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Study of the properties of biomedical materials based on cellulose mesylates

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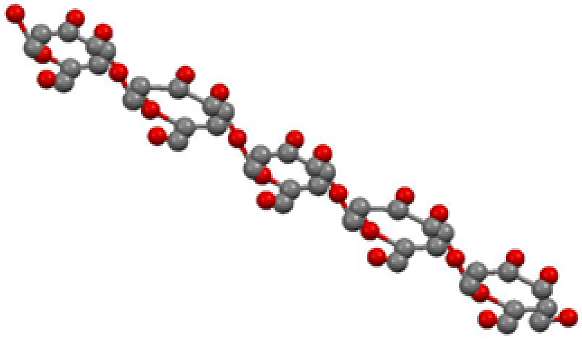
Russian Academy of Sciences

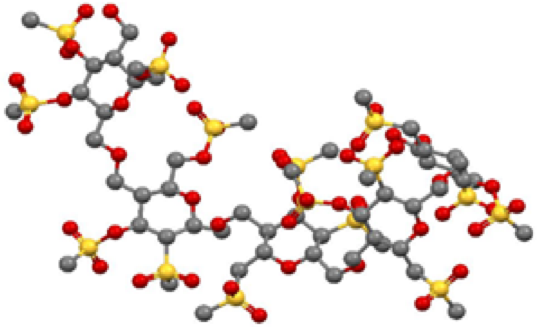
DAGESTAN STATE UNIVERSITY

Study of the properties of biomedical materials based on cellulose mesylates

Graphical Abstract



fragment cellulose



fragment cellulose of mesylate

Abstract: Currently, cellulose is positioned as the most popular natural high-molecular biopolymer, the modification products of which are used to obtain materials such as composites, films, fibers, membranes, nanofibers, nanogels, hydrogels, etc., which are widely used in medicine: tissue engineering , as a drug delivery system; cell technology, as matrices for the immobilization of enzymes and biologically active substances, etc. The demand for biomedical materials based on cellulose is due to such unique properties as its biocompatibility with various tissues, non-toxicity, high crystallinity and mechanical strength, etc. The object of scientific research is esters - cellulose mesylates, obtained by the author of the project by chemical and electrochemical modification in methanesulfonic acid (MSA) solutions. The advantage of using methanesulfonic acid as a solvent and medium for modifying cellulose in comparison with toluenesulfonic acid is its low toxicity compared to other acids; biodegradability - in the natural environment, MSA is part of the cycle of organic sulfur circulation in nature, and is destroyed with the formation of sulfur and carbon dioxides. It was found that it was found that the interaction of alcohol groups with the MSA molecule leads to the formation of esters - cellulose mesylates (MCC and NCC) and cellobiose.

Keywords: biomedical materials, drugs, cellulose mesylate, modification

Introduction

Cellulose is the most famous natural polymer in the world!

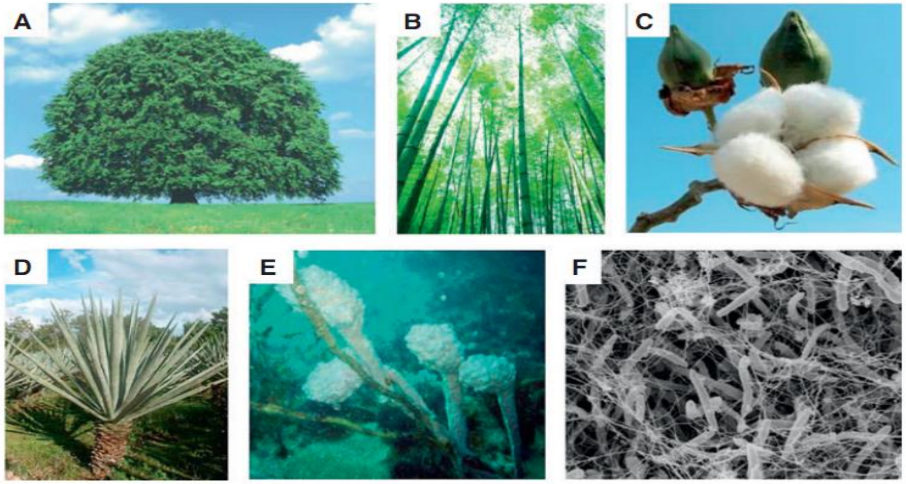
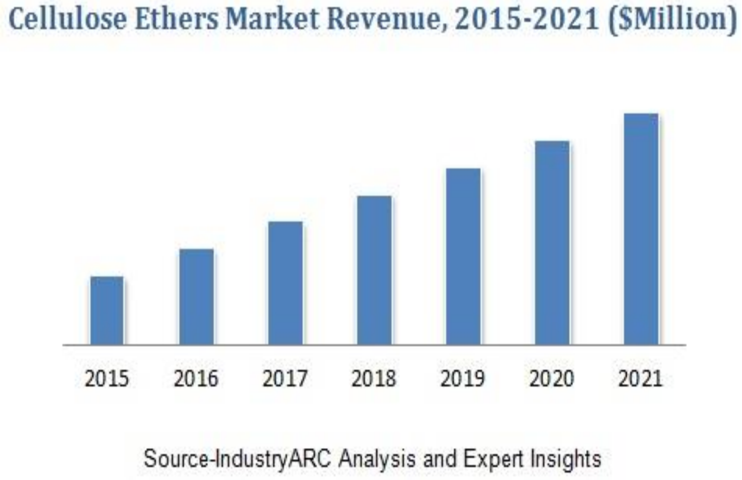


Fig. 1. Cellulose can be obtained from various sources, some examples: (A) beech tree, (B) bamboo, (C) cotton, (D) sisal, (E) tunicine, (F) Gluconacetobacter xylinum. Reproduced with permission from Ref. [1].



Source-IndustryARC Analysis and Expert Insights

Fig. 2. Cellulose Ethers Market - Forecast(2020 - 2025)

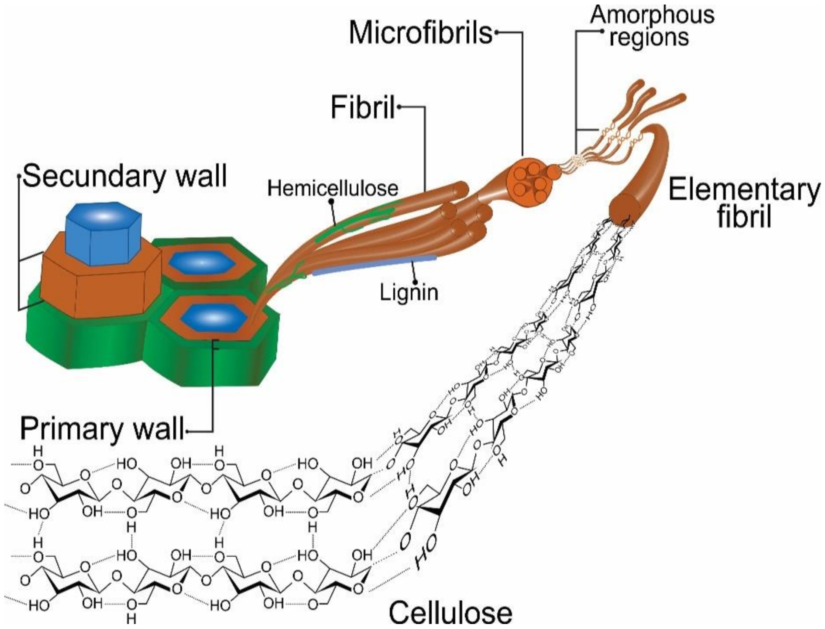
[1] Jedvert, K., & Heinze, T. Cellulose modification and shaping – a review. *Polymer Engineering*, 2017, vol. 37, N. 9. doi:10.1515/polyeng-2016-0272

[2] Cellulose Ethers Market Research https://www.industryarc.com/Report/11703/cellulose-ethers-market.html

Introduction

Cellulose chains show a very high tendency to selforder and so there are different structural levels of cellulose [1]. The cellulose chains arrange themselves into fibrils that have regions with varying degree of order [4]. The fibrils, in turn, organize themselves into structures of higher order, which results in arrangement into layers of varying texture and density. This unique and complex structure influences the properties and the reactivity of different cellulose materials [5].

