Controlled-Release Polymers for Delivery of Dipyridyls and Tetraalkyl Ammonium Hydroxide

Nathan A. Carrington,[1] D. Lynn Rodman,[1] Kisholoy Goswami,[2] Zi-Ling Xue[1]

[1]*Department of Chemistry, the University of Tennessee, Knoxville, Tennessee*
[2]*InnoSense LLC, 2531 West, 237th Street, Suite 127, Torrance, California*

ABSTRACT: A method to incorporate 2,2′-(or 4,4′-)dipyridyl and tetra-*n*-butylammonium hydroxide into poly(vinyl alcohol) (PVA) monoliths and the controlled-release properties of these polymer monoliths for delivery of the reagents are reported. The monoliths were prepared by heating PVA beads until they formed a viscous liquid and then loading the molten polymers with the desired reagents. Several freeze-thaw cycles were then carried out to provide the mechanically stable, reagent-loaded monoliths. The release of the reagents from the PVA monoliths was monitored by UV–vis spectroscopy, and the release was found to proceed in a controlled manner, yielding consistent results among different reagent-loaded PVA monoliths. In addition, the reagents underwent no chemical changes upon their release from the monoliths. Limitations of the use of the controlled-released chemicals as replenished reagents in Fujiwara reactions for the continuous monitoring of halocarbons are discussed. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 104: 1043–1048, 2007

Key words: controlled-release; poly(vinyl alcohol); hydrogels; heterogeneous polymers; sensor

INTRODUCTION

Controlled-release polymers (CRPs) have been intensively investigated for the delivery of various drugs, reagents, and biological species.[1–7] Several attributes including ease of synthesis, lack of chemical reactivity, cost effectiveness, and consistent delivery of reagents make CRPs very attractive for the delivery of reagents. Some CRPs have demonstrated the ability to deliver reagents at a constant rate over long periods of time.[2–5]

When poly(vinyl alcohol) (PVA) monoliths are prepared through freeze-thaw cycles, the monoliths contain small domains of crystalline polymer[8–13] that act as physical crosslinks between polymer chains.[3,9,10,14] As the number of freeze-thaw cycles is increased, the fraction of polymer in the crystalline domain increases, as does the mechanical strength of the polymer. The viscoelasticity of these polymers arises from polymer chains that are physically crosslinked and connected by amorphous chain segments.[3,9,10,14]

We have been interested in the delivery of 2,2′-dipyridyl (or 4,4′-dipyridyl) and tetra-*n*-butylammonium hydroxide (*n*-Bu$_4$NOH) using CRPs. These chemicals are reagents for the detection and quantification of halogenated hydrocarbons (HHCs) such as HCCl$_3$ by the modified Fujiwara reactions,[15] and they need to be replenished for continuous monitoring of HHCs. Studies have been conducted to replenish these reagents by a pump.[16] Herein, our recent studies to develop CRP monoliths of PVA for the delivery of 2,2′-dipyridyl, 4,4′-dipyridyl, and *n*-Bu$_4$NOH are discussed.

EXPERIMENTAL

Materials and instrumentation

Poly(vinyl alcohol) (PVA; Scientific Polymer Products, Ontario, NY) 99% hydrolyzed, MW 86,000), tetrahydrofuran (THF; Fisher, Pittsburg, PA, certified), 2,2′-dipyridyl (Acros, Morris Plains, NJ, 99+%), 4,4′-dipyridyl (Acros, 98%), and tetra-*n*-butylammonium hydroxide (*n*-Bu$_4$NOH) (Lancaster, Pelham, NH, 40% w/w aqueous solution) were used as received. Deionized water was used in the preparation of all PVA gels.

A Hewlett–Packard 8452 photodiode array UV–visible spectrophotometer was used with standard 1.0-cm quartz cuvettes. Standard THF solutions and calibration plots yielded the molar absorptivities (ε) of (1.22 ± 0.05) × 10^4, (1.18 ± 0.05) × 10^4, and (4.75 ± 0.19) × 10^3 M^{-1} cm^{-1} for 2,2′-dipyridyl, 4,4′-dipyridyl, and *n*-Bu$_4$NOH, respectively.

