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Preparation and Characterization of Intrinsically Fluorescent Polyphosphazene Microspheres

Simge METİNOĞLU ÖRÜM *[1]

Abstract

The novel polyphosphazene and cyclomatrix type microspheres were synthesized via a one-pot self-assembly polycondensation method. Octachlorocyclotetraphosphazene and two fluorescent compounds; fluorescein and curcumin were used as a crosslinker and monomers, respectively. The prepared microspheres were characterized by SEM, EDX, FTIR, XRD, UV-vis techniques. Also, the fluorescence properties of the microspheres were investigated. The microspheres exhibited fluorescence emissions both in ethanol and as solid-state when excited at 470 nm. The optimum pH was determined as 9.0 for fluorescence measurements. Owing to fluorescent properties of the microspheres, the delivery of curcumin from the prepared microspheres, and cell imaging can be investigated in the future. It is thought that the obtained intrinsically fluorescent polyphosphazene microspheres have the potential for use as sensors and labels, also.

Keywords: Polyphosphazene, fluorescence, fluorescein, curcumin, microsphere

1. INTRODUCTION

Polyphosphazenes are inorganic-organic hybrid polymers that include alternating –P=N– groups [1]. Cyclomatrix type polyphosphazenes are highly crosslinked materials that can be facilely prepared via a one-pot polycondensation and self-assembly process. A cross-linker phosphazene compound (hexachlorocyclotriphosphazene; HCCP or octachlorocyclotetraphosphazene; OCCP) and monomer including two or more donor atoms are used in their synthesis [2]. Owing to the substitution of organic side groups for phosphorous atoms of phosphazene rings, phosphazene compounds have been gain various features such as catalysts [3], flame retardants [4], adsorbents [5], protic ionic liquids (PILs) [6], organic light-emitting diodes [7], fluorescent chemosensors [8], bioactive agents (such as antituberculosis [9], anticancer [10], DNA cleavage and antimicrobial agents [11]), biomaterials [12]. Additionally, due to being biodegradable and biocompatible, they are used for tissue engineering [13], drug delivery [14] and controlled drug release [15] applications.

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In recent years, apart from these applications of the polyphosphazenes, their fluorescence properties and applications have been attracted attention. Especially, in the past decade, intrinsically fluorescent cyclomatrix and highly cross-linked polyphosphazene nano/microspheres were synthesized containing amine [16, 17] or hydroxyl [18-20] derivative monomers. Their fluorescent applications such as sensor to detection of metal ions (Fe^{3+}, Hg^{2+}) [17, 21], picric acid [22], nitroaromatic explosives [16], dopamine [23]; cell or tumor imaging [24, 25] and drug delivery [26] were investigated.

Fluorescein is the most popular organic fluorescent dye. It is generally used as a fluorescent sensor or label. But, it can not be used with all solvents and its photobleaching property is not good [27]. Also, its leakage from the host is still a serious problem when encapsulated in nanomaterials [28]. On the other hand, curcumin is a natural anticancer drug and biologically active compound besides, it is also a fluorescent molecule. It can be used for confocal imaging [29], cell tracking [30], and sensing [31].

The aims of this study are to obtain cross-linked polyphosphazene microspheres that are novel, highly cross-linked, intrinsically fluorescent, and containing an anticancer drug. For this purpose, novel cyclomatrix polyphosphazene microspheres were prepared by self-assembly polycondensation using fluorescein, curcumin, and OCCP as monomers and crosslinker. Fluorescein was used to gain fluorescence properties to the microspheres. Curcumin was chosen both as an anticancer drug and as a fluorescent compound. The microspheres were obtained just in 4 hours using an ultrasonic bath. The microspheres gained fluorescent features by means of monomers. It was determined that they exhibited fluorescence emissions both as ethanolic dispersion and as solid-state. The optimum pH was determined as 9.0. It is thought that the delivery of curcumin from the synthesized microspheres, and monitoring fluorescently can be investigated in the future. In addition, the prepared novel and intrinsically fluorescent polyphosphazene microspheres will open a gate for preparing new fluorescent polymers and they have great potential for sensor applications.

2. EXPERIMENTAL

2.1. Materials and Methods

Octachlorocyclotetraphosphazene (OCCP) was used after recrystallization using n-heptane. Curcumin, fluorescein, triethylamine (TEA), acetone and ethanol were purchased from Sigma-Aldrich.

