

Controlled Release of Polymer Conjugated Agrochemicals. System Based on Poly(Methyl Vinyl Ether-*alt*-Maleic Anhydride)

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ABSTRACT: Controlled release formulations were prepared by using commercially available poly(methyl vinyl ether-*alt*-maleic anhydride) (I) and 2,4-dichlorophenoxy acetic acid herbicide (2,4-D). The copolymer (I) was reacted with various diamines to produce amido-amine containing carboxylate copolymers. The produced copolymers were reacted with the acid chloride of herbicide 2,4-D as model herbicide for carboxylic group functionalized herbicides. The formulations produced were characterized by IR and elemental analyses. The release of the herbicide 2,4-D from the formulations was studied under different aqueous medium conditions and the effect of copolymer microstructure on release profiles was investigated. © 2001 John Wiley & Sons, Inc. *J Appl Polym Sci* 80: 415–421, 2001

INTRODUCTION

Controlled-release technology has emerged during the 1980s as a commercially sound methodology^{1,2} for administration of active principles of pharmaceuticals and agrochemicals. The predictable and reproducible release of an active agent in a specific environment over an extended period of time highly advantageous.

Controlled-release systems find good application in agriculture due to environmental concerns that impose severe restrictions on uses of mobile herbicides with high activity.^{3–11} In addition, controlled-release administration of agrochemicals has certain advantages over conventional methods of application of agrochemicals.³

In most controlled-release formulations, the biologically active agent is dispersed in, or combined with, polymeric matrices.^{3,12} i.e., i) physical mixing of an active agent with a polymer to yield a rate controlling device; or ii) chemical binding of

the active agent to the polymer matrix to act as carrier and subsequent release of the active ingredient is controlled by the chemical cleavage of polymer-active agent bond or by environmentally induced depolymerization. The choice of either method for achieving controlled-release in a particular application depends on the release rate required, properties of the active agent and the cost.³

We have reviewed the finding in this area through our research activities^{3,12} and a number of articles.^{4,13–21}

Recently, special reference has been made to environmentally acceptable biodegradable polymers^{22–29} and controlled release systems.^{5–8,30–32} In our current studies, we have used bioerodible poly (methyl vinyl ether-*alt*-maleic anhydride) as a carrier polymer for agrochemicals. This was modified by reacting it with various diamines to afford amido-amines containing carboxylate copolymers which were subsequently acetylated with 2,4-dichlorophenoxy acetic acid (2,4-D) as a model for carboxylic group containing herbicides (Table 1). The effect of structure of diamines used and pH of the release medium was investigated.

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Table I Acetylation of Aminated Copolymers With 2,4-D Acid Chloride

Polymer	Starting Aminated Polymer (mmol)	2,4-D Acid Chloride (mmol)	Yield	
			(g)	(%) ^a
V	II (15.38)	18.45	6.1	91.4
VI	III (11.56)	13.87	3.7	61.7
VII	IV (11.3)	13.52	3.2	50.7

^a Evaluated as 100 (actual yield/theoretical yield).

EXPERIMENTAL

Materials and Methods

Poly (methyl vinyl ether-*alt*-maleic anhydride) (Aldrich) was used as received. Ethylenediamine (Aldrich) was purified by distillation before use. Diethylenetriamine, p-phenylenediamine and tetrabutyl ammonium bromide (TBAB) (Aldrich) were used as received. 2,4-Dichlorophenoxy acetic acid (Aldrich) was recrystallised twice from benzene before use. Thionyl chloride (Aldrich) was distilled before use.

IR spectra were recorded on a Perkin-Elmer 1430 Ratio Recording Infrared Spectrophotometer using KBr pellets. Elemental analyses were recorded on a Perkin-Elmer 2400. The release studies were performed on a Shimadzu UV-2101 PC uv-vis Scanning spectrophotometer.

