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Synthesis, Characterization and Hydrolytic Degradation of Poly [bis (Methyl Glycolate Diethylamino) Phosphazenes] and Poly [bis (Ethyl Glycolate Diethylamino) Phosphazenes]

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Abstract

Poly[bis (methyl glycolate diethylamino) phosphazenes] (PMGDEAP) and poly[bis (ethyl glycolate diethylamino) phosphazenes] (PEGDEAP) were stepwise synthesized; the polydichlorophosphazenes (PDCP) was synthesized from hexachlorocyclotriphosphazene (HCCP) by ring opening polymerization (ROP) in the presence of $AlCl_3$ catalyst and in second step chlorine atoms of PDCP were substituted by methyl glycolate, ethyl glycolate and diethylamine as the side groups. Their structures and molecular weights were analyzed by nuclear magnetic resonance (NMR) and gel permeation chromatography (GPC). Moreover, hydrolytic degradation of PMGDEAP and PEGDEAP was investigated in acidic, basic and neutral medium at constant temperature (37°C).

Keywords:* *Polyphosphazenes; Synthesis; Characterization; Applications; Hydrolytic degradation

Introduction

From the past few decades, some inherent properties of degradable polymers especially biodegradable polymers trigger the researchers to explore their use in different potential applications like advanced drug delivery systems, short term medical implants and reconstructive implants, tissue engineering and different biomedical applications. Biodegradable polymers may be biopolymers or synthetic ones. Hydrolytic degradation is extensively studied and explored among other degradation

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processes like microbial; enzyme accelerated hydrolytic, oxidative or thermal rearrangement. Hydrolytically sensitive polymers that hydrolyse to harmless products are particularly interesting in different biomedical applications.

The synthetic biodegradable polymers like polyphosphazene have also gained repute in biomedical applications. The properties of polyorganophosphazenes can be tailored by varying the side groups on polyphosphazene Nitogen-Phosphorous [-N=P-] backbone in a wide range. The properties like *in vivo* as well as *in vitro* biodegradability, hydrolytic degradation, degradation rate, hydrophilicity, hydrophobicity, hydrophilicity-hydrphobicity balance, water solubility, glass transition temperature, mechanical strength can be introduced by the choice of side groups [1-12].

Soo-Chang Song et al. synthesized polyphosphazene/(diamine)platinum(II)/saccharides conjugates and studied their hydrolytic degradation at different pH values. They found that these conjugates are stable at neutral pH but degrade at a control rate at acidic and basic medium [13].

Olugbemisola Oredein-McCoy et al. substituted phosphazene with less bulky ethyl glycinato side groups to induce hydrolysis-sensitization for degradation along with the bulky phenylalanato side group to control the degradation rate [14,15]. Thrimoorthy Potta et al. synthesized biodegradable thermosensitive polyphosphazenes with hydrophilic side group's α-amino-ω-methoxypoly (ethylene glycol) as well as hydrophobic side group's isoleucine ethyl ester to get controlled degradation rate [16].

Polyphosphazenes can be sensitized to hydrolysis by the introduction of side groups like amino acid ester linkages or ethoxy groups but later group due to its small dimension, favours biologically important and high molecular weight polyphosphazene hydrolyze to harmless products like ethanol, phosphate and ammonia [16-20]. The first requirement of biodegradable, bioerodible and biocompatible is the end of hydrolysis into harmless products such as amino acids, ethanol, phosphate and ammonia [21-23].

Polyphosphazene backbone can be decorated with variety of side groups like amino acid ester linkages and amines for hydrolytic sensitization. Not only the hydrolytic products including ammonia, phosphate, amino acids and alcohols of these phosphazene derivatives are non-toxic but also make buffering medium which resist a change in pH of the medium. Hydrophilic side groups like glycolate derivatives, lactate, imidazole, glyceryl and amino acid ester in polyphosphazenes induces rapid hydrolysis and poor mechanical properties whereas hydrophobic side groups like alkoxy, fluoralkoxy or aryloxy introduce resistance to hydrolysis and good mechanical properties [20-24]. However, hydrolytic behavior cannot be clearly interpreted from the structure features and its mechanism is not very much clear.