Scanning Electron Microscopy (SEM) images and Energy-Dispersive X-ray analysis (EDX) of prepared microspheres were recorded by ZEISS geminiSEM 500 electron microscope at an accelerating voltage of 3 kV. Perkin Elmer FTIR Spectrometer Spotlight 400 Imaging System was used for Fourier Transform Infrared Spectroscopy (FTIR) measurements of the microspheres, OCCP, curcumin and fluorescein. X-ray diffraction (XRD) pattern was recorded by using a Bruker AXS, D8 Advance instrument equipped with Cu Kα radiation at 40 kV and 40 mA. The UV–vis spectra of curcumin, fluorescein and microspheres were measured by the PG Instruments T60 Model UV–vis spectrophotometer. The fluorescence experiments were performed by the LS-55 Fluorescence Spectrometers.

2.2. Synthesis of the Microspheres

Fluorescein (0.072 g; 0.216 mmol), curcumin (0.080 g; 0.216 mmol) and OCCP (0.100g; 0.216 mmol) were dissolved in 50 mL acetone in a round bottom flask using ultrasonic irradiation (53 kHz, 150 W). After 15 minutes, TEA (3mL) was added to the reaction. The colour of the reaction medium changed to red from orange. The reaction was finished 4 hours later. The precipitated yellow product was separated by centrifugation at 4500 rpm, for 10 min and washed with acetone, distilled water and ethanol, respectively. Finally, the obtained polyphosphazene microspheres were dried under vacuum at 45 °C.

3. RESULTS AND DISCUSSIONS

3.1. Preparation of the Microspheres

The synthesized reaction and crosslinked structure of the prepared microspheres are illustrated in Figure 1. The fluorescent compounds; fluorescein and curcumin were reacted with phosphazene; OCCP to obtain intrinsically fluorescent polyphosphazene microspheres via a one-pot self-assembly polycondensation. In the synthesis procedure, TEA was used as a catalyst and an acid acceptor which absorb HCl and form TEA.HCl salt during the reaction [32]. In the formation mechanism of the microspheres, hydroxyl groups of fluorescein and curcumin react with phosphorous atoms of OCCP rings. In this way, the crosslinked oligomeric species are formed. Then, the oligomers aggregate together and primary nucleus particles are obtained. The stable particles generate via aggregation of the primary nucleus particles by hydrogen bonds. The stable particles grow by absorbing oligomers and highly crosslinked, solid, inorganic-organic hybrid, and contained hydroxyl groups on their surfaces polyphosphazene spheres are obtained [33].

3.2. Characterization

The characterization of the microspheres was performed by SEM, EDX, XRD, FTIR, and UV-vis techniques. SEM images of the synthesized polyphosphazene particles are seen in Figure 2. It was determined that the particles were spherical and micro-sized. In Figure 3, EDX results show that the microspheres have fluorescein and curcumin in their structures due to including 60 % C, 19.48 % O. Phosphorus and nitrogen atoms belonging to OCCP rings were determined as 7.94 % and 10.25 %, respectively. Also, the microspheres contain just 2.32 % unreacted Cl atoms owing to steric hindrance. Thus, it was seen that the microspheres were highly crosslinked.

