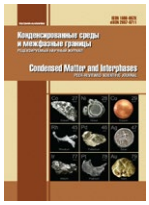

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Study of the influence of the nature and concentration of the solubilizer on the process of formation of solid dispersions of chloronitrophenol

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Abstract

Objectives: The aim of the work was to study the influence of surfactants on the release and solubility of chloronitrophenol (CNP) from solid dispersions in water. The object of study was a solid dispersion of chloronitrophenol with PEG 1500.

Experimental: The concentration of the pharmaceutical substance in solutions was determined spectrophotometrically at a wavelength of 410 nm. The study of the solubility and dissolution rate of pharmaceutical substances (PS) in the form of powder and in the composition of solid dispersed systems (SDS) was carried out according to the method proposed by I. I. Krasnyuk. The study of the optical properties of solutions of the initial compounds and solid dispersions was carried out using the method described in the study of V. V. Grikh. IR spectroscopy, differential scanning calorimetry, and electron microscopy were used for investigation of SDS.

Conclusions: The influence of solubilizers on the process of formation of solid dispersions of chloronitrophenol was studied. It has been shown that the presence of solubilizers allows the use of lower concentrations for the carrier when obtaining solid dispersed systems of chloronitrophenol. The conducted complex of physicochemical methods of analysis allows us to more accurately explain the phenomenon of increasing the solubility and dissolution rate of PS from solid dispersions in the presence of a solubilizer. Based on the conducted studies, it can be concluded that the production of solid dispersions based on a carrier polymer in the presence of a solubilizer allows to reduce or completely eliminate the crystallinity of the pharmaceutical substance, converting it into an amorphous state. The presence of the phenomenon of light scattering and the opalescent Faraday-Tyndall cone in solutions containing solid dispersions of CNP confirmed the assumption about a colloidal-dispersed state of the pharmaceutical substance in water when dissolving CNP from solid dispersions.

Keywords: Chloronitrophenol, Solid dispersions, Solubility, Crystallinity

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1. Introduction

Chloronitrophenol (CNP) is a medicinal substance used to treat fungal skin diseases, as well as mycosis of the external auditory canal. In high concentrations, CNP exhibits activity against gram-positive and gram-negative bacteria of the genera Proteus and Pseudomonas [1].

Due to its poor solubility in water, CNP exists on the pharmaceutical market as only one dosage form: an alcohol solution for external use. However, this dosage form has significant disadvantages.

To solve the problem of solubility of substances such as chloronitrophenol, a method for obtaining solid dispersions can be used. The method is easy to implement, economical, and versatile. It is used in the production of dosage forms for both internal and external use [2-13].

Another way to increase solubility is solubilization, a process of spontaneous transition of compounds that are insoluble or difficult to dissolve in a given solvent into a stable solution using surfactants. Sodium lauryl sulfate, alginates, proteins, lecithins, esters formed by fatty acids, and various glycols are effective surfactants [14].

Therefore, the purpose of our study was to study the influence of surfactants on the release and solubility of chloronitrophenol from solid dispersions (SD) in water.

2. Experimental

The object of study was a solid dispersion of chloronitrophenol with PEG 1500. Chloronitrophenol and PEG from Sigma, as well as sodium lauryl sulfate as a solubilizer, were used in the experiment. To prepare solid dispersions of chloronitrophenol with polymers, the solvent removal method was used [15].

The concentration of PS in solutions was determined spectrophotometrically at a wavelength of 410 nm [16].

The study of the solubility and dissolution rate of pharmaceutical substances in powder form and as part of solid dispersed systems was carried out according to the method proposed by I. I. Krasnyuk Jr. [17].

The study of the optical properties of solutions of the initial compounds and solid dispersions was carried out using the method described in the study of V. V. Grikh [18].

IR spectroscopy was performed in the Centre for Collective Use of Scientific Equipment of Voronezh State University using a VERTEX 70 IR Fourier spectrometer with the unit for measuring the absorption/transmission of thin-film samples (BRUKER).

Differential scanning calorimetry was carried out using an STA 449 F3 synchronous thermal analysis device (NETZSCH, Germany) in the Centre for Collective Use "Experiential Center" of Voronezh State University of Engineering Technologies. The studies were conducted under the following conditions: atmospheric pressure, maximum temperature of 473 K, temperature change rate of 5 K/min.

