



Novel Methacrylate Copolymers: Photosensitive Adhesives and Hydrogels

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ABSTRACT

Photosensitive methacrylate copolymers were studied as candidates for biomaterials in the fields of hydrogel-based drug delivery and bioadhesives. An acid-labile hydrogel was synthesized and found to exhibit a 100-150% increase in water uptake in the presence of aqueous acid or a photoacid generator. A photocrosslinkable methacrylate adhesive was also synthesized, and peel testing determined that a time-dependent reduction in peel strength of up to 100% occurs upon irradiation with sunlight in the presence of a photoinitiation system.

INTRODUCTION

Acrylates and methacrylates have a wide variety of uses, ranging from artists' paint to fake nails. In addition, the biocompatibility of certain methacrylates, including 2-hydroxyethyl methacrylate (HEMA, Figure 1a) makes these monomers ideal for a number of medical applications. Currently found in contact lenses, bone cements, and dental composites, HEMA can also potentially be used in other biomaterials, including hydrogels for drug delivery¹ and adhesives for bandages and wound dressings².

Both fields require materials that do not irritate or poison the body, and that also possess specific mechanical properties—adhesives must be sticky and hydrogels must be absorb water well. Innovative materials in these areas exceed these basic requirements by providing additional characteristics beneficial to their applications. For example, an acceptable hydrogel would be any biocompatible material that absorbs water; an excellent hydrogel would be not only biocompatible and hydrophilic, but would also allow for controlled long-term drug release at a specific site within the body.

How can this be accomplished? Hydrogel-based drug delivery systems require very specific properties because of their application. First, the hydrogel should be biodegradable so that it will not require surgical removal³. Second, the hydrogel and all degradation byproducts must be biocompatible to prevent adverse reactions in the body. Third, the hydrogel must produce sustained, controlled drug release—sustained to make the system worth implementing, and controlled to prevent dose dumping and maintain drug concentration within the therapeutic

window¹. In addition, control over the location and initiation of drug release can also be important when localized drug delivery is preferable⁴.

The composition and degree of crosslinking of a hydrogel, usually a copolymer of multiple biocompatible monomers, can be tailored to alter its release properties. For example, a study of lactoyl-functionalized poly(ethylene glycol) found that varying the molecular weight and number of lactoyl end groups resulted in different release profiles for the proteins studied³. The change in release profiles related directly to the calculated average mesh size of the hydrogels, the size of the holes or spaces formed by the network, which was controlled by the length of the polymer chains, the number of crosslinkable end groups, and the degree of swelling of the hydrogel. For mesh sizes much larger than the diameter of the protein being released, diffusion-controlled release was observed; however, for mesh sizes close to the diameter of the protein, the degree of swelling and network degradation strongly influenced protein release.

This clearly indicates that the mesh size of the hydrogel and its change over time with swelling and degradation are important in controlled drug release. One way to initiate release at a specific time and location within the body would therefore be to incorporate a pore-enlarging mechanism into the structure of the polymer, which could be accomplished easily by causing controlled degradation of the polymer.

Photoacid generation is one example of such a mechanism. Photosensitive compounds cause a variety of reactions upon exposure to light, including acid production and crosslinking, and many of these reactions can be used beneficially in biomedical applications. An acid-labile hydrogel that contains a photoacid generator (PAG) would begin to degrade and release drug upon exposure to light. This would be very beneficial in tumor treatment because the hydrogel could be implanted directly at the tumor site and then irradiated at the appropriate time to begin drug release. Local administration of the anti-tumor agent would ensure that the cancerous cells and surrounding tissue would receive the maximum possible dosage while systemic blood levels of the drug remained low, as most of the drug would remain close to the tumor site. Using such a hydrogel, higher doses of anti-cancer drugs could be administered with reduced systemic toxicity and side effects.

