JUSTIFICATION OF CONDITIONS OF SALICYLIC ACID INTRODUCTION INTO EMULSION OINTMENT BASE COMPOSITION

Zuykina E.V., Polovko N.P.

National University of Pharmacy
Department of Pharmaceutical Technology of Drugs

Introduction

Extemporaneous production in Ukraine revives, regulatory framework is improving and the material supply is re-equipped. However, to maintain the pace of development, it is necessary to update prescription prescriptions, to improve the technology of drugs, to study stability in the storage process to extend shelf life, etc. Previous studies have found that about 26 % of medicines, that are prepared in pharmacies about the stock, are semi-soild dosage forms [1]. Almost all of these forms are prepared on a vaseline base. It has many disadvantages compared to the modern emulsion bases that are widely used in European practice. Therefore, the creation and implementation of modern emulsion bases for semi-soild dosage forms is a promising direction for the development of pharmaceutical compunding in the country.

One of the most important requirements for the bases is the versatility – the ability to maintain stability and exhibit maximum biopharmaceutical properties when introducing different active substances into it.

Salicylic acid is widely used as a keratolytic component for the treatment of hyperkeratotic dermatoses. It is used in concentrations of 0.5 to 60 % with almost any base. At a concentration of up to 2 % salicylic acid has a keratoplastic action, in higher – keratolytic [2, 3]. Pharmacies prepare 2, 5 and 20 % ointments where vaseline is used as the basis.

Previous microbiological and chemical studies showed a high level of release and a wide range of antimicrobial activity of the experimental samples of 20 % salicylic ointment on the developed emulsion base in comparison with vaseline [4, 5].

Physical and chemical properties of active substances influence not only on the choice of the composition of the base, but also the technology of dosage forms.

The salicylic acid substance is white needle crystals or crystalline powder (Fig. 1), slightly soluble in cold water (1:500), soluble in hot (1:5), easily soluble in alcohol and other non-polar solvents (1: 3) [6].

