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Article

Hemostatic Nanobiocomposite Based on the Base Cellulose Derivatives

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Abstract: A method has been developed for producing a composite biodegradable hemostatic agent in the form of films based on sodium H carboxymethylcellulose (Na-H-CMC), oxycellulose (OC), nanocellulose (NC) and chemically bound calcium ions. The contents of the components in the hemostatic agent, in terms of dry matter, were 55% for Na-H-CMC 30% for OC, 4% for NC and 11% for calcium chloride. Biodegradable films 100 μm thick were obtained; their hemostatic time was 34 ± 2 s. Studies were carried out to determine acute and chronic toxicity and hematological and biochemical parameters of the blood of experimental animals. Based on these research results, the possibility of using hemostatic compositions in practical medicine has been established.

Keywords: oxycellulose, nanocellulose, sodium H carboxymethylcellulose, composite, hemostatic agent, IR spectroscopy, carboxymethyl and carboxylate functional groups.

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1. Introduction

Recently, interest in new hemostatic agents based on natural polymers and their derivatives has increased worldwide. This is because most natural polymers and their derivatives are organotropic, nontoxic, biodegradable compounds with hemostatic properties and are most often classified according to their mechanism of action [1]. When creating new hemostatic agents, polysaccharide cellulose and its derivatives, alginate, starch, amylopectin, protein polymers such as collagen, gelatin, aminopolysaccharides such as chitin, chitosan and its derivatives are of interest [2].

When creating hemostatic agents, a special place is given to cellulose and its derivatives due to their inert behavior, organotropy, low toxicity and biodegradability. By chemically modifying cellulose, particularly by including carboxyl and carboxymethyl groups in the macromolecule, it is possible to impart biodegradable and hemostatic properties. By chemically modifying cellulose, particularly by including carboxylate and carboxymethyl groups in the macromolecule, it is possible to impart biodegradable and hemostatic properties. After chemical modification cellulose can acquire its own biological activity and biodegradability, which allows it to be used as a medicinal material material without the addition of medicinal substances. For example, the cellulose derivative carboxymethylcellulose (CMC), which contains carboxymethyl functional groups, is capable of binding peptides in the wound environment and can suppress their activity [2, 3]. The high bioinertness and organotropy of CMC allow it to be used as a barrier agent for the prevention of abdominal adhesions in the postoperative period [4]. It has a stimulating effect on abstraction processes, accelerates the formation of granulation tissue, and actively influences the processes of fibrillogenesis. Na-CMC swells, forming transparent gels; after the gel dries, mucoadhesive films are formed that are used for hemostasis. The use of monocarboxylcellulose as a hemostatic drug is well known. OC absorbs blood and promotes the formation of a platelet and, subsequently, a fibrin clot [5].

One of the most widely used cellulose-based hemostatic drugs in surgical practice is monocarboxylcellulose. Monocarboxylcellulose is produced by the oxidation of native cellulose with nitrogen oxides, sodium hypochlorite or hydrogen peroxide. Currently, hemostatic agents made from oxidized cellulose (OC) are known and available under various trade names: "GelitaCel" in the form of powder, gauze and fiber; "Okcel" in the form of fabric of various weaves; "Trauma stem" in the form of powder and gauze; and "Okcel and Surgicel" in the form of fabric of various weaves, fibrous material and nonwoven fabric and "GuraCel" in the form of fiber [6]. These OC-based hemostatic agents are used in cardiovascular surgery, general surgery, traumatology, neurosurgery, and ENT surgery to stop capillary, venous, and even minor arterial bleeding.

OC acts on the wound as a caustic substance due to its acidity, introducing it into the hemostasis mechanism as a component of blood clot formation.

The low pH of oxidized cellulose causes lysis of red blood cells. In this case, hemoglobin released from erythrocytes reacts with oxidized cellulose to form hematin, and the average time to stop bleeding is 2-4 minutes [7,8].

Despite the fairly wide selection of local hemostatic implants, the search for and development of new products in this group remain relevant. This is due to the biological incompatibility of the components of hemostatic implants with surrounding tissues, their antigenic effect on the body, and their low efficiency in cases of blood clotting disorders.

