THE EFFECT OF POLY(N-HYDROXYMETHYL ACRYLAMIDE) CHAIN LENGTH IN POLY(N-VINYL PYRROLIDONE)-BLOCK-POLY(N-HYDROXYMETHYL ACRYLAMIDE) ON ITS SENSITIVITY TO pH

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ABSTRACT

The synthesis of pH-sensitive poly(N-vinyl pyrrolidone)-block-poly(N-hydroxymethyl acrylamide)s (PNVP-b-PNMA) was carried out using atom transfer radical polymerization by varying the amount of N-hydroxymethyl acrylamide to study its effect on pH. The success of polymerization was characterized using FT-IR and ¹H-NMR. The investigation of block copolymers sensitivity to pH was performed by observing the changes in particle sizes of copolymers at various pH. Particle sizes of PNVP-b-PNMA were affected by the pH, in which they became smaller (275.43 – 548.70 nm) at pH 9 and 12 than that in pH 3, 5, and 7 (394.86 – 694.56 nm). In addition, particle sizes increased along with the increasing monomer composition of N-hydroxymethyl acrylamide.

Keywords: pH-sensitive polymer, N-hydroxymethyl acrylamide, N-vinyl pyrrolidone, Block Copolymers, Particle Sizes.

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INTRODUCTION

Stimuli-sensitive polymers are polymers that can give responses to environmental changes, which have been known for a long time yet are still under development to study its properties and characteristics with various synthesis methods and techniques.¹ There are many types of stimuli-sensitive polymers, two of the most interesting types are temperature-sensitive polymer and pH-sensitive polymer. Some polymers can respond to the change of temperature by changing their physical properties and interacting with other molecules. Saxena and Bhatt studied interactions between poly(vinyl alcohol) (PVA) in an aqueous solution by investigating its ultrasonic speed, density, and viscosity. Its physical properties changed towards temperature because of interactions between PVA and water.²

pH-sensitive polymers can respond to the change of pH due to the presence of acidic functional groups, i.e., carboxylic or basic, i.e., amines, in their side chains. Much research about pH-sensitive polymers and their applications has been conducted. Wikantyasning *et al.* reported the incorporation of gold nanoparticles on agarose hydrogel, which was crosslinked by a pH-sensitive polymer of poly(acrylic acid). As a response to pH change, this hydrogel nanocomposite had peculiar swelling/deswelling properties response to pH, and thus, it is promising to be used as a nanosensor.³ Darjito *et al.* prepared chitosan–silica by sol-gel method and studied the adsorption of metal ions (Mn²⁺, Cu²⁺, Zn²⁺) in different pH solutions. It was found that there was a rise in the adsorption ability of all ions, which is more likely due to the repulsion of the positive charges between the metal ions and the adsorbent. The adsorbent, in particular chitosan, experienced protonation at low pH resulting in a positive charge in its amine groups.⁴

Another example of a pH-sensitive polymer is poly(N-hydroxymethyl acrylamide) (PNMA), and not many researchers have been investigated its sensitivity to pH.⁵⁻⁷ The monomer, N-hydroxymethyl acrylamide (NMA) can be copolymerized with N-vinyl pyrrolidone (NVP), which polymer has been known for its advantages, such as non-toxic, biocompatible, has good affinity to hydrophilic or hydrophobic substances, etc.⁸ Because of its advantages, poly(N-vinyl pyrrolidone) (PNVP) has been applied to various applications. For example, poly(N-vinyl pyrrolidone)-block-polycaprolactone micelles for nanocarriers of anti-TB drugs⁹, metal retention in various pH.¹⁰

To our knowledge, not many studies have been reported regarding the synthesis of PNMA based block copolymers and their pH sensitivity. We herein present the attempt to synthesize PNVP-b-PNMA using the macroinitiator approach of ATRP with PNVP as the first block and PNMA as the second block by varying the amount of NMA to investigate its effect on pH sensitivity. The functional groups in copolymers were characterized by FT-IR and the structure of the copolymers was characterized by $^1\text{H-NMR}$. Furthermore, the sensitivity of the copolymers towards pH was investigated using a particle size analyzer (PSA) in various pH.

EXPERIMENTAL

Material and Methods

NVP (Aldrich, 99%), NMA, ethyl α -bromoisobutyrate (EBiB), copper (I) bromide (CuBr, Aldrich, 98%), 2,2'-bipyridine (bpy, Merck, 99%), dichloromethane (DCM, Aldrich, 99%), chloroform (Aldrich, 99%) and diethyl ether (Aldrich, 99%) were used as received. The pH solutions were made from pH 5 and pH 7 phosphate buffer of potassium dihydrogen phosphate and dipotassium hydrogen phosphate. Then, the phosphate buffers were adjusted to pH 3, 9, and 12 with hydrogen chloride or sodium hydroxide.

