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MODELLING OF THE COMPOSITION OF EMULSION MEDICINES AND COSMETICS STABILIZED BY A BIOCOMPLEX OF SURFACTANT SUBSTANCES BASED ON RHAMNOLIPIDS *PSEUDOMONAS* SP. PS-17

Iryna Peleh-Bondaruk, Ivan Revyatskyy, Svitlana Bilous

The aim. *To study the biocomplex of surfactants based on rhamnolipids Pseudomonas sp. PS-17 (biocomplex PS) as an emulsifier and co-emulsifier by using the method of modelling the composition of emulsions for use in dermatology.*
Materials and methods. *The biocomplex PS is a biogenic surface-active complex synthesized by bacteria of the genus Pseudomonas, which is a viscous mass that includes rhamnolipids, which make up to 80 % of the biocomplex, as well as alginate and water. The methods of computer simulation of semi-automated selection of the composition of the oil phase and emulsifiers of medicinal or cosmetic emulsions developed in the MO Excel program were used. In modelling processes, the biocomplex PS was studied as an independent emulsifier in o/w type emulsions, as well as a co-emulsifier of this type of emulsions in combination with type II emulsifiers.*
Results*. The substantiation of the concentration of emulsifiers in the composition of emulsion medicinal and cosmetic products is mainly carried out based on experimental studies; therefore, it requires a long time and is expensive. To reduce the number of technological experiments in the development of emulsion products stabilized by a biocomplex of surfactants based on biocomplex PS, a method of computer simulation of the composition of emulsions in the MO Excel program was developed and used. A method based on the application of the hydrophilic-lipophilic balance system. Two examples of solving specific problems of choosing a complex emulsifier and the composition of the oil phase components of the emulsion product are given.*
Conclusions*. The use of a semi-automated modelling system provides a reasoned choice of the composition of the oil phase of the emulsion when using the PS biocomplex as an independent emulsifier or the choice of the ratio between the PS biocomplex and the type II emulsifier when using a complex emulsifier and allows rational experimental study*
Keywords*: emulsions, emulsifiers, rhamnolipids Pseudomonas sp. PS-17, medicines, cosmetics, hydrophilic-lipophilic balance, emulsions, emulsifiers, rhamnolipids Pseudomonas sp. PS-17, medicines, cosmetics, hydrophilic-lipophilic balance*

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1. Introduction

The development of the composition of medicinal or cosmetic emulsions, in particular the selection of the concentration of emulsifiers, is mainly carried out based on experimental studies [1, 2]. When conducting them, an empirical approach is most often used: several emulsion compositions with different emulsifiers in the same or well-known concentrations are made, and then emulsion compositions are made with the selected emulsifier in different concentrations [3, 4]. They are also investigating the possibility of combining emulsifiers of the I and II kind, studying various combinations of co-emulsifiers with a certain total content, which usually does not exceed 10 % [5]. Therefore, such studies are long-term and expensive.

The aim of the work is to study the biocomplex of surface-active substances based on rhamnolipids of *Pseudomonas* sp. PS-17 (biocomplex PS) as an emulsifier and co-emulsifier by using the method of modeling the composition of emulsions for use in dermatology.

2. Research planning (methodology)

In order to reduce the number of technological experiments at the first stages of the development of medicinal or cosmetic emulsion products, that is, to realize the possibility of theoretical justification of the qualitative and quantitative choice of an emulsifier or a mixture of emulsifiers, the most significant parameter is the hydrophilic-lipophilic balance (HLB) of the surfactants used in order to stabilize emulsions [6, 7]. In the experiment, it was planned to use modelling processes of semi-automated selection of the composition of emulsions. This approach will allow to reduce the financial and time costs of creating an emulsion medicinal or cosmetic product and will ensure the rational conduct of experimental research. Modelling the composition will be promising in the study

of new biogenic surfactants, which can be effective emulsifiers, safe for humans and the environment.

