1. Introduction

A self-emulsifying drug delivery system is a drug for oral administration that consists of an active pharmaceutical ingredient dissolved in a hydrophobic solvent and a combination of surfactants, primary and secondary. The main task of self-emulsifying drug delivery systems is to improve the solubility of poorly soluble substances in the aqueous environment of the gastrointestinal tract, as a result of which absorption is accelerated, the bioavailability and effectiveness of the drug increases [1].

During the development of new self-emulsifying drug delivery systems, along with numerous studies, biological tests are conducted to strengthen the results obtained in previous studies.

The main directions of these studies are usually the determination of bioavailability indicators by determining the amount of the active substance in blood serum by the method of high-performance liquid chromatography, and for some active substances, for which it is possible, confirmation of effectiveness. For example, for simvastatin, it should be a study of hypolipidemic effect by determining the amount of triglycerides, cholesterol and lipoproteins in blood serum.

For example, when developing a self-emulsifying system with exenatide, the antihyperglycemic activity was evaluated by measuring glucose in blood serum [2]. During the development of the system with nevirapine (antiretroviral drug), the profile of its in vivo release and biodistribution in the body, in particular in the liver and brain, were studied [3]. When developing an antimalarial drug, a self-emulsifying system with artemether, the antimalarial activity was also studied and it was established that the substance in the system is significantly more effective [4].

There are alternatives, such as when developing a self-emulsifying system with plant extracts. To confirm the antidiabetic effectiveness of the self-emulsifying system with garden thistle extract, an improvement in the quality of life of experimental animals was noted, which was manifested mainly in the cessation of body weight loss [5].

The aim of the research. Conducting biological tests to compare the hypolipidemic activity of the developed self-emulsifying drug delivery systems with simvastatin.

CONDUCTING BIOLOGICAL TESTS IN THE DEVELOPMENT OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS WITH SIMVASTATIN

Liubov Bodnar, Dmytro Lytkin, Nataliіa Polovko

The aim of the study was to compare the hypolipidemic activity of the developed self-emulsifying drug delivery systems with simvastatin with reference samples of the substance and the finished drug product of industrial production.

Materials and methods. The substance of simvastatin (India, s. DK40-2005021, 99.09 %, introduced into the composition of self-emulsifying compositions based on castor oil (Ukraine), polyethylene glycol 40 hydrogenated castor oil (India), Tween 80 (Ukraine), glycerol monostearate (Gustav Heess GmbH, Germany) or polyethylene glycol 100 stearate (ERCA, Italy). Reference samples were Simvastatin-Sandoz (Salutas Pharma, Germany, series LX5161) and simvastatin in pure form.

The experimental animals were Syrian hamsters aged 2 months. Hyperlipidemia was modeled by means of an alimentary load. To assess the state of lipid metabolism in animals, the content of triacylglycerols, total cholesterol, low-density lipoprotein and high-density lipoprotein in the blood serum was determined by colorimetric enzymatic methods using the appropriate standard reagent kits “Triacylglycerol F” HP022.02, “Cholesterol F” HP026.02, “Cholesterol-LDL F” HP026.05 and “Cholesterol-HDL F” HP026.04 (LLC SPE “Filitic-Diagnostics”, Ukraine) on a semi-automatic biochemical analyzer MapLab Plus (BSI, Italy).

Results. The reference samples had similar dose-dependent efficacy parameters. At the same time, the test samples, also having similar dose-dependent effects, in absolute terms at the maximum concentration reduced the amount of low-density lipoprotein and total cholesterol more effectively than the reference samples. When using the test samples in their average concentration, the level of triglycerols was significantly reduced, which is rather a concomitant effect of simvastatin.

Conclusions. The improvement of the overall efficacy of simvastatin when it is introduced into self-emulsifying drug delivery systems has been proved, which is associated with the modification of pharmacokinetic parameters by improving the solubility of the substance in the aqueous environment of the gastrointestinal tract

Keywords: self-emulsifying drug delivery systems, increased activity, improved solubility, simvastatin, biological tests

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with reference samples of the substance and the finished medicinal product of industrial production. At the same time, the authors do not aim to develop an improved drug specifically for the treatment of atherosclerosis. Research is being conducted exclusively to develop self-emulsifying compositions, and simvastatin was chosen as one example of active pharmaceutical ingredients due to its poor solubility in water, 0.1 M hydrochloric acid and low bioavailability.

