Intramolecular and Intermolecular Crosslinked Poly(vinyl alcohol)–Borate Complexes for the Sustained Release of Fertilizers and Enzymes

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ABSTRACT: Therapeutic agents or agricultural fertilizers captured in polymer colloids (PCs) give rise to interesting applications, which are typically related to sustained release. We synthesized crosslinked polymer structures with poly(vinyl alcohol) (PVA) and borax precursors. Fourier transform infrared spectroscopy showed that a polymer–boron ion complex was formed with the crosslinking reaction at the O—H site of PVA; thereby, PCs were formed. Field-emission scanning electron microscopy showed that a uniform mesoporous two-dimensional structure formed via intermolecular and intramolecular crosslinking. Trypsin enzyme and phosphate fertilizer were trapped in these PCs independently to study sustained release. Fertilizer-incorporated PCs were mixed with soil samples, in which seeds of fenugreek were sown, and the plant growth was monitored a duration of 15 days. The fertilizer release, studied with UV–visible spectroscopy, showed a sustained signature of the fertilizer (at 690 nm) in the water extracts of soil, with much healthier plant growth compared to the control. For the trypsin-incorporated PC samples, the released enzyme was made to interact with bovine serum albumin protein to monitor the released percentage with UV absorption spectroscopy. A systematic increase in the enzyme signature (at 280 nm) was observed for a duration of 60 min; this indicated the potential of PC for sustained drug release. The swelling calculations predicted that the mechanism involved was composed of pseudo-swelling behavior. We envisaged that the hydroxyl groups of the PC broke in water and formed a complex with water. This complex slowly dissolved in water to release the entrapped molecules. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 121: 2450–2457, 2011

Key words: biological applications of polymers; crosslinking; drug delivery systems; electron microscopy; FTIR

INTRODUCTION

Throughout various fields of science, a push toward the use of submicrometer-scale technology is well underway; this technology has the potential to produce low-cost, self-replicating systems that could revolutionize the scientific arena.[1–3] One area where this work is already well in progress is the field of sustained particle release. Conceptually, submicrometer/nanoparticles are entrapped in cagelike structures, which could be ruptured under different ambient conditions (e.g., pH, temperature, solvent) to release the trapped molecules in a steady fashion. The released particles may be composed of an inorganic nanomaterial or bioactive chemical to invite applications in the areas of novel pesticides, fertilizers, food preservatives, drugs, dust-free and corrosion free coatings, and microbe-resistant materials.[4–7] The systematic release of fertilizer materials for farming has been a solution, and different materials have been tried that supply fertilizers to plants in a sustained manner and for a longer duration of time to ensure proper usage.[8]

On the biomedical side, especially with traditional drug-delivery methods, there has been substantial demand in current times to improvise the drug delivery and administration.[9–13] As is known, traditional drug-delivery methods include oral and intravenous routes of administration; these are largely inefficient because of the need for exposure of the pharmaceutical agent to the complete metabolic system of the body. A low specificity for injectable drugs requires large amounts of a drug be injected into a patient; this creates a high concentration of the drug in the blood stream, which could potentially lead to toxic side effects. Submicrometer-sized drug delivery, with degradable and absorbable polymers, provides a more efficient, less risky solution to many drug-delivery challenges.[9,10] Additionally, they provide a high degree of biocompatibility for delivery systems.[11–13]

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In the search of such new materials, various attempts have been documented.[14–16] The efficacy of nanocapsules of polysiloxanes and copolysiloxanes as matrix materials for the slow release of 2-pyridine aldoxime chloride was investigated by Gupta et al.[14] at different pH's and temperatures. Aronna et al.[15] studied the biocompatibility and slow release of antibiotic materials in the treatment of periodontal disease, exploring poly(hydroxyethyl methacrylate) as a slow-release material for a few drugs. Indapamide-based slow-release pellets were synthesized and tested for different drug-release applications;[16] polystyrene beads were yet another candidate for a similar objective.[17] Mesoporous[18] silica nanospheres have been investigated the most in the domain of sustained drug release because of their biocompatible nature and ease of synthesis. Magnetic polymer particles have been studied as carriers of pharmaceutically active substances[17] for local concentration of a medicine in an organism or for slow release from a deposit with magnetic-field-assisted routing. Poly(vinyl alcohol) (PVA) is well known to be a polymer that can crosslink with boron as the linking agent, with its biocompatibility and biodegradable properties,[19] which are useful in various applications. For example, Orienti et al.[20] synthesized hydrogels using PVA for sustained drug-delivery release while it was mixed with Arabic gum to yield a similar system to release antimicrobial drugs.[21]