Thus, new hemostatic agents must meet the following requirements:

- high efficiency in stopping capillary and parenchymal bleeding within up to 2 minutes;
- high adhesiveness;
- preventing resumption of bleeding;
- biocompatibility (no irritating effect);
- lack of systemic effect on hemostasis;
- lack of toxicity;
- biodegradation within a specified time frame;
- possibility of sterilization using known methods;
- low cost;
- manufacturability;
- ease of use;

Currently, a number of hemostatic agents based on natural polymers, such as cellulose, cellulose derivatives, oxidized cellulose, gelatin, and collagen, are known [9-12]. However, these hemostatic agents do not fully meet the above requirements. Despite the availability of a large number of hemostatic agents, there is still no universal drug that meets the requirements of practical surgeons. This is probably due to the wide range of applications since various clinical situations require hemostatic agents with specific properties. According to this urgent task of chemists and physicians new highly effective, safe and biodegradable agents that ensure reliable hemostasis are needed [13,14].

The goal of this research was to create a new biodegradable composite film with mucoadhesive properties and high hemostatic properties.

2. Materials and Methods

Samples of OC, Na-H-CMC based on hemostatic composite films were studied using physicochemical methods: infrared spectroscopy, conductometric titration and determination of the thickness. The structure of the sample was determined using an Inventio-S IR spectrophotometer (Bruker, Germany) from 500 sm-1 to 4000 sm-1 [15]. The amount of carboxyl, carboxymethyl, and carboxylate groups formed in OC, Na-H-CMC, and based on hemostatic composite film was determined by conductometric titration using a Mettler Toledo benchtop pH conductometer [16]. The thickness of hemostatic composite films was determined using an MK-75 micrometer [17].

The following research objects were selected: Na-CMC, oxidized cellulose, nanocellulose, and calcium chloride as cross-linking agents with hemostatic properties [18].

3. Results

The CMC of a hemostatic biodegradable film should function as a hemostatic agent with mucoadhesive properties.

In CMC macromolecules, hemostatic properties increase due to the content of carboxylate groups, and mucoadhesive properties increase due to the content of carboxymethylate groups.

The hemostatic properties of CMC macromolecules increase due to the presence of carboxymethyl groups, and the mucoadhesive properties increase due to the presence of carboxylate groups. To determine the optimal ratio of carboxymethyl and carboxylate functional groups in the macromolecule, changes in the content of carboxymethyl functional groups were studied depending on the degree of substitution of Na-CMC.

Table 1 presents the calculated values of changes in the content of Na-carboxymethylate and carboxylate anion groups depending on the degree of substitution of the original Na-CMC.

Table 1

Changes in the calculated values of the content of carboxymethylate and carboxylate anionic functional groups depending on the degree of substitution of Na-CMC

№	Na-CMC		Average molecular weight of an elemental unit of Na-CMC	Content of H-carboxymethyl groups, %	Content of Na-carboxylate groups, %	Solubility in water, %
	Degree of substitution	Degree of polymerization				
1	1,0	560	242	33,4	27,7	100,0
2	0,85	640	230	27,7	24,8	100,0
3	0,70	710	218	24,1	21,5	96,3
4	0,65	830	214	22,8	20,3	92,6

As shown in Table 1, the selected samples of Na-CMC, purified from accompanying mineral and organic impurities, are soluble in water, and a decrease in their DSs monotonically decreases the calculated values of the content of carboxymethyl and carboxymethylate functional groups that provide mucoadhesive properties.

Next, studies were carried out on the changes in carboxyl functional groups depending on the degree of substitution of H-CMC.

Samples of H-CMC with various DSs and DP were obtained on the basis of Na-CMC by treating them in an aqueous solution of 20% average acid at a modulus of 1:10 at a temperature of 35°C for 120 minutes. In this case, H-CMC samples that are insoluble in water are formed from Na-CMC. The resulting H-CMC samples were washed with water until the reaction to sulfate ions was negative and dried at a temperature of 60°C.

Table 2 presents the calculated values of changes in the content of H-carboxymethyl and Na-carboxylate groups depending on the degree of substitution of the original CMC.

