Ф А 2.2.1-32-367

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
Pharmaceutical Faculty
Drug Technology Department

QUALIFICATION WORK

on the topic: «**RESEARCH TO IMPROVE THE SOLUBILITY OF SIMVASTATIN IN AN ORAL PREPARATION**»

Prepared by: higher education graduate of group Phm20(4.10d)eng-01
specialty 226 Pharmacy, industrial pharmacy
educational and professional program Pharmacy
Fadwa DILAI
Supervisor: head of the drug technology department, doctor of pharmacy, professor Liliia VYSHNEVSKA
Reviewer: head of the department of industrial technology of drugs and cosmetics, doctor of pharmacy, professor Olena RUBAN

Kharkiv – 2025

ANNOTATION

Theoretical studies have confirmed the feasibility and relevance of developing drugs for internal use with improved solubility of active pharmaceutical ingredients. For our own research, we chose a lipid delivery system.

During practical studies, we developed the composition and confirmed the effectiveness of the lipid delivery system for simvastatin.

The work is presented on 40 pages, contains 5 tables, 8 figures, 2 formulas and 30 references.

Key words: simvastatin, lipid delivery system, oral use, improve solubility, biopharmaceutical research.

CONTENT

LIST OF ABBREVIATIONS

API – active pharmaceutical ingredient;

ATC – anatomical and therapeutic chemical classification;

BCS – biopharmaceutical classification system;

BP – British Pharmacopoeia;

CAS – Chemical Abstracts Service;

DF – dosage form;

DMG – distilled monoglycerides;

GIT – gastrointestinal tract;

GMS – glycerol monostearate;

HCO – hydrogenated castor oil;

HNS – hydrophilic non-aqueous solvent;

SPU – State Pharmacopoeia of Ukraine;

PEG – polyethylene glycol;

PhEur – European Pharmacopoeia.

INTRODUCTION

Actuality of the topic. The solubility of active pharmaceutical ingredients (APIs) used to manufacture oral medicines is a crucial factor that determines the rate and completeness of absorption of the active substance in the gastrointestinal tract (GIT) and, as a result, bioavailability and efficacy.

According to various literature sources, the share of water-insoluble APIs ranges from 40 to 50 % of their total amount. Since gastrointestinal fluids are 80 % water and polar, the use of hardly soluble substances in oral medicinal products is difficult and has a number of disadvantages, including slow absorption and low absorption rate, as well as reduced bioavailability of the active substance. This leads to the need to use larger amounts of APIs to manufacture the drug or to increase the frequency of drug administration in order to achieve the required therapeutic effect. On the one hand, this has a negative impact on the economic part of the production of such drugs, and on the other hand, it has a negative impact on patient compliance. In some cases, such as cyclosporine, it is impossible to include such an active substance in oral medicinal products, which may be aggravated by the lack of alternatives in choosing a route of administration.

The factors described above make it important to develop oral medicines with hardly soluble APIs using methods to improve their solubility in the GIT.

The purpose of the study. Confirm the relevance of research on improving the solubility of APIs and develop a lipid-based drug delivery system using simvastatin.

Tasks of the study: - to review, analyse and summarise the literature on possible ways to improve the solubility of APIs, in particular lipid delivery systems;

- to theoretically substantiate the choice of simvastatin as a potential API for lipid delivery system;

- to analyse the prevalence of different methods of improving simvastatin solubility;

- to propose the composition of the lipid-based drug delivery system, to study its properties and quality indicators;

- to obtain a lipid drug delivery system with simvastatin and develop its technology;

- to control the main quality indicators of the lipid delivery system with simvastatin;

- to study the effect of excipients on the rate of dissolution and release of APIs in vitro.

Research objects: simvastatin, lipid solvents, surfactants, co-solvents; samples of lipid system bases, lipid drug delivery system with simvastatin.

The subject of research: quality studies and biopharmaceutical research of a lipid-based drug delivery system with simvastatin.

Research methods. General scientific theoretical methods, and physical, physicochemical, pharmacotechnological, and biopharmaceutical methods were used in the research.

Practical significance of the results. The composition of the drug with simvastatin was modified, which, based on the results of further clinical trials, can be introduced into practical pharmacy and medicine as a drug with improved pharmacokinetic parameters.

Approval of research and publications. The results of the study were presented at the XXXI International Scientific and Practical Conference of Young Scientists and Students «Topical Issues of New Drug Development» in the format of an oral report (Appendix C). The abstracts were published in the Proceedings of the XXXI International Scientific and Practical Conference of Young Scientists and Students «Topical Issues of New Drug Development» (Appendices A, B).

Structure and scope of qualification work. The work is presented on 40 pages, contains 5 tables, 8 figures, 2 formulas and 30 references.

CHAPTER 1. IMPROVING THE SOLUBILITY OF SIMVASTATIN (Literature review)

1.1 Review of methods for improving the solubility of active substances in oral medicines

To improve the solubility of hardly soluble substances in the aqueous environment of the gastrointestinal tract, techniques and methods are used that have a direct impact on the physical state of the substance or can modify the molecule of the active substance (Fig. 1). In this case, the therapeutic activity of the drug is increased by accelerating and increasing the absorption of the active substance, as well as increasing the bioavailability [11, 24, 28].

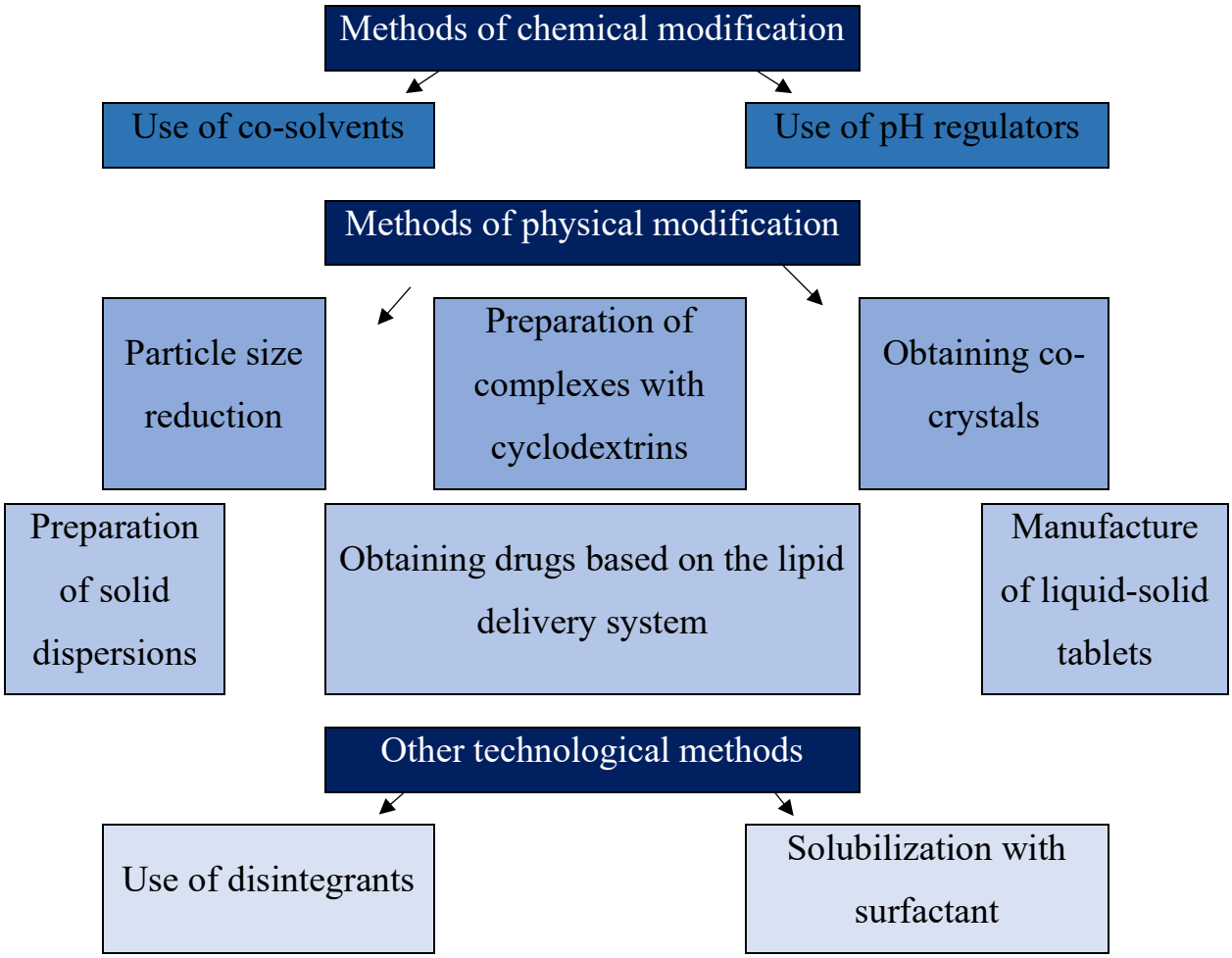

Fig. 1 Methods for improving the solubility of active substances

Methods of chemical modification. Substances that are difficult to dissolve in aqueous medium are hydrophobic by nature, and the use of hydrophilic co-solvents

allows improving their solubility by changing the polarity of the substance molecules. The main factors in providing a mechanism for improving solubility are the reduction of interfacial tension between the hydrophobic substance and the aqueous solution, the simultaneous reduction of mutual attraction of water molecules by small hydrocarbon regions in the solvent molecule and the promotion of solubility in water by hydrophilic hydrogen bonds. Examples of co-solvents that can easily dissolve some hydrophobic substances and at the same time mix with water are propylene glycol, ethanol, polyethylene oxides, etc [3, 20].

The latest substances that are considered as an alternative to organic solvents for use as co-solvents are ionic liquids. They have a number of advantages that make them promising excipients in modern pharmaceutical development. Ionic liquids can be optimised at the molecular level to achieve a specific task: improving the solubility of the active substance or accelerating its absorption. The structural properties of ionic liquids can be adapted by changing the anions and cations that make up their composition. In addition to improving pharmacokinetic parameters, options for improving pharmacodynamic properties are being considered, which allows us to obtain the most effective drugs with minimal adverse side effects [2].

Since the solubility of substances depends not only on their own properties but also on the dissolution medium, excipients can be used to improve solubility by adjusting the pH during the dissolution of active ingredients that are in an ionised state. The pH value of the diffusion layer is changed by H^+ or OH^- ions. For substances that have a weakly basic reaction during electrolytic dissociation, acids are used, for example, citric, tartaric, carbonate. For substances with an acidic reaction, it is advisable to create a basic microenvironment. When substances are added to the formulation that can affect the pH of the microenvironment of the active substance during its dissolution in gastrointestinal fluids, solubility is improved by increasing the period of the substance's residence in the ionised state [30].

Methods of physical modification. Each of the physical modification methods helps to reduce the particle size of substances in one way or another. It is known that with the reduction of particle size, the solubility of the active substance improves

and accelerates. A mechanical method of particle size reduction is grinding. This method is used in both extemporaneous manufacturing and industrial production of medicinal products. Auxiliary equipment is used to obtain particles of substance with a size from 0,16 to <0,1 mm (mortars, ball mills, screw grinders, etc.).

The mechanical grinding method is the simplest and is increasingly used only to achieve a uniform particle size throughout the substance, and subsequently in the drug product. This is due to the availability of more modern and more efficient ways to improve solubility, as well as the fact that the process of long grinding has some disadvantages. For example, high physical exertion and hyperthermic effects during grinding and friction during grinding [5,7,16].

More modern ways to reduce particle size are micronisation and nanoscale technologies. To obtain microparticles, a substance is dissolved in a volatile organic solvent or a dispersion is made with it and spray dried.