Sheme 1. Structure of cellulose

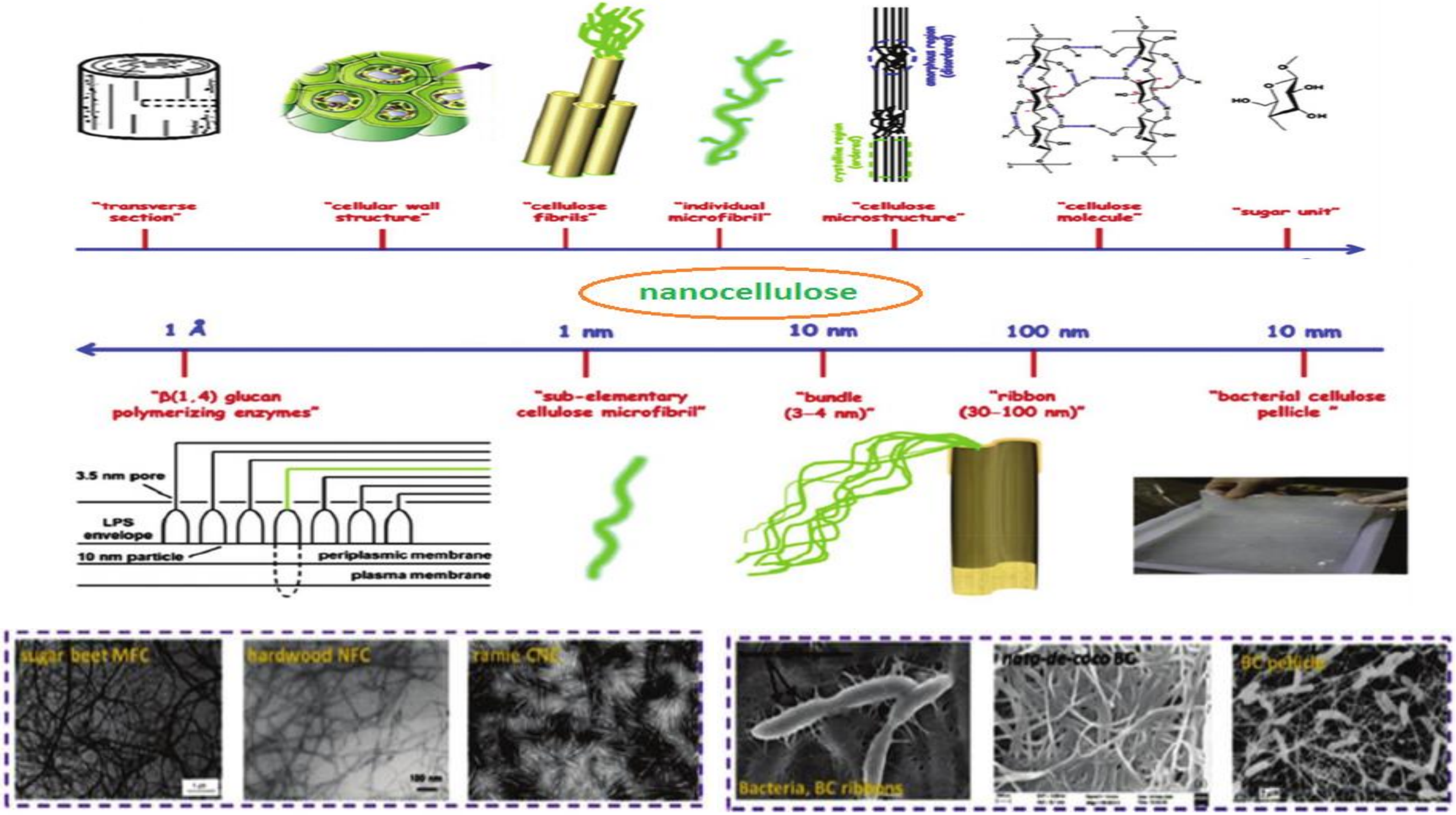


[3] O'Sullivan AC. Cellulose: the structure slowly unravels, *Cellulose,* 1997, vol.4, P.173–207

[4] The structure and physico-chemical properties of cellulose and nanocompositov based on them / ed. Aleshina L.A., Gurtov V.A., Melekh N.V. - Petrozavodsk: Publishing house of PetrSU, 2014. - 240 p.

Introduction

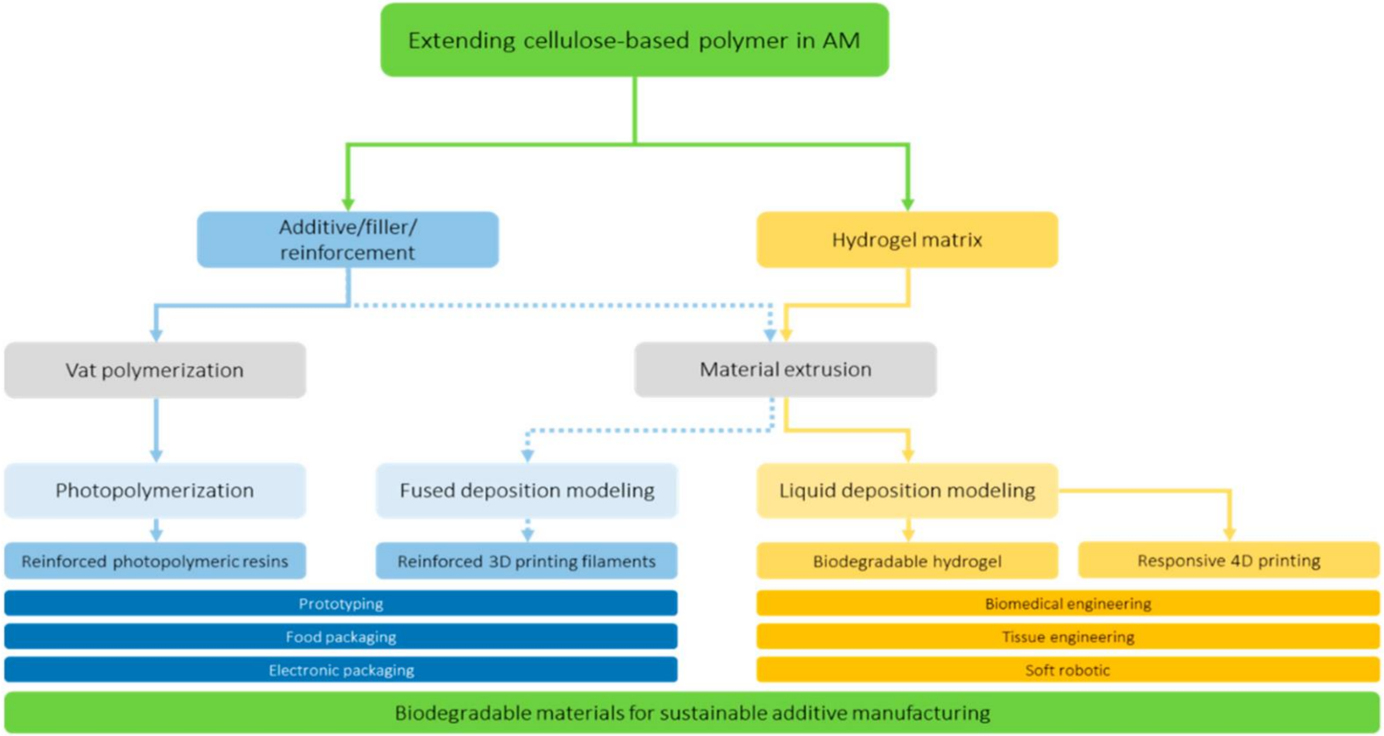
Sheme 2. Cellulose types [5]



[5] Mohammadinejad, R., Karimi, S., Iravani, S., & Varma, R. S. Plant-derived nanostructures: types and applications, *Green Chemistry*, 2016, vol. 18, N. 1, P. 20–52. doi:10.1039/c5gc01403d

Introduction

Sheme 3. The use of cellulose-based polymers for bioprinting technology [6]



Extending cellulose-based polymer in AM

Additive/filler/ reinforcement

Hydrogel matrix

Vat polymerization

Material extrusion

Photopolymerization

Fused deposition modeling

Liquid deposition modeling

Reinforced photopolymeric resins

Reinforced 3D printing filaments

Biodegradable hydrogel

Responsive 4D printing

Prototyping

Food packaging

Electronic packaging

Biomedical engineering

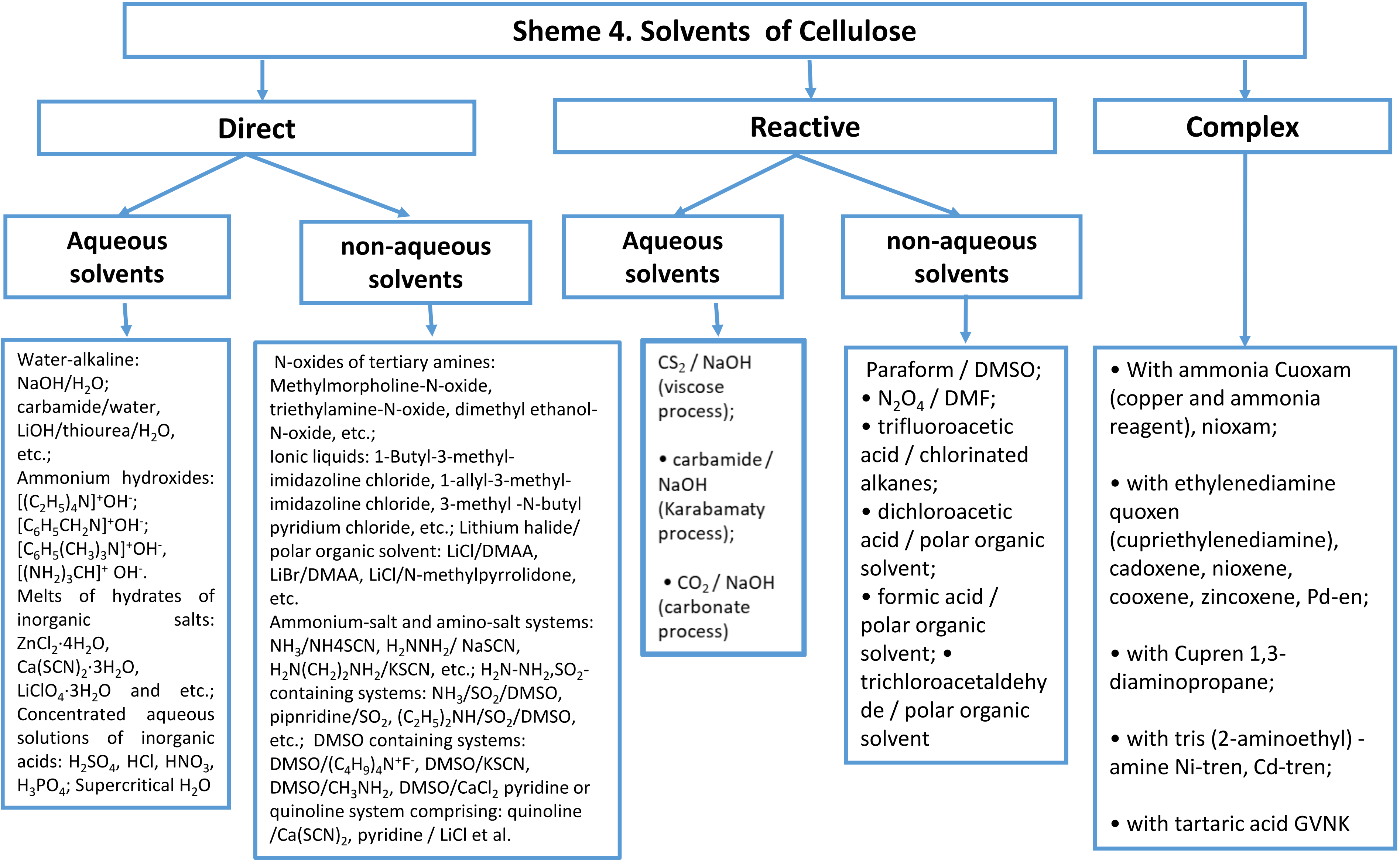
Tissue engineering

Soft robotic

Biodegradable materials for sustainable additive manufacturing

[5]. Mohan, D., Teong, Z. K., Bakir, etc. Extending Cellulose-Based Polymers Application in Additive Manufacturing Technology: *A* Review of Recent Approaches*. Polymers, 12(9), 1876.* doi:10.3390/polym12091876

Introduction



Sheme 4. Solvents of Cellulose

Direct

Aqueous solvents

Water-alkaline: NaOH/H_2O; carbamide/water, LiOH/thiourea/H_2O, etc.; Ammonium hydroxides: $[(C_2H_5)_4N]^+OH^-$; $[C_6H_5CH_2N]^+OH^-$; $[C_6H_5(CH_3)_3N]^+OH^-$, $[(NH_2)_3CH]^+ OH^-$. Melts of hydrates of inorganic salts: $ZnCl_2 \cdot 4H_2O$, $Ca(SCN)_2 \cdot 3H_2O$, $LiClO_4 \cdot 3H_2O$ and etc.; Concentrated aqueous solutions of inorganic acids: H_2SO_4, HCl, HNO_3, H_3PO_4; Supercritical H_2O

non-aqueous solvents

N-oxides of tertiary amines: Methylmorpholine-N-oxide, triethylamine-N-oxide, dimethyl ethanol-N-oxide, etc.; Ionic liquids: 1-Butyl-3-methyl-imidazoline chloride, 1-allyl-3-methyl-imidazoline chloride, 3-methyl -N-butyl pyridium chloride, etc.; Lithium halide/ polar organic solvent: LiCl/DMAA, LiBr/DMAA, LiCl/N-methylpyrrolidone, etc. Ammonium-salt and amino-salt systems: NH_3/NH4SCN, H_2NNH_2/ NaSCN, $H_2N(CH_2)_2NH_2$/KSCN, etc.; H_2N-NH_2,SO_2-containing systems: NH_3/SO_2/DMSO, pipnridine/SO_2, $(C_2H_5)_2NH/SO_2$/DMSO, etc.; DMSO containing systems: DMSO/$(C_4H_9)_4N^+F^-$, DMSO/KSCN, DMSO/CH_3NH_2, DMSO/$CaCl_2$ pyridine or quinoline system comprising: quinoline /$Ca(SCN)_2$, pyridine / LiCl et al.

