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Comparative Study of the Mucoadhesive Properties of Polymers for Pharmaceutical Use

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Abstract

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BACKGROUND: In recent years, mucoadhesive dosage forms due to their advantages have attracted the interest of researchers and developers. Polymeric excipients are included into the drug composition to give adhesion to the mucous membrane.

AIM: The aim of this research was to select a specific brand of pharmaceutical quality polymer that is promising for inclusion in the drug formulation.

METHODS: The article presents the results of studying the mucoadhesive properties of polymers on two models using mucin: By measuring the amount of adhesion and by the evaluation the sample movement speed.

RESULTS: According to the combination of two indicators, the highest mucoadhesive properties were shown by the brands of hydroxypropylmethylcellulose and xanthan gum. In addition, it was noted that hydroxyethylcellulose (HEC), sodium alginate, and hydroxypropylmethylcellulose (HPMC) also have good mucoadhesive properties. Polyethylene glycols proved to have the weakest mucoadhesive properties. The negative relationship between the average molecular weight and the sample movement speed of the HEC and HPMC was established. Obtained data showed no direct influence of the polymer average molecular weight on the amount of adhesion. It was also noted that there is no strong correlation between the amount of adhesion and the sample movement speed of the experimental samples.

CONCLUSION: Based on the results of the study, it was suggested that the complex influences of the physical and chemical properties of the polymer on its mucoadhesive properties.

Introduction

The choice of excipients and, first of all, polymers that provide adhesion to the mucous membrane should be based on specific indicators including the critical gelation concentration, optimal pH, rheological properties (plastic and dynamic viscosity, yield strength, and spreadability), as well as the characteristics of mucoadhesion. If the technological parameters of polymers, as well as their viscosity properties, are often presented in the specification, then the indicators of mucoadhesion are studied by researchers on a small group of polymers selected according to the design of the study. These conditions do not allow the valid screening of a specific excipient for the development of a mucoadhesive dosage form with optimal biopharmaceutical characteristics. Another task when working with mucoadhesive dosage forms is an adequate assess of the effectiveness of their ability to fix on the mucosa. To date, quite a lot of methods have been developed for evaluating the mucoadhesive characteristics of pharmaceutical composition and excipients [1], [2], [3], but none of the methods have become pharmacopoeia due to certain restrictions. At

the same time, the evaluation of the mucoadhesive properties of the dosage form is necessary for the scientifically based pharmaceutical development of drugs intended for application to the mucous membranes [3], [4].

The aim of the work was to study the comparative properties of various grades of pharmaceutical polymers used in the formulations of mucoadhesive dosage forms: Cellulose derivatives, sodium alginates, xanthan gums, carbomers, and polyethylene glycols.

Materials and Methods

Materials

The objects of research were the pharmaceutical quality polymers. Information about the chemical name, trade name and manufacturer, the range of recommended concentration, as well as information about the polymer viscosity according to the manufacturer is shown in Table 1.

