УДК 615.014.22:620.3
DOI: 10.15587/2519-4852.2019.158590

STUDY OF THE STABILITY OF ORGANOLEPTIC AND STRUCTURAL-MECHANICAL INDICATORS OF SEMI-SOLID PREPARATIONS WITH METAL NANOPARTICLES

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Мета. *Дослідження стабільності органолептичних та реологічних властивостей м'яких лікарських засобів з наночастинками срібла і золота.*

Методи. *Для дослідження органолептичних показників використано класичний метод визначення стабільності з періодичним контролем зразків лікарських форм при двох температурних режимах: 8–15 °С (прохолодне місце) та 15–25 °С (кімнатна температура). Для вивчення реологічних характеристик м'яких лікарських засобів використано ротаційний віскозиметр із системою коаксіальних циліндрів.*

Результати. *Досліджено три лікарських форми на основі наночастинок срібла - мазь, крем та гель, які можуть бути перспективними для застосування у дерматології, а також дві лікарські форми на основі наночастинок срібла і золота для застосування у стоматології і хірургії з метою лікування інфекційних, гнійно-запальних захворювань шкіри та слизових оболонок ротової порожнини. Протягом 24 міс зберігання зразків лікарських форм в захищеному від світла місці у банках із темного скла кожні 6 міс проводили контроль за такими показниками: однорідність, запах, колір та pH. Реологічні показники досліджували після виготовлення лікарських форм та через 24 міс зберігання. За реологічними показниками будували реограми плину м'яких лікарських засобів, а також розраховували показники механічної стабільності. Встановлено, що всі зразки є коагуляційними системами з псевдопластичним типом течії. Одержані реограми містять петлі гістерезису, які характеризують їх певний ступінь тиксотропності.*

Висновки. *За результатами досліджень встановлено стабільність органолептичних показників м'яких лікарських засобів при температурі зберігання 8-15 °С у захищеному від світла місці. За реологічною поведінкою досліджені зразки м'яких лікарських засобів характеризуються доброю здатністю до намазування на шкіру та екструзії з туб*

Ключові слова: *наночастинки срібла, наночастинки золота, мазі, креми, гелі, стабільність, реологічні властивості*

1. Introduction

Stability of quality indicators of drugs ensures the continuity of their therapeutic properties in the process of storage and use. Therefore, the study of stability should be the subject of special attention at the stage of pharmaceutical design of drugs [1, 2].

The development of a new medicinal product should be based on general methodological approaches to pharmaceutical design, taking into account the requirements for the dosage form [3].

In the development of soft drugs, considerable attention should be paid to the study of the rheological properties of ointment and gel bases, since conducting such studies can control the quality of the drug by introducing additional auxiliary substances, changes in modes and methods of the process [4].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Important indicators of stability of soft drugs are organoleptic parameters: appearance, colour, odour, homogeneity and rheological properties: marginal shear stress (yield strength) and structural viscosity. From a practical point of view, the study of properties such as smearing and extrusion from tubes, which are determined by the degree of thixotropy of samples, is important.

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author

At the Department of Technology of medicine and biopharmacy of the Lviv National Medical University named after Danylo Halytsky, was conducted research on the pharmaceutical development of drugs in which metal nanoparticles are used as active pharmaceutical ingredients [5].

Based on the study of the peculiarities of the course of the pathological process in infectious, purulent-inflammatory and burn skin diseases and the analysis of the results of microbiological studies, the composition of soft drugs with silver nanoparticles in various dosage forms (ointment, cream, gel) depending on the stage of the wound process was substantiated [6, 7].

The combination of silver and gold nanoparticles proved to be effective in purulent inflammatory diseases of the maxillofacial area in an in vitro and in vivo experiment. The high antimicrobial, anti-inflammatory activity and ability of the studied nanoparticles to stimulate the reparative processes of soft tissues and bones was estab-

lished [8]. On the basis of a colloidal solution of silver and gold nanoparticles, an ointment and gel have been developed for use in dentistry and surgery [9].

According to SPHU, soft drugs should be homogeneous in terms of weight and content, colour and odour in accordance with the specifications and have constant rheological characteristics throughout the shelf life [10].

