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Permeability of Responsive Polymer – Grafted Porous Membranes: Temperature, pH and Multi-Stimuli Response

By

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A thesis submitted in conformity with the requirements for the Degree of Doctor of Philosophy
Graduate Department of Chemical Engineering and Applied Chemistry
University of Toronto

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Permeability of Responsive Polymer – Grafted Porous Membranes: Temperature, pH and Multi-Stimuli Response

Doctor of Philosophy, 2000, Tao Peng,

Graduate Department of Chemical Engineering and Applied Chemistry, University of Toronto

ABSTRACT

A temperature-responsive polymer, poly(N-isopropylacrylamide) (PNIPAAm), and a pH-responsive polymer, poly(methacrylic acid) (PMAA), were singly grafted and co-grafted onto porous polyethylene (PE) membranes by photochemical means. Graft yield, graft location, co-graft yield and composition were varied by controlling grafting time, grafting solvent and monomer concentration.

Characterization of the PNIPAAm-g-PE membranes by X-ray photoelectron spectroscopy, scanning electron microscopy (SEM), and membrane thickness measurements shows that PNIPAAm is grafted on external membrane surfaces as well as inside membrane pores. Thickness changes with temperature are minimal at graft yields below 150%, but the thickness increases with further increasing graft yield. Characterization of the PMAA-g-PE membranes shows that methanol can increase grafting inside the pores in comparison with water solvent - presumably due to variations in pore wetting. Co-grafted membranes were prepared using a sequential co-grafting procedure. It is shown that the co-grafts are di-block in structure. Furthermore, differential scanning calorimetry results suggest that complexes between the two blocks are formed under certain conditions.

Permeation studies elucidate that low graft yield membranes show a lower permeability in the expanded state than in the collapsed state, explained by a pore control mechanism. High
graft yield membranes show the opposite phenomenon, a higher permeability in the expanded state, explained by a surface control mechanism. The transitional graft yield for the two mechanisms depends on the graft location and co-graft composition. In addition, permeability changes are reversible and reach a maximum at an intermediate permeant molecular weight.

A two-layer model is used to describe the permeation behavior of the grafted membranes. Polymers grafted inside the pores would close and open the pores by extension and contraction of the grafted chains. With increased grafting inside the pores, permeability decreases due to increased obstruction in the pores. Polymers grafted on the surface would form a surface layer to increase and decrease the permeability during swelling and de-swelling changes. With increased grafting on the surface, the membrane permeability becomes increasingly influenced by the surface layer.

Finally, the co-grafted membrane exhibits more sophisticated permeability changes, with more possible “set points”, than the singly grafted membrane.
Acknowledgments

I would like to thank my supervisor, Dr. Yu-Ling Cheng, for her guidance and help. Special thanks to Drs. Molly Shoichet and Kim Woodhouse for being advisors in my reading committee and to Prof. Kang-De Yao for his advice during my study in Canada. I am grateful to University of Toronto for financial support.

I also thank Hai-Hui Lin, Charlene Ng, Jennifer Smith-Hansen, Pina Turner, Josh Markham and other group members for their friendship, suggestions and help.

Last but not least, I wish to express my gratitude to my wife for her patience and understanding and to our parents for their encouragement and support. I am also thankful to my daughter for her teaching me thermodynamics when she is taking out her toys from a box and making a big mess, which reminds me that the phase transition of PNIPAAm in water is a entropy-driven process.
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Chapter 1  Introduction

This thesis addresses the subject of porous membranes on which stimuli-responsive polymers are grafted. Specifically, the effect of grafting parameters on graft yield, graft location and co-graft architecture is investigated, and the subsequent permeation characteristics are determined. Although it is well known in such membranes that the porous substrate provides mechanical support, while the grafted responsive polymers act as a permeation 'valve' by conformation transitions between collapsed and expanded states, a systematic study is needed to understand the effect of graft yield and location on the permeability change of the membrane. The study would reconcile conflicting reports in the literature and demonstrate possible applications for responsive release through the membrane. Moreover, the study allows us to develop a novel type of membrane by co-grafting two kinds of responsive polymers onto a porous substrate to achieve more sophisticated control over membrane permeability.

Controlled release is one of the most promising potential applications of responsive membranes. It is well known that drug delivery systems, capable of releasing an active agent at a constant rate (zero order) over a long period of time, improve therapeutic efficiency for some drugs. However, the constant drug release profile of such devices is not optimal for all drugs. It is more desirable to release certain drugs in a patterned manner, or in response to the body's needs. Examples include insulin for diabetes treatment, antiarrhythmics for heart disease therapy, gastric acid inhibitors for ulcer control, contraceptives for birth control, hormones, and drugs for immunization and cancer chemotherapy [Kost 1991]. A system comprised of a responsive membrane can be designed to deliver drug in response to disease signals or external stimuli.

Separation may be another potential application. Since the pore size of the membrane
can be changed in-situ by external stimuli a reversible separation process from microfiltration to ultrafiltration can be achieved [Liang 1999].

Recently, copolymers that respond to more than one stimulus have been investigated [Park 1999, Yuk 1997, Chen 1995]. The copolymer response triggered by different stimuli may be independent, or they may influence each other in either synergistic or antagonistic ways depending on the structure of the responsive copolymers. Random copolymers exhibit mutual influence on their stimuli responsiveness, while graft or block copolymers show independent responsiveness in each chain segment [Chen 1995].

More complex pulsatile release patterns can be achieved using multi-stimuli responsive copolymers in comparison with the on-off release pattern obtained with single-stimulus responsive polymers. For example, random copolymers of NIPAAm, butylmethacrylate and acrylic acid showed a lower critical solution temperature (LCST) which is dependent on pH due to the ionization properties of acrylic acid [Feil 1993]. Such copolymer beads were proposed for oral delivery of peptide drugs, such as human calcitonin [Serres 1996]. At pH 2, the LCST was below the body temperature. The polymer was insoluble, prevented drug release and thus prevented the peptide from gastric degradation in the stomach. At pH 7, the LCST increased above the body temperature at which the copolymer became soluble and allowed release of drug in the intestinal lumen.

In theory, multi-stimuli responsive membranes can be made from a copolymer or an interpenetrating polymer network, which contain different responsive components. They can also be prepared by grafting the responsive components onto a porous membrane. Reservoir devices for responsive drug release can then be designed using these membranes.

We are interested in multi-stimuli responsive membranes in order to achieve more
sophisticated control over permeability, leading to more distinct responsive release patterns. In addition, due to more control over membrane pore size, more effective separation of compounds with different sizes may be achieved utilizing such membranes. A novel method, which involves sequential co-grafting of two types of responsive polymers onto a porous substrate, was used to prepare a membrane with good mechanical strength, dimensional stability and multi-stimuli responsiveness.

1.1 Objectives

The thesis was designed to meet the following objectives:

1. To prepare responsive polymer singly grafted and co-grafted porous membranes. Specifically, a temperature-responsive polymer, poly(N-isopropylacrylamide) (PNIPAAm), and a pH-responsive polymer, poly(methacrylic acid) (PMAA) were singly grafted and co-grafted onto porous polyethylene (PE) membranes.

2. To investigate the effect of grafting parameters, e.g. grafting time, monomer concentration and grafting solvent, on the graft yield, graft location, co-graft yield and co-graft composition.

3. To understand the effect of the graft yield and location on the permeation control mechanisms in the responsive polymer grafted porous membranes.

4. To elucidate the co-graft architecture under different temperature and pH conditions.

5. To investigate the effect of co-graft yield and composition on the permeability of the co-grafted membrane.

6. To characterize and compare the temperature- or/and pH-responsive permeability changes of the responsive polymer singly grafted and co-grafted porous membranes.
1.2 Hypotheses

The permeability of a responsive polymer grafted porous membrane depends on the graft yield, graft location, co-graft yield and co-graft composition.

The responsive polymers can be grafted on the membrane surface (i.e. surface grafts) and inside the membrane pores (i.e. pore grafts). The polymers located on the membrane surface would show a different permeation control mechanism from those inside the membrane pores. Since the graft yield and location would affect the relative amount of the polymer grafted on the surface and inside the pores, the permeation control mechanism can be related to these two parameters.

The conformation of a copolymer grafted onto a porous membrane changes in response to stimuli, which leads to a difference in solute permeability. The conformation change would depend on the copolymer architecture which, in turn, is affected by the co-graft yield and composition.

1.3 Scope and Organization of the Thesis

To achieve the objectives and test the hypotheses stated in this thesis, membranes were prepared, characterized and membrane permeation experiments were conducted. Membranes were prepared by a photochemical graft polymerization method and characterized by scanning electron microscopy, X-ray photoelectron spectroscopy, differential scanning calorimetry, and swelling and thickness measurement. Membrane permeability under different temperature and pH conditions was measured.

The thesis is organized as follows: Chapter 2 provides a general literature review on the subject of stimuli-responsive polymer membranes, particularly as they are used in permeation
control applications and serves as background for the entire thesis. Chapter 3 describes the
general methods that were used throughout the thesis. Chapters 4, 5 and 6 represent the original
research work performed in this thesis; each of these chapters is presented in the format of a
journal paper, with abstract, introduction, results and discussion, conclusions and references.
Chapters 4 and 5 are modified from papers that have already been published [Peng 1998, 1999].
while Chapter 6 will be modified and submitted as a journal paper. Chapter 7 provides an
overall discussion of the results presented in Chapters 4, 5 and 6. General conclusions and
recommendations for future work are presented in Chapter 8.

