

Smart Polymer Layer by Layer Assembly

Major Qualifying Project Report

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Abstract

The utilization of smart polymers, in recent years, has achieved various reactions, such as swelling and changes in porosity, under a variety of external stimuli, such as temperature, pH, and heat. The use of multiple cross-linked smart polymers allows for tailoring of both the stimulus applied, and the degree of swelling and shrinking occur. Layer by layer (LbL) assembly, using polystyrene as a non-polar barrier, has been used to achieve controlled crosslinking throughout the polymer sample. The use of multilayered polymer hydrogels for the controlled release of a variety of substances placed within the structure of the gel are currently in research stages for cancer treatments. This project was undertaken assembly and characterizing both NiPAM and PAA hydrogels assembled layer by layer to analyze the characteristics of this mode of assembly, and characterized swelling through pH tests.

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1. Introduction

Smart polymers are materials which, when cross-linked and made into a hydro polymer gel, are affected in unique ways, such as swelling or changing porosity, by a number of different stimuli, such as temperature, pH, and magnetic fields. Polymers are composed of repeating structural units called mers which when linked together. These chains can then be linked together through cross-linking, usually using a combination of environmental factors, such as pH, temperature, or photo-irradiation, along with a cross-linking agent to help the process along.

PNiPAM, Poly (N-isopropyl acrylamide) is a thermal sensitive smart polymer which is popular in research due the fact that around human body temperature, the polymer changes from hydrophilic to hydrophobic. Thus this polymer is viewed as having great potential in future polymer based drug delivery systems. PAA, Poly (acrylic acid), is another smart polymer, which exhibits swelling and porosity change in response to changes in pH. This polymer has been researched in depth for over thirty years because of the ease with which these reactions are obtained.

There are several ways by which hydro-polymers can be assembled into useful constructs. Polymer printing essentially uses the polymer as the ink in an ink jet printer, deposits the polymer layer by layer, then the polymer is cross-linked to produce a usable construct. IPNs, or inter penetrating networks, can be assembled in various ways. Essentially two different polymer networks are intertwined with each other to make one layer with unique properties due to its intricate composition and structure. LbL, or layer by layer assembly, is the manual assembly of each layer of polymer gel to produce a usable construct.

This project aims to see the construction of a dual polymer structure made of inter-changing layers of NiPAM and PAA, using polystyrene as a non-polar barrier to keep the layers separate. The resulting construct would have alternating layers, capable of being impregnated with different

substances, thus producing a structure capable of reacting to both temperature, and pH changes in the environment around the construct.

2. Background Research

There are many methods to create and package hydropolymers as ongoing research is still yielding new results. The necessary methods to crosslink and package hydropolymers were researched in order to gain the necessary background information to formulate the procedures and methods to accomplish the objectives of this MQP.

2.1 Polymers and Gels

Polymers consist of monomers or repeating structural units to create long chains which consist of a carbon backbone and functional groups (the chemical mechanism responsible for most of the properties of the polymer). The mechanical properties of the polymer are largely dependent on the nature of the bonds which hold the polymer together. Hydrogen bonding is the attraction of the hydrogen atoms in a polymer forming weak bonds with other electro-negative atoms in other, or even the same, chains within the polymer structure. Covalent bonds makeup the majority of the chemical bonds which hold the polymer chains together.

2.2 Methods of Crosslinking Hydropolymers

The aim of creating a hydropolymer is to cross link the polymer chains in order to create a network capable of water retention. Crosslinking is achieved when the polymer chain is bonded to parallel polymer chains covalently rather than relying on the weaker hydrogen bonds. This project used hydrophilic polymers as opposed to those which are hydrophobic or repel water [2]. Different methods are used to achieve these ends, often using radiation, heat, or radiation, in conjunction with a chemical cross-linking agent, to achieve a degree of crosslinking capable of forming a hydropolymer.



Figure 1 – NIPAM Polymer Solution in initial stages of Crosslinking



Figure 2 – PAA Hydrogel taking shape after undergoing Thermal Crosslinking

2.2.1 Free Radical Polymerization

Published Journal Articles utilize simultaneous free radical polymerization (the process of creating the polymer chain from the monomer (mer) unit while adding chemical agents and catalysts to achieve a high quality hydropolymer. These procedures can be modified to achieve crosslinking by using preformed polymer chains obtained by a chemical supplier.

2.2.2 Thermal Crosslinking

Thermal crosslinking utilizes thermal energy and chemical agents to induce crosslinking among polymer chains. Convection oven or water baths are often used as a thermal energy source to the prepared polymer solution. The time and temperature allotted for the polymer solution control the degree of crosslinking. A water bath is ideal because it allows for more precise temperature regulation.



