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Review

Applications of Inorganic Polymeric Materials, III: Polyphosphazenes

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Summary. Polyphosphazenes form one of the most important and interesting classes of inorganic polymers having a backbone of alternating phosphorus and nitrogen atoms with phosphorus atom bearing two organic side groups. The most important feature of these polymers is the synthesis route which allows the side groups to be changed over a wide range to obtain a broad variety of products with different properties from elastomers to glasses, water soluble to hydrophobic polymers, bioinert to bioactive materials, and electrical insulators to conductors. In this paper, some novel applications of these polymers in biomedical materials and advanced devices are reviewed.

Keywords. Polyphosphazene; Synthesis; Elastomers; Biomedical.

Introduction

Polyphosphazenes comprise the largest class of inorganic–organic polymers with more than 700 variations which have very interesting properties and commercially promising applications [1]. Synthesis of the first polyphosphazene has been reported in 1964 [2].

The backbone of these polymers consists of alternating phosphorus and nitrogen atoms which each one attaches to organic or inorganic side groups (Scheme 1) [3]. The most interesting feature of these compounds is their synthesis procedure which allows changing of the side groups to obtain a wide variety of products with a broad range of properties. It is consisted of elastomers to glasses, hydrophilic to hydrophobic, bioinert to bioactive materials, and electrical conductors to insulators [4–6]. Thus, considering the structure-property correlations, one can even predict the properties of the compound yet to be prepared. The properties-structure relationship for some typical polyphosphazenes is shown in Table 1 [3].

As crystallization is a consequence of molecular symmetry, the microcrystallinity is only observed in polyphosphazene with a single type of substituent group. When different types of substitute groups are present, the required conditions with respect to symmetry do not meet. The aminophosphazene polymers are amorphous probably due to hydrogen bonding, for example. The elastomeric properties are exhibited when small or flexible substituents, *e.g.*, linear side groups such as $-OC_2H_5$, $-OCH_3-$ are present. Therefore, these polymers are used as low temperature elastomers.

Polyphosphazenes with trifluoroethoxy, alkyl, aryl, and organosilicon are also used for this application [7]. Also, polyorganophosphazenes are resistant to hydrolysis [8].

As, the molecular-property relationships play an important role in producing a wide range of advanced materials, some general relationships can be summarized as follows:

– Crystalline *versus* amorphous polymers: As mentioned earlier, presence of one type of side group results in molecular symmetry, microcrystallinity, and mixed substitutions end up with amorphous structure.
– Hydrophobic *versus* hydrophilic polymers: The presence of a hydrophilic side group such as

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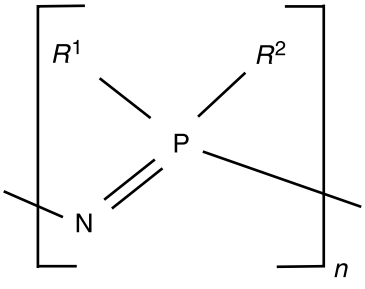
$-NHCH_3$, results in solubility of the polymer in water and side group such as $-OCH_2CF_3$ which is hydrophobic in nature leads to water repellency.
- Water stability *versus* water erodability: Most of the poly(organophosphazenes) are stable in water but, polymers containing amino acid ester side groups are unstable in water. Also, water-soluble polyphosphazenes with aminoalcoholic functions have been prepared by reaction of aminoalcohol with polydichlorophosphazene [9]. Poly[di(carboxylatophenoxy)phosphazene is a water soluble polymer and is used in aqueous microencapsulation [10].
- High T_g *versus* low T_g polymers: For different side groups as shown in Table 1, T_g can move up or down.

Far about 300 grades of polyphosphazenes have been made, and most of them are functionalized polyphosphazenes, which are bonded to other molecules or to other polymers to make novel materials. Polyphosphazenes form new promising engineering materials with a large number of possible different structures for specific applications. Some of these polymers are very hard, stiff, and have very good resistance to organic chemicals. Furthermore, this class of materials combines high temperature stability and low temperature flexibility with good toughness and inherent flame retardance [11].



Scheme 1. The chemical structure of backbone of polyphosphazene

These polymers are more resistant to thermo-oxidative decomposition than organic polymers. Several polyphosphazene materials have thermal stability above 400°C and are resistant to degradation in acidic media. DSC technique has been used to study thermal behavior of polyphosphazene homopolymers. The results show that polyphosphazenes have a single glass transition temperature and two first order phase transitions with a large mesophase temperature. When these polymers are obtained in solution, they exhibit 3D crystallinity and by heating above their mesophase transition they show 2D structure and when they are cooled to room temperature, their crystallinity will be at very high level. In these polyphosphazenes, the glass transition temperature is almost independent of the level of crystallinity. The nature and magnitude of mesophase transition temperature and melt temperature depend upon processing conditions [12]. Polyphosphazenes, especially those which contain aryloxy side groups, have very good temperature stability [13].