In this experiment, a HEMA-based methacrylate hydrogel with a novel crosslinking monomer was studied as a model drug delivery system to determine the effect of acid on degradation of the crosslinks. HEMA was chosen for its hydrophilicity, while the novel monomer, 2,5-dimethyl-2,5-hexanediol dimethacrylate (DHDMA, Figure 1b), was designed to possess two vinyl groups for crosslinking and two tertiary ester bonds that should be acid-degradable. As shown in Figure 2, the crosslinks formed by this monomer can be broken in the presence of acid—either from an external source, such as hydrochloric acid, or from a PAG such as diphenyliodonium nitrate (DPIN, $\lambda_{\text{max}} = 226 \text{ nm}$, Figure 1c) impregnated into the hydrogel network itself; similar crosslinking agents have been shown to undergo the proposed degradation⁵. Upon degradation of the crosslinks, the mesh size of the hydrogel and mobility of the polymer chains should increase, leading to increased drug release. Network degradation also leads to increased water uptake and swelling as more space becomes available for water molecules to enter the system. Thus, water uptake can be used as an indicator of the relative degree of crosslinking of the hydrogel after exposure to acid.

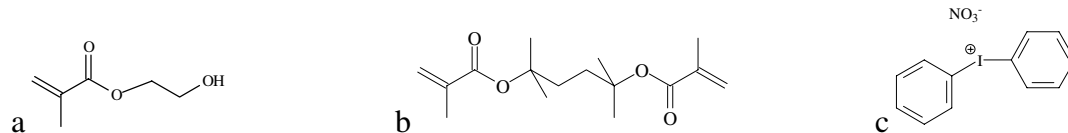


Figure 1: Structures of the hydrogel components: a) HEMA; b) DHDMA; c) DPIN.

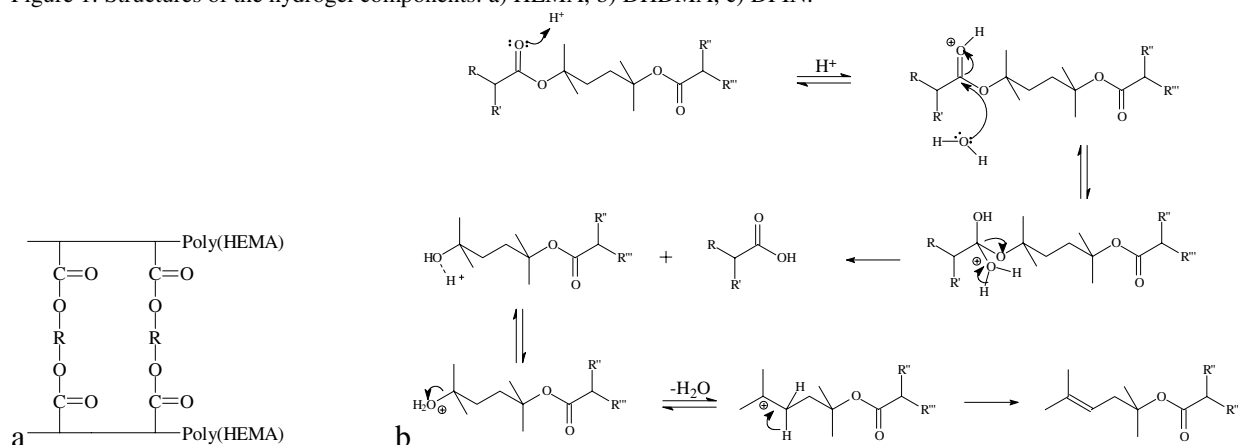


Figure 2: a) Schematic representation of the hydrogel; b) Proposed acid-catalyzed degradation mechanism of DHDMA. R, R', R'', and R''' represent chains of poly(HEMA) with other DHDMA crosslinks. The products of this reaction include a carboxylic acid, a tertiary alcohol or diol, and several vinyl or divinyl species, including 2,2',5,5'-tetramethyl-1,3-butadiene, a volatile conjugated hydrocarbon that should form favorably.

Another biomedical application of photosensitive polymers is the field of bioadhesives, compounds used to adhere bandages and wound dressings to human skin. An ideal pressure-sensitive adhesive (PSA) would be sticky for as long as the bandage was necessary, then “switch” to lose its tackiness just before removal. This type of PSA would eliminate the skin trauma now typically associated with bandage removal, particularly from patients with sensitive skin. One promising switching mechanism involves crosslinking polymers to raise their storage modulus above the Dahlquist Criterion, 10^5 Pa, the maximum storage modulus of an adhesive polymer⁶. Polymers with storage moduli below this value flow well and can wet substrates sufficiently to cause adhesion, but polymers with storage moduli above the Dahlquist Criterion are too stiff to be sticky.

