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Modification of Poly(maleic anhydride-co-styrene) with Hydroxyl Containing Compounds

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Soluble and cross-linked poly(maleic anhydride-co-styrene) copolymers were reacted with hydroxyl containing compounds such as salicylic acid, 2-phenyl ethanol, eugenol and paracetamole in acetone or dioxane solution at 50-80°C. The hydrolytic and controlled release behavior of the copolymers containing these compounds in water was studied. The extent of hydrolysis was found to be affected by the type of polymer support as well as time, temperature and the type of supported compound.

Introduction

Synthesis of polymerizable acetales, sulfonate esters[1] and carbamates[2]obtained from perfume alcohols, pesticides and herbicides and the controlled release function of the monomers and polymers there of have been studied before. Perfume alcohols have also been supported to polymer backbones and the controlled release properties have been investigated[3].

Copolymers of maleic anhydride with ethylene, methyl vinyl ether, styrene and vinyl chloride are avaible commercially[4,5]. The reaction of anhydride groups containing copolymers such as poly(N-vinyl pyrrolidone-co-maleic acide)[6], poly(methyl vinyl ether-co-maleic anhydride)[7] with hydroxyl compounds and amines were studied earlier.

In this article, we studied the supporting of hydroxyl containing medicinal compounds such as eugenol, paracetamole, 2-phenyl ethanol and salicylic acid to maleic anhydride copolymers. The controlled release of these compounds was also investigated. Both soluble and macroporous poly(styrene-co-maleic anhydride) copolymers were used in order to determine the effect of polymer solubilities and microstructures on the yields of coupling and hydrolyzing reactions.

Experimental

Equipment–FTIR spectra were recorded on a Jasco FTIR-5300 spectrophotometer as KBr pellets or films. Both ^{1}H NMR and ^{13}C NMR spectra were obtained from $(CD_3)_2CO$ solutions, on a Bruker AC-200 MHz spectrometer. Tetramethyl silane (TMS) was used as the internal standard. The maleic anhydride functional

group was analyzed by the morpholine method[8]. Molecular weight of soluble poly(maleic anhydride-co-styrene) was calculated from the single-point viscosity of its acetone solution at 25°C using the following equations[9]:

$$|\eta| = 8.69 \times 10^{-5} M_n^{0.74} \quad |\eta| = \frac{\eta_{sp}}{1 + 0.28x\eta_{sp}}$$

Softening point measurments were carried out with a melting point apparatus (Buchi). The sample was placed into a capillary glass tube and its softening point was measured.

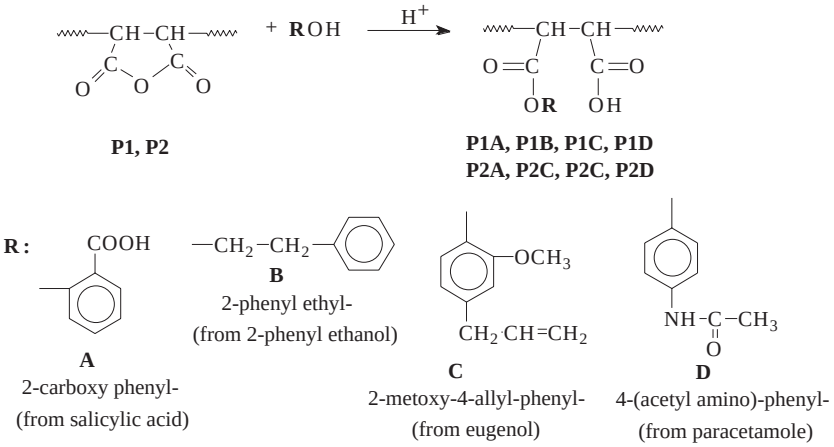
Materials–Polymerization grade styrene (Fluka, Switzerland), divinyl benzene (Fluka, Switzerland) and maleic anhydride (Fluka, Switzerland) and dibenzoyl peroxide (Fluka, Switzerland) were used as received. Salicylic acid (Merck, Germany), 2-phenyl ethanol (Fluka, Switzerland), eugenol (Fluka, Switzerland) and paracetamole (Merck, Germany) were reagent grade. Toluene (Merck, Germany), dioxane (Merck, Germany), acetone (Merck, Germany), glacial acetic acid (Merck, Germany) and methanol (Merck, Germany) were freshly distilled before use.