In the design of soft drugs, Ukrainian scientists pay close attention to studying the structural and mechanical properties of these dosage forms [11, 12].

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

The main indicator of drug stability is the quantitative content of active pharmaceutical ingredients, but for soft drugs, organoleptic parameters such as appearance, colour, odour, homogeneity, and rheological properties that characterize the consumer's properties of the medicinal product are equally important indicators of stability, the ability to smear and extrude the tubes.

5. Formulation of goals (tasks) of Article

The aim of the work is to study the stability of organoleptic and rheological properties of soft drugs with silver and gold nanoparticles.

6. Statement of the basic material of the study (methods and objects) with the justification of the results

Regardless of dosage form and specific drug requirements, all methods of stability research are designed to determine the term for which the components of the drug and the finished product will be stable [13].

Three drugs based on silver nanoparticles – ointment, cream and gel, which can be promising for use in dermatology, as well as two dosage forms based on nanoparticles of silver and gold for use in dentistry and surgery for the treatment of infectious, purulent, inflammatory diseases of the skin and mucous membranes of the oral cavity.

For the study of organoleptic parameters, a classic method for determining the stability with periodic control of dosage forms was used [14, 15]. The study was performed on 3 series of drugs stored in dark glass containers at two temperature regimes: 8–15 °C (cool place) and 15–25 °C (room temperature) in a place protected from light.

The study of the rheological characteristics of drugs in soft dosage forms with nanoparticles of metals was carried out after the preparation of dosage forms and after 24 months of storage on a rotary viscometer Myr VR 3000, manufactured in Spain, using a system of coaxial cylinders.

Characteristics of the studied soft dosage forms with nanoparticles of metals are given in Table 1.

Table 1

Studied drugs in soft dosage forms

No.	Characteristics of dosage forms
No. 1	Ointment with silver nanoparticles
No. 2	Cream with silver nanoparticles
No. 3	Gel with silver nanoparticles
No. 4	Ointment with silver and gold nanoparticles
No. 5	Gel with nanoparticles of silver and gold

During 24 months of storage, every 6 months, samples of drugs in soft dosage forms were monitored for the following parameters: homogeneity, odour, colour and pH. The results of the study of dosage forms are given in Table 2.

As a result of the research, it was found that drugs in soft dosage forms, which were stored at a temperature of 8–15 °C, were stable for the studied quality indices. In samples of gels, which were stored at a temperature of 15–25 °C, after 12–18 months of storage, stratification and liquefaction of gels were observed. These results indicate instability of gels during storage in such conditions.

Study of the rheological properties of soft drugs was carried out according to the methodology, which was as follows: the weight of the sample was placed in the chamber and immersed in the spindle TR-11; after this, the spindle was forced to rotate, starting at low speeds, and fixed the viscometer's visibility. Rheological indicators of samples of soft drugs after manufacturing dosage forms and after 24 months practically did not differ. The rheograms of the flow of soft drugs are shown in Fig. 1–4.

Table 2

Evaluation of the stability of drugs in soft dosage forms

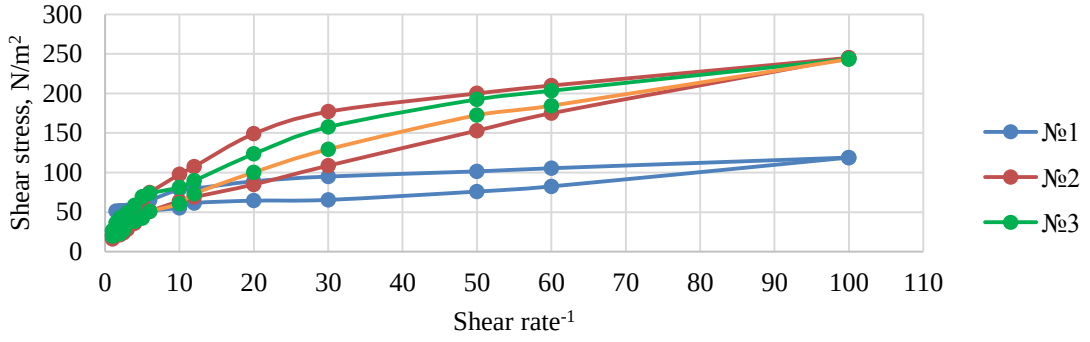
	Indicators	Requirements of MQC	Study period, months									
			0	6	12	18	24	0	6	12	18	24
			Storage in cool place, 8–15 ^{0}C					Storage at room temperature, 15–25 ^{0}C				
1	2	3	4	5	6	7	8	9	10	11	12	13
1	Appearance	Homogeneous soft mass	Homogeneous soft mass	+	+	+	+	Homogeneous soft mass	+	+	+	+
	Colour	Match the colour of the drug	White	+	+	+	+	White	+	+	+	+
	Odour	Match the odour of the drug	Odour less	+	+	+	+	Odour less	+	+	+	+
	pH	5.5–7.5	6.7±0.2	6.9±0.5	6.9±0.3	6.8±0.2	6.9±0.4	6.7±0.2	6.9±0.1	6.9±0.3	6.8±0.5	6.8±0.4

