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MODELING OF THE PROCESS OF EMULSIFIERS SELECTING IN EMULSION MEDICINES AND COSMETICS

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Abstract

The choice of emulsifiers and justification of their concentration in the composition of emulsion medicines and cosmetics based on experimental studies is time-consuming and expensive process. To reduce the number of technological experiments, a method of computer modeling of the composition of emulsions in MO Excel was developed and used, which is based on the use of hydrophilic-lipophilic balance system. An algorithm of modeling o/w emulsions compositions with a complex emulsifier is developed and an example of solving a specific problem of selecting the optimal composition of the emulsion components is given. The use of a semi-automated modeling system is quite effective because it provides a reasoned choice of the oil phase composition of the emulsion, the mixture of emulsifiers and the ratio between them, and allows conducting of experiments rationally.

Keywords: *emulsions, emulsifiers, medicines, cosmetics, hydrophilic-lipophilic balance.*

Introduction

In the development of emulsion medicines and cosmetics is extremely important the process of choosing excipients, including emulsifiers, provides a quality, effective and safe product. In practice, the choice of emulsifiers and justification of their concentration is mainly based on experimental studies, so it takes a long time and is expensive.

Most emulsifiers used to stabilize emulsion medicines and cosmetics are surfactants that have a diphilic structure and form a boundary layer on the surface of immiscible phases. A high stabilizing effect is observed when using two types of surfactants – hydrophilic and hydrophobic, which reduces the total hydrophilic-lipophilic balance (HLB) of the emulsifier mixture and increases the viscosity of the system at a relatively low content of surfactant mixture (up to 10%) [1, 2]. Therefore, at the stage of pharmaceutical development of emulsions, considerable attention is paid to the combination of I and II type emulsifiers, investigating their different ratio and total content [3].

To reduce the number of technological experiments, that is to realize the possibility of theoretical substantiation of qualitative and quantitative choice of oil phase composition and emulsifiers mixture, in the first stages of pharmaceutical development of emulsion medicines and cosmetics it is advisable to use modeling of emulsion composition taking into account the most important parameter – HLB. This approach reduces the financial and time costs of emulsion medicines and cosmetics creation and provides rational conduction of experimental studies.

The aim of our work was to substantiate the choice of the quantitative composition of the oily phase and the mixture of I and II type emulsifiers for stabilization of o/w emulsions by using the method of emulsions composition modeling.

Methods

The methods of computer modeling developed in the MO Excel program have been used for the semi-automated choice of the oily phase composition and a mixture of I and II type emulsifiers for emulsion medicines and cosmetics by selecting individual components based on the HLB value.

Results and Discussion

Choosing the most rational emulsifier in the emulsion is a difficult task, especially due to the rapid growth of their number. When choosing an emulsifier, developers of emulsion medicines and cosmetics, first, pay attention to the stability of which type of emulsion it provides, as well as the smallest amount of emulsifier or mixture that allows obtaining a stable emulsion. An important parameter in the choice of emulsifiers is their safety, as many surfactants that provide high stability of emulsion systems are classified as undesirable and even dangerous components of modern emulsion medicines and cosmetics. This mainly applies to cationic and anionic surfactants, which are the most common cause of various skin dermatitis [4]. The mildest and safest are nonionic surfactants – derivatives of fatty acids and polymer alcohols, fatty alcohols, lanolin alcohols, etc., and their oxyethylated derivatives [1, 5]. When choosing emulsifiers for stabilizing emulsion systems, the mechanism of their stabilizing action, pH value, chemical compatibility with other components of the emulsion and others are also taken into account. It is desirable that the emulsifier is odourless and colourless. Its financial value and affordability also play an important role. Taking into account all these factors may lead to the fact that even at the initial stage of pharmaceutical development will have to abandon the consideration of some potential emulsifiers [6].

The surfactant used to stabilize the emulsions is best characterized by the HLB value. This parameter characterizes not only the surfactant, but also the "necessary" HLB value for emulsification of the oil phase, depending on the type of emulsion (o/w or w/o) [1, 7, 8].

