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# Synthesis and characterization of poly(2-hydroxyethyl methacrylate)-1-naphthylacetic acid adduct

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## Summary

Poly(2-hydroxyethyl methacrylate) (PHEMA) functionalized with chloroacetate groups was obtained by reaction of PHEMA with chloroacetyl chloride using the 5% lithium chloride/N,N-dimethylacetamide system as solvent and pyridine as catalyst. The coupling of bioactive carboxylic acid (1-naphthylacetic acid) to PHEMA functionalized with chloroacetate groups was carried out by reaction with its the potassium salt. The structures of chloroacetylated PHEMA and PHEMA-1-naphthylacetic acid adducts were determined by means FTIR, $^{1}$H-NMR and $^{13}$C-NMR spectra. The degree of substitution was calculated from the chloride content and ranged from 13.4 to 98.1 mol% depending on the ratio of chloroacetyl chloride to PHEMA. The hydrolysis in the heterogeneous phase of PHEMA-1-naphthylacetic acid adducts showed that the release of the bioactive compound from tablets is dependent on hydrophilic character of adduct as well as on pH value of the medium.

## Introduction

In recent years, much attention has been directed to speciality polymers of the most useful materials [1]. Controlled release polymeric systems in which bioactive compounds are bound to a synthetic or natural polymeric backbone via covalent bounds have emerged as one approach promissing to solve the problems which accompany the use of biologically active agents [2]. The advantages of poly(vinyl alcohol) or polysaccharides as a macromolecular carrier for bioactive agents immobilization are well accepted, as is apparent from the literature data [3-9]. In most cases this polymers has been previously transformed into a suitable reactive derivative, in order to achieve the attachment of bioactive compound as well as to introduce a spacer between the carrier and the bioactive compounds. A gradual release of the bioactive agent can be achieved by hydrolytic or enzymatic cleavage of the linking bond. In this context, PHEMA with reactive hydroxyl groups may be used as polymeric carrier for coupling of bioactive compounds.
The aim of the present paper was to synthesize and characterize PHEMA-1-naphthylacetic acid adduct in a two-stage procedure. During the first stage, PHEMA was chloroacetylated with chloroacetyl chloride, while in the second stage,

chloroacetate groups reacted with a potassium salt of bioactive 1-naphthylacetic acid. A study of the hydrolysis of resulting adduct in the heterogeneous phase was also made in order to evaluate the realese of the bioactive acid.

## Experimental

### *Materials*

2-Hydroxyethyl methacrylate (HEMA) (Aldrich) was purified by distillation under reduced pressure and the fraction of bp 87—89°C/5 mm Hg was collected. Poly(2-hydroxyethyl methacrylate) (PHEMA) was prepared by polymerization of a 10% solution of monomer in isopropanol. The concentration of AIBN was 20% by wt. in relation to HEMA. The reaction temperature was 75°C, time 5.5 h. The polymer was precipitated with benzene-heptane mixture 1:1 by vol., washed with acetone, and dried under reduced pressure at a temperature of 50°C. The yield was 69%. The number average molecular weight of PHEMA was $M_n$ = 23.600 g/mol, ($DP_n$ = 181) and polydispersity was $M_w/M_n$ = 1.93.
N,N-dimethylacetamide (DMAc) (Aldrich), dimethylsulfoxide (DMSO) (Merck) was purified by distillation and then stored over 4 Å moleculare sieves. Chloride lithium (LiCl) (Aldrich) was dried under reduced pressure in the presence of phosphorus pentoxide. Chloroacetyl chloride (Aldrich) was purified before use by distillation under reduced pressure. Pyridine (POCh, Poland) was refluxed over $CaH_2$ under a nitrogen atmosphere and then distilled. 1-Naphtylacetic acid (NAA) (Fluka) was used without further purification. Potassium salt of 1-naphthylacetic acid was obtained by dissolving 9.3 g (0.05 mol) of the acid in 50 $cm^3$ of chloroform, then neutralized with 2.8 g (0.05 mol) of KOH dissolved in 50 $cm^3$ of ethyl alcohol. The product precipitated by pouring reaction mixture into 600 $cm^3$ of dry acetone. After filtration, the salt was dried under reduced pressure at 50°C to constant weight.