Continuation of the Table 2

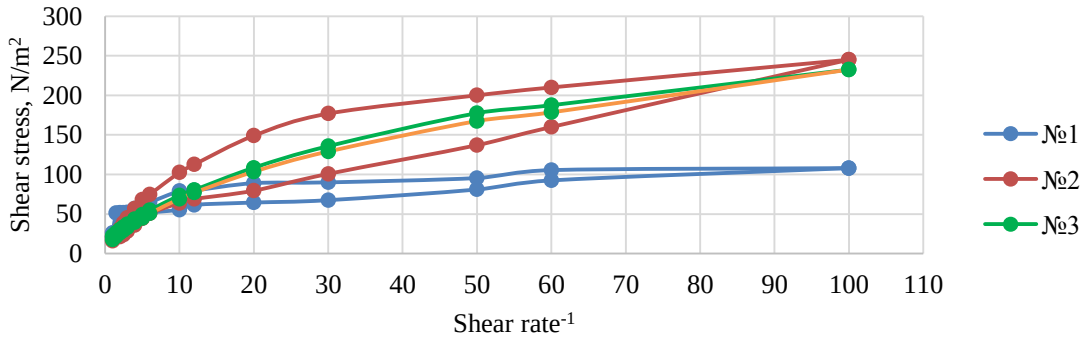
1	2	3	4	5	6	7	8	9	10	11	12	13
2	Appear pear-ance	Homoge-neous soft mass	Homo-gene-ous soft mass	+	+	+	+	Homo-gene-ous soft mass	+	+	+	+
	Colour	Match the colour of the drug	White	+	+	+	+	White	+	+	+	+
	Odour	Match the odour of the drug	Odour-less	+	+	+	+	Odour-less	+	+	+	+
	pH	4.5– 6.5	5.8±0.2	5.8±0.5	5.7±0.2	5.8±0.3	5.9±0.5	5.8±0.2	5.7±0.3	5.7±0.5	5.6±0.3	5.6±0.4
3	Appear pear-ance	Homoge-neous soft mass	Homo-gene-ous soft mass	+	+	+	+	Homo-gene-ous soft mass	+	+	-	-
	Colour	Match the colour of the drug	White opales-cent	+	+	+	+	White opales-cent	+	+	+	-
	Odour	Match the odour of the drug	Odour-less	+	+	+	+	Odour-less	+	+	+	+
	pH	5.5 –7.5	7.2±0.2	7.1±0.5	7.2±0.1	7.0±0.5	7.1±0.2	7.2±0.2	7.2±0.3	7.0±0.1	6.9±0.5	6.9±0.2
4	Appear pear-ance	Homoge-neous soft mass	Homo-gene-ous soft mass	+	+	+	+	Homo-gene-ous soft mass	+	+	+	+
	Colour	Match the colour of the drug	Light brown	+	+	+	+	Light brown	+	+	+	+
	Odour	Match the odour of the drug	Odour-less	+	+	+	+	Odour-less	+	+	+	+
	pH	5.5 – 7.5	6.4±0.3	6.5±0.4	6.5±0.3	6.6±0.2	6.5±0.5	6.4±0.3	6.4±0.5	6.3±0.2	6.2±0.3	6.3±0.4
5	Appear pear-ance	Homoge-neous soft mass	Homo-gene-ous soft mass	+	+	+	+	Homo-gene-ous soft mass	+	+	+	-
	Colour	Match the colour of the drug	Brown	+	+	+	+	Brown	+	+	+	+
	Odour	Match the odour of the drug	Odour-less	+	+	+	+	Odour-less	+	+	+	+
	pH	5.5 – 7.5	6.3±0.4	6.2±0.3	6.1±0.4	6.2±0.4	6.1±0.5	6.3±0.4	6.1±0.2	5.8±0.3	5.9±0.4	6.0±0.3