In this context, we report on the synthesis of novel polymer colloids (PCs) with PVA and sodium borate (borax) precursors to yield crosslinked polymer cages. The structural confirmation was done with Fourier transform infrared (FTIR) spectroscopy (PerkinElmer, spectrum 1B, Massachusetts, USA) and field-emission scanning electron microscopy (FESEM; Nova 600 NanoSEM, FEI, Germany). During this synthesis, two different materials, namely, the enzyme trypsin and a phosphate fertilizer, were incorporated into the PCs to yield particle-incorporated PC structures. The selection of these materials was done carefully to identify the agricultural and biomedical applications. Ultraviolet–visible (UV–vis) spectroscopy (model 1700, Shimadzu) and photoluminescence (PL) spectroscopy (Shimadzu RF-5301 PC spectrofluorometer) was used for the time-dependent release study of these entities.

EXPERIMENTAL

Chemicals and materials

PVA (molecular weight = 110,000), borax (molecular mass = 381.37), cadmium sulfate ($CdSO_4 \cdot 2.5H_2O$), 1-thioglycerol, ammonium sulfide, ammonium molybdate, stannous chloride, glycerol, and ammonium molybdate were obtained from Kemphasol (Mumbai, India) with 99.99% purity. Trypsin enzyme was obtained from bovine pancreas albumin; bovine fraction powder (pH 6–7), and perchloric acid were used as the basic biochemicals and were procured from Sigma-Aldrich (St. Louis, U.S.A.).

Experimental methods

Synthesis of PC

Deionized water (1 L) was kept on a stirrer and was heated to about 80°C. PVA powder (40.0 g) was slowly added to this hot water to dissolve it and prevent clumping. The solution was allowed to cool, and its yield was uniform and viscous. Independently, 4 g of borax was dissolved in 1 L of water at room temperature. These were the basic stock solutions, which were later mixed in the presence of the fertilizer/enzyme/nanoparticles; this is explained later.

Synthesis of the sample for FESEM:cadmium sulfide (CdS):PC

To enable good imaging, particles of known size were synthesized and entrapped in the PC matrix. CdS nanoparticles about 10 nm in size were chosen for this study. To synthesize CdS nanoparticles, the following procedure was followed:[22] $CdSO_4 \cdot 2.5H_2O$ was dissolved in 1 L of deionized water (the concentration was 2 m*M*). This solution was placed under stirring (200 rpm), and 18 mmol of 1-thioglycerol was added. Ammonium sulfide (30 mmol) was rapidly added at room temperature to form CdS nanoparticles. Dried powder of 3 mg of CdS nanoparticles was added to 3 mL of the borax solution (from the stock solution mentioned previously). The solution was then well sonicated for about 5 min and added to the PVA solution in a 1 : 1 volume ratio. As the PVA interacted with the borax crosslinker, it formed a PC structure, in which the CdS nanoparticles got trapped during synthesis. The final product had a yellowish tinge of CdS. The CdS:PC (2–3 drops) was dropped onto the glass slide, spin-coated (2000 rpm, 3 min), dried at room temperature, and used for FESEM studies.

Synthesis of trypsin:PC

In this approach, 3 mg of trypsin enzyme was added to 3 mL of borax solution. The solution was stirred for about 5 min to achieve uniformity. The solution was then well sonicated and added to the PVA solution at a 1 : 1 volume ratio. As PVA interacted with the borax crosslinker, it formed a PC structure, in which the trypsin molecules got trapped during synthesis.

Synthesis of fertilizer:PC

To prepare a standard solution of phosphate fertilizer, 25 g of ammonium molybdate was dissolved in

175 mL of distilled water, and 280 mL of concentrated sulfuric acid was dissolved in 400 mL of distilled water. Both of the solutions were mixed and diluted to 1 L. Second, 2.5 g of $SnCl_2$ (stannous chloride) was added to 100 mL of glycerol and boiled to get a clear solution. Potassium dihydrogen phosphate (K_2HPO_4; 4.388 g) was dissolved in 1000 mL of distilled water. This was then diluted 100 times to get a standard phosphate solution containing 10 mg of phosphate/L. To study the phosphate estimation, 10 mL of either the standard (containing a known concentration of phosphate) or the sample solution was taken. Ammonium molybdate (0.4 mL) was added to it. $SnCl_2$ (2 drops) was then added. A blue color developed. The absorbance of this was measured at 690 nm (a blank was set with distilled water + ammonium molybdate + $SnCl_2$ at the same concentration). The absorbance was measured after 5 min but before 12 min of the addition of $SnCl_2$. A standard graph was plotted and used to determine the concentration of phosphate in the sample solutions. This phosphate fertilizer (N : P = 15 : 15) was added to the PVA solution, and then, 5% borax was added to it slowly with stirring to form the PC. The fertilizer (1 g) was entrapped in 100 g of PC.

