THE SYNTHESIS AND CHARACTERIZATION OF POLYURETHANE POLY(ETHYLENE GLYCOL) BASED HYDROGEL FILMS AND MICROGELS FOR APPLICATIONS IN INDUSTRIAL COATINGS AND DRUG DELIVERY

Stacy Michele Trey
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by

Stacy Michele Trey

A Dissertation
Submitted to the Graduate Studies Office
of The University of Southern Mississippi
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

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August 2007
The University of Southern Mississippi

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ABSTRACT

THE SYNTHESIS AND CHARACTERIZATION OF POLYURETHANE POLY(ETHYLENE GLYCOL) BASED HYDROGEL FILMS AND MICROGELS FOR APPLICATIONS IN INDUSTRIAL COATINGS AND DRUG DELIVERY

by Stacy Michele Trey

August 2007

Although the area involving the application of polymeric hydrogels is rapidly maturing, little is reported about the preparation and response of discrete hydrogels within a hydrophobic coating matrix. It will be the objective of this research to determine how the structural variations in gels, both chemical and mechanical, will affect water absorption. In an effort to better understand this area, film preparation methods along with the composition and properties of both the hydrogels and continuous phase will be investigated. This investigation will be carried out by looking at film properties firstly and then follow with an examination of the responsiveness of the film to various external stimuli. These characteristics can then be related to the morphology and rheological properties of these films and their components. This developed technology can be used to further the research and development currently being conducted for application of hydrogels as separation systems, as active delivery materials, as actuators, and as biomimetic devices.
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CHAPTER I
INTRODUCTION TO HYDROGELS

Introduction

Hydrogels are environmentally responsive to their environment and thus have potential for applications including separation systems, active delivery, actuators, and biomimetic devices. However, by themselves they have poor physical properties and are shear sensitive. Therefore, the current trend is to incorporate hydrogel particles into coatings in order to retain mechanical properties of the film while lending the material stimuli responsive behavior.

Hydrogels consist of a hydrophilic polymer matrix that is rendered insoluble in water by crosslinking. In fact, they are considered to be particles of water, since these materials can hold over five times their weight in water when fully hydrated. In addition, hydrogels are considered as "smart materials" because of their response to environmental changes such as pH, light, magnetic field, and ionic strength. There are three classes of hydrogels; nonionic, polyelectrolyte, and polyampholyte. Nonionic hydrogels have no charge and are synthesized from a wide variety of monomers such as acrylamide, N-isopropylacrylamide, polyethylene oxide (PEO), polyvinyl alcohol (PVA), and 2-hydroxyethyl methacrylate. These gels are sensitive to ambient solvent compositions or temperature changes, undergoing large volume phase transitions under certain conditions.

Polyelectrolyte gels are network polymers possessing only positive or negative charges. Acidic or anionic polyelectrolytes are formed using either weakly acidic monomers (pKₐ of about 5.5) like acrylic acid and methacrylic acid or strongly acidic monomers.
monomers such as sodium styrene sulfonate and sodium 2-acrylamide-2-methyl-1-propane sulfonate (NaAMPS). Weakly cationic or basic hydrogels can be made using monomers containing tertiary amines such as 2-vinylpyridine where the network is charged once the amine functionality becomes protonated. Strongly basic gels are synthesized using quaternary ammonium salts like [3-(methacryloylamino)propyl]trimethylammonium chloride (MAPTAC). Networks containing these strongly basic functional groups remain dissociated over a wide pH range. Typically, polyelectrolyte gels de-swell at low ionic strengths in a neutral pH and collapse at high ionic strengths due to loss of osmotic pressure difference between the gel and the surrounding environment.

Polyampholyte hydrogels consist of positive, negative and sometimes neutral monomers in which the physical properties are determined by the concentration of positive or negative monomers. These gels typically collapse at low ionic strengths and swell at high ionic strengths when charge balanced.

In pH responsive hydrogels, the swelling is a result of ionization of functional groups in the gel. Here ionization depends on the concentration of ions as well as the functional group pKa value. Acid or basic functionalities undergo a change in hydration with pH, governed by the pKa of that group. This changes the hydration of the gel in response to electrostatic and osmotic forces that control diffusion in the network.

The solution salinity changes the inter and intramolecular interactions of the polyelectrolyte by shielding the charges on the polymer chain. Also, as the concentration of ions outside of the gel increase, the osmotic pressure within the gel decreases, leading to swelling. Anionic hydrogels have repulsion between charged groups which causes
the gels to swell.\textsuperscript{7} In their swollen state, the gels have large amounts of water along with surfactant and polymer aggregates that are freely dispersed throughout the network allow for greater water diffusion.\textsuperscript{8}

\textit{Stimuli Responsive Hydrogels}

The temperature dependence of hydrogels is characterized by their lower critical solution temperature (LCST), at which the polymer demonstrates a volume phase transition temperature (VPTT). At this temperature, the chains in the network change from a random coil to a globular state. These gels transform from a swollen to collapsed state as the temperature rises above the LCST. This temperature is determined by the physical and chemical makeup of the network.\textsuperscript{2} The VPTT of gels are theorized to be a combination of the mixing and the rubber elasticity free energies. In addition to these two components, osmotic contributions of the counterions are also a factor with ionizable or polar monomers.\textsuperscript{5}

Polymer gels are controlled by magnetic fields when being swollen with a complex fluid. Complex fluids are colloidal solutions of electrorheological fluids, magneto-rheological fluids, or ferrofluids. Whose apparent viscosity and yield stress change in the presence of an applied magnetic field. The particles in the nano or micrometer range create a collective change in the molecular conformation, causing a macroscale change via summation of forces. The field applied can be nonuniform or uniform, with the first resulting in aggregation, while the second causes particles to line up end to end, forming a pearl chain structure. Zrinyi et al. synthesized a magnetic field sensitive gel by incorporating magnetite nanoparticles into a poly (N-isopropylacrylamide) hydrogel (MNIPA) and is shown in Figure I-1.\textsuperscript{3}
Figure I-1. MNIPA under (a) no magnetic field, (b) a nonuniform magnetic field, (c) a homogeneous magnetic field.3

Ultraviolet (UV) and visible light responsive systems are being investigated as materials for faster responding gels. UV light initiates a response by initiating an ionization reaction in the gel, creating internal osmotic pressure which causes the gel to swell.9 Visible light creates a response in gels by direct heating of the network, which is faster than the UV light system.10 A light sensitive hydrogel was made by Suzuki in which the main component is N-isopropylacrylamide with a light sensitive chromophore specifically trisodium salt of copper chlorophyllin.

One type of chemically responsive hydrogel is based on immobilization of enzymes by ionic and hydrogen bonding, which respond to specific substances.11 Here the response is due to the recognition elements or enzymes experiencing a change of charge state when in contact with the interacting species, initiating a change in the volume and diffracted wavelength of the gel. The concentration of a reactive substance is measured directly by the change in refractive index.12 This enzymatic action also can cause a localized increase in pH and increase capacitance up to four orders of magnitude.13 This could lead to high sensitivity and fast responses for use in immunosensing.
Polymer gel electrolytes respond to an electric field due to the ion conductivity of the complexes. For example, electrochromic materials change optical properties in a reversible manner with applied voltage. Electrochromic switching is observed in poly(ethylene oxide) (PEO) derivatives crosslinked and swollen with KOH aqueous solution. Thin films having covalently crosslinked polyelectrolytes are conductive and used in antistatic coatings.\textsuperscript{14}

Hydrogel Applications

Hydrogels have many potential applications due to their responsive nature. One developed application is in separation systems or filters. Thin film gels are being developed for diffusive gradients in thin films (DGT) technique. In work done by Zhang \textit{et al.}, a polyacrylamide hydrogel permitted diffusional mass transport of an analyte when functional groups that interacted selectively with a specific species such as trace metal ions. The diffusive gradient lets the accumulation and mass transport to be quantified using Fick’s law of diffusion.\textsuperscript{15}

Active delivery using biocompatible hydrogels is also being researched. A dry hydrogel can be saturated with a solute or drug which is then incorporated into the network and released in the body under controlled conditions. The release of the solute is governed by the network relaxation as the polymer absorbs water and the drug diffusion across the water concentration gradient. Gels have shown to release solute at a rate of zero order and can target specific sites such as the small intestine.\textsuperscript{16}

Research of hydrogels for application as switches or actuators and reactive sites has received more attention recently. For example, N-isopropylacrylamide (NIPA) polymer gels have a large reversible change in volume with change in environmental
temperature. The gel is transparent and swollen at room temperature, but undergoes spinodal decomposition, collapsing to a cloudy material at 34°C. These gels are used in smart windows, ultrasonic attenuators, and optical displays.\(^\text{17}\)

In optical applications, crystalline colloidal arrays formed from polymer spheres (about 50 nm radius) within a hydrogel swell in response to pH, temperature, or trace metals. The crystalline component diffracts light at visible wavelengths. A color change occurs as the hydrogel swells because the diffraction wavelength of the crystalline colloidal array changes. This system has potential uses for monitoring cell cultures, process streams, and clinical diagnostics.\(^\text{5}\)

The use of hydrogels in electrochromic devices is currently being investigated for switchable windows, electromagnetic shutters, and light modulation devices. For instance, poly(ethylene oxide) materials crosslinked and complexed with alkali metal salts produce an electrolytic conductive gel used in high energy density batteries.\(^\text{18}\)

The most common use of hydrophilic gels is as absorbents in products ranging from disposable diapers to hydration of soil, transforming non-arable land.\(^\text{19}\) One class of hydrogels are superabsorbent polymers (SAPs), having higher water absorbing capacity than most water absorbing materials where absorbed water is not removable even under high pressures.\(^\text{20}\) In order to increase the water absorption capacity, gel strength, and absorption rate, researchers have studied the dependence of water absorbency on particle size and salinity.\(^\text{21}\)

**Synthesis of Gels**

The average functionality \(f_{avg}\) of a system as defined by Carothers is the average number of functional groups per monomer molecule for all monomers in the system.
This expression is given in Equation 1-1, where \( N_i \) is the number of molecules of monomer \( i \) with functionality \( f_i \).

\[
    f_{\text{avg}} = \frac{\sum N_i f}{\sum N_i} \quad \text{Equation I-1}
\]

At the point where the number average degree of polymerization approaches infinity, the critical extent of the reaction \( (p_c) \) at the gel point is expressed in Equation I-2. 23

\[
    p_c = \frac{2}{f_{\text{avg}}} \quad \text{Equation I-2}
\]

A typical method used to synthesize crosslinked hydrophilic polymer gels is by a thermally initiated free radical method. Here crosslinking is obtained in thermally initiated free radical reactions by having a system with an average functionality of greater than two, accomplished simply by adding a crosslinking agent. This was done in the synthesis of poly(acrylamidoglycolic acid-co-acrylamide) (poly-(AAGA-co-AAm)) gel by Li et al. where a molar ratio of 3:1 molar ratio of AAGA and AAm were reacted in solution with 2% agarose derived cross linker, ammonium persulphate for the initiator and \( N,N,N',N' \)-tetramethylethylenediamine (TEMED). 1

Radiation cure methods are essentially the same as thermally initiated free radical reactions, except that radicals are formed exposing polymers to ionizing radiation. If the excited state cannot be achieved by direct irradiation, a photosensitizer is used as a donor to transfer energy and form the excited state. 24

The photo-cross-linkable monomers containing a sensitizer are usually spin coated onto various substrates, controlling the thickness with solution viscosity, dried and then cross linked by some type of radiation. 5,25 Harmon synthesized a photo-cross-linked polymer film by spin-coating on different substrates using a cyclohexane solution.
containing 1-10% of photo-cross-linkable linear polymers based on N-isopropylacrylamide and 2-(dimethylmaleimido)-N-ethyl-acrylamide with 2 wt% thioxanthone sensitizer. The resulting films were dried under a vacuum and cross-linked by UV radiation using a 75-W high-pressure Hg lamp at a wavelength $\lambda > 300$ nm for 60 minutes.

Inverse suspension polymerization systems have the organic solvent as the continuous phase and from water soluble monomer in droplets throughout. These particles are on the size range of 50-500 μm in diameter, because surfactant content is only about 0.1% as compared to emulsion polymerizations (1-5%). Thus constant agitation is required, and the surfactant acts as a stabilizer to prevent particles from collapsing and forming conglomerates.22

Hydrogels are also made by nanoscale alternate layer deposition based on different types of chemical and physical interactions. One approach is to have each component or layer multiply charged, which can be deposited onto a substrate either in a swollen or deswollen state depending on the desired morphology of the film.23 This is done by functionalizing the glass with positive charged species, rinsing with water, and then exposing the surface to a dilute solution containing a negatively charged species.24 Deposition is tracked and quantified using chemical dies such as methylene blue. It has been shown that the outermost layer of layer by layer (LbL) assembly gives the properties of the corresponding polymer.25

Slow swelling kinetics have been a major drawback of gels, because as the outer layer of a gel swells upon exposure to a solvent, it becomes more difficult for the solvent to reach the inner layers of the gel and take advantage of the full swelling capacity.
Complex architectures of hydrogels have been examined in order to increase their swelling kinetics. Equilibrium swelling can require several hours to days in bulk hydrogels. Therefore, methods are being investigated that allows for fast hydrogel response. The swelling of conventional hydrogels can be described by Equation 1-3, where $\tau$ is equaled to the characteristic swelling time, $L$ is the characteristic length of the gel, and $D$ is the diffusion coefficient of the gel in the solvent.

$$\tau = \frac{L^2}{D} \quad \text{Equation 1-3}$$

The typical diffusion coefficients for hydrogels are about $10^{-7} \text{ cm}^2$/s and so for a hydrogel film with a thickness of 2 mm and a $L$ of 1 mm, the swelling will take about 1 day.

In one attempt to decrease slow swelling kinetics, open channels were formed using a gas blowing or foaming technique that allowed faster swelling to occur due to capillary wetting instead of slow diffusion through the glassy matrix of hydrogels. These pores are hundreds of micrometers in diameter in contrast to microporous (10-100 nm) or macroporous (100 nm -10 $\mu$m). Porous hydrogels can also be formed by a prosigen technique, phase separation, or crosslinking of individual microgels. The prosigen technique involves preparing hydrogel networks in an environment containing water soluble materials such as sucrose, sodium chloride, and PEG. These are removed after matrix formation, leaving behind a mesh. Water has been used in a freeze drying/hydration cycles of thermosensitive gels to increase the gel deswelling. This method produced honeycomb shaped pores from the formation of the hydrophobic bonds between polymer chains.

In the separation method, the solvent quality is decreased for a given polymer. The disadvantages of this method are that there are a limited number of materials
available and there is a lack of control over pore size and number. Crosslinking individual microgels to form very small pores can only be done with absorbent particles with chemically reactive functional groups on their surface. The way porous hydrogels are dried also affects their swelling kinetics. Drying gels in air causes pores to collapse, possibly irreversibly in some capillary channels. These channels are preserved using ethanol, which in turn makes the soft network hard and brittle due to possible precipitation of polymer chains in a poor solvent.

Bulk or monolithic hydrogels containing microstructure gels of either the same material as the continuous phase or of an altered composition are possible. In a microcomposite made entirely of poly(N-isopropylacrylamide) (pNIPAm), the microgel particles were first made by precipitation polymerization and then placed in a monomer solution immobilized between glass slides to form a thin film dispersed with microgels upon radiation curing. Here the equilibrium swelling rate of the gels increased with the concentration of microgels.

An example of a system containing microgels composed of differing material from the matrix, poly(N-isopropylacrylamide-co-acrylic acid) (pNIPAAm-AA) microgels were synthesized by a surfactant free emulsion polymerization method and placed in a homogeneous matrix of N-isopropylacrylamide monomer solution. This solution contained monomer, a crosslinking agent, and redox initiators. This formed an evenly dispersed microgel containing network. With the acrylic acid groups laying on the surface of the particles while the NIPAAm portions were sequestered inside. This prevented aggregation, increased particle stability, and allowed for the microgels to be
crosslinked to form an interpenetrating network (if desired). In addition, incorporating microgels in the network increased the rate and capacity of swelling.\textsuperscript{28}

Interpenetrating networks of pH and temperature sensitive gels have been made by a sequential UV polymerization method. Here the interpenetration of polymer chains yielded a material having properties of both polymer networks. In sequential UV polymerization, there are no chemical bonds between the two component networks and each component can be varied independently. This incorporation of two crosslink systems may also increase the modulus of the material.\textsuperscript{29,30}

Doping a starch grafted acrylamide polymer with ultra fine mineral powder or clay such as bentonite, kaolinite, montmorillonite, or sercite increased water absorption compared to undoped species.\textsuperscript{31} These minerals are all layered aluminum silicates with exchangeable cations and reactive surface hydroxyl groups. One micron mineral particles were combined with other components such as monomer, starch, and crosslinker and then heated for 2 hours to form these materials. The polymer containing kaolinite absorbed the most water because it could moderately disperse in the water and act as a crosslink point with the acrylamide and starch. This can be shown in Figure 1-2, with the kaolinite particles either chemically bonded with the polymer (A), functioning as a chemically bound terminal point (B), or simply physically filling in the network structure (C).
The time dependence of water vapor absorption of superabsorbent polymer clay composites was measured using a reaction calorimeter, which thermally monitored the heat of interaction of the liquid water with the composite hydrogel. A thermogravimetric analyzer was also used to measure the moisture absorption behavior.

Conductive hydrogels are made by trapping ions in a host matrix. If the polyelectrolyte exceeds a critical weight fraction, the material is conductive; if the weight fraction of monomer exceeds a critical value, the coating is unaffected by a water wash. Polyaziridine, a hydrogel, is strengthened when polymerized in the presence of a polyelectrolyte due to ionic bond formation between the electrolyte and the protonated polyaziridine host. In addition, the network is much more conductive in comparison to the polyaziridine alone because of the trapped but internally mobile counterion guest.

Sulfonation is a method for modifying polyolefins to enhance water absorption and ion exchange. In one case, sulfonated polyethylene has been studied for use in membrane separation. The swelling behavior is affected by the degree of sulfonation, the species of counterion, and the composition of the mixtures, for example H$_2$O and

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*Figure 1-2. A starch graft acrylamide/mineral powder.*

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ethylene glycol. Since the sulfonic acid salt is hydrophilic, swellability increases with sulfonation content.\textsuperscript{32}

Films treated with supercritical CO\textsubscript{2} (SC-CO\textsubscript{2}) which has moderate critical conditions (T\textsubscript{c}=31.1°C, P\textsubscript{c}=7.38 MPa) and adjustable solvent properties have also been investigated. Superabsorbents treated with SC-CO\textsubscript{2} have increased water absorption. Smaller particles show this same increase under this treatment which can be explained by the rules of solvent transportation in polymers. It is thought that in the presence of SC-CO\textsubscript{2} chains reorganize, producing more free volume and lowering the T\textsubscript{g} similar to a plasticizing effect. This increase in free volume allows for the uptake of more water into the polymer network.\textsuperscript{33}

\textit{Synthesis of Gel Particles}

Particles can be made by inverse suspension polymerization, where by spheres are formed instead of irregular shapes from grinding. It is known that particle size and morphology affect the overall behavior of the absorbent. Thus, as particles become more regular in shape and smaller in size, absorbency rate and capacity increases, due to increased surface area as well as an interstitial volume effect.

As particles become more regular in shape, water absorption increases because of a capillary effect. Here, water can be held both in the particles as well as in the free volume between the particles.\textsuperscript{34} In research by Schlenker et al., nanoparticles were synthesized from methacrylate substituted PEG-modified urethane acrylate (PMUA). As shown in Figure 4, 2,4-toluene diisocyanate (TDI) is reacted with poly(tetramethyleneglycol) (PTMG), of which the product is then reacted with 2-
hydroxyethyl methacrylate (2-HEMA) followed by poly(ethylene glycol)monomethacrylate (MA-PEG) (Mₙ=2000).³⁶ (Figure 1-3)

![Chemical structure of 2,4-TDI and PTMG with formulas and ratios]

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Mole Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-TDI</td>
<td>2:1</td>
</tr>
<tr>
<td>PTMG</td>
<td>1:1</td>
</tr>
<tr>
<td>2-HEMA</td>
<td>1.2:1</td>
</tr>
<tr>
<td>MA-PEG</td>
<td>0.8:1</td>
</tr>
</tbody>
</table>

**Figure 1-3.** Nanoparticles synthesized from methacrylate substituted PEG-modified acrylate (PMUA).³⁷

The resulting PMUA was melted and water added drop by drop while stirring at a ratio of 1:4, then heated to 35°C for 4 hours to promote crosslinking. The resulting particles were 70 nm in diameter at room temperature and 40 nm at 65°C as determined by dynamic light scattering.³⁵,³⁶

Many superabsorbents are sold as powders due to the ease of preparation and handling, along with low cost. A continuous mass is created by solution polymerization and then converted to particles by grinding.³²

Particles of hydrogel have been prepared by mechanically grinding films into particles using a hammer-type laboratory grinder.³⁴ In a study by Omidian, particles of a terpolymer (acrylic acid: sodium acrylate: acrylamide in a molar ratio of 1:3:4) were

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dried and ground using a hammer-type laboratory grinder. These particles were irregular in shape and ranged from dust (38-45 μm) to particles of 500 μm in size as observed in Figure I-4.

*Figure I-4.* SEM image of ground up absorbent with a scale bar of 1.00 mm.\(^{34}\)

Poly(ethylene oxide) (PEO) films have been doped with either electrolyte solutions or clays in order to fine tune the properties of the gel. Hirota used various KCl salt concentrations to dope polysaccharide gels in order to determine protein diffusion in various ionic strength environments.\(^9\) This can be done by polymerizing the monomer in the presence of the material to be doped by synthesis methods such as radcure\(^{37}\), thermally initiated free radical\(^1\), or using redox initiators.\(^{26}\)

**Characterization of Gel Particles**

Key parameters are required to understand the structure property relationship of gels include overall chemical composition, crosslink density and the resulting swelling behavior, mobility of the network, mechanical and thermal properties, and morphology. Chemical composition has been determined by solid state NMR spectroscopy in the case where a crosslinked network is not mobile enough once swollen in a deuterated solvent. FT-IR spectroscopy is also a complimentary method to NMR spectroscopy in expanding knowledge in areas such as the degree of hydrogen bonding.
The swelling behavior of gels based on their chemical composition has been used to determine the crosslink density, $M_c$, and the sol content. These properties can be confirmed by thermogravimetric analysis and the rubbery plateau of the storage modulus which is inversely proportional to the $M_c$. It is also important to understand the relationship between the chemical makeup and the thermal properties typically determined by DSC and TGA along with the thermal properties determined by DMA.

Imaging of phase domains within hydrogel films and gel composites systems over a range of hydration levels and temperatures is done using such methods as scanning electron microscopy (SEM), atomic force microscopy (AFM), phase contrast optical microscopy (PCOM), and small angle laser light scattering (SALS).

**Crosslink Density Determination**

Crosslink density of the gels is calculated using Equation 1-4, where $M_c$ is the average molecular weight between crosslinks, $M_n$ is the number average molecular weight of the uncross-linked polymer, $V$ is the molar volume of the solvent (18 cm$^3$/mol), $v$ is the specific volume of the solvent, $v_2$ is the polymer volume fraction in the equilibrium swollen gel and $\chi$ is the polymer-solvent interaction parameter (0.426 for PEO in water).\textsuperscript{38}

$$\frac{1}{M_c} = 2 \frac{\nu \left( \ln(1 - v_2) + v_2 + \chi v_2^2 \right)}{M_n \left( \frac{1}{v^2} - \frac{v_2}{2} \right)} \quad \text{Equation 1-4}$$

The average mesh size of the polymer network, $\xi$, can be found using Equation 1-5, where $(r^2)^{1/2}$ is the root mean squared end-to-end distance of a randomly coiled
polymer of n bonds with a bond length \( l \) (1.54 Angstroms) and a characteristic ratio \( C_n \) (4.0).\(^{38}\)

\[
\xi = \nu_2^{-1/3} (r^2)^{1/2}
\]  

Equation I-5

where

\[
(r^2)^{1/2} = \chi C_n^{1/2} n^{1/2} l
\]  

Equation I-6

and

\[
n = \frac{3M_n}{44}
\]  

Equation I-7

**Water Absorption**

Determining the rate of absorption and maximum water absorption of each hydrogel material is important. Hu *et al* measured the swelling kinetics of a polymeric absorbent by taking 0.050 g of the dry absorbent, packing it into tea bags, and soaking each of them in 50 ml of distilled water. At specific time intervals the bag was removed, blotted with tissue paper to remove excess water, and then weighed. An empty tea bag was used as the blank. The amount of swelling was then calculated using Equation I-8, where \( M_{t,1} \) is the mass of swollen absorbent at time \( t \), \( Q \) is the sorbability at equilibrium, and \( M_\infty \) is the initial mass of absorbent.\(^{39,40}\) Plots of absorbent swelling as a function of time were then plotted.

\[
\frac{M_{t,1} - M_\infty}{M_\infty} = Q
\]  

Equation I-8
The sol fraction (S) is measured using Equation I-9, where a solvent is used to extract any uncrosslinked species is extracted by Soxhlet extraction or soaking. \( M_{t,2} \) is the weight after extraction.\(^{40}\)

\[
\frac{(M_\infty - M_{t,2})}{M_\infty \times 100} = S
\]

\textit{Equation I-9}

\textbf{Fluorescence Microscopy}

Fluorescence microscopy has proven valuable in determining the degree of hydration by using a fluorescent probe to measure changes in the ionic strength and water content. For example, Hu studied an ionic polyacrylamide gel and a linear poly (acrylamide), having a side chain dansyl fluorescent probe, at varying acetone concentrations in water.\(^{41}\) The gel is in the swollen, random coil state until going through a volume phase transition at 60% acetone at 20°C. The probes fluorescence intensity and peak wavelength responds to environmental changes in viscosity, polarity, and mobility.\(^{4}\) This experiment by Hu is shown in Figure I-5.
Figure I-5. (a) Absorption spectra of the dansyl probe attached to the gel at acetone contents of 10-90% in intervals of 10% going from (a) to (j) respectively. (b) Fluorescence emission spectra with the same sequence as the absorption spectra. Excitation wavelength is 345 nm.\(^\text{41}\)

The fluorescent probe method is useful in observing changes in the physical properties and microenvironments, provided the probe molecules are homogeneously distributed throughout the system, and the probe is not subject to photodegradation under experimental conditions. Also, chemical structure is not determined, only change in the physical structure. Finally, the probe is not efficient at looking at macroscopic changes, requiring other methods for obtaining that information.\(^\text{4}\)

Composite Film Formation

The \(T_g\) of films are adjusted using the Fox Equation, shown in Equation I-10, where \(w\) is the weight fraction of each component with the corresponding \(T_g\) as the denominator.\(^\text{42}\) (Assuming a random incorporation of monomers.)
\[
\frac{1}{T_g} = \frac{w_1}{T_{g,1}} + \frac{w_2}{T_{g,2}} + \frac{w_3}{T_{g,3}} + \frac{w_4}{T_{g,4}}
\]  

Equation I-10

The theoretical value is compared with the experimental \(T_g\) as measured by DSC.