Note: + – no changes during storage; – – changes during storage are presence

All samples are coagulation systems with a pseudoplastic flow type. The obtained rheograms contain loops of hysteresis, which characterize their certain degree of thixotropy. As can be seen from figures No. 1 – No. 2, with increasing displacement voltage in samples No. 1, No. 4 there is a sharp loss of structural and mechanical parameters in comparison with samples No. 2, No. 3, No. 5. Samples of gels are more slowly deformed under the influence of mechanical action with complete system restoration. Unlike the sample No. 4, which has a line of flow at No. 5 s^{-1}, sample No. 5 requires more external forces and is capable of restoring the structure during their termination. Samples No. 1-No. 3, No. 5 have a denser system. The degree of structuring of the system decreases in the number No. 2 → No. 1 → No. 3 → No. 5, as evidenced by the area of hysteresis loops.

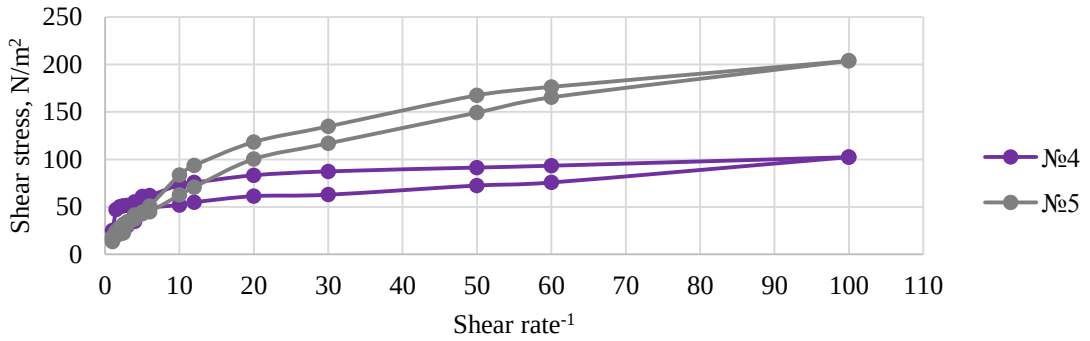


a

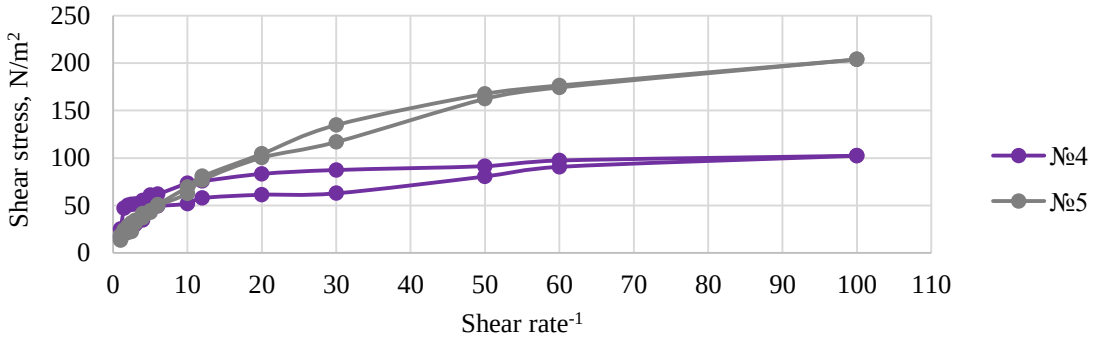


b

Fig. 1. Rheograms of a stream of drugs in soft dosage forms with nanoparticles of silver: *a* – after preparation; *b* – after 24 months of storage

