



Synthesis and characterization of temperature sensitive P-NIPAM macro/micro hydrogels

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ABSTRACT

A thermo responsive macro porous poly(N-isopropylacrylamide) hydrogel was synthesized using free radical polymerization. The reaction was optimized by varying the reaction temperature, monomer, cross-linker and initiator based on the strength and swelling characteristics of the hydrogel. The morphology of the macro hydrogel was observed using scanning electron microscope (SEM). The swelling behavior of the macro hydrogel was performed gravimetrically and found that the gel synthesized at 36 °C had maximum deswelling ratio of 34.5 (–). These optimized values were further used to synthesize micro hydrogels using water–oil (w/o) emulsion technique. The morphology of the micro hydrogels were observed through SEM. Effect of water–oil ratio and stirrer speed on the mean particle size of the micro hydrogels were studied. Micro hydrogels synthesized at 1:1.5 w/o ratio and at 800 rpm had perfect spherical shape and had least particle mean diameter of 0.74 μm, with SD of 0.5. Dye release kinetics with respect to temperature and time were studied using methylene blue solution. The release kinetic studies of micro hydrogel showed higher sustained release for 56 h compared to the macro hydrogel.

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1. Introduction

Hydrogels are three dimensional polymeric networks that are able to absorb and retain large amounts of water and other biological fluids. These conventional hydrogels exhibit volume or phase transitions in response to slight environmental changes, such as temperature [1], pH [2], ionic strength [3], light [4], electric [5] and magnetic fields [6]. Depending on the design of the hydrogel matrices, the volume change may occur continuously over a range of stimulus values or intermittently at a critical stimulus level. Because of these special characteristics, they can be widely applied in biomaterials such as controlled drug-release, delivery systems [7–9], on–off switching materials [10], artificial muscles, sensors [11–13], chemical separations [14,15] and adsorptive materials.

Recently, much attention has been paid to the development of thermo responsive hydrogels, especially for biomedical applications, due to their unique properties, such as biocompatibility, biodegradability and biological functionality [16]. As a typical temperature-sensitive hydrogel, poly(N-isopropyl acrylamide) (PNIPAM) hydrogel undergoes a dramatic volume change at lower critical solution temperature (LCST, about 32 °C) [17], which is the result of rather complex polarity of this molecule. Below the LCST, the amide functionality binds water molecules via hydrogen

bonding, thus imparting both water solubility and surface activity. However, moving above the transition temperature breaks these hydrogen bonds, and the polymer expels water molecules and undergoes a coil-to-globule transition, thereby precipitating and forming particles. The LCST close to physiological temperature makes the polymer a good candidate for applications in biotechnology and in medicine [18–20].

In recent times, the importance of size scale of hydrogels used has become increasingly evident. Thus, micro hydrogels have become highly popular due to their improved potential uses in cell-based therapies, tissue engineering [21], liquid microlenses, and drug delivery systems [7–9]. They are particularly useful because they can reach areas of the body not accessible to macro scale hydrogels and enter the cytoplasm of cells. However, in this paper, we wish to synthesize and characterize temperature-sensitive poly-(N-isopropylacrylamide) hydrogel sheets and micro hydrogels using novel method with the scope of exploitation as matrix for medical applications especially as drug carriers. In this present study, hydrogel sheets were synthesized and their physical strength and accessibility were tuned by varying the composition of monomer, cross linker, initiator and reaction temperature. The behavior of the hydrogel was characterized by its swelling ratio and the morphology was characterized using scanning electron microscope (SEM). Further micro hydrogels were synthesized using the optimal conditions derived during macro hydrogel production. The effect of water–oil ratio and speed of the stirrer on mean diameter of the micro hydrogels were investigated. The particle size distribution and the swelling behavior of micro hydrogels were

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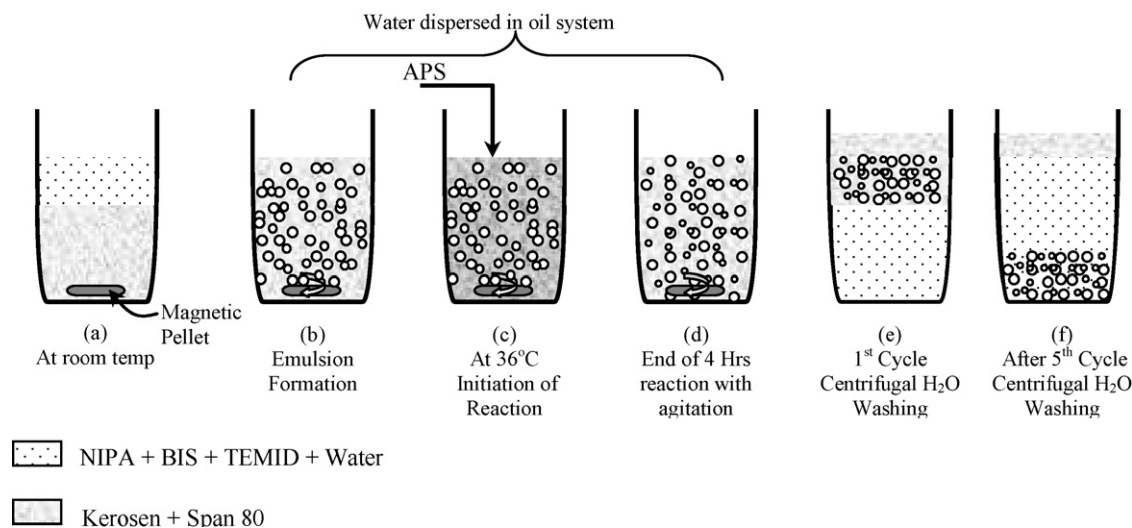


Fig. 1. Water–oil emulsion polymerization to produce micro particles.

characterized by dynamic light scattering (DLS) particle analyzer and by absorption studies.

