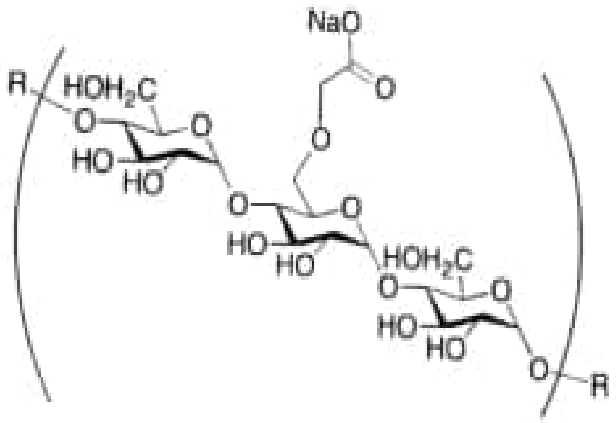

Fig. 2.5. Chemical structure of sodium starch glycolate

Swelling capacity of sodium starch glycolate is up to 300 times its volume. Particle size distribution is D_{50} = 35 – 45 μm depending on grade, 100% ≤ 110 μm.

PROSOLV® SMCC (from JRS Pharma) is silicified microcrystalline cellulose or a combination of microcrystalline cellulose and colloidal silicon dioxide. This excipient with multiple functions for tablets requires less complex processing, has proper functionality. PROSOLV® SMCC passes its functionality on to the tablets formulation.

PROSOLV® SMCC exhibits plastic deformation characteristics and also brittle fracture, leading to good properties as binder agent. This excipient imparts both superior flow and optimum compaction to tablets formulations. The technology of PROSOLV® SMCC leads to much finer homogenous colloidal silicon dioxide particle size distribution. These results in a five-fold excipient specific surface area increase, also a 30–50% compaction increase compared to traditional microcrystalline cellulose. The increased excipient surface area enables excellent flow and increased compaction. Also it results in improved content (active components) stability and uniformity in the tablets formulation.

Compositions with excipient PROSOLV® SMCC produce uniform and cost effective tablets. This multifunctional excipient is available in a number of grades [7]. PROSOLV SMCC® 50 is the most compactible grade of this excipient. The particle size is from 45 to 80 μm. It accomodates poorly compactible active ingredients, delivers good compactibility in high drug-loading compositions, and

excels in the compaction process of tablets presses with the roller. This excipient can be used in the wet granulation process [25].

Magnesium stearate or magnesium octadecanoate is the excipient with the chemical formula $Mg(C_{18}H_{35}O_2)_2$. Its chemical structure is shown in Fig. 2.6. It is a soap, consisting of salt containing one magnesium cation (Mg^{2+}) and two equivalents of stearate (the anion of stearic acid). Magnesium stearate is a water-insoluble powder. Applications this excipient exploit its softness, and low toxicity. It is used as lubricant in the production of pharmaceuticals in solid dosage forms.

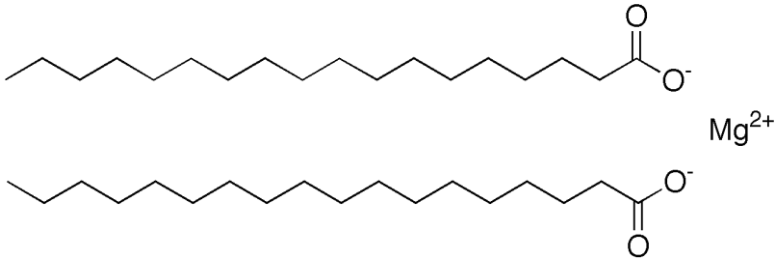

Fig. 2.6. The chemical formula of magnesium stearate (source: Wikipedia).

2.2 Methods of researches

2.2.1 Evaluation of properties of the turmeric root powder, black pepper extract, granules and tablets

Moisture content or specific humidity of the granules with the turmeric root powder and black pepper extract was determined by a loss-on-drying test (LOD) using a MoistureTester Sartorius MA50 at a temperature of 105 °C. Each batch of granules was dried to a target moisture content corresponding to the LOD value of the dry blend after the wet granulating step.

The size analysis of developed granules was measured by sieve analysis using the test standart sieve shaker.

Bulk and tapped density of active ingredients, granules of the turmeric root powder and black pepper extract was determined by a Bulk Density tester based on Ph.Eur Method.

Bulk density is measured by pouring the estimating powder into a measuring glass cylinder, the initial weight was noted. This initial volume of a powder is called the bulk volume. The bulk density of a powder is calculated according to the formula 2.1. It is expressed in g/ml and is given by

$$D_b = m / V_b, \quad (2.1)$$

where, m is the powder sample mass;

V_b is the powder sample bulk volume.

For the tapped density the first volume measured with tapping the powder sample 100 times in a bulk density apparatus, tapping is continued for 1250 times and the tapped volume was noted if the difference between these two volumes is less than 2 %. The tapped density is expressed in g/ml also and is given by

$$D_t = m / V_t \quad (2.2)$$

where, m is the powder sample mass;

V_t is the powder sample tapped volume.

Hausner's ratio is an special index of ease of powder samples flow. Hausner's ratio is calculated by following formula 2.3:

$$\text{Hausner's ratio} = D_t / D_b \quad (2.3)$$

where, D_t is powder sample tapped density of,

D_b is powder sample bulk density.

The compressibility index or Carr's Index of powder samples was determined by using equation 2.4 [7]:

$$\text{Carr's Index (\%)} = [(D_t - D_b) \times 100] / D_t, \quad (2.4)$$

The tablet resistance to crushing or mechanical strength was evaluated with a tablet multifunctional tester. The tablet resistance to crushing is the force required to break the tablet in a diametric compression. It is measured in Newtons. Usual range of resistance to crushing for big tablets should be preferably more than 60 N.

