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Poly(vinyl alcohol)-nalidixic acid adducts

Synthesis and controlled release behaviour

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SUMMARY

This work deals with the coupling of nalidixic acid (NAL) to poly (vinyl alcohol) (PVAL) functionalized with chloroacetate groups by reaction with its potassium salt. The structure of the resulting adducts was determined by means of ^{1}H and ^{13}C NMR spectroscopy. The obtained results show the reaction to occur in a quantitative way. The hydrolysis in the heterogeneous phase of PVAL-NAL adducts showed that the release of the bioactive compound is dependent on the hydrophilic character of the adduct as well as on the pH value of the medium.

INTRODUCTION

Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) is a synthetic drug used to control several gram-negative microorganisms, specially those that are responsible for infections of the urinary system (1). However, this compound, as all quinolone antibiotics, exhibits adverse side effects, which limit their applications to a large extent. Un attempt of Ghosh to avoid those problems by incorporating nalidixic acid (NAL) to poly (vinyl alcohol) (PVAL) and poly (allyl alcohol) in the presence of bicyclohexylcarbodiimide proved unsuccesful (2). On the other hand, the transformation of NAL in their acid chloride to synthetize monomeric derivatives is not feasible because of the oxidation of the aromatic methyl group to trichloromethyl group resulting from that reaction(2).

The present paper deals with an efficient method to link NAL to chloroacetylated PVAL, a reactive derivative of PVAL. A study of the hydrolytic degradation of the resulting PVAL-NAL adducts in the heterogeneous phase was also made, in order to evaluate the release of the active compound.

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EXPERIMENTAL

Materials

The PVAL was a commercial product (Gohsenol NL-O5), thoroughly hydrolyzed. Its molecular weight, as measured by osmometry, was 22000 g/mol, and purification was performed by a conventional reprecipitation method using a water/methanol mixture as solvent/precipitant system. The purified polymer was dried in vacuo in the presence of phosphorus pentoxide to constant weight. N-Methyl-2-pyrrolidone (Fluka) and dimethyl sulfoxide (DMSO) (Ferosa) were distilled under vacuum and then dried for a few days with a Merck 4 Å molecular sieve. Chloroacetyl chloride (Fluka) was purified prior to use by distillation under normal pressure. Pyridine (Ferosa) was purified by a conventional method (3). NAL (Fluka) was used without further purification. Potassium salt of NAL was obtained by dissolving 0.1 mol of the acid in 100 ml of chloroform, then neutralizing with 0.1 mol of KOH dissolved in 80 ml of ethyl alcohol. The solution was precipitated by pouring into 1500 ml of dry acetone. After filtration, the salt was dried in vacuo in the presence of phosphorus pentoxide.

Reaction of PVAL with chloroacetyl chloride

PVAL partially chloroacetylated were obtained as described earlier (4). Shortly, equimolecular concentrations of chloroacetyl chloride and pyridine were reacted at 25°C with 4 g (0.091 mol OH) of PVAL using 200 ml of N-methyl-2-pyrrolidone as solvent. The modification extent was controlled by the amount of chloroacetyl chloride used. The modified polymers were isolated by precipitation using distilled water as precipitant. It was purified by reprecipitation using acetone or THF/methanol (4:1 by vol.) mixture as solvent and distilled water or isopropyl alcohol as precipitant, and then dried in vacuo in the presence of phosphorus pentoxide. Characterization of chloroacetylated PVAL was carried out as indicated previously (4).

Reaction of chloroacetylated PVAL with the potassium salt of NAL

The chloroacetylated PVAL was dissolved in DMSO at 50°C. The calculated amount of potassium salt of NAL was added while stirring. All the reactions were performed at constant temperature during 10 h. The polymer remained soluble throughout the process. The modified polymers were isolated by precipitation using distilled water as precipitant. All samples were purified by reprecipitation, using THF/DMF (1:1 by vol.) mixtures as solvent and distilled water as precipitant, and then dried in vacuo in the presence of phosphorus pentoxide.

Characterization of PVAL-NAL adducts

The ^{1}H NMR spectra were registered in DMSO-d_6 at 70°C using a 200 MHz Bruker AM-200 spectrometer. ^{13}C NMR spectra were obtained from a Bruker AM-200 spectrometer operating

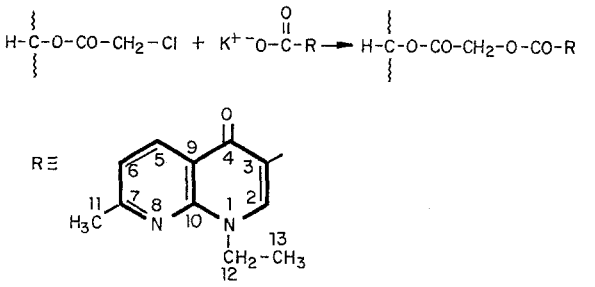
at 50.4 MHz in DMSO-d_6 at 70°C. The modification extent was determined by ^{1}H NMR.