2. Materials and methods

2.1. Materials

N-isopropylacrylamide (NIPA), 99%, purchased from Acros Organics, New Jersey was used without further purification. N,N'-methylenebisacrylamide (BIS, $\geq 98\%$, Sisco Research Laboratories Pvt. Ltd., India), N,N,N',N'-tetramethylethylenediamine (TEMED, 99%, Spectrochem Pvt. Ltd., India), ammonium peroxydisulfate (APS, $\geq 98\%$, Merck Ltd., India), Span 80 (Loba Chemie Pvt. Ltd., India), Kerosene (Sigma–Aldrich, USA). Methylene blue dye (MB, Loba Chemie Pvt. Ltd., India), were used without further purification. Distilled water was used for all the experiments.

2.2. Synthesis of bulk hydrogels

Known quantities of NIPA, BIS and TEMED were dissolved in distilled water in a separate beaker and known quantity of APS was dissolved separately in distilled water. Both the mixtures were brought to the reaction temperature using refrigerated circulating water bath (Hummber, Germany). Then, both the contents were mixed thoroughly in a 100 ml beaker and maintained at the reaction temperature for 4 h. The polymerization reaction temperature was varied from 5 °C to 50 °C. Hydrogels synthesized at 5 °C, 28 °C, 32 °C, 34 °C, 36 °C, 42 °C, 45 °C and 50 °C were named as T5, T28, T32, T34, T36, T42, T45 and T50 respectively. After the polymerization reaction, the hydrogel was immersed in distilled water for 48 h at room temperature and the water was replaced for every 2 h once, in order to allow the un-reacted chemicals to leach out from the hydrogel. The feed compositions of the monomers and other reactants were optimized for the production of stable, good strength, and high swelling ratio hydrogels. Stability and strength of the synthesized hydrogel were visually observed.

2.3. Synthesis of micro hydrogels

The micro hydrogels were synthesized by precipitation–emulsion polymerization technique. A schematic representation of water–oil emulsion polymerization is shown in Fig. 1. The precursor emulsion was prepared by mixing 6.525 g of kerosene and 1.975 g of span 80 [22]. Initially the optimized

composition of monomer (NIPA–400 mg), cross linker (BIS–8 mg) and terminator (TEMED–120 μL) were dissolved in 2 ml distilled water and then added to the precursor emulsion.

The contents were agitated well using a magnetic stirrer and the polymerization reaction was initiated by adding APS solution to the precursor. APS solution was prepared by dissolving 80 mg of APS in 2 ml distilled water separately. The reaction was carried out for 4 h at optimized temperature i.e. at 36 °C and then the contents were cooled to room temperature. The formed particles were initially filtered using wet Wattman filter paper to remove kerosene, span 80 and unreacted chemicals. The micro hydrogels were then subjected to 5 cycles of repeated centrifugal washing. In individual cycles, the hydrogel particles were immersed in pure distilled water and then centrifuged at 15,000 rpm for 30 min to remove kerosene, span 80 and unreacted chemicals. The effect of w/o ratio on the size of the micro hydrogels was studied by varying the weight ratio of w/o from 1:1 to 1:2.5. The effect of stirrer speed was studied by varying the speed from 300 rpm to 900 rpm.

2.4. Morphology observations

The bulk hydrogel sheets were characterized using SEM, to analyze the internal pore structure and pore size. The bulk hydrogel sheet which were under equilibrium in distilled water, were quenched and freeze in a deep freezer and then the gel was dried in a lyophilizer for 10 h to completely sublimate the water with out disturbing the internal pore structure of the hydrogel. Prior to SEM analysis the samples were properly cut and coated with platinum and observed using JEOL, JSM-6360 LV analytical SEM.

Morphology and shape of the micro hydrogels was studied preliminarily by inverted microscope (Olympus CX 31) connected with the NIS software.

2.5. Measurements of deswelling ratio of bulk hydrogels

The behavior of hydrogel with respect to the temperature was analyzed by calculating the deswelling ratio of the hydrogel, where the deswelling ratio (DSR) is defines as follows;

$$\text{DSR} = \frac{W_t}{W_d}$$

where, W_t is the weight of the water in the shrunken sample at a given temperature, W_d is the weight of the sample at dry state. Deswelling ratio of the hydrogel was measured by initially

soaking the hydrogel in the distilled water for 48 h. Then completely swollen hydrogel was transferred in to a Petri dish and the whole Petri dish was partially dipped in the temperature controlled water bath. Before fixing the temperature of the water bath, the water sticking on the surface and the sides of the hydrogel was gently wiped out using wet tissue paper. Then the temperature of the water bath was fixed at a set value and left it for 45 min. After 45 min, the squeezed water from the hydrogel was removed using wet tissue paper and then the hydrogel was weighed using weighing balance. Further the same procedure was followed for different temperature from 30 °C to 70 °C.

2.6. Particle size

Size of the hydrogel plays a major role in the application of the hydrogel. The mean size and size distribution of the micro hydrogels were measured using dynamic light scattering (DLS WCIS-50, Ankersmid). All DLS measurements were done with a wavelength of 633.0 nm at 25 °C. Each sample was measured thrice and the values reported in this article were the mean values.

