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# Influence of reaction parameters on synthesis of temperature-sensitive materials in supercritical carbon dioxide by precipitation polymerization

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## Summary

Temperature-sensitive materials were prepared by free radical precipitation copolymerization of N-isopropylacrylamide (NIPA) with acrylic acid (AA) or 1-vinyl-2-pyrrolidone (VP) in supercritical carbon dioxide ($scCO_2$). Dry, fine, powdered, nano-sized polymer product was produced at 70°C and pressures ranged from 150 to 400 bar. The resulting high yield (>96%) of temperature-sensitive microgels was obtained in the absence of stabilizer. The effects of comonomer, reaction pressure and reaction time on the yield and morphology of the copolymers have been investigated. It was found that solubility of NIPA in $scCO_2$ was remarkably enhanced in the presence of comonomers. The morphology of polymers could be controlled conveniently by changing reaction parameters. In addition, the reaction could be completed in short time in the presence of divinyl monomer.

**Keywords:** Copolymerization; crosslink; Precipitation polymerization; Supercritical carbon dioxide; temperature-sensitive polymers.

## Introduction

"Intelligent" or "smart" materials exhibit large property changes in response to small physical or chemical stimuli. Stimuli responsive polymers have been studied as smart materials aiming at the applications in biomedical fields or chemomechanical devices. The representatives of the stimuli-sensitive polymers are P (N-isopropylacrylamide) (PNIPA) and its copolymers, in which the coil-globule transition based on hydration-dehydration behavior is induced in response to temperature [1]. PNIPA have been one of the most commonly studied thermoreversible systems, with a low critical solution temperature (LCST) in water of 32°C. Temperature-and pH-sensitive hydrogels are the most investigated, because of the easy control and wide-ranging applicability of these signals such as biotechnology, chemical processing, and medical fields [2-3].
These many applications require the PNIPAM material to be very pure and free from residual solvent. However, temperature-sensitive microgels is usually produced by radical polymerization in aqueous solutions or several conventional organic solvents [4-7]. Such product need to be precipitated into diethyl ether and then rinsed

thoroughly with distilled water, which generate large quantities of wastewater and require substantial quantities of energy to dry the polymer product. Thus purification stage for the polymers is often energy intensive and therefore expensive.

Recently, the use of supercritical carbon dioxide ($scCO_2$) as an alternative to traditional aqueous and organic solvents has attracted much attention in the fields of extraction, polymer synthesis and materials processing [8-10]. Carbon dioxide is inexpensive, nontoxic, and non-flammable, and it has an easily accessible critical point with a $T_c$ of 31.1°C and a $P_c$ of 73.8 bar [11]. $scCO_2$ can exhibit the best features of two worlds: they can have gaslike diffusivities and liquidlike densities. In the vicinity of the fluid's critical point, its density is highly sensitive to modest changes in pressure or temperature. Higher $scCO_2$ diffusivities have important implications in polymerization kinetics and in polymer processing (i.e., diminishing the "cage effect" associated to the initiator decomposition in free radical polymerization processes). The thermodynamic and transport properties of $scCO_2$ can be easily tuned by adjusting the pressure or temperature. Polymers can be isolated from the reaction mixture by a simple depressurization, resulting in a clean, dry polymer product.

Based on above mentioned, provided such stimuli responsive polymers made in a non-toxic solvent, whose solvation properties can be tuned, creates great potential in all of the biomedical fields and drug delivery. For example, if a bioactive substance could be incorporated in these polymers during or after polymerization with the aid of $scCO_2$ would be very interesting.

Many polar or hydrophilic molecules, such as water, proteins, amides, ionic species, sugars, etc., exhibit very poor solubility in $CO_2$. So far, Limited research efforts have been reported on the polymerization of water-soluble vinylic monomers containing amides in carbon dioxide, including inverse emulsion polymerization of acrylamide [12], emulsion polymerization of N-ethylacrylamide [13], dispersion copolymerization of N, N-dimethylacrylamide [14].