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Chapter 2  Literature Review

2.1 Introduction

Polymer membranes have been used in many diverse fields, such as the chemical, biotechnological, pharmaceutical and medical industries where the membrane acts as a thin barrier between the two phases as shown in Figure 2.1 [Bungay 1983]. Mass transport of components across the membrane occurs due to the presence of driving forces, such as concentration gradient $\Delta C$, pressure and temperature difference $\Delta P$, $\Delta T$, and electric field $\Delta E$ [Mulder 1991].

![Polymer membrane diagram](image)

Figure 2.1 Schematic representation of a two-phase system separated by a polymer membrane.

Normally, membrane properties are fixed once the membrane has been fabricated. In some applications, however, it would be desirable for the structural and functional properties of the membrane to change in response to stimuli such as changes in temperature and pH of the
surrounding environment. Such membranes, called intelligent or stimuli-responsive membranes, have become the focus of increasing attention in the past few years. In particular, membranes with stimuli-responsive permeability have been widely investigated. The stimuli-responsive membranes may be made from a large variety of polymers, and may be made to be responsive to a number of different stimuli (Table 2.1).

This chapter provides a review of stimuli-responsive membranes whose permeability to solutes can be controlled by the conditions of the external environment. The review is divided into sections according to membrane type, i.e. hydrogels, liquid crystalline polymers, crystallizable polymers, conductive polymers, and porous substrate membranes with adsorbed or grafted responsive polymers. Within each section, discussion is organized according to the stimuli and mechanism used to control permeability, i.e. temperature, pH, electric field, light, and chemical and biological species. Potential applications are presented where appropriate. Multi-stimuli responsive polymers are reviewed separately in section 2.7.

Table 2.1 Different types of stimuli-responsive membranes and their environmental stimuli

<table>
<thead>
<tr>
<th>Types of membrane</th>
<th>Environmental stimuli</th>
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<tbody>
<tr>
<td>Homogeneous hydrogel membranes</td>
<td>Temperature, pH, electric field, light, chemical or biological species</td>
</tr>
<tr>
<td>Heterogeneous hydrogel membranes</td>
<td>Temperature and pH</td>
</tr>
<tr>
<td>Liquid crystalline polymer membranes</td>
<td>Temperature and electric field</td>
</tr>
<tr>
<td>Polymer dispersed liquid crystal membranes</td>
<td>Temperature and electric field</td>
</tr>
<tr>
<td>Crystallizable polymer membranes</td>
<td>Temperature</td>
</tr>
<tr>
<td>Conductive-polymer based membranes composed of a conductive polymer and a substrate</td>
<td>Electric potential or current</td>
</tr>
<tr>
<td>Polymer-adsorbed or grafted porous membranes</td>
<td>Temperature, pH, electric field, light, chemical or biological species</td>
</tr>
</tbody>
</table>
2.2 **Hydrogel Membranes**

Hydrogels are crosslinked polymer networks capable of absorbing large amounts of water while retaining their three dimensional structures. The degree of swelling, a measure of the water content in hydrogels, is considered an important factor that influences many hydrogel properties, including permeability, and mechanical strength [Peppas 1986]. The properties of responsive hydrogels, most notably their degree of swelling, change in response to external stimuli. It is known that four fundamental interactions, i.e., van der Waals forces, hydrophobic interaction, ionic force and hydrogen bonding, play an essential role in determining the degree of swelling of hydrogels [Tanaka 1992]. The balance of these competing interactions can be disturbed by various stimuli, thus leading to a change in the degree of swelling of responsive hydrogels. Excellent reviews on responsive hydrogels have been published [Dusek 1993a, b and De Rossi 1991].

Hydrogels have been used as membranes to allow selective solute permeation from one compartment to another [Bell 1994]. A number of hydrogel membranes exhibit reversible swelling-shrinking transitions that translate into solute permeability changes in response to applied stimuli. It is known that water in the hydrogel serves as a pathway for solute diffusion through the hydrogel [Bell 1994, Gehrke 1993]. The mesh size, defined as the distance between two neighboring crosslinks or junctions in the hydrogel network, determines whether a solute of a certain size can pass through the space between polymer chains. As the water content of the gel decreases, so does its average mesh size, the obstruction of solute increases resulting in a decrease in hydrogel permeability. There are a number of theories and models that describe the relationship between the swelling of a hydrogel membrane and its permeability to a solute [Amsden 1998, Gehrke 1997]. Theoretical predictions of hydrogel membrane permeability have

One major disadvantage of hydrogel membranes is their poor mechanical strength [Peppas 1986]. A number of approaches have been used to improve the mechanical strength of hydrogels including formation of interpenetrating polymer network (IPN) structures [Frisch 1998], combination of hydrogels with a stronger inert membrane substrate (i.e. composite structure) [Sun 1999, Trank 1987], and dispersion of hydrogels in a matrix [Yam 1999, Turner 1998].

In the following discussion, hydrogel membranes are classified by the nature of the stimuli to which they show responsiveness. In each type of hydrogel membrane, the discussion is subdivided by the membrane structure, i.e. copolymer, IPN, composite and particle-containing structures.

2.2.1 Temperature-Responsive Membranes

Several families of polymeric hydrogels are known to exhibit swelling-deswelling transitions at upper or lower critical solution temperatures, and thus exhibit significant permeability changes at their critical temperatures. Based on this property, the temperature-responsive permeability has been achieved using the hydrogel membranes with various structures.

2.2.1.1 Copolymer Membranes

The most extensively studied temperature responsive hydrogel membranes are composed of copolymers of poly(N-isopropylacrylamide) (PNIPAAm) with other polymers.
PNIPAAm is a polymer within the family of polyamides - many of which show temperature-responsiveness [Plate 1999]. It is known that aqueous solutions of PNIPAAm exhibit a dramatic soluble-insoluble change at a lower critical solution temperature (LCST) of around 31~33°C, a temperature close to the physiological range [Heskins 1968, Yoshida 1994, Kaneko 1995]. The LCST can be shifted to lower or higher values by random copolymerization of NIPAAm with other hydrophobic or hydrophilic monomers, respectively [Feil 1993]. For example, it has been found that poly(N-isopropylacrylamide-co-butyl methacrylate), poly(NIPAAm-co-BMA) had a lower LCST than PNIPAAm due to the hydrophobic characteristics of the BMA units. In addition, the BMA units would reduce membrane swelling to improve mechanical strength of the copolymer membrane relative to the PNIPAAm homopolymer membrane.

The permeation of solutes of various sizes through poly(NIPAAm-co-BMA) hydrogel membranes was investigated as a function of temperature to assess their potential applicability for separation [Feil 1991]. It was found that permeability decreased with increasing temperatures due to decreased swelling of the membranes. The permeability of uranine (molecular weight=376) was the highest at all temperatures followed by the permeability of dextrans with molecular weight of 4,400 and 150,000. Based on these temperature and solute size-dependent permeation properties, separation of the three solutes was achieved by a step-wise change in temperature to allow for the sequential selective permeation of each solute. The free volume theory was able to describe the temperature-responsive permeability of the membranes.

Complete ON-OFF permeation control of glucose and insulin across poly(NIPAAm-co-BMA) membranes, in response to step-wise temperature changes between 20°C and 30°C, was
observed by Okano et al. [Okano 1990]. Upon a temperature change from 20°C to 30°C, permeation could be blocked quickly which was explained by dense surface layer formation in deswelling at 30°C. The surface layer formation is consistent with that reported by Yoshida et al. who studied the permeation of indomethacin through copolymer membranes of NIPAAm with alkyl methacrylates of different alkyl side chain lengths [Yoshida 1992]. Moreover, it was observed that the membranes containing longer side chain lengths formed the skin layer faster and showed lower membrane permeability than those composed of shorter side chains.

To make membranes thin and strong, graft copolymer membranes based on N-isopropylacrylamide-grafted poly(vinyl alcohol) were prepared and their temperature-responsive permeability was observed [Kurihara 1996, Nonaka 1994, Ogata 1994]. The membranes were prepared by casting the copolymer solution in dimethyl sulfoxide followed by annealing above 100°C or crosslinking with glutaraldehyde. The permeation of solutes with different molecular size and hydrophobicity such as lithium ion, methylene blue and poly(ethylene glycol)s. and butyl alcohols through the membranes could be regulated at temperatures below and above the transition temperature of 33°C.

Microcapsules containing PNIPAAm also showed temperature-responsive permeability. D’Emanuele et al. prepared indomethacin loaded microcapsules by emulsion polymerization followed by drug loading from solution [D’Emanuele 1995]. They found that thermo-responsive release of indomethacin from the microcapsules could be achieved.

Another type of thermo-responsive microcapsules was prepared by grafting PNIPAAm onto the surface of polypeptide microcapsules [Kidchob 1998]. It was shown that a dense skin layer of PNIPAAm was formed on the microcapsule surface at 40°C, resulting in a lower release rate of dextran than at 25°C.
Thermoresponsive polymers not based on PNIPAAm have also been studied. The permeability of temperature-responsive membranes made from poly(N-acryloyl pyrrolidine-co-hydroxyethyl methacrylate) was measured at 27°C and 37°C using insulin as a solute [Bae 1989]. The membrane exhibited temperature-dependent permeability similar to the poly(NIPAAm-co-BMA) membranes. Insulin permeation fell to less than half its original value as the volume transition of the gel took place at around 35°C.

2.2.1.2 IPN Membranes

Interpenetrating polymer networks (IPN) of PNIPAAm and poly(tetramethylene ether glycol) (PTMEG) were synthesized. The reaction involved a crosslinking polymerization of NIPAAm monomer to form a network and a condensation reaction between PTMEG and a triisocyanate to form the second network. Thermo-responsiveness was demonstrated by decreased membrane swelling and decreased release rate of indomethacin through the membrane as temperature was increased above the transition temperature of around 30°C [Okano 1990].

