Poly(2-hydroxyethyl methacrylate)-Based Hydrogels for Slow Release of Pralidoxime Chloride

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ABSTRACT: Pralidoxime chloride (PAM-Cl)-loaded poly(2-hydroxyethyl methacrylate) (PHEMA)-based hydrogels were prepared by bulk copolymerization of 2-hydroxyethyl methacrylate (HEMA) with different mol fractions (0.02–0.10) of trimethylsilyl methacrylate. Characterization of the gels was done by dynamic swelling measurements. It was found that copolymerization does not alter the swelling mechanism of PHEMA and it essentially remains Fickian in nature. *In vitro* drug-release studies show the increase in release time from 6 to 12 h on incorporation of a 0.1 mol fraction of trimethylsilyl methacrylate on the PHEMA backbone. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **66:** 267–270, 1997

Key words: hydrogels; poly(2-hydroxyethyl methacrylate); pralidoxime chloride; swelling

INTRODUCTION

Organophosphorus (OP) compounds are generally used as insecticides. There is also the threat that some of the highly toxic OP compounds may be used as chemical warfare agents. These OP compounds irreversibly inhibit an enzyme known as acetylcholine esterase (AChE), leading to the accumulation of acetylcholine in the nervous synapse. Accumulation of AChE induces several toxic symptoms and death may also result. 2-Pralidoxime chloride (PAM-Cl) is used as the reactivator of the inhibited AChE.[1,2] PAM-Cl in conjunction with atropine has generally been adopted for the treatment of poisoning by organophosphorus esters, i.e., nerve agent poisoning. The PAM-Cl antidote must be administered in limited but multiple doses over a period of not more than 48 h. Multiple doses can be replaced by its slow-release formulations using a polymeric matrix system loaded with PAM-Cl.

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Poly(2-hydroxyethyl methacrylate) (PHEMA)-based hydrogels are increasingly being used as a swellable matrix system for the release of different classes of bioactive agents because of their biocompatibility characteristics.[3–6] The permeability of hydrogels can be tailored over a wide range to release a bioactive agent at a desired rate. Copolymerization of 2-hydroxyethyl methacrylate (HEMA) with other comonomers including crosslinkers is done for the tailor-making of PHEMA.[7–9] Therefore, in the present studies, an attempt was made to explore the possibility of using PHEMA and its copolymeric hydrogels with trimethylsilyl methacrylate for the slow release of PAM-Cl. Trimethylsilyl methacrylate was chosen as a comonomer to introduce some amount of hydrophobicity in an otherwise hydrophilic PHEMA system.

EXPERIMENTAL

Materials

2-Hydroxyethyl methacrylate (HEMA, Aldrich) was purified by vacuum-distillation. Ethylene gly-

col dimethacrylate (EGDMA), a crosslinker, was synthesized in the laboratory by direct esterification of HEMA and methacrylic acid in the presence of catalytic amounts of *p*-toluenesulfonic acid.[10] PAM-Cl was prepared in the laboratory by the reported procedure.[11] Trimethylsilyl methacrylate (Aldrich) was used as such without further purification.

Preparation and Characterization of Gels

A free-radical polymerization method was used to prepare cylindrically shaped crosslinked hydrogel samples of PHEMA and its copolymers with trimethylsilyl methacrylate. Gels were prepared by copolymerization of HEMA with different mol %, 2, 5, and 10, of trimethylsilyl methacrylate in the presence of 25% (w/v) water and 0.5% EGDMA. The required quantities of monomers were mixed with water in a three-necked flask fitted with a magnetic stirrer and a water condenser at 80°C. Nitrogen gas was flushed for 10 min, then polymerization was initiated by adding 0.2% (w/w) of benzoylperoxide (BPO) as an initiator. The reaction was allowed to proceed for about 10–15% conversion as determined by a gravimetric method, after which ~ 20–25% (w/w) of the drug PAM-Cl was mixed with stirring at a high speed. The reaction mixture was cooled to 45°C. The contents were then transferred to a glass test tube and polymerization was completed at this temperature in about 72 h. After polymerization, the gels were taken out by breaking the glass tubes. The samples so obtained were cut into ~ 1 mm thin discs with a sharp-edged blade and finally dried under a vacuum to a constant weight at room temperature.