The tablet friability was studied using also a multifunctional tablet tester with friabilator. The friabilator subjects tablets to the combined effect of shock and abrasion in a plastic chamber that revolve at 25 rpm. Preweighed samples of tablets was placed in the friabilator and were subjected to 100 revolutions [7]. Then tablets were dusted using a soft cloth and reweighed. The friability (F) is given by the formula 2.5 below.

$$F = (W_{initial} - W_{final})/W_{initial} \times 100 \quad (2.5)$$

Both uncoated and coated tablets of the turmeric root powder and black pepper extract were tested on disintegration time in the purified water and with disks according to the Ph.Eur with a multifunctional tablet tester.

2.2.2. Determination of shape and surface of particles of the turmeric root powder and and black pepper extract, and dominant fractions of active ingredients

The shape of particles and the approximate size of particles of powders were estimate by the luminescent microscope "Lumam R1", that allows observing and photographing the image of different objects in passing light. The shape of the particles was estimated in relation to an average width to an average length of the particles.

2.2.3 Determination of the flowability of the turmeric root powder and and black pepper extract

The flowability of powders depend upon many factors, some of which are some related to the process of determination and particle related. Monitoring the

flowability of powders through an orifice of funnel has been proposed as a better measure of flowability. However, determination of the flowability through a funnel orifice is useful only with freeflowing powders.

Allow the powder to flow through a funnel orifice of special apparatus onto a horizontal surface below. The angle of conical heap so formed can be estimated from geometry [7]. The angle of repose (θ) is an symptomatic of flow properties of the material.

2.2.4. Weight variation of tablets of the turmeric root powder and black pepper extract

Tablets are considered to contain a definite amount of substance in a specific amount of tablet composition. Average weight of 20 tablets of the turmeric root powder and black pepper extract were selected randomly from the batch and weighed individually. Not more than two from the individual tablets masses deviate from the average weight of tablets with the turmeric root powder and black pepper extract by more than 5 % deviation and none deviates by more than twice that 5 %.

2.2.5. Thickness of tablets with the turmeric root powder and black pepper extract

The thickness of pre-weighed 10 tablets was measured by a calipers. It is measured by placing the tablet between two anvils and rotating the sliding knob until the tablet with the turmeric root powder and black pepper extract was tightly fitted and the reading was noted. The tablet thickness must be controlled within a ± 5 % variation of a standard thickness value.

Conclusions to chapter 2

1. Thorough methodological approaches to the development of coated tablets with the turmeric root powder and black pepper extract are suggested.

3. The characteristics of the turmeric root powder, black pepper extract and different special excipients which were used in the development of tablets are presented.

4. The methods of technological researches, basic, sufficient and necessary for creation of composition and development of rational technology of tablets with the turmeric root powder and black pepper extract are shown.

CHAPTER 3.
EXPERIMENTAL PART.
RESEARCH FOR DEVELOPMENT OF PREPARATION COMPOSITION IN FORM OF TABLETS WITH THE TURMERIC ROOT POWDER AND THE BLACK PEPPER EXTRACT

3.1. Study of physicochemical and pharmaco-technological properties of the turmeric root powder and the black pepper extract

The microstructure of powdery materials (particles sizes, their shape and the surface nature), including substances, determines their pharmaco-technological characteristics**:** flow and volume properties, compressibility and other. Powders structure researches allow to predict the choice of excipients, composition and a technology method of tabletes obtaining with medicinal substances.

All powdery materials consist from polydisperse systems with various shapes and sizes of particles.

For the choice of optimum and necessary technological parameters and modes of tablets obtaining we studied structure characteristics, physicochemical and pharmaco-technological properties of two powders: the turmeric root powder and the black pepper extract. Pharmaco-technological properties of two active ingredients mix were examined also.

The real structure of pharmaceutical powder (also dry extracts or ground powder) can be studied by a microscopic method. Analising of shape and sizes of powder particles, and the middle size of their dominant fraction was carried out with the microscope (images taken at 75–400x magnification).

Microscope observations which were carried out have demonstrated that the turmeric root powder and the black pepper extract were polydisperse powders, the particles of which have a close to isometric shape. The surface of particles of two powders is rough (Fig. 3.1, 3.2). This is reason to assume that substances of the

turmeric root powder and the black pepper extract due to the difficult surface of particles, have insufficient pharmaco-technological properties such as flowability.

