STUDY OF NEW POLYMER FORMS OF INTERFERON INDUCTOR WITH ANTI-VIRAL ACTIVITY

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Abstract*. This article examines the possibility of obtaining a polymer form of new preparations of interferon inducers based on carboxymethylcellulose dialdehyde and gossypol. By chemically combining the dialdehyde of water-soluble carboxymethylcellulose with the natural polyphenol gossypol, water-soluble polymer derivatives of gossypol with interferon-inducing and antiviral properties were obtained.*

Water-soluble, purified Na-carboxymethylcellulose (Na-CMC) with a degree of polymerization DP=650±20 and a degree of substitution DS=0.85±3 were selected as research objects. The physico-chemical and medico-biological properties of a new antiviral drug against viral influenza and ARVI were studied. The optimal ratios of components were selected to obtain the polymer form of the antiviral drug.

Keywords*: interferon, influenza; antiviral activity, ARVI, carboxymethylcellulose.*

INTRODUCTION

One of the most common groups of viral diseases are respiratory diseases, which pose a danger primarily due to rapid transmission from person to person (mainly by airborne droplets). Viruses have many tools for changing their properties due to the high rate of reproduction, the speed of the mutation process and the diversity of emerging variants [1]. Because of this feature, there is a high risk of resistance to existing chemotherapy drugs, as well as the emergence of new, pandemic strains with increased virulence. To combat viral infections, both supportive treatment and etiotropic therapy aimed directly at the cause of the disease - the virus - are actively used [2]. One of the approaches that brings researchers closer to the search for such universal antiviral agents is the use of a promising class of antiviral substances - water-soluble polyelectrolytes, which make it possible to synthesize on their basis new polymers of a given molecular weight and architecture with a wide variation of functional groups, high molecular weight polyelectrolyte compounds that block binding of the virus to cell surface receptors. Due to the non-specificity of this mechanism of action, polyelectrolytes should prevent infection of cells by a wide range of viruses. Such compounds include, for example, the drug catapol, which has extensive antiviral and antibacterial properties against pathogens of many infectious diseases [3]. The antiviral properties of sulfur-containing polymers against several enveloped viruses, including influenza virus, have also been described [4]. Various phosphate containing polymers have antiviral activity against SARS-CoV-2 and HIV (Corona virus 2 associated with severe acute respiratory syndrome and human immunodeficiency virus) [5,6]. Natural polymers, phosphates and sulfates of polysaccharides [7], as well as synthetic anionic polyelectrolytes [8, 9], exhibit high antiviral activity. Their activity is due to the ability to block the interaction of the virus with the “host” cell, induce the body’s production of interferon, activate macrophages and stimulate the body’s nonspecific resistance to external infections. Among the large number of different polyanions, sodium polystyrene sulfonate has been studied in detail [10, 11]. It targets respiratory viruses and

is active as an anti-HIV agent. Today, the pharmaceutical market offers a wide range of interferon preparations, which contain not only the interferon protein itself, but also other medicinal components, such as antioxidants (Viferon), immunoglobulins (Kipferon), hyaluronic acid salt (“Geaferon”), antimycotics (“Mikoferon”, “Vagiferon”), purine nucleoside with lidocaine (“Gerpferon”), antihistamines (“Grippferon with loratadine”), corticosteroids (“Allergoferon”), etc. [12, 13] . The work of domestic authors shows that the drug of recombinant interferon in the form of a substance has its advantages, it allows for a prolonged effect of the drug, rarely causes allergies, is well absorbed, especially in the form of a substance, which increases the effectiveness of the drug, and also has a moisturizing effect, which allows use them in adult children in the complex therapy of acute respiratory viral infections and influenza. According to the authors, the effect of interferon is more effective the earlier it begins to be synthesized or enter the body from the outside [14]. As a result of targeted screening, it is possible to obtain drugs with desired properties. Compared to synthetic interferon inducers, preparations based on plant substances have a significant advantage due to the possibility of obtaining them from cheap raw materials using fairly simple technologies.

Such natural inducers include polyphenols, in particular gossypol and its derivatives. Due to its relatively simple structure and the possibility of various chemical transformations, gossypol is a convenient model for determining the relationship of the chemical structure with the ability to induce interferon, antiviral activity and non-toxic properties.