Synthesis of the *PVA* monolith and incorporation of reagents

The method used to make the PVA monoliths (Fig. 1) is similar to the reported method.[3] Monoliths of various
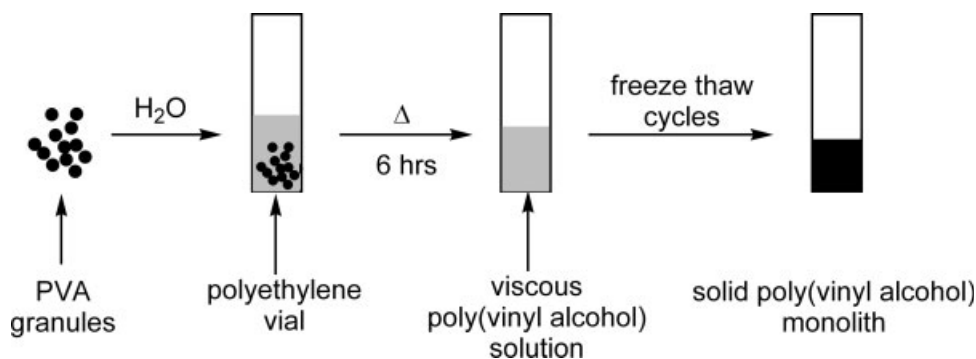
Figure 1 Schematic of the procedure used in the preparation of the PVA monoliths.

sizes were made using a 15% w/w solution of PVA beads in deionized water contained in a 50-mL polyethylene vial. The vial containing the PVA beads and water was placed into a 90°C water bath for 6 h to give a viscous liquid. The vial was then removed from the bath, and the mixture in the vial was stirred using a glass rod. The viscous PVA solution was then loaded with 0.3–6.3% w/w of 2,2′-dipyridyl, 0.6–2.5% w/w of 4,4′-dipyridyl, or 2.0–9.9% w/w of n-Bu$_4$NOH, and stirred thoroughly to give a homogeneous reagent/PVA mixture. The vial was then reinserted into the 90°C water bath for 15 min so that any bubbles trapped in the molten polymer could escape.

After the monoliths were removed from the water bath and allowed to slowly cool to 25°C for 1 h, the vials containing the gels were placed into a −20°C freezer for 18 h. They were then allowed to thaw to 25°C for 6 h. This freeze-thaw cycle was repeated a total of five times to give mechanically stable, reagent-loaded PVA monoliths (Fig. 2).

Controlled-release studies

THF was chosen as the solvent.[8] At least two separate experiments were conducted for each controlled-release study. The following PVA monoliths containing the reagents and solvent were used in the studies: (1) A monolith (2.0243 g PVA + 11.5 g H$_2$O) loaded with 0.2525 g of 2,2′-dipyridyl immersed in 1000 mL of pure THF in a sea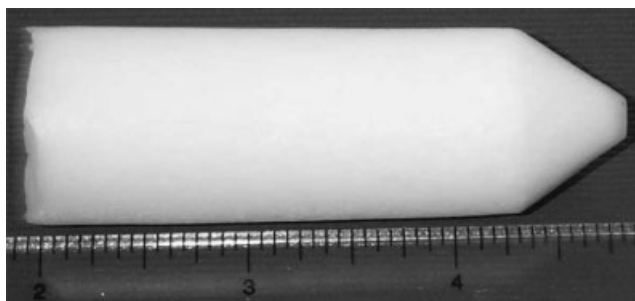led flask; (2) A monolith (6.0040 g PVA + 34.0 g H$_2$O) with 0.7654 g of 4,4′-dipyridyl immersed in 100 mL of THF in a sealed flask; (3) A monolith (2.6497 g PVA + 13.0 g H$_2$O) with 2.000 g of 40% w/w aqueous n-Bu$_4$NOH immersed in 100 mL of THF in a sealed flask. The percentage of reagents diffused from a reagent-loaded monolith into solution was studied by the process discussed below using 2,2′-dipyridyl as an example.

