Controlled Release from a Composite Silicone/Hydrogel Membrane

Zhibing Hu,* Changjie Wang,* Kevin D. Nelson,† and Robert C. Eberhart†

To enhance the drug uptake and release capacity of silicone rubber (SR), N-isopropylacrylamide (NIPA) hydrogel particles have been incorporated into a SR membrane. The NIPA particles were thoroughly blended with uncured SR with a certain ratio at room temperature. The mixture was then cast in a Petri dish to 1 mm thickness and cured 10 hours at 90°C. The SR/NIPA composite gel can absorb water approximately equal to its dry weight. Brilliant blue, used as a mock drug, was loaded into the composite gel. Drug release increased exponentially to a final value that is temperature dependent: low at T> =34°C, and high at T< 34°C. This finding is because the hydrophobicity of NIPA changes with temperature. Pulsed release in response to temperature switching between 20 and 39°C has been achieved. Drug uptake and release capability strongly depends upon the structure of the composite gel. The optimal range of NIPA composition is between 75 and 87% by volume. In the cited range, the NIPA particles form an interconnected network that provides a channel for diffusion of drug solution. The SR/NIPA composite gel has promising attributes as a wound dressing and other uses. *ASAIO Journal* 2000; 46:431–434.

Numerous dressings have been applied to wounds in past centuries with properties of hemostasis, protection, support, and absorption.[1] Currently, many dressing types are available, including films, hydrocolloids, hydrogels, alginates, and composite dressings.[1–4] These types provide a wide variety of dressings based on wound type.[4,5] A dressing is no longer a passive adjunct to healing but is an active element of wound management, aimed at removal of necrotic tissue, elimination of infection, absorption of excess exudate, maintenance of a moist wound surface, as well as provide thermal insulation and protect the healing wound from trauma and bacterial invasion.[1–4]

Silicone rubber is used in wound healing dressings, it has good strength and flexibility, is generally considered to be biocompatible, and has gained acceptance in the management of hypertrophic and keloid scars.[6–10] Although the mechanism is not completely understood, both physical and chemical effects are believed to be involved. The water impermeability of silicone rubber has been shown to reduce evaporation fluid loss and maintain the moisture level.[7] It has also been reported that vitamin E added to a silicone rubber sheet improved wound healing over simple silicone gel.[6] However, the water absorption of silicone rubber is almost zero, which strongly limits silicone rubber from fully functioning as a drug releasing wound dressing or for exudate absorption.

In this study, poly(N-isopropylacrylamide) (NIPA) hydrogel microparticles were synthesized and incorporated into silicone rubber. The NIPA gel is hydrophilic and swells in water for $T<T_c$, where T_c (=34°C) is the volume phase transition temperature. For $T>T_c$, it becomes hydrophobic and collapses into a small volume.[11] Such unusual properties suggest varied applications, including controlled drug delivery[12,13] and sensors.[14,15] In this SR/NIPA composite membrane, absorption ability has been markedly enhanced. The composite gel can absorb water equal to approximately its dry weight. Furthermore, as a drug delivery system, this membrane's release rate changes due to changes in environmental temperature.

Materials and Methods

The synthesis of composite silicone rubber membranes consisted of two steps. First, NIPA microgels were prepared, then NIPA microgels were incorporated into the silicone gel.

NIPA microgels were prepared by the suspension method. A mixture of 7.8 g of N-isopropylacrylamide monomers (Acros Organics), 133 mg of methylene-bis-acrylamide as a crosslinker, and 240 μL of tetra-methyl-ethylene-diamine as an accelerator (both from BIO-RAD Laboratories), were dissolved in 100 mL of deionized and distilled water. Nitrogen gas was bubbled through the solution to remove dissolved oxygen. The polymerization was initiated by adding 40 mg of ammonium persulfate (Aldrich Chemical Company). This pregel solution was poured into the prepared mixture of 300 g of cyclohexane (EM Science) and 5 g sorbitan monooleate (Aldrich Chemical Company). The suspension was stirred and bubbled with nitrogen for approximately 3 hours and kept overnight. Afterward, NIPA particles were washed to remove cyclohexane and sorbitan monooleate. An optical microscope was used to check the NIPA gel particles. The average size of the NIPA gel particles was approximately 100 μm in diameter when fully swollen in water at room temperature. NIPA microgels were found to swell below T_c = 34°C and shrink above T_c, as expected.