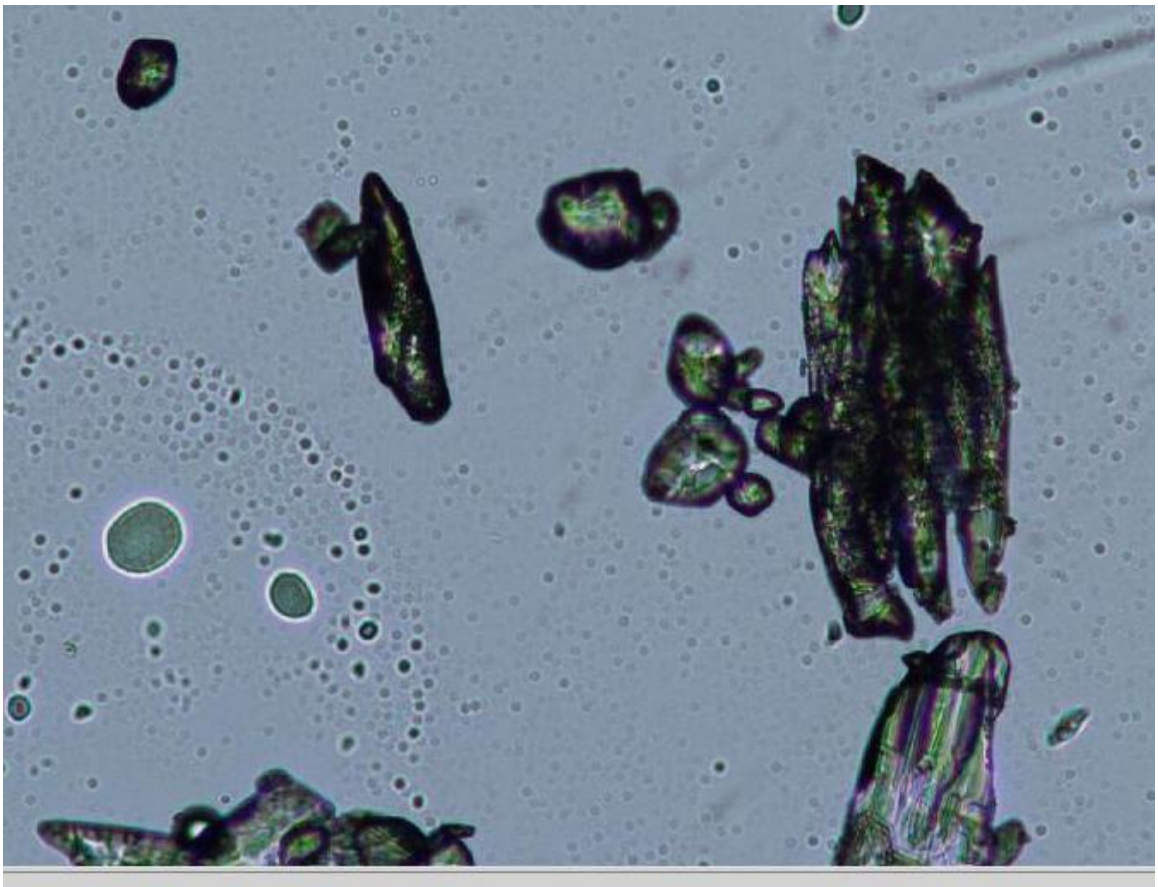


Fig. 1. Crystallographic characteristics of salicylic acid

In the general technology of semi-solid dosage forms, this substance is administered by the type of suspension [7].

In the technology of drugs in the conditions of pharmacies to obtain a drug of good quality, it is necessary to provide a rational way of introducing the active substances to the base, so it is necessary to justify the parameters of the manufacture of ointment with salicylic

DOI: 10.5281/zenodo.3885073

acid in the conditions of pharmacies.

The purpose of our study was to justify the method of introduction of salicylic acid in semi-solid dosage forms (SSDF) on different emulsion bases and to develope the rational ointment technology.

Materials and methods

Previous studies substantiated the use of emulsion bases to create SSDF from 20 % salicylic acid. The following baseline formulations were selected for the study: sample 1 (based on first-grade emulsion) contained 10 % corn oil, 4 % Olivem 1000 (Cetearyl Olivate / Sorbitan Olivat) and purified water up to 100 %. Sample 2 (second-grade emulsion) contained 40 % corn oil, 2 % Span 80, (Sorbitan oleate); Span 60, 3 % (Sorbitan monostearate), 5.5 % cetyl stearyl alcohol and purified water to 100 %. Determination of the degree of dispersion of the oil phase and salicylic acid at the base was performed using a "NIKON ECLIPSE CI-S" triocular digital usb microscope with a built-in camera (the lens 40 X / 0.65 160 / 0.17; eyepiece WD 0,56) with 40x magnification [8, 9].

Results and discussion

During the work it was necessary to justify experimentally the introduction of salicylic acid to the emulsion bases – the carrier. It is important to consider the solubility of API in the appropriate liquids (water, glycerol, oils, ethanol, etc.), which are the components of the base when developing the technology of emulsion-based drugs.. Based on the physical and chemical properties of salicylic acid, the following technology options were proposed.

In the first embodiment, the pre-weighed emulsifier (or mixture of emulsifiers) was melted in a water bath at a temperature of 80 ± 5 °C, and weighed corn oil was added. After melting the oil phase, salicylic acid was introduced to obtain a homogeneous solution, transferred to a heat-resistant container, gradually added the calculated amount of heated to (80 °C) purified water, homogenized using a laboratory homogenizer (Homogenizer HG - 15A) for 20 min at 3000 rpm. Cooled for 30 minutes with stirring [10].

In the second embodiment, a pre-weighed emulsifier (or mixture of emulsifiers) was melted on a water bath with corn oil. After melting, the oil phase was placed in a heat-resistant container, gradually adding the calculated amount of heated to (80 °C) purified water, homogenized using a laboratory homogenizer (Homogenizer HG-15A) for 20 minutes at 3000 rpm to a homogeneous consistency. To the prepared base salicylic acid, pre-ground with 95 % ethanol and, according to Deriagin's rule, with half of its weight base, was added. Stirring continued for 30 minutes.

The obtained samples were labeled as follows:

1. А. emulsion base of the first kind;

1. Б. the base of the first kind with 20 % salicylic acid, dissolved in oil;

1. В. the base of the first kind with 20 % salicylic acid introduced by the type of suspension according to the Deriagin rule;

2. А. emulsion base of the second kind;

2. Б. base of the second kind with 20 % salicylic acid dissolved in oil;

2. В. base of the second kind with 20 % salicylic acid introduced by the type of suspension according to the Deriagin rule.

