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Thermo-Sensitive Hydrogel: Control of Hydrophilic-Hydrophobic Transition

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***Abstract*—**The study investigated the hydrophilic to hydrophobic transition of modified polyacrylamide hydrogel with the inclusion of *N*-isopropylacrylamide (NIAM). The modification was done by mimicking micellar polymerization, which resulted in better arrangement of NIAM chains in the polyacrylamide network. The degree of NIAM arrangement is described by N_H number. The hydrophilic to hydrophobic transition was measured through the partition coefficient, K, of Orange II and Methylene Blue in hydrogel and in water. These dyes were chosen as a model for solutes with different degree of hydrophobicity. The study showed that the hydrogel with higher N_H values resulted in better solubility of both dyes. Moreover, in temperature above the lower critical solution temperature (LCST) of Poly(*N*-isopropylacrylamide) (PNIAM)also caused the collapse of NIPAM chains which results in a more hydrophobic environment that increases the solubility of Methylene Blue and decreases the solubility of Orange II in the hydrogels with NIPAM present.

***Keywords*—**Thermo-sensitive hydrogel, partition coefficient, the lower critical solution temperature (LCST), micellar polymerization.

I. Introduction

DUE to its biocompatibility, hydrogels are suitable for the use in biological systems [1]. As a result, hydrogel technology has been widely studied in many biomedical applications over the past few decades [2]. Examples of such applications include controlled drug delivery [3], enzyme immobilization and tissue engineering [4]. The high water content in hydrogel allows it to be flexible and resemble biological tissues [1]. The water content of the hydrogel fills up the hydrogel pore space allowing selective diffusion of solutes through the hydrogel matrix. This characteristic of the hydrogel is desired for controlled release drug delivery systems [3, 5, 6]. Other desired characteristics of hydrogel for controlled release drug delivery system include its response to the change in the environment such as the change in temperature [7-10] and pH [11-13].

In the past few decades, the hydrogel of Poly (N-isopropylacrylamide) (PNIPAM) has been extensively studied because of its response to temperature change [7, 9, 10, 14, 15]. It demonstrates an immediate transition from a hydrophilic to a hydrophobic structure at the temperature known as the lower critical solution temperature (LCST) [14]. This is due to the presence of the hydrophilic amide groups and the hydrophobic isopropyl group on its side chain. When the temperature is below LCST [9], the hydrophilic chains are hydrated and the hydrogel became swollen. As the temperature increases past LCST, the hydrophobic interaction becomes stronger, thus the balance between hydrophilic/hydrophobic interactions break down, causing the gel to collapse. This allows the solute to diffuse outside the gel [9]. The normal range of the LCST for PNIPAM is around 30-33 °C, which is close to physiological condition and make it applicable in a wide range application [7, 9, 10, 15].

However, PNIPAM has exhibited a strength setback, which it tends to collapse when became highly swollen. The low mechanical strength problem is, then, overcome by the trapping the PNIPAM in a structure such as Polyacrylamide (PAM) to form semi-interpenetrating network, (semi-IPNs). This is proven to be stable and preserve the thermal- sensitive property [2]. The hydrophobic structure in the PNIPAM plays a crucial role for the control of molecular release mechanism. Since, the semi-IPNS of PNIPAM trapped in PAM appears in random orientation; a better control of release mechanism and a wider range of LCST hence use for wider applications can be achieved through a better control of PNIPAM arrangement. We proposed a better method to control the arrangement PNIPAM chains in PAM hydrogels through mimicking micellar polymerization [16, 17], which is a technique used to synthesize hydrophobically-modified polyacrylamide (hmPAM) [18] used as a thickening material.

The principles of micellar polymerization were first described by Candau *et al.* [17] based on the technique developed by Turner *et al.* [19] for water-based polymer syntheses with hydrophobic comonomer by using surfactants. The process is depicted in Fig. 1. The hydrophobic monomer is soluble inside the surfactant micelles, while the hydrophilic monomer is soluble in the aqueous continuous medium. The reaction is a microheterogeneous copolymerization system where micelles act as microdomains where the hydroprobes concentrate. This system differs from solution polymerization where the hydrophobic and hydrophilic monomers are polymerized in a random order, whereas the micellar polymerization results in addition of hydrophobes on the hydrophilic backbone in a block-like structure [17, 18].

