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Sustained release of hydrophilic drug from polyphosphazenes/poly(methyl methacrylate) based microspheres and their degradation study

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ABSTRACT

Drug delivery system is referred as an approach to deliver the therapeutic agents to the target site safely in order to achieve the maximum therapeutic effects. In this perspective, synthesis of three new polyphosphazenes and their blend fabrication system with poly(methyl methacrylate) is described and characterized with ^{1}H NMR, ^{31}P NMR, GPC and DSC. Furthermore, these novel blends were used to fabricate microspheres and evaluated for sustain release of hydrophilic drug (aspirin as model drug). Microspheres of the two blends showed excellent encapsulation efficacy (about 93%), controlled burst release (2.3% to 7.93%) and exhibited sustain in vitro drug release (13.44% to 32.77%) up to 218 h. At physiological conditions, the surface degradation of microspheres and diffusion process controlled the drug release sustainability. Furthermore, it was found that the degree of porosity was increased with degradation and the resulting porous network was responsible for water retention inside the microspheres. The percentage water retention was found to be interrelated with degradation time and percentage drug release.

1. Introduction

Drug encapsulation with polymeric materials is a technical approach to deal with the problems associated with solubility, bioavailability and bio-distribution [1]. Polymeric drug delivery system (DDS) has increased the therapeutic efficacies of many drugs by maintaining the optimum therapeutic concentration level for long terms at local disease site [2,3]. For control release applications of therapeutic agents, polymeric vehicles such as micelles, microspheres or nanofibers are used to encapsulate and release them at control rate for a long time ranging from weeks to months. Among other polymeric drug delivery vehicles, polymeric microspheres provide sustain release profile, inhibit the sudden sharp increase concentration of drugs and can be used for inject or organ-target release [4]. Polyphosphazenes (PPHOSs) have a unique potential for biomedical applications, especially for DDS [5] and being evaluated for many biomedical applications [6] and tissue engineering [7]. PPHOSs are hybrid organic–inorganic macromolecules, containing conjugated nitrogen and phosphorus atoms in polymeric backbone and two organic groups directly attached with phosphorus via covalent bond. The precursor of PPHOSs is highly reactive intermediate poly(dichlorophosphazenes) (PDCP), which can be synthesized via ring opening polymerization of hexachlorocyclophosphazene (HCCP) in the presence of Lewis acid ($AlCl_3$) [8–10] or living cationic polymerization of phosphoranimine [11,12]. The desired properties for PPHOSs can be easily attained due to its versatile synthetic flexibility and the non-covalent binding ability of polymeric backbone to self-assembled supramolecular structures makes these polymers favorable for biological systems [13].

Caliceti et al. prepared the PPHOSs based microspheres with three different solvent evaporation methods and loaded therapeutic agent i.e. insulin. The resulting microspheres exhibited in vitro fast and slow release profiles for insulin [14]. In another study, Andrianov et al. synthesized poly[di-(carboxylatophenoxy)phosphazene] and sulfonated PPHOSs. Microspheres and nanospheres were fabricated for the control release of spermine [15]. Gudasi et al. synthesized the poly[bis(4-methoxy benzylamino)polyphosphazene] and poly[bis(4-methoxyphenethylamino)polyphosphazene] and checked their encapsulation and sustain release abilities of prepared microspheres for hydrophobic indomethacin and 5-fluorouracil hydrophilic drugs [16]. However, polymeric microspheres have integral problems like incapability to show variant drug release kinetics [17] and initial burst release [18]. The higher initial burst release increases the drug concentration level higher than optimum therapeutic concentration level, which causes cytotoxicity and is not physiologically favorable.

Another approach to achieve the required properties is the blend fabrication. Polymer blends have the ability to produce such materials,

