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Synthesis of Water-Soluble Polyethylene Glycol Fumarates for Biomedical Applications

Polyethylene glycol fumarate (PEGF) with controlled structural composition has been obtained for further synthesis of double network cross-linked hydrogels for biomedical applications. The copolymer has been synthesized by polycondensation reaction of fumaric acid and polyethylene glycol (PEG-600). Molecular weight of PEGF has been determined by gel permeation chromatography to be approximately 6000 Da with gel permeation chromatography. The polycondensation of fumaric acid and PEG-600 was studied throughout the reaction process. The structure of the reaction product has been evidenced using FTIR- and 1H NMR-spectroscopy. The quantitative ratios of the amount of –C=C– bonds and –COO groups to –C=O groups in the obtained PEGF have been estimated from IR-spectra for different synthesis time. The time-dependence of molar ratio of double bonds to methyl groups in PEGF has been obtained from corresponding 1H NMR-spectra. FTIR and 1H NMR-spectroscopy, both, demonstrate that after the end of reaction the unsaturated –C=C– double bonds remain in the structure of the macromonomer, that is essential for further preparation of cross-linked hydrogels. The addition of the tightly cross-linked network of polyvinyl alcohol leads to formation of highly tough biocompatible material for preparation of the artificial meniscus which can further be used as a solution in the treatment of diseases such as osteoarthritis.

Keywords: polyethylene glycol, polyethylene glycol fumarate, fumaric acid, polyester resin, macromonomer, hydrogels, FTIR- spectroscopy, 1H NMR-spectroscopy.

Introduction

The creation of novel materials with sufficient mechanical properties for use in various areas of science and industry is of great importance. Due to their unique properties such materials have a wide range of applications starting from additives for building materials to use in medicine [1–16]. Varieties of copolymers have been studied to obtain the systems used in medicine for different purposes [17–29], e.g. in tissue engineering [18, 22, 27], metallic nanocomposites [25, 26], double network stimuli-responsive hydrogels [23, 30] and so on. Among other polymers the oligo-/polyethylene glycol fumarates are recommended and investigated as medical hydrogel systems for tissue regeneration and drug delivery purposes due to their best mechanical properties [13, 14, 24]. Besides, the cryogels based on oligo-/polyethylene glycol fumarates were effectively synthesized for the biomedical applications [27]. High elasticity and simplicity of the synthesis of polyethylene glycol fumarates make them an interesting and promising object for the development of hydrogels for the biomedical application. Biocompatible soft materials made of hydrogels with high toughness based on double polymer networks can be used for the replacement of the soft tissue with endoprosthesis which could be a solution for the treatment of such severe disease as osteoarthritis [5–9]. Such gels consist of two compartments: the first should have rigid and highly cross-linked structure, while the other must be weakly-crosslinked and possess elasticity [6] to be able to restore after huge deformations applied to a knee joint. In this regard, polyesters can serve as building blocks for the second elastic network. For instance, oligo/polyethylene glycol fumarates were suggested in the literature as promising polymers for hydrogels in medicine [10–12]. Thus, it could be used for the preparation of biocompatible hydrogels based on a of double crosslinked network. In this case, polyvinyl alcohol could be a material for the first rigid network [13–16].

The present article focuses on the synthesis of water-soluble polyethylene glycol fumarate (PEGF) of controlled structural composition and the investigation of the changes of the process parameters on the structure, composition and properties of the final product.

Experimental

Materials

Polyethylene glycol with molecular weight of 600 Da (PEG-600) and fumaric acid were purchased from Sigma Aldrich. Milli-Q water was used in all the experiments.

Synthesis of PEGF

Polyester resin was synthesized by direct polycondensation reaction of PEG-600 with fumaric acid at a molar ratio of the monomers of 1:1 in three-necked round bottom flask equipped with magnetic stirrer, condenser with Dean-Stark nozzle, thermometer and vacuum outlet. The system was submerged into glycerin or silicone bath to provide uniform heating and was blown with nitrogen. The reaction flask was heated to 160–170 °C for 4–8 hours and then under high vacuum (147.1 millimeters of mercury) for 10 minutes at the same temperature. The reaction was stopped when the calculated amount of water was collected.