3. Materials and methods

Biocomplex PS is a biogenic surface-active complex synthesized by bacteria of the genus *Pseudomonas*, which is a viscous mass that includes rhamnolipids, which make up to 80 % of the biocomplex, as well as alginate and water [8].

The methods of computer simulation of semi-automated selection of the composition of the oil phase and emulsifiers of medicinal or cosmetic emulsions developed in the MO Excel program were used. In modelling processes, the PS biocomplex was studied as an independent emulsifier in emulsions of the o/w type, as well as a co-emulsifier of this type of emulsions in combination with type II emulsifiers.

4. Research results

Emulsions as dispersed systems with a developed surface of phase separation, which has an excess of free surface energy, are characterized by thermodynamic instability in the form of coalescence, when individual phases of the emulsion are separated. The stability of emulsions depends on such factors as the nature of the dispersion medium and the dispersed phase, the amount of surface tension, and the viscosity of the system [9, 10].

Most of the emulsifiers used to stabilize emulsion medicinal and cosmetic products are surfactants that have a diphilic structure and form a boundary layer on the surface of immiscible phases. However, many surfactants, which ensure high stability of emulsion systems, are classified as undesirable and even dangerous components of modern medicinal and cosmetic products. This mainly applies to cationic and anionic surfactants, as they are most often the cause of various skin dermatitis [11].

Non-ionic surfactants – derivatives of fatty acids and polymer alcohols, fatty alcohols, lanolin alcohols, and their oxyethylated derivatives [5, 12] are among the mildest and safest.

Choosing the most rational emulsifier is a difficult task, especially in connection with the rapid increase in the number of emulsifiers. When choosing an emulsifier, developers of medicinal and cosmetic products, first of all, pay attention to the stability of which type of emulsion it provides, as well as the smallest amount of emulsifier that allows obtaining a stable emulsion. When using one type of emulsifier, stabilization of emulsions occurs at high concentrations of surfactants (over 30–50 %), which is not technologically rational and can cause side effects, in particular allergic reactions, and change the permeability of skin cell membranes [11]. A high stabilization effect is observed when using two types of surfactants – hydrophilic and hydrophobic, which accordingly reduces the total *HLB* of the mixture of emulsifiers and increases the viscosity of the system at a rather low content of the surfactant mixture (up to 10 %) [5, 12].

When choosing emulsifiers to stabilize emulsion systems, it is necessary to consider not only the *HLB* of emulsifiers, but also the mechanism of their stabilizing effect, toxicity, pH value, chemical compatibility with other emulsion components, etc. It is desirable that the emulsifier is odourless and colourless. Its financial value and affordability also play an important role. Considering all these factors may lead to the fact that even at the initial stage of pharmaceutical development, it will be necessary to abandon the consideration of some potential emulsifiers [13].

The value of HLB characterizes not only the surfactant, but also the "necessary" value of HLB for the emulsification of the oil phase, depending on the type of emulsion (o/w or w/o) [12, 13]. Knowing the HLB values necessary for emulsification of individual oil components of the emulsion, the total HLB value of the fat system can be calculated using the following formula:

$$HLB = \sum_{i=1}^{n} \left(HLB_i \cdot \frac{X_i}{100} \right),$$

where *HLB* – the hydrophilic-lipophilic balance of the mixture of oil components;

X_i – percentage content of a specific component in the oil phase;

HLB_i – hydrophilic-lipophilic balance of a specific component;

n is the number of components.

As a result of such calculations, the *HLB* value will indicate that an emulsifier with the same *HLB* value is needed to emulsify the fat system. However, this does not mean that every emulsifier or mixture of emulsifiers with the corresponding *HLB* will be optimal, as chemical incompatibility with the components of the emulsion or other reasons for the unacceptability of a given emulsifier are possible. However, we can be sure that performing experimental studies, we will get more optimal results quickly if we experiment in the required *HLB*±1. It would be necessary to spend more time to try other mixtures of emulsifiers, choosing them randomly [13].

