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BIOPHARMACEUTICAL JUSTIFICATION OF THE CREATION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS WITH SIMVASTATIN

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The aim of the research – to conduct biopharmaceutical tests of capsules with a self-emulsifying delivery system of simvastatin to confirm the effectiveness and feasibility of introducing into the composition of self-emulsifying drug delivery systems active pharmaceutical ingredients that are difficult to dissolve in the gastric juice environment.

Material and methods. Substances, excipients, reagents and materials used during research were simvastatin (India, p. DK40-2005021, 99.09 %), castor oil (Ukraine), polyethylene glycol 40 hydrogenated castor oil (India), Tween 80 (Ukraine), glycerol monostearate (Gustav Heess GmbH, Germany), polyethylene glycol 100 stearate (ERCA, Italy), hard gelatin capsules No. 3 white (China), 0.1 M hydrochloric acid solution (made from concentrated hydrochloric acid), ethanol 96 % (Ukraine), filter paper 90 mm white tape (Ukraine). The reference drug is “Simvastatin-Sandoz” (Salyutas Pharma, Germany, series LX5161).

An Evolution 60S spectrophotometer (USA) was used to carry out studies by absorption spectrophotometry.

Results. Preliminary study of the absorption spectra of absorption of the substance, bases, gelatin capsules, developed self-emulsifying systems and the reference drug made it possible to predict and optimize the conduct of biopharmaceutical research. The study of the release of simvastatin from the developed delivery systems and the reference drug, which was carried out at a temperature of 37 °C in an environment of 0.1M hydrochloric acid, showed that the introduction of simvastatin into the composition of the investigated self-emulsifying compositions allows to increase its solubility in this solvent by five times, compared to the reference drug.

Conclusions. The obtained results indicate the effectiveness of the introduction of simvastatin into the composition of self-emulsifying drug delivery systems and the feasibility of using such systems to improve the solubility and accelerate the release of a poorly water-soluble active pharmaceutical ingredient into the gastric juice environment

Keywords: self-emulsifying drug delivery systems, accelerated release, increased solubility, simvastatin capsules

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1. Introduction

Accelerating the solubility and increasing the amount of the medicinal substance released into the gastric juice environment are relevant for poorly water-soluble active pharmaceutical ingredients (APIs), because improving these parameters allows increasing the bioavailability of such APIs when taken orally [1].

One of the ways to improve and accelerate the dissolution of APIs in the aqueous environment of gastric or intestinal juice is to introduce them into self-emulsifying drug delivery systems. The main advantage of self-emulsifying systems over conventional drugs for oral use is that in them the API is in a dissolved state, which ensures an increase in the overall effective contact area of the substance with the environment of gastric or intestinal juice. Surface-active substances (SAS), which are part of the systems, provide the actual self-emulsification process, which contributes to a quick and effective transition to the API absorption process [2].

The classic composition of a self-emulsifying composition is a mixture of a solvent in which the API dissolves best, SAS, which ensures the formation of an

emulsion of the first kind, and co-SAS, which enhances the effect of the main one [3].

As an API, we were interested in simvastatin (Fig. 1) – a substance that is sparingly soluble in water and very easily soluble in methylene chloride and easily soluble in ethanol. According to the biopharmaceutical classification system, simvastatin is (1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl]2,2-dimethylbutanoate) belong to class II (has low solubility and high permeability), when taken orally, its bioavailability is 5 % [4].

Confirmation of the effectiveness of the introduction of sparingly soluble APIs into self-emulsifying in vitro drug delivery systems is usually performed through biopharmaceutical trials. API release speed and completeness are being investigated. For gastric-dissolving drugs, the environment of gastric juice is simulated (0.1 M solution of hydrochloric acid at a temperature of 37 °C without the use of intensive shaking techniques), for enteric-dissolving drugs, conditions of an alkaline environment are created accordingly [5].