Obtained polymer was purified from low molecular substances by dialysis by submerging the dialysis membrane (MWCO 3500 Da (Sigma Aldrich)) into deionized water at room temperature and constant mixing at 250 rpm for 3 days. The deionized water was changed every 6 hours.

The samples were then dried in a vacuum oven at 80 °C for several days until the copolymer with constant weight was obtained.

Molar weight estimation

Molar weights (number-average (Mn) and weight-average (Mw) molecular weights) of the oligo-/polyesters obtained during the reaction after 4, 5, 6 and 8 hours of polycondensation have been determined by gel permeation chromatography (GPC) on a Malvern chromatograph equipped with a Viscotek 270 max dual detector (polystyrene was used as a standard; the standard deviation of the molecular weight was ±100-120). The samples of PEGF were dissolved in water, filtered and analyzed by GPC.

Bromatometry

Bromatometry is an analytical method based on the determination of the amount of bromine released into the medium as a result of the reaction with unsaturated double bonds [31]. For the analysis 1 g of the sample (PEGF) was dissolved in 10 ml of water or the organic solvent and left for 24 hours. Then the mixture of KBr and $KBrO_3$ solution was then poured into the sample solution which had been preacidified with 0.1 N solution of HCl. In acidic medium the bromine molecules react with the unsaturated double bonds in the system. So, the bromide-bromate mixture is then left for 4 hours in a dark place. The access of bromine is titrated with the 0.1 N solution of $Na_2S_2O_3$ in the presence of indicator phenolphthalein using microburette. The sample containing PEGF was analyzed in parallel with the control sample. The bromine index corresponds to the amount of bromine which can be added to 100 g of the substance analyzed.

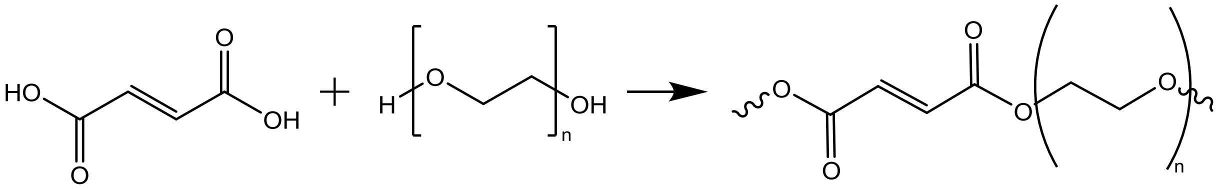
FTIR- and 1H NMR-spectroscopy

The structure of obtained copolymers has been confirmed by FTIR-spectroscopy on a device FSM 2201, using standard procedure by preparation of KBr tablets in the wavenumber range 4000–400 cm^{-1} with a resolution of 1 cm^{-1}.

^1H NMR-spectroscopy has been performed on a device Bruker AMX-400 spectrometer at 22 °C. For the analysis 0.01 g of dried sample was dissolved in deuterium oxide within 24 hours followed by exposure to US-homogenization at 200 W for 10 min. The peak of chemical shift of D_2O (4.79 ppm) was used as a reference. The frequency range was 950-4100 Hz. This signal was taken as indicated in the references [32, 33].

Results and Discussion

The synthesis of PEGF has been carried out by polycondensation reaction of PEG-600 and fumaric acid at the molar ratio of PEG 600 and fumaric acid of 1:1 according to the scheme:



As was measured by GPC, after 8 h of reaction the macromonomer with molecular weight around 6000 Da was formed (Fig. 1).

