Mishina Marina M., Vekshin Vitaliy A., Burov Andrey N., Grabovetskaya Evgeniya R. Investigation of physico-chemical characteristics of carboxymethylcellulose colloidal carriers for medical preparations. Journal of Education, Health and Sport. 2021;11(1):202-218. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2021.11.1.020
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.1.020
https://zenodo.org/record/4540129

8

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 25.12.2020. Revised: 14.12.2020. Accepted: 29.01.2021.

INVESTIGATION OF PHYSICO-CHEMICAL CHARACTERISTICS OF CARBOXYMETHYLCELLULOSE COLLOIDAL CARRIERS FOR MEDICAL PREPARATIONS

Marina M. Mishina[1], Vitaliy A. Vekshin[1]✉, Andrey N. Burov[1]
Evgeniya R. Grabovetskaya[2]

[1]Kharkiv National Medical University, Kharkiv, Ukraine,
[2]V. N. Karazin Kharkiv National University, Kharkiv, Ukraine

Vitaliy A. Vekshin - Central Scientific and Research Laboratory of Kharkin National Medical University, Ukraine; Address: Nauki ave., 4, Kharkiv, 61000, Ukraine
E-mail: myposta2014@gmail.com; Phone +380509027452

Marina M. Mishina - Department of Microbiology, Virology and Immunology named by D.P. Grynyov. Kharkin National Medical University, Ukraine; Address: Nauki ave., 4, Kharkiv, 61000, Ukraine; E-mail: mishina1969mmm@gmail.com; Phone +380506082117

Andrey N. Burov - Department of Microbiology, Virology and Immunology named by D.P. Grynyov. Kharkin National Medical University, Ukraine; Address: Nauki ave., 4, Kharkiv, 61000, Ukraine; E-mail: burov129@ukr.net; Phone +380983564540

Evgeniya R. Grabovetskaya - Departement of biochemistry of V.N.Karazin Kharkin National University, Ukraine; Address: Svobody Sq., 4, Kharkiv, 61022, Ukraine
E-mail: e.graboveckaya@gmail.com; Phone +380506835178

Abstract

Introduction. Physico-chemical peculiarities of processes of preparation and aging of colloidal carriers (gels) based on carboxymethylcellulose (CMC) for medical preparations which are planned to be used as a treatment for burn wounds are considered in the article. Studies were conducted in the Central Scientific Research Laboratory of the Kharkiv National

Medical University in 2019.

The objectives of the study. The objective was to study the applicability of CMC solutions and their modified analogues for the gel-based pharmaceutical preparations.

Material and methods. Experimental studies were carried out under laboratory conditions using equipment for viscosity and pH measuring.

Results. The influence of concentration, temperature, and acidity on viscosity of gels was investigated. The gels were tested on aging during storage. The stability of these solutions and syneresis process were investigated. The influence of added modifiers – glycerol and ascorbic acid on the consistency, acidity, susceptibility to contamination and term of storage of the gels was determined.

Conclusions. It is shown that unmodified solutions have the highest viscosity and the greatest stability. Increasing of temperature reduces duration of dissolution of CMC and viscosity of the gels. Modification by ascorbic acid significantly reduces viscosity and pH of gels, while addition of glycerol does not affect the stability but increases susceptibility of these solutions to contamination. Storage of obtained solutions for three months under normal conditions at room temperature leads to syneresis and total loss of initial consistency. The gels modified by ascorbic acid are shown to be the least stable. Graphic dependences of these processes are obtained and functions are calculated on the basis of experimental research with the use of mathematical modeling methods. The obtained models will allow to predict physical and chemical properties of gels in order to define the necessary parameters of preparation at the stage of development.

Keywords: gels; syneresis; thixotropy; modifiers; carboxymethylcellulose; viscosity.

Abbreviations: CMC – carboxymethylcellulose.

Résumé

Étude des indicateurs physiques et chimiques des milieux colloïdes à base de carboxyméthylcellulose pour médicaments

Introduction. Le papier examine les particularités physico-chimiques de la préparation et de vieillissement de la carboxyméthylcellulose (CMC) colloidale de préparations pharmaceutiques, qui devraient être utilisés pour le traitement des brûlures. Des études ont été menées au laboratoire central de recherche de l'université de médecine nationale de Kharkov en 2019.

Les objectifs de l’étude. La possibilité d'utiliser des solutions de CMC et leurs analogues modifiés pour la création de préparations pharmaceutiques à base de gel a été étudiée.

Méthodes. Des études expérimentales ont été menées dans des conditions de laboratoire en utilisant un équipement de détermination de la viscosité et du pH.

Résultats. L'influence de la concentration, de la température et de l'acidité sur la viscosité des colloïdes est étudiée. Il a été déterminé comment la stabilité des gels change en fonction de leur temps de stockage. La stabilité de ces solutions et leur aptitude à la synérèse sont déterminées. L'influence de l'addition de modificateurs, de glycérine et d'acide ascorbique, sur la consistance, l'acidité, la résistance à la contamination et la durée de conservation de ces gels est déterminée.