Analysis of the morphology and size of the obtained samples of solid dispersed systems (SDS) was performed using a JEOL JSM-6380LV scanning electron microscope (JEOL Ltd., Japan) in the Centre for Collective Use of Scientific Equipment of Voronezh State University.

3. Results and discussion

During the first stage of the study, the solubility of solid dispersions of chloronitrophenol with PEG 1500 was studied. The results are presented in Fig. 1.

Obtaining SD in the ratio of 1:1, 1:2, and 1:5 did not lead to an increase in the solubility of chloronitrophenol. Experimental data demonstrated that in the presence of PEG-1500 in a ratio of 1:15 and 1:20, the concentration of released chloronitrophenol was maximal. SDS with a ratio of 1:10 also showed good results in solubility.

In SD prepared using sodium lauryl sulfate, the solubility of chloronitrophenol was higher. As can be seen (Fig. 2), the use of a solubilizer allowed to increase the solubility of the CNP SD.

Studies have shown that solutions of solid dispersions with this polymer exhibit opalescence and demonstrate the Tyndall-Faraday effect. Unlike solutions containing only the chloronitrophenol or polymer substance, or their physical mixture, when a thin beam of light passes through a solution of a solid dispersion, the light flux is scattered.

The effect of the opalescent Tyndall-Faraday cone in solutions of solid dispersions is associated with their colloidal-dispersed state.

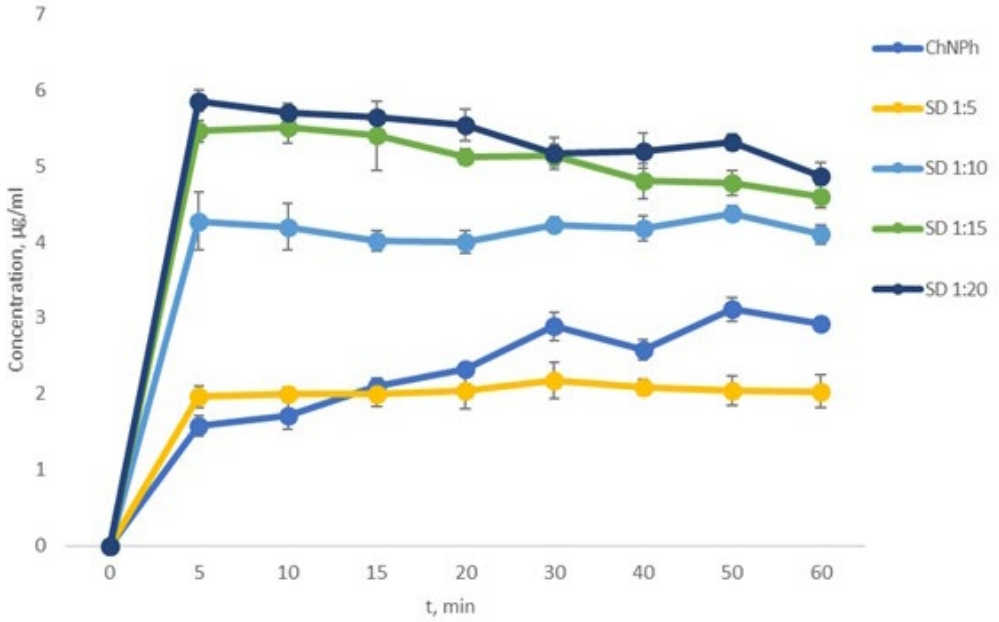


Fig. 1. Dissolution kinetics of chloronitrophenol solid dispersions with PEG 1500