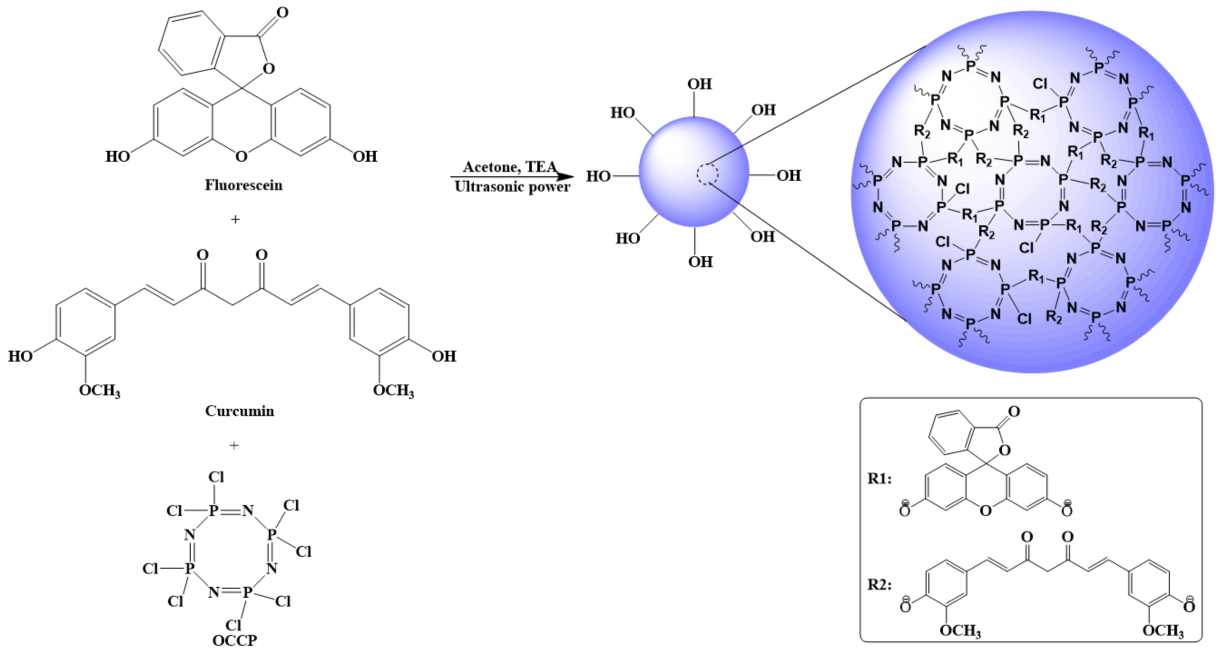


Figure 1The synthesis reaction and crosslinked structure of the polyphosphazene microspheres

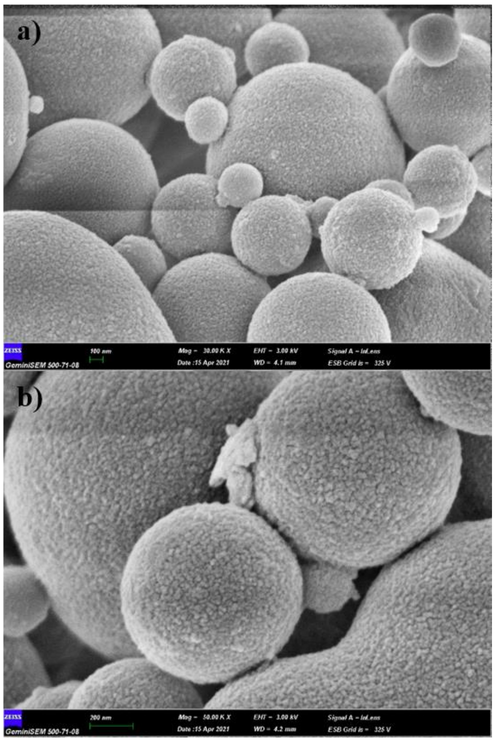
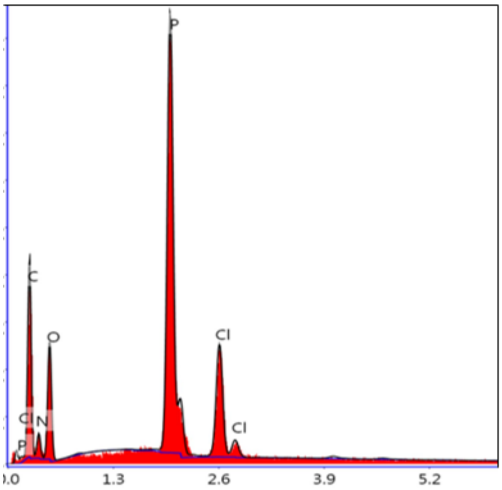


Figure 2 SEM images of synthesized polyphosphazene microspheres at different magnifications a) 30.00 KX, b) 50.00 KX.



Element	Weight %	Atomic %
C K	47.91	60
N K	9.55	10.25
O K	20.72	19.48
P K	16.34	7.94
ClK	5.48	2.32

Figure 3 EDX results of the microspheres

XRD pattern of the microspheres is illustrated in Figure 4. The wide diffraction peak at about 24 θ showed that the microspheres were amorphous. The peaks of the fluorescein, curcumin and TEA.HCl salt were not seen in the XRD pattern. Hence, it is seen that the microspheres were purified from monomers and salt [34].

