

Research Article

Semibath Polymerization Approach for One-Pot Synthesis of Temperature- and Glucose-Responsive Core-Shell Nanogel Particles

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Herein, we report a simple and easy procedure for the synthesis of core-shell structures of glucose-sensitive 3-acrylamidophenylboronic acid (APBA) and temperature-responsive P(NIPAm-AAc) shell nanogel particles using MBA as a cross-linker via free radical polymerization. The synthesized particles were approximately 100 nm and were cross-linked to one another. The shell thickness of the nanogel particles was adjusted by increasing the concentrations of NIPAm through the semibath approach during the process of polymerization. The synthesized colloidal nanogel particle shows thermoresponsive behaviors. The dynamic light scattering technique also confirmed the change in the size of particles dispersed in an aqueous solution upon increase/decrease in temperatures, which is the result of its volume phase transition temperatures (VPTT). The size and morphology of the particles were characterized by TEM, FE-SEM, and AFM. The sensitivity of these nanogel particles to temperature and glucose suggests that they have the potential for applications related to the delivery of self-regulated insulin.

1. Introduction

Stimuli-responsive polymeric nanogels are cross-linked structures of colloidal particles in nanometer sizes, which can contract and expand in response to changes in the external environment, such as temperature, pH, or ionic strength [1–3]. Due to their exceptional features and extensive scope of applicability, these materials have drawn considerable attention over recent decades [2]. The thermoresponsive polymer known as poly-*N*-isopropylacrylamide (PNIPAm) is among the most widely researched stimuli-responsive polymers. The applications of PNIPAm are mainly related to the areas of drug delivery [3–5] and the immobilization as well as adsorption of enzymes and proteins [6]. This is partially due to inherent physical properties, which are modulated by the reversible phase separation behavior. Upon arrival at the lower critical solution temperature (LCST),

the “phase separation behavior” is triggered and the cross-linked polymer chains undergo the process of volume phase transition (VPT). The nanogels expand below their LCST and contract above their LCST.

Diabetes mellitus is one of the serious health issues worldwide [7, 8]. Thus, diabetes mellitus still cannot be cured completely. As a result, life-long treatment is needed for maintaining the level of blood glucose concentrations at normal levels and avoiding severe complications. Currently, daily injections or infusions of insulin form the best approach to treat insulin-dependent diabetes mellitus patients [9]. This is a significant burden on diabetic patients. Hence, finding an alternative methodology for the treatment of diabetes would be of great significant. In particular, this treatment should be able to deliver and release insulin in a self-regulated manner in light of the instability of blood glucose concentration. In the past few decades, a glucose-sensitive material, phenylboronic acid

(PBA), has attracted great interest due to its wide applications in self-regulated insulin delivery for the treatment of diabetes mellitus. Kitano et al. [10] have reported on the synthesis and application of PBA-based glucose-sensitive materials through the formation of a complex between the copolymers PBA and diol or polyvinyl alcohol. Zhang et al. [11] also investigated the modification of glucose-responsive nanogels based on APBA and PNIPAm-co-AAc via carbodiimide coupling and studied their glucose and thermoresponsive behaviors at various pH and temperatures. Farooqi et al. [12, 13] made outstanding contributions to the synthesis and functionalization of glucose-sensitive PBA with 4-vinylpyridine (4VP) and NIPAm when working at the physiological pH and temperature. They found that the incorporation of the 4VP unit into the PBA-based copolymer microgels significantly reduces the pKa of the PBA unit by Lewis acid-base interactions, increases the VPTT, and enhances glucose sensitivity at the physiological pH and temperature. There has also been data regarding the sugar-responsive polymer fluorescent nanospheres based on NIPAm and PBA [14], the particles of which swell in the presence of sugar. The nanospheres were in their nonswollen state without sugar, while the fluorescent donor and acceptor were in close juxtaposition for effective fluorescence resonance energy transfer (FRET) effect. Degradable multifunctional [15] and injectable dextran [16] containing microgels composed of glucose-responsive PBA of several hundred nanometers in diameter were synthesized and studied for insulin loading and levels of release in response to glucose. PNIPAm, APBA, and its copolymers have also been studied by many research groups [17–21].

In the context of alterations in blood glucose levels, the potential of the glucose molecule is widely acknowledged with respect to the medical applications in this area [18]. Recently, the development of a glucose-responsive polymeric scheme for the treatment of diabetes through self-regulated insulin mechanisms has progressed significantly [15, 19]. However, to the best of our knowledge, no work has yet been reported on the synthesis of core-shell structures of APBA-based thermoresponsive polymers through semibath polymerization approach. In this present study, we established a simple and straightforward method for preparing the core-shell structures of nanogel particles, which are composed of a copolymer of thermoresponsive moiety PNIPAm-AAc with a glucose-sensitive APBA component. The addition of acyclic acid (AAc) as a copolymer causes the system to be extremely sensitive to pH and well dispersed in water in addition to being temperature- and glucose-sensitive components. Furthermore, the prepared nanogel particles in an aqueous solution were studied using dynamic light scattering (DLS), which found that the sizes of these particles are greatly influenced by temperature and glucose concentration. The nanogel particles developed through this approach may be used in important applications in drug delivery for the treatment of diabetes mellitus.

