

COPOLYMER OF 1-(ACETYLSALICYLYLOXY)ETHYL METHACRYLATE AND ITS HYDROLYSIS*

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ABSTRACT

The copolymers of 1-(acetylsalicylyloxy)ethyl methacrylate (HEMA-ASA) with methacrylic acid (MA) have been prepared and their hydrolysis in dioxane-H₂O either in acidic or alkaline medium, at 60°C or 37°C have been investigated. It is found that the chief product of hydrolysis is always aspirin with minor amount of salicylic acid. Due to its neighbouring group effect, the hydrolysis rate of (HEMA-ASA)-MA copolymer markedly depends on its composition and the pH value of hydrolysis medium, i.e. the hydrolysis rate increases with increasing mole fraction of MA in the copolymer and pH value of hydrolysis medium.

INTRODUCTION

The anticoagulation effect of blood platelet of ordinary analgesic and antipyretic drug aspirin has recently aroused much interest. From the study on hydrolysis of the hydrophilic acrylic polymers having aspirin moieties, it is indicated that these polymers would act as the biocompatible release systems with controlled release of aspirin^[1-4]. In this study, the copolymers of 1-(acetylsalicylyloxy)ethyl methacrylate (HEMA-ASA) with methacrylic acid (MA) have been prepared and the hydrolysis of these copolymers in dioxane-H₂O either in acidic or alkaline medium, at 60°C or 37°C have been investigated. The chief hydrolysis products of HEMA-ASA homopolymer either in acidic or in alkaline medium are aspirin and salicylic acid, evidenced by UV spectrum analysis^[3]. It is expected that the hydrolyzed backbone polymer would be biocompatible since poly(β -hydroxyethyl methacrylate) is a well-known biocompatible material and poly(methacrylic acid) and its Na salt are polymeric electrolytes^[5]. Besides, it is also anticipated that the release of aspirin species would be influenced by its neighbouring group due to the incorporation of methacrylic acid moieties. Thus, the release rate of aspirin could be further controlled through different compositions of copolymers.

EXPERIMENT

The synthesis of HEMA-ASA was carried out as mentioned previously^[1].

Copolymer (HEMA-ASA)-MA.

Monomers HEMA-ASA and MA were dissolved in benzene to around 20% in concen-

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tration and AIBN was added. The polymerization of this mixture was carried out at 60 °C under N_2 atmosphere. Then, it was poured into methanol and filtered. After washing and drying, the yield is about 70 %. The composition of the copolymer was determined by electrometric titration.

The hydrolysis reaction and hydrolysis products were studied and determined as mentioned previously^[1].

RESULTS AND DISCUSSION

About the hydrolysis products of P(HEMA-ASA)-co-MA

The content of aspirin in the hydrolyzed products of copolymer is always higher than salicylic acid no matter with the component of the copolymer, pH value of medium and temperature in hydrolysis. Fig. 1 shows the hydrolysis of the copolymer with 69.5% MA in pH 7.70 at 60 °C. It can be seen that the content of aspirin in the hydrolyzed products of copolymer in alkaline medium is about 6 times as high as salicylic acid, but the content of aspirin is similar to salicylic acid as the hydrolysis of HEMA-ASA homopolymer in the same conditions^[3].

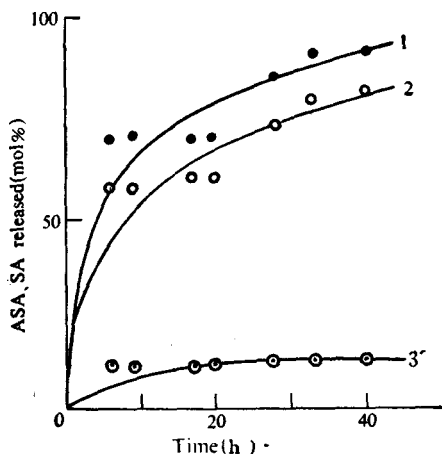


Fig. 1 Hydrolysis of P(HEMA-ASA)-co-MA (69.6:30.4) in dioxane- H_2O , 60°C, pH 7.70
1 Total 2 ASA 3 SA

The effect of pH value of medium on hydrolysis

The hydrolysis rate of these copolymers varies with the pH value of the medium. From curve 3 and 2 in Fig. 2, illustrating the hydrolysis of P(HEMA-ASA)-co-MA with same composition either in pH 7.70 or in pH 1.20 at 60 °C with total amount of release of aspirin and salicylic acid vs. time, it can be seen that the total amount of the copolymer with 69.5% of MA in hydrolysis is about 60 % at pH 1.20 in 10 h. and becomes about 76 % at pH 7.70 in the same time. This may be ascribed to that more $-COO^-$ anions would be formed from