It should also be considered that the values of HLB required for the emulsification of individual oil components of the emulsion in different literature sources may differ slightly, depending on the test conditions. With the help of calculations, you can choose several pairs of mixtures of emulsifiers of different chemical groups, each of which will form the desired *HLB*. Mixtures of any two (or three or more) surfactants can be investigated, except for mixing anionic and cationic surfactants. Experimental studies in such a case will be limited to testing the same amount of each mixture of emulsifiers and choosing the best one, for example, with a lower cost, or the one that thickens the emulsion better [13, 14].

The analysis of the composition of excipients of soft emulsion-type medicines presented on the pharmaceutical market of Ukraine showed that polysorbates are mainly used as emulsifiers of the 1st kind to create emulsion medicines, and cetostearyl alcohol and cetostearyl alcohol are most often used as emulsifiers of the 2nd kind lanolin [15].

Recently, biosurfactants of microbiological origin are common objects of study due to several advantages over synthetic surfactants, in particular, their biodegradability, low toxicity and the ability to manifest their properties when

used in low concentrations [16]. An important advantage of biosurfactants is also the possibility of their industrial synthesis using cheap raw materials available in large quantities. It can be waste from the food industry (oil and fat, alcohol, dairy), agriculture (starch-containing waste) [17, 18].

Among the wide spectrum of promising surfactant-producing microorganisms, representatives of the genus *Pseudomonas*, which synthesize extracellular surface-active glycolipids with high surface, emulsifying, foam-forming activity, deserve great attention. This producer is well-studied, very easily and quickly cultivated, which allows obtaining a significant amount of the initial product in a fairly short period of incubation [17].

Pseudomonas aeruginosa biosurfactant is a mixture of rhamnolipids of different structures, the main part of which consists of di- and monorhamnolipids, which consist of a hydrophilic "head" represented by one or two molecules of rhamnose, and a hydrophobic "tail" of one or two fatty acid chains [19, 20]. Today, rhamnolipids are of great practical interest from the point of view of bioremediation of soils contaminated by oil spills, however, rhamnolipids synthesized by *Pseudomonas aeruginosa* also have a wide range of biological activity, in particular, they have antimicrobial and antitumor effects [21].

In the process of modelling the composition of emulsifiers to stabilize the investigated emulsions, we used biocomplex PS – a biogenic surface-active complex synthesized by bacteria of the genus *Pseudomonas*, which is a viscous mass consisting of rhamnolipids, which make up 80 % of the biocomplex, alginate and water. The advantages of this form of the product are its concentrated form, the possibility of long-term storage, convenience in transportation and use. This biosurfactant has low values of surface (27.9–29.8 mN/m) and interfacial tension (0.01–0.5 mN/m), high emulsifying and suspending activity (emulsification index – 65–85 %) [8].

Given that the available literature sources do not contain accurate information about the HLB of the PS biocomplex, we conducted a study of its solubility in water to establish this indicator, as well as theoretical calculations of the *HLB* of the PS biocomplex, based on the known *HLB* values of rhamnolipids.

Studies based on water solubility provide an approximate estimate of HLB, but in many cases this is sufficient for screening work. Table 1 shows the relationship between the ability to dissolve (disperse) surfactants in water and the *HLB* value [5, 13].

Table 1

HLB value of surfactant depending on solubility in water

Solubility of surfactants in water	*HLB*
Does not disperse	0–3
Disperses poorly	3–6
Stable dispersion with strong mixing	6–8
Turbid dispersion	9–13
Semi- or transparent solution	More than 13

The study of the solubility of the PS biocomplex in water was carried out at a room temperature of 20±5 °C.

As a result of studying the solubility, it was established that the PS biocomplex when dispersed in water at a concentration of 1–2 % initially forms a translucent solution, and when the concentration increases (3–5 %) – a cloudy dispersion, so it can be assumed that its *HLB* is close to 13.