Procedure of sustained-release testing

CdS:PC. CdS:PC (7 g) was taken and kept independently in a conical flask. Water (100 mL) was added to the sample and kept on shaker with high speed. This was done to check the release of the nanoparticles in water from the PC cages after definite time intervals. Every 10 min, the flask was removed from the shaker, 5 mL of the solution was removed, and the flask was returned to the shaker. These samples were collected for 60 min; this yielded six samples. The whole procedure was repeated four times to get the final values, check the repeatability, and ensure the correctness of the data.

Trypsin:PC. Bovine serum albumin (BSA) lyses activity was used to estimate trypsin release. A protocol explained by Spencer et al.[23] was used for the same for determination of this proteolytic activity of trypsin against BSA. The trypsin:PC sample (3 g) was taken and kept in a conical flask. Water (100 mL) was added to the sample and kept on the shaker at high speed. Every 10 min, the flask was removed from the shaker. a 5-mL solution was removed from the flask, and the flask was again put on the shaker. These samples were collected for 60 min; this yielded six samples, which were subjected to interaction with BSA.

Test tubes containing supernatant solution were incubated in a water bath at 30°C. After 5 min, 1 mL of 1% (w/v) BSA solution in 0.05*M* phosphate buffer (pH 7.4, of the same temperature) was then added to each tube. The mixture was incubated at 30°C for 10 min without shaking. The reaction was stopped by the addition of 5 mL of a 10% (w/v) perchloric acid, and samples were allowed to stand at 25°C for 1 h. After centrifugation at 5000 rpm for 15 min, the supernatant was filtered through Whatman No. 1 paper, and its absorbance was determined at 280 nm with a UV spectrophotometer. Perchloric acid added to the trypsin was prepared in parallel for all treatments and was used as a standard reference. A mixture containing 1 mL of buffer was used as blank and was treated in the same manner. Enzymatic activity was calculated as the difference in the supernatant absorbance, as compared to the reference. One unit of protease activity is defined as the amount of trypsin that liberates 1 μM of tyrosine/min under experimental conditions. The whole procedure was repeated four times to get the final values, check the repeatability, and ensure the correctness of the data.

Fertilizer:PC. Three 250-mL funnel flasks were taken, in which the first funnel contained 100 g of soil, the second funnel contained 100 g of soil in which 1 g of soil contained fertilizer:PC, and the third funnel had 100 g of soil + 10 mg of fertilizer. The funnels were placed with filter paper at the bottom. The effective concentration of fertilizer was kept the same. Every day, distilled water was added on top of the soil, and then, the filtrate was collected in the flask. This filtrate was then subjected to the phosphate estimation experiment as described previously.

For experiments on plants to monitor the plant growth, Methi (Fenugreek, *Trigonella foenum-graecum*) plants were chosen because of their rapid germination and growth. Soil (1 kg) was placed in four pots. In each pot, 55 seeds were sewn. All pots were kept in same environment and were watered equally everyday. The seeds germinated in 4 days. On the 4th day, either the PC, the fertilizer, or the fertilizer:PC was added to the pots. The first pot had control plants (only soil), the second pot had plants sewn in soil + 10 g of plain PC, the third pot had soil + fertilizer:PC, and the fourth plant had soil + fertilizer (0.1 g). The plant growth was monitored for 15 days, with regular and equal watering for every pot.

Various percentages of fertlizer:PC were also chosen to obtain a better understanding of the effect of PC on the plant growth. Keeping the PC quantity the same as in earlier studies (10 g in 1 kg of soil), the fertilizer percentage in the encapsulated in PC was varied as 0.03, 0.05, 0.08, and 0.1 g. The fertilizer:PC effect on the growth was monitored for 15 days on all four of these pots and was compared with the plant growth in the presence of only fertilizers of same quantities in the similar 1 kg of soil. The results were also compared with the plant grown only in soil (i.e., without the fertilizer or fertilizer:PC).