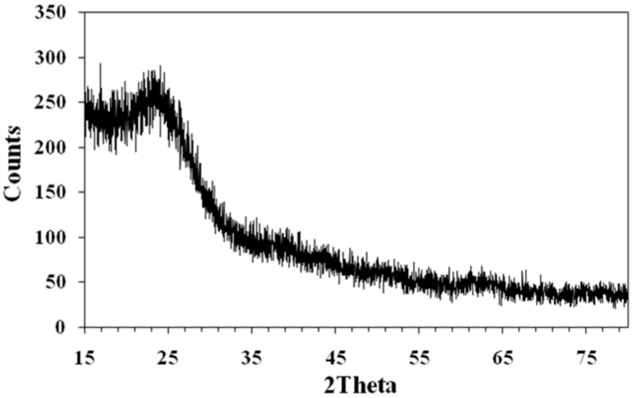


Figure 4 XRD pattern of the microspheres

The FTIR spectra of the curcumin, fluorescein OCCP and the obtained microspheres were recorded to explain the bonding of monomers with OCCP (Figure 5). The peak at 1766 cm^{-1} (a) indicates the carbonyl group arising from the lactone ring based on fluorescein. It is understood that the microspheres have fluorescein moieties. The absorbance at 1600 cm^{-1} (b) is attributed to the C=C bond. It is seen that the absorbances at 1498 cm^{-1} (c) and 1155 cm^{-1} (f) which corresponded to C=O and C-O ($O-CH_3$) bonds of curcumin, respectively, demonstrated including curcumin of the microspheres. The peaks at 1239 cm^{-1} (d) and 1213 cm^{-1} (e) belong to the P=N group of the OCCP ring in the crosslinked structure of the microspheres. The most important absorbance at 970 cm^{-1} (g) is attributed to P-O-Ar shows that bonded of curcumin and fluorescein to OCCP rings. Also, the peak at 494 cm^{-1} (h) corresponds to the P-Cl bond demonstrating that the microspheres have a few amounts of unreacted chloride atoms owing to steric hindrance. It is understood from the FTIR results that the bonding and polycondensation between OCCP, curcumin and fluorescein were accomplished successfully.

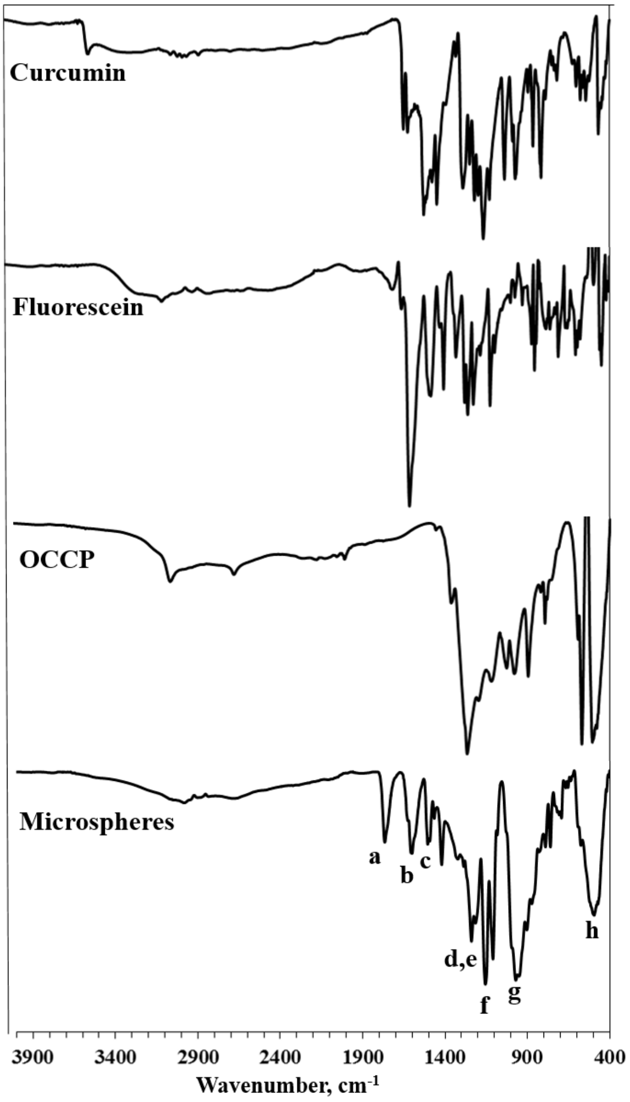


Figure 5 FTIR spectra of curcumin, fluorescein, OCCP and the microspheres

In Figure 6, UV-vis spectra of the microspheres, fluorescein and curcumin in ethanol are seen. It was determined that fluorescein, curcumin and the microspheres demonstrated absorbance peaks at 457, 485; 425; 458 nm, respectively. Due to the highly crosslinked structure, the microspheres show a wide absorbance spectrum.