Preparation of Buffer Solutions

a) Buffer Solution pH = 4. Buffer solution pH 4 was prepared as follows: To 100 ml of 0.4 M Boric acid (H₃BO₃) was added 100 ml of 0.4 M acetic acid and 100 ml of 0.4 M H₃PO₄, followed by addition of few drops of sodium hydroxide solution (10%) to reach the required pH. The mixture was completed with distilled water to 1 L.

b) Buffer Solutions pH 9 and 7. These buffer solutions were prepared by dissolving a tablets supplied by BDH England for each buffer solution in 100 ml of distilled water.

Amidation of Poly(Vinyl Methyl Ether-Maleic Anhydride) Copolymer

Amidation with ethylenediamine. A mixture of 40 ml (599 mmol) of ethylenediamine and catalyst 0.2 g (0.62 mmol) of tetrabutyl ammonium bromide (TBAB) was stirred until complete dissolution of TBAB. A 1.5 g (8.0 mmol) of poly (methyl

vinyl ether-*alt*-maleic anhydride) copolymer (I) in 5 ml dimethylformamide was added dropwise to the diamine solution while stirring. The reaction mixture was heated, while stirring, at 95°C for 9 hr in a water bath. The product, amido-aminated copolymer (II), was filtered and washed several times with ethanol and then dried under vacuum; a yield of 1.7 g (92%) was obtained. The product was characterized by elemental analysis and IR (Table 2). The IR spectra showed prominent bands centered at: 3400 cm⁻¹ (γ NH₂); 3300 (γ NH₃⁺); 1650 cm⁻¹ (γ CONH). The presence of the quoted bands was accompanied by the disappearance of γ C=O.

Amidation with Diethylenetriamine. Copolymer (I) (1.0 g; 5.3 mmol of repeat units), TBAB (0.2 g) and diethylenetriamine (20 ml) were reacted while stirring for 11.5 h to give amido-amine containing polymer (III) (1.5 g yield, 89%) which was characterized by elemental microanalysis and IR. The elemental microanalysis data are reported in Table 2. The IR spectra showed prominent bands centered at: 3500–3300 cm⁻¹ (γ NH₂, γ NH₃⁺); 1625 cm⁻¹ (γ CONH); 2300 cm⁻¹ (γ CH₂); 2100 cm⁻¹ (γ NH₃⁺). The presence of the quoted bands was accompanied by the disappearance of γ C=O.

Amidation with P-Phenylenediamine. The amino-amidation with p-phenylenediamine was done as previously described for copolymer II.: copolymer (I), 1.0 g, TBAB (0.2 g) and p-phenylenediamine (4.32 g; 40 mmol). Copolymer (IV) was produced (1.1 g yield, 58%) and characterized by elemental microanalysis and IR. The microanalysis data are given in Table 2. The IR showed prominent bands centered at 3450 cm⁻¹ (γ NH₂), 1700 cm⁻¹ (γ CONH), 1590 (γ NH₃⁺); 750 cm⁻¹ (substituted aromatic ring). The presence of the

Table II Elemental Microanalysis for Aminated and Acetylated Polymers

Polymer	Analyses (%)			
	C	H	N	Cl
II	50.1	8.8	11.9/12.3, 12.3/12.7	—
III	52.1	9.5	14.0	—
IV	58.9	5.9	9.0	—
V	49.3	5.8	11.12	17.5/15.8
VI	50.3	6.7	13.0	19.1/19.4
VII	58.0	4.8	8.6	1.9

quoted bands was accompanied by the disappearance of γ C=O.

Synthesis of Acid Chloride of 2,4-Dichlorophenoxy Acetic Acid (2,4-D)

The acid chloride of 2,4-D was prepared as described elsewhere.⁴ Accordingly 2,4-D (26.5 g, 120 mmol) was added to thionyl chloride (14.6 ml, 200 mmol) and the reaction mixture was heated to 100°C for 5 hours. The residual thionyl chloride was distilled off and its last traces were removed by co-distilling off with toluene. The product was finally dried under vacuum at room temperature.