Knowing the HLB values required for emulsification of individual oil components of the emulsion, it is possible to calculate the total HLB value of the oily system by the following formula:

$$\mathrm{HLB} = \sum_{i=1}^{n} \left(\mathrm{HLB}_i \bullet \frac{X_\mathrm{i}}{100} \right)$$

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

X_i –percentage of a particular component in the oil phase;

HLB_i – hydrophilic-lipophilic balance of a particular component;

n –number of components.

The HLB of the emulsifier mixture is calculated by a similar formula.

An emulsifier or a mixture of emulsifiers with the same HLB value is required for emulsification of the oily system [1, 6, 7]. However, this does not mean that each emulsifier or mixture of emulsifiers with a suitable HLB will be optimal, as there may be a chemical incompatibility with the components of the emulsion or other reasons for the unacceptability of this emulsifier.

It should also be taken into account that the HLB values required for emulsification of individual oily components of the emulsion in different literature sources may differ slightly, depending on the test conditions and be given with an error ± 1 [6]. Accordingly, based on the above, it becomes obvious that the optimal results of the experimental study will be obtained faster, taking into account possible errors in the HLB values for the components of the oily phase and surfactants. Without the use of this indicator, economic, resource and time costs increase significantly due to the growing number of experiments.

In the model built by us, with the help of calculations, it is possible to choose several pairs of emulsifier mixtures of different chemical groups, each of which forms the desired HLB. At this stage, the model calculates the ratio of components in the selected mixture of emulsifiers. Mixtures of any two (or, if necessary, three or more) surfactants may be investigated, except for the mixing of anionic and cationic surfactants. Experimental studies, in this case, will be necessary to test the same amount of each emulsifier's mixture and choose the best one taking into account safety, quality of emulsion, financial value, etc. [6, 9].

Analysis of the composition of semi-solid preparations of the emulsion type, presented on the pharmaceutical market of Ukraine, showed that as I type emulsifiers are mainly used polysorbates, as I type emulsifiers are the most common cetostearyl alcohol and lanolin [10].

In the process of modeling the composition of emulsion medicines and cosmetics to stabilize the studied emulsions, we used emulsifiers of I and II type, for which the available scientific literature has information about their HLB [6, 11]. The list of investigated components of the oily phase and emulsifiers is given in table 1 [5, 9, 11].

Given the well-known approaches to the use of emulsifiers in the maximum amount up to 10% in emulsions [1, 12], when modeling the composition of emulsions, we considered acceptable for further studies those emulsion compositions in which a mixture of emulsifiers are used with a total content up to 10%.

When performing any modeling, the starting parameters must be set, so when building a semi-automated model for selecting oily phase components and emulsifiers of stable o/w emulsion, we used the following starting parameters entered by the user (emulsion medicines or cosmetics developer):

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

The parameter "Desirable content of the emulsifier mixture" provides the ability to perform inverse calculations. Depending on the task, only one of the two parameters will be taken into account in the calculations: "Desirable content of the oil phase" or "Desirable content of the emulsifier mixture".

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

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Fig. 1 shows our algorithm for modeling the composition of emulsions.

After modeling, the developer experimentally determines the optimal total concentration of emulsifier mixture, preparing several compositions of the emulsion using two types of emulsifiers in a certain ratio calculated by the program (for example, in the ratio of two emulsifiers 40:60 with a total concentration of emulsifier mixture 2, 4, 6, 8 and 10 %).

To test the modeling system, we set the following task – to choose the optimal quantitative composition of components for the following prescription:

Oil phase 20% (olive oil 10%, lanolin anhydrous X %, cocoa butter Y %)

Complex emulsifier (glycerol monostearate: polysorbate 80)

Purified water up to 100.0

For this task, the specified parameters include the number of components of the oily phase – 3; the desirable concentration of the oil phase in the composition – 20%. The initial amount of the finished product 100 g, and the number of emulsifiers – 2.