Considering that mono- and dirhamnolipids are part of the PS biocomplex in a ratio of 90:10 [22], and the HLB of monorhamnolipid and dirhamnolipid, calculated based on their chemical structure, are 13 and 21, respectively [23], the *HLB* of the PS biocomplex was also calculated as follows as follows:

$$HLB_{biocomplex\ PS} = (90 \cdot 13 + 10 \cdot 21)/100 = 13.8.$$

Thus, according to the *HLB* indicator, the PS biocomplex is similar to polysorbates (the *HLB* of polysorbate 80 is 15), which indicates the ability of the PS biocomplex to form stable emulsions of the o/w type, that is, to be used as an emulsifier and co-emulsifier.

We have developed in the MO Excel program a semi-automated system for modelling the composition of o/w type emulsions with PS biocomplex as an independent emulsifier or co-emulsifier.

Considering the generally known approaches to the use of emulsifiers in a maximum amount of up to 10 % in the composition of emulsions, when modelling the composition of emulsions, we considered those emulsion compositions acceptable for further research, in which it is possible to use the PS biocomplex in this maximum concentration as an independent emulsifier, as well as in of the complex emulsifier with a total content of up to 10 %.

When performing any modelling, starting parameters must be set, therefore, when building a semi-automated model for the selection of components of the oil phase and emulsifiers of a stable o/w type emulsion, we used the following starting parameters, which are entered by the user [24]:

1. Initial amount of the finished product (g).
2. Number of emulsifiers to be used (1 or 2).
3. The desired number of components of the oil phase (pcs).
4. Desired oil phase content (%).
5. Desired content of emulsifier or mixture of emulsifiers (%).

Entering the desired values does not mean that exactly such parameters will be obtained at the output. They are introduced to ensure the implementation of automated calculations in the model to offer the user possible options for qualitative and quantitative selection of components of the oil phase and emulsifiers.

Also, the list of components of the oil phase and emulsifiers, given in the Table 2, were included in the model for approval [12, 13].

The algorithm for modelling the composition of emulsions is shown in Fig. 1.

After completing the modelling, the developer experimentally establishes the optimal concentration of the biocomplex PS as an independent emulsifier or the concentration of a complex emulsifier, producing several emulsion compositions with different concentrations of the biocom-

plex PS or complex emulsifier in a certain ratio calculated by the program between the biocomplex PS and the type II emulsifier (for example, in a ratio of 40 : 60 with a total concentration of complex emulsifier 2, 4, 6, 8, 10 %).

To test the modelling system, we set two tasks. In all tasks, the initial amount of the finished product will be 100 g.

Task 1: choose the optimal quantitative composition of components for the following recipe:

– oil phase 30 % (grape seed oil, paraffin);

– complex emulsifier (glycerol monostearate: biocomplex PS);

– water up to 100.0.

In this recipe, the concentration of any component of the oil phase is not known. Having noted grape seed oil and paraffin in the model, the developer obtains a graph of the dependence of the HLB value required for the emulsification of the oil phase on the two components (Fig. 2). Such a dependence has a linear character. Representation of this type of information in the model was implemented using a combined diagram using an auxiliary axis and series in the form of lines and histograms (the main axis is the value of *HLB*, the auxiliary axis is the concentration of components, %).

Table 2

Oil phase components and emulsifiers

Oil phase components	HLB at which emulsification occurs	Emulsifiers	*HLB*
Stearyl alcohol	15.0	Polysorbate 20	16.7
Cetyl alcohol	15.0	Polysorbate 80	15.0
Vaseline oil	10.0	Polysorbate 60	14.9
Paraffin	10.0	Biocomplex PS	13.8
Beeswax	9.0	Sorbitan monolaurate (Spen-20)	9.0
Lanolin anhydrous	9.0	Diethylene glycol monolaurate	6.0
Grape seed oil	7.0	Sorbitan monostearate	4.7
Olive oil	7.0	Sorbitan monooleate (Spen-80)	4.0
Cocoa butter	6.0	Glycerol monostearate	3.8
Mink fat	5.0	Sorbitan tristearate (Spen-65)	2.0

