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Abstract

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PREPARATION OF CARBOXYMETHYLCELLULOSE PREPARATIONS FOR BLOOD-SUBSTITUTE SOLUTIONS

(Presented by Academician A. V. Topchiev, 3 VII 1958)

The sodium salt of carboxymethylcellulose (Na-CMC), as a plasma substitute, was first used by Hopper ([1]). According to his data, the introduction even of highly excessive amounts of Na-CMC (up to 600 ml of a 0.25% solution per 1 kg of body weight) does not cause a significant change in the composition of the blood or in the organs of animals. However, upon internal administration of Na-CMC, Hopper observed a hypotensive effect, which led him to give this preparation an overall negative assessment.

In view of the fact that CMC preparations can be obtained with different values of the degree of polymerization (DP) and degree of etherification (DE) ([2]), it seemed advisable to obtain preparations that would also satisfy requirements from the standpoint of their hemodynamic properties.

This work was begun by the Moscow Petroleum Institute jointly with the Central Institute of Hematology and Blood Transfusion (TsOLIPK) in 1953.

We synthesized more than 40 different CMC preparations, which were tested at TsOLIPK as blood-substitute solutions.

The degree of polymerization of CMC was determined by Wurz' s method ([3]), and the degree of etherification by iodometric determination of copper in the copper salt of CMC.

The DP of the initial cellulose was determined from the intrinsic viscosity of its solutions in a quaternary ammonium base ([4]).

CMC preparations with different DE and DP values were obtained by etherifying comminuted alkali cellulose, previously pressed free of excess aqueous alkali, with sodium monochloroacetate. The degree of etherification was regulated

by changing the quantitative ratio of etherifying reagent to cellulose ([2]), while the DP was regulated by the temperature regime and duration of preliminary degradation of the alkali cellulose.

The amount of etherifying reagent necessary to achieve the required degree of etherification depends on the DP of the initial alkali cellulose.

The data of Table 1 show that, with a decrease in the DP of alkali cellulose, higher values of the degree of etherification are attained at the same reagent ratio (experiments Nos. 1–3). At the same time, it is shown that the required DE can be achieved with a lower consumption of sodium monochloroacetate by lowering the DP of the initial alkali cellulose (experiments Nos. 4 and 5).

For the preparation of blood-substitute solutions, only chemically purified CMC preparations are suitable. We used the following method for purifying CMC preparations. The preparation precipitated from aqueous solutions with alcohol and filtered was treated with a 5% alcoholic solution of hydrochloric acid. Iron compounds dissolved in the acid were removed

with subsequent filtration and washing of the cellulose-glycolic acid formed, which was then dissolved in an aqueous alkali solution, precipitated again with alcohol, and washed free of impurities by extraction. This method of purification does not cause a change in the DP of CMC and ensures the preparation of products of a high degree of purity.

Table 1

Change in DS of CMC as a function of the DP of alkali cellulose

Experiment No.	DP of alkali cellulose	Ratio $C_6H_{10}O_6$:$CH_2ClCOONa$ (in moles)	DS of CMC
1	315	1 : 1.35	71.0
2	215	1 : 1.35	73.0
3	170	1 : 1.35	77.6
4	116	1 : 1.30	75.2
5	100	1 : 1.25	75.3

To ensure complete solubility, the DS of CMC must be high. However, as tests of our CMC preparations carried out at TsOLIPK showed, fluctuations in the DS value from 70 to 85 do not produce a substantial effect on the blood-substituting properties of CMC ([5]).

In order to study the influence of DP, a series of CMC preparations with DP from 240 to 58 was prepared. The most effective were CMC preparations with the viscosity of 3% aqueous solutions in the range 3.5–5.0 centipoises, which corresponds to DP values from 70 to 100. More highly molecular preparations, as well as preparations with a lower DP, have poorly expressed hemodynamic

properties. This fact is not consistent with the data of G. M. Miklavskaya and E. D. Buglova ([6]), who used higher-molecular-weight CMC preparations for blood-substitution purposes.

Of great importance is the choice of a rational method for obtaining CMC preparations with a low degree of polymerization. Low-polymerized carboxymethylcellulose can be obtained either by preliminary destruction of the initial cellulose or alkali cellulose, or by additional cleavage of ready-made CMC preparations.

As our studies have shown, preliminary cleavage of cellulose with an aqueous HCl solution causes a number of technological difficulties during mercerization of the cellulose and its subsequent use, and cannot be recommended.

Oxidative destruction of alkali cellulose by atmospheric oxygen, as can be seen from Table 2, is a very prolonged process even at an elevated temperature of preliminary aging of the alkali cellulose.