An implant grade liquid silicone rubber (LSR) 10:1 system was purchased from Applied Silicone Corporation. It is a two-part, pourable, dimethyl silicone elastomer and is designed to mix with 10 parts base (part A) to 1 part crosslinker (part B). The mixture will cure to a high strength, clear, and flexible elastomer. The NIPA microgels were thoroughly blended with uncured SR at room temperature. The concentration ratio of NIPA over SR/NIPA by volume varied from 75 to 87%. After complete mixing with help of a centrifuge, the mixture was cast in a Petri dish to approximately 1 mm thickness and cured for 10 hours at 90°C. The composite membrane was then

From the *University of North Texas, Denton, Texas; the †University of Texas at Arlington and University of Texas Southwestern Medical Center at Dallas, Texas.

Submitted for consideration June 1999; accepted for publication in revised form December 1999.

Reprint requests: Dr. Zhibing Hu, Physics Department, University of North Texas, Denton, TX 76203.

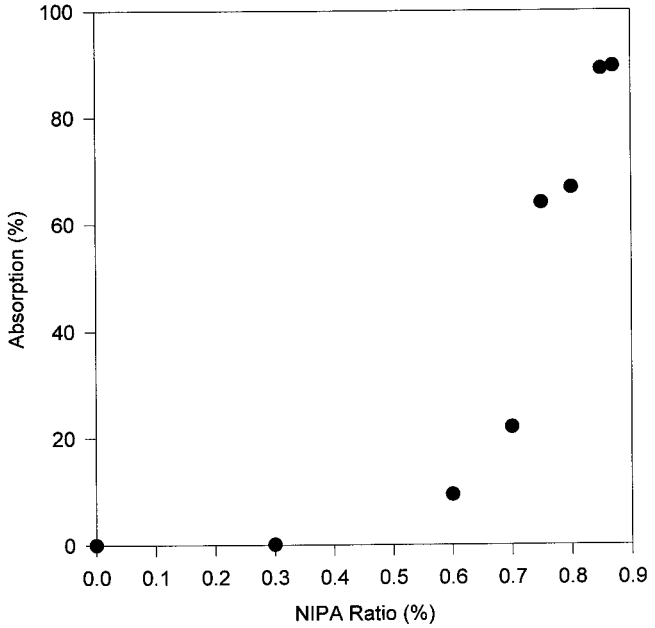

Figure 1. The water absorption of the silicone rubber/N-isopropylacrylamide (SR/NIPA) composite material was measured as a function of the ratio of NIPA particles incorporated over the composite material in volume. The threshold of absorption was identified at a ratio of approximately 75%.

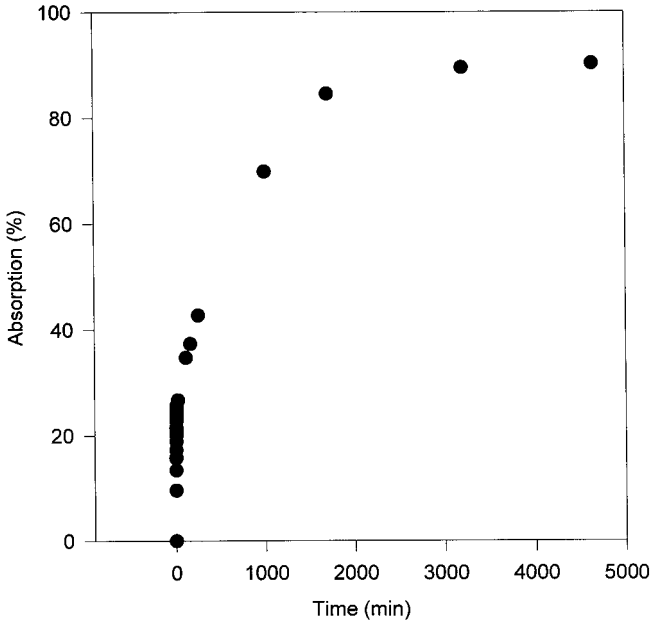

Figure 2. Water absorption of the composite membrane at an 85% ratio, with a thickness of 0.65 mm, was measured as a function of time. The absolute absorption time depends upon the ratio of NIPA to SR and the thickness of the composite membrane.

washed with deionized water. By immersing the sample in warm water (T = 37°C), the membrane would reversibly become opaque compared with its transparent state at room temperature. This demonstrated that the NIPA microgels were incorporated into the silicone rubber, because the opacity is caused by the volume phase transition of the NIPA gel at 34°C.[16]

Results and Discussion

Water absorption of the SR/NIPA composite material is measured as a function of the NIPA ratio as shown in **Figure 1**. The ratio is defined as the volume of NIPA microgel to the volume of whole composite material (SR + NIPA) when the sample is prepared. If the ratio is lower than approximately 75%, the absorption is very low. If the ratio is higher than 90%, the silicone rubber can no longer form a good matrix, resulting in poor mechanical strength. From the curve, the threshold at which the water absorption exhibits a sharp increase is approximately 75%.