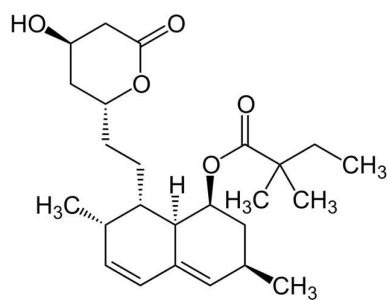


Fig. 1. Simvastatin

Qualitative and quantitative analysis of the released substance is carried out by various methods: thin-layer chromatography, spectrophotometry in the ultraviolet or visible range of light, potentiometric titration [6].

This direction of research is not sufficiently developed in Ukraine, but foreign scientists have managed to achieve significant success. During the development of a self-emulsifying drug delivery system with acyclovir, it was found that *in vitro* API release is 4.92 times more efficient, compared to API release not placed in a self-emulsifying system (Mahmood et al., 2022) [7]. When developing a self-emulsifying system with dalargin, it was possible to achieve 92.1 % release of the active substance within 30 minutes (Zupancic et al., 2017) [8]. A delivery system of dimenhydrinate was developed, from which the release is 2.8 times more efficient, compared to the pure substance (Leichner et al., 2019) [9]. It was also possible to develop a self-emulsifying delivery system for azithromycin, which allows the release of 7.99 times (liquid form) and 4.63 times (solid form) more API, compared to the release of the substance not placed in the system (Assi et al., 2020) [10]. Conducted research on the development of self-emulsifying systems for MPRM extracts, for example, the development of a self-emulsifying delivery system for Commiphora wightii extract, which releases 98.14 % API within 60 minutes (Singh et al., 2021) [11].

The research results described above refer to enteric-dissolving drugs. They are the most common among self-emulsifying systems, as they allow you to use the mechanism of lymphatic absorption of API and avoid the effect of the first passage through the liver, which also contributes to increased bioavailability [12]. Our chosen substance, simvastatin, is transformed in the liver with the formation of active metabolites, so such a popular type of self-emulsifying system is inappropriate in this case [13].

An example of the development of gastric-soluble self-emulsifying systems is the creation of a self-emulsifying system for the delivery of dolutegravir sodium (an antiretroviral drug), it was found that the introduction of API into the composition of the system allows to increase the release into the environment of 0.1 N hydrochloric acid solution by 2.8 times, compared to the release of the pure substance (Giddam et al., 2022) [14].

The aim of the research. Conducting biopharmaceutical tests of capsules with a self-emulsifying delivery system of simvastatin to confirm the effectiveness and feasibility of introducing into the composition of

self-emulsifying drug delivery systems active pharmaceutical ingredients that are difficult to dissolve in the environment of gastric juice.

2. Research planning (methodology)

In vitro biopharmaceutical testing is one of the stages of complex research on the development of the composition and technology of self-emulsifying drug delivery systems.

The effectiveness and expediency of introducing simvastatin into self-emulsifying systems was confirmed by conducting a comparative analysis between the tested samples and the reference drug. Two stages of research were planned:

I – carrying out studies on the adaptation of the method of quantitative determination of simvastatin to the conditions of further biopharmaceutical trials;

II – biopharmaceutical tests study of the dynamics of the release of the active substance from the test samples and the reference drug with the subsequent determination of the rate and amount of the release of the active substance from the test samples and the reference drug.

3. Materials and methods

Substances, auxiliary substances, reagents and materials used during research were simvastatin (India, p. DK40-2005021, 99.09 %), castor oil (Ukraine), polyethylene glycol 40 hydrogenated castor oil (PEG-40 Hydrogenated Castor Oil) (India), Tween 80 (Polysorbate 80) (Ukraine), glycerol monostearate (Glycerol monostearate(90 %)) (Gustav Heess GmbH, Germany), polyethylene glycol 100 stearate (PEG-100 Stearate) (ERCA, Italy), hard gelatin capsules No. 3 white (China), 0.1 M hydrochloric acid solution (made from concentrated hydrochloric acid), ethanol 96 % (Ukraine), filter paper 90 mm white tape (Ukraine). The reference drug is “Simvastatin-Sandoz” (Salyutas Pharma, Germany, series LX5161) [4, 15, 16].