Reactive

Aqueous solvents

CS_2 / NaOH (viscose process);

- carbamide / NaOH (Karabamaty process);
- CO_2 / NaOH (carbonate process)

non-aqueous solvents

Paraform / DMSO;
- N_2O_4 / DMF;
- trifluoroacetic acid / chlorinated alkanes;
- dichloroacetic acid / polar organic solvent;
- formic acid / polar organic solvent; • trichloroacetaldehyde / polar organic solvent

Complex

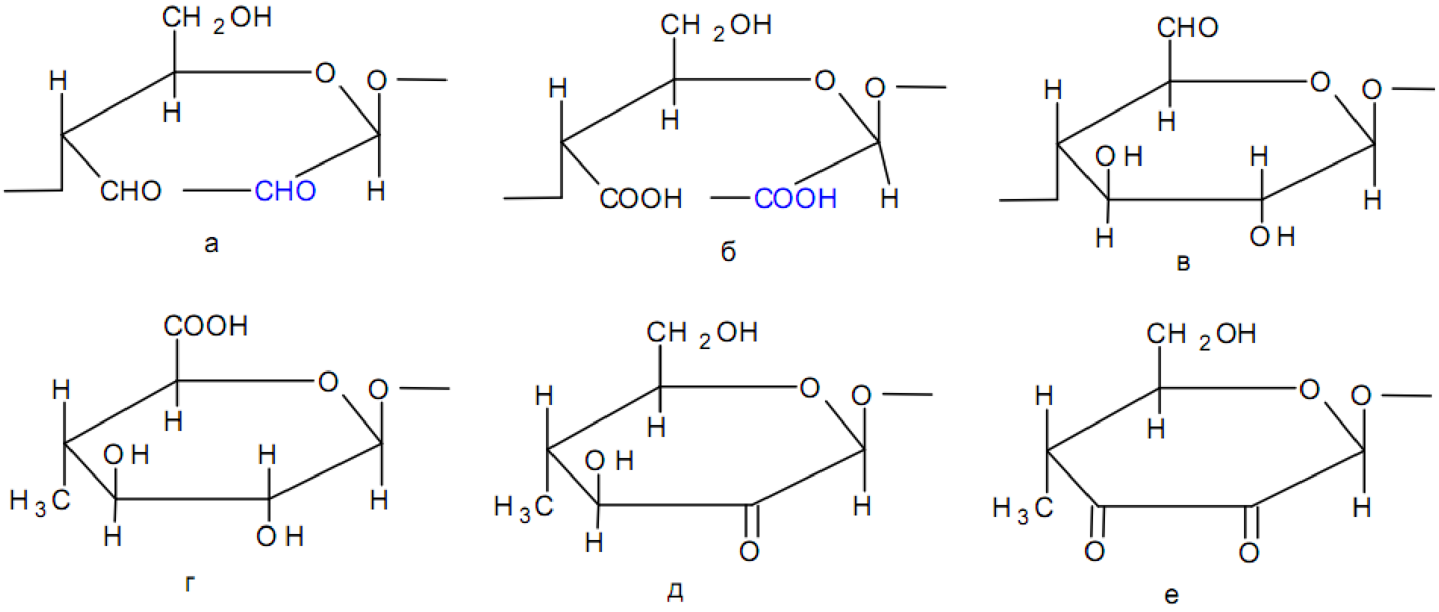
- With ammonia Cuoxam (copper and ammonia reagent), nioxam;
- with ethylenediamine quoxen (cupriethylenediamine), cadoxene, nioxene, cooxene, zincoxene, Pd-en;
- with Cupren 1,3-diaminopropane;
- with tris (2-aminoethyl) -amine Ni-tren, Cd-tren;
- with tartaric acid GVNK

[6] Berezin, A. S., Tuzhikov, O. I. Dissolution mechanisms of cellulose in direct aqueous solvents. (review), *Izvestia of VolgGTU,* 2010, vol. 62, N. 2, P. 5-23

Introduction

Cellulose oxidation products are used for various medical purposes and pharmaceuticals [7-9], as well as in organic synthesis to protect hydroxyl groups [8].

Scheme 5. Cellulose modification



[7] KhidirovSh.Sh., Akhmedov M. A., Khibiev Kh.S., Akhmedov Sh.V., Electrochemical modification of cellulose, *Helard oF DSU, 2015, vol. 30, N. 6*
[8] Budaeva V.V., Mitrofanov R.Yu. and others. Ways complete and environmentally friendly processing of renewable plant materials, *Polzunovsky Vestnik*– 2010. Vol. 4, No. 1. - P.158-165.
[9] Dier, T. K. F., Rauber, D., Durneata, D., Hempelmann, R., & Volmer, D. A. (). Sustainable Electrochemical Depolymerization of Lignin in Reusable Ionic Liquids. Scientific Reports, 2017, vol. 7, N.1. doi:10.1038/s41598-017-05316-x

Introduction

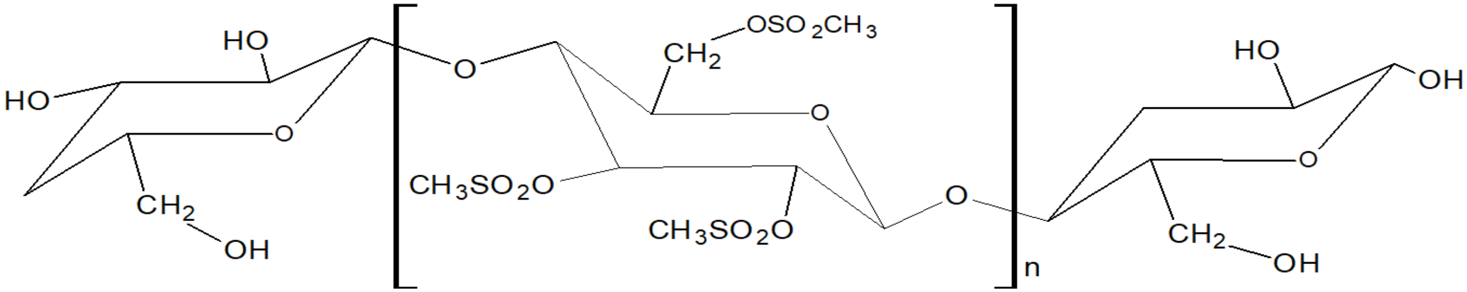


Fig. 3. Cellulose mesylate structure [10]

Cellulose mesylates are a well-known class of organic compounds related to esters, with the general formula [C6H7O2 (OH) 3-X (SO3CH3) 3] n, reactive, subject to exchange reactions and nucleophilic substitution (SN2); is of interest primarily as a starting product for the synthesis of new classes of cellulose and carboxycellulose derivatives [11].

[10] Sh.Sh. Khidirov, Kh.S. Khibiev, M.A. Akhmedov, *Pharm. Chem. J.,* 2017, 50, 817; DOI: 10.1007/s11094-017-1539-x.

[11] N. Bykles, L. Segal, *Cellulose and its derivatives*. Part 2, Ed. Z. A. Rogovina, Mir, Moscow, 1974, 510 p.

Introduction

Research objectives

1. Development of new methods for organic and electrochemical synthesis of cellulose mesylates;
2. Modification and study of the properties of biomedical materials and preparations based on cellulose mesylates.

The specified purpose of the work will require the solution of the following tasks:

1. Selection of systems of organosulfur solvents for dissolving cellulose.
2. Study of the composition of the products of acid hydrolysis of cellulose in methanesulfonic acid solutions.
3. Synthesis and study of the properties of cellulose mesylate, cellobiose and glucose.
4.Development of methods for isolation and purification from solutions of methanesulfonic acid - microcrystalline and nanocrystalline cellulose.
5. Investigation of cellulose electrooxidation in methanesulfonic acid solutions.
6.Synthesis of biomedical materials and preparations obtained by C-OH functionalization of cellulose mesylate

Results and discussion

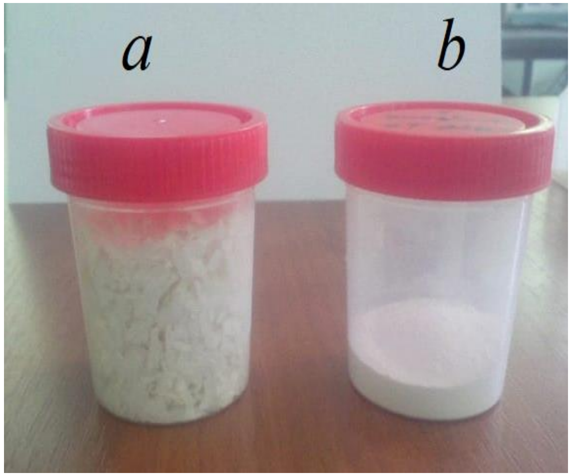


Fig.4. Cellulose original image (a) microcrystalline cellulose and (b).