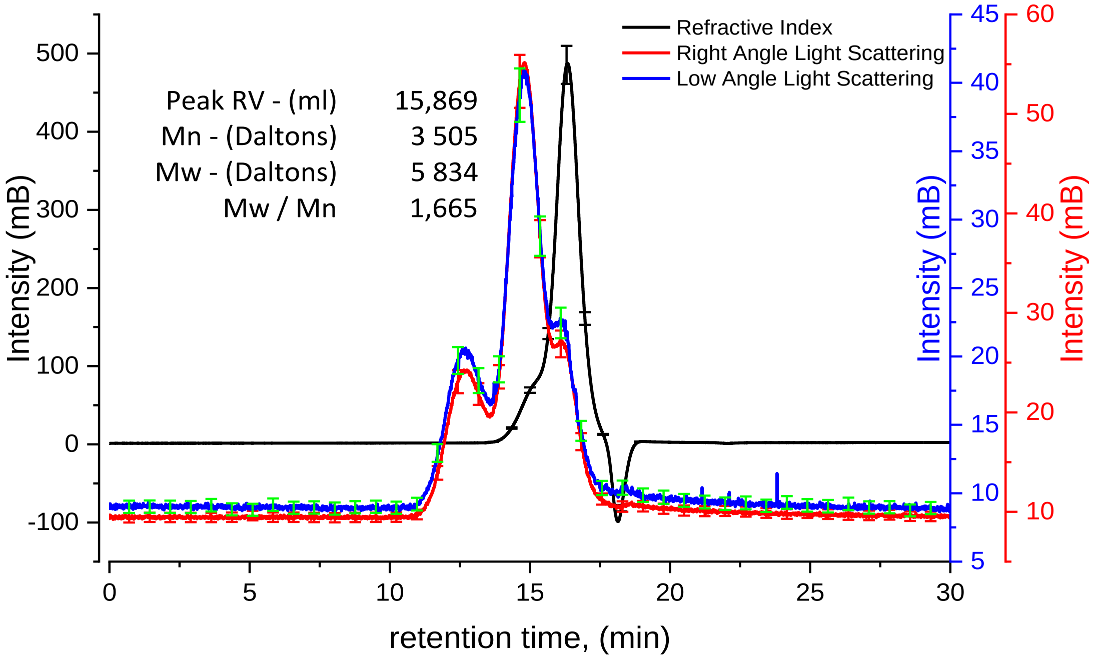


Figure 1. Molecular mass of the final product of PEGF obtained after 8 hours of polycondensation

In order to study the influence of the duration of reaction on the chemical structure of PEGF, the samples were removed from the reaction mixture after a certain time. The obtained purified products were analyzed by FTIR-spectroscopy for the presence of active double bonds necessary for the formation of double network hydrogels. Figure 2 shows the FTIR-spectra of PEGF formed after 1–8 h of polycondensation.

The FTIR spcterum of PEFG has typical –C–O– signal of the ether bond in PEG at 1100 cm^{-1}, in addition, it contains the peaks at 1730 and 1640 cm^{-1} which respectively correspond to the –C=O and –C=C– groups of the fumaryl moiety [12] (Fig. 2). From the FTIR-spectrum of the macromonomer it is obvious that with the time the intensity of –C=C– bond decreases, whereas the signal of ester bond –O–C=O– increases gradually with deepening the conversion. Note, after 8 h of polycondensation process in PEGF there are still active double bonds that are required for further polymerization and the preparation of hydrogels containing cross-linked network [12].

From Figure 2, the ratios of number of carboxylic groups –O-C=O– and unsaturated double bonds –C=C– to the –C=O bonds for different duration of polycondensation reaction were calculated (Fig. 3). The dependence shows decreasing number of double bonds and, simultaneously, increasing number of ester bonds during the reaction. This effect was previously observed in literature [9].

