Ionotropic Crosslinking of Sodium Carboxymethylcellulose and Sodium Carboxymethylcellulose-Gelatin Matrices and Their Erosion Properties

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SYNOPSIS

Hydrophilic sodium carboxymethylcellulose (NaCMC) matrices were chemically modified into hydrophobic gels by ionotropic crosslinking with cupric or ferric ion under ambient temperature and pH. Insoluble matrices were also prepared using an interactive polymer gelatin in combination with NaCMC. These matrices underwent erosion at the crosslinks, followed by matrix erosion when released in water. The matrix erosion in water was influenced by the gelling agent, initial crosslinker density, and gelatin content in the insolubilized matrices. The apparent diffusion coefficients of fenthion ranged from 7.2×10^{-9} to 175.6×10^{-9} cm^2/sec, with matrices prepared under different conditions. These erosion-controlled matrices can be used for the controlled release of various biologically active agents. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

Chemical derivatives of natural polymers find wide applicability in the development of controlled release systems of various biologically active compounds.[1-5] Sodium carboxymethylcellulose (NaCMC), an anionic polyelectrolyte, is highly water soluble and this semisynthetic cellulose derivative requires further chemical modification to be useful as controlled release systems of mosquito larvicides.[6,7]

Different insolubilization procedures have been reported using formaldehyde,[8] dimethylol urea,[8] or epichlorohydrin[9] as crosslinking agent under highly alkaline or acidic conditions and at higher temperatures. These procedures have limited usefulness in the development of controlled release systems, as the incorporated active agent may undergo chemical degradation under these conditions. The insolubilization reaction of NaCMC with multivalent ions involves the ion exchange process.[10] NaCMC is compatible with certain nonionic polymers[11] and forms an interactive polymer network with gelatin, below its isoelectric point.[12]

This article deals with the insolubilization of NaCMC with two gelling agents, copper sulfate or ferric chloride, at two concentrations, and at different durations of crosslinking, in order to study the influence on the crosslinker density of the resulting matrices and the diffusion property of fenthion, an organophosphorus mosquito larvicide. The study was also extended to NaCMC-gelatin (10 : 1 and 4 : 1) matrices.

EXPERIMENTAL

Preparation of the Crosslinked Polymer Samples

The NaCMC used for this study was obtained from Gujchem Distillers India Ltd., Gujarat, India. The molecular weight of the sample was 5.5×10^4 and the viscosity of a 5% neutral aqueous solution was 140 cp (Haake Viscometer: VT 02, Germany). Gelatin powder (bacteriology grade) was obtained from Loba Chemie, Bombay, India. Other chemicals used were Analar grade materials.

A 20% neutral aqueous slurry of NaCMC was spread uniformly over a glass plate and was allowed

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to dry in air at room temperature (30 ± 1°C) to obtain the dry polymer sheet of NaCMC. Dry polymer sheets of NaCMC-gelatin, at proportions of 10 : 1 and 4 : 1, were also made. The dried sheets of 4 mm thickness, thus obtained, were cut into squares that were 4 × 4 cm in size.

Crosslinking of the slabs of NaCMC and NaCMC-gelatin, thus obtained, was carried out by immersing the slabs in an aqueous solution of the gelling agent, that is, copper sulfate or ferric chloride. Crosslinking was performed with 0.5 and 1.0 M concentrations of the gelling agents. Each sample was exposed to 75 mL of the gelling medium and was withdrawn at intervals *viz.*, 3, 6, 9, 12, 24, and 48 h. The withdrawn samples were washed with distilled water and were dried to constant weight in an air oven at 50°C. All samples were prepared in duplicate.

Estimation of Crosslinker Densities

The crosslinker density, expressed as the percentage of metal ions present in the crosslinked samples, was obtained by the estimation of the percentage of metal ion present in the samples, obtained with different gelling media and durations of crosslinking.

The estimation of cupric ion was done by digesting the polymer samples in 25 mL of 1 : 1 HCl over a steam bath. The digest was cooled and filtered into a standard flask (100 mL). To 20 mL of this solution, ammonia solution was added dropwise until a deep blue color was observed. Glacial acetic acid was added until acidic (pH = 6.0). Then 2 mL in excess was added, and was cooled to 15–20°C. A 10% solution of potassium iodide (10 mL) was then added and was titrated against standard sodium thiosulfate in the presence of potassium thiocyanate and starch until the blue color disappeared. The percentage of copper was estimated, using the formula:

$$\text{Copper content (\%)} = (0.0635 \times V1 \times N1 \times 100 \times 100)/(20 \times W1) \quad (1)$$

where V1 and N1 are the respective volume and normality of thiosulfate and W1 is the weight of the polymer sample.