Table 1: Physicochemical characteristics of polymers

Trade name, manufacturer	Recommended concentration, %	Viscosity
Hydroxyethylcellulose (HEC)		
NATROSOL™ 250L Pharm, Ashland	4–8	0.075–0.150 Pa·s (5% solution)
NATROSOL™ 250G Pharm, Ashland	4–8	0.25–0.4 Pa·s (2% solution)
NATROSOL™ 250M Pharm, Ashland	4–8	4.5–6.5 Pa·s (2% solution)
NATROSOL™ 250H Pharm, Ashland	4–8	1.5–2.5 Pa·s (1% solution)
NATROSOL™ 250HHX Pharm, Ashland	4–8	3.5–5.5 Pa·s (1% solution)
Hydroxypropylmethylcellulose (HPMC)		
Benece™ K100LV PH DC, Ashland	2–10	0.08–0.12 Pa·s (2% solution)
Benece™ E4M Pharm, Ashland	2–10	2.7–5.04 Pa·s (2% solution)
METOLOSE® 60SH, Shin-Etsu Chemical Co	2–10	0.05–10 Pa·s (2% solution)
Benece™K100MPH DC, Ashland	2–10	75–140 Pa·s (2% solution)
Hydroxypropylcellulose (HPC)		
Klucel™ GF Pharm, Ashland	5–20	0.15–0.4 Pa·s (2% solution)
Sodium carboxymethylcellulose (sodium CMC)		
Blanose® 7LPEP, Ashland	4–8	0.025–0.05 Pa·s (2% solution)
Blanose® 7MF PH, Ashland	4–8	0.4–0.6 Pa·s (2% solution)
Blanose® 7HF PH, Ashland	4–8	1.5–2.5 Pa·s (1% solution)
Blanose® 9M31F PH, Ashland	4–8	1.53.1 Pa·s (2% solution)
Sodium alginates		
Protanal® CR 8133, FMC BioPolymer	5–10	0.1–0.3 Pa·s(2% solution, pH 7.5)
Protanal® CR8223, FMC BioPolymer	5–10	0.6–0.9 Pa·s(1.25% solution, pH 7.5)
MANUCOL®LX, IMCD LTD	5–10	0.06–0.17 Pa·s(1% solution, pH 7.5)
Xanthan gums		
Grindsted® Xanthan 80, Dupont Nutrition & Health	0.05–0.5	1.2–1.6 Pa·s(1% solution in 1% KCl)
XANTURAL® 180 XANTHAN GUM,CP Kelco	0.05–0.5	1.2–1.6 Pa·s(1% solution in 1% KCl)
Carbomers		
CARBOPOL®ETD 971P NF, Lubrizol	0.5–0.7	4–11 Pa·s (0.5% solution at pH 7.5)
CARBOPOL® 974P NF, Lubrizol	0.5–0.7	29.4–39.4 Pa·s (0.5% solution at pH 7.5)
CARBOPOL® ETD 2020 NF, Lubrizol	0.5–0.7	47–77 Pa·s(0.5% solution at pH 7.5)
Polyethylene glycols (PEG)		
Polyglycol 400, «IREA2000»	1–10	0.000039–0.000045 m ² /s (kinematic viscosity at t 40 ± 0.3°C)
Polyglycol®400S, Clariant	0.5–20	0.000065–0.0001 m ² /s (kinematic viscosity at t 90 ± 0.3°C)

The polymer specifications specify the viscosity of solutions of different concentrations, which makes it impossible to compare the rheological characteristics of the samples to establish their relationship with the mucoadhesive properties. For some polymers, the specified range of average molecular weight is too large (sodium alginate), which makes it impossible to determine the effect (or lack thereof) of this characteristic on the indicator of mucoadhesion. Therefore, for some polymers, the dynamic viscosity was determined experimentally in accordance with the requirements of European Pharmacopeia using capillary viscometer method on a suspended level viscometer. The experiment was conducted at a temperature of $23 \pm 0.5^\circ\text{C}$. The viscosity of samples of sodium alginates and carbomers was measured at pH 7.5.

Conditionally studied polymers can be divided into semisynthetic and synthetic. The first group includes cellulose derivatives, sodium alginates, and xanthan gums; the second group includes carbomers and polyethylene glycols.

Methods for obtaining the experimental samples are shown in Table 2.

To make a solution of 20% and 4% mucin (mass-volume concentration), type II porcine stomach mucin was used (Sigma-Aldrich, catalog number M 2378), which is a mixture of glycoproteins [1] secreted by the digestive glands of a pig. The content of N-acetyl neuramic acid in the used mucin was 0.5%. This substance looked like a white powder with a yellowish tinge. Mucin when mixed with water gives a yellow muddy solution. As the concentration increases, it will turn into a sticky mass of light yellow color. To obtain solutions, the accurately weighed quantity of mucin was dissolved in water for injections.

Table 2: Methods for obtaining the experimental samples [4]

Polymer	Method
Sodium CMC	The accurately weighed quantity of the sodium CMC was slowly added to the funnel, which was obtained by vigorously mixing purified water on a magnetic stirrer EKROS ES-6120 (Russia). Mixing was continued until complete dissolution of the polymer.
HEC, HPC	The accurately weighed quantity of HEC or HPC was added to purified water preheated to a temperature of about $45\text{--}50^\circ\text{C}$. Mixing was continued until complete dissolution of the polymer.
HPMC	One-third of the total volume of purified water was heated to 80°C , then the accurately weighed quantity of the polymer was added and thoroughly mixed. The remaining volume of purified water was cooled to a temperature of $5\text{--}10^\circ\text{C}$ and added to the resulting dispersion of the HPMC. Mixing was continued until complete dissolution of the polymer.
Sodium alginates	The accurately weighed quantity of sodium alginate was dispersed in one-third of the total volume of purified water heated to a temperature of 80°C . The mixture was left to swell. Then, the remaining two-thirds of the purified water was added while stirring.
Xanthan gums	The accurately weighed quantity of xanthan gum was carefully poured on the surface of the purified water and mixed until a homogeneous sample was obtained.
Carbomers	The accurately weighed quantity of polymer was shifted on the surface of purified water and left to swell at room temperature for 30 min. Then, the neutralization was performed with 0.1 N sodium hydroxide solution to form a stable system.
PEG	The accurately weighed quantity of polymer was melted in an oil bath IKA HB 10 (Germany) at a temperature of 80°C . Then, the purified water was added. The resulting system was mixed, cooled for 15 min, and weighed. The loss in mass due to evaporation was compensated by adding purified water.