To obtain nanoparticles, a nanosuspension is first prepared by homogenisation under high pressure, microfluidisation, wet grinding, supercritical fluid technology and ultrasonic dispersion. In order to facilitate the introduction of such substances into the composition of solid drug products, lyophilic drying is performed.

Cyclodextrins are cyclic oligoglycosides that are able to accept small hydrophobic molecules due to the presence of a non-polar cavity in the centre of the ring of their molecule. At the same time, hydrophilic groups are located on the outside of the ring, which provide high affinity for the hydrophilic solvent. This results in the formation of clathrates, which have improved solubility, physical and chemical stability, absorption in the gastrointestinal tract and bioavailability.

Cyclodextrins are divided into α, β and γ structures, depending on the number of glycosidic groups in the molecule. β-cyclodextrins are commonly used to produce complexes [8, 19].

Co-crystallisation is a method of solubility improvement based on the formation of hydrogen bonds between the API and the coformer to obtain a multicomponent crystalline compound with specified physical and chemical

properties. The peculiarity of this method is the possibility of improving the organoleptic properties of the substance, in addition to improving its solubility.

The co-crystals are obtained by grinding and mixing the dry substances for a rather long time, sometimes up to 45 minutes. Citric acid, glutaric acid, benzoic acid, adipic acid, cinnamic acid, urea, sodium acetate, succinate, sodium saccharinate, etc. are used as coformers [21].

The preparation of solid dispersions is the most popular method of improving the solubility of crystalline and large crystalline substances among scientists conducting research in this area. For their manufacture, the technology of dispersing a substance with polymeric substances in a powdered state is used. Polymeric substances, also known as carriers or matrices, must be water-soluble to be effective in improving the solubility of hydrophobic substances. The main advantage of solid dispersions is that the hardly soluble substance in their composition has an amorphous state, due to which it has higher solubility indicators compared to its crystalline state [4, 14].

Carriers used to obtain solid dispersions: high molecular weight polyethylene glycol, polyvinyl pyrolidone, hydroxypropyl methyl cellulose starch glycolate, croscarmellose. Methods: evaporation of the solvent, which is usually a volatile organic substance, freeze-drying or spraying and the use of supercritical liquid technologies.

In the manufacture of liquid-solid tablets, a substance that is hardly soluble in water enters the drug in an already dissolved state. The main requirement is the minimum amount of solvent to make it easy to introduce the solution to the tabletmass, so it is important to choose a solvent in which the substance is very easily or easily soluble. To introduce a solution of the active substance into the tablet mass, it is mixed with substances that can easily absorb moisture (silicon dioxide), add disintegrants (up to 5 % of the total mass), if necessary, lubricants (up to 1 % of the total mass). Tablets are prepared either by direct compression or by compression with preliminary wet granulation.

Often in the sources of literature there is information on the combination of some methods of physical modification. This can be the manufacture of solid dispersions with complexes with cyclodextrins, or the use of ionic liquids for the manufacture of self-emulsifying systems, the manufacture of liquid-solid tablets for self-emulsifying systems, the production of solid dispersions with lipid drug delivery systems [9, 17, 26].

Other technological methods. Surfactants in oral preparations help to reduce surface tension at the interface between the phase separation of the hydrophobic substance and the aqueous dispersion medium. Due to this, surfactants have a positive effect on the solubilization of hydrophobic substances in the gastrointestinal medium. An additional advantage of this method is the economic component, the relatively low cost distinguishes it from other methods of improving the solubility or absorption of API. Therefore, despite some shortcomings, for example, an increase in the size of molecules due to the inclusion of the active substance in the micelle of surfactants, both scientists and manufacturers (Fluconazol-Darnitsa (pharmaceutical company Darnitsa, Kyiv, Ukraine), Omeprazol (Arterium Corporation, Kyiv, Ukraine) widely use the introduction into the composition of surfactants. Sodium lauryl sulfate, poloxamers, polysorbates and the like are commonly used.

The release of the active substance is accelerated by the introduction of disintegrants into the preparations. They provide mechanical destruction of solid DF when they enter the gastrointestinal tract, which accelerates the processes of disintegration, dissolution and release of API. Most often, cellulose derivatives, crospovidone, croscarmellose sodium, silicon dioxide and starch are used.

1.2 Lipid-based drug delivery systems: a promising development

Lipid drug delivery systems are represented by microemulsions, solid lipid nanoparticles, liposomes and self-emulsifying drug delivery systems. The uniqueness of lipid-based drug delivery systems lies in their ability to improve not only the solubility of the substance, but also its absorption in the gastrointestinal

medium. Therefore, lipid delivery systems are most often used to improve the solubility of substances that are classified as class IV according to the biopharmaceutical classification system (BCS). Such substances are hardly soluble in water and difficult to penetrate biological membranes. Lipid drug delivery systems for APIs are also often used, which are classified as class II by BCS (have only low solubility in water) and sometimes as class III by BCS (have only low absorption rates).

Microemulsions are microheterogenic isotropic disperse systems whose particle size ranges from 10-200 nm. Compared to conventional emulsions, microemulsions have increased stability, require the introduction of more PAR, sometimes using co-PAR, and have differences in a number of other properties. In most cases, surfactants that have high hydrophilic-lipophilic balance values (15 to 18) are used to prepare microemulsions [1].

In addition to traditional homogenization methods, microemulsions can be obtained by ultrasound. Microemulsions, as well as conventional emulsions, can be of the oil-in-water, water-in-oil type, and a bi-continuum emulsion can be formed if the ratio of oil to water phases is 1:1.

When developing microemulsions for oral use, not only hydrophobic substances are introduced into their composition in order to improve their solubility, but also hydrophilic substances in order to improve their absorption into the gastrointestinal tract, because emulsion preparations, especially with such a small particle size of the dispersed phase, can facilitate the passage of API through biological membranes. This property of microemulsions makes their use relevant in preparations for external use [6].

Solid lipid nanoparticles are second only to solid dispersions in their popularity. The composition of solid lipid nanoparticles is identical to emulsions: lipid phase, aqueous phase and surfactant. The lipid phase includes steroid compounds, diglycerides, triglycerides or mixtures thereof (0,1-30 %). The peculiarity is that the substances of the lipid phase at room temperature and at body

temperature are in the solid state. surfactant is added to solid lipid nanoparticles at concentration 0,5-5 %.

The type of structure of solid lipid nanoparticles depends on the composition, solubility profile of API and the technological process [18].

Type I is a homogeneous matrix that is characteristic of APIs of a very lipophilic nature. The production method is cold or hot homogenization. In the case of cold homogenization, the active substance is dissolved in a lipid matrix, homogenization is carried out under high pressure, which causes the formation of mechanical breaks and, as a result, nanoscale particles. In hot homogenization, nanoparticles are formed in a similar way, the difference is the dissolution of the active substance in the lipid matrix at an elevated temperature.

Type II - the active substance is localized in the shell of lipid nanoparticles. This type of structure is used in preparations for external use when it is necessary to improve the permeability of the API transdermally. The production method is hot homogenization. After combining the substance with a lipid base, cooling is carried out, during which lipid molecules first precipitate, forming the nucleus of the future structure, after which the concentration of API in still molten lipids increases, the solubility limit of API is reached and the outer shell is formed due to crystallization of the formed mixture.

Type III is a structure with the maximum concentration of API in the nucleus of a solid lipid nanoparticle. It can be formed when the concentration of the active substance close to the solubility limit is immediately in the entire volume of the lipid, and the first lipid precipitates with the maximum concentration of API, forming the nucleus. To form the shell, a lipid with a low concentration of the active substance remains.

The particle size of the solid lipid nanoparticles may be less than 100 nm. This is achieved not only due to the above-described features of the technology, but also due to the optimally selected components and their ratios. Glycerol tribegenate, myristyl myristate, oleic acid, cetyl palmitate and the like are generally used as lipid components. Polysorbates, lecithins can be used as surfactants [25].

In addition to oral and topical preparations, solid lipid nanoparticles are used in DF for parenteral and inhalation administration.

Liposomes are diphilic structures whose shell consists of phospholipids, and the internal medium is aqueous (concentric vesicles of spherical shape, ranging in size from 20 nm to several microns). They are used to making drugs not only with hydrophobic, but also with hydrophilic APIs. The main direction of the function of liposomes is to improve the absorption of the active substance, in addition, liposomes are able to protect the substances contained in them from damage. They can also be used to make controlled-release drugs or targeted drug delivery [26, 29].

1.3 Review of methods to improve the solubility of simvastatin

The main general criteria for selecting an active substance for inclusion in lipid systems are as follows:

- availability for use in Ukraine;
- presence in the list of approved APIs;
- availability of information on the safety of the API for oral administration;
- availability of information on reproducible quality control methods.

Characteristic criteria for selection of APIs for inclusion in medicinal products with improved API solubility

- poor solubility in water and 0,1 M hydrochloric acid solution (for gastric soluble forms), 0,1 M sodium hydroxide solution (for intestinal soluble forms);
- low bioavailability;
- absence of life-threatening side effects that may be enhanced by modification of pharmacokinetic parameters associated with improved API solubility.

The API we chose, simvastatin, meets all of the above criteria. However, when conducting studies on the development of lipid system with simvastatin, it is worth considering such an undesirable side effect as myopathy and conducting additional studies to assess the risks of its occurrence.

Simvastatin is an antihyperlipidemic drug belonging to the group of statins and is a semi-synthetic compound. Simvastatin substance is highly insoluble in water and readily soluble in 96 % ethanol.

Improving the solubility of simvastatin in the gastrointestinal tract is important because, despite its easy absorption in the intestine, the substance remains highly insoluble in the stomach, where the process of drug breakdown and dissolution begins. Simvastatin is a non-polar substance with a fairly high lipophilicity index Log P=4,7. It is metabolised in the small intestine and liver by cytochrome P450 3A with the formation of active and inactive metabolites. When it enters the bloodstream, a significant amount of the active form of simvastatin binds to plasma proteins. The bioavailability of simvastatin is about 5 %. The half-life is 1,3-3 hours.

The relevance of improving the solubility of simvastatin is also confirmed by studies in this area. For example, the introduction of simvastatin into solid lipid nanoparticles, incorporation of simvastatin into polymeric carrier matrices, preparation of solid dispersions with simvastatin, and addition of surfactants to the drug [13, 15, 27].

There is also information on studies of lipid systems for simvastatin. Scientists use substances in their composition that are difficult to obtain for the Ukrainian raw materials market. The composition of the composition containing a solution of simvastatin in a mixture of surfactants (Capryol 90 and Tween 80), which does not contain a lipophilic phase, is proposed, which is significantly different from the traditional approach to the creation of lipid systems (use of a hydrophobic solvent, surfactant and co-surfactant or co-solvents).

Therefore, the positive experience of using various methods to increase the solubility of simvastatin was an additional factor in choosing it for our studies, which will allow us to objectively assess the effectiveness of the developed composition of the self-emulsifying composition. Thus, simvastatin is a suitable API to demonstrate the effectiveness of the introduction of hardly soluble drugs into lipid systems.

CONCLUSIONS TO CHAPTER 1

1. Analysis of available literature on the development of oral preparations with improved solubility of hardly soluble APIs has shown that various methods are used to improve the solubility of substances depending on the chemical structure, molecular weight and properties of the selected substance.

2. One of the factors in choosing a method is economic feasibility, since manufacturers prefer more cost-effective methods (introduction into the composition of the drug surfactant). Scientists most often use the formation of solid dispersions and solid lipid nanoparticles, which is confirmed by the vast majority of publications on these methods of improving solubility.