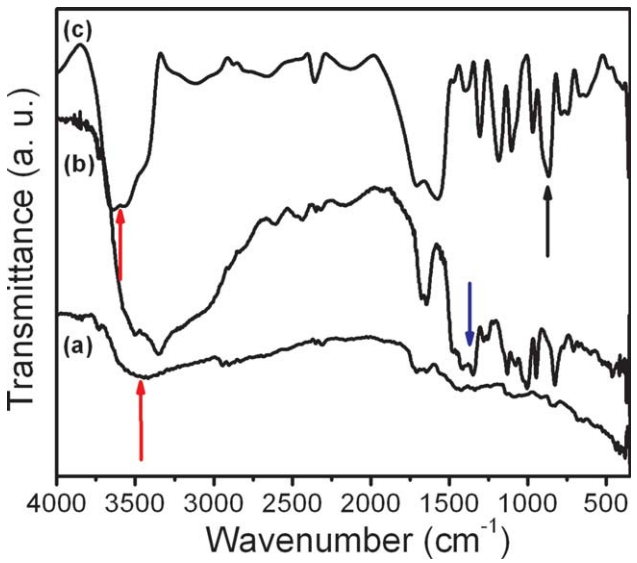


Figure 1 FTIR of (a) PVA, (b) sodium borate, and (c) PC. The red arrows show the O—H signature shifted in the PC structure. The blue arrow shows the B—O—B bond in sodium borate being weakened in PC. The black arrow shows the persistent signature of B—O in PC. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Analyses

Confirmation of PC formation was done with FTIR spectroscopy. The PC morphology was observed with FESEM images of the CdS:PC samples. A sustained release mechanism was checked with PL for the CdS nanoparticles and UV–vis spectrometry for trypsin–BSA interaction and phosphate release estimation. To understand the swelling mechanism of PC, a simple procedure was followed. Dried powder (5 g) of PC was kept in porous sintered glass tube. The glass tube was immersed in a distilled water bath for 24 h at 25°C. The excess water was removed by centrifugation at 5000 rpm for 5 min. The degree of swelling (S_W) was calculated according to the following formula:

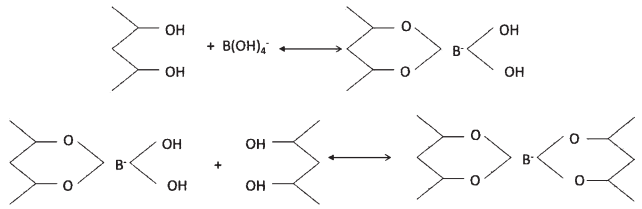
$$S_W = (W_2 - W_1)/W_1$$

where W_2 and W_1 are the weights of the water-absorbed PC and dried-powder PC, respectively. This experiment and these calculations were repeated three times for better confirmation.

RESULTS AND DISCUSSION

PC formation studies

Figure 1 shows the FTIR of PVA, sodium borate, and PC. As shown in Figure 1(a,b), broad O—H stretching vibrations were observed around 3450 cm^{-1}.[24] The signatures showed a clear shift to 3650 cm^{-1} in the PC that was formed; this indicated that the modification in the O—H bonding upon the interaction. This is shown by red arrows in the online version of the figure. The B—O—B signature shown in Figure 1(b) at 1400 cm^{-1} weakened upon PC formation [Fig. 1(c)]; this indicated the weakening of this bond (shown by a blue arrow in the online version of the figure). The signature at 848–1050 cm^{-1} [Fig. 1(b)], however, seemed to persist in Figure 1(c), which is essentially of B—O (shown by a black arrow).[25,26] This indicated that the B-O-B vibration frequency got modified upon PC formation, with borax working as a crosslinker. As is known from the basic studies of the PVA–borax system,[27] PVA is capable of forming a polymer–ion complex, and the mechanism of the crosslinking reaction with borate ions is shown by the following equations:



It is also well known that borax totally dissociates into equal quantities of boric acid [$B(OH)_3$], borate ion [$B(OH)_4^-$], and Na^+.[28] The borate ions and PVA molecules formed crosslinked complexes, which induced electrostatic charges on the polymeric chains. The Na^+ ions had a shielding effect on the charges of the polymer chains. Thus, the conformation of the polymer chains was a consequence of the balance of the excluded volume of the polymers, the electrostatic repulsion among the charged complexes bound on the polymeric chains, and the shielding effect of free Na^+ ions on the charged complexes. Initially a borate ion was attached to a polymer chain and later was bound to another diol unit at a crosslinking point, and a PVA–borate PC was formed.