The estimation of iron was made by digesting the dried polymer samples with 25 mL of 4.0 N H_2SO_4 over a steam bath. The digest was cooled and neutralized with ammonia solution to the formation of a brown precipitate. The precipitate was dissolved in 1.0 N sulfuric acid, which was added in excess (10 mL). The solution was then heated on a steam bath with zinc dust (1.0 gm) until the mixture did not show a blood red coloration with potassium thiocyanate solution. The solution was cooled and made up to 100 mL. A 20 mL portion, with 10 mL of 1.0 N H_2SO_4, was titrated against standard $KMnO_4$ solution until a permanent pale pink color appeared. The quantity of iron present in the polymer sample is expressed as

$$\text{Iron content (\%)} = (0.05584 \times V2 \times N2 \times 100 \times 100)/(20 \times W2) \quad (2)$$

where V2 and N2 are the respective volume and normality of permanganate solution and W2 is the weight of the polymer sample.

Erosion of the Crosslinks and Matrix Erosion

Samples for the erosion studies were prepared by crosslinking NaCMC and NaCMC-gelatin (10 : 1 and 4 : 1) in 1.0 M solution of the gellants for 12, 24, and 48 h. The samples were withdrawn and dried to constant weight. The weighed samples were released in distilled water and they were withdrawn after 3 months. The samples were dried to constant weight. The weight loss of each sample was noted and the results were expressed as percentage weight loss. The metal ion content of the different polymer samples, thus obtained, was determined and the loss in crosslink density was estimated.

Preparation of Matrices Containing Fenthion

The controlled release matrices, containing fenthion, were prepared by aqueous solution casting of the neutral aqueous slurries of NaCMC or NaCMC-gelatin (4 : 1), containing the required amount of fenthion (20% with respect to NaCMC), followed by crosslinking in 1.0 M solution of each gelling agent for 12, 24, and 48 h.

The diffusion coefficient of fenthion from these matrices in water was determined using the release data under laboratory conditions. The apparent diffusion coefficient of fenthion (Di) from these matrices was calculated from the equation,[13]

$$k = 4(\text{Di}/\pi d^2)^n \quad (3)$$

where d is the thickness of the slab, k is a constant incorporating the structural and geometric characteristics of the matrices, and n is the release exponent obtained from the equation,[14]

$$\text{Mt}/\text{Mz} = kt^n \quad (4)$$

where Mt/Mz is the fraction of fenthion released at time t. The values of k and n were calculated from the linear regression of $\log(Mt/Mz)$ on $\log(t)$. The X-coefficient of the regression equation, thus obtained, was taken as n and the constant as $\log(k)$.

RESULTS AND DISCUSSION

Ionotropic network formation, through chemical reaction or ion-exchange, due to ionic crosslinking of polyionic chains with multivalent counter ions, is an important technique for the development of erodible controlled release systems, resulting in porous and water swellable matrices.[15,16] The addition of an aqueous solution (1.0 M) of the gellant into an aqueous slurry of NaCMC resulted in gelling, followed by local precipitation. In an alternative procedure for preparing water insolubilized matrices of carboxymethylcellulose, dried sheet was initially made from a neutral aqueous slurry by aqueous solution casting, followed by the insolubilization in solutions of the gelling agents.

Studies on Crosslinker Densities

The variation in crosslinker density, with respect to the time of insolubilization of polymer samples in copper sulfate as the gelling agent at two concentrations, 1.0 and 0.5 M, is given in Figure 1. The crosslinker density was found to increase rapidly up to 12 h. Polymer samples, crosslinked in 0.5 M solution, showed relatively lower crosslinker densities

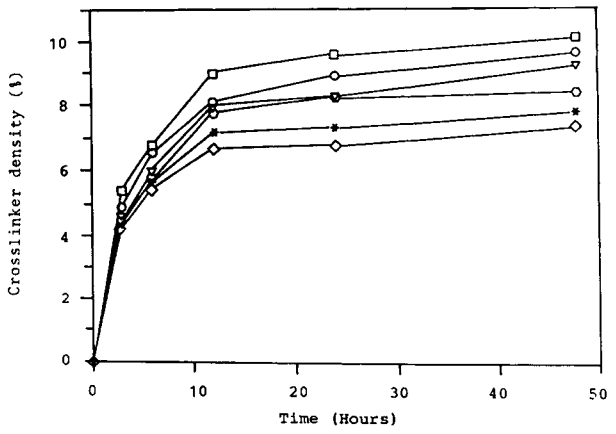

Figure 1 Crosslinker densities of NaCMC (□), NaCMC-gelatin (10 : 1) (○) and NaCMC-gelatin (4 : 1) (▽), insolubilized in 1.0 M copper sulfate and NaCMC (○), NaCMC-gelatin (10 : 1) (✱), and NaCMC-gelatin (4 : 1) (◇), insolubilized in 0.5 M copper sulfate.