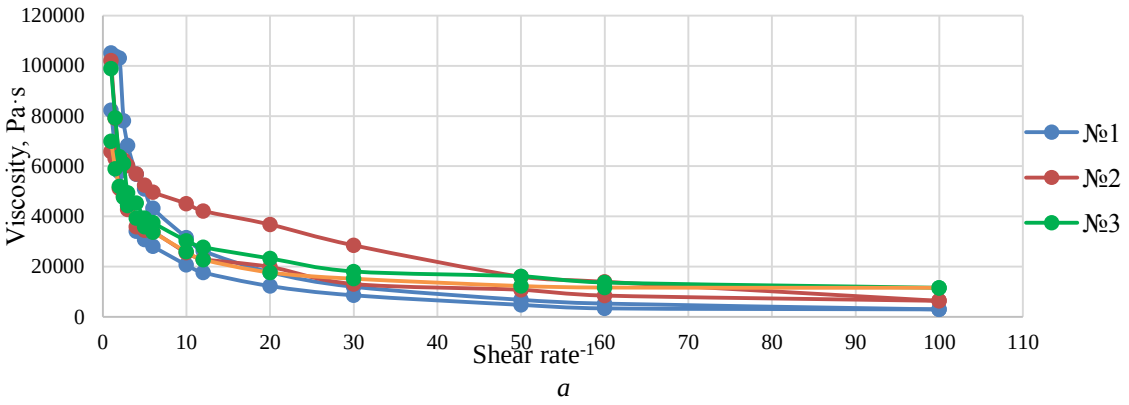


a

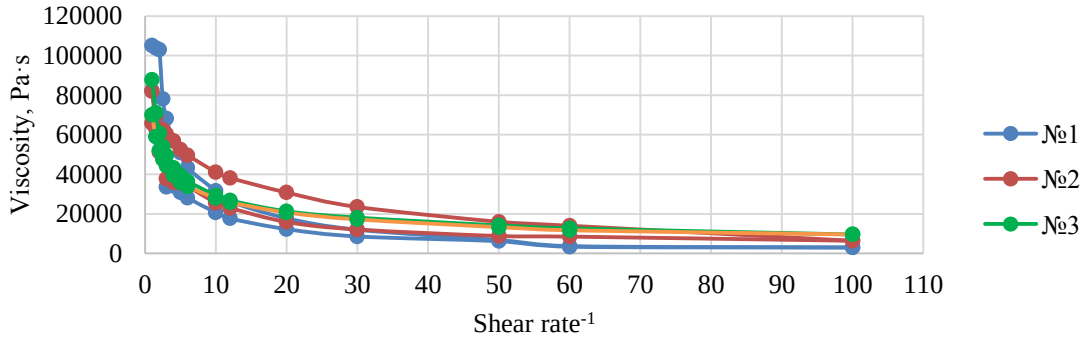


b

Fig. 2. Rheograms of a stream of drugs in soft dosage forms with nanoparticles of silver and gold: *a* – after preparation; *b* – after 24 months of storage