These polymers in general are synthesized in a two steps process: first, linear polydichlorophosphazene is produced *via* either a ring-opening process from a commercially available phosphonitrilic chloride trimer or a condensation procedure. The second step is nucleophilic substitution of the backbone with the suitable alkoxide or aryloxide [14]. Several of the potential applications of these polymers are in fuel cells, medicine, hydrogels, and membranes. Some of the novel applications will be present in more details in the following sections.

Table 1. Relationship of properties-structure for some polyphosphazenes

Formula	Properties	T_g/°C	T_m/°C
$[NP(NHC_6H_5)_2]_n$	Glass	+91	–
$[NP(OC_6H_5)(OC_6H_4C_6H_5\text{-}p)]_n$	Glass	+43	–
$[NP(OC_6H_5)(OC_6H_4C_6H_5\text{-}o)]_n$	Glass	+24	–
$[NP(OC_6H_4COOEt)_2]_n$	Microcrystalline thermoplastic (films)	+7.5	+127
$[NP(OC_6H_5)_2]_n$	Microcrystalline thermoplastic (films, fibers)	−8	+390
$[NP(OC_6H_5)(OC_6H_4C_2H_5)]_n$	Elastomer	−10	–
$[NP(O(CH_2)_8CH_3)_2]_n$	Elastomer	−56	–
$[NP(OCH_2CF_3)_2]_n$	Microcrystalline thermoplastic (films, fibers)	−66	+242
$[NP(OCH_3)_2]_n$	Elastomer	−76	–
$[NP(OC_2H_5)_2]_n$	Elastomer	−84	–
$[NP(OC_3H_7)_2]_n$	Elastomer	−100	–
$[NP(OCH_2CH_2CH_2CH_3)_2]_n$	Elastomer	−105	–

Novel Applications of Polyphosphazenes

Optical Applications

Polyphosphazenes are resistant to photolytic cleavage, because the phosphorus – nitrogen backbone is transparent. Therefore, optical transparent polymers that have high refractive index are made from them [15, 16]. Due to the relatively high electron density in the backbone structure, polyphosphazenes are able to produce high refractive index value. Refractive indices are independent of the molecular weights of polyphosphazenes. Polyphosphazenes are conjugated to aromatic polymers in high refractive index applications and the [N=P] repeating unit has a linear polarizability near to conjugated C=C bonds [17].

In a research work [18], optical properties of poly(aryloxyphosphazenes) as a function of the side group has been studied. The results show that the aromatic side groups produce high refractive indices. Also, the type of side group can effect on transparency. The refractive indices ranges were from 1.561 to 1.686 at $\lambda = 632$. Polyphosphazene with a carbazolyl side group is used for charge photogeneration and transport properties. In a recent study [19] polyphosphazene with 9-(2-hydroxycthyl)carbazolyl side groups has been synthesized and its structure has been studied.

Recently, a new photoreactive polyphosphazene based on carbazole has been synthesized by post azo coupling reaction and shows a glass transition temperature at 50°C and is used as an optically transparent film with long-term stability [20].

A new photosensitive polyorganophosphazene with coumarin as side group has been synthesized through polymeric substitution reaction of poly(dichlorophosphazene) with the sodium salt of 7-(2-hydroxyethoxy)-4-methylcoumarin. The obtained results show that this polymer is stable up to 280°C. Also, under UV irradiation, photodimerization occurred and the gel content increased with increasing irradiation intensity. This polymer can be used as photoresistant and photorecording device [21].

A novel high T_g photoreactive polyphosphazene has been synthesized. This polymer with an imidazole based chromophore is prepared by a two steps method and has high photoinduced birefringence value, good optical transparency, high T_g (170°C), and good solubility in common organic solvents. This method can be used for preparation of other polymers containing heteroaromatic based and multidipolar chromophores for nonlinear optical applications [22].

Flame Retardants and Thermosensitive Polyphosphazenes

Polyorganophosphazenes are used as flame retardants. By blending of polyphosphazene derivatives flame retardant materials are produced [23]. A blend of polyurethane/poly[bis(carboxylatophenoxy)phosphazene] has been made, and its thermal degradation studied. It was found that at amounts of larger than 20% polyurethane in the mixture, flame retardancy is significantly increased [24] and a novel aryloxyphosphazene is produced. Halogenated organophosphates are used as the phosphorylating agents. These agents react with hydroxyl groups. Phosphorylated cyclic trimers are synthesized and are used as flame retardant additives to polystyrene [25].

Trichlorotri(dimethylamino)cyclotriphosphazene which has been prepared from hexachlorocyclotriphosphazene is used as curing agent for epoxy resins and fire resistant applications [26].

A novel polyphosphazene containing C_{60} moieties has been synthesized. The phosphonitrile trimer molecules obtained *via* thermal ring-opening polymerization in the presence of C_{60} molecules, contain C_{60}-poly(dichlorophosphazene). This polymer has high thermal stability and good solubility in common organic solvents [27].

