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Hydrogels based on polysaccharides for biomedical application

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The aim of this work is the development of a new composite hydrogel material based on gellan for biomedical applications. There are two types of biomedical materials that were developed during this research: hydrogels and eye drops. As hydrogel material components the following substances were used: gellan polysaccharide and synthetic nonionic polymers - polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA). Selection of these components is due to the fact that gellan has properties of thickening agent, and it is inexpensive comparatively with other polysaccharides. The main advantage of natural materials is undoubtedly their high biocompatibility and biodegradability. The value of PVP and PVA is due to the fact that these polymers are biologically inert - such polymers, which are successfully used in medicine. Synthetic polymers decisive advantages are high probability of final material properties prediction at the synthesis stage, lightness and cheapness.

Methods of hydrogels obtaining gellan-PVP and gellan-PVA are based on the unique property of gellan to form a three-dimensional network with temperature increase to sol-gel transition point [1]. This unique property allows gellan to simplify and cheap hydrogels synthesis due to the lack of additional components in the system (e.g., crosslinking agent), and reduce the number of synthesis steps. In obtaining of hydrogels based on gellan and nonionic polymers gellan concentration varied from 1 to 2 wt. %, and concentration of nonionic synthetic polymers (PVP, PVA) varied in range - 3, 5 and 7 wt. %.

Hydrogel synthesis represents gradual dissolution of nonionic polymer, and gellan after that with following gradual heating and mixture stirring at temperature of 80°C - the temperature of the sol-gel transition of gellan macromolecules. Upon reaching this temperature, the mixture was kept under stirring for 10 minutes and allowed to cool to room temperature. In result mixture loses its fluidity, gaining gel elasticity. Further physicochemical properties of hydrogels samples gellan-PVP and gellan-PVA were studied by different analysis techniques.

Swelling kinetics was studied on hydrogels samples based on gellan and nonionic polymers in water and isotonic solution. It was found that hydrogels based on gellan and synthetic polymers show the greatest swelling in water than in isotonic solution. Also with increase of nonionic polymer concentration in gellan-PVP and gellan-PVA compositions hydrogels swelling degree decreases in geometric order almost 2 times. It can also be noted that there is a trend hydrogels sorption properties decrease (for ≈2 g/g) with increase of gellan concentration in composite. Swelling of hydrogels based on gellan and PVA is higher than swelling of hydrogels based on gellan and PVP.

Mechanical properties were studied for compression of hydrogels based on gellan and synthetic polymers. The maximum load applied to the studied hydrogels was 7.5 kg. As a result, hydrogels based on gellan and non-ionic polymers PVP and PVA are not strong, but flexible materials. However, at the time τ = 2.5-3 seconds all hydrogels were destructed. Based on obtained data mechanical compression limit was calculated for each hydrogel polymer sample. Hydrogels gellan-PVP-have higher mechanical compressive limit values than hydrogels gellan-PVA. Also it should be noted that hydrogel mechanical strength increases with increase of components total concentration in composite material. Thus, results of mechanical analysis of hydrogel samples based on gellan and synthetic polymers correlate with data on obtained samples swelling kinetics.

Obtained hydrogels porosity has been studied by optical microscopy at 20 times zoom. For this purpose equilibrium swollen hydrogels gellan-PVP and gellan-PVA were preliminarily frozen and

dried by freeze dryer to constant weight to keep hydrogels pores size. It was shown that pores size of gellan-PVA hydrogels greater than pores size of gellan-PVP hydrogels. Thus, one can conclude that physicochemical properties of hydrogels based on gellan and polyvinylpyrrolidone and polyvinyl alcohol polymers are under influence of nonionic polymer nature, components concentration and, as a consequence, hydrogel network density.