2,2′-dipyridyl (0.2525 g) was uniformly loaded into a PVA monolith to give a total mass of 13.777 g. This monolith was then cut into two cylindrically-shaped pieces, and one piece of 8.191 g was used in controlled-release studies. The mass of 2,2′-dipyridyl in this piece was 0.1501 g (or 59.45% of 0.2525 g). This PVA monolith was immersed in THF (1000 mL) in a sealed flask at 25°C (Fig. 3). A monolith containing no reagents in a separate flask was used as a control. Samples were periodically removed by micropipette and replaced with the same volume of fresh THF. The samples were placed in sealed volumetric flasks, and, at the conclusion of study, all samples were diluted to the mark with the THF. UV–visible spectra were then collected with each control sample as the reference for each corresponding reagent sample. The concen-
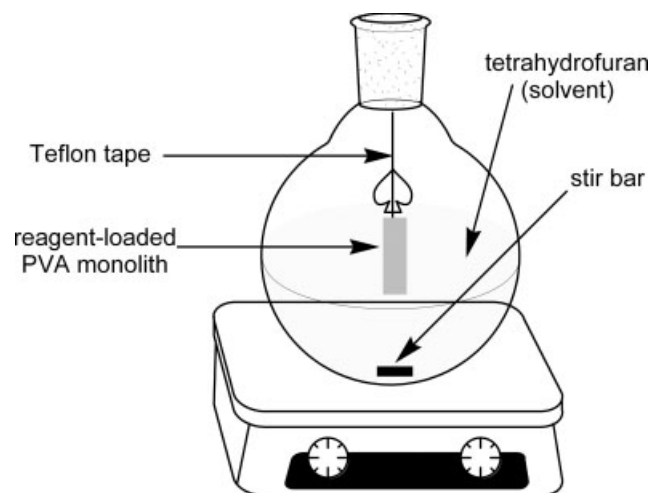

Figure 2 Image of a PVA monolith used in the current studies. Units on scale are in inches.

Figure 3 Schematic of the experimental setup used in the diffusion experiments with the PVA monoliths.
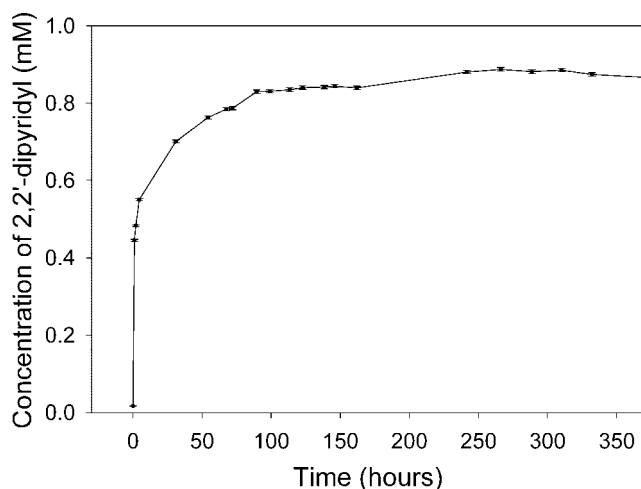
Figure 4 Concentration of 2,2'-dipyridyl in a THF solution during the release of 2,2'-dipyridyl from a PVA monolith. The monolith had a mass of 8.2 g, a length of 62 mm, and a diameter of 13 mm.

trations of 2,2'-dipyridyl were calculated using Beer's law and monitored as a function of time. In 332 h (Fig. 4), the concentration of 2,2'-dipyridyl diffused into solution reached a maximum of ∼ 0.88 m*M*. The amount of 2,2'-dipyridyl released from this PVA monolith into the 1000-mL solution is thus 0.14 g, and the percentage of the release is (93 ± 4)%.

RESULTS AND DISCUSSION

Reagent loading and the properties of the reagent-loaded *PVA* monoliths

It is well known that aqueous solutions of PVA gradually gel and exhibit a small increase in elasticity upon standing at room temperature.[14] The gelation of aqueous solutions of PVA through freeze-thaw cycles results in the formation of a viscoelastic polymer with increased mechanical strength and high elasticity, often stretching to 5–6 times their original size.[3,8,9,14] The current work has focused on the development of a method for incorporating reagents into the PVA monoliths and monitoring the release characteristics of the reagents. Upon loading reagents, no visual change in mechanical properties of the PVA monoliths was observed.

Whether the PVA monolith was dissolved in THF was investigated. Literature data indicate that PVA is insoluble in THF.[17] A PVA monolith was immersed in THF for 1 week. UV–visible spectra of this THF solution showed very little variation from that of pure THF, indicating that there is indeed little or no dissolution of the PVA monolith in THF.