### *Esterification of PHEMA with chloroacetyl chloride*

The typical procedure, of the esterification was as follow: 3.9 g (30.0 mmol, -OH groups) PHEMA was dissolved in 60 $cm^3$ DMAc/LiCl solvent system. The solution was then charged into a three-necked flask equipped with a nitrogen inlet and outlet, dropping funnel, magnetic stirrer and thermometer. Pyridine 3.1 $cm^3$ (39.0 mmol) was added to the flask as an acid acceptor. DMAc solution (10 $cm^3$) containing chloroacetyl chloride 2.9 $cm^3$ (36.0 mmol) was then added dropwise at about 0°C with stirring. The reaction mixture was heated at 25°C for 8 h and after the solution was poured into a large amount of cold 2M HCl to precipitate the product. The precipitated product was filtered and washed several times with cold distilled water. It was purified by reprecipitation using THF as solvent and cold distilled water as precipitant, then dried under reduced pressure at 50°C to constant weight. Yield was 84%.

### *Reaction of chloroacetylated PHEMA with the potassium 1-naphthylacetate*

The typical procedure, of the reaction was as follow: The chloroacetylated PHEMA 2.1 g (10 mmol $ClCH_2CO$- groups) was dissolved in 20 $cm^3$ DMSO at room temperature and then of potassium 1-naphthylacetate 3.15 g (14 mmol) was added while stirring. The reaction was performed at 30°C and under stirring for about 5 h.

The product was isolated by precipitation using distilled water as precipitant and then ethanol washed to remove unreacted potassium salt of acid. All samples were purified by reprecipitation, using DMSO as solvent and ethanol as precipitant and then dried under reduce pressure at 60°C to constant weight. Yield was 76%.

*Study of heterogeneous hydrolysis of PHEMA-1-naphthylacetic acid adduct*

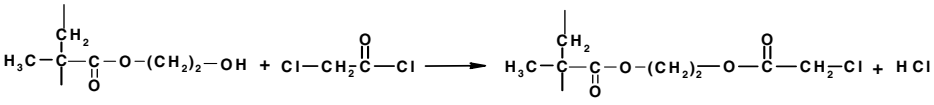
Samples of the PHEMA-1-naphthylacetic acid adduct, about 0.1 g, (containing from 13.4 to 98.1 mol% 1-naphthylacetate groups) in the form of powder were pressed in steel cylindrical cell with a diameter of 12 mm in a hydraulic press under a pressure of about 12 MPa to make disks. The resulting disk was placed in conical flasks with 100 $cm^3$ water solution of NaOH (pH = 12.7 ÷ 13.7). Flaskes were put into water bath headed to the 25°C temperature. At fixed intervals, solution specimens were taken from the liquid above the padded of tables samples. The homogeneous solution contained the released bioactive agent, which was quantitatively determined by UV spectroscopy at the absorption wavelength of 1-naphthylacetic acid ($\lambda$=281 nm) using calibration curves (aqueous solution of sodium hydroxide as solvent). Tests were performed for different hydrophilic character of adducts and various pH values of reaction environment.

*Measurements*

Infrared spectra were recorded using Perkin-Elmer 2000 (FTIR) instrument (Beaconsfield, England). $^1$H-NMR and $^{13}$C-NMR spectra were obtained using Bruker DPX 250 MHz spectrometer (Kalsruhe, Germany) with $CDCl_3$ as solvent and TMS as an internal reference. The UV-VIS spectra were obtained using Perkin Elmer UV/VIS Lambda 2 spectrometer (Überlingen, Germany). The degree of the substitution of the PHEMA was determined from the elemental analysis of chloride. The values of number average molecular weight ($M_n$), average molecular weight ($M_w$) and the polydispersity ($M_w/M_n$) of the PHEMA were determined by gel permeation chromatography (GPC). Chromatogram in DMF at 35°C was obtained in Waters modular system (Milford, USA) using Ultrastyragel Linear Column and RI-detector Waters 410 Average molecular weight was calculated on the basis of a polystyrene calibration curve.