An important parameter used in micellar polymerization is the number of hydroprobes per micelle (referred to as N_H number), which can be determined from the equation (1) [17, 20]. The degree of blockiness depends on this value.

$$N_H = \frac{[Hydrophobes]}{[Micelles]} = \frac{[Hydrophobes]}{\left(\frac{[surfactant]-cmc}{N_{agg}}\right)} \quad (1)$$

Where cmc is a critical micellar concentration of surfactant, N_{agg} is a surfactant aggregation number.

A higher N_H value means more hydroprobes are incorporated at a time, which results in higher degree of blockiness whereas a lower number results in more evenly distribution of hydroprobes along the backbone (see Fig. 2) [17].

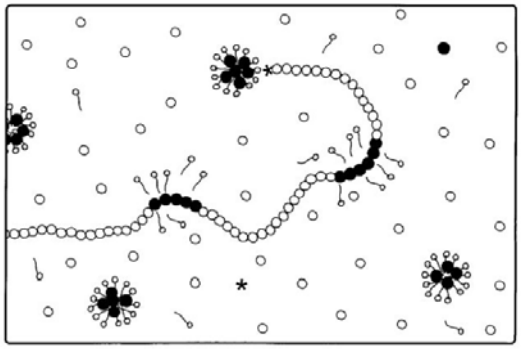

Fig. 1 Micellar polymerization process. ○ represents hydrophillic monomers; • represents hydrophobic monomers; ⌒ represents surfactants (Excerpt from [17])

By employing the micellar polymerization technique, it is possible to synthesize hydrophobically-modified polymer with the same degree of hydrophobic substitution but different degree of blockiness. These polymers exhibit unique rheological characteristics [16, 17, 21, 22] due to interaction among the hydrophobic side chains. Hydrophobically-modified polymer with the different degree of blockiness exhibits different side chain interaction even if the degree of hydrophobic substitution remains the same.

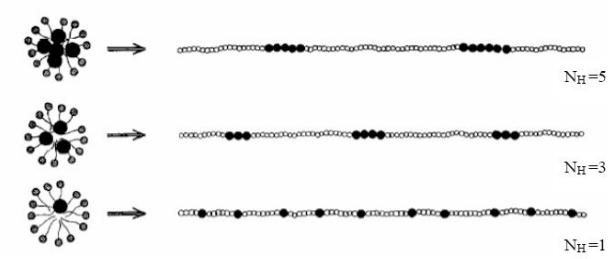

Fig. 2 Different N_H values reflect different arrangement of hydrophobic monomers on the polymer chain (Excerpt from [14])

Fig. 4 shows the plot of the viscosity of hydrophobically-modified polyacrylamide (hmPAM) at 0.5wt% as a function of surfactant concentration [22]. The increase in viscosity of the polymer solution is the result of the associations between hydrophobic side chains of the polymer and surfactant molecules (sodium dodecyl sulfate was the surfactant used in this experiment [18]. In general, a plot of viscosity of the mixture of hm-polymers and surfactants contains two critical surfactant concentrations (C_1 and C_2), which is determined from the solution viscosity. C_1 and C_2 divide the plot into 3 regions (Fig. 3) [16, 18, 23]. Region 1: where a small amount of surfactant ($C < C_1$) is added to the hm-polymer solution, the surfactant molecules aggregate with the hydrophobes on the polymer chains similar to micelle formation. Because of the relatively small amount of surfactant molecules and considerably more available hydrophobic units, one surfactant molecule associates with more than one hydrophobic unit. As a result, the surfactant molecules act as a physical but reversible crosslink between the hm-polymer chains. This leads to an increase in the solution viscosity.