Several methods of loading reagents into the PVA monoliths were tested, including addition of the reagent before and at various points during the initial heating of the PVA beads. Addition of *n*-Bu₄NOH before

and during the heating process often resulted in color change. The nature of the reaction between the base *n*-Bu₄NOH and PVA under heating is not clear. However, *n*-Bu₄NOH is expected to form hydrogen bonds with PVA in the monoliths, and *n*-Bu₄NOH is known to be corrosive.[18] Unlike addition of *n*-Bu₄NOH, incorporation of 2,2'-dipyridyl or 4,4'-dipyridyl in the early stages of the heating process resulted in no observable chemical reaction between the dipyridyl and PVA. Addition of all reagents near the conclusion of the heating process resulted in no observable chemical reaction between the reagents and PVA. Reagents were therefore added near the conclusion of the heating process to avoid chemical reaction with PVA.

Controlled-release studies

To have a useful CRP, it is necessary that the concentration of reagents released into solution from the CRP monolith reach a constant value. For the study involving 2,2'-dipyridyl (Fig. 4), the early stages show rapid diffusion of 2,2'-dipyridyl from the PVA monolith. The rapid increase in concentration is likely due to the rapid diffusion of the 2,2'-dipyridyl molecules near the surface of the monolith. As the length of time increases, the concentration of 2,2'-dipyridyl reaches a constant value with little change. A study of the amount of 2,2'-dipyridyl released from a PVA monolith revealed that (93 ± 4)% of 2,2'-dipyridyl that had been loaded in the monolith was released into the solution. The spectra of 2,2'-dipyridyl released into THF match closely with those of 2,2'-dipyridyl in THF (Fig. 5), indicating that there is no chemical change of 2,2'-dipyridyl during the controlled-release process.

In the 4,4'-dipyridyl study, the early stages show gradual diffusion of 4,4'-dipyridyl from the PVA monolith (Fig. 6). The increase in concentration is
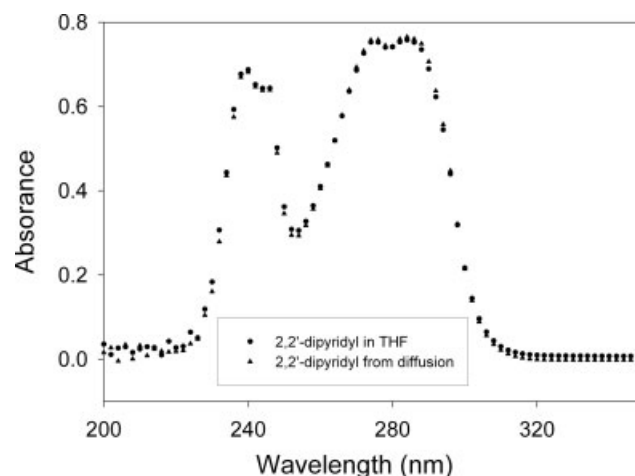

Figure 5 A comparison of the UV–visible spectrum of a freshly-prepared solution of 2,2'-dipyridyl dissolved in THF (●) with that of a solution of 2,2'-dipyridyl released into THF from a PVA monolith (▲).
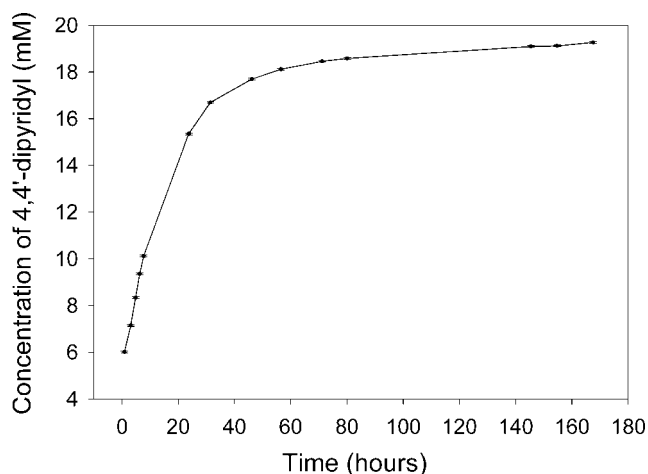
Figure 6 Concentration of 4,4′-dipyridyl in a THF solution resulting from the release of 4,4′-dipyridyl from a PVA monolith. The monolith had a mass of 29.9 g, a length of 72 mm, a diameter of 23 mm, and 0.723 g of 4,4′-dipyridyl.