2. Research planning (methodology)

Prerequisites for conducting biological research: we previously developed self-emulsifying drug delivery systems with simvastatin in the form of hard gelatine capsules and conducted their biopharmaceutical tests. It was determined in vitro that the developed samples of self-emulsifying compositions allow to accelerate and increase the solubility of simvastatin in 0.1 M hydrochloric acid by almost five times [6, 7].

Therefore, this stage (in vivo) is a continuation of a consistent research plan for the development of self-emulsifying drug delivery systems with simvastatin. For its implementation, a theoretical search was conducted and experimental animals were selected, and a preliminary research scheme was constructed (Fig. 1).

![Fig. 1. Scheme of biological tests](image)

3. Materials and methods

As experimental animals for drugs with simvastatin, it is advisable to choose Syrian hamsters. Most rodents have an antitherogenic lipoprotein profile. Unlike other rodents, the percentage of lipoproteins in Syrian hamsters is as close as possible to that of humans, which makes them the best object for modelling dyslipidaemias among small laboratory animals, but a significant proportion of their cholesterol is still in the form of high-density lipoproteins. This complicates the interpretation of the obtained data due to relative indicators, such as the atherogenicity coefficient or the ratio of low-density lipoprotein/high-density lipoprotein but allows reliable evaluation of the results in absolute values of the sum of all fractions of cholesterol and other lipids [8, 9].

The study was conducted for 13 weeks (from March 13, 2023 to June 11, 2023).

The experimental study was carried out on 84 male Syrian hamsters, aged at the time of the experiment, 2 months, weighing 90±10 g. Conditions of keeping experimental animals: in the vivarium of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy in accordance with sanitary and hygienic standards. The animals were housed in separate polypropylene cages in a room with a natural day-night light regime at a temperature of 19–24 °C and a humidity of 50–60 %. The standard diet of the animals was modified depending on the experimental group (or was unchanged), the animals had free access to water and food [10].

Each of the stages of this research was carried out in compliance with the principles of Directive 2010/63/EU of the Council of the EU “On the protection of animals used for scientific purposes” (Brussels, 2010) and “General ethical principles of animal experiments” (Kyiv, 2001), which were agreed with the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1985) and the Code of Ethics of the World Medical Association (Helsinki, 1964) [11]. The conclusion regarding the compliance of research with modern scientific standards and ethical principles was obtained at the meeting of the Commission on Bioethics of the National Pharmaceutical University, protocol No. 5 dated March 25, 2021.

Animals belonging to intact control groups during the experiment and all animals during the adaptation period were kept on a balanced standard diet for rodents (320 Kcal/100 g, 12 % fats, TU.U157-2123600159-001; 2007). After the adaptation period, the animals were divided into groups and the diet was changed:

1) negative control (NC), a group of animals maintained on a standard diet (n=6);
2) positive control (PC), a group of animals maintained on a hypercaloric hypercholesterol diet (n=78).

To reproduce hyperlipidaemia, animals were kept on a hypercaloric hypercholesterol diet for 6 weeks instead of standard feed, which consisted of: 89.8 % standard ground rodent feed, 0.2 % dietary cholesterol, and 10 % unsaturated fats (margarine, lard, coconut oil) by mass [8, 12].

After 4 weeks from the beginning of the diet change, samples were started to be used. Daily doses for each of the samples were given in terms of simvastatin content. Animal-equivalent daily doses of simvastatin were calculated according to FDA recommendations, considering average therapeutic daily doses for humans and interspecies differences in body mass and surface area [13]. The initial therapeutic daily doses for humans were chosen to be 10, 20, and 40 mg for recalculation, the calculated equivalent doses for animals were, respectively, 1.25, 2.50, and 5.00 mg/kg with rounding [14].