## Results and discussion

PHEMA modified with chloroacetate groups with different degrees of substitution were synthesized in a homogenous medium by using the method followed in the chloroacetylation of poly(vinyl alcohol) [8] according to the reaction presented by the Scheme 1:



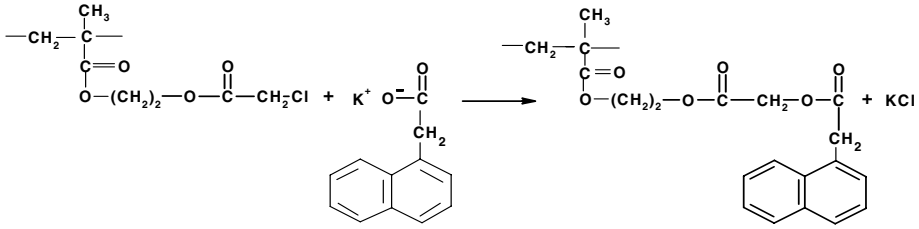
Scheme 1

The effect of reaction conditions on degree of substitution is summarized in Table 1. As follows from the date in Table 1, the extent of modification increases with an increase in the ratio of chloroacetyl chloride to PHEMA. For example, the degress substitution increases from 13.4 to 98.1 mol% chloroacetate groups as chloroacetyl chloride/hydroxy groups of PHEMA increase from 0.4 to 1.2.

**Table 1.** Effect of reaction conditions on the degree of substitution for the esterification of PHEMA with chloroacetyl chloride at 25°C

| Sample | $ClCH_2COCl$ /-OH mole/mole | Cl % | Degree of substitution mol % |
|---|---|---|---|
| 1 | 0.4 | 3.32 | 13.4 |
| 2 | 1.0 | 14.89 | 80.5 |
| 3 | 1.2 | 16.95 | 98.1 |

The coupling of bioactive carboxylic acid to PHEMA functionalized with chloroacetate groups was carried out by using the potassium 1-naphthylacetate according to the following Scheme 2:



Scheme 2

The elementary analysis of the products obtained from chloroacetylated PHEMA with various degrees of substitutions and potassium 1-naphthylacetate showed the absence of chlorine, which allowed one to assume its total replacement with the substitution degree of the adduct being the same as that for corresponding chloroacetylated derivatives of PHEMA.

Figure 1 (a-c) shows exemplary FTIR spectra of unmodified PHEMA, chloroacetylated PHEMA (98.1 mol% of chloroacetate groups) and PHEMA-1-naphthylacetic acid adduct (98.1 mol% of 1-naphthylacetate groups). As is seen, the spectrum of chloroacetylated PHEMA (Figure 1b), unlike the spectrum of PHEMA (Figure 1a), has a new absorption band at 1760 $cm^{-1}$ of carbonyl groups in $–COO-CH_2-Cl$, which is superimposed on the spectrum of >C=O band of ester groups of PHEMA. There is also visible an absorption peak of $–CH_2Cl$ groups at 760 $cm^{-1}$. On the other hand, there disappears the band within the range 3630 - 3050 $cm^{-1}$ derived from hydroxyl groups. Moreover in spectrum (Figure 1c) of the adduct PHEMA-1-naphthylacetic acid absorption band appears at 1560, 1513 and 790 $cm^{-1}$, which results from scissoring vibrations bands >C=C< and C-H in the naphthyl ring [10].

The $^1$H-NMR spectrum of the same chloroacetylated PHEMA (Figure 2a) shows a characteristic band of protons of chloroacetate groups at 4.25 ppm, which is superimposed on one of the signals of $–OCH_2CH_2O-$ groups. There are also visible

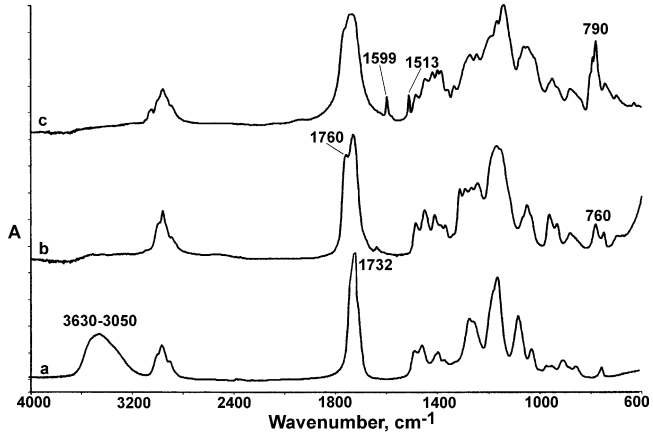



**Figure 1.** FTIR spectra of: a - PHEMA, b - chloroacetylated PHEMA (98.1mol% of chloroacetate groups), c - adduct of PHEMA-1-naphtylacetic acid (98.1 mol% of 1-naphthylacetate groups)