Water uptake of the composite membrane can be understood from the connectivity of both silicone rubber and NIPA microparticles. For lower ratios, NIPA microgels have no contact with each other. That is, almost all NIPA microgel particles are isolated within the silicone rubber matrix. The permeability of such low ratio material is nearly zero, because the permeability of the silicone rubber is almost zero. As the concentration of NIPA microgel increases, neighboring microgels will begin to be in physical contact. As this continues to increase with increasing microgel concentration, a pathway is soon formed wherein most of the microgels are in physical contact. At this point, there is direct communication existing throughout the SR matrix, including the surface. At this point, water is readily absorbed from the surface and taken up within the SR matrix. This process is described mathematically by the percolation theory, as described below.

Suppose the silicone rubber has a three-dimensional lattice of sites, and gel microparticles are in contact between every pair of neighboring sites with probability p. At a threshold value of p_c, one cluster will span the lattice, meaning that there is a connected path across the lattice through a single spanning cluster. Only above this threshold does the water uptake of the composite membrane become available. By using the percolation model in the three-dimensional site problem,[17] the threshold is found to be 74% under the assumption that all microgel particles are spherical and have the same size. Our experimental result is in good agreement with this theoretic value.

Water absorption kinetics was measured for a composite SR/NIPA membrane with an 85% NIPA ratio and a thickness of 0.65 mm. The results are shown in **Figure 2**. The absolute absorption rate depends upon the NIPA ratio, size of the microgel particles, and the thickness of the membrane.

The mechanical strength of the composite material is much better than that of the NIPA gel. The shear modulus of the sample is measured by uniaxially stretching the sample with different weights (F) attached to the bottom. When the volume of the sample is kept constant, one can obtain[18]

$$F/A_0 = G(\lambda - 1/\lambda^2)$$

where G is the shear modulus and A_0 is the cross-sectional area of the undeformed sample; λ is the z-direction elongation ratio of the gel. By plotting F/A_0 *versus* $(\lambda\text{-}1/\lambda^2)$, the slope G of the sample is obtained as shown in **Figure 3**. It is found that the shear modulus is 3.6×10^5 dyn/cm^2 for a membrane with 87% NIPA. The shear modulus of the pure silicone gel is 8.2×10^6

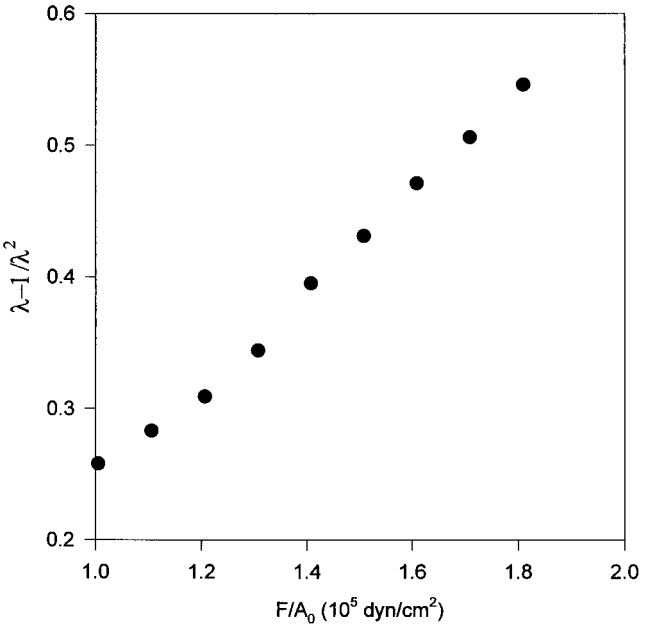

Figure 3. The shear modulus of the composite material was measured by the tensile method and found to be 3.6×10^5 dyn/cm^2 for the sample containing 85% NIPA.

dyn/cm^2. There is no significant difference for samples with NIPA ranging from 75 to 87%. Compared with pure NIPA gel's shear modulus of 2.2×10^4 dyn/cm^2,[19] the mechanical strength of the composite membrane is drastically enhanced.