2. Experimental

Core-shell nanogel particles were prepared via surfactant-free emulsion polymerization reactions in a semibath fashion.

A 100 mL round bottom flask equipped with a condenser, a N₂ flow pump, and a magnetic stirrer was employed for carrying out the reactions. Typically, 60 mL of the aqueous solution containing 0.14 g NIPAm (Aldrich), 10 μ L AAc (Aldrich), and 3.3 mg N'N'-methylene-bis-acrylamide (MBA, Aldrich) was charged, stirred, and degassed for a period of 30 minutes and heated at 60°C for a period of 5 minutes. Subsequently, 1 mL of the (5 mg/mL) 2,2'-azobis(2-methylpropionamide) dihydrochloride (AAPH, Sigma) initiator was introduced into the solution. After 5 minutes of reaction, 16 mg of APBA dissolved in 1 mL of methanol was injected into the reaction compartment and the temperature was elevated to 70°C. After 4 h of reaction, 5 mL of the resulting opaque solution was withdrawn from the reaction flask with a syringe and allowed to cool down to ambient temperature. This sample was denoted as NG-1. A second reaction was carried out to grow a thicker PNIPAm shell. Firstly, in a 20 mL glass cuvette, 0.075 g of the NIPAm monomer, and 1.8 mg of MBA were dissolved in 5 mL of distilled water and degassed for 15 min. This was followed by the injection of the solution into the reaction carafe. The unutilized free radical initiator left in the reaction carafe was used to start polymerizing NIPAm monomers. After an hour of reaction time, 5 mL of the opaque solution was removed and labelled as NG-2. This second shelling step was replicated once, with the resulting end product denoted as NG-3. The volume in all samples was diluted with 20 mL of distilled water, before cleansing through 45 minutes of centrifugation at 6000 rpm. After repeating this redispersion and centrifugation in water three times, the final products were freeze-dried for further characterization.

2.1. Measurements. A JEOL 1010 microscope at 80 kV accelerating voltage was employed to carry out transmission electron microscopy (TEM). A drop of the colloidal solution was drop casted onto the carbon-coated Cu grids, allowed to dry overnight, and observed under the TEM. Field emission scanning electron microscopy (FE-SEM) was performed on a JEOL JSM 7600F microscope at 5–10 kV. A drop of colloidal solution was drop casted on a precleaned glass substrate, dried overnight, coated with Pt, and observed under FE-SEM. The FTIR spectra were recorded with ATR-FTIR, using the Bruker Vertex-80 spectrometer. A few drops of colloidal solution samples were dropped onto the precleaned ATR-crystal unit and the FTIR was measured at the ambient temperature. Particle size analysis was performed using Malvern Nano ZS dynamic light scattering (DLS) at a pH of 8.5 in all experiments, unless otherwise mentioned. All the measurements were performed at a scattering angle of 90°C. The sample temperature was regulated with a build-in Peltier temperature controller, varying from 20°C to 45°C. AFM was recorded with a Veeco Nanoscope V multiscope atomic force microscope. AFM was performed by depositing a diluted (2 μ L) colloidal solution of nanogels on a precleaned glass substrate, which were dried overnight at the room temperature and observed under AFM with tapping mode. The ¹H-NMR spectra of the nanogel were studied using a JEOL RESONANCE 500 MHz spectrometer.

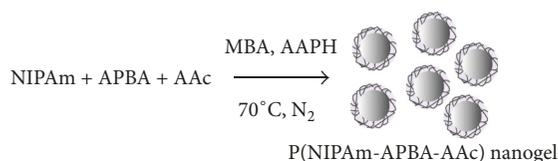


FIGURE 1: Schematic illustration of the preparation of nanogel.

3. Results and Discussion

Copolymerization of APBA with NIPAm, AAc, and MBA was carried out in an aqueous solution at 70°C to form cross-linked thermo- and glucose-sensitive nanogel particles via free radical polymerizations without the use of surfactant in a semibath fashion. Due to its insolubility in water, APBA was first dissolved in 1 mL of methanol. Upon addition to an aqueous solution of comonomers, it was observed to be completely miscible. The aliquot of APBA showed no evidence of precipitation or aggregation after addition to the monomer solution. Upon elevation of the solution temperature, the monomer solution evolved to a white and turbid suspension. This change in the solution appearance corresponds to the polymerization of the monomers into cross-linked hydrogel nanoparticles. It has been confirmed that the consumption of APBA is much faster than that of NIPAm in the PNIPAm gel particle formation by polymerization through precipitation [20]. Therefore, the APBA monomers would be completely utilized during the process of polymerization creating core-shell nanogel particles. In order to obtain polymer shells with homogenous cross-linking throughout the shell, we performed the polymerizations in a semibath manner with a continuous feeding of NIPAm monomers and MBA into the reaction chamber during the reaction. The schematic diagram of the synthesis procedure is described in Figure 1.