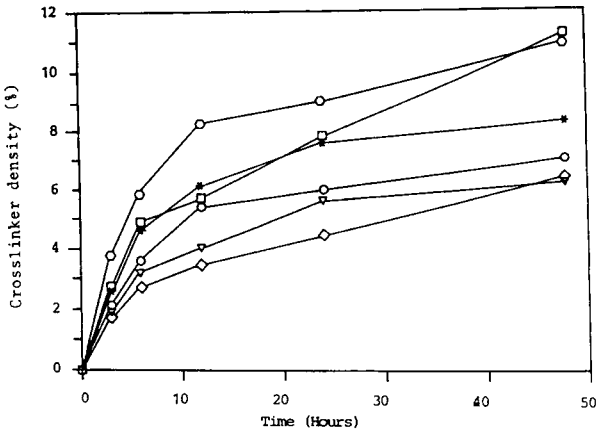

Figure 2 Crosslinker densities of NaCMC (□), NaCMC-gelatin (10 : 1) (○) and NaCMC-gelatin (4 : 1) (▽), insolubilized in 1.0 M ferric chloride and NaCMC (○), NaCMC-gelatin (10 : 1) (✱), and NaCMC-gelatin (4 : 1) (◇), insolubilized in 0.5 M ferric chloride.

than the samples obtained with the 1.0 M solution of the gelling agent.

When ferric chloride was used as the gelling agent, the crosslinker density was found to increase more slowly than with copper sulfate, as shown in Figure 2. Polymer samples, crosslinked in 0.5 M solution, showed relatively higher crosslinker densities than in the 1.0 M solution during the initial hours of insolubilization (Fig. 2). The higher values of crosslinker density in the 0.5 M solution, compared to 1.0 M solution observed in the case of the ferric ion, may be due to the formation of more networks with trivalent ferric ion than the divalent copper ion and the crosslinked network formed on the surface of the polymer sample with 1.0 M solution would have prevented the further permeation of ferric ions into the inner portions of the matrix.

Erosion of the Crosslinks and Matrices

Matrices, obtained by hydrophobic crosslinking of water soluble polymers when placed in water, undergo erosion of the crosslinks as well as the polymer.[17,18] This erosion process controls the physical integrity and the diffusional property of the incorporated active agent. The insolubilized matrices, obtained from NaCMC, were found to undergo matrix erosion when placed in water. Therefore, the erosion of the crosslinks and matrices was monitored after a period of three months in water.

The cupric ion crosslinked matrices, obtained below the crosslinking duration of 12 h, were found to disintegrate completely within three months.

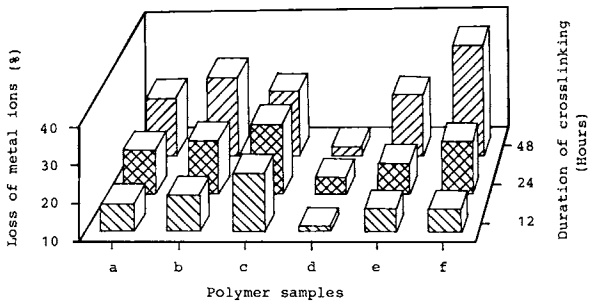

Figure 3 Percentage erosion of crosslinking agents after releasing in water for three months. (a) CuCMC, (b) CuCMC-gelatin (10 : 1), (c) CuCMC-gelatin (4 : 1), (d) FeCMC, (e) FeCMC-gelatin (10 : 1), and (f) FeCMC-gelatin (4 : 1).

Therefore, matrices crosslinked for a duration of 12 h and above, were studied for monitoring the erosion properties. The results of the percentage erosion of the crosslinks and matrices, after releasing in water for three months, are presented in Figures 3 and 4, respectively.

These matrices were found to swell in water to achieve the equilibrium swelling ratio. The hydrophobic crosslinks were found to be hydrolytically unstable. The interaction of these matrices with water suggests that, initially, water molecules form hydrogen bonding with hydroxyl groups of cellulose. As the content of water increases, some of the hydrogen bonds are weakened and hydration of the metal ion takes place, resulting in the hydrolysis of the crosslinks.[19]

CuCMC matrices showed lower values of percentage matrix erosion than the matrices containing gelatin. The percentage of matrix erosion was found to be relatively higher with the ferric ion crosslinked matrices of NaCMC-gelatin (4 : 1).