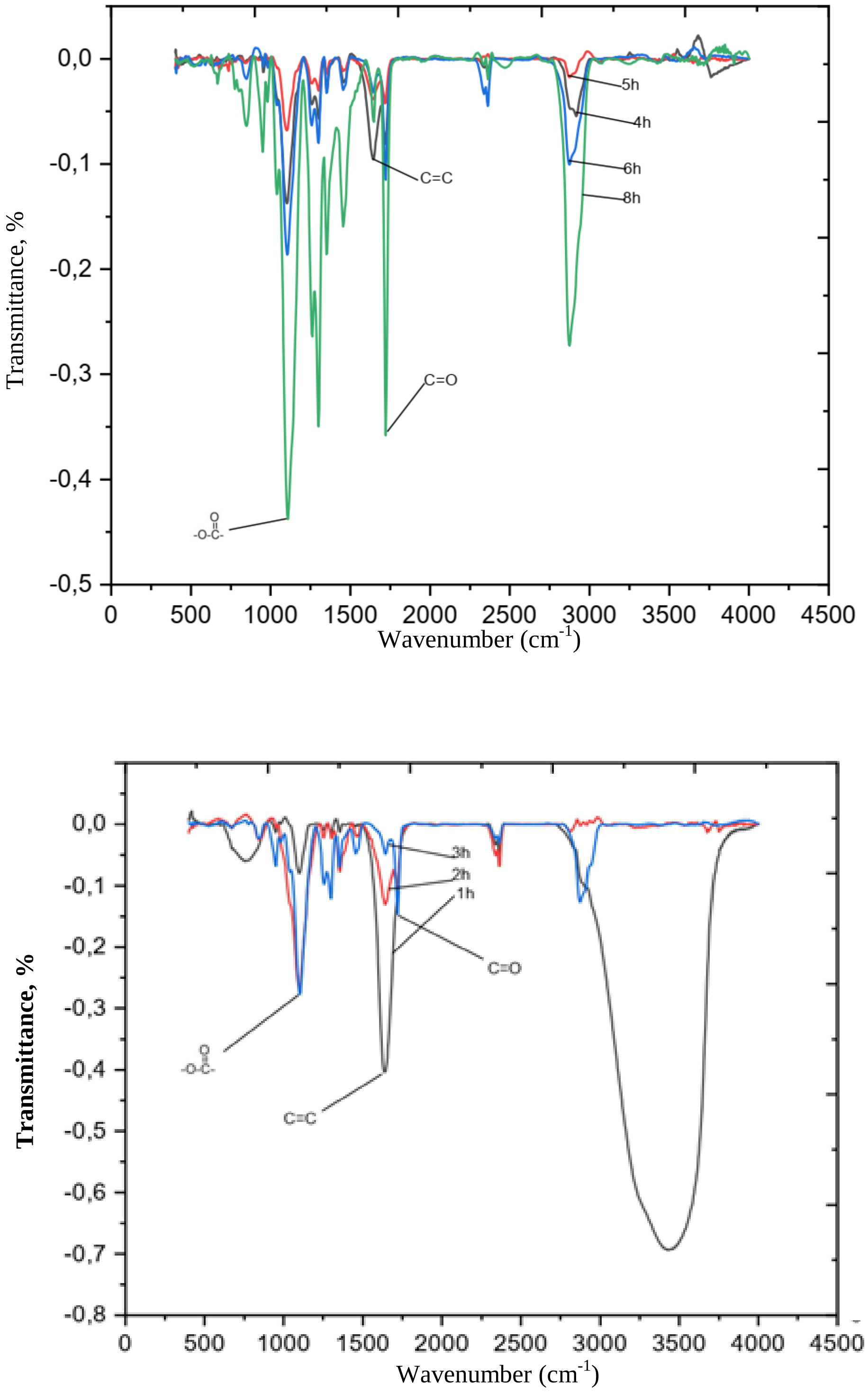


Figure 2. FTIR-spectra of PEGF obtained after different time of polycondensation of PEG-600 and fumaric acid