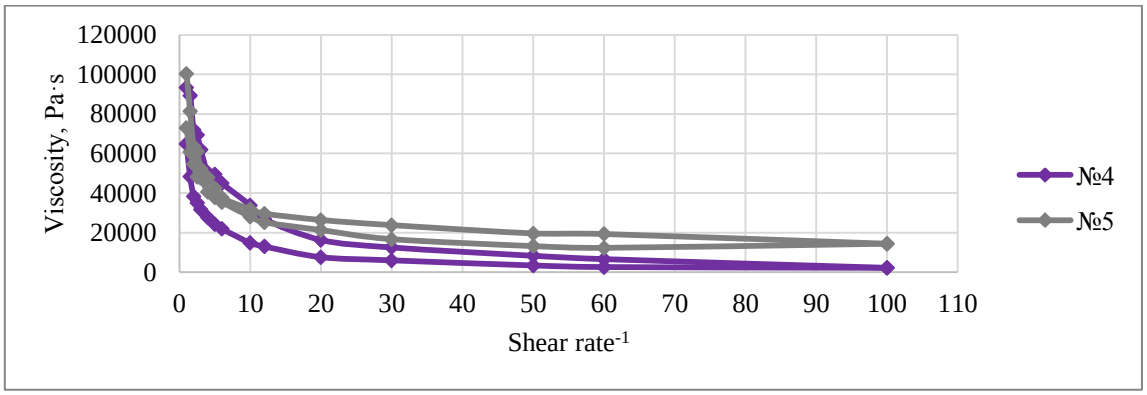


a

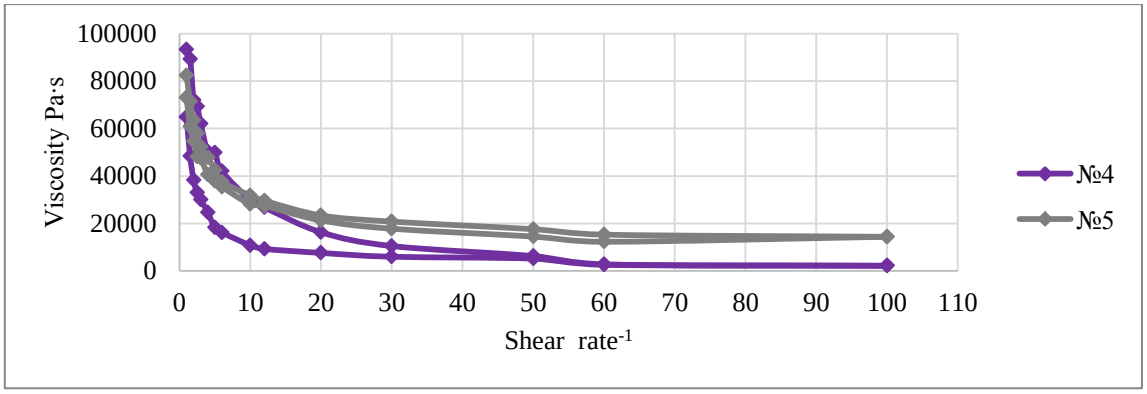


b

Fig. 3. Dependence of dynamic viscosity on shear stress in samples of drugs in soft dosage forms with nanoparticles of silver: *a* – after preparation; *b* – after 24 months of storage



a



b

Fig. 4. Dependence of dynamic viscosity on shear stress in samples of drugs in soft dosage forms with nanoparticles of silver and gold: *a* – after preparation; *b* – after 24 months of storage

As can be seen from Fig. 3 and 4, in all investigated samples there is inversely proportional dependence of the values of dynamic viscosity on the values of shear rate in the whole range of velocities.

Initial viscosity differs considerably in specimens, depending on their composition and decreases in the number No.1 → No.4 → No.3 → No.2 = No.5. The viscosity of the restored structure of almost all samples slightly exceeds the initial, the maximum value is the sample No.4 (almost 1.5 times).

Also, indicators of mechanical stability were calculated as the ratio of the value of the strength to the fracture (τ1) and the value of the strength after the destruction (τ2) by the formula τ1 / τ2 (Table 3).

Table 3

Indicators of mechanical stability of samples

No.1	No.2	No.3	No.4	No.5
1.27	1.09	1.12	1.37	1.11

Samples of drugs in soft dosage forms are characterized by the same ability to structure and have indicators of mechanical stability approaching 1. According to rheological behavior, the samples studied differ from each other depending on their composition. The presence of upward and downward curves on rheograms (hysteresis loops) indicates that the studied drugs in soft dosage forms have thixotropic properties, which characterizes the good ability to smear on the skin and the ability to extrude from tubes.

7. Conclusions from the conducted research and prospects for further development of this field

1. According to the results of the research the stability of organoleptic parameters of soft drugs at a storage temperature of 8–15 °C in a place protected from light was established.

2. According to the results of rheological studies, it was found that the samples of tested drugs in soft dosage forms have a good ability to smear on the skin and extrusion from tubes.

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Рекомендовано до публікації д-р фарм. наук, професор Калинюк Т. Г.
Дата надходження рукопису 29.01.2018

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