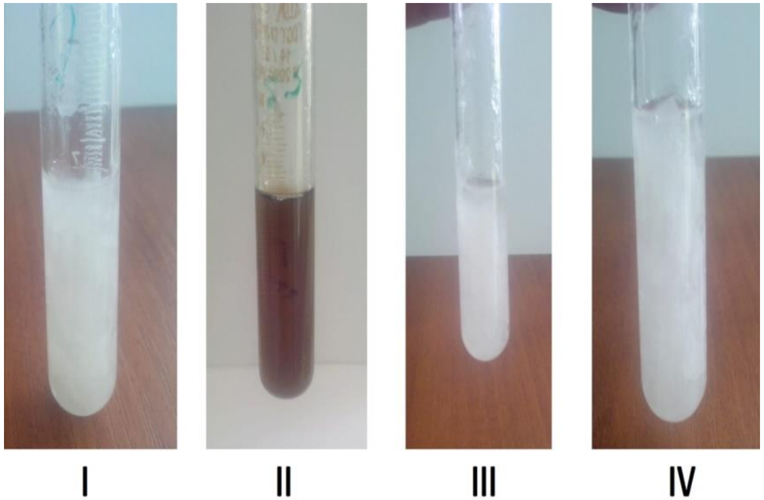


Fig.5. Cellulose solutions: I - in 10.0 M MSC solution; II - in 15.0 M MSC solution; III –10.0 M DMSO solution; IV - in the system of 5.0 M solutions of MSC and DMSO at a ratio of 1 ÷ 1.

Results and discussion

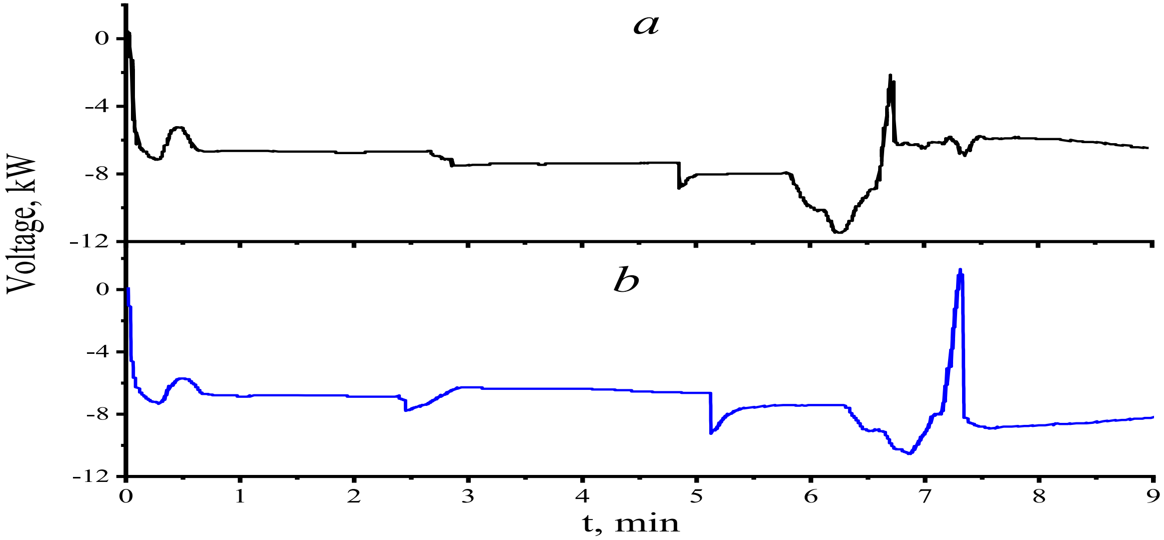
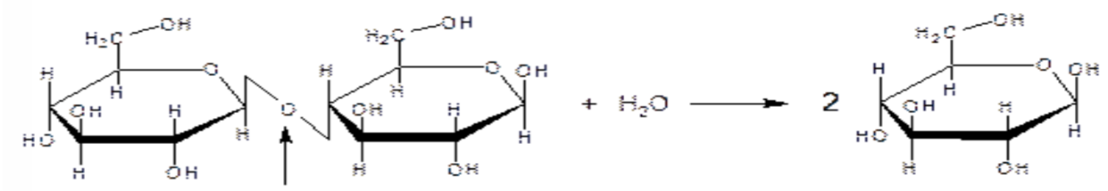


Fig.6. Electropherogram of a solution of cellobiose (1) and glucose (2) obtained after hydrolysis of cellulose in 15.0 M MSC solution.



Results and discussion

Data of analysis

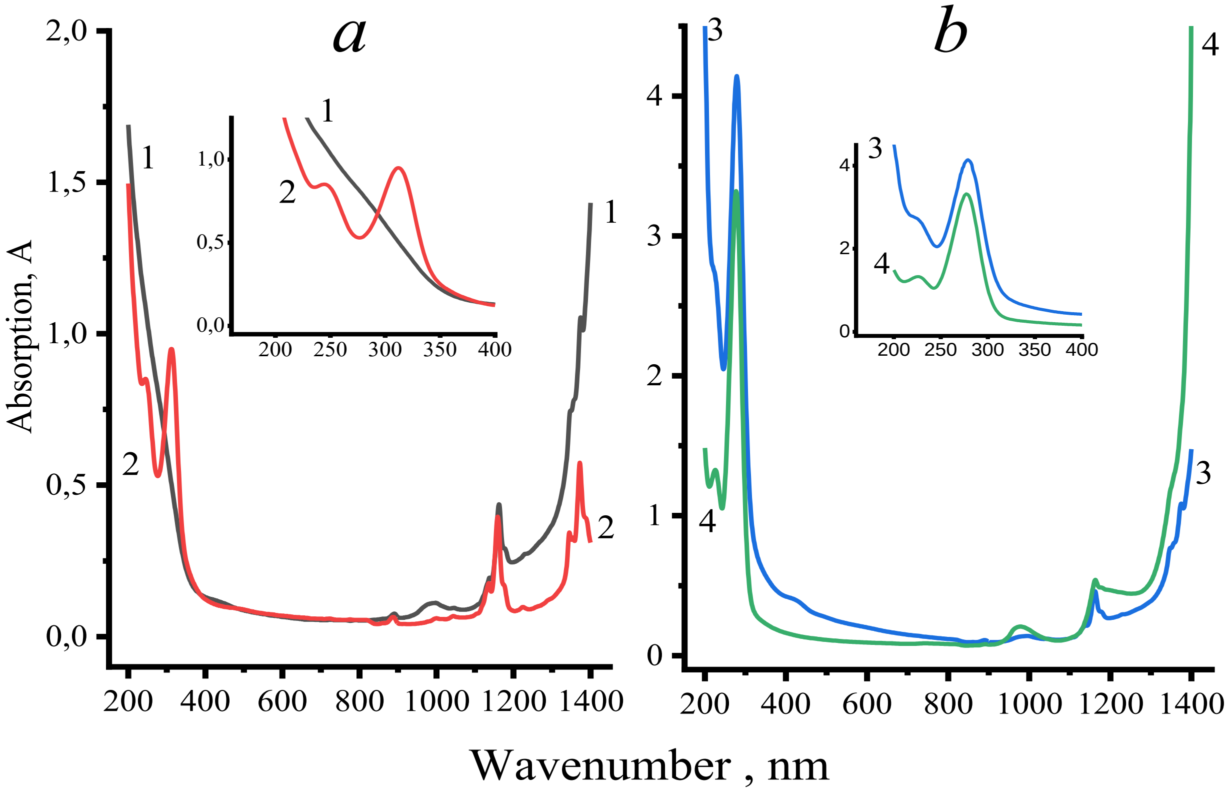


Fig. 7. UV and Near IR spectra: a –10 M (1) and 15 M (2) MSA solutions; b - 10.0 M MSA-10 g / l cellulose (3) and 15.0 M MSA-10 g / l cellulose (4).

Results and discussion

Data of analysis

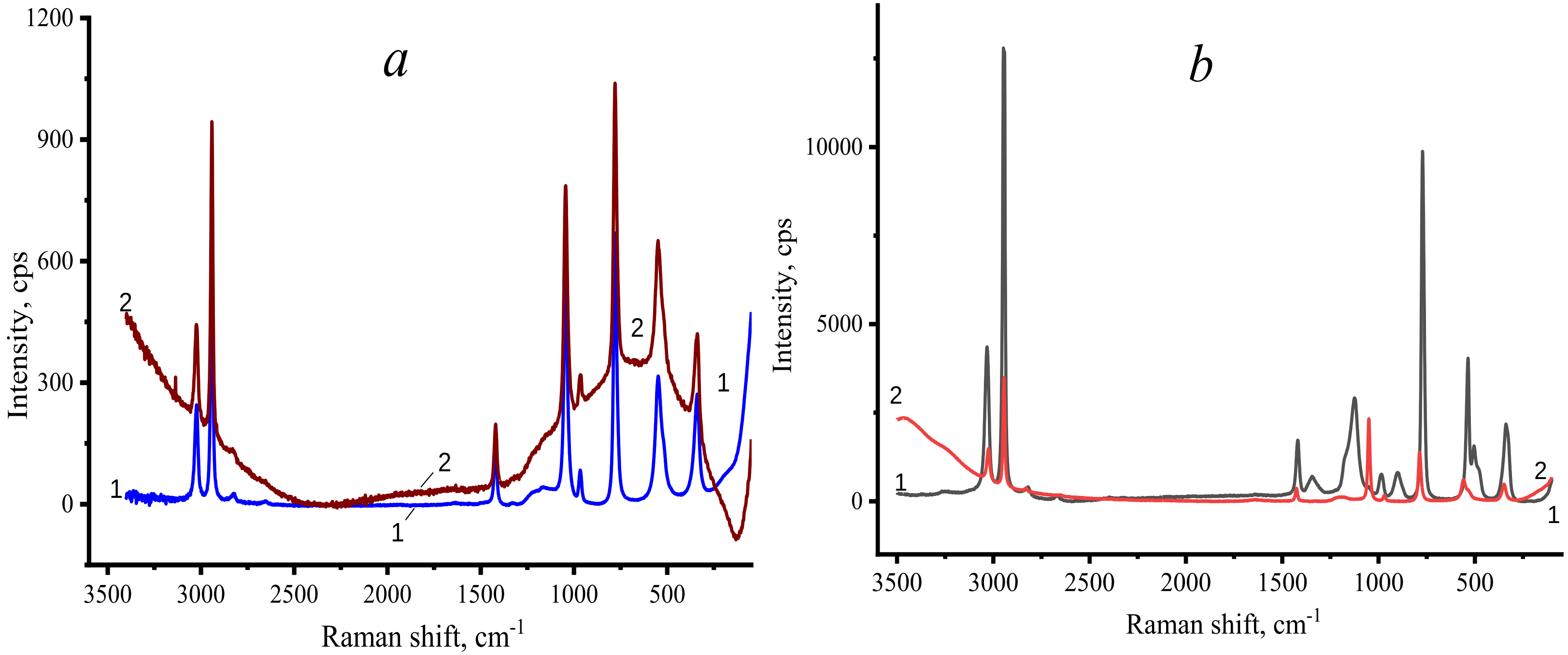


Fig. 8. Raman spectra: *a* - 10 M MSA solution (1) and in the presence of 10 g / L cellulose; *b* - 15 M MSA solution and in the presence of 10 g /l cellulose. Excitation source solid-state laser 532 nm.

