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Production physical and chemical analysis of the «Propolis» eye drops

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Abstract
The technology of obtaining propolis water-soluble fraction which does not require use of highly flammable liquids has been developed for the first time ever. The developed technology will help to avoid accidents during industrial production and compounding of certain types of medicines, in particular of intravenous solutions, eye drops and other types which have to meet the requirements of sterility and standards foreseen by the regulatory documents.
Physical and chemical properties (pH, surface tension, refraction index, viscosity, absorbance, etc.) were identified to choose the optimum amount of biologically active compounds in "Propolis" eye drops having water-soluble fraction as their base.

Keywords: Physical, Chemical, Propolis, eye drops

Introduction
Mathematization of pharmaceutical sciences and wider use of computers in laboratories occur the creation of new medicines based on different chemical development parameters, including those involving classic methods of Rosentours fractional extraction. At the same time, technological processes of obtaining medicines with predefined properties and the procedure of identifying connections between content and effect are simplified.
For the moment, several scientific approaches to mathematical studies of unknown phenomena exist [1, 2].
At one point, a simplified experimental model is taken and certain differential, integral and other analytical dependences are applied. Their selection can be proven once the results of the study are even partly known. At other point, having the results of analysis as a starting point, the corresponding models are created, based in their turn on the results of statistical processing of data and dropping of "low-impact" factors. This was the approach we used in our study [3, 4].
The points we have described above helped us to get biologically active propolis water-soluble fraction (license 97076, bul. 4 from 25.02.2015) and further develop the eye drops technology and study their physical and chemical properties [5].
Physical and chemical properties of propolis water solution (pH, surface tension, refraction index, viscosity, absorbance) had to be identified in order to find out a necessary concentration of phenolic compounds in the proposed dosage form ("Propolis" eye drops).
The data we have received further were used to identify the critical micelle concentration (CMC) of water solution of the drops we study [6, 7].
Results of surface tension measurement of the solution let us speak about good adsorption ability of phenolic compounds which are contained in the drops.
As follows from the concentration dependence of the surface tension of studied solutions, the components contained in the drops possess quite high surface activity, thus they will be adsorbed well on the surface of phase separation.
As the concentration of phenolic compounds increases, the surface tension of a solvent (water) changes from 70.66×10^{-3} J/m^2 to 44.54×10^{-3} J/m^2, which is one of the criterions to evaluate the level of absorption of a medicine by body tissues regardless of the way it gets into a human organism.
The experiments let us say about good therapeutic effect of medicines containing propolis phenolic compounds.
Studying of the pH is one of the most important quality criterion of the "Propolis" eye drops. It has been proved that pH of the drops decreases from 4.77 to 4.11 as the concentration of phenolic compounds increases. It supports the fact that the components contained in the drops have acid-base character.

It is widely known that the refraction index depends on a nature, density and concentration of components, type of a solvent, temperature and other factors. The refraction index is considered to be an extremely useful physical and chemical parameter. Thus, we studied the interrelation between the refraction index and the concentration of water solutions (nD = f ($\omega_{propolis}$)), which consists of three linear sections in a wide concentration range.

It can be seen on a Fig. 1 that the refraction index increases as the concentration of phenolic derivatives and phenolcarboxylic acids grows.