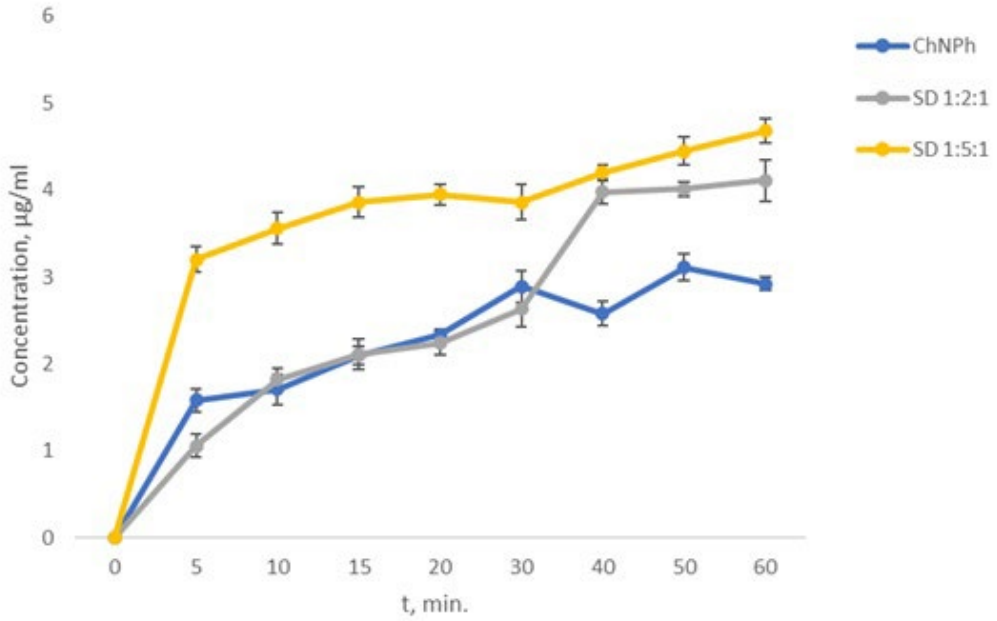


Fig. 2. Dissolution kinetics of chlornitrophenol solid dispersions with PEG 1500 in the presence of a solubilizer

To identify the reasons for the increased solubility of chloronitrophenol in a SDS composition, physicochemical methods were used.

According to scanning electron microscopy data (Fig. 3), the chloronitrophenol substance consists of square and rectangular crystals of approximately the same size. PEG 1500 is a homogeneous, transparent mass without a pronounced internal structure (Fig. 4).

The SD with PEG (Fig. 5) had a non-crystalline structure. Typical crystals of CNP were not observed.

Solid dispersions of CNP with PEG 1500 in the presence of a solubilizer (1:5:1) also represent an amorphous structure in the absence of crystalline structures (Fig. 6).

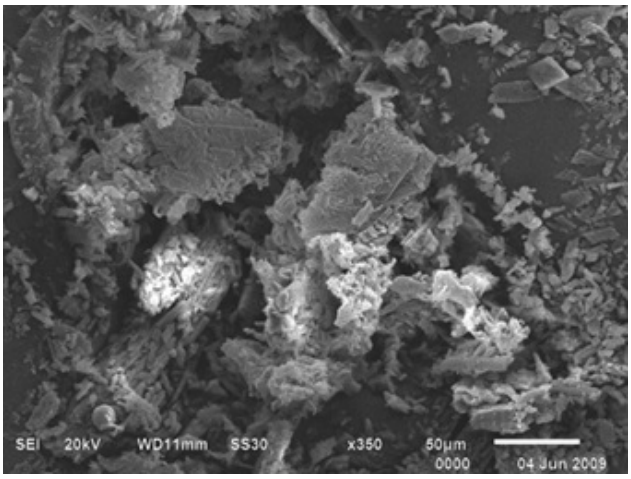
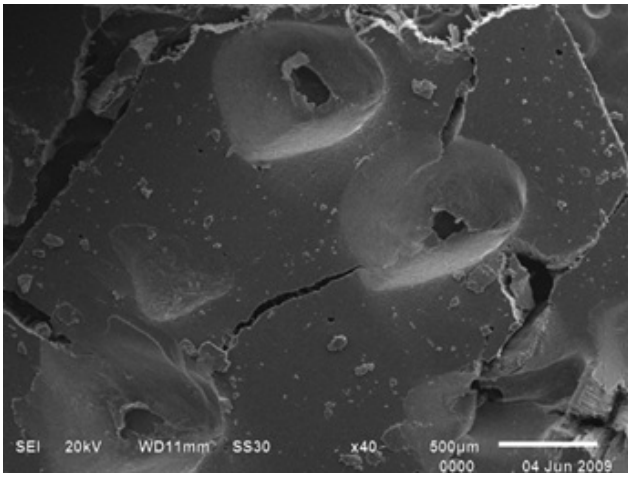


Fig. 3. Scanning electron microscopy of chloronitrophenol substance

Several studies indicate the possibility of using thermal methods, including differential scanning calorimetry for the analysis of solid dispersions [19, 20]. When conducting differential scanning calorimetry of chloronitrophenol, a peak at 112 °C was observed, for PEG 1500 it was 51 °C (Fig. 7, 8), which corresponds to the literature data. For the CNP SD with PEG-1500, a shift of the melting peak to the left at 41 °C was observed (Fig. 9). For SD in the presence of a solubilizer, even greater mixing and broadening of the peak (up to 38 °C) was observed (Fig. 10).