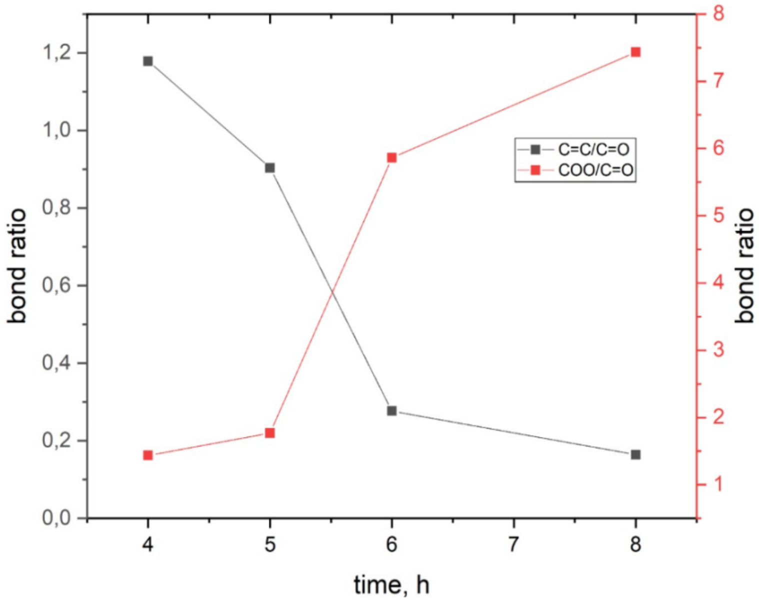


Figure 3. The dependence of the ratio of number of double bonds –C=C– and carboxylic groups –COO– to the –C=O bonds in chemical structure of PEGF, obtained at different time of polycondensation of PEG-600 and fumaric acid

The average degree of unsaturation of the samples obtained at different time of the reaction determined by bromatometry decreases from 7.5 to 5.1 % as the the reaction time increases (Fig. 4). The results of bromatometric analysis are in good correlation with the FTIR-spectroscopy data also indicating on the decrease of the number of double bonds during the reaction (Fig. 4). Thus, after 8 h of polycondensation, only 5 % of double bonds which are essential for further preparation of the double network remain unchanged.

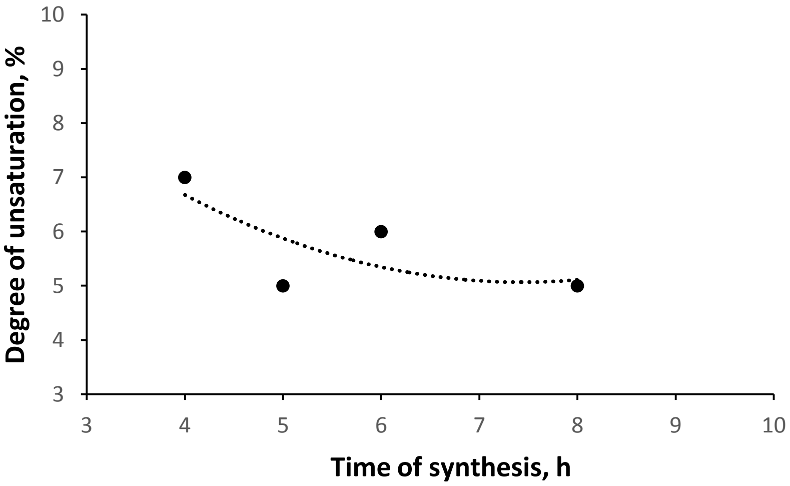


Figure 4. Degree of unsaturation for the samples of PEGF obtained at a different time of polycondensation of PEG-600 and fumaric acid

The following chemical shifts are observed on the spectra of the macromonomer [13]: 1) 3.7–3.9 ppm — the peak of methylene protons (related to $–CH_2–$ groups conjugated with the ether groups); the peak is characteristic for molecules of polyethylene glycol, built-in the structure of PEGF; 2) 4.3–4.5 ppm — the groups of peaks of methylene protons (related to $–CH_2–$ groups conjugated with the ester groups); 3) 6.7–6.8 ppm — signal related to the protons of double bond of fumaric acid built-in the structure of PEGF (polyester). These peak positions are consistent with the ^{1}H NMR data presented in the works [9, 12] for PEGF. Thus, NMR data confirm the chemical structure of the synthesized macromonomer (Fig. 5).