Figure 3 - Preparation of Polymer Solution



Figure 4 - Thermal Crosslinking of Polymer Solution in Washburn Labs

2.2.3 Photo-Irradiation Crosslinking

Photo-irradiation can be used to achieve both polymerization and crosslinking of the polymer. In order to crosslink the polymer a source of radiation (UV light) is used in while a photo-reactive agent and catalysts are necessary chemical additives. Studies have shown the amount of UV irradiation governs the degree of crosslinking, making this process ideal for controlling the degree of cross-linking of the hydropolymer [3].

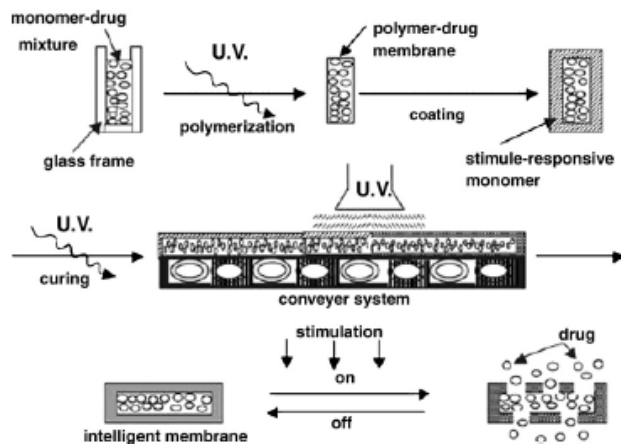


Figure 5 – Process for Drug Release Mechanism by Photo-Crosslinking

2.3 Smart Polymers

Creating hydrogels with smart polymers enable the hydrogel to respond to different external stimuli (i.e. temperature, pH, ionic concentration, electromagnetism, and heat). This MQP group studied Poly(N-isopropylacrylamide (NIPAM) and Poly Acrylic Acid (PAA) which are temperature and pH reactive, respectively.

2.3.1 NIPAM

NIPAM is a thermal sensitive smart polymer with a Lower Critical Solution Temperature (LCST) in the range of 30 °C to 35 °C as the polymer is hydrophilic below this range and hydrophobic above. NIPAM is cross-linked when heated above the LCST in a prepared solution of either *N,N'*-methylene-bis-acrylamide (MBA) or *N,N'*-cystamine-bis-acrylamide (CBA) [2]. MBA is the crosslinking agent used for this project because of its widespread use in published research attributing to its validity and also allowing for multiple procedures to be adopted. The relevancy of NIPAM in ongoing research is attributed to its swelling behavior in the range of temperature similar to the human body allowing for easy application to drug delivery systems.

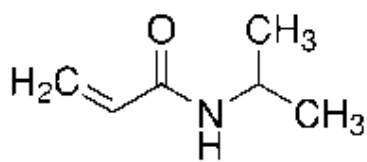


Figure 6 – Chemical structure of NIPAM

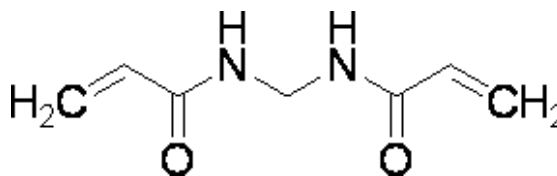


Figure 7 – Chemical structure of MBA

2.3.2 PAA

PAA is polyelectrolyte polymer which contains an electrolytic functional group. Its pH sensitivity allows swelling and porosity change with varied pH levels. PAA has also yielded research applicable to drug delivery systems and the biomedical industry. Research determined it necessary to co-polymerize

PAA with Poly (vinyl alcohol) (PVA) in order to create a quality hydrogel [4]. The best candidate for a crosslinking agent was determined to be Glutaraldehyde due to its superiority over Glyoxal in a research study [5].

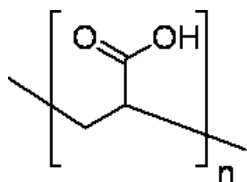


Figure 8 – Monomer structure of PAA

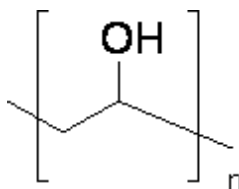


Figure 9 - Monomer structure of PVA

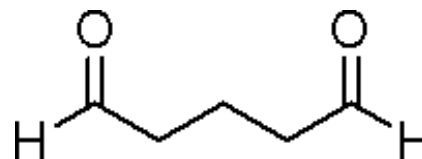


Figure 10 - Chemical structure of Glutaraldehyde [12]

2.4 Methods of Assembling Hydro-polymers

The application of hydro-polymers can be determined by which the method they are assembled or packaged. The different packaging techniques can achieve different results for different applications.