Table 2

Changes in the calculated values of the content of H-carboxymethylate and Na-carboxylate functional groups depending on the degree of H-CMC substitution

№	H-CMC		Average molecular weight of an elemental unit of H-CMC	Content of H-carboxymethyl groups, %	Content of Na-carboxylate groups, %	Solubility in water, %
	Degree of substitution	Degree of polymerization				
1	1,0	510	220,0	26,8	20,4	99,3
2	0,85	600	211,3	27,9	21,3	98,5
3	0,70	580	202,6	29,1	22,1	96,4
4	0,65	790	199,7	29,6	22,5	95,4

As shown in Table 2, the obtained H-CMC samples are insoluble in water and by decreasing their DS values, the calculated values of the content of carboxymethyl and carboxylate functional groups, which provide their mucoadhesive and hemostatic properties, increase.

Next, to create a composite biodegradable film that is soluble in water and expected to have high hemostatic properties, Na-H-CMC carboxymethylcellulose, which was obtained through acid titration of 2% solutions of Na-CMC with different DSs and calculated amounts of 1.0 M hydrochloric acid solution, was selected. The resulting solutions were precipitated with acetone. The precipitate was washed with alcohol until the reaction for chlorine ions was negative and then was dried at 75°C.

Table 3 presents the DSs and DP values of the water-soluble Na-H-CMC samples containing various amounts of carboxymethyl and carboxyl functional groups.

Table 3

Changes in the content of carboxymethylate and carboxyl functional groups in Na-H-CMC with various degrees of substitution

№	Na-H- CMC		Average molecular weight of an elemental unit of Na-H-CMC	Content of carboxymethyl groups, %	Content of carboxylate groups, %	Solubility in water, %
	Degree of substitution	Degree of polymerization				
1	1,0	530	228,8	25,7	19,7	100
2	0,85	620	218,7	26,9	20,6	100
3	0,70	670	208,8	28,3	21,6	96,1
4	0,65	800	205,4	28,7	22,0	94,5

As shown in Table 3, Na-H-CMC with DSs = 0.85 and DP = 620 and a ratio of carboxymethylate to carboxylate functional groups of 40:60 is completely soluble in water can provide the necessary mucoadhesive properties and contains 26.9% carboxymethyl groups in terms of the 20.6% carboxylate groups providing hemostatic properties.

The content of carboxyl groups in oxidized cellulose was 23.4% which is greater than its theoretical value of 25.56%.

When creating a biodegradable composite hemostatic film, nanocellulose was chosen according to a previously reported method [19], where the content of carboxyl groups was 2.0%.

The next component in the structure of the biodegradable hemostatic composition was calcium ions, which act as cross-linking agents and simultaneously help to increase the hemostatic properties of the hemostatic composition [13].

Furthermore, by changing the content of the components, the optimal ratios of Na-H-CMC, oxycellulose, nanocellulose and calcium chloride in the structure of a biodegradable composite hemostatic film with high hemostatic and mucoadhesive properties were determined.

Subsequently, the following optimal composition of the hemostatic film in weight percent was established: Na-H-CMC – 55%; oxycellulose – 30%; nanocellulose – 4%; and calcium chloride – 11%. By sequentially dissolving the components of the hemostatic mixture in water at the above weight ratios, a 2% solution with a pH = 6,4 was obtained.

The composite solution was poured into 56:84 and 140 ml glass or chrome-plated trays measuring 20x14 cm and dried for 72 hours at a temperature of 33±3°C. The thicknesses of the hemostatic films were 40:60 and 100 microns.