Acetylation of Amido-Amine Containing Carboxylate Copolymers with Acid Chloride of 2,4-D

Acetylation of Aminated Co-Polymer (II). Acetylation of the aminated copolymer was achieved by treating it with the acid chloride of 2,4-D in dry chloroform. General procedure for acylation of amido-amine containing carboxylate copolymers (II) was as follows: a suspension of aminated copolymer (II) (11.56 mmol of repeat unit) and 30 ml of anhydrous chloroform was stirred under nitrogen for 5 hours, then the reaction mixture was cooled in an ice-bath for 10 min while stirring. Triethylamine (4.2 ml: 30 mmol) was added to the cooled reaction mixture, 2,4-D acid chloride (18.45 mmol) was slowly added while the temperature was kept at 5°C and the reaction mixture was stirred for 5 h at room temperature. The solid product was filtered off, washed several times with anhydrous ethanol and then dried at 30°C under vacuum to yield 6.1 g of polymeric product (V).

The acetylated product (V) was analyzed by elemental microanalysis and IR. The microanalysis data are shown in Table 2. The IR spectra showed prominent bands centered at: 2750 cm^{-1} (γ n CH_2); 1050 cm^{-1} (in plane bending band of aromatic ring C—H bonds); 800, 850 cm^{-1} (out of plane bending of the aromatic ring C—H bonds) and 650 cm^{-1} (γ C—Cl vibration). The presence of the quoted bands was accompanied by the partial disappearance of (γ NH_2). In Table 1, the quantities of reactants, products and yield are summarized.

Acetylation of Aminated Co-Polymer (III). The acetylation was done as described for acetylation of aminated copolymer (II). The product, copolymer (VI) was characterized by elemental microanalysis and IR. The microanalysis data are given

in Table 2. The IR spectra showed prominent bands centered at: 750, 800 cm^{-1} (out of plane bending band of the aromatic ring C—H bonds); 600 cm^{-1} (γ C—Cl vibration); and 1100 cm^{-1} (in plane bending of aromatic ring C—H bonds).

Acetylation of Aminated Co-Polymer (IV). Procedures similar to the ones described for the synthesis of copolymers (V) and (VI) were followed for the preparation of acetylated copolymer (VII) from amido-amine containing carboxylate copolymer (IV). Copolymer (VII) was characterized by elemental microanalysis and IR (Table 2). The IR spectra obtained showed prominent bands centered at: 850 cm^{-1} (out of plane bending band of aromatic C—H bonds) and 650 cm^{-1} (C—Cl vibration).

Hydrolytic Release of 2,4-D From Polymeric Formulations. Release studies were carried out as described elsewhere.⁴ Accordingly 100 mg of 2,4-D acetylated co-polymer samples (V–VII) were kept in a flask containing 100 ml buffer, and in a water bath at 25°C, without stirring. A sample from the release medium was periodically withdrawn and analyzed by UV at 283 nm to determine the amount of the released 2,4-D. Buffer solution was withdrawn from the flask after each analysis and replaced by fresh buffer except for the first few days. A calibration curve was constructed with software built in the computerized UV spectrophotometer and the amount (mg) of the released 2,4-D were determined directly from the software using the calibration curve. The release studies were carried out on media with different pH (4, 7 and 9) for all formulations. The experimental release profiles are shown in Figures 1–6.

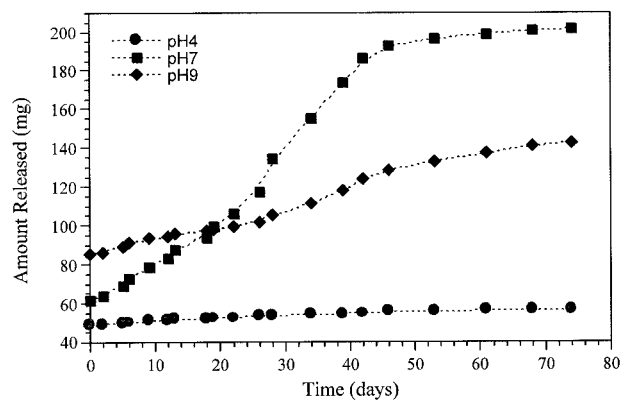


Figure 1 Release profile of the active ingredient 2,4-dichlorophenoxy acetic acid herbicide (2,4-D) from copolymer V at different pH.