Because of the low solubility of the majority of polymers in supercritical carbon dioxide, special $CO_2$-philic stabilizers have been developed and used in various dispersion and emulsion polymerization of monomers. However, the presence of stabilizers that cannot be easily removed from the polymer becomes a concern for some applications. Precipitation polymerization is an alternative approach, which produces stabilizer-free polymers [15]. In a precipitation polymerization, an initially homogeneous mixture of monomer, initiator, and solvent becomes heterogeneous during the reaction as insoluble polymer chains aggregate to form a separate polymer phase. Primary radicals are formed from thermally promoted fragmentation of the initiator. These primary radicals rapidly react with monomer molecules to produce polymer chains that are insoluble in the continuous phase.

To our knowledge, no previous attempt has been made to study the temperature sensitive materials in supercritical carbon dioxide. The objectives of the study are to find a new route towards materials that can be applied in biomedicine. In this work, the influence of comonomers, reaction pressure and reaction time have been investigated.

## Experimental

### *Materials*

N-isopropylacrylamide (NIPA) was purchased from Acros (99%) and was used as received. 1-vinyl-2-pyrrolidone (VP) (99%) and Acrylic acid (A.R. grade) were distilled at reduced pressure prior to use. 2,2′-AzoBIS(isobutyronitrile) (AIBN) was supplied by Shanghai Chemical Agent fourth Factory and was recrystallized twice from methanol. N,N-methylenebisacrylamide (BIS) was analytical reagent grade and supplied by Tianjin Chemical Reagent Company. Carbon dioxide gas was purchased from Guangzhou Gas Factory with >99.9% purity. High-pressure reactions were carried out in a 300 mL stainless steel reactor equipped with sapphire windows used for observation of the phase behavior during the reaction process. The pressure in the reactor was measured using a pressure gauge in the range of 0-400 bar.

The temperature of the reactor was measured with a platinum resistance thermometer (model WMZK-01, produced by Shanghai medical instruments Factory). A magnetic stirrer was used for mixing.

### *Precipitation polymerization*

In a typical polymerization reaction, the autoclave was charged with 1.0 g of NIPA, 0.2 g of comonomers, and the desired amount of AIBN. The reactor immersed in an ice bath was first purged with a flow of $CO_2$ to remove air for 20 min and then filled with liquid $CO_2$ to desired amount. The autoclave was gradually heated to 70°C, on average, it took approximately 120 min to heat from room temperature to 70°C, and the pressure was gradually increased to desired pressure, the polymerization was allowed to proceed for 3 h as stir bar agitated the mixture. At the end of the reaction, the autoclave was cooled to room temperature and the $CO_2$ was slowly vented through a pressure release valve. A white, dry, flow powdered polymer product was collected, no purification was necessary before the storage of the polymer product.

### *Characterization*

The products were treated with subcritical carbon dioxide by high pressure Soxhlet extractor to remove the unreacted monomers until the mass of the products did not change. The yield of these polymerizations is above 95%, which is calculated according to the mass of final products and added monomer. Scanning Electron Microscopy (SEM) images were obtained using a JSM-6330 FE SEM (JEOL LTD, Japan). FTIR spectra of samples were taken in KBr pellets using a Bruker/VECTOR 22 FTIR spectrophotometer (Bruker Optics Inc,Germany). The VPTTs of the microgels were determined by measuring the light transmittance (at 500 nm) of a microgel dispersion between 24 to 50°C using CARY 100 UV-vis Spectrophotometer (Varian Inc, USA), equipped with a circulating water bath. The pH sensitivity was measured by swelling ratios in different pH buffers. Lightly crosslinked copolymer particles were immersed in the buffers of various pH values from 1 to 11 for a week.

## Results and discussion

### *FT-IR Spectra*

FTIR spectra were used to identify the chemical components of the copolymers. Fig. 1 shows the FTIR spectra of cross-linked PNIPA and the cross-linked copolymers of NIPA with AA or VP. In Fig. 1, the stretching vibration peak due to CO groups in AA is observed at 1721 $cm^{-1}$. The bending vibration peak due to amide groups (i.e., amide I: C=O stretching and amide II: N-H bending) of cross-linked NIPA-*co*-AA are in the ranges of 1651-1653 and 1550-1552 cm$^{-1}$, respectively. The characteristic peaks of VP in the FTIR spectra appeared at 1288 cm$^{-1}$, and a broad absorption band characteristic of VP at 1672 cm$^{-1}$, where an increment in the intensity of vibration peak in the case of a crosslinked NIPA-co-VP sample. Therefore, it can be concluded from FTIR spectra that cross-linked copolymer formation occurred.