In this present study, in the first step of polymerization process, a core-shell structure composed of P(NIPAm-APBA-AAc) was obtained. At 70°C, they are in a collapsed state and serve as a “core” for further shell growth. After this, the shell was synthesized by polymerization of a mixture of NIPAm and MBA in the presence of the “core.” Upon the first layer of shell growth, a cloudier colloidal solution was observed compared to the first parent core-shell sample (NG-1). This observation provides further evidence that the PNIPAm shell grows over the “core” particles upon polymerization. The shelling process was repeated to obtain a thicker layer of the PNIPAm shell. Monodispersed PNIPAm-APBA submicrometric microgel particles with a well-controlled size were also prepared by polymerization through precipitation by Lapeyre et al. [20, 21]. In their case, they first prepared PNIPAm core microgels by an aqueous free radical polymerization through precipitation. Following this, the shell was synthesized by the polymerization of a mixture of NIPAm-MBA-APBA in the presence of the core as seeds. They have made outstanding contributions to the synthesis of microgel particles and studied their properties, such as VPTT at different temperatures and pH; swelling properties in the presence of glucose; and insulin loading and releasing rate. However, the core-shell structural morphology was not clearly visible from their TEM

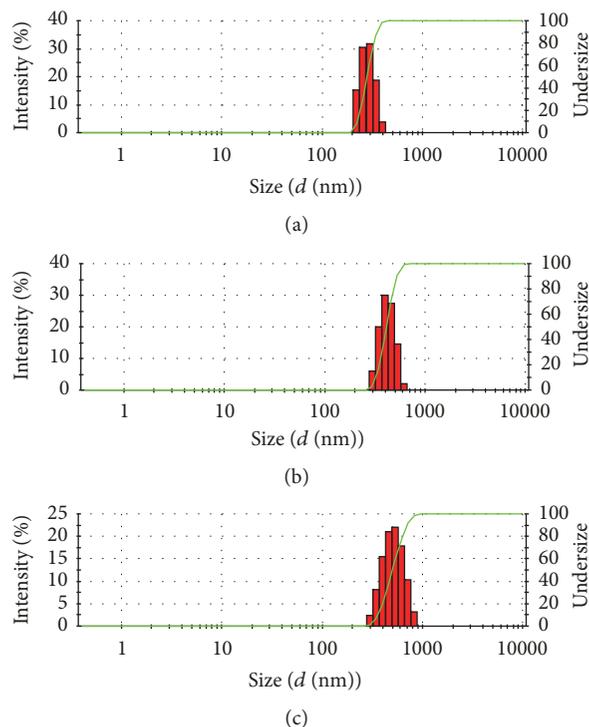


FIGURE 2: Hydrodynamic diameter obtained by DLS of (a) NG-1, (b) NG-2, and (c) NG-3 samples at 20°C and pH of 8.5.

images. On the contrary, our current method of preparation of core-shell structures of nanogels is much easier, straightforward, and controllable. Furthermore, this method forms a distinctive core and shell structural morphology. To further confirm the PNIPAm shell growth over the “core” nanogel, we obtained the DLS measurement of all three samples at 20°C (Figure 2) in the fully swollen state. It can be seen from the DLS data that the size of the particles in Figures 2(b) and 2(c) are larger than the parental nanogels. The average particle diameter in the swollen state was found to be 396 nm, 470 nm, and 620 nm for NG-1, NG-2, and NG-3 samples, respectively. DLS analysis also demonstrates that the size distribution is the same between the parental nanogel sample (NG-1) and NG-2 and NG-3 samples as they are all in the range of 15–30%. There is no evidence for a new particle population created from the second or third polymerization steps [22]. This observation provides evidence for the formation of layers of shells on the parental P(NIPAm-APBA-AAc) nanogel.

