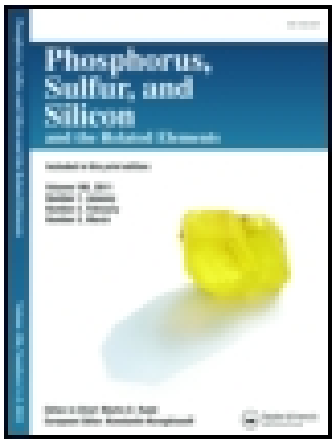

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A pH-Sensitive Drug Carrier Based on Maleic Acid-Substituted Cyclotriphosphazene

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A pH-SENSITIVE DRUG CARRIER BASED ON MALEIC ACID-SUBSTITUTED CYCLOTRIPHOSPHAZENE

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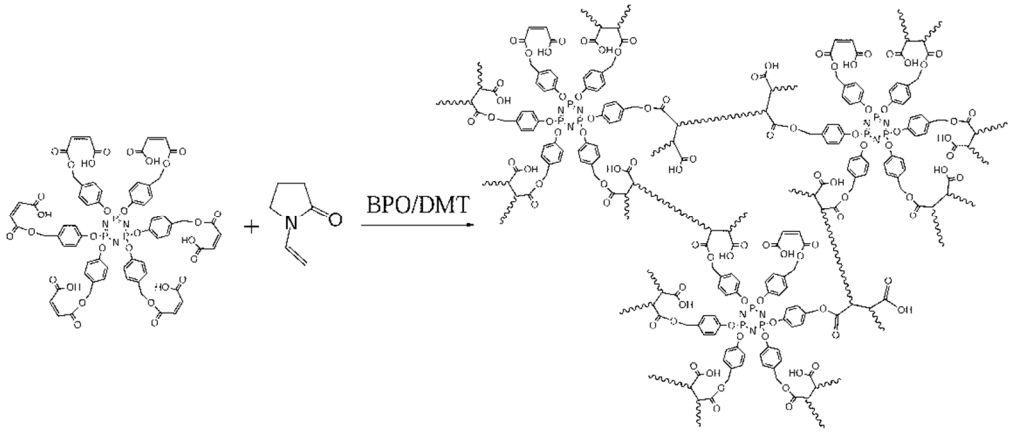
Abstract The cyclotriphosphazene derivative $N_3P_3[OC_6H_4$-*p*-$CH_2O(CO)CH=CH(CO)OH]_6$ bearing maleic acid groups was synthesized and characterized by NMR, FTIR spectroscopy and MS. A cross-linked network was produced by free radical copolymerization of this phosphazene derivative with *N*-vinyl-2-pyrrolidone. Swelling experiments indicated that the cross-linked network was highly sensitive to pH environments. In-vitro release studies have been performed in 2.0 and 7.4 pH media to simulate gastric and intestinal conditions. The results indicated a dependence on the pH of the release media and extent of crosslinking.



Keywords Cyclotriphosphazene; pH-controlled release; cross-linker; swelling; maleic acid

INTRODUCTION

Phosphazenes are a class of compounds having chemical structures based on repetitive P=N units. The class includes cyclic derivatives with three or four such units and polymers with a linear or branched skeletal structure. Phosphazenes have recently received a great deal of attention as potential biomaterials due to their synthetic flexibility,[1] high biocompatibility and distinctive degradation property.[2] The synthetic flexibility of phosphazenes has enabled the development of a wide range of phosphazene derivatives with a variety of physiochemical and biological properties. The degradable phosphazenes release phosphate, ammonia from the backbone and free organic side groups through hydrolysis reactions.[3] The produced phosphate can be metabolized and the ammonia excreted [2] The phosphate-ammonia solution creates a nearly neutral, pH-buffered medium. Blending a poly(Ŭ-hydroxyester) with a polyphosphazene provides a viable improvement to biomaterials based on acid-releasing organic polymers because the degradation products of the polyphosphazene neutralizes the acidic degradation products of the poly(Ŭ-hydroxyester).[3-7] Moreover, the degradation rate of the phosphazene can be tuned by choosing various side groups or changing co-substituent ratios.[2, 8]

Much research has been focused on developing polyphosphazenes for the purpose of tissue engineering and drug carrier applications.[7, 9-14] However, it is difficult to control exactly and reproducibly the purity and molecular weight of polyphosphazene because organic reactions carried out on polymer side groups are nearly always more challenging than on small molecules. Small molecule model cyclophosphazene reactions usually were carried out for providing a basis to plan the substitution reactions of poly(dichlorophosphazene).[10, 15-17]. The purity and molecular weight of the cyclophosphazene derivatives are easy to control, and thus reduce the

difficulty of synthesis. In this regard, design and synthesis of cyclophosphazene derivatives for the purpose of biomedical applications are preferable.