bands at 1.63 – 2.46 ppm, which belong to protons of $–CH_2-$ in the main chain, and a signal of protons of $\alpha–CH_3$ groups at 0.65 - 1.51 ppm. The spectrum of the PHEMA-1-naphthylacetic acid adduct (Figure 2b) shows additional signals at 7.26 – 8.31 ppm derived from the protons of naphthyl ring [11].

The $^{13}$C-NMR spectrum of chloroacetylated PHEMA (Figure 3a) is characterized by chemical shifts at 40.73 and 167.17 ppm, which correspond to chloromethyl and carbonyl carbon atoms of chloroacetate groups, respectively. The spectrum of the

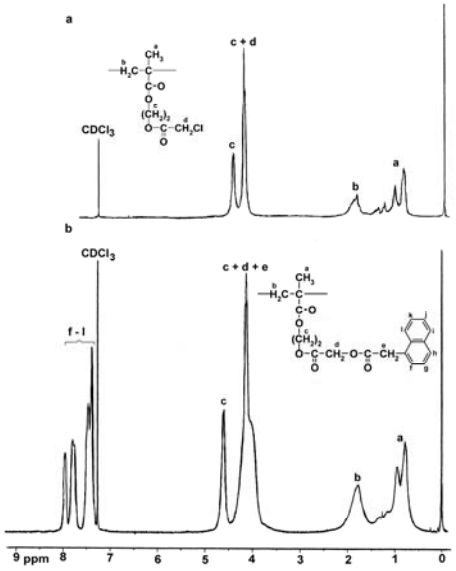



**Figure 2.** $^1$H-NMR spectra of: a - chloroacetylated PHEMA (98.1 mol% of chloroacetate groups) in $CD_3Cl$, b - adduct of PHEMA-1-naphthylacetic acid (98.1mol% of 1-naphthyl-acetate groups) in $CD_3Cl$

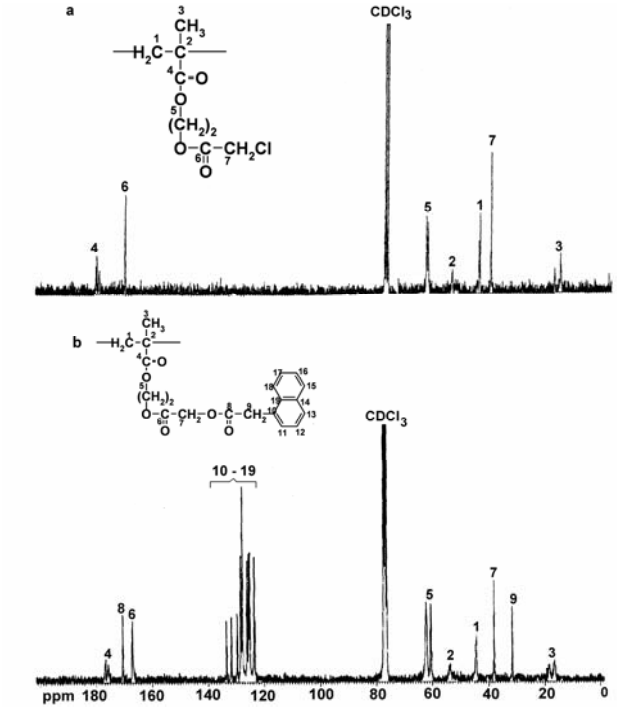



**Figure 3.** $^{13}$C-NMR spectra of: a - chloroacetylated PHEMA (98.1 mol% of chloroacetate groups) in $CD_3Cl$, b - adduct of PHEMA-1-naphthylacetic acid (98.1 mol% of 1-naphthyl-acetate groups) in $CD_3Cl$

PHEMA-1-naphthylacetic acid adduct (Figure 3b) shows additional peaks between 121.58 and 134.51 ppm, which due to the resonance of carbon atoms in the naphthyl ring and the signal at 170.77 ppm can be assigned to the $C_{10}H_7$-$CH_2$-$\underline{C}O$- groups.