The method of making a solution of simvastatin standard sample (SS): 0.050 g (exact weight of the substance) is placed in a measuring flask with a capacity of 50.0 ml, dissolved in 20 ml of ethanol 96 % and brought up to the mark with the same solvent. 1.0 ml of the resulting solution is placed in a volumetric flask with a capacity of 200.0 ml, and the volume of the solution is brought up to the mark with a 0.1M hydrochloric acid solution.

To confirm compliance with the Bouguer-Lambert-Beer law, from 0.1 ml to 0.9 ml of the obtained solution of simvastatin in ethanol is placed in volumetric flasks with a capacity of 10.0 ml, brought up to the mark with a 0.1 M solution of hydrochloric acid. Compensation solution: 0.1 M hydrochloric acid solution.

The absorption spectra and optical density of the investigated solutions were recorded using a spectrophotometer using quartz glass cuvettes with a layer thickness of 10 mm against the background of the compensating solution.

Statistical analysis of the obtained results was carried out using Excel2010 software in accordance with SPbU requirements [17].

The stability of the solution obtained under the same conditions was investigated for 60 minutes by measuring the optical density every 5 minutes. The solution is considered stable if the change in optical density does not exceed $\pm 1\%$.

For the next stage of research, pre-made samples of self-emulsifying bases were used, the composition of which is given in Table 1 based on one dose.

Table 1
The composition of the studied self-emulsifying bases

Composition	Castor oil	PEG-40 HCO	Tween-80	GMS	PEG-100 stearate
1	0.016	0.004	0.025	0.005	–
2	0.016	0.004	0.025	–	0.005

The method of making a solution of the investigated bases: an exact weight of the self-emulsifying base, equivalent to the weight of one dose, is placed in a measuring flask with a capacity of 100.0 ml, brought up to the mark with a 0.1 M solution of hydrochloric acid. Dissolution without intensive shaking is carried out at a temperature of 37 ± 0.5 °C. Already after 4 minutes, an emulsion is obtained, which is quite cloudy. Filter through a paper pleated filter. The resulting filtrate is used to record the absorption spectrum of absorption.

The preparation of a solution of hard gelatine capsules is carried out according to a method similar to the preparation of a solution of the investigated bases.

Preparation of samples of self-emulsifying drug delivery systems: 10 mg of simvastatin is added to the proposed bases. When preparing a self-emulsifying system, the required amount of castor oil and PEG-40 HCO is heated in a water bath to 80 °C (as shown by the results of previous studies, simvastatin dissolves well in this mixture when heated) [18]. Dissolve simvastatin in the resulting mixture, add GMS or PEG-100 stearate without cooling (if necessary, you can additionally use a water bath to accelerate their melting), add Tween 80, mix until homogenous, 0.060 g (precisely weighed) of the studied samples are placed in a hard gelatine capsule No. 3.

The method of making a solution of the studied samples: 1 capsule is placed in a glass flask with 100.0 ml of a 0.1 M solution of hydrochloric acid. Dissolution is carried out without the use of intensive shaking methods. After some time, an emulsion is obtained, which is quite cloudy. Filter through a paper pleated filter. 2.0 ml of the filtrate is placed in a volumetric flask with a capacity of 10.0 ml, brought up to the mark with a 0.1 M solution of hydrochloric acid. The resulting solution is used to measure the optical density and obtain an absorption spectrum. As a compensating solution, a solution of a capsule filled with an exact amount of self-emulsifying base, prepared according to the same method, is used.

The method of making a solution of the reference drug: an exact amount of the drug, equivalent to 10 mg of simvastatin, is placed in a glass flask with 100.0 ml of a 0.1 M solution of hydrochloric acid. Dissolution is carried out without the use of intensive shaking methods. Filter through

a paper pleated filter. The resulting filtrate is used to measure the optical density and obtain the absorption spectrum.

Compensation solution: 0.1 M hydrochloric acid solution.