A new copolymer of poly *N*-isopropylacrylamide grafted polyphosphazene has been synthesized. This polymer is thermosensitive and is prepared through co-substitution reaction of poly(dichlorophosphazene) with amino terminated *N*-isopropylacrylamide oligomer and glycin ethyl ester [28].

By nucleophilic displacement of activated nitro groups of tri(4-nitrophenoxy)tri(phenoxy)cyclotriphosphazene and hexa(*p*-nitrophenoxy)cyclotriphosphazene with the hydroxyl groups of bisphenol A, novel cyclomatrix network polymers of phosphazene have been synthesized. The results show that these polymers have very good thermal stability and flame retardancy, if a cross-linked phosphorous oxynitride structure is formed during pyrolysis or combustion [29].

Hydrogels and Drug Delivery Systems

The substitution of certain groups such as amines, amino acids, or alkoxy substituents can change poly-

phosphazenes to biodegradable materials. Also, high biocompatibility combined with their ability to exhibit controlled erosion times through macromolecular substitution makes them attractive materials for drug delivery systems [30].

Polyphosphazenes with alkyl ether side groups are soluble in water. When cross-linked by γ-radiation, they absorb water and swell to hydrogels. These hydrogels show a lower critical solution temperature (LCST) property [31]. Polyphosphazenes with LCST are used for thermosensitive drug release. Below this temperature they are expanded and above that they are contracted. For some of these hydrogels, the LCST is near to temperature of human body which means they can be used for membranes, and drug delivery systems. Also, poly[bis(methoxyethoxyethoxy)-phosphazene], *MEEP*, and its derivatives can be used in hydrogels, membranes, and drug release systems [32].

Polyphosphazene with carboxylatophenamino groups (*PCPAP*) was prepared from substitution reaction of ethyl *p*-aminobenzonate with poly(dichlorophosphazene). Its properties were determined by IR, ^{1}H NMR, DSC, and elemental analysis. By incremental increase of *PCPAP* or $CaCl_2$ in concentration, erosion duration of the beads at *pH* 7.4 and 37°C is extended. At *pH* 8.0 buffer within 34 days, 39.4% of sample degradation was observed into macromolecular segments by breakage of the backbone, which can prevent the accumulation of this compound in the body, furthermore these properties of *PCPAP* are useful in controlled drug delivery [33].

When polyphosphazene is added dropwise into $CaCl_2$/chitosan solution, chitosan coated polyphosphazene-Ca^{2+} hydrogel beads are produced. In this state, polyphosphazene is a water soluble degradable polyanion (*PCPAP*). On the backbone of this polymer, two carboxylatophenamino groups are presented on each phosphorus atom. The *PCPAP*/chitosan complex made at $pH = 6.5$ dissociates slowly in $pH = 7.4$ phosphate buffered solution. By improving of drug loading efficiency, coating of *PCPAP*/chitosan complex on the surface of beads is possible. In addition, at higher gelling solution *pH*, the drug delivery efficiency is improved. Therefore, the chitosan-coated polyphosphazene-Ca^{2+} beads can be used for drug controlled released [34].

Polyphosphazene hydrogels are used as carriers for a variety of prophylactic and therapeutic agents. These hydrogels have good biocompatibility and can produce any combination of properties for specific biomedical applications. Microspheres based on phosphazene polyelectrolytes have strong immunostimulatory activity, therefore they are used in vaccine delivery facility. Organic solvents must be used for making synthetic microspheres [35].

Hydrogels are produced when poly[bis(carboxylatophenoxy)phosphazene] (*PCPP*) interacts with salts of divalent cations as calcium chloride in aqueous media. Beads with diameter size of 24 nm of fluorescent polystyrene with varying molecular weights were encapsulated in polyphosphazene microspheres to investigate the ability of the *PCPP* hydrogel matrix to release a macromolecular substrate. To produce a poly-L-lysine (*PLL*) outer membrane coating around the *PCPP* microsphere, the spheres were treated with *PLL* solution. By varying the molecular weights, the concentration of *PLL*, and reaction time between *PCPP* microsphere and *PLL*, the release profiles can be controlled [36].

Poly[di(carboxylatophenoxy)phosphazene] (*PCPP*) can form hydrogel microcapsules and has useful immunoadjuvant properties. The mixed substitute copolymers of *PCPP* and polyphosphazenes with hydrophilic alkyl ether alkoxy groups were prepared. As a result, the solubility range of polyphosphazene containing carboxylatophenoxy groups and also hydrophilicity were increased [37].

Poly[di(ethyl glycinato)phosphazene], poly[di(ethyl alanato)phosphazene], and poly[di(benzyl alanato)-phosphazene] were prepared for drug delivery systems. Films cast from tetrahydrofuran solutions of each polymer were kept in aqueous media at $pH = 7$ and temperature of 25 and 37°C for 1400 h, and the release of the small molecules, was studied by UV/Vis spectroscopy technique. It was found that poly [(amino acid ester)phosphazene] can be used as substrate for controlled release of small molecules [38].