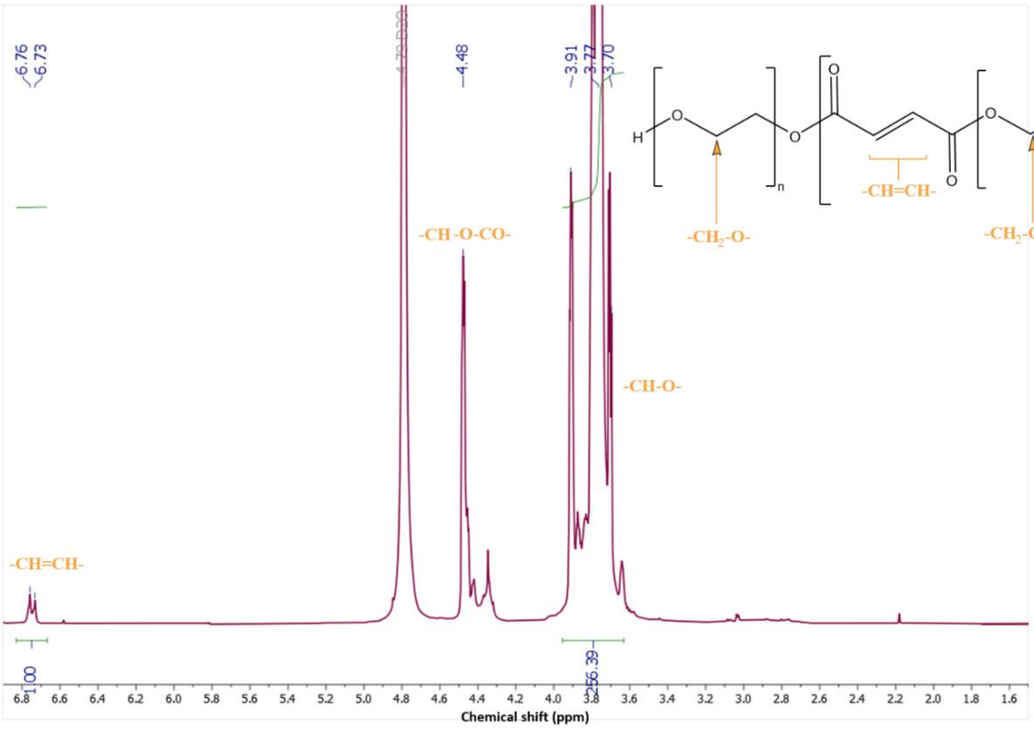


Figure 5. ^{1}H NMR-spectra of PEGF obtained after 8 h of polycondensation

From the NMR spectrum, the ratio of integrals of the peaks of double bonds and of methylene groups of PEG600 was calculated, which is equal to 0.004. The obtained amount of the double bonds in PEGF is 11 % of that theoretically estimated for the “ideal” structure of PEGF to be obtained in polycondensation. Therefore, NMR data are in semi-qualitative agreement with the FTIR and bromatometry results presented above, and they show that a certain fraction of double bonds remains in the PEGF structure after synthesis.

Thus, ^{1}H NMR- and FTIR-spectroscopies confirmed the formation of PEGF by polycondensation of PEG and fumaric acid. At high conversions (after more than 4 hours of polycondensation) the degree of unsaturation of PEGF decreases, so that after 8 h of reaction the amount of unsaturated double bonds in its structure is sufficiently reduced.

Conclusions

Macromonomers of PEGF with the molecular weight of about 6 kDa has been synthesized by polycondensation of PEG-600 with fumaric acid for 8 h. The time-dependence of the structure of PEGF was analyzed using bromatometry and FTIR- and ^{1}H NMR-spectroscopies. According to bromatometric analysis and IR-spectroscopy, the amount of unsaturated –CH=CH– groups of fumaric acid in PEGF decreases from 4 to 8 h of synthesis. After 8 h of polycondensation the bromatometry and ^{1}H NMR-spectroscopy both indicate the sufficiently smaller amount of unsaturated double bonds that are required for further polymerization of PEGF for the formation of hydrogels for biomedical purposes.

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Author Contributions

All authors contributed to the preparation of the manuscript. All authors approved the final version of the manuscript. CRediT: **Yerkeblan Muratovich Tazhbayev** conceptualization of the research, discussion of the results, review and editing the draft; **Akerke Temirgalievna Kazhmuratova** writing an original draft preparation, review and editing; **Lyazzat Zhanybekovna Zhaparova** writing an original draft, preparation, review and editing; **Ulugbek Borashevich Tuleuov** carrying out the experiments; **Yermauyt Nassikhatuly** analysis of the samples on FTIR-spectrometer and GPC; **Elizaveta Sergeevna Mitricheva** analysis of the samples on ^{1}H NMR-spectrometer; **Alexander Lvovich Kwiatkowski** discussion of the results, review and editing the draft; **Andrey Vladimirovich Shibaev** discussion of the results, review and editing the draft.

Conflicts of Interest

The authors declare no conflict of interest.

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