Semi-IPN membranes with temperature-responsive permeability were also prepared by crosslinking polymerization of N. N-dimethylacrylamide (DMAAm) in the presence of a protein called zein [Bromberg 1996]. Thermo-induced aggregation of hydrophobic groups on the protein left crosslinked poly(DMAAm) networks open, leading to a two-fold increase in the permeability of methyl orange through the membrane as temperature was raised from 20°C to 60°C.

2.2.1.3 Composite Membranes

Composite hydrogel membranes made of crosslinked poly(NIPAAm-co-N-
acryloxysuccinimide-co-2-hydroxyethyl methacrylate) on nonwoven polyester were synthesized [Sun 1999]. Starch was incorporated into the hydrogel as a macropore forming agent to decrease response time. The membrane showed a change of swelling ratio from 2.4 at 20°C to 1.4 at 40°C with a midpoint of 34°C. The permeability of maltose through the membrane at 20°C and 40°C was $1.98 \times 10^{-4}$ and $4.06 \times 10^{-5}$ cm$^2$/s, respectively. The membrane may be used as an enzyme support and a separation medium simultaneously. This has been demonstrated in a membrane reactor with temperature cycling operation for starch hydrolysis using the membrane with immobilized α-amylase [Chen 1998].

2.2.1.4 Particle-Containing Membranes

Particle-containing membranes were prepared by in situ polymerization of entrapped NIPAAm in vacant spaces of glutaraldehyde-crosslinked gelatin matrix [Chun 1996]. It was found that the entrapped PNIPAAm in the composite membrane could act as a gate valve by swelling and shrinking in response to temperature. The permeation rate of 4-acetamidophen at 40°C was 1.5 times higher than at 25°C when the PNIPAAm was swollen, giving rise to a decrease in effective pore size of the membrane.

A similar permeation control mechanism was observed in a nanoparticle-dispersed polymer membrane [Yam 1999]. The nanoparticle was synthesized by aqueous dispersion polymerization of NIPAAm and methacrylic acid (MAA). The membrane was prepared by casting a solution of hydrophobic polymer dispersed with the particles. The ratio of the permeability at 45°C to that at 20°C was determined as 2.2, 2.88 and 11 for acetaminophen, theophylline, and vitamin B$_{12}$, respectively. In contrast, chymotrypsin did not permeate at all at either temperature, due to its very large molecular size. Size exclusion effect on the membrane
permeation was suggested.

2.2.2 pH-Responsive Membranes

Two mechanisms are involved for pH-responsive membranes: pH-dependent swelling and complexation. If the polymer chains making up a hydrogel contain ionizable groups such as \(-\text{COOH}, \text{-NH}_2\), ionization of these groups would lead to electrostatic repulsion, and hence increased equilibrium swelling of the hydrogels. Hydrogels with ionizable groups would therefore be sensitive to the pH and ionic strength of the surrounding solution. Extensive research has been conducted on pH-sensitive hydrogels, mostly focusing on swelling and membrane permeability as a function of solution pH and ionic strength. It has also been found that some polymers with ionizable groups, in particular poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA), may form complexes with other polymers via hydrogen bonding [Scranton 1992]. Such a complex can be dissociated by ionization of PAA or PMAA in solution at a pH less than their \(pK_a\) values. This type of complex structure has been incorporated into graft copolymers and IPN hydrogels to design membranes with pH-dependent permeability.

Both synthetic polymers composed of acrylic acid (AA), methacrylic acid (MAA) or maleic acid and biological polymers composed of glutamic acid are used to prepare pH-sensitive hydrogel membranes. They have been combined with other monomers or polymers in the form of copolymers, interpenetrating polymer networks (IPN) and particle-dispersed membranes.

2.2.2.1 Copolymer Membranes

Ultrafiltration membranes composed of random copolymers of acrylonitrile (AN) with acrylic acid or methacrylic acid have been prepared [Oak 1997]. It was confirmed that the AN
segments act as membrane-forming sites, while the AA and MA segments control the membrane permeability in response to environmental pH. The permeability increased as the AA and MA groups became ionized, resulting in an increase in membrane swelling.

Ionizable groups can also be incorporated into a membrane via macromolecular reaction. For example, by esterification of poly(vinyl alcohol) (PVA) with maleic anhydride, carboxylic acid groups were attached to the PVA backbone [Liou 1996]. Hydrogel membranes were prepared from the material by crosslinking or heat treatment, giving rise to two types of permeation profiles as a function of pH. For crosslinked membranes, the permeability of glucose increased when pH was raised from 2 to 7, while no significant change was noticed between 7 and 12. In contrast, for heat-treated membranes, the permeability increased in both pH ranges. The difference was explained by the fact that the dissociation constant of the maleic acid groups in the crosslinked membrane was within a rather narrow range, whereas, the dissociation constant for the heat-treated membrane changed gradually with the degree of acid dissociation.

Hydrogel membranes comprised of biological polymer components also showed pH-responsive permeation due to sensitivity of their conformations to environmental pH. For example, in the membranes composed of a poly(butyl methacrylate)-poly(L-glutamic acid) or poly(L-aspartic acid) graft copolymer, the hydrophilic polypeptide microdomain within the membrane serves as a permeating pathway [Chung 1986]. The permeability of sugars, such as glucose, lactose and raffinose, and styrene glycol across the membrane, was much more diminished in the region of low pH than in the region of high pH. This was ascribed to the reversible dissociation of the carboxyl groups on the polypeptide resulting in the changes in conformation structure and hydrophilicity of the permeating domains. Moreover, they also
investigated the effect of Ca$^{2+}$ on the permeability of the membrane with poly(L-glutamic acid) (PGA) domains [Kinoshita 1995]. It was shown that the membrane permeability was reduced 10 times in the presence of the divalent cation Ca$^{2+}$ which would induce coil-to-helix transitions in the PGA domain.

Solute effects on the permeation mechanisms for the polypeptide membranes were also proposed [Kinoshita 1983, 1980]. pH-responsive permeability changes for ionic solutes across the polypeptide membrane with poly(L-glutamic acid) (PGA) domains were found to be different from those for non-ionic solutes. For example, the permeation study of sucrose and KCl through a crosslinked poly(L-glutamic acid) membrane indicated that the permeability of sucrose gradually increased with pH below pH 5, and steeply increased above pH 5. This was explained in terms of a pH-induced increase in the hydration of the membrane. The ionic salt permeability of KCl decreased when the pH was raised up to 5 and then gradually increased with a further increase in pH. The decrease was due to the dissociation of the carboxyl group of polypeptide below pH 5, resulting in electrostatic repulsion between the membrane and KCl, and the increase was due to the increase in the hydration of the membrane above pH 5, which when balanced against the electrostatic repulsion, resulted in a gradual increase in permeability.

Amphiphilic copolypeptide membranes which consist of hydrophobic leucine (Leu) and hydrophilic N-substituted β-aminoethyl L-glutamine (Gln(EtNH$_2$)) residues have also been studied [Kinoshita 1994]. It was reported that the degree of hydration of the membranes with various (Gln(EtNH$_2$)) contents increased steeply with pH changes from alkaline to weak acid pH values due to ionization of the (Gln(EtNH$_2$)) residues. However, a further decrease in pH induced a significant deswelling of the membrane due to the formation of hydrophobic clusters between the leucine moieties. Therefore, the membrane showed a maximum permeability at pH 4.5.
Based on the complexation mechanism, pH-responsive membranes were investigated using graft copolymers of PMAA-g-PEG [Bell 1994, 1996]. The permeation of vitamin B₁₂, lysozyme, chymotrypsinogen, ovalbumin, bovine serum albumin and different molecular weight FITC-dextrans through the membrane was responsive to solution pH, due to the formation and dissociation of the complexes between PMAA backbone and PEG grafts. Separation of solutes was achieved based on their size. However, the membrane cracked in permeation tests under dynamic pH conditions, indicating poor mechanical strength.

pH-responsive permeability based on the complexation mechanism was found in microcapsules composed of poly(acrylic acid) and poly(ethyl enimine) as well [Kono 1993]. The permeability changes in response to pH depend on the charge properties of a solute. For a neutral solute, the permeability from the capsule was low under neutral or weakly acidic environments, but increased strongly under acidic or alkaline conditions due to swelling changes of the capsule membrane. In contrast, the permeability of an anionic permeant was low under an alkaline condition due to the ionization of the permeant, resulting in electrostatic repulsion, and was increased by lowering pH due to the reduced electrostatic repulsion between the membrane and the solute. This suggests that in addition to the membrane swelling, the pH-dependent ionization of permeants also affects greatly the permeability change via the electrostatic interaction.

2.2.2.2 IPN Membranes

IPN membranes made from poly(vinyl alcohol) and PAA were studied [Gudeman 1995a, b, Peppas 1996]. The degree of crosslinking and ionic content was varied to control the mesh size of the network. The permeation of solutes with different molecular sizes, including urea, L-
tryptophan, vitamin B₁₂, myoglobin and dextran, was investigated as a function of solution pH. It was demonstrated that for ionizable solutes, the permeation was mainly affected by solute interaction with the membrane rather than by membrane swelling. For example, although the membrane swelling was lower at pH 3 than at pH 6, permeability of L-tryptophan through the membrane was higher at pH 3 than at pH 6 due to repulsion of the solute by the negatively-charged membrane at pH 6. On the other hand, permeability of neutral solutes was lower at pH 3 than at pH 6 due to lower membrane swelling at pH 3. In addition, the smaller the size of the solute the faster the permeation rate. The free volume theory proposed by Peppas was used to describe the permeation behavior of the neutral solutes [Peppas 1996].