Results and discussion

Data of analysis

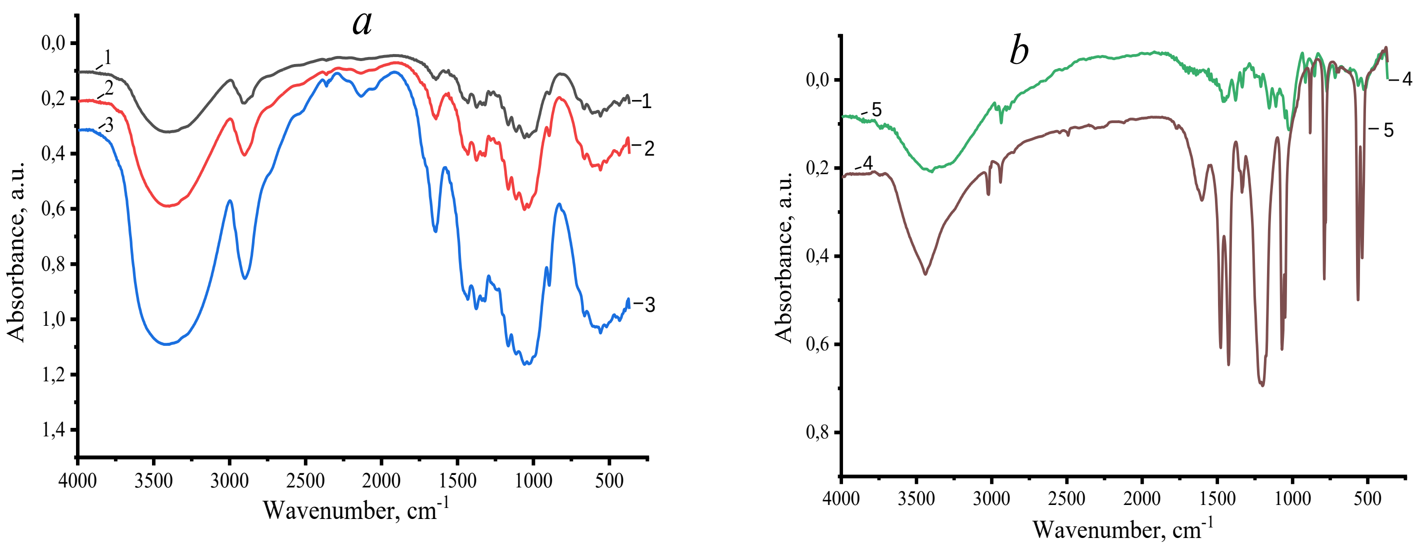


Fig. 9. IR spectra of the initial cellulose (1) and solid products obtained as a result of its modification in MSC solutions: MCC (2); NCC (3), dehydrated cellobiose (4) and glucose (5).

Results and discussion

Data of analysis

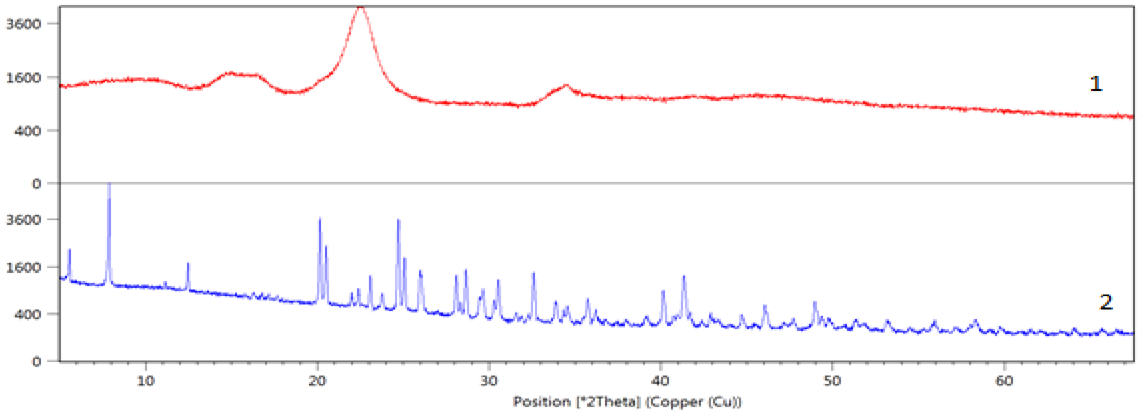
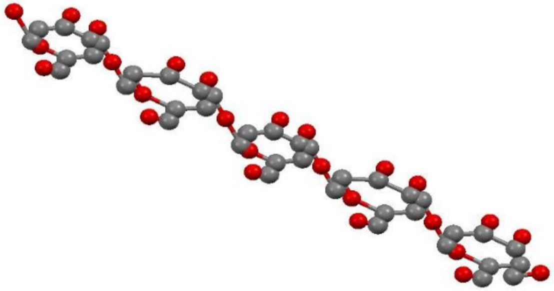
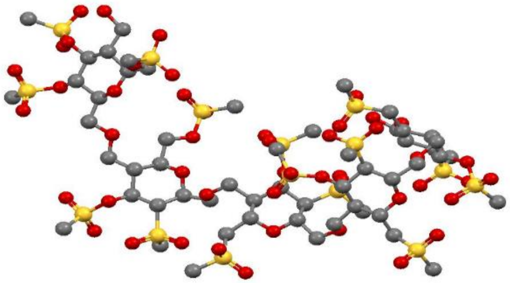


Fig.10. X-Ray analysis of the original cellulose (1) and cellulose of mesylate (2)

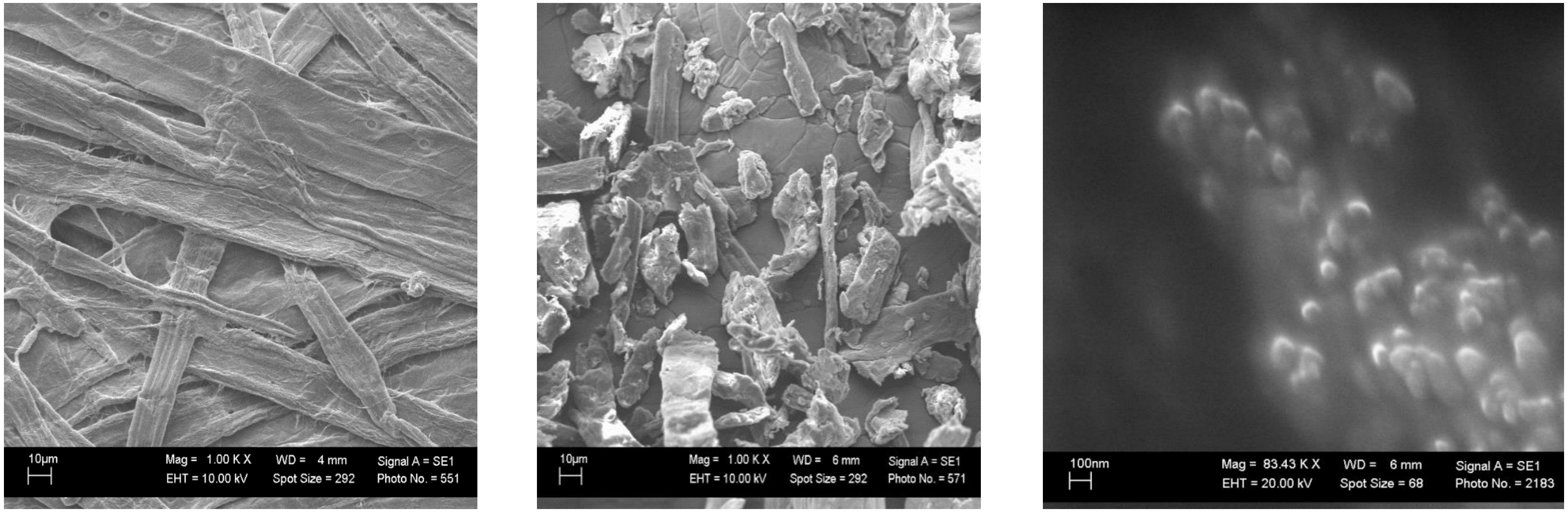


fragment cellulose



fragment cellulose of mesylate

Data of analysis

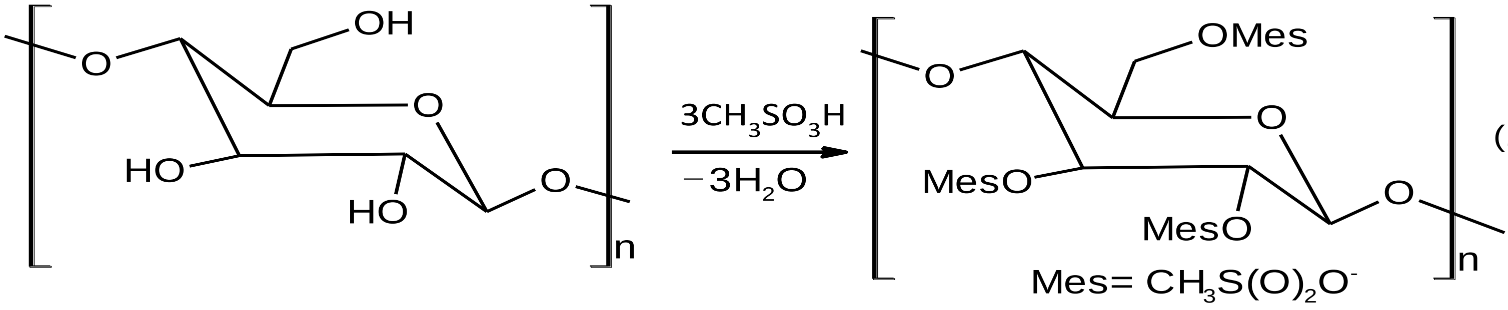


a *b* *c*

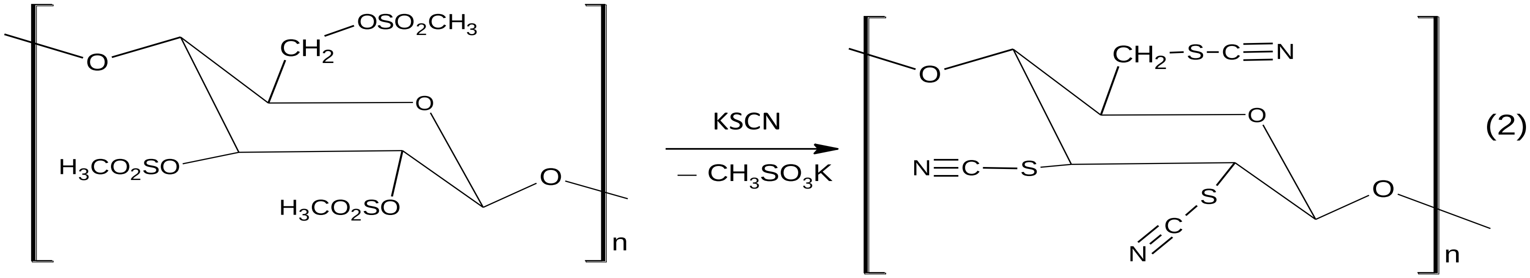
Fig.11. Image of scanning electron microscopy of the surface of the initial cellulose (a) and the products of its hydrolysis in MSC solutions: MCC (b) and NCC (c).