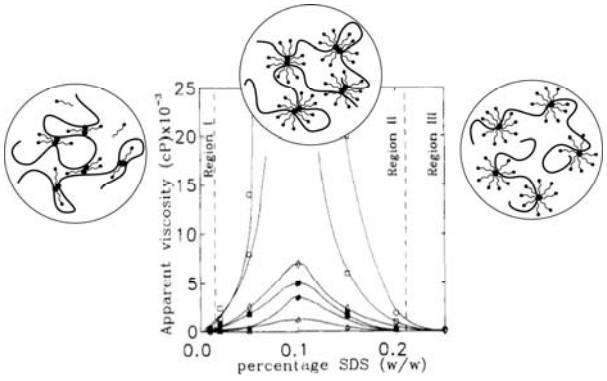

Fig. 3 The apparent viscosity of hydrophobically-modified polyacrylamide solutions a function of surfactant (SDS) concentration for polymer with different a degree of hydrophobic substitution (concentration of polymer in solution = 0.5% (w/w), shear rate = 0.5 s^{-1}). Adapted from [16]

In region 2, as the concentration of the surfactant increases ($C_1 < C < C_2$), the number of the physical crosslinks increases, which leads to a further increase in viscosity. In region 3, where the concentration is higher than C_2 ($C_2 < C$ where C_2 is the critical micellar concentration of the pure surfactant), there is enough surfactant to form micelles around each hydrophobic chain, and the physical crosslinks are no longer prevalent. This leads to a dramatic drop in viscosity [66, 71].

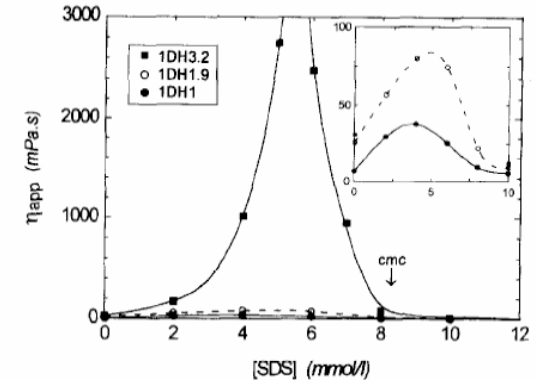

Fig. 4 Apparent viscosity as a function of SDS concentration of 3 samples of hydrophobically-modified PAM with the same hydrophobic content (1 mol%) with different degree of blockiness (Excerpt from [22])

Fig. 4 shows the viscosity of hydrophobically-modified polyacrylamide (hmPAM) as a function of the surfactant (sodium dodecyl sulfate-SDS) concentration. For the same amount of surfactant, the hmPAM with higher N_H number (N_H= 3.2) showed an increase of 3 orders of magnitudes in the apparent viscosity when compared to the solution of hmPAM with lower N_H number [17, 20]. This suggests that the hm-polymer with a higher N_H number (higher degree of blockiness) provided stronger hydrophobic interactions with the surfactant molecules than hm-polymer with the lower N_H value even if the polymers have the same degree of hydrophobic substitution [16, 17].

As shown by Candau *et al.*, interactions amount the hydrophobic side chains can be moderated through the degree of blockiness. We will use the same technique to moderate the interaction among the NIAM chains in the PAM hydrogels. Coupled the micellar polymerization technique with the thermo-sensitive properties of the NIPAM, we proposed a method of preparing a modified PAM hydrogel with the micellar polymerization technique. As such, we can produce modified PAM hydrogels with different properties, depending on the degree of blockiness (designated by different N_H values). In particular, we examine the effects of the arrangement of N-isopropyl acrylamide (NIAM), through the use of micellar polymerization technique [13, 14], on the thermo-sensitive properties of the modified PAM hydrogel. The schematic of the proposed modified PAM hydrogels is shown in Fig. 5.