Conclusions. Il est démontré que les solutions préparées sans additifs ont la plus haute viscosité. Des études ont montré que les solutions préparées sans additifs présentent la viscosité la plus élevée. Ils présentent également la plus grande stabilité. Il est montré que l'augmentation de la température réduit la durée de dissolution du CMC et la viscosité des gels. La modification avec l'acide ascorbique réduit considérablement la viscosité des gels et leur pH. L'ajout de glycérine n'affecte pas la stabilité, mais rend ces solutions instables à la contamination. Le stockage des solutions pendant trois mois dans des conditions normales à la température ambiante entraîne une synérèse et une perte totale de consistance initiale. Les moins stables étaient les gels auxquels on a ajouté de l'acide ascorbique. Sur la base de recherches expérimentales et en utilisant les méthodes de modélisation mathématique, des dépendances graphiques et des fonctions calculées de ces processus sont obtenues. Les modèles obtenus permettront de prévoir les propriétés physiques et chimiques des gels afin de déterminer les paramètres technologiques au stade de la conception.

Mots clés: gels; synérèse; thixotropie; modificateurs; carboxyméthylcellulose; viscosité.

Introduction

Recently, intensive studies of new drugs with improved properties are very actual in the field of pharmacology. However, there is still a problem with the choice of material which can be used as a carrier for therapeutic drugs at all stages of the inflammatory process [1]. Extremely promising option is the design of coatings based on natural polymeric substances [2 – 6].

Nowadays, colloidal solutions of carboxymethylcellulose (CMC) and its sodium salt are becoming very popular as ointment bases. They are non-toxic, capable of dissolving in water and other polar solvents, resistant to light, temperature, and stable in respect with biological contamination [7, 8]. Moreover, CMC-based ointments have high osmotic effect, which helps in wounds cleansing by adsorption of their contents and sloughing [9]. Gel ointment bases prepared with CMC are surface active, which leads to such positive effects as cooling the skin and reducing itching [10]. They can be used in case of acute inflammation due to the drying effect [11]. These gels are especially useful when fat-based ointments cannot be applied, and they are also preferable for mucous membranes [12, 13].

Preparation of CMC gels is based on the inexpensive raw materials of cotton production, which makes them cost effective [14, 15]. Carboxymethylcellulose is non-allergenic and does not provoke skin reactions. However, the formulation of gel-based drugs is rather problematic as there are some important properties which must be strictly maintained. These are: biological availability, completeness of active substance release, and stability of the dispersed system [16]. Finding the ways to provide desired levels of concerned characteristics will lead not only to the creation of effective medicinal product but also to extension of its term of storage.

Nowadays, the multicomponent compositions with additives are of particular importance [17]. Additives can increase solubility, viscosity of solutions, and biological availability of substances, which will allow formulation of new medicines with a minimal content of active substances and excipients, and greater therapeutic efficacy, as well as will allow optimization of some technological processes [18, 19]. Thus, the concerned investigations can be very perspective.

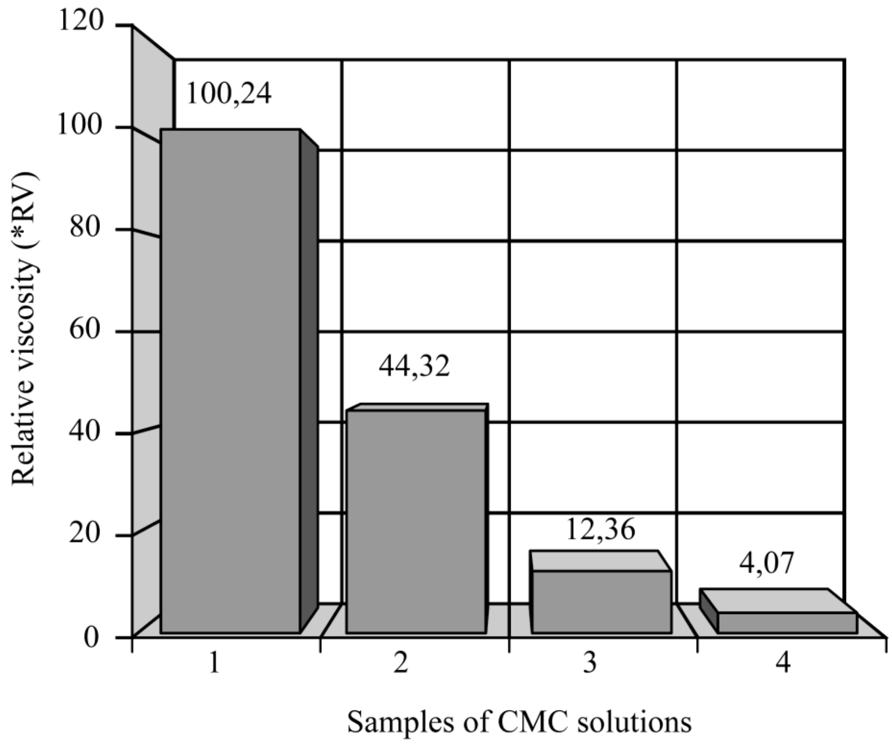
Objectives

The purpose of this work was to study physico-chemical properties of carboxymethylcellulose colloidal solutions prepared from pure CMC (the manufacturer "Ester MT", Ukraine), and with added modifiers - glycerol and ascorbic acid. Taking into consideration that this gel is intended to be used as a carrier for the treatment of burn injuries, the studies were conducted based on the requirements inherent to the bases of medicinal products, namely: the substance should be spreadable, that is, it should possess necessary consistency properties such as viscosity, plasticity, fluidity, thixotropy, etc., it should be able to absorb medicinal substances; it should remain unchanged under the influence of external factors such as light, air, temperature, to be chemically inert, and pharmacologically indifferent. It should not have irritating and sensitizing action, should maintain the normal pH of the skin and mucous membranes. It should be resistant to contamination, water rinsable, should not be too sticky. The properties of the carrier should be consistent with the purpose of the drug, quickly dry and tightly adhere to the surface of the skin, the base of topical ointments should not be absorbable [20].