A new biodegradable polyphosphazene that contains glycine ethyl ester and benzyl ester of amino acethydroxamic acid (*PGBP*) has been synthesized. *In vitro* degradation studies at varied *pH* show that the degradation of *PGBP* is *pH* sensitive and occurs in two stages. The polymer first is degraded to water soluble components with the fast breakage of side groups and then the backbone is broken. This property of *PGBP* can be used in drug delivery systems [39].

A novel drug carrier has been synthesized from an amphiphilic graft polyphosphazene with a molar ratio

0.54:1 of poly(*N*-isopropylacrylamide) (*PNIPAm*) to ethyl glycinate. This copolymer exhibits two phase transitions in aqueous solution which indicates aggregate morphology (at T_{ph1}) and the collapse of *PNIPAm* chains (at T_{ph2}), respectively. At temperatures below T_{ph1} network micelles are produced and at temperatures above T_{ph2} dispersed nanoparticles are formed. When the hydrophobic drug, for example ibuprofen, is solubilized into polymeric aggregates, drug loaded nanospheres are formed [40].

Membranes

Polyphosphazenes have been used for preparing different kinds of membranes such as uncharged pervaporation membranes for organic/water separation, carboxylated ion-exchange, and sulfonated cation-exchange membranes for electrodialysis and battery/fuel cell applications [41]. The membranes prepared from polyphosphazenes containing amino acids as side groups have shown promise for treatment of periodontal diseases. Polyphosphazene membranes have been prepared with alanine ethyl ester and imidazole (in the molar ratio of 80/20) as side groups. It was found that degradation rate of these membranes corresponds to the healing of the bone defect. Polyphosphazene microsphere has been produced using phenylalanine ethyl ester as substitute on the phosphorus atom and loaded with succinylsulphathiazole or naproxen which is useful for bone formation [42].

Poly[bis(methoxyethoxyethoxy)phosphazene] (*MEEP*) cross-linked when exposed to γ-rays and connected to water swellable membranes and hydrogels. By incremental increase of irradiation dose, the degree of cross-linking increases [43].

Different polymeric materials were prepared by reaction of $(NPCl_2)_n$ with 2-hydroxyethylacrylate and different primary and secondary amines and converted to membranes by casting, mixing mill method, and ultraviolet radiation. The oxygen gas permeability of these membranes was determined and it was found that poly[diethylaminobutyl(aminophosphazene)] has the highest gas permeability [44].

Ion exchange membranes from poly[(4-ethylphenoxy)(phenoxy)phosphazene] (*PEPP*), with benzophenone (*BP*) as a photoinitiator, have been made. After mixing of photoinitiator with polyphosphazene polymer, a thin film was prepared by solvent casting and irradiation with UV light. The results show that half-life of *BP* in films with thickness of 50 μm is 20 min. By incremental increase of molar ratio of *BP-PEPP*, T_g increases. Also swelling in dimethylacetamide at 25°C decreases [45].

A cyclolinear polyphosphazene has been produced to make a nanofiltration membrane, by considering of organic and inorganic properties. This polymer is put in a zirconia ultrafiltration layer which is used as inorganic matrix. This ultrafiltration membrane is used for removing organic dyes from water and its efficiency depends on its charge density [46]. Membranes with multicomponents which contain polyphosphazene coatings are used for gas separation [47].

Also, a new procedure has been used to measure diffusion coefficients of methanol in several polyphosphazene based cation exchange membranes [48]. Sulfonated poly[bis(3-methylphenoxy)phosphazene] membranes with an ion exchange capacity of 2.1 mmol/g have been synthesized. The results show that the base polymer, poly[bis(3-methylphenoxy)-phosphazene], has semicrystalline structure and for the sulfonated polymer the three dimensional crystal structure disappeared [49].

Ten new polyphosphazenes have been synthesized and their gas permeability has been studied [50]. These polymers which are used in membranes contained both the aromatic and the polyether components that are attached to the backbone and a random terpolymeric structure is yielded. Permeabilities of the six gases, such as CO_2, Ar, CH_4, O_2, N_2, and H_2 have been studied. CO_2 is the most permeable gas through any of these phosphazenes. A correlation has been observed between the polymer glass transition (T_g) and the CO_2 permeability that polymers with lower T_g show higher CO_2 transport. By addition of higher amounts of polyether to the polymers, T_g decreases and a positive correlation is observed between the polymer polyether content and the CO_2 permeability.