The study of the dynamics of the release of the active substance from self-emulsifying drug delivery systems and the reference drug was carried out for 50 minutes in a medium of 0.1 M hydrochloric acid solution at a temperature of 37 ± 0.5 °C according to the method described above, an aliquot of 5.0 ml was taken every 10 minutes from subsequent renewal of the selected volume with the same solvent. The choice of medium and dissolution temperature is dictated by the method of application of the tested drug (for oral use).

The concentration of the obtained solutions (C , mg/ml) was calculated according to the formula (1):

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

where A – optical density of the investigated solution;

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

C_{st} – concentration of the standard sample, mg/ml;

b – dilution.

The total amount of simvastatin that went into the solution (X_n , mg) is calculated according to the formula (2):

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

where C_n – concentration of simvastatin in the solution after n minutes of the experiment, mg/ml;

V_p – total volume of the studied solution, ml;

X_{n-1} – the total amount of simvastatin that went into the solution in $n-1$ minutes, mg;

V_a – the volume of the aliquot selected for research, ml.

4. Research results

For further biopharmaceutical tests, it was necessary to adapt the spectrophotometric method of quantitative determination of simvastatin. The literature describes spectrophotometric methods of quantitative assessment of simvastatin in tablet dosage forms [19] and blood plasma by its own light absorption using methanol as a solvent [20].

To create a similar environment of gastric juice, the test was carried out in a 0.1 M solution of hydrochloric acid. It was established that the absorption spectrum of a 0.001 % solution of simvastatin in a 0.1 M solution of hydrochloric acid in the region from 220 nm to 270 nm is characterized by the presence of absorption maxima at wavelengths of 232 nm, 239 nm, and 248 nm (Fig. 2).

To select the analytical wavelength of absorption, the subordination of solutions of simvastatin in a 0.1 M solution of hydrochloric acid to the basic law of light absorption at wavelengths of 232 nm, 239 nm, and 248 nm was determined (Table 2).

It was established that at wavelengths of 232 nm, 239 nm and 248 nm in concentrations from 0.0004 % to 0.0018 %, the subordination of standard solutions of sim-

vastatin in a 0.1 M solution of hydrochloric acid to the Bouguer-Lambert-Beer law is observed (Table 2). To confirm the linear dependence of the wavelength on the concentration of the investigated solution, the specific absorption index was calculated, the values of which were subjected to statistical processing.

Table 2

The results of determining the optical density and specific absorption rates of simvastatin in a 0.1 M solution of hydrochloric acid at wavelengths of 232 nm, 239 nm, 248 nm

C, %	232 nm		239 nm		248 nm	
	A	A _{1cm} ^{1%}	A	A _{1cm} ^{1%}	A	A _{1cm} ^{1%}
0.0002	0.112	560	0.121	605	0.085	425
0.0004	0.174	435	0.186	465	0.127	318
0.0006	0.296	493	0.323	538	0.221	368
0.0008	0.410	513	0.452	565	0.309	386
0.0010	0.468	468	0.512	512	0.348	348
0.0012	0.594	495	0.655	546	0.448	373
0.0014	0.702	501	0.772	551	0.530	379
0.0016	0.787	492	0.866	541	0.600	375
0.0018	0.866	481	0.953	529	0.667	371

Further studies of the main metrological characteristics of the average value of the specific absorption index (Table 3) showed that the method is reproducible at all selected wavelengths. The values obtained at 239 nm have the smallest relative error of the average result, further studies were carried out precisely at this wavelength (Fig. 3).

The results of the study of the stability of 0.0004 % of simvastatin in a 0.1M solution of hydrochloric acid at a wavelength of 239 nm indicate that the solution is stable for 1 hour (the relative deviation of the obtained optical densities of the solution is 0.54 %).

Absorption spectra of absorption of self-emulsifying bases and gelatine capsule in 0.1 M solution of hydrochloric acid (Fig. 4) indicate the presence of substances in them, which at a wavelength from 220 nm to 270 nm increase the intensity of the optical density of the active compound. To prevent measurement error, a solution of one capsule filled with an exact weight of self-emulsifying base in a 0.1 M solution of hydrochloric acid was used as a compensation.