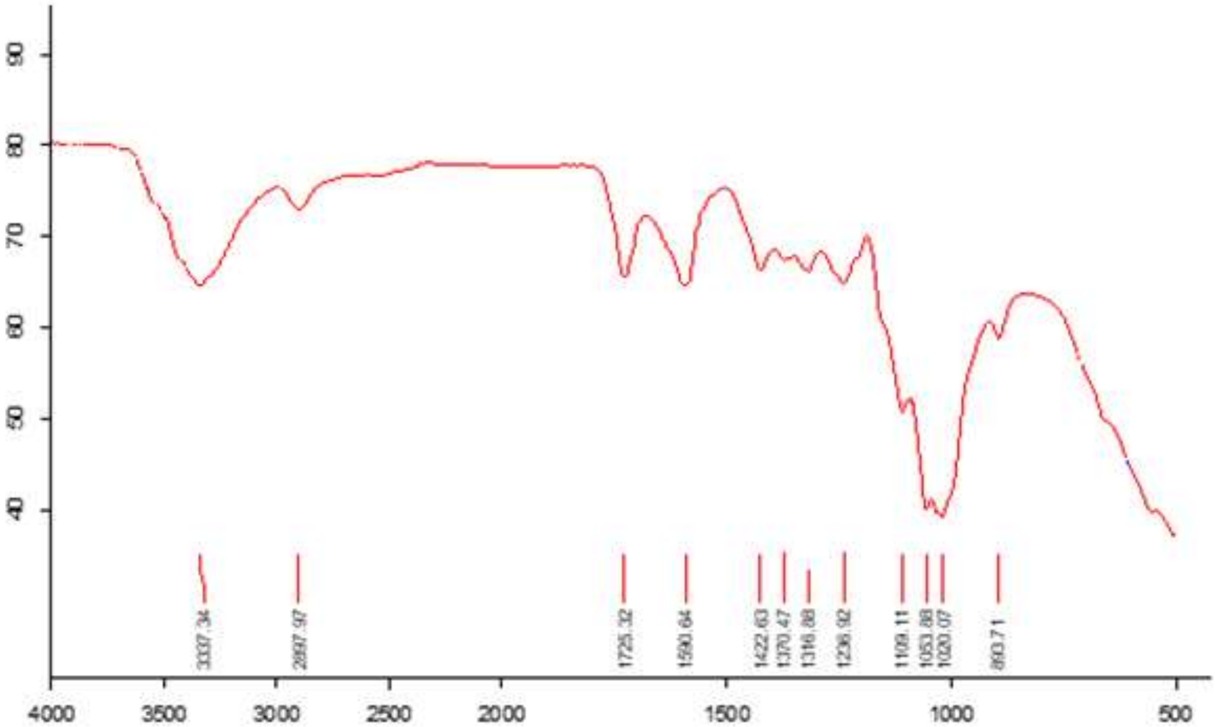

Figure 1 shows the IR spectra of thecomposite hemostatic films.

As shown in Figure 1, in the IR spectra of hemostatic agents obtained on the basis of cellulose and calcium chloride derivatives, the intensity of the peaks is in the region of the carboxyl group (–COOH) at 1725 sm-1, and the absorption regions of the carboxylate group (–COONa) are observed at 1590 sm-1.

In this case, the carboxylate group (–COOH) moves from 1740 sm-1 to 1725 sm-1, and the carboxylate group (–COONa) moves from 1600 sm-1 to 1590 sm-1, forming a bond with the calcium ion through chemical bonds. It is also clear from the IR spectrum that the intensity of the peak in the region of 1725 sm-1, belonging to –COOH, and the intensity of the peak in the region of 1590 sm-1, belonging to –COONa, show a ratio of 40:60.

4. Conclusion

For the first time, a method has been developed for producing biodegradable composite hemostatic films based on Na-H-CMC, OC, NC and calcium chloride in the form of biosoluble films.

Physicochemical and medical-biological tests of the composite hemostatic films were carried out and the possibility of their use in medical practice as biodegradable films was shown.

The hemostatic properties of the developed biodegradable film are superior to those of imported hemostatic agents obtained on the basis of polysaccharides and their derivatives.