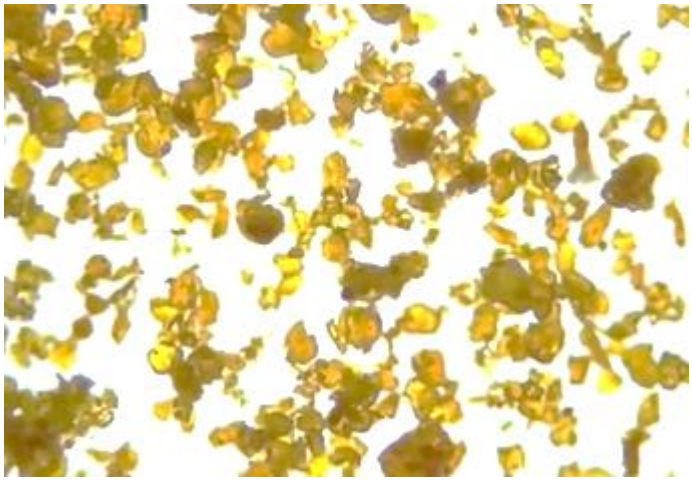

Fig. 3.1 Microphotograph of particles of the turmeric root powder

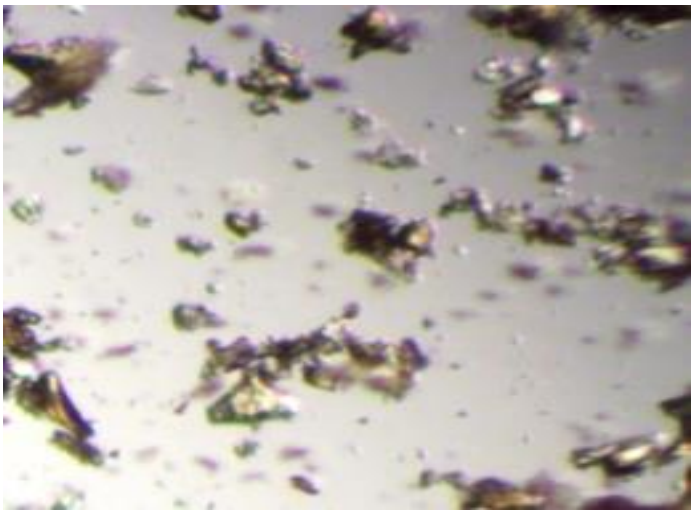

Fig. 3.2 Microphotograph of particles of the black pepper extract

The results of conducted researches of physicochemical and pharmaco-technological properties of the turmeric root powder, the black pepper extract and blend of two active ingredients are presented in a table 3.1.

As the table 3.1 information indicates the turmeric root powder and its mix with the black pepper extract has low flowability (68 sec /100 g of a sample or 1,47 g/sec and 69 ± 3 g of a sample or 1,45 ± 0.07 g/sec respectively), about what

the angle of repose showed also. The flow character is poor for the turmeric root powder and blend of the substances and very poor for the black pepper extract on indicators Hausner's ratio and Carr's Index.

Table 3.1

Pharmaco-technological and physicochemical properties of the turmeric root powder, the black pepper extract and blend of substances

Investigated characteristics of substance	Turmeric root powder	Black pepper extract	Blend of substances
1. Bulk volume, ml	270.0 ± 0.5	162.0 ± 0.2	268.0 ± 0.7
2. Bulk density, g/ml before with compaction (m/V_{1250})	 0.37±0.04 0.53±0.06	 0.43±0.02 0.67±0.08	 0.39±0.05 0.54±0.04
3. Flowability, sec/100 g of powder sample or (g/sec)	68 ± 3 (1,47 ± 0.07)	74 ± 3 (1.35 ± 0.05)	69 ± 3 (1,45 ± 0.07)
4. Angle of repose of powder sample, degree	60 ± 1	54 ± 1	59 ± 1
5. Hausner's ratio	1.43±0.02	1.56±0.03	1.38±0.03
6. Carr's Index, %	30.19	35.82	27.78
7. Compressibility, N	9 ± 1	16 ± 1	9 ± 1
8. Ejection pressure, MPa	10.0 ± 0.56	15.0 ± 0.23	11.0 ± 0.47
9. Disintegration of tablet in water, sec	1700 ± 46	1820 ± 29	1710 ± 49
10. Moisture content, %	4.25 ± 0.40	2.37 ± 0.05	4.15 ± 0.20

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

According to bad compressibility of the turmeric root powder (9 N), the dose of which was very high (750 mg), and low flowability direct compression with most modern commonly used excipients did not bring acceptable properties of tablets.

The dose of the black pepper extract is very small (5 mg) and the extract, did not make any significant changes in the technological properties of the blend of substances, as expected.

The moisture absoptions determination of the blend with the turmeric root powder and the black pepper extract was carried out at different relative humidity of air.

For researches the sample of blend with the turmeric root powder and the black pepper extract (750:5) was added to desiccator at 45 %, 75 % and 100 % relative humidity of air during 12 hours. Experimental information of moisture absorption kinetics of the blend with the turmeric root powder and the black pepper extract is presented on a fig. 3.3.

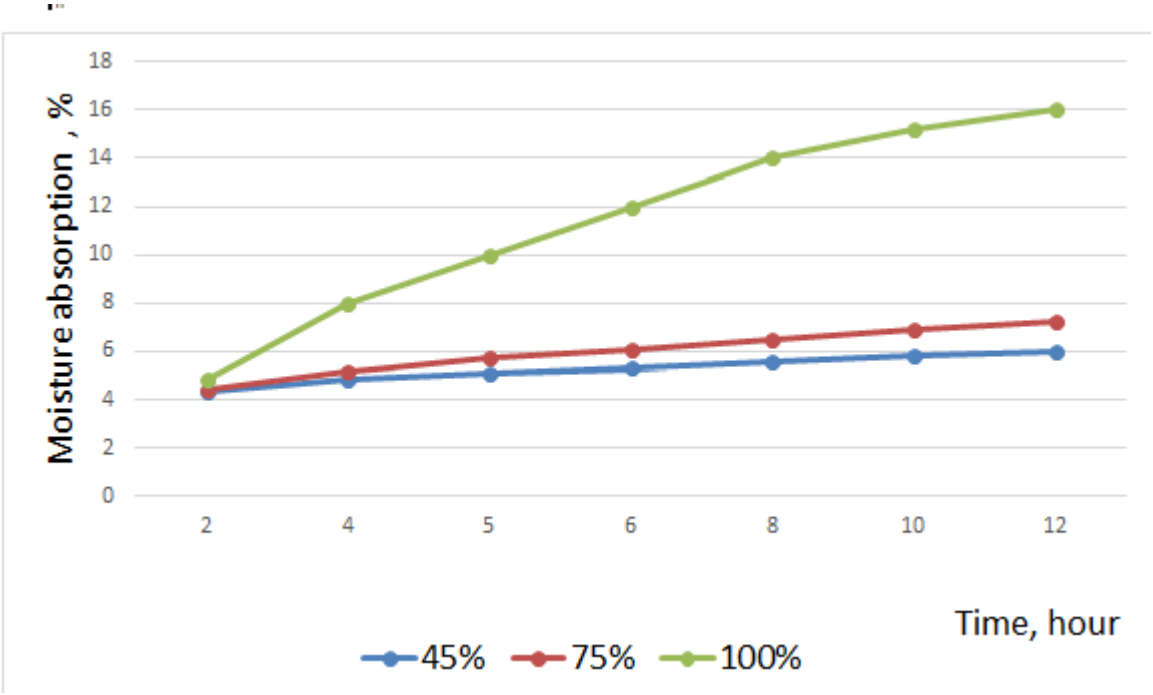

Fig. 3.3. Kinetics of moisture absorption of the blend with the turmeric root powder and the black pepper extract at different relative humidity of air: 1 – at 100 % relative humidity of air; 2 – at 75 %; 3 – at 45 %.

