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BIOMEDICAL APPLICATIONS OF POLYMERIC MATERIALS FOR HUMANITY

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Abstract
At present biomedical applications are more attractive and significant due to their dire need in this modern age for humanity. Many types of materials have been investigated for biomedical applications but polymers are the largest and versatile class of biomaterials being extensively applied in multitude of biomedical applications. Polymers for biomedical application are non- toxic, biodegradable, biocompatible and meet the required specification for which they are intended because it has direct contact with the human body. In this study, poly[bis(p-oxyazobenzoic acid)phosphazenes](POABAP) was synthesized and used for biomedical applications such as hydrolytic degradation for drugs delivery etc for the social benefit of human beings.

Keywords: Polyphosphazenes, synthesis, characteristics, azobenzene, biomedical applications

1. Introduction

Polymers showed applications in various fields such as biophysics, medicine, electronics, and other branches of science and technology. Among these polymers, biomedical polymers are specially mentioned due to their less toxicity in vivo, easy to process and sterilized, better shelf life, light weight, and remarkable properties suited to the applications **[1-3]**. Utilization of polymers has greatly impacted the advancement of modern medicine. Applications are wide ranging with degradable polymers being used clinically as surgical sutures and implants. To fit functional demand, materials with desired physical, chemical, biological, and degradation properties must be selected. Fortunately, a wide range of natural and synthetic degradable polymers has been investigated for biomedical applications with novel materials constantly being developed to meet new challenges **[4-6].**
Polyphosphazenes, among inorganic polymers is a unique, attracting and most interesting topic in polymer due to their novel characteristics and applications because of inorganic main chain structure. These compounds are basically combination of organic and inorganic parts, so have wide range of application as hydrogels, drug delivery, membranes, biomaterials, fiber and film forming, elastomers, ionic conductors, flame retardant, and optical applications **[7-10]**. Polyphosphazenes have

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inorganic backbone of nitrogen and phosphorus atoms (-N=P-) and two organic groups can replace halogen which is attached with phosphorus. These side groups can be changed over wide range, organic, inorganic or organometallic so properties vary such as hydrophobic, hydrophilic, elastomers, biomaterial and conductors etc. Polyphosphazenes ring have availability for different groups and so wide range of compounds can be synthesized, more than 1500 different polymers have been synthesized **[11-15]**.

Polyphosphazenes with same side groups have microcrystalline or crystalline properties while different groups have amorphous or elastomeric properties **[16, 17]**. Hydrophobic groups such as $–OCH_2CF_3$ is water repellent while hydrophilic side groups such as $–NHCH_3$ soluble in water. Many polyphosphazenes are stable in water but amino acid ester as substituents is stable in water **[18-20]**. Polyphosphazenes is synthesized in two steps, in first step, hexachlococyclotriphosphazenes (HCCP) was converted into polydichlorophosphazenes (PDCP) by thermal ring opening polymerization heating upto 250^{o}C under vacuum **[21-23]**.

In this study, we synthesized poly[bis(p-oxy azobenzoic acid)phosphazene] (POABAP) by thermal ring opening polymerization in the presence of $AlCl_3$ catalyst and in second step chlorine from PDCP was substituted by hydroxy group of azobenzoic acid as side groups.

2. Experimental

2.1 Materials

Hexachlorocyclotriphosphazene (HCCP) was purchased from Nibo Boyuan Cailiao.Co.Ltd.. Tetrahydrofuran (THF) is refluxed over potassium and distilled in nitrogen atmosphere. Molecular weight and molecular weight distribution were determined by gel permeation chromatography (GPC) with a laser scattering detector and an ultrastyral gel column with pore size of 10^3-10^5Å. ^{1}H NMR, and ^{31}PNMR were obtained from a 400 MHz AVANCE NMR spectrometer (model DMX400). For protons, the chemical shifts were relative to tetramethylsilane at δ=0 ppm.

2.2. Synthesis of PDCP from HCCP and Synthesis of Poly[bis(p-oxy azobenzoic acid)phosphazene]

Monomer HCCP (2.0g, 5.75mmol) introduced and then catalyst $AlCl_3$ (0.1g, 0.75mmol) is added respectively. The tube is evacuated at 0.1Pa for 5 hrs at 50^{o}C and then sealed under vacuum. The sealed ampule tube is placed in oil bath at 250^{o}C for 5 hrs. During heating, HCCP converted into PDCP by changing physical states from clear melting mixture to highly viscous and mobile phase **[4-10]**. Reaction is shown in Figure 1. Sample tube is broken and connected with schlenk line. PDCP is purified by dissolving in refluxed toluene (10ml) through sonication and precipitated in refluxed n-hexane (150ml=50x3). After this, n-hexane is removed, unreacted HCCP trimer is weighed and the amount of PDCP is calculated (1.4g, 70%). Finally, PDCP is dissolved in refluxed tetrahydrofuran THF in the presence of inert atmosphere.