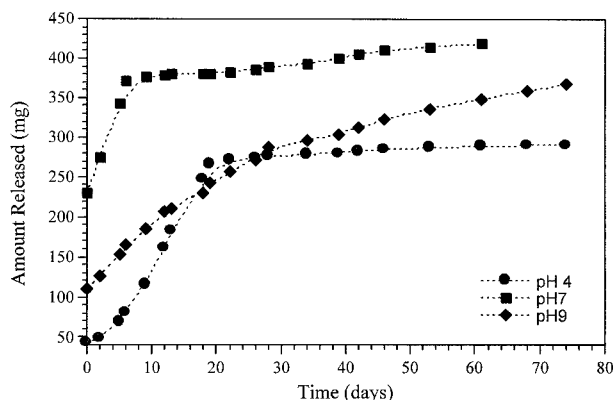


Figure 2 Release profile of the active ingredient 2,4-dichlorophenoxy acetic acid herbicide (2,4-D) from copolymer VI at different pH.

RESULTS AND DISCUSSION

Modification of Poly (Methyl Vinyl Ether-*Alt*-Maleic Anhydride) (I) with Various Diamines

Poly (methyl vinyl ether-*alt*-maleic anhydride) copolymer was modified with diamines of various structures as described in the experimental part. The objective of these modifications was to study the effect of the structure of the side chain on the release rate of the active ingredient. It is worth mentioning that when stoichiometric amounts of diamines were used, crosslinked polymers were produced, probably due to the reaction of both diamino groups with two anhydride groups of the two polymer chains forming two amido groups. Therefore it was better to add the copolymer to an excess diamine to avoid or at least minimize the crosslinking arising from multi-transamidation with various diamines. The modification reac-

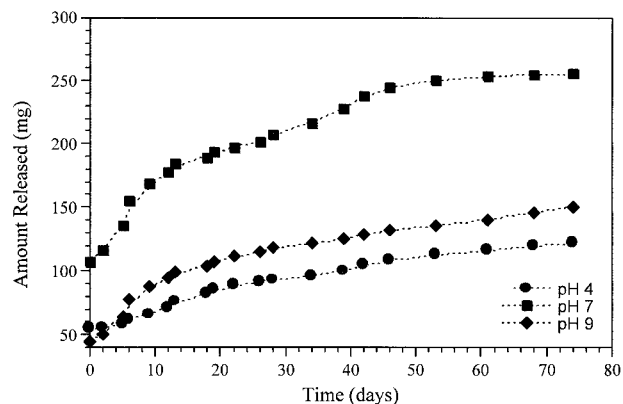


Figure 3 Release profile of the active ingredient 2,4-dichlorophenoxy acetic acid herbicide (2,4-D) from copolymer VII at different pH.

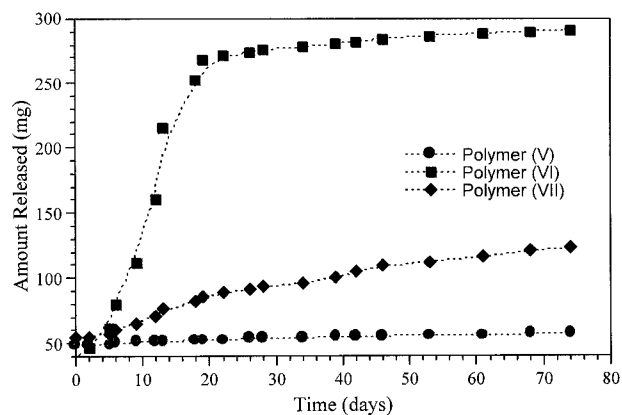


Figure 4 Release profiles of active ingredient 2,4-dichlorophenoxy acetic acid herbicide (2,4-D) from copolymers V, VI, and VII at pH 4.

tions are outlined in Scheme 1. The amido-aminated copolymers were analyzed by microanalysis and IR. The IR spectra showed a band at $3300\text{--}3500\text{ cm}^{-1}$ for the amino group which indicates introduction of the amino groups to the copolymers and formation of amide at $1625\text{--}1700\text{ cm}^{-1}$. Also, the results of the elemental microanalysis indicated relatively high % of introduction of amino groups.