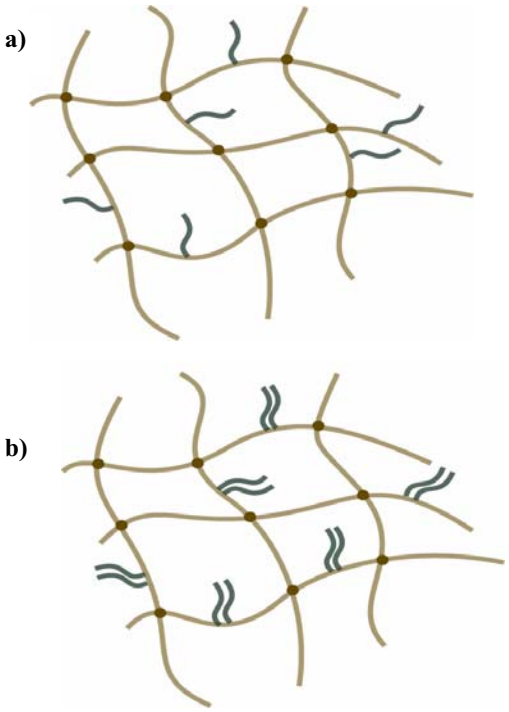

Fig. 5 a) Schematic of Polyacrylamide (PAM) hydrogel with interpenetrating network (IPN) of N-isopropyl acrylamide synthesized in [7]. b) Schematic of Polyacrylamide (PAM) hydrogel with interpenetrating network of poly (N-isopropyl acrylamide) polymerized with micellar polymerization technique

II. Experimental Details

A. Synthesis of PNIAM-Acrylamide Hydrogel

The modified PAM hydrogel synthesis was carried out following the example of Guilherme *et al.* [2] with the addition of a surfactant during polymerization, where the surfactant sodium dodecyl sulfate (SDS) was used. The hydrophillic acrylamide (Fluka, 01200) monomer was used as received. To synthesize hydrogels, two aqueous solutions were prepared. Solution, A, was prepared with 2.5 M of acrylamide and degassed for 1 hour. Later, 0.02 M (1.3 wt %) of *N*-isopropylacrylamide (NIPAM, Acros Organics, 412780250) and an appropriate amount of SDS (Fluka, 75370) were added to solution A. Degassing was continued for the next 30 minutes [17]. Subsequently, 50 µmol/ml of Methylene-bis-acrylamide (MBAM, Fluka, 66670), used as a cross-linking agent and 3.2 µmol/ml N,N,N,N-Tetramethylenediamine (TEDEM, Sigma-Aldrich, T22500) as an accelerator were added and continued to gas for another 15 minutes. Solution B, was prepared with 42 µmol/ml sodium persulfate (NaPS, Fluka, 71890) as an initiator, and degassed for 20 minutes. After degassing, 90 mL of solution A was mixed with 10 mL of solution B. The mixture was quickly injected between two glass plates separated by a rubber O-ring [2]. The concentrations of PNIPAM and SDS for the synthesis are described in Table I.

TABLE I
Concentration of Acrylamide (AM), N-Isopropyl Acrylamide (PNIAM), the Initiator (MBAM), and Sodium Dodecyl Sulfate (SDS) used for Synthesis of Hydrogel

Batch	Hydrogel	PNIPAM [µmol/ mL]	SDS [mmol/mL]	N_H
1	[2.5-0-L]	0	0	0
2	[2.5-0-H]	0	0	0
3	[2.5-1-L]	20	1.21	1
4	[2.5-1-H]	20	1.21	1
5	[2.5-5-L]	20	0.24	5
6	[2.5-5-H]	20	0.24	5

The mixture was allowed to set for 24 hours at room temperature. After the gel was formed, it was removed from the mold, and washed with excess methanol 3 times to remove excess SDS. The gel was rinsed with excess water in the final step before using in the partition coefficient measurements.