Characterization of these crosslinked hydrogels was not possible by spectroscopic methods and molecular weight determination. Therefore, gels were characterized by their swelling behavior. Dynamic swelling measurements were done by a gravimetric method at 37 ± 1°C by immersing about 0.5 g of the polymer sample (without the drug) in phosphate buffer (pH 7.4). Swelled gels were periodically removed, patted dry, and weighed at regular intervals with an analytical balance until equilibrium was attained. The % equilibrium swelling (water uptake at equilibrium/dry mass × 100) was calculated from the swollen and dry mass of the gels.

Drug-release Studies

Dry drug-loaded polymer samples (~ 0.2 g) were placed in a 100 mL phosphate buffer (pH 7.4) in different beakers at 37 ± 0.5°C under an unstirred condition. The release of the drug in the medium was determined by taking out an aliquot portion (0.05 mL) of it at different time intervals and measuring its absorbance after suitable dilution at the λ_{max} of the drug using a Shimadzu UV-visible spectrophotometer. Concentration of the released drug was then computed by comparing the absorbance with the standard curves prepared.

RESULTS AND DISCUSSION

A PAM-Cl-loaded and unloaded pure PHEMA homopolymer and its copolymeric gels were prepared by polymerizing HEMA with 2, 5, and 10 mol % of the comonomer trimethylsilyl methacrylate by a free-radical polymerization technique. All the samples prepared were transparent, slightly brownish in color, and insoluble in common organic solvents, thereby indicating the formation of a highly crosslinked structure. Characterization of the gels (without the drug) was done by swelling measurements and the data are expressed in terms of equilibrium swelling % (Table I). The values of the equilibrium swelling % for P(HEMA-*co*-trimethylsilyl methacrylate) increased as the amount of HEMA, the more hydrophilic component in the copolymer, increased. Fig-

Table I Equilibrium Swelling % of Copolymers Having 0.5% EGDMA

Sample Designation	Mol Fraction of Trimethylsilyl Methacrylate	No. Samples Tested	Equilibrium Swelling % (37 ± 1°C)
HS1	0.00	5	47
HS2	0.02	5	44
HS3	0.05	5	39
HS4	0.10	5	35

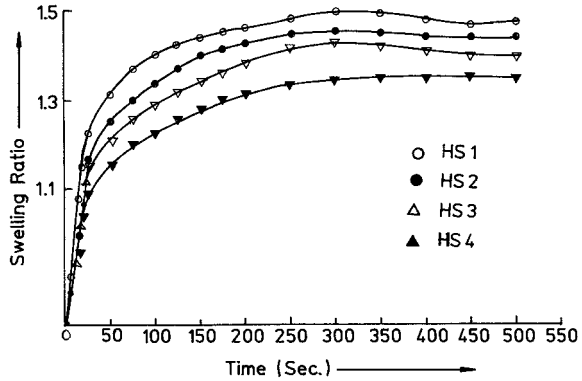

Figure 1 Swelling ratio (swollen mass/dry mass) vs. time plots of poly(HEMA-*co*-trimethylsilyl methacrylate).

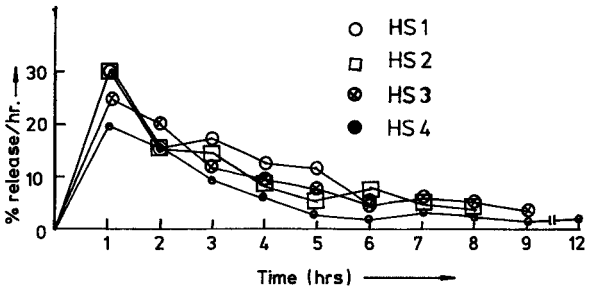

Figure 2 Release of PAM-Cl from HEMA–trimethylsilyl methacrylate copolymer gels.