The presented information shows that the blend with the turmeric root powder and the black pepper extract tends to moisture absorption. During development of technology of solid dosage form it is necessary to take into account that tablets with the blend with the turmeric root powder and the black pepper extract also will have ability to moisture absorption. Therefore, coating of tablets is needed with the purpose of their protecting from the factors of external environment.

3.2. Development of tablets-cores technology of the turmeric root powder and the black pepper extract by the method of wet granulation

For the improvement of pharmaco-technological properties of mass for tabletting the components of medicinal form exposed to wet granulation.

Further experiments obtaining of tablets of the turmeric root powder and the black pepper extract by wet granulation process have provided medicine in solid form with good parameters of the quality. Granulation of the powders blend for even distribution of large number of different particles in each granule is also one of solutions of segregation problems used for low dose unit dosage forms. The dose of a black pepper extract is very small (5 mg) and this extract was previously mixed with silicified microcrystalline cellulose PROSOLV SMCC® 50.

Povidone was dissolved in water for obtaining solutions with different concentrations and added with spraying to the well-blended mixture of the turmeric root powder, a black pepper extract in PROSOLV SMCC® 50 and a superdisintegrant sodium starch glycolate EXPLOTAB®.

After granulation, drying (up to 1.5 %) and calibration of granulate Mg-stearate (0.3 mm) was added to granulate, and blended.

As previous researches of physicochemical and technological properties of substances blend shawed, it is necessary to include silicified microcrystalline cellulose PROSOLV SMCC® 50 to the composition of tablets — for providing of sufficient hardness of tablets, sodium starch glycolate EXPLOTAB® — for

providing of tablets disintegration in optimum time. Introduction of magnesium stearate is needed with the purpose of improvement of gliding properties of tablet mass. The amount of components of medicinal form was counted for the tablets mass 0,9 g. The resulting final blend of components was compressed into tablets using capsule-shaped, biconvex punches.

For the study of influence of concentration of a binder solution on pharmaco-technological properties of granules and indexes of quality of the obtained tablets as binder polymer was used 10–20 % povidone [21, 34]. Amount of a binder solution was in every case determined experimentally to the obtaining of easily plastigage mass. Granulation was carried out after moisturizing of blend and carefully mixing to the even distributing of components in the mass through a net in granulator with the diameter of orifices 1-1.5 mm. Then drying, dry granulation and powdering of the granules was carried out. Determined technological characteristics of the obtained granules is resulted in table 3.2.

Table 3.2

Technological characteristics of granules with the povidone

Investigated characteristics of granules	Units of measure	Concentration of povidone in binder solution, %		
		10	15	20
1	2	3	4	5
Bulk density of granules sample before / after compaction (m/V_{1250})	g/ml	0,65±0,03/ 0,71±0,03	0,57±0,03/ 0,72±0,03	0,73±0,02/ 0,76±0,02
Flowability of granules sample	sec/100 g of sample or (g/sec)	17,6±0,7 (5,68±0,1)	16,1±0,4 (6,21±0,1)	11,0±0,5 (9,09±0,1)

Table 3.2 (continued)

1	2	3	4	5
Compressibility	N	45±3,3	53±3,5	71±4,0
Ejection force	MPa	9,0±1,0	8,6±1,0	9,2±1,0

Note: n=5

Table 3.2 indicates that technological indexes of granules, that obtained with a 20 % solution of povidone, were better. Therefore, exactly this povidone concentration is rationally to utilize in a binder solution.

The amount of silicified microcrystalline cellulose PROSOLV SMCC® 50 in tablets was determined by an experimental way. Tablets mixtures samples, containing from 1 % to 8 % PROSOLV SMCC® 50, were estimated for this aim. The results of researches are presented in a fig. 3.4.