The purpose of the study is to develop a synthesis method, establish the chemical structure of DACMC (carboxymethylcellulose dialdehyde) of the polymer modification of gossypol and study the correlation between the nature of the carrier polymer, the content of bound gossypol, the type of chemical bond and biological activity. This article presents the results of physico-chemical and medico-biological tests of a new polymeric, water-soluble interferon inducer with antiviral activity, obtained by chemically combining the Na derivative - carboxymethylillulose with a natural polyphenol - gossypol. It is known that gossypol is an interferon inducer, but due to its rather high toxicity and hydrophobicity it is not used in practical medicine. In order to reduce toxicity by blocking part of the active functional groups and imparting water solubility, we investigated the possibility of modifying gossypol with reactive derivatives of another derivative of the natural polymer Na - carboxymethylcellulose (Na-KMC).

MATERIALS AND METHODS

Water-soluble Na-CMC, of high purity, was obtained according to the SZ and SP methods. Na – CMC was determined according to the method [15] Na-carboxymethylcellulose (CMC) according to Ts 19515439-01:2017 “ASDACELL” Carboxymethylcellulose (CMC). Quality indicators at the CMC:

A) Degree of substitution for carboxymethyl groups in the range of 0.61 and 0.80

B) Degree of polymerization 550 and 750 and the degree of their required purity

-Iodic acid (HIO4□2H2O) analytical grade. company "Reonal" Budapest (Hungary)

-acetone grade "ch" or "khch"

-hydrochloric acid "reagent grade" or "pure grade"

- potassium iodide KI grade "ch"

- potato starch

- DACMC obtained from 100g NKMC

- Gossypoacetic acid (GUA)

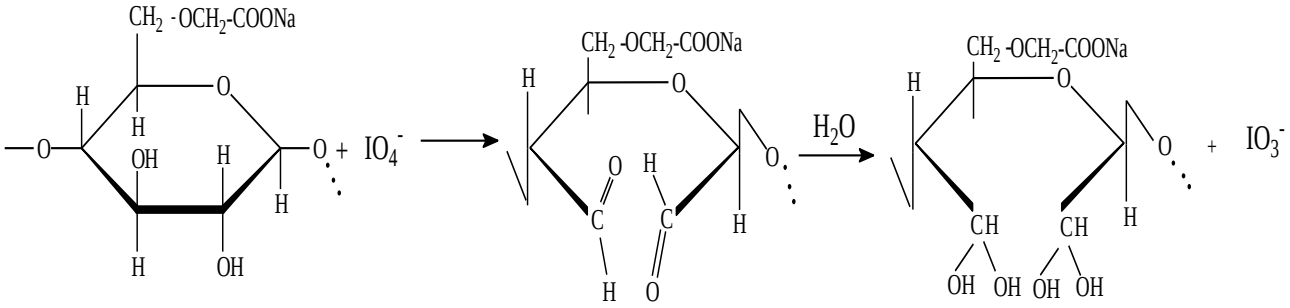
- Caustic sodium "h" and "khch"
- Acetone "h" and "khch"
- Iced acetic acid "ch", "khch"
- Rectified ethyl alcohol
- Distilled water

Methodology for obtaining NKMC. To obtain NCMC, a 20% H2SO4 solution was prepared. We weighed 100 g of Na CMC and added 107 ml of sulfuric acid to 1 liter of distilled water. The prepared solution is left for 16 hours. After time, the solution is filtered and the precipitate is washed several times with water until the remaining SO4-2 ions are completely removed. The test is carried out with a BaCl2 solution. The process of selective oxidation of H-CMC was carried out in a wet state with an aqueous solution of periodate acid with a concentration of 0.1 M at a modulus of 1:10, at a temperature of 25±1°C for 24-48 hours. The substance of the drug “CelAgrip”, its quality indicators were determined in accordance with the pharmacopoeial article FS 42 Uz -1554-2021 from 09/29/2021. The synthesis of the substance "CelAgrip" was carried out in a glass reactor (high-speed mixer Erweka SW 1/S with A403 nozzle). The filtered and wet DACMC sample is transferred to a glass crystallizer, loosened, and 20 g of gossypol acetic acid powder is added evenly on top of the DACMC. The resulting mixture is stirred until smooth. The resulting mass is passed 3 times by grinding through a sieve with a hole size of 1-2 mm made of stainless steel. The resulting mass is transferred to a glass reactor with a stirrer (5000 rpm). While stirring at room temperature, the mixture of DACMC and HUA is titrated with a NaOH solution with a concentration of 1.5 N. The first portion of the NaOH solution in a volume of 125 ml is poured quickly. Next, stirring is continued until a uniformly viscous mass is obtained (without large grains). At the end of mixing, a homogeneous yellow viscous mass similar to mother-of-pearl is formed. Next, titration is continued until a dark brown solution is obtained. The transition from yellow to brown, that is, the end point of the titration can be controlled by taking 1 ml of the mixture and dissolving it in 20 ml of distilled water. This should result in a fairly transparent light brown solution. If there is noticeable turbidity, add an alkali solution to the mixture and mix. At the end of the titration, the resulting solution must be quickly passed through a filter with a mesh size of 65-100 microns. The process of neutralizing the mixture of DACMC + HUA with NaOH solution and its filtration should not exceed 30 minutes, especially pay attention that from the moment the brown solution is obtained until the completion of its filtration should not exceed 5-6 minutes. The resulting solution is precipitated with a thin stream into a volume of acetone, which is 5 times larger than the volume of the precipitated solution. The precipitation process is carried out with constant stirring of the resulting precipitate. At the end of precipitation, a resinous mass is formed in the reactor, which gradually hardens due to stirring. After 30-45 minutes, the upper acetone is drained from the reactor by decantation and the sediment is filled with a new portion of acetone. The mixing process is continued for another 30 minutes. Next, the acetone is drained off, the precipitate is transferred to a porcelain ball mill and, by squeezing out under a layer of acetone, stirring is continued, periodically draining and pouring in new portions of acetone. The thick mass is poured with 1 liter of acetone and crushed for 10-12 hours. Every 4 hours, the acetone is drained by decantation and a new portion is poured. The resulting powder is filtered on a Buchner funnel under vacuum. The resulting powder is transferred to a glass crystallizer and dried in air, stirring occasionally. Dry CelAgrip powder is dried in a vacuum oven at a temperature of 45□50C until acetone vapor is removed. The pH of the solution of the resulting