Remarkable progress has been achieved in recent decades in the synthesis and application of cyclotriphosphazenes for biomedical applications. A variety of novel cyclotriphosphazene derivatives, such as cyclotriphosphazenes containing vitamins,[16] oligopeptides,[18-20] drugs,[21-24], amino acids[15] and amino acid esters[25], or which can take on the form of hydrogels,[21-22, 25] micelles[19-20] or microspheres, has been developed.[24]

In this paper, we describe a new kind of degradable cyclophosphazene derivative, $N_3P_3[OC_6H_4$-*p*-$CH_2O(CO)CH=CH(CO)OH]_6$ (HMCP, Scheme 1), which can be used as a cross-linker to form a three-dimensional network. Maleic acid side groups provide double bonds that act as the cross-linking sites. Although maleic acid does not homopolymerize because of the polar effects, copolymerizations of this compound are possible.[26] The phosphazene backbone and the ester group provide hydrolytic instability. The ionization of carboxyl groups imparts water solubility and the capacity of forming a dual cross-link system with bivalent metallic ions. In this study, we investigated the cross-linking reaction of HMCP with *N*-vinyl-2-pyrrolidone (NVP) (Scheme 2) and the pH sensitive performances of the formed HMCP-NVP network. Preliminary results on the HMCP-NVP network as pH-dependent drug controlled release matrix are also reported.

RESULTS AND DISCUSSION

Synthesis and characterization of HMCP

HMCP was synthesized according to Scheme 1. DMAP was used as a MA ring-opening reaction catalyst for improving the yield. The oily product was purified by re-precipitation into diethyl ether, no further purification measures were taken.

The structure of the HMCP was confirmed with ^{1}H, ^{13}C, ^{31}P NMR, FTIR spectroscopy, and MS. The ^{1}H NMR spectrum (Fig. S1 in the Supplemental materials SM) of the HMCP showed a singlet at 5.16 ppm for methylene protons ($ArCH_2O$). The multiplets at 6.38-6.43 ppm were assigned to the ethenyl protons (CH=CH). Resonances appearing at 6.90-6.87ppm and 7.30-7.32 ppm were assigned to the aromatic protons. In the corresponding ^{13}C NMR spectrum (Fig. S2 in the SM), the carbonyl carbon atoms of ester and carboxy groups were observed at 165.6 and 167.0 ppm, respectively. The double bond carbon (C=C) resonated at 130.2 and 132.5 ppm. ^{13}C NMR spectra of the methylene groups showed resonance at 65.9. Other chemical shifts (ppm) were assigned to the aromatic carbon resonances: 150.2 (CO), 133.2 (C), 128.6 (CH), 120.9 (CH). In the ^{31}P NMR spectrum of HMCP (Fig. S3 in the SM), a singlet appearing at 8.91ppm indicated that the substituted reaction onto CP ring was complete. In the FTIR spectrum of HMCP (Fig. S4 in the SM), the characteristic absorption bands due to the maleic acid moiety were observed at 1735 cm^{-1} (C=O stretching vibration), 1643 cm^{-1} (C=C stretching vibration), 3000-2500 cm^{-1} (OH stretching vibration), 1198 cm^{-1} (symmetric stretching of C-O-C), 1417 cm^{-1} (asymmetric bending of CH_2). The wave numbers from 700 to 900 cm^{-1} and at 1507 cm^{-1} are assigned to the disubstituted benzene ring. Two strong absorption peaks located at 957 cm^{-1} and 1163 cm^{-1} are due to stretching of P-O-Ar and N=P, respectively. The MALDI-TOF mass spectrum confirmed the expected chemical composition with a *m/z* value of 1484.18, corresponding to the $(M+Na)^{+}$ ion.