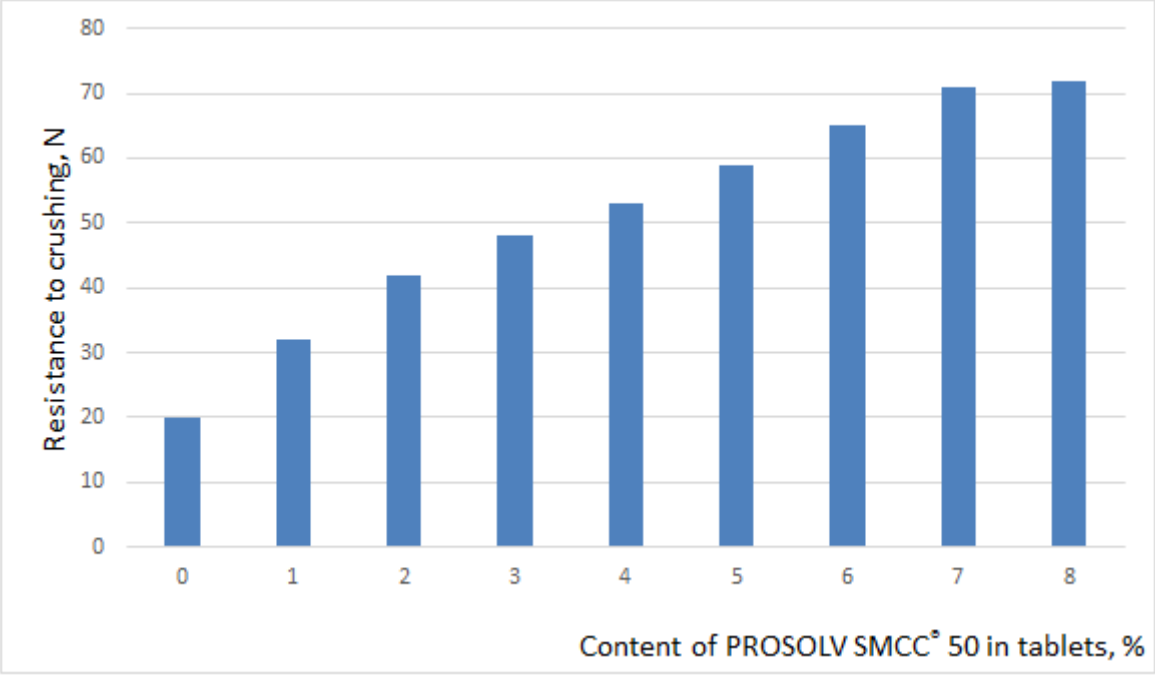

Fig. 3.4. Dependence of resistance to crushing of tablets from PROSOLV SMCC® 50 content in them

It is seen from a fig. 3.4, that sufficient hardness (resistance to crushing of tablets) is provided by 7 % of PROSOLV SMCC® 50.

Study of compositions of tablets of the turmeric root powder and the black pepper extract, containing 83.33 % turmeric root powder, 0.56 % black pepper

extract, 7.0 % PROSOLV SMCC® 50, 6.11 % povidone, 2 % EXPLOTAB® and 1.0 % magnesium stearate shawed that tablets disintegration with this composition is within the limits of 12–14 min. This is satisfactory for tablets-cores which must be coated.

Thus, the next composition of tablets-cores with the turmeric root powder and the black pepper extract 0,9 g was offered:

Composition of tablet-cores**:**

Description of components	g	%
1. Turmeric root powder	0.750	83.33
2. Black pepper dry extract	0.005	0.56
3. Povidone (Eu.Ph.)	0.055	6,11
4. PROSOLV SMCC® 50 (Eu.Ph.)	0.063	7,00
5. EXPLOTAB® (Eu.Ph.)	0.018	2.00
6. Magnesium stearate (Eu.Ph.)	0.009	1.00
Weight of tablet:	**0.900**	**100.0**

For determination of time of wet granules drying of the turmeric root powder and the black pepper extract researches of kinetics of drying process were carried out at shelf type dryer. Esperimental information of drying process of wet granules of the turmeric root powder and the black pepper extract is resulted in a fig. 3.5. The thickness of granules layer was made 0.8–1 cm. The loss of moisture was determined as described in the chapter 2.

Loss of moisture in granules take place first 30 min intensively enough, this process is slow further. For the obtaining granules with necessary properties time of drying must be 8 hour at a temperature of 55±5 ^{0}C.

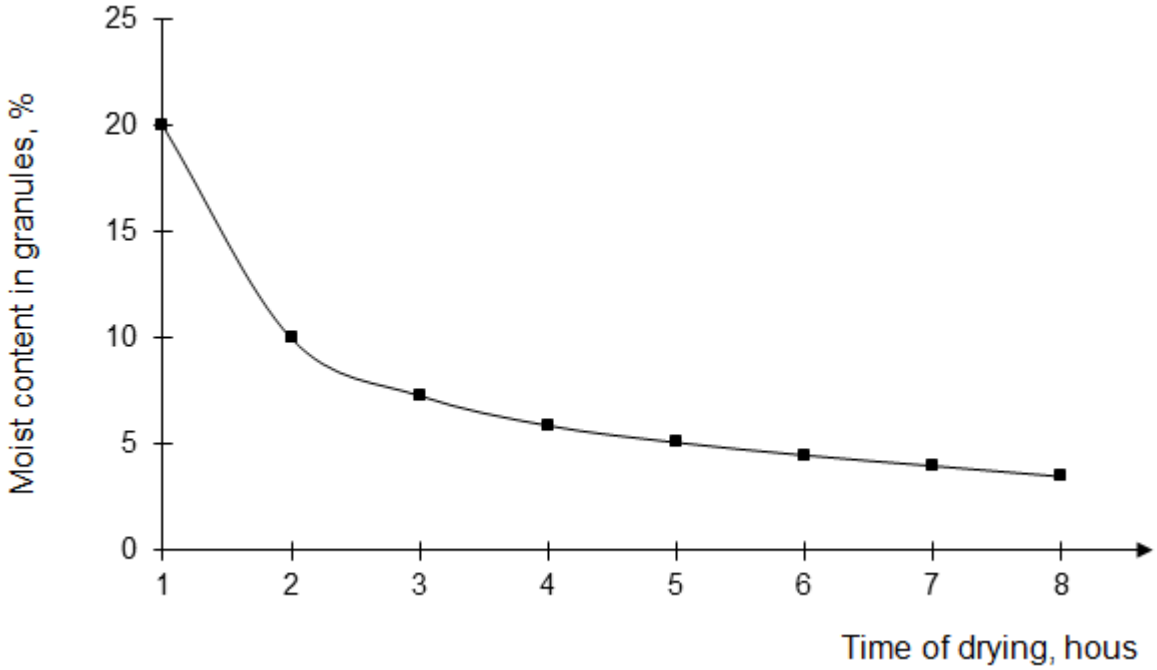

Fig. 3.5. Kinetics of drying process of granules with the turmeric root powder and the black pepper extract in the shelf type dryer

Residual moisture of tablets mass had considerable influence on the resistance to crushing of tablets that was determined at the development of the tablet's technology. The optimum residual moisture of mass was detected by the examination of tablets masses with different moisture content. The results of researches are shown in table 3.3.

As shown in these table 3.3, that there is not quality appearance of tablets and there is tablets adhesion to press-tools at content of moisture in tablets mass more than 5 %. Thus, the optimum residual moisture of tablets mass must be within the limits of 4.5±0.1 %. If there is insufficient moisture, the tablets can delaminate,

It was necessary to coat tablets with the moisture-resistant film in connection with a hygroscopicity of blend of the turmeric root powder and the black pepper extract and coloring properties of turmeric.