3. The development of drugs based on lipid systems is a promising direction of pharmaceutical development, as it will expand the range of studies conducted by Ukrainian scientists in order to improve the solubility of hardly soluble substances. In the future, lipid systems can replenish the range of domestic preparations for oral use with improved release and increased therapeutic activity of API.

CHAPTER 2. MATERIALS AND METHODS

2.1 Materials of the research

The study materials were samples of the bases of lipid systems with a lipophilic solvent, surfactants and co-solvents, and a lipid delivery system with simvastatin.

Simvastatin (SPU, BP, PhEur, USP, CAS №: 79902-63-9). Series DK40-2005021, China. Crystalline or amorphous powder of white or almost white color, practically insoluble in water, easily soluble in ethanol 96 %, very easily soluble in methylene chloride, thermostable. Gross formula: $C_{25}H_{38}O_5$ (Fig. 2). Molecular weight – 418,6. BCS class is the second.

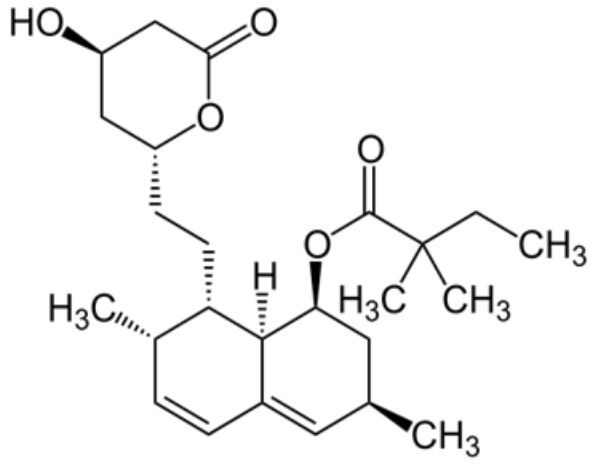

Fig. 2 Structural formula of simvastatin

ATC classification code – C10A A01. Simvastatin – prodrugs (inactive lactone form is metabolized in the liver with the formation of an active β-hydroxy acid form). The active form is a 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor, inhibits the synthesis of total cholesterol, triglycerides, low density lipoproteins and very low density lipoproteins.

0,1 M chloride acid solution made from concentrated chloride acid (37%) and purified water.

Concentrated chloride acid (SPU, BP, PhEur, USP, CAS №: 7647-01-0). Transparent, colorless, smoky liquid. Content is not less than 35,0% (w/w) and not

more than 39,0% (w/w). Easily mixed with water. The relative density is 1,18. Chemical formula: HCl. Molecular weight – 36,46 [12].

Purified water (SPU, BP, PhEur, USP, CAS №: 7732-18-5). Clear, colorless liquid without taste and smell, obtained by distillation. Gross formula: H_2O. Molecular weight – 18,02. pH – 5,0-7,0 [12].

Purified water is a pharmacologically and chemically indifferent substance. Used as a solvent. It is used in many industries, most often in the chemical, pharmaceutical, food industry, mechanical engineering.

Propylene glycol (SPU, BP, PhEur, USP, CAS №: 57-55-6). Transparent, colorless, viscous liquid, hygroscopic. Easily mixed with water and ethanol 96 %. Boiling point – 184-189 °C. Chemical structure: propane-1,2-diol. Gross formula: $S_3N_8O_2$. Molecular weight – 76,1 [12].

It is used in the pharmaceutical, cosmetic and food industries. In pharmacy, most often as a solvent for some hardly water-soluble APIs, for example, anesthesin, barbituric acid derivatives, fat-soluble vitamins, etc. It is also often used as a stabilizer (oxytetracycline solution for intramuscular injections), a preservative and a moisturizing component.

Glycerol triacetate (BP, PhEur, USP, CAS №: 102-76-1). Transparent, colorless, viscous liquid, has a specific smell. It is mixed with water, chloroform, toluene, ethanol 96 %. Boiling point – 258 °C. Chemical structure: 1,2,3-propanetriol triacetate. Gross formula: $C_9H_{14}O_6$. Molecular weight – 218,21 [12].

In pharmacy, it is used as a hydrophilic plasticizer, it is part of capsules, granule shells, tablets. In the cosmetic and food industry, it is used as a solvent and for fixing aroma.

Polyethylene glycol 400 (PEG 400) is a colorless, transparent, viscous liquid with a faint characteristic odor. Organic HNS. Hygroscopic, has high osmotic activity. It is mixed with water, methylene chloride, chloroform. It is used to dissolve some hardly water-soluble APIs, for example, benzoic and salicylic acid, anesthesin, sulfonamides, etc [12].

Polysorbate 80 (PhEur, USP, CAS №: 9005-65-6). A mixture of partial complex esters of fatty acids, mainly oleic, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The oily liquid is colorless or brownish-yellow, transparent or somewhat opalescent. It is mixed with water, ethanol, ethyl acetate, methanol, at room temperature practically does not mix with fatty oils and mineral oil. The relative density is about 1,10. Viscosity – about 400 mPa·s at a temperature of 25 °C [12].

Used as a stabilizer, emulsifier (non-ionic surfactant, forms emulsions of the first kind).

Polyethylene glycol 40 hydrogenated castor oil (PEG 40 HCO) (BP, USP, CAS №: 61788-85-0). At room temperature, a thick, viscous substance of white or almost white color, has a specific smell. Soluble in water, ethanol and fatty oils. It is characterized by a decrease in its viscosity with an increase in temperature.

In pharmacy, it is used as a solubilizer, stabilizer, viscosity regulator, emulsifier (non-ionic, forms emulsions of the first kind). It is widely used in the production of cosmetics in most cases in order to dissolve essential oils, lipid perfume components and other hydrophobic substances. In addition, with external use, it helps to soften the skin.

Glycerol monostearate (GMS) (BP, PhEur, USP, CAS №: 31566-31-1). The solid, waxy substance or powder is uniform, or the flakes are white or almost white. Practically insoluble in water, soluble in ethanol (96 %) and fatty oils at a temperature of 60 °C. Melting point – 58-62 °C. Gross formula: $S_{21}N_{42}O_4$. Molecular weight – 358,6 [12].

GMS is a mixture of monoacylglycerols, mainly monostearoylglycerol, together with a variable content of di- and triacylglycerols. The total content of monoacylglycerols is in the range of 40-55 %, diacylglycerols – 30-45 %, triacylglycerols – 5-15 %.

In the manufacture of drugs and cosmetics, it is used as a plasticizer, stabilizer, emollient, emulsifier (non-ionic, forming emulsions of the second kind).

Distilled monoglycerides (DMG) (CAS №: 123-94-4). White or flesh-white powder or granular solid, tasteless and odorless. Easily soluble in fatty oils and ethanol, insoluble in water. They have a composition similar to GMS, but contain 90 % monoacylglycerols. Gross formula: $C_{21}H_{42}O_4$. Molecular weight – 358,56.

Refined ricin oil (PhEur, CAS №: 8001-79-4). Fatty oil obtained from ricin of ordinary seeds by cold pressing followed by pressing. Transparent, colorless or slightly yellow, viscous liquid, hygroscopic. It is mixed with ethanol (concentration above 90 %), glacial acetic acid, difficult to mix or not at all mixed with petroleum products. The relative density is about 0,958. Viscosity – about 1000 mPa·s. The refractive index is about 1,479 [12].

It is used as API (ATC A 06A B 05), which has a laxative effect when using 15-30 g of oil internally. With external use, it has a softening effect on the skin, strengthens the hair, and is also used to treat wounds, burns, ulcers, dandruff. As an excipient, it is used in small quantities as a solvent for hydrophobic APIs.

Refined sunflower oil (BP, PhEur, USP, CAS №: 8001-21-6). Fatty oil obtained from sunflower seeds by pressing or extraction is then refined. Clear, light-yellow liquid. It is practically not mixed with water and ethanol (96 %), it is mixed with oil refining products. The relative density is about 0,921. The refractive index is about 1,474 [12].

It is used in the food, paint and varnish industry, cooking, soap making. In pharmacy, it is the main component of the oil phase of classical pharmaceutical emulsions. It is also included in liniments, creams, ointments as a solvent, filler, softening, liquefying substance.

Refined corn oil (PhEur, USP, CAS №: 8001-30-7). Fatty oil obtained from corn seeds by pressing or extraction followed by refining. Clear, light yellow or yellow oil. It is practically not mixed with water and ethanol (96 %), it is mixed with oil refining products and methylene chloride. The relative density is about 0,920. The refractive index is about 1,474 [12].

It is widely used in the food industry, cooking, as well as sunflower oil. In pharmacy, it is used for the manufacture of tablets and capsules as a binding

substance, as well as a solvent in preparations for internal, external and parenteral use.

2.2 Methods of the research

Solubility of the active substance. The study was conducted at a temperature of 20±2 °C. On electronic scales weighed simvastatin solution, added to the corresponding minimum amount of solvent (1/2 of the weight of simvastatin solution). Further, under constant visual control, the solvent was gradually added until the solubility limit was reached, which was visually reflected by the complete solubility of the active substance (positive result), or until the maximum amount of the solvent was reached (ratio 1: x >10.000).

The result was considered negative if, at the maximum ratio of substance to solvent, undissolved particles on the filter material were observed after filtration. When a negative result was obtained, the test was repeated with heating in a water bath. Simvastatin is a thermostable substance, however, given the peculiarities of the use of surfactants, heating was carried out to a temperature of 65 ℃, temperature control was carried out using a laboratory thermometer. Interpretation of the results obtained during the study was carried out according to the data provided in the SPU.

The thermal stability study was carried out in accordance with State standard 4765:2007 Cosmetic creams. General specifications. Three tubes of 14×120 mm by 2/3 volume were filled with the emulsion, preventing aeration of the contents of the tubes. Kept in a thermostat at a temperature of 40-42 ℃ for 24 hours.

Stability was evaluated visually. The sample is considered stable if no more than one drop of water or no more than 0,5 cm of oil layer is released in three test tubes after thermostat.

The effect of changing the pH value on the properties of the samples was investigated by adding concentrated hydrochloric acid (37 %) to reduce the pH value and a pre-made aqueous sodium hydroxide solution to increase the pH value. The study was conducted in compliance with safety rules when working with concentrated acids and alkalis.

Gradually, solutions were added to the emulsion by drops, periodically controlling the pH using universal indicator strips (litmus), which in a strongly acidic medium acquire a pink color, in alkaline - blue. Changes in the systems were determined visually. The study is considered positive if no more than one drop of the aqueous or oil phase is released when the pH value changes.

The effect of dilution was investigated by adding purified water gradually to achieve a sample : water ratio of 1:100. Temperature of purified water – 37±2 °C. Changes in the systems were determined visually. The sample stability during dilution is indicated by its uniform distribution throughout the volume of purified water.

Sedimentation and aggregation resistance studies were carried out for test samples diluted with 100 ml of 0,1 M chloride acid solution, temperature – 37±2 °C. Observations were carried out for 60 minutes, stirring periodically without the use of intensive mixing techniques and maintaining the required temperature with a water bath. Stability is confirmed by uniform distribution of emulsion particles in 0,1 M chloride acid medium for 60 minutes.

Dissolution test. It was used as part of biopharmaceutical tests. It was carried out in accordance with the methodology given in the Order of the Ministry of Health of Ukraine № 426 "Procedure for the examination of registration materials for medicinal products submitted for state registration (re-registration), as well as examination of materials on amendments to registration materials during the validity of the registration certificate" in the version approved by Order № 3 of the Ministry of Health of Ukraine dated 04.01.2013. A device with rotating blades Pharma Test DT 70 (Germany) was used. The dissolution medium was 0,1 M chloride acid. Speed – 50 rpm. Temperature – 37±0,5 °C.