Morphological and sustained release studies

Figure 2 shows FESEM of the CdS:PC sample, which clearly showed a uniform two-dimensionally stretched PC sample with CdS nanoparticles embedded in the matrix. A few of the nanoparticles are shown by a yellow outline for better clarity. The particle size was about 10 nm, which is the size of the CdS synthesized nanoparticles. This gave us a hint that while the PC was getting formed, the nanoparticles got bundled up in the matrix and, thereby, formed a nanoparticle-encapsulated PC sample. The inset shows the PL spectrum of CdS nanoparticles released by CdS:PC with time. With excitation given

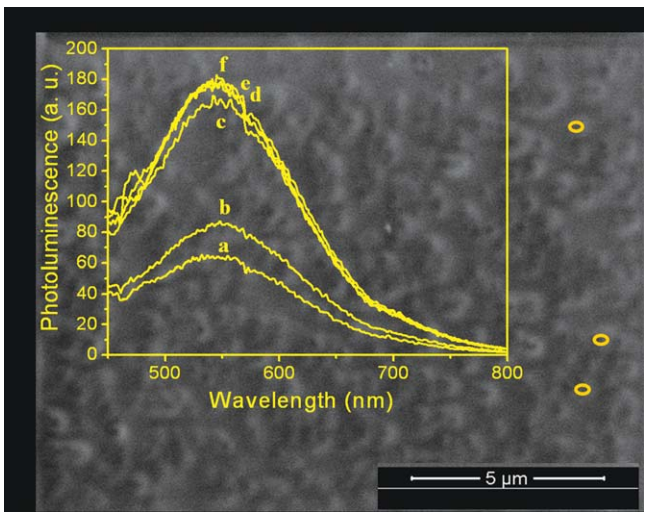


Figure 2 FESEM of the trapped CdS nanoparticles in PC. The few entrapped cavities are highlighted with circles. The inset shows the PL emission spectrum of the CdS nanoparticles released in aqueous medium by CdS:PC with time after (a) 10, (b) 20, (c) 30, (d) 40, (e) 50, and (f) 60 min. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

at 360 nm, the standard emission of CdS nanoparticles was obtained at about 542 nm; this matched well with standard references.[29] Because the same quantity of supernatant was taken at each time instant, the intensity of the peak at 542 nm was directly related to the concentration of CdS nanoparticles. Indeed, we did see an increase in the intensity of the CdS signature peak with time with the total release in 50 min [Fig. 2(a–f)].

Figure 3 shows the graph of the interaction between the released trypsin with BSA. As mentioned in the synthesis procedures, the released trypsin was carefully collected and further processed to interact with BSA protein. The UV spectrometer reading of the absorbance at 280 nm showed the strength of this interaction, which was dependent on the enzymatic activity of trypsin with BSA.[23] Figure 3 shows a clear increase in the absorption with time and indicates the extent of the interaction of released trypsin with BSA. Because the concentration of BSA was kept constant in all of the reactions, the increase in the absorption was directly proportional to the available trypsin at that time. The inset shows the linear fitting of the data and confirms the enzymatic action. Indirectly, this segment also gave a hint that the PC structures would be biocompatible, which enabled the positive interaction of an enzyme and a protein. As is well known, BSA as a protein can be denatured rapidly if subjected to toxic materials; this was apparently not observed.

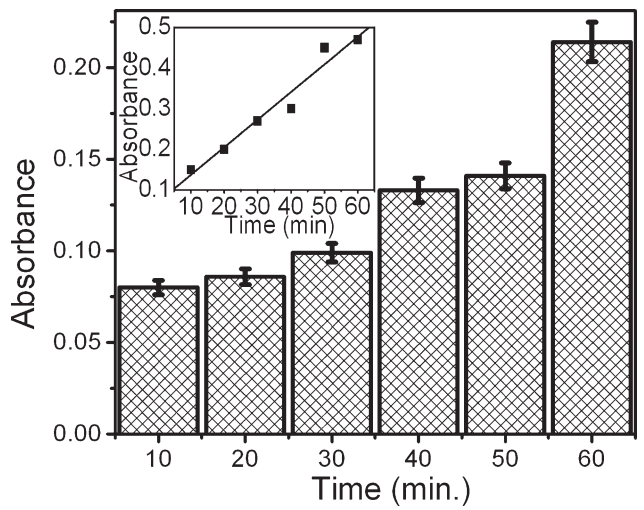


Figure 3 UV–vis absorption data at 280 nm showing a clear increase in the absorption with time, indicating the extent of interaction of released trypsin with BSA. The inset shows the fit data points, indicating the rate of released trypsin from PC to be linear in nature.