Methods

Mucoadhesion was determined by two ways: By the amount of adhesion (first method) and by the rate of the sample movement speed (second method) [2], [5], [6]. First method is based, apparently, on the strength of physical and chemical bonds formed between polymer and mucin molecules without taking into account its ability to move through the mucosa. The second method is important because it allows evaluating the retention time of the dosage form on the mucosa, which to some extent allows taking into account the physiological conditions. Consequently, it is advisable to use both methods for better evaluation of mucoadhesion.

First method: Evaluation of the amount of adhesion or the "Pull-off experiment"

The experiment used a lever mechanism, on the left shoulder of which there were movable (upper) and fixed (lower) parts, on the right – a place for cargo placement. Previously, non-woven material of the spunbond type was attached to the lower and upper part of the lever mechanism. About 20% mucin solution was applied to the lower part, and a test gel sample was applied to the upper part. In this case, the mucin layer thickness was controlled, it was 0.1 mm, which lies within the range of the mucus layer thickness under physiological conditions [7]. The plates were held together for 1 min. Then, a load was placed on the platform and the weight was recorded at which the upper plate was completely detached from the lower one. Mucoadhesion was determined at a temperature of $20 \pm 0.5^\circ\text{C}$. The amount of adhesion was calculated as the product of the mass of the load and the acceleration of gravity ($g = 9.81 \text{ m/s}^2$) and was expressed in Newton. Based on the average values of five measurements, the rate of mucoadhesive was calculated.

Second method: Evaluation of the sample movement speed or the "Experiment on a plane"

A borosilicate glass fiber membrane with a density of 125 g/m^2 (AND, Japan) with a size of $70 \times 100 \text{ mm}$ was impregnated with 4% mucin solution, which corresponds to the physiological norm of its content in mucus [7] and placed on the plane of a glass plate, fixed at an angle of 45° relative to the horizontal surface. The thickness of the mucin layer, which was 0.1 mm, was controlled using a GRIFF MKC 25 micrometer (Russia). The experiment was performed at a temperature of $20 \pm 0.5^\circ\text{C}$. Using an applicator, 1 ml of the experimental sample was taken and applied to the upper edge of the treated membrane. The value of mucoadhesion was expressed in units of the movement speed of the polymer solution sample by calculating the average of five consecutive measurements (mm/s).

Results and Discussion

Semisynthetic polymers

Cellulose derivatives are hydrophilic, water soluble, and have many alcohol hydroxyl groups in their structure that determines the ability to form intermolecular hydrogen bonds. The cellulose derivatives used in this work differ not only in the nature of substituents but also in their viscosity and average molecular weight. The latter one according to manufacturers was calculated based on the solution viscosity [8].

NATROSOL – hydroxyethylcellulose (HEC) is an hydroxyethyl ether of cellulose. This is a non-ionic and water-soluble polymer (Figure 1).

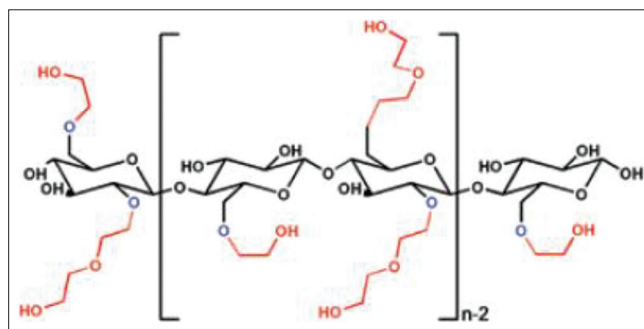


Figure 1: Structural formula of hydroxyethylcellulose [8]

The results of the study of various NATROSOL™ brands shown in Table 3 indicate that all of them have a sufficiently high amount of adhesion, which is independent of the average molecular weight. For example, NATROSOL™ 250L Pharm with the lowest average molecular weight showed the maximum amount of adhesion. The sample movement speed varied over a wide range and logically decreased in proportion to the growth of the average molecular weight and viscosity of the sample. According to the combination of two indicators, NATROSOL™ 250H Pharm and NATROSOL™ 250HHX Pharm can be considered as the leaders. It can also be noted the good mucoadhesive properties of NATROSOL™ 250M Pharm, which combine an acceptable amount of adhesion and sample movement speed.