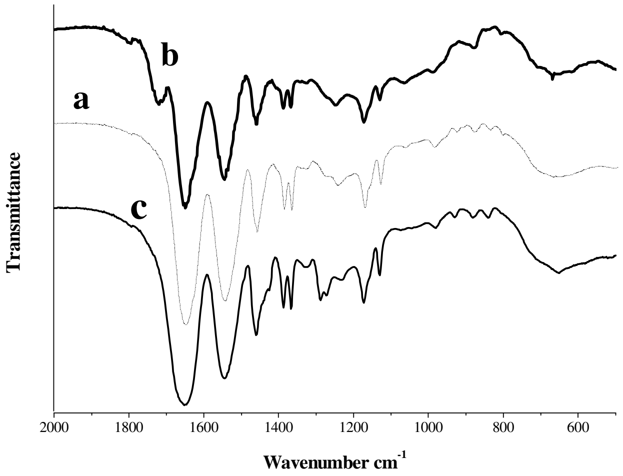


**Figure 1** FTIR spectra of (a) cross-linked of PNIPA and their copolymers(b)NIPA-co-AA(c)NIPA-co-VP synthesized in present study.

### *Phase Behavior of the Reaction Mixture*

The phase of the $CO_2$/monomers system was investigated by coupling visual observation of the mixture to the recording of the pressure trend inside the fixed volume view autoclave as a function of the temperature during the slow heating of the reaction system. At room temperature, all the investigated systems were composed of two fluid phases (solid NIPA and liquid $CO_2$, comonomers), which merged into a single phase during the heating cycle.

This simple static synthetic method was repeated for all initial feed compositions of the reaction mixture adopted in this work, all of which were initially composed of a single phase under the operating conditions adopted to perform the polymerization.

During copolymerization of NIPA with AA (VP) with or without BIS, the polymerization mixture was initially all clear and homogeneous. After a relatively short time (around 1 h), the growing polymer could be seen precipitating out of solution and coalescing on the cell window. Therefore, it would appear that under these conditions the nature of the reaction is a precipitation polymerization.

### *Effect of comonomers*

Our experiments found that NIPA had a relatively low solubility in $CO_2$. Precipitation polymerization of NIPA results in poor yield of a slightly yellow, hard and glassy material. A scanning electron microscope (SEM) picture of such a sample is shown in Figure 2. To investigate the effect of comonomers on the copolymerization, two

**Table 1** Effect of comonomers on polymerization (Reaction condition: 400 bar, 1.0g NIPA, 0.2g comonomer, 0.04gBIS, 70°C, 8h.)

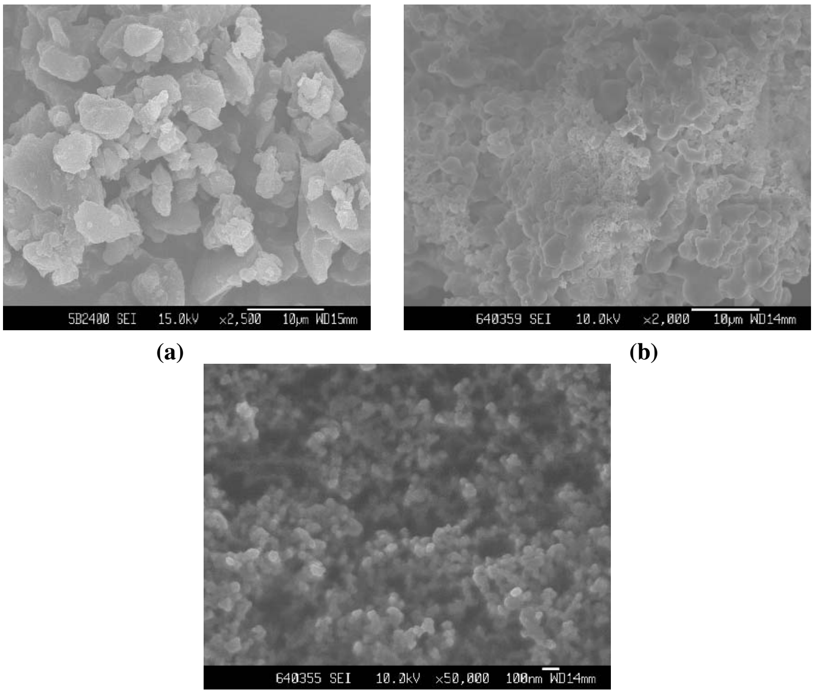
| Entry | comonomers | Yield/% | Polymer Morphology [a] |
|---|---|---|---|
| 1 | AA | 97 | Lower density, dry, White, powder |
| 2 | VP | 37 | Aggregate |
| 3 | BIS | 99 | Dry, White ,fine powder |
| 4 | AA+ BIS | 99 | Dry, White, fine powder |
| 5 | VP+BIS | 99 | Aggregate |
| 6[b] | - | 41 | Glassy solid |