Figure 3(a) shows the ATR-FTIR of the prepared APBA and corresponding P(NIPAm-APBA-AAc) nanogels. After modification with APBA, the P(NIPAm-APBA-AAc) nanogels with the spectrum of the parent (NIPAm-AAc) nanogel exhibited strong amide I and amide II bands at 1638 cm^{-1} and 1543 cm^{-1} , respectively. There was also a weak amide III band at 1261 cm^{-1} (N-H bending and C-N stretching in the plane) [23]. The disappearance of a peak at 900–1100 cm^{-1} of the vinyl group implies that the C=C from APBA has been completely reacted with NIPAm-AAc monomers. In addition to the absorption maxima of amide

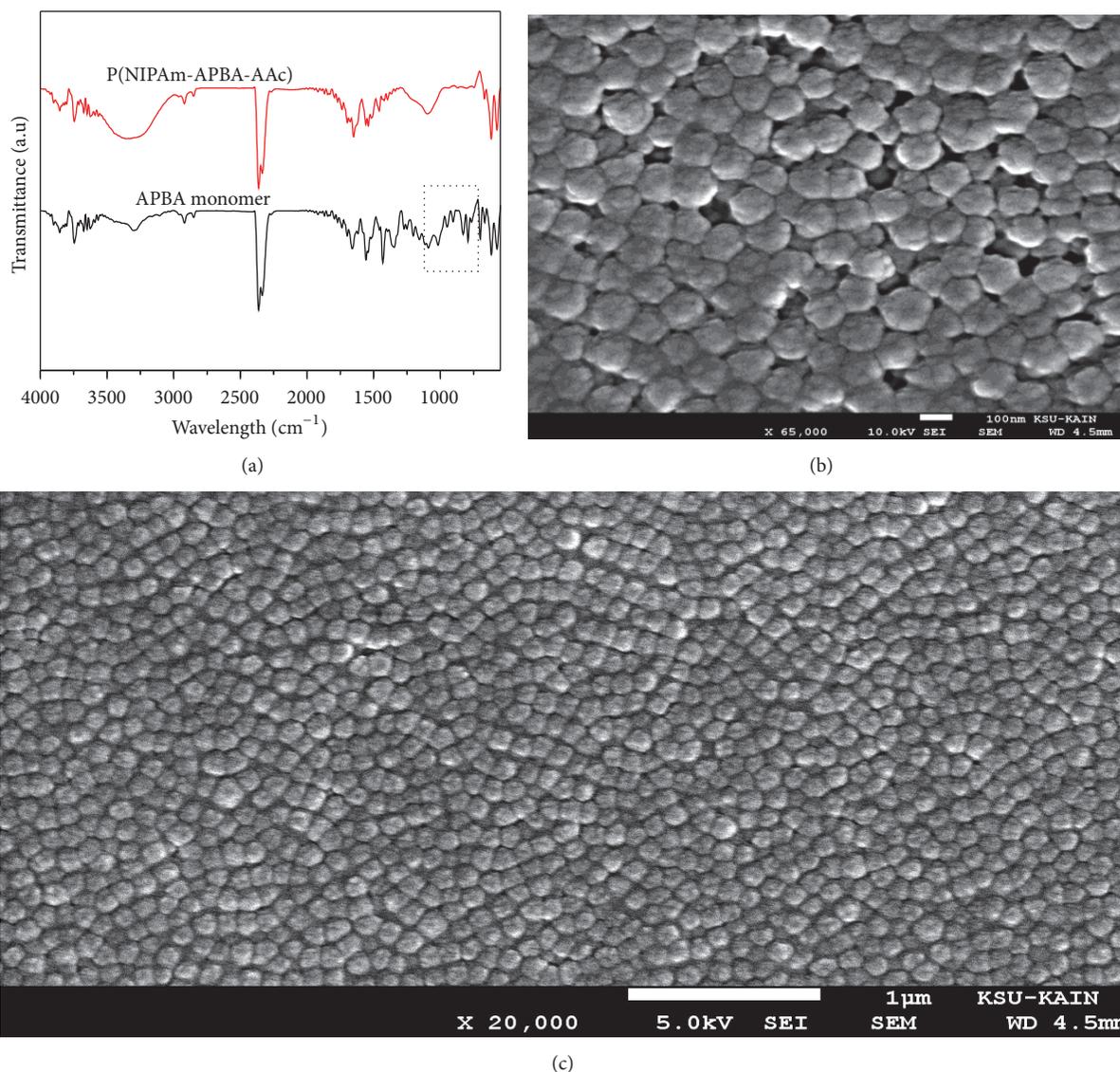


FIGURE 3: (a) FTIR spectra of APBA monomers and prepared nanogel particles. (b and c) are the FE-SEM results of low and high magnification images of the prepared nanogel [NG-1 sample] deposited on a glass substrate, which shows well-oriented nanometer-sized particles.