Our purpose in this paper focuses on the synthesis of polyphosphazenes derivatives (PMGDEAP and PEGDEAP), their characterization and study of their properties especially hydrolytic degradation due to their biocompatibility and nontoxic characteristics. The chlorine atoms on poly (dichlorophosphazene) are replaced methyl glycolate diethyl amine and ethyl glycolate diethyl amine separately to introduce hydrolytic degradability for the use in enhanced biomedical applications. The hydrolytic degradation rate was investigated in acid, basic and neutral media at body (37°C) temperature. Later, these polymers will be applied for drug delivery applications.

Experimental

Materials

Methyl glycolate, ethyl glycolate and hexachlorocyclotriphosphazene (HCCP) were purchased from Acros organics and used as such. Diethylamine (Et_2NH) was distilled over calcium hydride CaH_2. Tetrahydrofuran (THF) was refluxed over potassium and distilled under nitrogen atmosphere.

Synthesis of PDCP from HCCP

HCCP (2.0 g, 5.75 mmol) and catalyst $AlCl_3$ was $AlCl_3$ (0.1 g, 0.75 mmol) were introduced in sample tubes and sealed under vacuum. The sealed ampule tube was placed in oil bath at 250°C for 5 h. During heating, HCCP was converted into PDCP by changing physical states from clear melting mixture to highly viscous and mobile phase [20]. Reaction was shown in FIG. 1. Sample tube was cut and PDCP was purified by dissolving in toluene (10 ml) and precipitated in n-hexane. After this, the amount of PDCP was calculated (1.4 g, 70%) [20].

Synthesis of poly [Bis (methyl glycolate diethylamino) phosphazenes] (PMGDEAP)

The synthesis of PMGDEAP was based on the method reported in the literature [21,22]. In typical synthesis, purified PDCP (2.0 g, 17.24 mmol) was dissolved in THF and in another flask, methyl glycolate (8.422 g, 68.97 mmol) (Cl:OH, 1:2) was dissolved in THF. After this, methyl glycolate solution was transferred into PDCP solution. Finally, diethylamine (Et_2NH) (9.65 ml, 68.97 mmol) was added in the mixture. Reaction mixture was stirred and refluxed at 67°C for 48 h as shown in FIG. 2. The resultant mixture was filtered and solution was precipitated in n-hexane and final product was dried to constant weight (2.23 g, % yield 45).

Synthesis of Poly [bis (ethyl glycolate diethylamino) phosphazenes] (PEGDEAP)

The synthesis of PEGDEAP was based on the method reported in the literature [21,22]. PDCP (2.0 g, 17.24 mmol) was dissolved in THF [23]. Ethyl glycolate (8.422 g, 68.97 mmol) (Cl:OH, 1:2) dissolved in refluxed THF. After this, ethyl glycolate solution was transferred into PDCP solution. Finally, diethylamine (Et_2NH) (9.65 ml, 68.97 mmol) was added in mixture. Reaction mixture was stirred and refluxed at 67°C for 48 h as shown in FIG. 2. The resultant mixture was filtered. The solution was concentrated and precipitated in n-hexane. At the end, polymer was dried till constant weight (2.23 g, % yield 45).

Equipment

Molecular weight of the polymer was determined by gel permeation chromatography (GPC). The eluent was DMSO at a flow rate of 1.0 ml min^{-1}. ^{1}H NMR and ^{31}P NMR were obtained from a NMR spectrometer (model DMX 300). Hydrolytic degradation was studied with magnetic stirrer at constant temperature.

Results and Discussion

HCCP monomer was purified by recrystallization and analyzed by ^{31}PNMR that pure PDCP showed sharp single peak at 20 ppm [3-6]. PDCP was synthesized from HCCP by ring opening polymerization at 250°C under vacuum using catalyst $AlCl_3$ as the details were described in our previous work [3-6]. The synthesis scheme was given in FIG. 1. The details are given in TABLE 1.