The synthesis of POABAP is based on the method reported in the literature with modification.

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In typical synthesis, 250ml three neck flask is equipped with reflux condenser and flask is dried under vacuum by heating at flame to remove moisture and oxygen and then nitrogen gas introduced respectively. This process is repeated for 3-times. PDCP (2.0g, 17.24mmol) is purified by dissolving in toluene and precipitating in n-hexane, finally dissolved in THF. In another flask, p-hydroxy benzoic acid (8.422g, 68.97mmol) (Cl:OH, 1:2)is dried under vacuum for 5 hours at 50^{o}C and dissolved in refluxed THF. After this, p-hydroxy benzoic acid solution transferred into PDCP solution by syringe. Finally, triethylamine (Et_3N) (9.65ml, 68.97mmol) catalyst is added dropwise into the mixture. Reaction mixture is stirred and refluxed at 67^{o}C for 48hrs shown in Figure 3. The resultant mixture filtered, and residue washed with water many times to remove salt and impurities. Residue dried in vacuum oven for 24 hours. Excess THF from filtrate is removed by rotatory evaporator, added into n-hexane dropwise and stirred by magnetic stirrer. Flask cooled down by ice bags. Stirring process stopped and n-hexane poured out. Again, the resultant product dissolved in minimum amount of THF (10ml) and added into fresh n-hexane (100ml) dropwise and this process repeated for 2-times and then precipitated in ethanol (100ml) 2-times to ensure purification. At the end, polymer is dried under vacuum to constant weight (2.23g, %yield 45).

3. Results and Discussion

HCCP monomer was purified by crystallization and sublimation and finally analyzed and confirmed by ^{31}PNMR indicated peak at 20ppm. PDCP was synthesized from HCCP by thermal ring opening polymerization at 250^{o}C under vacuum using catalyst detail is given in table 3.1 **[24]**. For the synthesis of PDCP, we introduced HCCP sample (2.0g, 17.24mmol) and catalyst(0.1g, 0.75mmol) (5% wt), sealed tube under vacuum and put in oil bath at 250^{o}C, the sample phase altered during heating from melting to highly viscous and mobile. The product phase depends on the amount of catalysts and reaction time, when catalyst amount is more than 3%, then viscous phase PDCP was obtained and content of catalyst less than 2% result mostly crosslinked product. Reaction time also varied from 3hours to 10 hours. PDCP purified in refluxed n-hexane because HCCP can easily dissolve in n-hexane while PDCP could not dissolve. After purification of PDCP, we calculated the amount of PDCP (60-70% yield). Reaction is shown in Figure 1. In this reaction, $AlCl_3$ acts as initiator for thermal ring opening polymerization, but in excess amount of catalyst, reaction stopped due to formation of stable acid base adduct with HCCP. Reaction time and catalyst depends upon each other, it is concluded that when catalyst amount increased then reaction time decreased and vice versa **[24]**. Reaction mechanism is shown in Figure 12.

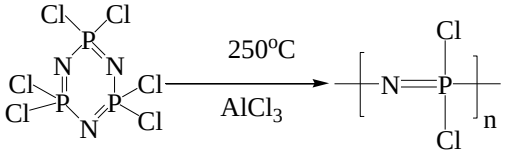

Figure 1. Synthesis of PDCP from HCCP in the presence of catalyst

3.2. Synthesis of poly[bis(p-oxy azobenzoic acid)phosphazene] and Hydrolytic Degradation

In second step, POABAP is synthesized by the replacement of chlorine from PDCP with

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hydroxyl group of p-hydroxybenzaldehyde in THF solvent by refluxing 48 hours in the presence and absence of triethylamine TEA catalyst. From the ^{1}HNMR and ^{31}PNMR, it is concluded that when substitution reaction occurred in the presence of TEA, then TEA also reacted and interfered with PDCP that is proved by two extra peaks appeared in ^{1}HNMR and ^{31}PNMR. The resultant polymer is difficult to dissolve in any solvent. While, when reaction happened in the absence of TEA, no extra peaks presented in ^{1}HNMR and single sharp peak appeared in ^{31}PNMR and resultant product is soluble in THF and other solvents. Initially, PDCP was purified and dissolved in THF, and after this 4-hydroxynebaldehyde dissolved in THF and triethylamine was introduced respectively.