The process of modeling the oily phase composition is shown in Fig. 2, 3, 4, 5.

As can be seen in Fig. 2, the developer of emulsion medicines or cosmetics adds 10 g of olive oil to the model. The program automatically shows in the top line: the total mass of all selected components (currently only one is selected), their concentrations in emulsion product and in the oil phase (10.0, 10.0 and 100.0, respectively). HLB required for emulsification of this component (7.0) and predicted HLB for components selected in the oil phase (3.5). In the planned preparation the concentration of olive oil in the oily phase is 50% (= 10*100/20). According to the above formula, the required HLB of olive oil in the oily phase will be 3.5 (= 7*(50/100) = 7*0.5). The other 50% the model will evenly distribute among the probable other components in the forecast columns – 25% (= (100 – 50) / (3 – 1) = 50/2). Based on this value, the projected HLB indicator for each component will be calculated, as well as adjusted for already selected components.

In accordance with the conditions of the task in the oily phase must be available lanolin anhydrous and cocoa butter. Anhydrous lanolin is emulsified at a higher HLB, so an increase of its concentration will lead to an increase of the HLB required to emulsify the oil phase. If we choose each of the components equally, the required HLB of the oily phase will be 7.25 (Fig. 3).

In addition to predicting the value of HLB with a uniform distribution, we have included in the model the possibility of plotting the dependence of HLB on two components with an unknown number. This dependence is linear (Fig. 4).

Representation of such information in the model was realized using a combined diagram with auxiliary axis and rows in the form of lines and histograms (main axis – the HLB value, auxiliary axis – the concentration of components, %) (Fig. 4, 5, 6).

Also in the model, we implemented the ability to take into account, when constructing this type of graph, the presence of components with known concentration (Fig. 5).

If the oil phase contains three or more components with unknown concentration, the dependence will not be linear. An example of constructing such diagram for a task with the assumption that concentration of olive oil is unknown is shown in Fig. 6. In the model built by us, the concentration interval in modeling the quantitative content of components can be different, such one that would best meet the objectives of the study (in Fig. 6, the interval is 10%). To implement a more correct selection from fewer permissible combinations, additional conditions for the relationship between the components can be introduced into the model. For example, mandatory presence (eliminates the possibility of missing one or more components) or a specified range of permissible concentrations of each component. Thus, in accordance with our task, the concentration of olive oil is 50% of the oil phase. The result of selection based on this criterion is shown in Fig. 5.

From the diagram (Fig. 5) it is possible to see that to select the optimal composition of the oily phase using each specified component, can be choose the following variants:

HLB = 8.0: olive oil 50%, lanolin anhydrous 50%, cocoa butter 0%;

HLB = 7.7: olive oil 50%, lanolin anhydrous 40%, cocoa butter 10%;

HLB = 7.4: olive oil 50%, lanolin anhydrous 30%, cocoa butter 20%;

HLB = 7.1: olive oil 50%, lanolin anhydrous 20%, cocoa butter 30%;

HLB = 6.8: olive oil 50%, lanolin anhydrous 10%, cocoa butter 40%;

HLB = 6.5: olive oil 50%, anhydrous lanolin 0%, cocoa butter 50%.

Having received with the help of the program the following recommendations of the oily phase composition, the developer of emulsion medicines or cosmetics will be able to adjust easily the amount of each component to the required weight, concentration or HLB value.

Based on the obtained data and in the absence of additional criteria for the selection of components in the task, we chose a uniform amount of anhydrous lanolin and cocoa butter. The HLB required to emulsify this oil phase, as noted above, is 7.25.

The next stage of modeling is the selection of emulsifiers. According to the task, the composition of emulsifiers includes glycerol monostearate (HLB = 3.8) and polysorbate 80 (HLB = 15) and it is defined by the prescription, so in this example, the selection of emulsifiers in the model is not used. It is necessary to calculate the ratio between emulsifiers only. In automated calculations, the ratio of emulsifiers was obtained: 69:31 (Fig. 7).