[a] Appearance of the polymer after venting

[b] Without comonomers or BIS

hydrophilic monomers AA or VP and crosslinker BIS were used as comonomers for the precipitation copolymerization of NIPA in $CO_2$. Their structures are shown in Figure 3. The polymerizations were carried out on a scale of 1.0 g NIPA, (0.3w/v% monomers in $CO_2$), 8.3wt.-% AIBN, the reaction conditions were kept at 400 bar at 70°C and only the comonomers were changed. The results obtained are summarized in Table 2. In most case, the monomer conversion is >96%, however, the copolymerization with VP, lower conversion was obtained, Suggesting that AA has a higher reactivity ratios when copolymerization with NIPA in $scCO_2$ than that for VP. Besides, AA worked effectively as cosolvent to some extent that solubility of NIPA in $CO_2$ can be remarkably altered by adding a little amount of AA. Philip G. Jessop [16] reported that the difference between solid solubilities in a given SCF depends mainly on the solid vapor pressure and intermolecular interactions between solvent and solute. In this studied system, suggesting that the solubility of AA is much larger than that for VP or NIPA under similar conditions mainly because of the difference in their vapor pressures (NIPA=0.0881 Torr, VP=0.132 Torr, AA=3.42 Torr at 25°C). The additional Lewis acid-base type interaction between $CO_2$ and monomers govern the solubility of them.

In the absence of divinyl monomer BIS, the precipitation polymerization of NIPA in $scCO_2$ resulted in poor yield (Table 1, entry 6). In the presence BIS, a little amount of BIS (0.04g) can induce higher conversion of NIPA. Figure 2 shows the effect of the amount of the BIS on the morphology of the polymer particles. Because the crosslinking structure reduced the solubility of PNIPA chains in sc $CO_2$, the polymers with a higher degree of crosslinking precipitated out of the $CO_2$ fluid phase faster. Therefore, the increase in the concentration of the BIS increased the number of nuclei generated in the reaction system and reduced the particle diameter, as shown in Figure 2. We also think that the formation of microspheres in our samples attributes to the rigidity of the polymers. Since the copolymerization of NIPA with VP in absence of BIS was also studied, a little, white, aggregate microgel was obtained. The morphology is very different from cross-linked samples. The fact that the lightly cross-linked polymers did not form microspheres is consistent with this idea. The particles formed from higher BIS samples (Fig 2c) were significantly less agglomerated than those formed from lower BIS samples (Fig 2b), perhaps because the highly cross-linked particles were more rigid, and therefore less prone to aggregation. Such similar phenomena are also found by other works. [17-19]



**(a)** **(b)**

**(c)**

**Figure 2** Effect of BIS ratios on polymerization NIPA-co-VP in $scCO_2$. (a) 0g BIS (b) 0.025 g BIS (c) 0.08g BIS.

*Effect of reaction time*

The reaction time has a strong effect upon the conversion and morphology of the resulting polymer. In an effort to gain insight into the reaction progress as a function of time, Polymerization of cross-linked P (NIPA-co-AA) was chosen as a model system. Samples were obtained by stopping the reactions at various intervals. Table 2 depicts the results from this study. Figure 4 shows the conversion increase with reaction time. When the reaction time is increased up to 50 min, it was observed the formation of particles although with larger aggregation. After 1 h, a white, dry, fine powder was obtained with yields around 90%. For diffusion-controlled kinetics in free-radical polymerization, as expected, when the autoacceleration effect is more pronounced, the polymerization rate is much faster, and the polymerization fully completed within 2 h.