Crosslinking reaction and compressive testing

The cross-linked network of HMCP-NVP was prepared in the composition as listed in Table 1. Upon the HMCP, NVP and free radical initiator mixing and increasing the temperature to 37 °C, the solutions will rapidly solidify in 10 min due to the free radical polymerization mechanism (Scheme 2). The specimens were kept at 37 °C for 24 h in order to get a complete reaction of the monomer. The extent of cross-linking of HMCP-NVP network was evaluated by compressive testing. The compressive strength at yield, fracture strength and compressive modulus of the cross-linked specimens were measured (Table 1). An increase in HMCP provided more cross-linking points and resulted in shorter poly NVP cross-links, which created a more densely cross-linked polymeric network. Therefore, an increase in the HMCP/NVP ratio resulted in an increase in compressive strength at yield, compressive modulus, and fracture strength. The compressive strengths and compressive modulus of the sample with equal HMCP and NVP in mass were 11.5 MPa and 215.2 MPa, values which were closer to those of human cancellous bone.[27] Therefore, the HMCP-NVP copolymer could be used as a potential injectable bone repair material for replacing the non-degradable PMMA bone cement. Further improvement of the mechanical property of the HMCP-NVP network may be brought about by reinforcement with hydroxyapatite. Although the mechanical properties of specimens with low HMCP/NVP ratio were insufficient for replacement of human bone, they hold promise for the engineering of softer orthopedic tissues such as cartilage. The mechanical property study demonstrated the feasibility of the cross-linked network with tailored mechanical properties by varying the HMCP/NVP ratio.

Equilibrium swelling studies

The pH-dependent equilibrium swelling of the HMCP-NVP networks were studied both in the simulated gastric and intestinal pH conditions using pH 2.0 and pH 7.4 phosphate buffer, respectively (Fig. 1 and Fig. 2). The HMCP-NVP network swelled in pH 7.4 PBS but shrank in pH 2.0 PBS. This different swelling behavior in acidic and neutral media clearly indicated that the matrix was pH sensitive. The swelling ratio in water has a relation to extent of cross-linking and the affinity of the matrix to water. At pH 7.4, the ionization of carboxyl groups increased the hydrophilic nature of the matrix. The lowered intermolecular interaction force by the dissociation of hydrogen bonds, together with the electrostatic repulsion between the ionized groups created a large swelling force and brought about a significant swell. At pH 2.0, the deprotonated carboxyl groups in HMCP decreased the hydrophilic nature of cross-linked network and lowered the affinity of the matrix to water. Moreover, the hydrogen bond between carboxyl groups increased the intermolecular interaction force, increasing the network shrink force. The unreacted monomer and homopolymer of NVP dissolved into water under the shrink force, which led to the shrinkage of the sample. The different crosslinking density also leads to differences in equilibrium swelling. An equilibrium swelling of 71.2% was observed for samples with low content of HMCP compared with 40.2% of samples with high content of HMCP in pH 7.4 media. In this research, HMCP played the role of a multifunctional cross-linker, so more cross-linking structure should be formed as more HMCP was used, which resulted in the lowest swelling ratio. At the same time, more cross-linking structure would decrease the formation of water-soluble homopolymer of NVP, therefore lowered the shrink ratio of cross-linked samples in pH 2.0 media.

pH-Sensitive drug release behaviors

To understand the drug release behaviors from the 5-FU-loaded HMCP-NVP cross-linked network, in vitro release experiments were carried out under gastric and intestinal pH conditions. 5-FU loading concentration was 100 mg/g. The initial weight of the drug-loading sample was 0.1040±0.0011g. Fig. 3 and Fig. 4 showed that the release profiles of 5-FU from HMCP-NVP network at pH 7.4 and pH 2.0 at 37 °C as a function of time. In general, it was found that the HMCP-NVP network in neutral media had a shorter half drug release time. The percentage of drug released increased with an increase in pH of PBS, within 1 h, 54.6% of 5-FU was released from the samples with high crosslinking density (HMCP/NVP = 1.0/1.0) at pH 7.4 but 13.9% at pH 2.0. This behavior showed that drug release profiles of HMCP-NVP network were pH-sensitive.

The swelling characteristics of HMCP-NVP network have a significant influence on the diffusion behavior of drug molecules through the matrix. At pH 7.4, the loose network due to the swelling and the hydrophilic nature of matrix raised the permeation ability of the drug. On the contrary, in acidic media, the compact matrix arising from the shrinking and the higher hydrophobicity hindered the drug transport. The initial burst effect may be attributed to the release of drug entrapped towards the surface of the matrix. For different formulations in the same pH medium, as the ratio of HMCP/NVP increased, the HMCP-NVP had a longer half drug release time due to the higher crosslinking density. To some extent, the release rate of 5-FU can be tuned by the ratio of HMCP/NVP.

CONCLUSIONS

A new multifunctional cyclic trimeric phosphazene derivative containing maleic acid was synthesized and a biodegradable HMCP-NVP cross-linked network based on this compound was

prepared by free radical polymerization. The mechanical property measurement suggested that this network might find applications as injectable tissue engineering scaffolds. The equilibrium swelling measurements and in vitro release behavior of 5-FU in simulated fluids indicated the pH responsive nature of this network. The results implied that the HMCP-NVP network could be exploited as potential drug carriers for the localized oral drug delivery to the gastric environment.