**Characterization of Hydrogel Composite Films**

In work done by Melekaslan, polyelectrolyte hydrogels based on acrylamide and 2-acrylamido-2-methylpropane sulfonic acid sodium salt were studied in a polymer melt of poly (ethylene glycol) (PEG) to observe the effect of PEG segment size in relation to the volume of the hydrogel. It was found that linear polymers can penetrate into the network, leading to a contraction of the gel.\(^{43}\)

To obtain colloidal stability, electrostatic repulsion is needed to force functional groups to orient along the surface of the particle in order to prevent aggregation. This was shown by Cai using gel particles made from polyisopropylacrylamide-co-acrylic acid microgels in isopropylacrylamide gel matrix.\(^{27}\) Aggregation is also avoided by having a stabilizing medium such as surfactant or a suspension in a more viscous solution than monomer. Gels have also been dispersed with monomer on a substrate or between glass plates in order to be radiation cured.\(^{11}\)

**FT-IR and NMR Spectroscopy**

Films containing a range of hydrogel compositions can be determined by Fourier-transform infrared spectrometry (FTIR) and proton and carbon nuclear magnetic resonance spectroscopy (\(^1\)H and \(^{13}\)C NMR).\(^{9,33,37}\) FTIR spectroscopy is useful because it reduces signal to noise ratio and measures all wavelengths at once. 2-D NMR methods such as correlation spectroscopy (COSY) can be used to observe the chemical shift and
spin-spin coupling separately. Solid state NMR can also be used to characterize crosslinked polymer samples of gel particle material and continuous matrix material.

*Scanning Electron Microscopy (SEM)*

SEM images a surface via electron beam which is reflected by the sample surface as backscattered electrons, secondary electrons, and X-rays. Large samples of several centimeters in size can be used while examining surfaces on the micron level. Disadvantages of studying polymers with SEM is that there needs to be a conductive coating applied to the surface of the sample. In addition, polymers can be damaged by the electron beam, generating artifacts. This can be circumvented by Environmental SEM, however the resolution is not as precise.

The morphology of microgels in coatings has been imaged by SEM. For poly(N-isopropylacrylamide-co-acrylic acid (NIPAAm-AA) microgels in NIPAAm gel matrix, a minimum gel content of 9.2% are observed. However, at a maximum of 54.2% microgel, a porous sponge is seen and the swelling response to temperature was greatest for this system. (Figure I-6)
Placing a hydrated sample in a vacuum can change its morphology, especially in the case of hydrogels. This can be circumvented by freeze drying the samples or freezing them in liquid nitrogen. Xia froze swollen samples of sulfonated polyethylene with water and froze them with liquid nitrogen to -50°C. The samples were then sputter coated with a Au/Pd alloy, and the sample was placed in a vacuum chamber on a cold stage in order to take the image. These sulfonated polyethylene samples can be seen in their swollen state in Figure I-7.
Atomic Force Microscopy (AFM)

Atomic force microscopy (AFM) will be used to image the topology of the films. In order to avoid damaging softer film samples, tapping mode is used whereby the cantilever oscillates vertically close to its resonance frequency. This application was used by Martin et al. to image a coating with hydrogel fragments, about 12 nm thick, lying on the surface. (Figure I-8) An advantage of this method is that usually no surface preparation is needed.

Figure I-7. SEM images of the morphology of swollen sulfonated polyethylene membranes.34

Atomic Force Microscopy (AFM)

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AFM images of hydrogel particles on a coating surface (2.5 μm x 2.5 μm). AFM is ideal for determining the morphology of microgels in different industrial coatings systems as a function of percent microgels, hydrophilicity, and monomer composition of the matrix.

**Optical Microscopy**

Optical microscopy has been extensively used to determine film thickness and microgel size. Optical microscopy was used by Nayak et al. to show a (pNIPAm) hydrogel film deswelling using a water/film interface, and a film/glass interface as designated by the white dashed lines in Figure 1-9 where the scale bar is 20 μm.
Figure 1-9. Optical Microscopy images of film deswelling from left to right with dashed white lines showing water/film interface (left) and film/glass interface (right).

Optical microscopy has also been used to study the phase domain behavior of composite films as well as determine the degree of interaction in blends via analysis of crystalline character in semi-crystalline blends.\textsuperscript{45,46,47,48} Phase contrast microscopy permits for determination of phase domains in a sample. Here contrast is resulting from changes in the relative strengths of diffracted and transmitted light due to the change in refractive index from one region to another. Phase domain studies of a polymer composite as the temperature or relative humidity change, can provide insight into the effect of the composite on matrix properties.

Birefringent optical microscopy is useful for observing differences in relative crystallinity of a sample due to heat, composite composition, or humidity. Birefringence occurs when the velocity of light through the sample is altered in respect to the plane of polarization. In polymers, molecular orientation or crystalline lamella is the source of birefringence with the degree of orientation increases the degree of birefringence.\textsuperscript{53}
Small Angle Light Scattering (SALS)

Phase domain changes in polymer blends due to blend composition, hydration levels, and heat have been previously examined by small angle laser light scattering. The scattering of a laser by the polymer sample due to phase separation exhibits a scattering pattern in the shape of a halo, with the radius inversely proportional in size to the phase separated domains. Increasing phase separation is indicated by an increase in the intensity of the scattered light as a function of the humidity, temperature, or blend composition.49-52

Thermal Gravimetric Analysis (TGA)

The thermal stability of hydrogels and of synthesized films with and without hydrogels has been determined using thermogravimetric analysis (TGA). TGA measures the mass of a sample with an increase in temperature and is able to measure the weight losses that occur due to volatiles and degradation.47

Dynamic Mechanical Thermal Analysis (DMTA)

The physical properties of the films such as modulus have been measured using dynamic mechanical thermal analysis (DMTA). DMTA measures the relaxation behavior of a material by deforming the sample cyclically under forced vibration conditions.53 Here, $T_g$, ratio of loss modulus to storage modulus, and small scale transitions such as the beta and gamma transitions are observed in the loss tangent ($\tan \delta$) versus temperature curve. This is a useful technique for determining the effect of microgel composites on films elasticity and relaxations with increasing temperatures.
Also hydrogel film mechanical properties can be investigated as a function of heat and hydration.

Conclusion

Hydrogels are environmentally responsive materials that are made up of crosslinked hydrophilic monomers that form a highly hydrophilic network that is not soluble in water. These “smart” materials respond to pH, temperature, radiation, electric fields, and magnetic fields; however they have poor physical properties such as a low modulus and sensitivity to shear. Therefore, there is a need to incorporate hydrogel particles into a polymer matrix in order to obtain a coating that has the stimuli responsive character of hydrogels and the mechanical properties of the continuous phase.

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CHAPTER II
PREPARATION AND CHARACTERIZATION OF POLY(ETHYLENE GLYCOL) BASED HYDROGEL FILMS

Abstract

Chemical and mechanical variations in discrete hydrogels affect water absorption and retention. A series of poly(ethylene glycol) (PEG) based hydrogel thin films were prepared by crosslinking PEG diols with molecular weights ranging from 400 to 6000 g/mol with an isocyanurate trimer of hexamethylene diisocyanate (PHDI). Their hydration behavior was investigated by absorption studies and thermal gravimetric analysis (TGA). Results showed that water retention was proportional to PEG $M_n$ in the films and the sol content decreased with the unreacted PEG diols. $T_m$, $T_c$, and the degree of crystallinity ($\chi_c$) increased with PEG number average molecular weight ($M_n$) in the hydrogel films. $T_m$ was lower after crosslinking, with the product based on PEG 400 $M_n$ having non crystalline chain mobility in the network structure, as determined by $^{13}$C NMR spin-lattice relaxation times and fluorescence spectroscopy. In addition, the soft segment mobility is proportional to hydration, temperature, and PEG $M_n$.

Hydrogels have potential applications for tissue engineering as hosts for cell growth network structures. In addition, microgels within a coating matrix would provide a hydrated environment where enzymes could carry out their inherent functions. Properties such as hydration and network mobility variation with PEG $M_n$ in these systems are of utmost importance to ensure that sufficient diffusion of biological activities occurs or to allow enough mobility for proper folding of proteins that may be incorporated.
Introduction

Hydrogels consist of a crosslinked polymer matrix that is highly water absorbent due to the hydrophilic polymer backbone. As a result of either physical or chemical crosslinking, hydrogels are insoluble in water. They are considered particles of water since these materials are able to hold over 200-300 times their weight in water. Superabsorbent hydrogels (those based on starches and acrylamide) are able to accommodate up to 4000 times their weight in water when fully hydrated.\textsuperscript{1,2}

Polyurethanes (PU) are currently one of the most widely studied materials in biological applications since the 1960s owing to their biocompatibility and physical properties. Polyurethanes are typically formed by the reaction of poly functional isocyanates (f>2) and hydroxyl containing co-reactants. The ease of this reaction gives access to a diverse range of thermoplastics and crosslinked structures. Polyether based polyurethanes are relatively stable towards hydrolytic degradation. However, they can easily be modified to allow degradation, through hydrolysis and oxidative cleavage of the polyether to result in carboxylic ester and acid groups.\textsuperscript{3}

PEG based oligomers and their derivatives are ideal candidates for synthetic biomaterials as a result of their non-toxicity and biocompatibility. They have found use in biomedical applications such as coatings for biosensors, wound dressings, drug delivery vehicles, and contact lenses.\textsuperscript{5} Hydrogels are similar to natural tissue with respect to physical and mechanical properties. They also allow permeability of small molecules such as nutrients, oxygen, and water soluble metabolites.\textsuperscript{4,5} These similarities have stimulated interest for their use in regenerative tissue engineering of bone, cartilage, and tendons.
Specifically, the use of PEG based hydrogels as cell scaffolds for tissue regeneration is possible by incorporating specific peptide sequences such as Arg-Gly-Asp (RGD) that can stimulate native osteoblast adhesion and spreading in an effort to produce an extracellular matrix.\(^6\) Also, hydrogels containing modified mesenchymal stem cells have been shown to secrete an extracellular matrix within degradable PEG hydrogel scaffolds.\(^7\)

The crosslink density of PEG hydrogels can be varied thereby allowing tailoring of polymer permeability, modulus, elasticity, and equilibrium water content. These physical properties can be further modified using additional PEG copolymers, adjusting the crosslink density, and changing the polymerization conditions.\(^8\) The crosslink density of the covalently linked networks is directly proportional to the gel-modulus and inversely proportional to the water absorption. Additionally, the PEG molecular weight is key in modifying the mechanical strength of oligo((polyethylene glycol) fumarate) hydrogels.\(^9\)

Investigation of different systems involving PEG polyurethane hydrogels is needed as the physical properties of the gels are still not predictable because of inherent variation in hydrogel formation due to conversion dependent reactivity, cyclization, and spatial gel inhomogeneity.\(^4\) Better understanding of these gel systems will yield insight into the ways these materials affect enzymes and living cells. For example, diffusion coefficients will vary with hydration and temperature in these systems, allowing migration or loss of the confined host. Modification in the internal network motion will alter the transport of nutrients through the polymer network and cell waste out, thereby allowing optimum cell functioning. In the case of an enzyme guest, too much structural
confinement and limited network mobility will result in improper protein folding and a loss of enzyme function. Furthermore, PEG hydrogels are being studied for applications as a host in controlled release drug delivery. In these cases, it is imperative to have a full understanding of how network mobility affects diffusion and in turn the intended dose.  

The work reported in this section develops a base understanding of PEG-based hydrogel physical structure and morphology as a function of chemical composition. PU hydrogels were prepared by reaction of a polyisocyanate with a series of PEG diols of differing molecular weight. Subsequent characterization probed the effect of reactant molecular weight and sol content on bulk gel properties such as swelling capacity and mobility of the network.

Experimental

Materials, Compounds, and Sources

Tetramethyl rhodamine cadaverine (5,6 isomer) (TRC) was supplied by Molecular Probes, Eugene, OR. Dibutyltin dilaurate (DBTDL) and PEG of Mₐ 400, 1000, 3400, and 5,000-7,000 g/mol, were purchased from Sigma-Aldrich Chemical Inc. in St. Louis, MO. The trimer of hexamethylene diisocyanate, designated PHDI, (Desmodur® N3600) was supplied by Bayer MaterialScience in Pittsburgh, PA. Methyl ethyl ketone (MEK), dimethyl sulfoxide (DMSO), and methanol were received from Fisher Chemicals in Fair Lawn, NJ. All chemicals were used as received.

Hydrogel Preparation

In an example hydrogel preparation, PUPEG 1000 (Figure II-1), 0.953 grams of PHDI (0.0052 equiv), was charged to a 100 mL flask under N₂ with 2.42 grams of MEK.
solvent (density=0.805g/cm³) and 2.047 grams of PEG 1000 (0.0041 OH equiv). 1 drop of DBTDL as added. The reaction mixture was drawn down on to polypropylene plates at 2 wet mils and heated for 1 h at 80 °C to give a colorless clear film. Gel films from PEG diols of Mn 400, 3400, and 6000 g/mol were prepared similarly. In all cases an isocyanate to hydroxyl index of 1.2/1.0 was used. Such a ratio ensures complete incorporation of the PEG diol with excess NCO reacting with water.

\[
\text{NCO} \quad \text{(CH}_2\text{)}_6 \quad \text{N} \quad \text{+} \quad \text{OH} \quad \text{(CH}_2\text{)}_n \quad \text{OCN} \\
\text{PHDI} \quad \text{PEG} \\
\text{1. MEK/DBTDL} \\
\text{2. 80 °C/N}_2/1\text{h} \\
\]

Figure II-1. PHDI reaction with PEG.

Fluorescent Probe Modified Hydrogel

The molecular probe tetramethyl rhodamine cadaverine (TRC) was used for fluorescent studies to determine the motion of the crosslinked networks at varying
temperatures and hydrated states. (Figure II-2) This probe was added at a concentration of $1.5 \times 10^{-5}$ M. The primary amine of TRC was chemically bound to the polymeric films by reaction with Desmodur N3600, the isocyanurate of hexamethylene diisocyanate (HDI), at a concentration of 0.1 M in DMSO. This afforded a light pink viscous reaction mixture. Films were prepared as described previously. This concentration was kept constant in order to only modify the crosslink density in a relative manner, changing the same number of chain ends in each film in the series.

Unreacted TRC and impurities were extracted from the films by soaking them in water for 48 hours. The intensity of the fluorescence of TRC in aqueous solution was then measured using a fluorimeter. The extract aqueous solution showed a greater intensity (25%), at an excitation wavelength of 512 nm, than the water alone which was negligible. This indicates that some of the TRC or impurities were not incorporated into the film effectively.

Figure II-2. Zwitterionic molecular probe: tetramethyl rhodamine cadaverine (mixed 5,6 isomers) (TRC).

**Thermal Gravimetric Analysis (TGA)**

Weight loss as a function of temperature was measured using a Q500 TA Instruments TGA at a heating rate of 5 °C/min and a nitrogen flow of 40 mL/min.
Platinum measuring pans were used, with a typical weight of 10-12 mg. The TGA temperature was calibrated using a nickel standard, and the weight calibration was performed in the range of 200 mg to 1 g with a pan weight of slightly over 200 mg. Water loss was determined by calculating the weight change that occurred below 100°C, at which point the weight loss profile begins to plateau. The degradation temperature (Td) was determined using the onset function in Universal Analysis Software (2002). Here 2 points are selected, one at a plateau point before weight loss and the other at the point maximum in the derivative peak. A line is drawn tangent to the curve at each point, and the intersection of these 2 lines was designated as the onset of degradation.

**Dynamic Scanning Calorimeter (DSC)**

T<sub>g</sub>, T<sub>c</sub>, and T<sub>m</sub> were determined with a Q1000 Dynamic Scanning Calorimeter (DSC) from TA Instruments with heating/cooling rate of 10°C/min, a scan range from -90 to 150°C and a 5 minute isothermal hold at 150°C to erase thermal history. Temperature calibration was performed using indium and zinc standards, and heat flow calibration was established using sapphire standards. Values reported for the melting (T<sub>m</sub>) and crystallization temperatures (T<sub>c</sub>) are those at the minimum and maximum of endothermic and exothermic peaks, respectively and are taken from the second heat. The fractional degree of crystallization (X<sub>c</sub>) was calculated by taking the observed heat of fusion (∆H<sub>obs</sub>) from the DSC experiments of the hydrogel films and dividing it by the heat of fusion (188.95 J/g) for 100% polyethylene oxide. The samples were run in duplicate to determine the reproducibility.
The degree of crystallinity, $X_c$, was calculated using Equation II-1, where $\Delta H_{\text{obs}}$ is the heat of fusion observed by DSC, $\Delta H^0_f$ the standard heat of fusion of 100% crystalline PEG (188.95 J/g), and $\omega$ the weight fraction of PEG in the films. The $\omega$ term accounts for PEG being the only component in the film that will crystallize.\textsuperscript{12} For the PEG diols, $\omega$ was assigned to be 1.

$$X_c = \frac{(\omega \Delta H_{\text{obs}})}{\Delta H^0_f}$$  \hspace{1cm} \text{Equation II-1}

\textit{NMR}

Solid-state NMR spectroscopy, were obtained using a Varian Unity Inova 400 spectrometer equipped with a standard Chemagnetics 7.5 mm PENCIL-style probe. Relaxation studies were performed in sealed rotors over a range of temperatures. The rotors were tested for solvent leaks at temperatures up to 80°C by filling the rotor with water, spinning for 2 h and comparing the initial and final weights. The initial and final weights of the water filled rotors were the same, indicating that relaxation measurements of hydrated samples were not affected by water loss. All samples were run in triplicate, and the average was reported with $T_1$ values having reproducibility of $\pm 0.01$ s.

Samples were loaded into zirconium rotor sleeves and sealed with special leak-proof Teflon™ caps. Spectra for dry films were acquired using the standard cross-polarization/magic angle spinning (CP/MAS) technique using high-power proton decoupling during data acquisition.\textsuperscript{13} Instrumental parameters included a $^1\text{H}$ 90° pulse width of 4.0 $\mu$s with a cross-polarization contact time of 1 ms, an acquisition delay of 6.4 $\mu$s, an acquisition time of 45 ms, and a recycle delay of 3 seconds. Data for hydrated films were obtained using a Bloch decay sequence (i.e. 90° pulse followed by data...
acquisition under proton-decoupling conditions) in which the $^{13}$C 90° pulse width was 4 μs.

Spin-lattice relaxation ($T_1$) experiments were performed using the inversion-recovery sequence where the recycle delay was set to ~5X the $^{13}$C $T_1$ value of the ethylene oxide carbons. For this work, delays ranged from 1.5 - 6 seconds. Typically 22 to 24 different delay times were used, with the final value equal to the recycle delay ($\sim$5XT₁ of the PEG moiety). The $T_1$ values were measured at 25, 40, 60 and 80°C for hydrated and dehydrated polyurethane materials. The peak intensities were fit to Equation II-1 in order to find $T_1$ for each material and environment, where $^{13}$C magnetization of nuclei are inverted using a 180° pulse, allowed to recover for some period $t$, and the resulting signal is observed using a 90° pulse. Recovery magnetization before equilibrium is $M(t)$, and equilibrium magnetization is $M_0$. The surroundings are called the lattice and the characteristic life-time of a spin in an upper state is the spin-lattice relaxation time or $T_1$.

$$M(t) = M_0 - 2M_0 \exp(-\frac{t}{T_1}) \quad \text{Equation II-2}$$

**Fluorescence measurements**

Fluorescence spectra were obtained using a Tecan Safire 96-well multifunctional plate reader (Tecan U.S., Durham, NC) to observe the fluorescent behavior of the molecular probe. The gel films were cut in 1 cm² pieces and placed on a glass cover slip used as a stage in a 24 well aluminum plate. The plate was equilibrated for 10 min at each temperature (30 and 40°C) and the samples were hydrated with 3 drops of deionized water. Blanks of water, TRC in DMSO and water mixture, and the glass alone were all

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evaluated for their intensities. Five replicates of each experiment were performed and the average reported.

The gel networks range of relative motion was also characterized using the TRC fluorescent probe. TRC-based films were cast onto a 24-well plate with glass cover slips placed in the wells to act as a stage. Films were dehydrated under vacuum in a desiccator containing phosphorous pentoxide for 24 hours. The intensity of the buffer, the film, the glass, and deionized water were measured as blanks. A fluorescent scan over a range of emission (200-800 nm) and excitation wavelengths (200-800 nm) was then performed on the buffer solution containing TRC to determine the optimal wavelength of excitation and emission. An excitation wavelength of 512 nm was chosen, with the resulting emission between 540 and 600 nm depending on the probe’s environment.

*Sol Content Determination*

To determine the sol content (S) of unreacted diols left in the gel networks, the as prepared polymer films were soaked in deionized water for 48 hours then methanol for 48 hours to swell the networks, and allow diffusion of uncrosslinked aqueous and organic soluble reactants. S was calculated using Equation 11-3 where $M_{t,2}$ is the weight after extraction, and $M_0$ is the weight of absorbent or gel before extraction. The sol fraction determined will affect the final product by plasticizing the network and affect characteristics including crosslink density, mesh size, swelling kinetics, and swelling capacity. The sol level is also important to establish because it may not be biocompatible and thus must be eliminated from the hydrogel films before use in biological applications.¹⁴
\[
\frac{(M_o - M_{t,2})}{M_o} \times 100 = S \quad \text{Equation II-3}
\]

The degree of swelling (sorbability) by the gel samples was determined by immersion of dry extracted films in water for 48 hrs. Sorbability (Q) was then calculated using Equation II-4, where \(M_t\) is the mass of swollen film, and \(M_\infty\) is the initial mass.\(^{15}\)

\[
\frac{M_t - M_\infty}{M_\infty} = Q \quad \text{Equation II-4}
\]

To confirm the calculation for water absorption, the hydrogel series was measured using TGA. The weight loss of the dehydrated sample and hydrated gel films were measured from 25-200°C at 10°C/min.

**Wide Angle X-ray Diffraction (WAXD)**

WAXD were obtained for the films in order to determine the relative crystallinity using a Rigaku Ultima III X-Ray diffractometer with a Cu K\(_\alpha\) radiation, \(\lambda=1.54\ \text{Å}\), at room temperature. A scan speed of 2 deg/min was used with a sampling width of 0.1 mm and a range of 2-30 2\(\theta\) was measured with a tube current of 44 Ma, a tube voltage of 40 kV and a power of 1.76 kW. The reactants and thermoset films were in powder/pellet and film form respectively.

**Dynamic Mechanical Analysis (DMA)**

The visco-elastic properties of the films were measured using a TA Q800-0193 Dynamic Mechanical Analysis (DMA) instrument equipped with a tension/film clamp. The settings were such that a temperature ramp/frequency sweep was performed at a strain of 0.1%, a preload force of 0.01 N, a force track of 125%, an initial frequency of 1
Hz, a temperature range of -90 to 160°C at 2°C/min. The Poisson ratio was set at 0.444 with minimum dynamic force of $1 \times 10^{-5}$ N and the clamp was floated using an air bearing.

Results and Discussion

Structure Characterization

The structure of the polyurethane PEG based hydrogels is be confirmed by solid state $^{13}$C NMR spectroscopy. A representative spectrum of a hydrogel film based on PEG 400 is shown in Figure II-3. The peak at 158 ppm is characteristic of the urea carbonyl bond formed when PHDI reacts with water. This is the result of the excess isocyanate reacting with water either in the system or in the air.
Figure II-3. Solid State $^{13}$C of 400 PEG based hydrogel film.
Thermal Properties

The measured thermal properties of the PEG diols and crosslinked hydrogel films are listed in Table II-1 and

Table II-2 respectively as measured by DSC (Figure II-4) and TGA. The hydrogel films have less crystalline content when compared to the PEG diol reactant. This is a result of the decreased mobility of the chains that are covalently crosslinked and unable to order to the same extent as the unbound diol. The impact of the reacted immobilized end groups also decreases with the increase in PEG $M_n$. This relationship of crystallinity as a function of PEG $M_n$ is crucial to understand because a guest has been shown to diffuse slower out of PEG based films containing more crystallinity due to the lamella barriers providing a more tortuous path.\(^{16}\)

As the PEG $M_n$ increases from 1000 to 6000 g/mol higher $T_m$ and $T_c$ were found, indicating that the longer PEG chains have the ability to pack more efficiently, elevating the degree of crystallinity as well as the size of the crystal domains. The degree of crystallinity, $X_c$, calculated using $\Delta H_{\text{obs}}$ is also higher with PEG molecular weights used to form these hydrogel films. This increase in crystallinity causes the films to have more mechanical integrity or physical strength when dehydrated as a xerogel. This increase in $X_c$, inherently indicates that more chains are ordered in lamella and fewer chains are in the amorphous region giving rise to less chain entanglement overall.
Additionally, the resulting films can be observed to have a lower melt temperature than the PEG reactant alone as can be expected similar to the effect of impurities lowering the $T_m$ of a pure substance.

Figure II-4. DSC trace of PEG 6000 reactant.

Table II-1.

Thermal Transitions of PEG Diols.

<table>
<thead>
<tr>
<th>Thermal Property</th>
<th>PEG 400</th>
<th>PEG 1000</th>
<th>PEG 3400</th>
<th>PEG 6000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m$ (°C) ±0.4</td>
<td>1.16</td>
<td>38.6</td>
<td>59.8</td>
<td>63.0</td>
</tr>
<tr>
<td>$T_c$ (°C) ± 0.2</td>
<td>-11.6</td>
<td>26.2</td>
<td>38.5</td>
<td>38.7</td>
</tr>
<tr>
<td>$\Delta H_{obs}$ (J/g)± 1.2</td>
<td>30.78</td>
<td>151.8</td>
<td>184.9</td>
<td>185.5</td>
</tr>
<tr>
<td>Crystallinity (%)± 0.1</td>
<td>16.3</td>
<td>80.3</td>
<td>97.9</td>
<td>98.2</td>
</tr>
<tr>
<td>$T_d$ (°C) ± 1.2</td>
<td>236</td>
<td>312</td>
<td>334</td>
<td>356</td>
</tr>
</tbody>
</table>
Table II-2.

*Thermal Transitions of Hydrogel Film Series.*

<table>
<thead>
<tr>
<th>Thermal Property</th>
<th>PU-PEG 400</th>
<th>PU-PEG 1000</th>
<th>PU-PEG 3400</th>
<th>PU-PEG 6000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$ (°C) ±0.3</td>
<td>-38.6</td>
<td>-47.5</td>
<td>-40.5</td>
<td>-41.5</td>
</tr>
<tr>
<td>$T_m$ (°C) ±0.5</td>
<td>No $T_m$ detected</td>
<td>10.5</td>
<td>41.0</td>
<td>51.0</td>
</tr>
<tr>
<td>$T_c$ (°C) ±0.8</td>
<td>NA</td>
<td>13.2</td>
<td>39.2</td>
<td>50.8</td>
</tr>
<tr>
<td>$\Delta H_{obs}$ (J/g) ± 1.5</td>
<td>NA</td>
<td>10.8</td>
<td>77.3</td>
<td>101</td>
</tr>
<tr>
<td>$\omega$</td>
<td>0.462</td>
<td>0.682</td>
<td>0.880</td>
<td>0.928</td>
</tr>
<tr>
<td>Crystallinity (%) ± 0.07</td>
<td>NA</td>
<td>3.90</td>
<td>36.0</td>
<td>49.6</td>
</tr>
<tr>
<td>$T_d$ (°C) ± 1.2</td>
<td>316</td>
<td>315</td>
<td>342</td>
<td>361</td>
</tr>
</tbody>
</table>

The scan showed no crystallization for the film based on PEG 400 by DSC and hence no values are reported for $T_c$, $T_m$, or $X_c$. This is due to the high crosslink density restricting the mobility of the chains between crosslinks, preventing formation of significant organized structures.

The degradation temperatures ($T_d$), by TGA, of the PEG based networks increase with $M_n$ 400 to 6000. This degradation temperature is higher in hydrogel films compared to the corresponding PEG reactant. The increase in thermal stability results from the binding of lower $M_n$ components to the network. No trend was found in $T_g$ as a function of PU-PEG $M_n$.  

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**Crystallinity by Wide Angle X-ray Diffraction (WAXD)**

The crystalline pattern of the reactant PEG diols compared to that of the crosslinked hydrogel films can also be seen by wide angle x-ray diffraction. The WAXD spectrum of PEG reactants in their as received form can be seen in Figure II-5. No crystalline peaks were observed for P400 sample, with only an amorphous halo obtained. This is not surprising given the $T_m$ of 1.6°C measured by DSC.