Spectrophotometric study, was used as part of biopharmaceutical tests. Determination of the optical density of the prepared solutions of the test samples, and then the API quantification was carried out in accordance with the procedure of Article SPU 2.2.25. Absorption spectrophotometry in the ultraviolet and visible regions. Taking into account the specificity of API light absorption, studies were

conducted in the visible area of light. An Evolution 60S spectrophotometer (USA) with quartz glass cuvettes and a layer thickness of 10 mm was used.

CONCLUSIONS TO CHAPTER 2

1. The physicochemical properties of the active and excipients that were used to develop the composition of the lipid system for simvastatin are presented.

2. The research methods used in the development and determination of basic quality indicators of the base and experimental samples of the lipid drug delivery system were selected and analysed.

CHAPTER 3. RESEARCH ON THE DEVELOPMENT OF A LIPID DELIVERY SYSTEM FOR SIMVASTATIN

3.1 Development of lipid base composition

The development of the composition of the base of the lipid system is based on the choice of a solvent that ensures the maximum solubility of the API with the minimum amount of the solvent itself, and the choice of surfactants and their ratio, which fully and quickly provide the homogenization process in the GIT medium.

Solvent selection criteria:

- safety during oral administration;
- chemical indifference to API and other excipients;
- pharmacotherapeutic indifference;
- maximum dissolution of the active substance with a minimum amount of solvent;
- physical compatibility with surfactants;
- availability of raw materials in the domestic market;
- economic accessibility.

Selection criteria of surfactants that are introduced into lipid systems:

- safety during oral administration;
- pharmacotherapeutic indifference;
- chemical indifference to API and other excipients;
- ensuring the homogenization process in an acidic medium at a temperature of 37 ℃ without intensive mixing;
- ensuring proper rate of uniform distribution;
- availability of raw materials in the domestic market;
- economic accessibility.

Solvent selection was performed by examining the solubility of simvastatin (Table 1).

The results obtained indicate the possibility of using a combination of ricin oil with glycerol triacetate 4:1 as a solvent.

Table 1

Solubility of simvastatin

Solvent	Ratio
Purified water	1 : 15000
0,1 M chloride acid solution	1 : 20000
Propylene glycol	1 : 200
Glycerol triacetate	1 : 5 – ↑◦t[1]
PEG 400	1 : 90; 1 : 3 – ↑◦t
Castor oil	1 : 100
Sunflower oil	1 : 20000
Corn oil	1 : 20000
Polysorbate 80	1 : 100; 1 : 3 – ↑◦t
GMS	1 : 2 – ↑◦t
DMG	1 : 2 – ↑◦t
PEG 40 HCO	1 : 2 – ↑◦t
Castor oil + PEG 40 HCO 5 : 1	1 : 3 – ↑◦t
Castor oil + GMS 3 : 1	1 : 3 – ↑◦t
Castor oil + PEG 400 3 : 1	1 : 4 – ↑◦t
Castor oil + DMG 3 : 1	1 : 3 – ↑◦t
Castor oil + Glycerol triacetate 4 : 1	1 : 2 – ↑◦t
Castor oil + Polysorbate 80 3 : 1	1 : 3 – ↑◦t

Note: 1 – at a temperature increased to 65 °C

According to the selection criteria, Polysorbate 80, DMG, GMS, PEG 400 were selected as surfactants. In order to establish the optimal ratio of solvent : surfactant, a study was conducted on the rate of uniform distribution of the mixture in 0,1 M chloride acid medium (modeling of gastric juice medium by pH). The studied ratios were chosen according to literary sources.

The results showed that the solvent : surfactant ratio of 1 : 1,5 with such surfactants as PEG 400 and Polysorbate 80 provides the fastest uniformity of distribution (4 minutes). Therefore, for further research, we obtained samples of this composition (Table 2).

Table 2

Composition of the test samples

Ingredients	Sample №1, g	Sample №2, g
Castor oil	0,4	0,4
Glycerol triacetate	0,1	0,1
PEG 400	0,75	-
Polysorbate 80	-	0,75

For the samples obtained, the main indicators of their quality were monitored: thermal stability, stability under pH changes (this is important for drugs for internal use), stability when diluted and sedimentation and aggregation stability of the diluted sample (this is important for understanding the uniform distribution of the substance throughout the entire period of stay in the stomach) (Table 3).

Table 3

Quality control of the test samples

Quality indicators	Sample №1	Sample №2
Thermal stability	Stable	Stable
Stability under pH changes	Stable	Stable
Stability in dilution	Stable	Stable
Sedimentation and aggregation stability	Stable	Unstable

The results of the study showed that sample №1 remains stable under all conditions and retains sedimentation and aggregation resistance for 60 minutes.

Sample №2 is also stable, but retains sedimentation and aggregation stability for no more than 25 minutes, which is insufficient for the time spent in the stomach, so we conclude that it is unstable.

3.2 Preparation and study of the lipid system with simvastatin

Based on the results of preliminary studies, a mixture of castor oil, glycerol triacetate and PEG 400 was chosen as the basis for the lipid delivery system. The next step is to add simvastatin to the base.

Here is a description of the stages of the technological process of manufacturing model samples of lipid delivery systems with simvastatin in the laboratory:

1. Weighing of APIs and excipients.
2. Preparation of the solvent by mixing castor oil and glycerol triacetate in a ratio of 4: 1. Since glycerol triacetate has a more viscous consistency than castor oil, the mixture should be placed in a water bath to speed up the time of this operation.
3. Dissolution of the active substance in the resulting mixture by heating in a water bath (t = 65 °C). Stir slowly to accelerate dissolution and promote uniform distribution of the active substance. It should be noted that intensive stirring is undesirable as it may lead to the formation of air inclusions.
4. Adding surfactants. PEG 400 (thick liquid) was added without removing from the water bath at a temperature (t = 60-70 °C).
5. The stage of homogenisation of the mixture (without intensive stirring; speed – 40-50 rpm, at a speed < 40 rpm the homogenisation time increases, at a speed > 50 rpm the degree of aeration of the mixture increases, which leads to the need to use additional equipment for deaeration).
6. Visual inspection of the appearance of the test samples to confirm the complete dissolution of the active ingredient and homogeneity of the mixture.

Based on the results of the described technology, we propose a technological scheme for the manufacture of lipid drug delivery systems with simvastatin in the laboratory (Fig. 3).

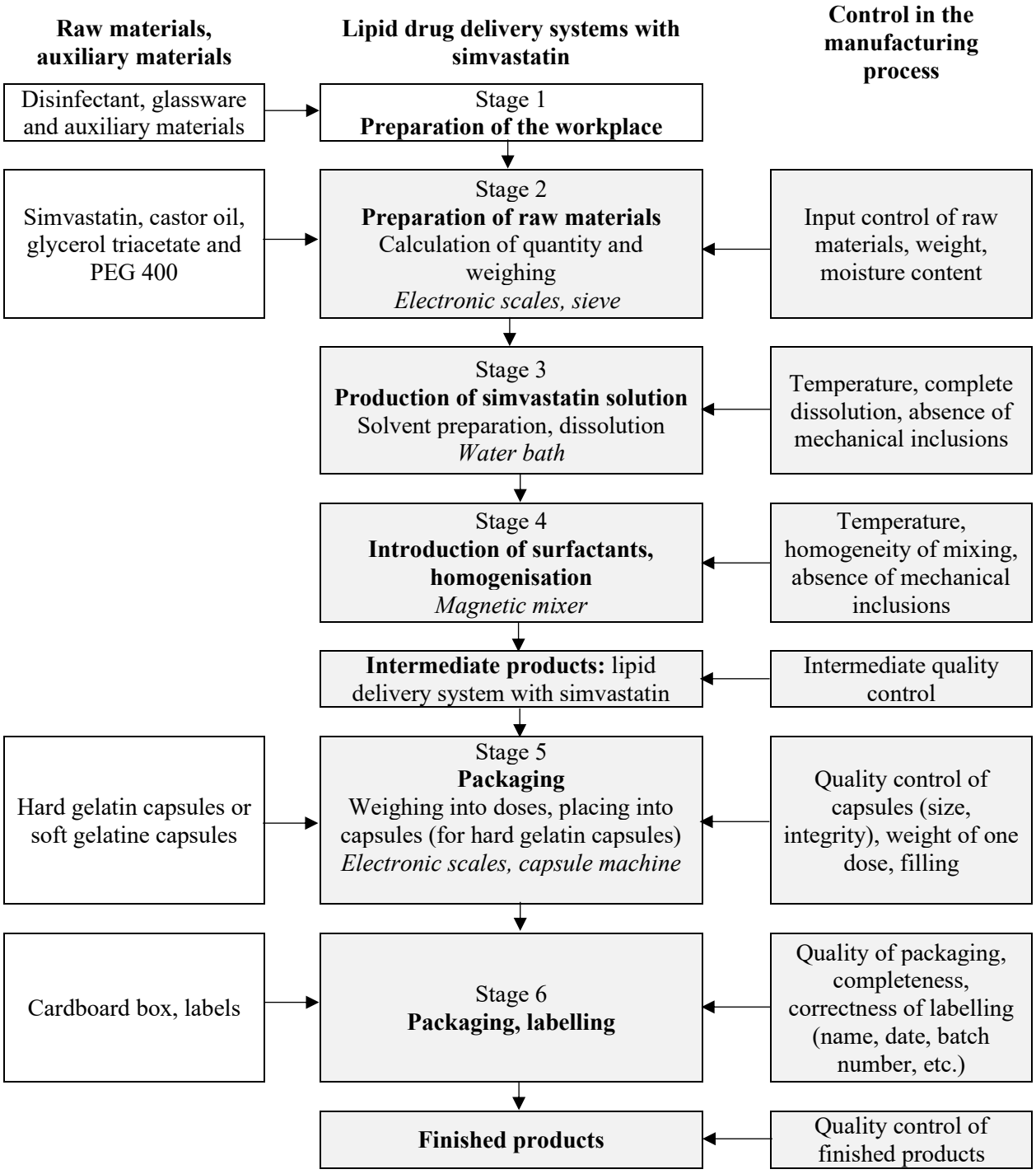

Fig. 3 Technological scheme for the manufacture of lipid drug delivery systems with simvastatin

To implement stages 5 and 6, it is necessary to determine the DF for the lipid system. For the composition we have presented, it is advisable to use hard gelatin capsules (for laboratory and pharmacy conditions) or soft gelatin capsules (for industrial manufacturing conditions). In this case, intermediate quality control consists of conducting studies of the main quality indicators of lipid systems, which were presented in the previous subsection. Finished product quality control involves conducting studies of lipid and pharmacotechnological quality parameters of capsules. Pharmacotechnological studies of capsules include weight homogeneity for a unit of dosed drug and capsule disintegration time.

The next step is to study the effect of APIs on the quality of the lipid system. Therefore, for the system with simvastatin obtained by the described technology, the main quality indicators were monitored (Table 4).

Table 4

Quality control of the lipid system with simvastatin

Quality indicators	Sample
Appearance	Liquid homogeneous mass with a slightly noticeable yellow tint, has a completely dissolved API without mechanical and air inclusions
Thermal stability	Stable
Stability under pH changes	Stable
Stability in dilution	Stable
Sedimentation and aggregation stability	Stable (60 minutes)

It was found that the introduction of simvastatin into the developed lipid system had no negative effect on its quality indicators.

Thus, based on the results of the studies on the development of the composition and technology of the lipid system with simvastatin, the following composition was proposed (Table 5).