2.7. Methylene blue dye release using micro-hydrogels

Release kinetics of the bulk and micro hydrogels were studied using known concentration of methylene blue solution. Methylene blue absorption studies were performed at 30 °C by dispersing known quantity of hydrogels in known concentration of methylene blue solution. The hydrogels were left undisturbed for 48 h, so as to reach its equilibrium with the dye solution. After 48 h, the hydrogels were filtered and washed with distilled water to remove dyes solution from the surface of the hydrogel. The washed hydrogels were placed in known quantity of distilled water at 28 °C in a temperature controlled water bath. Initial concentration of the distilled water was measured spectrophotometrically and noted. Then the temperature was increased to 30 °C and left undisturbed for 30 min and then, 1 ml of distilled water was pipette out and the dye released was determined. This procedure was repeated for every 2° raise in the bath temperature and the concentration was plotted against temperature.

3. Results and discussion

3.1. Bulk hydrogel sheets

The compositions of monomer, cross linker, accelerator and terminator were optimized to produce bulk hydrogel sheet with good swelling ratio and better stability. The stability and the swelling ratio of the hydrogel depend on the composition of the monomer and the other reactants in the reaction mixture and the degree of polymerization reaction. Therefore, the compositions were initially optimized by conducting 35 experimental trials and the optimized compositions were used for further studies. The swelling behavior was improved by further optimizing the reaction temperature. The reaction temperature was varied from 5 °C to 50 °C. In general, hydrogel acts as hydrophobic above LCST and acts as hydrophilic below LCST. When the temperature is below LCST [23,24], the hydrophilic chains are hydrated and the hydrogel becomes swollen. As the temperature increases above LCST, the hydrophobic interaction becomes stronger and thus the balance between hydrophilic/hydrophobic interactions breakdown causing the gel to collapse. In this study, hydrogels were produced and characterized both above and below LCST temperatures.

Visual observation of the synthesized hydrogel above LCST was opaque in nature and the hydrogel synthesized below LCST was transparent. At LCST, which was equal to room temperature, the

synthesized hydrogel had higher water content and low refractive index contrast relative to that of water, and low mechanical stiffness. When the temperature was increased above the critical temperature, the gel volume reduced several folds, and the refractive index increased. Thus, combination of refractive index and porosity changes caused the gel to appear opaque above critical temperature and transparent below the critical temperature [25]. Fig. 2 shows the image of hydrogel produced above and below LCST. Further, the hydrogel was subjected to the deswelling studies, which was done by gravimetric method.

Hydrogels synthesized at 45 °C and 50 °C were not stable and the rest of the hydrogels synthesized at 28 °C, 32 °C, 34 °C, 36 °C and 42 °C were stable. The stable hydrogels were subjected to the deswelling studies and the morphological changes were observed through microscope. From the experiment, it was found that the hydrogels synthesized below LCST showed abrupt change in its diameter, whereas the hydrogels synthesized above LCST showed change in terms of thickness when temperature was raised during the deswelling experiment. This may be due to formation of thick dense layer on the surface of the hydrogels synthesized below LCST and this dense layer does not allow water to diffuse from the upper layer of the hydrogel and hence the hydrogel shrunk radially [26] as shown in Fig. 3, whereas hydrogel synthesized above LCST shrunk axially due to the presence of micro and nano pores on the surface of the hydrogel. Based on the observation, we could able to conclude that the hydrogel synthesized above LCST reduced in terms of its thickness and hydrogel synthesized below LCST reduced in terms of its size.

3.2. Morphology of bulk hydrogel sheet

The hydrogels synthesized above and below LCST were observed under microscope to further confirm the behavior discussed in Section 3.1. Fig. 4 shows the SEM image of hydrogels synthesized above and below LCST. From the figure it was observed that the hydrogel synthesized at 5 °C (Fig. 4(A)) was compact and had nonporous surface under its swollen state. Hydrogel synthesized at 5 °C was subjected to deswelling studies where the hydrogel shrunk radially, by squeezing its water content in its sides. As the reaction temperature increased from 5 °C to 28 °C, slight pore formation happened on the surface of the hydrogel (Fig. 4(B)). At reaction temperature 36 °C maximum micro and nano pore were formed on the surface of the hydrogel (Fig. 4(D)), where during deswelling experiment the hydrogel reduced its size in terms of its thickness by squeezing its water content through its surface. Further, the interconnected micro and nano porous structure, which made the water to diffuse more easily within the gel matrix during the deswelling and reswelling processes led to a rapid response rate.

From the above discussed results we could able to conclude that, as the polymerization reaction temperature increased (up to few degrees above LCST) the number and size of the pores also increased and the formation of the dense layer on the hydrogel could be avoided and thus we could able to increase the water diffusivity and response rate of the hydrogels.

3.3. Measurement of deswelling ratio of bulk hydrogels

In general, properties of the hydrogel are quantified in terms of its swelling capacity. The hydrogels were subjected to a continuous temperature change and the deswelling behavior was quantified by gravimetric method. The temperature was increased from 30 °C to 70 °C and for every 10 °C increase, the hydrogels were weighed by wiping the squeezed water using wet tissue paper. Fig. 5 shows the deswelling characteristic of hydrogel synthesized at various temperatures. From the figure it was observed that, all the hydrogels exhibited a similar temperature-dependence that lost water