Figure 8 Concentration of n-Bu$_4$NOH in a THF solution from the release of n-Bu$_4$NOH from a PVA monolith. The monolith had a mass of 12.5 g, a length of 33 mm, and a diameter of 23 mm.

likely due to the rapid diffusion of the 4,4′-dipyridyl molecules near the surface of the monolith. A study of the amount of 4,4′-dipyridyl released from a PVA monolith revealed that $(42 \pm 0.6)\%$ of 4,4′-dipyridyl that had been loaded in the monolith was released into the solution, reaching a concentration of about 19.3 mM (for a 100-mL solution). In comparison, the end concentration of the diffusion studies involving 2,2′-dipyridyl was about 0.85 mM (for a 1000-mL solution). Perhaps the solution in the 4,4′-dipyridyl studies was so concentrated that the diffusion of 4,4′-dipyridyl into and out of the monolith is close to an equilibrium, thus reducing the percentage of 4,4′-dipyridyl released from the monolith. The spectra of 4,4′-dipyridyl released into THF match closely with those of 2,2′-dipyridyl in THF (Fig. 7), indicating that there is
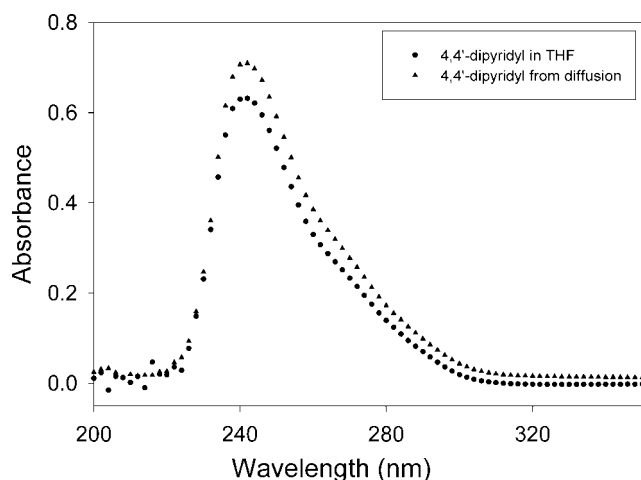
no chemical change of 4,4′-dipyridyl during the controlled-release process.

Repeated experiments showed a slower diffusion of n-Bu$_4$NOH from the PVA monolith (Fig. 8) than that of 2,2′- or 4,4′-dipyridyl. n-Bu$_4$NOH may form hydrogen bonds with the —OH groups in the PVA monolith, making its release difficult. n-Bu$_4$NOH is an ionic compound, and it may also dissociate into cation/anion, contributing to its slower diffusion from the PVA monolith. A study of the amount of n-Bu$_4$NOH released from a PVA monolith revealed that $(73 \pm 3)\%$ of n-Bu$_4$NOH that had been loaded in the monolith was released into the solution.[19] The spectra of n-Bu$_4$NOH released into THF match closely with those of fresh n-Bu$_4$NOH in THF (Fig. 9), indicating that there is no chemical change of n-Bu$_4$NOH during the controlled-release process.

Figure 7 A comparison of the UV–visible spectrum of a freshly-prepared solution of 4,4′-dipyridyl dissolved in THF (●) with that of a solution of 4,4′-dipyridyl released into THF from a PVA monolith (▲).
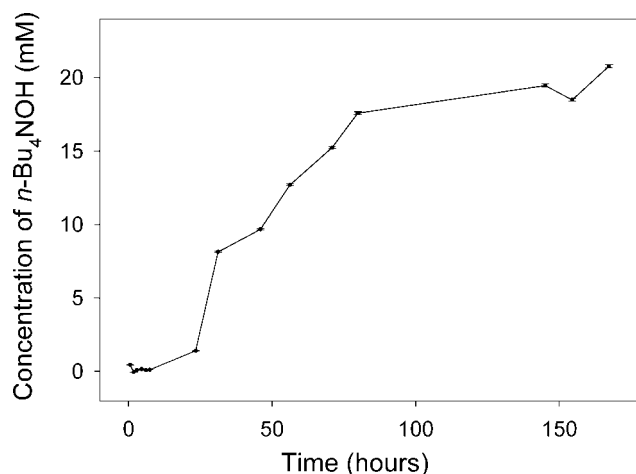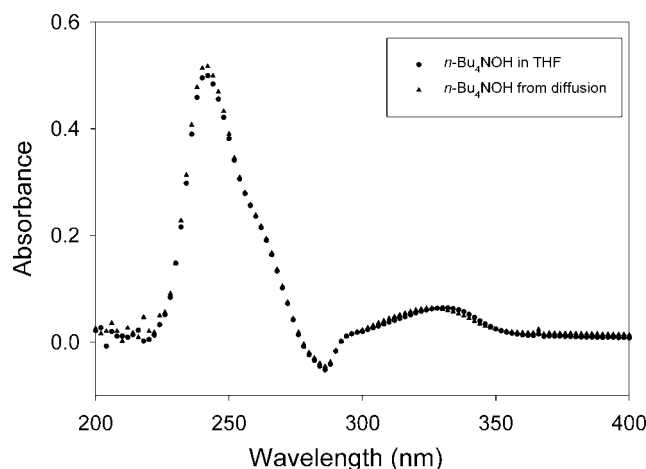