substance was determined according to the method laid down in FS 42 Uz -1554-2021. The resulting preparation is ground in a ball mill. The powdered preparation is sifted through a sieve with a pore size of 0.1 mm. The yield of the substance "CelAgrip" is determined. The quality of the substance is assessed by IR and UV spectroscopic methods.

DISCUSSION OF RESEARCH RESULTS

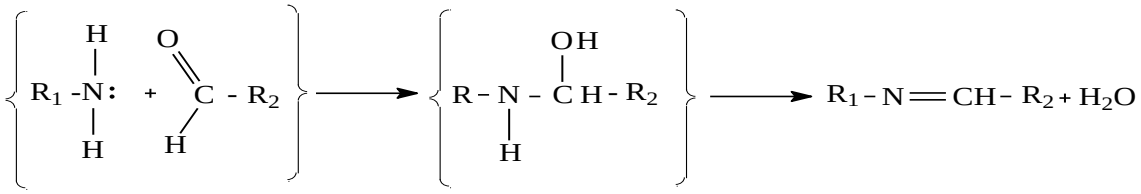
In this work, we used reactive derivatives obtained by oxidation of Na-KMC of varying degrees of substitution (DS) with an aqueous solution of periodic acid. For the oxidation of Na-CMC in an aqueous environment, purified samples were used. To increase the efficiency of the Na-CMC purification process, it was converted into the N-CMC form by treating it with aqueous solutions of mineral acids. To functionalize Na-CMC macromolecules, a method was chosen for selective oxidation of free glycol groups of anhydroglucose units of the CMC macromolecule using periodic acid. To be used as a carrier of PAS in the creation of graft-type polymers, Na-CMC is chemically modified by periodate oxidation under homogeneous or heterogeneous conditions. Periodate oxidation of free glycol groups was carried out both in aqueous solutions of Na CMC and in an aqueous medium, and the oxidation process was studied under homogeneous conditions. Homogeneous oxidation is carried out in laboratory conditions under small operating conditions. Heterogeneous conditions are more often used in factory settings in semi-industrial installations. However, this method is labor-intensive, it uses a large amount of precipitant - acetone dialdehyde Na-CMC, the yield of the target product is reduced due to the partial dissolution of low molecular weight fractions of dialdehyde in a mixture of aqueous-organic systems of the precipitant. DACMC is obtained by periodate oxidation of n-carboxymethylcellulose. It is known that during the selective pereodate oxidation of CMC, the glucopyranose rings of elementary units containing free glycol groups at positions C2 and C3 are irreversibly broken with the formation of two aldehyde groups according to the following scheme.



I Link CMC ***II DACMC*** ***III Gemdiol DACMC***

The resulting dialdehyde unit of CMC, in the presence of water, quickly transforms into hemdiol structure III, which has several other structures, and the equilibrium DACMC ↔hemidiol DACMC shifts completely to the right, which is confirmed by the absence of absorption bands of carbonyl groups in the region of 1610 cm-1 in the IR spectra of DACMC. Equilibrium shift towards structure II can be achieved by interacting the structure of DACMC III with nucleophilic drugs of high nucleophilicity such as R-NH2.