IR spectra of the chloronitrophenol substance, polymer, and solid dispersions with PEG 1500 showed that no new absorption bands were observed for the SD compared to the PS, which may indicate the absence of covalent bonds between the PS and the polymer in the SD (Fig. 11).



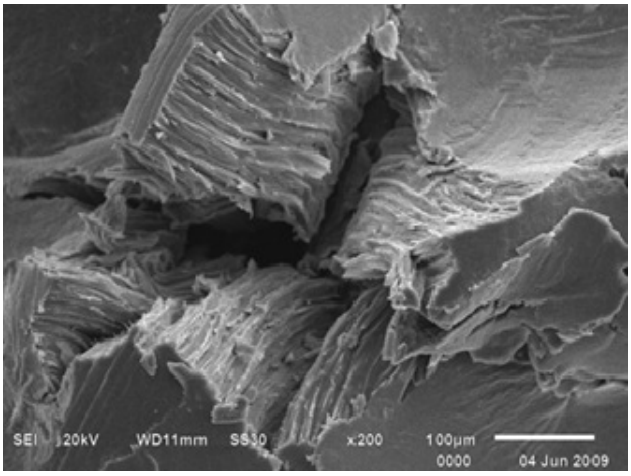


Fig. 4. Scanning electron microscopy of PEG 1500

4. Conclusions

Thus, the influence of solubilizers on the process of dissolution of chloronitrophenol from SD was studied. It has been shown that the

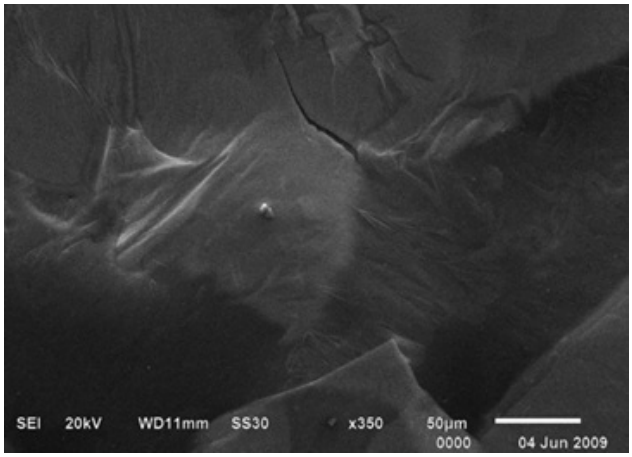


Fig. 5. Scanning electron microscopy of CNP solid dispersions with PEG 1500 (1:10)

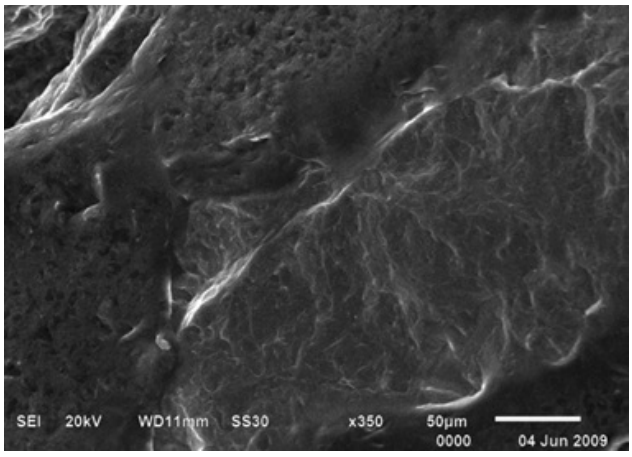


Fig. 6. Scanning electron microscopy of CNP solid dispersions with PEG 1500 in the presence of a solubilizer (1:5:1)