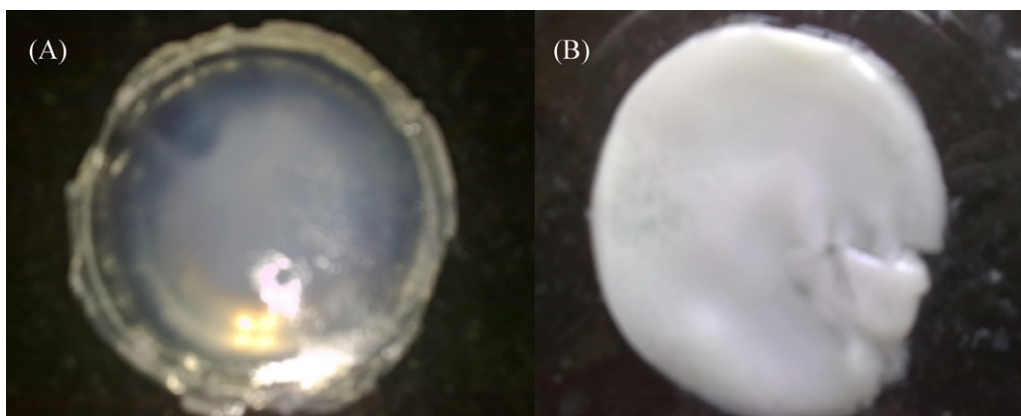


Fig. 2. Bulk hydrogel sheet synthesized below LCST (A) and above LCST (B).

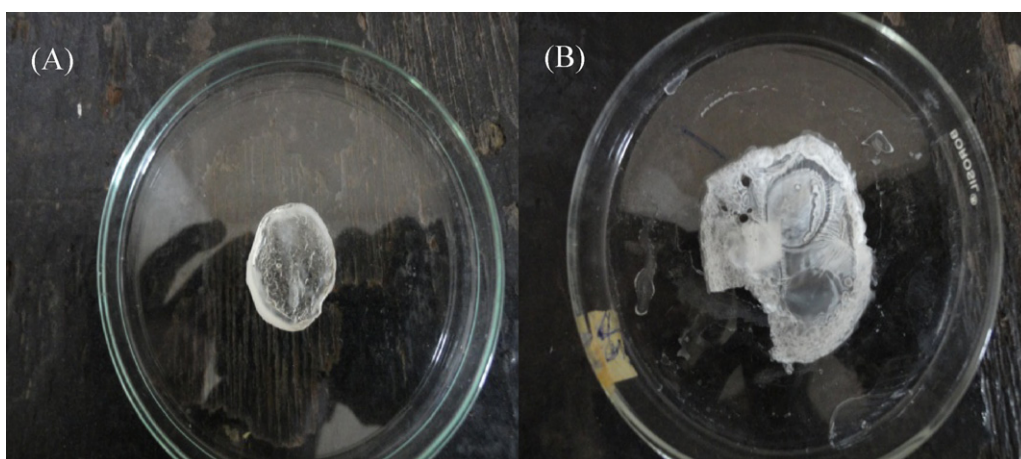


Fig. 3. Hydrogel after complete deswelling: (A) below LCST and (B) above LCST.

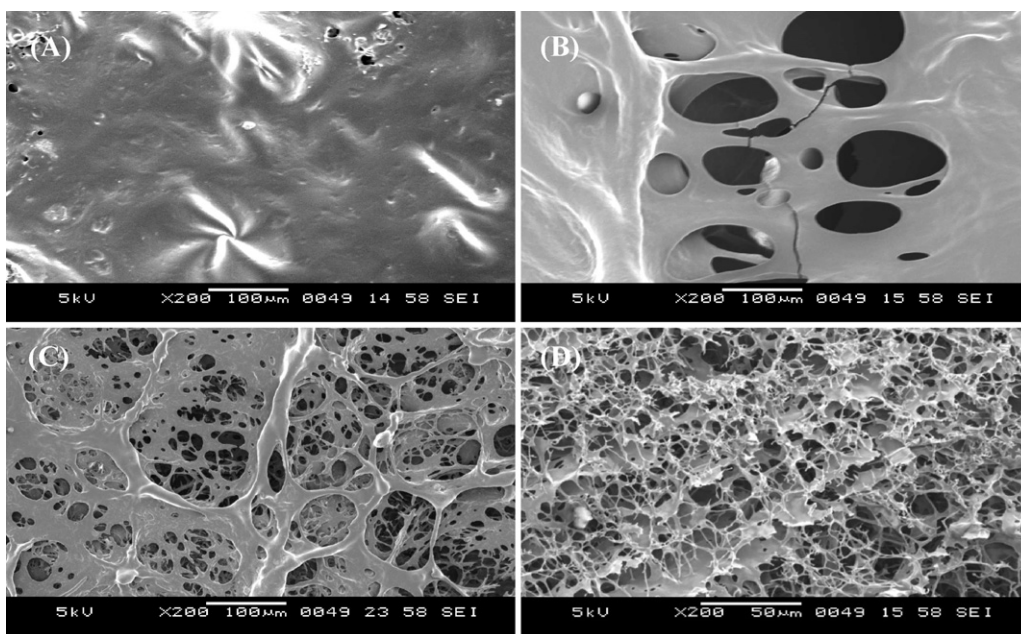


Fig. 4. SEM micrographs of the PNIPAA hydrogels synthesized at different temperature: (A) at 5 °C; (B) at 28 °C; (C) at 32 °C; and (D) at 36 °C.