ure 1 represents the dynamic swelling curves for the four systems. These plots show the general trend of increased swelling for the more hydrophilic materials in the series. In PHEMA and two of the poly(HEMA-*co*-trimethylsilyl methacrylate copolymers, i.e., HS1, HS2, and HS3, a maximum value of swelling ratio is observed which then decreased to the final, lower equilibrium value. This behavior may be due to uncrosslinked polymer chains diffusing out of the swollen polymer network.[5] Designing polymer matrix-based controlled-release dosage forms requires control of the degree of swelling of the hydrogel and predicts the rate of release of active ingredients, which, in turn, necessitates an understanding of the swelling kinetics of the polymer matrices. The increasing rate of swelling on decreasing the comonomer content, i.e., going from HS4 to HS1 (Fig. 1), suggests that not all the curves can be fitted to an equation with the same functional dependence on time (t). Therefore, to elucidate the transport mechanism, the swelling curves were fitted for values up to $M_t/M_\infty = 0.8$ to $M_t/M_\infty = Kt^n$, where M_t is the water uptake at any time t; M, is the water uptake at equilibrium; M_t/M_∞, the fractional water uptake by the polymer; t, the diffusion time; K, a constant characteristic of the system; and n, an exponent characteristic of the mode of transport of the penetrant.[5] The values of n were found to be 0.5 ± 0.04 in all the cases (Table II), which indicates the Fickian nature of the diffusion. It has been suggested that for cases of Fickian transport the rate of approach to the equilibrium can be characterized by a diffusion coefficient value "D" which can be calculated from the equation[3]

$$M_t/M_\infty = (4/\pi^{0.5})\,(Dt/L_0^2)^{0.5}$$

Diffusion coefficient values are given in Table II. A slightly lower value of the diffusion coefficient for HS3 as compared to HS4 may be due to the difference in the crosslink density of these two systems.[12] Increased swelling of HS3 can be explained as a combined effect of its high hydrophilicity and low crosslink density in comparison to HS4.

Drug-release Studies

The drug-loaded polymer matrix systems were subjected to *in vitro* drug-release studies to obtain an idea of their ability to function as a slow-release delivery systems. In all cases, an initial burst of drug release was observed in which some of the drug is released at an initially high rate, followed by a uniform release rate of the PAM-Cl drug (Fig. 2). The release rate decreased continu-

Table II Diffusion Coefficient Values for PHEMA-based Hydrogels

Sample Designation	Wt % EGDMA	Kinetic Exponent	Diffusion Coefficient $D \times 10^5$ cm^2 min^{-1}
HS1	0.5	0.50 ± 0.01	5.02
HS2	0.5	0.50 ± 0.05	4.41
HS3	0.5	0.50 ± 0.02	1.96
HS4	0.5	0.50 ± 0.05	2.00

Table III *In vitro* Drug-release Studies of PAM-Cl

Sample Designation	Weight of the Sample (mg)	Amount of the Drug Incorporated (mg)	Time Taken for ~ 90% Release (h)	Time Taken for Complete Release (h)
HS1	200	50	6	36
HS2	210	55	8	30
HS3	198	48	9	29
HS4	225	60	12	24

ously with time until an ~ 90% release was over in 6–12 h. Thereafter, the release of the drug became very slow and complete release was over in 24–36 h (Table III). No erosion of the matrix system was observed until the release was over. Thus, it appears that in these systems drug release occurs purely by a diffusional process. It is observed that the time taken for release of 90% of the drug increases on increasing the comonomer content. This may be due to the increased hydrophobicity of the matrix system on increasing the comonomer content. Also, it is evident from the dynamic diffusion studies that the swelling is greater for the more hydrophilic (PHEMA) system, thereby making the release of the drug faster by diffusion through the water-filled pores that form as water is imbibed from the surface of the device to replace the active agent that leaches out. On the other hand, complete release of PAM-Cl from the PHEMA hydrogel took a longer time (36 h) as compared to its copolymers with trimethylsilyl methacrylate (24–30 h). Polar–polar interactions between highly polar PAM-Cl and more hydrophilic PHEMA hydrogels may be responsible for retaining residual drug for a longer time as compared to copolymeric hydrogel systems having a hydrophobic comonomer.

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