When nucleophilic agents of the indicated structure are added to solutions of DACMC, the carbonyl group is attacked at high speed by a nucleophilic agent to form the primary addition product IV. This is followed by the acid-catalyzed stage of dehydration of the addition product, which limits the rate of the entire process and leads to the final product V according to the equation:



IV ***V***

When obtaining the final product with structure V, low molecular weight medicinal compounds containing primary amino groups with different nucleophilicity can be used as a nucleophilic agent. The oxidized form of carboxymethylcellulose is widely used as a drug carrier polymer.

Studies of selective oxidation in a solution of Na-CMC with periodic acid were carried out. The results of changes in the degrees of oxidation, substitution and polymerization of Na-CMC in 2% aqueous solutions during homogeneous selective oxidation are presented in Table 1.

Changes in the degrees of oxidation, substitution and polymerization of Na-CMC in 2% aqueous solutions during homogeneous selective oxidation

(Concentration of aqueous solutions of Na-CMC is 2 mass%, the concentration of periodic acid solution is 0.1 M; temperature 25±1°C; oxidation time is 4 hours)

Table 1.

Original Na-KMC		Content of aldehyde groups, mol %			Number of free glycol groups in CMC, mol%
NW	SP	Based on oxidizer consumption	Based on the iodometric method.	According to the Wilson and Padit method	
84	600	23,6	18,5	17,6	9,0
80	650	31,2	27,2	26,4	13,4
72	720	34,6	29,4	28,6	14,6
54	740	38,0	31,9	30,6	15,7
43	870	40,7	34,5	33,8	17,1
34	920	47,9	38,1	37,6	19,0

As can be seen from Table 1, at high C3 values of Na-CMC, a decrease in the degree of oxidation is observed, which is explained by a decrease in the content of free glycol groups in the glucopyranose units of Na-CMC at positions C2 and C3. A side reaction that occurs during the oxidation of Na-CMC is the hydrolysis of macromolecules, leading to a decrease in molecular weight. It has been established that, along with the hydrolysis of macromolecules, another side reaction occurs—the subsequent oxidation of the forming aldehyde groups to carboxyl groups, which is confirmed by an increase in the SD values in the oxidized Na-CMC samples.

It is known that during the periodate oxidation of cellulose ether Na-carboxymethylcellulose, due to the selective cleavage of unsubstituted glucopyranose rings containing free glycol groups in the C2 - C3 position, their dialdehyde derivatives are formed. The presence of periodate oxidized Na-CMC dialdehyde and hydroxyl functional groups contributes to the spontaneous flow inside and intermolecular chemical transformations with the formation of hemiacetal and acetal bonds during their drying at high (80-100 0C) temperatures. By oxidizing H-CMC with a solution of periodic acid and depending on the degree of substitution and the degree

of polymerization, samples of DACMC were obtained containing from 23 to 38 mol% of aldehyde groups.

Change in the degree of oxidation depending on the SP and SD of the initial H-CMC under heterogeneous conditions

Table 2

№	N-KMC		Periodic acid concentration %	Oxidation time hour	DACMC	
	NW	SP			Oxidation state mol%	Polymerization degree
1	0,61	750	5	24	38	76
2	0,61	750	10	12	30	58
3	0,80	550	5	22	23	41
4	0,80	550	10	12	19	37

As can be seen from Table 2, the degree of oxidation of H-CMC depends on the concentration of periodate acid and oxidation time. In this case, a significant decrease in the DP of the original NCMC is observed due to its oxidative destruction. It was established that the values of the degree of oxidation of NCMC – 38 and 23 mol% are the limiting values for the oxidation of all free glycol groups of the original N-CMC. The IR spectrum of the original gossypol contains a characteristic absorption band of stretching vibrations of the carbonyl group of the aldehyde group in the region of 1740 cm-1, however, it is not possible to use this band for the quantitative determination of gossypol in the polymer, since it overlaps the absorption band of the carboxyl group of the carrier polymer