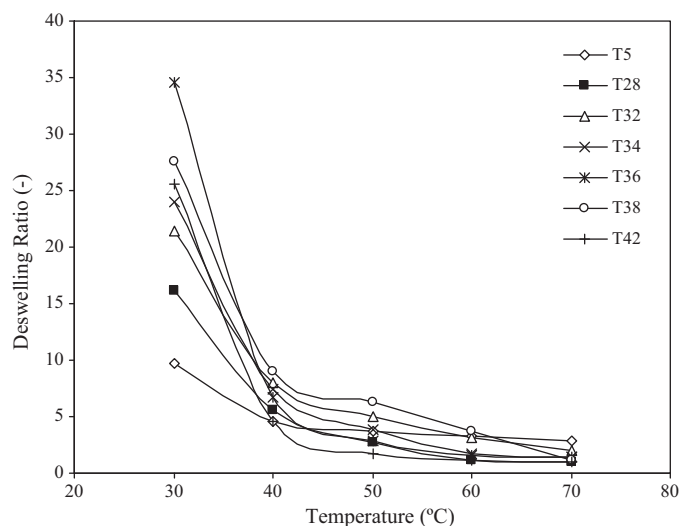


Fig. 5. Deswelling ratio of PNIPA bulk hydrogels as a function of temperature.

and shrank in volume [27]. All hydrogels synthesized at different temperature undergoes volume-phase transition by squeezing its water content as the temperature was raised. While increasing the temperature from 30 °C to the next higher level, the extent of hydrophobic interaction increased and particularly above LCST, these hydrophobic interactions dominated and led to the collapse of the PNIPA hydrogels. Similar behavior was observed in all the hydrogel, but the degree of volume-phase transition varied (Fig. 5). On the other hand, due to the increased thermal energy (at the temperature above LCST), the thermal motion of the polymer chains gets enhanced.

The attractive forces induced by the increased hydrophobic interactions also derived the chains to collapse and tangle with each other and the structured water was excluded as free water. During this course the entropy of the polymer chains was decreased and the entropy of the pristinely structured water surrounding the polymer chains of gel gets increased. But as a whole, the total entropy of the gel system, including the polymer chain and the surrounding water was increased. The phase transition of the temperature sensitive gel was an entropy increasing driven process i.e. the phase separation phenomena of PNIPA gel could be elucidated by the second law of thermodynamics.

From the figure (Fig. 5) it was observed that the hydrogels T5 and T28 exhibited slow shrinking rate. From the previous discussion regarding the entropy, we could conclude that, at swollen state due to expanded polymer chains of hydrogels (T32, T34, T36, T38 and T42), the number of structured water molecules decreased. Thus the expanded gel network shrinks easily and undergoes phase separation according to the second law of thermodynamics. When the temperature was raised above the LCST, the expanded polymer chains quickly dehydrated and the hydrogel exhibited rapid deswelling rate or display abrupt phase transition [28].

The deswelling property of the hydrogel also depends on the morphology of the hydrogel. From the SEM analysis, we could able to find dense layer on the surface of few hydrogel sheets (T5 and T28). From Fig. 5, we could find that those hydrogels (T5 and T28) showed lower swelling ratio. During deswelling process, the dense layer present on the surface of the hydrogel acted as resistance for the flow of liquid and hence the deswelling ratio was low. From Fig. 5 we could able to conclude that the hydrogel synthesized at 36 °C has better deswelling ratio of 34.5 and further for the synthesis of micro hydrogel 36 °C was used as reaction temperature.

Table 1
Particle size of the micro-hydrogels under various w/o ratio.

S. no.	w/o ratio (wt:wt)	Mean diameter (μm)	SD (μm)
1	1:1	0.77	0.43
2	1:1.5	0.75	0.08
4	1:2	-	-
3	1:2.5	-	-

Table 2
Effect of stirrer speed on size of micro-hydrogel.

S. no.	Speed of the stirrer (rpm)	Mean diameter (μm)	SD (μm)
1	300	2.43	1.74
2	400	0.93	0.38
3	500	1.04	0.45
4	600	1.30	1.00
5	700	0.78	0.14
6	800	0.74	0.05
7	900	0.74	0.05

3.4. Micro-hydrogels

Micro hydrogels were synthesized using the compositions which were optimized during bulk hydrogel synthesis. Micro hydrogels were synthesized using water–oil emulsion technique. Initially NIPA, BIS and TEMED were added to the precursor emulsion consisting of kerosene and span 80. Then the reaction was initiated by adding APS solution to the mixture. The mixture was continuously stirred using magnetic stirrer. While adding APS solution the color of the solution changed into pale pink for initial few minutes, which indicates phase transition of the monomer and further turned into milky white which confirmed the polymerization reaction. The formed micro hydrogels were subjected to seven cycle of centrifugal washing to remove unreacted chemicals, kerosene and span 80. The size of the micro-hydrogel was optimized by tuning the stirrer speed.

3.5. Effect of water–oil ratio on size of micro-hydrogels

The effect of w/o ratio on the size of the micro hydrogels was studied by varying the weight ratio of w/o from 1:1 to 1:2.5. The particle size distribution of NIPA micro-hydrogels prepared with various w/o ratio's (weight ratios) were characterized by Dynamic Light Scattering particle analyzer. Table 1 shows the influence of the water–oil ratio on the mean diameter of the micro-hydrogels. From Table 1, it was observed that the diameter of each sample was smaller than 770 nm. Moreover, the diameter distribution of the micro-hydrogels was least at 1:1.5. For w/o ratio of 1:2 and 1:2.5, Dynamic Light Scattering particle analyzer showed error. From repeated experiment at 1:2 and 1:2.5, we could able to conclude that beyond 1:1.15; the water/oil emulsion technique is not suitable for synthesis of micro-hydrogel. Below 1:1.5, the particle size distribution is not uniform. For w/o ratio of 1:1, the standard distribution is 0.43, which confirmed the irregular particle size distribution.