New composite salts in polymer electrolyte membranes have been synthesized using poly[(bis(2-methoxyethyl)amino)(*n*-propylamino)phosphazene] (*BMEAP*) with dissolved $LiCF_3SO_3$ and dispersed Al_2O_3 nanoparticles. The obtained membranes have good mechanical stabilities. Also, these electrolytes show a large enhancement of the ionic conductivities by two orders of magnitude upon addition of Al_2O_3 nanoparticles [51].

Novel dimensionally stable membranes have been synthesized through a solution casting and free radical cross-linking process using 2-(2-methoxyethoxy) ethanol (*MEE*), 4-methoxyphenol, and 2-allylphenol

as pendant groups. As homopolymer, 4-methoxyphenol produces poor membranes due to high brittleness. But, upon addition of both pendant groups, *MEE* and 4-methoxyphenol onto the polymer, an amorphous elastomer with good film forming properties is obtained. Membranes from heteropolymers are used for pervaporation membranes [52].

Recently, new proton conducting membranes have been synthesized *via* sulfonated poly[bis(phenoxy)-phosphazene] that is trapped in a cross-linked interpenetrating hydrophilic and three dimensional network of hexa(vinyloxyethoxyethoxy)cyclotriphosphazene (*CVEEP*). The *CVEEP* network increases the hydrophilicity of the membranes which is due to polyether chains. Furthermore, these chains act as a plasticizer. These membranes have good mechanical and thermal stabilities and exhibit high ion exchange capacities [53].

The use of polyphosphazene membranes in mass spectroscopy has been reported [54]. Membrane introduction mass spectrometry (MIMS) is a very good analytical instrument that can measure analytes in the parts per trillion ranges. The membrane controls the selectivity, sensitivity, and flux of the analyte into the mass spectrometer. The results show that polyphosphazene membranes can separate organics from water and pass them into the mass spectrometer for detection.

Biomaterials

By evaporating of poly[bis(ethyl alanato)polyphosphazene] around a capillary with a diameter of 1.3 mm, tubes are obtained. These tubes are used for nerve regeneration [55]. Polyphosphazenes with amino acid ester side groups are used as biodegradable materials. By suitable selection of side groups, the rate of degradation can be controlled. Also, the degradation rate of poly[(amino acid ester)phosphazene] is controlled by hydrolysis of the sensitive amino acid ester side groups or by blending [56].

A novel biodegradable polyphosphazene has been produced from poly[(50% ethyl glycinato)(50% *p*-methylphenoxyphosphazene] (*PPHOS*)-hydroxyapatite (*HA*) composite. This composite is used for bone tissue engineering. Porous matrices of *PPHOS* are made using a salt leaching procedure. These matrices have three dimensional structure and high cell number. These novel composites retain their mechanical properties during degradation. Also, the *PPHOS*/*HA* composites support cellular reproduction [57].

In the study of surface modification of poly[bis(trifluoroethoxy)phosphazene] with polyethylene glycols, the metathetical exchange reaction between the $-O-CH_2CF_3$ segments of poly[(bis(trifluoroethoxy)-phosphazene] (*PTFP*), as slightly swollen films, and the alkoxide ions derived from methoxypolyethylene glycol (*MPEG*) of molecular mass in the range of 350–5000 g/mol was investigated. In all cases, the surface biocompatibility was increased [58].

A novel biodegradable polymer blend of polyphosphazene including 50:50 poly(lactide-*co*-glycolide) (*PLAGA*) and a 50:50 ratio of the following polyphosphazenes (*PPHOS*) poly[(25% ethyl glycinato)-(75% *p*-methylphenoxy)phosphazene], poly[(50% ethyl glycinato)(50% *p*-methylphenoxy)phosphazene], and poly[(75% ethyl glycinato)(25% *p*-methylphenoxy)phosphazene] was developed to obtain blends A, B, and C, using a mutual solvent technique. Degradation studies showed blends A and B losing 10% of their mass after two weeks and blend C degrades more rapidly, 30% loss during the same period of time. Therefore, these novel biodegradable *PLAGA*/*PPHOS* blends are useful for biomedical applications [59].

A degradable poly[(methylphenoxy)(ethyl glycinato)phosphazene] has been prepared and a three dimensional (3D) matrix system produced using a salt leaching method. This degradable 3D matrix has been used as a construction for skeletal tissue regeneration. Then, the 3D polyphosphazene polymer matrix system was nucleated with osteoblast cells for production of a cell-polymer matrix material. This 3D matrix contains an average cell diameter of 165 μm. This novel porous 3D polyphosphazene polymer matrix is suitable as biodegradable scaffold to reproduce skeletal tissue [60].

A biodegradable poly(organophosphazene) nanoparticles surface which is modified by adsorption of a novel poly(organophosphazene)-poly(ethylene oxide) has been developed. The data of biodistribution of poly(organophosphazene) was compared to poly(lactide-*co*-glycolide) nanoparticles which are coated with poloxamine 908. This copolymer is poly(ethylene oxide)-poly(propylene oxide) ethylene diamine. The results indicate that in the rat model, the poly(organophosphazene) nanoparticles with poloxamine 908 coating were taken up by the liver. But in the rabbit model, lifetime of circulation

in blood is longer and adsorption by liver is reduced [61].