Table 2

Dependence of the DP of CMC on the duration and temperature conditions of the preliminary aging process of alkali cellulose

Preparation No.	Preliminary aging conditions	DP of CMC
1	100 h at 20°	270
2	12 h at 50° + 32 h at 20°	130
3	12 h at 55° + 32 h at 20°	125
4	17 h at 50° + 32 h at 20°	120

Note. Mercerization was carried out with a NaOH solution (230–235 g/l) at 20° for 1.5 h. The alkali cellulose was preliminarily ground for 2.5 h at 50° (in experiment No. 1, at 35°).

In order to accelerate the process of destruction of alkali cellulose, additions of hydrogen peroxide to the mercerization bath or to the alkali cellulose during its grinding were used.

The results of the experiments are given in Table 3.

CMC samples prepared from alkali cellulose destroyed with the use of H_2O_2 behaved differently when tested as blood-substituting solutions: the introduction of small amounts of hydrogen peroxide (up to 1.5% into the grinder and the mercerization bath) does not have a negative effect on the blood-substituting properties of CMC. Pre-

Table 3

Destruction of alkali cellulose in the presence of hydrogen peroxide

Preparation No.	Amount of H_2O_2 in the mercerization bath: H_2O_2 concentration in the alkali, %	Amount of H_2O_2 in the mercerization bath: H_2O_2, % of cellulose weight	Amount of H_2O_2 added to the grinder, % of cellulose weight	Maturation conditions	DP of CMC
5	1.5	45	—	3 hours at 40°	167
6	1.5	45	—	6 hours at 40°	130
7	1.5	45	—	5 hours at 45°	130
8	1.5	45	1.5	4 hours at 40°	140
9	—	—	3.5	4 hours at 40°	110
10	—	—	3.5	4 hours at 45°	100

Note. Mercerization was carried out at 35° for 1.5 hours; grinding of the alkali cellulose was carried out at 37° for 2.5 hours.

Preparations Nos. 5–8, obtained in this way, gave satisfactory results in animals. The addition of larger amounts of H_2O_2 directly to the alkali cellulose during its grinding leads to the appearance of toxic properties in the CMC preparations: preparations Nos. 9–10 caused the death of animals when administered intravenously.

The data from the study of the chemical composition of cellulose subjected to oxidative destruction, presented in Table 4, show that preparations Nos. 9 and 10, which caused the death of animals, differ little from preparations Nos. 5 and 8 in the content of carboxyl groups in the cellulose, determined by the *O*-nitrophenolate method ([7]). The content of aldehyde groups, determined from iodine numbers ([8]), is insignificant in all preparations (taking into account their degree of polymerization). According to the hydroxylamine method for carbonyl groups ([9]), practically no change in the pH of the solution was detected. Consequently, ketone groups were also absent in the cellulose samples studied.

Table 4

Change in functional groups in cellulose during oxidative destruction

Preparation No.	Number of glucose residues per one group: –COOH	Number of glucose residues per one group: –COH
5	89	554
8	75	585
9	73	394
10	69	235

Therefore, the increase in toxic properties in preparations Nos. 9 and 10 cannot be explained by a change in the average chemical composition of the cellulose. Most likely, it is a consequence of the nonuniformity of the destruction process, as well as the accumulation of some amount of highly oxidized cellulose, which gives rise to the toxic properties of the CMC preparations. On this basis, it should be concluded that the use of hydrogen peroxide for the purpose of accelerating the destruction process of alkali cellulose and attaining the required DP must be undertaken with great caution.

To obtain CMC preparations with a DP value below 100, additional destruction of the finished product was carried out by hydrolytic cleavage with an aqueous solution of hydrochloric acid at 65–70°. The duration of the hydrolysis process depends on the initial DP of the CMC preparations.

Experience with the use of high-molecular-weight CMC preparations (DP 250) for this purpose gave unsatisfactory results: preparations Nos. 12 and 13, obtained in this way, as can be seen from Table 5, proved to be toxic, whereas samples obtained by additional degradation of comparatively low-molecular-weight CMC preparations (DP about 130) gave positive results.

Table 5

Influence of the duration of hydrolysis of CMC with HCl solution on the blood-substituting properties of the preparations

Preparation No.	DP of initial CMC	Duration of CMC hydrolysis, min	DP of CMC after hydrolysis	Results of biological tests
2	130	80	80	+
3	125	75	80	+
6	130	75	90	+
7	130	80	80	+
11	130	85	67	+
12	250	300	70	–
13	240	300	60	–

The negative results may apparently be explained by the fact that, during hydrolytic cleavage of high-molecular-weight CMC preparations in a heterogeneous medium, some of the highest-molecular-weight fractions remain insufficiently degraded, which adversely affects the blood-substituting properties.

The investigations carried out make it possible to outline ways of developing a technology for obtaining Na-CMC preparations possessing blood-substituting properties.

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Note: Figure translations are in progress. See original paper for figures.