For pharmacocorrection of experimental hyperlipidaemia, test and commercial samples containing simvastatin as an active ingredient were used:

1) Simvastatin substance, white amorphous powder (India, p. DK40-2005021, 99.09 %) (reference No. 1);
2) Simvastatin Sandoz, tablets, film coated 40 mg each, series No. LXS161 (reference No. 2);
3) self-emulsifying delivery system with simvastatin (sample No. 1);
4) self-emulsifying delivery system with simvastatin (sample No. 2).

For the manufacture of the studied samples (Table 1), we used the substance simvastatin (India, p. DK40-2005021, 99.09 %), castor oil (Ukraine), polyethylene glycol 40 hydrogenated castor oil (PEG-40 Hydrogenated Castor Oil) (PEG-40 HCO) (India), Tween 80 (Polyborate 80) (Ukraine), Glycerol monostearate (90 %) (GMS) (Gustav Heess GmbH, Germany) [15, 16], polyethylene glycol 100 stearate (PEG-100 Stearate) (ERCA, Italy) [17].

Table 1

<table>
<thead>
<tr>
<th>Components</th>
<th>Purpose</th>
<th>Sample No. 1</th>
<th>Sample No. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>Active substance</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Main solvent</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>PEG-40 HCO</td>
<td>Surfactant – co-solvent</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Tween-80</td>
<td>Main surfactant</td>
<td>0.0125</td>
<td>0.0125</td>
</tr>
<tr>
<td>GMS</td>
<td>Co-surfactant</td>
<td>0.0025</td>
<td>-</td>
</tr>
<tr>
<td>PEG-100 Stearate</td>
<td>Co-surfactant</td>
<td>-</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

For pharmacocorrection, animal group 2 was divided into subgroups:
1) positive control (PC), a group of animals that continued to be kept on a hypercaloric, hypercholesterol diet (n=6).
2) group of animals on a hypercaloric hypercholesterol diet received reference No. 1 (P_API) in doses of 1.25 mg/kg (n=6), 2.50 mg/kg (n=6) and 5.00 mg/kg (n=6);
3) group of animals on a hypercaloric hypercholesterol diet received reference No. 2 (P_Drugs) in doses of 1.25 mg/kg (n=6), 2.50 mg/kg (n=6) and 5.00 mg/kg (n=6);
4) group of animals on a hypercaloric hypercholesterol diet received test sample No. 1 (TS_1) in doses of 1.25 mg/kg (n=6), 2.50 mg/kg (n=6) and 5.00 mg/kg (n=6);
5) a group of animals on a hypercaloric hypercholesterol diet received test sample No. 2 (TS_2) in doses of 1.25 mg/kg (n=6), 2.50 mg/kg (n=6) and 5.00 mg/kg (n=6).

Appropriate doses of the studied samples were dispersed in purified water and administered intragastrically using a special probe once a day during the last two weeks of observation. Animals from the negative control group received solvent.

Euthanasia of experimental animals was carried out 6 weeks after the start of keeping animals on a model diet, after a two-week treatment period. Animals were removed from the experiment humanely using a CO₂ box. Blood was collected by intracardial puncture.

Blood serum was obtained according to the standard method by incubating freshly collected blood for 30 minutes at 37 °C, after which the blood was centrifuged for 15 minutes at 1000 g. All received serum samples were stored at -20 °C.

To assess the lipid metabolism of animals, the content of triacylglycerols (TG), total cholesterol (CHL), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) was determined in blood serum. A colorimetric enzymatic method was used applying the appropriate standard sets of reagents “Triacylglycerols F” HP022.02, “Cholesterol F” HP026.02, “Cholesterol-LDL F” HP026.05 and “Cholesterol-HDL F” HP026.04 (ToV NVP “Filisit-Diagnostics”, Ukraine) on a semi-automatic biochemical analyzer MapLab Plus (BSI, Italy).

Statistical processing of the results was carried out using the basic package of programs MS Excel 2007 and IBM SPSS Statistics 22. When determining the nature of the distribution, the Shapiro-Wilk test was applied, since this test shows the greatest power and is appropriate for samples with numerical values, and the sample size does not exceed 60. The result was expressed as arithmetic mean (M) and standard error of the mean (SEM). For further comparison of the samples, parametric a priori (ANOVA) and post-hoc (Tukey’s HSD test) methods were used, since the samples are characterized by a normal data distribution. Differences were considered probable at the level of significance p<0.05 [18].