Table 5

Composition of the developed lipid drug delivery system with simvastatin

Ingredients	Purpose	Sample, g[1]
Simvastatin	API	0,010
Castor oil	Solvent	0,016
Glycerol triacetate	Surfactant that promotes the dissolution	0,004
PEG 400	Surfactant	0,015

Note: 1 – the dosage of simvastatin is selected in accordance with the minimum dosage of the drug (tablet) available on the pharmaceutical market, and the amount of excipients is also changed accordingly

3.3 Biopharmaceutical studies for the lipid delivery system of simvastatin

Since the introduction of APIs into lipid systems is carried out to improve the solubility of APIs in the gastric juice environment, it is advisable to conduct biopharmaceutical studies. Biopharmaceutical studies are conducted to confirm the effectiveness of the developed system *in vitro* [23].

Biopharmaceutical research is an important element of pharmaceutical drug development. It is thanks to biopharmaceutical research that we are able to produce medicines with maximum efficacy and minimal unwanted side effects. Such research is an intermediate stage between the development of a new drug or improvement of an existing drug and it's *in vivo* pharmacological testing. Creating conditions as close as possible to those of a living organism during in vitro biopharmaceutical research helps to optimise and minimise research on experimental animals. In addition, by conducting appropriate tests specific to each of the drug substances, biopharmaceutical studies allow predicting the

bioavailability of the API, obtaining the results of the API release in vitro, which will have a correlation with similar indicators *in vivo*.

The bioavailability of an active substance is primarily influenced by the release of the API into the application medium. The choice of research method depends on the type of DF.

When developing drugs for oral administration, biopharmaceutical studies allow us to study the dependence of the rate and completeness of API release on various biopharmaceutical factors, which is especially relevant for the development of drugs using methods to improve the dissolution of the active substance [10].

Equally important is the choice of analytical method for the quantitative determination of the content of the active substance in the dissolution medium. According to the SPU, the quantitative determination of simvastatin is performed by liquid chromatography. However, our chosen spectrophotometric method has a number of advantages for use in the «Dissolution test»: fast sample preparation and results, no need for additional reagents, and optimisation of the study process, since spectrophotometry is also used for detection in liquid chromatography. In addition, the structure of the simvastatin molecule allows for direct spectrophotometric studies, as it contains double bonds (chromophores), which characterise its ability to absorb light.

Biopharmaceutical studies were conducted by comparing the kinetics of API release from the developed systems and the reference drug [22]. Simvastatin-Sandoz film-coated tablets from Salutas Pharma GMBH, Germany (series LX5161) were chosen as the reference drug.

The reference product contains simvastatin 40 mg and excipients: pregelatinised starch, microcrystalline cellulose, lactose monohydrate, butylhydroxyanisole (E 320), citric acid, magnesium stearate; coating components: hypromellose, talc, titanium dioxide (E 171), iron oxide red (E 172), ethanol 96% (evaporated during production), water (evaporated during production). In accordance with the above composition, simvastatin in this product is unchanged. The tablet contains standard excipients for such a drug, none of which improve the

solubility of the active substance: fillers, baking powder, antioxidant, acidity regulator, and antifriction agent. The film coating is gastric soluble.

Before conducting biopharmaceutical studies, preliminary studies were conducted to develop a spectrophotometric method for the quantitative determination of simvastatin and to establish the specifics of sample preparation for the quantitative determination of APIs in the lipid system using the developed method.

There are data on a spectrophotometric method for the quantitative determination of simvastatin in blood plasma using methanol as a dissolution medium. Since the systems we are developing are oral drugs, the methodology needs to be modified and refined to transfer to a 0,1 M hypochlorous acid solution.

The solution of the simvastatin standard was prepared according to the following procedure: an exact 0,050 g weight of the substance weighed on an electronic analytical balance was placed in a 50 ml volumetric flask, dissolved in 20 ml of 96 % ethanol, and brought to the mark with the same solvent. 1,0 ml of the resulting solution is placed in a 200 ml volumetric flask, the volume of the solution is made up to the mark with 0,1 M hydrochloric acid solution.

The absorption spectrum and optical density of the solution under study were determined according to the method described in Chapter 2. The study was carried out in the visible light region, at wavelengths from 220 nm to 270 nm, against the background of a compensation solution: 0,1 M hypochlorous acid solution.

It was found that the absorption spectra of simvastatin at a concentration of 0,001 % in 0,1 M hydrochloric acid at wavelengths from 220 nm to 270 nm were characterised by the presence of absorption maxima at wavelengths of 232 nm, 239 nm, 248 nm (Fig. 4).

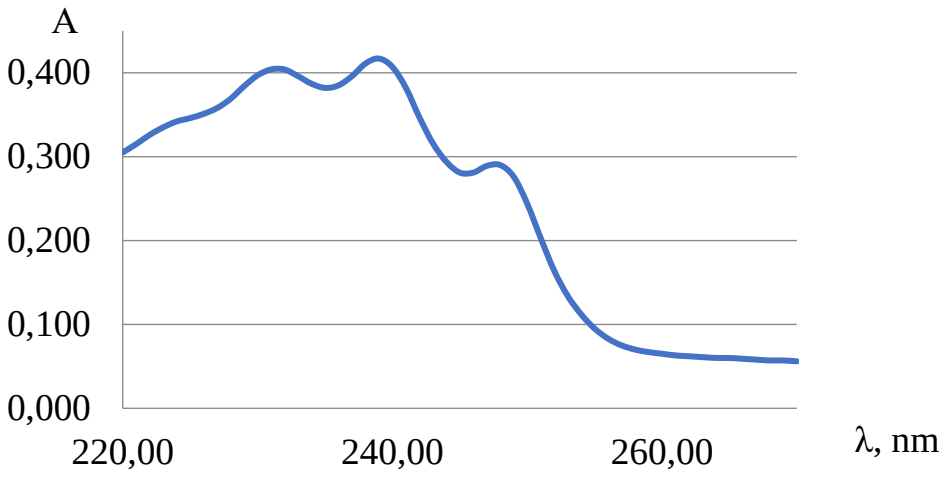

Fig. 4 Absorption spectrum of 0,001% simvastatin in 0,1 M hydrochloric acid

To confirm the obedience to the Bouguer-Lambert-Behr law, the optical density of the studied simvastatin solutions was determined according to the following method: 50 ml of 0,1% ethanol solution of simvastatin was obtained according to the method described above, 0,1 ml to 0,9 ml of the resulting solution was placed in a 10 ml volumetric flask, the volume of the solution was brought to the mark with 0,1 M hydrochloric acid solution. Compensation solution – 0,1 M hydrochloric acid solution.

To establish a linear dependence of the optical density on the concentration of the solution under study, the corresponding graph was constructed (Fig. 5).

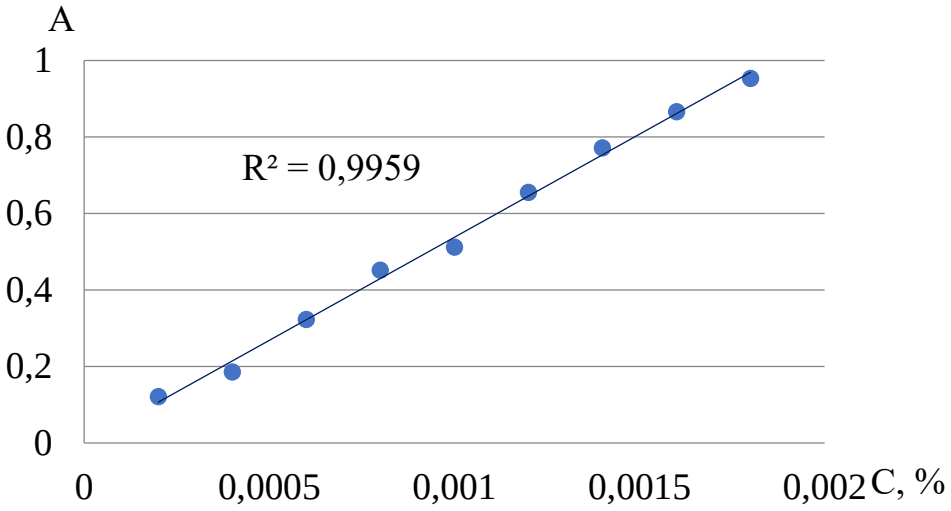

Fig. 5 Graph of the dependence of optical density on simvastatin concentration at the maximum absorption at a wavelength of 239 nm

It was found that at a concentration of 0,0004 % to 0,0018 %, the solution of simvastatin in 0,1 M hydrochloric acid followed the Bouguer-Lambert-Behr law, and the proposed method was reproducible.

The stability of the solution obtained according to the above method for the preparation of a standard solution of simvastatin was studied for 60 minutes, and the optical density was recorded every 5 minutes. The solution was considered stable if the deviation of the optical density values did not exceed ± 1 %. The study was performed at a wavelength of 239 nm. The results obtained indicate the stability of 0,0004 % solution of simvastatin in 0,1 M hydrochloric acid for 60 minutes, since the relative deviation of the obtained optical density values was 0,54 %.

The method can be used for the quantitative determination of simvastatin.

It is also advisable to study the absorption spectra of the lipid base (Fig. 6) and the reference drug (Fig. 7).

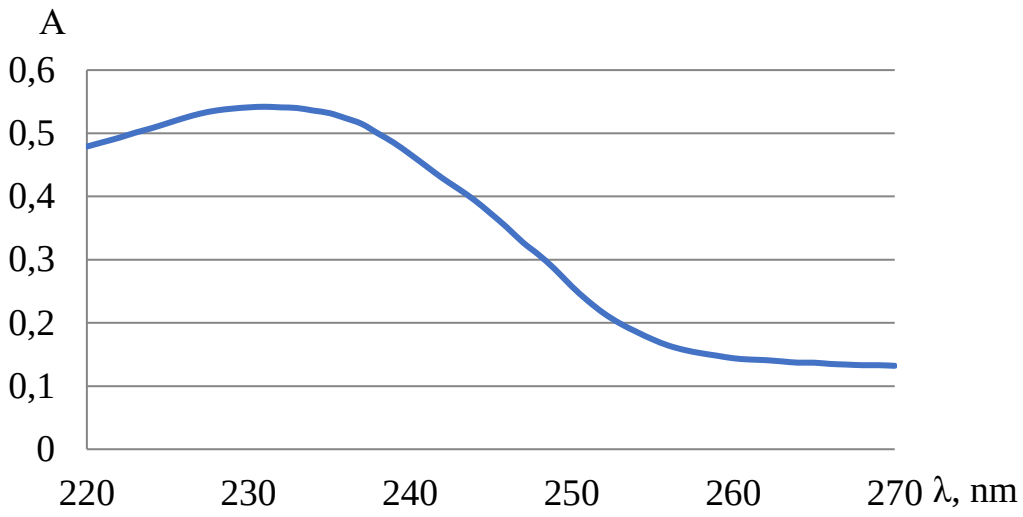

Fig. 6 Absorption spectra of the lipid system base in 0,1 M hydrochloric acid

The obtained results indicate the presence of substances in the composition of the base, which, over a wavelength of 220 to 270 nm, can increase the optical density, which will adversely affect the reliability of the data obtained for the quantitative determination of the active substance.

To mitigate the effects of these substances in order to avoid measurement errors, it was decided to produce a compensation solution for research with a lipid system by dissolving the bases in 0,1 M chloride acid solution.