Thus, when using the method of modeling, the developer of emulsion medicines or cosmetics will need to confirm experimentally only the optimal choice of the total concentration of emulsifier mixture.

Conclusions

To reduce the number of technological experiments at the stage of emulsion medicines or cosmetics development, it is advisable to use the method of computer modeling of the emulsions composition, based on the HLB system, for example, in MO Excel. This approach can be quite effective, as it will provide a reasoned choice of the oily phase composition, the mixture of emulsifiers and the ratio between them, and will allow conducting experimental studies rationally.

Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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Table 1. Oily phase components and emulsifiers

Oily phase components	HLB required for emulsification
Stearyl alcohol	15.0
Cetyl alcohol	15.0
Vaseline oil	10.0
Paraffin	10.0
Beeswax	9.0
Lanolin anhydrous	9.0
Grape seed oil	7.0
Olive oil	7.0
Cocoa butter	6.0
Mink fat	5.0

Emulsifiers	HLB
Polysorbate 20	16.7
Polysorbate 80	15.0
Polysorbate 60	14.9
Polysorbate 85	11.0
Sorbitan monolaurate (Spen-20)	9.0
Diethylene glycol monolaurate	6.0
Sorbitan monostearate	4.7
Sorbitan monooleate (Spen-80)	4.0
Glycerol monostearate	3.8
Sorbitan tristearate (Spen-65)	2.0

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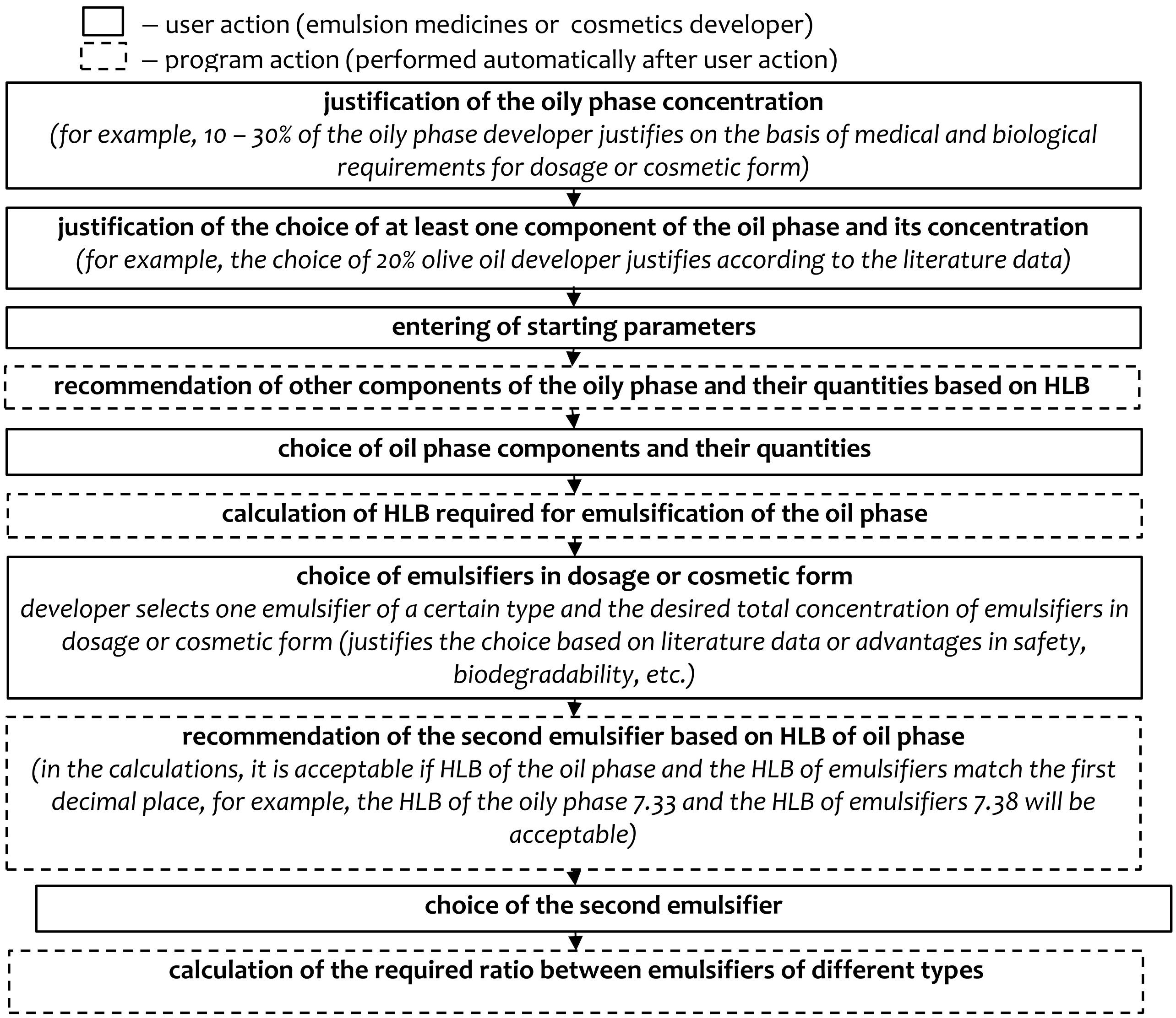