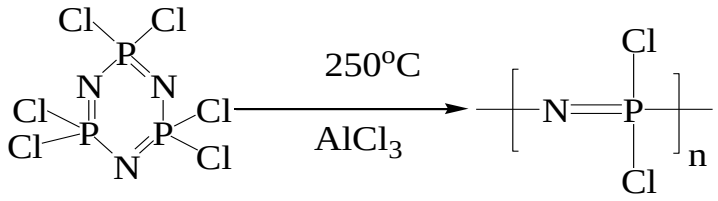

FIG. 1. **Synthesis scheme of PDCP from HCCP.**

In second step, PMGDEAP was prepared by the replacement of chlorine from PDCP with methyl glycolate with NaH in first step and then diethylamine in second step respectively. The synthesis scheme of PMGDEAP is given in FIG. 3(A) and details are given in TABLE 1. The possible synthesis mechanism is given in FIG. 3(B).

^{1}H NMR of PMGDEAP represented peaks at a=3.05 ppm, b=1.32 ppm, c=3.35 ppm, d=3.65 ppm, as shown in FIG. 4(A). ^{31}P NMR showed single peaks at 1.35 ppm. GPC showed molecular weight of the polymer as showed in TABLE 1. From NMR and GPC, successful synthesis of PMGDEAP is found. PEGDEAP was synthesized with ethyl glycolate and diethylamine as side groups. Possible synthesis mechanism is given in FIG. 3(B).

^{1}H NMR of PEGDEAP represented peaks at a=3.12 ppm, b=1.24 ppm, c=3.47 ppm, d=4.26 ppm, 4.43 ppm as shown in FIG. 5. ^{31}P NMR showed single peak at 2.58 ppm. GPC showed molecular weight as given in TABLE 1. From the NMR and GPC, successful synthesis of PEGDEAP was found. The glass transition temperature of the PMGDEAP was 36.27°C, and PEGDEAP 38.30°C respectively.

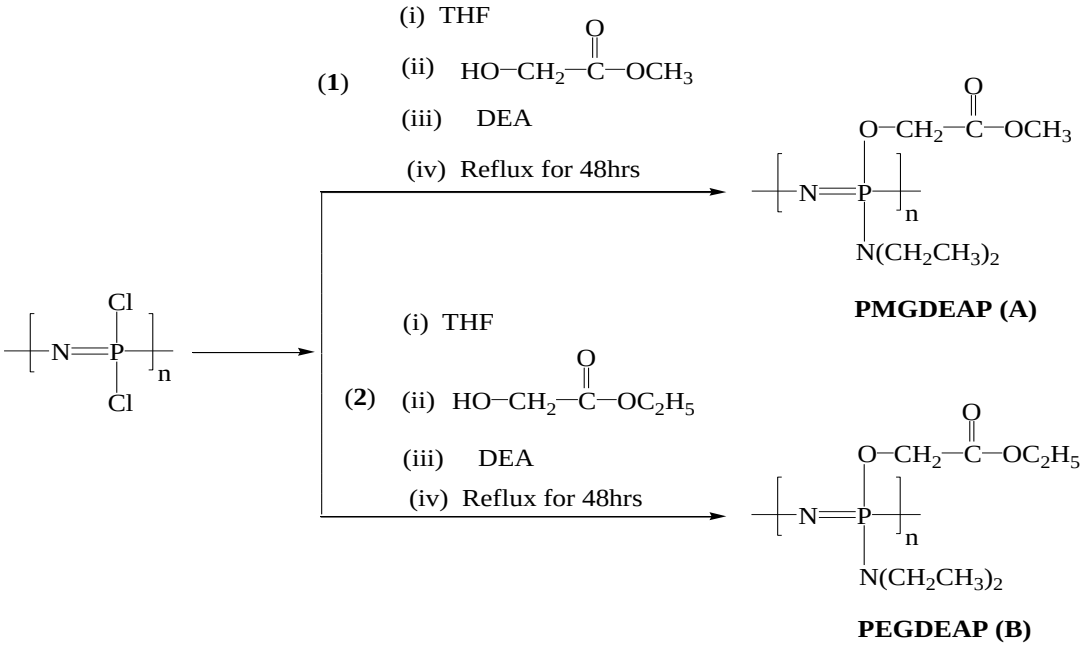

FIG. 2. **Synthesis scheme of PMGDEAP (A) and PEGDEAP (B).**

TABLE 1**. Synthesis and characterization of PMGDEAP (A) and PEGDEAP (B).**

Sample	HCCP			$AlCl_3$			PDCP			Glycolate		DEA	Mw
	G	mmol		g	mmol		G	mmol		ml	mmol	ml	----
A	1.230	3.54		0.065	0.489		0.86	7.42		10.0	46.68	10.0	13647
B	0.542	1.56		0.038	0.281		0.48	4.14		4.26	19.89	2.75	10872