Results and discussion

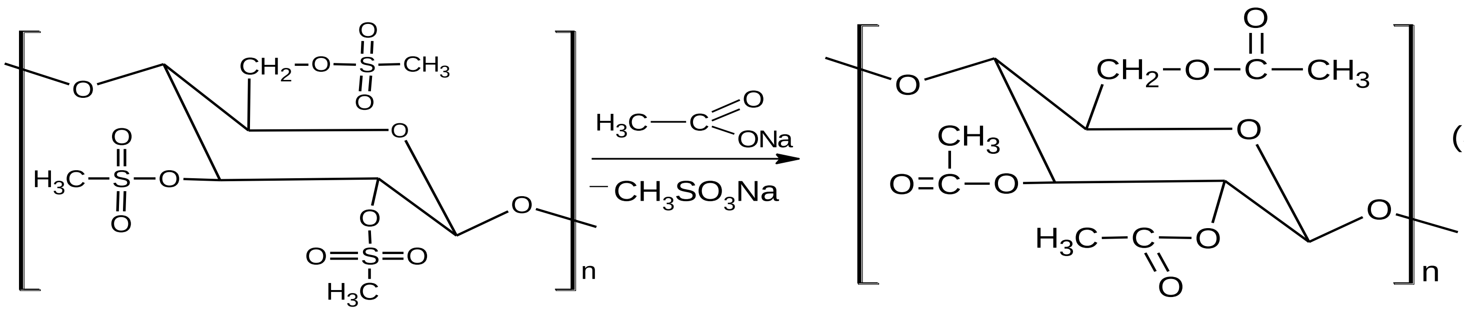
Cellulose modification



(1)



(2)



(3)

Results and discussion

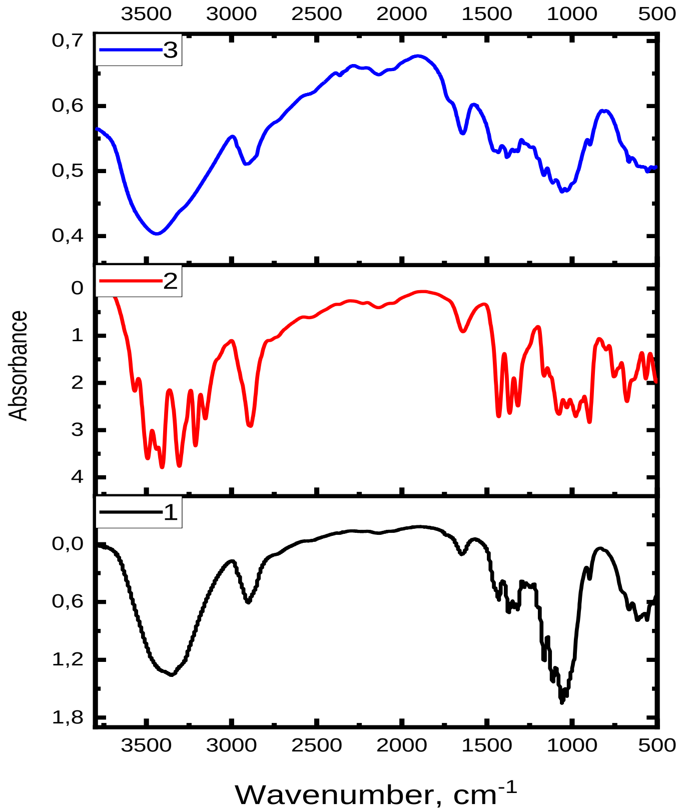


Fig. 16. IR spectra of nucleophilic substitution products microcrystalline cellulose: microcrystalline cellulose (1); cellulose thiocyanate (2) and cellulose acetate (3).

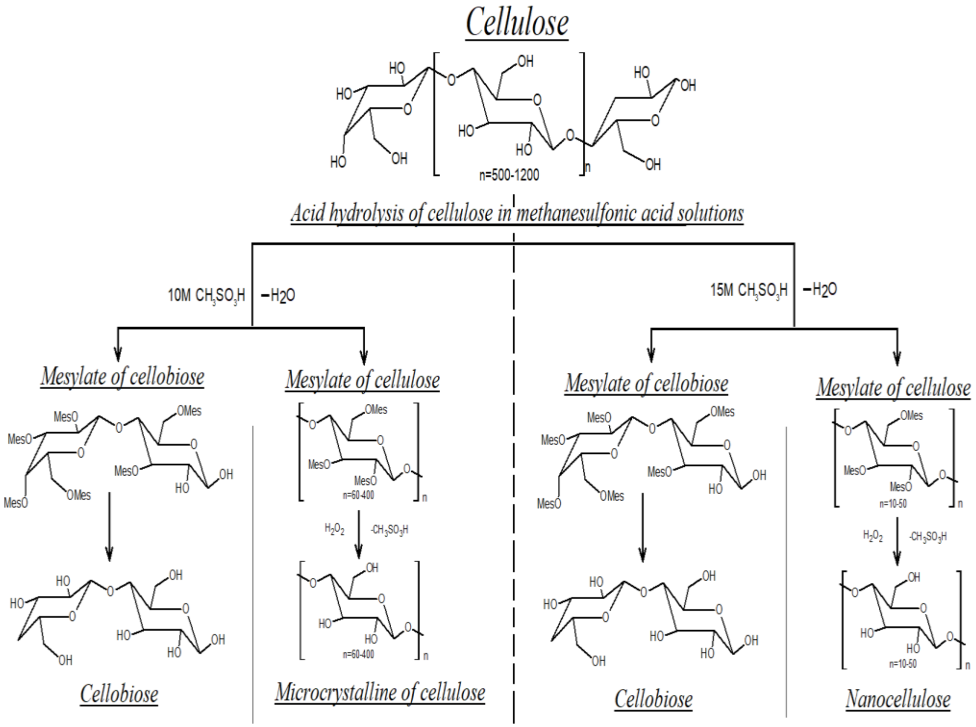
Table 2.

Comparative characteristics of the absorption bands of the IR spectrum of the products of nucleophilic substitution of MCC

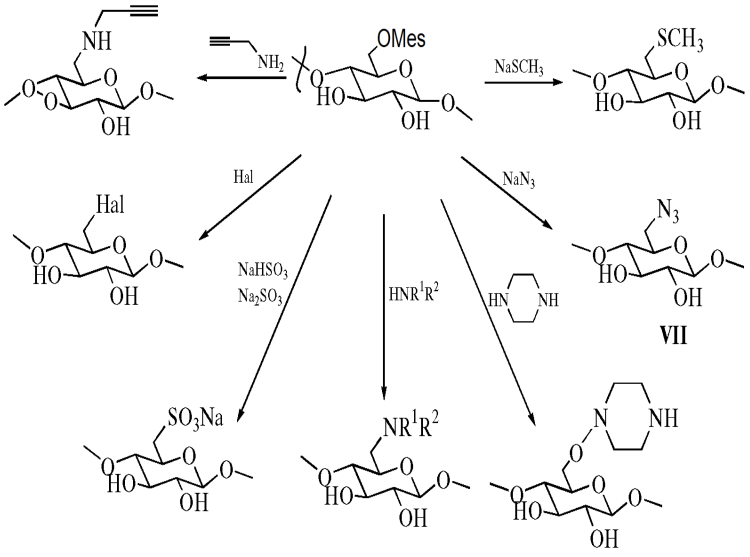
Cellulose of thiocyanate	
Functional groups	**Absorption bands, cm^{-1}**
C-C	585-540
C-(H)S-C	705—590
S-C	785—710 830-790
C-(H)OH	930-840
C-O	1340-1210
C-(H) S- C≡N	2075-1900 2200-2080
S-C≡N	2300-1900
C≡N	1710-1520
C – (OH)	3000-2780
OH-	3180-3130 3245-3190 3360-3250 3540-3600
Acetylcellulose	
Functional groups	**sorption bands, cm^{-1}**
C-C	1035
C-(H)OH	955-890
C-O	1320-1210
COO$^-$	1640-1725
OH-	3000-2780
OH-	3700-3050