Fig. 1 Algorithm for modelling the composition of emulsions

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HLB f – actual HLB of mixture of selected components
HLB p – predicted HLB of mixture components

amount of the component: the actual (g)	of the total (%)	in oil phase (%)	oil phase ingredients: name	HLB	HLB f	predicting: in oil phase (%)	value of HLB	HLB p
control totals: 10	10	100			7.00			3.5
0	0	0	Stearyl alcohol	15	0.00	25	3.75	0
0	0	0	Cetyl alcohol	15	0.00	25	3.75	0
0	0	0	Vaseline oil	10	0.00	25	2.5	0
0	0	0	Paraffin	10	0.00	25	2.5	0
0	0	0	Beeswax	9	0.00	25	2.25	0
0	0	0	Lanolin anhydrous	9	0.00	25	2.25	0
0	0	0	Grape seed oil	7	0.00	25	1.75	0
10	10.0	100.0	Olive oil	7	7.00	50	3.5	3.5
0	0	0	Cocoa butter	6	0.00	25	1.5	0
0	0	0	Mink fat	5	0.00	25	1.25	0

Fig. 2 Selection of at least one component of the oily phase

HLB f – actual HLB of mixture of selected components
HLB p – predicted HLB of mixture components

amount of the component: the actual (g)	of the total (%)	in oil phase (%)	oil phase ingredients: name	HLB	HLB f	predicting: in oil phase (%)	value of HLB	HLB p
control totals: 20	20	100			7.25			7.25
0	0	0	Stearyl alcohol	15	0.00	0	0	0
0	0	0	Cetyl alcohol	15	0.00	0	0	0
0	0	0	Vaseline oil	10	0.00	0	0	0
0	0	0	Paraffin	10	0.00	0	0	0
0	0	0	Beeswax	9	0.00	0	0	0
5	5.0	25.0	Lanolin anhydrous	9	2.25	25	2.25	2.25
0	0	0	Grape seed oil	7	0.00	0	0	0
10	10.0	50.0	Olive oil	7	3.50	50	3.5	3.5
5	5.0	25.0	Cocoa butter	6	1.50	25	1.5	1.5
0	0	0	Mink fat	5	0.00	0	0	0