B. Partition Coefficient Measurements

The partition coefficient measurements were done following the procedure detailed by *Guilherme et al.* [2]. Aqueous solution of Methylene Blue and Orange II (Fluka, 75370) were prepared in the concentrations of 148 µmol/mL and 140 µmol/mL, respectively. The hydrogels prepared in part A, were cut into equal size and immersed in 25 mL of the dye solution. After 24 hours of immersion, the concentration of the reminiscent dye in the aqueous solution was determined

by UV-Vis spectroscopy at wavelength 486 and 664 nm for Orange II and Methylene Blue, respectively. The partition coefficient, K, was determined by the following equation.

$$K = \frac{[\text{dyes in hydrogel}]}{[\text{dyes in water}]} \quad (2)$$

The partition coefficients were determined at temperature 25 °C and 45 °C.

III. Result and Discussion

Based on the molecular structure (see Fig. 6) and experimental studies, Guilherme *et al*. has illustrated that the Orange II exhibits a more hydrophilic character than Methylene Blue [2]. This character will greatly influence the solubility of these dyes in the modified hydrogels, which were observed in term of the partition coefficients, K.

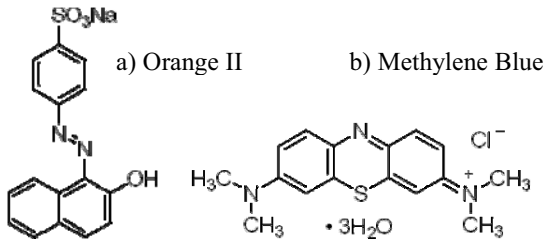

Fig. 6 Molecular Structure of a) Orange II and b) Methylene Blue

The partition coefficients, K, of Orange II and Methylene Blue in the modified hydrogels were measured at two different temperatures, and the results are plotted in Fig. 7 and Fig. 8, respectively. In Fig. 7, the partition coefficient for Orange II in the PAM hydrogel before the addition of the hydrophobic NIPAM decreases from 2.10 to 2.00 as the temperature increases from 25 °C to 45 °C. This follows similar trend seen by Guilherme *et al.*, which showed that the partition coefficient K of Orange II decreased from 0.75 to 0.35 as the temperature increased from 25 °C to 40 °C [2].

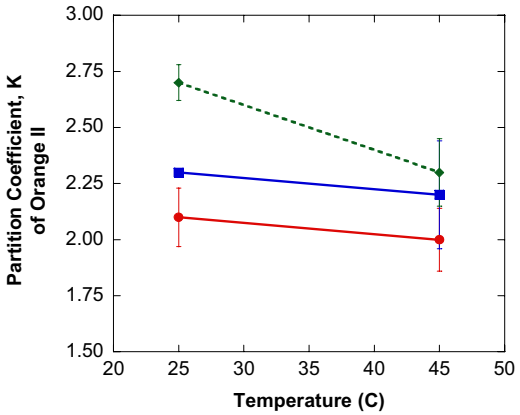

Fig. 7 The partition coefficient, K, of Orange II in hydrogels a function of temperature. ● represents K values for PAM hydrogel, ■ represents K values for modified PAM hydrogel with $N_H = 1$, and ◆ represents K values for modified PAM hydrogel with $N_H = 5$

The same trend is seen in the modified PAM hydrogels with the addition of NIAM for both $N_H = 1$ and $N_H = 5$. That is the partition coefficient for Orange II in the modified PAM hydrogel decreases as the temperature increases from 25 °C to 45 °C. Because Orange II is relatively hydrophilic, the decrease in the partition coefficient demonstrates the hydrophilic to hydrophobic transition as the temperature increases past the LCST for PNIPAM (31 – 33 °C) [7, 9, 10, 15]. At temperature below the LCST, the hydrophilic-hydrophobic interaction between the acrylamide and the hydrophobic N-isopropyl acrylamide is in balance; and the modified PAM hydrogel stays hydrated [2]. As the modified hydrogel is warmed and temperature increased past the LCST of PNIPAM, the hydrophobic interaction among the NIAM side chains become stronger, and the hydrophobic chains collapse creating a more hydrophobic environment making the modified hydrogel become less hydrophilic [2, 24]. As a result, the solubility of Orange II in the modified hydrogel was reduced as the temperature exceeded 33 °C.

