Novel pH-responsive hydrogels based on chemically modified Arabic Gum polysaccharide.

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Statement of Purpose: Natural polymers are preferred over synthetic materials for colonic drug delivery because they are more susceptible to microbial biodegradation. Particular attention has been paid to drug delivery devices based on polysaccharides [1]. However, the high solubility of polysaccharides in aqueous media is often responsible for the premature release of solutes. Natural polymers such as dextran, pectin, guar gum, and inulin have been chemically modified in an attempt to tailor desired applications. An important fact is that hydrogels prepared by cross-linking a modified polysaccharide have high potential application to colon-specific drug delivery, because they are susceptible to enzymatic biodegradation by the bacteria present in the colon environment [2]. The main objective of this work is to develop an alternative procedure for the chemical modification of Arabic Gum (AG) and prepare hydrogels based on the modified polysaccharide for acting as drug carrier.

Methods: Reaction of glycidyl methacrylate (GMA) with purified Arabic Gum (AG) was performed in a mixture of water-DMSO 1-2 (v:v). The reaction was catalyzed by TEMED. Aqueous solution (15 wt-%) of modified polymer (AG-MA) was prepared and 0.1 mMol sodium persulfate was added, stirred for 15 min, transferred to a test tube and heated to 70 °C for 30 min. A consistent gel was formed. The gel was taken out and immersed in water. The water was renewed every 8 h for 72 h, after which the hydrogels were dried at room temperature. The raw polymer (purified AG), modified polymer (AG-MA) and the hydrogels were lyophilized and FT-IR, ^{1}H NMR and ^{13}C NMR analyses were carried out. FT-IR spectra were taken on a Bomem FT-IR model MB100 spectrometer. Powdered samples were prepared into pellets with KBr. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian spectrometer model Oxford 300 at 300 MHz. The relaxation time length and the angle pulse used in 1H NMR and 13C NMR spectra were 30 s and 90º, and 1 s and 30°, respectively. Solid-state ^{13}C-CP/MAS NMR spectra were obtained on a Varian spectrometer model Oxford 300 at 74.47 MHz. The samples were placed in a 4-mm rotor; other important parameters were adjusted as follows: pulse angle $\theta = 37$ º, spinning rate of 12 kHz, contact time of 3 ms, and relaxation time of 3 s. Morphologies of AG films and hydrogel were analyzed using a Shimadzu scanning electron microscope (SEM). Water uptake (Wu) as a function of pH, in several ionic strength, were measured. The dependence of Wu to the pH was determined by using buffer solutions with pH ranging from 2 to 10 at 37 ºC. The mechanism of water uptake (Wu) was investigated using classical model [3].

Results and Discussion: FTIR spectra of AG-MA presents a band at 1719 cm^{-1} attributed to the C=O stretching frequency of the conjugated ester groups from GMA. This band is an evidence of the modification of AG. The NMR spectra of AG-MA show signals at δ 6.20 ppm and δ 5.79 ppm attributed to the vinyl hydrogen from GMA. The modification of AG with GMA was also confirmed by ^{13}C NMR analysis. Signals at δ 136.62 and δ 128.39 ppm were attributed to the vinyl carbons. The signals at δ 170.19 ppm and δ 20 ppm were assigned to the carbonyl groups and methyl carbons, respectively. The hydrogel formation occurs through the C=C bonds on AG-MA as followed by the solid-state 13C-CP/MAS NMR spectra. The absence of signal at 140-120 ppm, attributed to C=C groups in AG-MA, on the hydrogel spectrum indicates the consumption of C=C groups during cross-linking. AG-MA film showed a tight structure while the AG-MA hydrogel had a porous structure due to the formation of voids. The pores that became visible on the surface of the hydrogel were attributed to solvent evaporation during dry freezing. The Wu of the AG-MA hydrogel showed significant pH-dependence. The hydrogel Wu increased with the increase in the pH of supernatant. At pH values higher than the hydrogel pKa (4-5), the COOH groups dissociate to COO-, increasing the number of fixed ionized groups within the hydrogel structure. This generates electrostatic repulsion forces between the adjacent ionized groups in the polymer network, which increases the AG-MA hydrogel Wu significantly. The parameter ***n*** was determined from the slope of the *ln*(Wu) *vs* ln(t) plots. It was observed that the ***n*** values were on the order of $0.45 < \boldsymbol{n} < 0.89$, which indicates that the water absorption mechanism of the AG-MA hydrogel is governed by anomalous transport in the pH range studied. As the pH of the supernatant increased from 1.2 to 10, the values *of* ***n*** increased significantly from 0.51 to 0.60. It could be pointed out that at higher pH the water uptake profile becomes more dependent on the polymer relaxation. This effect was attributed to the increased ionization of COOH groups of glucuronic acid segments of the hydrogel at high pH. An increase in the number of fixed ionized groups within the hydrogel raises the polymer relaxation.

Conclusions: AG-MA was obtained by reaction with glycidyl methacrylate in an appropriated solvent mixture. The cross-linking reaction of AG-MA forms AG-MA hydrogels that showed significant pH dependence, which had considerable effect on the water absorption transport mechanism. In the pH range studied, it was found that the water uptake mechanism of the AG-MA hydrogel was controlled by polymer relaxation (anomalous transport). The AG-MA hydrogels exhibited pH-responsive, which makes them a potential polymeric drug carrier.

References: 1 - Na K *et al.* Eur. J. Pharm. Sci 2003,18:165. **2** - Vervoort L *et al.* Pharm. Res. 1997,14:1730. **3** - Ritger PL and Peppas NA, J. Control. Release 1987,5:23.

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