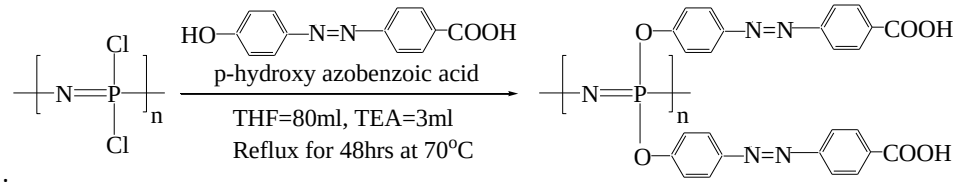

Figure 2. Synthesis of poly[bis(p- oxy azo benzoic acid)phosphazenes]

The ^{1}H NMR spectrum showed peaks with the following shifts: 6.60-6.80ppm (2H of C_6H_4), 7.10-7.35ppm (2H of C_6H_4), 7.55-7.65ppm (2H of C_6H_4), 7.72-7.85ppm (2H of C_6H_4), 8.12-8.22ppm (1H of C_6H_4), and from 13.44-13.55ppm (1H of -COOH) as shown in Figure 3. Molecular weight of polymer was Mw, 575987, PDI 2.8, Mn, 14929 as shown in Figure 4.

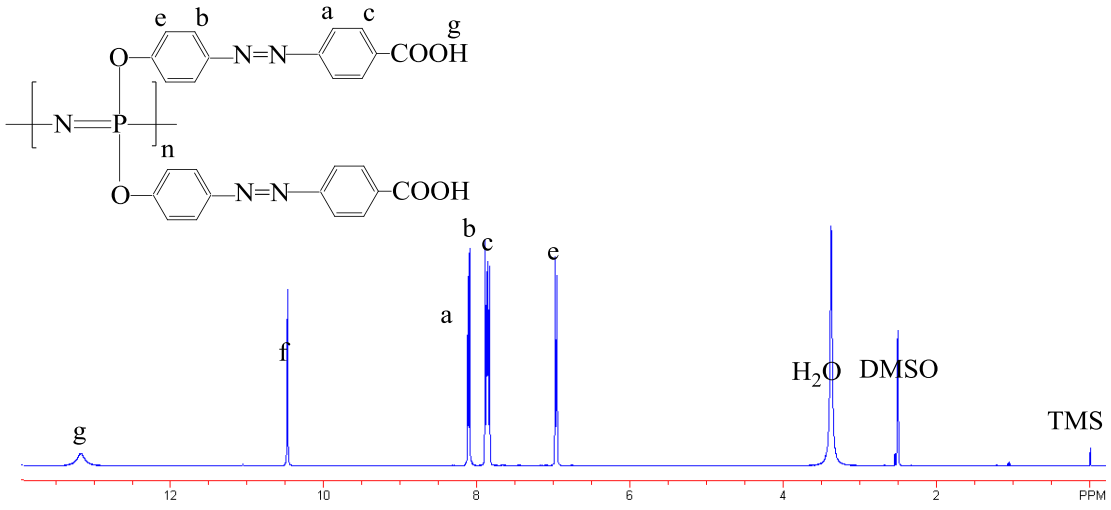

Figure 3. ^{1}H NMR of poly[bis(p- oxy azo benzoic acid)phosphazenes]

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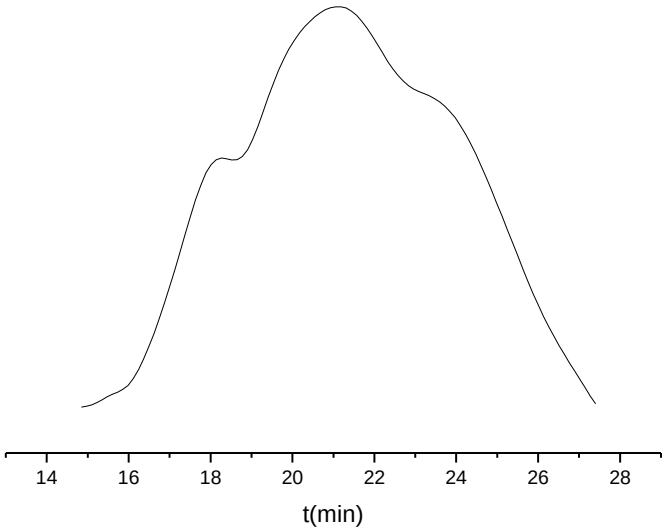