It is known that gellan cations of the dissolved salt could enforce gelation process [1]. In this regard, the obtained hydrogels gellan-PVP and gellan-PVA were prepared in presence of NaCl or $MgCl_2$ salt. For preparation of hydrogels instead of distilled water saline solutions [NaCl] = 0.1 and 0.5 M and [$MgCl_2$] = 0.1 M were used. Effect of salt was investigated by study of hydrogels physicochemical properties. It should be noted that sorption properties of hydrogel materials in sodium chloride presence decrease comparatively to the same hydrogels swelling properties, which do not contain dissolved salt in its composition. The higher concentration of NaCl, which is contained in hydrogel sample, the more decrease in composite material swelling degree. It was found that sorption properties of hydrogel material obtained in presence of magnesium chloride is much lower. Compared with mechanical properties of samples of composite materials not containing sodium chloride, hydrogels, obtained in presence of salts are also not rugged enough and at the same time lose their elasticity. In this case, destruction of occurs at τ = 2-2,5 seconds. The hydrogels strength values are much (2-3 times) higher than values of hydrogels compressive strength limit which do not containing sodium chloride. Destruction of hydrogels containing magnesium chloride occurs at $\tau \approx 1.5$ seconds. These hydrogels strength value is 4 times higher than compression limit strength values for hydrogels containing no salt and 1.5 times higher than compression limit strength values for gels containing NaCl. Thus, it can be concluded that the presence of cations in composite materials gellan-PVP and gellan-PVA promotes densification of hydrogel network and, as a result, affects to physical and chemical properties of hydrogels: lower swelling properties, reduction in pores of hydrogels and increased material strength.

The use of hydrogel for biomedical application was studied as a drug carrier of brilliant green (BG) as model drug. The immobilization and release of BG were measured by turbidimetry at a wavelength of 580 nm and a temperature of 25°C. The immobilization process of brilliant green occurs during 5-5.5 hours. In this case BG was immobilized by 80-90%. Also it should be noted that immobilization of model MS on gellan-PVA hydrogel occurs a little more intensive than in case with gellan-PVP hydrogel. Release kinetics of MS were studied by direct diffusion method. The release process occurs within 5.5-6 hours. BG release from hydrogel samples based on gellan and synthetic polymers flows prolonged, which is an advantage in the use of composite materials as drug carriers. Also it should be noted that the percentage of release of BG is about 80%.

The eye drops were developed at Pharmaceutics laboratories of University of Reading. It was proposed that when putting the gellan solution to eye, cations containing the tear fluid would enforce the gelation process of polymer. Thus, the retention time of eye drop would be increased. Firstly, the viscosity properties of gellan solution were studied. For this gellan solution were prepared with concentration of polymer 0.2; 0.4 and 0.6 wt. %. Also as a variable the drug pilocarpine hydrochloride was added in concentration 0.25; 0.5; 0,75; 1 and 1.25 wt. %. So, the viscosity of gellan solution increases within the increase of polymer concentration, as well as the higher concentration of pilocarpine hydrochloride leads to higher viscosity values.

The next step of eye drops' development was the modification of gellan by adding the mucoadhesive groups to main polysaccharide chain. As modifying agent, methacrylic anhydride was used according to [2]. Briefly, 0.5 g of gellan was dissolved in 100 mL of deionized water by stirring at 90°C during 20-30 min. Then temperature of system was decreased to 50°C, after which different amounts of methacrylic anhydride were added depending on desired degree of substitution (DS) of final product: low DS 1 mL; medium DS 2.5 ml; high DS 4 mL. The reaction lasted 6 hours at 50°C, pH was adjusted to 8.0 by adding 5.0 M sodium hydroxide solution. The final product was purified by dialysis

in distilled water during 3 days and freeze dried. The structure of modified polymer was determined by ^1H NMR spectroscopy. The peaks in the double bond region (δ 5.50-7.00 ppm) and a peak of $-CH_3$ in the methacrylate groups (δ 2.09 ppm) confirm the methacrylation of gellan. The modified gellan was also used for preparation solution for using as eye drops containing pilocarpine hydrochloride.

Thus, materials based on polysaccharide gellan could be used for biomedical application.

References:

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