Material and methods

One of the fundamental factors influencing the structure of the colloidal solution is its viscosity, which, in turn, depends on a number of technological parameters, whose changing determines the final properties of the resulting hydrogel [21]. Determination of relative viscosity was carried out using the viscometer VBR-1 by timing the flow of the solution from a hole with a 5 mm diameter. This technique is simple and allows to obtain relative viscosity parameters by determining the ratio of duration of gel flow to the duration of flow of the same amount of distilled water. The research was carried out using colloidal solutions of pure carboxymethylcellulose and solutions with addition of glycerol, ascorbic acid and their mixture. The initial concentration of CMC was 3%.

The studies were conducted under laboratory conditions at room temperature. The results are shown in Figure 1.



1 – 3% CMC; 2 – 3% CMC + 1% glycerol;

3 – 3% CMC + 1% ascorbic acid;

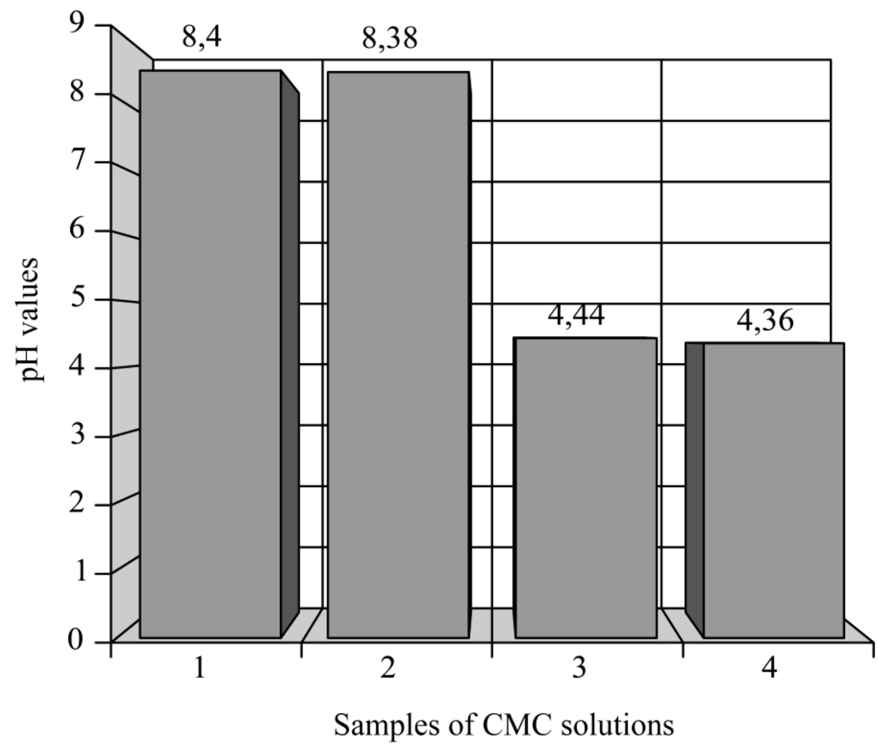
4 – 3% CMC + 1% ascorbic acid + 1% glycerol

Fig. 1. Dependence of relative viscosity on the composition of solution

The diagram shows the highest relative viscosity of 3% CMC water solution. Added glycerol reduces the relative viscosity more than two-fold. Solutions modified by ascorbic acid have even lesser viscosity. Simultaneous addition of ascorbic acid and glycerol makes the solution extremely liquid and unsuitable for use as a base for ointments.

It is known [22, 23] that the structural viscosity of gels increases proportionally to the increasing concentration, molecular mass, nature of substance, and pH of the medium, therefore the next step was to study the influence of these parameters on the physical and chemical properties of gel. The physical and chemical properties of the gel were studied, namely, the qualitative characteristics: appearance, color, smell, pH, temperature and aggregative stability under long storage.

The pH values were determined by means of pH meter "Eutech-510". Figure 2 shows the dependence of pH of obtained solutions on the nature of modifier.



1 – 3% CMC; 2 – 3% CMC + 1% glycerol;

3 – 3% CMC + 1% ascorbic acid;

4 – 3% CMC + 1% ascorbic acid + 1% glycerol

Fig. 2 Dependence of pH on the composition of solution

The samples prepared from pure CMC or modified with glycerol are shown to have slightly basic medium. They have almost identical pH value which is about 8.40. Added ascorbic acid causes a sharp decrease in pH almost two-fold. Solutions modified by ascorbic acid and its glycerol mixture also have almost identical pH which is slightly acidic and ranges from 4.44 in the solution containing ascorbic acid to 4.36 in the solution containing mixture of ascorbic acid with glycerol. This means that ascorbic acid has the greatest influence on the acidity of the medium, whereas the influence of CMC and glycerol is insignificant.

It is known that the dissolution of CMC directly depends on the temperature of the solvent, therefore the next step of the research was to study dependence of the gel viscosity on water temperature, with the definition of the function of dissolution process using regression analysis. The research was carried out by means of a viscometer using unmodified 3% CMC solution, the temperature was simultaneously recorded by a thermometer. The results were processed by the Statgraphics Centurion statistical program. The results of experimental studies are shown in Table. 1, calculations of regression analysis are given in Figure 3.