The samples were controlled for organoleptic (appearance, color, odor, homogeneity) indicators, and their stability was evaluated (Table 1) and microscopic studies were performed.

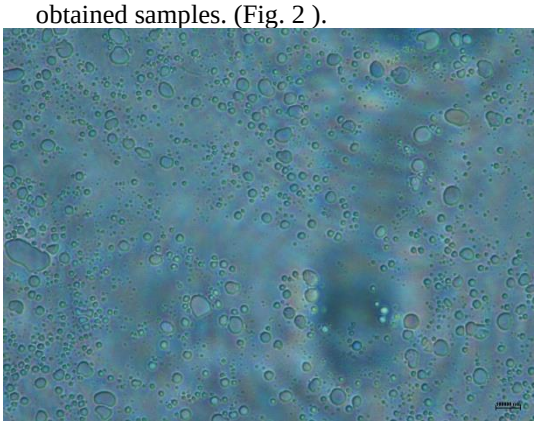
Table 1 Organoleptic properties of the studied samples

Indicators	Samples					
	1. А.	1. Б.	1. В.	2. А.	2. Б.	2. В.
Appearance	Creamy consistency, well distributed and absorbed	Creamy consistency, well distributed and absorbed, palpable presence of salicylic acid particles when applied	Light creamy consistency, well distributed and absorbent; palpable presence of salicylic acid particles when applied	Dense creamy consistency, well distributed	Dense creamy consistency, well distributed palpable presence of salicylic acid particles when applied	Dense creamy consistency, well distributed palpable presence of salicylic acid particles when applied
Color	White with a light creamy tint	White color	White with a light grayish tint	Ivory color	Ivory color	Ivory color
Odor	Neutral	Neutral with a barely perceptible odor of salicylic acid	Neutral with a barely perceptible odor of salicylic acid	Neutral with a tangy taste of corn oil	Neutral with a tangy taste of corn oil	Neutral with a tangy taste of corn oil
Homo-geneity	+	-	-	+	-	-

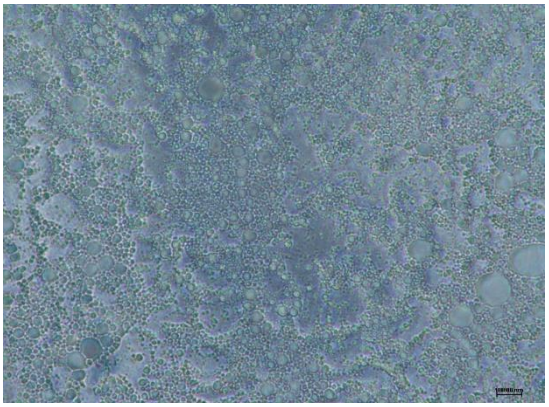
DOI: 10.5281/zenodo.3885073

The microscopic examination observed the preservation of the sizes and shapes of their particles in the obtained samples. (Fig. 2).

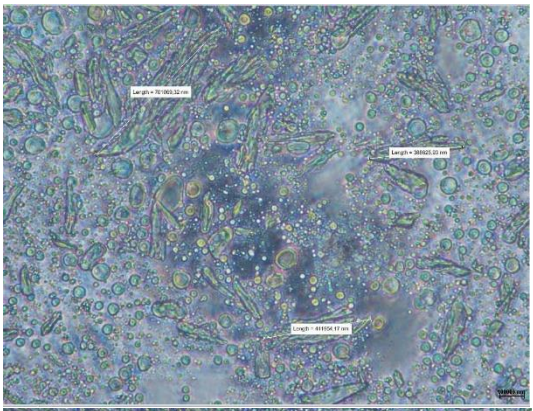
1. A.



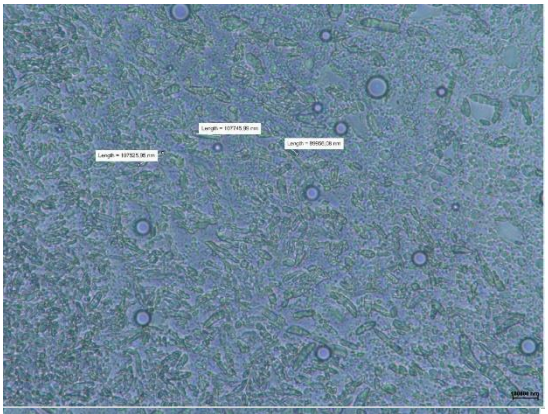
2. A.