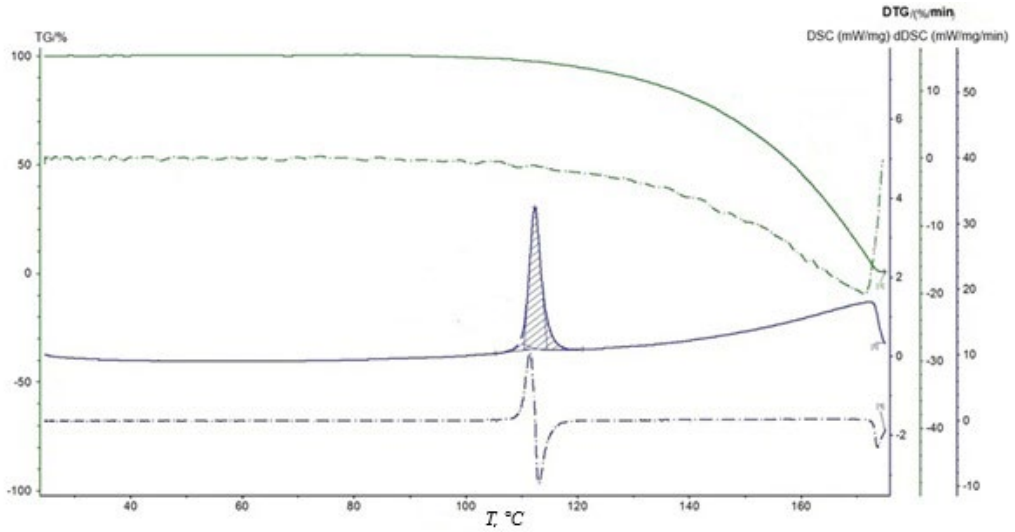


Fig. 7. DSC curve of chloronitrophenol

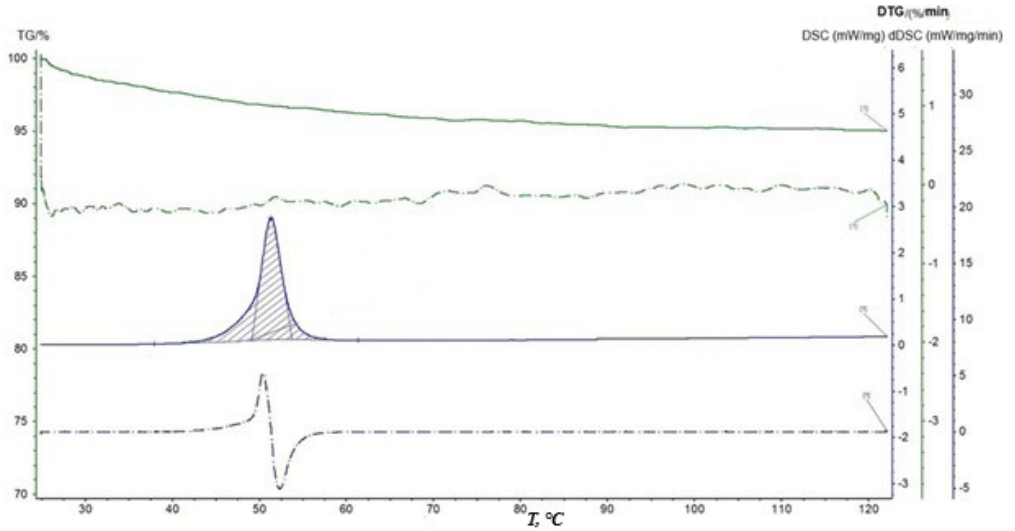


Fig. 8. DSC curve of PEG 1500

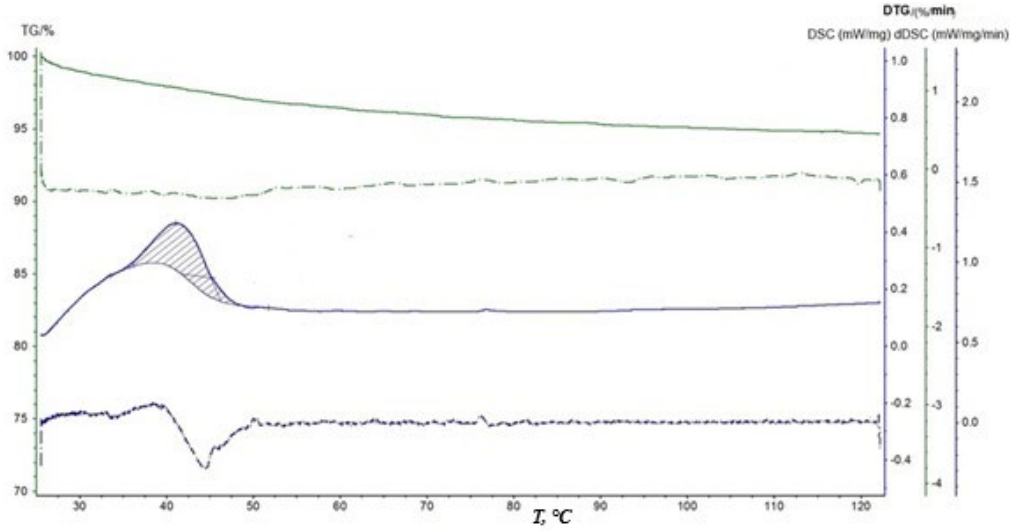


Fig. 9. DSC curve of chloronitrophenol solid dispersions with PEG 1500 (1:10)

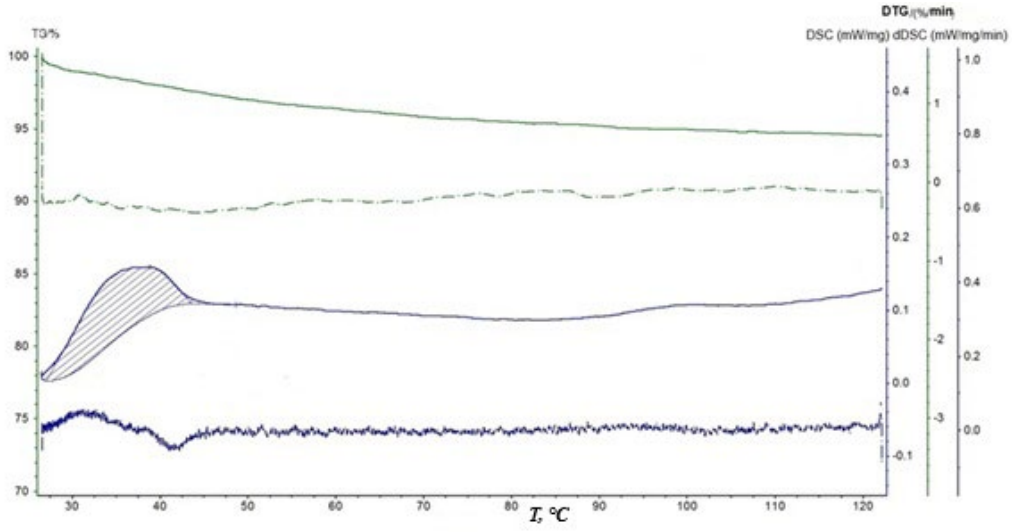


Fig. 10. DSC curve of chloronitrophenol solid dispersions with PEG 1500 in the presence of a solubilizer (1:5:1)

presence of solubilizers allows the use of lower concentrations of the carrier when obtaining SDS.

Based on the conducted research, it can be concluded ibn the production of solid dispersions of chloronitrophenol with a solubilizer, the crystallinity of the PS decreases, increasing the solubility. The properties of chloronitrophenol in the presence of a solubilizer do not change, but its solubility and dissolution rate are modified.

Contribution of the authors

The authors contributed equally to this article.