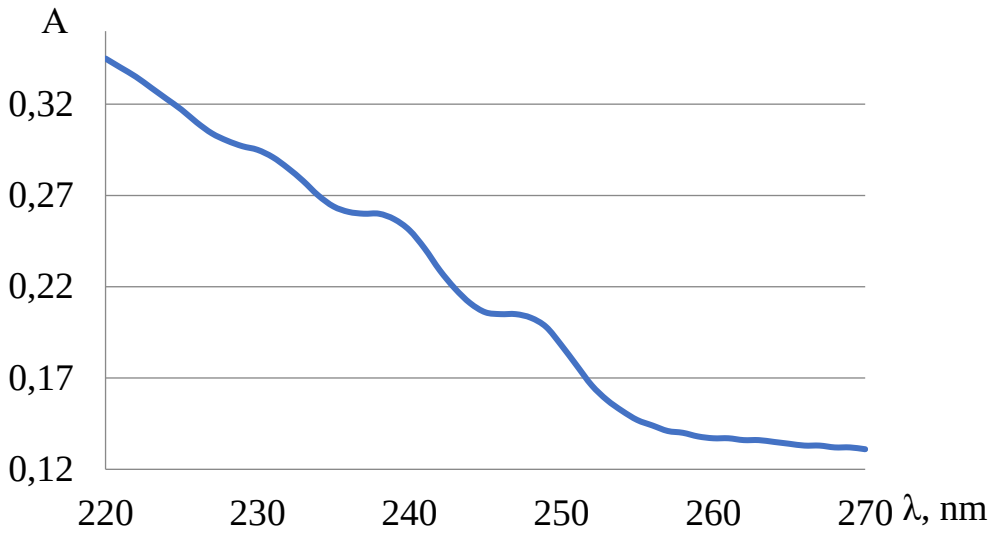

Fig. 7 Absorption spectra of the reference drug in 0,1 M hydrochloric acid

The obtained absorption spectra of the reference drug in the medium of 0,1 M chloride acid at wavelengths from 220 to 235 nm differs from the spectrum of the standard sample. The increase in optical density in this wavelength range is due to the influence of excipients that are part of the preparation, for example, butyl hydroxyanisole, in the chemical structure of which there is an aromatic carbohydrate compound. Nevertheless, the absorption maxima that are characteristic of the reference standard are maintained at wavelengths of 239 nm and 248 nm. Since the 239 nm wavelength has been determined analytically, the selected preparation can be used as a reference.

The basis of biopharmaceutical tests was a comparative study of the kinetics of API release from the developed systems and the reference drug using the Dissolution test. The study conditions were selected according to the method of use of the drug. Since the developed system is a preparation for oral use a 0,1 M solution of chloride acid (500 ml) at a temperature of 37±0,5 °C was used as a dissolution medium. Analytical solutions were prepared according to the procedures described

above. Aliquots (5 ml) were taken to determine the API concentration in the solution every 10 minutes, each time restoring the selected volume, for 50 minutes.

The concentration of the resulting solutions (C, mg/ml) was determined by the formula (1):

$$C = \frac{A \cdot C_{st} \cdot b}{A_{st}}, \quad (1)$$

where:

A – optical density of the test solution;

A_{st} – optical density of the standard solution;

C_{st} – concentration of the reference solution, mg/ml;

b – dilution.

The total amount of API that passed into the solution (X_n, mg) was determined by formula (2):

$$X_n = C_n \cdot V_s + \frac{X_{n-1}}{V_s} \cdot V_a, \quad (2)$$

where:

C_n – concentration of API in the solution after n minutes of the test, mg/ml;

V_s – total volume of the test solution, ml;

X_{n-1} – the total amount of API that passed into the solution in n-1 minutes, mg;

V_a – volume of aliquots selected for studies, ml.

Based on the results of the calculations, kinetics of API release were plotted from the test sample and the reference drug (Fig. 8).

The reference preparation is characterized by a gradual increase in the amount of simvastatin in solution for 50 minutes from 0,0906 to 0,1389 mg. The amount of simvastatin in the test sample solution increases rapidly from 10 to 20 minutes. Further, the indicators are reduced, which is associated with the peak concentration at 20 minutes and the subsequent dilution of the solution with each renewal of the selected aliquot.

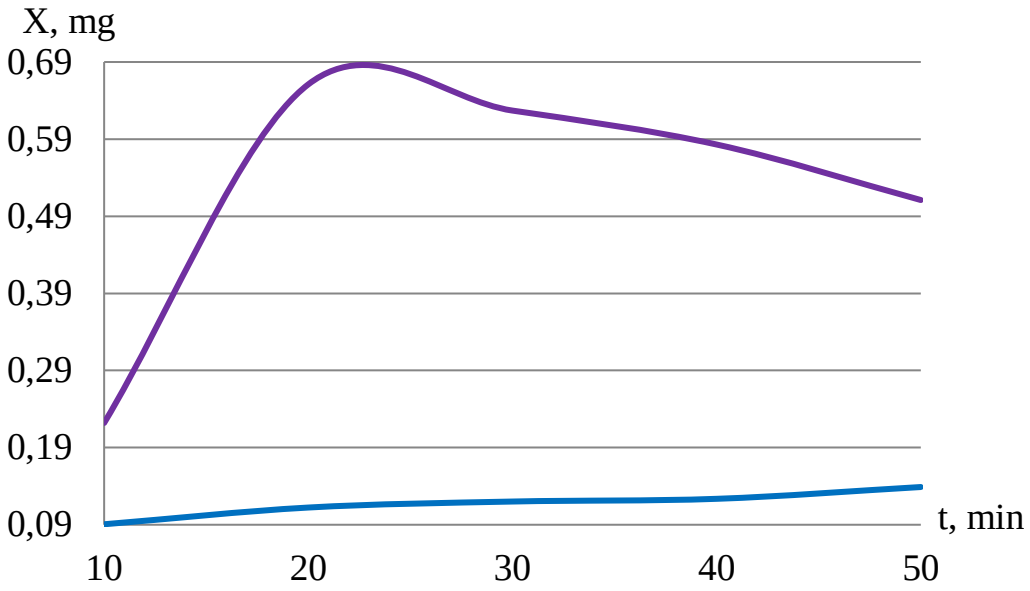

Fig. 8 Kinetics of API release from lipid system and reference drug samples

In addition, the amount of simvastatin in the test sample solution as early as 10 minutes is greater than in the reference drug solution after 50 minutes. It was also found that the introduction of simvastatin into the lipid system not only improved its solubility, but also significantly accelerated. This is indicated by reaching the maximum API concentration in the lipid system solution 30 minutes faster than the reference drug. It should be noted that according to visual observations, the process of dissolving the lipid system and tablets of the reference drug occurred simultaneously, which confirms the influence of the characteristics of the composition of the drug and the state of the active substance in the drug on the studied parameters.

CONCLUSIONS TO CHAPTER 3

1. The basis for the lipid delivery system was developed and the main indicators of its quality were studied. The composition of the base includes castor oil, glycerol triacetate, PEG 400.

2. The invention proposes technology of lipid drug delivery system with simvastatin. The quality control of the obtained system was carried out, it was

established that the API introduction into the system does not have a negative impact on its quality indicators.

3. Methods for the quantitative determination of simvastatin by absorption spectrophotometry in the visible region of light have been developed and it has been established that this method is reproducible and can be used for the quantitative determination of simvastatin.

4. A preliminary spectrophotometric study was carried out and the features of sample preparation for samples of the developed lipid systems, hard gelatin capsules and reference preparation were determined.

5. With the help of the Dissolution test, using absorption spectrophotometry in the visible area of light for API quantification, a comparison was made of the speed and completeness of the release of simvastatin from the test sample and the reference product. It was found that the introduction of simvastatin into the lipid system helped to accelerate its dissolution almost twice and increased the amount of release of the active substance into the medium of 0,1 M chloride acid, compared with the reference preparation, by almost five times.

GENERAL CONCLUSIONS

1. Analysis of available literature on the development of oral preparations with improved solubility of hardly soluble APIs has shown that various methods are used to improve the solubility of substances depending on the chemical structure, molecular weight and properties of the selected substance.

2. One of the factors in choosing a method is economic feasibility, since manufacturers prefer more cost-effective methods (introduction into the composition of the drug surfactant). Scientists most often use the formation of solid dispersions and solid lipid nanoparticles, which is confirmed by the vast majority of publications on these methods of improving solubility.

3. The development of drugs based on lipid systems is a promising direction of pharmaceutical development, as it will expand the range of studies conducted by Ukrainian scientists in order to improve the solubility of hardly soluble substances. In the future, lipid systems can replenish the range of domestic preparations for oral use with improved release and increased therapeutic activity of API.

4. The physicochemical properties of the active and excipients that were used to develop the composition of the lipid system for simvastatin are presented.

5. The research methods used in the development and determination of basic quality indicators of the base and experimental samples of the lipid drug delivery system were selected and analyzed.

6. The basis for the lipid delivery system was developed and the main indicators of its quality were studied. The composition of the base includes castor oil, glycerol triacetate, PEG 400.

7. The invention proposes technology of lipid drug delivery system with simvastatin. The quality control of the obtained system was carried out, it was established that the API introduction into the system does not have a negative impact on its quality indicators.

8. Methods for the quantitative determination of simvastatin by absorption spectrophotometry in the visible region of light have been developed and it has been established that this method is reproducible and can be used for the quantitative determination of simvastatin.

9. A preliminary spectrophotometric study was carried out and the features of sample preparation for samples of the developed lipid systems, hard gelatin capsules and reference preparation were determined.

10. With the help of the Dissolution test, using absorption spectrophotometry in the visible area of light for API quantification, a comparison was made of the speed and completeness of the release of simvastatin from the test sample and the reference product. It was found that the introduction of simvastatin into the lipid system helped to accelerate its dissolution almost twice and increased the amount of release of the active substance into the medium of 0,1 M chloride acid, compared with the reference preparation, by almost five times.

LIST OF REFERENCES

1. An Innovative Approach on Microemulsion: A Review / P. Vishvakarma et al. *European Chemical Bulletin*. 2023. Vol. 12, № 4. P. 11710–11733.

2. Assessing Fatty Acid Profiles of Macadamia Nuts / T. J. O'Hare et al. *HortScience horts*. 2019. Vol. 54, № 4. P. 633-637.

3. Bhattacharya S., Mishra S., Prajapati B. G. Design and Development of Docetaxel Solid Self-Microemulsifying Drug Delivery System Using Principal Component Analysis and D-Optimal Design. *Asian Journal of Pharmaceutics*. 2018. Vol. 12, № 1. P. 122–144.

4. Bhattacharya S., Prajapati B. G. Formulation Approach of Self Emulsifying Drug Delivery System. *International Journal of Pharmaceutical Formulation and Analysis*. 2015. Vol. 6, № 1. P. 15.

5. Bist V., Faruk A. Recent Advancement in Self Emulsifing Drug Delivery System. *Journal for Research in Applied Sciences and Biotechnology*. 2023. Vol. 2. P. 89-101. DOI: 10.55544/jrasb.2.2.14.

6. Darusman F., Amalia F., Priani S. Development and Characterization of Orally Ibuprofen Self Emulsifying Drug Delivery Systems (SEDDS). *Indonesian Journal of Pharmaceutical Science and Technology*. 2022. Vol. 9. № 65. DOI: 10.24198/ijpst.v9i2.31508.

7. Development and characterization of clove oil nanoemulsions and self-microemulsifying drug delivery systems / K. Kheawfu et al. *Journal of Drug Delivery Science and Technology*. 2018. Vol. 46. P. 330–338.

8. Development and optimization of a self-microemulsifying drug delivery system for atorvastatin calcium by using d-optimal mixture design / D. W. Yeom et al. *International Journal of Nanomedicine*. 2015. Vol. 10. P. 3865–3878.