Out of the 18 samples studied for their matrix erosion, the minimum value of the percentage matrix erosion was observed with CuCMC matrix, obtained by crosslinking in a 1.0 M gelling agent for 48 h, and the erosion was maximum in the case of NaCMC-gelatin (4 : 1), obtained by crosslinking for 12 h in 1.0 M ferric chloride. The matrix erosion was found to decrease with an increase in crosslink density and was found to increase with an increase in gelatin content in the matrices.

The results obtained from the erosion properties of the insolubilized matrices showed that the ionotropic crosslinking of NaCMC with cupric and ferric ions is reversible. The insolubilized and hydrophobic matrices undergo matrix erosion when a sufficient number of crosslinks are cleaved. These matrices were found to undergo heterogeneous surface erosion rather than the bulk erosion.

Diffusion Coefficients of Fenthion

The apparent diffusion coefficients of fenthion from these matrices are presented in Table I. The values were found to be higher when the interactive biopolymer gelatin was incorporated in the matrices. The maximum values of 16.48×10^{-9} and 175.64×10^{-9} cm^2/sec were observed with the NaCMC-gelatin (4 : 1) matrix, crosslinked for 12 h with cupric and ferric ions, respectively. The values of the percentage erosion of the respective matrices, after three months in water, are also presented in Table I. The apparent diffusion coefficients of fenthion from these matrices were found to be influenced by the extent of crosslinking and erosion of the crosslinks, followed by the matrix erosion, as observed with other matrices.[17,18,20]

CONCLUSIONS

The present study shows that the hydrophilic NaCMC matrices could be chemically modified to a hydrophobic gel by ionotropic crosslinking with cupric and ferric ions under ambient conditions of temperature and pH. Matrices, with different crosslinker densities and erosion properties, could be achieved by altering the crosslinking conditions. The incorporation of an interactive polymer, gelatin, followed by crosslinking with cupric ion, also resulted in matrices with improved matrix stability, whereas the ferric ion crosslinked matrices underwent erosion at a faster rate. The apparent diffusion coefficient of fenthion from these matrices was found to be proportional to the erosion of the matrices.

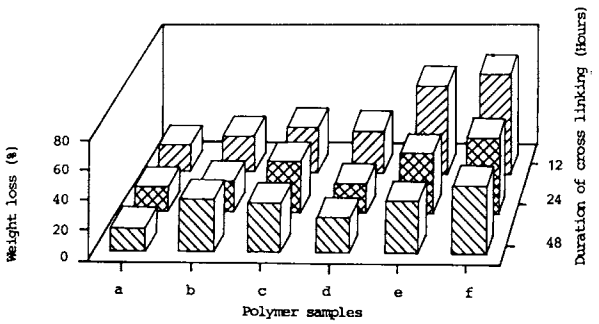

Figure 4 Percentage erosion of matrices after releasing in water for three months. (a) CuCMC, (b) CuCMC-gelatin (10 : 1), (c) CuCMC-gelatin (4 : 1), (d) FeCMC, (e) FeCMC-gelatin (10 : 1), and (f) FeCMC-gelatin (4 : 1).

Table I Matrix Erosion and Apparent Diffusion Coefficient (Di) of Fenthion from the Insolubilized Matrices of CMC and CMC-Gelatin

Matrices of Fenthion	Gelling Medium (1.0 M)	Duration of Gelling (h)	Matrix Erosion (%)	Di $\times 10^9$ (cm^2/sec)
NaCMC	$CuSO_4$	12	17.25	8.88
NaCMC	$CuSO_4$	24	15.68	7.47
NaCMC	$CuSO_4$	48	15.69	7.21
NaCMC	$FeCl_3$	12	27.41	32.92
NaCMC	$FeCl_3$	24	19.44	36.52
NaCMC	$FeCl_3$	48	23.11	26.22
NaCMC-Gel (4 : 1)	$CuSO_4$	12	29.60	16.48
NaCMC-Gel (4 : 1)	$CuSO_4$	24	33.55	12.64
NaCMC-Gel (4 : 1)	$CuSO_4$	48	33.08	11.83
NaCMC-Gel (4 : 1)	$FeCl_3$	12	65.61	175.64
NaCMC-Gel (4 : 1)	$FeCl_3$	24	50.05	135.49
NaCMC-Gel (4 : 1)	$FeCl_3$	48	44.95	81.22

These matrices can be utilized for the controlled release of various biologically active agents, with varying durations of activity and release rates, according to the processing conditions, and they may be more acceptable as the matrices are erodible and biodegradable in the environment.

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