Conflict of interests

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

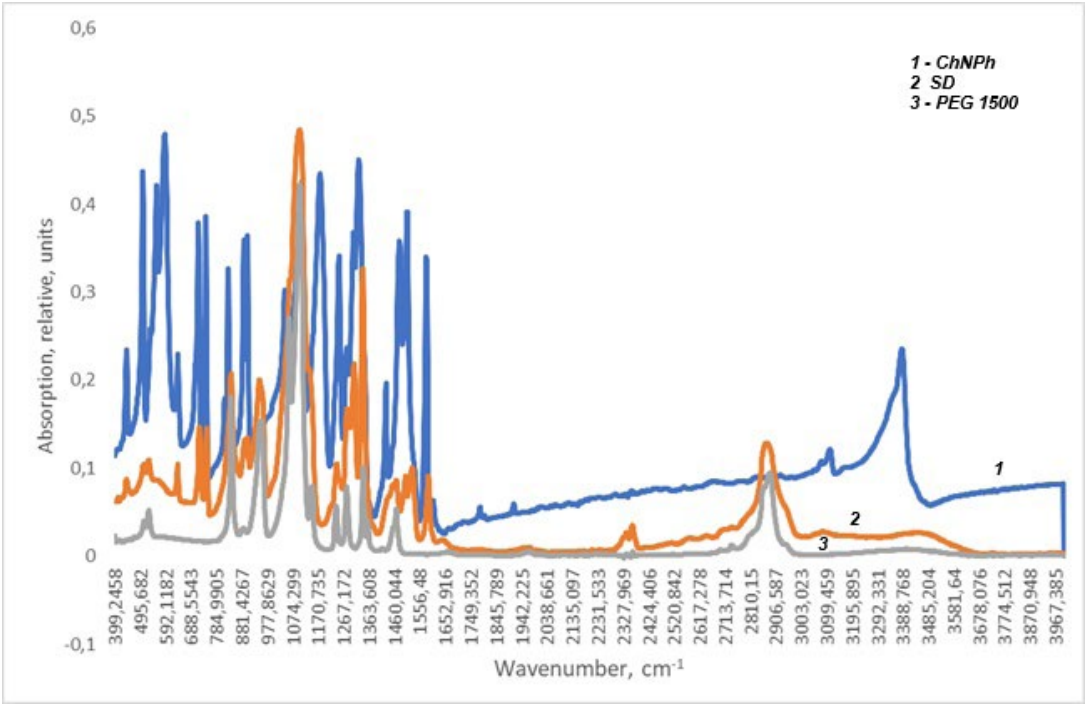


Fig. 11. IR spectrophotometry of chlornitrophenol substance, PEG 1500, solid dispersions of chlornitrophenol with PEG 1500 in the presence of a solubilizer (1:5:1)

References

1. *Register of medicinal products*. (in Russ.). Available at: https://www.rlsnet.ru/active-substance/xlornitrofenol-819

2. Censi R., Gigliobianco M. R., Dubbini A., Malaj L., Di Martino P. New nanometric solid dispersions of glibenclamide in neusilin® UFL2. *AAPS PharmSciTech*. 2016;17(5): 1204–1212. https://doi.org/10.1208/s12249-015-0457-z

3. Khabriev R. U., Popkov V. A., Reshetnyak V. Yu., Krasnyuk I. I. (ml.), Manakhova O. V. Increasing the solubility of an angioprotector by the method of solid dispersions. *Pharmaceutical Chemistry Journal*. 2009;43: 472–476. https://doi.org/10.1007/s11094-009-0326-8

4. Krasnyuk I. I. (ml.), Manakhova O. V., Khabriev R. U., Popkov V. A., Reshetnyak V. Yu., Krasnyuk O. I. Increasing the solubility of phenazepam by obtaining its solid dispersions. *Pharmaceutical Chemistry Journal*. 2010;44(5): 274–277. https://doi.org/10.1007/s11094-010-0448-z

5. Terentyeva O. A, Teslev A. A., Loginov K. Yu. Modern approaches to enhancing the bioavailability of poorly water-soluble drugs. *Sciences of Europe*. 2016;7(7): 27–31. (in Russ.). Available at: https://www.europe-science.com/wp-content/uploads/2020/10/VOL-2-No-7-7-2016.pdf

6. Kolpaksidi A. P., Dmitrieva M. V., Orlova O. L., Ektova L. V., Krasniuk I. I. Application of solid dispersion technology to obtain a model of injectable dosage form of indolocarbazole derivative. *Drug Development & Registration*. 2022;11(4): 73–78. (in Russ.). https://doi.org/10.33380/2305-2066-2022-11-4-73-78

7. Krasnyuk (Jr.) I. I., Naryshkin S. R., Krasnyuk I. I., … Vorobiev A. N. Effect of solid dispersions on the solubility of metronidazole. *Pharmacy & Pharmacology*. 2021;9(3): 195–204. https://doi.org/10.19163/2307-9266-2021-9-3-195-204