4. Research results

Under the influence of a high-caloric diet with cholesterol, combined hyperlipidemia was observed in all animals in the PC group. The level of TG increased by 2.60 times, and the level of total cholesterol – by 1.93 times compared to the conventional norm in the negative control (p<0.05). The increase in the level of cholesterol in this group occurred both at the expense of LDL and at the expense of HDL (Table 2).

All studied doses of the reference substance simvastatin led to a decrease in LDL content, which was accompanied by a noticeable dose-dependent effect: at a dose of 1.25 mg/kg, this indicator decreased by 19.11 %, at a dose of 2.50 mg/kg - by 29.96 % and in a dose of 5.00 mg/kg – by 36.86 % (p<0.05 vs. PC). There were no clear patterns of the drugs effect on HDL content in hamsters. In the maximally used dose, the simvastatin substance also contributed to a probable decrease in CHL content by 31.51 % and TG content by 32.42 % compared to similar indicators in the PC group (Table 2).

The drug simvastatin led to similar results as the substance, the indicators had no statistical differences relative to the P_API group. In addition, all the results of the relative comparison with other groups were the same in both groups P_API and P_Drug.

A similar picture was observed against the background of the use of the studied sample No. 1 (TS_1). There was also a dose-dependent effect on the reduction of LDL content: by 17.75 % at a dose of 1.25 mg/kg, by 25.26 % at a dose of 2.50 mg/kg and by 41.30 % at a dose of 5.00 mg/kg (p<0.05 vs. PC). In the highest dose of sample No. 1, which corresponds to 5.00 mg/kg of simvastatin, CHL content was also reduced by 29.32 % and TG content by 43.93 % compared to similar indicators in the PC group (Table 2). However, a statistically significant decrease in TG content against the background of the use of
TS_1 was observed even at a dose of 2.50 mg/kg, in contrast to the reference agent (by 27.27 %, \( p<0.05 \) vs. PC).

Test sample No. 2 (TS_2) against the background of use in animals with experimental hyperlipidemia at all tested doses contributed to a probable dose-dependent decrease in both LDL content and TG content, compared to similar indicators in the PC group. Thus, in a dose of 1.25 mg/kg, the content of LDL decreased by 19.45 %, and TG – by 28.79 %; in a dose of 2.50 mg/kg LDL – by 29.35 %, and TG – by 34.55 %; in a dose of 5.00 mg/kg LDL – by 44.03 %, and TG – by 51.21 %. At the same time, at the maximum dose of 5.00 mg/kg, the TG content in the serum of animals of the TS_2 group was even statistically lower than against the background of the use of the reference agent simvastatin (both in the form of a substance and in the form of a finished medicinal product) in the corresponding dose (\( p<0.05 \) vs. P_API; \( p<0.05 \) vs. P_Drug). In addition, under the conditions of using the maximum studied dose in this group, the content of CHL probably decreased by 38.62 % from the indicator of the positive control (Table 2).

The graphs of the dynamics of the decrease in the level of the investigated indicators were built, which allow a visual comparison of the results obtained when using the reference means and the tested samples with the group of positive control (Fig. 2).

### Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>Daily dose of simvastatin, mg/kg</th>
<th>TG content, mmol/l</th>
<th>CHL, mmol/l</th>
<th>LDL, mmol/l</th>
<th>HDL, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>–</td>
<td>1.27±0.19</td>
<td>2.84±0.29</td>
<td>1.54±0.08</td>
<td>0.92±0.10</td>
</tr>
<tr>
<td>PC</td>
<td>–</td>
<td>3.30±0.23(^a)</td>
<td>5.49±0.32(^a)</td>
<td>2.93±0.13(^a)</td>
<td>1.30±0.06(^a)</td>
</tr>
<tr>
<td>P_API</td>
<td>1.25</td>
<td>2.75±0.22(^a)</td>
<td>4.55±0.56(^a)</td>
<td>2.37±0.14(^b)</td>
<td>0.98±0.10(^a)</td>
</tr>
<tr>
<td></td>
<td>2.50</td>
<td>2.59±0.16(^a)</td>
<td>4.34±0.31(^a)</td>
<td>2.14±0.07(^b)</td>
<td>1.17±0.06(^a)</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>2.23±0.06(^a)(^b)</td>
<td>3.76±0.39(^a)</td>
<td>1.85±0.13(^a)</td>
<td>1.01±0.04(^a)</td>
</tr>
<tr>
<td>P_Drug</td>
<td>1.25</td>
<td>2.73±0.13(^a)</td>
<td>4.58±0.27(^a)</td>
<td>2.39±0.09(^b)</td>
<td>0.98±0.07(^a)</td>
</tr>
<tr>
<td></td>
<td>2.50</td>
<td>2.69±0.13(^a)</td>
<td>4.40±0.13(^a)</td>
<td>2.22±0.05(^b)</td>
<td>1.03±0.08(^a)</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>2.27±0.07(^a)(^b)</td>
<td>3.65±0.35(^a)</td>
<td>1.82±0.09(^a)(^b)(^c)</td>
<td>1.08±0.05(^a)</td>
</tr>
<tr>
<td>TS_1</td>
<td>1.25</td>
<td>2.58±0.20(^a)</td>
<td>4.65±0.53(^a)</td>
<td>2.41±0.09(^b)</td>
<td>0.88±0.10(^a)</td>
</tr>
<tr>
<td></td>
<td>2.50</td>
<td>2.40±0.19(^a)(^b)</td>
<td>4.45±0.33(^a)</td>
<td>2.19±0.08(^b)</td>
<td>1.03±0.12(^a)</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>1.85±0.12(^a)(^c)</td>
<td>3.88±0.32(^a)</td>
<td>1.72±0.08(^a)(^d)(^e)</td>
<td>0.99±0.07(^a)</td>
</tr>
<tr>
<td>TS_2</td>
<td>1.25</td>
<td>2.35±0.19(^a)(^b)</td>
<td>4.57±0.51(^a)</td>
<td>2.36±0.11(^b)</td>
<td>1.12±0.10(^a)</td>
</tr>
<tr>
<td></td>
<td>2.50</td>
<td>2.16±0.12(^a)(^c)</td>
<td>4.48±0.33(^a)</td>
<td>2.07±0.08(^b)</td>
<td>1.10±0.07(^a)</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>1.61±0.06(^a)(^c)(^d)(^e)</td>
<td>3.37±0.35(^a)</td>
<td>1.64±0.13(^a)(^d)(^e)</td>
<td>1.14±0.07(^a)</td>
</tr>
</tbody>
</table>

Note: \(^a\) – differences are statistically significant (\( p<0.05 \)) relative to the corresponding value in the negative control group (NC); \(^b\) – differences are statistically significant (\( p<0.05 \)) relative to the corresponding value in the positive control group (PC); \(^c\) – differences are statistically significant (\( p<0.05 \)) relative to the corresponding value in reference group No. 1 (P_API), corresponding to a similar dose of the active substance; \(^d\) – the differences are statistically significant (\( p<0.05 \)) relative to the corresponding value in reference group No. 2 (P_Drug), corresponding to a similar dose for the active substance; \(^e\) – the differences are statistically significant (\( p<0.05 \)) relative to the dose of 1.25 mg/kg in the groups of reference samples, TS_1 and TS_2, corresponding to a similar sample; \(^\#\) – the differences are statistically significant (\( p<0.05 \)) relative to the dose of 2.50 mg/kg in the groups of reference samples, TS_1 and TS_2, corresponding to a similar sample.

**Fig. 2.** Graphs of the dynamics of lowering the level of TG (a), CHL (b), LDL (c), HDL (d) in doses of 1.25 mg/kg (1), 2.5 mg/kg (2), 5.0 mg/kg (3)
5. Discussion of research results

The results of the study indicate that in terms of antihypercholesterolemic effect, the tested samples No. 1 and No. 2 were comparable to each other and the reference sample (simvastatin substance). And although according to the absolute indicators of the reduction of proatherogenic fractions, sample No. 2 was the leader, in any case, its advantage was not reflected in statistically significant differences from other studied samples.