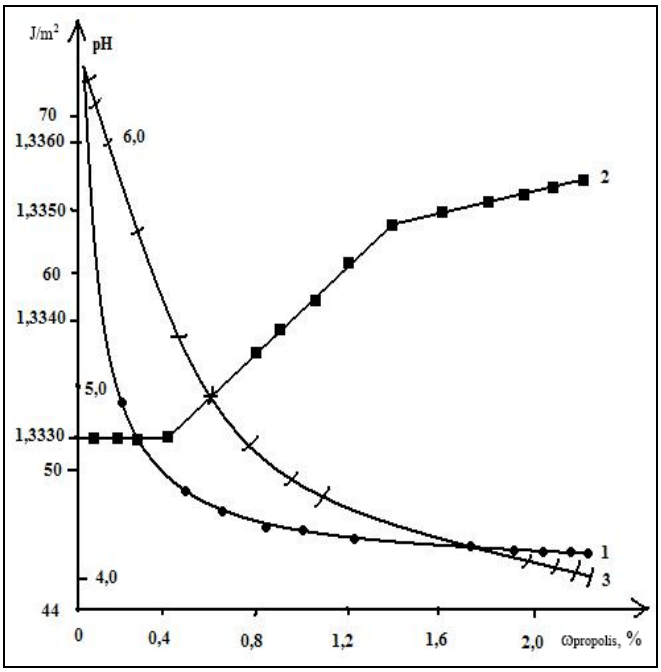

Fig 1: Dependence of a surface tension (1), refraction index (2) and a pH (3) on a concentration of Propolis water solutions

The refraction index is directly connected with concentration of the solution, and this correlation is widely used in pharmaceutical science during quantitative analysis of dosage forms.

During the experiment we analyzed the precipitation in water solutions with a mass content of over 1.0% ($\omega_{propolis}$) as the disperse system is created. The following experiments were conducted with the solutions where the concentration changed from 0.1 % to 1.0 %.

Adsorption of the water solutions of phenolic compounds was measured by photoelectric colorimeter KFK-2 (Table 1). The wavelength was 490 nm.

Based on adsorption data the turbidity was calculated with a formula:

$\tau = (2,3\times D)/\iota$, where ι is a thickness of a system layer

The data in a table show that as the concentration of propolis phenolic compounds in water solutions of increases, the turbidity grows as well, which says about better diffusion of light. At the same time solubility of propolis in the water worsens.

However we shoned note that the photoelectric colorimeter has limited number of color filters, which does not let us measure the adsorption in wide wavelength spacing.

To measure the operating wave length we made photos of the UV absorption spectrums of PCP water solutions with ω from 0.1 to 1.0% on a Specord M-40 spectrometer. The received spectrums are presented on the Fig. 2 and in the table. They show that the maximum wavelength is 282 nm.

Critical micelle concentration (CMC) is the concentration above which the micelles start to appear in the solution. It is the most essential parameter which describes the solutions` properties, especially while producing stable liquid dosage forms.

Studied interrelations of concentration and physical and chemical properties of PCP water solutions let us identify the critical micelle concentration (CMC) for the surface-active agents which are contained in the "Propolis" eye drops.

Table 1: Results of adsorption and turbidity measurements in Propolis water solutions

#	$\omega_{propolis}$, %	KFK-2		Specord M-40
		D	τ, sm^{-1}	D
		λ= 490		λ = 290
1.	0.10	0.139	0.032	0.0300
2.	0.20	0.240	0.055	0.1018
3.	0.30	0.361	0.083	0.1422
4.	0.35	0.420	0.097	0.2074
5.	0.40	0.487	0.112	0.2867
6.	0.45	0.541	0.124	0.2404
7.	0.50	0.570	0.131	0.2656
8.	0.55	0.683	0.157	0.3849
9.	0.60	0.722	0.166	0.3174
10.	0.65	0.754	0.173	0.3995
11.	0.70	0.800	0.184	0.4747
12.	0.80	0.900	0.270	0.4683
13.	0.90	1.000	0.230	0.4841
14.	1.00	1.200	0.276	0.5110

Note: The table presents measurement averages of 5 parameters. The maximum ration error is 0.3%

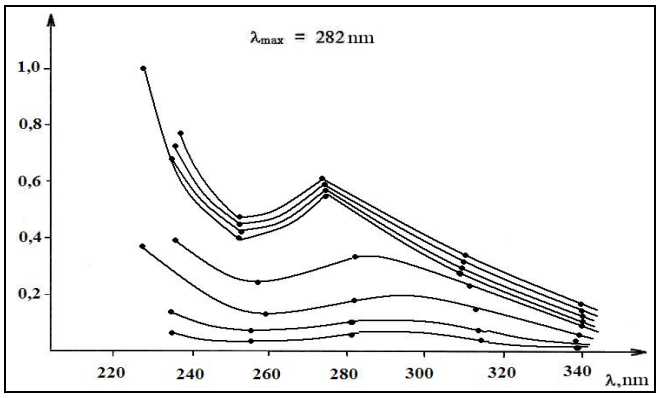

Fig 2: Dependence of adsorption on the wavelength in propolis water solutions

We conducted the experiments using optical methods (refractometric and turbidimetric) and also the method based on surface tension measurement.