8. Gulyakin I. D., Nikolaeva L. L., Obolova N. A., … Bunyatyan N. D. Common methods increasing the solubility of poorly soluble hydrophobic substances. *Drug Development & Registration*. 2016;(2): 52–59. (in Russ.). Available at: https://www.pharmjournal.ru/jour/article/view/83

9. Silaeva S. Yu., Belenova A. S., Slivkin A. I., Chupandina E. E., Naryshkin S. R., Krasnyuk I. I. Use of solid dispersion systems in pharmacy. *Condensed Matter and Interphases*. 2020;22(2): 173–181. https://doi.org/10.17308/kcmf.2020.22/2820

10. Dmitrieva M. V., Kolpaksidi A. P., Orlova O. L., … Krasnyuk I. I. Development of a technology for producing a stable injectable dosage form of a hydrophobic indolocarbazole derivative. *International Journal of Applied Pharmaceutics*. 2021;13(6): 232–235. https://doi.org/10.22159/ijap.2021v13i6.42685

11. Nair A. R., Lakshman Y. D., Anand V. S. K., Sree K. S. N., Bhat K., Dengale S. J. Overview of extensively employed polymeric carriers in solid dispersion technology. *AAPS PharmSciTech*. 2020;21(8): 309. https://doi.org/10.1208/s12249-020-01849-z

12. Dahiya S. Studies on formulation development of a poorly water-soluble drug through solid dispersion technique. *The Thai Journal of Pharmaceutical Sciences*. 2010;34: 77–87. https://doi.org/10.56808/3027-7922.2171

13. Akiladevi D., Shanmugapandian P., Jebasingh D., Sachinandan B. Preparation and evaluation of paracetamol by solid dispersion technique. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2011;3(1): 188–191.

14. Gladyshev V. V., Davtyan L. L., Drozdov A. L., Biryuk I. A., Kechin I. L. *Biopharmacy**. Dnipro: ChMP "Economy Publ.; 2018. 250 p. (in Russ.)

15. *Measurement of concentrations of harmful substances in the air**. Collection of methodological guidelines MUK 4.1.1706-03 "Spectrophotometric measurement of mass concentrations of 4-nitro-2-chlorophenol (nichlorfen, nitrofungin, chloronitrophenol) in the air of the working area." Moscow: Federal Center for Hygiene and Epidemiology of Rospotrebnadzor; 2007. 287 p. (in Russ.). Available at: http://libnorm.ru/Files2/1/4293755/4293755416.pdf

16. Silaeva S. Yu., Belenova A. S., Zvyagintseva T. K., Tsivilka M. V. Selection of carriers for obtaining solid dispersions of chloronitrophenol*. In: *Ways and forms of improving pharmaceutical education. Topical issues of development and research of new drugs. Collection of works of the 8th International Scientific and Methodological Conference, March 31 – April 02, 2022. Voronezh*. VSU Publishing House; 2022. p. 476–479. (in Russ.)

17. Krasnyuk I. I. *Increasing the bioavailability of dosage forms using solid dispersions**. Dr. pharm. sci. diss. Moscow: 2010. 298 p. (in Russ.). Available at: https://www.dissercat.com/content/povyshenie-biodostupnosti-lekarstvennykh-form-s-primeneniem-tverdykh-dispersii

18. Grikh V. V. *Development of dosage forms of nifedipine using solid dispersions**. Cand. pharm. sci. diss. Moscow: 2018. 151 p. (in Russ.). Available at: https://www.dissercat.com/content/razrabotka-lekarstvennykh-form-nifedipina-s-primeneniem-tverdykh-dispersii

19. Karolewicz B., Gajda M., Pluta J., Gorniak A. Dissolution study and thermal analysis of fenofibrate–Pluronic F127 solid dispersions. *Journal of Thermal Analysis and Calorimetry*. 2016;125(2): 751–757. https://doi.org/10.1007/s10973-015-5013-2

20. Gorniak A., Gajda M., Pluta J., Czapor-Irzabek, H., Karolewicz B. Thermal, spectroscopic and dissolution studies of lovastatin solid dispersions with acetylsalicylic acid. *Journal of Thermal Analysis and Calorimetry*. 2016;125(2): 777–784. https://doi.org/10.1007/s10973-016-5279-z

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