Klucel™ – hydroxypropylcellulose (HPC) is a simple cellulose ether in which some of the hydroxyl groups in repeating glucose units are replaced by hydroxypropyl groups: $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3$. It is a non-ionic water-soluble polymer with surfactant properties (Figure 2). It is soluble not only in water but also in some organic solvents: Isopropyl alcohol, dioxane, methanol, etc.

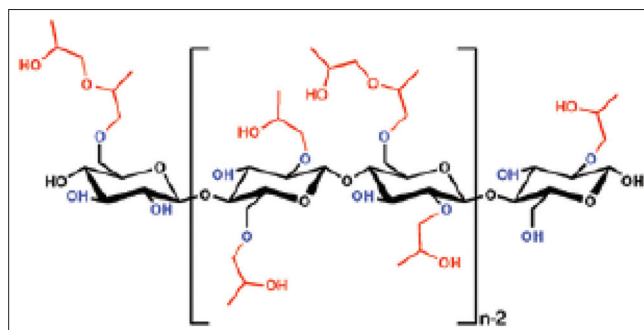


Figure 2: Structural formula of hydroxypropylcellulose [8]

Amount of adhesion (Table 3) of the HPC fitted into the range of values of the HEC amount of adhesion. The sample movement speed of Klucel™ GF Pharm with the average molecular weight of 370,000 Da was also comparable to the data for the Natrosol™ 250G PHARM, which has the similar average molecular weight (300,000 Da). Based on these data, it can

Table 3: Results of determining of mucoadhesion of 2% solutions of hydroxyethylcellulose of various brands and solution of hydroxypropylcellulose

Trade name	Average molecular weight*, Da	Dynamic viscosity of the solution, Pa·s	The amount of adhesion, N±SD	The sample movement speed, mm/s ±SD
Hydroxyethylcellulose (HEC)				
NATROSOL™ 250L Pharm	90,000	0.0074 ± 0.003 (2.0% solution)	35.264 ± 0.008	77.4 ± 1.14
NATROSOL™ 250G Pharm	300,000	0.3414 ± 0.0173 (2.0% solution)	21.667 ± 0.013	33.10 ± 0.24
NATROSOL™ 250M Pharm	720,000	0.3669 ± 0.0182 (1.0% solution)	32.140 ± 0.009	8.75 ± 0.01
NATROSOL™ 250H Pharm	1,000,000	6.4031 ± 0.3204(2.0% solution)	24.33 ± 0.013	0.380 ± 0.005
NATROSOL™ 250HHX Pharm	1,300,000	8.5205 ± 0.4261(1.5% solution)	24.577 ± 0.015	0.050 ± 0.005
Hydroxypropylcellulose (HPC)				
Klucel™ GF Pharm	370,000	—	25.865 ± 0.013	28.51 ± 0.22

*According to the manufacturer. **Dynamic viscosity was not measured.

be assumed the comparability of the mucoadhesive properties of the HEC and HPC.

Hydroxypropylmethylcellulose (HPMC) (Benecel™ and METOLOSE®) contains 20–30 % methoxyl and 2–12% hydroxypropyl groups (Figure 3). Having a relatively hydrophobic methyl and hydroxypropyl groups, HPMC is soluble in water, in some organic, as well as in complex solvents (water mixed with organic solvent). According to manufacturers, the water solution of this polymer has high surfactant properties.