Table *3.3*

The influence of a residual moisture content of tablet masses with the turmeric root powder and the black pepper extract on the tablets compressing and quality

Moisture content in the tablets mass, %	Quality indexes of obtained tablets		Observations
	The resistance to crushing, N	Disintegration, min	
5.0 ± 0.1	72±0.4	12±0.5	Tablets shine is absent
4.0 ± 0.1	71±0.3	11±0.5	Tablets appearance is good. Adhesion is absent
3.0 ± 0.1	65±0.5	10±2.0	Tablets exfoliation
2.0 ± 0.1	63±0.6	10±2.5	Tablets exfoliation

Note: n=5

3.3 Coating of tablets of the turmeric root powder and the black pepper extract

The Opadry II 85F Yellow supplied by Colorcon (USA) was utilized as film-forming material for the tablets-cores with the turmeric root powder and the black pepper extract. The followings components are in the composition of the Opadry II: hydroxypropylmethyl cellulose (HPMC), talc, polyvinyl alcohol, polyethylene glycol, titanium dioxide, and colorants: iron oxide yellow and iron oxide red.

In accordance to information of firm-producer of film-forming coat material a concentration of Opadry II 85F Yellow powder must be 12–15 % in the film-forming system. Therefore, the 15 % concentration was used.

A plasticizer in film-forming coat material (polyethylene glycol) gives film elasticity, improves the wettability of film-forming solution.

Polyviol is used in the composition for coat as moisture-resistant component.

Titanium dioxide is a pigment of the film-forming system, provide full opacity of the dry film.

Talc is included in the composition of the film-forming system with the purpose of more even distributing of coat system on the surface of tablets-cores.

Thus, on the basis of the carried out researches for the tablets of the turmeric root powder and the black pepper extract a moisture-resistant coat was offered, technology of tablets coating is resulted below.

3.4 Technological process of tablets from the turmeric root powder and the black pepper extract

The process of tablets production from the turmeric root powder and the black pepper extract must be carried out given sanitary-hygenic requirements. The flow-chart of technological process of production of coated tablets of the turmeric root powder and the black pepper extract, is resulted on a fig. 3.6.

Technology of tablets-cores

Components on the stage of raw material preparation, must be accompanied the documents of entrance control, which confirm accordance of their quality a reference documentation, also must be tested on a microbiological cleanness.

Batch is formed to the capacity of mixer, for example, on 100 kg of tablet mass. Weigh the components on scales and sift them on vibrosieve: through a sieve with the size of orifices (0.5 ± 0.05) mm.