It is clear that the peak positions from the WAXD profiles of P3400 and P6000 in Figure II-5 are almost identical to those found by Huang et al. (Figure II-6), who analyzed the unit-cell structure parameters and indexed the main peaks. They found that they were consistent with a monoclinic crystal system whose interplanar spacing of the $(hkl)$ reflection planes is given by Equation II-9. Through the insertion of the values of $\lambda$(1.542 Å), $\beta$ (125.4°), and the peak positions of (120), (032), and (024) reflection planes, the unit cell parameters $a$, $b$, and $c$ can be determined by Equation II-5.

\[
\left( \frac{1}{d_{hkl}} \right)^2 = \left( \frac{2 \sin \left( \frac{\theta_{hkl}}{2} \right)}{\lambda} \right)^2 = \frac{1}{\sin^2 \beta} \left( \frac{h^2}{a^2} + \frac{k^2 \sin^2 \beta}{b^2} + \frac{l^2}{c^2} - \frac{2hl \cos \beta}{ac} \right) \quad \text{Equation II-5}
\]
Figure II-5. WAXD pattern for PEG reactants as received.

Figure II-6. (a)WAXD pattern and (b) peak deconvolution of the WAXD profile of pure PEO.\textsuperscript{17}
The same trend can be seen in the PUPEG 3400 and 6000 films as with the PEG components in terms of crystallinity. (Figure II-7) The diffraction peak corresponding to the (120) plane of the PEG crystallite was observed in the WAXD spectrum in P3400 and P6000.\(^{18}\)

The PUPEG films of higher \(M_n\) possessed stronger intensities than the PEG components, as a result of the longer amount of time given to the chains to organize upon curing in comparison to PEG quenching in manufacturing. The same monoclinic unit cell is observed for the crosslinked films as with the reactants based on the observation of 5 major peaks in the PUPEG 3400 and 6000 data. This indicates the PEG chains are still able to organize into lamella even when confined into crosslinks. Therefore, the PEG unit cell structure is not affected by the urethane hard segments. However, the PUPEG 400 film has a much lower amorphous halo indicating less orientation of the chains in the amorphous state. In addition, the PUPEG 400 and 1000 films exhibit no crystallization because the \(T_m\), as determined by DSC is below room temperature.

![WAXD patterns for PUPEG films.](image)

*Figure II-7. WAXD patterns for PUPEG films.*
Elasticity, Modulus, and Thermal Transitions by Dynamic Mechanical Analysis

The DMA plots for PUPEG 400-PUPEG 6000 are shown in (Figure II-8). The PUPEG 400 film is almost 1:1 PHDI to PEG by mole %, with a region of chain mobility around -40°C and -10°C. Thus transition of -40°C and -10°C are attributed to the PEG and the urethane hard segment T_g respectively. PUPEG 1000 has a much larger volume fraction of PEG, causing the tan δ maximum around -30°C and a small shoulder in the region of PHDI mobility. PUPEG 3400 and 6000 have a much higher crystalline content than amorphous and therefore show little mobility before their melt temperature around 50°C.

![Figure II-8. Tan δ plot of dehydrated PUPEG films.](image)

The elasticity of the dehydrated films are determined from the storage modulus plot in Figure II-9. The PUPEG 400 and 1000 exhibit increases in the storage modulus at around -40 and -10°C. These are attributed to increased mobility of chains that enables crystalline lamella to form. A large drop off in elasticity is observed above the T_g of both
the hard and soft segments. The plateau from 25°C is typical of crosslinked systems, where and the magnitude is proportional to the crosslink density. In this case PUPEG 400 is slightly higher than PUPEG 1000 because of the increased crosslink density. The high amorphous character of PUPEG 400 and PUPEG 1000 films make them very rubbery and flexible compared to the highly crystalline PUPEG 3400 and PUPEG 6000 materials in the dehydrated state.

![Graph](image)

*Figure II-9.* Elasticity and thermal transitions of dehydrated PUPEG films.

In the hydrated film there is a transition as expected around 0°C whose intensity increases with the PEG Mn component. PUPEG 6000 was not measured because of the lack of integrity of the hydrated film. A high degree of crystallinity is lost in these films upon hydration, and because more water is absorbed by the PUPEG 3400 and PUPEG 6000 films upon hydration, they have little mechanical integrity. Since PUPEG 400 and 1000 films have lower water absorption, the change in mechanical properties in the presence of water is reduced.
Figure II-10. Tan δ of hydrated PUPEG films.

The storage modulus of the hydrated films in (Figure II-11) illustrates the loss of elasticity in the films as the absorbed water melts. The peak in PUPEG 400 indicates the enhanced mobility, and thus a small degree of cold crystallization takes place due to mobility in the system at the hard segment T_g. (DMA heating rate of only 2°C/min) The same is true of PUPEG 1000 with the higher volume % of PEG. Once the soft segment T_g, there is enough mobility for crystallization to occur.
Figure II-11. Storage modulus as a function of temperature for hydrated PUPEG films illustrating cold crystallinity an elasticity.

Water Absorption

The water absorption ($Q_{\text{grav}}$) and sol content (S) of the PU hydrogel series were measured gravimetrically, and summarized in Table II-3.

Table II-3.

Network Characteristics Derived From Water Sorption.

<table>
<thead>
<tr>
<th></th>
<th>PU-PEG 400</th>
<th>PU-PEG 1000</th>
<th>PU-PEG 3400</th>
<th>PU-PEG 6000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{\text{grav}}$ ($25 , ^\circ C$)</td>
<td>0.33</td>
<td>0.53</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>±0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q_{\text{TGA}}$ ($25 , ^\circ C$)</td>
<td>0.35</td>
<td>0.55</td>
<td>0.91</td>
<td>0.74</td>
</tr>
<tr>
<td>±0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q_{\text{grav}}$ ($50 , ^\circ C$)</td>
<td>0.29</td>
<td>0.56</td>
<td>0.85</td>
<td>0.86</td>
</tr>
<tr>
<td>±0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% S (sol content)</td>
<td>1.50</td>
<td>1.58</td>
<td>0.913</td>
<td>0.655</td>
</tr>
<tr>
<td>±0.02%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Q_{GRAV} data was compared to values obtained from TGA experiments (Q_{TGA}). An example of the TGA data is shown in Figure 4, where the amount of water absorbed by a sample of PUPEG 400 was measured. The amount of water absorbed by PUPEG 400 was 22.5 wt % as determined by the weight loss below 100 °C, and another large weight loss is not observed until the degradation temperature around 300°C. Since PEG has a higher volume fraction in the formulation, the relatively larger weight loss at 300°C is attributed to the PEG segments, with weight loss at 400°C attributed to the degradation of the urethane crosslinker. There is no bound water as evidenced by no detectable significant weight loss step between 100 and 200°C.

![Graph showing normalized weight loss against temperature](image)

*Figure II-12.* PU-PEG 400 hydrogel weight loss profile measured by TGA.

Weight loss before and around 100°C is due to water. However, it is interesting to note the increase in T_d of the hydrated sample as seen in Figure II-12. This could be the result of residual bound water. TGA results give a percentage of water in the sample,
or more specifically the amount of water the hydrogel was capable of holding. These are consistent with those calculated values for Q using dehydrated and hydrated weights.

The sorbability measurements $Q_{grav}$ and $Q_{TGA}$ taken for each film were comparable and show the trend of increasing equilibrium water content with increasing PEG chain lengths in the polyurethane hydrogel. The exception to this trend is PUPEG 6000, which decreases in its ability to hold onto water or swell in comparison with PUPEG 3400. This is attributed to PUPEG 6000 having a higher degree of crystallinity than the other hydrogels in the series. Therefore, the water is not able to break up and infiltrate these crystalline domains of the gel, leaving them as relatively dehydrated packets within the film. This is confirmed when hydrogels are saturated with water and heated to 50°C. The resulting $Q_{grav}$ is higher for PUPEG 6000 at 50°C in relation to 25°C, although relatively the same for the other films. This indicates that the crystalline domains dissolve at higher temperatures by the water, as the $T_m$ of the material is approached, enabling further swelling of the PUPEG 6000 hydrogel film.

This trend of increasing water content with increasing PEG units between crosslinks is consistent with what is expected due to the hydrophilicity and complexation of ethylene oxide with water. However this is an effective method to quantify the amount of water these materials can contain at equilibrium.

The sol content or unbound diol remaining within the gel network decreases from PU-PEG 400 (1.50%) to PU-PEG 6000 (0.655%). This finding is a possible result of the increased mobility as the PEG chains get longer (from $M_n$ 400 to $M_n$ 6000) since the solids content in MEK was identical for each, creating a more viscous environment the lower the PEG $M_n$. This is credited to the larger ratio of crosslinker to PEG reactants, due
to the molecular weight between crosslinks, which increases the hydrogen bonding in the system, reducing the motion of the chains. It is interesting to note that as molecular weight between crosslinks increases, a higher percentage of chains is expected to be unreacted at this concentration due to mobility issues.

**Fluorescence Spectroscopy**

The molecular mobility of the crosslinked networks is of utmost importance in biomaterials used for tissue engineering applications. The hydrogel must provide sufficient confinement to keep the host or guest in place, however there must be enough freedom in the network to allow accurate protein folding and cell activities to take place. The mobility of the network in the hydrated and dehydrated states for the series of polyurethane hydrogels with PEG Mₙ ranging from 400-6,000 g/mol was then observed with a fluorimeter. In order to observe changes in network mobility with temperature, probe emission intensity within the film was observed in 30 and 40°C environments in both the dehydrated and hydrated states. These temperatures were chosen with end use applications in mind including industrial coatings containing enzymes and biomaterials containing cellular components. Blank measurements were performed on the glass cover slips, deionized water, DMSO, the TRC probe in water all of which showed a relative intensity of less than 15 (arbitrary units). TRC probe in DMSO (Figure II-13 and Figure II-14) was also measured in the same concentration as TRC covalently attached to the PU films.
Figure II-13. Emission of TRC (covalent) in a dehydrated PU-PEG 400 film at 30 and 40°C.

Figure II-14. Emission of TRC (covalent) in a hydrated PU-PEG 400 film at 30 and 40°C.

Compared to the dehydrated film in Figure II-13, the relative intensity of TRC in the hydrated film of Figure II-14 is about 10% lower than the dehydrated relative
intensity of 1100. In Figure 11-14, at 580 nm, the intensity of TRC drops drastically from 1000 to 550 relative intensity with an increase of 10°C of the hydrated film. The same trend occurs with the relative intensity of TRC in the dehydrated films with a temperature increase. These results indicate the bound probe is self-quenching. Fluorescence quenching refers to any process that decreases the intensity of a sample with the most common type being collision or dynamic quenching which results from interactions between a fluorophore and another atom or molecular entity of the same species in the ground state. An increase in collisions of TRC with itself expends the energy that would have been emitted, creating a decrease in detected intensity. This confirms that an environment of increased temperature and enhanced hydration within the film increases the mobility of the ethylene oxide chains between crosslinks in the system.

NMR

The solid-state NMR spectra of hydrated gels were compared to the spectra of dehydrated gels. Here the peaks narrowed as the gel became more hydrated due to increased mobility. It is important to note that relaxation data could be fit to one $T_1$ value indicating that water absorption affected all parts of the network equally, and that there is no phase separation. This is confirmed by the presence of only one $T_g$ in the DSC plot of the gels.

Carbon spin-lattice relaxation times ($T_1$) were determined for the dehydrated and hydrated crosslinked networks. $T_1$ values of the ethylene oxide carbons were measured at 25, 40, 60 and 80°C of hydrated and dehydrated polyurethane materials. Table II-4 summarizes these results.
Table II-4.

*PEG-PU* $T_1$ Values as a Function of Hydration, Temperature, and PEG $M_n$.

<table>
<thead>
<tr>
<th>PUPEG film</th>
<th>Dehydrated 25°C</th>
<th>Hydrated 25°C</th>
<th>Hydrated 40°C</th>
<th>Hydrated 60°C</th>
<th>Hydrated 80°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUPEG 400</td>
<td>0.24</td>
<td>0.22</td>
<td>0.24</td>
<td>0.33</td>
<td>0.46</td>
</tr>
<tr>
<td>PUPEG 1000</td>
<td>0.32</td>
<td>0.34</td>
<td>0.44</td>
<td>0.47</td>
<td>0.72</td>
</tr>
<tr>
<td>PUPEG 3400</td>
<td>0.25</td>
<td>0.59</td>
<td>0.80</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>PUPEG 6000</td>
<td>0.23</td>
<td>0.69</td>
<td>0.87</td>
<td>1.2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

$T_1$ increases with temperature because of enhanced mobility in the gel. In addition, in agreement with fluorescence work, $T_1$ increase with PEG molecular weight. This suggests the mobility of the PEG segments increases as the number of ethylene oxide units between crosslinks increases. This more mobile network structure at higher temperatures and longer PEG segments between crosslinks will provide a more spacious environment for entrapped cells in an extra-cellular matrix that would allow for cellular activity by allowing enhanced diffusion.
The relaxation time increases with the $M_n$ of the PEG or the number of ethylene oxide repeat units between crosslinks. (Figure II-15)

The overall increase in slope of PUPEG 400 to PUPEG 6000 from 25 to 80°C indicates that there is greater change in mobility of the network or a more dramatic increase of freedom for the chains as they are subjected to higher temperatures. The gravimetric sorbability ($Q_g$) value increased as the PUPEG 6000 was soaked in $H_2O$ at higher temperatures. This was not detected gravimetrically with PUPEG 400 through PUPEG 3400.

Increased mobility, as evident by larger $T_1$ values, is also observed when the gels are placed in an equilibrium swelling state from a dehydrated state. The exception to this is PUPEG 400, where the motion of the network decreases with hydration ($T_1$ values slightly decrease). This could be due to the higher level of chain entanglement since there is no crystallinity seen and all the chains are in the amorphous state as opposed to those hydrogels of higher $M_n$ PEG where fewer chains are in the amorphous region. This could
also be ascribed to enhanced hydrogen bonding of the network with increasing PEG $M_n$ that could crowd or confine the network below a certain level of swelling seen in the hydration studies of PU-PEG 1000 to PU-PEG 6000.

Conclusions

The different characterization methods reveal the link between physiochemical interactions and their behaviors. In this study we have found that with increasing soft segment or PEG $M_n$ in polyurethane crosslinked hydrogel systems, there is an increase in $Q$ or water uptake due to the lower degree of crosslink density and higher degree of solubility. Also by DSC it was found that there was an enhanced degree of crystallinity as PEG $M_n$ increased in the hydrogel films. Also the melting temperatures of the hydrogels are lower than the PEG reactant alone which is consistent with the addition of impurities and removal of crystallization.

The molecular motion of the dehydrated and hydrated PEG chains at various temperatures in these hydrogel films is imperative to understand if they are to be used in future studies as hosts to enzymes and cells. Also by examining the $T_1$ relaxation times of the ethylene oxide carbons it is observed that the relative degree of motion in the system is greatly affected with an alteration in PEG $M_n$, temperature, and/or hydration as shown by the increasing $T_1$ times. Also by measuring a bound molecular probe in the system by fluorescence, it is determined that a decrease in the observed emission intensity with higher temperatures and hydration is consistent with self-quenching probes and indicates enhanced movement within the system.

References

CHAPTER III
HYDROPHILIC MICROGELS

Introduction

In the surface coatings industry, microgel research is a direct result of the movement from solventborne to waterborne coatings in order to reduce or eliminate volatile organic compounds. This is accomplished by increasing solid content and using microgels to control the resulting change in viscosity. Microgels were first used as additives in the late 1960s by Smith to obtain non-Newtonian rheological properties since microgels are usually pseudoplastic. They also have an effect on the resulting physical properties of the cured films such as enhancing impact flexibility and elasticity. This is a result of the microheterogeneous structure of the composite film and the gel particles' high molecular weight which allows enhanced dissipation of impact energy as compared to the homogeneous film alone. Current research on microgels in coatings focuses on shelf stability of the mixture, interactions of the microgels with pigments, drying times of the films, and the resulting film morphologies.

Hydrogels have been researched for a wide variety of applications in fields ranging from biomedical applications to architectural coatings. Synthetic hydrogels allow adjustment of the material properties more readily than natural physical crosslinked gels such as alginate, a viscous gum that is abundant in the cell walls of brown algae. Properties such as crosslink density can be tuned with synthetic hydrogels affecting the resulting gel’s modulus and degree of swelling in water. Controlling these properties is advantageous for use in applications such as drug delivery, where the drug’s release rate is altered by varying the composition, density, and crosslinking groups. Also material
engineering is desirable in applications for artificial semi-permeable membranes where regular and controlled pore sizes are advantageous.\textsuperscript{9-11}

PEG based hydrogels can be obtained by free-radical polymerization of bifunctional acrylate PEG monomers.\textsuperscript{12,13} The amphiphilic nature of hydrophobic methacrylic end capped PEG-based macromonomers in aqueous media results in self-organization, producing microgels with more desirable physical properties than those prepared in organic solvents. These hydrogels were found to be ideal semi-permeable membranes in artificial pancreases, due to the ability to control the diffusion coefficient of glucose by altering the PEG content.\textsuperscript{14}

Traditionally, polyurethane dispersions are prepared in a process where polyurethane prepolymers with hydrophilic pendant groups are first dispersed and then chain extension is employed to increase the molecular weight.\textsuperscript{15,16} However, they have also been prepared in a method where urethane acrylates are emulsified and the free radical polymerization results in crosslinked polyurethane latexes. PEG modified urethane acrylate latexes have been researched for use in soil remediation of polycyclic aromatic hydrocarbons.\textsuperscript{17}

Reduced amount of surfactant and improved water dispersability of urethane acrylate monomers was achieved by Kim and Suh. This was accomplished by incorporating reactive surfactants by addition of hydrophilic groups into the chain ends. They combined hydrophobic poly(tetramethylene glycol), hydrophilic PEG, and residual isocyanate groups of urethane acrylate end capped with vinyl groups. In addition, the typical neutralization step was not needed because the hydrophilic group was
This work is beneficial because this is a viable method in which reactive surfactants may be used for the aqueous synthesis of polyurethane microgels.

High throughput experimentation (HTE) has been utilized to analyze multiple variables affecting the resulting material properties. The large amount of data resulting from these experiments can be effectively analyzed using statistical analysis tools. These tools allow for more efficient data dissemination, and screening experiments such as the Taguchi design effectively evaluate whether a large number of factors affect the measured response by looking at only the maximum and minimum setting of each factor. The overall effect of each factor on the responses is evaluated by the change in the response at the low setting compared to the high setting. The significant factors can be further evaluated to determine if their effects are linear or non-linear based on the response. This is established by designs such as central composite designs or the Box Behnken design in which there are three settings for each factor. A model that is a good fit also allows for prediction of which factors and their settings will result in the desired material properties.

For this research, a Taguchi screening design was utilized to establish the chemistries and reaction conditions that effect urethane acrylate free radical microgel synthesis in aqueous media.

Here, the macromonomer prepolymer was synthesized with a hydrophilic PEG soft segment and an isophorone diisocyanate (IPDI) or lysine diisocyanate (LDI) hard segment followed by end capping with acrylates. This prepolymer was then dispersed in aqueous media, without the use of surfactant due to its amphiphilic character, and crosslinked. PEG, IPDI, and LDI are all generally regarded as safe components that are nonionic. This work is beneficial because this is a viable method in which reactive surfactants may be used for the aqueous synthesis of polyurethane microgels.

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currently being researched for application in biodegradable medical materials. The synthesized microgels were based on PEG of \( M_n \) 400 g/mol (P400), 3400 g/mol (P3400) and 6000 g/mol (P6000) and correspond to microgels based on P400 (mP400), P3400 (mP3400), P6000 (mP6000).

**Experimental**

*Materials, Compounds, and Sources*

2,2-Azobisisobutyronitrile (AIBN) and dibutyl tin dilaurate (DBTDL) was received from Sigma-Aldrich Chemical, Milwaukee, WI. Isophorone diisocyanate, Desmodur I, was obtained from Bayer in Pittsburgh, PA and lysine diisocyanate was supplied by Kyowa Hakko U.S.A. in New York, New York. Monomethacrylate PEG of \( M_n \) 2000 g/mol was supplied by Monomer-Polymer & Dajac Labs, Inc. in Pike Feasterville, PA. All were used as received.

*Taguchi Design of Experiments of Crosslinked Microgel Polymerization*

Listed in Table III-1 are the eight factors chosen to evaluate their low (-1) and high (+1) settings. In order to determine the effects of composition and reaction conditions on the particle size (PS) and particles size distribution (PSD) of the formed microgels, a screening design of experiments (Taguchi L12) was utilized. The prepolymer in acetone were added to water under the conditions established in the design (Table III-1). The suspensions were formulated at 10 or 30 wt % solids, temperature was set at 80 or 100 °C in a closed system in order to prevent boiling off of acetone, and the stir rate was either 60 or 300 rpm. The volume in the 100 mL round bottom flask was kept constant at 5 mL, and an egg shaped stir bar of dimensions 1/2 x
5/8 in. was used. Temperature was controlled using a heating mantle connected to a variable transformer, and the reaction time was held constant at 4 hours. The success of the reaction was determined by the detection of particles using DLS. The particles were placed in methylene chloride and THF at a range of temperatures in order to confirm that crosslinking occurred. An example reaction is shown in Figure III-1.

![Reaction Scheme](image)

**Figure III-1.** Synthesis of PEG based microgels using LDI as the hard segment.

The resulting crosslinked microgels were characterized by dynamic light scattering (DLS) to determine how the hydrodynamic PS and PSD are affected by these factors.

**Table III-1.**

*Taguchi L12 Factors and Levels.*

<table>
<thead>
<tr>
<th>Factors</th>
<th>Symbol</th>
<th>Level -1</th>
<th>Level +1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stir rate (rpm)</td>
<td>A</td>
<td>60</td>
<td>300</td>
</tr>
<tr>
<td>PEG M_n</td>
<td>B</td>
<td>400</td>
<td>6000</td>
</tr>
<tr>
<td>PEG diol wt %</td>
<td>C</td>
<td>5</td>
<td>65</td>
</tr>
<tr>
<td>Solids wt % in H_2O</td>
<td>D</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Addition rate</td>
<td>E</td>
<td>Dropwise</td>
<td>Continuous</td>
</tr>
<tr>
<td>Diisocyanate</td>
<td>F</td>
<td>IPDI</td>
<td>LDI</td>
</tr>
</tbody>
</table>

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The Taguchi L12 (resolution level 4 where no main effects are aliased) screening design of experiments was planned and results statistically analyzed using DOE Pro Software.

**Dynamic Light Scattering (DLS)**

Dispersion PS and PSD were determined by dynamic light scattering (DLS) performed on a Microtrac UPA 250 ultrafine particle analyzer. The samples were diluted to the required concentration with distilled water before measurement. The analysis was carried out with estimated solution parameters as follows: refractive index of 1.5, particle density of 1.0 g/mL, and viscosity between 0.797 and 1.002 mPa·s. The time for each analysis was fixed at 360 s, and a minimum of two analyses were performed and the average reported.

**Thermal Gravimetric Analysis (TGA)**

Weight loss as a function of temperature was measured using a Q500 TA Instruments TGA at a heating rate of 5°C/min and a nitrogen flow of 40 mL/min. Platinum measuring pans were used, with a typical weight of 10-12 mg. The TGA temperature was calibrated using a nickel standard, and the weight calibration was performed in the range of 200 mg to 1 g with a pan weight of slightly over 200 mg. Water loss was determined by calculating the weight change that occurred below 100°C, at which point the weight loss profile begins to plateau. The degradation temperature (Td) was determined using the onset function in Universal Analysis Software (2002). Here 2
points are selected, one at a plateau point before weight loss and the other at the point maximum in the derivative peak. A line is drawn tangent to the curve at each point, and the intersection of these 2 lines was designated as the onset of degradation.

*Dynamic Scanning Calorimeter (DSC)*

\( T_g, T_c, \) and \( T_m \) were determined with a Q1000 Dynamic Scanning Calorimeter (DSC) from TA Instruments with heating/cooling rate of 10°C/min, a scan range from -90 to 150°C and a 5 minute isothermal hold at 150°C to erase thermal history. Temperature calibration was performed using indium and zinc standards, and heat flow calibration was established using sapphire standards. Values reported for the melting \( (T_m) \) and crystallization temperatures \( (T_c) \) are those at the minimum and maximum of endothermic and exothermic peaks, respectively and are taken from the second heat. The fractional degree of crystallization \( (X_c) \) was calculated by taking the observed heat of fusion \( (\Delta H_{obs}) \) from the DSC experiments of the hydrogel films and dividing it by the heat of fusion \( (188.95 \text{ J/g}) \) for 100% polyethylene oxide.\(^{22}\) The samples were run in duplicate to determine the reproducibility.

The \( \omega \) term accounts for PEG being the only component in the film that will crystallize.\(^{23}\) For the PEG diols, \( \omega \) was assigned to be 1.

\[
X_c = \frac{(\omega \Delta H_{obs})}{\Delta H_f^0}
\]

*Equation III-1*

*NMR*

Solution NMR spectra were obtained using 5 mm o.d. tubes on a Varian Unity (500 MHz) or a Bruker AC-300 (300 Hz) spectrometer at 25°C. All solutions were at a
concentration of 10% (w/w) in deuterated chloroform (CDCl₃) (Aldrich Chemical Co.) containing tetramethylsilane as an internal reference. Chemical shifts were referenced from the solvent resonance signals (¹H 7.26 and ¹³C 77.0). All spectra were processed using Varian 6.0 software. All 1D and 2D-NMR technique parameters were set accordingly to the standard Varian ChemPack macros, with modifications listed accordingly.

**FT-IR Spectroscopy**

Sample specimens were analyzed using a BioRad Diffuse Reflectance Attachment in combination with the IR spectrometer. Potassium bromide was used as the IR background with 64 scans performed. The protocol for sample characterization included using three averaged spectra, each obtained at 128 scans with a resolution set to 4 cm⁻¹. The spectra were adjusted to form a common baseline, and peak height normalized to the C-H bending peak at 1319 cm⁻¹.

**Prepolymer Synthesis**

Acrylate-functionalized polyurethane prepolymers (Figure III-1) were prepared by adding IPDI or LDI to PEG (of Mn 400 or 6000 g/mol) at a molar ratio of 1.05:1, and this product was used at levels of 5 or 65 wt % of the final formulation. The remainder of the formulation (95 or 35 wt %) was composed of the same diisocyanate with monomethacrylate PEG in a 1:2 mole ratio. The prepolymers were formulated at 50 wt % solids in acetone to reduce the viscosity.

A representative prepolymer preparation (based on PEG 3400) (Figure III-1) included charging 4.97 g of PEG 3400 (0.0029 OH equiv), 2.70 g of monomethacrylate
PEG (0.0014 OH equiv) into a 100 mL flask under N\textsubscript{2} with 8 grams of anhydrous acetone and 0.35 g of Desmodur I (IPDI) (0.0032 equiv). 1 drop of DBTDL was added, and the reaction contents were heated for 3 h at 60 °C. Prepolymers from PEG diols of M\textsubscript{n} 400, 3400, and 6000 were prepared in a similar fashion. In all cases, an isocyanate to hydroxyl index of 1.05/1.0 was used. Such a ratio ensures complete incorporation of the PEG diol with excess NCO reacting with trace atmospheric and PEG monomer water content.