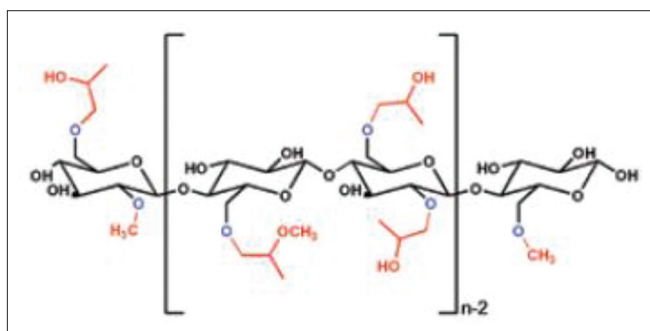


Figure 3: Structural formula of hydroxypropylmethylcellulose [8]

It should be noted that the mucoadhesive characteristics of HPMC was higher than the similar characteristics of HEC and HPC (Table 4). It is possible that a complex of physical and chemical characteristics of the polymer provides with the presence of both methoxyl and hydroxypropyl groups in combination with hydrophobic fragments of molecules, which are capable of forming hydrophobic interactions. The surface activity of molecules can also contribute to the rapid spreading of the polymer solution and wetting of the surface treated with mucin.

The results show a relationship between the average molecular weight of the HPMC and the mucoadhesion indicators obtained by two methods. The amount of adhesion of HPMC polymers with the average molecular weight in the range up to 550,000 Da was the highest among the cellulose derivatives used in the experiment, despite differences in the value of dynamic viscosity. The Benecel™ K100M PH DC sample with the average molecular weight of 1,000,000

Da had the amount of adhesion almost 2 times lower, which may be due to the spatial configuration of large molecules.

The sample movement speed of the Benecel™ K100M PH DC sample with the highest average molecular weight of 1,000,000 Da and maximum viscosity (100 Pa·s according to the manufacturer) was minimal. The highest value of sample movement speed was for Benecel™ K100LV, with the minimum average molecular weight and viscosity (164,000 Da and 0.1 Pa·s, respectively). The sample movement speed for samples with the average molecular weight of 400,000 and 550,000 Da (Benecel™ E4M Pharm and METOLOSE® 60SH, respectively) was close. The Benecel™ K100LV PH DC sample is less promising for use in the formulations of mucoadhesive dosage forms due to the high sample movement speed in comparison with the rest of the studied samples.

Blanose® CMC polymers are cellulose ethers in which each unit of glucopyranose monomers contains three hydroxyl groups (Figure 4). In sodium carboxymethylcellulose, hydrogen is replaced with sodium in some hydroxyl groups. The degree of substitution is indicated by a digital index in the brand name, for example, "DS Type 7" has a degree of substitution of 0.7. Sodium CMC is an anionic water-soluble polymer.

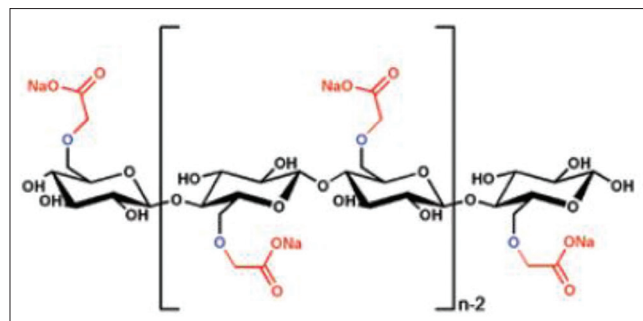


Figure 4: Structural formula of sodium carboxymethylcellulose [8]

The amount of adhesion of sodium CMC varied from high for samples of Blanose® 7MF PH and Blanose® 9M31F PH to low for Blanose® 7HF PH and did not depend on the average molecular weight,

Table 4: Results of determining of mucoadhesion of 2% solutions of hydroxypropylmethylcellulose

Trade name	Average molecular weight*, Da	Dynamic viscosity of the solution, Pa·s	The amount of adhesion, N±SD	The sample movement speed, mm/s ±SD
Benecel™ K100 LV PH DC	164,000	0.0975 ± 0.0016 (2% solution)	41.160 ± 0.007	72.0 ± 0.8
Benecel™ E4M Pharm	400,000	3.6973 ± 0.1848 (2% solution)	38.019 ± 0.007	1.87 ± 0.01
METOLOSE® 60 SH	550,000	1.9245 ± 0.0966 (2% solution)	44.178 ± 0.004	2.93 ± 0.01
Benecel™ K100M PH DC	1,000,000	1.9782 ± 0.0981 (1.0% solution)	21.84 ± 0.025	0.05 ± 0.007

*According to the manufacturer.

degree of substitution, and viscosity (Table 5). A high sample movement speed was detected for samples with an average molecular weight of 90,500 and 250,000 Da. For samples with a higher average molecular weight, the indicator was lower, but there was no direct relationship. The obtained data show the possibility of using Blanose® 7MF PH and Blanose® 9M31F PH as a mucoadhesive excipient in the composition for which the sample movement speed is of little importance.