On the other hand, in the studied samples (especially in TS 2), an enhancement of the antihypertriglyceridemic effect was noted at various exposures compared to the reference agent (simvastatin substance). Simvastatin and similar agents primarily affect the biosynthesis of cholesterol and the formation of low-density lipoproteins and inhibit the formation of very low-density lipoproteins and reduce the content of triglycerides. Since the simvastatin molecule in the studied samples was not modified, the increase in the effects of the active substance in absolute terms for the studied samples No. 1 and No. 2, as well as a statistically significant increase in the antihypertriglyceridemic effect of sample No. 2 is associated with an increase in the bioavailability of the active substance.

The bioavailability of simvastatin is only 5% of the orally received dose, while the nature of the diet does not affect the bioavailability of the drug [19]. Metabolism of simvastatin is very complex, and bioavailability is affected by many processes in addition to intestinal absorption. Simvastatin is a prodrug in which the inactive lactone form is well absorbed in the intestine by passive diffusion due to high lipophilicity. At the stage of presystemic metabolism, a significant amount of the absorbed agent is lost, and the amount of the substance that did not have time to metabolize forms an equilibrium in the blood between the inactive lactone and active hydroxyacid forms [20].

There are data that pathological changes in the small intestine can lead to changes in the pharmacokinetics of simvastatin. First, thickening and fibrosis of the intestinal wall is a common feature of inflammatory bowel diseases associated with hyperlipidemic conditions, such as non-alcoholic fatty liver disease, which in turn complicates the course of passive diffusion. In addition, fibrosis of the intestinal wall is associated with a decrease in local blood flow, which also reduces intestinal absorption. Secondly, hypercholesterolemic conditions are characterized by an increase in the accumulation of cholesterol in the membranes of the intestinal epithelium, as a result of which the fluidity and permeability of the membranes decreases. Such modulation may also explain the lower absorption of simvastatin in the small intestine of Syrian hamsters with experimental hyperlipidemia. In addition, hyperlipidemic conditions can lead to increased expression of P-glycoprotein protein (efflux of simvastatin from epitheliocytes into the intestinal space) and carboxylesterase-1 activity (acceleration of simvastatin metabolism at the time of absorption); but it is unlikely that the dosage form of samples No. 1 and No. 2 affected the latter factors in a certain way [20].

Also interesting is the fact that the drug simvastatin did not differ in the severity of the effect from the substance. Given that the drug was studied in the form of a film-coated tablet, it is obvious that the film coating was damaged during sample preparation for in vivo studies, and this method of administration did not exactly correspond to what was intended by the manufacturer. However, it also indicates that none of the auxiliary ingredients under the film is likely to improve the absorption of the active ingredient.

Thus, it can be assumed that either the proposed new dosage form contributes to a shift in the balance towards the formation of the hydroxyacid form of simvastatin at the stage of wall metabolism, or creates conditions for improving the intestinal absorption of the lactone form of simvastatin.

Study limitations. It was possible to establish the effectiveness of the drug, but this research method does not provide for studying toxicity and predicting the exacerbation of unwanted side effects, which is necessary for moving to the next stage of research.

Prospects for further research. The obtained results indicate the prospect of conducting clinical studies with the aim of establishing the recommended dose and frequency of administration of the new drug.

6. Conclusions

Considering all information above, it can be concluded that the strengthening of the effect in the groups receiving the studied sample No. 2 is related to the modification of the composition of the drug, namely the use of simvastatin in an already dissolved form and in combination with surface-active substances (Tween-80 with PEG-100 Stearate), which accelerated and improved its transition into the gastrointestinal tract environment.

Therefore, the conducted studies allowed to confirm the advantages of self-emulsifying drug delivery systems compared to conventional drugs for oral use. But they point to the prospects of introducing such drugs into industrial production.

Conflict of interests

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

Financing

The study was conducted without financial support.

Data availability

The manuscript has data included as electronic supplementary material.

Use of artificial intelligence technologies

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.
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13. Liubov Bodnar, Postgraduate Student, Department of Pharmaceutical Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

14. Dmytro Lytkin, PhD, Educational and Scientific Institute of Applied Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

15. Nataliia Polovko*, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmaceutical Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

*Corresponding author: Nataliia Polovko, e-mail: polovko.np@gmail.com