**Table 2** Effects of reaction time on polymerization (Reaction condition: 400 bar, 1.0 g NIPA, 0.2 g AA, 0.1 g AIBN, 0.04 g BIS. 70°C.)

| Entry | Time / h | Yield / % | Polymer Morphology[a] |
|---|---|---|---|
| 7 | 1.3 | 51 | aggregate |
| 8 | 1.8 | 95 | Dry,white,fine powder |
| 9 | 2.0 | 99 | Dry,white,fine powder |
| 10 | 2.5 | 99 | Dry,white,fine powder |

[a] Appearance of the polymer after venting

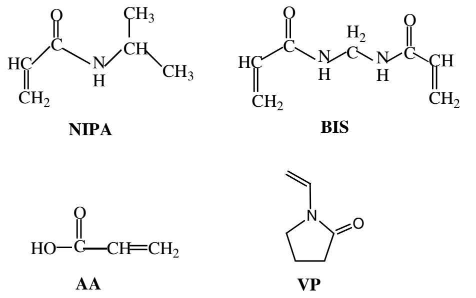


**Figure 3** Chemical structures of monomers.

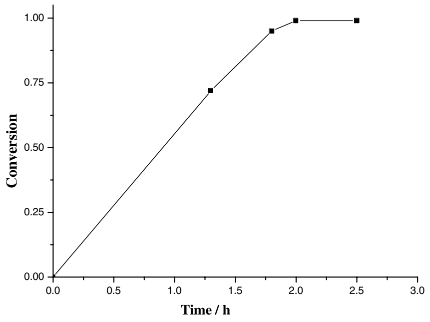
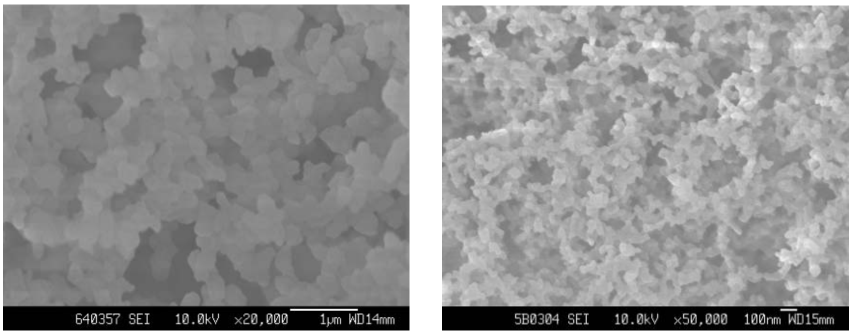


**Figure 4** Effect of reaction time on conversion.

### *Effect of reaction pressure on polymer distribution*

An opportunity unique to supercritical fluids as a reaction medium is the ability to adjust its solvent quality through its easily tunable density and dielectric constant by simply changing either pressure or temperature. Moreover, for free-radical reactions, $CO_2$ offers no chain transfer to solvent and high free-radical initiation efficiency with acceptable initiator decomposition kinetics [20]. The precipitation copolymerization of NIPA with AA or VP in $scCO_2$ was conducted at four different pressures; the results are collected in Table 2.