Results and discussion

Sheme 6. Cellulose hydrolysis in methanesulfonic acid solutions



Scheme 7. Nucleophilic substitution of cellulose mesylates



$R^1 = H$ $R^2 = H$

$R^1 = H$ $R^2 = (CH_2)_2CH_3$, Ph

$R^1 = H$ $R^2 = (CH_2)_n$-NH_2, PhNH

$R^1 = H, CH_3$ $R^2 = CH_3$

$R^1 = Ph$ $R^2 = C_2H_5$

Polarization measurements

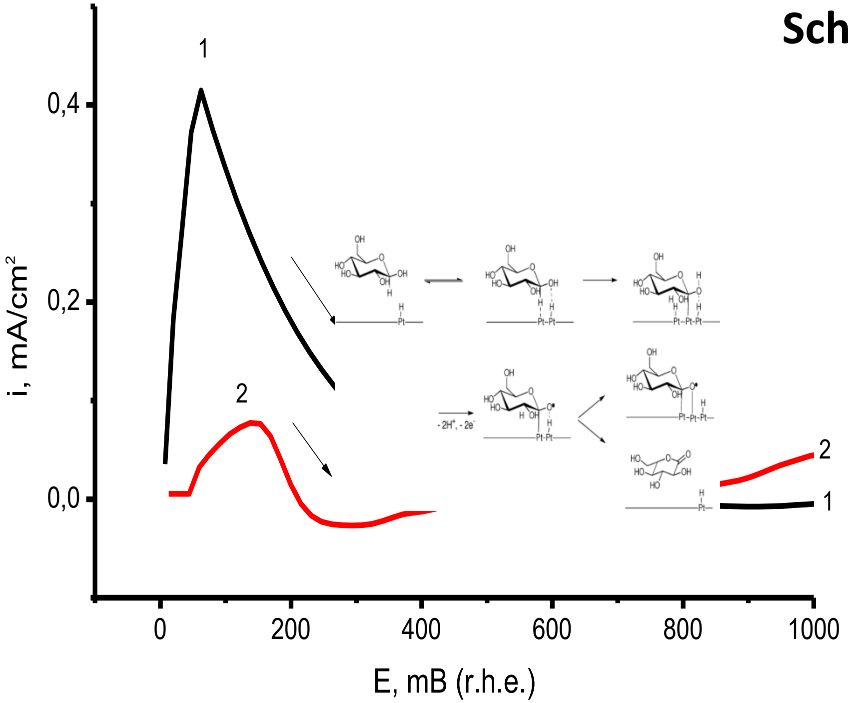
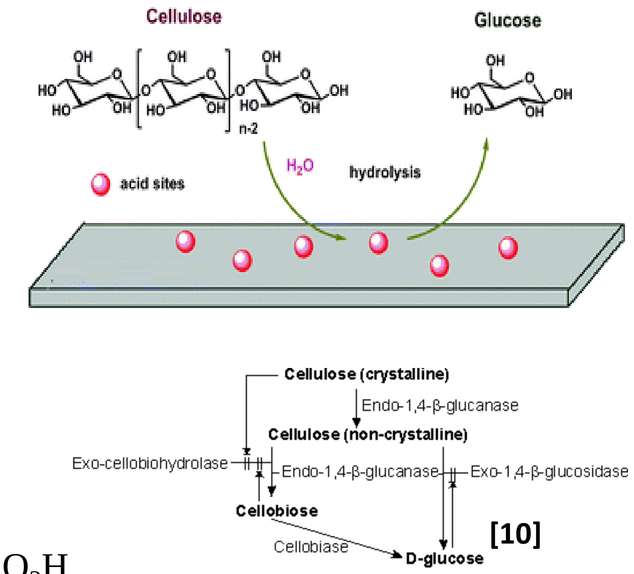


Fig.17. CVA of flat Pt-electrode in the 10.0 M solution of CH_3SO_3H и в присутствии целлюлозы , г/л: 1 (2). At scanning speed of potential 100 mB/s.

Scheme 8. Mechanism of cellulose hidrolysis



[11] Park, S., Boo, H., & Chung, T. D. (). Electrochemical non-enzymatic glucose sensors. Analytica Chimica Acta, 2006, vol.556, N.1, P.46–57. doi:10.1016/j.aca.2005.05.080

[12] Huang, Y.-B., & Fu, Y. (). Hydrolysis of cellulose to glucose by solid acid catalysts. Green Chemistry, 2013, vol. 15, N.5, P. 1095. doi:10.1039/c3gc40136g

Polarization measurements

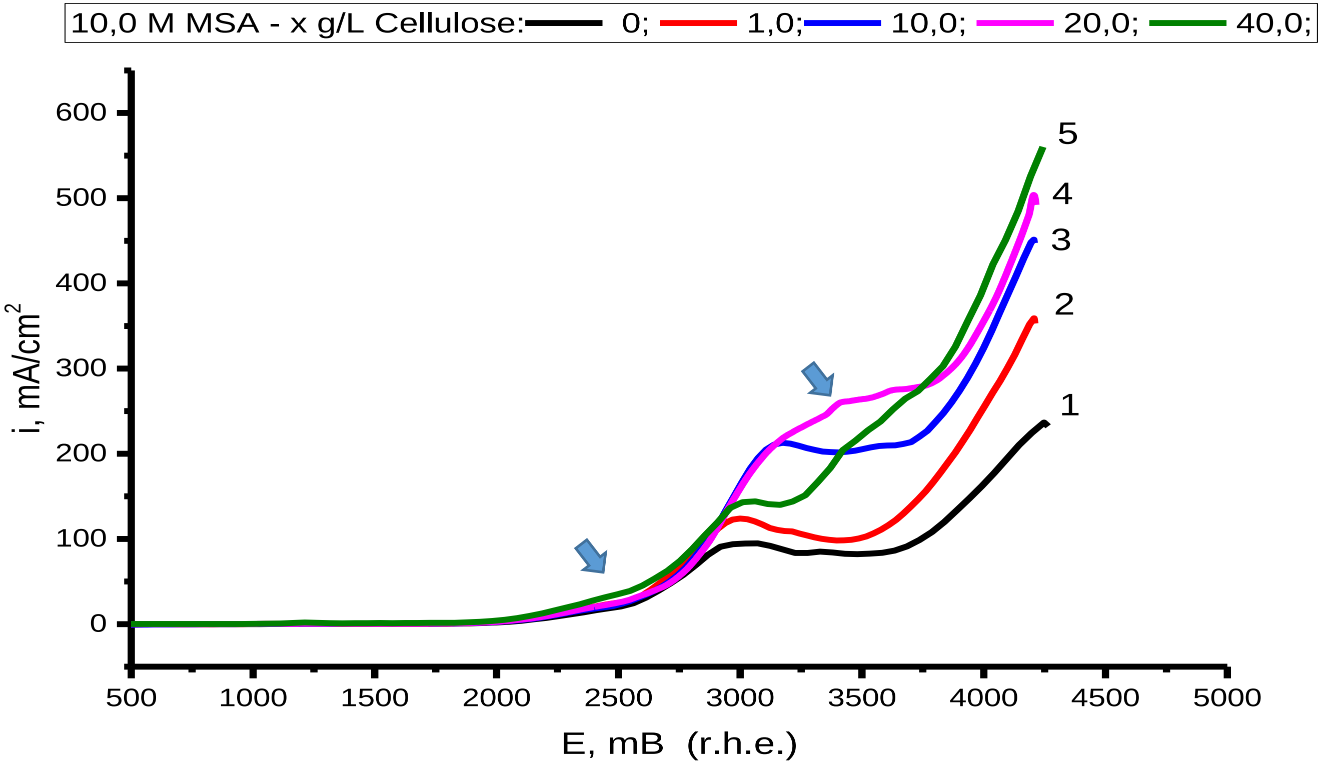


Fig.18. CVA of flat Pt-electrode in the 10.0 M solution of CH_3SO_3H ***и в присутствии целлюлозы , г/л: 1 (2); 10 (3); 20 (4); 40 (5)*** At scanning speed of potential 100 mB/s.

Analysis of products

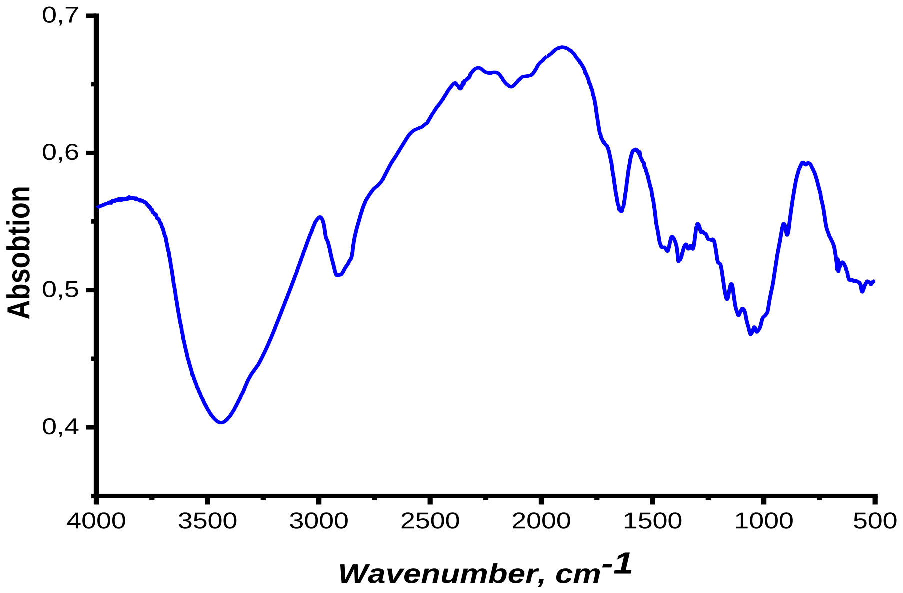


Fig. 20. IR spectra after electrolysis at 0.1 A / cm2 and E≥3.0 V in 10.0 M MSC solution.

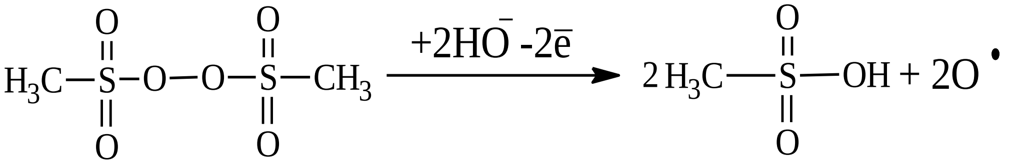
Cellulose carboxylate is a cellulose derivative with a carboxyl group (-CH2-COOH) linked to some hydroxyl groups of glucopyranose monomers, which make up an open cellulose chain, and is widely used in the preparation of various filters, sorbents, as well as in the preparation of pharmaceuticals.