The results of regression analysis show that viscosity of the CMC colloidal solution decreases with increasing temperature of the solvent, and the function of this process is quadratic. However, if the temperature range is insignificant, the classical interpolation methods may be used for determination of the gel viscosity.

The above-mentioned studies will help to optimize the temperature conditions for the CMC dissolution up to the formation of the gel with desired consistency.

Table 1. Dependence of the relative viscosity of the pure CMC gel on the temperature of the solvent (H_2O)

T_{CMC}, °C	Time of the gel flow, sec	Relative viscosity (*RV)
43	49,7	4,69
42	56,3	5,31
40	58,3	5,50
38	62,5	5,90
36	66,0	6,23
34	67,0	6,32
32	68,6	6,47
30	72,5	6,84
28	74,9	7,07
26	79,6	7,51

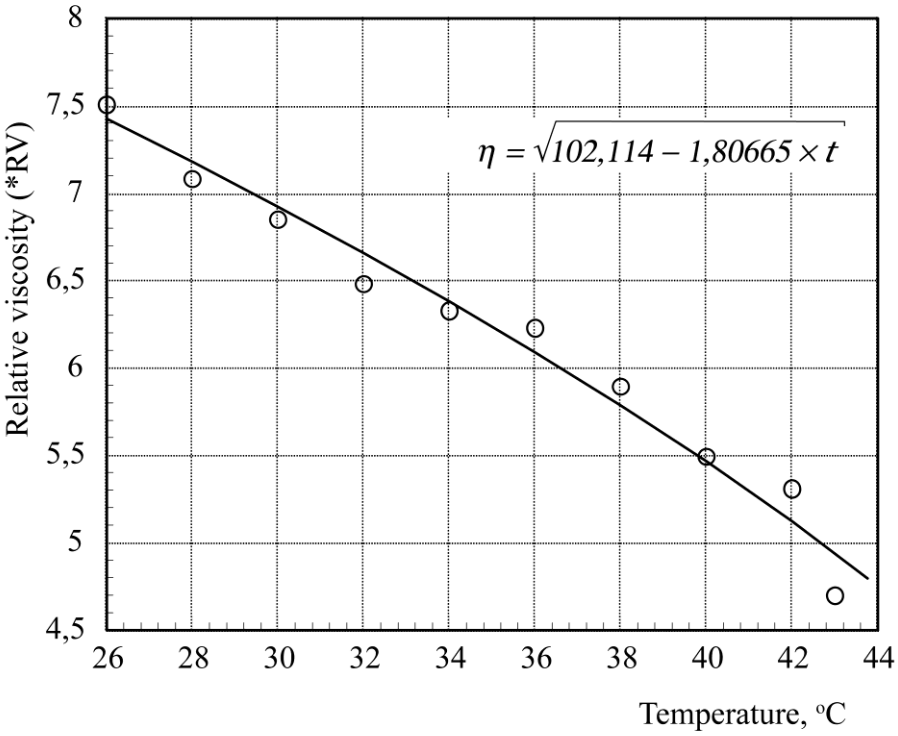


Fig. 3 Dependence of relative viscosity of CMC gel on solvent temperature. Results of regression analysis

Concentration of CMC solution is also an important characteristic for gel preparation[24]. It influences not only physical and chemical properties of the gel but also the ability of the solution to maintain its stability for the required time, therefore the next step was to study the influence of CMC concentration on the viscosity of the resulting gel. The dependence of the relative viscosity of the gel on the CMC concentration is given in Table 2.

Table 2. Dependence of the relative viscosity of unmodified gel on the CMC concentration (T = 18 °C)

$C_{(CMC)}$, %	Time of the gel flow, sec	Relative viscosity (*RV)
0,5	81,5	4,69
0,25	26,1	2,46
0,125	15,6	1,47
0,060	12,5	1,18

Determination of viscosity of concentrated solutions of polymers is rather complicated task. It is impossible to use viscometers for such gels because of their high viscosity, therefore such measurements require specific equipment, which is often not available in non-specialized laboratories. Determination of empirical dependencies of viscosity of diluted

CMC gels can be helpful in this respect. Such solutions are of liquid consistency, therefore, they are quite capable of passing through the viscometer opening but their practical application as ointment bases is doubtful because of unsatisfactory mechanical characteristics. Experimental data allow creating a regressive model which can be used for determination of the viscosity of more concentrated solutions. Figure 4 shows the graphical dependence of the gel viscosity on solution concentration and the mathematical model of this process.

The data presented in Fig. 4 show that increase in the concentration of dissolved CMC contributes to increase in the gel relative viscosity and this dependence is quadratic. The empirical function calculated by regression analysis enables to apply the usual mathematical methods for predicting the gels relative viscosity for different CMC concentrations when its direct measuring by means of a viscometer is impossible.