Reaction temperature; PDCP was synthesized at 250°C for 5 h and PMGDEAP (A) and PEGDEAP (B) was synthesized at 70°C. The glass transition temperature of the PMGDEAP was Tg=36.27°C, and PEGDEAP Tg=38.30°C.

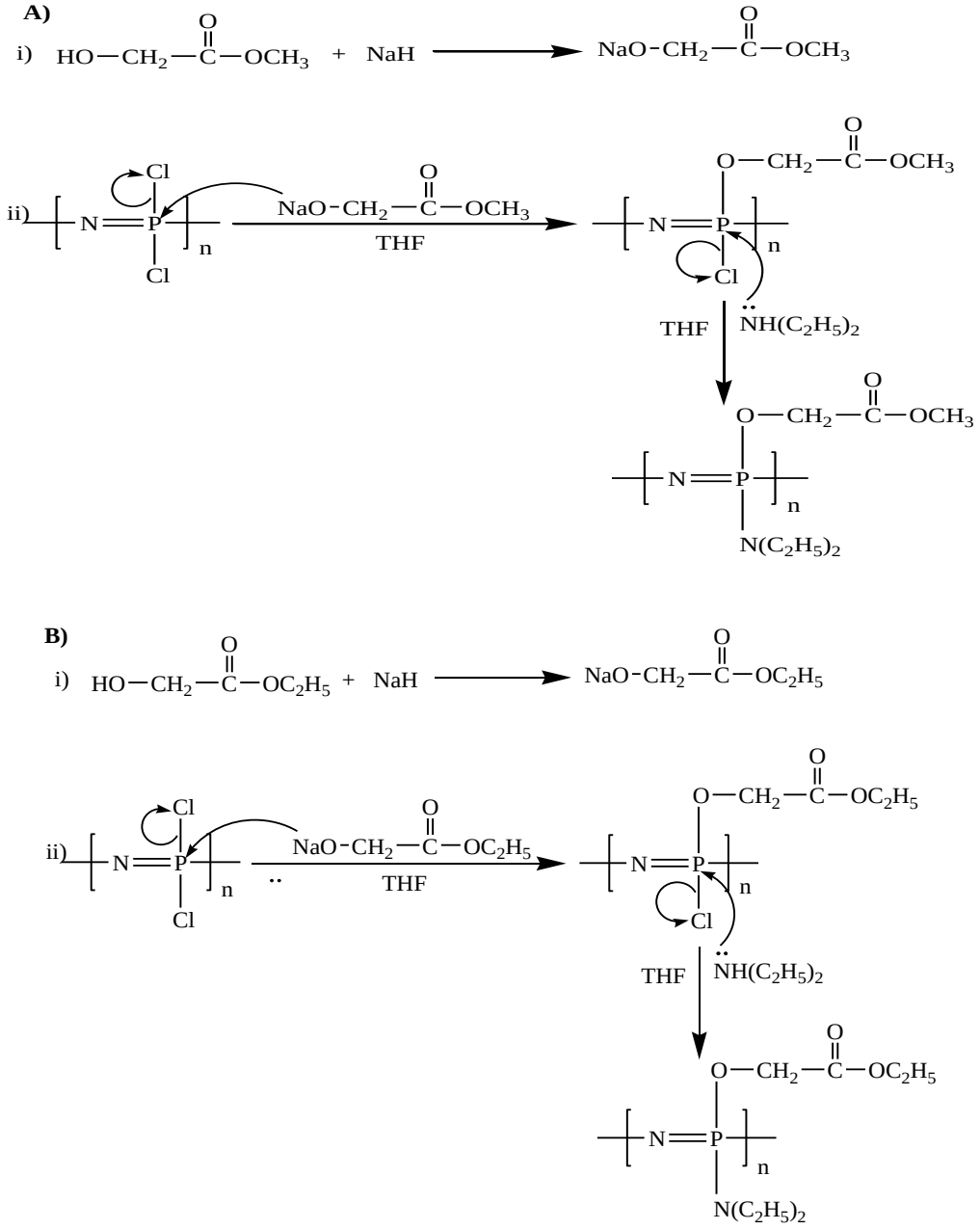

FIG. 3. **Possible synthesis mechanism of PMGDEAP (A) and PEGDEAP (B).**

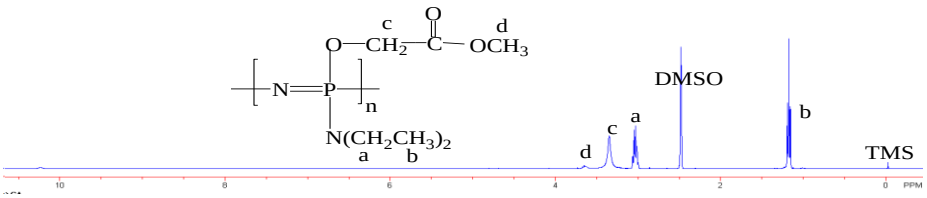

FIG. 4. **[1]HNMR of poly [bis (methyl glycolate diethylamino)] phosphazenes.**

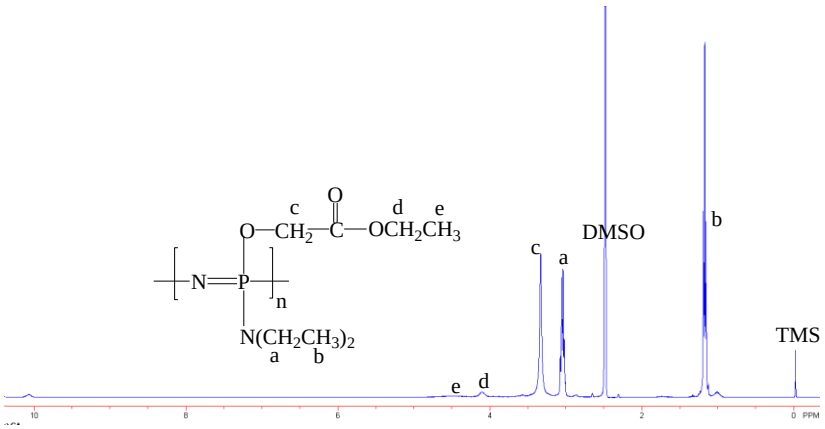

FIG. 5. **[1]HNMR of poly [bis (ethyl glycolate)] phosphazenes.**

Hydrolytic degradation

The degradation of PMGDEAP and PEGDEAP was examined on time dependent in different buffer solutions at 37°C. PMGDEAP and PEGDEAP (20 mg) were dissolved in buffer solutions (acetate buffer of pH 5, phosphate buffer of pH 7.4, and carbonate buffer of pH 10), which was incubated in a water bath at 37°C. Time-dependent hydrolytic behavior of the PMGDEAP and PEGDEAP were determined in terms of weight decrease of the polymers after every week. Moreover, hydrolytic degradation was investigated by ^{31}PNMR. It was found that ^{31}PNMR showed more than one peak that indicated that polymers were degraded after one week. Degradation behavior was given in FIG. 6.

The weight loss and percentage mass remaining of PMGDEAP and PEGDEAP were studied as shown in FIG. 7. It was found that PMGDEAP degraded rapidly as compared to PEGDEAP. After 7 weeks, it was found that percentage mass remaining of PMGDEAP was 8% while PEGDEAP percentage mass remaining was 15%. This was may be due to effect of side groups that PEGDEAP has larger side groups as compare to PMGDEAP.

Possible degradation mechanisms of PMGDEAP (A) and PEGDEAP (B) were given in FIG. 8. From this mechanism, it was found that during the hydrolysis, PMGDEAP and PEGDEAP backbone chain and side groups attached undergo degradation. Release of side groups and decrease in molecular weights of the polymer chain is the base of degradation study PMGDEAP

(A) and PEGDEAP (B). Hydrophilic groups are the base of hydrolysis which was studied in acidic, basic and neutral medium at body (37°C) temperature. There was decline in molecular weight and the decline increases with the time.