The formation of HMCP-NVP network showed that the multifunctional cyclic trimeric phosphazene was an effective network-forming molecule for the creation of degradable polymer networks. It should be appropriate for crosslinking with any acrylate or other vinyl monomers by free radical polymerization. By varying the vinyl monomer, it should be possible to get cross-linked polymer materials with various properties and applications in biomedical field.

EXPERIMENTAL

Materials. Hexachlorocyclotriphosphazene was synthesized according to the literature,[28] and was recrystallized from dry hexane followed by sublimation (60 °C, 0.05 mm Hg) before use. Maleic anhydride (MA), 4-dimethylaminopyridine (DMAP), tetrahydrofuran (THF), $NaBH_4$, benzoyl peroxide (BPO), 4-hydroxybenzaldehyde, methanol, and K_2CO_3 were gained from Sinopharm Chemical Reagent Co., Ltd., China. 4-Hydroxybenzaldehyde was purified by recrystallization from water. $K_2CO_3$was dried at 140 °C. THF was freshly distilled under nitrogen from sodium-benzophenone ketyl. NVP was purchased from Merck Company and purified by distillation. *N,N*-Dimethyl-*p*-toluidine (DMT) was acquired from Acros. 5-Fluorouracil (5-FU) was obtained from Tianjin Central Pharm. Co., Ltd.

$N_3P_3(OC_6H_4$-*p*-CHO)$_6$ was prepared according to the literature[29] with minor modification. 4-Hydroxybenzaldehyde (25.20 g, 0.206 mol) was dissolved in dry THF (300 mL). To this solution was added K_2CO_3 (45.50 g, 0.33 mol). The mixture was stirred at room temp. for 30 min. A solution of hexachlorocyclotriphosphazene (10.00 g, 0.0288 mol) in THF (50 mL) was added drop-wise to the reaction mixture over 1h. After stirring at refluxing temperature for 48 h, the reaction mixture was concentrated in a rotary evaporator and washed with 800 mL of water. The crude product was then recrystallized from ethyl acetate to yield white crystalline $N_3P_3(OC_6H_4$-*p*-CHO)$_6$. Yield 77.5%, m. p. 160-162 °C. ^{1}H NMR (DMSO-d$_6$, TMS, ppm): 9.95(1H, CHO), 7.19-7.82(4H, dd, ArH). ^{13}C NMR (DMSO-d$_6$, TMS, ppm): 192.0 (C=O), 154.1 (C-O), 134.1 (C-C), 131.9 (CH), 121.5(CH). ^{31}P NMR (DMSO-d$_6$, ppm): 7.64.

Reduction of $N_3P_3(OC_6H_4$-*p*-CHO)$_6$ was carried out following the literature procedure[30] with minor modification. $N_3P_3(OC_6H_4$-*p*-CHO)$_6$ (6.00 g, 7 mmol) was dissolved in dry THF-methanol (400 mL, 1:1). To this solution was added $NaBH_4$ (1.70 g, 0.045 mol), and the mixture was stirred at room temperature for 14 h. The solvent was evaporated by a rotary evaporator. The residue was recrystallized from EtOH-H_2O (9:1) to give 3.93 g white crystalline $N_3P_3(OC_6H_4$-*p*-$CH_2OH)_6$. Yield 65.5%, m. p. 228~231 °C, ^{1}H NMR (DMSO-d$_6$, TMS, ppm): 7.21-6.80 (4H, dd, ArH), 5.23 (1H, OH), 4.48-4.47 (2H, CH_2). ^{13}C NMR (DMSO-d$_6$, TMS, ppm): 149.1 (C-O), 139.9 (C-C), 128.2 (CH), 120.6(CH), 62.8 (CH_2). ^{31}P NMR (DMSO-d$_6$, ppm): 8.88.

$N_3P_3[OC_6H_4$-*p*-$CH_2O(CO)CH=CH(CO)OH]_6$. $N_3P_3(OC_6H_4$-*p*-$CH_2OH)_6$ (3.00 g, 3.44 mmol) was added in 240 mL dry THF (240 mL). The mixture was refluxed until the formation of a homogeneous solution. To this solution was added MA (3.03 g, 0.0309 mol) and DMAP in 60 mL THF over 30 min. After refluxing for 24 h, the reaction mixture was cooled and filtered. The

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filtrate was concentrated with a rotary evaporator; the residue was purified by reprecipitation into ethyl ether (three times) to yield 2.19 g yellowish oily product. Yield 43.6 %.