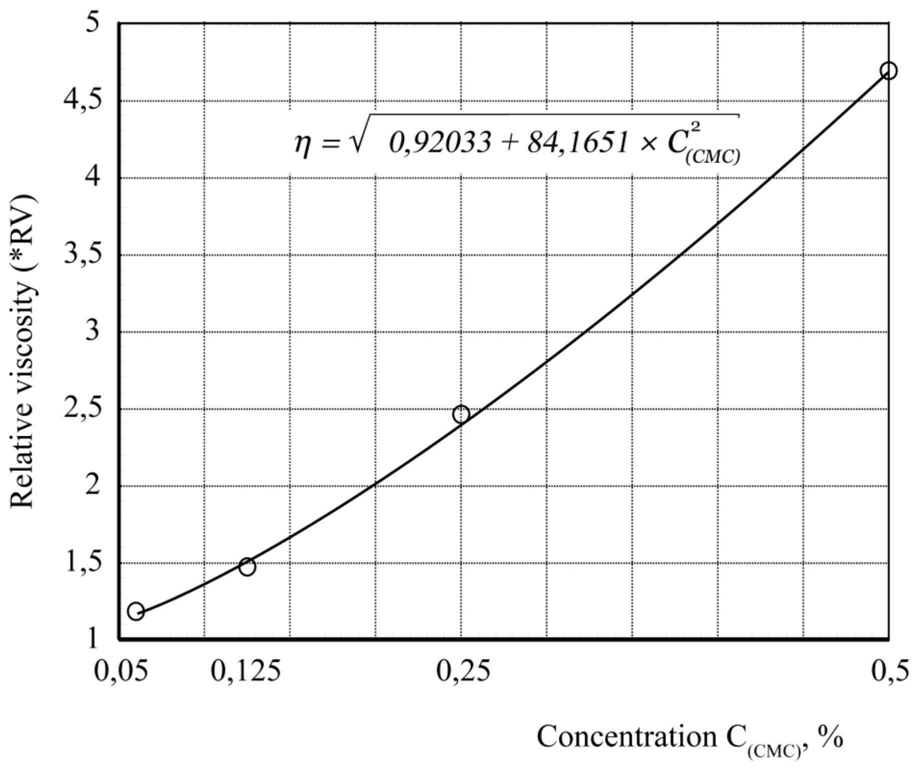


Fig. 4 Dependence of the gel relative viscosity on the concentration of CMC. Results of regression analysis

Stability of medicinal gels is one of the main features that characterize the feasibility of their use. Industrial production and application of unstable gels as commercial preparations which quickly lose their consistency do not make any sense[25]. Therefore, the next step of this scientific work is entirely devoted to determination of the stability of obtained colloids.

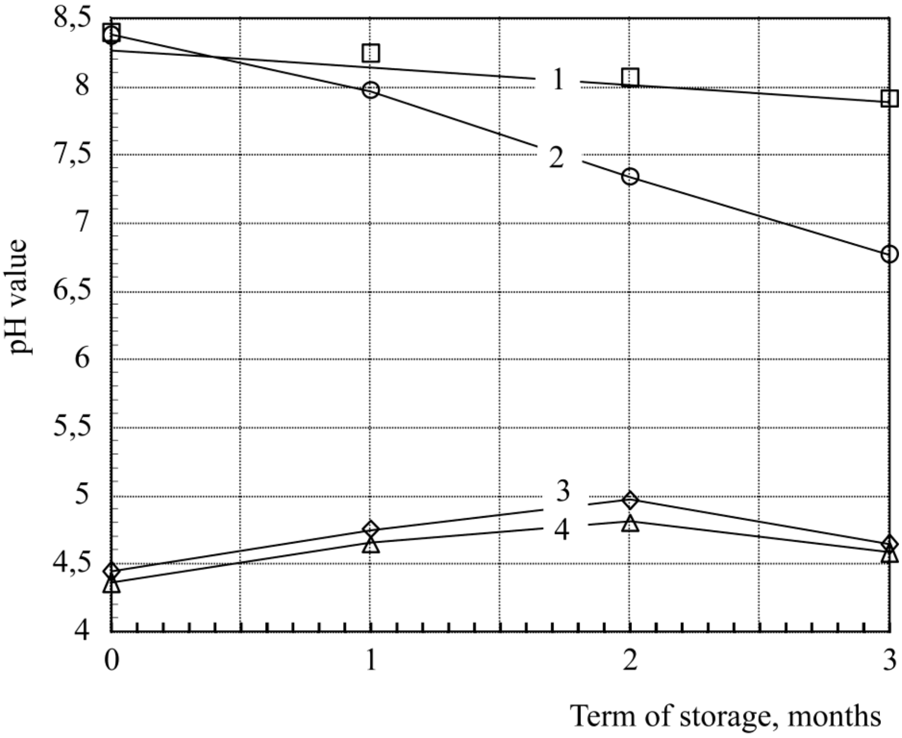
The main purpose of the following studies was to determine the stability of the preparation by the aging under normal conditions, with subsequent prediction of its term of storage. The evaluation of stability of samples was based on the following test parameters: appearance, pH and viscosity. The density of solutions was also determined but it appeared to be constant during all period of observation. The research was carried out until the significant changes in the above parameters began to be observed. The results of studies are shown in Table 3.

Table 3. Alterations of characteristics of gel samples depending on the term of storage

Term, months	CMC		CMC+glycerol		CMC+ascorbic acid		CMC+ascorbic acid+glycerol	
	pH	$\nu_{rel.}$ (*RV)	pH	$\nu_{rel.}$ (*RV)	pH	$\nu_{rel.}$ (*RV)	pH	$\nu_{rel.}$ (*RV)
Start	8,40	100,24	8,38	44,32	4,44	12,36	4,36	4,07
1	8,25	81,84	7,96	51,63	4,74	2,55	4,65	1,10
2	8,07	31,67	7,33	17,72	4,97	1,18	4,81	1,10
3	7,92	10,35	6,76	7,25	4,64	1,08	4,58	1,06
	Color and smell are not changed		Color is changed to yellow. Putrefactive smell appears		Color is changed to dark yellow. Mucus formation is observed. The smell remains the same		Color is changed to dark yellow. Mucus formation is observed. The smell remains the same	

The study of the gels appearance shows that the most stable was solution of pure unmodified CMC. During the whole period of aging (3 months) the external parameters of this gel were the same. Addition of glycerol resulted in color change to pale yellow and solution began to emit putrefactive smell. Other solutions differed from the two previous ones in that they were prepared with the addition of ascorbic acid. Added ascorbic acid made the primary gels yellow but during the subsequent storage the color became darkened and turned into almost brown. Mucus appeared in the volume of solutions. The smell was the same.