Fig. 7 also shows that for the modified PAM hydrogel with higher N_H values ($N_H = 5$), the transition from higher K values at lower temperature to lower K value at high temperature, is more dramatic than the unmodified hydrogel or the modified hydrogel with lower N_H values ($N_H = 1$). The result suggests that by having the NIAM side chains arranged in block-like manner enhances the hydrophobicity of the modified PAM hydrogels. The results are similar to the thickening properties of hmpolymers seen by Candau *et al.*[17, 20, 25]

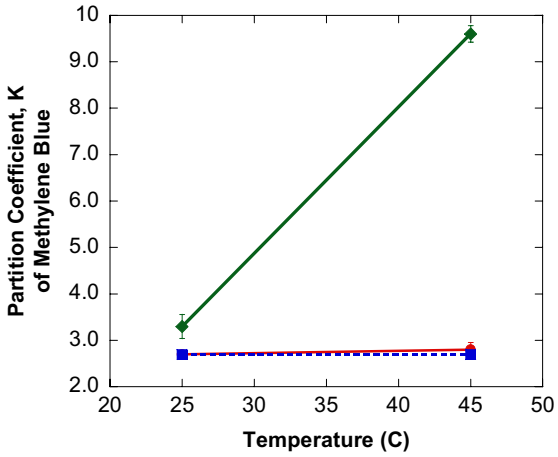

Fig. 8 The partition coefficient, K, of Methylene Blue in hydrogels a function of temperature. ● represents K values for PAM hydrogel, ■ represents K values for modified PAM hydrogel with $N_H = 1$, and ◆ represents K values for modified PAM hydrogel with $N_H = 5$

An opposite trend is seen in Fig. 8. The partition coefficient, K, for Methylene Blue in the modified PAM hydrogel increases as the temperature increases from 25 °C to 45 °C. As in the case of Orange II, this increase in the partition coefficient values demonstrates the hydrophilic to hydrophobic transition as the temperature increase from below the LCST of PNIAM to above the LCST. Note that the

transition is more dramatic in the modified PAM hydrogels with $N_H = 5$. The value of the partition coefficient at 45 °C is 3 times the value of the partition coefficient at 25 °C. This shows that the solubility of Methylene Blue within the modified hydrogel increase as the N_H value increases. This is consistent with the argument made for the change in the partition coefficients of Orange II. For the same amount of NIPAM included in the modified PAM hydrogel system, the higher solubility Methylene Blue can be obtained with the higher degree of blockiness of hydrophobicity groups in the modified hydrogel. Having the hydrophobes closer together in a block-like structure enhances their interaction with Methylene Blue. Thus for the same degree of hydrophobic addition, the modified PAM hydrogel with $N_H = 5$ exhibits more hydrophobic characters. As a result, Methylene Blue is more soluble in the modified PAM hydrogel with $N_H = 5$. The result becomes more dramatic at 45 °C.

The dependence of the partition coefficients, K, Orange II and Methylene Blue on the degree of blockiness, N_H, and the temperatures are illustrated in Fig. 9 and Fig. 10. The plots of partition coefficient displayed similar trend for both Orange II and Methylene Blue as the partition coefficients, K, increase with the degree of blockiness, N_H. In Fig. 9, the partition coefficient, K, of Orange II is less dependent on N_H values at 45˚C, whereas the dependence on N_H is more dramatic at lower temperature (25 °C). In Fig. 10, a dramatic trend is observed. The partition coefficient, K, of Methylene Blue is strongly dependent on N_H values at 45˚C.