Characterization

The structure of the compounds was verified by solution-state ^{1}H, ^{13}C and ^{31}P NMR spectroscopy using a Bruker AV400 NMR spectrometer at a proton frequency of 400 MHz as well as the corresponding phosphorus frequency at room temperature. FT-IR spectra were recorded in KBr matrix using a Bruker VERTEX 70 spectrometer in the 4000ï 400 cm^{-1} range. The molecular weight of $N_3P_3[OC_6H_4$-*p*-$CH_2O(CO)CH=CH(CO)OH]_6$ was analyzed using time-off light mass spectroscopy with positive-mode electrospray ionization on a Bruker Daltonics Inc. MALDI-TOF. Figures S 1 ï S 4 (Supplemental Materials) provide sample NMR and FT-IR spectra for HCMP

Crosslink reaction and compressive testing

The HMCP was dissolved in the appropriate amount of NVP. DMT was added into the solution, followed by the BPO, which was dissolved in the remaining NVP. The mixture was placed in the Teflon molds (ū 6×12 mm). After a 24 h period at 37 C in order to get a complete reaction of the monomer, the cylinders were removed. The mechanical properties were measured according to ISO5833:2002(E) and carried out on a universal WDW-20 Electronic Materials Testing System at room temperature. The cross-linked samples were compressed at a cross-head speed of 1 mm min^{-1} until failure, with the stress versus strain curve recorded throughout. Five replicate specimens were prepared for compression testing.

Swelling studies

The cross-linked samples (Φ4.5×5 mm) were incubated in 20 ml of 0.1M PBS with pH was 7.4 or 2.0. The swelling study was carried out at 37 °C until equilibrium was attained. The percentage equilibrium swelling was equal to $[(W_t-W_0)/W_0]\times100\%$, where W_0 is the initial weight and W_t is the weight of the sample at time t.

***In vitro* drug release studies**

In order to incorporate a model drug into the system, the crosslinking reaction was performed in the presence of the drug. In this work, a model drug, 5-FU, was mixed in the monomer mixture at a concentration of 10 wt %. Upon polymerization, the network was formed and the drug was trapped inside the matrix. The resulting samples were washed with distilled water, dried, and stored until further use. The in-vitro release of the entrapped 5-FU was carried out by placing the samples (Φ4.5×5 mm) into 20 ml of PBS with pH = 7.4 or 2.0 at 37 C and shaken at 60 r.p.m. on an orbital shaker. At predetermined time points, the PBS medium was replaced and tested at 265 nm using UV-VIS spectrophotometer (Shimadzu UV-2550).

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Table 1 Composition and mechanical properties of the HMCP-NVP network formulations.

Formulation	HMCP/NVP (g/g)	BPO (wt%)	DMT (wt%)	Compressive Yield Strength (MPa)	Compressive Modulus (MPa)	Fracture Strength (MPa)
F1	0.50/1	1	1	2.7±0.3	30.6±7.1	77.4±4.5
F2	1/1	1	1	11.5±0.2	215.2±28.9	160.6±3.3