2.4.1 Polymer Printing

Recent advances in inkjet printing technology have allowed for the adoption of polymer printing using the equivalent technology found in commercial printers. Previous MQP groups at WPI have designed and implemented polymer printers to print polymers from a designed polymer solution [6]. The advantage of Polymer Printing allows for the gradient control of layers. The printer deposits a thin film over multiple iterations to produce a three dimensional polymer structure. The gradient control achieved by polymer printers has great potential in the biomaterial industry and drug application.

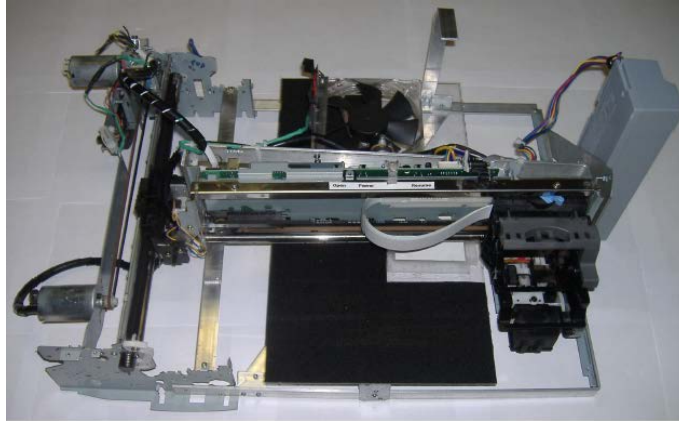


Figure 11 - Polymer Printer Developed by Multilayer Polymer Inkjet Printing MQP [6]

2.4.2 IPN

An IPN or semi-IPN is composed of two or more distinct polymer networks. The polymer chains are entangled, but not covalently bonded to one another. The creation of an IPN improves the mechanical property of the hydrogel when not swollen, however this is not true when the hydrogel undergoes swelling [7]. It is easier to produce because of the structural interdependence of the two polymer networks on one another. The IPN allows for the integration of multiple polymers which increase the capabilities and application of the produced hydropolymer. However, the application of a drug delivery system is complicated by the increased number of polymer networks.

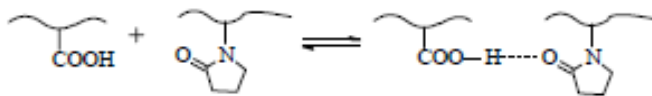


Figure 12 –Chemical Representation



Figure 13 –IPN process of PAA and PVP [8]

2.4.3 LbL

LbL assembly produces multilayered films through a simple and versatile process. The modern process was originally developed by Decher and co-workers in 1991 and has been further developed by additional research groups to form a collective set of procedures allowing for the widespread applicability of LbL [1].

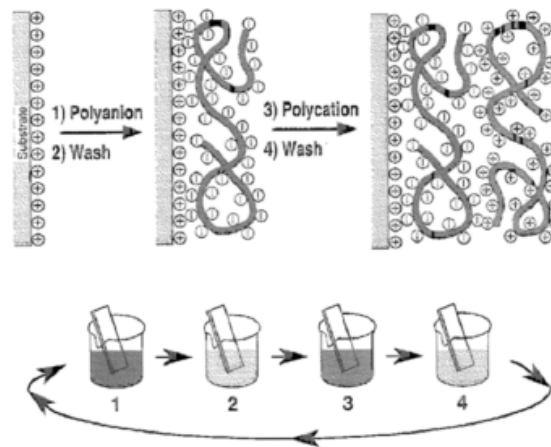


Figure 14 - LbL Assembly Method for Multilayered Films by alternate dipping method [9]

Layer by layer assembly allows for the containment of multiple different hydro polymers, each with a different set of drugs contained within. This allows for different substances to be released by a different trigger for each different polymer in the multiple layer construct. The ability of LbL assemblies to contain alternating layers, each with different drugs would allow for greater customization of treatment.