3.6. Effect of stirrer speed on size of micro-hydrogels

The effect of stirrer speed on the particle size distribution of micro-hydrogels was studied. Table 2 and Fig. 6 show the effect of the stirring rate on the mean diameter of micro-hydrogels. From the figure it was observed that the increase in the stirrer speed decreased the particle size. With increasing the stirring rate, the shear force in fluid increased and this resulted in the reduction of latex droplets size correspondingly the mean diameter of the micro-hydrogels became smaller [29]. As the stirrer speed

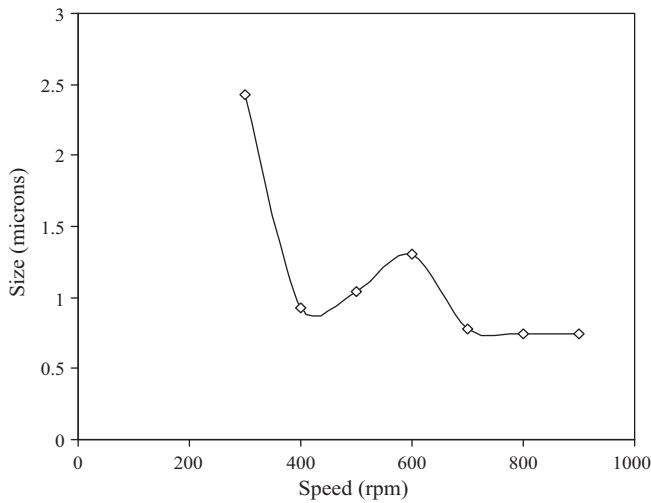


Fig. 6. Effect of stirrer speed on mean diameter of the micro-hydrogels.

increased from 300 to 400 rpm, the particle size reduced from 2.43 to 0.81 with a standard deviation of 0.38. The standard deviation (SD) value confirmed the irregular particle size distribution.

This could be due to the upper laminar condition prevailed during the agitation and further increase from laminar to transition, the particle size and SD value increased. As the stirrer speed was increased from 600 to 700 rpm, the particle size got reduced and further increase to 800 rpm the SD value reduced to 0.05. From this we could able to conclude that 400 and 800 rpm were suitable for producing micro-hydrogel, but 800 rpm give uniform size particles compared to 400 rpm.

3.7. Morphology of micro-hydrogels

Fig. 7 shows the morphology of micro-hydrogel synthesized at 800 rpm and w/o ratio of 1: 1.5 (optimized value). From the figure, we could able to conclude that the water oil emulsion technique is capable of producing perfect spherical hydrogel micro particles.

3.8. Dye absorption kinetic studies

In order to study the deswelling behavior of the micro-hydrogels, dye release studies were performed using methylene blue. Prior to the dye release studies, calibration chart was prepared for methylene blue at $\lambda = 312$ nm. Fig. 8 shows the dye release kinetics of both bulk and micro hydrogels, at different temperatures in 40 ml distilled water, which were prior equilibrated with 5 ppm

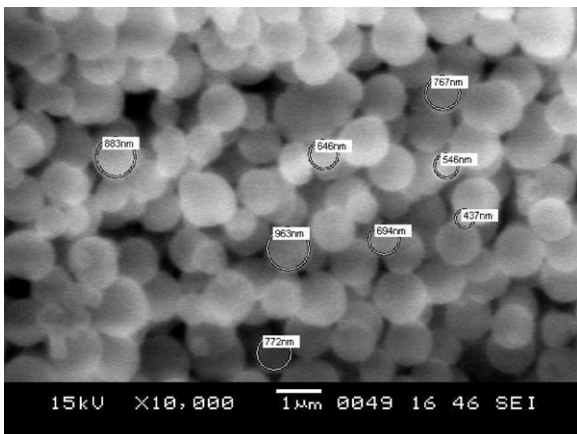


Fig. 7. Microscope images of micro-hydrogels synthesized at 800 rpm.

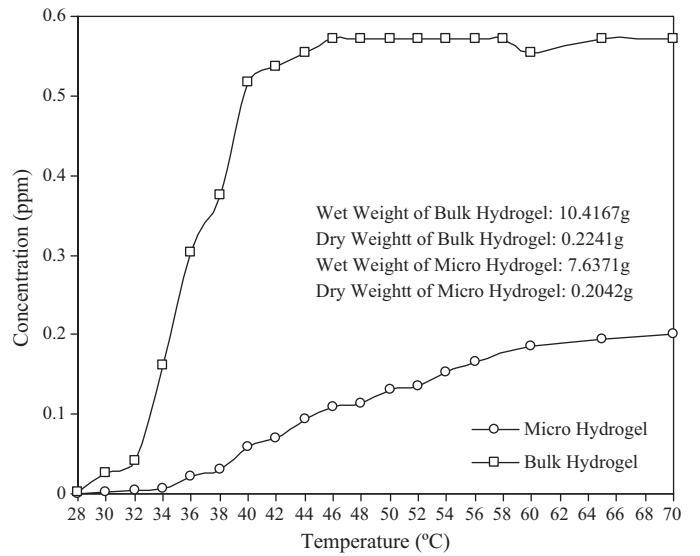


Fig. 8. Effect of temperature on methylene blue dye release.

methylene blue solution. Both bulk and micro hydrogels were prepared using the optimized compositions as mentioned in the early sections. From the figure; it was observed that, below LCST the response of both bulk and micro hydrogel was poor compared to the response above LCST. The hydrophilic nature of the hydrogel could be the reason for the poor response below LCST. Further increase in the temperature, increased the release rate and the dye concentration reached a maximum value of 0.57 ppm for bulk hydrogel and 0.21 ppm for micro hydrogel.