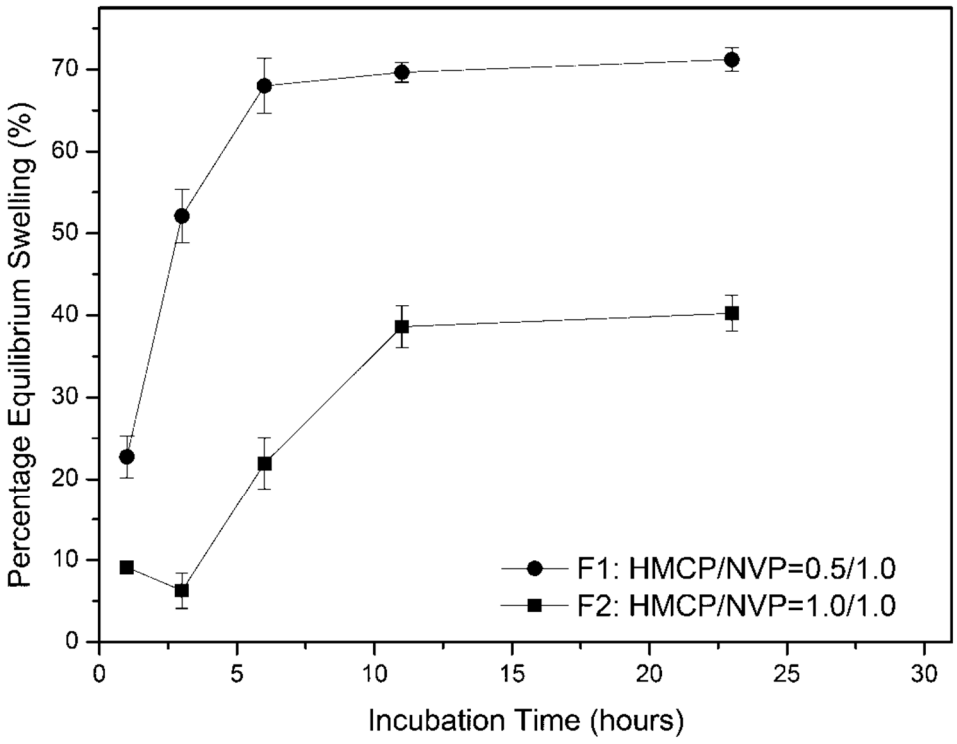


Figure 1 Effect of HMCP/NVP on swelling of cross-linked products in pH=7.4 PBS. Data represents the mean ± SD.

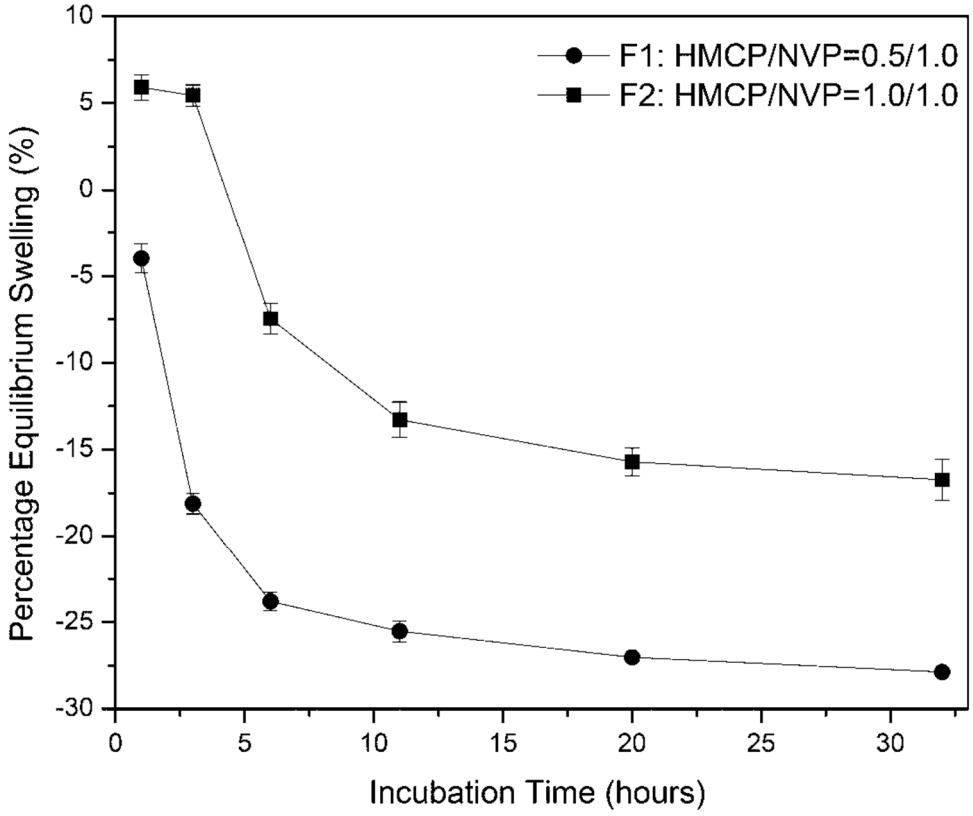


Figure 2 Effect of HMCP /NVP on swelling of cross-linked products in pH=2.0 PBS. Data represents the mean ± SD.