The obtained absorption spectra of the absorption of the studied samples using the prepared compensation solution coincide with the spectrum of the SS of simvastatin (Fig. 5).

The absorption spectrum of the absorption of the reference drug in a 0.1 M solution of hydrochloric acid in the region from 220 to 235 nm differs slightly from the spectrum of the standard sample,

which is due to the influence of auxiliary substances that are part of the drug. At the same time, at wavelengths of 239 nm and 248 nm, maxima are observed, which correspond to simvastatin absorption maxima (Fig. 6).

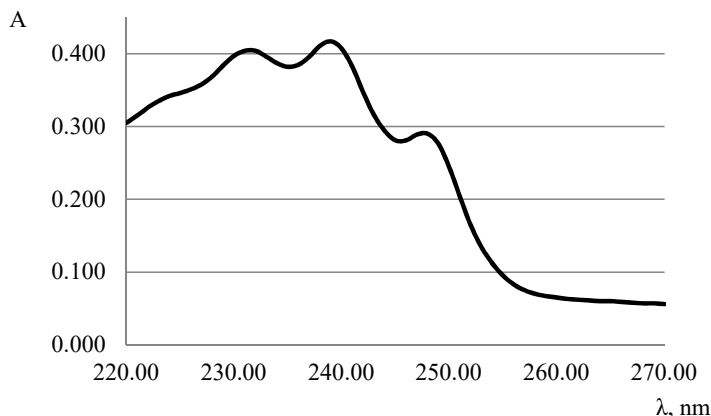


Fig. 2. Absorption spectrum of absorption of 0.001 % solution of simvastatin in 0.1M solution of hydrochloric acid

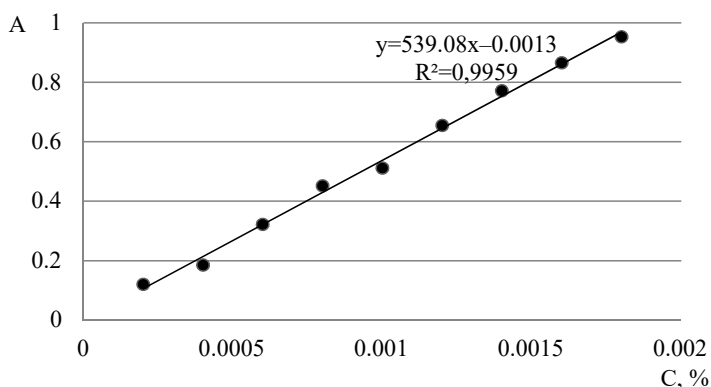


Fig. 3. Graph of dependence of optical density on the concentration of simvastatin in the absorption maximum at a wavelength of 239 nm

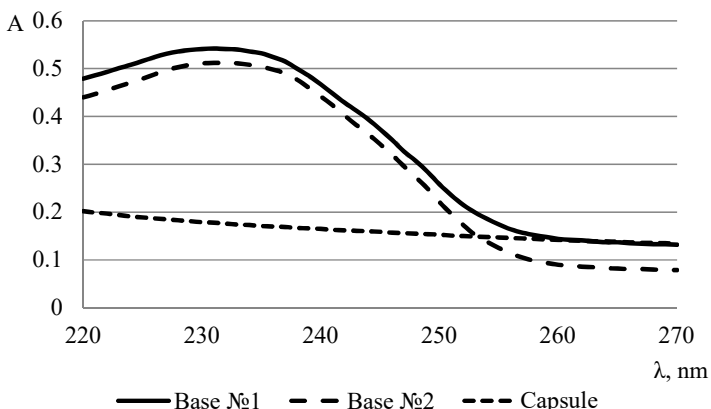


Fig. 4. Absorption spectra of absorption of self-emulsifying bases and gelatine capsule in 0.1 M solution of hydrochloric acid