*Representative Prepolymer Dispersion and Microgel Formation (based on prepolymer of PEG 3400)*

8 g of prepolymer was charged to a 100 mL flask under N\textsubscript{2} by dropwise addition to 8 g of (Teflon stir bar) de-ionized water while mixing with a stir bar at 80°C for 3 hours. The presence of microgel particles in the range of 100 nm - 4 µm was detected by DLS. The mixture is then freeze dried to yield a powder which is insoluble in solvents including tetrahydrofuran, hexanes, and water.

The two difunctional isocyanates, LDI and IPDI, are shown in Figure III-2.

*Figure III-2. Structure of LDI and IPDI.*

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Polymers containing IPDI in their backbone are much more rigid than those containing LDI and also have shorter dust-free times because of this characteristic.

*Gel Permeation Chromatography (GPC)*

Molecular weights and molecular weight distributions (MWD) of prepolymer were characterized using a Waters Alliance 2695 Separations Module, an on-line multiangle laser light scattering detector (MiniDAWN™, Wyatt Technology Inc.) and an interferometric refractometer (Optilab DSP™, Wyatt Technology Inc.). Freshly distilled THF served as the mobile phase and was delivered at a flow rate of 1.0 mL/min. Sample concentrations were 10 mg/mL in freshly distilled THF, and the injection volume was 100 μL.

**Results and Discussion**

The regression table from the results of the study is shown in Table III-2, where \( P_{(2 \text{Tail})} \) calculates the significance of the factors, with values less than 0.05 being highly significant and values from 0.05-0.1 being significant. The coefficient indicates the impact either positively or negatively of the factor on the desired response. \( R^2 \) is a measure of the fit, with 1.0 being a perfect fit.

Table III-2.
Regression Table for PS and PSD.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Name</th>
<th>PS</th>
<th>Coeff</th>
<th>P (2 Tail)</th>
<th>PSD</th>
<th>Coeff</th>
<th>P (2 Tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Const</td>
<td></td>
<td></td>
<td>8.401</td>
<td>0.000</td>
<td>2.988</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Stir rate</td>
<td>-0.134</td>
<td>0.032</td>
<td>-0.284</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Temperature</td>
<td>0.082</td>
<td>0.561</td>
<td>-0.383</td>
<td>0.071</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>PEG Mn</td>
<td>0.548</td>
<td>0.001</td>
<td>0.297</td>
<td>0.153</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>PEG wt %</td>
<td>0.474</td>
<td>0.004</td>
<td>-0.118</td>
<td>0.558</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Addition rate</td>
<td>2.574</td>
<td>0.056</td>
<td>-1.905</td>
<td>0.300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Solids wt %</td>
<td>1.348</td>
<td>0.001</td>
<td>-0.891</td>
<td>0.091</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Diisocyanate</td>
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<td>0.000</td>
<td>0.728</td>
<td>0.002</td>
<td></td>
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<tr>
<td>H</td>
<td>Initiator</td>
<td>-0.421</td>
<td>0.008</td>
<td>0.140</td>
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</tr>
<tr>
<td></td>
<td>R²</td>
<td>0.861</td>
<td>0.7135</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table III-2 shows which factors affect each response and the $R^2$ value of PSD is fairly low which could indicate that a factor is missing from the model. However, most of the factors do have a significant effect on particle size with the exception of the temperature, addition rate, the initiator content, PEG Mn and prepolymer wt % on particle size distribution.

The most significant factor that affects PS is the diisocyanate monomer used with a $P_{(2\text{Tail})}$ value of 0 and since this factor is categorical, IPDI was arbitrarily assigned as the low value of 0 and LDI was assigned as the high value of 1. The coefficient is a positive integer of 0.768 indicating that LDI causes larger particle size as compared to IPDI a lower particle size. This observation is attributed to the more flexible, linear, and more
hydrophilic monomer LDI which would create more swollen particles in comparison to microgels based on IPDI. The same trend is seen with the particle size distribution being broadest with LDI and narrowest with IPDI. This may be due to differences in reaction rates and needs to be investigated further.

The solids wt % of the prepolymer dispersed in water has a significant effect on the particle size and a proportional relationship exists. The increase in PS with increasing solids content is attributed to the solution becoming more concentrated. These results need to be examined further in order to fully understand why narrower PSD is formed with decreasing prepolymer wt %. The molecular weight of the PEG oligomer precursor is the next most significant factor affecting particle size. As the PEG molecular weight increases, the particle size increases. As PEG $M_n$ increases, the volume % increases, causing enhanced hydrophilicity of particles and increased hydrodynamic volume. The particle size distribution is not affected by PEG $M_n$ indicating that hydrophilicity is not a factor and other characteristics such as a threshold size or reaction rate is the determining factor.

The next significant factor that affects particle size is addition of the initiator AIBN. From the negative coefficient it can be seen that there is an inverse relationship between the addition of AIBN and the particle size. This could be a result of AIBN increasing reaction kinetics and hence allowing for particles to build up more before precipitating out of solution. There is no effect of the initiator on particle size distribution, with a $P_{2\text{tail}}$ value of above 0.1.

The stir rate is the next factor that has an effect on the particle size. As the stir rate is decreased from 300 to 60 rpm, the particle size increases. This contradicts the
assumption that larger particles are due to more collisions and less organized chains creating microgels with more defects such as loops and unreacted methacrylate groups. Higher shear effects on the particles could cause the particles to precipitate out of solution sooner. This could also explain the large effect that increased stir rate has on decreasing the particle size distribution.

Since the addition rate of prepolymer to water $P_{2\text{mol}}$ value is above 0.05, there is less of an effect of addition rate on particle size and particle size distribution. However, it can be said from the coefficient values that addition of prepolymer in a continuous stream versus dropwise addition creates larger particles with a smaller particle size distribution. Further studies are needed in order to determine the explanation behind this behavior.

A predictive equation is formed from this table in order to set conditions at appropriate settings to minimize, maximize, or optimize the responses of PS and PSD. The two predictive equations that can be formed from this regression table are seen in Equations III-1 and III-2. $\hat{y}$ (y-hat) is the desired response (PS in Equation III-1, PSD in Equation III-2) and the letter coefficients correspond to significant factors that can be set between -1 and 1.

\[
\hat{y}(PS) = 8.401 - 0.133A + 0.548C + 0.474D + 2.574E + 1.348F + 0.768G - 0.421H
\]

Equation III-2

\[
\hat{y}(PSD) = 2.99 - 0.284A - 0.383B - 0.891F + 0.728G
\]

Equation III-3
These equations allow for selection of the proper conditions to get the desired PS and PSD. For example based on Equation 1, small microgel PS is favored by a high stir rate of 300 rpm (A=+1), small PEG $M_n$ such as 400 (C=-1), a small PEG % (D=-1), a dropwise addition of prepolymer (E=-1), a solids content of 10% (F=-1), IPDI as the diisocyanate (G=-1), and the addition of initiator (H=+1). Looking at Equation 2, particles of a narrow PSD will most likely be formed in a reaction where conditions are set at a high stir rate of 300 rpm, a water temperature of 100 °C, a solids quantity of 30 wt %, and when IPDI is used as the hard segment.

These predictive equations are also shown in bar plot form (Figure III-3). Where the high and low setting of each factor is listed on the abscissa and the absolute intensity of the bar is proportional to the significance of the factor on minimization of the particle size. Reaction conditions and reactants were optimized in order to obtain particles around 1 μm. The chosen settings based on the Taguchi results are shown in Figure III-3 in which addition of prepolymer to water is dropwise, the solids wt % of prepolymer in water is 30 wt %, the isocyanate chosen is IPDI, the stir rate is set at the high level of 300 rpm, and no AIBN is used.
Factor (-1,1)

<table>
<thead>
<tr>
<th>stir rate</th>
<th>PEG Mn</th>
<th>PEG wt%</th>
<th>prep add rate</th>
<th>solids wt%</th>
<th>disocyanate</th>
<th>initiator ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>dropwise, continuous</td>
<td>60,300</td>
<td>400,600</td>
<td>5.65</td>
<td>10,30</td>
<td>IPDI, LDI</td>
<td>0,100</td>
</tr>
</tbody>
</table>

**Chosen Parameters**

- Add Rate = dropwise
- Solids = 30
- Isocyanate = IPDI
- Initiator = 0
- Stir rate = 300 rpm
- PEG = Vary

*Figure III-3.* Reaction settings to minimize particle size illustrated by a bar graph.

This concept can be illustrated further by looking at the coded low (-1) and high (+1) level averages (Marginal Means Plot, Figure III-4 and Figure III-5). In these plots, the steeper the slope, the greater the impact or significance of the factor on the responses of PS and PSD. In order to minimize PS and PSD, the high level (+1) will be used for those factors with a negative slope and the low level (-1) for plots with a positive slope in reaction conditions. In optimizing particles of around 1 μm, significant factors are indicated by steeper slopes. (Figure III-4) Since C,D,E,F, and G have positive slopes, the low level condition is recommended. A and H can also be observed as significant due to their steeper slopes compared to B, but have negative slopes indicating that the high level will give smaller PS.

In setting conditions to minimize PSD, A, B, and F high levels are used (negative slopes) and G high level is suggested. While PEG Mₙ (C), PEG wt % (D), dropwise vs.
continuous addition of prepolymer to water (E), initiator content to the aqueous free radical reaction (H) are all insignificant factors due to their shallower slopes.

Figure III-4. Marginal Means plots for PS. Stir rate (A), temperature (B), PEG Mn (C), PEG wt % (D) dropwise vs. continuous addition of prepolymer to water (E), prepolymer wt % (F), diisocyanate (G), initiator content to the aqueous free radical reaction (H).

Figure III-5. Marginal Means plots for PSD: Stir rate (A), temperature (B), PEG Mn (C), PEG wt % (D) dropwise vs. continuous addition of prepolymer to water (E), prepolymer wt % (F), diisocyanate (G), initiator content to the aqueous free radical reaction (H).

Once these factors and their effect on particle size and particle size distribution were determined, a reaction based on IPDI was chosen to determine the effects of PEG $M_n$ on the microgel’s properties. This reaction is illustrated in
mp400, mP3400, mP6000= crosslinked microgels based on PEG Mn 400, 3400, and 6000 g/mol respectively

Figure III-6 and shows that the acrylate end-capped urethane ether prepolymer is the product. This prepolymer is then dispersed in water and a thermally initiated free radical reaction pursues in which the methacrylate groups are crosslinked to form microgel particles in the size range of 100 nm to 4 μm in size.

Figure III-6. Formulation based on IPDI and PEG using a chosen set of conditions.
Figure III-7. $^1$H NMR spectrum of mP6000 prepolymer (before being dispersed in water and heated) in DMSO-$d_6$, with (a) being the methacrylate peaks and (b) the ethylene oxide peak.
Figure III-8. \(^1\)H NMR spectrum of dehydrated mP6000 microgels (after being dispersed in water and heated at 80°C for 4 h) dispersed in DMSO-\(d_6\) with (a) being the methacrylate peaks and (b) the ethylene oxide peak.

The particles were then freeze dried and dispersed in DMSO-\(d_6\) in order to perform \(^1\)H NMR spectroscopy. This was possible because the microgels swell sufficiently in DMSO-\(d_6\) that the microgels have enough mobility to obtain a spectrum. When the methacrylate bonds of PEG-monomethacrylate, located at 5.6-6.1 ppm (peak a), are followed over the course of the reaction and integrated with respect to the constant ethylene oxide peak (peak b), it is found that about 80% of the double bonds react once the prepolymer is dispersed in water and heated over 3 hours. (Figure III-7)

The \(M_n\) and the polydispersity index (PDI) of the prepolymer are summarized in Table III-3. It is important to note that although the PEG reactant \(M_n\) spans a large range, 400 to 6000 g/mol, the resulting prepolymer, which will be the molecular weight between crosslinks once dispersed in water, with the exception of 20% residual methacrylate end groups, is not over such a wide range. The resulting
prepolymer $M_n$ is from 3,358 to 4,648 to 8,284, as expected due to the addition of monomethacrylate PEG of $M_n$ 2000 g/mol.

Table III-3.

$M_n$ and PDI of Prepolymers Based on PEG $M_n$ 400, 3400, and 6000 g/mol.

<table>
<thead>
<tr>
<th>Prepolymer/Property</th>
<th>mP400</th>
<th>mP3400</th>
<th>mP6000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_n$ (±5%)</td>
<td>3,358</td>
<td>4,648</td>
<td>8,284</td>
</tr>
<tr>
<td>PDI</td>
<td>1.33</td>
<td>1.23</td>
<td>1.31</td>
</tr>
</tbody>
</table>

Dehydrated powders of mP3400 and mP6000 are shown in Figure III-9, and the urethane versus urea content of these microgels remains independent of PEG $M_n$ reactant used. This is illustrated by the consistent ratio of amide II peak at 1530 cm$^{-1}$ compared to the urethane carbonyl at 1720 cm$^{-1}$. 

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**Figure III-9.** Urethane versus urea content.

Observation of the $\equiv$C–H stretch from 3070 to 3100 cm$^{-1}$, appear as a small shoulder (Figure III-10) confirming the presence of 20 % residual methacrylate groups, previously found by $^1$H-NMR.
After prepolymer dispersion and crosslinking in water, the resulting particles were analyzed by DLS. It was found that the PS and PSD did not vary significantly with varying PEG $M_n$. (Figure III-11)
Figure III-11. Particle size distribution plots as determined by DLS of (a) mP400, (b) mP3400 and (c) mP6000.
The microgels were also characterized in terms of their degradation behavior by TGA. This degradation behavior can be directly correlated to the oxidative stability of the particles over time as they are stored in the dehydrated state. The thermal degradation behavior of mP400 and mP6000 and the starting ingredients, P400 and P6000, provided for comparison, are shown in Figure III-12.

Figure III-12. TGA showing thermal mass loss from dehydrated PEG reactants P400 and P6000 in comparison to the freeze dried crosslinked microgel product, mP400 and mP6000.

Figure III-12 gives additional insight into the molecular weight effect of PEG on microgel thermal properties. P400, being a smaller molecule in comparison to P6000, begins to degrade slightly above 200 °C. However, mP400, as a result of the crosslinking chemistry, does not begin to volatilize until after 250 °C. Moreover, a small shoulder can be seen around 375 °C, indicating further deblocking of the urethane hard segment and volatilization of the PEG soft segment.24
The opposite trend is apparent in the degradability of P6000 versus mP6000. P6000 does not begin to volatilize until after 400 °C as a result of the entire volume consisting of 6000 g/mol whereas the corresponding microgel contains monomethacrylate PEG Mₙ 2000. This results in shorter chains that volatilize earlier than P6000. mP400 volatilizes 50 °C lower than mP6000 because of the higher small molecule content, however the degradation temperature differences of mP400 versus mP6000 as a function of PEG Mₙ used cannot be clearly deduced from this test.

Looking at the relative crystallinity of the microgels by DSC, (Figure III-13) it can be seen that there is a comparable melting endotherm for mP3400 and mP6000, with mP3400 having slightly more crystallinity. This could be attributed to mP3400 chains between crosslinks are mobile enough, but not overly so, allowing an upper limit degree of crystallization in the given time frame.

The lengths of chains between crosslinks of mP6000 are too mobile and there is less crystallinity observed during the time period of 10 °C/min temperature ramp. mP400 has the smallest degree of crystallinity and broadest endotherm indicating that there is a range of lamella sizes.

The first cool and second heat of the mP series allows for more differentiation of the thermal behavior of these microgels (Figure III-13). Because of the longer chains between crosslinks, mP3400 and mP6000 have enough mobility to organize into crystalline lamella and exhibit a crystalline exotherm at 27 °C. However, because of mP400’s shorter relative chain length between crosslinks, there is less mobility and lamellas are not able to form while cooling.
Figure III-13. First cool and second heat of mP DSC thermograms.

However when heat is being added to the system, mP400 has enough energy and mobility in order to organize into crystalline lamella at -30 °C. All of the chains have been given ample time to crystallize on cooling in mP3400 and mP6000 as indicated by the lack of a similar exotherm as mP400 during the second heat. This information suggests that the preparation of these microgels and the time they are allowed to cool will greatly affect their crystalline properties, as expected. Adjusting the crystalline properties allows for a wide range of control over these materials corresponding water sensitivity and water uptake kinetics.

In comparison to PEG reactants, the microgels based on PEG 3400 and PEG 6000 have less crystallinity and lower melting temperatures attributed to the hard segment crosslinker that breaks up PEG chain packing. (Table III-1)
Table III-1.

*Percent Crystallinity of PEG Reactants and Microgels.

<table>
<thead>
<tr>
<th>Thermal Property</th>
<th>PEG 400*</th>
<th>mP 400</th>
<th>PEG 3400*</th>
<th>mP 3400</th>
<th>PEG 6000*</th>
<th>mP 6000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m$ ($^\circ$C) ±0.4</td>
<td>1.16</td>
<td>40.4</td>
<td>59.8</td>
<td>52.9</td>
<td>63.0</td>
<td>55.6</td>
</tr>
<tr>
<td>Crystallinity (%)*± 0.1</td>
<td>16.3</td>
<td>29.1</td>
<td>97.9</td>
<td>82.4</td>
<td>98.2</td>
<td>78.2</td>
</tr>
</tbody>
</table>

Relative crystallinity was also observed by WAXD, in which the PEG reactants were compared to the corresponding microgels. In Figure III-14, P400 shows a large amorphous halo and sharp crystalline peaks are absent indicating the lack of any crystalline peaks.

![WAXD profile of PEG reactants as received.](image)

*Figure III-14. WAXD profile of PEG reactants as received.*

The WAXD profile of the microgels in Figure III-15 indicates the same diffraction pattern as the PEG reactants in Figure III-14. It is clear the peak positions from the WAXD profiles of P3400 and P6000, in Figure III-14 and Figure III-15, are...
identical to those found by Huang et al. (Figure III-16) who analyzed the unit-cell structure parameters and indexed the main peaks of PEG. They found that they were consistent with a monoclinic crystal system whose interplanar spacing of the \((hkl)\) reflection planes is given by Equation II-4. Through the insertion of the values of \((1.542 \, \text{Å})\), \(b (125.4^\circ)\), and the peak positions of \((120)\), \((032)\), and \((024)\) reflection planes, the unit cell parameters \(a\), \(b\), and \(c\) can be determined by Equation III-3.

\[
\left( \frac{1}{d_{hkl}} \right)^2 = \left( \frac{2 \sin \left( \frac{\theta_{hkl}}{2} \right)}{\lambda} \right)^2 = \frac{1}{\sin^2 \beta} \left( \frac{h^2}{a^2} + \frac{k^2 \sin^2 \beta}{b^2} + \frac{l^2}{c^2} - \frac{2hl \cos \beta}{ac} \right)
\]

Equation III-4

![WAXD profile of microgels based on PEG and IPDI.](image)

**Figure III-15.** WAXD profile of microgels based on PEG and IPDI.
Since the same planes are seen in the microgels as in the pure PEO diffraction pattern, it is apparent that the crystalline content is a result of PEG moieties forming lamella. As suspected, there is no contribution of the hard segment. However, in mP400 two low intensity sharp peaks appear that are consistent with the 120 and 032 planes of PEG. This is attributed to the added monoP2000 content which adds longer PEG chains and enhanced mobility. In every case the microgels exhibit much more crystallinity than the PEG reactants which is attributed to the preparation of the microgels. This more

*Figure III-16. (a) WAXD pattern and (b) peak deconvolution of the WAXD profile of pure PEO.\textsuperscript{25}*

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regular structure outweighs the negative effect on crystallinity, of the crosslinker disrupting crystallinity of the PEG chains by way of decreasing the mobility and breaking up the packing of the chains.

The water uptake of the microgels over a range of relative humidity’s was also determined gravimetrically by TGA (Figure III-17). Microgels were exposed to each RH atmosphere for 48 h.

![Graph showing water uptake vs. relative humidity for microgels mP400, mP3400, and mP6000.](image)

*Figure III-17. Water uptake of microgels with varying relative humidity.*

It is of interest to note that at 50 and 75% RH, mP400 takes up significantly more water from the air than mP3400 and mP6000. mP400 has lower crystallinity than mP3400 and mP6000 allowing a higher number of PEG units in mP400 to be available for association with water from the air. However, at a RH of 100%, signature WAXD peaks of PEG are no longer seen in mP3400 and mP6000 and water uptake is proportional to PEG Mₙ as expected. Water uptake varied from 25, 35, and 55 wt % of the microgel weight for mP400, mP3400, and mP6000 respectively. This is as predicted

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since crystallinity is no longer present and every PEG repeat unit is available to complexes with 2 water molecules.\textsuperscript{26}

Conclusions

The Taguchi L12 screening design is used to identify the important factors out of a large pool of reaction conditions and reactants that effect PS and PSD determined by DLS. A regression table was created to determine significant factors and the settings that would minimize PS and PSD in this microgel synthesis. Future studies will involve confirming the current predictive equation with more reactions and a more narrow nonlinear modeling DOE such as Box Benken or Central Composite Design of significant factors.

Additionally, after optimizing the microgel synthesis, a set of parameters was chosen. The PEG M\textsubscript{n} was varied from 400, 3400, and 6000 in order to determine the characteristics of these microgels. It was established that there is an optimum maximum degree of crystallization of mP3400 as a result of the chain length between crosslinks, as determined by DSC and WAXD. Furthermore, water sensitivity and absorption of the microgels is proportional to the degree of crystallinity of the microgels and the PEG M\textsubscript{n}.

References


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CHAPTER IV
MICROGELS IN A POLYURETHANE MATRIX VIA AQUEOUS DISPERSIONS

Abstract

The following work investigates the addition of polyurethane PEG based microgels (at 5, 25 and 45 wt %) to a polyurethane dispersion in an effort to determine miscibility and interactions of the dispersion and properties as a thin film. The viscosity must be fully understood in order to determine the amount of interaction and dispersability of the gels within the dispersion. In the formed composite films, the modification of thermal, mechanical, and water sensitivity should be understood. In NMP based polyurethane systems, the viscosity effect on the dispersion and the plasticizing effect on the film should be quantified.

Introduction

Microgels have been widely studied in the past 35 years for a variety of applications including drug delivery, coatings technology, and as a template for the synthesis of metal nanoclusters.¹

In the area of drug delivery, microgels have been researched for carriers of drugs including bioactive molecules, replacement of soft tissues, wound healing, ophthalmologic applications, and materials for medical devices.²³

In coatings technology, microgels are of interest because of their rheological behavior in latex formulations and their reinforcing properties in cured films. The particle size and swellability can be easily tuned by altering the microgel crosslinking density and the monomer composition. This allows for a range of behaviors that can
result from microgel addition to formulations. Microgels having low swellability because of the monomer composition and high degree of crosslinking can result in low degrees of viscosity modification even at high solid content, while microgels having high swellability as a result of low crosslink density and monomer composition result in a large effect on a formulations pseudoplastic behavior. The first species are suitable as binders in high-solid paints, and the second type can be used as rheology control agents in high-solid and water based systems. This viscosity behavior of microgel containing paints helps to improve application properties, especially to achieve high film thickness without sagging and flake orientation in metallic coatings.4

For similar reasons of viscosity modification, microgels have been added to UV-curable coatings in order to reduce the viscosity of the formulation instead of typical reactive diluents that are usually linear polymers or oligomers.5-9

Porter filed the first patents in 1978 indicating the rheological properties of microgel dispersions10 and then Backhouse in 198211. Porter demonstrated that the combination of acrylic resins and acrylic polymer microgels increased film thickness in solvent- or waterborne paints eliminating sagging or popping. This resulted from the orientation in solventborne metallic top coats. Backhouse’s research involved the addition of swellable crosslinked polymer microparticles with diameters in the range of 0.01-10 μm to a waterborne base coat in a process involving a base coat/clear coat multilayer coating.

Densely crosslinked microgels lead to improved film properties when they are used as fillers in place of inorganic particles. These properties include mechanical properties like elasticity, hardness and stone chip resistance or impact flexibility. The
presence of pre-crosslinked polymer structure and the existence of separate microphases in the polymer film, allow for enhanced energy dissipation during impact. Early on, in 1967 ICI demonstrated the use of crosslinked microgels, with a low $T_g$, in coating formulations to improve mechanical properties.

In other research involving latex biocatalytic coatings, microgels are being added to coatings in order to host living organisms and enhance their stability and efficiency of use. These systems are being looked at for applications in biosensors, bioelectronic devices, and industrial biocatalysts. This type of polymer coating was first investigated in the early 1980s by Eastman Kodak, specifically, coatings containing enzymes and antibodies with color indicators for use in dry reagent clinical chemistry.

Gel based microbial immobilization systems are not ideal because of their poor mechanical properties, their thicknesses of 100's of microns which limits mass transfer, and their pore size is typically larger than the microorganism. In addition, storage of these materials containing enzymes has shown to be limited, where after a specified time, large losses in activity occur. Currently whole cells are being looked at as biocatalysts in the chemical process industry, and this type of formulation would enable a more robust whole cell with storage and shipping made possible without loss of activity. It has proven very difficult to trap living organisms such as bacteria, yeast or fungi into a nanoporous matrix of partially coalesced polymer particles. This is a result of many factors or variables being involved such as film thickness, microstructure, diffusion properties, cell density, and manufacturing processes.

Microgels as composites within organic coatings alter the final film elastic modulus significantly. In work by Gindre and coworkers, styrene based particles of
different cross link densities, formed by emulsion polymerization were studied. It was found that increasing the crosslink density of the particles led to a rise in the elastic modulus.21

In terms of rheological impact of microgels in polymer films, addition of microgels has been a method used in the coatings industry since the 1970's. There are also many other ways to modify the rheology of formulations. Microgels have the advantage of giving the formulation pseudoplastic qualities which are of particular interest in waterborne systems. Microgels in electro-deposition coatings have shown to perturb the flow of the surrounding fluid in a low shear field during the curing process which in turn provides edge protection.22-24

Microgel modifications of crosslink density and size allow fine tuning of the shear thinning behavior and alter elasticity.25,26 Swelling ratio and microgel concentration affect steady shear and dynamic properties of the formulations.27,28,29 The volume the microgels occupy in the formulation as well as the degree of aggregation among the particles are key parameters in altering rheological properties of organic coatings.30-36

In this research, fully crosslinked, ready made poly(ethylene glycol) polyurethane microgels have been added to a polyurethane dispersion and the effect of the composite microgel on the dispersion rheological properties and final film properties have been examined. Also the microgel water absorption is characterized by phase contrast microscopy and compared to microgel water absorption unconstrained in the film matrix.
Experimental

**PU Dispersion Preparation**

Butyl adipate phthallene (Desmophen S1019-120 Polyol 1000 MW 120 OHV),
dicyclohexylmethane diisocyanate, Desmodur® W was provided by Bayer in Pittsburgh,
PA. 2-Methylpentamethylenediamine (DYTEK® A), triethyl amine (TEA), 1-methyl-2-
pyrrolidone (NMP), PEG 400 and 6000, and acetone were purchased from Sigma-Aldrich
in St. Louis, MO. 1,4-Cyclohexane di-methanol (CHDM) from Eastman Chemicals in
Kingsport, TN. Dimethylolpropionic acid (DMPA) and dibutyl tin dilaurate (DBTDL)
from Aldrich in Milwaukee, WI.

**Phase Contrast Optical Microscopy (PC-OM)**

PC-OM was completed with a Nikon OptiPhoto II scope operating in phase
contrast mode with a Nikon Digital Eclipse DXM 1200 CCD camera. A Mettler FP90
hot stage was utilized in combination with the Nikon OptiPhoto II scope operating in
birefringence mode in order to determine the degree of crystallinity as a function of
temperature.

**Scanning Electron Microscopy (SEM)**

FEI Quanta 200 Scanning Electron Microscope (SEM) was used under high
vacuum, with a spot size of 4-4.5. Samples were prepared by adhering films with epoxy
to AFM specimen discs of 12 mm and sputter-coated using an Emitech k550X gold
sputterer with a thickness of 10 nm under argon gas. A coating current of 25 mA was
used. The films were cooled to -100°C using a Leica EM FC6 microtome with the low
temperature liquid nitrogen, a cryo 45° Diatome diamond knife, and the knife holder, Leica Ultracut UC6. The films were sliced in order to observe the cross section by SEM.