Figure 4. GPC of poly[bis(p- oxy azo benzoic acid)phosphazenes]

In this process, hydrolytic degradation of Poly[bis(p- oxy azo benzoic acid)phosphazenes] was studied in neutral, acidic and basic media and it was found that polymer degraded faster in acidic medium, then basic and moderate in neutral medium at 37^{o}C **[11-15]**. Polymer sample 10g was dissolved in buffer solution and degradation study was observed with the loss of weight of polymer by balance.

It was noted that after degradation, ammonia, phosphate and amino acid was produced at the end. To verify, Nin hydrin test was performed by the appearance of yellow color with silver nitrate and intense violet color was appeared.

From the graph and results, this was found that degradation of polymer was dependent on side groups. From the results, it was studied that rate of degradation of polymer was very fast as compared to basic and neutral medium. For mechanism hydrolytic degradation mechanism, it was also observed that some unreacted chlorines can initiate degradation and backbone was break down. After degradation, there are some common products such as carboxylic acids, ammonium, phosphate and alcohol. Possible degradation mechanism of polymer is shown in Figure 5. Moreover, this data will be analyzed by mathematical and computational modeling.

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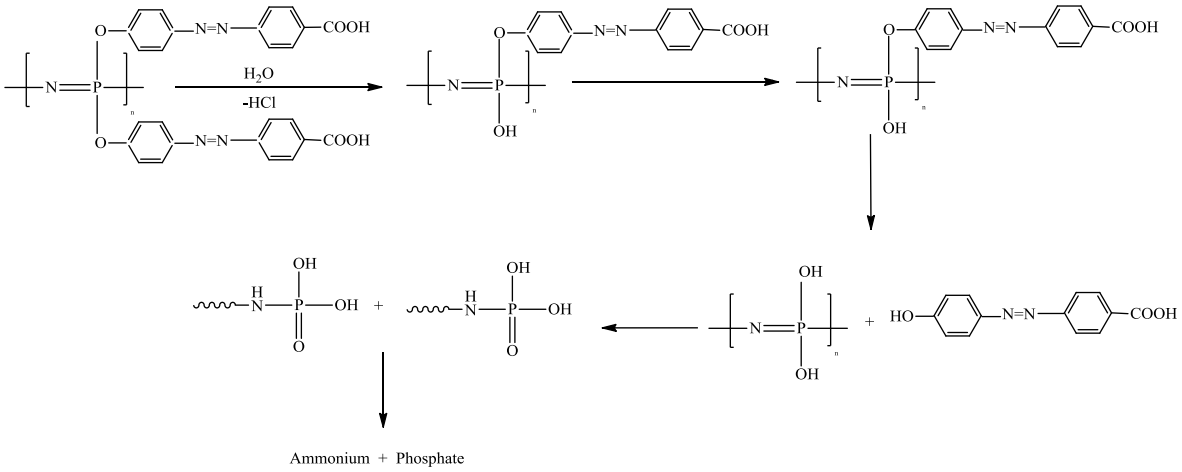

Figure 5. Possible degradation mechanism of polymer

Conclusion

Poly[bis(p- oxy azo benzoic acid)phosphazenes] (POABAP) was synthesized in two steps. In first step, the polydichlorophosphazenes (PDCP) was synthesized from hexachlorocyclotriphosphazene (HCCP) by thermal ring opening polymerization in the presence of $AlCl_3$ catalyst and in second step chlorine atoms from PDCP were substituted by hydroxy groups of 4-hydroxy azo benzoic acid. Further, degraded polymeric data will be analyzed by mathematical modeling. The applications of biodegradable polymers are very effective and significant because these are non-toxic and safe and applied for surgical sutures, medical implants, tissue engineering scaffolds, and drug encapsulating. Some materials are used for drugs delivery applications and some other applications such as cardiopulmonary bypass surgery. Due to the rapid development and applications of biomaterials, it is becoming increasingly important to understand the structure, processing and properties of biomedical polymers and their medical applications for human beings.

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