A new biodegradable polyphosphazene/poly(α-hydroxyester) blend has been produced whose degradation products are less acidic than those of the poly(α-hydroxyester) alone. Also, a blend of poly (lactide-*co*-glycolide) (50:50 *PLAGA*) and poly-[(50% ethyl glycinato)(50% *p*-methylphenoxy)phosphazene] (*PPHOS-EG*50) has been prepared. Circular matrices (14 mm diameter) of these materials have been degraded in non-buffered solutions ($pH = 7.4$). The results showed that the blend degraded at a rate intermediate to that of the original polymers and the degradation products of the polyphosphazene have neutralized the acidic degradation products of *PLAGA* [62].

A complex of platinum(II) and derivatives of phosphazene polymers have been synthesized and used to *in vitro* and *in vivo* tests for antitumor activity [63]. Different poly[(amino acid ester)phosphazenes] with biomedical applications have been prepared. The crystalline structure and hydrolysis behavior in solution and solid states have been studied [64]. Water soluble phosphazene polyacids have been synthesized and it is found that these polymers are able to enhance the immune response to influenza virus as compared to vaccine alone [65].

Recently, a bioresorbable blend of a polyphosphazene consisting of amino acid ester side groups and poly(lactide-*co*-glycolide) has been synthesized. *In vitro* studies showed that this polymer is able to increase adhesion and numbers of osteoblast-like cells on the surface. Also, some methods have been used for preparing porous matrices using poly(lactid-*co*-glycolide). These matrices have been formed *in vitro* as a scaffold for proliferation by sintered microsphere procedure. This polymer is used for bone regeneration [66].

A novel composite has been synthesized using biodegradable polyphosphazene, poly[bis(ethyl alanato)phosphazene] (*PNEA*) and poly[(50% ethyl alanato)(50% methylphenoxy)phosphazene] ($PNEA_{50}$ mPh_{50}) and calcium incomplete hydroxyapatite at physiological temperature. The results showed that surface morphology of the composites was similar to porous microstructure. The adhesion and number of osteoblast cells have increased on these composites and these materials can be used for bone tissue engineering [67].

A novel and biodegradable polymer, poly(2-dimethylaminoethylamino)phosphazene (*P*(*DMAEA*)-*ppz*), has been synthesized. This polymer is non-toxic and can be used for gene therapy. In this research, biodistribution of polyplexes consisted of plasmid *DNA* and *P*(*DMAEA*)-*ppz* has been studied and compared with polyplexes based on the non-biodegradable polyethylenimine (*PEI* 22 kDa). Both polyplex systems showed arrangement in the liver and the lung. As a result of interaction between polyplexes and blood components the lung disposition occurred, *P*(*DMAEA*)-*ppz* polyplexes did not show considerable gene expression in the lung [68].

In a recent study novel blends of poly[bis(ethyl alanato)phosphazene] (*PNEA*) and poly(lactide-*co*-glycolide (*PLAGA*) with ratio of $LA{:}GA = 85{:}15$ have been prepared. Two compositions with weight ratios of $PNEA{:}PLAGA = 25{:}75$ and 50:50 were considered for blends 1 and 2. The osteocompatibilities of blends 1 and 2 have been studied by considering adhesion of rat osteoblast cells on two dimensional polymer and films of blends in culture over a 21 day period of time. The results showed that blend films have much higher cell numbers on the surface compared to *PLAGA* and *PNEA* films alone [69].

A new blend of poly[bis(glycine ethyl ester)phosphazene (*PGP*) with poly(D,L-lactide-*co*-glycolide) (*PLAGA*) with molar ratio of 80:20 and poly[sebasic anhydride-*co*-trimellitylimidoglycine)-block-poly(ethylene glycol)] (*PSTP*) with molar ratio of 30:50:20 has been synthesized. *In vitro* and *in vivo* degradation of the polymer blends have been studied. The results show that *PGP*/*PLAGA* blends have higher activity [70].

A novel polyphosphazene, poly[di(sodium carboxylatoethylphenoxy)phosphazene] (*PCEP*), has been synthesized to increase antigen specific immune responses. Adjuvant activity of this polyelectrolyte was compared to poly[di(sodium carboxylatophenoxy)-phosphazene] (*PCPP*) and the known adjuvant alum. This novel polyphosphazene is able to increase antigen specific immune responses and its adjuvant activity is higher than *PCPP* and alum. Also, it provides desirable attributes of a novel vaccine adjuvant [71].