Detailed studies of the pH levels during aging showed that the pH of unmodified CMC solutions and colloids with glycerol was evenly reduced (Figure 5). It is evident that decreasing of pH value in the second sample is more pronounced than in the unmodified sample. The pH of the first gel decreased by 5.7% but remained in the weakly basic medium, while pH of the modified gel decreased by 19.3% and shifted from weak alkaline medium to the slightly acidic one.



1 – 3% CMC; 2 – 3% CMC + 1% glycerol; 3 – 3% CMC + 1% ascorbic acid;
4 – 3% CMC + 1% ascorbic acid + 1% glycerol

Fig. 5 Dependence of pH value on the term of gels storage

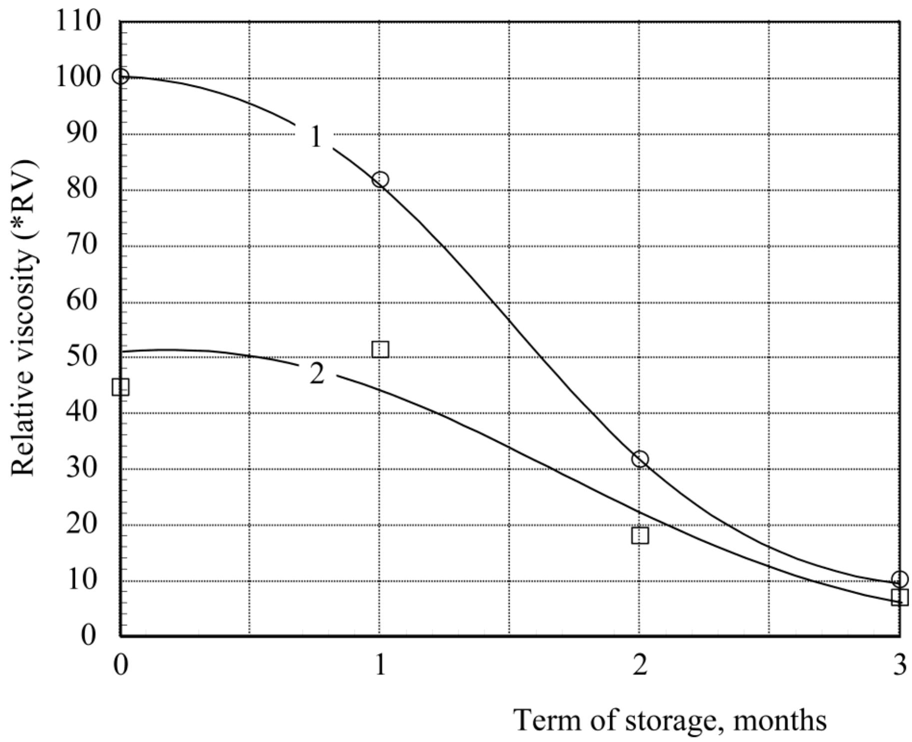
Solutions modified with ascorbic acid and its mixture with glycerol demonstrated another type of dependency. In this case, the pH value increases for two months, and then reduces. The pH changes for these two samples are linear and almost the same: over two months there is an even increasing of pH followed by an even decreasing. However, the pH variations in these solutions are insignificant and do not exceed 0.5 units. This proves that such gels can stably maintain pH within weakly acidic medium. Functions describing the change in pH of gels depending on the time of storage are given in Table 4.

The functions in the table are linear which means an even change in the gels acidity.

The next step in determination of the obtained colloids stability was the study of changes in viscosity during aging. These studies can be considered as basic ones among all the tests because viscosity is the main characteristic that determines the quality of the gels. Analysis of data given in Table 3 shows that the tendency of viscosity changing of gels modified by ascorbic acid significantly differs from solutions prepared from CMC and glycerol, so the functions of these processes were considered separately. Figure 6 shows graphical dependencies of changing of relative viscosity (*RV) of gels obtained from pure CMC and modified with glycerol.

Table 4. Regression analysis of the functions of pH changing of gels during aging

Solution	Function	
CMC	*pH = 8,403 – 0,162×Mic* R^2*=99.86*	
CMC+Glycerol	*pH = 8,431 – 0,549×Mic* R^2*=99.39*	
CMC+Ascorbic acid	Before 2 months	*pH = 4,45167 + 0,265×Mic,* R^2*=99.42*
	After 2 months	*pH = 5,63 – 0,33×Mic*
CMC+Ascorbic acid+Glycerol	before 2 months	*pH = 4,38167 – 0,225×Mic* *R2=97.29*
	After 2 months	*pH = 5,27 – 0,23×Mic*



1 – 3% CMC; 2 – 3% CMC + 2% glycerol

Fig. 6 Dependence of relative viscosity of gels prepared without ascorbic acid on duration of storage

The curves indicate that aging of gels prepared without ascorbic acid proceeds slowly during the first month. Viscosity decreases insignificantly and in the sample modified with glycerol even slightly increases. Then, until the second month there is a sharp decrease in viscosity 2,5-3-fold from initial values followed by slow decreasing. A general view of the functions of this process can be represented as sigmoidal relationships which result in asymptote. Regression analysis showed that both dependencies were exponents which can be described in detail by the following models:

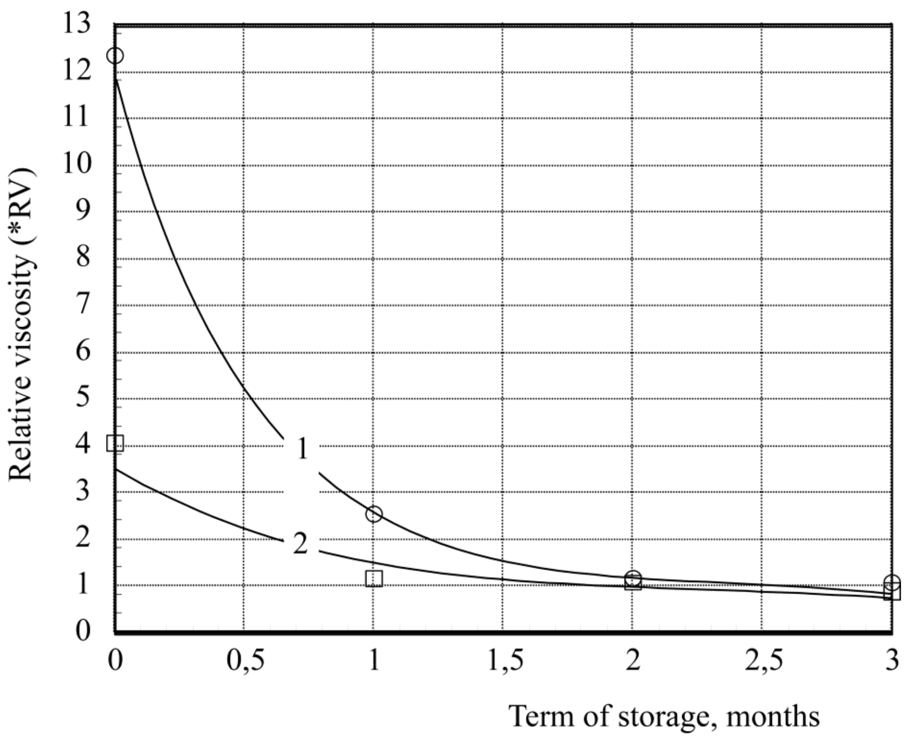
For CMC gel: $\eta = e^{4,59812-0,256271 \cdot \tau^2}$ R^2= 99.38%

For CMC+Glycerol gel: $\eta = e^{3,91905-0,220356 \cdot \tau^2}$ R^2= 95.77%

where: η – relative viscosity (*RV)

τ – term of storage, months

Samples modified by ascorbic acid show different specificity of aging. Graphic interpretation is given in Figure 7.



1 – 3% CMC + 1% ascorbic acid;

2 – 3% CMC + 1% ascorbic acid + 2% glycerol

Fig. 7 Dependence of relative viscosity of gels modified by ascorbic acid on the term of storage

Graphic dependencies show that solutions modified by ascorbic acid have low initial viscosity, almost 10 times lower than that of unmodified gels. They are also subjected to a sharp decrease in viscosity during rather short term of storage. Viscosity of such solutions reduces 1.5-2.5 times in two weeks, and after 2 months it becomes equal to the viscosity of distilled water. Mathematically these functions can be described by the following models:

For CMC gel: $\eta = e^{2,4607-1,48321\sqrt{\tau}}$ R^2= 97.96%

For CMC+Glycerol gel: $\eta = e^{1,25471-0,811889\sqrt{\tau}}$ R^2= 85.71%

Results

The following conclusions can be drawn based on the research carried out.

The most stable solutions are those prepared from pure CMC without any additives. They have an initial viscosity that meets the requirements for pharmaceuticals and keep their properties for a month. Addition of glycerol to the given solution almost does not change its pH, however, reduces the initial viscosity and contributes to the reduction of stability. In addition, as shown by the tests, the solution modified by glycerol is more susceptible to contamination. Addition of ascorbic acid shifts the pH into acidic medium, which results in a sharp decrease in the initial viscosity and acceleration of the syneresis process. Attempts to adjust the stability of such solutions by addition of glycerol were not successful.

Conclusions.

Thus, the solutions studied lose their consistency by changing physico-chemical properties during three months of storage under normal conditions.

Based on the tests carried out, the following conclusions can be made: the term of storage is not enough for design of commercial medicines, and the given technology cannot be offered for manufacturing on an industrial scale. However, the developed technique is quite acceptable for use in specialized medical facilities for the creation of products that can be used without long-term storage under normal conditions for the treatment of burn wounds.

Thus, research in this area is rather promising for finding new modifiers for the design of gels concerned, and the results obtained are of great interest.

Compliance with Ethics Requirements:

«The authors declare no conflict of interest regarding this article»

«The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law.»

«All institutional and national guidelines for the care and use of laboratory animals were followed»

«No funding for this study»

References

1. Wnek GE, Bowlin GL, Encyclopedia of Biomaterials and Biomedical Engineering, vol. 1. New York, Marcel Dekker, 2008: 448.

2. Chandra WP, Sharma P. Chitosan and alginate wound dressings: a short review. *Trends Biomater. Artif. Organs*. 2004; 18(1): 18–23.