I at 1650 cm^{-1} and amide II at 1525 cm^{-1} , P(NIPAm-APBA-AAc) nanogels had a peak at 1706 cm^{-1} with a shoulder at 1724 cm^{-1} , which was assigned to the carboxylic group of AAc units. The morphology and the particle size of the prepared P(NIPAm-APBA-AAc) nanogel sample 1 (NG-1) were characterized by FE-SEM. From Figures 3(b) and 3(c), it was observed that a distinct nanometer-sized spherical shape of particles was formed. To further investigate the chemical structure of the synthesis of copolymers, we obtained the NMR of a nanogel sample (NG-1). A representative $^1\text{H-NMR}$ spectrum of the copolymer is shown in Figure 4. The typical proton signals around 1.0 ppm attributed to the $-\text{CH}_3$ protons of the NIPAm units were observed in the $^1\text{H-NMR}$ spectra of the copolymers, while the signal at 1.4–2.0 ppm was caused by the polymer backbone assigned to the $(-\text{CH}_2-\text{CH}-)$ protons [24]. The peak at 3.8 ppm was ascribed to the $(\text{CH}-(\text{CH}_3)_2)$ of the NIPAm units. The peaks at 7.2–7.4 ppm

were attributed to the phenyl protons of the APBA groups, confirming the successful introduction of APBA groups in the copolymer [25].

TEM images of the prepared P(NIPAm-APBA-AAc) nanogel sample show a uniformly distributed spherical shape for the cross-linked particles (Figures 5(a) and 5(b)). Figure 5(c) is the high-resolution image of the P(NIPAm-APBA-AAc) nanogels, which shows that the core-shell structures of the poly-APBA core have a size of approximately 100 nm and a thin layer P(NIPAm-AAc) shell was formed by cross-linking particles. Furthermore, we have prepared different batches of P(NIPAm-APBA-AAc) nanogels by growing PNIPAm shells. This involves injecting a specific quantity of NIPAm monomers with MBA into the prepared P(NIPAm-APBA-AAc) during the reaction. Subsequent to each reaction, a 5 mL sample was withdrawn after each reaction, which was analyzed for shell growth using DLS and TEM analysis. These