Modification of Amido-Amine Containing Carboxylate Copolymers with 2,4-Dichlorophenoxy Acetic Acid (2,4-D)

Polymers bound 2,4-D, V–VII, were synthesized by reaction of the acid chloride of 2,4-D with the amido-aminated polymers II, III, IV as outlined in Scheme 2. The reactions were carried out at sub ambient temperature (5°C) using triethylamine

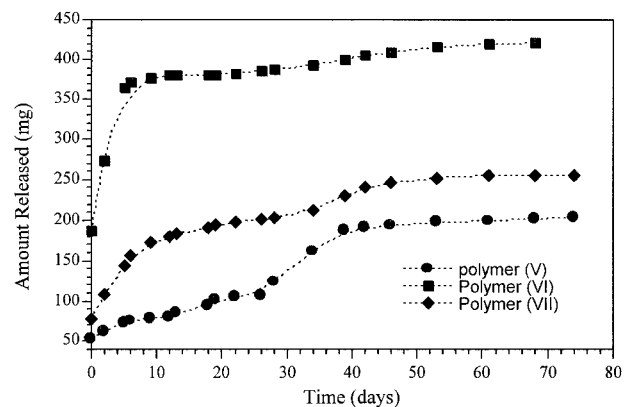


Figure 5 Release profiles of active ingredient 2,4-dichlorophenoxy acetic acid herbicide (2,4-D) from copolymers V, VI, and VII at pH 7.

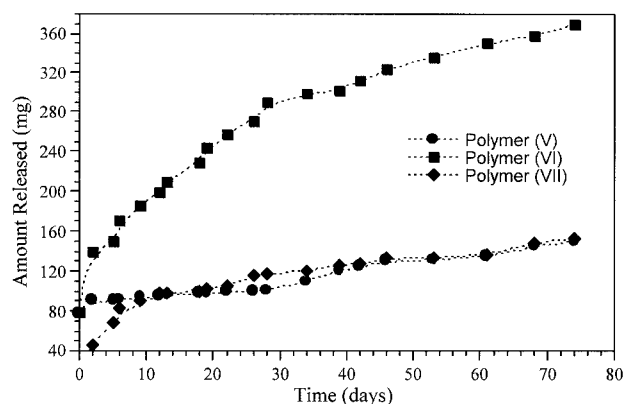


Figure 6 Release profiles of active ingredient 2,4-dichlorophenoxy acetic acid herbicide (2,4-D) from copolymers V, VI, and VII at pH 9.