3. Objectives

1. Crosslink PAA and NIPAM
2. Create a functional hydrogel polymer
3. Assemble PAA and NIPAM into a structure; utilizing Polystyrene as a (non polar or polar) barrier
4. Investigate the effects of swelling under temperature and pH changes

4. Methodology

The Project began under the pretense of layer by layer assembly using a polymer printer, however after several mechanical failures a new printer would have been needed the project was sent in the direction of solvent casting. Solvent casting in the broadest term is the dissolving of a material to make into a certain shape, through way in a medium, called a solvent, the resulting solution is poured into a mold of some kind and the solvent is removed. This was the technique through which PAA was cross-linked with PVA, to make a hydro-gel, which is a cross-linked network, in which 2 polymers have been chemically mixed together, often exhibiting cross-linking density of 5 to 15%, in an aqueous solution.

A variety of molds were designed to contain the polymer during cross-linking. Plaster molds coated in paraffin wax were the first attempt, however it was found that the layers would break up after two to three uses causing the solution to absorb into the mold, resin molds were next, due to cracking over repeated cycling in the oven, silicone molds were found to cause sticky residue, due to over curing, increasing the difficulty to handle the polymer, causing sticking to the mold after extended times in the oven. Non-stick aluminum foil was finally shaped to the inside of a beaker and found to be adequate.

4.1 PAA

PAA, supplied by Aldrich with no further purification, was mixed in a solution of 75% water 25% isopropyl alcohol, the isopropyl alcohol, being intended to assist the PAA to dissolve in the water, which was found to be unneeded, due to PAA being hydrophilic. Initial tests used solutions with 5, 10, 15, 20 and 25 wt% PAA.

Samples below 20 percent lacked concentration to separate out from the water in a reasonable amount of time, 25% solution was found to gain similar results to 20wt% PAA.

The first laboratory procedure with PAA involved heat treating it at 60°C for 6 hours, removing some, others were heated again at 80C for 1 hour. The PAA was found not to reliably form testable discs. PVA was introduced, through the literature review, using a proportion of 5/1 PAA/PVA, with Gluteraldehyde as a cross-linking agent [10].

Non-stick aluminum foil lined beakers were used as containment vessels, the samples were heat treated at 60C for 60 minutes, dried, then heated to 80C for 30 to 45 minutes, followed by increasing the temperature up to 120C over 5 to 10 minutes, the samples were then allowed to reach room temperature.



Figure 15 - PAA Hydropolymer

4.2 NiPAAM

NiPAAM, supplied by Aldrich and used without further purification, was mixed with distilled water in varying weight concentrations (5, 10, 15, 20, 25%), with samples between 5 and 15 total grams, for at least a day, until in full solution. The samples were then heated just above LCST, around 40°C for between 20 minutes and 8 hours, with 1wt% MBA cross-linking agent, then allowed to reach room temperature [4].

4.3 Swelling test preparation

Preparation for swelling tests started by dissolving polystyrene, Styrofoam was used, into acetone, heating to around 40°C for between 1 and 4 hours, separating the finished solution into 2 beakers. Two to three drops of food coloring were then dropped in each beaker, as shown below.



Figure 16 - Dissolving Styrofoam(Polystyrene) in acetone



Figure 17 - PAA/PVA samples after coatings applied

One sample was dipped into one of the beakers of polystyrene solution, some were layered in alternating colors, stacked then dried at 120°C. More than three layers put together at once caused the layers to fall apart during drying.

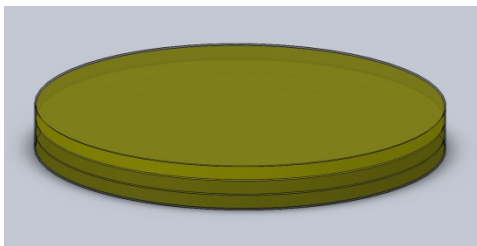


Figure 18 - View of Cad Model

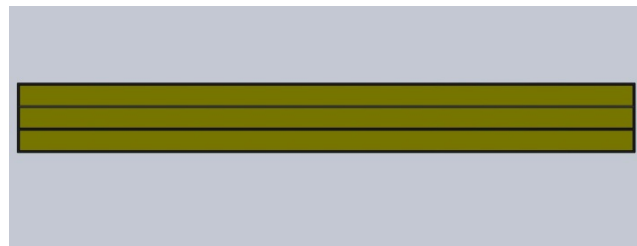


Figure 19 - Cross Sectional View of Cad Model

4.4 Swelling test

Samples were tested by being exposed to 1 molar HCL with data being recorded about every half hour until the sample stopped expanding. The samples were then put in distilled water for between

10 and 45 minutes, dried , then put through the above test but with 1 molar NaOH until shrinking ceased.