9. Development of Triptolide Self-Microemulsifying Drug Delivery System and Its Anti-tumor Effect on Gastric Cancer Xenografts / M. Xie et al. *Frontiers in Oncology*. 2019. Vol. 9. DOI: 10.3389/fonc.2019.00978.

10. Devhare L. D., Kore P. K. A Recent Review on Bioavailability and Solubility Enhancement of Poorly Soluble Drugs by Physical and Chemical Modifications. *Research Chronicle in Health Sciences*. 2016. Vol. 2, № 5. P. 299–308.

11. Dhoble P., Tekade B., Bodke V., Kale M. A Systematic Review of Solubility Enhancement Techniques Used for BCS Class II & IV. *International Journal of Research in Pharmaceutical Sciences*. 2024. Vol. 15. P. 1–11. DOI: 10.26452/ijrps.v15i1.4658.

12. European Pharmacopoeia. 8th ed. Strasbourg: European Department for the Quality of Medicines. 2013. 3655 p.

13. Fatima S., Usman S., Jamil S. Effect of surfactant on dissolution of simvastatin tablets; comparison with USP. *World Journal of Pharmacy and Pharmaceutical Sciences*. 2014. Vol. 3, № 3. P. 142–150.

14. Formulation Development of Albendazole-Loaded Self-Microemulsifying Chewable Tablets to Enhance Dissolution and Bioavailability / S. Sawatdee et al. *Pharmaceutics*. 2019. № 11 (134). DOI: 10.3390/pharmaceutics11030134.

15. Formulation for Enhancement of Solubility and Dissolution Rate of Simvastatin using Solid Dispersion / G. Kumar et al. *Research Journal of Pharmaceutical Dosage Forms and Technology*. 2023. P. 143–148. DOI: 10.52711/0975-4377.2023.00024.

16. Formulation Studies of Solid Self-Emulsifying Drug Delivery System of Ivermectin / P. P. Vipul et al. *Folia Medica*. 2018. Vol. 60, № 4. P. 580–592. DOI: 10.2478/folmed-2018-0024.

17. Gahlawat N., Verma R., Kaushik D. Recent Developments in Self-microemulsifying Drug Delivery System: An Overview. *Asian Journal of Pharmaceutics*. 2019. Vol. 13, № 2. P. 59–72.

18. Gupta S., Kesarla R., Omri A. Formulation Strategies to Improve the Bioavailability of Poorly Absorbed Drugs with Special Emphasis on Self-Emulsifying Systems. *ISRN Pharmaceutics*. 2013. DOI: 10.1155/2013/848043.

19. Improved Antioxidant Capacity of Optimization of a Self-Microemulsifying Drug Delivery System for Resveratrol / Y. Chen et al. *Molecules*. 2015. Vol. 20. P. 21167–21177.

20. Improved Oral Bioavailability Using a Solid Self-Microemulsifying Drug Delivery System Containing a Multicomponent Mixture Extracted from Salvia miltiorrhiza / X. Bi et al. *Molecules*. 2016. Vol. 21, № 456. DOI: 10.3390/molecules21040456.

21. Incorporating valsartan in sesame oil enriched self-nanoemulsifying system-loaded liquisolid tablets to improve its bioavailability / K. M. El-Say et al. *International journal of pharmaceutics*. 2023. Vol. 639. DOI: 10.1016/j.ijpharm.2023.122966.

22. Indrayan A., Malhotra K. R. Medical biostatistics. 4th ed. Boca Raton : CRC Pres. 2018. 685 p.

23. In Vitro Evaluation of A Self-Emulsifying Drug Delivery System (SEDDS) for Nasal Administration of Dimenhydrinate / C. Leichner et al. *Drug Delivery and Translational Research*. 2019. Vol. 9, № 11. DOI: 10.1007/s13346-019-00634-1.

24. Kumar S., Singh P. Various techniques for solubility enhancement: An overview. *The Pharma Innovation*. 2016. Vol. 5, № 1. P. 23–28.

25. Mahapatra A. K., Murthy P., Swadeep B., Swain R. Self-emulsifying drug delivery systems (SEDDS): An update from formulation development to therapeutic strategies. *International Journal of PharmTech Research*. 2014. Vol. 6. P. 546–568.

26. Nigade P. M., Patil S. L., Tiwari Sh. S. Self-emulsifying drug delivery system (SEDDS): a review. *International Journal of Pharmacy and Biological Sciences*. 2012. Vol. 2, Issue 2. P. 42–52.

27. Nirmala D., Bhavani K., Sudhakar M. Formulation and Evaluation of Simvastatin Nanoparticles. *Asian Journal of Pharmacy and Technology*. 2023. P. 183–188. DOI: 10.52711/2231-5713.2023.00033.

28. Poorly Water Soluble Drugs: Change in Solubility for Improved Dissolution Characteristics a Review / B. Dhillon et al. *Global Journal of Pharmacology*. 2014. Vol. 8, № 1. P. 26–35.

29. Recent Advancements in Self-emulsifying Drug Delivery Systems (SEDDS) / B. Singh et al. *Critical Reviews in Therapeutic Drug Carrier Systems*. 2014. Vol. 31, № 2. P. 121–185.

30. Reza J. Self-Emulsifying Drug Delivery Systems: A Review. *International Journal of Pharmaceutical and Life Sciences*. 2013. Vol. 2, Issue 2. P. 80–84.

APPENDICES

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

СЕРТИФІКАТ УЧАСНИКА

Цим засвідчується, що

Dilai Fadwa

Scientific supervisor: Vyshnevska L.I.

брав(ла) участь у роботі

XXXI 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

23-25 квітня 2025 р, м. Харків

Appendix B

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

МАТЕРІАЛИ
XXXI МІЖНАРОДНОЇ НАУКОВО-ПРАКТИЧНОЇ
КОНФЕРЕНЦІЇ МОЛОДИХ ВЧЕНИХ ТА СТУДЕНТІВ

23–25 квітня 2025 року
м. Харків

Харків
НФаУ
2025

Continuation of app. B

One of the main representatives of biologically active substances of the willow family is phenolic glycosides, the aglycone of which is salicylic alcohol. The first phenolic glycoside isolated from plants – salicin (salicoside), is a β-glucoside of salicylic alcohol. It was obtained from willow bark by the French scientist A. Leroux (1829). The main types of action of willow – anti-inflammatory, analgesic, and antipyretic – are associated with salicin.

Thus, the use of Salix Viminalis L. extract as an API for the preparation of gels is relevant. Further studies are planned to clarify the concentration of the extract and investigate the severity of antimicrobial activity.

Conclusions. Considering the above, we consider it rational and relevant to develop soft dosage forms with extracts of Lemon balm and Willow bark for the treatment of wounds of various etiologies. The focus on natural APIs with antimicrobial, anti-inflammatory, soothing and moisturizing properties emphasizes the transition to a more holistic and effective treatment of wounds and demonstrates a strategic approach to creating a stable and suitable semi-solid dosage form.

PROSPECTS FOR THE DEVELOPMENT OF MEDICINAL PRODUCTS WITH IMPROVED SOLUBILITY OF THE ACTIVE SUBSTANCE

Dilai Fadwa
Scientific supervisor: Vyshnevska L.I.
National University of Pharmacy, Kharkiv, Ukraine
atl@nuph.edu.ua

Introduction. Oral route of drug administration is the simplest and most convenient, but at the same time there is a problem of bioavailability of active substances, in particular poorly soluble in water. One of the options for solving this problem is the introduction of poorly soluble substances in the composition of self-emulsifying compositions (SEC). In this case, the possibility of oral administration is preserved, and solubility, absorption in the gastrointestinal tract and bioavailability are increased. This effect is achieved by proper ratio of excipients such as solvent, surfactant (surfactant) and co-surfactant (co-surfactant).

Aim. Research of prospects for the development of medicinal products with improved solubility of the active substance.

Materials and methods. Literature sources were analyzed in order to study the peculiarities of composition, technology, research of SEC, as well as the prospects for the development of a new drug based on SEC.

Results and discussion. SEC are special drug delivery systems f or oral administration, the active pharmaceutical ingredients (API) of which are insoluble or poorly water-soluble substances. In a classical embodiment, an SEC consists of a solvent, a surfactant and a co-surfactant. The solvents depend on the nature of the AFI. They can be fatty acids, vegetable oils, more modern – acetylated mono-, di-, triglycerides of fatty acids. Among surfactants, sodium lauryl sulfate and polysorbates are more common. Co-surfactants are polyethylene glycol-400 and poloxamers.

Additional substances found in modern literature are emollients and enhancers (glycerin, isopropyl myristate, diethylene glycol). They accelerate the absorption of active substances in the stomach. Due to this composition, when entering the stomach, SEC under the action of gastric juice spontaneously emulsifies, forming a microemulsion of oil-in-water type. Reduction of the particle

size leads to an increase in the interfacial surface, which, in turn, improves the absorption of active substances in the gastrointestinal tract and leads to an increase in bioavailability.

The following stages of SEC development are distinguished: study of API dissolution in excipients, construction of ternary phase diagrams, direct preparation of SEC, evaluation of quality parameters. Study of API dissolution in auxiliary substances is carried out in order to select the most suitable solvent, surfactant and co-surfactant, which will ensure maximum dissolution of API. Construction of ternary phase diagrams is used to determine the best ratio of auxiliary substances, at which the most persistent effect of self-emulsification is observed.

Preparation of SEC includes stages of API dissolution, preparation of surfactant and co-surfactant solution, mixing and homogenization of the obtained solutions.

Assessment of quality parameters consists of studying the effect of dilution and pH change on emulsion stability, as well as thermodynamic stability, determination of particle size, observation of particle morphology, measurement of density (turbidimetry), viscosity (viscometry), determination of refractive index (refractometry) and transmittance (UV spectrophotometry), study of release profile in vitro to predict bioavailability and directly determine bioavailability by in vivo method.

Many foreign scientists have achieved significant results in the development of SEC and drugs based on them. SEC are developed for fat-soluble vitamins, chemotherapeutic agents, nonsteroidal anti-inflammatory, hypoglycemic, hypolipidemic, anti-epileptic, antihypertensive agents, hepatoprotectors and others. Both synthetic (ivermectin, candesartan, valsartan, paclitaxel, butylphthalide, verapamil, ibuprofen, glibenclamide, acyclovir, atorvastatin, carvedilol, fenofibrate, etc.) and natural (silymarin, berberine) substances are chosen as APIs. Experimental data confirm the feasibility of introducing insoluble or poorly water-soluble APIs into the composition of SEC, as it is confirmed that they improve solubility, accelerate absorption in the gastrointestinal tract and increase bioavailability.

Scientists from the USA, India, China, South Korea, Germany, Switzerland and the UK are engaged in the development and research of SEC. Some of the drugs have already entered the pharmaceutical market and are actively used. For example, Sandimmune Neoral (Novartis, Switzerland, active substance cyclosporine), Norvir (Abbott Laboratories, USA, active substance ritonavir), Fortovase (Hoffmann-LaRoche inc, Switzerland, active substance saquinavir), Convulex (Pharmacia, Russia, active substance valproic acid), Rocatrol (Roche, Switzerland, active substance calcitriol), Lipirex (Genus, UK, active substance fenofibrate), Targretin (Ligand, USA, active substance bexarotene).

Conclusions. Thus, SEC is an innovative drug delivery system that allows oral administration of insoluble or poorly water-soluble drugs, while improving their dissolution and increasing bioavailability. Creation of new drugs based on SEC is relevant to expand the range of drugs with increased bioavailability in the pharmaceutical market.