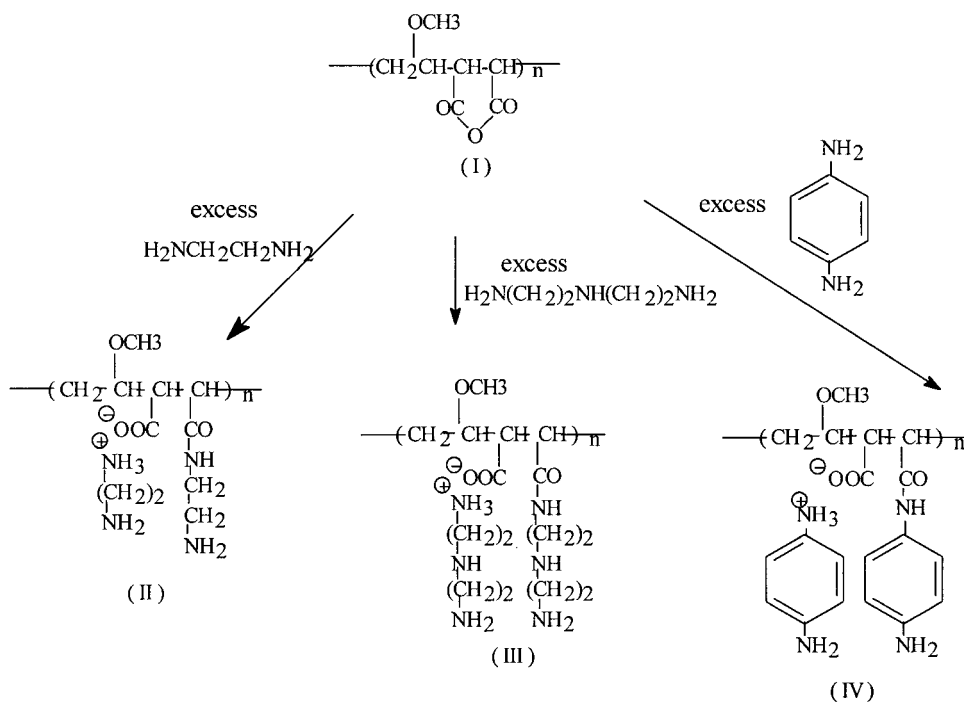
as a base. The extent of reaction was fairly high in the case of aminated copolymers II, III whereas a lower yield was recorded in the case of polymer IV. The extent of modification was checked by the chlorine microanalysis (Table 2).

Hydrolysis of 2,4-D Containing Copolymers

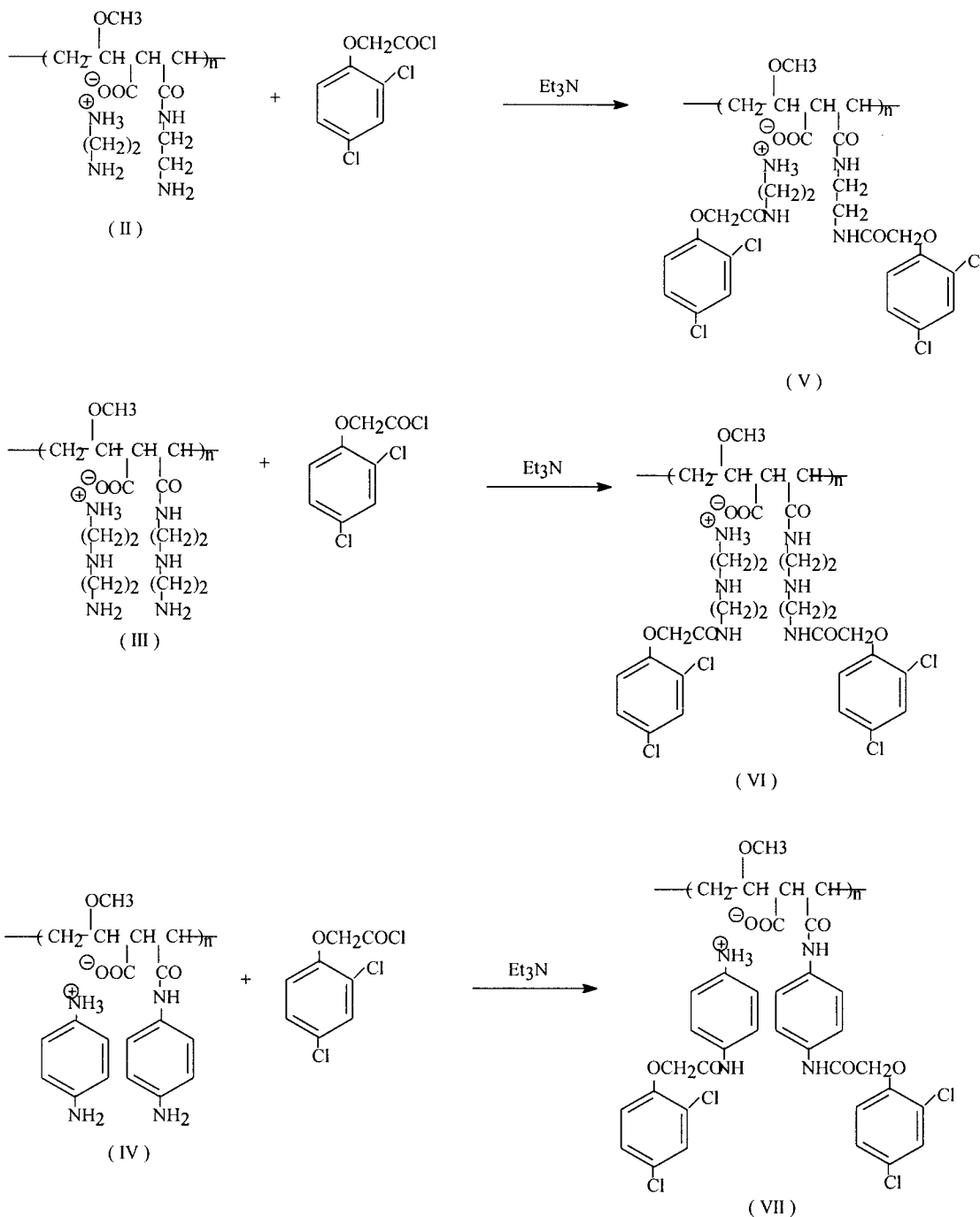
In most cases of chemically controlled release formulations, the mechanism of release of the active agent implies the hydrolysis of the active agent-