Sharp fractures on the curves $n_D = f(-\lg \omega_{PCP})$, $\sigma = = f(-\lg \omega_{PCP})$, $\tau = f(-\lg \omega_{PCP})$ on the concentration range from 0.40 to 0.55 % is connected with the change of the state of the system components (Fig. 3).

With the concentration lower than 0.40 % we get a true solution; the CMC corresponds the true solubility of surface-active agents which are contained in the drops. As the concentration grows above 0.55%, the micellar colloidal system appears.

Physical and chemical properties of propolis water solutions change rapidly as the micelles appear.

The results of systematic studies of surface-active agents let us

suggest that as the critical concentration of the solution (which corresponds to the curves fractures) is achieved, part of molecules unites into bigger associates or micelles. Those micelles are made up of dozens and hundreds molecules of surface-active agents.

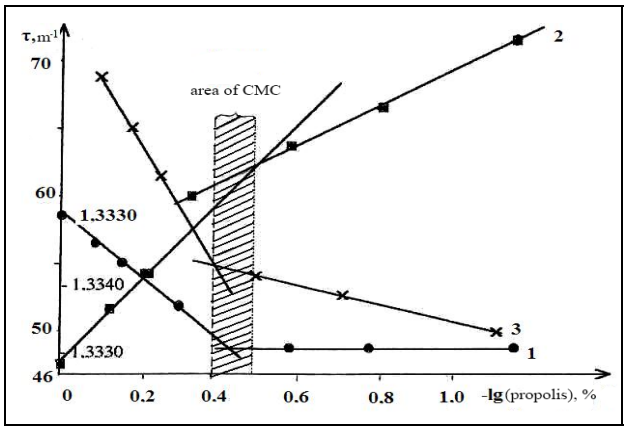

Fig 3: Dependence of the refraction index on surface tension (2) and turbidity (with λ = 490 nm) (3) and the concentration logarithm in propolis water solutions

The received experimental data are in line with the phase theory of micelle formation which states that during micelle formation new limiting dispersed phase appears.

Moreover, the precipitation in the solutions with propolis weight percentage of above 0.50% has been proved experimentally. This goes to show that a thermodynamically-unstable system appears which goes in line with a modern theory of dispersion systems.

Based on the data we received, we may conclude that the process of micellar formation of phenolic compounds occurs in the propolis solutions between 0.40 to 0.55%.

Correctness of the graphical values of CMC obtained through experimental physical and chemical measurements has been proved by the method of computer-assisted evaluation of parameters of discontinuous semilinear regression model.

The calculated CMC value amounts to 0.50%. Selection of the optimum concentration ranges was based on the application of refractometric and turbidimetric methods and on the method based on surface tension measurements. The received correlation indices are quite high, in particular for:

- Refractometric method – 0.99686 (CMC= 0.51%);
- Turbidimetric – 0.99850 (CMC= 0.60%);
- Method based on surface tension measurements – 0.99527 (CMC= 0.55%).

Critical micelle concentration of propolis water solutions (0.50%) was identified after application of a computer-assisted estimation model. The ratio error of physical and chemical measurements is ±10%.

During elaboration of the content and technology of the «Propolis» eye drops the concentration found experimentally was selected as maximum for our studies.

As the results of the studies we have obtained transparent sterile stable aqueous extract which was packed in bottles and registered according to the requirements of the State Pharmacopoeia of Ukraine as a medicine for treatment of toxic, chemical and mechanical eye injuries.

Conclusions

1. Selection of the dosage form with propolis water solution has been grounded.
2. The technology of "Propolis" eye drops based on water-soluble fraction has been proved theoretically and experimentally.
3. Physical and chemical properties of propolis water solutions have been analyzed: pH, surface tension, refraction index, viscosity, absorbance. Correspondence of the medicine to the requirements of the SPU has been confirmed.

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