Sodium alginates

The specifications for the different trade names of alginates used in this work indicate the same characteristics: These substances are sodium salts of alginic acid with the same ratios of G (guluronic acid) and M (mannuronic acid) blocks, which give the alginate molecule strength and flexibility, respectively (Figure 5). This ratio for these samples is 30-40/60-70. However, it is currently known that alginates are a whole family of linear copolymers and may differ depending on the raw material not only in the content of M - and G-blocks but also in their length. The ratio of M-/G-blocks, sequence, segment length, and molecular weight are critical factors for the physical properties of alginates and the hydrogels they form. In addition, the physical and chemical characteristics of these biopolymers strongly depend on the density and types of cross-linking: Ionic, covalent, or other [9]. The presence of hydroxyl and carboxyl groups, in which hydrogen is replaced by sodium, determines the ability to form intermolecular hydrogen bonds and possibly electrostatic.

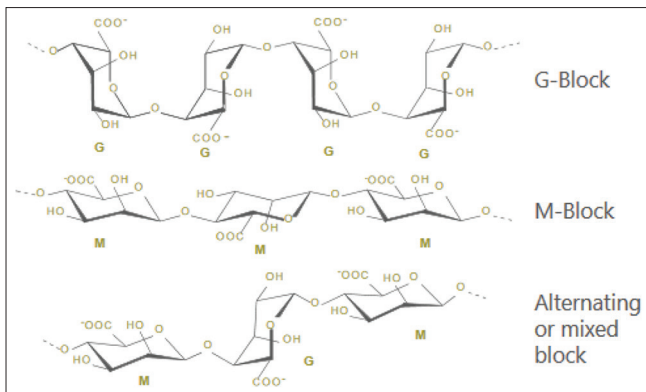


Figure 5: Structural formula of different types of sodium alginate blocks [9]

The exact value of the average molecular weight of biopolymers depends on the processing technology of natural raw materials and is not regulated by the manufacturer. The range specified in the specifications is too large, and it is from 15,000 to 170,000,000 Da. Therefore, the main technological characteristic of alginates in this case is the viscosity.

Experimental data on the study of alginates (Table 6) show that the sample movement speed decreased as the viscosity of the sample increased, while the relationship between the viscosity and the amount of adhesion was not found. The differences in the results obtained are undoubtedly determined by a combination of the critical factors mentioned above. However, the value of the dynamic viscosity of the studied samples allows predicting the value of their mucoadhesive properties obtained in the experiment on the plane. According to the results obtained, MANUCOL® LKX showed the best mucoadhesive characteristics.

Xanthan gum is a polysaccharide obtained by fermentation using the bacterium *Xanthomonas campestris*. The main chain of the polymer is identical to the cellulose molecule, the difference being the trisaccharide side chains, each of which contains a glucuronic acid residue between the two mannose links (Figure 6).

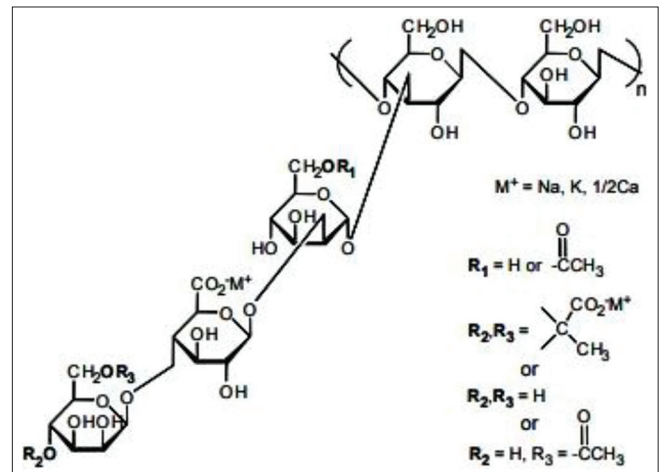


Figure 6: Structural formula of xanthan gum

Most end links of mannose contain a 4,6-bound pyruvate fragment. The number of pyruvate groups determines the viscosity of xanthan water

Table 5: Results of determining of mucoadhesion of 2% solutions of sodium carboxymethylcellulose (sodium CMC)

Trade name	Average molecular weight*, Da	Dynamic viscosity of the solution, Pa·s	The amount of adhesion, N±SD	The sample movement speed, mm/s ±SD
Blanose® 7LP EP	90,500	0.0231 ± 0.0011 (2% solution)	19.12 ± 0.02	77.0 ± 0.8
Blanose® 7MF PH	250,000	1.4657 ± 0.0732 (2% solution)	28.288 ± 0.013	42.8 ± 0.3
Blanose® 7HF PH	725,000	3.4901 ± 0.1745 (1.5 % solution)	13.77 ± 0.13	0.28 ± 0.004
Blanose® 9M31F PH	395,000	0.9187 ± 0.0459 (2% solution)	27.57 ± 0.013	16.7 ± 0.1

*According to the manufacturer.