Fig. 1. Algorithm for modelling the composition of emulsions

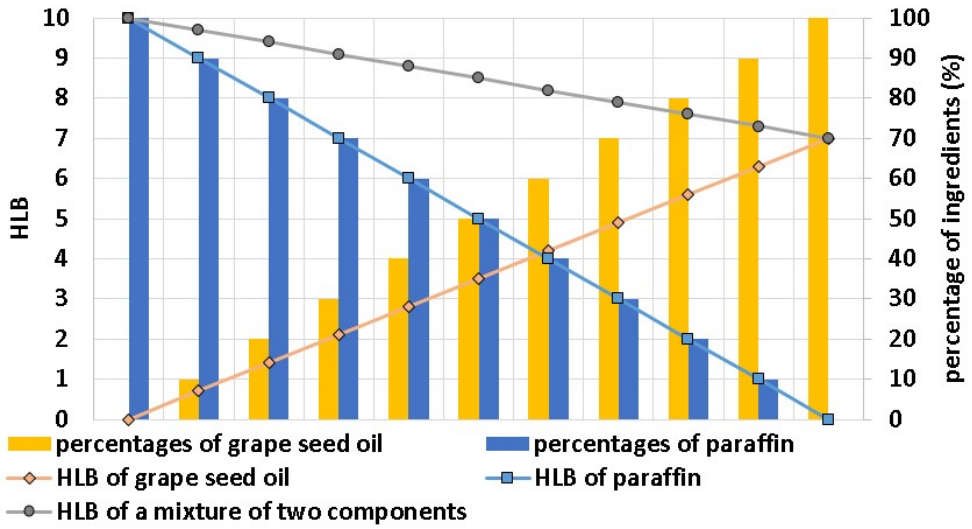


Fig. 2. Linear dependence of the amount of required *HLB* on two components (grape seed oil, paraffin)

Having chosen from the displayed options the most optimal option in terms of the ratio of components and the value of *HLB*, the developer notes the selected quantities in the model.

For example, the developer decided to choose an option with the following quantitative composition of the components of the oil phase: grape seed oil 25 g and paraffin 5 g, which will be 83.3 % and 16.7 % of the oil phase, respectively. The *HLB* required for emulsification of this oil phase will be 7.5 (Fig. 3).

In this task, the selection of emulsifiers in the model is not used, the emulsifiers are defined by prescription, only the calculation of the ratio between emulsifiers is required. The concentration of the oil phase and its composition are of decisive importance for choosing the ratio between emulsifiers of the I and II kind. With automated calculations, the proportions of emulsifiers glycerol monostearate and biocomplex PS were obtained: 63:37 (Fig. 4).

Task 2: Select the optimal quantitative composition of the components of the oil phase for the following recipe:

– oil phase 30 % (grape seed oil, paraffin, cetyl alcohol);

– emulsifier: biocomplex PS;

– water up to 100.00.

control totals		
30	30	100
amount of the component		
the actual (g)	of the total (%)	in oil phase (%)
0	0	0
0	0	0
0	0	0
5	5.0	16.7
0	0	0
0	0	0
25	25.0	83.3
0	0	0
0	0	0
0	0	0

HLB f – actual HLB of mixture of selected components

HLB p – predicted HLB of mixture components

oil phase ingredients		7.50	predicting		7.50
name	HLB	HLB f	in oil phase (%)	value of HLB	HLB p
Stearyl alcohol	15	0.00	0	0	0
Cetyl alcohol	15	0.00	0	0	0
Vaseline oil	10	0.00	0	0	0
Paraffin	10	1.67	16.7	1.67	1.67
Beeswax	9	0.00	0	0	0
Lanolin anhydrous	9	0.00	0	0	0
Grape seed oil	7	5.83	83.3	5.83	5.83
Olive oil	7	0.00	0	0	0
Cocoa butter	6	0.00	0	0	0
Mink fat	5	0.00	0	0	0