Figure 9 A comparison of the UV–visible spectrum of a freshly-prepared solution of n-Bu$_4$NOH dissolved in THF (●) with that of a solution of n-Bu$_4$NOH released into THF from a PVA monolith (▲).
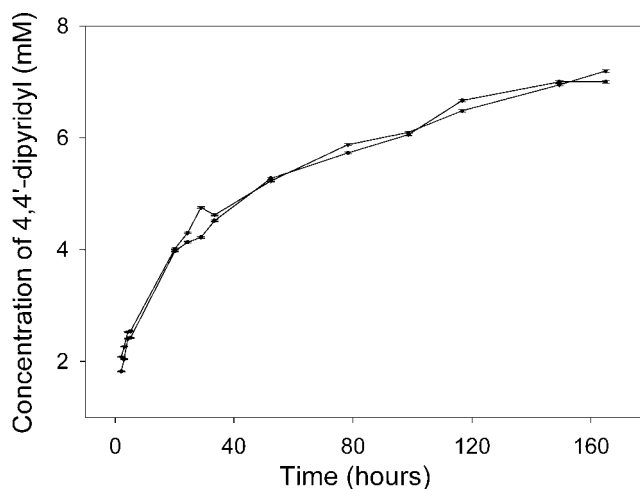
Figure 10 Comparison of the controlled-release study results of two similarly-prepared PVA monoliths containing 4,4′-dipyridyl. Both monoliths had a mass of 10.3 g, a length of 24 mm, a diameter of 23 mm, and 0.251 g of 4,4′-dipyridyl.

Studies were conducted to test the consistency in the rate of reagent release among different reagent-loaded PVA monoliths. A PVA monolith was prepared (6.0013 g PVA + 34.0 g H_2O) and loaded with 0.502 g of 4,4′-dipyridyl. This monolith was then cut into two identical circular pieces, each weighing 10.3 g with 0.251 g of 4,4′-dipyridyl. The diffusion properties of the two reagent-loaded monoliths are similar (Fig. 10), suggesting that the reagent was dispersed evenly throughout the original monolith. Although not tested, similar consistency in results is expected for the diffusion properties of other reagent-loaded monoliths. The consistency in reagent release characteristics from these reagent-loaded monoliths indicates that, at least in the case of 4,4′-dipyridyl, such reagent-loaded polymer monoliths may be mass-produced for delivery and sensing applications.

It is worth noting that both Figures 6 and 10 involve controlled- release studies of 4,4′-dipyridyl. The former was conducted with a monolith (29.9 g with 0.723 g of 4,4′-dipyridyl) that was about three times longer (and thus larger in volume, as both have the same diameter of 23 mm) and contained about three times more 4,4′-dipyridyl than the latter (10.3 g with 0.251 g of 4,4′-dipyridyl). It is thus perhaps not surprising that the controlled-release studies of the former (Fig. 6) showed a faster release than the latter (Fig. 10). In addition, at 160 min, the concentration of 4,4′-dipyridyl released from the former (19.3 m*M*) is nearly three times that released from the latter (ca. 7 m*M*).