The microscopic structures of samples were examined by a scanning electron microscope (SEM) (**Figure 4**). The sample was first dried and then sputter-coated with gold to achieve satisfactory conductivity with minimal damage to the specimens. The coated specimens were observed in the scanning electron microscope (Model JSM-T300, JEOL), and the scanning images were photographed on Polaroid PN/52 films. From the pictures, one can see that the NIPA microgel particles are trapped and exposed to the surface of the silicone rubber membrane. The NIPA microgel particles must also be connected in a three dimensional cluster inside the silicone, as demonstrated by absorption kinetics.

Brilliant blue (Aldrich), used as a mock drug, was loaded into the composite membrane. The drug loaded composite was then transferred to a water bath, with temperature controlled by a thermostat. The brilliant blue was eventually released into water. The molecular mass of brilliant blue G was 854.04 daltons and completely dissolved in water without aggregation at the concentration that we used. If considering brilliant blue G molecules as spheres, their diameters should be smaller than 1 nm. The concentration of brilliant blue in the water bath was monitored through spectrophotometric measurement of turbidity (Spectronic 301, Milton Roy, Ltd.) operating at a wavelength of 555 nm. The results are shown in **Figure 5**. Drug release increased exponentially to a final value that is temperature dependent: low at $T > T_c$ and high at $T < T_c$. This finding is because the hydrophobicity of the NIPA changes with temperature. In such a thermo-sensitive system, hydrophobic drugs tend to be immobilized in the polymer network above T_c, and diffuse out at temperatures below T_c.[20] Some released brilliant blue G tends to be retaken up by the

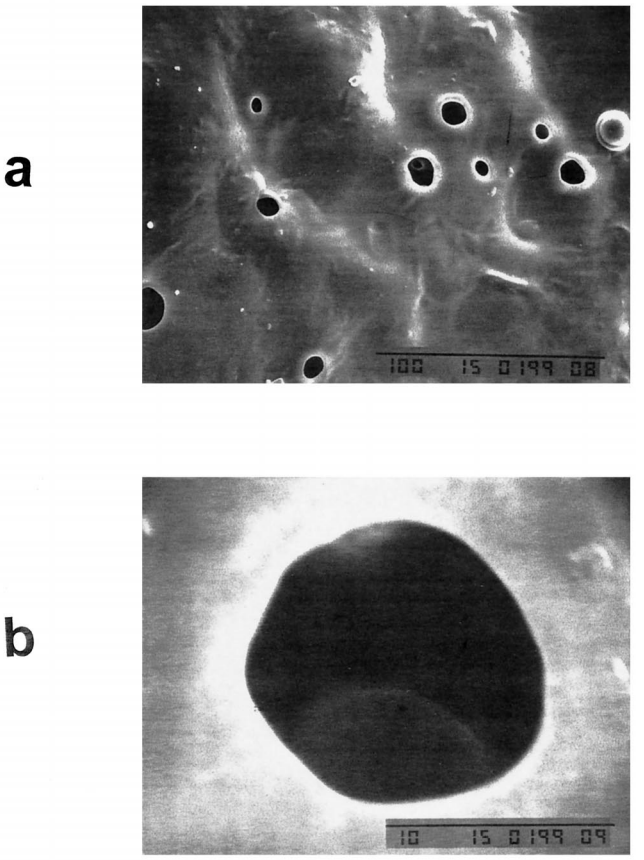

Figure 4. The surface of the composite membrane was studied by scanning electron microscopy. Samples were first dried and then coated with gold. (a) Attached inside the voids of silicone rubber are NIPA gel particles in the dehydrated state. (b) Close-up of a single NIPA particle embedded in the surface of the silicone rubber membrane.

membrane above T_c because of hydrophobic interaction of the NIPA gel with this mock drug. Pulsed release in response to the temperature switching between 20 and 39°C has been achieved. Drug uptake and release capability strongly depends upon the structure of the composite gel. The optimal range of the NIPA composition was found to be between 75 and 87% by volume. In the cited range, the NIPA particles form an interconnected network that provides a channel for diffusion of a drug solution.

Conclusions

The SR/NIPA composite membrane combines the strength of silicone rubber and the wetability of the NIPA gel. The hydrophobic SR provides strong mechanical support, whereas the hydrophilic NIPA hydrogel enhances the wetability of the system. The NIPA particles form an interconnected network that provides a channel for diffusion of a drug solution. The composite membrane could be used to release drug under external stimuli such as temperature and pH, and has promising attributes as a wound dressing and other applications.