Heterogeneous hydrolysis reactions

For this study we used some PVAL-NAL adducts containing different amounts of bioactive compound, which are insoluble in water. Polymer samples of approximately 0,1 g in disk form were obtained by casting from DMF/THF (1:1 by vol.) mixture solutions containing the appropriate amounts of the adduct. After evaporation of nearly all the mixture solvent at room temperature, the resulting film was detached and disks, each of diameter 13 mm cut out with a cork-borer. The obtained disks were dried to constant weight in a vacuum oven at 40°C.
In order to determine the release rate, the disk was introduced into a small wire-basket which was entirely permeable to water. This device was placed in pyrex stoppered test tubes, each one containing 25 ml of an aqueous buffer solution. The tubes were then immersed at the desired temperature in a thermostat bath. A periodic assay of samples was obtained by removing the metallic device, stirring the solution and pipetting a 1-ml sample. The wire-basket was quickly re-inserted, making sure that the disk remained completely immersed throughout the hydrolysis study. The volume pipetted for each sample was replaced by an equivalent volume of fresh solvent, with corrections being applied in the calculations. The concentration of NAL released was determined by UV at 255 nm ($\epsilon = 2.80.10^4$ l.mol^{-1}. cm^{-1}). Note that PVAL-NAL adducts remain insoluble in the reaction medium along the whole hydrolysis process investigated.

RESULTS AND DISCUSSION

PVAL modified with chloroacetate groups with different modification extent were synthesized in a homogeneous medium, following a previously used method. The structure of the resulting polymers was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopies. The obtained results enable us to conclude that the reaction of PVAL with chloroacetyl chloride in the presence of pyridine was practically quantitative.
The covalent attachment of NAL to chloroacetylated PVAL through ester bonds was performed according to the following scheme:



The structure of the resulting polymers was confirmed by ^{1}H and ^{13}C NMR spectroscopies. Table 1 shows the characteristic bands of the pendant bioactive groups. These assignments are supported by those previously reported for ^{1}H NMR of NAL (5) and ^{13}C NMR of sodium nalidixate (1).

Table 1. Characteristic data of the ^{1}H and ^{13}C NMR spectra of pendant nalidixic groups of PVAL-NAL adducts.

H/C atom	^{1}H NMR (ppm)	^{13}C NMR (ppm)
2	8.7	148.7
3	-	109.8
4	-	172.5
5	8.3	135.4
6	7.2	120.5
7	-	161.8
9	-	120.5
10	-	147.8
11	2.6	24.0
12	4.7	45.0
13	1.3	14.1

Table. 2 shows satisfactory couplings for the reaction between chloroacetylated PVAL and NAL. The modification extent was determined from ^{1}H NMR spectra by comparing the integrated intensities of the sum of the bands centered at 8.7; 8.3 and 7.2 ppm (corresponding to the three ring protons of NAL) with the signal at 5.2 ppm (ascribed to methine protons of modified units, whether containing nalidixic groups or unreacted chloroacetate groups). It is seen from Table 2 that virtually all the chloroacetate groups were quantitatively converted to nalidixic groups.

Table 2. Reaction of chloroacetylated PVAL with the potassium salt of NAL at 50°C using DMSO as solvent[a]

Reaction	Chloroacetate groups (mol-%)	Nalidixic groups (mol-%)
1	61.3	58.0
2	38.4	35.6
3	25.2	24.8

a: [potassium salt of NAL]/[chloroacetate groups] = 1.13, Time of reaction = 10h.

In order to study the active ingredient release, two PVAL-NAL adducts with different composition were hydrolyzed in the heterogeneous phase at 37°C and pH = 8.0 or 7.6 (Figure 1). As may be seen from Figure 1, enhanced release rate is observed at pH 8.0 for the two adducts. On the other hand, the total release of the active compound at the two pH values was reached more quickly in the case of the adduct with lower extent of modification. That feature may be explained in terms of the interaction of the polymers with water. Decreasing the content of nalidixic groups renders the polymers more hydrophilic and, therefore, facilitates the entry of hydrolytic species into the tablet to the active sites, effectively increasing the relative hydrolysis rates.

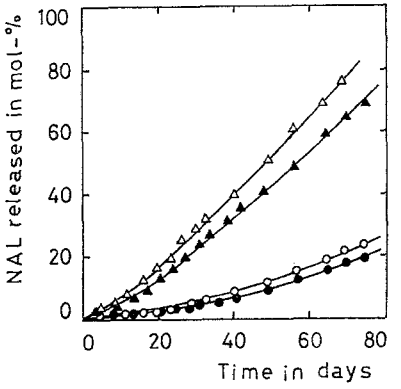


Figure.1 Heterogeneous hydrolysis of two PVAL-NAL adducts at 37°C and pH 8.0 or 7.6; (○): 35.6 mol% of NAL, pH 8.0, (△): 24.8 mol% of NAL, pH 8.0, (●): 35.6 mol% of NAL, pH 7.6, (▲): 24.8 mol% of NAL, pH 7.6.

It may be noteworthy that release experiments at 37°C and pH 8.0 of a PVAL-NAL (58.0 mol% of NAL) adduct showed that no significant hydrolysis takes place under the conditions employed.

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