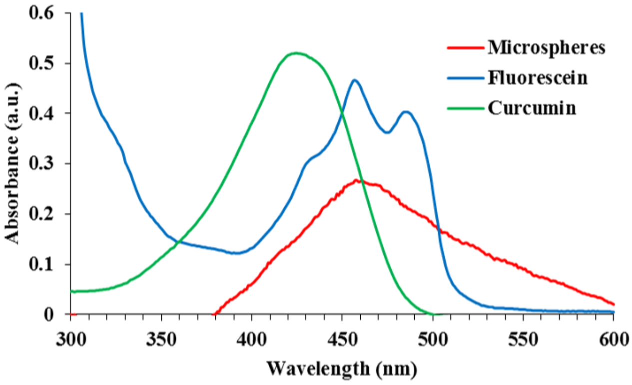


Figure 6 Uv-vis spectra of the microspheres (1.0 mg/mL), fluorescein and curcumin

3.3. Fluorescence Studies

The fluorescence emissions of the microspheres, fluorescein and curcumin were compared in ethanol and solid-state, in Figure 7. As can be seen in Figure 7a, the microspheres, fluorescein and curcumin exhibited fluorescence emissions at 528, 515 and 525 nm, in ethanol, when excited at 470 nm light, respectively. It was thought that the fluorescence emission peak of the microspheres is red-shifted due to the bonding of curcumin and fluorescein changing the energy gap for the electron transition of curcumin and fluorescein in the microspheres [24].

The microspheres exhibited wide fluorescence emission at 536 nm as solid when excited at 470 nm, in Figure 7b. The fluorescein and curcumin showed very weak fluorescence emissions at 619 and 562 nm, respectively, due to aggregation-induced quenching when compared with the microspheres.

The OCCP rings are nonconjugated systems for electron transfer without any resonance between alternating P−N and P=N bonds. Thus, they are photochemically inert and act as spacers to isolate fluorescein and curcumin in the microspheres [26]. So, the electron and energy transfer between the fluorescein and curcumin were blocked effectively in microspheres. Hence, the microspheres exhibited fluorescence emissions-reducing fluorescence quenching in both ethanol and solid states.

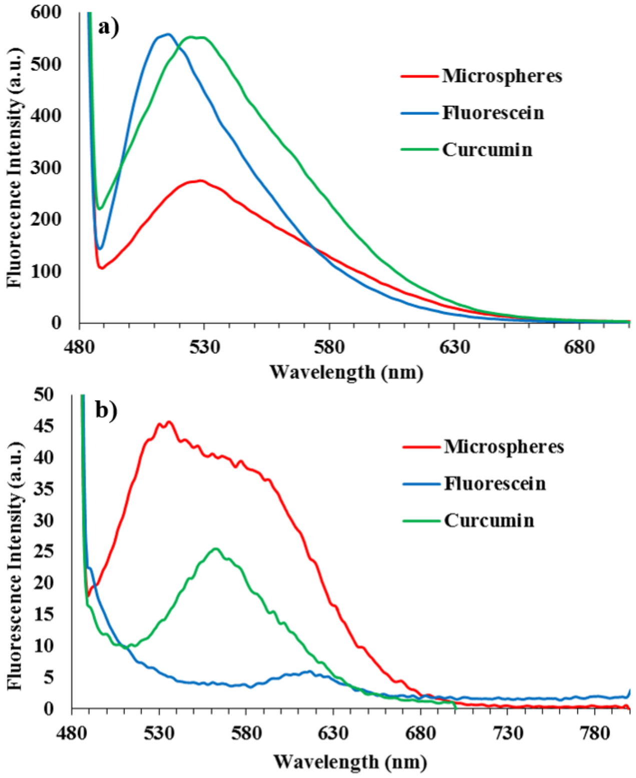


Figure 7 a) Fluorescence emission spectra of synthesized microspheres (1.0 mg/mL), fluorescein and curcumin in ethanol and b) solid state

The fluorescence emissions of aqueous dispersions of the microspheres dependent on pH were investigated between pH 3-10, in Figure 8a and 8b. The hydroxyl groups of the curcumin and fluorescein, and nitrogen atoms of the OCCP in the microspheres have lone-pair-electrons. The hydroxyl groups and nitrogen atoms can transfer electrons to curcumin and fluorescein in a basic medium. So, the microspheres exhibited higher fluorescence emissions at the basic medium and showed a maximum emission peak at pH: 9.0. But, in an acidic medium, owing to the protonation of hydroxyl groups and nitrogen atoms, the electron transfer is eliminated and weakened fluorescence emissions are observed [17].