Table 6: Results of determining of mucoadhesion of 2% hydrogels of sodium alginate

Trade name	Average molecular weight*, Da	Dynamic viscosity of the solution, Pa·s	The amount of adhesion, N±SD	The sample movement speed, mm/s ±SD
Protanal® CR8133	15,000–170,000,000**	0.1013 ± 0.0059 (2% solution, pH 7.5)	20.125 ± 0.007	6.77 ± 0.03
MANUCOL® LKX	15,000–170,000,000**	0.3957 ± 0.0193 (2% solution, pH 7.5)	25.713 ± 0.032	2.43 ± 0.02
Protanal® CR8223	15,000–170,000,000**	2.4614 ± 0.1231 (2% solution, pH 7.5)	15.06 ± 0.09	1.87 ± 0.02

*According to the manufacturer. **The exact value of the molecular weight of biopolymers depends on the processing technology of natural raw materials and is not regulated by the manufacturer.

solutions. The mannose closest to the main chain usually contains a 6-bound acetyl ether or may also be unsubstituted. Numerous studies have shown that the average molecular weight of xanthan gum is about 2 million Daltons, which corresponds to about 2000 repeating units per polymer molecule [10].

Two brands of gums were studied in the experiment. It was showed that both substances had high mucoadhesive properties (Table 7). The greatest amount of adhesion (41.688 ± 0.003 N) had XANTURAL[®] 180 XANTHAN GUM, which makes it the strongest mucoadhesive in the series of semi-synthetic polymers. Grindsted[®] Xanthan showed the highest sample movement speed.

Table 7: Results of determining of mucoadhesion of 2% solutions of xanthan gum

Trade name	Dynamic viscosity of the solution, Pa·s	The amount of adhesion, N ± SD	The sample movement speed, mm/s ± SD
Grindsted [®] Xanthan 80 (2% solution)	1.3845 ± 0.0691	25.87 ± 0.008	0.0042 ± 0.0003
XANTURAL [®] 180 XANTHAN GUM (2% solution)	1.2961 ± 0.0653	41.688 ± 0.003	0.0091 ± 0.0003

The extreme branching of the molecules, as well as the presence of hydroxyl, carboxyl, and ester groups, that provide a powerful coupling with mucin molecules of mucus, may determine the obtained values. At close values of viscosity, established experimentally, the amount of adhesion of samples differed by 2 times. The sample movement speed had the same exponent of a number with minimal values in the series of polymers studied in the work.

Thus, the gums, showing high rates of the amount of adhesion, demonstrated the lowest sample movement speed, which together shows their prospects for introducing mucoadhesive dosage forms into the formulations.

According to the European Pharmacopoeia, carbomers (CARBOPOL[®]) by chemical structure are the polymers of acrylic acid, cross-linked polyalkyl esters of sugars or polyalcohols. This polymer contains from 56.0 to 68.0% of carboxyl (-COOH) groups calculated with reference to dried substance. Carbomers do not dissolve in water but only swell, forming during hydration and neutralization colloidal dispersions characterized by apparent viscosity. Perhaps, this is the reason that the mucoadhesive properties of this group of polymers are relatively low, and the adsorption at the first stage of interaction of the polymer with the mucosa and subsequent diffusion in the solution proceeds faster and easier compared to the dispersion. However, Carbopol[®] polymers due to carboxyl groups are able to form hydrogen bonds with other components that are hydroxyl donors. According to the manufacturer [11], this is a slow process that takes up to several hours.

According to Table 8, CARBOPOL[®] 971P and CARBOPOL[®] 974P had similar values of the amount of adhesion, the average values in the range

of studied polymers. These grades of Carbopol are homopolymers of different types: A and B, respectively. Despite the different degree of cross-linking, it was not possible to detect a significant difference in the characteristics of mucoadhesion in the experiment.