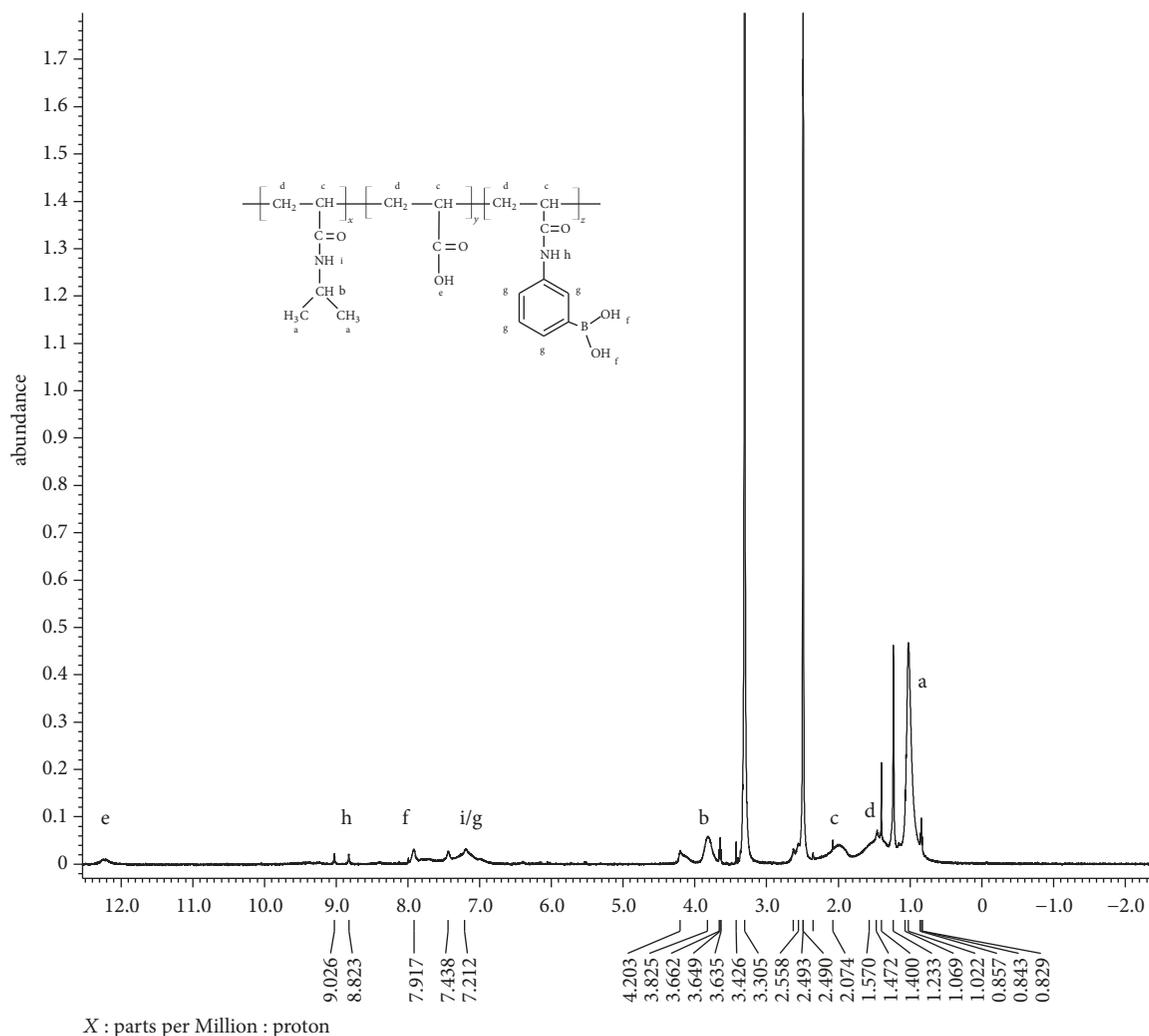


FIGURE 4: Chemical structure and ^1H -NMR spectrum of the P(NIPAm-APBA-AAc) nanogel sample NG-1 using DMSO-d_6 as the solvent.

samples are named NG-1, NG-2, and NG-3. The epitaxial growth of the shell was verified by TEM as shown in Figures 5(d) and 5(e). It was observed from the TEM images that thicker shells were grown onto the parent P(NIPAm-APBA-AAc) nanogel particles. TEM images at low resolutions did not show clear core-shell structures due to the low contrast between the polymer and the background. However, we could clearly observe the formation of thicker layers of PNIPAm shells after further shell growth in NG-2 and NG-3 samples in the high-resolution TEM (HR-TEM) images (Figures 5(d) and 5(e)). The AFM further confirmed that the as-prepared nanogel particles (NG-1) were approximately 100 nm in diameter and exhibited spherical shape and ordered structure with a cross-linked network (Figures 5(f) and 5(g)).

PNIPAm is one of the most important thermoresponsive polymers that undergo a reversible transition from a random coil to a dissolved globular state at about 32°C . This change is due to the disruption of hydrogen bonds at higher temperatures (just above to its VPTT), causing water to act as a poor solvent for the polymer chain [25–28]. When this polymer becomes cross-linked and forms a covalent gel, the

gel shows a volume phase transition from a swollen state to a crumpled state at or close to its VPTT. The width of this transition relies upon the degree of cross-linking of the gel [27]. The temperature-induced change in the size of the P(NIPAm-APBA-AAc) nanogel particles with different shell thickness was investigated by DLS. Figure 6(a) shows the variation of the hydrodynamic diameter of the various composites as a function of the temperature in the range of 20 – 45°C . As expected, they all exhibit thermoresponsive volume phase transition characteristics, which is essentially a decrease in hydrodynamic diameter with an increase in temperature. As shown in Figure 6(a), when fully swollen, all three nanogel samples present a hydrodynamic diameter of approximately 405 nm, 470 nm, and 620 nm for NG-1, NG-2, and NG-3 samples, respectively. The hydrodynamic diameter is reduced to approximately 160 nm, 220 nm, and 285 nm, respectively, when fully collapsed. This finding confirmed the thermoresponsive characteristics of nanogel particles with PNIPAm. Furthermore, this is an effect on the fast volume changes due to the presence of more hydrophilic AAac units into the nanogel [24]. By changing the composition of the