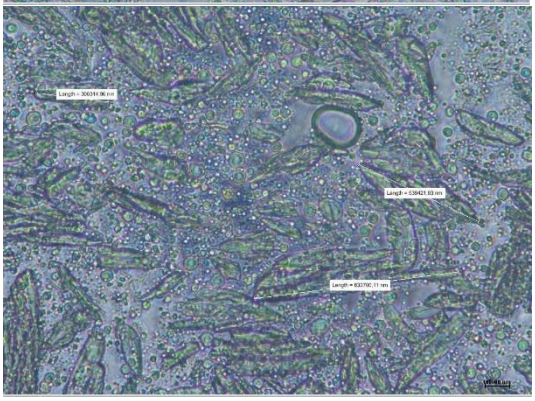
1. B.



2. B.



1. C.



2. C.

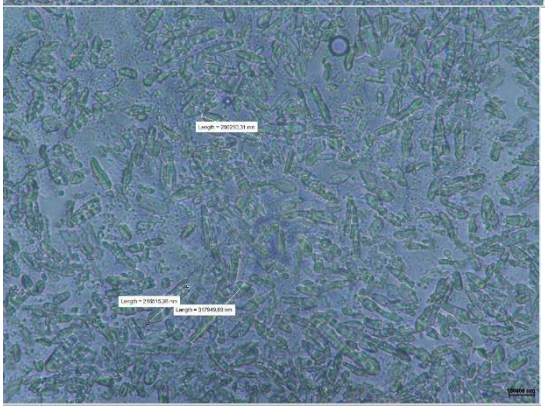


Fig. 2. Microscopic image of the samples

The size of the largest crystals (n=3) and the distribution of the active substance were determined during microscopic examination. The data obtained are shown in the table 2.

Table 2 Results of microscopic examination of samples

Base Type and Technology / Parameters	1. B. the base of the first kind with 20 % salicylic acid dissolved in oil	1. C. the base of the first kind with 20 % salicylic acid introduced by the type of suspension according to the Deriagin's rule	2. B. the base of the second kind with 20 % salicylic acid dissolved in oil	2. C. the base of the second kind with 20 % salicylic acid introduced by the type of suspension according to the Deriagin's rule
The average size of crystals (n = 3)	511 μm	558 μm	102 μm	262 μm

DOI: 10.5281/zenodo.3885073

Evenness of distribution	Uneven distribution	Uneven distribution, accumulation of crystals	Even distribution	Even distribution, moderate accumulation of crystals

The microscopic image of the test samples shows that the average size of crystals in the base of the first kind is 5 times larger than the base of the second kind. Visually visible more uniform distribution of the active substance in the sample with the base of the second kind – 2. B.

Therefore, the study showed that when using the emulsion base of the second kind the more complete dissolution and uniform distribution of salicylic acid is noted, since the base has a greater amount of oil, in which has the active substance is well-soluble, compared to the emulsion base of the first kind. Microscopic studies confirmed the feasibility of dissolving the active substance directly in the oil when preparation of the dosage form. The dissolution of salicylic acid in the oil made it possible to obtain a uniform distribution of drugs in an emulsion base. According to the results of the research, a technological scheme of preparation of 20 % salicylic ointment in the conditions of the pharmacy was developed, which layed in the basis of the technological instruction (Fig. 3).