Our Previous study [21] suggested that in the reaction system (300 mL), where a rather high initiator concentration is necessary to achieve good monomer conversions in $scCO_2$. Based on above discussion, batch reactions were performed with the same amount of monomers, initiator (8.3wt.-% based on the monomers weight), at 70°C for 10h, although most reactions were fully completed with 3h. During the reactions, the corresponding $CO_2$ densities were 0.508, 0.738, 0.823, 0.857g·mL$^{-1}$.Table 3 gives the results of overview morphology of the cross-linked NIPA-co-AA and NIPA-co-VP produced from the reactions with different $CO_2$ pressure. When the pressure was increased from 150 to 400 bar, the polymer products mainly distribute dominates changing from top to bottom of the autocalve, and the higher pressure, the more isolated, the higher particles densities obtained. This suggests that the polymerization of cross-linked NIPA copolymers in $scCO_2$ is extremely sensitive to the density of the continuous phase. An interesting behavior was found during the synthesis of cross-linked polymers, when the pressure is 150 bar, the dry, soft polymer products filled the whole reactor volume instead of bottom of view cell. But above 250 bar, white, dry, fine powders was obtained in bottom of the autoclave. Similar results were obtained in most batch process. Scanning electron microscopy (SEM) was employed to investigate the polymer morphologies with different pressure. It can be clearly seen by comparing Fig.5 (a) with Fig.5 (b) that the polymers produced from higher pressure 250 bar, resulted in lightly aggregated polymers and their particles size were in 50 nm. However, the polymer product formed in larger diameter size when prepared at 150 bar. A similar trend was found in other works [22-23]. It may be ascribed that the propagating macro-radical will aggregate and precipitate faster at a lower pressure, and then the polymer particles precipitate in the wall of chamber, from which point the polymerization mainly took place in polymer-rich phase. The monomer and radicals diffuse into the polymer particle and led to larger particle aggregates.



(a) (b)

**Figure 5** SEM images of cross-lined NIPA-co-VP particles from the reactions at the $CO_2$ pressure of (a) 150 bar, (b) 250 bar Reaction conditions: 1.0g NIPA; 0.2gVP; 0.1g AIBN; 70°C; 10 h; 0.04 g BIS.

**Table 3** Effects of reaction pressure on polymerization( Reaction condition: 400 bar, 1.0 g NIPA, 0.2 g VP, 0.1 g AIBN, 0.04 g BIS. 70°C.)

| Entry | Pressure/ bar | Yield / % | Polymer Morphology[a] |
|---|---|---|---|
| 11 | 150 | 99 | Aggregate |
| 12 | 250 | 98 | Dry, yellowish ,fine powder |
| 13 | 250[b] | 97 | Dry, white ,fine powder |
| 14 | 350 | 96 | Dry, yellowish ,fine powder |
| 15 | 400 | 98 | Dry, yellowish ,fine powder |
| 16 | 350[b] | 99 | Dry, white ,fine powder |
| 17 | 400[b] | 99 | Dry, white ,fine powder |

[a] Appearance of the polymer after venting
[b] comonomer=0.2 g AA

*Demonstration of the stimuli-responsive properties of the microgels*

One of the aims of this study was the preparation of materials with thermosensitivity, the end-use properties of the cross-linked copolymers obtained at different comonomers were compared by measuring microgels dispersion absorbency observed at $\lambda = 500$ nm at different temperatures. There has been a sharp increase in the absorbency when the temperature was in the period of 32~40°C. It suggested that the VPTT of the copolymers could be altered by slight modifications of the copolymer composition.

In order to demonstrate the pH sensitivity of cross-linked NIPA-co-AA polymers, the swelling ratios of these samples in different pH solutions were measured At the pH value above 5, significantly higher swelling was observed in the crosslinked polymers. As pH approached 11, maximum swelling of 60~90 times was observed, this indicates possibly complete ionization of carboxylate groups.

## Conclusions

This study indicates that cross-linked NIPA copolymer can be produced in supercritical carbon dioxide. Cross-linker effectively worked as surfactant in the stabilization of the cross-linked microparticles to some extent. It is possible to obtain monodispersed nano-sized spherical particles with narrow size distribution and in short reaction times, by changing the initial concentrations of initiator, cross-linker and $CO_2$ pressure as well as reaction time. The polymers were obtained in high yield as dry, fine and free flowing material directly from the reaction vessel. No contamination of monomer was obtained in the final product by continuously washing the polymer at the end of the reaction with high-pressure $CO_2$. Future work will focus on the impregnation of cross-linked copolymer with water-insoluble drug in $scCO_2$ and investigate their adsorption behavior.

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