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

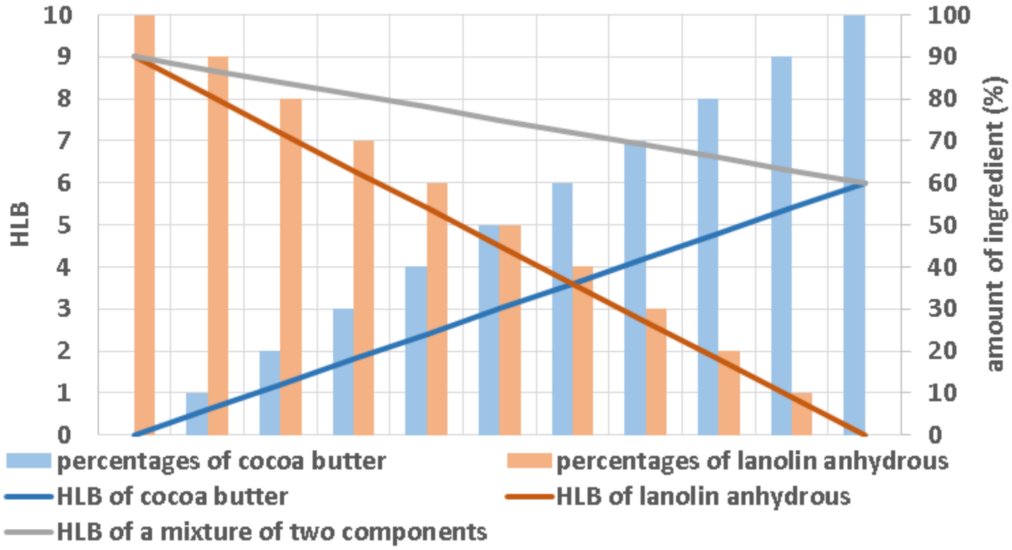

Fig. 4 Linear dependence of the required HLB on two components with unknown concentration

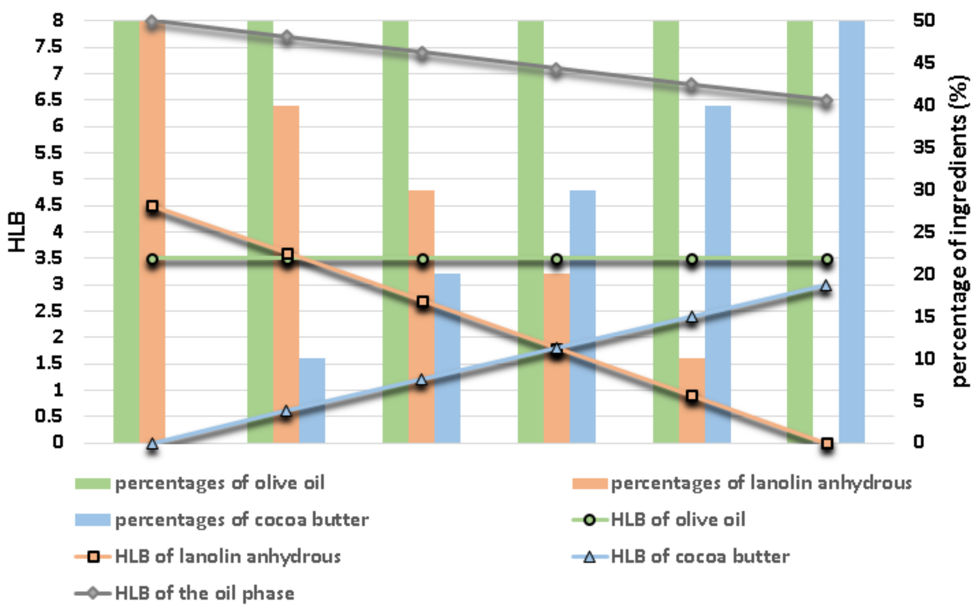

Fig. 5 Linear dependence of HLB value on two components with unknown (variable) concentrations and other components with known concentrations (constant for a specific task)