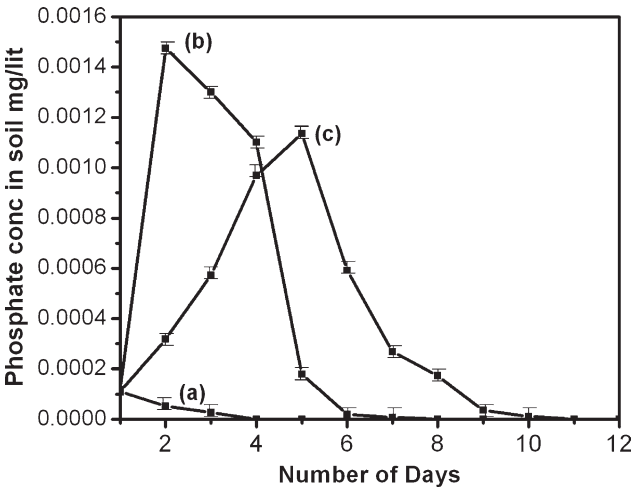


Figure 4 Release of phosphate from (a) soil, (b) soil + fertilizer, and (c) soil + fertilizer:PC.

The most telling results are depicted in Figure 4–7, which are related to fertilizer release and further availability for plant growth. Figure 4 shows the results of the funnel experiments and phosphate estimation for a duration of days. Figure 4(a) shows the phosphate fertilizer content in the sample with only soil, Figure 4(b) shows the same with soil + fertilizer, and Figure 4(c) shows that with soil + fertilizer:PC. The content of fertilizer was negligible for the entire duration of time for the soil-only sample. For the sample in which only fertilizer was mixed with soil, the phosphate release was maximum in the first 2 days. Later, the availability went down rapidly, and hence, its availability to plants decreased rapidly with time. Comparatively, the fertilizer released from PC showed sustained release for over 10 days, with the maximum release in 5 days or so. The decrease (and, hence, lower availability of the fertilizer) was seen to also have a low slope; this indicated that the PC structures released