Synthesis of PNVP-Br Macroinitiator

The synthesis method was adapted from others.^{9,11-14} First, the solvent (20 mL H_2O) was purged with nitrogen. Then, CuBr (1.40 mmol) and bpy (1.40 mmol) were added to the solvent and stirred. NVP (70.00 mmol) was then added into the mixture and purged with nitrogen. EBiB (1.40 mmol), was added to the mixture and the polymerization was allowed to proceed for 12 h at 70°C . After 12 h, the mixture was exposed to air to stop the polymerization. Purification was done by passing the polymer solution through the alumina column, followed by precipitation in diethyl ether. The obtaining polymer was dried in an oven at 60°C . As a reference, PNMA was synthesized using a similar procedure.

Synthesis of PNVP-b-PNMA

PNVP-b-PNMA was synthesized by using PNVP-Br as a macroinitiator. First, the solvent was purged with nitrogen. After that, CuBr and bpy were added to the solvent and stirred. Various amount of NMA was added into the mixture and was purged with nitrogen. Then, the macroinitiator PNVP-Br was added to the mixture. The polymerization was carried out at 70°C for 6 h. The mixture was exposed to air to stop the polymerization. Purification was conducted by passing the polymer solution through alumina followed by precipitation in diethyl ether. Finally, the polymers were dried in an oven at 60°C . The synthesis of PNVP-b-PNMA method was adapted from others.^{9,13-14}

Characterization Method

Functional groups of the products were characterized using Shimadzu Fourier Transform-Infrared Spectroscopy (FT-IR) with KBr at $400\text{ cm}^{-1} - 4000\text{ cm}^{-1}$. The structure and repeating units (ru) of the products were characterized using $^1\text{H-NMR}$, which were recorded using Bruker-Avance 500 MHz Nuclear Magnetic Resonance in D_2O as the solvent. The number average molar masses (M_n) of the products were calculated from its repeating unit using end group analysis as in eqn.-1.

$$M_n = M_{\text{end group}} + (M_{\text{ru macroinitiator}} \times \text{ru macroinitiator}) + (M_{\text{ru second block}} \times \text{ru second block}) \quad (1)$$

The particle sizes were characterized using Horiba-Sz 100Sz particle size analyzer in pH 3, 5, 7, 9, and 12 at room temperature.

RESULTS AND DISCUSSION

Molecular Structure Analysis of PNVP-Br Macroinitiator and PNVP-b-PNMA

The PNVP-Br macroinitiator synthesized to act as the first block and the second block would be formed by chain extension of this macroinitiator. The FT-IR spectrum of PNVP-Br is shown in Fig.-1, which shows that vinyl peak does not appear. This concludes that the polymer was formed. In comparison with FT-IR spectrum of PNVP that previously had been characterized by other researchers, PNVP-Br in this research gave similar peak positions.¹⁵⁻¹⁶ Nonetheless, the existence of a hydroxy peak might be caused by the presence of water in the PNVP-Br spectrum.¹⁶

Fig.-1: FT-IR Spectra of PNVP-Br, NMA, PNMA-Br and PNVP-b-PNMA

PNVP-Br was used as a macroinitiator and acted as the first block in PNVP-b-PNMA, while the second block was formed by varying the amount of NMA. Figure-1 shows that PNVP-b-PNMA has the same functional groups in PNMA-Br, that is, N-H and C-O functional groups. Since in FT-IR spectrum of PNVP-Br does not have those functional groups, suggesting that NMA was incorporated into PNVP. Moreover, there are no clear signs of vinyl peaks and these FTIR spectra of PNVP-b-PNMA gave similar peak positions to FT-IR spectrum of PNVP-co-PNMA that prepared by Marambio *et al.*¹⁰

The ¹H-NMR spectrum and the chemical structure of PNVP-Br are shown in Fig.-2(a). It shows that the signals were similar to the ¹H-NMR spectrum of PNVP-Br synthesized by Haaf *et al.* and Luan *et al.*¹⁷⁻¹⁸

Fig.-2: ¹H-NMR spectra of (a) PNVP-Br; and (b) PNVP₅₀-b-PNMA₇₅

The repeating unit of PNVP-Br was obtained by comparing the integration of the protons at repeating unit (I_5) to the integration of end group (I_1), which come to 40 repeating units, and, thus, number average molar mass (M_n) of PNVP-Br is 4155 g/mol. However, there is a chemical shift $\delta_H = 6.85$ ppm that belongs to the proton from vinyl group, suggesting the presence of residual monomers in the product.