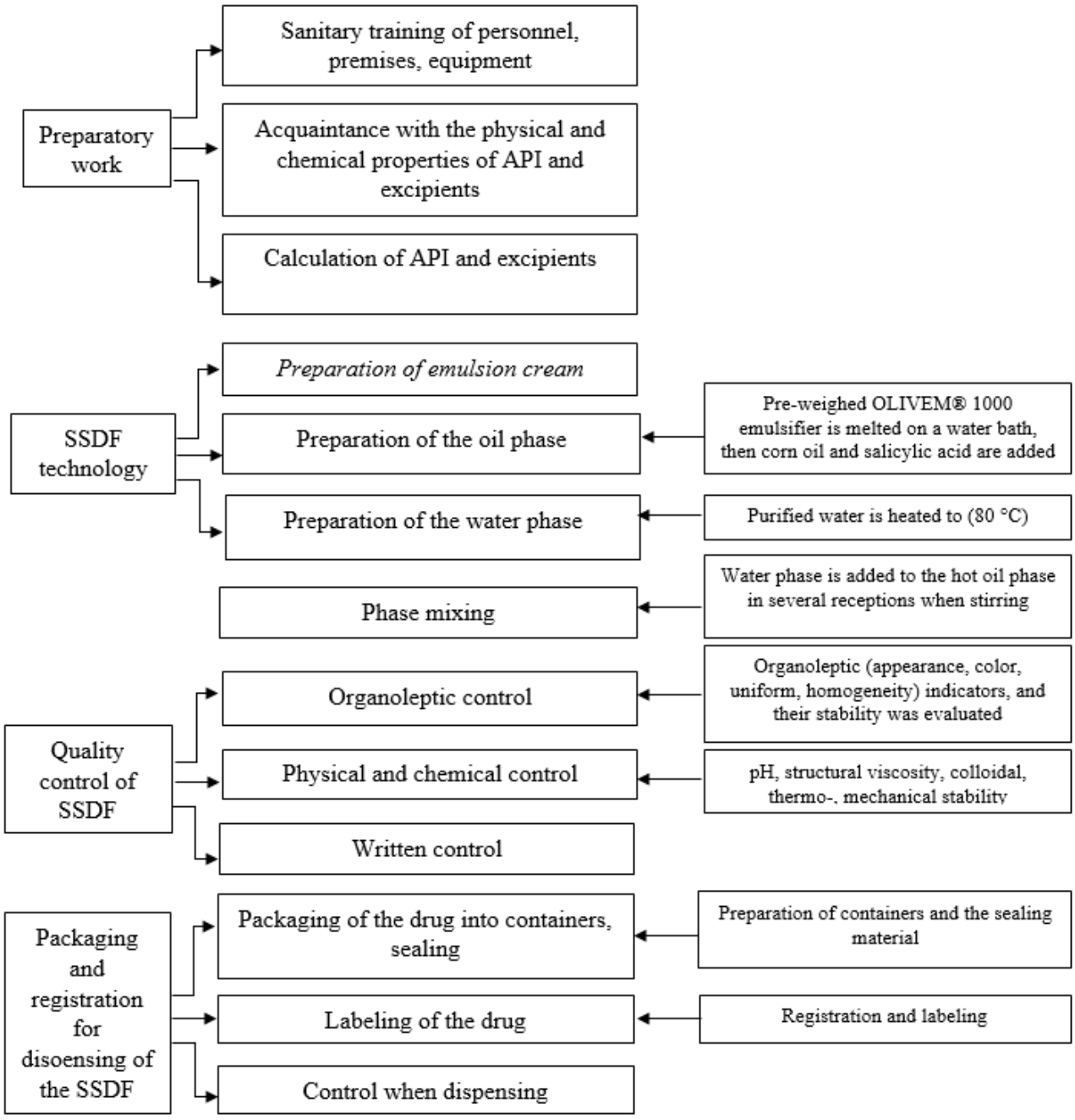


Fig. 3 Technological scheme of preparation of SSDF in the pharmacy.

DOI: 10.5281/zenodo.3885073

Key words: technology, semi-solid dosage forms, microscopic examination, emulsion base.

Conclusions

Physical-chemical and microscopic studies justified the method of introducing salicylic acid into the emulsion base. The dependence of the degree of dispersion and distribution of salicylic acid on the kind of selected emulsion base is shown. It is shown that API is advisable to dissolve in oil, since it promotes less dispersion and a more homogeneous distribution of salicylic acid. The technological scheme of preparation of 20 % salicylic ointment in the conditions of pharmacy is developed, which is layed the basis of the technological instruction.

Justification of conditions of salicylic acid introduction into emulsion ointment base composition

Zuykina E.V., Polovko N. P.