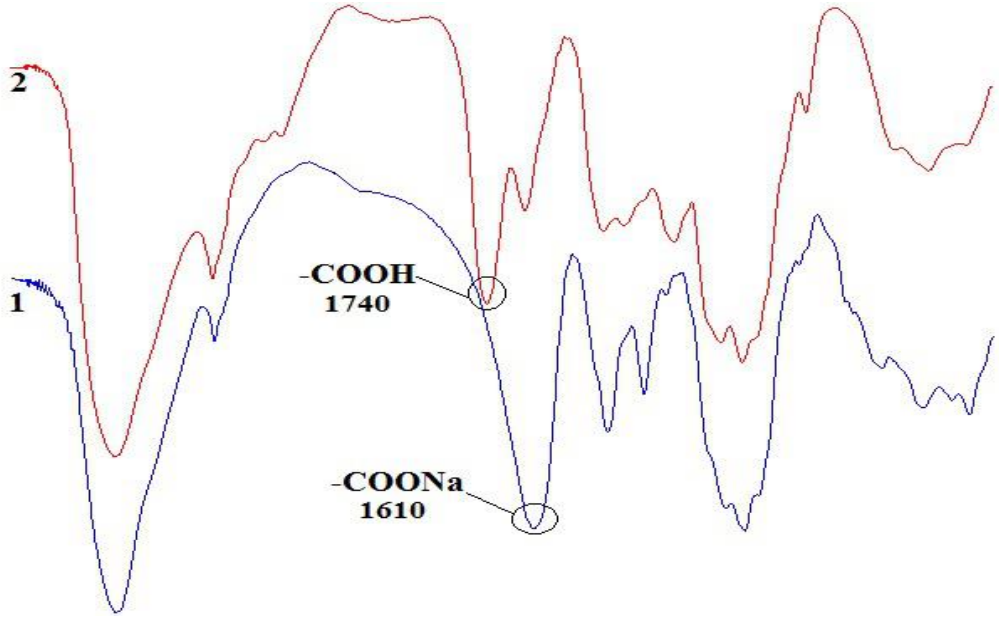


Fig.1. IR spectra: 1. NaCMC 2. NKMC

In the figures you can see the resulting NCMC with NaCMC. As a result of the analysis of the spectra, the peak at 1610 cm-1, related to vibrations of COONa, as well as the absorption band of the COOH group at 1740 cm-1 were selected as analytical bands. In the spectra of the products of the addition of Na CMC to NCMC, obtained under heterogeneous conditions using acetone as a precipitant.

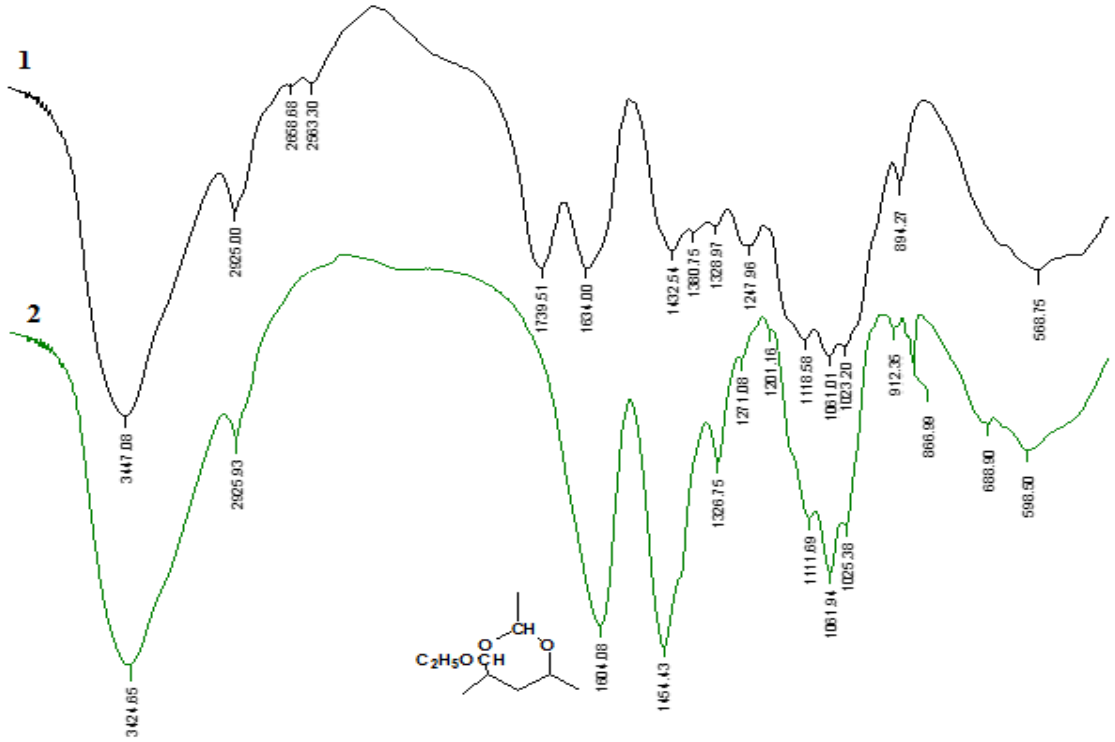


Figure. 2 – Fourier IR – spectra: 1-DAKMC, 2-CelAgrip

Figure 2 shows the vibration spectra of the original DACMC and CelAgrip. FT-IR spectroscopy allows you to clearly identify different samples and their functionality.