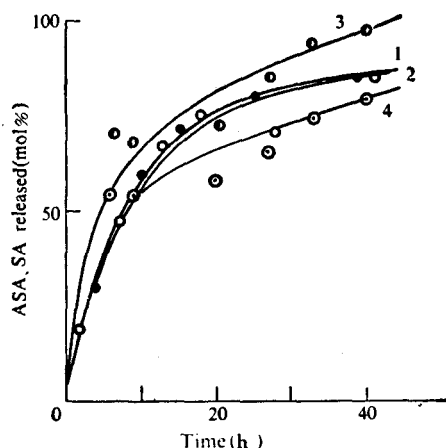
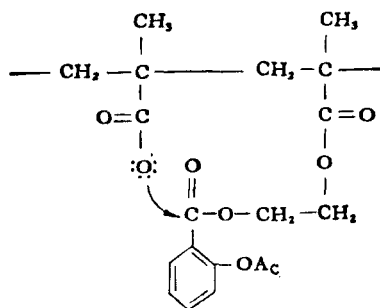


Fig. 2 Hydrolysis of P(HEMA-ASA)-co-MA with different composition (MA in copolymer) 60°C

1 79.4%, pH 1.20	2 69.6%, pH 1.20
3 69.6%, pH 7.70	4 58.1%, pH 7.70

the carboxy group of methacrylic acid at higher pH medium with the result of a nucleophilic attack on the ester group by neighbouring group effect to enhance its hydrolysis as follows:



The effect of copolymeric component on hydrolysis

Fig. 2 illustrated the hydrolysis of P(HEMA-ASA)-co-MA with different components in dioxane-H₂O medium at pH 1.20 and pH 7.70 at 60°C. From curve 1 and 2, it is shown that the total released amount of aspirin and salicylic acid is almost independent on the component of copolymer at pH 1.20. This may be attributed to that all the carboxy groups along the copolymer chain are in the state of carboxylic acid at lower pH medium, thus the rate of hydrolysis reaction is hardly influenced. However, the hydrolysis rate of the copolymer with more content of methacrylic acid is quicker than that with less content of that at pH 7.70 as the curve 3 and 4 in Fig. 2. It is quite evident that more —COO⁻ anions are produced from the copolymer with more carboxy groups in the higher pH medium, and the rate of hydrolysis will be accelerated by the neighbouring group effect.

In addition, comparing the hydrolysis of homopolymer and copolymer, the copolymer always possesses higher rate of hydrolysis than that of homopolymer independent on pH value of medium and temperature of hydrolysis as in Figs. 3 and 4. The rate of hydrolysis of P(HEMA-ASA) homopolymer is slower at first and it is only in 10 hours that the rate will start to increase, but the rate of hydrolysis of the copolymer is quicker at first as in Fig. 3. The total release of aspirin and salicylic acid in the hydrolysis of P(HEMA-ASA)-co-MA is about 3.5 times as long as P(HEMA-ASA) homopolymer in pH 1.20 medium at 37°C as shown in Fig. 4.

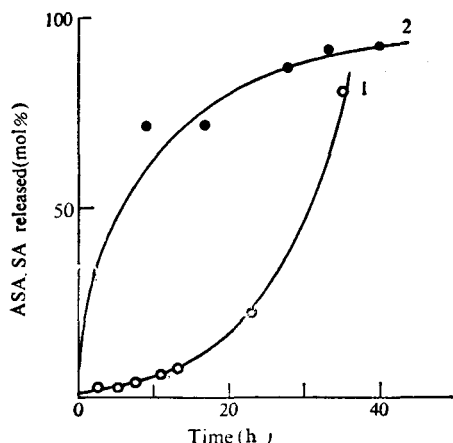


Fig. 3 Hydrolysis of P(HEMA-ASA) and its copolymers in dioxane-H₂O 60°C, pH 7.70

- 1 P(HEMA-ASA)
- 2 P((HEMA-ASA)-co-MA)(MA: 69.6%)

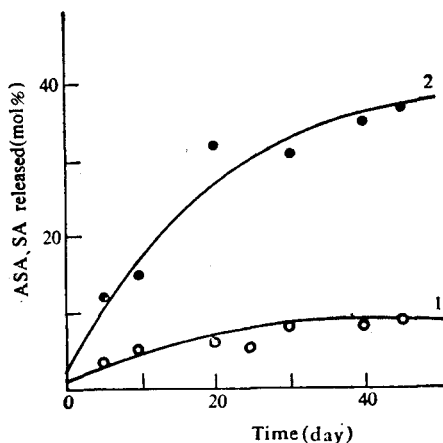


Fig. 4 Hydrolysis of P(HEMA-ASA) and its copolymers in dioxane-H₂O 37°C, pH 1.20

- 1 P(HEMA-ASA)
- 2 P((HEMA-ASA)-co-MA) (MA: 58.1)

Thereby, in case of the copolymer of HEMA-ASA with hydrophilic monomer MA, the component may effectively influence the rate of hydrolysis, i. e. the release of aspirin. Such a system may provide a possibility for controlled release of aspirin.

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