The feasibility study to obtain flat or tubular matrices using biocompatible poly[(ethylphenylalanato)(1.4)(ethyl glycinato)(0.6)phosphazene] by electrospinning process has been performed. The effect of different parameters on the diameter of nano-

fibers has been studied. The adhesion and growth of rat cells that have been cultured on sheets and tubes with an average diameter of 850 ± 150 nm has been studied. Microscopic tests show that after 16 days of incubation, endothelial cells form a monolayer on the whole surface. These results demonstrate that tubes of biodegradable polyphosphazenes can be used in human tissues such as vessels or cardiac valves [72].

A novel amphiphilic poly(organophosphazene) has been synthesized *via* stepwise nucleophilic substitutions of a hydrophilic methoxy poly(ethylene glycol) and a hydrophobic glycyl-L-glutamate as side groups. Then, an antitumor (dach) platinum(II) moiety has been conjugated to the polymer using the dipeptide as a spacer. This polymer is accumulated in the tumor tissue larger than in the normal tissue. This is due to the long blood circulating properties such as high plasma half-life. This polymer also exhibits high *in vitro* cytotoxicity comparable to cisplatin against human tumor cells that have been tested [73].

Poly[bis(4-methoxybenzylamino)polyphosphazene] (*POP*-1) and poly[bis(4-methoxyphenethylamino)-polyphosphazene] (*POP*-2) are two novel organo-polyphosphazenes that have been synthesized and characterized by spectral and thermal techniques. Microspheres have been prepared by incorporating indomethacin (water insoluble) and 5-fluorouracil (water soluble) drugs, and *in vitro* release has been studied. The results obtained show that at higher amounts of indomethacin the release is faster. After clinical and toxicological characteristics testing, these matrices can be used in biomedical and *in vivo* applications [74].

Poly(organophosphazenes) with a lower critical solution temperature (LCST) below body temperature have been synthesized. These polymers are biocompatible and thermosensitive and have been prepared by including short chain tri- or tetraethylene glycol as a hydrophilic group and a dipeptide as hydrophobic group into the backbone of polyphosphazene. *In vitro* studies show that the entrapment efficiency of human growth hormone (as a model drug) by the polymer decreases when polymer concentration increases [75].

In a recent research three polymers, poly[bis(ethyl alanato)phosphazene] (*PNEA*), poly [(50% ethyl alanato)(50% methyl phenoxy)phosphazene] ($PNEA_{50}$ mPh_{50}), and poly[(50% ethyl alanato)(50% phenyl-phenoxy)phosphazene] ($PNEA_{50}$ $PhPh_{50}$), have been used for evaluation of biocompatibility in a rat model. By a solvent evaporation technique polymer disks with a diameter of 7.5 mm were prepared and were implanted subcutaneously in rats. After 2, 4, and 12 weeks tissue responses were studied. Shape and structure of these polymers are remained intact during the experiments and have very good tissue compatibility and *in vivo* biodegradability which make them suitable for biomedical applications [76].

Two novel biodegradable polyphosphazenes have been synthesized. These polymers are poly[(ethyl oxybenzoate)phosphazene](*PN-EA*/*EOB*) and poly [(ethyl alanato)(propyl oxybenzoate)phosphazene] (*PN-EA*/*POB*). Biodegradability and percentage of water uptake of the polymers have been studied. Degradation and water absorption of *PN-EA*/*POB* is higher than of *PN-EA*/*EOB*. Both polymers support the adhesion and proliferation of rat osteoblast cells *in vitro*. Thus, these biodegradable amino acid based polyphosphazenes can be used for self-setting bone cements [77].

Ionic Conductors

Poly[bis(methoxyethoxy)ethoxy]phosphazene], *MEEP*, is the first polyphosphazene that exhibits ionic conductivity. It was made in 1984 [78]. A new series of electrolyte materials based on poly(organophosphazene) has been produced. The results show that the conductivity is decreased with the length of alkyl group side chain. These polymers have properties similar to *MEEP* and low dimensional stability. The branched polymers have bulk dimensional stability greater than those with linear side groups [79, 80]. Two new series of polymer electrolytes based on poly(bis(pentylaminophosphazene) (*PPAP*) and poly(bis(hexylamino)phosphazene) (*PHAP*) have been prepared with lithium perchlorate, $LiClO_4$. These electrolytes have good dimensional stability and ionic conductivity. The highest ionic conductivity is 7 times larger than that of the original polymer and is similar to the one of polyethylene oxide (*PEO*), at room temperature [81]. Dissolving lithium salts in *MEEP* results in an ionic conductor. This material is used for rechargeable lithium batteries. These batteries are non-flammable and have a low T_g [82]. Poly[bis(2,2,2-trifluoroethoxy)phosphazene], poly[bis(methoxyethoxyethoxy)phosphazene], and

poly[bis(4-hydroxyphenoxy)phosphazene] have been used as phosphazene substrates and in combination with metal alkoxide to produce three dimensional networks. The results show that ionic conductivity is increased when these materials are doped with Li^+ or Ag^+ triflates [83]. When sulfone or sulfoxide functional groups are introduced into the side groups of polyphosphazene, the attractive forces produced by these functional groups result in alkyloxy substituted polyphosphazene with high T_g. These materials are used as polymer electrolytes [84].