Permeability of a PAA and poly(oxyethylene) (POE) IPN membrane having equimolar composition could be controlled by adjusting pH and ionic strength of buffer solutions, due to the complex formation and dissociation between PAA and POE [Nishi 1986]. The membrane showed very limited swelling at pH 2.5, where the PAA protonated, resulting in the complex formation. On the other hand, the membrane showed significant swelling at pH 7, where the PAA was ionized, resulting in the complex dissociation. Due to the complex formation and dissociation, the membrane showed pH-dependent permeability. However, the hydraulic permeability was high at the low pH, but decreased by 1500 times at the high pH. The phenomenon was opposite to most observations, in that permeability increased with increasing swelling of a hydrogel membrane. This was explained by the fact that the membrane was first swollen at pH 7 in an unrestrained condition, reaching an equilibrium state, and then was fixed on ultrafiltration cells. Therefore, when pH was lowered to 2.5, the fixed membrane could not shrink as expected in the unrestrained condition. As a result, channels or pores should be created to release internal stresses in the membrane, resulting in increased membrane permeability.
model was proposed to calculate the number of the channels and their average radius from the membrane swelling and permeation data. The calculation was based on the assumption that the volume of the created channels corresponded to the difference between the swelling ratio at pH 7 and pH 2.5, and that the channel flow obeyed the Hagen-Poiseuille law.

### 2.2.2.3 Particle-Dispersed Membranes

pH-sensitive heterogeneous gel membranes were developed by dispersing PMAA gel particles within a poly(dimethylsiloxane) network [Turner 1996, 1998]. Hydration and the extent of connectivity (percolation) of the PMAA gel particles were varied with pH leading to the permeability response. Much larger permeability changes were obtained compared to pure PMAA gel membranes. For example, the permeability ratio for vitamin B\textsubscript{12} between pH 7 and 3 was 125 for the heterogeneous membrane in comparison with 7 for the PMAA membrane.

It should be noted that the permeation mechanism for the PMAA particle-dispersed membrane is opposite to that for the membrane containing PNIPAAm copolymer particles. The difference may be due to the method involved in the membrane preparation that results in different membrane morphologies. For example, in Yam's work, the responsive particles were dispersed in a hydrophobic matrix [Yam 1999], which is similar to Turner's work where the gel particles were dispersed in a polydimethylsiloxane network [Turner 1998]. However, the former work showed an increase in the permeability as the gel particles collapsed, in contrast to a significant decrease in the permeability shown in Turner's work. The opposite permeation control mechanism may occur because of different membrane morphologies. Porous structure was observed in the former type of membranes and the particles might be isolated in both the swollen and collapsed states. As a result, the swollen particles occupied the porous spaces, while
the collapsed particles left the spaces to be filled with water. The water-filled pores would be more permeable than the pores occupied by the swollen particles. In contrast, the porous structure might not exist in the membrane reported by Turner and the particle loading may be such an amount that the swollen particles became connected to form a very permeable pathway, while the collapsed particles became isolated to close the permeation pathway.

2.2.3 Electric-Field Responsive Membranes

The most relevant effects that result from electric fields on a swollen ionic hydrogel have been summarized by Osada [Osada 1987]: orientation of dipolar species, deformation of polarizable species and orientation of induced dipoles, influence on the degree of dissociation of weak acids and bases, motion and redistribution of mobile charged species, and electrochemical reaction at interfaces.

The electrotransport of ionic and neutral solutes across hydrogel membranes has been widely investigated [Osada 1987, Peppas 1996, Grodzinsky 1985]. The effective mesh size and permeability of a hydrogel membrane can be altered by electrically induced ionization or swelling of the membrane which would increase solute diffusion [Grodzinsky 1990, Crimshaw 1989]. The electrostatic repulsion forces between membrane molecules and fibrils would change the interstitial separation distances determining the effective pore size of the membrane. This suggested that the electric field acted as a switch to control the membrane permeability to neutral or charged solutes. For example, sucrose flux through collagen membranes can be changed up to 25% under an applied electric field, which could alter intramembrane ionic profiles in collagen membranes via an electrodiffusion process, changing the membrane's permeability to sucrose [Eisenberg 1984]. Grodzinsky et al. demonstrated reversible changes in the uniaxial swelling of
PMAA membranes as well as by electrodiffusion control of intramembrane ionic strength [Nussbaum 1987]. Electrically controlled size specific transport of fluorescent solutes through PMAA membranes was also investigated [Weiss 1986]. The experimental results showed that large and reversible size specific permeability changes were induced in response to applied electric currents that gave rise to the electrolysis reaction at a platinum cathode, changing solution pH and hence, membrane swelling. In one example, a 16-fold increase in solute flux of Lissamine-Maltoheptaose conjugate was achieved. The electro-induced permeability changes were smaller for solutes of smaller size. Additionally, the membrane with higher crosslinking density exhibited a much lower permeability.

2.2.4 Light-Responsive Membranes

Photo-responsive molecules, such as an azobenzene and its derivatives, or spirobenzopyrans, show photo-induced trans-cis isomerization or neutral-ionic dissociation [Anzai 1994]. Polymers containing such photo-responsive components may undergo conformational and property changes upon irradiation. Two approaches towards photo-regulation of hydrogel membrane permeability have been investigated. One involves the direct control of membrane properties by incorporating photo-responsive moieties into a polymer membrane. The other provides indirect control of liposomal (bilayer) membrane properties by photo-regulating the conformation of the polymer that interacts with the membrane.

Photo-induced permeation of proteins across a poly(2-hydroxyethyl methacrylate) membrane containing 2 mole% p-phenylazobenzoyl side groups was studied [Ishihara 1984a]. A 50-80% reduction in the permeability of chymotrypsin ($M_w=23200$), lysozyme ($M_w=14500$), and insulin ($M_w=6000$) was observed when the membrane was subject to UV irradiation. The larger
the molecular size of the protein, the larger the reduction attained. The UV-induced decrease in the permeability was because of the deswelling of the membrane, caused by a decrease in polarity of the p-phenylazobenzoyl groups. The polarity change was due to their isomerization from trans-form to cis-form by UV.

Sato et al. [Sato 1988a] reported a 50% increase in the permeability of styrene glycol through a membrane made of poly(L-glutamic acid) carrying 15.5 mole% pararosaniline pendant groups (a triphenylmethane leucohydroxide derivative) by UV irradiation. The irradiation produced cationic side chains along the polypeptide backbone due to the photo-dissociation of the leucohydroxide, giving rise to an electrostatic repulsive force among the cationic side chains. This created force changed the polymer conformation from a random coil to a helix, resulting in increased swelling of the membrane and increased permeability.

Kodzwa et al. investigated photo-responsive permeation of neutral and anionic solutes across a poly(acrylamide) hydrogel containing 0.5 mole% triphenylmethane leucohydroxide groups [Kodzwa 1999]. The permeability of an anionic permeant, methyl orange, increased about two-fold under UV. However, no significant change was observed in the permeability of the neutral permeant, 4-dimethyl amino pyridine. It is known that the triphenylmethane leucohydroxide dissociates into a leuco cation on irradiation with UV. Moreover, it was observed that this photo-dissociation caused a three-fold increase in swelling of the poly(acrylamide) hydrogel. Based on these facts, the UV-induced permeability changes were attributed mainly to changes in the fixed charge concentration in the membrane and not simply to changes in the membrane swelling. A model based on Donnan equilibrium and the Nernst-Plannck equation was developed to predict the permeability of UV irradiated and non-irradiated membranes.
Liposomal membranes combined with photo-responsive polymers can show permeability changes under photo irradiation as well. For example, a dipatmitoylphosphatidylcholine liposome into which a photo-responsive polymer was incorporated showed significant release of encapsulated carboxyfluorescein [Ohya 1998]. The amount increased with UV irradiation time. The polymer with an amphiphilic structure consisted of a lipid chain and a spiropyran moiety. The spiropyran moiety was attached to the hydrophobic end of the lipid chain. Under UV, the spiropyran moiety dissociated into an ionic group and the structure turned into two hydrophobic groups at the two ends, connected by a hydrophobic chain. The polymer became more hydrophilic and unstable in the hydrophobic environment in the liposome. As a result, the polymer would rearrange to locate its hydrophilic group in the hydrophilic aqueous phase on the surface of the liposome. The liposomal membrane was perturbed by this rearrangement, resulting in increased permeability.

2.2.5 Glucose-Responsive Membranes

In theory, many different chemical or biological molecules may be used as a stimulus to trigger structural changes in hydrogels. In practice, glucose is the most commonly studied triggering chemical due to its role in the pathology of diabetes. An insulin delivery device using glucose as the trigger would have enormous potential in diabetes treatment. Various schemes have been proposed for a glucose-responsive insulin delivery system [Schwartz 1998, Imanishi 1995]. Only one of these schemes involved permeability changes of a hydrogel membrane in response to glucose by immobilizing glucose oxidase in a pH-responsive hydrogel. As glucose in the solution surrounding the membrane diffused into the hydrogel, the glucose oxidase catalyzes its conversion to gluconic acid. The process lowered the pH within the hydrogel
microenvironment, which caused swelling of the membrane and an increase in the permeability. Using this principle, Kost et al. [Kost 1985] immobilized glucose oxidase on crosslinked poly(hydroxyethyl methacrylate-co-dimethylaminoethyl methacrylate) (poly(HEMA-co-DMAEMA) hydrogels. Permeability of small molecules, such as ethylene glycol and iodide ion through the membrane increased with glucose concentration. The permeability change was similar to that induced by external pH changes. The parallel trend indicated the above glucose-responsive mechanism. In addition, the permeability in log scale decreased linearly with inverse membrane hydration, following the free volume theory. However, insulin permeability through the membrane was too low to be measured.