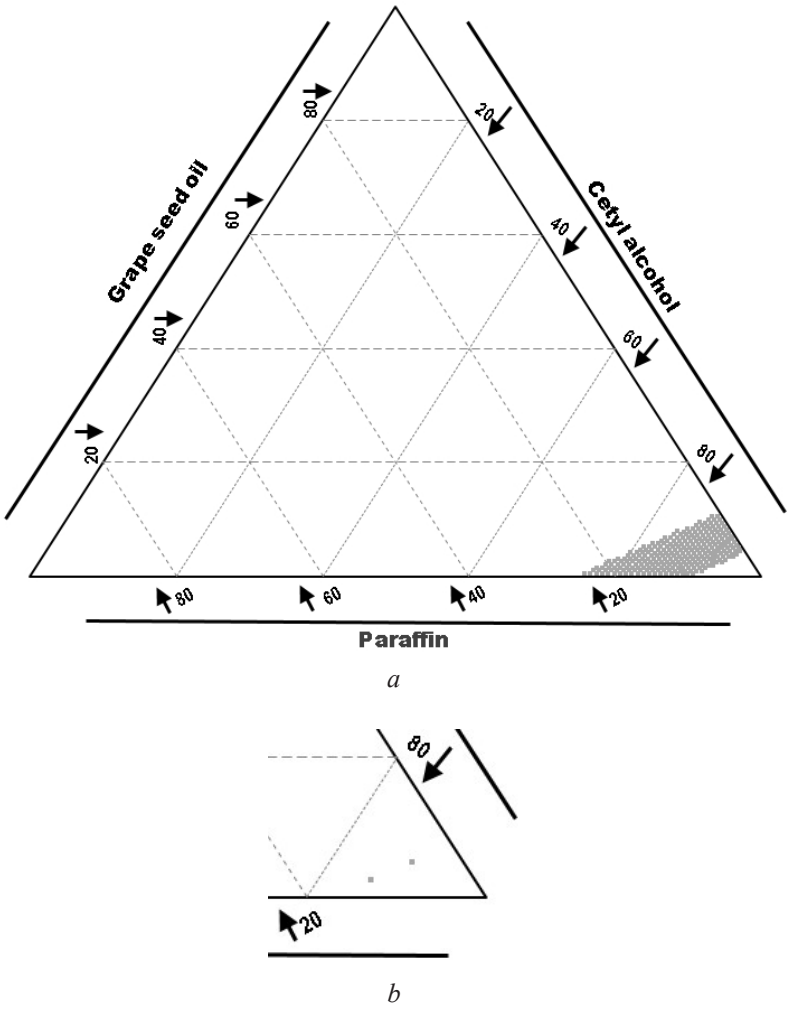
Fig. 3. Calculation of the HLB required for the emulsification of the oil phase

Names of emulsifiers	HLB of emulsifiers	HLB of the oil phase	The amount of emulsifiers at the desired emulsifier content 10% (g)	Ratio between emulsifiers (%)
biocomplex PS	13,8		3,70	37,01
		7,50		
glycerol monostearate	3,8		6,30	62,99
			10,00	100,00

Fig. 4. Calculation of the ratio between two types of emulsifiers

In this prescription, only biocomplex PS (*HLB* 13.8) is used as an emulsifier and the share of any component of the oil phase is unknown. The *HLB* values required for emulsifying the components of the oil phase are as follows: grape seed oil – 7, paraffin – 10, cetyl alcohol – 15.

To calculate the optimal concentration of substances in the three-component oil phase, we used a graph showing the relationship between three variables (Ternary Plot) (Fig. 5). Given that each of the three components is present in the oil phase, and based on a concentration interval of one percent, the total number of allowable combinations was 4,754 (component ratio range from 1:1:98 to 98:1:1).



a

b

Fig. 5. The relationship between the concentrations of the three components when obtaining the *HLB* value of the oil phase:
a – in the range from 13.3 to 14.3 (13.8±0.5); *b* – in the exact value of 13.8

In addition to the graphical representation of the results (Fig. 5), the model developed by us also produces numerical results – the graph is built precisely on their values. The model implements the possibility of selecting the values of the results based on the criteria specified by the user. Thus, having selected the results in accordance with the task for the exact value of *HLB* 13.8 (corresponding to the *HLB* of the PS biocomplex) (Fig. 5, *b*), we will get the following automatically calculated results of the ratio of components: olive oil:paraffin:cetyl alcohol – 10:8:82 or 5:16:79

The total amount of the oil phase is 30 g. Then, in accordance with the task, the mass fraction of each of the components will be: olive oil:paraffin:cetyl alcohol – 3.0:2.4:24.6 or 1.5:4.8:23.7.