Introduction. The revival of extemporaneous production requires the updating of prescriptions, the improvement of the technology of drugs, the study of stability in the process of storage in order to extend the shelf life. Semi-solid dosage forms, which take more than 25 % of medicines prepared in pharmacies about the stock, are currently prepared on a vaseline base. It has many disadvantages compared to the modern emulsion bases that are widely used in European practice. Therefore, the creation and implementation of modern emulsion bases for semi-soled dosage forms is a promising direction for the development of pharmaceutical compouding. To obtain the drug of good quality, it is necessary to provide a rational way of introducing the active substances to the base, so it is necessary to justify the parameters of the ointment with salicylic acid preparation in the conditions of pharmacies. **Material & methods** The samples of the emulsion bases of the first and second kinds, into the composition of which 20 % of salicylic acid was introsuced by the different technology, were investigated. Determination of the degree of dispersion of the oil phase and salicylic acid in the base was carried out using a "NIKON ECLIPSE CI-S" triocular digital usb microscope with a built-in camera (the lens 40 X / 0.65 160 / 0.17; eyepiece WD 0,56) with 40x magnification. **Results & discussion** Microscopic imaging of the test samples showed that the average size of crystals in the base of the first kind was 5 times larger than in the base of the second kind. A more uniform distribution of the drug substance in the sample with the base of the second kind was established. It is shown that the more complete dissolution and uniform distribution of salicylic acid in the base are observed when dissolving the drug substance in the emulsion base of the seconf kind. **Conclusion.** Physico-chemical and microscopic studies substantiated the method of introducing salicylic acid into the emulsion base. The dependence of the degree of dispersion and distribution of salicylic acid on the type of selected emulsion base is shown. It was shown that API is advisable to dissolve in oil, since it promotes less dispersion and a more homogeneous distribution of salicylic acid. The technological scheme of preparation of 20 % salicylic ointment in the conditions of pharmacy is developed, which is layed in the basis of the technological instruction.

References

1. Polovko NP Zuykína YeV. Stan ekstemporal′noyi retseptury ukrayiny ta problemy sohodennya. Collection of scientific works of employees of NMAPE named after PL Shupik. Kyiv, № 32 2018. P. 294 - 307.
2. Kolyadenko VH Do problemy likuvannya psoriazu. Suchasni likars′ki zasoby ta yikhnya efektyvnist. Ukr. zhurn. dermatolohiyi, venerolohiyi, kosmetolohiyi. № 4. 2008. P. 11-13.
3. Andrashko YuV Sharkan′ IY Suchasnyy pohlyad na mistse keratolityka v kompleksnomu likuvanni psoriazu. Ukrayins′kyy zhurnal dermatolohiyi, venerolohiyi, kosmetolohiyi. Vol. 3. № 38. 2010. P.42 – 46.
4. Nordström FL & Rasmuson Å C Solubility and melting properties of salicylic acid. Journal of Chemical & Engineering Data. 2006. Vol. 5. № 51 1668-1671.
5. Polovko NP Zuykina YeV Yssledovanyya po razrabotke émul′syonnykh osnov s émul′hatoramy marky olivem. Nauchnyy zhurnal «Nauka y ynnovatsyya». №. 3 2018 P. 82 – 86.
6. Nordström FL & Rasmuson AC. Solubility and melting properties of salicylic acid. Journal of Chemical & Engineering Data. Vol. 5. № 51. 2006 P. 1668-1671.
7. Tikhonov AI Yarnykh TG Tekhnologiya lekarstv: Ucheb. dlya farmats. vuzov i fak. pod red. Izdvo NFaU Zolotyye stranitsy. Kharkov 2002. P 704.
8. Tzoumaki MV Moschakis T Kiosseoglou V & Biliaderis CG Oil-in-water emulsions stabilized by chitin nanocrystal particles. Food hydrocolloids. Vol. 6. № 25. 2011. P 1521-1529.
9. Helgason T Weiss J McClements DJ Gislason J Einarsson JM Thormodsson FR & Kristbergsson K Examination of the interaction of chitosan and oil-in-water emulsions under conditions simulating the digestive system using confocal microscopy. Journal of Aquatic Food Product Technology. Vol. 3. № 17. 2008. P 216-233.
10. Anton N Gayet P Benoit JP Saulnier P Nano-emulsions and nanocapsules by the PIT method: an investigation on the role of the temperature cycling on the emulsion phase inversion. Int. J. Pharm. Nov Vol. 1. № 344 2007. P 44–52.

DOI: 10.5281/zenodo.3885073