The glucose-responsive permeability was also demonstrated by a membrane sandwich made from poly(acrylamide) with entrapped glucose oxidase placed next to a poly(N, N-dimethylaminoethyl methacrylate-co-2-hydroxypropyl methacrylate) [Ishihara 1984b]. The permeability of insulin increased with increasing glucose concentration following the same glucose response mechanism as discussed above.

Mathematical models have been derived to describe the diffusion and reaction in the glucose-responsive membranes [Klumb 1992, Albin 1987]. The model indicated two important points: (1) glucose response could be achieved only with a sufficiently low glucose oxidase loading, otherwise depletion of oxygen caused the membrane to become insensitive to glucose. (2) pH decrease resulting from the enzymatic reaction could be significant to change membrane swelling and permeability only if the concentration of ionizable groups, such as amine, in the membrane was sufficiently low to prevent a buffering effect.
2.3 Liquid Crystalline Membranes

Attempts have been made to exploit the temperature-induced phase transition and electric-field induced orientation characteristics of liquid crystalline materials. This has been done by either using polymers that contain side chain mesogens, by incorporating low molecular weight liquid crystalline molecules into polymer matrices, or by filling the pores of porous substrate membranes with low molecular weight liquid crystalline molecules. Thermally and electrically responsive permeability of these membranes has been shown.

2.3.1 Thermally-Responsive Liquid Crystalline Membranes

Liquid crystal (LC) molecules and liquid crystalline domains undergo phase transitions between a liquid-crystalline state and a crystalline or amorphous state, or an isotropic, liquid or gel state, within a narrow range of temperatures. The type of the phase transition depends on the nature of liquid crystal molecules or liquid crystalline mesogens. The phase transition property presents an opportunity to control the membrane permeability by temperature, which has been illustrated in several types of the liquid crystalline membranes.

Polymer-dispersed liquid crystal membranes combined the phase transition property of low-molecular-weight liquid crystals and polymers with their capacity to form membranes. Depending on the polymer concentration, which can be as large as 70% or as small as 2%, the properties of the membrane are varied significantly [Crawford 1992].

Most work deals with the thermal response of gas permeation across the membrane [Kajiyama 1992, Blumstein 1994]. In these instances, the LC components were conventional low molar mass nematics and the polymers were poly(vinyl chloride) (PVC) or polycarbonate (PC). The composite film was prepared by casting from a common solvent. The membrane
typically displays interpenetrating co-continuous morphology with the LC component dispersed as a low viscosity diffusing phase within the polymer matrix. Despite high LC content (more than 60 wt% is necessary for a significant thermal response), a thin film with excellent mechanical stability and ductility was formed. A distinct jump in permeability coefficient of the gas (nitrogen and oxygen) near the crystal-nematic phase transition temperature of embedded LC was observed over a temperature range of several degrees.

Two other types of thermo-responsive membranes composed polymers and the liquid crystals were prepared by Nozawa et al. [Nozawa 1991a]. One, called polymer alloyed membranes, was obtained by polymerization of acrylic monomers in the presence of polyoxyethylene trimethylolpropane distrarate (PTDS) as the LC component with or without a crosslinker. The other, called LC-adsorbed membrane, was prepared by soaking a porous hydrophobic membrane in the LC (e.g. PTDS) solution. The drug permeability (indomethacin) of two types of membranes was investigated at two temperatures (32°C and 38°C) below and above the LC phase transition temperature. It was found that the ratio of the permeability coefficients at 38°C to 32°C for the polymer-alloyed membrane (120) was different from that observed for the membrane which was not LC alloyed (2.0 to 3.4). It was concluded that the content of LC in the membrane was one of the key factors for the thermo-response efficacy. Because the polymer itself had no thermo-sensitivity, high response efficacy could not be reached if the LC was not a continuous phase.

Liquid crystals can also be incorporated into porous polymer matrices to prepare the liquid crystalline membranes showing temperature-responsive permeability. For example, a thermo-responsive membrane was prepared by pouring a solution of monooxyethylene trimethylolpropane tristearate (MTTS) in ethanol/water between two porous polypropylene films
Since this solution had a gel to liquid crystal phase transition temperature at 35-36°C, it was expected that the permeation of chemicals through this immobilized liquid crystal membrane could be controlled by a temperature change around the transition temperature. Such an on-off switching permeation behavior was confirmed by measuring the difference of non-steroidal anti-inflammatory drugs (indomethacin, ketoprofen) and antipyretic drugs (acetaminophen, ethenzamide) across the membrane in response to a temperature cycle between 32 and 38°C.

Biological membranes are the most ubiquitous of LC/polymer composite membranes where a continuous bilayer matrix of lipid LCs was incorporated by proteins in a cell membrane [Blumstein 1994]. The continuous double layer of lipid LCs undergoes gel-liquid crystal phase transitions leading to changes in their permeation properties. Synthetic lipid vesicles were similarly constructed on this principle. The transport properties of the membranes were reversibly controlled by the crystal-LC phase transition of the lipid bilayer. However, the membranes may be too weak and fragile under the dynamic changes of outside effects, such as temperature, near the phase transition from solid to liquid crystalline state. Lipid bilayer-containing capsule membranes were developed, where the pores of physically strong, ultrathin nylon membranes were filled with lipid bilayers composed of dialkyl amphiphiles [Okahata 1986a]. The bilayer acted as a permeation valve in response to environment signals. Permeation of water soluble substances, such as NaCl, glucose and fluorescent probes encapsulated inside the capsule, was reversibly controlled by outside effects, such as temperature and electric field, due to changes in the physical state of the lipid bilayer.

In the case of the capsule membrane corked with anionic phospholipid bilayers (transition temperature = 50°C), the permeability was reversibly changed by a factor of 10 between 40 and
50° C due to the phase transition of the corving bilayers from a rigid crystalline state to a fluid liquid crystalline state. A similar thermo-sensitive permeation change was observed for glucose and large, water-soluble naphthalene probes, which indicated increased permeability changes with increasing molecular size.

Polymers that contain liquid crystalline mesogens in the main-chain or side-chain are known as liquid crystalline polymers. They present another way to combine the properties typical of liquid crystals with those peculiar to polymers. These polymers showed the phase transitions due to the liquid crystalline mesogens and membrane forming capacity, dimensional stability and mechanical strength due to macromolecular structures. By solution casting techniques, membranes could be made from the liquid crystalline polymers.

Diffusion flux of salicylic acid across liquid crystalline side-chain polysiloxane elastomer membranes was investigated [Loth 1988]. It was confirmed that the permeability was greatly varied by modifying their composition, such as the type of the main chain, crosslinking degree, as well as the structure and amount of the liquid crystalline side-chain. For example, the diffusion coefficient of salicylic acid could be decreased by more than 3 orders of magnitude by increasing the mass fraction of the mesogen from 0 to 0.7. Changes in the diffusion coefficient were also observed at the phase transition temperature between the liquid crystalline state and amorphous state.

Further study on the solute permeation across the liquid crystalline side-chain polysiloxane elastomer membranes was accomplished recently [Loth 1998]. The membrane structure could be varied by the content and length of the methoxy-polyethoxy side chain and by the length of the crosslinker. The permeability increased with increasing the length of the side-chain and the crosslinker, respectively. Only the membrane with a relatively low degree of
crosslinking and a high side-chain content showed a liquid crystalline phase, due to the high mobility and closeness of the side-chain. Consequently, the membrane showed temperature-responsive permeability.

2.3.2 Electrically-Responsive Liquid Crystalline Membranes

Due to anisotropy of dielectric property, electric fields induce orientational phase transitions in liquid crystalline molecules or mesogens. If liquid crystalline domains are relatively impermeable in comparison with amorphous polymer phases, the orientation would have a direct effect on the permeability of liquid crystalline membranes on the basis of path length for diffusion, as shown in Figure 2.2 [Kajiyama 1992, Blumstein 1994]. In the case of a well-oriented state under an electric field, a permeant can diffuse along a nearly straight path, resulting in a greater flux. There have been some investigations of electro-effects on transport properties of the membranes containing the liquid crystalline mesogens or liquid crystals.

![Figure 2.2 Schematic representation of the path for diffusion of permeant molecules in the oriented and disoriented liquid crystalline membranes containing liquid crystals or liquid-crystalline mesogens [Kajiyama 1992].](image-url)
The voltage dependence of the permeation of n-C₄H₁₀ and iso-C₄H₁₀ through a poly(vinyl chloride) (PVC)/4-cyano-4'-phentylbiphenyl (CPB) composite membrane has been reported [Kajiyama 1992]. CPB molecules within the membrane could be oriented preferentially in the direction of the electric field. Since the liquid crystal aggregated in a continuous phase, the orientation would change the diffusivity of gas molecules through the composite membrane. It was observed that as the applied voltage was increased, permeability for both n-C₄H₁₀ and iso-C₄H₁₀ gradually increased. This was attributed to the relative difference of diffusion path length. As shown in Figure 2.2, gas molecules diffused along a fairly straight path in an oriented composite membrane, while they diffused along a tortuous path in a disoriented membrane. On the other hand, permselectivity for two gases was also increased, indicating that the distribution of channel dimensions among LC molecules became narrower as a result of a stronger molecular orientation perpendicular to the membrane surface.