Film Preparation

Films used for dynamic mechanical analysis (DMA), rheology studies, and mechanical testing were prepared by adding 0-45 wt % based on solids of dehydrated crosslinked microgel particles in powder form to the final polyurethane dispersion. These solutions were then mixed for 48 hours in a Heidolph Reax 2 rotating mixer. Films were then drawn at a thickness of 5 mils on polyolefin plates. The films were then air dried for 48 hours, placed in a vacuum oven at 50°C for 48 hours and mechanical properties were characterized. Further treatment of films involved soaking them in 100 mL of de-ionized water for 48 hours.

To determine extractable content in the films, various solvents including hexanes and acetone were used to swell the films over 48 h and extract both polar and nonpolar small molecules. These solvents were then analyzed by a Varian FID TSD CX Series Star 3400 Gas Chromatograph with 120 Volts and 50/60 Hzs.

Rheological Measurements

The viscoelastic measurements were done Physica MCR 501 rheometer with Couette and 25 mm diameter cup. To prevent dehydration of the PU-hydrogel dispersions, a thin layer of low-viscosity silicone oil was applied to the air/sample interface. In this study, the following rheological experiments were performed:

1. Strain sweep at a constant temperature and frequency range of 0.1-100 rad/s to obtain the linear viscoelastic range of the dispersions.
2. A time sweep at a constant temperature and frequency to obtain steady state and thus ensure that the measurements were carried out under equilibrium conditions.

3. Frequency sweep at a constant temperature (20 °C) in the linear viscoelastic region (strain amplitude ≤10% strain) to obtain the dynamic shear viscosity. The zero shear viscosities ($\eta_0$) of the dispersions were calculated by fitting the $|\eta^*|$ versus $\omega$ data to the Cross model by the following Equation:

$$\eta = \frac{\eta_0}{1 + (\omega / \omega_c)^\beta}$$

Equation IV-1

where $\eta_0$ is the zero-shear viscosity, $\omega_c$ is the critical shear frequency value at which the viscosity decreases to half its initial value and $\beta$ is a material constant that depends on the nature of the dispersion. Equation 1 was used to calculate $\eta_0$ as a fitting parameter to the experimental results using non-linear regression analysis.

**PU Dispersion Synthesis (PUD)**

PU preparation was carried out in a 500 mL four-necked flask with a mechanical stirrer, thermocouple, a condenser equipped with a nitrogen bubbler, and a pipette outlet. To the reactor, 65.7 g of the polyester diol (0.071 hydroxyl equiv), 8.74 CHDM, and 8.8 g of DMPA (0.046 hydroxyl equiv, 0.023 acid equiv) were charged. While mixing, 74.9 g of NMP was added, and stirring was continued until a homogeneous mixture was obtained. Dicyclohexylmethane diisocyanate (81.1 g, 0.19 isocyanate equiv) and 4 drops of DBTDL were added dropwise with continued stirring at 60 °C for 1 h and then raised to 85°C approximately 4 h until the theoretical NCO value of 3.6% was reached. Upon reaching the theoretical NCO value, the prepolymer was chain extended with 2-methyl-
pentamethylene 1,5-diamine (9.3 g, 0.053 hydroxyl equiv), and the reaction was allowed to continue for 2 h to finish the polymerization. The final polymer was neutralized by the addition of 6.6 g of TEA (0.023 equiv) and stirred for 30 min while maintaining the temperature at 55 °C. (Figure IV-1) The particle size was unimodal with a range of particle sizes from 30-400 nm with the majority having a size of 50 nm.

**Figure IV-1.** Synthesis of PU dispersion by prepolymer preparation.

Results and Discussion

Microgel impact on the zero shear viscosity ($\eta_0$) of the polyurethane dispersion (PUD) is such that there is a small effect on viscosity with the addition of 5% microgels based on PEG 3400 (mP3400). (Figure IV-2) In Figure IV-3, zero shear viscosity is on
the ordinate and PUD weight % solids is on the abscissa and each line represents mP6000 microgels at 5, 25, and 45 wt % based on PUD solids. However, once 25% mP3400 are added to the PU dispersion there is a large jump in $\eta_0$. As the mP3400 content was increased further to 45 wt %, there was a less drastic increase. This indicates that there is a maximum amount of interaction that can occur between the microgels and the PU dispersion. Also as expected, as the number of particles in solution increases, so does the $\eta_0$ in which the relationship between the two can be see in the Einstein Equation.

![Figure IV-2. Zero shear viscosity as a function of polyurethane solids %](image-url)
Figure IV-3. Zero shear viscosity as a function of microgel wt % in PU dispersions of 20-30% solids.

In Figure IV-3, zero shear viscosity, $\eta_0$ is on the ordinate, PEG $M_n$ reactant to the microgels on the abscissa, and 45 wt % microgels in 20, 25, and 30 wt % PUD represented by each line. It is interesting to note that there is a small change in viscosity with 400 and 3400 PEG $M_n$ based microgels; however, with mP6000 there is a drastic increase in viscosity and a large change with a small increase of 5 wt % PUD solids. This indicates more interactions are taking place between the mP6000 microgels and the PUD particles which may be a result of the larger mesh size of mP6000 relative to mP3400 and mP400.
Figure IV-4. Zero shear viscosity as a function of microgel PEG M₆ component at 45 wt % microgels in blank solids % PU dispersion.

In Figure IV-4, η₀ is on the ordinate, wt % of mP6000 in PUD is on the abscissa from 0 to 45 wt % and each line represents 20, 25, and 30 wt % PUD particles. Even though the results are as expected, i.e. η₀ increases as more particles are added, it is interesting to note that the effect of 25 wt % microgels is much more significant than the increase that takes place from 25 to 45 wt %. This indicates that there may be a maximum or optimum amount of interactions that can take place and further addition of microgels has minimal effect on the η₀.
Figure IV-5. Relative crystallinity of microgels determined by WAXD.

The relative crystallinity of the microgels was determined by wide angle x-ray diffraction. A small degree of crystallinity exists for mP400 and a much larger degree with mP3400 as the distance between crosslinks increases. (Figure IV-5)

Once the microgels are added to the films, crystallinity can be seen in the films by optical microscopy in birefringent mode. (Figure IV-6) The PU films containing 0% microgel exhibits no birefringence and no light appears in the image. However, as microgels are added, there is increasing birefringence in the images from 5-45 wt %. This indicates that the microgels are not strongly interacting with the PUD in film form because they are not inhibited from forming crystalline lamella.
Soaking of the PU films in water revealed a counterintuitive effect of microgel addition on the equilibrium weight in water, obtained after 3 weeks. The inclusion of 5 wt % microgels had the expected effect of increasing water uptake of the PU films.

(Figure IV-7)
The films containing 5 wt % microgels showed an 11 to 17.5% increase in weight as a result of microgels in the polyurethane films. This compares with a 10 wt % mass increase in the film without microgels. The film containing 0% microgels took up 9.7 wt % mass at equilibrium absorption in water which is lower than the film containing 5% microgels. It should be noted that at 5 wt % the water uptake does not follow the trend of equilibrium swelling of the microgels unconstrained in a film. Instead of increasing equilibrium swelling as the PEG \(\text{M}_n\) reactant increases, the microgels in the PU films swell with water from 3400 to 6000 to 400 PEG \(\text{M}_n\) of the microgels. This indicates that there are other factors involved in the increased water uptake of the films besides the microgels themselves. These factors could include enhanced free volume, more permeable films, or the increase surface area of the PU phase domains allowing for more swelling of the PU matrix. However, once microgel content increases to 25%, instead of an expected increase in water absorption, there is a decrease in mass % in water.

The unexpected loss in mass can be traced back to morphology. At higher gel contents there is the formation of a continuous microgel phase. The continuous network created at 25 wt % microgels in the films allows for those microgels on the surface and close to the surface to migrate out of the film since there is no chemical bond between the film and microgels. Generally the mass of \(\text{mP3400}\) is lower than \(\text{mP400}\) and \(\text{mP6000}\) as a result of the more porous nature and enhanced aggregation as seen by SEM images of freeze dried cross section of films in Figure IV-8.
It is apparent from Figure IV-8 that gel particles appear homogeneous throughout the film, create a continuous phase at 45 wt % and mechanical properties are more spongy when dehydrated.

There is a large degree of aggregation of the microgels taking place in these films as can be seen in Figure IV-9, where at 5% mP3400. The large particle size distribution from 100 nm to 4 microns can be seen, but also the aggregation of larger particles is apparent.

Figure IV-8. (a) Film with 45% mP400, (b) 45% mP3400, (c) and 45% mP6000.
The films containing 25 wt% dehydrated microgels also demonstrated homogeneous distribution of microgels over the cross section of the film, but also areas of localized aggregation (Figure IV-10).

The same trend can be seen in films containing 45 wt% of mP3400. There are regions of continuity emerging in the film between the microgel phase and the polyurethane dispersion matrix. (Figure IV-11) There are also regions of aggregation that create voids in the film cross section. This results from the microgels not being
covalently linked and easily dislodging from the film as the diamond knife cuts the sample.

*Figure IV-11.* 45% 3400 microgels in PU film illustrating multiple aggregates creating continuous porous matrix, homogeneously distributed in the cross section of the film.
Phase Domain Determination by Phase Contrast Optical Microscopy (PC-OM) and Small Angle Light Scattering (SALS)

Phase domain behavior of PU films after storage over a range of relative humidities can be observed using phase contrast optical microscopy (PC-OM). PC-OM images of PU films containing mP3400 microgels from 0-45% at 0, 75, and 100% RH are shown in Figure IV-12 and Figure IV-13. There is no visible change in the films by PC-OM at 25 and 50% RH in comparison to 0% RH, but at 75% RH there is a large change in the films.

![PC-OM images with inset CFT detailing phase behavior of microgels in films with varying RH, scale bar = 50 μm.](image)

*Figure IV-12.* PC-OM images with inset CFT detailing phase behavior of microgels in films with varying RH, scale bar = 50 μm.

In Figure IV-12 and Figure IV-13, the PU film containing 0 wt % microgels shows typical phase separation behavior of hard and soft domains in the film giving no macroscopic phase separation. The difference in phase domains of just 5 wt % microgels at 100% RH compared to the film containing 0 wt % mP3400 from 0 to 100 % RH
indicates the drastic difference in water sensitivity with the addition of the microgels to the PU films. (Figure IV-12)

Once microgels are added to the film, smaller domains are observed and attributed to the microgels that are well dispersed, yet create small heterogeneities in the film. As the wt % of microgels increases from 5 to 45 wt %, there are a proportional number of phase domains that appear, indicating more and more heterogeneities created in the film. (Figure IV-13) This is also confirmed by PC-OM, in which the control film shows no indication of phase separation, but once the microgels are added, film defects occur.

As the relative humidity increases, the presence of phase domains becomes apparent as water rich regions develop and then grow at 100% RH. These large domains are also very apparent in the PC-OM pictures at 25 and 45 wt % where the darker regions indicate the phase separation and water rich domains.

Figure IV-13. Phase behavior of mP3400 at 25 and 45 wt % in films with varying RH, scale bar = 50 μm.
Conclusions

The addition of hydrophilic microgels to an anionic polyurethane dispersion was found to yield stable aqueous solutions that showed a large increase in viscosity with hydrogel at 25 or higher wt %. This indicates a large degree of interaction between the two systems, particularly between mP6000 and the PUD as a result of the larger mesh size. Films formed from these products showed a relatively even distribution of the microgels across the film. Soaking the films in water at 5 wt % microgels resulted in enhanced water uptake and little diffusion of the microgels trapped in the film. However, soaking the 25 and 45 wt % microgel containing films in water resulted in the formation of a porous structure, as the microgels appeared to have diffused out of the film. This mobility shows that there was no significant interaction of the microgels with the continuous phase. Microgel addition created a more water sensitive film as seen by the increase in water rich domains as demonstrated by PC-OM images at RH of 0-100%. Also the phase domain size and number is significantly altered by the addition of microgels over the range of humidities.

References


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CHAPTER V

MICROGELS IN UV POLYMERIZED CROSSLINKED FILMS

Abstract

UV-curable thiol-ene and hexaacrylate films were prepared with thiol:ene:acrylate ratios of 8:8:3 (37 wt% hexaacrylate) and 8:8:5 (62 wt% hexaacrylate). To these films, polyurethane poly(ethylene glycol) (PEG) based crosslinked microgels were dispersed in the monomer solutions with varying PEG Mₙ and wt% of microgels. Properties including crosslink density, heterogeneity of the network, and morphology of the microgels in the matrix were studied as a function of composition. Resulting thermal and mechanical properties including water absorption were also studied. Addition of microgels into the UV cured films resulted in increased heterogeneity in the crosslinked network along with reduced crosslink density ($\overline{M}_c$) as determined by DSC and DMA. In addition, the microgels changed the morphology of the cross section of the films, as concluded by AFM phase imaging. The water absorption was enhanced with larger PEG Mₙ of the microgels and with increasing microgel content. Conversion rates and equilibrium conversions of thiol-ene and acrylate functional monomers were not significantly affected by the addition of microgels.

Introduction

The use of UV-curable coatings are rapidly expanding in industry to replace thermally cured coatings as a result of their high solids content, lack of volatile organic compounds, speed of cure, and energy efficiency. These coatings result in higher productivity and an alternative way to coat heat sensitive substrates. Radiation cured
coatings can be found in products ranging from wood, plastic, and metal, to varnishes, inks, and adhesives.\textsuperscript{1} Moreover, UV formulations contain no solvents which lend to an environmentally friendly process along with cost savings for the consumer and the manufacturer. In order to decrease the viscosity of these systems, reactive low molecular weight multifunctional diluents are added.\textsuperscript{2} However, these additives dramatically change the resulting film properties. An alternate route to modifying the solution viscosity is beginning to emerge.\textsuperscript{3} Polymer microgels decrease the viscosity of formulations more efficiently than linear additives because of their compact structure. Furthermore, to obtain thixotropic or shear-thinning behavior, a large volume fraction of microgels can be added to the system without significantly increasing the low shear viscosity.\textsuperscript{4-7}

There are typically two stages of network formation in the photopolymerization of polyfunctional acrylates. First, the heterogeneous formation of nanoscale gelation occurs forming highly crosslinked localized gels in monomer solution, then these microgels link together to form a less densely crosslinked network. This process creates a very heterogeneous network.\textsuperscript{8-10} As a result, networks formed from multifunctional monomers in an acrylate polymerization have inherent problems with the control of size of the cluster, the molecular weight between crosslinks (\(M_c\)), and the density distribution. Information about the morphology can be found by light scattering techniques.\textsuperscript{11,12} While information about the average molecular weight between crosslinks can be found by analysis of the modulus in the rubbery plateau region by dynamic mechanical analysis.\textsuperscript{13}

Urethane acrylates are often used in UV systems because of their combination of characteristics including high abrasion resistance, toughness, tear strength, and also
desirable low temperature properties. They also are known for their optical properties and weatherability.\textsuperscript{14-16} In work done by Michelle and coworkers, urethane acrylates greatly enhanced the fracture toughness and puncture resistance of optical fiber coatings.\textsuperscript{17}

\textit{Figure V-1.} Mechanism of thiol-ene polymerization.\textsuperscript{18}

Thiol-ene systems have very uniform crosslinked networks due to high conversion as a result of the high degree of mobility throughout the polymerization. This high degree of mobility is a result of the late onset of gelation due to the reaction following a step growth path (Figure V-1) which involves gelation at higher conversions than for acrylates. This can be illustrated by the narrow tan δ peak of the film obtained by photocuring a mixture of a 1:1 molar ratio of trimethylolpropane tri(3-mercaptopropionate) with triallyl ether and 1 wt % DMPA. (Figure V-2)
Another important quality of thiol-ene systems is their resistance to oxygen inhibition. This is a result of the hydrogen abstraction of a thiol hydrogen by peroxy radicals that are formed by the reaction of carbon-centered propagation radicals with oxygen. The resulting thiyl radicals add to vinyl bonds to maintain propagation.\textsuperscript{18,19} This allows thiol-ene systems to photopolymerize rapidly in air as opposed to inert conditions as needed for acrylate photopolymerizations.\textsuperscript{20-22}

In this work we have evaluated the structure and morphology of films containing PEG based hydrophilic microgels in UV cured crosslinked films composed of thiol-ene and acrylate moieties. The impact of thiol, ene, and acrylate conversion in the UV film with the addition of microgels was determined. Furthermore, the moisture uptake, physical, and thermal properties were determined as a function of the composition.
Experimental

Materials, Compounds, and Sources

Trimethylolpropane tri(3-mercaptopropionate) and pentaerythritol triallyl ether were supplied by Sigma-Aldrich in St. Louis, MO. Hexaacrylate CN 968 was supplied by Sartomer Company Inc. in Exton, PA. Irgacure 651, dimethoxy-2-phenylacetophenone, was received from Ciba Specialty Chemicals. Steel Q panels, type R, cold rolled steel, 3’x5’, of 0.8mm thickness, and meeting ASTM specifications A1008/1010 were received from Q-Lab Corporation in Cleveland, Ohio.

Film Preparation and Irradiation

Films of thiol-ene and acrylate were drawn out on Q panels of 3’ x 5’ using a draw down bar to give a 5 mil wet film thickness. Films were cured on a Fusion curing line system with a D bulb (3.0 W/cm², belt speed= 3.05 m/min, five passes). Thick samples (4-mm thick) were irradiated with a low-intensity, 254-nm, low-pressure mercury lamp (0.1mW/cm²) in air.

Real-Time Infrared (RTIR)

Real-time infrared (RTIR) spectra were recorded on a modified Bruker 88 spectrometer. UV light from an Oriel lamp system equipped with a 200 W, high-pressure mercury-xenon bulb was channeled through an electric shutter and fiber-optic cable into the sample chamber. Photoreactions were conducted by sandwiching samples between two sodium chloride salt plates at a thickness of 20 μm. The salt plate edges were sealed with vacuum grease to suppress monomer leakage, and the optics chamber was purged for 10 min in dry air before irradiation. Light intensity measurements were made with an
IL-1400 calibrated radiometer from International Light. Infrared absorption spectra were obtained under continuous UV irradiation at a scanning rate of 5 scans/s. The unfiltered light intensity at full arc was 187 mW/cm². All samples contained 1 wt% photoinitiator, Irgacure 651 (2,2-dimethoxy-2-phenylacetophenone).

The characteristic infrared absorbance bands used to monitor the disappearance of the reactant and monomer during the photoreactions were as follows: acrylate at 812 cm⁻¹, thiol at 2570 cm⁻¹, and ene at 3080 cm⁻¹. The reactant conversions calculated from the change in the peak area with time have an approximate error of 2%.

**Dynamic Mechanical Analysis (DMA)**

The visco-elastic properties of the films were measured using a TA Q800-0193 Dynamic Mechanical Analysis (DMA) instrument equipped with a tension/film clamp. The settings were such that a temperature ramp/frequency sweep was performed at a strain of 0.1%, a preload force of 0.01 N, a force track of 125%, an initial frequency of 1 Hz, a temperature range of -150 to 100°C at 2°C/min. The Poisson ratio was set at 0.444 with minimum dynamic force of 1x10⁻⁵ N, and the clamp was floated using an air bearing.

**Differential Scanning Calorimeter (DSC)**

Thermal properties were measured using a Q1000 DSC from TA Instruments with nitrogen flow of 22 mL/min at a heating rate of 10 °C/min and a scan range from -80 °C to 150 °C. Thermal properties resulting from the first heating scan were reported. Calibration was performed using indium and zinc standards, and the heat flow calibration was established using sapphire standards. Values reported for the melting (Tₘ) and
crystallization temperatures ($T_c$) are those at the minimum and maximum of endothermic and exothermic peaks, respectively.

**Results and Discussion**

The chemical structures of trithiol, trimethylolpropane tri(3-mercaptopropionate), and the tri-ene, pentaerythritol triallyl ether, are shown in Figure V-3.

![Figure V-3](image1.png)

Figure V-3. (a) Trimethylolpropane tri(3-mercaptopropionate) and (b) pentaerythritol triallyl ether, thiol-ene UV monomers tri functional thiol and ene.

The acrylate component, dipentaerythritol hexaacrylate, is shown in Figure V-4. Because of the high functionality of the hexaacrylate, the crosslink density of the trifunctional thiol-ene system increases with its incorporation.

![Figure V-4](image2.png)

Figure V-4. Idealized structure of dipentaerythritol hexaacrylate.
The thermal properties of the cured thiol-ene films (TE-A0), hexaacylate (A100), (Figure V-5) and acrylate thiol-ene films (37 and 62 wt% hexaacylate content: TE-A37 and TE-A62 respectively) were analyzed by DSC. (Figure V-6)

![DSC spectrum of (a) A100 and (b) TE-A0.](image)

*Figure V-5.* DSC spectrum of (a) A100 and (b) TE-A0.

As more acrylate content is added to the thiol-ene, the $T_g$ becomes broader indicating an increasingly heterogeneous network, which is typical of acrylate photo-cured films.$^{18}$

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Figure V-6. DSC traces of TE-A37 and TE-A62.

Since the transitions of the films in Figure V-6 are very close to the freezing point of water, the possibility that water may be absorbed by the films and plasticizing them was investigated by TGA. (Figure V-7) Less than 1% of volatile content is lost before 200 °C and less than 2% is lost before 350 °C. This indicates that the T_g seen in Figure V-6 is not significantly plasticized by water.
128

The microgels were readily dispersed (10 wt%) into the 1:1 thiol-ene monomer mixture. However, upon photopolymerization phase separation occurred and the microgels partitioned into a powder layer on the substrate. (Figure V-8)

Figure V-7. TGA spectrum of TE-A37.

Figure V-8. (a) Thiol-ene (1:1 molar ratio of functional groups) film with powdery surface, (b) residue on glass slide, (c) powdery nature of residue.

It was confirmed by DSC that the residue on the glass slide was mP6000 due to the $T_m$ at 50 °C that is characteristic of microgels based on PEG of $M_n$ 6000 (mP6000). The dehydrated microgel’s thermal transition, before being placed in the monomer solution, is shown in Figure V-9. The DSC trace of the residual layer remaining on the glass after
curing is almost identical indicating that this layer is mP6000, which was partitioned out of the thiol-ene network. The thiol-ene network with 0 wt% microgels shows only a T_g. (Figure V-10). However, the film formulated with 10 wt% indicates that not all microgels migrated out of the thiolene film as indicated by the appearance of a T_m at 50 °C. (Figure V-11) Approximately 1/3 the original weight of microgels was collected from the glass slide surface indicating 2/3 of the microgels were trapped in the film. This was only true of samples cured on glass substrates. When polyolefin was used as the substrate, all of the microgels migrated to the surface of the film.

Figure V-9. DSC illustrating the T_m of mP6000 before being added into thiol-ene films.
Figure V-10. DSC of thiolene film with 0 wt% mP6000, 10 wt% mP6000, and residue left on glass slide after UV cure.

Figure V-11. Thiol-ene film formulated to contain 10 wt% mP6000.

It was found that 37% hexaacrylate was sufficient to lock the microgels in the film, leaving no powder layer on the substrate. (Figure V-12) Moreover, clear films
(Figure V-13) were formed (whereas TE-A0 films containing 10 wt% mP6000 were opaque, signifying a large degree of phase separation).

<table>
<thead>
<tr>
<th>wt% hexaacylate:</th>
<th>0%</th>
<th>37.5%</th>
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</table>
| @10 wt% microgels | ![Image](image)

*Figure V-12.* Illustration demonstrating behavior of microgels in UV films with varying wt% of hexaacylate in thiol-ene films.

*Figure V-13.* Clear TE-A37 film containing 10 wt% mP6000.

Microgels, from 0.1 to 10 wt%, were dispersed in the monomer mixture of 37 wt% hexaacylate with the thiol-ene (TE-A37). The films were then drawn and cured. The resulting thermal transitions, measured by DSC, are shown in Figure V-14. The PEG Tₘ attributed to mP6000 becomes evident as 5 and 10 wt% microgels are added to the film. This crystallization is confirmed by the presence of birefringence that disappears around 50 °C as the films are heated due to melting of the microgels in the film, determined by optical microscopy.
Figure V-14. DSC plot of TE-A37 containing various amounts of mP6000 microgels. The same trend is seen in thermal properties of TE-A62 film. As microgels are added, the mP6000 $T_m$ at 50 °C becomes more apparent.

Figure V-15. DSC plot of films of TE-A62 containing various amounts of mP6000 microgels.

TE-A0 has a defined and abrupt drop in the storage modulus around 0 °C due to the regular crosslink density. A100 film was too brittle for mechanical measurements to
be performed by DMA below room temperature with the tensile film clamp. It can be
deduced, however, that the crosslink density is much higher for A100 than TE-A0 as seen
by the higher value of the rubbery plateau which is proportional to the crosslink density
($\bar{M}_c$). (Figure V-16) This relationship is expressed in Equation I, where R is a constant,
T is the temperature at which the storage modulus is observed, $\rho$ is the density of the
material, and $G'$ is the storage modulus rubbery plateau value at a specified temperature.

$$G' \propto \frac{1}{\bar{M}_c}$$

Equation V-1

Addition of acrylate content, results in a higher crosslink density as demonstrated by the
increasing value of the storage modulus at 100 °C in the rubbery plateau region. (Figure
V-16)

![Graph showing storage modulus and acrylate effect](image)

*Figure V-16.* Storage modulus and the effect of acrylate on thiol-ene films.

Modulus measurements by DMA of TE-A37 with 0.1-10 wt% microgels confirm that as
microgels are added to the films, heterogeneity increases in the network. This
heterogeneity is indicated by the decreasing value of the rubbery plateau at 100 °C with
increasing mP6000 concentration (0-10 wt %). (Figure V-17)
Figure V-17. Storage modulus of 37 wt% hexaacrylate films in thiolene with addition of 0-10 wt% mP6000.

Figure V-18. Effect of microgels content on TE-A37 films storage modulus plateau at 100 °C.

The tan δ plots of TE-A0 is characterized by a sharp transition or peak before 0 °C for the thiol-ene film, while A100 has a very broad transition over the measurement temperature range of 25 °C to 125 °C. (Figure V-19) Once again, with the addition of
hexaacylate, there is a shift in the $T_g$ to higher temperatures and the transition broadens, indicating a more heterogeneous structure.

![Graph](image)

**Figure V-19.** Tan $\delta$ plot of increasing hexaacylate wt% in thiolene films.

The tan $\delta$ maximum temperature of 10 wt % mP400, mP3400, and mP6000 in TE-A37 and TE-A62 does not shift significantly, indicating that there is no significant difference in $T_g$ as PEG $M_n$ increases. (Figure V-20 and Figure V-21)
Figure V-20. Tan δ maximum of TE-A37 films as a function of microgel content.

Figure V-21. Addition of mP400, mP3400 and mP6000 at 10 wt% in TE-A37.

Microgels of Mn 400, 3400, and 6000 (mP400, mP3400, and mP6000 respectively) were next added to the TE-A37 and TE-A62 film and the storage modulus rubbery plateau at 100 °C (st) and the tan δ maxima (td) were measured by DMA and are summarized in
Table V-1. There is a reduction in crosslink density, demonstrated by the decreasing rubbery plateau value at 100 °C of the films from mP400, to mP6000, to mP3400 which coincides directly with the degree of crystallinity of the microgels.

Table V-1.