Webster^{2,7,8} takes advantage of this concept in his work on photoswitchable adhesives, specifically visible-light-initiated crosslinking of acrylate/methacrylate copolymers. Acrylates are widely used as adhesives in both medical and non-medical applications due to their inherent stickiness, good mechanical properties, and resistance to weathering⁶. Webster built upon these characteristics by incorporating pendant vinyl groups into the polymer structure, providing the potential to crosslink upon initiation. Using vinyl-functionalized copolymers of HEMA, *n*-butyl acrylate (BA, Figure 3a), itaconic anhydride, and 2-ethylhexyl methacrylate with Irgacure 784 as a visible photoinitiator, he has reported photoinduced adhesive switching of up to 86%, as calculated by the formula

$$\text{Percent switch} = [1 - (P_e/P_u)] * 100 \quad (1)$$

where P_e represents the peel strength of a sample exposed to light and P_u represents the peel strength of an unexposed sample². These results indicate that crosslinking acrylate/methacrylate

copolymers can in fact significantly reduce the peel strength (tackiness) of the polymers, suggesting that the concept should be further explored.

This experiment aimed to do just that. Based on the same ideas, this study involved a simpler polymer, a different synthetic scheme, and a different photoinitiator. Again, the goal was to synthesize a high-molecular-weight, highly adhesive polymer containing pendant crosslinkable vinyl groups, but just two monomers were used: BA and HEMA. BA is a sticky and biocompatible monomer. As previously mentioned, HEMA is also biocompatible⁹, and its bifunctionality makes it very versatile. The vinyl group allows for free radical polymerization, while the primary alcohol can be used as a nucleophile in a number of reactions, including esterification with acryloyl chloride (AC, Figure 3b)—the second step of the adhesive synthesis.

Like Webster's work, the photoinitiation system in this study involved a visible-light-active compound, but the components were chosen for other important characteristics as well. The photoinitiator, camphorquinone (CQ, Figure 3c), is currently widely used in dental applications, and its use within the body is FDA-approved. CQ requires a tertiary amine as a co-catalyst, and dimethylaminoethyl methacrylate (DMAEM, Figure 3d) was selected because it possesses both the tertiary amine and a vinyl group, which can be incorporated into the polymer backbone to avoid leaching into the body.



Figure 3: Structures of the adhesive a) comonomer, BA, and b) functionalization group, AC, and the photoinitiating system c) initiator, CQ, and d) co-catalyst, DMAEM.

The design of an ideal bandage incorporating the photosensitive polymer is shown in Figure 4. Though similar to current bandages, this dressing requires one additional component, which would have minimal contact with the patient's skin. To prevent switching before the desired removal time, an opaque top layer would completely cover the photosensitive adhesive. This layer, attached by a fairly weak adhesive (so that it could be peeled away without disturbing the rest of the bandage) would be pulled off just before the desired removal time, causing light exposure through the transparent backing.

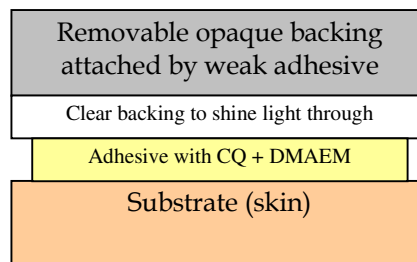


Figure 4: An ideal photoswitchable bandage.

EXPERIMENTAL

Materials

HEMA, BA, and DMAEM (all Aldrich) were purified by column chromatography to remove inhibitor and stored under N₂ at -5 °C. Triethylamine (TEA, Aldrich) was also stored under N₂ at -5 °C. AC, DPIN, CQ, 2,5-dimethyl-2,5-hexanediol, methacryloyl chloride and 2,2'-azobisisobutyronitrile (AIBN) were stored at -5 °C and used as received from Aldrich. HPLC-grade tetrahydrofuran (THF, Burdick & Jackson) was used as received for all free-radical

polymerizations and distilled over sodium to remove water for all acid chloride reactions. 95% ethanol (EtOH, Aager) was used as received. Distilled H₂O was used for all precipitations.

Methods

Synthesis of acrylate-functionalized HEMA/BA (AFHB). The preparation of AFHB involved three steps, shown in Figure 5: 1) free-radical polymerization of 10 mol% HEMA/90 mol% BA; 2) reaction of the HEMA/BA with AC; and 3) purification of the product to remove excess acid chloride and TEA-HCl salt.