An investigation of voltage control of solute diffusion through a polymeric membrane containing embedded liquid crystals was reported [Roberts 1994]. The membrane was prepared by casting a solution of polyvinylchloride and liquid crystal in tetrahydrofuran. The diffusion of methylene blue across the membrane in an aqueous solution under the influence of DC and AC 100Hz electric field stresses (1 V/mm) was studied. The results suggested that the permeation rate could be controlled by the polarity of the applied DC electric field and by the application of the AC field. Specifically, the application of DC voltage with a positive electrode in the donor cell stopped the diffusion of methylene blue across the membrane. However, the subsequent reversal of the field polarity increased the diffusion across the membrane up to two-fold. The phenomena were explained by the fact that the applied field caused a reorientation of the liquid crystalline molecules from a cubic phase or similar system in the aqueous pores to a field aligned
structure, which limited the diffusion. The reversal of the field may cause a disordering of this orientated structure which facilitated the diffusion before the liquid crystal could realign in the opposite direction. In contrast, the effect of the AC field resulted in a three-fold increase in membrane permeability. This was explained in terms of the disruption of the cubic phase adopted by the embedded liquid crystal to prevent complete realignment as observed on the initial application of the DC field. On removal of the AC field, the original diffusion rate without the field was recovered, suggesting that the liquid crystal was able to readopt the initial cubic phase structure.

Bhaskar et al. developed a liquid crystalline membrane composed of a 23% w/v solution of poly(γ-benzyl-glutamate) (PBLG) in dichloromethane [Bhaskar 1985]. An electrically induced cholesteric to nematic phase transition of PBLG was observed. Experimental results showed that the flux of small organic permeants, methylene blue (charged) and phthalyl alcohol (neutral), through the membrane increased 50-60 percent when a voltage of 40V was applied across the membrane of 1mm thickness.

An alternative technique was proposed using thermotropic side chain liquid crystalline polymers [Ly 1997, 1993]. The liquid crystal domain within the polymer would act as a threshold in the diffusion path. It was switched ON and OFF by an electric field which could change the orientation of the liquid crystal domain. Depending on dielectric anisotropy of the liquid crystalline mesogens, the membrane permeability could be enhanced (positive) or reduced (negative) by the applied electric field. In one example, a mesogenic side chain, allyloxyphenyl p-methoxy benzoate, was grafted to poly(hydrogen methylsiloxane) to synthesize a side chain liquid crystalline polymer with a flexible spacer. The permeability of the membrane made from this polymer was tested in distilled water at 50°C, selecting p-aminoacetophenone as a permeant.
It was revealed that the permeability of the membrane increased with DC field strength and decreased with AC frequency. Specifically, a 28-fold increase in membrane permeability was obtained under a field strength of 4200 V/cm and a 26-fold range in permeation rate was attained between 0.001 Hz and 10 KHz at a field strength of 4900 V/cm. Moreover, a permeation rate ranging from 3x10^{-9} cm^2/s to 1.8x10^{-7} cm^2/s could be obtained by changing the electric field strength and frequency. A geometric model was derived to predict the effective diffusivity of the side-chain liquid crystalline membranes [Ly 1997]. The model was consistent with random walk simulations and valid to estimate the permeability change of the membrane induced by a DC electric field.

Among liquid crystalline polymer membranes, the reversibility in response to temperature has been better characterized than that in response to electric fields [Mohr 1992]. Reversible structure changes of side chain liquid crystalline polymers have been confirmed in a repeated process of heating/cooling for 10 cycles [Aindersson 1994]. On the other hand, electro-optical switching characteristics have been observed for side chain liquid crystalline polymers [Yamane 1997]. A reversible response with some hysteresis was confirmed by 2-4 response cycles and the response time was several seconds [Abe 1995].

2.4 Crystallizable Polymer Membranes

It is known that phase transitions between a crystalline state and a molten phase occur in semi-crystalline polymers and polymers containing small-molecule crystals at a melting temperature. Based on the reversible transition between the two states, another class of permeability variable membranes was developed. Hydrocarbons and ε-caprolactone segments have been reported to show such behavior and have been incorporated into membranes.
Poly(acrylic ester) membranes showed a sharp transition between a crystalline state and a melted state due to the hydrocarbon side chains, as shown in Figure 2.3 [Greene 1993]. The transition temperature increased with the length of the side chains and could be set anywhere between 0°C and 65°C. A nicotine transdermal delivery system was developed using the membrane. A 1000-fold change in the membrane permeability was observed over a 2.5°C temperature change across the transition temperature. An on and off switch on nicotine permeation through the membrane was obtained in response to resistive heating, yielding more than two orders of magnitude difference in drug release. The work demonstrated the feasibility of constructing a novel release device using a temperature-responsive permeability membrane.

![Figure 2.3 The transition of poly(acrylic ester) between crystalline and amorphous phase in response to a temperature change](Reprinted with permission from Greene 1993. Copyright 1993 American Chemical Society).

Another example of a crystallizable polymer membrane is crosslinked polyester membranes made of poly(ε-caprolactone) homopolymer and its block copolymers with L-lactide [Aoyagi 1994]. The membrane exhibited a phase transition temperature due to melting of the ε-caprolactone segment. The transition temperature and crystallinity increased with the length of the ε-caprolactone segment. The permeability of a model drug, indomethacin, increased
dramatically at around the phase transition temperature. Moreover, the increase was mainly ascribed to the increase of partition coefficients rather than diffusion coefficients. In addition, the higher the membrane crystallinity, the larger the permeability changes. Since the solute could permeate through the amorphous phase and the crystalline phase played a responsive function, a membrane with high crystallinity might be preferable. On the other hand, due to the presence of hard poly(L-lactide) segments, the mechanical strength of the block copolymer membrane was greater than that of the poly(ε-caprolactone) homopolymer membrane. It is interesting that in contrast to the block copolymer, the random copolymer exhibited no phase transition because the sequence of the ε-caprolactone segment was too short. Rapid - on the order of minutes - and reversible control of drug permeation through the block copolymer membrane was observed.

In addition to chemical attachment, hydrocarbons may be incorporated into a polymer by physical methods such as dispersion and absorption. For instance, a porous polyethylene membrane filled with hydrocarbons was studied to develop a temperature responsive system for treating penile erectile dysfunction [Ng 1999]. The phase transition of the embedded hydrocarbons between a parallel crystal and an amorphous liquid gave rise to two orders of magnitude difference in membrane permeability for a model drug of DL-propranolol hydrochloride. The transition temperature could also be varied by mixing hydrocarbons with different chain lengths.

2.5 Conductive Polymer-Based Membranes

Conductive polymer-based membranes can be produced by electro-polymerization of monomers or by solvent casting of polymer solution onto a substrate composed of electrodes
and/or a porous membrane, as shown in Figure 2.4, or by embedding a porous electrode inside the polymer via electro-polymerization. A conductive polymer was switched between oxidation and redox states by an applied electric current, which implied a different response mechanism during permeability changes from hydrogel and liquid crystalline membranes.

Figure 2.4 A conductive polymer-deposited membrane.

Figure 2.5 Ionic permeability response of a switchable ion gate membrane to an applied potential [Reprinted with permission from Burgmeyer 1984. Copyright 1984 American Chemical Society].
An ion gate membrane in which the ionic resistance of the membrane can be dynamically and reversibly varied by electrochemical control of redox states within the polymer membrane is expected for electrically modulated drug release devices [Burgmeyer 1984, 1983, 1982]. The mechanism for permeability changes is illustrated in Figure 2.5. For the reduction of the membrane from a polycationic to a neutral polymer, the ion permeability drops to some low value, or conversely, the ionic resistance of the membrane increases. On reoxidation of the membrane to a polycationic form, the initial permeability or resistance is restored. Ideally, the cycle of low-high (on-off) ion permeability can be repeated many times by controlling the embedded electrode potential.

Poly(pyrrole) is a typical conductive polymer that can be cycled electrochemically between charged and neutral states, and it shows ion exclusion on reduction to the neutral polymers. Poly(pyrrole) was deposited onto a gold minigrid sheet by electro-polymerization to prepare such a membrane. Electrochemical control of ion permeability of the membrane was illustrated by AC impedance and DC resistance. Moreover, direct analytical permeability measurements revealed that the membrane permeability was cyclically changed in response to applied potentials. The anionic permeability of oxidized polypyrrole (polycationic) was very high, whereas that of reduced (neutral) polypyrrole was lower by >1000 fold. However, a fast ion gate switching time between ON and OFF is required for potential applications. A devised electrode with smaller pore size was used to lower the polymer membrane thickness required for pore-filling, and thus, decrease the time required for changing the membrane oxidation state, i.e., the switching time. The electrode was composed of a polymer filter with a pore size from 5 to 0.03 μm, and vapor deposited by gold in layers from 2.5 to 20 μm. It was evident that the rate of switching ion permeability across the electrode-filter membrane was strongly dependent on
the electrode pore size. The electrodes with smaller pores changed ionic resistance at a much faster rate. In addition, the response time of the gold minigrid-based electrode membrane was faster than the porous filter-based electrode membrane, though the electrodes had approximately the same pore size (5.0µm). This was explained by the fact that the minigrid electrode had more actual electrode area exposed to the polymer (both sides of the electrode), which might help to change the polymer faster.

Another type of conductive polymer membrane was developed by depositing a conductive polymer poly(3-hexylthiophen) galvanostatically at a current density of 2 mA/cm² on a commercially available membrane (Durapore, Millipore, average pore size 0.1 µm) onto which a thin gold layer was sputtered in advance [Stassen 1995]. After polymerization, the film was cycled in deaerated 0.1M aqueous NaClO₄. Using dopamine, a neurotransmitter, as a model permeant, the controllable permeability of the membrane was tested by applying various potentials to the membrane system. Depending on the oxidation states of the conducting polymer switched by the applied potential between +700 mV/SCE and -200 mV/SCE, differences in the rate of permeation were attained, and up to a 40% difference in permeability was achieved. In the oxidized state, the membrane was less permeable as a result of the incorporation of the perchlorate anions into the polymer that caused the swelling of the membrane and a decrease in the pore size.