The degradation rate of polymer PMGDEAP was observed to be faster as compared to polymer PEGDEAP; this might be due to the presence of difference of side group of PMGDEAP and PEGDEAP. This methyl glycolate diethylamine may be more susceptible to hydrolysis than ethyl glycolate diethylamine due to smaller side group. The percent mass remaining of PMGDEAP was 8% while PEGDEAP percentage mass remaining was 15% after 7 weeks.

The presence of degradation products like ammonia, amino acids and phosphate group was confirmed by ninhydrin test with resulting violet color and yellow color of silver phosphate, respectively. This degradation phenomenon is shown in FIG. 6.

Moreover, it was observed from possible degradation mechanism that substitution of chlorine atoms in PDCP by glycolate derivatives was usually not 100% and the presence of unreacted chlorine atoms make the polymer susceptible to hydrolysis, the so called hydrolytic sensitization. Therefore, degradation rate depends upon the ratio of side groups and it increases with the increase in chlorine side groups.

There are many varieties of ways for the degradation of polyphosphazene derivatives and so the mechanisms but we can explain possible mechanism. In first step of mechanism, chlorine being more sensitive to hydrolysis is attacked by water and in the second step; hydroxyl group was hydrolyzed and was broken from the chain.

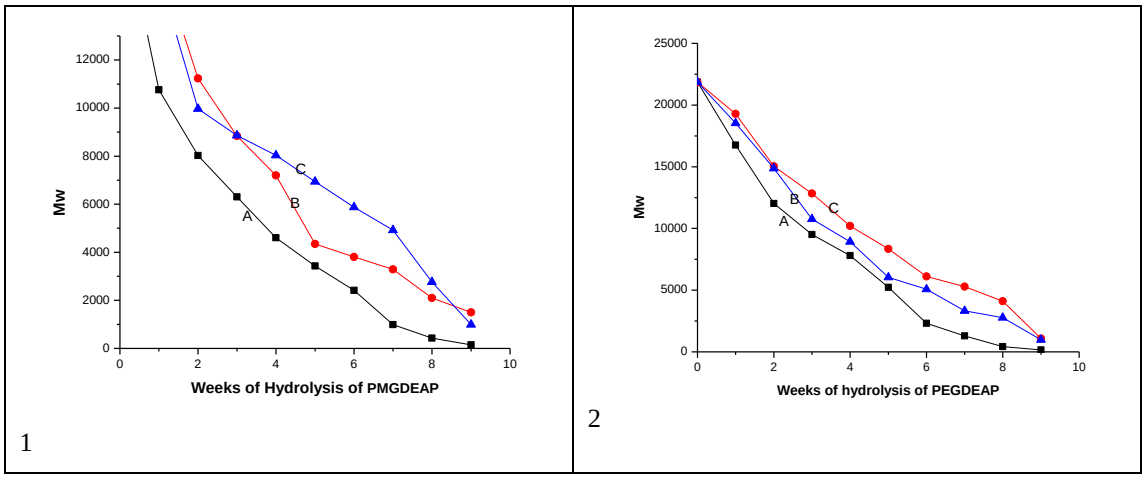

FIG. 6. **Degradation of PMGDEAP (1) and PEGDEAP (2) in acidic, basic and neutral media.**

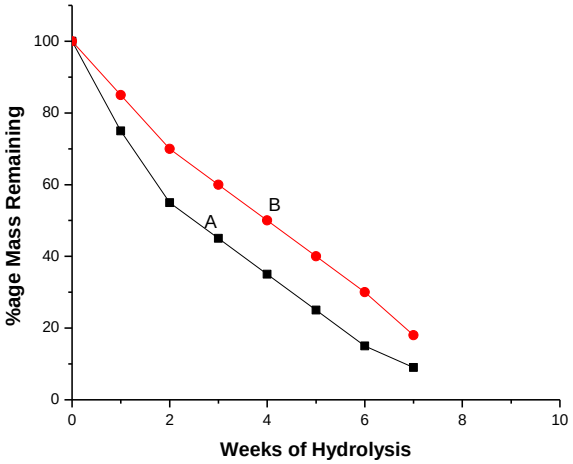

FIG. 7. **Percentage mass remaining of PMGDEAP (A) and PEGDEAP (B)**.