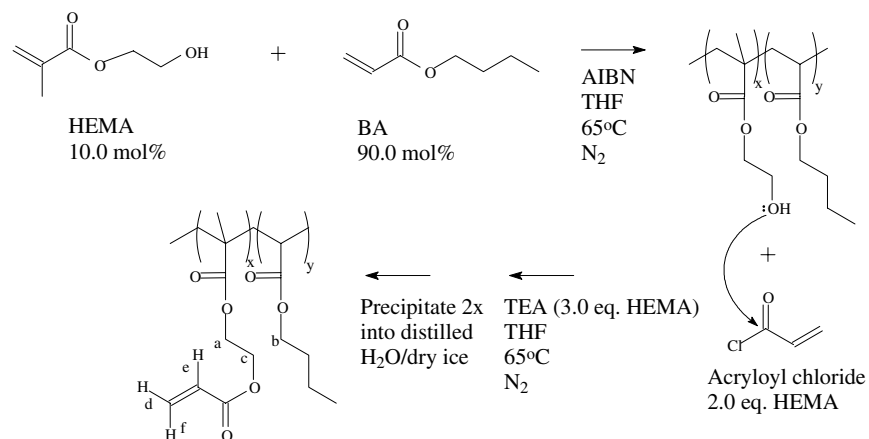


Figure 5: Synthesis and purification of AFHB. Lowercase letters a-f label protons used for NMR characterization.

First, 1.0 eq. HEMA and 9.0 eq. BA were syringed into a flask containing AIBN (0.5 wt% of monomers) and THF (50 wt% of total reaction). The mixture was sparged with N₂ for 5 minutes and heated to 65 °C for 24 hours with stirring. The product was carried on to the second step without purification or exposure to air. Additional THF (approximately four times the amount added in the first step) was added to decrease the viscosity of the solution, which was stirred to homogeneity. TEA (3.0 molar eq. of HEMA) was then syringed into to the reaction flask, which was placed into an ice bath. Finally, AC (2.0 molar eq. of HEMA) was syringed dropwise into the flask, and the mixture was allowed to react with stirring for 24 hours. To purify the product, it was precipitated into a beaker of distilled H₂O and dry ice, redissolved in THF, and reprecipitated into H₂O/dry ice, then dried in a vacuum oven for 24 hours.

NMR with a Varian Unity 400 produced peaks at δ 4.0 and δ 3.8 corresponding to the methylene protons a+b and c, respectively (see Figure 5 for labeling). These were used to determine the HEMA:BA molar ratio, 11:89. After functionalization, the c peak shifted from δ 3.8 to δ 4.2, and peaks from the vinyl protons d, e, and f appeared at δ 5.8, δ 6.2, and δ 6.4, respectively. The average of the integration of the vinyl protons was used to calculate the conversion, 60-80%, of the HEMA alcohol to an ester.

Peel testing sample preparation. A stock solution of 0.0251 g CQ and 0.0275 mL DMAEM in 10.0 mL THF was prepared. 0.1 g AFHB was placed on one end of a glass microscope slide (VWR, 25 x 75 mm, polished with Kimwipes). For samples containing photoinitiator, 0.4 mL of CQ/DMAEM solution was syringed onto the end of the slide such that every slide contained 1.0 wt% each of CQ and DMAEM¹⁰. The samples were placed in chambers completely covered with aluminum foil to block out light and the THF was allowed to evaporate for 18 hours. A

Mylar strip (30 x 100 mm) was placed on each slide as shown in Figure 6, and 35 lbs. of weight were placed on the samples for 45 minutes.