Table 8: Results of determining of mucoadhesion of 2% dispersions of Carbopol

Trade name	Average molecular weight*, Da	The amount of adhesion, N ± SD	The sample movement speed, mm/s ± SD
CARBOPOL [®] 971P	3,000,000	19.607 ± 0.015	0.0074 ± 0.0004
CARBOPOL [®] 974P	4,000,000	23.379 ± 0.005	0.0032 ± 0.0004
CARBOPOL [®] ETD 2020	4,500,000	16.657 ± 0.073	0.0042 ± 0.0003

*According to the manufacturer.

CARBOPOL[®] ETD 2020 NF is a B-type copolymer consisting of a block of copolymer of polyethylene glycol and an ester with a long chain alkyl substituent $R = C_{10-30}$ and H_{21-61} . The amount of adhesion of this polymer was the smallest for the studied carbomers. It is possible that the presence of a large radical in the molecule creates diffusive difficulties when interacting with mucosa.

The sample movement speed of dispersions of all used carbomers was extremely slow, which indicates a high mucoadhesive ability. In addition, this indicator practically does not depend on the molecular weight, viscosity, or structure of the polymer and is not consistent with the amount of adhesion. Obviously, the large number of carboxyl groups in the carbomer molecule determines this property.

PEG is a water-soluble non-ionic polymer obtained by polymerization of ethylene oxide, having one hydroxyl group in each molecule (Figure 7).

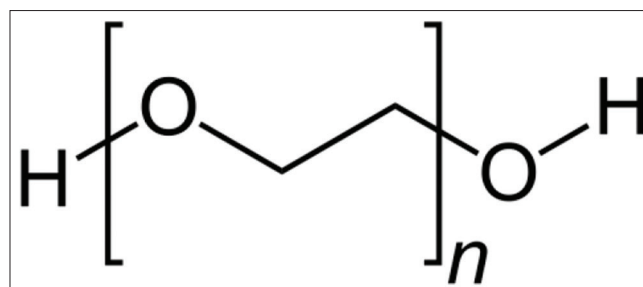


Figure 7: Structural formula of polyethylene glycol

Perhaps, this was the reason for the relatively weak mucoadhesive properties of PEG (Table 9),

Table 9: Results of determining of mucoadhesion of 3% solutions of polyethylene glycol

Trade name	Average molar weight*, g/mol	Dynamic viscosity of the solution, Pa·s	The amount of adhesion, N±SD	The sample movement speed, mm/s ± SD
Polyglycol 400	400	0.00303 ± 0.00015 (3% solution)	12.228 ± 0.011	77.0 ± 1.27
Polyglycol [®] 400S	4,000	0.00405 ± 0.0002 (3% solution)	12.156 ± 0.008	36.666 ± 0.1967

*According to the manufacturer

which were inferior to the samples of other polymers discussed above. The difference in the values of the dynamic viscosity of the samples did not affect the

amount of adhesion, but it was noticeable by the sample movement speed: As in the case of other polymers, a PEG sample with a lower viscosity moved faster.

Conclusion

The analysis of the obtained data shows a wide range of values of mucoadhesion indicators of different polymer brands, even in a row of the same chemical group. The amount of adhesion and the sample movement speed of the studied polymers do not correlate with each other. According to the combination of two indicators, hydroxypropylcellulose (Benecel™ E4MPharm and METOLOSE® 60 SH) and xanthan gum (XANTURAL® 180 XANTHAN GUM) showed the highest mucoadhesive properties. It can also be noted that NATROSOL™ 250H Pharm and NATROSOL™ 250HHX Pharm hydroxyethylcellulose, MANUCOL® LKX sodium alginate, Grindsted® Xanthan 80 xanthan gum, and CARBOPOL® 974P have good mucoadhesive properties. It is noteworthy that the studied brands of xanthan gum and carbomers showed extremely low sample movement speed, while the other polymers have this characteristic vary in a wide range. Polyethylene glycols proved to be the weakest mucoadhesive excipients.

The obtained results demonstrate the absence of direct influence of the average molecular weight of polymers of different structures on the amount of adhesion. It is possible to conclude that the physical and chemical properties of polymers have a complex influence on this characteristic. The sample movement speed of HEC and HPMC increases with increasing average molecular weight.

The obtained experimental data may be of interest for the pharmaceutical development of formulations of dosage forms with optimal mucoadhesive properties and intended for application to mucous membranes.

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