Results and discussion

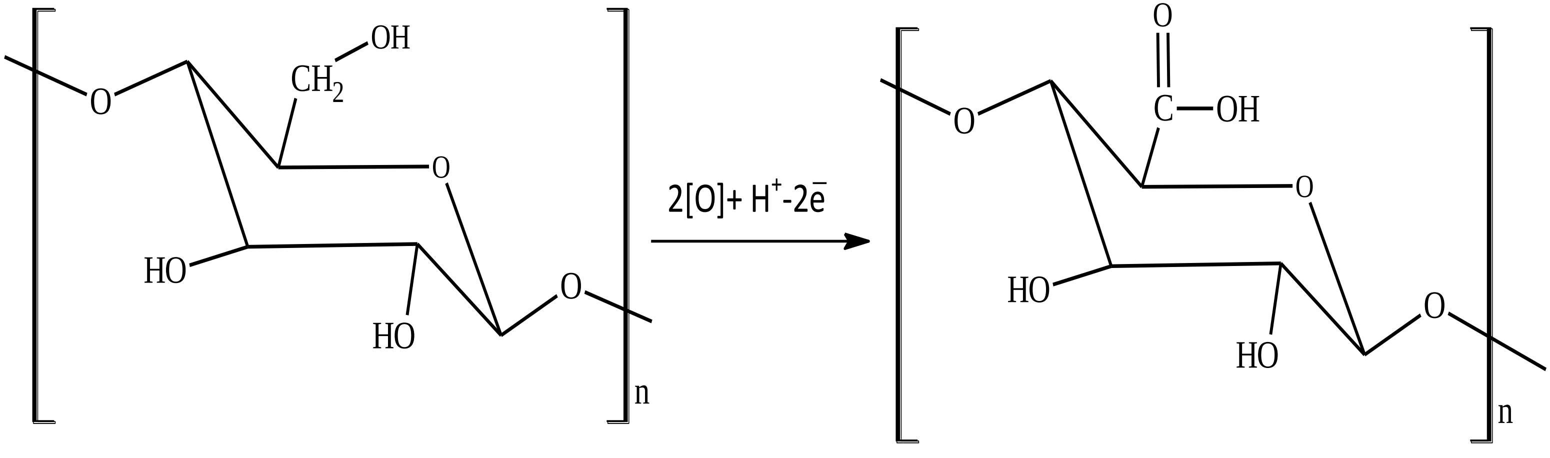
Scheme 7. Mechanism of the formation of cellulose carbaxylate from MCC:

$$H_2O - \bar{e} = OH_{ads} + H^+ \qquad (6);$$

$$OH_{ads} - \bar{e} = O_{ads} + H^+ \qquad (7)$$



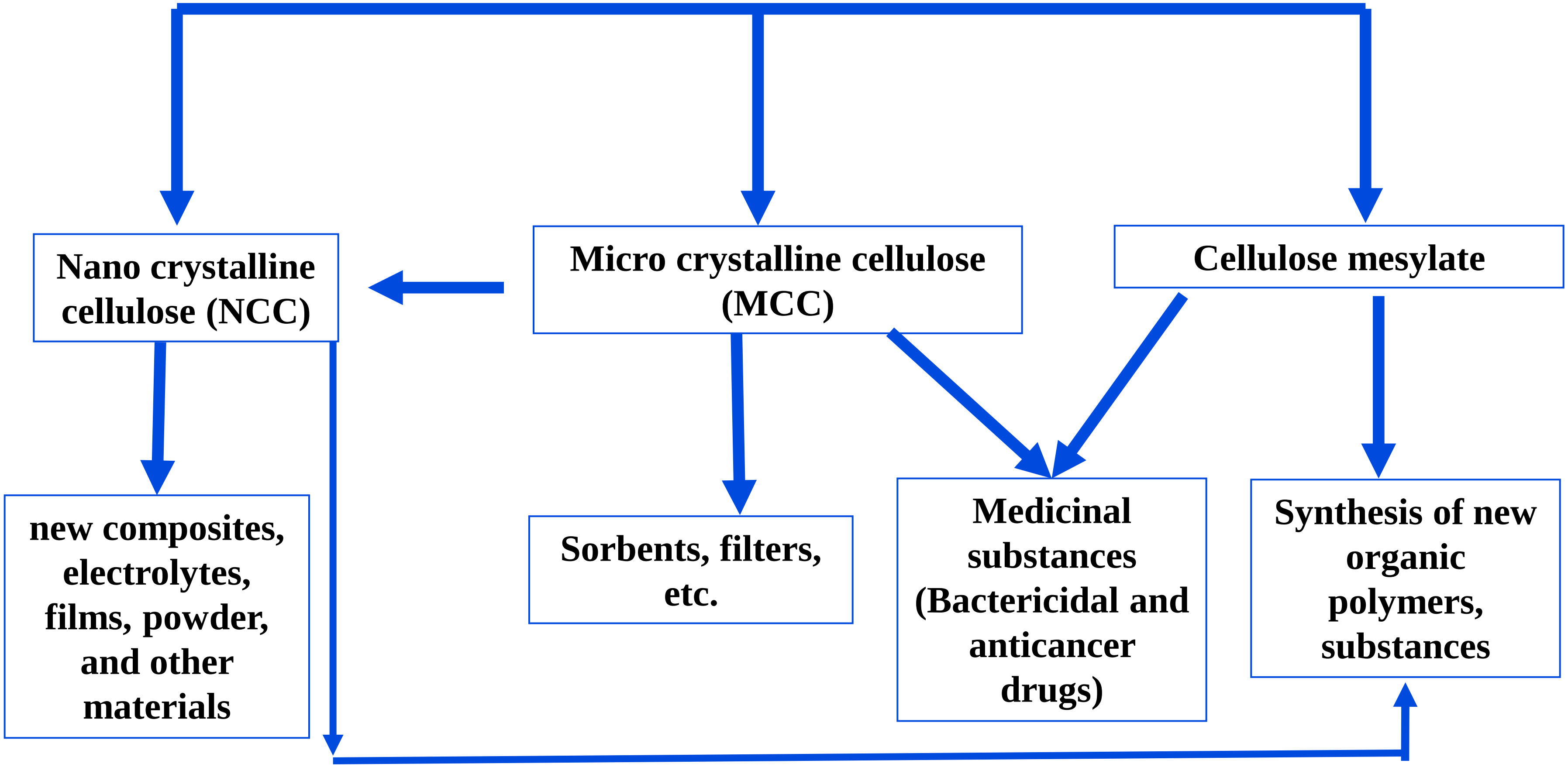
$$H_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CH_3 \xrightarrow{+2H\bar{O}\ -2\bar{e}} 2\,H_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OH + 2O^{\bullet} \qquad (4.8)$$



(4.9)

Results and discussion

Scheme 9. Modification of Cellulose



Nano crystalline cellulose (NCC)

Micro crystalline cellulose (MCC)

Cellulose mesylate

new composites, electrolytes, films, powder, and other materials

Sorbents, filters, etc.

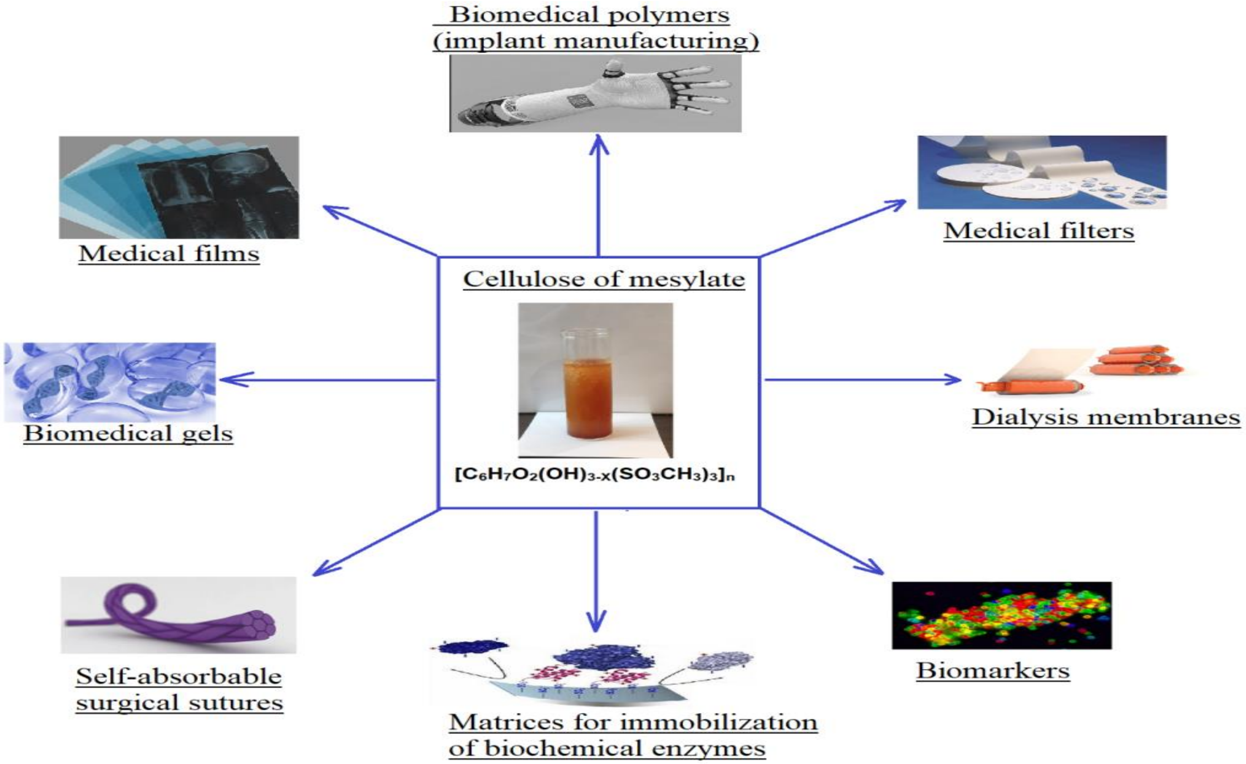
Medicinal substances (Bactericidal and anticancer drugs)

Synthesis of new organic polymers, substances

Results and discussion

Perspectives for researcher

Scheme 9. Preparation of various biomedical materials based on cellulose of mesylates



Conclusions

1. It was found by the methods of physicochemical analysis that the dissolution of cellulose in 10 and 15 M methanesulfonic acid solution is accompanied by incomplete hydrolysis, the main products of which are glucose, cellobiose, microcrystalline (MCC), and nanocrystalline cellulose. It was found that the interaction of alcohol groups with MSCs leads to the formation of esters - mesylate of cellulose, cellobiose and glucose.
2. As a result of chemical modification of cellulose in methanesulfonic acid solutions, 3 products were obtained and analyzed by IR spectroscopy methods - mesylate, thiocyanate, and cellulose acetate.
3. It was found that cellulose mesylates on the platinum electrode also undergo further electrochemical modification by anodic oxidation of the CH2OH group to the COOH group with the formation of cellulose monocarbaxylate.
4. Nucleophilic substitution reactions involving mesylate and other cellulose sulfonates, as well as bromine-containing cellulose derivatives, make it possible to obtain a large number of regioselectively functionalized derivatives, the subsequent modification of which can lead to the creation of new functional materials.
5. Electrochemical modification of cellulose mesylate does not lead to polymer destruction, but electrooxidation of C-OH groups of both aldehyde / ketone groups and carboxyl (COOH) occurs.

Achievements

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