Limitations of the *PVA* monoliths for use in the Fujiwara reaction

The PVA monoliths here have been shown to release reagents at a consistent rate, making the monoliths

attractive in chemical sensor development. However, the PVA monoliths in this study are composed of 80–90% w/w water.[14] As reported previously,[15] the modified Fujiwara reactions must be conducted in a low-moisture environment. When a large amount of water is present, it competes with pyridine for the carbene $:CX_2$ intermediate, decomposing $:CX_2$ before it reacts with pyridine to give the colored product in the modified Fujiwara reactions.[19] Solutions of *n*-Bu₄NOH and 2,2′- or 4,4′-dipyridyl resulting from controlled-release studies were thus found unsuitable for the Fujiwara reactions. No colored products were observed when chloroform was added to the solutions of released *n*-Bu₄NOH and 2,2′- or 4,4′-dipyridyl.

To rule out interference of dry PVA beads with the Fujiwara reactions, qualitative experiments were carried out in which dry PVA beads as received were added to a mixture of 2,2′-dipyridyl and *n*-Bu₄NOH. This combination of PVA beads and reagents was allowed to stand for 24 h. After 24 h, a small amount of chloroform was added to the vessel, and subsequently the characteristic color of the modified Fujiwara reaction product was observed. This test rules out interference of PVA and indirectly suggests that the water released from PVA monoliths had decomposed carbene intermediates in the Fujiwara reactions. In other words, the process developed here and controlled-release of the reagents could be used in other reactions that are not sensitive to the presence of water.

CONCLUSIONS

A method for the development of CRPs containing 2,2′-dipyridyl, 4,4′-dipyridyl, or *n*-Bu₄NOH has been developed. The method by which the reagents were incorporated into the polymer matrix was found to be a critical step in the development of the CRPs. The release characteristics of the reagents from the polymer monoliths were also found to proceed in a controlled manner. Release characteristics of reagents from reagent-loaded PVA monoliths were also found to be consistent. The methodology for reagent delivery developed here could have potential applications in chemical sensing applications that are not sensitive to the presence of water.

References

 1. Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. Chem Rev 1999, 99, 3181.
 2. Mandal, T. K. Eur J Pharm Biopharm 2000, 50, 337.
 3. Peppas, N. A.; Scott, J. E. J Control Release 1992, 18, 95.
 4. Luo, S.; Walt, D. R. Anal Chem 1989, 61, 174.
 5. Barnard, S. M.; Walt, D. R. Science 1991, 251, 927.
 6. Hassan, C. M.; Stewart, J. E.; Peppas, N. A. Eur J Pharm Biopharm 2000, 49, 161.

7. Agayn, V.; Walt, D. R. Immunomethods 1993, 3, 112.

8. Ricciardi, R.; Auriemma, F.; Gaillet, C.; De Rosa, C.; Laupretre, F. Macromolecules 2004, 37, 9510.

9. Hassan, C. M.; Peppas, N. A. Macromolecules 2000, 33, 2472.

10. Ricciardi, R.; Mangiapia, G.; Lo Celso, F.; Paduano, L.; Triolo, R.; Auriemma, F.; De Rosa, C.; Laupretre, F. Chem Mater 2005, 17, 1183.

11. Willcox, P. J.; Howie, D. W., Jr.; Schmidt-Rohr, K.; Hoagland, D. A.; Gido, S. P.; Pudjijanto, S.; Kleiner, L. W.; Venkatraman, S. J Polym Sci Part B: Polym Phys 1999, 37, 3438.

12. Yokoyama, F.; Masada, I.; Shimamura, K.; Ikawa, T.; Monobe, K. Colloid Polym Sci 1986, 264, 595.

13. Ricciardi, R.; Auriemma, F.; De Rosa, C. Macromol Symp 2005, 222, 49.

14. Peppas, N. A.; Stauffer, S. R. J Control Release 1991, 16, 305.

15. Rodman, D. L.; Carrington, N. A.; Qiu, H.; Goswami, K.; Xue, Z.-L. Anal Chim Acta 2005, 548, 143.

16. Milanovich, F. P.; Brown, S. B.; Colston, B. W., Jr.; Daley, P. F.; Langry, K. C. Talanta 1994, 41, 2189.

17. O'Neil, M. J. In The Merck Index, 13th ed.; O'Neil, M. J., Smith, A., Heckelman, P. E., Eds.; Merck: Whitehouse Station, NJ, 2001; p 1362.

18. Material Safety Data Sheet for n-Bu$_4$NOH. http://www.alfa.com/MSDSPDF/English/110445.pdf

19. Hine, J. J Am Chem Soc 1950, 72, 2438.