Synthesis of poly(maleic anhydride-co-styrene) (P1)–A 500 ml round-bottomed three-necked flask equipped with a mechanical stirrer, a thermometer and a reflux condenser was charged with 300 ml toluene, 10 ml (0.086 mole) styrene, 9.8 g (0.1 mole) maleic anhydride and 0.1 g (0.4 mmole) dibenzoyl peroxide. The mixture was stirred at room temperature for about 0.5 hours and a homogeneous solution was achieved. The mixture was then heated up to 80°C and stirred for one hour. It was then cooled to room temperature, and the precipitated copolymer (P1) was collected by filtration as white powder. The copolymer (P1) was rapidly washed with alcohol at room temperature and dried at 50°C in vacuo overnight. The yield was about 95% and the calculated molecular weight was 22 000 g/mol.

Synthesis of macroporous cross-linked poly(maleic anhydride-co-styrene) (P2)–A 250 ml round-bottomed three-necked flask equipped with a mechanical stirrer, a thermometer and a reflux condenser was charged with 150 ml toluene, 5 ml (0.043 mole) styrene, 4.9 g (0.049 mole) maleic anhydride, 0.25 ml (1.8 mmole) divinyl benzene and 0.05 g (0.2 mmole) dibenzoyl peroxide. The mixture was stirred at room temperature for about 0.5 hours, then heated up to 80°C while stirring. The stirring was continued for another hour. Then the mixture was cooled to room temperature. The white cross-linked copolymer (P2) powder was collected by filtration, washed with acetone and dried at 50°C in vacuo overnight. The yield was 95% .

The reaction of maleic anhydride-styrene copolymers with hydroxyl compounds–A round-bottomed two-necked flask equipped with a magnetic stirrer, a thermometer and a reflux condenser was charged with 2 g copolymer P1 (0.01mole anhydride group), 0.01mole hydroxyl compounds (i.e. salicylic acid, 2-phenyl ethanol, eugenol or paracetamole), 50 ml solvent (acetone or dioxane) and a few drops of concentrated H_2SO_4. The homogenous mixture was heated up to a selected temperature and stirred for 24 hours. The products (P1A, P1B, P1C or P1D) were precipitated with toluene, collected by filtration, washed with alcohol+water, cold alcohol and ether and dried in vacuo. Conversion was defined as the percent age of anhydride units reacted with hydroxyl compounds.

The same procedure described above was applied to the mixture of 2 g cross-linked poly(styrene-co-maleic anhydride) (P2) and 0.01 mole hydroxyl compounds. The products P2A, P2B, P2C, P2D were collected as white powders.



Hydrolysis–A 0.5 g polymer supported hydroxyl compound was put into 50 ml water and the pHwas brought to 3 by dropwise addition of H_2SO_4 to imitate the gastric condition. The mixture was let to stand at 20, 50 and 80^0C for a period of 3 to 96 hours The released compounds were extracted with ether and dried over anhydrous sodium sulfate. Ether was then evaporated and the residue, i.e., salicylic acid, 2-phenyl ethanol, eugenol or paracetamole was weighed to determine the extent of hydrolysis.

Results and Discussion

Two different type of maleic anhydride copolymers were synthesized in order to study the reaction between anhydride groups of copolymers and hydroxy containing compounds. They were soluble poly(maleic anhydride-co-styrene) (P1) and crosslinked poly(maleic anhydride-co-styrene) (P2). The soluble copolymer was suitable for spectroscopic examination of the reaction and its solution properties. The copolymer (P1) was soluble in dioxane and acetone and insoluble in aromatic and chlorinated hydrocarbons. Macroporous cross-linked poly(maleic anhydride-co-styrene) (P2) was swollen in dioxane and acetone.

The copolymers (P1) and (P2) were treated under the same experimental conditions without any hydroxyl containing compounds for blank experiments. This enable us to determine the effect of reaction conditions on anhydride groups.

The reactions of hydroxyl containing medicinal compounds such as salicylic acid, 2-phenyl ethanol, eugenol and paracetamole with (P1) and (P2) were carried out under anhydrous conditions and the results are summarized in Table 1. The mole ratio of the hydroxyl group to the anhydride group was taken as 1. The reaction yield was varied between 22 and 95% and was dependent on temperature, time and solvent type. For example, the yield increased from 47% to 83% in dioxane if the time increased from 24 to 48 hours (P1C). A yield of 94% was achieved in dioxane (P1D). Under the same conditions, the reaction yield of the cross-linked polymer of (P2) with hydroxyl compounds of (A), (B) and (C) decreased (Table 1). This was probably due to the diffusion effects of solvent in the swollen cross-linked polymer P2. The diffusion of hydroxyl compounds through pores of polymer P2 controls the reaction rate. However, for compound (D), the reaction yields of polymer P1 and polymer P2 were somewhat higher than those of compounds (A), (B) and (C). This diference is probably due to the local concentration of anhydride of macroporous polymer which favours reaction with compound B and D with higher reaction rate rather than A and C. Besides the formed ester structure, the effect of the random coil formation in solution and in the cases of B and D

and the chemical reactivity of neighbouring anhydride groups in reacted polymers P1B and P1D would be decreased in soluble St/MA copolymers.