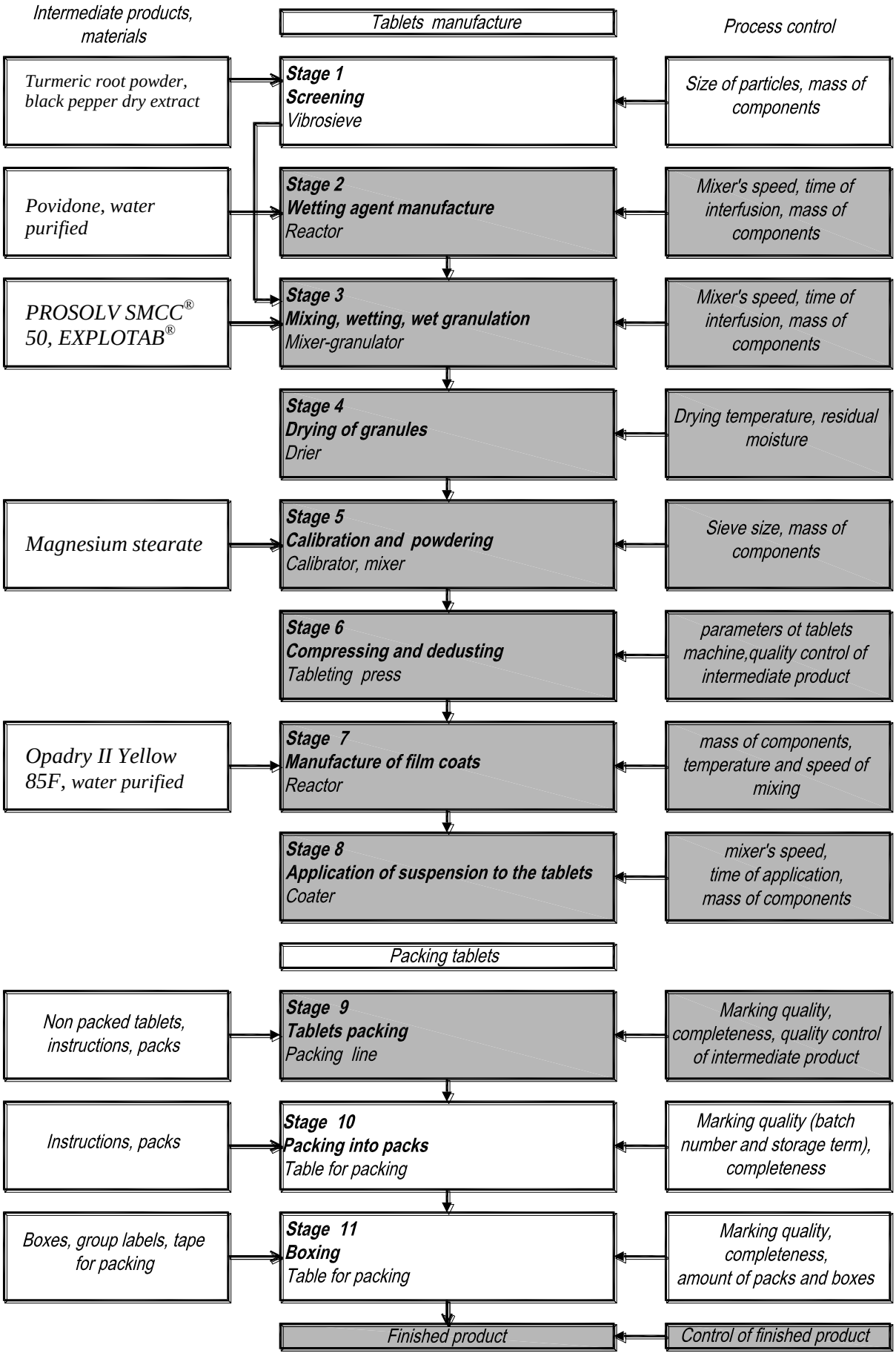

Fig. 3.6 The flow chart of coated tablets manufacture

For obtainig binder solution weigh the necessary amount of povidone, dissolve it in a measured amount of water purified, with a temperature 45 ± 2 °C, cool to the room temperature and filter through a net with the size of orifices (0.2 ± 0,03) mm.

Mixing of components of medicinal form is carried out in the blender. For this purpose load the components of tablet mass: the turmeric root powder, and the black pepper extract with silicified microcrystalline cellulose PROSOLV SMCC® 50, EXPLOTAB® in a necessary amount and then mix carefully. Then moisten the mixture with a 10 % povidone solution. Make wet granulation through a net with the size of orifices 2 mm in granulator. Drying of wet granules is carried out in the shelf type dryer at a temperature 55 ± 5 °C to the moisture (4.5±0.1) %.

After the calibration through a mesh 2 mm and powdering of the masses with magnesium stearate, tablets-cores with the turmeric root powder and the black pepper extract compress into tablets with average mass 0.9 g±5% using capsule-shaped, biconvex punches of the rotor tablet press.

Technology of tablets coating

Preparation of the film-forming system

The weighed amount of dry powder Opadry II white 85F add to the and mix by a mixer. Then film-forming system is filtered through a net № 38 with the size of orifices (0.192±0,021) mm.

Coating of tablets-cores of the turmeric root powder and the black pepper extract

Tablets-cores in an amount 15–16 kg put into a dragée pan, plug it in work and give air with a temperature (18–20) ^{0}C. Then turn on heating and warm up tablets-cores during 10–15 min to the temperature (30–35) ^{0}C. Speed of film-forming solution spraying from 25 to 30 ml/min.

Cool tablets to the room temperature after coatig and pack to blister packaging from tape of polyvinylchloride and foils aluminium, printed, lacquered.

A film coating is formed through the application of a thin, even, and continuous film around the surface of a tablet. The film coating serves numerous purposes, from making it waterproof to easy identify and take by swallowing.

3.5. Researches of parameters of quality of obtained tablets with the turmeric root powder and the black pepper extract

The parameters of quality of coated tablets of the turmeric root powder and the black pepper extract were determined using standard methods of the European Pharmacopoeia.

The criteria of estimation of quality were: original appearance, average weight of tablets, disintegration:

1) Original appearance: tablets with yellow color of biconvex capsule-shaped;

2) Average weight of tablet of 0,9 g ± 5%;

3) Homogeneity of tablet weight: only two tablets from 20 can have deviations from average weight on a size more than ± 5%, but not one of tablets can have deviation from average weight on more ± 5 %.

4) Disintagration time: tablets must disintegrate in water no more than 30 min

Coated tablets of the turmeric root powder and the black pepper extract were estimated on stability. The results of researches are presented in a table 3.4.

From information of table it is seen that pharmaco-technological properties of tablets remain stable during 18 months (observation time).

The stability monitoring continues.

Table 3.4

Researches on a stability of tablets with the turmeric root powder and the black pepper extract in storage conditions 15-25 °C

Characteristics	Freshly made	Storage time, month		
		6	12	18
1. Appearance	Yellow coated tablets with uniform surface			
2. Average weight, g	0,910	0,912	0,915	0,914
3. Disintegration, min (tablets must disintegrate during no more than 30 min)	19.0 ± 4	20.0 ± 5,1	19.5 ± 4,3	19.4 ± 5,4
4. Specific humidity, %	4.3 ± 0,2	4.4 ± 0,3	4.2 ± 0,1	4.3 ± 0,1

Note: n=5.

CONCLUSIONS TO CHAPTER 3

1. The composition and technology of phytopreparation with the turmeric root powder and the black pepper extract are developed in the form of coated tablets as a result of theoretical and experimental researches.
2. Influence of excipients is studied on the indexes of technological characteristics of tablet masses and indexes of quality of the obtained coated tablets.
3. With the purpose of defence of tablets from influence of moisture of environment water system coat was used, providing uniformity of coat distribution on the core and stability of the prepared tablets in storage.

GENERAL CONCLUSIONS

1. Osteoarthritis is a condition that affects over a third of the population of the world, and is a large source of healthcare costs. Results from this literature review suggest that curcumin in turmeric root powder can be considered by physicians as an adjunctive therapy to traditional therapies for osteoarthritis, as it does appear to offer benefit in pain relief compared to placebo. Although more evidence is needed to support curcumin in turmeric root powder as a replacement for NSAIDs. However, curcumin appears to be a safe and effective addition to osteoarthritis treatments for patients, and should not be overlooked by physicians. Also, the combining black pepper extract with piperine and turmeric root powder with curcumin in enhances curcumin absorption.

2. The complex of different theoretical and experimental researches is carried out to development of composition of one from pharmaceuticals with the turmeric root powder and the black pepper extract in the tablets form.

3. Physical and chemical and also pharmaco-technological properties of the turmeric root powder and the black pepper extract and their mix, allowing to justify the composition and rational technology on its basis, are investigated.

4. A high dose tablet formulation of turmeric root powder with low dose of the black pepper extract was developed and evaluated using silicified microcrystalline cellulose PROSOLV SMCC® 50 and sodium starch glycolate EXPLOTAB® in a wet granulation process.