*Tan δ Peak Maxima (°C) and Storage Modulus Rubbery Plateau's (MPa) Reported as a Function of Acrylate Content and Microgel Content.*

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Storage modulus (st) reported in MPa, tan δ (td) reported in °C

In tan δ plots of mP6000 from 0-10 wt% in TE-A37 and TE-A62, as microgel content increases, the Tg indicated by the tan δ maximum at 60° for TE-A37 and 80 °C for TE-A62 significantly broadens. This correlates to a greater distribution of molecular weight between crosslinks or a more heterogeneous matrix.

AFM phase images of the TE-A62 film, obtained by hard tapping, exhibit phase morphology with yellow regions attributed to higher Tg presumably with higher acrylate
content. This morphology demonstrates the regular, yet heterogeneous, structure of the film. (Figure V-22)

*Figure V-22. Phase image of 1 μm control TE-A62 film.*

With the addition of 1 wt % mP400 (Figure V-23) and 10 wt% mP400 (Figure V-24) there is a large change in morphology to a more "pebbly" texture with the white regions indicating the presence of microgels. The irregular regions increase in number and size as microgel content increases. At 10 wt%, microgels begin to aggregate. (Figure V-23)

*Figure V-23. Phase image of 1% mP400 in TE-A62 films.*
Phase Domain Behavior by Small Angle Laser Light Scattering (SALS) and Phase Contrast Optical Microscopy (PC-OM)

The effect of added microgels on water uptake behavior and resulting phase domain formation of these UV films over a range of relative humidities (RH) can be examined using PC-OM and SALS. (Figure V-25) The TE-A37 films were observed over a range of RHs with 0-10 wt% microgels. At 0 % RH there is no appearance of phase domains due to microgel addition indicating that the microgels are homogeneously distributed throughout the film or that they have a refractive index that is too similar to the surrounding matrix and are not discernible. (Figure V-25a)

There is little difference seen in the films from 0 to 50 % RH. Once the films are exposed to 75% RH, phase domains appear in the films containing 5 and 10 wt% mP3400. (Figure V-25b) The water rich domains appear uniform throughout the film with 5 wt% microgels, but at 10 wt% the domains appear larger and their locations more heterogeneous. This appearance of large and scattered water rich domains is a result of aggregates of mP3400 within the film at 10 wt% mP3400. These dark regions confirm that water is localizing in mP3400 regions. (Figure V-25) The film containing 0 wt% mP3400...
mP3400 at 75% RH undergoes little visible change with the exception of slight surface deformation with water uptake.

\[\text{Figure V-25. (a) 0\% RH, (b) 75\% RH, (c) 100\% RH TE-A37 films containing mP3400.}\]

At 100 \% RH, there is little phase contrast in the PC-OM images as the thiol-ene acrylate matrix takes up more water. This is a result of the water rich regions becoming the continuous phase.
Equilibrium water absorption of TE-A37 films is proportional to PEG $M_n$ of the microgels as found by gravimetric studies. (Figure V-26a) However, once microgel water equilibrium water content is accounted for, it is apparent that PEG $M_n$ has little affect on water uptake of the films. (Figure V-26b) There is increased water uptake with increasing microgel content which confirms that there are other factors that are contributing to water uptake including micro cracks, voids, and increased surface area.

*a.*  
*Figure V-26.* (a) Equilibrium water absorption of TE-A37 UV films containing microgels and (b) normalized for microgel content.

*b.*  
*Figure V-27.* (a) Equilibrium water absorption of TE-A62 UV films containing microgels and (b) normalized for microgel content.
Because the hexaacrylate is more hydrophilic than the thiolene, TE-A62 takes up about 2% more water than TE-A37. Equilibrium water absorption of TE-A62 films containing microgels does not appear to be proportional to PEG Mn. This is most likely a result of a large degree of film defects such as microcracks and voids in the film containing mP400. Also, at 1 wt% microgel content, there is less water uptake than the film with 0 wt% microgels. This can be explained by the fact that the microgels may densify the heterogeneous network and also be restricted by the surrounding matrix from absorbing water. However, at higher wt% of microgels, the network may become more porous and have a higher number of film defects such as cracks and voids, along with higher surface area. This conclusion can be confirmed by the increase in water uptake % of the matrix containing mP400 and mP6000, once microgels and their water uptake are accounted for.

The reaction conversion plots of TE-A37 and TE-A62 films containing the functionalities thiol, ene, and acrylate, were measured by real-time FTIR. 10 wt% mP6000 slows the rate of conversion of all functionalities slightly and reduces the terminal conversion of the thiol and acrylate moieties concomitantly. (Figure V-28)

It is interesting to note that the acrylate double bonds at 812 and enes at 3080 cm\(^{-1}\) with TE-A62 films, react at a slower rate and have a lower terminal conversion than the TE-A37 film. This is due to the reduced mobility resulting from the higher percentage of hexaacrylate in TE-A62 films causing gelation early in the polymerization,
Figure V-28. Real time IR of (a) thiol 2570 cm⁻¹ (b) ene 3080 cm⁻¹ (c) acrylate 812 cm⁻¹.
Conclusions

UV cured films based on a hexaacrylate and thiol-ene mixtures at ratios of 3:8 (37 wt%) and 5:8 (62 wt%) were prepared. The addition of the hexafunctional acrylate to thiol-ene at a minimum content of 37 wt % allowed for the early gelation of the system and eliminates phase partitioning behavior once polyurethane PEG based microgels were added to the matrix. The PEG $M_n$ of the microgels was varied in order to determine the impact of this factor on the morphology of the microgels and the resulting thermal and mechanical properties of the films.

Addition of microgels to the UV films resulted in increased heterogeneities in the crosslinked network along with reduced crosslink density ($\bar{M}_c$) as seen by DSC and DMA. In addition, the microgels changed the morphology of the cross section of the films via AFM phase imaging. The water absorption properties increased with larger PEG $M_n$ of the microgels and with increasing microgel wt%. Conversion rates and equilibrium conversions of thiol-ene and acrylate functional monomers were not significantly affected by the addition of microgels.

References


CHAPTER VI
MICROGELS IN BIODEGRADABLE POLYESTER MATRIX PREPARED BY
SOLUTION CASTING

Introduction

Biodegradable polymer research has grown considerably due to the need for such materials in biomedical and environmental arenas. There is a long history of degradable polyesters and co-polyester research as a result of their physical properties and hydrolytic degradation which make them applicable in the areas of orthopedics, drug delivery matrices, and degradable sutures. The biodegradable polyesters commonly used in these applications are poly(lactic acid), poly(glycolic acid), and poly(ε-caprolactone), which primarily decompose into absorbable products by hydrolysis of the ester bond in aqueous environments. In addition, polylactide has been the focus of degradable polyesters research because of its adequate physical properties, degradation characteristics, and benign degradation products.

Polymer degradation can occur either by heterogeneous surface erosion or by homogeneous bulk erosion. In surface erosion, water is not able to readily infiltrate the bulk polymer and degradation occurs primarily in the outermost layers. In bulk eroding systems, water uptake is as fast as or faster than degradation. With the entire system in a hydrated state, polymer chains are hydrolyzed throughout. In this bulk hydrolysis, cleavage of the ester bonds occurs randomly. The parameters that most strongly affect the overall degradation rate of the polymer are the amount of absorbed water in the polymer, the diffusion coefficient of the contained oligomers within the polymer, and the solubility of degradation products. In poly(D,L-lactic acid) (PDLLA) systems, hydrolysis
of the ester bonds occurs throughout the matrix at the same rate. Degradation creates a higher concentration of carboxylic acid chain ends. Only chains that are soluble in aqueous media and close to the surface will leach out. Chains in the core of the film remain, lowering the pH in the polymer matrix, further speeding hydrolysis in these regions.9

The hydrolytic degradation kinetics of PDLLA have been well documented under specified conditions.10,11 The effect of end group functionality, either hydroxyl or carboxylic acid, on degradation rates is well known.12 It has been shown in multiple cases that as the content of mobile carboxylic acid groups increases within a system, hydrolytic degradation increases along with the rate of moisture uptake.13-15 The temperature and pH of the solution can also affect hydrolysis rates, with acidic media causing faster hydrolysis than neutral media.16,17,18

The progression of polymer degradation is monitored most commonly by dehydrated and hydrated mass loss as a function of time. Additionally, hydrolysis is quantified by gel permeation chromatography (GPC) with the appearance of low molecular weight oligomers.19 Also differential scanning calorimetry (DSC) is used to observe the change in thermal transitions over time as the polymer's oligomer content increases.18,20

Addition of Polyether Urethane Microgels and Their Degradation in Aqueous Media

Polyurethanes, specifically segmented polyurethanes consisting of hard or rigid urethane segments and soft or flexible polyether or polyester segments are suitable for many different types of applications including biomedical devices. Polyurethanes have been used as soft tissue interfacing materials since the 1970s and now have use in
pacemaker leads, diagnostic catheters, and compliant vascular grafts. Because of this application to biomedical devices, the susceptibility of polyether urethanes to hydrolysis and degradation has been thoroughly studied. In terms of hydrolysis in aqueous environments, hydrolysis of hard segments is one order of magnitude slower than the hydrolysis of ester groups. Therefore, poly(ether urethanes) are generally much more stable in aqueous environments. Their hydrolytic stability is largely dependant on the hydrophilicity and permeability to water, which are proportional to the degradation rate.

The type of isocyanate reactant used also affects the rates of polymer hydrolysis. Aromatic diisocyanates have proven to be less stable than aliphatic diisocyanates to hydrolysis in moderately acidic environments. The degradation of materials containing the hard segment dicyclohexylmethane diisocyanate (H12MDI) was compared to those containing methylene diphenyl diisocyanate (MDI). The material based on H12MDI had less crystallinity due to poor packing of chains, as a result of the mix of isomers. Conversely, the MDI based materials had efficient packing allowing for a higher degree of order within the hard segments. The material based on MDI also exhibited a lesser degree of degradation due to the extensive hydrogen bonding occurring between the hard segments, protecting the urea and urethane linkages from degradation. While relatively stable in comparison to poly(ester urethanes), poly(ether urethanes) are subject to oxidative degradation including environmental stress-cracking and metal ion oxidation.

In this research, poly(ether urethane) microgels are incorporated into a PDLLA matrix in order to determine the impact on thermal and mechanical properties. Additionally, an understanding of the diffusion pathways of water into the matrix and
oligomers out of the matrix is accomplished. Rates of degradation are determined and correlated to microgel content and chemical makeup (PEG $M_n$ of 400 vs. 6000).

Experimental

Materials, Compounds, and Sources

Isophorone diisocyanate (IPDI), (Desmodur I), was received from Bayer in Pittsburgh, PA. Monomethacrylate PEG of Mn 2000 was supplied by Monomer-Polymer & Dajac Labs, Inc. in Pike Festerville, PA. (DLLA), 1,2 propanediol, tin (II) ethyl hexanoate (Sn(Oct)$_2$), PEG of $M_n$ 400 (P400), $M_n$ 6000 (P6000) and acetone were provided by Sigma-Aldrich in St. Louis, MO. Methylene chloride was supplied by Fischer Chemical in Fair Lawn, NJ. D,L-lactide was provided by Ortec, Inc. in Easley, South Carolina.
**PDLLA Synthesis**

In a typical experiment, 209.97 g (1.46 mols) of D,L-lactide, 0.29 g (3.8 mmols) of 1,2-propanediol and 0.20 g (0.49 mmols) of Sn(Oct)$_2$ were added to a 250 mL, 1-neck round bottom flask equipped with an overhead stirrer. (Figure VI-1)

![Chemical reaction diagram]

**Figure VI-1.** PDLLA synthesis.

The polymerization was carried out by the immersion of the flask in a 130° C thermostated oil bath contained within a dry N$_2$ atmosphere glove box, for 19 hr, after which the molten reactor contents were poured into a Teflon® dish to cool. The polymer was then mechanically ground into a coarse powder. Weight average molecular weight (M$_w$), number average molecular weight (M$_n$), and molecular weight distribution (MWD) of the polylactide were determined to be 46,290 g/mol, 38,140 g/mol and 1.22, respectively, by GPC.

**Film Preparation**

To test thermal and physical properties of microgels in PDLLA, polylactide films containing 0, 1, 5, and 10 wt% of microgel particles composed of P400 (mP400) and
P6000 (mP6000) were prepared. These films were cast in 20 wt% solutions in CH$_2$Cl$_2$ in Teflon® Petri dishes and placed in an enclosed environment (glass case) with a small beaker of approximately 40 mL of methylene chloride. This environment was chosen to ensure slow evaporation and reduce defect formation. After 1 week, the films were placed under a slight vacuum for 4 days. The vacuum on the films was slowly increased for another 4 days. The films were stored in vacuo to prevent moisture uptake.

*Gel permeation chromatography (GPC)*

$M_n$ and $M_w$, and MWD were determined on starting materials using a gel permeation chromatography (GPC) system equipped with a Waters Alliance 2690 separation module, a Waters 484 tunable absorbance detector operating at 265 nm, an online multi-angle laser light scattering (MALLS) detector fitted with a Gallium arsenide laser (power 20 mW) operating at 690 nm (MiniDawn, Wyatt Technology Inc.), an interferometric refractometer (Optilab DSP, Wyatt Technologies Inc.) operating at 35°C and 690 nm, and two PL gel (Polymer Laboratories Inc.) mixed E GPC columns (pore size range 50-10$^3$ Å, 3 μm bead size) connected in series. THF was used as the mobile phase at a flow rate of 1 ml/min. Sample concentrations were approximately 5-10 mg/mL in freshly distilled THF with an injection volume of 100 μL. Detector signals were simultaneously recorded and absolute molecular weights and MWDs were calculated using ASTRA 4.0 software (Wyatt Technologies Inc.)

*Atomic Force Microscopy (AFM)*

Specimens were prepared for AFM analysis by cutting a smooth surface of the cross section of the bulk sample with a diamond knife at temperatures of -80°C at an
angle of 6° to the knife and a speed of 1.5-3.5 mm/s on a Reichard-Jung Ultracut E microtome.

Tapping mode-phase AFM was performed using a Digital Dimension 3000 Nanoscope IIIa instrument. Tapping/phase is particularly appropriate, as this mode interrogates morphology on the basis of local viscoelastic properties (hard vs. soft regions). The tapping frequency was approximately 1 Hz or less. In order to minimize artifacts, all bulk sample surfaces were smoothed using a diamond knife prior to acquiring the phase images. Tapping mode was used to preserve the surface topography of the sample so that the results were reproducible in both height and phase images.

Scanning Electron Microscopy (SEM)

FEI Quanta 200 Scanning Electron Microscope (SEM) was used under high vacuum, with a spot size of 4-4.5. Samples were prepared by adhering films with epoxy to AFM specimen discs of 12 mm and sputter-coated using an Emitech k550X gold sputterer with a thickness of 10 nm under argon gas. A coating current of 25 mA was used. The films were cooled to -100°C using a Leica EM FC6 microtome with the low temperature liquid nitrogen, a cryo 45° Diatome diamond knife, and the knife holder, Leica Ultracut UC6. The films were sliced in order to observe the cross section by SEM.

Degradation Studies

PDLLA diol having a molecular weight of approximately 38,000 g/mol was degraded by exposure to phosphate-buffered aqueous solution (7.4 pH, 0.05 M) at 37°C. Polymer discs were stored in 100 mL of buffer solution in 125 mL Fisherbrand jars with
a Teflon face-lined cap. The jars were then stored in a Fisher Scientific Model 146E incubator at 37°C.

The percent mass was calculated by carefully taking 2 discs of the same polymer, patting the surface of excess water with a Kimwipe and weighing the sample to the nearest 0.1 mg. The percent change in mass was calculated according to Equation VI-1, where \( m_h \) is the hydrated mass and \( m_i \) is the initial mass

\[
\text{% Change in mass} = \frac{m_h - m_i}{m_i} \times 100
\]

Equation VI-1
Results and Discussion

The PDLLA films with and without microgels were imaged by SEM before being placed in buffer to determine the morphology of the gels in the films. After microtoming, most films contained cavities or holes where the microgels had been pulled out, and they are not attributed to air bubbles because the film containing 0 wt% microgels lack these holes. (Figure VI-2). Although the microgels readily disperse in PDLLA/methylene chloride solution, since the microgels are not covalently attached to the surrounding PDLLA matrix, they do not interact enough with the surrounding matrix to be held in place below the systems $T_g$ during microtoming. The average size of these pores appears to be about 1 micron in diameter; however they can be as large as 5 microns and are spherical in shape.
After the PDLLA film containing 0 wt% gel particles are placed in standard buffer solution, pock marks are evident after 22 days. (Figure VI-2b) This is in contrast to the smooth cross section of the original film and is indicative of the effect of hydrolysis on the material. (Figure VI-2a)

The control film after 69 days in buffer is significantly more porous, but still exhibits more bulk porosity compared to the surface. This is due to the autocatalytic hydrolysis induced by trapped oligomers having acid end groups on the interior of the film. (Figure VI-2d)
From Figure VI-3a, it can be seen that in both the films containing 10 wt% mP400 and mP6000 at t=0, that there are areas of aggregation. However, looking at a larger view of the film cross section (Figure VI-3a inset), it appears that the distribution of the microgels is homogeneous from the surface to the interior of the film and there is no collection of microgels at either air or substrate interface.

As expected, the PDLLA films with 10 wt% mP400 is much more porous after being in buffer for 35 days. The pore size has increased to approximately 25 μm and the pores start running into each other in some places. Also, the smaller pores seen in the control film after 35 days in buffer are not visible in 10 wt% mP400. This could mean

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that oligomers are either able to migrate out of the film, or they are concentrating in the large pores which would cause the degradation of the PDLLA in these pores, creating larger pores over time as seen in Figure VI-3c.

From images of PDLLA films containing 10 wt% mP400, over 69 days, it can be seen that the cross section has gone from clean circles or cavities to distorted circles of much larger diameter. Some cavities are up to 10 μm in diameter, double in size to the film at zero time in buffer. (Figure VI-3d) This indicates that the microgels are acting as pockets of water within the film and increase the internal surface area of the PDLLA, leading to enhanced physical degradation of the film in comparison to the control film containing 0 wt% microgels.

Observing a corner cross section of the PDLLA film containing 0 wt% microgels after 35 days in buffer, the inner portion of the film becomes visibly porous, while a 50 μm thick perimeter at the surface remains relatively nonporous. (Figure VI-4) This less degraded perimeter decreases significantly in the film, from 50 μm to 10 μm once 10 wt% mP6000 are added. This demonstrates that addition of microgels can affect the bulk degradation of the film, providing more degradation per film volume. The higher porosity in the interior of the film due to trapped oligomers is also apparent in the film containing 10 wt% mP6000 by the larger pore size on the interior after 35 days in buffer.
Figure VI-4. (a) Cross section of PDLLA with 0 wt% mP6000 and (b) PDLLA film containing 10 wt% mP6000, t=35 days.

This same trend of interior degradation occurring at an accelerated rate in the films of 10 wt% mP400 as can be seen in Figure VI-5. A smooth cross section can no longer be obtained by microtoming lyophilized degraded sample because of the increased brittleness and chalkiness of the films at 69 days of buffer solution contact. (Figure VI-5 a and b)

Figure VI-5. Cross section of PDLLA film with (a) 10 wt% mP400 and (b) 10 wt% mP6000 after 69 days in buffer.

From the SEM images there is no significant difference in films containing microgels based on PEG $M_n$ 400 vs. PEG $M_n$ 6000. However, the film with microgels of
more PEG repeat units does appear slightly more porous. This may be a result of the increased hydrophilicity of the microgels as the soft segment PEG increases in length.

Images of the cross section of a PDLLA film with 10 wt% mP6000 before being placed in buffer are observed by a height image using AFM. Clean spherical craters are apparent with areas of greater height or peaks in the films, indicating the presence of microgels just below the surface in the 2D image. (Figure VI-6)

![Figure VI-6. AFM height scale of cross section of PDLLA film containing 10 wt% mP6000.](image)

The same AFM image in 3D, gives a topological view of the surface. (Figure VI-7) In this case it is much easier to see the presence of microgels below the surface which lead to peaks in the film of up to 400 nm, and valleys created by the pulling out of microgels from the PDLLA matrix by the diamond knife.
Figure VI-7. AFM 3-D height image illustrating peaks and valleys created by microgels.

To determine the effect of microgel addition to the PDLLA films, thermal properties were determined by DMA. (Figure VI-8) The PDLLA with 0% microgels has a large drop in storage modulus due to the $T_g$ of PDLLA around 60°C. This drop off occurs at 30°C with the addition of 10 wt% microgels. This is a result of the added dehydrated microgels having a small percent of residual water 0.2-0.3%, as measured by a Karl Fisher titration, which is plasticizing the film. This small molecule content is not detectable by TGA however.
Figure VI-8. Storage Modulus of PDLLA films before being soaked in buffer with increasing wt% of mP6000.

PDLLA controls containing 0 wt% microgels shows a drastic change in the glassy modulus or stiffness after being placed in buffer solution as demonstrated by the lowering of the plateau before the onset of chain motion around 60°C. (Figure VI-9)

Figure VI-9. Control from zero days in buffer to 35 days.
In comparison, the films with 10% mP6000 from 0 to 35 days in buffer have similar glassy modulus profiles over 35 days. (Figure VI-10) Therefore, microgel addition does not significantly affect the glassy modulus of PDLLA over time.

\[ \text{Figure VI-10. PDLLA films with 10 wt% mP6000 from 0 to 35 days in buffer.} \]

The tan δ profile of films with 10 wt% mP6000 measured by DMA show more clearly the shift in T_g to lower temperatures with the addition of more microgels confirming plasticization of PDLLA from the added water the microgels have brought into the system. (Figure VI-11) Not until microgel content reaches 10 wt% in the films does there start to appear the presence of two thermal transitions, the first being the T_m of the microgel particles around 45°C and the second the T_g of PDLLA.
Figure VI-11. Films with 10 wt% mP6000 at t=0 days.

The control film before being placed in buffer shows a single peak around 65°C that is representative of the T_g of PDLLA, but as the film is in buffer for 22 days, there is a shoulder that emerges at 57°C. This shoulder indicates the presence of smaller chains forming that are more mobile at lower temperatures.
Figure VI-12. Control film over 0-35 days in buffer.

The film with 10 wt% mP6000 shows the two peaks before being placed in buffer, one at 45°C indicating the presence of microgel Tm and the other around 60°C due to PDLLA’s Tg. After 22 days in buffer there is a shifted PDLLA Tg to higher temperatures, resulting from loss of a small number of microgels that allows for more efficient chain packing of the PDLLA. Also after 35 days the sample is very brittle and because of the small oligomer chains present, there is an abrupt transition at 55°C due to enhanced chain mobility. (Figure VI-13)
The film containing 10 wt% mP6000 exhibits a $T_g$ around 50°C before being placed in buffer, but also has a shoulder due to the plasticizing effect of trace amounts of water brought into the matrix by the dehydrated microgels. (Figure VI-14) A small crystallization exotherm is seen at -40 and -20°C for 22 and 35 day samples. This is attributed to the oligomer concentration increasing and allowing for organization of these chains.
For the microgels based on PEG Mn 6000, T_m is seen at 55°C, but is not detected in the PDLLA film containing 10 wt% mP6000. (Figure VI-15) This confirms that PDLLA is significantly inhibiting the microgel’s ability to crystallize, indicating that there is interaction between the two systems.
Figure VI-15. Thermal transitions of microgels determined by DSC.

Examining the percent water uptake of the films allows for determination of water absorption properties, oligomer migration rates, and microgel migration from the films over time. This can then be correlated to the structural properties measured by DMA and DSC, along with morphology determined by SEM. All films containing microgels, regardless of the PEG $M_n$ that those microgels are based on, take up more water than the film alone. Water uptake of the films containing microgels is proportional to the PEG $M_n$ the microgels are based on and proportional to the microgel content. (Figure VI-16) Films containing mP400 from 1-10 wt% exhibit decreased initial water uptake over the first 20 days. This is due to the fact that PDLLA is a better hydrogel or absorbs more water than the polyurethane microgels. Eventually the control begins to lose weight due to oligomer migration. The films with microgels loss weight more rapidly in this period than the control because microgels are being lost from the surface along with oligomers migrating from the film.
The films containing mP3400 had a large increase in water uptake compared to the control film due to the increased soft segment content and the number of PEG repeat units per volume in the microgels. (Figure VI-17) Once the water uptake is normalized for microgel content, there is a slight effect of the porous structure and increased surface area observed on PDLLA water uptake. (Figure VI-18) After 290 days the percent water absorption eventually drops down to about the same for all wt% of microgels in the film. This is attributed to the fact that as the films become more porous and swollen with water, thereby allowing a larger number of microgels to migrate out of the film along with trapped oligomers.
Figure VI-16. PDLLA films containing microgels, mass loss profile in aqueous solution, not normalized for microgel content.

Figure VI-17. PDLLA films containing microgels, mass loss profile in aqueous solution, normalized for microgel content.

After the hydrated films were removed from buffer and their mass recorded, the films were freeze dried. Their resulting mass was compared to their original mass before being placed in buffer in order to quantify the amount of microgels and oligomers that have migrated from the film and determine the degree of physical degradation. It was found that in films containing 5 wt% mP400, mP3400, and mP6000 there was not a significant mass loss until 240 days. (Figure VI-18) After this point mass loss is proportional to the PEG $M_n$ of the microgels. This is most likely due to the increased
water absorption and thus swelling of the films with increasing PEG Mn. This increased water content would lend the polymer network more mobility resulting in more facile migration of oligomers and microgels from the matrix. Also decreased physical integrity of the film occurs with higher water absorption, resulting in small pieces of the film breaking away from the more delicate structure.

![Graph](image)

**Figure VI-18.** PDLLA films containing 5wt% mP400, mP3400, and mP6000 microgels, mass loss profile after being removed from aqueous solution and dehydrating.

Increasing the mP6000 content in the films also affects mass loss of the dehydrated films over time. Films containing 10 wt% mP6000 begin to lose weight more rapidly than the other films at 140 days. (Figure VI-19) 10 wt% is lost from this film at 220 days, and this is due to microgel migration out of the water swollen matrix. At 290 days, mass loss is proportional to the wt % of mP6000 due to a more porous structure and a higher degree of swelling with increasing microgel content.
Figure VI-19. PDLLA films containing 0, 1, 5, and 10 wt% mP6000 microgels, mass loss profile after being removed from aqueous solution and dehydrating.

Analysis of the films and how the molecular weight changes over time can also be measured by GPC. The control goes from 41,000 to about 24,000 $M_n$ over 69 days and the PDI, as expected increases to about 1.5, as there becomes a broader distribution of chain lengths. (Figure VI-20)
Figure VI-20. PDLLA with 0% microgels, $M_n$ and PDI over 69 days in buffer solution.

The $M_n$ and PDI of films containing 10 wt% mP6000 can be seen in Figure VI-21. Only PDLLA with 10 wt% shows increased hydrolysis with a $M_n$ of 19,000 after 69 days. This could be due to the enhanced water uptake of mP6000 compared to mP400 that is also allowing more mobility in the film which may give the acidic oligomers more mobility to concentrate in the pores, enhancing hydrolysis.
In analysis of the phase behavior of the films containing microgels over a range of RH, PC-OM can provide a large amount of information involving the effect of microgels. In PDLLA films with 0% microgels, there is no phase separation or phase domains present. However, once mP3400 is added in at 1 wt%, a small number of film defects appear. (Figure VI-22) At 5 wt% mP3400 there appears to be phase domains attributed to the microgels homogeneously dispersed throughout the film over a range of sizes as indicated by the dark speckles throughout the film. As the wt % of mP3400 is increased to 10 wt%, there is aggregation of dark water rich domains detected by CP-OM.
There is little change seen from 0% RH to 25 and 50% RH by PC-OM. (Figure VI-23) However, at 75% RH, there is a marked difference in the phase behavior of the films. There is a small amount of film deformation taking place in the film with 0% mP3400, but little phase separation occurring as seen by PC-OM. With the addition of microgels there are large water rich regions, credited to the growing microgels as they swell with water that concentrates in these regions. This is most dramatic for 5% mP3400 at 75% RH and then decreases with 10 wt% mP3400, attributed to the interconnected water rich regions.