Table 3

Metrological characteristics of the average value A _{1cm} ^{1%} at each of the analytical wavelengths											
λ, nm	v (n-1)	P, %	\bar{x}	S ²	S	S _x	t (P, n)	t (P, v)	Δ \bar{x}	$\bar{\epsilon}$, %	
232	7	95	484.7500	579.6429	24.0758	8.5121	1.57	2.36	13.4350	2.7715	
239			530.8750	950.1250	30.8241	10.8990	1.07		11.6673	2.1977	
248			364.7500	477.6429	21.8550	7.7269	1.19		9.1924	2.5202	

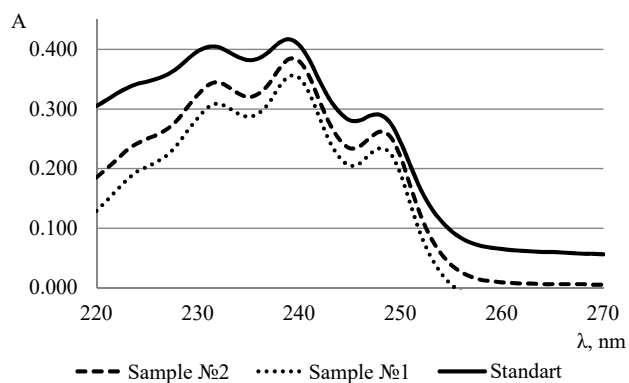


Fig. 5. Absorption spectrum of the absorption of the studied samples and the standard sample of simvastatin in a 0.1 M solution of hydrochloric acid

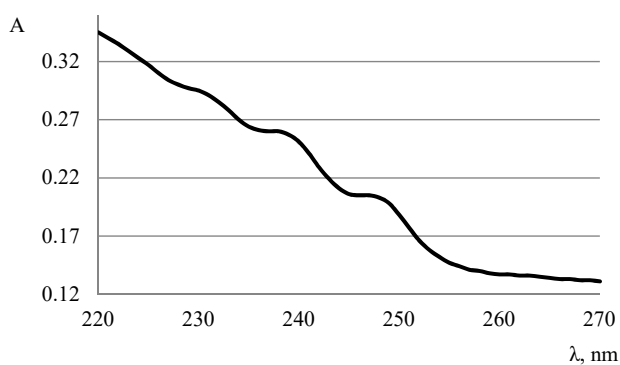


Fig. 6. Absorption spectrum of absorption of the reference drug in a 0.1 M solution of hydrochloric acid

According to the results obtained during the calculations of the total amount of simvastatin that went into the solution, graphs of the dependence of the released amount of simvastatin on time were constructed for the studied samples and the reference drug (Fig. 7). Studies of the kinetics of the release of simvastatin in the medium of 0.1 M hydrochloric acid solution showed that both self-emulsifying bases contribute to the release of almost five times more simvastatin, compared to the reference drug (Fig. 8).

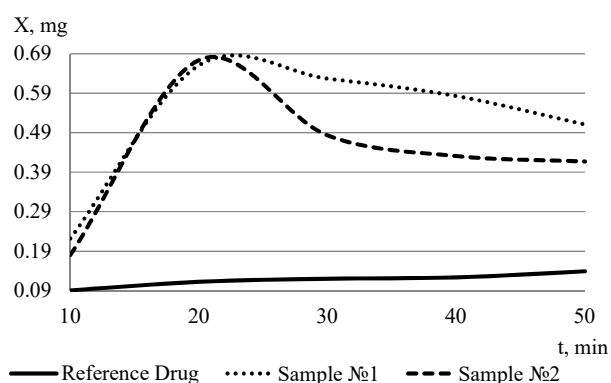


Fig. 7. Kinetics of simvastatin release from the tested samples and the reference drug

The results obtained during biopharmaceutical tests were subjected to statistical processing. With the help of a two-sample t-test for samples of the percentage ratio of the released active substance between the tested

samples and the reference drug, it was determined that the difference between the data obtained during the study of sample No. 1 and sample No. 2 is not statistically significant ($p=0,4458$, $p>0,05$).