Exposure to light. The samples were irradiated through their microscope slide backings by one of two methods. For 487 nm light, samples were placed 0.5" from the tip of an Oriel

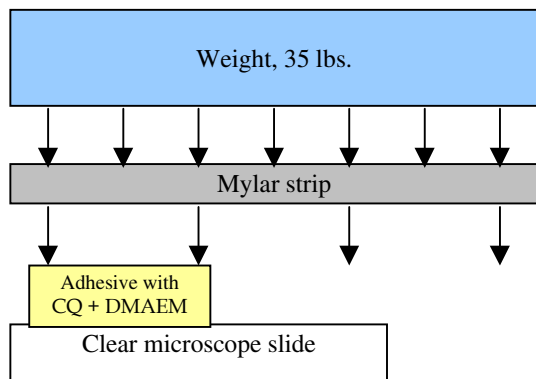


Figure 5: Preparation of peel testing samples.

photoreactor with a mercury lamp source and a 487 nm light-pass filter and irradiated for 10, 20, or 30 minutes. For a broader spectrum, samples were exposed to direct sunlight with an intensity of 2.55-4.26 mW/cm², measured using an Oriel Instruments Goldilux UV-A Photometer (Model 70234) for 5, 10, or 20 minutes. Peel test results were obtained within two hours of exposure.

Peel testing. An Instron 4411 Universal Testing Rig was used to perform an ASTM Method D903 180° peel test at a peel rate of 5"/minute at room temperature. Tests were performed in duplicate

and the results are reported as an average of the data obtained.

DHDMA synthesis. 1.0 eq. 2,5-dimethyl-2,5-hexanediol was reacted with 2.0 eq. methacryloyl chloride in dichloromethane (Burdick & Jackson) at 0 °C using TEA as an acid sponge. The product was purified three times by column chromatography.

Hydrogel coating preparation. 97.0 mol% HEMA (4.37 mL) was mixed with 3.0 mol% DHDMA (0.25 mL) and AIBN (0.0251 g, 0.5 wt% of monomers). Either 17.7 v/v% EtOH (1.0 mL) or DPIN (0.0501, 1.0 wt% of monomers) dissolved in 1.0 mL EtOH was added to the monomer mixture, which was then sparged for 5 minutes with N₂. To prepare coatings, pre-cleaned glass microscope slides were wiped with Kimwipes and placed in an airtight chamber fitted with a gas line and rubber septum. To remove oxygen, the chamber was purged with N₂ for 20 minutes, then filled with N₂ for 10 minutes. 0.5 mL monomer mixture was then syringed onto each slide and the chamber was placed in a water bath at 65 °C for 4 hours. For slides containing DPIN, the entire chamber was wrapped in aluminum foil to prevent exposure to light. The coatings (attached to microscope slide backings) were dried in the vacuum oven at room temperature for 18 hours prior to use in water uptake studies.

Water uptake studies. The coatings were weighed upon removal from the drying oven to determine the dry weight (w_d) and, if applicable, exposed to unfiltered light from a mercury lamp source in the Oriel photoreactor. Each sample was placed in a 60-mL sample jar containing 50 mL of either distilled water or 1.0 M HCl. The sealed jars were immersed in a water bath at 60 °C and weighed at regular intervals to determine the water uptake of the hydrogel. Before weighing, each coating and slide was patted dry with a Kimwipe¹¹. The degree of swelling (DS) at a given time was determined by the equation

$$DS = (w_s - w_d)/w_d \quad (2)$$

where w_s represents the swollen weight of the hydrogel at that time⁴. In all cases, the wet and dry weights of the polymer itself were calculated by subtracting the total weight of the hydrogel and the slide minus the weight of the slide as determined before preparation of the hydrogel coating.

RESULTS AND DISCUSSION

As the crosslinks of a crosslinked polymer degrade, the polymer chains gain mobility and the entire network becomes more flexible. In the case of a hydrogel immersed in water, this should result in an increase in the ability of the hydrogel to absorb water due to increased space within the network for the water molecules. Thus, it would be expected that if the ester bonds in DHDMA are in fact acid labile, a HEMA/DHDMA coating exposed to acid would absorb more water and attain a greater equilibrium degree of swelling (DS_{eq}) than a coating exposed only to water.

Exposure to acid could occur through one of two methods: immersion in an acid solution (1.0 M HCl), which at any given time within the experiment would only expose the part of the hydrogel that had already taken up the acid solution, or impregnation with DPIN followed by exposure to light. In this case, assuming that the coating was thin enough to allow even exposure throughout the hydrogel, every bond in the hydrogel would be exposed to acid at the same time. The difference in exposure of internal ester bonds could result in a different method of degradation (bulk as opposed to surface), which could alter the kinetics of water uptake; however, regardless of the type of exposure, both acid-exposed hydrogels should exhibit a greater DS_{eq} than a coating exposed only to water. In addition, a hydrogel impregnated with DPIN but not exposed to light should exhibit identical a water uptake profile to that of the hydrogel without DPIN that was exposed only to water.