polymer bond. The hydrolysis rate of the bioactive agent from the polymer depends on pH of the medium, the temperature, the accessibility of the nucleophiles to the hydrolyzable bond and the distance between the active ingredient and the polymer backbone. The copolymer microstructure plays an important role in the release of the active ingredient from the polymeric formulations.^{3,19,20}

The hydrolysis of 2,4-D from the polymeric formulation was followed by UV-spectrophotometer at 25°C in aqueous media having 4, 7 and 9 pH). The release profiles of 2,4-D from the formulations within 74 days are shown in Figures 1–6. In all cases it was found that the release rate of 2,4-D was faster in neutral medium (pH 7) than that in basic or acidic media. This may be due to the fact that the polymer structure has a salt as a side chain which has more tendency to solubilize the polymer or act as a phase transfer agent to make the polymer more hydrophilic. In acidic and basic media, protonation of the amino groups and formation of carboxylate amine could be respectively envisaged. From the release profiles plotted in Figures 4–6 it is found that, copolymer VI showed faster release rate than copolymers V and VII. This could be due to the higher length and hydrophilicity of the side chain.² The release rate is relatively fast at early stages of experiments,



Scheme 1 Amidation of poly(vinyl)methyl ether/maleic anhydride) copolymer with various diamines.



Scheme 2 Reaction of 2,4-dichlorophenoxy acetyl chloride with the amidated copolymers.

which is necessary for field applications since at the beginning high doses are usually required to control the weeds.^{33,34}

CONCLUSIONS

Controlled release formulations based on poly(methyl vinyl ether-*alt*-maleic anhydride) copoly-

mer have been synthesized. It was demonstrated that the commercially available copolymer (I) could be a useful support for the formulations of polymer supported herbicides for the carboxy functionalized herbicides. During the formulation of these systems there was some possibility of small amount of crosslinking during the amidation reaction due to the reaction of the bifunctional amine with the anhydride groups in two

polymer chains. These drawbacks could even be useful to provide some hydrogel character for the system. However it could be minimized by using a higher ratio of the diamine. The release of the active ingredient 2,4-D was found to be faster in the neutral media than in basic and acidic media. In addition the spacer group between the active ingredient and polymer backbone was also an important parameter: the longer the spacer group, the faster the release rate. Its anticipated that, when these polymers degrade after releasing the herbicide 2,4-D, the degradation products could be useful as a nutrient to enrich the soil with nitrogen.

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