In the IR spectra of DACMC in the regions of 3400-3000, 2918, 2879, 1637, 1432, 1377, 1243, 1119, 1062 and 895 cm-1, regions characteristic of the absorption bands of CMC were observed, while in the region of 1739 cm-1 a peak characteristic of the aldehyde group C = O which is formed when the ring breaks.

In the IR spectra of CelAgrip, an intense absorption band is observed in the region of 1610 cm-1, which characterizes the total absorption lines of the aldehyde of the gossypol group and the carrier polymer, on the basis of which it is impossible to determine the amount of gossypol. According to the absorption bands in the region of 1441 cm-1 and 1326 cm-1, characteristic of deformation vibrations of the cycle, it is possible to conclude about the presence of intra- and intermolecular bonds in the compound of gossypol with DACMC and carry out a quantitative assessment. The absorption bands of aldehyde groups can explain intramolecular and intermolecular interactions with the formation of hemiacetal and acetal bonds on the one hand, as well as the hydration of free aldehyde groups to hemdiols on the other hand. However, taking into account the dynamic equilibrium of hemiacetal, acetal hemdial structures with primary aldehyde and hydroxyl functional groups, as a result of the interaction of these structures with reagents having strong nucleophilicity, the equilibrium shifts towards the formation of new structures of hemiacetal and acetal nature.

The change in the chemical structure and the position of the absorption peaks of the gossypol molecule in the electronic spectrum is associated with enolization leading to a change in the conjugation chain.

As can be seen from the experimental data, absorption bands are observed in the UV spectra of DACMC at wavelengths of 202 nm and 221 nm, corresponding to π-π* electronic transitions of the carboxyl and aldehyde groups. The UV spectra of gossypol exhibit intense, well-separated absorption bands at 389 nm, 252 nm, and a shoulder at 311 nm, as well as a weak intensity

absorption band at 207 nm, which indicates the stable two tautomeric forms of gossypol (aldehyde and lactone form) Fig. 2.