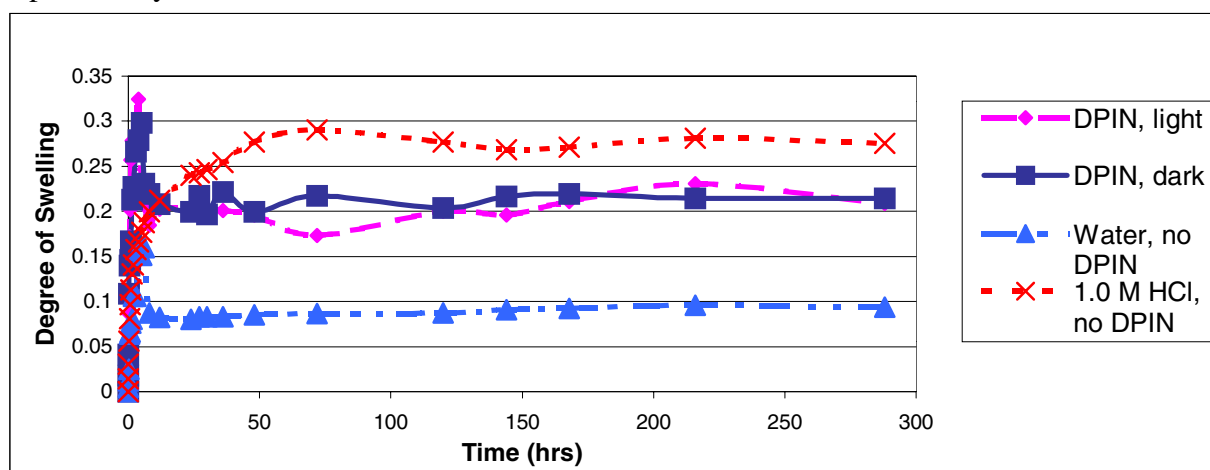


Figure 7: Hydrogel water uptake results as a function of time.

Figure 7 shows the results of the water uptake study, which was repeated three times with similar results (data not shown). A comparison of the water uptake of the hydrogel in water to the hydrogel in acid clearly the effect of the acid: DS_{eq} for the hydrogel in 1.0 M HCl is nearly three times that of DS_{eq} for the hydrogel in water. Similarly, DS_{eq} for the hydrogel with DPIN

exposed to light is greater than twice that of DS_{eq} for the hydrogel in water. This strongly suggests that the ester bonds in DHDMA are indeed acid labile and can be broken under these conditions.

However, while the hydrogels exposed to acid did in fact attain a greater DS_{eq} than those exposed only to water, the DPIN-containing hydrogel kept in the dark exhibited water uptake kinetics nearly identical to those of the DPIN-containing hydrogel that was exposed to light. This result suggests one of three conclusions: first, the stock DPIN had already generated acid before synthesis of the coatings, such that acid was incorporated into the hydrogel network along with the DPIN; second, the DPIN-containing hydrogels meant to remain in the dark were inadvertently exposed to light; or third, a light-independent mechanism is responsible for the network degradation evidenced by the elevated DS_{eq} of the hydrogel left in the dark. If the third is true, then the light-independent mechanism was likely also responsible for the degradation of the hydrogel exposed to light, as the uptake profiles of the two are nearly identical.

Interestingly, all three of the samples in water reach equilibrium at nearly the same time, between eight and twelve hours into the study, and all three seem to uptake water to some sort of breaking point four to five hours after initial water exposure, then collapse and lose some water to reach equilibrium. Only the hydrogel in aqueous HCl exhibits different behavior, taking up water non-linearly until reaching equilibrium without collapse around 48 hours after exposure. This again suggests that DPIN does not act on the hydrogel by the same mechanism as HCl, or that there is a secondary mechanism at work, but the DPIN mechanism could not be determined in this study.