PROSPECTS OF BISACODYL USAGE IN VETERINARIAN PRACTICES

Kamal Saeed
Scientific supervisor: Semchenko K.V.
National University of Pharmacy, Kharkiv, Ukraine
tolochko.kv@gmail.com

Introduction. Bisacodyl is a powerful laxative that stimulates intestinal motility and is used to treat constipation in both humans and animals. Although its use in veterinary practice is less common, it can be useful in cases of severe constipation in dogs, cats, and some other species.

Appendix C

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
РАДА МОЛОДИХ ВЧЕНИХ
СТУДЕНТСЬКЕ НАУКОВЕ ТОВАРИСТВО

ПРОГРАМА

XXXI Міжнародної науково-практичної конференції молодих вчених та студентів «АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»

23-25 квітня 2025 р.

Харків – 2025

Continuation of app. C

10 **Порівняльний аналіз кремів для обличчя від бренду "MR SCRUBBER"**
Доповідач: Германова Дар'я
Науковий керівник: Боднар Л.А., PhD, асистент

11 **Арніка в гомеопатії та фітотерапії: від синців до стресу**
Доповідачі: Орловська Олександра, Васильченко Вікторія, Гуторка Микита, Лісаченко Єгор, Мекленбурцев Олександр
Науковий керівник: Олійник С. В., к. фарм. н., доц.

12 **Психологічні аспекти терапії дерматологічних захворювань**
Доповідач: Демяновська Аліна
Науковий керівник: Боднар Л.А.,, PhD, асистент

13 **Дослідження впливу супозиторної основи на вивільнення парацетамолу з дитячих супозиторіїв**
Доповідач: Крюкова Тетяна
Науковий керівник: Семченко К.В. д фарм. н., проф.

14 **Дослідження з покращення розчинності симвастатину**
Доповідач: Ділай Фадуа
Науковий керівник: Вишневська Л.І., д. фарм. н., проф.

15 **Розроблення складу екстемпорального засобу для терапії акне**
Доповідач: Дабло Тетяна
Науковий керівник: Олійник С. В., к. фарм. н., доц.

16 **Development of the composition of veterinary drop for the treatment and prevention of cat urolithiasis**
Доповідач: Черноусенко Катерина
Науковий керівник: Половко Н.П. д фарм. н., проф.

17 **Дослідження показників якості протизапального препарату з тієнофлогіном**
Доповідач: Рибак Наталя
Науковий керівник: Вишневська Л.І., д. фарм. н., проф.

18 **Composition substantiation and technology development of extemporaneous gel with Lemon balm and Willow bark extracts**
Доповідач: Замахшарі Малак
Науковий керівник: Буряк М.В., к. фарм. н., доц.

19 **Composition substantiation and technology development of extemporaneous gel with Lemon balm and Willow bark extracts**
Доповідачі: Bida Bogdana, Fomenko Inna
Науковий керівник: Половко Н.П. д фарм. н., проф.

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty pharmaceutical
Department drug technology
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational and professional program Pharmacy

APPROVED
The Head of Department

Liliia VYSHNEVSKA

"30" August 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Fadwa DILAI

1. Topic of qualification work: «Research to improve the solubility of simvastatin in an oral preparation», supervisor of qualification work: Liliia VYSHNEVSKA, Doctor of Pharmaceutical Sciences, Professor

approved by order of NUPh from "27" of September 2024 № 237

2. Deadline for submission of qualification work by the applicant for higher education: May 2025.

3. Outgoing data for qualification work: simvastatin, lipid drug delivery system, quality studies and biopharmaceutical research of a lipid drug delivery system with simvastatin.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): to review, analyse and summarise the literature on possible ways to improve the solubility of APIs, in particular lipid delivery systems; to theoretically substantiate the choice of simvastatin as a potential API for lipid delivery system; to analyse the prevalence of different methods of improving simvastatin solubility; to propose the composition of the lipid-based drug delivery system, to study its properties and quality indicators; to obtain a lipid drug delivery system with simvastatin and develop its technology; to control the main quality indicators of the lipid delivery system with simvastatin; to study the effect of excipients on the rate of dissolution and release of APIs in vitro.

5. List of graphic material (with exact indication of the required drawings): tables 5, pictures 8.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Liliia VYSHNEVSKA, head of the drug technology department	05.09.2024	05.09.2024
2	Liliia VYSHNEVSKA, head of the drug technology department	01.11.2024	01.11.2024
3	Liliia VYSHNEVSKA, head of the drug technology department	11.02.2025	11.02.2025

7. Date of issue of the assignment: "30" August 2024

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Justification of the research design	September 2024	**done**
2	Analysis of literature sources	October-November 2024	**done**
3	Conducting experimental research	November-December 2024	**done**
4	Analysis, interpretation, and synthesis of the results	January-March 2025	**done**
5	Designing a work	April 2025	**done**

An applicant of higher education _____ Fadwa DILAI

Supervisor of qualification work _____ Liliia VYSHNEVSKA

ВИТЯГ З НАКАЗУ № 237
По Національному фармацевтичному університету
від 27 вересня 2024 року

Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу Фм20(4,10д) 2024-2025 навчального року, освітньо-професійної програми – Фармація, другого (магістерського) рівня вищої освіти, спеціальності 226 – Фармація, промислова фармація, галузь знань 22 Охорона здоров'я, денна форма здобуття освіти (термін навчання 4 роки 10 місяців), які навчаються за контрактом (мова навчання англійська та українська) згідно з додатком № 1.

Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі аптечної технології ліків**				
Ділай Фадуа	Дослідження з покращення розчинності симвастатину у складі препарату для перорального застосування	Research to improve the solubility of simvastatin in an oral preparation	проф. Вишневська Л.І.	проф. Рубан О.А.

Ректор
Вірно: Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«05» травня 2025 р. № 331121695

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Ділай Фадуа, групи Фм20(4.10д)англ-01, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Дослідження з покращення розчинності симвастатину у складі препарату для перорального застосування / Research to improve the solubility of simvastatin in an oral preparation», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

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

Ф А 2.2.1-32-353

REVIEW

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

Fadwa DILAI

on the topic: «Research to improve the solubility of simvastatin in an oral preparation»

Relevance of the topic. The solubility of active pharmaceutical ingredients in oral medicinal products determines the rate and completeness of absorption of the active substance in the gastrointestinal tract, as well as bioavailability and efficacy. Given the predominant number of hydrophobic substances, it is important to conduct research to improve their solubility in the aqueous environment of the gastrointestinal tract.

To improve the solubility of such substances, physical and chemical modification methods and other technological methods are used. Among them, the method of introducing hydrophobic substances into a lipid drug delivery system is promising. This has a number of advantages: the substance is in a dissolved state at the time of entry into the stomach, the speed and uniformity of distribution of the active substance in the gastric juice environment, and in some cases, the levelling of the effect of the first passage through the liver.

The expediency of developing drugs with improved solubility and the prospects of working on lipid-based drug delivery systems confirm the relevance of this work.

Practical value of conclusions, recommendations and their validity. The qualification work describes in detail the key approaches to improving the solubility of hydrophobic active pharmaceutical ingredients. Particular attention was paid to lipid-based drug delivery systems and simvastatin as a substance that can be used as an example for this development.

The result of the presented qualification work is the substantiation of the optimal composition of the lipid drug delivery system with simvastatin and its biopharmaceutical studies.

Assessment of work. The qualification work in terms of theoretical and practical research fully meets the requirements for qualification works.

General conclusion and recommendations on admission to defend. Fadwa DILAI's qualification work can be submitted for defense to the Examination Commission of the National Pharmaceutical University for the assignment of the educational qualification level of Master of Pharmacy.

Scientific supervisor _____ Liliia VYSHNEVSKA

«15» of May 2025

Ф А 2.2.1-32-356

REVIEW

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

Fadwa DILAI

on the topic: «Research to improve the solubility of simvastatin in an oral preparation»

Relevance of the topic. Improving the solubility of active pharmaceutical ingredients that are difficult to dissolve in the aqueous environment of the gastrointestinal tract is an important issue when developing oral medicines with hydrophobic substances of active ingredients. Such substances have a number of disadvantages when administered orally: due to their difficult solubility, the amount of absorbed substance decreases, and they have low bioavailability and therapeutic activity. Therefore, to obtain the optimal concentration of APIs in the blood and the desired efficacy of the drug, various methods of improving the solubility of the active substance are used when developing drugs with hardly soluble substances. One of these methods is to incorporate them into lipid-based drug delivery systems.

Lipid systems are oral drug delivery systems that, due to their composition, can improve the solubility of hydrophobic substances in the aqueous environment of the gastrointestinal tract, promote their absorption, which leads to increased bioavailability and therapeutic activity. Lipid systems are based on a hydrophobic solvent (oil or organic) and surfactants, the optimal ratio of which implements the above functions of the systems.

Theoretical level of work. New and deepened existing theoretical approaches to solving the urgent problem of increasing the solubility of hardly soluble active substances by physical modification of the substance, in particular, its introduction into lipid drug delivery systems.

Author's suggestions on the research topic. The author independently chose the method of improving the solubility of the substance. The choice was made on the basis of studying and summarising the literature. The components to be selected for the lipid

drug delivery system are proposed. The main research methods have been selected and processed.

Practical value of conclusions, recommendations and their validity. The composition of the lipid drug delivery system with simvastatin is proposed, which is an addition to the studies conducted in this area. Biopharmaceutical studies have confirmed the effectiveness of the developed composition in vitro.

Disadvantages of work. The content of the work contains spelling mistakes and technical errors. However, this does not reduce the value of the work.

General conclusion and assessment of the work. Fadwa DILAI's qualification work can be submitted for defense to the Examination Commission of the National Pharmaceutical University for the assignment of the educational qualification level of Master of Pharmacy.

Reviewer _____ prof. Olena RUBAN

«16» of May 2025

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 17
«19» травня 2025 року
м. Харків
засідання кафедри
аптечної технології ліків
(назва кафедри)

Голова: завідувачка кафедри, професор Вишневська Л.І.
Секретар: докт. філ., ас. Боднар Л.А.

ПРИСУТНІ:

проф. Половко Н.П., проф. Семченко К.В., проф. Зуйкіна С.С., доц. Ковальова Т.М., доц. Буряк М.В., доц. Ковальов В.В., доц. Олійник С.В., доц. Марченко М.В., ас. Іванюк О.І.

ПОРЯДОК ДЕННИЙ:

1. Про представлення до захисту кваліфікаційних робіт здобувачів вищої освіти.

СЛУХАЛИ: проф. Вишневську Л. І. – про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт здобувачів вищої освіти.

ВИСТУПИЛИ: Здобувач вищої освіти групи Phm19(4,10d)eng-01 спеціальності 226 «Фармація, промислова фармація» Fadwa DILAI – з доповіддю на тему «Research to improve the solubility of simvastatin in an oral preparation» (науковий керівник, проф. Лілія ВИШНЕВСЬКА).

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу.

Голова
Завідувачка кафедри, проф. _____ Лілія ВИШНЕВСЬКА
(підпис)

Секретар
Асистент _____ Любов БОДНАР
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Fadwa DILAI до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Research to improve the solubility of simvastatin in an oral preparation»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____/ Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Fadwa DILAI представила кваліфікаційну роботу, яка за об'ємом теоретичних та практичних досліджень повністю відповідає вимогам до оформлення кваліфікаційних робіт.

Керівник кваліфікаційної роботи

_____ Лілія ВИШНЕВСЬКА

«15» травня 2025 р.

Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри
аптечної технології ліків

_____ Лілія ВИШНЕВСЬКА

«19» травня 2025 р.

Qualification work was defended

of Examination commission on

« ___ » of June 2025

with the grade _____

Head of the State Examination commission,

Doctor of Pharmaceutical Sciences, Professor

_____ / Volodymyr YAKOVENKO /