Though both bulk and micro hydrogels were subjected to same concentration of methylene blue solution (5 ppm), the final concentration in 40 ml distilled water during release studies varied significantly by 0.36 ppm (i.e. 0.57–0.21 ppm). Since, wet weight of bulk hydrogel was higher (10.47 g) than the wet weight of micro hydrogel (7.637 g), the final concentration of methylene blue in 40 ml distilled water varied significantly during release study, though the dry weight of both bulk and micro hydrogels were same. From this, we could able to observe that the bulk hydrogel could hold slightly higher amount of dye solution compared to

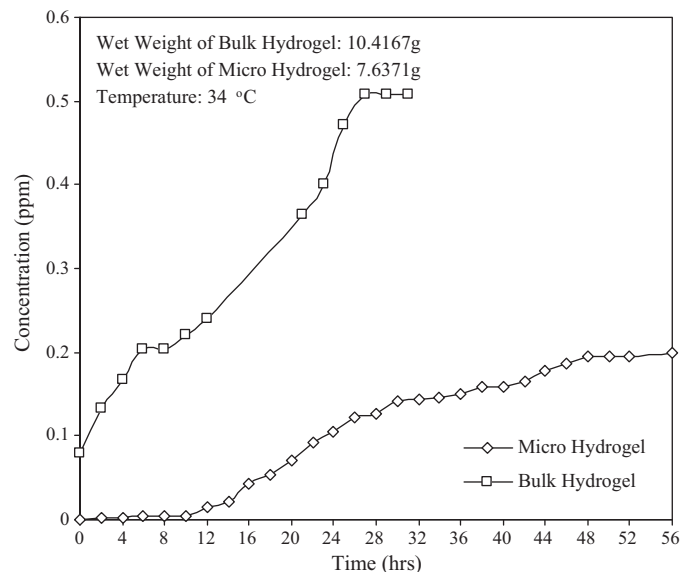


Fig. 9. Release kinetics of dye with respect of time.

the micro hydrogel, because of its well defined pore structure and lesser surface area.

The difference between the wet and dry weight of the micro hydrogel could be defined as the holdup of the micro hydrogel and from the experiment we could find it to be 7.43 g of 5 ppm methylene blue solution prior to release studies. When 7.43 g of 5 ppm dye solution dissolves in 40 ml of distilled water (during release studies) would give a final ppm of 0.48, and from the experiment we could be able to get final concentration as 0.21 ppm, which showed a maximum release of the dye [30]. From this we could be able to conclude that the micro-hydrogel produced by water–oil emulsion technique showed better deswelling characteristics.

To study the release kinetics and equilibrium time of the bulk and micro hydrogel at constant temperature, the hydrogels were permanently placed in known quantity (40 ml) of distilled water at 34 °C. Amount of dye released from bulk and micro hydrogel in 40 ml distilled water was measured in terms of concentration at regular time interval. Fig. 9 shows the release kinetics of both bulk and micro hydrogel with respect to time. From the figure it was observed that for the bulk hydrogel the final concentration reached 0.517 ppm, which exactly matched with the final concentration obtained during temperature effect. Similarly, for micro hydrogel the final concentration during time effect (0.197 ppm) matched with the final concentration during temperature effect (0.201 ppm). Though the final concentration in both temperature effect and time effect were same, the time duration varied significantly. The bulk hydrogel took 31 h to reach final equilibrium concentration where as micro hydrogel took 56 h to reach final equilibrium concentration. This could be because of the internal pore distribution and the overall available surface area of the bulk and micro hydrogels. In micro hydrogel because of size reduction the pores were less compared to the bulk hydrogel but overall surface area increased. From this, we could be able to conclude that the micro hydrogel had very slow release rate with respect to time, compared to the bulk hydrogel, where these micro hydrogels could be potentially used in the drug delivery system.

4. Conclusions

In this study, the poly(N-isopropylacrylamide) bulk hydrogel were successfully synthesized using free radical polymerization. Water–oil emulsion technique was successfully used to synthesize micro hydrogel. The composition of monomer, cross linker, initiator for the production of bulk hydrogel was optimized based on the deswelling behavior of hydrogel by conducting 35 different trials. Further the optimized reaction temperature was found to be 36 °C, where maximum deswelling ratio of 34.5 was achieved. From the deswelling behavior, it was observed that the gel synthesized below LCST responded radially and the gel synthesized above LCST responded axially. Based on the optimized values, micro hydrogel was synthesized using different water–oil ratio at different rpm. The water–oil ratio of 1:1.5 and stirrer speed of 800 rpm were found to be suitable for the production of micro hydrogels, where a minimum mean diameter of ~0.74 μm with SD of 0.5 were achieved. The SEM results of the micro hydrogel confirmed the synthesis of mono dispersed spherical shaped hydrogel particles. The dye release studies of the hydrogel with respect to temperature showed a maximum deswelling property and the dye release studies with respect to the time showed a sustained release of the dye for duration of 56 h.