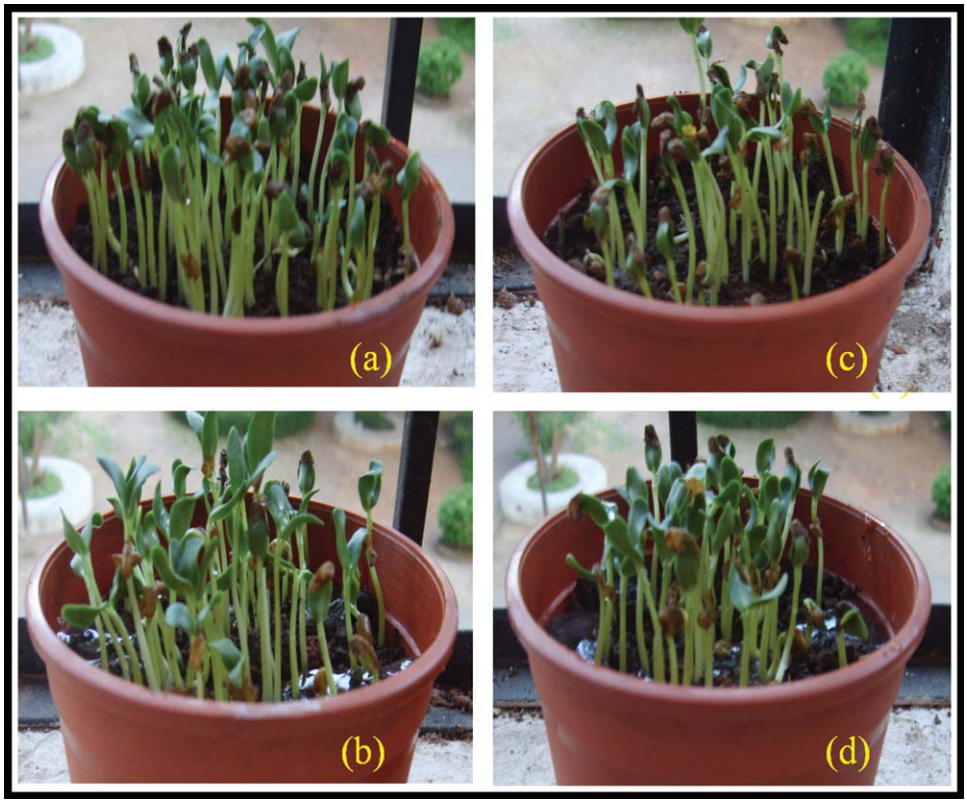


Figure 5 Plant growth pictures: (a) only soil, (b) soil + PC, (c) soil + fertilizer, and (d) soil + fertilizer:PC for the duration of 4 days. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the sample in a sustained fashion for longer durations.

Figure 5 and 6 shows the plant growth pictures in only soil, soil + PC, soil + fertilizer, and soil + fertilizer:PC for the durations of 4 and 15 days, respectively. All of the samples grew equally well over 4 days. However, in 15 days time, the plants (soil + fertilizer:PC) were fresher [Fig. 5(d)] and greener compared to the rest. The rest of the pots showed plants with a few leaves turning yellow and the growth exhibiting less leaves on shoots. Figure 7 shows the comparison of plant growth in 15 days with different concentrations of fertilizers encapsulated in PCs. Clearly, as the percentage of fertilizer:PC increased, the growth was better. Furthermore, with the comparison with the fertilizer-only data, we observed that the growth of the plant with fertilizer:PC (0.1 g) showed healthy plant growth, with bigger size of leaves and also enhanced growth as compared to the same quantity without PC. The same can be said with the comparison of fertilizer:PC with the soil-only data. It is important to mention here that higher quantities (>0.1 g) of fertilizers could not be incorporated in the PCs. At that percentage, PVA did not form a PC with boron, and hence, lower percentages were selected.

The swelling calculations depicted that the values of S_W were in the range 8.1–8.9 for all of the samples, that is, PC, fertilizer:PC, trypsin:PC, and CdS:PC. This gave us a hint that this PC displayed a pseudo-swelling behavior, in which no real physical swelling occurred. Instead, in the presence of water, the PC started to form a complex with water. For lower water contents and short contact times, the complex-forming process appeared to be like swelling. However, at higher water contents and after longer contact times, the PC chains eventually dissolved, and the encapsulated molecules are liberated. Similar findings were depicted by Omidian and Park.[30] In fact, such pseudo-swelling behavior is the major mechanism of controlled drug release through medicinal tablets, with which our findings also agree.

Lin et al.[31] studied PVA–borax systems in aqueous solutions and documented that they behaved as weak colloids. Studying the interaction of PVA with chitosan, Mucha et al.[32] documented that good compatibility of the components resulted from the presence of hydrogen bonds between specific groups (e.g., hydroxyl, amide) of chitosan and PVA chains; this caused an increase in molecular packing and, thus, a decrease in the pore volume and rate of water diffusion. The interaction between water