Table 1. The reaction yield of poly(maleic anhydride-co-styrene) with hydroxy compounds.

Modified polymer	Solvent	Time (hr.)	Temp. (°C)	Conversion (%)
P1A	gl.acetic acid	24	80	72
P1A	dioxane	24	80	74
P2A	gl.acetic acid	24	80	46
P2A	dioxane	24	80	60
P1B	acetone	24	50	50
P1B	acetone	48	50	54
P1B	acetone	72	50	88
P2B	acetone	24	50	71
P1C	dioxane	24	80	47
P1C	dioxane	48	80	83
P2C	dioxane	48	80	56
P1D	dioxane	24	25	22
P1D	acetone	48	50	80
P1D	dioxane	48	80	94
P2D	acetone	48	50	92

The intrinsic viscosity, softening point and solubilities of the products P1A, P1B, P1C and P1D and the swellability of the products P2A, P2B, P2C and P2D are shown in Table 2 and 3. All of the reaction products (P1A-P1D) were insoluble in water, ether, aromatic hydrocarbon and chlorinated hydrocarbons. P1D was insoluble in acetone. As seen in Tables 2 and 3, the softening points of the reaction products were much higher than those of their base copolymers (P1) and (P2). After coupling of the organic compounds, the products P1A-D and P2-D are completely different copolymers than P1 and P2 as they have much higher softening points (Tables 2, 3).

Table 2. Physical properties of poly(maleic anhydride-co- styrene) and modified poly(maleic anhydride-co- styrene).

Modified	s.p	Solubility						
polymer	(°C)	water	alcohol	acetone	ether	dioxane	toluene	chloroform
P1	190	i	s^h	s	i	s	i	i
P1A	220	i	s^h	s	i	s^h	i	i
P1B	200	i	S	s	i	s	i	i
P1C	285	i	s^h	s	i	s^h	i	i
P1D	>300	i	sl^h	i	i	s^h	i	i

Table 3. Physical properties of cross-linked poly(maleic anhydride-co-styrene) and modified cross-linked poly(maleic anhydride-co-styrene).

Modified	s.p	Swellability					
polymer	(°C)	alcohol	acetone	eter	dioxane	toluene	chloroform
P2	230	nsw	sw	nsw	sw	nsw	nsw
P2A	270	sw	sw	nsw	sw^h	nsw	nsw
P2B	220	nsw	sw	nsw	sw	nsw	nsw
P2C	>300	sw^h	nsw	nsw	sw^h	nsw	nsw
P2D	>300	sw	nsw	nsw	sw^h	nsw	nsw

Soluble copolymer P1 and its reaction products P1A, P1B, P1C and P1D were studied with FTIR and NMR. Cross-linked copolymer P2 and its reaction products P2A-D were only examined with FTIR.

In the FTIR spectrum of the copolymer P1 and P2 and their reaction products P1A-D and P2A-D, peaks due to anhydride groups appear at 1855 cm^{-1}, 1775 cm^{-1} (cyclic anhydride C=O) and 1220 cm^{-1} (cyclic C-O-C). As expected, the higher the conversion of anhydride to ester groups after the reaction with hydroxyl containing compounds, the lower the residual anhydride absorption intensities of peaks at 1855 cm^{-1} and 1775 cm^{-1}. In all of the reaction products (P1A-D and P2A-D), the characteristic absorption peaks at about 1730 cm^{-1} due to the ester carbonyl and 1180 cm^{-1} due to the acyclic C-O band are present. Peaks due to unreacted anhydride groups (1855 cm^{-1} and 1775 cm^{-1}) in the FTIR spectrum of (P1A-C) and (P2A-C) are clearly seen. The FTIR spectrum of P1D shows a hydrogen bonded N-H stretching band at 3325 cm^{-1}, amid C=O stretching at 1650 cm^{-1}, NH bending and CN stretching at 1560 cm^{-1} and 1310 cm^{-1} respectively.