2.6 Polymer-Adsorbed or Grafted Porous Membranes

As mentioned in the section 2.2, the mechanical strength of hydrogels can be improved by combining an inert support membrane with a responsive polymer or hydrogel. For example, the responsive component can be either adsorbed or grafted to a porous membrane. The porous
substrate would provide strong mechanical support and be impermeable to a solute, while the conformational changes of the responsive component would give rise to the permeability change.

2.6.1 Responsive Polymer-Containing Porous Membranes

Responsive polymer-containing porous membranes are prepared by either crosslinking polymerization of monomers in the presence of porous membranes or adsorbing polymers from solution onto membrane pore surfaces. The crosslinking polymerization may occur inside the membrane pores, giving rise to a hydrogel-filled membrane. For example, Kapur et al. showed that the pores of a membrane could be filled with crosslinked poly(acrylamide) hydrogels and the permeation of proteins through the membrane could be regulated as ionic strength changed [Kapur 1997]. The authors reported that the hydrogel was absorbed to the membrane pore surfaces rather than being grafted, and the pores could be filled completely with the hydrogel.

Permeability changes of a porous cellulose acetate membrane with adsorbed responsive poly(L-glutamic acid) (PGA) were also observed [Sato 1988b]. The adsorption of PGA onto cellulose acetate took place through hydrogen bonds between the carboxylic acid groups of PGA and residual hydroxyl groups of cellulose acetate. Hydraulic permeability of the membrane decreased steeply at around the conformational transition pH of PGA in solution; this was attributed to an interfacial conformational transition of PGA on the pore surfaces that correlated with a pH-induced helix to coil conformational transition of PGA in solution. Moreover, a photo-responsive polymer was prepared by incorporating azobenzene sulfonate groups as side chains onto PGA. UV induced trans to cis isomerization of the azobenzene sulfonate groups resulted in an immediate decrease in the hydraulic permeability [Sato 1988b].

Electrically-activated ‘chemical valve’ hydrogel membranes, which reversibly expand
and contract the pore size in response to the electric stimulus, were reported as well [Osada 1990]. The membrane was prepared by polymerization of 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) on a porous poly(vinyl alcohol) sheet with 0.8 μm pore size. An increase in water permeation through the membrane was observed when 6.5 V of DC was imposed. It was expected that if the electro-induced chemomechanical contraction was developed isometrically, i.e., membrane dimensions remained constant, the contractile stress appearing in the membrane should expand the pore channels through which water and solute permeate. This was consistent with the experimental result that the increase in water permeability was proportional to DC current. This type of membrane may be used as an electrically-controlled variable permeability membrane for drug delivery.

2.6.2 Responsive Polymer-Grafted Porous Membranes

Compared to a porous membrane physically combined with a polymer, polymer-grafted membranes should exhibit increased durability [Ratner 1976]. As shown in Table 2.2, a large amount of work has been reported on stimuli-responsive permeability membranes prepared by grafting responsive polymers onto porous membranes via various techniques.

The permeability response mechanism for the grafted membranes has been visualized by atomic force microscopy studies [Yoshida 1996, Ito 1997a, b, Iwata 1998, 1997], as well by scanning electron microscopy studies [Omichi 1997, Yoshida 1996]. All these studies showed the opening and closing of membrane pores due to chain expansion and collapse of graft polymers. Moreover, it was observed that the pores could be completely occupied by expanded graft chains, with some grafts being squeezed out from the pores, resulting in a surface graft layer [Iwata 1997].
2.6.2.1 Characteristics of Grafted Polymers

In theory, all the polymers used for responsive hydrogels can be grafted onto a porous membrane. As summarized in Table 2.2, temperature-, pH- or photo-sensitive polymers have been grafted onto a porous substrate and their stimuli-responsive properties give rise to permeability changes. However, the membrane shows higher permeability in collapsed states than in expanded states which is opposite to hydrogel membranes [Ito 1997c, Park 1997].

The graft polymer membranes may show a faster permeability response than their corresponding hydrogels. Since each grafted chain has one freely mobile end, distinct from the typical network structure in a hydrogel where both ends of a polymer chain segment are crosslinked and relatively immobile, more rapid swelling-shrinking transitions are expected for the graft polymer [Yoshida 1995, Takei 1994]. Moreover, direct contact between the grafted chains and surrounding environment may also lead to more rapid response since the molecular diffusion of a stimulus in the polymer network of the hydrogel could limit the response process. It was reported that PNIPAAm grafted on a crosslinked PNIPAAm network collapsed well before the collapse of the crosslinked PNIPAAm [Yoshida 1995]. It was observed that the grafted porous membranes showed permeability changes within minutes [Park 1998a, 1997, Ulbricht 1996, Iwata 1991].
Table 2.2 Stimuli-responsive membranes obtained by graft polymerization onto porous substrates

<table>
<thead>
<tr>
<th>Membrane matrix</th>
<th>Grafted polymer</th>
<th>Grafting method</th>
<th>Graft location</th>
<th>Graft amount</th>
<th>Response Signal</th>
<th>Permeation</th>
<th>Permeant</th>
<th>Highest ON/OFF ratio</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(vinylidene difluoride) (pore size 0.22 μm)</td>
<td>butylmethacrylate-co-methacrylic acid</td>
<td>plasma-initiated</td>
<td>surface</td>
<td>not available</td>
<td>glucose-induced pH changes</td>
<td>hydraulic</td>
<td>glucose in citric acid-azide-NaCl buffer</td>
<td>1.2 after adding 1000 mg% glucose</td>
<td>Cartier 1995</td>
</tr>
<tr>
<td>High density polyethylene</td>
<td>methacrylic acid</td>
<td>UV-irradiated</td>
<td>?</td>
<td>26%</td>
<td>pH, solvent composition species</td>
<td>hydraulic</td>
<td>water/KCl</td>
<td>3.3</td>
<td>Islam 1992</td>
</tr>
<tr>
<td>Poly(vinylidene fluoride) (pore size 0.22 μm)</td>
<td>N-isopropyl-acrylamide or its copolymer with acrylamide or n-butylmeth-acrylate</td>
<td>plasma treatment followed by UV-radiation</td>
<td>surface</td>
<td>not available but grafting was confirmed by XPS</td>
<td>temperature</td>
<td>hydraulic</td>
<td>water</td>
<td>4</td>
<td>Iwata 1991</td>
</tr>
<tr>
<td>Poly(tetrafluoroethylene) (pore size 0.8 μm)</td>
<td>spiropyran-containing methacrylate</td>
<td>plasma-initiated</td>
<td>surface</td>
<td>not available but graft was confirmed by XPS</td>
<td>photo</td>
<td>hydraulic</td>
<td>water/methanol (1/9 v/v)</td>
<td>6</td>
<td>Chung 1994</td>
</tr>
<tr>
<td>Polycarbonate (pore size 0.2 μm)</td>
<td>acrylic acid, methacrylic and ethacrylic acid</td>
<td>plasma-initiated</td>
<td>surface</td>
<td>density of carboxyl groups: 0.9-13×10^{-7} mol/cm²</td>
<td>pH</td>
<td>hydraulic</td>
<td>pH buffer solution</td>
<td>10</td>
<td>Ito 1992, 1990</td>
</tr>
<tr>
<td>Poly(vinylidene fluoride) (pore size 0.22 μm)</td>
<td>acrylic acid</td>
<td>plasma-initiated</td>
<td>surface</td>
<td>91.3 μg/cm²</td>
<td>pH, solvent composition species</td>
<td>hydraulic</td>
<td>citrate-phosphate buffer</td>
<td>10</td>
<td>Iwata 1988</td>
</tr>
<tr>
<td>Low density polyethylene (pore diameter 0.19-0.47 μm)</td>
<td>4-vinylpyridine</td>
<td>UV-initiated</td>
<td>surface/inside pores</td>
<td>34.5%-125.3%</td>
<td>pH</td>
<td>hydraulic</td>
<td>water/NaCl</td>
<td>1000</td>
<td>Mika 1995</td>
</tr>
<tr>
<td>Material Description</td>
<td>Initiator</td>
<td>pH/ionic strength</td>
<td>pH/diffusional</td>
<td>Hydr/NaCl</td>
<td>pH/ionic strength</td>
<td>pH/diffusional</td>
<td>Hydr/NaCl</td>
<td>pH/ionic strength</td>
<td>pH/diffusional</td>
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</tr>
<tr>
<td>Polypropylene (pore diameter 0.2-0.47 μm)</td>
<td>4-vinylpyridine</td>
<td>UV-induced</td>
<td>surface/inside pore</td>
<td>40.7%-126.2%</td>
<td>pH</td>
<td>hydraulic</td>
<td>water/NaCl</td>
<td>1000</td>
<td>Mika 1995</td>
</tr>
<tr>
<td>Porous poly(vinyl alcohol) sheet (4 μm pore size)</td>
<td>methacrylic acid</td>
<td>plasma</td>
<td>?</td>
<td>18%-189%</td>
<td>pH, ionic strength, metal ions: Cu²⁺, Cr³⁺</td>
<td>hydraulic</td>
<td>water/NaCl</td>
<td>1000</td>
<td>Osada 1986</td>
</tr>
<tr>
<td>Poly(vinylidene fluoride) (pore size 5 μm)</td>
<td>acrylic acid</td>
<td>radiation-induced</td>
<td>surface/inside pores</td>
<td>0-93%</td>
<td>pH, ionic strength</td>
<td>diffusional</td>
<td>water/KCl</td>
<td>1000</td>
<td>Hauto-Jarvi 1996</td>
</tr>
<tr>
<td>Polyamide (pore size 0.2 μm)</td>
<td>methacrylic acid, acrylic acid</td>
<td>plasma and UV-initiated</td>
<td>?</td>
<td>1.8%-17.9%</td>
<td>24.5%-37.7%</td>
<td>pH</td>
<td>diffusional</td>
<td>riboflavin</td>
<td>1.41</td>
</tr>
<tr>
<td>Poly(vinylidene fluoride) (pore size 0.22 μm)</td>
<td>acrylic acid</td>
<td>plasma-induced</td>
<td>surface</td>
<td>3.5-21.7 mol/cm²</td>
<td>pH</td>
<td>diffusional</td>
<td>riboflavin</td>
<td>1.5</td>
<td>Lee 1996</td>
</tr>
<tr>
<td>Cellulose filters (pore size 0.2 μm)</td>
<td>acrylic acid</td>
<td>initiator plasm-initiated</td>
<td>?</td>
<td>35%-50%</td>
<td>3%-37%</td>
<td>glucose-induced pH change</td>
<td>diffusional</td>
<td>insulin</td>
<td>1.7</td>
</tr>
<tr>
<td>Polyamide (pore size 0.2 μm)</td>
<td>N-isopropylacrylamide</td>
<td>UV-initiated</td>
<td>?</td>
<td>1.6%-3.1%</td>
<td>temperature</td>
<td>diffusional</td>
<td>riboflavin</td>
<td>1.7</td>
<td>Lee 1995</td>
</tr>
<tr>
<td>Glass-fiber membrane (diameter of filtration limit &lt; 0.3 μm)</td>
<td>copolymer of N-isopropylacrylamide and bis(4-(dimethylamino) phenyl (4-vinylphenyl) methyl leuco cyanide</td>
<td>initiator-initiated</td>
<td>surface/inside pores</td>
<td>185%</td>
<td>photo</td>
<td>diffusional</td>
<td>poly (ethylene glycol) 600</td>
<td>2.3</td>
<td>Kurihara 1995</td>
</tr>
<tr>
<td>Material Description</td>
<td>Initiator or Trigger</td>
<td>Surface/Inside Pores</td>
<td>Permeability</td>
<td>Duration in Days</td>
<td></td>
<td></td>
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<tr>
<td>Glass-fiber membrane (diameter of filtration limit &lt; 0.3 μm)</td>
<td>copolymer of N-isopropylacrylamide and bis(4-(dimethylamino)phenyl (4-vinylphenyl)methyl leuco cyanide</td>
<td>initiator-induced</td>
<td>185%</td>
<td>temperature</td>
<td>diffusional</td>
<td>poly (ethylene glycol) 600</td>
<td>4</td>
<td>Kurihara 1995</td>
<td></td>
</tr>
<tr>
<td>Cellulose (pore size 0.2 μm)</td>
<td>N-acryloyl glycine</td>
<td>initiator-induced</td>
<td>?</td>
<td>not available, grafting was confirmed by FT-IR</td>
<td>glucose-induced pH change</td>
<td>diffusional</td>
<td>insulin</td>
<td>10% permeated versus 0 in 4.5 days</td>
<td>Barbucci 1991</td>
</tr>
<tr>
<td>Porous Nylon capsule membrane</td>
<td>N-isopropylacrylamide</td>
<td>initiator-initiated</td>
<td>surface/inside pores</td>
<td>10%</td>
<td>temperature</td>
<td>diffusional</td>
<td>naphthalene disulfonate</td>
<td>15</td>
<td>Okahata 1986b</td>
</tr>
<tr>
<td>Porous Nylon capsule membrane</td>
<td>acrylic acid, methacrylic acid, 4-vinylpyridine; initiator-initiated</td>
<td>surface/inside pores</td>
<td>15%-100% 30%-385% 35%-275%</td>
<td>pH</td>
<td>diffusional</td>
<td>NaCl, naphthalene</td>
<td>38 225</td>
<td>Okahata 1987</td>
<td></td>
</tr>
</tbody>
</table>
2.6.2.2 Diffusional Permeability Response