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REFERENCES

1. Belova A.V., Yudanova T.N., Galbraikh L.S. Preparation of biologically active cellulose fibers modified by treatment with xybethene-cel. Chemistry of plant materials. 2010. №4. pp. 11–15.
2. Budko E. V., Chernikova D. A., Yampolsky L. M., Yatsyuk V. Ya. Local hemostatic agents and ways to improve them. Russian Medical and Biological Bulletin named after Academician I.P. Pavlova. 2019. V. 27. №2. pp. 274-285.
3. Treskova V. I., Shipina O. T., Romanova S. M., Nikitin V. G. Chemical modification of carboxymethylcellulose with diaminofurazan. Bulletin of the Technological University. 2016. V.19, №12 P. 172-175.
4. Sarymsakov A.A., Yunusov KhE. Preparation and properties of antistatic hydrogel "Aspike". Pharmaceutical journal. 2015. № 3. pp. 60-65.
5. Grigoriev I.A., Morozov S.V., Tkacheva N.I., Pankrushina N.A., Chernyavsky A.M., Tarkova A.R. A method for producing a hemostatic agent based on oxidized cellulose using microwave exposure. Published: 09/20/2015. Bull. № 26.
6. Lipatov V.A., Severinov D.A., Saakyan A.R. Local applicational blood reestablishing instruments in surgery of the XXI century (literary review). Innova. 2019;(1):16-22.
7. Tarkova A.R. The effectiveness of various forms of local hemostatic materials based on oxidized cellulose in the experiment “Bulletin of Surgery named after. I.I. Grekova." - 2015. -V. 174. - № 6. - P. 56-60.
8. Bicer A.S. Bayram, O. Gurbuz et al. Assessment of the efficacy of bioabsorbable oxidized regenerated cellulose for prevention of post-operative pericardial adhesion in the rabbit model. J. Int. Med. Res. - 2008. № 36. - P. 1311-1318.
9. Lipatov V.A., Lazarenko S.V., Severinov D.A., Saakyan A.R. Modeling of injuries in a study of the applicative of hemostatic sponge implants in the in vivo experiment. ENI Transbaikal Medical Bulletin, № 1/2019. pp. 155-166.
10. Gabay, M and Boucher B.A. An essential primer for understanding the role of topical hemostats, surgical sealants, and adhesives for maintaining hemostasis. Pharmacotherapy – 2013 – 33(9) – p 935-55.
11. Sharma J.B., Zangmo R., Kumar S., Roy K.K. Use of oxidized regenerated cellulose (Surgicel Nu-Knit) as a hemostat in laparoscopic endometriotic cystectomy: a case report. Int Reprod Contracept Obstet Gynecol. -2015 – 4(1) –P. 283-285.
12. Struszyk M. H., Wilbik - Halgas B., Miklas M., et al. Estimation of the performance stability of the newly developed topical hemostatic agents based on the chitosan/alginate fibrids. Text Res J – 2017 – 87 – P. 780-789.
13. Kholturaev B.Zh. dis. ... can. chem. Sci. Tashkent: Institute of Chemical Physics of the Academy of Sciences of the Republic of Uzbekistan, 2023.
14. Ismoilov B.A. Dis... can. honey. Sci. Tashkent: RNIMC, 2019.
15. Youngjun A., Jong H.J., Chul S.B., Young H.Y., Thriveni Th., Ji Whan A., and Choon H. / Synthesis and Non-Isothermal Crystallization Behaviors of Maleic Anhydride onto High Density Polethylene// Journal of the Korean Ceramic Society//Vol. 53, No. 1, pp. 24-33, 2016.
16.]. Han Ya, Yefei Zh, Ryo K, Stuart J. Preparation of cellulose nanofibers from Miscanthus x. Giganteus by ammonium persulfate oxidation. 2019. Pages 30-39.
17. Konduri, M. K. R., Koteswarareddy, G., Rohini Kumar, D. B., Venkata Reddy, B., & Lakshmi Narasu, M. (2011). Effect of pro-oxidants on biodegradation of polethylene (LDPE) by indigenous fungal isolate, Aspergillus oryzae. Journal of Applied Polymer Science, 120(6), 3536–3545.

18. Kholturaev B.Zh., Sarymsakov A.A., Atakhanov A.A. Biodegradable hemostatic agent “Geprocel”. “Pharmaceutical bulletin of Uzbekistan” № 1, 2021. P. 62-67.
19. Sarymsakov A.A., Kholturaev B., Yunusov KhE., Oksengendler B.L., Nurgaliev I.N., Letfullin R.R2. The Role of Electron Structure of Polymers at Their Biodegradation in Living Organisms. Drug Design Development and Delivery Journal. Volume: 3.1. C. 1-6.