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References

- [1] Y. Hirokawa, T. Tanaka, Volume phase transition in a nonionic gel, *J. Chem. Phys.* 81 (1984) 6379–6380.
- [2] G.H. Chen, A.S. Hoffman, Graft copolymers that exhibit temperature-induced phase transitions over a wide range of pH, *Nature* 373 (1995) 49–52.
- [3] J. Ricka, T. Tanaka, Swelling of ionic gels: quantitative performance of the Donnan theory, *Macromolecules* 17 (1984) 2916–2921.
- [4] S. Nayak, L.A. Lyon, Soft nanotechnology with soft nanoparticles, *Chem. Mater.* 16 (2004) 2623–2627.
- [5] Z.B. Hu, X.M. Zhang, Y. Li, Synthesis and applications of modulated polymer gels, *Science* 269 (1995) 525–527.
- [6] M. Zrinyi, Intelligent polymer gels controlled by magnetic fields, *Colloid Polym. Sci.* 27 (2) (2000) 98–103.
- [7] Y.H. Bae, T. Okano, S.W. Kim, Temperature dependence of swelling of crosslinked poly(N,N-alkyl substituted acrylamides) in water, *J. Polym. Sci. Polym. Phys. Ed.* 28 (1990) 923–936.
- [8] R. Yoshida, K. Sakai, T. Okano, Y. Sakurai, Y.H. Bae, S.W. Kim, Surface-modulated skin layers of thermal responsive hydrogels as on-off switches: I. Drug release, *J. Biomater. Sci. Polym. Ed.* 3 (2) (1991) 155–162.
- [9] R. Yoshida, K. Sakai, T. Okano, Y. Sakurai, Surface-modulated skin layers of thermal responsive hydrogels as on-off switches: II. Drug permeation, *J. Biomater. Sci. Polym. Ed.* 3 (3) (1992) 243–252.
- [10] Y.H. Bae, T. Okano, R. Hsu, S.W. Kim, Thermo-sensitive polymers as on-off switches for drug release, *Makromol. Chem. Rapid Commun.* 8 (1987) 481–485.
- [11] Z.B. Hu, Y.Y. Chen, C.J. Wang, Y.D. Zheng, Y. Li, Polymer gels with engineered environmentally responsive surface patterns, *Nature* 393 (1998) 149–152.
- [12] B. Panchapakesan, D.L. DeVoe, M.R. Widmaier, R. Cavicchi, S. Semancik, Nanoparticle engineering and control of tin oxide microstructures for chemical microsensor applications, *Nanotechnology* 12 (3) (2001) 336–349.
- [13] H. van der Linden, S. Herber, W. Olthuis, P. Bergveld, Development of stimulus-sensitive hydrogels suitable for actuators and sensors in microanalytical devices, *Sens. Mater.* 14 (2002) 129–139.
- [14] H. Kawaguchi, K. Fujimoto, Smart latexes for bioseparation, *Bioseparation* 7 (1998) 253–258.
- [15] A. Kondo, T. Kaneko, K. Higashitani, Development and application of thermo-sensitive immunospheres for antibody purification, *Biotechnol. Bioeng.* 44 (1994) 1–6.
- [16] J.T. Zhang, K.D. Jandt, A novel approach to prepare porous poly(N-isopropylacrylamide) hydrogel with superfast shrinking kinetics, *Macromol. Rapid Commun.* 29 (2008) 593–597.
- [17] R. Pelton, Temperature-sensitive aqueous microgels, *Adv. Colloid Interface Sci.* 85 (2000) 1–33.
- [18] B. Jeong, S.W. Kim, Y.H. Bae, Thermosensitive sol–gel reversible hydrogels, *Adv. Drug Deliv. Rev.* 54 (2002) 37–51.
- [19] T. Okano, N. Yamada, M. Okuhara, H. Sakai, Y. Sakurai, Mechanism of cell detachment from temperature modulated, hydrophilic–hydrophobic polymer surfaces, *Biomaterials* 16 (1995) 297–303.
- [20] D. Liang, S. Zhou, L. Song, V.S. Zaitsev, B. Chu, Copolymers of poly(N-isopropylacrylamide) densely grafted with poly(ethylene oxide) as high-performance separation matrix of DNA, *Macromolecules* 32 (1999) 6326–6333.
- [21] R.A. Stile, W.R. Burghardt, K.E. Healy, Synthesis and characterization of injectable poly(n-isopropylacrylamide)-based hydrogels that support tissue formation in vitro, *Macromolecules* 32 (22) (1999) 7370–7379.
- [22] Wenjiang Li, Xiaoxiang Sha, Wenjun Dong, Zichen Wang, Synthesis of stable hollow silica microspheres with mesoporous shell in nonionic W/O emulsion, *Chem. Commun.* (2002) 2434–2435.
- [23] W. Xue, I.W. Hamley, Thermo reversible swelling behaviour of hydrogels based on N-isopropylacrylamide with a hydrophobic comonomer, *Polymer* 43 (2002) 3069–3075.
- [24] Moon Sik Shin, Hyung seok Kang, Tae Gwan Park, Ji-Won Yang, Synthesis and characterization of pH/temperature sensitive hydrogels based on chitosan derivative, *Polym. Bull.* 47 (2002) 451–456.
- [25] J. Wang, Z. Chen, M. Mauk, K.-S. Hong, M. Li, S. Yang, H.H. Bau, Self-actuated, thermo-responsive hydrogel valves for lab on a chip, *Biomed. Microdev.* 7 (4) (2005) 313–322.
- [26] Y. Kaneko, R. Yoshida, K. Sakai, Y. Sakurai, T. Okano, Temperature-responsive shrinking kinetics of poly(N-isopropylacrylamide) copolymer gels with hydrophilic and hydrophobic comonomers, *J. Membr. Sci.* 101 (1995) 13–22.
- [27] X.C. Xiao, Effect of the initiator on the thermosensitive rate of poly(N-isopropylacrylamide) hydrogels, *Exp. Polym. Lett.* 1 (4) (2007) 232–235.
- [28] X. Zhang, R. Zhuo, Y. Yang, Using mixed solvent to synthesize temperature sensitive PNIPAA gel with rapid dynamics properties, *Biomaterials* 23 (2002) 1313–1318.
- [29] Xin-Cai Xiao, Liang-Yin Chu, Wen-Mei Chen, Shu Wang, Rui Xie, Preparation of submicrometer-sized monodispersed thermoresponsive core–shell hydrogel microspheres, *Langmuir* 20 (2004) 5247–5253.
- [30] M.M. Perju, E.S. Dragan, Removal of azo dyes from aqueous solutions using chitosan based composite hydrogels, *Ion Exchange Lett.* 3 (2010) 7–11.