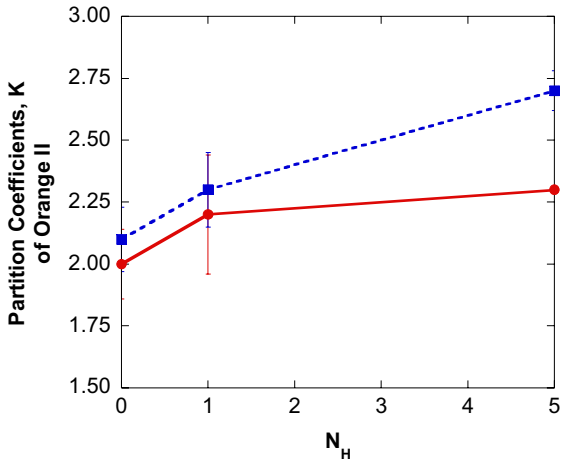

Fig. 9 The partition coefficient, K. of Orange II in hydrogels a function of N_H at two different temperatures. ● represents K values at 45 °C and ■ represents K at 25 °C

A sharp dependence of the partition coefficients of Methylene Blue on the N_H numbers is as expected because as N_H values increases, the solubility of Methylene Blue in the modified hydrogel increases due to the increase in hydrophobic character of the hydrogel. In addition, this character is enhanced at temperature higher than the LCST of PNIAM. However, the dependence of the partition coefficient of Orange II on N_H values is contrary to the earlier discussion.

This can be explained that having the hydrophobic NIAM side chains allows stronger interaction between the benzene ring of Orange II and the hydrophobic NIAM. Thus, this facilitates better solubility of Orange II into the hydrogel matrix. In addition, the NIAM arrangement in a block-like manner enhances this interaction. As a result, the interaction increases as the value of N_H increase. It manifests itself into higher partition coefficients as the N_H values increase.

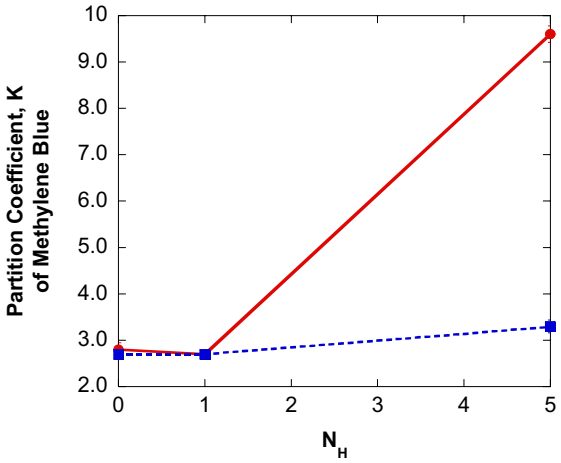

Fig. 10 The partition coefficient, K. of Methylene Blue in hydrogels a function of N_H at two different temperatures. ● represents K values at 45 °C and ■ represents K values at 25 °C

IV. Conclusion

The effect of the modification of the PAM hydrogel with *N*-isopropylacrylamide (NIPAM) included through micellar polymerization was observed through partition coefficient, K of Orange II and Methylene Blue at different temperatures and degree of blockiness of the hydrophobic NIAM, designated by N_H. The study showed that the modified PAM hydrogel retains the thermal sensitivity of Poly(N-isopropylacrylamide), which was observed that as the temperature increases above the LCST, the hydrophobic dye, Methylene Blue had higher solubility than the hydrophilic dye, Orange II. In addition, the hydrophilic to hydrophobic transition is more dramatic with the modified PAM hydrogel with higher N_H values.

At temperature lower than its LCST, the NIPAM chains remain swollen. As the temperature exceeded LCST (31-33 °C) the NIPAM chain collapsed to induce a more hydrophobic environment to the gel. The temperature has little effect for the gel absent of PNIPAM. The including of PNIPAM into the network with arrangement of the hydrophobic chains result in higher partition coefficients of both dyes with the higher in N_H, the higher solubility can be obtained.

The result is explained taken into the account that the arrangement of the hydrophobic molecules in 'block like' structure contribute to the more grouping of the same type of group on gel network resulting in the more space different in hydrophobicity. The results found in this work show that hydrophobic interaction can be moderated through the organization of the hydrophobic chains in a block-like

structure, and the thermo-sensitive property of Poly(N-isopropyl acrylamide) is retained.

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