Acknowledgments

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the US

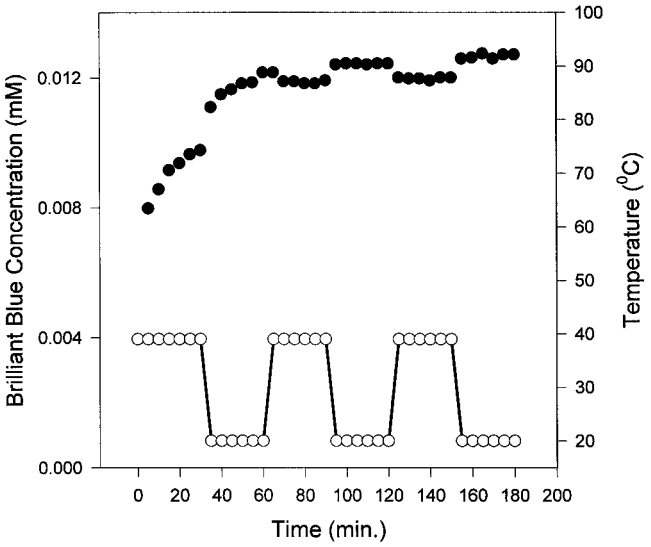

Figure 5. The composite membrane loaded with brilliant blue was transferred to a thermal bath. The concentration of brilliant blue in the bath was monitored by determining turbidity of the bath by using a spectrophotometer. Drug release increased exponentially to a final value that is temperature dependent.

Army Research Office under Grants DAAG55–98-1–0,175, for support of this research.

References

1. Hayward PG, Morrison WA: Current concepts in wound dressings. *Aust Prescriber* 19: 11–13, 1996.
2. Findlay D: Modern dressings: What to use. *Aust Fam Physician* 23: 824–839, 1994.
3. Ryan TJ: Wound dressing. *Dermatologic Clin* 11: 207–213, 1993.
4. Baranoski S: Wound dressings: Challenging decisions. *Home Healthc Nurse* 17: 19–25, 1999.
5. Hall CM: Wound dressings: use and selection. *Geriatr Nurs* 18: 266–267, 1997.
6. Palmieri B, Gozzi G, Palmieri G: Vitamin E added silicone gel sheets for treatment of hypertrophic scars and keloids. *Int J Dermatol* 34: 506–509, 1995.
7. Clugston PA, Vistnes MD, Perry LC, Maxwell GP Fisher J: Evaluation of silicone-gel sheeting on early wound healing of linear incisions. *Ann Plast Surg* 34: 12–15, 1995.
8. Gold MH: A controlled clinical trial of topical silicone gel sheeting in the treatment of hypertropic scars and keloids. *J Am Acad Dermatol* 30: 506–507, 1994.
9. Ahn ST, Monafo WW, Mustoe TA: Topical silicone gel for the prevention and treatment of hypertropic scar. *Arch Surg* 126: 499–504, 1991.
10. Sproat JE, Dalcin A, Weitauer N, Roberts RS: Hypertropic sternal scars: silicone gel sheet versus Kenalog injection treatment. *Plast Reconstr Surg* 90: 988–992, 1992.
11. Hirotsu S, Hirokawa Y, Tanaka T: Volume-phase transitions of ionized N-isopropylacrylamide gels. *J Chem Phys* 87: 1392–1395, 1987.
12. Chen G, Hoffman AS: Temperature-induced phase transition behaviors of random vs. graft copolymers of N-isopropylacrylamide and acrylic acid. *Macromolecular Rapid Communication* 16: 175–182, 1995.
13. Kim YH, Bae YH, Kim SW: pH/temperature-sensitive polymers for macromolecular drug loading and release. *J Controlled Release* 28: 143–154, 1994.
14. Ilmain F, Tanaka T, Kokufuta E: Volume transition in a gel driven by hydrogen bonding. *Nature* 349: 400–401, 1991.
15. Hu Z, Zhang X, Li Y: Synthesis and application of modulated polymer gels. *Science* 269: 525–527, 1995.
16. Hu Z, Chen Y, Wang C, Zheng Y, Li Y: Polymer gels with engineered environmentally-responsive surface patterns. *Nature* 393: 149–151, 1998.
17. Efros AL: *Physics and Geometry of Disorder: Percolation Theory*. Moscow, Mir Publisher, 1986.
18. Treloar LRG: *The Physics of Rubber Elasticity*. Oxford, Clarendon Press, 1975.
19. Zhang X, Hu Z, Li Y: The phase transition and shear modulus of ionic N-isopropylacrylamide gels in concentrated salt solutions. *J Appl Polym Sci* 63: 1851–1856, 1997.
20. Schild HG: Poly (N-isopropylacrylamide): Experiment, theory and application. *Prog Polym Sci* 17: 163–249, 1992.