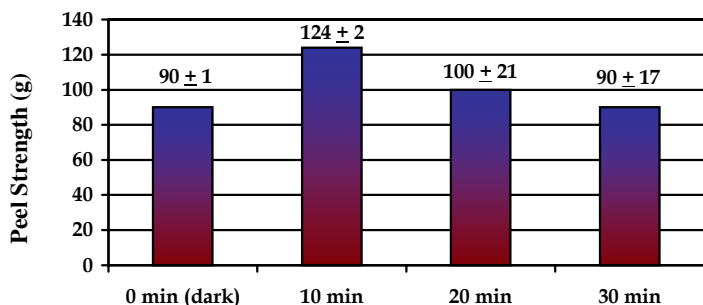


Figure 8: Peel strengths of adhesives exposed to 487-nm light.

The AFHB copolymer peel testing results are more conclusive, though likewise somewhat surprising. It was qualitatively observed that higher molecular weight polymers were stickier. Therefore, an AFHB with an M_w of 63,500 g/mol and M_w/M_n of 3.21 (determined by GPC with a Waters SEC using THF as a solvent and polystyrene standards) was used for all peel testing. In

addition, this polymer exhibited a T_g of -43 °C (quenched sample measured by DSC on a Perkin Elmer Pyris 1 instrument under helium at a heating rate of 20 °C/min), which falls well within the range accepted for adhesive polymers.

As Figure 8 illustrates, exposing AFHB samples containing CQ and DMAEM to 487 nm light for 10-30 minutes did not substantially alter the peel strength of the copolymer, given the experimental error inherent to peel tests and the fact that only two data points were obtained for each exposure time. Since CQ is widely known react upon exposure to light around 470 nm, this result is unexpected. However, several factors could account for the observed lack of crosslinking. First, the light from the photoreactor may have been at slightly too high a wavelength— λ_{max} for CQ occurs at 468 nm, and 487-nm light was being used. Second, light from the photoreactor may not have been sufficiently intense, as the filter does block about 50%

of the intensity. Lastly, irradiation occurred through the glass microscope slide, which may have also blocked some of the light.

The first or second option is more likely, as the results of exposure to sunlight, shown in Figure 9, indicate. P_u for AFHB containing CQ and DMAEM was 90 g; P_e after 10 minutes of exposure through the glass microscope slide, P_e dropped to 11 g, 88% switching. After 20 minutes, 100% switching was observed. Though further work must be performed to elucidate the switching kinetics and optimal conditions, particularly at body temperature, these preliminary results are reproducible and extremely encouraging.

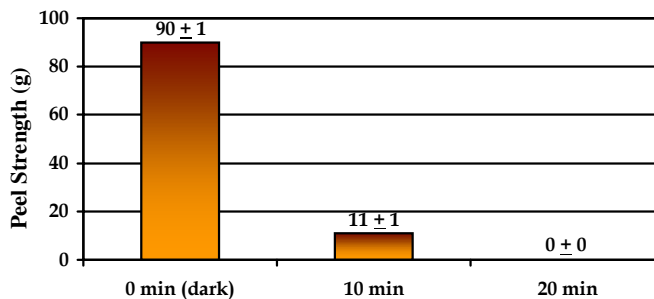


Figure 9: Peel Strengths of adhesives exposed to sunlight.

CONCLUSIONS

The water uptake of a model hydrogel drug delivery system was studied and found to increase significantly upon exposure to acid as the result of network degradation from acid-catalyzed ester bond cleavage. The addition of a photoacid generator, DPIN, also resulted in a significant increase in water uptake by the hydrogel. However, since DPIN-containing hydrogels that were and were not exposed to light exhibited identical water uptake profiles that were significantly different from that of a hydrogel exposed to aqueous HCl, it is clear that the major mechanism of DPIN-induced degradation/water uptake does not occur via the expected light-induced pathway. Further studies must be performed to determine the cause of the unusual behavior observed.

Peel testing of 10:90 HEMA/BA functionalized with acryloyl chloride in the presence of a CQ/DMAEM photoinitiation system produced very encouraging results. Blue light exposure must be further examined using a 468-nm filter and a higher-intensity light source, with an appropriate instrument (such as the Oriel Instruments Goldilux Photometer, Model 70235) available to measure visible light intensity. However, sunlight caused 88% switching after 10 minutes and 100% switching—complete loss of adhesive properties—after 20 minutes of exposure, which fully meets the goals of the project. Clearly, photoinitiated crosslinking of an acrylate copolymer containing pendant vinyl groups is a viable method of significantly decreasing polymer peel strength.

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