5. Results and Discussion

5.1 PAA

The resulting samples were extremely brittle, and were unable to measurably swell or contract in acid or base.

5.2 PAA/PVA

Sample #	Exposure type	Dilation (mm)	change in T (mm)	effective time (min)
1	HCl	1.4		48
1	NaOH	-0.5		41
2	HCl	-1	2	115
2	NaOH	-0.5	-1	79
3	HCl	1	-1	58
3	NaOH	0	-1	28

Table 1- Swelling Test Results

The table showed that both the amount of expansion, shrinkage, and effective time were primarily related to the volume, this were not so evident due to the holes in the data, the thicknesses of the first sample was 3.5 mm. Due to the lack of samples, further discussion will be qualitative.

These tests showed that NaOH reliably caused shrinking, and HCL caused expanding, in the samples although strange geometries of the various samples caused numbers to have some unforeseen results. The degree to which each sample expanded and shrank was variable relative to the thickness, diameter, and irregularity of the geometry of the samples.

5.3 NiPAAM

Samples would often begin the process of cross-linking, but lack of temperature control did not allow for storage of samples overnight, variance of temperature in oven, along with lack of atmospheric control, caused inhibiting of cross-linking making any completed samples useless [10].

5.4 Multiple layer tests

The polystyrene coatings didn't have a calculable effect on the swelling, however measurements were relatively crude, measured with a ruler, as of such further testing and analysis would be needed to confirm any effects that a PS coating have on the polymer samples.

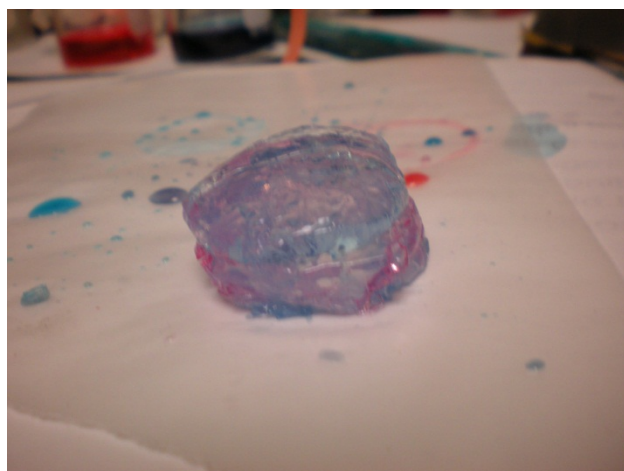


Figure 20 – multiple layer hydrogel construct



Figure 21 – construct after exposure to acidic solution

Once a procedure was found that allowed layers to stick together, through further heat treating, the PS coatings caused deflection in the layers, which eventually caused the multi-layer constructs to disassemble, however there was not enough time to do further testing to find the amount of time it took, or the maximum number of layers we could assemble in a stable structure.

6. Conclusion

Experimental procedures were implemented to crosslink NIPAM and PAA into functional hydrogels in order to create the desired components in Design A. Iterations of experimentation yielded a functional and non-functional hydropolymer for PAA and NIPAM respectively. Design B was developed and implemented to adapt to the results obtained during testing in order to demonstrate the LbL principle using repeating layers of the same hydrogel encased in a thin coating of polyethylene, as opposed to the alternating layers achieved by Design A. Both the singular samples and LbL assembled hydrogels were tested for swelling under different pH conditions.

Assembled polymer structure was created using three repeating layers of PAA hydrogel, encased in a thin coating of PE (polyethylene). The hydrogels were created utilizing heat treatments with chemical additives.

The assembly of a multi-layered polymer sample was accomplished through cross-linking, although this sample was not functional, the properties of the layers has been shown to be reliable, if not very predictable, paving the way for future projects to build a printer which can print out layer by layer, allowing for quick consistent assembly, allowing for proper characterization of PAA/PVA smart polymer.

Research for applications of the research done during this project include multiple triggered, multi-drug delivery systems capable of various rates of release on each layer, allowing for long term treatment of various illnesses could be treated with the application of a patch, or graft. Further research in the area could un-cover smart polymers which respond to new stimuli, such as applied forces, or unique combinations of inputs, in order to trigger changes in properties from thermal conductivity, to electrical conductivity, from Young's modulus toughness.

This project has seen many obstacles, from a complete change of premise, to the trial and error adjustment of the laboratory procedures needed to produce a functional hydro polymer with the facilities supplied. In the end the project saw the collecting of valuable data and experience by the team,

paving the way for future teams in the direction of researching the properties of different co-polymers, and even nano-polymers.

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