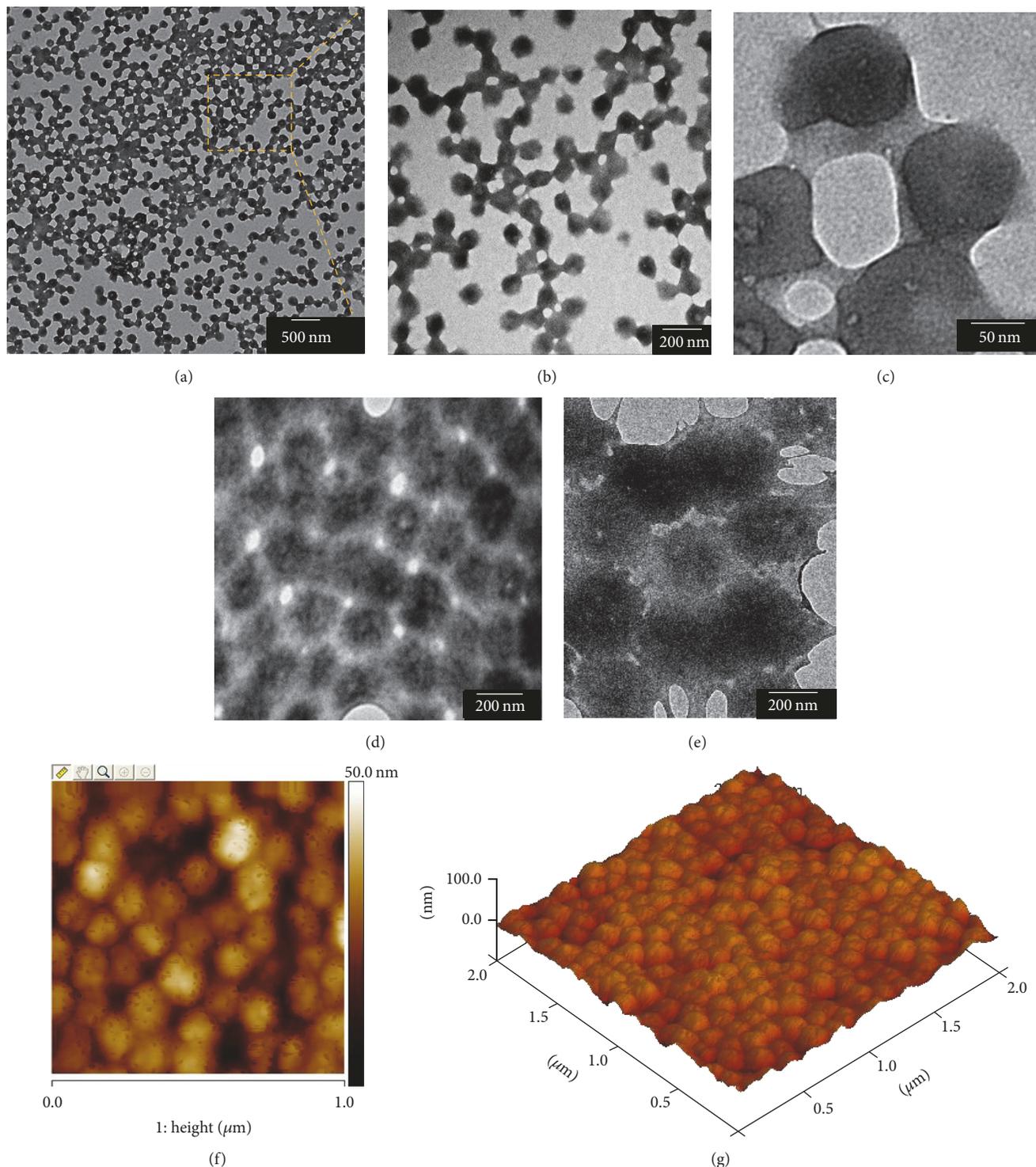


FIGURE 5: (a–c) are the TEM images of P(NIPAm-APBA-AAc) nanogels [NG-1 sample] of different magnifications showing core-shell particles. (d) and (e) are the HR-TEM images of NG-2 and NG-3 samples, respectively. (f) and (g) represent the AFM (height profile) and 3D images, respectively, of NG-1 sample deposited on a glass substrate scanned with the tapping mode.

polymer shells, the VPTT could be subtly changed from 28°C to 33°C. The VPTT of the prepared nanogels particles depends on the hydrophilic/hydrophobic balance in the copolymer chain as well as the hydrogen-bonding capabilities from its chemical structure [24]. DLS measurement of the

diameter of the nanogel particles was seen to be sizeable in comparison to those of TEM and SEM. This can be explained by the fact that DLS assesses the particle size in an aqueous solution under wet conditions and the gels are expected to be in a contracted state at a higher temperature. However, TEM