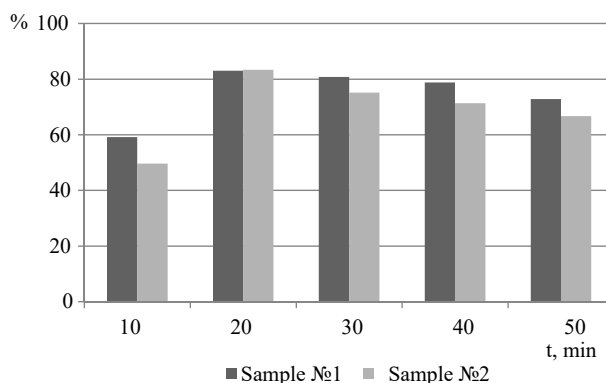


Fig. 8. The difference in the percentage of the active substance released from self-emulsifying bases in relation to the reference drug

5. Discussion of research results

During preliminary studies, it was confirmed that simvastatin solution obeys the Bouguer-Lambert-Beer law in concentrations from 0.0004 % to 0.0018 %. The stability of simvastatin in 0.1 M hydrochloric acid solution for 60 minutes has been proven. It was established that the method of absorption spectrophotometry can be used to conduct biopharmaceutical studies of self-emulsifying drug delivery systems with simvastatin.

When conducting biopharmaceutical tests, it was established that the release of simvastatin from the studied bases occurs faster, compared to the reference drug. Graphs of the dynamics of the release of the active substance, built according to the results of the studies, demonstrate the gradual dissolution and release of simvastatin from the reference drug throughout the study period. While the most saturated solution was obtained from the tested samples already at the twentieth minute, further renewal of the selected aliquot led to a certain dilution of the solution, and after 20 minutes the amount of simvastatin released into the solution of the tested samples was almost five times greater than after 50 minutes in a solution obtained from the reference drug. The increase in the release rate of simvastatin in a 0.1 M solution of hydrochloric acid is due to the presence of surfactants in the experimental samples, which ensure the process of self-emulsification, which contributes to the rapid and effective transition of the API into the solution and subsequently accelerates the absorption process of the API [2].

The obtained results can be compared with the results of scientists who were engaged in the development of enteric forms of self-emulsifying systems, and it can be concluded that gastric-dissolving systems are no less effective. Compared to the self-emulsifying system developed by scientists [14], which is gastric soluble, we managed to obtain higher API release rates.

The analysis of the obtained data does not allow to single out one of the studied samples, since the obtained results of the study of dissolution and release of the active

substance for composition No. 1 and No. 2 are practically identical. Therefore, the next stage of research, confirmation of the efficiency and safety of the investigated drug delivery systems *in vivo*, should be carried out with both samples as well.

Study limitations. The proposed research methods should be used for *in vitro* research. At the later stages of research (*in vivo*), it is more effective to use the method of high-performance liquid chromatography to identify or quantify simvastatin in the blood serum of laboratory animals [21].

Prospects for further research. After the biopharmaceutical research, the next step is to confirm the effectiveness of the introduction of simvastatin into self-emulsifying drug delivery systems by the *in vivo* method. Currently, comparative pharmacological studies of experimental samples and the reference drug have been started on the basis of the Educational and Scientific Institute of Applied Pharmacy, Kharkiv.

6. Conclusions

The results of biopharmaceutical tests of capsules with a self-emulsifying delivery system of simvastatin *in vitro* confirm the effectiveness and feasibility of intro-

ducing poorly water-soluble active pharmaceutical ingredients into the composition of self-emulsifying drug delivery systems. Using the example of simvastatin, it is shown that self-emulsifying drug delivery systems provide a more complete and rapid release of the active pharmaceutical ingredient compared to the reference drug. It was determined that the amount of simvastatin released into a solution of 0.1 M hydrochloric acid from the tested samples of self-emulsifying API mixtures is almost five times higher than in the solution of the reference drug.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, including financial, personal, authorship or other nature, which could affect the research and its results presented in this article.

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Availability of data

The manuscript has data included as electronic supplementary material.

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