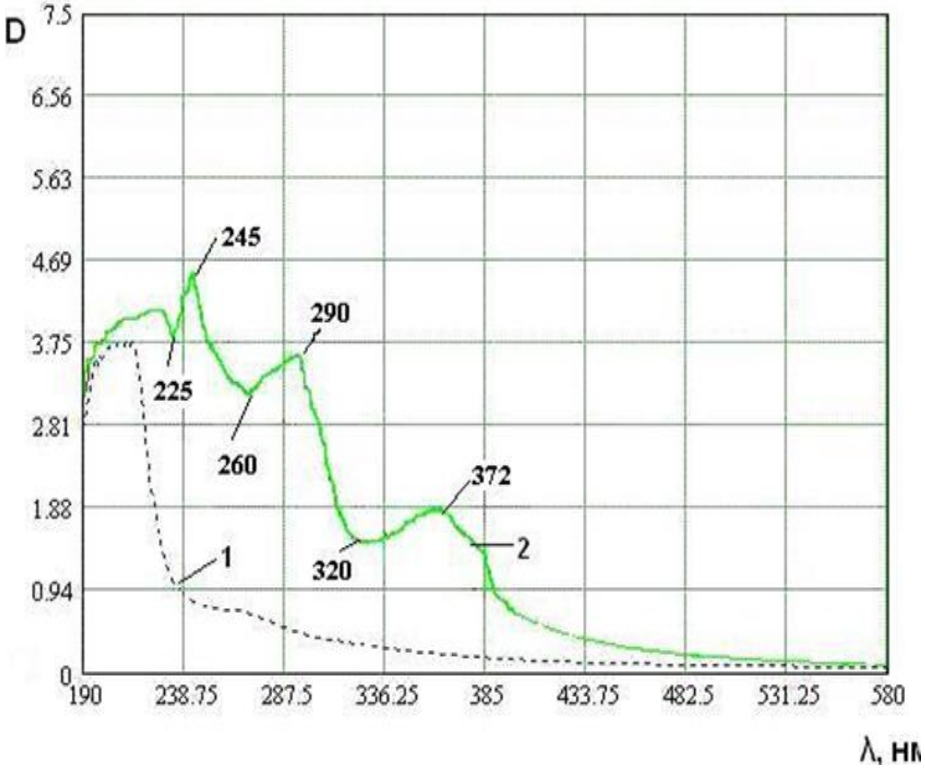


Fig. 3 UV spectrum Electronic absorption spectrum of 1.Na CMC and 2.CelAgrip

When obtaining the product of the addition of HAA to DACMC, the UV spectra show a bathochromic shift in the absorption band of the initial components, which indicates the formation of a chemical bond between DACMC and gossypol.

The electronic absorption spectrum of Na CMC and CelAgrip is shown in Figure 3. UV in the region from 220 nm to 700 nm should have absorption maxima at (245±5) nm, (290±5) nm, (372±5) nm and minima absorption at (225±5) nm, (260±5) nm and (32 0±5) nm. In an aqueous environment, when acidity changes, the main absorption peaks in the spectrum undergo a bathochromic shift. Its value depends on the pH of the solution. The absorption maximum of gossypol in a non-polar solvent is in the region of 401 nm.

In the spectra of the products of the addition of gossypol to DACMC, obtained under heterogeneous conditions using acetone as a precipitant, in all samples, there are two main absorption peaks: λ1 = 217 nm and λ2 = 312-324 nm.

By chemical combination of oxidized Na-KMC samples of different SZ, derivatives containing covalently bound gossypol with the following structure were obtained.

The presence of this structure was confirmed by IR, UV, NMR and ESR spectroscopic methods.

It is known that the dialdehyde CMC and gossypol contain identical functional groups in structure - aldehyde and hydroxyl, differing in electrophilicity. It has been experimentally established that in an alkaline environment, the more electrophilic aldehyde groups of the CMC aldehyde react with the less “acidic” hydroxyl groups of gossypol to form a hemiacetal bond with the structure 2,21 diacetal (1,6,7 trioxy, 3 methyl-5-isopropyl-8 - naphthaldehyde) 2, 3 dialdehydes 6-O-carboxymethylcellulose.

The reaction products containing 1-5 mol% of bound gossypol were readily soluble in water and had an intrinsic viscosity of - 0.08 - 0.12.