The final possible products of hydrolysis accompanied by the cleavage of backbone chain were alcohol, carboxylic acids, ammonium and phosphate [1-6].

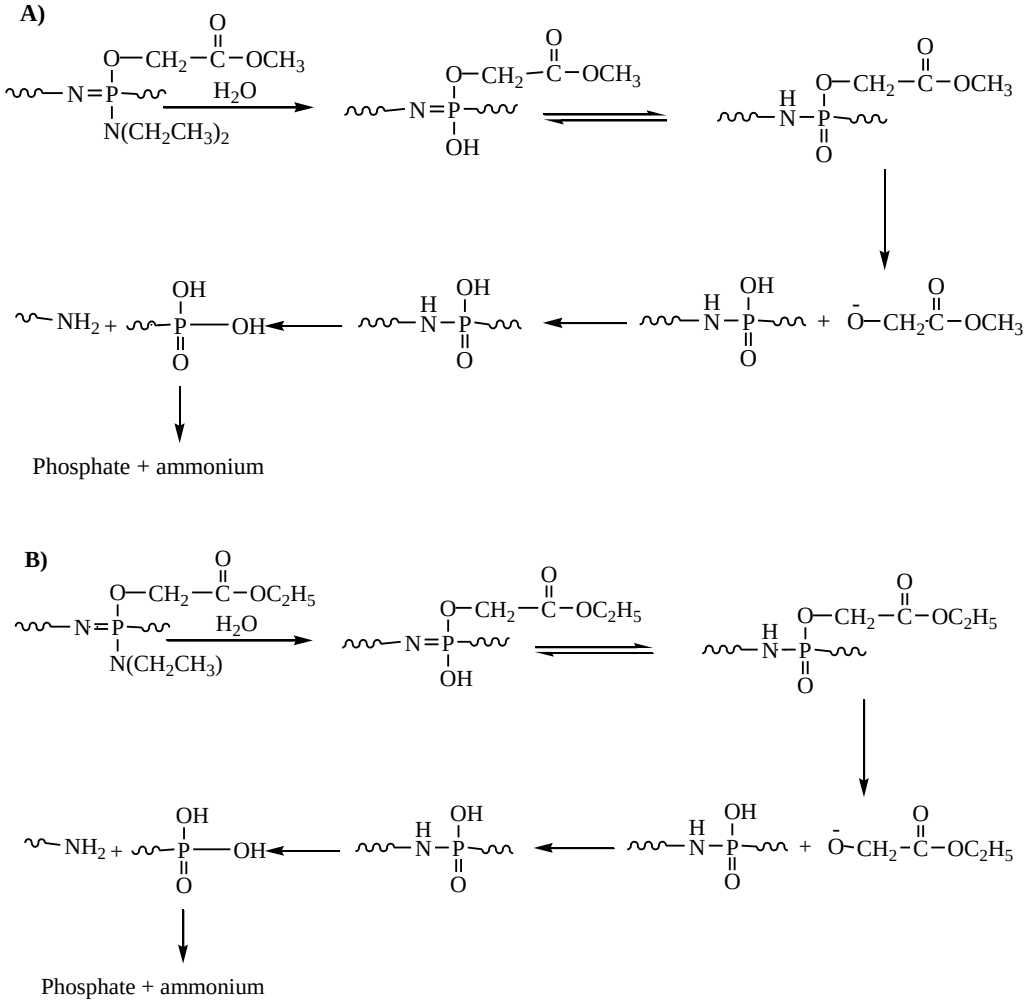

FIG. 8. **Possible degradation mechanism of PMGDEAP (A) and PEGDEAP (B).**

Conclusion

It was concluded that PMGDEAPP and PEGDEAPP were synthesized successfully *via* substitution of PDCP chlorines with methyl glycolate and ethyl glycolate. Their structures and molecular weight were elucidated by NMR and GPC respectively. These polymers are biodegradable and their hydrolytic degradation was investigated in acidic, basic and neutral medium at constant temperature. Moreover, it was concluded that polymer with smaller side groups were degraded rapidly as compared to larger side groups.

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