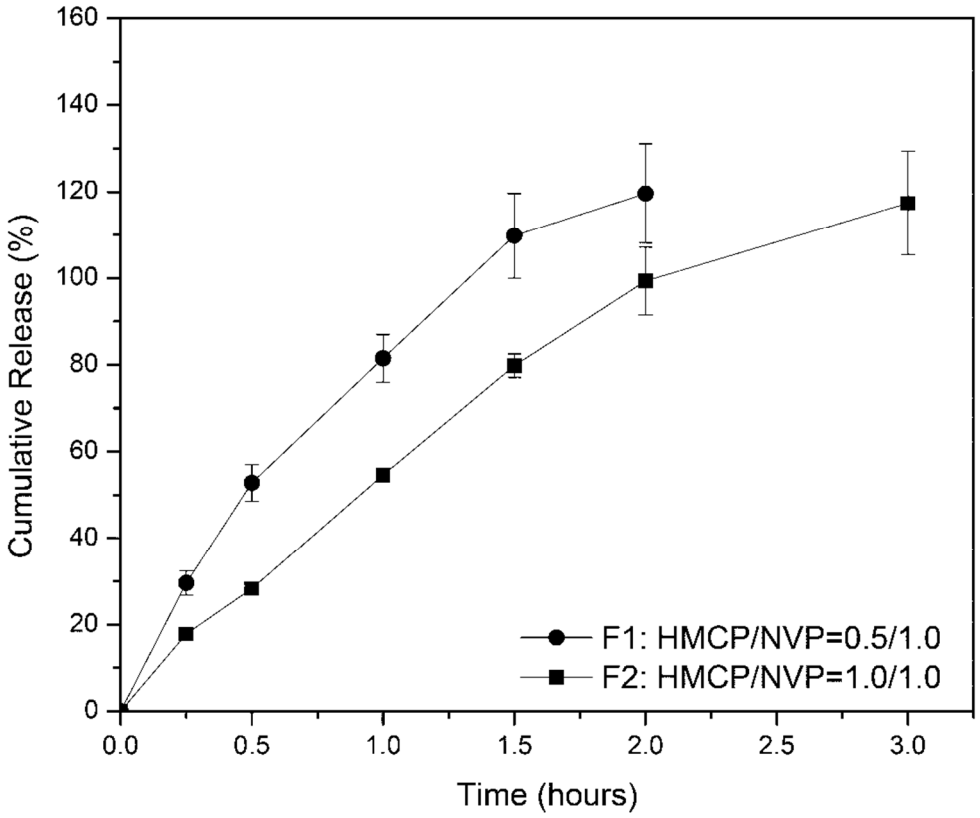


Figure 3 Effect of HMCP /NVP on drug release of cross-linked products in pH=7.4 PBS. Data represents the mean ± SD.