The initial stage of the heterogeneous hydrolysis of PHEMA-1-naphthylacetic acid adducts at various solution pH values and different composition adducts were also investigated. Figure 4 shows the release behaviour of naphthylacetic acid at 25°C and pH=12.7 from three PHEMA-1-naphthylacetic acid adducts with various compositions, containing from 13.4 to 98.1 mol% of naphthylacetate groups. From the course of kinetic curves it follows that the release of the active compound is the quickest in the case of the adduct with the lowest content of naphthylacetate groups. This seems to be connected with interaction between the polymer and water. The decreased content of naphthylacetate groups makes the polymer more hydrophilic and consequently facilitates the penetration of hydroxyl ions to active sites in the tablet, effectively increasing the relative of hydrolysis rates.

Figure 5 shows a typical course of the heterogeneous hydrolysis of PHEMA-1-naphthylacetic acid adduct (containing 98.1 mol% of naphthylacetate groups) in alkaline medium from pH=12.7 to 13.7 at 25°C. The presented results clearly indicate the increase in the release of bioactive carboxylic acid with the increase in the alkalinity of reaction medium. The hydrolysis rate of adduct is the lowest at pH = 12.7. This is consistent with the results obtained by Arranz *et al.* [8] for the poly(vinyl alcohol)-1-naphthylacetic acid adduct.

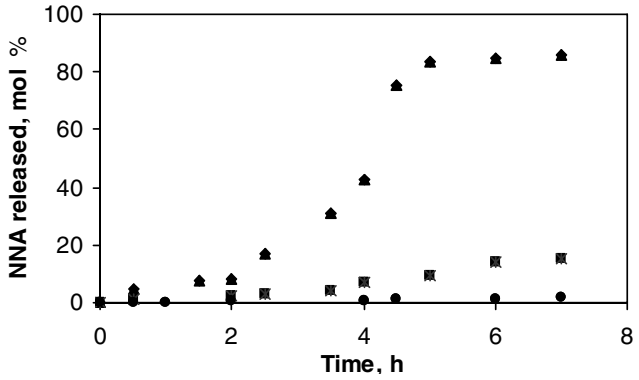



**Figure 4.** The release of the bioactive compound (NAA) with 1-naphthylacetate PHEMA derivative depending on different composition adducts: (▲) 13.4 mol% 1-naphthylacetate groups; (■) 80.5 mol% 1-naphthylacetate groups; (•) 98.1 mol% 1-naphthylacetate groups (pH = 12.7 at 25°C)

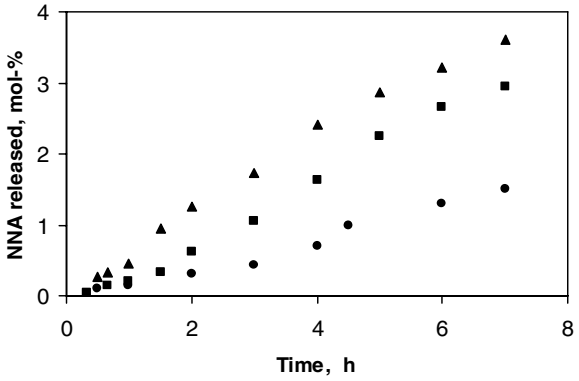



**Figure 5.** The release of the bioactive compound (NAA) with 1-naphthylacetate PHEMA derivative depending on pH value of reaction environment: (•) pH = 12.7, (■) pH = 13.0 and (▲) pH = 13.7 (98.1 mol% 1-naphthylacetate groups, at 25°C)

## Conclusions

As the result of esterification of PHEMA with chloroacetyl chloride, using pyridine as catalysts and DMAc/LiCl system as solvent, PHEMA with chloroacetate groups was produced. The presence of chloroacetate groups was used to obtain adduct with bioactive carboxylic acid during the reaction with its potassium salt. On the basis of the results of adduct heterogeneous hydrolysis, it was stated that the rate of biocide release depends on pH of reaction environment and composition adducts of PHEMA-1-naphthylacetic acid.

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