3. Chiu T, Burd A. «Xenograft» dressing in the treatment of burns. *Clin Dermatol*. 2005; 23(4): 419–423.

4. Harish Prashanth KV, Tharanathan RN. Chitin/chitosan: modifications and their unlimited application potential-an overview. *Trends in Food Science&Technology*. 2007; 18: 117–131

5. Haytmetova SB, Shomurotov ShA, Turaev AS. Sintez i izuchenie svoystv polimernyih kompleksov etatsizina s karboksimetiltsellyulozoy. *Himiya rastitelnogo syirya*. 2017; 4: 23–30. (in Russian).

6. Kulish EI, Chernova VV, Vildanova RF, Volodina VP, Kolesov S.V. O prichine fermentativnogo gidroliza hitozana pod deystviem nekotoryih nespetsificheskih fermentov. *Vestnik Bashkirskogo universiteta*. 2011; 3(16): 681–683. (in Russian).

7. Ogay MA, Stepanova EF, Dzyuba VF, Morozova EV. Ispolzovanie polimernyih osnov v mazyah dlya lecheniya i profilaktiki patologii «Diabeticheskaya stopa». *Nauchnyie vedomosti BelGU*, Seriya Meditsina. Farmatsiya. 2010; 22 (93): 5-9. (in Russian).

8. Kulikowska A, Wasiak I, Ciach T. Synthesis of carboxymethylcellulose nanoparticles using various coiling agents. Prosimy cytować jako: *Inż. Ap. Chem*. 2014; 53(4): 268–269.

9. Rahman AuR, Anjum S, Frontiers in Stem Cell and Regenerative Medicine Research, vol. 8. Bentham Science Publishers – Sharjah, UAE, 2018: 178.

10. Harsha Kharkwal, Kumud Bala, Deepshikha Pande Katare. Biodegradable Polymers, Role in Enhancing Bioavailability of Drug. *Asian Journal of Biomedical and Pharmaceutical Sciences*. 2011; 1 (5): 1–11.

11. Vinklárková L, Masteiková R, Vetchý D, Doležel P, Jurga Bernatonié J. Formulation of Novel Layered Sodium Carboxymethylcellulose Film Wound Dressings with Ibuprofen for Alleviating Wound Pain. *BioMed Research International*. 2015; 1–11.

12. Tanaka A, Furubayashi T, Matsushita A, et al. Nasal Absorption of Macromolecules from Powder Formulations and Effects of Sodium Carboxymethyl Cellulose on Their Absorption. *PLOS ONE*. 2016; 6: 2–11.

13. Popa V, Volf I, Biomass as Renewable Raw Material to Obtain Bioproducts of High-Tech Value, Elsevier, 2018: 401.

14. Ibrahim H Mondal. Carboxymethyl Cellulose: Synthesis and Characterization, Volume I. New York, Nova Science Publishers, Inc., 2019: 84.

15. Niekraszewicz A. Chitosan medical dressings. *Fibres &Textiles in Eastern Europe*. 2005; 6(54): 16–18.

16. Kamel S, Ali N, Jahangir K. , Shah SM, El-Gendy AA. Pharmaceutical significance of cellulose: A review. *eXPRESS Polymer Letters*. 2008; 2 (11): 758–778.

17. Mali KK, Dhawale SC, Dias RJ, Dhane NS, Ghorpade VS. Citric Acid Crosslinked Carboxymethyl Cellulose-based Composite Hydrogel Films for Drug Delivery. *Indian Journal of Pharmaceutical Sciences*. 2018; July-August: 657–667.

18. Zhilyakova ET, Popov NN, Novikova MYu, Novikov OO, Fadeeva DA. Izuchenie fiziko-himicheskih i tehnologicheskih harakteristik kombinirovannogo prolongatora natriy karboksimetiltsellyulozyi i polivinilovogo spirta s tselyu sozdaniya prolongirovannyih lekarstvennyih form s zhidkoy dispersionnoy sredoy. *Nauchnyie vedomosti*. Seriya Meditsina. Farmatsiya. 2011; 22 (117): 69-79. (in Russian).

19. Bishop SM, Walker M, Rogers AA. et al. Importance of moisture balance at the wound-dressing interface. *J. Wound Care*. 2003; 12(4): 125–128.

20. Leszek AD, Biomaterials in Regenerative Medicine, Books on Demand, 2018: 290.

21. Ghorpade V, Mali K, Dias R, Karande P. Carbopol and Sodium Carboxymethylcellulose Based Methylsulfonylmethane Gels for Treatment of Osteoarthritis: In-vitro and In-vivo Evaluation. *Ind J Pharm Edu Res*. 2012; 46(3): 235–242.

22. Morozova RF, Spatlova LV. Izuchenie strukturnoy vyazkosti gelya na primere lekarstvennogo preparata «Geparin». *Innovatsionnaya nauka*. 2018; 5, 38-41. (in Russian).

23. Mahdavinia G, Afzali A, Etemadi H, Hosseinzadeh H. Magnetic/pH-sensitive nanocomposite hydrogel based carboxymethyl cellulose-g-polyacrylamide/montmorillonite for colon targeted drug deliver. *Nanomed Res J*. 2017; 2(2): 111–122.

24. Ornanong S. Kittipongpatana, Siriporn Burapadaja, Nisit Kittipongpatana. Development of Pharmaceutical Gel Base Containing Sodium Carboxymethyl Mungbean Starch. CMU. *J. Nat. Sci*. 2008; 7(1): 23–32.

25. Sannino A, Demitri C, Madaghiele M, Biodegradable Cellulose-based Hydrogels: Design and Applications. *Materials*. 2009; 2: 353–373.