At 100% RH, the PDLLA film softens up enough to take on many more smaller and larger water rich domains. (Figure VI-24) By PC-OM, the large range of water rich domains can be seen throughout in the 5 and 10% mP3400 films. This data confirms the fact that there are more water rich domains in the PDLLA films with the addition of...
microgels over a range of relative humidities, making the PDLLA films more water sensitive.

Figure VI-24. 100% RH films containing mP3400 (scale bar= 50 μm).

Conclusions

Polyurethane PEG based hydrogel particles added to lactide films at 1 and 5% did not alter the T_g of the films significantly. However, it was found that the crystallization of the mP400 gels is kinetically controlled and that these thermal transitions are not disrupted once the gels are added to a polylactide matrix. However, mP6000 interacts strongly with the polylactide matrix chains, as indicated by the loss of crystalline content once mP6000 is added to polylactide.

Also with the addition of microgels to the polylactide films, the storage modulus was greatly enhanced, creating materials that store elastic energy more efficiently, correlating to less brittle films. The microgels created more water rich domains over a larger range of sizes within the film compared to the PDLLA film without microgels. Once the films were placed in water, films containing microgels did absorb more water, but hydrolysis rate of PDLLA was not significantly affected by addition of microgels. However, in the films containing microgels, there was a porous scaffold remaining in the films, allowing faster mechanical breakdown.
References


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CHAPTER VII
INCORPORATION OF ACYCLOVIR INTO POLYURETHANE POLY(ETHYLENE GLYCOL) BASED MICROGELS AND THE EFFECT OF DRUG ON THERMAL AND MECHANICAL PROPERTIES

Abstract

A series of polyurethane based hydrophilic microgels were produced by the free radical polymerization of acrylate terminated polyethylene glycol (PEG) prepolymers. Acyclovir, a hydrophobic small molecule derivative of imidazole, was incorporated into these microgels at a target of 10 wt%, bound by urethane and ester linkages. The microgel series of differing PEG molecular weights was prepared from PEG diols of Mn 400, 3400 and 6000. Incorporation of acyclovir is confirmed by $^{13}$C NMR and FT-IR. In addition properties of the microgels were altered with addition of the drug, including the hydrodynamic particle size decreasing with the addition of acyclovir as determined by dynamic light scattering. Also the crystallinity of the dehydrated microgels was disrupted with the addition of acyclovir which affects the dry powder character and will allow for faster dispersability rates in water.

Introduction

Vitreoretinal disorders are the leading cause of blindness in the developed world. Acyclovir (acycloguanosine), a synthetic analogue of purynic nucleosides $^2$ - deoxiguanosine is the main compound used in treatment of these intraocular pathologies as an inhibitor of herpes simplex virus (types I and II) varicella zoster, retinitis, Epstein-Barr virus, cytomegalovirus, and acute retinal necrosis.$^1$ The main mode of action of
acyclovir has been shown to be the inhibition of the Herpes virus DNA replication. The structure of acyclovir is shown in Figure VII-1.

![Figure VII-1. Structure of Acyclovir.](image)

The most popular method of drug delivery, because of its convenience, is by topical administration of eye drops which collect in the lower cul-de-sac. However, as a result of the eyes natural protective barriers such as the solution drainage, lachrymation, and diversion of exogenous substances into the systemic circulation by the conjunctiva, less than 5% of the drug reaches the target. Acyclovir is usually formulated as an ointment because of poor water solubility and this causes impairment of vision in the patient for up to 30 min, reducing patient compliance. The poor patient compliance combined with the drugs poor water and lipid bilayer solubility combined afford an overall ineffective treatment. Other methods of local treatment include ointments and hydrogel particles in the form of polymeric gels, but these methods encounter the same barriers to drug delivery as the eye drops.

Peri- and intraocular injections are much more efficient in delivering high drug concentration to the vitreous cavity. Vitreous humor, a hydrophilic gel within the ocular cavity, is composed of 99% water and 1% collagen, hyaluronic acid, and other organic compounds. This media has been shown to be comparable to water in allowing drugs to diffuse through it. These intraocular injections allow for treatment of diseases of the
retina or cornea and are carried out by a transvitreal approach or by creating a tunnel in
the sclera.\textsuperscript{8}

The frequency of these injections causes complications such as detached retinas,
endophthalmitis, cataract, vitreous hemorrhage, and infections in those afflicted who
already have compromised immune systems. As a result, polymer microspheres and
microcapsules have been widely researched for controlled long term release in order to
eliminate frequent intravitreous injections. These microcapsules have a drug core that is
surrounded by a polymer film and the microspheres are mixed in with the polymer
matrix.\textsuperscript{9} Very little research has been done on the covalent attachment of a drug to the
polymer matrix with the goal of zero order constant long term delivery. However,
microencapsulation and microspheres mixed with drug formulations have been studied
for ophthalmic drug delivery for long acting injectable drug delivery for the past 20
years.\textsuperscript{10-17}

Biodegradable polymers studied in the past include gelatin, albumin,
polyorthoesters, polyanhydrides, polyesters, and most commonly poly(D,L-lactic acid)
(PLA) and poly(glycolic acid) (PLGA) along with copolymers of these two (PLGA).\textsuperscript{18-21}
These systems, especially PLGA, have been investigated so much because the copolymer
is biocompatible and the degradation products, lactic and glycolic acids are metabolized
readily.\textsuperscript{22,23} Microspheres are commonly formed by spray-drying and by different types
of emulsions polymerizations. These include inverse emulsions for encapsulation of the
drug with the most commonly targeted and drug loading being 10 wt\%.\textsuperscript{24-28}

In research by Conti, PLGA particles prepared by the spray-drying technique
released 100\% of the drug in 8 h and showed a strong burst effect.\textsuperscript{29} Conversely, PLA
microspheres did succeed in sustained release over 14 days. PLGA microspheres prepared by solvent evaporation from an emulsion polymerization released drug up to 49 days, but almost nothing was released in the initial stages after injection. From ethyl cellulose microspheres synthesized by emulsion polymerization and solvent evaporation, release rates were sustained, but only for 12 h. In PEG coated poly(ethyl-2-cyanoacrylate) nanospheres encapsulating acyclovir, almost 100% of the drug was released over the short period of only 4 hours.

In this research, polyurethane PEG based microgels containing 10 wt% covalently attached acyclovir having PEG $M_n$ of 400, 3400, and 6000 and drug bound by either urethane or ester bond is synthesized and the microgel properties characterized. This is in an effort to obtain microgels that would provide controlled release kinetics with a minimal burst effect from treatment with only a single intravitreous injection.

**Experimental**

**Materials, Compounds, and Sources**

Acycloguanosine and (methyl sulfoxide)-$d_6$, PEG $M_n$ 400 (PEG 400) and $M_n$ 6000 (PEG 6000), acetone, and ε-caprolactone were provided by Sigma-Aldrich in St. Louis, MO. Isophorone diisocyanate (IPDI), Desmodur I, was received from Bayer in Pittsburgh, PA. Monomethacrylate PEG of $M_n$ 2000 was supplied by Monomer-Polymer & Dajac Labs, Inc. in Pike Festerville, PA.

**Microgel Preparation**

 Representative prepolymer preparation (based on PEG 400).
1.86 grams of PEG 3400 (0.0011 OH equiv), 0.63 grams of monomethacrylate PEG (3.2 x 10^{-4} OH equiv) and 0.31 grams of acyclovir (0.0013 OH equiv) was charged to a 50 mL flask under N\textsubscript{2} with 8 grams of anhydrous DMSO solvent and 0.28 grams of Desmodur I (IPDI) (0.0025 equiv). 1 drop of DBTDL was added. The reaction mixture was heated for 3 h at 60°C. Prepolymers from PEG diols of M\textsubscript{n} 400, 3400, and 6000 were prepared similarly. In all cases an isocyanate to hydroxyl index of 1.2/1.0 was used. Such a ratio ensures complete incorporation of the PEG diol with excess NCO reacting with water.

Representative Prepolymer Dispersion and Microgel Formation (Based on Prepolymer of PEG 400)

8 grams of prepolymer was charged to a 100 mL flask under N\textsubscript{2} by dropwise addition to 8 gram of agitated (Teflon stir bar) 80°C de-ionized water. The mixture was heated at 80°C for 3 hours. The mixture was then placed in dialysis tubes and the water renewed 4 times over 72 hours. The presence of microgels was detected by DLS to be in the range of 100 nm – 4 \mu m. The mixture was then freeze dried to yield a powder which was insoluble in solvents including THF, hexanes, and water.
Figure VII-2. (a) Acyclovir (10 wt % of the total formulation and 10 mole% of the hydroxyl functionality) (b) PEG (55 mole % hydroxyl functionality) (c) monomethacrylate PEG (35 mole% hydroxyl functionality) and (d) IPDI.

In order to modify the bond with which acyclovir is covalently attached to the polymer, acyclovir was not only bound by urethane bonds by reacting acyclovir with IPDI, but also acyclovir is combined with ε-caprolactone and further reacted with IPDI in order to link the drug to the polymer with an ester bond. This modification allows for microgels with variable properties and esters have been shown to readily hydrolyze in comparison to slower hydrolyzing urethane linkages due to enhanced hydrogen bonding.

Preparation of ring opened caprolactone by acyclovir. 2.25 grams of acyclovir (0.001 OH equiv) and 1.14 grams of ε-caprolactone (0.001 equiv) were charged to a 10 mL flask under N₂ in a 0.1 M solution of NMP and 100 ppm SnO₂. The reaction mixture was heated for 4 h at 70°C. The reaction to couple acyclovir to ε-caprolactone is shown in Figure VII-3, where acyclovir is in a 1:1 molar ratio with ε-caprolactone and behaves as an initiator for ring opening polymerization.
Figure VII-3. Coupling of acyclovir and ε-caprolactone.

The product shown in Figure VII-3 was found not to be the product by $^{13}$C NMR, in which the spectrum of acyclovir is shown in Figure VII- 4, the spectrum of ε-caprolactone in Figure VII- 5, and the product spectrum in Figure VII- 6. It is important to note that the reaction did not occur and when NMP was pulled off by vacuum, the unreacted ε-caprolactone was also. This results in no shifting of the acyclovir peaks and signature peaks of NMP being 19, 29, 31, 49, and 175 ppm are all present. (Figure VII- 6) This was confirmed by spiking the sample with more NMP and a rise in intensity of these peaks was observed.
Figure VII-4. $^{13}$C NMR spectrum of acyclovir in DMSO-d6.

Figure VII-5. $^{13}$C NMR spectrum of $\varepsilon$-caprolactone in CDCl$_3$. 

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Figure VII- 6. $^{13}$C NMR spectrum of acyclovir bound to caprolactone in DMSO-d6.

Once the prepolymer containing acyclovir is synthesized in DMSO, (Figure VII-7) the prepolymer is dispersed dropwise in agitated de-ionized water at 90°C for 4h. The resulting product is microgels of 100 nm to 4 microns as determined by dynamic light scattering. The microgels were then placed in dialysis tubes and the water changed 4 times over 72 hours to eliminate the residual DMSO and other small molecule contaminants.
Results and Discussion

It was confirmed by FT-IR that acyclovir is contained within the lyophilized microgel particles. (Figure VII-8) The microgels formulated with 0 wt% acyclovir have a peak around 1720 cm\(^{-1}\) due to the carbonyl of the urethane group, 1640 cm\(^{-1}\) is attributed to the carbonyl of the urea group, and the small peak at 1650 cm\(^{-1}\) is due to the residual alkenes present in the system. With the addition of 10 wt% acyclovir, the guanine group appears at 1662 cm\(^{-1}\) and 1637 cm\(^{-1}\). This data confirms the presence of acyclovir in the microgels after dialysis, however quantitative information must be observed by NMR.
Figure VII- 8. FT-IR of mP3400 containing 0% acyclovir, 10 wt% acyclovir, and 10 wt% acyclovir bound to caprolactone.

The dialyzed and freeze dried microgels were then dispersed in D$_2$O and quantitative acyclovir incorporation of 2.44 wt% was confirmed by integration of $^1$H NMR by comparing microgels without (Figure VII- 9) and with acyclovir (Figure VII-11). Peak f at 10.9 ppm (Figure VII- 10) was compared with the ethylene oxide peak (3.4-3.8 ppm) in the spectrum of microgels containing acyclovir (Figure VII- 11).
Figure VII-9. $^1$H NMR of microgels containing no acyclovir in DMSO-d$_6$. 

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Figure VII-10. $^1$H NMR spectrum of acyclovir in DMSO-$d_6$.

Figure VII-11. $^1$H NMR spectrum of microgels containing 10 wt% acyclovir (mP(PEG $M_n$)A) in DMSO-$d_6$.

From Figure VII-11, it can be seen that acyclovir is still contained within the microgels even after dialysis of the microgels as seen by peaks of acyclovir spectrum, Figure VII-10, that appear in the microgels. These peaks include 10.8, 7.9, and 2.2 ppm.
indicated with an asterisk. It can not be confirmed by $^1$H NMR if acyclovir is covalently attached because the end group hydroxyl proton is drowned out by the high intensity ethylene oxide peak around 3.6 ppm.

In analysis of the microgels and how attaching acyclovir (mP(PEG Mn)A) and acyclovir coupled with caprolactone (mP(PEG Mn)A,C) will affect the properties, it was discovered that this modification did affect the particle size and particle size distribution in aqueous media. (Figure VII-12) The microgel containing no drug has a particle size from 100 nm to 6 μm with the majority around 1 μm. (Figure VII-12a.) However, because each acyclovir molecule complexes with 2 water molecules, once acyclovir is incorporated into the microgels, more water is drawn into the particle as a result of enhanced hydrophilicity, and the particle size increases to the majority being around 3 μm and a much smaller fraction below 1 μm. (Figure VII-12b)
Figure VII-12. mP3400 containing (a) 0 wt% acyclovir and (b) 10 wt%.

The thermal properties of the microgels with and without drug have been measured by DSC. (Figure VII-13)
Figure VII-13. DSC spectra of mP400 without and with acyclovir and acyclovir alone.

Although PEG of $M_n$ 400 by itself is typically liquid, the microgels based on PEG $M_n$ 400 (mP400) exhibit thermal transitions that are typical for PEG above $M_n$ 1000. These transition of mP400 are a $T_g$ around -50°C, a $T_c$ around -20°C, and a $T_m$ around 30°C. This $T_m$ is slightly lower than PEG’s typical $T_m$ of 50°C due to the crosslinks that allow for smaller crystals to be formed.

Once acyclovir is incorporated, crystallinity of the soft segment PEG is reduced as evidenced by the reduced exotherm of crystallization. Also there is no longer a $T_m$ of the soft segment, but there is a $T_m$ that is consistent with acyclovir’s $T_m$ of 50°C, indicating that the acyclovir is segregated within the microgels.

Figure VII-14. WAXS spectra of mP400 microgel series and acyclovir.

The relative crystallinity of the microgels that was observed by DSC can be further confirmed and clarified by WAXS. The presence of the drug in the amorphous
phase versus the crystalline phase cannot be determined by WAXS because there are no signature peaks of acyclovir alone that occur in the microgels containing acyclovir. (Figure VII-14)

It is clear that the peak positions from the WAXD profiles of P3400 and P6000 in Figure VII-14 are a result of the crystallization of PEG in which the reflection planes were found by Huang et al. (Figure VII-15) who analyzed the unit-cell structure parameters and indexed the main peaks. They found that they were consistent with a monoclinic crystal system whose interplanar spacing of the \((hkl)\) reflection planes is given by Equation VII-1. Through the insertion of the values of \(l\) (1.542 Å), \(b\) (125.4°), and the peak positions of (120), (032), and (024) reflection planes, the unit cell parameters \(a\), \(b\), and \(c\) can be determined by Equation VII-1. The main peaks from PEG seen in Figure VII-14 are 120, 032, and 024, although the peaks are barely visible because of the large amorphous halo indicating microgels based on PEG 400 have little crystallinity at room temperature.

\[
\left( \frac{1}{d_{hkl}} \right)^2 = \left( \frac{2 \sin \left( \frac{\theta_{hkl}}{2} \right)}{\lambda} \right)^2 = \frac{1}{\sin^2 \beta} \left( h^2 + \frac{k^2 \sin^2 \beta}{b^2} + \frac{l^2 c^2}{ac} \right) + \frac{2hl \cos \beta}{ac} \]  
Equation VII-1
Figure VII-15. (a) WAXD pattern and (b) peak deconvolution of the WAXD profile of pure PEO.33

Figure VII-16. WAXD spectra of mP3400 microgel series and acyclovir.

The same trend was observed in mP3400 spectrum (Figure VII-16), which showed higher crystallinity of PEG due to the presence of more reflection planes of PEG,
120, 112, 032, 024, and 131 in the WAXD spectrum than mP6000, only 120, 032, and 024 (Figure VII-17). This is attributed to PEG 3400 chains not being so long as to inhibit crystallization within the given time frame, but long enough to allow enough mobility to form significant lamella.

Since the same planes are seen in the microgels as in the pure PEO diffraction pattern, it is apparent that the crystalline content is a result of PEG forming lamella and no contribution of the hard segment or acyclovir, as suspected. In every case the microgels exhibit much more crystallinity than the PEG reactants which is attributed to the preparation of the microgels allowing the chains to organize into a much more regular conformation as opposed to the PEG reactant. This more regular structure outweighs the negative effect of the crosslinker which disrupts crystallinity of the PEG chains by decreasing the mobility and breaking up the long chains.

*Figure VII-17. WAXD spectra of mP6000 series.*
The intensity of the peaks for mP6000 is much lower in comparison to mP3400. (Figure VII- 17) This confirms that as a result of the lengthy chains between crosslinks, there is too much mobility limiting the amount of lamella organization and crystallization that can occur. This information correlates to the dispersability rates of dehydrated microgels in aqueous solution, with higher crystallinity making the microgels less susceptible to hydration and dispersability in water.

![Graph](image)

*Figure VII- 18.* TGA spectra of acyclovir and mP6000 microgels with and without 10 wt% acyclovir.

More information about the thermal properties including thermal stability can be determined by TGA. (Figure VII- 18) Once 2.44 wt% acyclovir is incorporated into microgels, we see 5 wt% water is lost before 100°C. This is consistent with literature showing that acyclovir has been shown to complex with 2 water molecules. This difference in water content of the freeze dried microgels may affect the dispersability rates and drug diffusion out of the microgels in release studies.

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The difference in thermal stability of the microgels containing 0 and 10 wt% acyclovir is interesting to note. The microgels containing no acyclovir have fully degraded into smaller components that have volatilized by 400°C. On the other hand, the microgels containing 2.44 wt% acyclovir still have 20 wt% remaining at 400°C. This degradation behavior can be correlated to long term stability of the dehydrated microgels in which the particles containing acyclovir bound by urethane bonds are less susceptible to degradation than microgels with 0 wt% drug.

Conclusions

Microgels have been synthesized with IPDI and various PEG Mn from 400 to 6000. These microgels, with a synthesis target of 10 wt%, were confirmed by ¹H NMR to contain around 2.5 wt% acyclovir after dialysis and lyophilization. The PEG Mn used and also the addition of acyclovir do change the thermal properties including the degree of crystallization of the microgels. This crystallization in turn affects the dehydrated microgel powder flow, water sensitivity, and dispersability rates in water. The stability of microgels containing acyclovir was also found to be enhanced. Future studies will involve analysis of the drug release from these microgels and how it changes with PEG Mn, effectively altering the mesh size.

References


4. Bacyens, V.; Percicol, C.; Zigaani, M.; Deshpande, A. A.; Kaltsatos, V.; Gurny, R.


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CHAPTER VIII
INFLUENCE OF MOLECULAR WEIGHT ON ITRACONAZOLE INCORPORATED HYDROXYPROPYL CELLULOSE HOT-MELT EXTRUDED FILMS: RELEASE AND FILM PROPERTIES

Abstract

The treatment of onychomycosis by oral delivery is problematic and there is need of an alternative. If available, a topical transcuticular route would be preferred as it would avoid exposure of other organs to high concentrations of antimicrobials such as itraconazole. Reported here is the preparation and analysis of a series of hot-melt extruded hydroxypropyl cellulose (HPC) based films (MW 80k-850kDa) containing 10% of the anti-fungal drug itraconazole and 5% α-tocopherol (vitamin E succinate) for the assessment of topical onychomycosis therapies. The extruded films exhibited uniform post-processing drug content as evidenced by the absence of the crystalline exotherm of itraconazole in DSC measurements. This was confirmed by X-ray diffraction measurements, which also revealed a higher degree of crystallinity in samples with higher molecular weight. The itraconazole release rates were studied and found to trend directly with the degree of hydration in humid environments and inversely to HPC molecular weight. As the crystalline content of the films increased proportionally with the molecular weight of HPC, drug release declined, as measured by a Hanson SR8-Plus dissolution unit (USP XXVIII Apparatus 5). Also the films based on higher HPC molecular weights exhibited zero order release kinetics due to the large crystalline domains creating a more tortuous path for drug dissolution and therefore resulting in a constant release of the antifungal agent.
General Background

Onychomycosis

A significant percent of the world population has onychomycosis (*tinea unguium*), a fungal infection that causes the nails to thicken, discolor or split. This widespread problem occurs in approximately 1 in 5 people and accounts for half of all reported nail problems.\(^1,2\) The majority of those infected include the elderly, diabetic, military personnel, farmers, ranchers, and those in the medical field. Men are primarily affected with smokers being prone to contracting the disease on their fingernails.\(^3\) This disease also has a high rate of recurrence and is progressive.

Itraconazole

Itraconazole, the model drug used in this study, is currently one of the handful of drugs used to treat onychomycosis through oral administration. It is an imidazole antifungal agent whose mode of action is primarily by way of binding to proteins such as albumin in circulating blood where it eventually concentrates in fat cells, skin, and nails. It is a low aqueous solubility class II compound due to its weakly basic character with a \(pK_a\) of 3.7 and is used to treat the primary fungi of this disease, *Trichophyton rubrum* and *Trichophyton mentagrophytes*.\(^4\) Itraconazole binds to the fungal p450 enzymes and stops the fungal cell’s synthesis of ergosterol, the main component of the cell wall.

Disadvantages of Itraconazole Oral Delivery

Itraconazole is moderately effective against onychomycosis, however there are some issues that contribute to the common recurrence of the disease. Patient non-compliance is a serious issue in the treatment of this fungal disease since the patient must take an oral dose of itraconazole 2-3 times a day for 3-6 months. Patients are reluctant to
take itraconazole as a result of side effects such as nausea and vomiting. In addition, oral
delivery of itraconazole is plagued with other barriers that inhibit effective delivery to the
affected site, the nail bed. Even prescribed dosages can overload the metabolic capability
of the liver leading to damage of the liver and heart failure in some cases.\(^5\)

Due to the low solubility of the drug, significant concentrations are stored in fat
cells, reducing the amount available for the targeted nail bed.\(^6\) Solubility decreases if the
patient is taking antacids, which eliminate the acidic environment that itraconazole needs
to be solubilized. As a direct result of low aqueous solubility, complications encountered
that inhibit the oral bioavailability of the drug include: slow dissolution in the
gastrointestinal (GI) tract, metabolism in the liver, low membrane permeability and
complex formation as a result of interactions with the substances in the GI tract. These
factors have given impetus to formulation changes that improve solubility, including
surfactants, inclusion complexation and solid dispersion techniques.

*Topical Therapy*

An additional approach to formulation changes is to apply the drug by site
directed delivery or topical delivery. This is an alternative to oral and systemic
treatments, which reduce the total drug dose to the patient. To eliminate previously
discussed problems with oral delivery, HPC extruded patches are being studied in this
research to effectively deliver itraconazole topically, by site directed delivery. This
topical method would also reduce non-target site toxicities by concentrating the dosage
directly on the source rather than indirectly.\(^7\)

For topical therapy of drugs, a polymer is typically used as a carrier of the active
compound in which modification to the polymer can control the dosage form’s release
rate and location. The controlled release of itraconazole can be modified by changing the polymer vehicle properties such as the molecular weight, crystallinity and hydrophilicity of the material and hence the miscibility of the contained drug in the film. Additional variations are derived from the preparation method of the film (e.g. hot-melt extrusion).

Topical Considerations

Since onychomycosis affects the nail bed, in order to employ topical delivery of itraconazole through the nail plate, the nail structure must be thoroughly understood. The nail is made up of 25 layers of dead, keratinized cells of which 80% are the harder hair type keratin and 20% are the softer skin-type keratin. The cells are bound by intercellular links such as cystine rich proteins having hydrogen bonding, disulfide linkages, and ionic bonding.\(^8\)

There are 3 main keratin layers, dorsal:intermediate:ventral, with the relative thicknesses of the layers being 3:5:2. The top dorsal surface is made up of cells that overlap to form a smooth hard surface (Figure VIII- 1a). The intermediate layer is softer and accounts for the bulk of the nail and is made up of hair-like keratin filaments. These filaments are oriented perpendicular to the growth axis and combine into “keratin sandwiches” that swell and de-swell, acting as a hydrogel, with 10-30% water depending on the environment (Figure VIII- 1b.). The ventral layer is closest to the nail bed and is the thinnest layer.
In actual use, it is expected that these extruded films will be applied to the nail once the dorsal layer has been filed or otherwise compromised, allowing the drug to diffuse most efficiently to the nail bed.

Hot melt extrusion (HME) has recently shown to be a viable method for preparing drug delivery systems and has benefits over film cast delivery systems in that, solvents are unnecessary and there are fewer processing steps. Additionally, particles are more uniformly dispersed due to intense mixing, and therefore bioavailability is improved. This enhanced bioavailability has been shown to be a result of the molecular level solubilization of the drug in the polymer carrier.

During the HME process, the drug, thermoplastic polymers, and other excipients are fed into a heated barrel consisting of either a single rotating screw or two screws, which aid in transferring the polymeric-drug blend to the end of the heated barrel. The polymer melts at the elevated temperature and the molten mass is continually pumped through a die attached to the end of the heated barrel. The molten mass rapidly cools as it passes over a chilling apparatus and is collected using a wind-up roll in the case of films. Since HME precludes the use of solvents, especially water, the potential for drug degradation in the solid state is minimized.
Hydroxypropyl cellulose (HPC), a thermoplastic, hydrophilic, water-soluble polymer was used in this study as a sustained release matrix forming polymer. As supplied HPC is an amorphous non-ionic polymer that is a hydrogel and swells to a large extent in water. However, when extruded and highly crystalline, HPC does not quickly form a gel layer in the presence of minor amounts of water. This property of the polymer can be advantageous when fabricating a delivery system for poorly soluble drugs.

An appropriate choice of polymer molecular weight (chain length) may result in a desired erosion rate and hence a release rate that provides predictable salivary or blood levels of the drug. The molecular weight of HPC, along with processing conditions can be used to alter the crystallinity of the resulting films. The range of crystallinity within the HPC films allows for tuning the hydrophilicity of the HPC matrix and hence the release rates of a drug such as itraconazole. It has been found that the bioavailability of a drug can be improved when it is dispersed at the molecular level by extrusion techniques, indicating that this is a promising method of delivering compounds that are highly hydrophobic.