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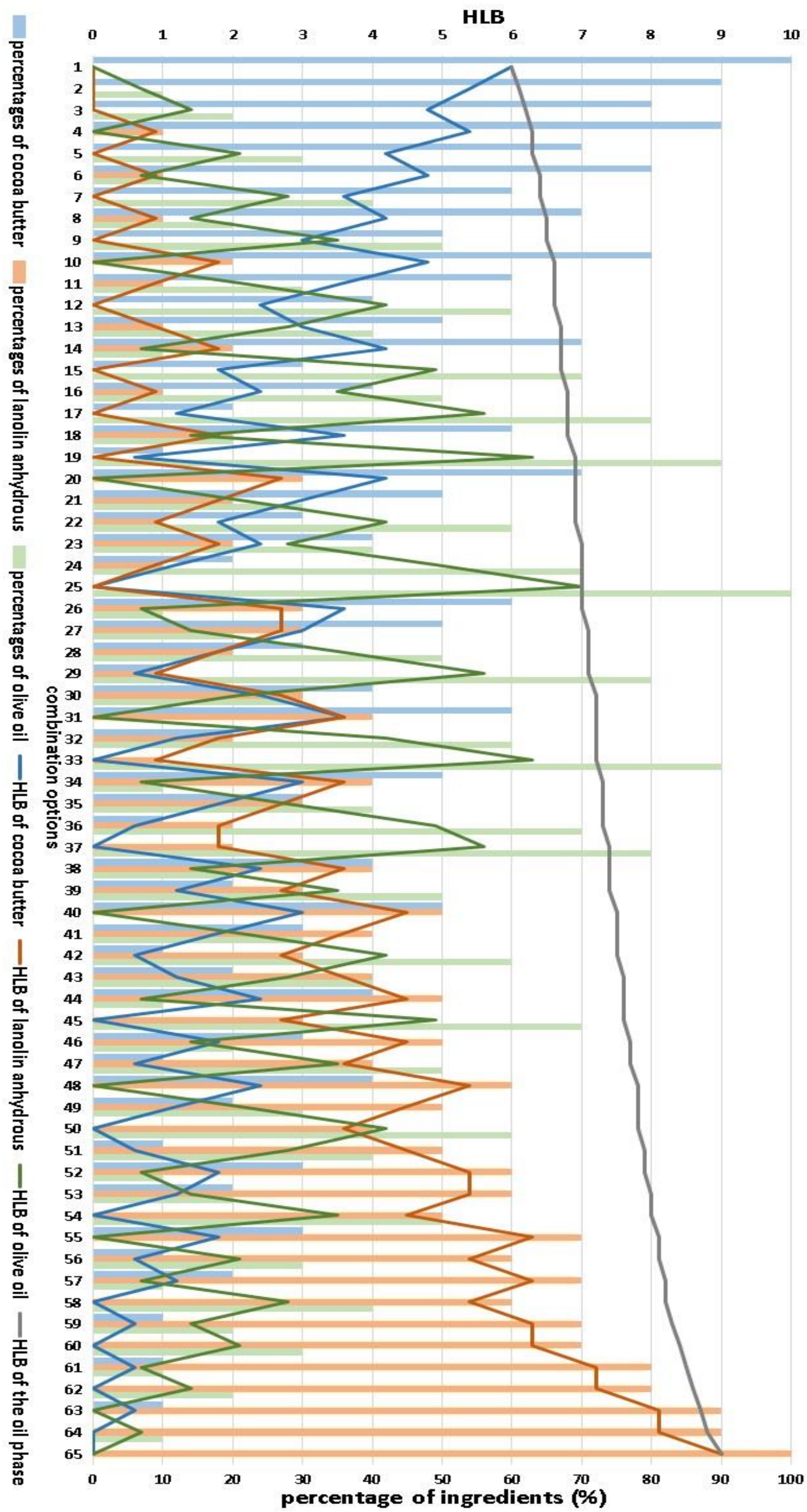

Fig. 6 Dependence of the HLB value required for emulsification of the oily phase on the variants of components combinations with a concentration interval 10%

Polysorbate 80	15.0		3.45	30.80
	HLB	7.25		%
glycerol monostearate	3.8		7.75	69.20
			11.20	100.00

Fig. 7 Calculation of the ratio between two types emulsifiers

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