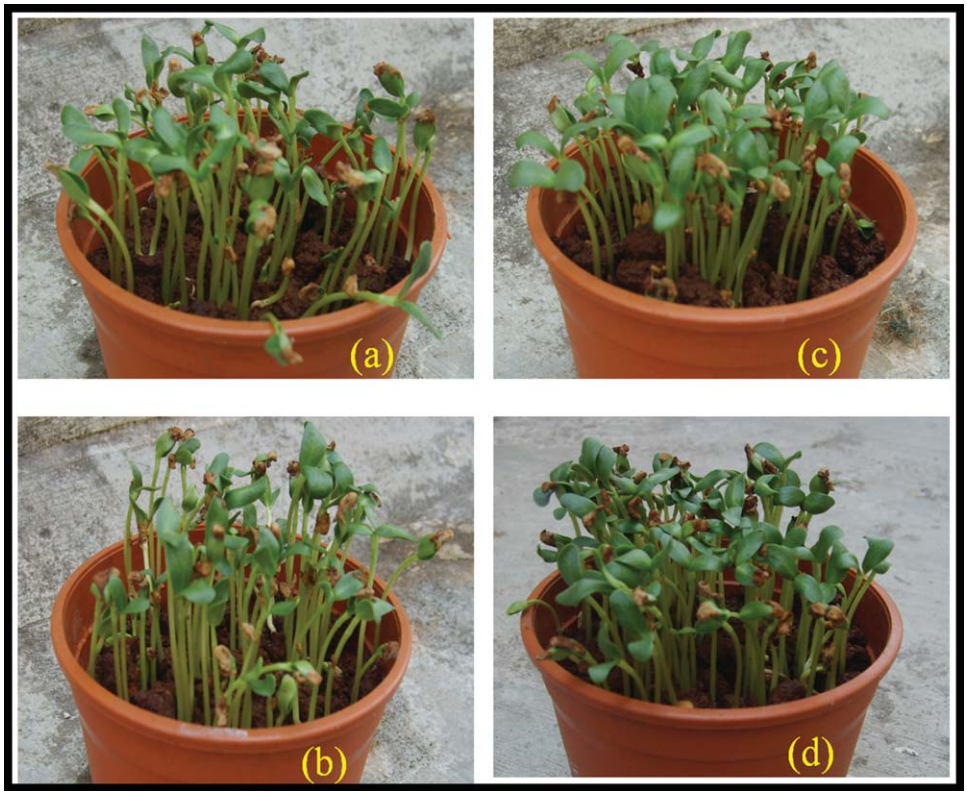


Figure 6 Plant growth pictures: (a) only soil, (b) soil + PC, (c) soil + fertilizer, and (d) soil + fertilizer:PC for the duration of 15 days. In 15 days time, the plants (soil + fertilizer:PC) were much fresher and greener compared to the rest. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

molecules and PVA–borax was a favored because of hydrophilic PVA, whereas on other side, with increasing content of the crosslinking agent, there was a hydrophobic character to the system as well. We, hence, envisaged in our case that the PVA–borax crosslinking process was in concurrence with the presence of either the nanoparticles, trypsin, or phosphate fertilizer. Colloid formation occurred around these materials, encapsulating them in the whole complex formation process. They, hence, formed a PC, in which the materials got arrested. As the PC came into the vicinity of water, the hydroxyl groups on the colloid surface interacted with water molecules to form a complex and exhibited a pseudo-swelling process; this, thereby, loosened the encapsulated entities, which were trapped inside. The process slowly released the materials in the medium; these could then be available to plants, a biomedium, or any other miscible medium. This release process was directly dependent on the competition between the tight bonding and conformational morphologies of the crosslinked polymers, mainly via boron ions (their ratio in the precursors) and the availability of the water medium to the hydrophilic ends (hydroxyl groups), which were active as primary water-sorption and complex-formation sites.

CONCLUSIONS

In conclusion, the use of PVA as a good candidate for sustained release was highlighted. The chemistry

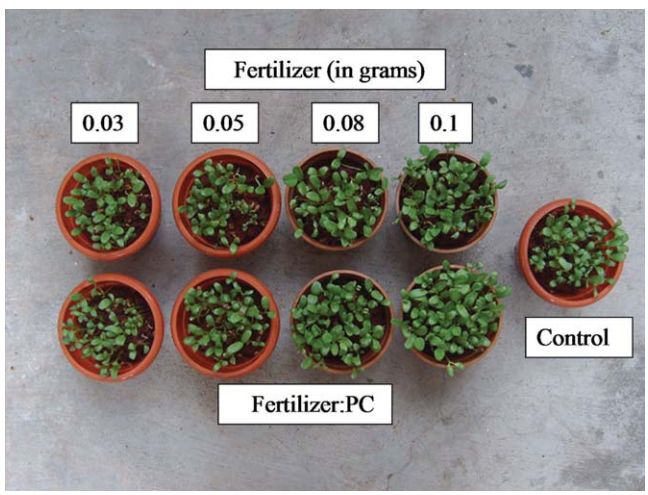


Figure 7 Growth of plants in 1 kg of soil after 15 days. The comparison was made of fertilizer:PC (the fertilizers weights varied from 0.1 to 0.03 g) with the corresponding data for only fertilizer. The pot labeled as *control* shows the plant growth with only soil. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

involved, the swelling calculations, and the release mechanism were discussed. This was demonstrated by the use of an enzyme, a nanoparticle, and a fertilizer as candidates. FESEM showed uniformly stretched two-dimensional structures of PCs with mesoporous cages. The fertilizer release showed a sustained signature of fertilizer in the water extracts of soil for more that 10 days in PC samples with much healthier plant growth compared to the control. For trypsin-incorporated PC samples, the enzyme was released systematically for a duration of 60 min; this indicated the potential of the PC as a sustained-drug-release candidate. Pseudo-swelling of PC in water ambience to release the trapped molecules in competition with the hydrophobic boron crosslink agent was envisaged to be the key to this process.

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