The goal of this study involves improving treatment modalities for onychomycosis. The purpose of the present study is to explore a potential topical drug delivery approach via HPC hot-melt extruded films as an alternative route to toxic systemic delivery systems. This research also studied release rates of itraconazole as a function of HPC molecular weight, which were correlated to the thermal and mechanical properties of the HME films.
Experimental

Materials, Compounds, and Sources

Hydroxypropyl cellulose (HPC) (Klucel® grades EL, LF, JF, GF and MF) was kindly supplied by the Aqualon Company, Wilmington, DE. Itraconazole was obtained from Hawkins Chemical Inc., Minneapolis, MN. Diethylamine, α-tocopherol and sodium lauryl sulfate (SLS) were obtained from Spectrum Chemical Mfg. Corp., Gardena, CA. Acetonitrile was purchased from Fisher Scientific, Pittsburgh, PA.

Preparation of Films

A single-screw Randcastle Microtuder® (Model RCP-0250) was used to prepare thin polymer films containing itraconazole, α-tocopherol and HPC grades that spanned the MW range of 80 to 850 kDa. The films were prepared from a blend of the components: 5 wt% α-tocopherol (vitamin E), 10 wt% itraconazole, and 85 wt% HPC. Screw speed was controlled to afford films of dimensions 45 mm in width by 0.1 mm in thickness.

α-Tocopherol, and the polymer were geometrically diluted through dry blending and dried in an oven at 55° C for 24 h and then introduced into a V blender and mixed at 100 rpm for 15 min. The resultant blend was fed into the extruder. The extrusion parameters are given in Table VIII-1.
Table VIII-1.

*Formulation and Extrusion Conditions for Preparation of HME Films.*

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</tr>
</tbody>
</table>

*High Performance Liquid Chromatography (HPLC)*

HPLC used for the drug quantification was performed on a system consisting of a Waters 600 pump and a dual wavelength Waters 2487 UV detector. The analytical column used was a 150 x 4.6 mm I.D., Inertsil ODS-2 column (Alltech Associates Inc.,) with a particle size of 5μm.

Random samples (n=4) were taken from all of the batches immediately after extrusion and at pre-determined intervals analyzed for drug concentration using HPLC. The samples were weighed and dissolved in 10 ml of acetonitrile, sonicated for 10 min or until the entire film was dissolved. After being centrifuged for 18 min at 4000 rpm, the supernatant was removed and filtered using a 0.45 μm nylon filter and injected into the chromatographic system. The mobile phase for HPLC was prepared by mixing HPLC grade acetonitrile, nanopure water and diethylamine in the ratio of 70:30:0.05. This mixture was vacuum filtered using a 0.2 μm nylon filter in a Millipore vacuum filtration assembly. The filtered solvent mixture was then degassed using a vacuum assembly,
simultaneously stirred using a magnetic stirrer until no bubbles were observed. Chromatography was performed with the filtered degassed mobile phase at a flow rate of 1.0 mL/min and an injection volume of 20 μL. The effluent was monitored at 261 nm.

For the calibration curve, stock solution of itraconazole at a concentration of 500 μg/mL was prepared in clean and dry volumetric flask by dissolving an appropriate amount of analyte in acetonitrile. Subsequent calibration standards were prepared by serially diluting the stock solutions with acetonitrile. A calibration curve was prepared by plotting the area under the curve (AUC) of the peak against the concentration.

**Stability Tests**

Stability testing provides evidence on how the quality or quantity of an active substance varies with time as a function of a variety of environmental factors, such as temperature and humidity. From this testing recommended storage conditions, re-test periods and shelf-lives can be established. Stability studies were performed on films stored in an unpackaged condition at 25°C/60% RH. Films were analyzed for the drug content using FIPLC at time zero, three months and six months to determine the stability of the drug within the HME films.

**In Vitro Release Studies**

Release studies were performed using a Hanson SR8-Plus™ dissolution test system according to USP XXVIII Apparatus 5, paddle over disk method. 900 milliliters aqueous solution containing 0.5-1.0% SLS at 37°C was used as dissolution media and the paddle rotation speed was 75 rpm. Samples were collected at predetermined time intervals, filtered using a 0.45μ nylon syringe filter and analyzed using HPLC. These
studies were performed in triplicate. The release studies were fitted to first-order, square root, and zero-order models, to ascertain the drug release kinetics from the matrices.

Results and Discussion

Stability Studies

The drug content remaining in the films stored at 25°C/60% RH for 6 months is illustrated in Figure VIII-2. The post-extrusion content remaining in the five films ranged from 84.5% (±1.7) of itraconazole added to the blend for the Klucel® MF (MW: 850 kDa) film to 94.2% (±3.0) for the Klucel® JF (MW: 140 kDa) film. In spite of extruding the films at temperatures well above the melting point of itraconazole there was less than 10% degradation of the drug observed in three of the film batches. This is due to the high thermal stability of itraconazole and short residence time of the drug inside the barrel of the extruder. The drug content remaining in the five film batches when measured after 3 months and 6 months is shown in Figure VIII-2.

Figure VIII-2. Retained itraconazole in HPC films

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In-Vitro Release Studies

Approximately 52% (±0.8) and 43% (±0.1) of drug was released at the end of 10h from the 370 k and 850 k films, respectively; whereas 80% (±2.0) release occurred from 80 and 95 k films at the same time interval (Figure VIII-3). The release profile was only carried out to 10 h for the lower molecular weight films 80k and 95k; this is due to the plateau of drug release at this point as the films were mostly dissolved. The films prepared from the 140, 370, and 850kDa HPC samples all retained visual mechanical integrity until 25 h and continued to demonstrate drug release.

Figure VIII-3. Release profiles of itraconazole from HPC films.

The release profiles in Figure VIII-3 show a clear retardation as the HPC molecular weight increases beyond 95 kDa. Such release profiles suggest that the process is carrier controlled and the physical properties of the drug are of minimal importance and imply that the release of the drug from the HME HPC films can be tailored by altering the molecular weight without affecting the mechanism of release.
The release data were fit to three different models, the kinetics of drug release for the HPC film of 80 kDa was found to be 1st order indicating that the concentration behind the poly(tetrafluoroethylene) (PTFE) membrane in the Hanson dissolution test decreases significantly over time. The 95 k film was found to have the kinetics of Higuchi-square root kinetics in which diffusion is controlled by the matrix of the film, in which there is a diffusion layer present. The three films of higher molecular weight HPC, 140 k, 370 k, and 850 k, were determined to have zero-order release rates (Figure VIII-4). In zero order kinetics there is a constant supply of drug or a saturated concentration behind the PTFE membrane in the Hanson Dissolution Test. The zero-order kinetics is desirable for controlled release dosage forms as a constant concentration of drug is released over time.11

\[ R^2 = 0.999 \]
\[ R^2 = 0.9989 \]
\[ R^2 = 0.9966 \]

Time (hrs)

% Drug Released

\( \bullet \) HPC 80 kDa
\( \boldsymbol{\bullet} \) HPC 370 kDa
\( \triangle \) HPC 850 kDa

Figure VIII-4. HPC 140, 370, and 850 k itraconazole release plots fit to zero order kinetics.

To observe the solubility of drug in the films, X-ray diffraction was used to assess the reactants in comparison to the final film (Figure VIII-5). The data suggests that there is drug content uniformity within the films because there are no sharp crystalline peaks.
resulting from itraconazole in the final film. However it cannot be determined from this data if the α-tocopherol is homogeneously distributed throughout the sample. This solubility of itraconazole in the films can also be observed in the DSC spectra of an extruded film and the components of the film (Figure VIII-6).

*Figure VIII-5.* X-ray diffraction spectra of HPC film, HPC powder, α-tocopherol, and itraconazole.

*Figure VIII-6.* DSC spectra of HPC powder, HPC film, α-tocopherol, and itraconazole.

With no endotherm attributable to itraconazole in the extruded film, it is assumed to be solubilized within the film and no longer in a separate crystalline drug phase. However there is a thermal event in the final film indicative of α-tocopherol. The endotherm is small as it makes up only 5% of the total components in the film. The
melting temperature is lower however, dropping from its neat melting point of 80°C to 60°C in the film indicating some degree of mixing.

X-ray measurements were made to look at how the crystallinity of the films differs as a function of HPC molecular weight and how extrusion changed the properties of HPC. The crystallinity of the received powders was very low, with only weak diffraction patterns evident in the diffraction patterns (Figure VIII- 7a). Within the as received samples, crystallinity appears to decrease with increasing MW. This is contrary to the trend found in samples after extrusion. (Figure V-7b)

These observations are most likely the result of powder formation in which the materials were forced to cool very fast resulting in less time for the crystal domains to organize, with less mobility at higher molecular weights. Once extruded, the HPC films have a much higher degree of crystallinity compared to the powders and it can be seen from the two main ordering or crystalline regions at 2Θ = 10 and 20 degrees, that as the molecular weight of HPC increases in the films, there is increase in crystallization. Crystalline lamella are also increasing in size as a function of molecular weight as can be
seen from the broader peaks with increasing HPC molecular weights. This formation of larger and more crystalline lamella in the films would result in a more tortuous path for drug diffusion and would most likely result in zero order release kinetics. However, the lower molecular weight films with less crystallinity and smaller lamella provide a more facile route for the entrapped host, demonstrating 1st order and Higuchi square root kinetics.

*Figure VIII- 8.* Influence of crystalline lamella on drug diffusion pathways.

*Figure VIII- 9.* Differences in amorphous ordering of 80 k HPC films compared to that of 850 k films.
Thermal Properties

In order to predict how the hydrophilicity of the HPC has changed by combining it with α-tocopherol and itraconazole along with increasing the overall crystallinity post extrusion, the HPC powders and final extruded films water uptake was measured after 5 days and after 3 months at 60% RH by TGA. HPC powders and films were dehydrated by placing them in a desiccator under vacuum containing P₂O₅ for 48 hours. These results are summarized in Table VIII-2.

Table VIII-2.

Water Content of HPC Powders, %H₂O (± 0.2 %).

<table>
<thead>
<tr>
<th>Condition/Film</th>
<th>80k</th>
<th>95k</th>
<th>140k</th>
<th>370k</th>
<th>850k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydrated Powder</td>
<td>1.2</td>
<td>1.3</td>
<td>1.1</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Powder 5 d</td>
<td>1.3</td>
<td>2.4</td>
<td>1.6</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Powder as received</td>
<td>1.8</td>
<td>2.6</td>
<td>1.8</td>
<td>2.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

From the data in Table VIII-3, it can be inferred that as the HPC powder molecular weight increases (crystallinity decreases as determined by XRD) hydrophilicity increases. The same method was applied to the HPC films. (Table VIII-3)

Table VIII-3.

Water Content of HPC Extruded Films %H₂O (±0.2%).

<table>
<thead>
<tr>
<th>Condition/Film</th>
<th>80k</th>
<th>95k</th>
<th>140k</th>
<th>370k</th>
<th>850k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydrated Film</td>
<td>0.38</td>
<td>0.80</td>
<td>0.55</td>
<td>0.60</td>
<td>0.57</td>
</tr>
<tr>
<td>Film 5 d RH</td>
<td>1.0</td>
<td>1.1</td>
<td>0.98</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Extruded Film (as received)</td>
<td>3.0</td>
<td>2.8</td>
<td>1.4</td>
<td>1.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>
It can be observed from these TGA measurements that the hydrophilicity decreases with increasing HPC molecular weight and with increasing crystallinity content causing more difficulty for water vapor to penetrate due to the higher content and larger crystalline lamella. In terms of utilizing these films (patches) for the desired application, higher molecular weight HPC films with higher crystallinity will absorb water at a slower rate and hence release itraconazole with zero order kinetics.

In order to determine if the extrusion process degrades the HPC to produce modified molecular weight films, the degradation temperature was measured of the powder HPC before being extruded and post extrusion. The onset point of the degradation temperature of the powders, as seen by taking the intercept of the lines tangent to the weight loss curve, was compared to that of the films by TGA to determine if modification occurred during extrusion. These results are summarized in Table VIII-4.

Table VIII-4.

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Form & 80k & 95k & 140k & 370k & 850k \\
\hline
Powder (±0.2 °C) & 374.6 & 375.9 & 377.3 & 377.3 & 383.3 \\
Film (±0.2 °C) & 374.7 & 378.4 & 378.5 & 380.8 & 380.8 \\
\hline
\end{tabular}
\end{table}

Using the t test, it was determined that processing did not affect the degradation temperature of HPC powder. This indicates that there was little or no degradation of the HPC upon extrusion.
Conclusions

HME is a viable technology to produce thin, stable, and homogenous drug-incorporated HPC films. Data from these studies indicate that the matrices produced via HME utilizing various Klucel® HPC grades can be used for the controlled-release of poorly water-soluble drugs.

References

CHAPTER IX

CONCLUSIONS AND RECOMMENDATION FOR CONTINUED STUDIES

Conclusions

The research results from this project clearly show the need to understand the fundamental structure property relationships of poly(ethylene glycol) (PEG) polyurethane hydrogel films and microgels. Also important to understand is the behavior and properties of the microgels once modified with the covalent attachment of a hydrophobic small molecule for drug delivery applications. We have also examined the behavior of microgels in various matrices including more hydrophobic and constrained environments such as UV curable thiolene/acrylate films and more hydrophilic and porous environments such as a polyurethane dispersion and poly(D,L-Lactic Acid) films. The effect of the microgels on the morphology, thermal and mechanical properties, along with the degree of interaction between the microgel and matrix in each case has been studied.

The research completed to date has addressed PEG based hydrogel films and their structure/property relationship both hydrated and dehydrated. Also the synthesis of microgels based on similar chemistries as the films and the effect of reagents such as isocyanate and soft segment diol Mₙ, along with reaction conditions such as temperature, stir rate, and prepolymer concentration in the dispersion have effected the microgel particle size and particle size distribution. Several important conclusions can be drawn from the body of knowledge generated during the course of this research.

In PEG based films different characterization methods reveal the link between physiochemical interactions and their behaviors. In this study we have found that with increasing soft segment or PEG Mₙ in polyurethane crosslinked hydrogel systems, there
is an increase in Q or water retention due to the higher ratio of hydrogen bonding sites. Also by DSC it was found that there was an enhanced degree of crystallinity as PEG $M_n$ increased in the hydrogel films. Also the $T_m$s of the hydrogels are lower than the PEG reactant alone which is consistent with the addition of impurities.

In IPDI based microgels and PEG of molecular weights 400, 3400, and 6000, it was determined that there is a increase in relative crystallization from mP400 to mP3400 and a slight decrease from mP3400 to mP6000 as determined by DSC and WAXD. Also the water absorption is proportional to the PEG molecular weight used.

The addition of these microgels to coatings systems has resulted in films that in all cases have been modified in their thermal, mechanical, water sensitivity, and morphological properties. In the case of more hydrophobic thiolene/acrylate films, the resulting composite exhibited increased heterogeneities in the crosslinked network along with reduced crosslink density ($\overline{M}_c$) as seen by DSC and DMA. In addition, the microgels changed the morphology of the cross section of the films as seen by AFM phase imaging. The water absorption properties increased with larger PEG $M_n$ of the microgels and with increasing microgel wt%. Conversion rates and equilibrium conversions of thiol-ene and acrylate functional monomers were not significantly affected by the addition of microgels.

In examination of the hydroxy propyl cellulose extruded films, HME is a viable technology to produce thin, stable, and homogenous drug-incorporated HPC films. Data from these studies indicate that the matrices produced via HME utilizing various Klucel® HPC grades can be used for the controlled-release of poorly water-soluble drugs.
Recommendations for Continued Research

Future work with PEG based hydrogel films that would allow a more quantitative examination of the chain motion with temperature and heat can concentrate on determination of PEG chain motion using neutron labeled PEG chains in order to perform small angle neutron scattering experiments.

Microgel synthesis understanding will involve confirming the current predictive equation with more reactions and a more narrow nonlinear modeling DOE such as Box Benken or Central Composite Design of significant factors. Also examination of prepolymer Mₙ kinetics and behavior in relation to the Taguchi factors examine will yield a large amount of understanding about this system.

After observing the effect of microgels on the thermal and mechanical properties of polylactide films, continued research should address the morphology of the gels in the matrix by saturating the hydrogels with water containing an aqueous dye. Also the change in hydrolysis kinetics and the effect of gel particles on the diffusion pathways of water entering the film and oligomers resulting from hydrolysis migrating out of the film is of great interest. This can be determined gravimetrically and the diffusion pathways examined by SEM. The resulting thermal and mechanical properties monitored at different stages of hydrolysis will also yield a large amount of structure/property understanding.

Studies involving the covalent bonding of hydrophobic small molecule acyclovir to the PEG based microgels have set the stage for future drug release examinations. This includes studies will involving analysis of the drug and degradation products released.

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from these microgels over time and how it changes with PEG $M_n$, which effectively alters the mesh size. Also the drug bond moiety to the polymer, either urethane or ester and its effect on small molecule elution should be examined.

Recommended future work on hydroxy propyl cellulose films includes studies to increase the initial drug content by preventing the formation of solid bridge at the throat of the hopper. “Starve feeding” or a force-feeding/controlled feeding device will be used in future research for the extrusion of HPC.
A. APPENDIX

The prepolymer reaction was monitored by $^1$H NMR in which it was found that over 3 hours, 84.15% of the urethane groups are formed, by monitoring the conversion of the primary amine on IPDI to urethane formation at 8.2 ppm in Figure A-A-2 when integrated with respect to the ethylene oxide peak which remains constant throughout the reaction at 3.4-3.8 ppm. This is assuming that 100% of the isocyanate groups have reacted in the spectrum of the resulting microgels. (Figure A-A-1)

*Figure A-A-1.* $^1$H NMR spectrum of the P6000 prepolymer at t=0 hours.
Figure A-A-2. $^1$H NMR spectrum of the P6000 prepolymer at T=3 h.
B. APPENDIX

Once films were drawn out and placed in the vacuum oven for 48 h at 50°C, it was found that there was still residual NMP within the films. NMP was identified first by gas chromatography and then confirmed gravimetrically by TGA (Figure IV-1) to be at 19.2 wt% remaining in the film. Such a low temperature of 50°C for 48 h was chosen so as not to degrade the polyurethane and to minimize a change in conformation or morphology of the microgel composite within the film. This residual NMP acted as a plasticizer within the film, but to what degree it has an effect on the mechanical properties is of importance. Once placed in deionized water for 24 h, the films swelled in water and once dehydrated, it was confirmed by GC that the films contained only 4.01 wt% of the film. Mechanical properties of the two films containing 2 levels of NMP, the thermal and mechanical effect of microgels on the polyurethane films, microgel morphology, and mass loss over time in an aqueous environment were measured.

*Figure A-B-1. 19.2% small molecule left by TGA in 40°C vacuum oven for 48 hrs, 4.01% found in 48 h water soaked films.*
As mentioned previously, the films contained 19% NMP after being placed in the vacuum oven for 48 h at 50°C. This low temperature prevents significant degradation of the materials from taking place, but also is not very effective in ridding the film of a high boiling solvent like NMP at 204.3°C. It is also very interesting from a scientific standpoint to quantify the effect of NMP as a plasticizer on the composite systems mechanical properties.

Looking at the mechanical properties of films containing 19% and 0-45 wt% mP3400, (Figure A-B-2), microgel addition to the films creates overall lower elasticity at temperature below 0°C. This is a result of the microgels adding crystallinity to the system and also this indicates little interaction between the microgels and the surrounding polyurethane matrix.

![Storage Modulus vs Temperature](image)

**Figure A-B-2.** mP3400 series in films containing 19% NMP.
In films containing 0-45 wt% mP6000 (Figure A-B-3), there is a slight increase in the elasticity of the films at temperatures below 0°C which could be a result of larger mesh sizes in the microgel because of the high PEG Mₙ that would allow more interaction of the polyurethane dispersion chain ends with the hydrated microgel. Since there is not a continuous phase at 5%, as seen by SEM, of the microgels then there is a synergistic effect of the microgels in the polyurethane matrix in terms of elasticity as illustrated by the rise in the storage modulus in the glassy region.

![Graph showing storage modulus vs. temperature for different mP6000 concentrations](image)

*Figure A-B-3. mP6000 series of films containing 19% NMP.*

After films have been soaked in water for 24 h in an effort to further extract NMP, 4.01% NMP remained in the films. This reduction of NMP lowers the storage modulus of the films greatly below 0°C (Figure A-B-4). However the films containing only 4% NMP maintain their elasticity for 25°C past that of the films containing 19% NMP.
The same trend is seen in films containing microgels based on PEG $M_n$ 6000. Because of this very similar mechanical behavior with films containing mP400 and mP6000, it can be concluded that the increased crystallinity that mP6000 adds to the films does not significantly affect the mechanical properties of the film meaning that the mechanical properties of the microgels do not affect the composite film properties. This also suggests a lack of interaction of the surrounding matrix with the microgels.
Figure A-B-5. Films containing mP6000 series.
C. APPENDIX

Experimental

Small Angle Light Scattering (SALS)

SALS images were obtained by use of incident light from a 3 mW He-Ne laser (\(\lambda=632.8\) nm, Oriel Corp., model 6697). A \(V_v\) scattering pattern was projected onto a sheet of paper and the image collected with a Photometrics SenSys 1401E CCD camera interfaced with a computer. Polar Version 2.6.6 was used to integrate the pattern and translate the values into Intensity vs. \(q\) (1/nm). Scattered light intensity is reported as a function of wavenumber \(q=(4\pi/\lambda)\sin(\theta/2)\), where \(\lambda\) is the wavelength, and \(\theta\) is the scattering angle in the medium. Peakfit Version 4.12 was then used to fit the peaks according to a Savitsky-Golay smoothing method to quantify the resulting peaks. ImageJ version 1.37 was then used to quantify domain size of the phase contrast optical microscope images (PC-OM) that were correlated to the SALS data for each sample. (Figure A-C-1)
Figure A-C-I. Example of quantifying peaks of integrated SALS pattern (Intensity vs. q) in Peakfit software.

The resulting peak maxima from the smoothed SALS pattern in Peakfit were then measured. The first peak from the center of the diffraction pattern or from 0 is attributed to the laser beam. Only the second and third peak from the center of the diffraction pattern peak, or the diffraction halo, is considered to contain relevant information about domain sizes. The inverse of q was then taken to find the correlation length or domain size, L, which is plotted as a function of relative humidity and wt % microgels.

Results and Discussion of PU Films
PU films with 0 wt % microgels over a range of RHs from 0-100 % exhibit little change in phase domain size and number by SALS. (Figure A-C-2) Looking at the second and third peaks only, since the 1st peak is a result of the beam, it appears that there is little change in domain size. However by PC-OM, there is evidence of film deformation around 75% RH indicating that the water rich regions could have too similar a refractive index compared to the continuous matrix to be detected by these methods. (Figure A-C-3)
In films containing 5 wt % microgels over a range of RHs, there is enough of a refractive index difference between the microgels and the PU continuous matrix for the phase domains to be visible by PC-OM. (Figure A-C-5) By SALS at 0 % RH, there is a correlation to PC-OM, with aggregates of microgels having domain sized of around 70 um, and single microgels being around 20 um. (Figure A-C-4) At 75% and 100% RH,
the domains that grow larger with water uptake run into the 1st peak, or the beam, while the smaller water rich regions are in a range of 20-30 μm.

![Graph showing L-domain size vs. Microgel content](image)

**Figure A-C-6.** Control PU film containing 0-45 wt% mP3400 at 0 % RH.

![Images of PC-OM](image)

**Figure A-C-7.** PC-OM images of films containing 0-45 wt % microgels at 0 % RH.

In PU films containing 0-45 wt % microgels at 0 % RH, 0, 25, and 45 wt% microgels all show similar phase domain sizes by SALS (20-30 μm). (Figure A-C-6)

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This is a result of the microgels forming their own continuous phase within the film, resulting in little change in the scattering pattern compared to the bulk PU sample. Also by PC-OM images it appears that there is little difference in the refractive index of the two polymers. (Figure A-C-7) However, at 5 wt% gels there is an increase in phase domain size at 70 μm. This is due to most of the microgels being discrete, with aggregates or pockets occurring within the matrix.

Results and Discussion of TE-A37 UV Cured Films

![Graph showing L-domain size vs RH]

*Figure A-C-8.* TE-A37 UV film containing 0 wt% mP3400 at 0-100 % RH.

![Three images showing PC-OM images of films]
a.) b.) c.)

*Figure A-C-9.* PC-OM images of films containing 0 wt % at a.) 0, b.) 75, and c.) 100 % RH.
There is little difference in the phase domains of TE-A37 films until 75% RH when water rich regions push the 1st beam peak to larger domains of around 180 um. (Figure A-C-8) This is not seen in PC-OM so there is not a large difference in refractive index of water rich domains and the continuous matrix. (Figure A-C-9)

![Figure A-C-10. TE-A37 UV films containing 5 wt % mP6000 at 0-100% RH.](image)

![Figure A-C-11. TE-A37 UV films containing 5 wt % mP6000 at 0-100% RH](image)
In films containing 5 wt% mP6000, there are domains of 40 um observed by SALS Figure A-C-12 which correlate to the PC-OM image (Figure A-C-13). However, at 75 % RH the domains become too large and run into the beam or 1st peak making them undeterminable by SALS. There is enough of a refractive index difference between water rich regions and the continuous matrix to make these domains visible by PC-OM, where domains are on the order of 25 um.

![UV film 0-10 wt% microgels (0 RH)](chart)

*Figure A-C-12.* TE-A37 UV films containing 0-10 wt% mP3400 at 0 % RH.

![PC-OM images of TE-A37 containing 0-10 wt% mP3400 at 0 % RH.](image)

*Figure A-C-13.* PC-OM images of TE-A37 containing 0-10 wt% mP3400 at 0 % RH.
In both the SALS and PC-OM data, there is not a significant change in the phase domain size of 20-37 μm in TE-A37 films containing 1-10 wt% microgels.

Results and Discussion of PDLLA Films

Figure A-C-14. PDLLA film containing 0 wt% mP3400 at 0-100 % RH

Figure A-C-15. PC-OM images of PDLLA containing 0 wt % mP3400 at a.)0, b.) 75, and c.) 100 % RH.

PDLLA films containing no microgels have very hydrophilic properties and take up water at 25 % RH. This is demonstrated by the increasing domain size from 20 to 40 μm in the SALS results. (Figure A-C-14) At 50-100 %RH, the presence of the halo

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disappears because the domains have gotten so large that the halo runs into the 1st peak resulting from the beam. (Figure A-C-15)

![Graph showing changes in L-domain size (um) with RH (%)](image)

**Figure A-C-16.** PDLLA films containing 5 wt% mP3400 at 0-100 % RH.

![Images of PC-OM](image)

**Figure A-C-17.** PC-OM images of PDLLA films containing 5 wt% mP3400 at a.) 0, b.) 75, and c.) 100 % RH.

In PDLLA films containing 5 wt% mP3400, the SALS data shows a second halo (third peak) attributed to the domains created by the presence of microgels. (Figure A-C-16) As these regions grow with RH, there is evidence of larger domains in both SALS data, indicated by the second and third peak running into the beam halo, and PC-OM images. (Figure A-C-17) At 100 % RH, the water rich domains are dispersed homogeneously throughout the matrix, and result in new domains from 20-30 μm.
In films containing 0 wt % mP3400 at 0 % RH, there are domains of 20 µm, as determined by SALS, (Figure A-C- 18) however there is no phase separation seen by PC-OM. (Figure A-C- 19) With 1 wt % of mP3400 there the appearance of a second halo (peak3) that is due to the microgels. The domain size changes very little in the SALS data with increasing mP3400 content, but from PC-OM it can be seen that a larger number of aggregates is present, at 10 wt % mP3400.
D. APPENDIX

**Figure A-D-1.** PDLLA with 1 wt% mP400, M_n and PDI over 69 days in buffer solution.

**Figure A-D-2.** PDLLA with 10 wt% mP400, M_n and PDI over 69 days in buffer solution.

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Figure A-D-3. PDLLA with 1 wt% mP6000, $M_n$ and PDI over 69 days in buffer solution.