Novel polyphosphazenes as solid polymer electrolytes with aryloxy and oligoethyleneoxy side groups have been synthesized. Both types of polymers contain 50:50 molar ratios of aryloxy/oligoethyleneoxy groups, but they exhibit different properties. The co-substituent polymers have lower glass transition temperatures and better ionic conductivities and single substituent polymers have higher toughness and make very good films, however, have lower ionic conductivities [85].

New comb-like polymers with polyphosphazene backbone and poly(propylene oxide) side chains have been synthesized and characterized in the form of cross-linked salts in polymer electrolyte membranes. The ionic conductivities of these polymers are almost as high as those in *MEEP*-based polymer electrolytes [86].

Ionic conductivities of solid polymer electrolytes prepared from low molecular weight poly(organophosphazenes) with cross-linkable oligo(oxyethylene) have been studied. In this research the effects of the length of the oligo(oxyethylene) chain and the degree of cross-linking on the ionic conductivity have been investigated. The maximum ionic conductivity measured for all solid polymer electrolytes was 2.92×10^{-4} s/cm at 25°C [87].

Fiber and Film Forming Polyphosphazenes

The low T_g, flexibility, and microcrystallinity are necessary for good fiber and film forming. Recently, poly[bis(2,2,2-trifluoroethoxy)phosphazene] nanofibers have been produced by electrospinning tetrahydrofuran, methyl ethyl ketone, and acetone solutions. These fibers exhibit contact angles towards water in the range of 135–159° [88]. Also, poly[bis(trifluoroethoxy)phosphazene], *PBFP*, films from tetrahydrofuran solution have been produced and its fracture surface morphology has been studied by SEM (scanning electron microscope). Obtained results indicate that its morphology is similar to Kevlar [89]. In the other study, it was found that (poly[bis(4-benzylphenoxy)phosphazene], *PBPP*, has semicrystalline behavior and the mechanical properties of *PBPP* films depend on the amount of crystallinity. Also, these polymers in crystalline and amorphous forms show elastomeric properties and have strain-at-break higher than 350% [90].

Recently, producing nanofibers using polyphosphazenes and the feasibility of developing a bead free nonwoven nanofiber mesh from poly[bis(*p*-methylphenoxy)phosphazene] (*PNmPh*) by electrospinning has been studied. In this research, the results show that a solution of *PNmPh* in chloroform at a concentration range of 7–9% (w/v) can be electrospun to produce bead free fibers at room temperature. The average diameter of the fibers is 1.2 μ. The electrospun nanofibers mats supported the adhesion and proliferation of osteoblast cells [91].

Phosphazene Elastomers

Three types of molecular structures in polyphosphazene are known to impart elastomeric properties to the compound. If the side groups were single atoms such as F, Cl, Br, inherent flexibility results in elastomeric behavior. Linear side groups such as $-OCH_3$ and $-OC_2H_5$ provide chain flexibility due to polymer chain motions, molecular voids, and free volume. Also, the presence of alkoxy, aryloxy, and organosilicon units lead to rubbery properties. Fluorophosphazene is a fuel resistant elastomer at low temperature. Polymer composition and mole percent of fluorine are the controlling factor of optimum performance. This elastomer is used in military applications in a large range [92]. On the other hand, polyphosphazene elastomers are classified as polyhalophosphazenes and polyorganophosphazenes. Some of the polyorganophosphazenes have found commercial applications [93]. Fluorinated polyphosphazene elastomers are suitable for applications such as in the oil field [94]. Poly(fluoroalkoxyphosphazene) fluoroelastomers have very good stress-strain properties, low temperature flexibility, and thermal stability. These elastomers are suitable for seals, O-rings, and gaskets [95].

Polyphosphazen elastomers exhibit four times lower peak heat release rate than the polyurethane elastomers [96].

Conclusion

Polyphosphazanes with a wide range of interesting properties and applications comprise one of the most important classes of inorganic polymers. Some of the challenging areas of biomedical and advanced applications of these polymers are outlined as follows:

These polymers have been used to enhance selectivity and overall performance of thermally, mechanically, and chemically stable membranes. They also have found applications in electrodialysis, microfiltration, ultrafiltration, and reverse osmosis. In addition, they are used in water purification, fuel cell technology, and in the separation of mixtures of alcohols and various organic compounds and ions. Polyphosphazenes make ideal medical polymers. They are also the essential components in drug delivery systems and able to accept grafts of active components to create a carrier molecule for the pharmaceutical.

Polyphosphazenes are used as flame retardants, additives, performance polymers, and in special applications. Some more general applications of these polymers are O-rings, fluoroelastomeric seals, gaskets, insulating foams, and they are used in optic devices, polymer conductors, coatings, fiber and film formations, and rubbers.

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