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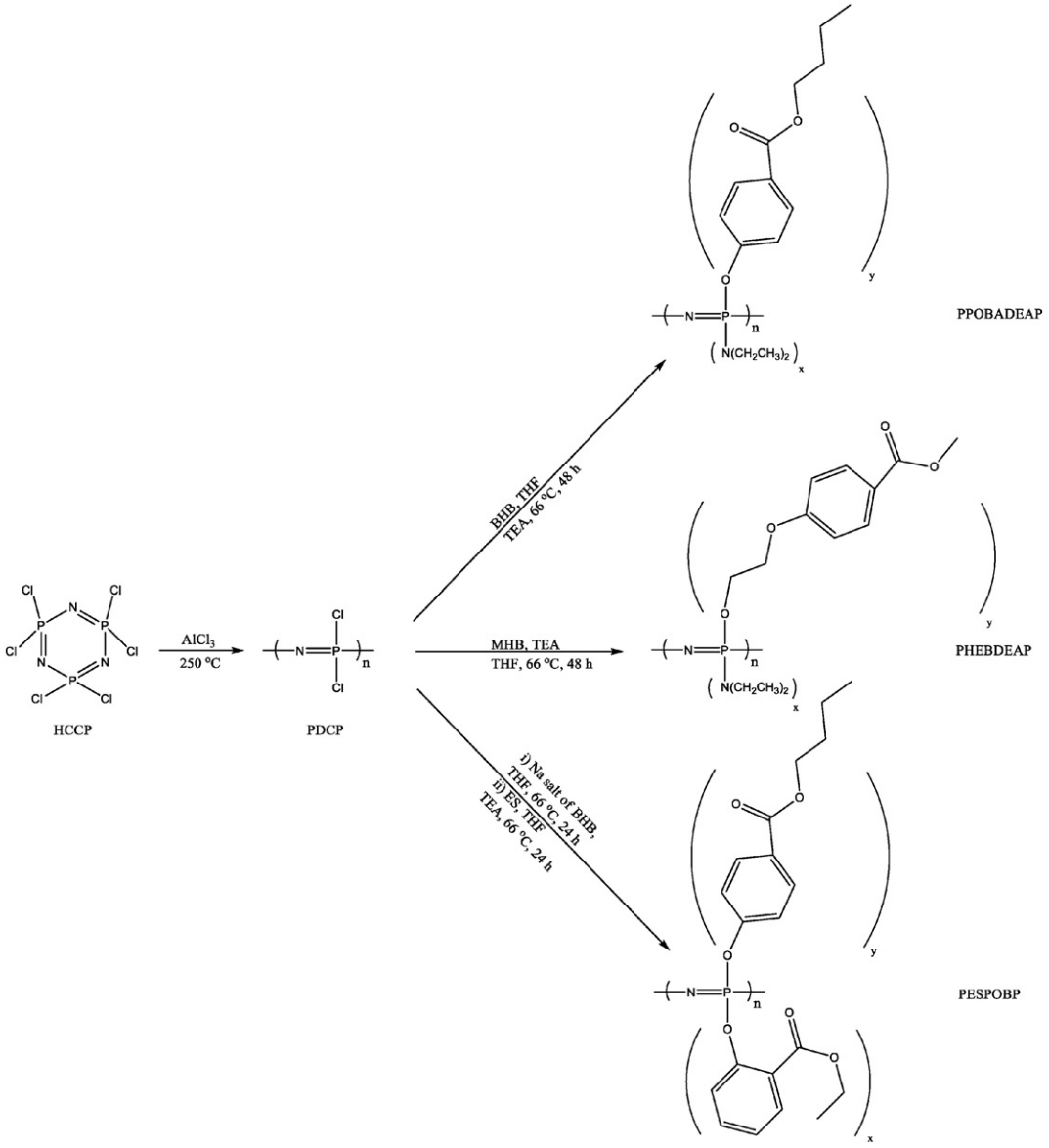

Scheme 1. Synthesis of PPOBADEAP, PEBDEAP and PESPOBP via macromolecular substitution of PDCP.

which are mechanically more stable and exhibited superior properties than their parent polymers [19]. Thus the degradation rate of PPHOSs can be controlled either by composition of side groups or the blend composition [20]. PPHOSs/poly(lactic-*co*-glycolic acid) (PLGA) blends have been used for many biomedical applications such as bone regeneration. However, PLGA produce acidic by-products, which are not physiologically favorable [21–23]. While, poly(methyl methacrylate) PMMA is hydrophobic, is a highly biocompatible polymer and has shown long in vivo tolerance in rats [24]. Previously PMMA was used to prepared cisplatin loaded cement/microparticles for local chemotherapy in bone tumor (malignant lesions in bone). Cisplatin was released from PMMA reservoirs via diffusion and targeted the tumor cells in bone [25–27]. Recently, the hydrophilic derivatives and nanocomposites of PMMA have been synthesized to prepare implants for local drug release and many other biomedical applications [28–32]. Furthermore, mechanical properties of microspheres prepared by PPHOSs/PMMA have significant influence in biomedical applications [33,34]. Therefore, it was hypothesized that the blending of PMMA with 75% of the degradable PPHOSs will prepare suitable drug loaded microsphere with control drug release properties for bone disease.

Here in this article considering the mechanical properties of PMMA and taking the idea of blending, three different PPHOSs were synthesized using different hydrophobic side groups and PMMA was selected for blend fabrication with these three synthesized polymers. In addition, microspheres were fabricated from these blends and aspirin was loaded. Previously, water soluble form of doxorubicin (DOX.HCl) [35] and cisplatin [36,37] was loaded to the polymeric microspheres and their tumor efficiency was evaluated. Here in this study, aspirin was chosen as a model hydrophilic drug. Moreover, drug release kinetics and in vitro degradation behavior were investigated.

Table 1
Characterization of PPOBADEAP, PHEBDEAP and PESPOBP.

Polymers	Molar ratio					Solubility	
	x	y	Mn	Mw	PDI	DMSO	$CHCl_3$
PPOBADEAP	0.67	1.32	1.12×10^4	2.09×10^4	1.85	Good	Good
PHEBDEAP	0.19	1.82	1.12×10^4	2.54×10^4	2.27	Good	Poor
PESPOBP	0.83	1.17	5.7×10^3	1.18×10^4	2.05	Good	Good