5. Discussion of research results

When developing emulsion medicinal and cosmetic products, the process of selecting auxiliary components, in particular surface-active substances, which ensure the creation of a high-quality, effective, and safe product, is extremely important [25, 27]. In practice, the choice of emulsifiers and justification of their concentration is mainly based on experimental studies [26, 28], therefore it requires a long time and is expensive.

Recently, mainly on the websites of companies engaged in the retail trade of raw materials for soap making and cosmetic products presented "online calculators". They can be easily found using a search engine on the Internet. These calculators allow you to calculate the concentration of fatty components and alkali to obtain soap with given characteristics or the concentration of a specific emulsifier (based on a fixed list) depending on the proposed composition of the cream, however, the correctness of the data used in such calculations is not confirmed.

Modelling the composition of emulsions, considering the most significant parameter *HLB*, allows to reduce the financial and time costs of creating a tool and rationally conduct experimental studies [24].

Our proposed model allows the developer to obtain predicted variants of the qualitative and quantitative composition of the oil phase components to achieve the planned *HLB* value, as well as, after that, predicted variants of emulsifiers or their mixtures to achieve emulsion stability. The model also allows the developer to publicly expand the database of lists of both oil phase components and emulsifiers, and edit all quantities.

Thus, when using the modelling method in task 1 given in the article, the developer will only need to experimentally confirm the choice of the optimal concentration of the complex emulsifier of glycerol monostearate and biocomplex PS (63:37), and in task 2 – only choose one of the options of the oil phase proposed by the model, which will allow to significantly reduce the number of technological experiments.

Further production of emulsion agents for experimental confirmation of their optimal composition can be carried out using different types of mixers, which will also affect the final choice of emulsifier concentration or mixture of emulsifiers.

Study limitations. The application of computer simulation of the composition of emulsions cannot be

carried out in the absence of information about the *HLB* required for emulsifying the components of the oil phase and the *HLB* of surface-active substances that are planned to be used as emulsifiers.

Prospect for further research. Computer modelling is promising for use at the first stages of developing the composition of medicinal or cosmetic emulsion products to realize the possibility of obtaining maximum results through theoretical justification of the qualitative and quantitative composition of the oil phase of the product, the choice of an emulsifier or a mixture of emulsifiers.

The article describes general approaches to the development of emulsion medicinal or cosmetic products stabilized by the biocomplex PS, using computer modelling of the composition of emulsion products. The next stage of research is planning the development of the composition and technology of a multi-component medicinal or cosmetic product with a specific direction of action.

6. Conclusions

The use of a semi-automated computer modelling system provides a reasoned choice of the composition of the oil phase of the emulsion when using the PS biocomplex as an independent emulsifier, or the choice of the ratio between the PS biocomplex and the type II emulsifier when using a complex emulsifier, and allows rational experimental research.

Conflict of interests

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

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Data availability

Data will be made available on reasonable request.

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Iryna Pelekh-Bondaruk, Postgraduate Student, Department of Drug Technology and Biopharmaceutics, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

Ivan Revyatskyy*, PhD, Department of Management and Economy of Pharmacy, Medicine Technology and Pharmacoeconomics, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

Svitlana Bilous, Doctor of Pharmaceutical Sciences, Department of Drug Technology and Biopharmaceutics, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

***Corresponding author:** Ivan Revyatskyy, e-mail: iwan.revyatskyy@gmail.com*