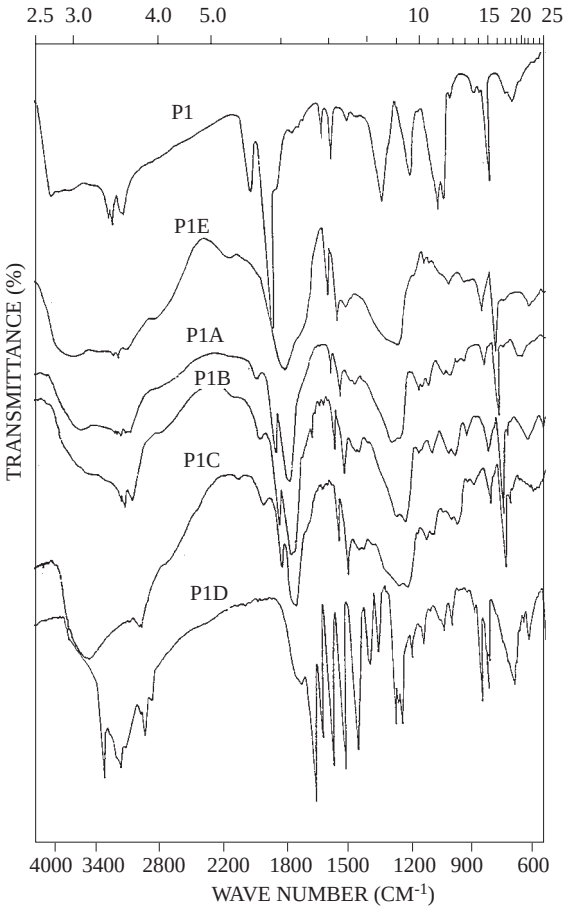


Figure 1. FTIR spectra of poly(maleic anhydride-co-styrene) and modified poly(maleic anhydride-co-styrene)
P1: Poly(maleic anhydride-co-styrene),
P1A: Salicylic acid modified poly(maleic anhydride-co-styrene)
P1B: 2-Phenyl ethanol modified poly(maleic anhydride-co-styrene)
P1C: Eugenol modified poly(maleic anhydride-co-styrene)
P1D: Paracetamole modified poly(maleic anhydride-co-styrene)
P1E: Hydrolyzed poly(maleic anhydride-co-styrene) (blank experiment)

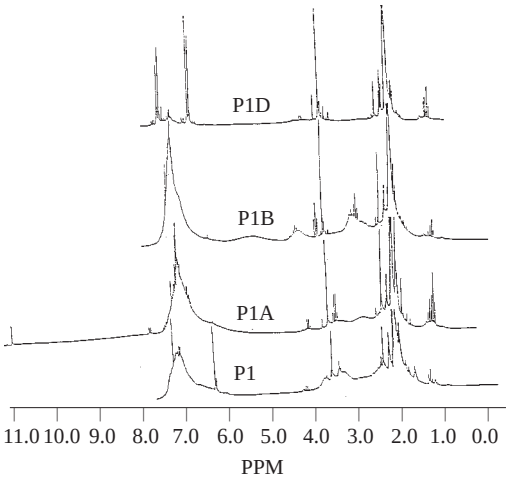


Figure 2. ^{1}H NMR spectra of poly(maleic anhydride-co-styrene) and modified poly(maleic anhydride-co-styrene) in $(CD_3)_2CO$

P1: Poly(maleic anhydride-co-styrene) ,

P1A: Salicylic acid modified poly(maleic anhydride-co-styrene)

P1B: 2-Phenyl ethanol modified poly(maleic anhydride-co-styrene)

P1D: Paracetamole modified poly(maleic anhydride-co-styrene)