Similar peaks of residual monomers (signal 15, 16, 17) and impurities from the solvent were also found in the ¹H-NMR spectrum of PNVP-b-PNMA, as shown in Fig.-2(b). These unexpected peaks in the product might happen because of the poor purification process. Nevertheless, it can be seen from the spectrum that the polymerization occurred, and the block copolymer was formed because of the presence of the signals from protons at numbers 4 (-CH₂-), 5 (-CHN-), 9 (-CHCO) and 13 (-CH₂-), which belong only to the backbone of the polymers. Scheme-1 shows the polymerization of PNVP-b-PNMA. PNMA repeating units in PNVP-b-PNMA were expected to reach 25, 50, 75 units. Nevertheless, based on ¹H-NMR spectra calculation¹⁹, the repeating units of PNVP-b-PNMA were obtained to be 15, 17, 20 units (Table-1). This

could happen because of the short polymerization time and the possibility of oxygen leak inside the reactor, which caused the ATRP catalyst to be oxidized and the polymerization led to the deactivation of the catalysts.²⁰

Scheme-1: ATRP polymerization of PNVP-b-PNMA via macroinitiator approach

Table-1: Overview of PNVP-b-PNMA

Polymer	NMA:PNVP-Br in feed ^a (mol ratio)	Repeating units ^b (units)		M _n ^c (g/mol)
		PNVP	PNMA	
PNVP ₅₀ -b-PNMA ₂₅	25:1	40	15	5265
PNVP ₅₀ -b-PNMA ₅₀	50:1	40	17	5413
PNVP ₅₀ -b-PNMA ₇₅	75:1	40	20	5635

^aThe CuBr and bpy to initiator mol ratio was 1:1 in all cases

^bDetermined by ¹H-NMR

^cDetermined by ¹H-NMR via end group analysis

pH Sensitivity of PNVP-b-PNMA

Typically, pH-sensitive polymers consist of polyacids or polybases that can form polyelectrolytes (polyanion for polyacids and polycation for polybases). Due to protonation or deprotonation of the chemical structure of polyelectrolytes in acidic or basic solution, their particle sizes²¹ would change. For instance, the transformation of carboxylic acids into carboxylate anions and vice versa in different pH results in a reversible change of particle sizes since the carboxylate anions have better interactions with water molecules than carboxylic acid does. Thus, polyelectrolytes with carboxylate anions exist in the form of a coil, while polyelectrolytes with carboxylic acid moieties are present in the form of a globule. In the case of PNMA, since PNMA bearing an amide group, it might undergo hydrolysis in acid or base environment into carboxylic acid²² and carboxylate anions²³, respectively, and thus, the particle sizes change as described earlier.

It was previously reported that hydrogel of P(NVP-co-NMA) has an increasing swelling property at pH 3-7.^{6-7, 10} Therefore, the change of particle sizes was predicted to take place around those pH ranges. The results from the particle size analyzer for the PNVP-b-PNMA in various pH solutions are presented in Fig.-3a, while the illustration of PNVP-b-PNMA pH-sensitivity on the particle sizes is shown in Fig.-3b.

Figure-3a shows that PNVP₅₀-b-PNMA₂₅ has an increasing particle size at pH 3-7 with maximum particle sizes occurring at pH 7, then the particle sizes decreased at pH 7-12. The increase of particle sizes of PNVP₅₀-b-PNMA₂₅ and PNVP₅₀-b-PNMA₅₀ between pH 3-7 could be explained because the interactions between the polymer chains increased. At neutral pH, the concentration between H⁺ and OH⁻ are equal. Therefore, the interaction between polymer chains would be more dominant than that within a single polymer or with the solvent resulting in an increase in particle sizes. Such behavior also happened in the PNMA homopolymer.

Meanwhile, PNVP₅₀-b-PNMA₇₅ had a maximum particle size at pH 3 which could be reasoned because of hydrolysis of the amide group in PNMA to form a carboxylic acid. The -COOH in PNMA block becomes hydrophobic at low pH since there was no polyanion presence in the polymer chains. As a consequence, the PNMA block prefers to interact with itself to water (hydrophobic effect) and behave as macrosurfactants that can aggregate to form micelles²⁴, and thus, the particle sizes became large. In addition, the particle size tended to decrease after pH 7 because of the deprotonation of a carboxylic acid into carboxylate anions that makes both PNVP and PNMA blocks hydrophilic and preferred to interact with water, and thus, the particle sizes became small (Fig.-3b).

Fig.-3: (a) The change of particle sizes in various pH; (b) illustration of PNVP-b-PNMA pH-sensitivity

In general, the increasing NMA content in PNVP-b-PNMA promoted larger particle sizes of the block copolymers in acid and base environments. The end group analysis of the ¹H-NMR showed that block copolymers of PNVP-b-PNMA obtained similar repeating units. Nonetheless, the PSA results showed a major difference in the change of particle sizes of PNVP-b-PNMA in various pH. Presumably, this might be due to residual monomers that could influence the change of particle sizes.

CONCLUSION

PNVP-b-PNMAs were prepared using ATRP via the macroinitiator approach. The existence of functional groups in FT-IR and some signals belonging to PNVP-Br or PNVP-b-PNMA in ¹H-NMR indicated that the polymerization occurred. PNVP-b-PNMAs show responsiveness in different pH through the change of particle sizes. In general, PNVP-b-PNMA in pH 3, 5, and 7 had larger particle sizes (394.86 – 694.56 nm) than in pH 9 and 12 (275.43 – 548.70 nm). The more NMA content in block copolymers of PNVP-b-PNMA was, the larger particle sizes could be obtained.

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