Fluorescein as an organic fluorescent dye can leak from the host when encapsulated in nanomaterials. In this study, this problem was eliminated due to the bonding of fluorescein covalently to phosphorus atoms of OCCP rings by a nucleophilic substitution reaction.

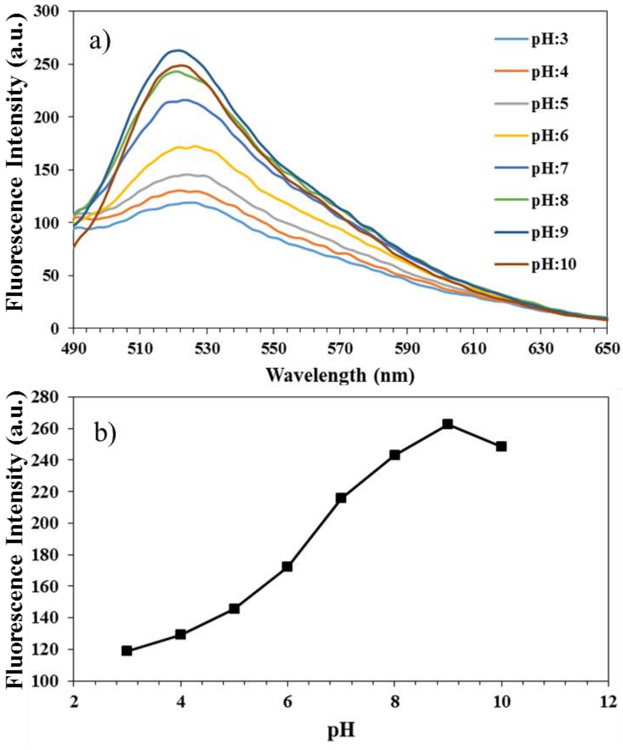


Figure 8 a)The pH dependent fluorescence spectra of the microspheres in different pH (1.0 mg/mL). b) the graph of fluorescence intensity versus pH

The prepared microspheres have hydroxyl groups on their surfaces due to fluorescein and curcumin compounds. In previous reports, hydroxyl derivated crosslinked polyphosphazene nano/microspheres such as including oxyresveratrol [18], phloroglucinol [19], 4,4′-sulfonyldiphenol [20] were synthesized and fluorescence properties were investigated. In addition, the applications of the prepared polyphosphazene nano/microspheres using the monomers containing lone-pair electrons arising from amine or hydroxyl groups, such as fluorescence sensors to detect Fe^{3+}, Hg^{2+} metal ions [17, 21], nitroaromatic explosives [16] and dopamine [23] were investigated.

By taking into consideration above studies, when the prepared microspheres interacted with metal ions, chemical or biological compounds, the fluorescence intensity of the microspheres can be quenched or increased by compounds. Hence, it is thougth that the obtained polyphosphazene microspheres have great potential for sensor applications due to having hydroxyl groups.

In the literature, curcumin was reacted with hexachlorocyclotriphosphazene (HCCP) and researched usage as a fluorescent sensor for the detection of picric acid [22]. Besides, the hollow polyphosphazene nanospheres were synthesized using fluorescein and HCCP. The cell imaging and drug delivery properties of the synthesized fluorescent nanospheres were investigated [26]. In this study, OCCP was used as a crosslinker instead of HCCP. Curcumin and fluorescein were reacted together with OCCP to synthesize microspheres. In this way, the microspheres both gained fluorescent properties and contained curcumin as an anticancer drug. Thus, the curcumin delivery from the synthesized microspheres and cell imaging owing to fluorescence property of the microspheres can be investigated as a further study.

3. CONCLUSIONS

In summary, the one-pot synthesis of the novel polyphosphazene microspheres was performed via polycondensation polymerization. The microspheres were obtained facilely with bonding between OCCP and fluorescent compounds; fluorescein and curcumin in an ultrasonic bath, for just 4 hours. They were characterized by SEM, EDX, FTIR, XRD, and UV-vis techniques. The microspheres gained fluorescence property through fluorescein and curcumin bonding to phosphorous atoms of the OCCP rings. The microspheres exhibited fluorescence emissions in both ethanol and as solid-state. The optimum pH was determined as 9.0. The prepared highly crosslinked and fluorescent polyphosphazene microspheres have the potential to be used as sensors to detect metals, and biological or chemical compounds, and also to deliver curcumin, and to image cells due to the fluorescence properties.

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The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the author.

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