5. Researches are carried out on stability of phytopreparation of the turmeric root powder and the black pepper extract in the form of tablets.

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APPENDIX

Appendix A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ГРАМОТА

за участь

отримав(ла)

Ісаме Сукейна

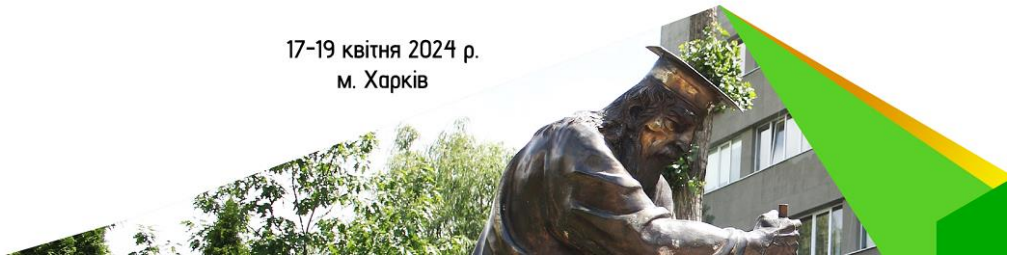
у секційному засіданні студентського наукового товариства кафедри технологій фармацевтичних препаратів

XXX Міжнародна науково-практична конференція молодих вчених та студентів **"Актуальні питання створення нових лікарських засобів"**

В.о. ректора
Національного фармацевтичного університету

Алла КОТВІЦЬКА

17-19 квітня 2024 р.
м. Харків



Appendix B


CERTIFICATE
is awarded to
Icame Soukaina
for being an active participant in
V International Scientific and Practical Conference
"EUROPEAN CONGRESS
OF SCIENTIFIC ACHIEVEMENTS"
24 Hours of Participation
(0,8 ECTS credits)
BARCELONA
20-22 May 2024
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INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE
EUROPEAN CONGRESS OF SCIENTIFIC ACHIEVEMENTS
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20-22 MAY 2024

Appendix C

SCI-CONF.COM.UA

EUROPEAN CONGRESS OF SCIENTIFIC ACHIEVEMENTS

PROCEEDINGS OF V INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE MAY 20-22, 2024

BARCELONA 2024

Appendix C (continued)

Appendix C (continued)

PHARMACEUTICAL SCIENCES

DEVELOPMENT OF THE TABLETS-CORE COMPOSITION AND TECHNOLOGY WITH TURMERIC ROOT POWDER AND BLACK PEPPER EXTRACT

Icame Soukaina,
Higher education graduate
Sichkar Antonina Anatoliivna,
PhD (Pharmacy), Associate Professor
Kryklyva Iryna Oleksandrivna,
PhD (Pharmacy), Associate Professor
Ponomarov Yelisei Serhiyovych,
Higher education applicant
National University of pharmacy,
Kharkiv, Ukraine

Introductions. The important task of modern pharmacy is the creation of new medicines based on medicinal plant raw materials, which have centuries-old experience of use, but the nomenclature of medicines with such plant extracts remains limited. Curcuma longa L. or turmeric and Black pepper (Piper nigrum L.) can be called promising sources for obtaining phytopreparations for the treatment of osteoarthritis (OA).

Osteoarthritis is a degenerative joint disease characterized by progressive inflammation leading to pain, limited joint function, and loss of social activity. Synthetic medicines are ineffective for patients in many cases, and are usually associated with gastrointestinal side effects (for example non-steroidal anti-inflammatory drugs).

The bioactive compound of Curcuma longa such as curcumin exert chondroprotective effects against OA. Curcumin is as effective as ibuprofen for the treatment of pain in knee OA. Black pepper possesses diverse biological activities

Appendix C (continued)

including anti-inflammatory properties.

The active phenolic component in black pepper, piperine, has the anti-inflammatory activity in human OA chondrocytes. Also, the combining piperine in black pepper extract with curcumin in turmeric root powder enhances curcumin absorption.

The whole turmeric root powder may be more beneficial than the curcumin extract: only very small amounts of curcumin are absorbed into the bloodstream. The turmeric root powder stays in the digestive tract longer than curcumin, releasing curcumin along with other beneficial substances.

Aim. Development of the composition of tablets-cores with a turmeric root powder and a black pepper extract for further coating.

Materials and methods. Dried and ground turmeric root was used as the turmeric root powder with curcumin content 3-4% (India). The dry extract of Black pepper, standardized to contain ≥ 95 % piperine (Ukraine) was used as second active ingredient. The studies on the quality of tablets were determined using standard methods of the European Pharmacopoeia.

Results and discussion. According to bad compressibility of the turmeric root powder (9 N), the dose of which was 750 mg and was very high, and low flow ability (68 sec /100 g or 1,47 g/sec) direct compression with most commonly used modern excipients did not bring acceptable properties of tablets. Further experiments obtaining of tablets by wet granulation process have provided medicine in solid form with good parameters of the quality.

Granulation of the powder mix for even distribution of large number of different particles in each granule is also one of solutions of segregation problems used for low dose unit dosage forms. The dose of a black pepper extract is very small and this extract was previously mixed with silicified microcrystalline cellulose PROSOLV SMCC® 50 (JRS PHARMA).

Povidone was dissolved in water and added with spraying to the well-blended mixture of the turmeric root powder, a black pepper extract in PROSOLV SMCC® 50 and a superdisintegrant sodium starch glycolate EXPLOTAB®. After granulation,

Appendix C (continued)

drying (up to 1.5 %) and calibration of granulate Mg-stearate (0.3 mm) was added to granulate, and blended. The resulting final blend was compressed into tablets using capsule-shaped, biconvex punches.

Conclusions. On the basis of pharmaco-technological research, the composition and technology of tablet cores with the turmeric root powder and black pepper extract were developed.