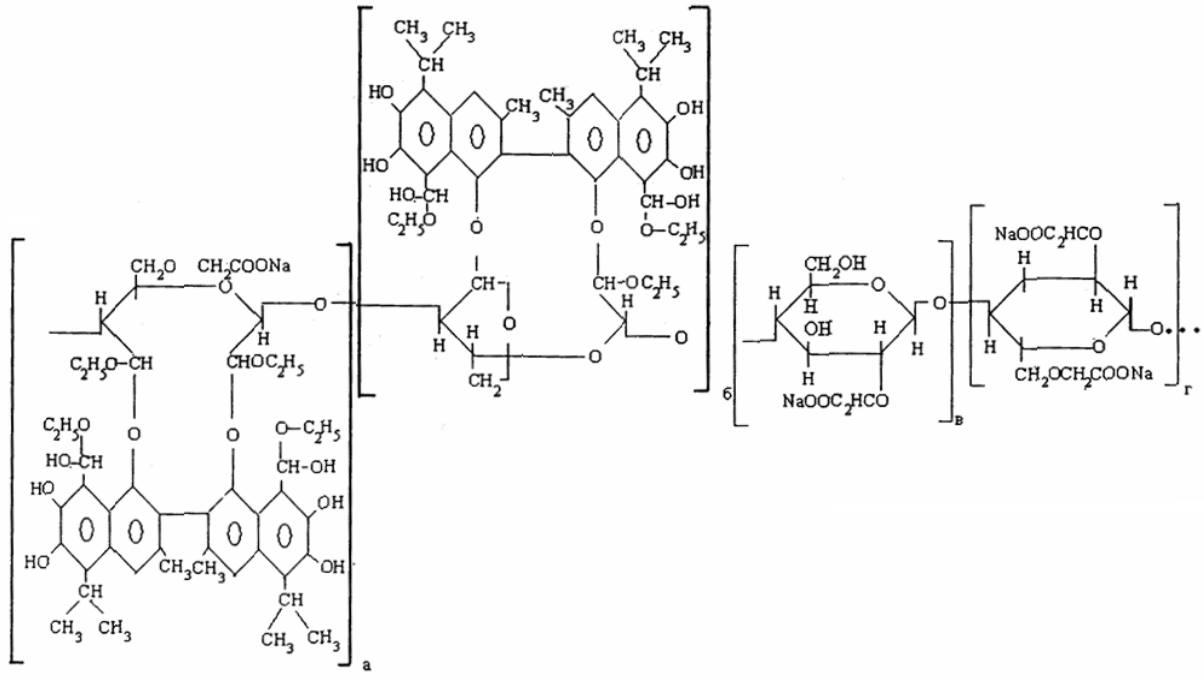


Fig 4. Structure: Copolymer of sodium salt of carboxymethylcellulose and gossypol CelAgrip - sodium salt of 2,3-diethoxy-6-0-carboxymethyl-(1→4)-β-D-oxyglucose-diethoxygossypolate-2-ethoxy-(1→4) -β-D-hydroxy-glucose-diethoxygossypolate-2-0-carboxymethyl-(1→4)-β-D-glucose 2,6-0-dicarboxy-methyl-(1→4)-β-D-glucose [(C46H57017 Na)a (C42H50O12)b (C8H11 O7Na)c (C10H12O9Na2)g]n, a: b: c: g = (2-3)a: (1-2)b (70-65)c (27 -30)g M.m. 120,000-130,000; n=50-60

On the basis of the Institute of Chemical Physics of the Academy of Sciences of the Republic of Uzbekistan, a drug was obtained that has high activity for the prevention and treatment of viral influenza and acute respiratory viral infections based on water-soluble polysaccharide derivatives and biologically active gossypol. The polymeric, water-soluble form of the drug has passed the full stage of biomedical, preclinical and clinical trials. Preclinical trials of the drug “CelAgrip” in Uzbekistan were carried out at the Research Institute of Virology of the Ministry of Health of the Republic of Uzbekistan, the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan, and the National Influenza Center. Clinical studies of the drug “CelAgrip” were carried out at the Department of GP Therapy with Allergology TMA and approved by the Pharmacopoeial Committee of the State Unitary Enterprise “State Center for Expertise and Standardization of Medicines, Medical Products and Medical Equipment” as a therapeutic and prophylactic agent (tablets) under the name “CelAgrip”. A general technology for the synthesis of polymer derivatives of gossypol has been developed, which makes it possible to reduce toxicity and increase the duration and direction of action; an original polymer water-soluble interferon inducer has been created, which has antiviral activity against a wide range of CelAgrip viruses. The drug induces late interferon and circulates in the bloodstream at a therapeutic level for one week. It does not have acute or chronic toxicity and does not accumulate in the body. Technological regulations and technical specifications have been developed for the substance of the drug under the chemical name, carboxymethylcellose gossypolate. The substance “CelAgrip” is intended for the production of a dosage form of the drug “CelAgrip” in the form of tablets,

blister packaging intended for the prevention and treatment of viral influenza and ARVI and herpes. Based on the results of medical and biological tests, it was established that interferon, which induces the activity of a drug containing 3 mol% bound gossypol, depends on the dose and method of its administration to the body. With intraperitoneal and intramuscular administration of the inducer at a dose of 100 mg/kg body weight, maximum interferon titers (1280 units/ml) are observed in the blood serum. When administered subcutaneously, the maximum production of serum interferon reaches 640-1280 units/ml at a dose of 50 mg/kg body weight. When the inducer is administered orally, sufficiently high interferon titers (640-1280 units/ml) are recorded in the bloodstream of animals at an inducer dose of 10 mg/kg body weight after 48 hours. The interferon response of the animal body to the introduction of this inducer is characterized by prolonged circulation (up to 72-96 hours) of interferon in the bloodstream.

CONCLUSION

The relationship between the degree of substitution and the degree of selective oxidation of Na-CMC, which determines the structure and physicochemical properties of oxidation products and regulates the content of the biologically active component responsible for the results of medical and biological tests of the final product, has been studied. The composition, structure and properties of Na-CMC dialdehydes were studied using modern physicochemical methods and the values of the degree of substitution, the degree of their Na-CMC polymerization and the degree of their periodate oxidation were selected, facilitating the production of polymeric forms of antiviral drugs with high rates of therapeutic activity at relatively low toxicity values . The first showed the possibility of obtaining polymeric water-soluble derivatives of natural water-insoluble gossypol through chemical combination with DACMC, where a covalent acetal bond is formed between gossypol and DACMC. Using IR-UV and NMR spectroscopy, the formation of an intermolecular covalent acetal bond between gossypol and DACMC was confirmed.

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