In the ^{1}H NMR spectrum of copolymer (P1) and the products (P1A-D), broad overlapping peaks between 1.1 and 2.4 δ ppm and peaks between 7.1 and 7.3 δ ppm are due to methylene/methine and aromatic ring hydrogens of styrene respectively. Methine protons of maleic anhydride appear between 3.4 and 3.7 δ ppm as the multiplet Styrene/maleic anhydride ratio of the copolymer (P1) was calculated from the integration ratio of the peaks at 7.1-7.3 δ ppm and 3.4-3.7 δ ppm. This ratio was about 0.95:1. As expected, an alternating copolymer was produced under the experimental conditions used in this work. The ^{1}H NMR spectrum of the products (P1A-P1D) showed characteristic peaks due to the hydroxyl compounds (A-D), formed ester groups and carboxylic acid groups as well as peaks of copolymer (P1). Salicylic acid modified copolymer (P1A) showed a peak due to carboxylic acid at 11.1 δ ppm as well as typical peaks of the (P1) copolymer. The peaks between 6.9 and 6.97 δ ppm were due to hydrogen ortho and para positions to ester groups and the peaks between 7.85 and 7.95 δ ppm were due to aromatic hydrogen ortho to carboxylic acid groups. Modified copolymer (P1B) showed peaks between 2.55-2.98 δ ppm and at about 3.75 due to Ar-CH_2- and Ar-C-CH_2-O respectively. Paracetamole modified poly(maleic anhydride-co-styrene), P1D showed peaks between 6.6-6.9 δ ppm due to hydrogens ortho to the ester groups and the peaks between 7.4 and 7.6 δ ppm were due to hydrogens ortho position to the acetyl amino groups. The peaks appeared between 1.1-2.4 δ ppm were due to both methyl protons of acetyl group and methylene and methine protons of styrene units. The spectra were in line with the propose structure. Using the integrated intensities of the appropriate resonances it was found that most of anhydride units are esterified (fig. 2). By using their ^{1}H-NMR spectrum the ratios of the compound (A-D) to the polymer (P1) in the supported polymers (P1A-P1D) were calculated. The ratio of salicylic acid, 2-phenyl ethanol, eugenol and paracetamole to styrene were about 0.5 : 1, 0.7 : 1, 0.6 : 1 and 1 : 1 respectively. Besides the ^{13}C NMR spectrum of eugenol modified poly(maleic anhydride-co-styrene), (P1C) showed peaks at 206 ppm due to carboxylic acid carbon, 174 ppm

due to carbon of ester carbonyl , 126-141 ppm due to aromatic carbons of the styrene and eugenol and 13-74 ppm due to aliphatic carbons rspectively.

Table 4. Hydrolysis of modified copolymers P1A-D and P2A-D with water

Compound	Modified Polymer	Time (h)	Temp. (°C)	Yield (%)
Salicylic acid (A)	P1A	24	80	7
	P1A	48	80	8
	P1A	72	80	12
	P2A	24	80	29
	P2A	48	80	91
2-phenyl ethanol (B)	P1B	48	50	12
	P1B	96	50	19
	P1B	24	80	55
	P2B	24	80	33
	P2B	48	80	72
	P2B	72	80	75
Eugenol (C)	P1C	72	50	1
	P1C	96	50	2
	P2C	72	50	100
Paracetamole (D)	P1D	24	20	16
	P1D	24	80	95
	P1D	36	80	99
	P1D	48	50	97
	P2D	36	80	96

Controlled release–The products P1A, P1B, P1C, P1D, P2A, P2B, P2C and P2D were hydrolysized with water in the presence of acid catalyst in order to eludicate their controlled release properties. After hydrolysis reaction, the products i.e. A, B, C and supporting polymers (P1) and (P2) were examined with FTIR and the amount of released products and hydrolysis were calculated. As seen in the table 4, the hydrolysis rate was affected by the time and the temperature and the type of compounds of A, B, C and the supporting copolymer (P1) and (P2). For the compound P1D, appreciably amount of hydrolysis was achieved at room temperature. The hydrolysis of the paracetamole modified crosslinked poly(maleic anhydride-co-styrene), (P2D) under the condition of gastric fluid (pH= 3, temp. $\sim$ 36°C) showed that the liberation yield of paracetamole was about 40 % in 4 hours. In case of salicylic acid, the extent of hydrolysis of P1A was affected insignificantly by time and temperature while hydrolysis of P2A was nearly completed in 48 h at 80°C. The hydrolysis yield of P1B was affected by the temperature rather than the time. The controlled release of P1 showed rather different behaviour. Even for 96 h at 50°C, hydrolysis yield of P1C was very low (2%) while the hydrolysis of P2C was about 100% in 72 hours at 50°C. This was probably due to polymer P1 and P2 coupled with eugenol were not swollen by water thus hydrolysis could only occur in the macroporous of polymer P2 and the eugenol molecules chemically trapped inside of the precipited polymer could not be extracted by water. On the other hand eugenol molecules are chemically bonded only on the active anhydride sites of macroporous PS/MA on its macropore surfaces where water molecules easily diffuse.

Conclusions

Hydroxyl containing medicinal compounds such as salicylic acid, 2-phenyl ethanol, eugenol and paracetamole could be coupled with both soluble and insoluble poly(maleic anhydride-co-styrene) copolymers. The coupling reaction yields were generally higher for soluble polymers. On the contrary, the hydrolysis yields of coupled macroporous copolymers, P2A, B, C, D were considerably higher compared to the non-porous copolymer P1A, B, C, D which were obtained by precipitating from a non-solvent.

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