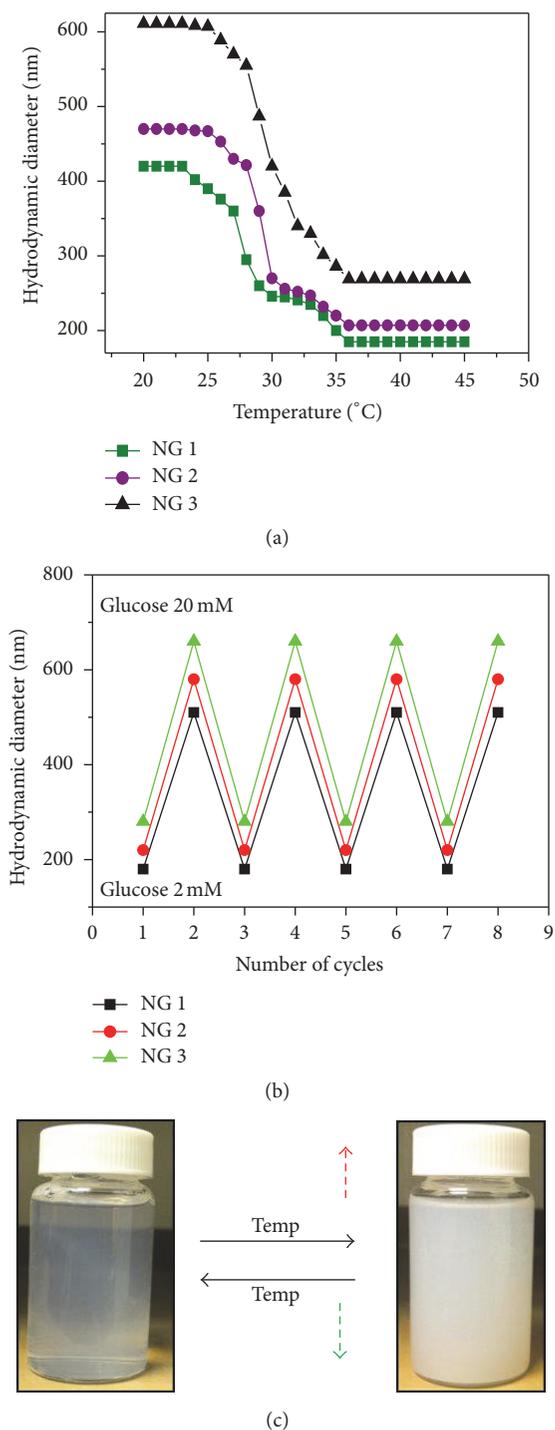


FIGURE 6: (a) Temperature-dependent hydrodynamic diameter of P(NIPAm-APBA-AAc) nanogels at a pH of 8.5. (b) Reversible hydrodynamic values of the nanogels as a function of glucose concentrations at the ambient temperature and a pH of 8.5. (c) Digital photograph of colloidal nanogel showing reversible temperature-dependent changes in water.

and SEM measurements were taken from particles in the dry state under a high vacuum where the gel undergoes complete dehydration process [24, 28, 29].

The changes in the hydrodynamic diameter of the nanogels upon glucose exposure were examined at two different glucose concentrations. The experiment was carried out at room temperature at a fixed pH of 8.5. Figure 6(b) shows the reversible swelling and shrinking behavior of the nanogel as a function of glucose concentration. At low glucose concentrations of 2 mM, the nanogel did not show any changes in hydrodynamic size. However, as the concentration increased to 20 mM, the hydrodynamic diameter of the nanogel greatly increased to be approximately 600 nm. It has also been previously reported [20] that PNIPAm-modified PBA derivative particles were found to be sensitive to glucose at a pH close to the pKa value of APBA (pH of 8.5). The degree of swelling was proportional to the concentration of glucose. At a pH of 8.5, the formation of the complex induces a shift in the charge equilibrium, which causes counterion osmotic pressure and gel swelling [19, 20]. Figure 6(c) shows the digital photograph of the prepared sample (NG-1) showing a reversible temperature-dependent dispersion (swollen state)/aggregation (shrunken state) at its VPTT in water. The prepared nanogel samples were highly stable at room temperature and did not have any changes in color or precipitation, even after storage for several months. Figure S1 (Supplementary Materials) shows a digital photograph and its TEM image of the stored nanogel sample (NG-1). The TEM experiment was performed for the same sample and it can be concluded from the image that no aggregation of the particles was observed.

4. Conclusions

In summary, we have developed a simple synthetic route to prepare thermo- and glucose-sensitive P(NIPAm-APBA-AAc) core-shell nanogel particles by free radical polymerization, which has a diameter of 100 nm. A series of characterization techniques were applied to characterize and confirm the structures and the formation of copolymer nanogel particles. The shell thickness of the nanogel particles can be controlled by increasing the concentrations of NIPAm through the semi-bath approach during the course of polymerization. These particles displayed both thermoresponsive properties and glucose sensitivity. The changes in hydrodynamic diameter as a function of temperature and glucose were also demonstrated. The developed nanogels are highly versatile and can maintain their stability for months if kept under an ambient temperature. The sensitivity of these nanogel particles to temperature and glucose suggests that they have potential applications related to the delivery of self-regulated insulin.

Conflicts of Interest

The authors declare no conflicts of interest with other researchers or groups.

Authors' Contributions

Aslam Khan conceived, designed, and performed the experiments and analyzed the data; Mahmoud Hezam performed

the AFM; Mukhtar Ahmed and Joselito Puzon Labis performed the TEM; Ahmed Mohamed El-Toni, Javed Alam, Ali Aldalbahi, and Tansir Ahamad contributed reagents/materials/analysis tools; Aslam Khan wrote the paper. All authors have read and approved the final manuscript.

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Supplementary Materials

Figure S1. (a) Digital photograph of the P(NIPAm-APBA-AAc) nanogels [NG-1 sample] after 4 months of storage at room temperature and (b) its corresponding TEM image. (Supplementary Materials)

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