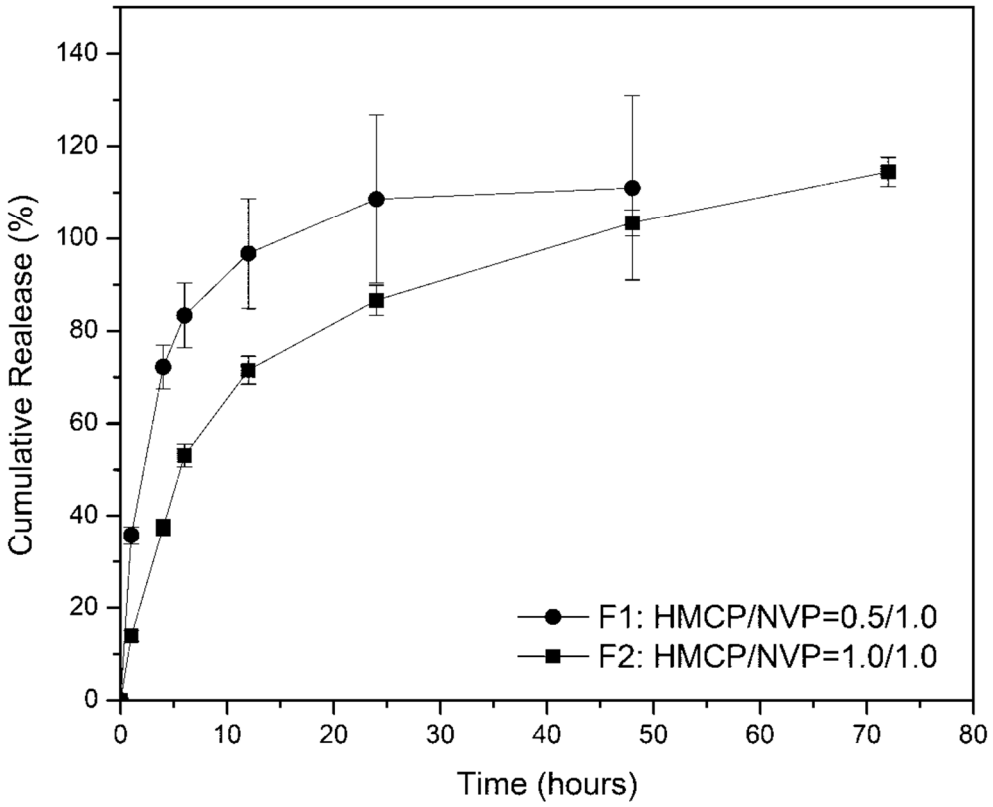
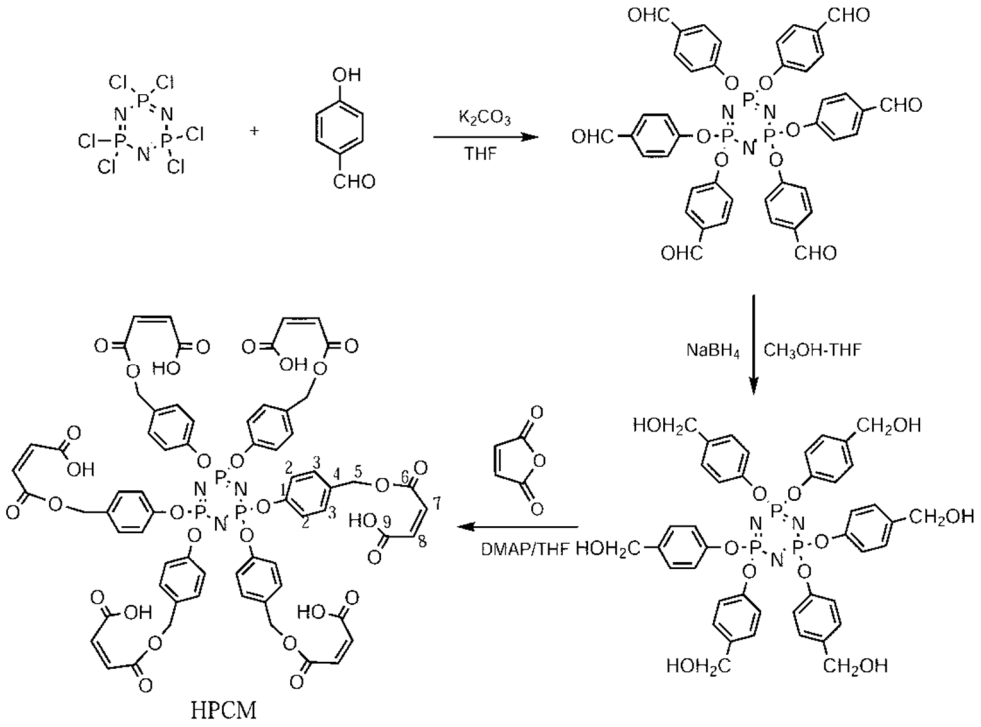
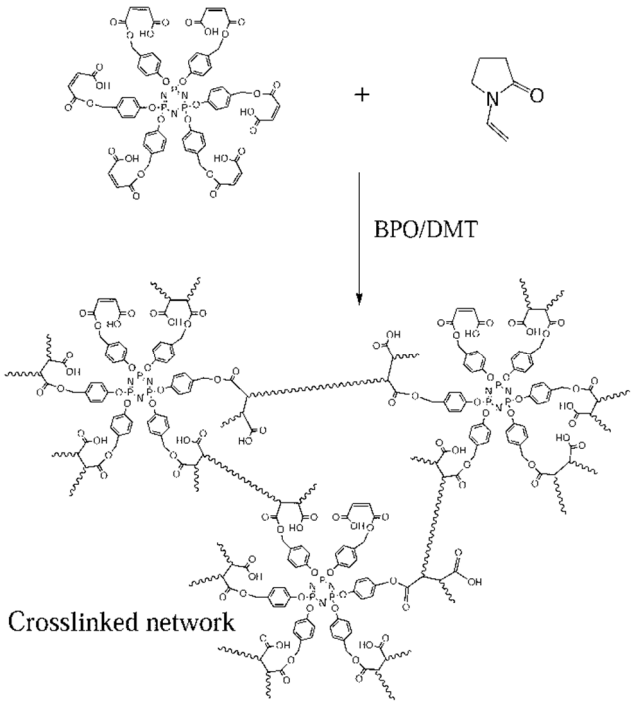


Figure 4 Effect of HMCP/NVP on drug release of cross-linked products at pH = 2.0 PBS. Data represents the mean ± SD.



Scheme 1: Synthesis route for $N_3P_3[OC_6H_4$-*p*-$(CH_2O(CO)CH=CHCOOH)]_6$.



Scheme 2: Cross-linking reaction of HMCP and NVP.