Table 2.2 shows that stimuli-responsive changes in both hydraulic permeability (i.e. pressure-driven flow of liquids) and diffusional permeability (concentration-driven diffusion of molecular solutes) can be achieved. For some applications, such as drug delivery, mass transport usually occurs via diffusion driven by concentration difference. It has been stated that the conformational changes of the graft polymer could have a stronger effect on hydraulic permeability than on the diffusional permeability, since the flow rate is related to the fourth power of the pore radius. \( R^4 \) [Cartier 1995], while diffusional transport through porous membranes is less affected by changes in pore size [Bell 1994].

Experimentally, it has been observed that the hydraulic permeability of a poly(acrylic acid)-grafted porous poly(vinylidene fluoride) membrane changed by three orders of magnitude when pH was lowered, in contrast with much smaller diffusional permeability change (2.4 times) in studies using the same membrane [Hautojarvi 1996]. The summary of literature reports in Table 2.2 further shows that hydraulic permeability ON/OFF ratios often reach as high as 1000, while most diffusional permeability ON/OFF ratios are less than 5, except for two studies by Okahata et al. in which ON/OFF ratios of 15 to 225 were reported.

2.6.2.3 Parameters Affecting Permeability Response

Some theoretical studies on ionizable polymer brushes (ionizable polymer chain including weak polyacid or polybase grafted at one end onto a planar surface) have been conducted to correlate properties (e.g., brush height, ionization degree) of the polymer chain with its surrounding solution quality (pH and ionic strength) [Zhulina 1995, Israels 1994]. It was predicted that the graft polymer would be more effective at controlling the diffusion of long or
bulky molecules than that of small species. Moreover, the pH dependence of the valve behavior could be tailored by varying the initial pore size of a porous membrane and graft spacing [Israels 1994].

Ito et al. investigated the effect of chain length and density of grafted polymers on the pH-dependent hydraulic permeability of a poly(acrylic acid) grafted straight pored polycarbonate membrane [Ito 1990]. It was concluded that the permeability response was most marked in membranes with an intermediate graft density and degree of polymerization. In another study with poly(acrylic acid)-grafted porous cellulose membranes with average pore size of 0.2 μm, it was found that the diffusional response was larger in membranes with higher graft yields [Ito 1989]. The effect of graft yield on permeability response from these two studies appears to be different. However, the different grafting methods and substrates used in the two studies may affect graft location and yield, and make it difficult to compare the findings. Recently, it has been reported that different methods used to prepare a polymer-grafted membrane result in different permeation control mechanisms [Park 1998b]

Hautojaru et al. found that the pH response in diffusional permeability decreased with increasing graft yield (0 to 93%) for poly(vinylidene fluoride) membranes with 5 μm pore size grafted with poly(acrylic acid) by electron beam irradiation [Hautojaru 1996]. More recently, Lee et al. found the largest pH sensitivity in membranes with the lowest graft yield. The membrane was also made of poly(vinylidene fluoride) substrate, but with a pore size of 0.22 μm, and plasma-induced surface grafting of poly(acrylic acid) [Lee 1996].

Okahata et al. developed pH- and temperature-responsive polymer-grafted porous nylon capsule membranes with large diffusional permeability changes (up to a factor of 225) [Okahata 1986b, 1987]. They reported that the permeability response was not affected by graft yield,
which ranged from 35% to 275% when hydrophobic poly(4-vinyl pyridine) was grafted. In contrast, when the graft polymer was relatively hydrophilic, the pH response decreased with increasing graft yield. This trend was observed for poly(acrylic acid), with a graft yield ranging from 15% to 100%, and poly(methacrylic acid) with a graft yield of 30% to 385%. Moreover, they found that the diffusional permeability was higher with the graft polymer in the ionized and swollen form, which was opposite to what other researchers have reported. The authors attributed this valve behavior to the chain length of graft polymers and membrane pore size. The contracted graft polymers covered the inner small pores (1 to 2 nm) of the capsule membrane instead of opening the pores. Conversely, in the swollen state, the expanded graft chains extended out from the membrane surface, leading to a pathway for permeation.

In addition to the graft density and the initial pore size, the permeability response also depends on the solute size. It was found that as the polyoxylethylene solute size increased from molecular weight of 1,000 to 20,000, the pH-dependent permeability response of poly(acrylic acid) grafted porous cellulose membranes increased [Ito 1989].

Graft location may be another factor that would greatly affect the permeability response, but it has not drawn much attention. The grafted polymers could be located mainly on membrane surfaces [Lee 1995, Iwata 1991, 1988] or both on the surface and inside membrane pores [Winnik 1998, Mika 1997, 1995], depending on initiation methods and grafting conditions. For example, in plasma-induced graft polymerization, polymers would be preferentially grafted onto the membrane surface [Lee 1995, Iwata 1991, 1988]. Hosoya et al. [Hosoya 1994] showed that the location of grafted PNIPAAm onto porous polymer beads could be controlled by using a proper porogenic solvent. The process involved the addition of NIPAAm monomer and a watersoluble initiator to a dispersion of polystyrene particles in the porogenic solvent and water.
NIPAAm polymerized in the aqueous phase, but soon precipitated out because the reaction temperature (80°C) exceeded the lower critical solution temperature of PNIPAAm. If cyclohexanol was used as the porogen for the dispersed beads, PNIPAAm dissolved in the cyclohexanol and was able to penetrate all pores of the beads, leading to grafting on the internal surface of the beads. If toluene was the porogen, PNIPAAm was insoluble in the porogen and unable to penetrate the pores, leading to grafting on the external surface.

2.7 Multi-Stimuli Responsive Membranes

Multi-stimuli responsive membranes are responsive to more than one stimulus. They are made from random, block, graft copolymers, IPNs, as well as polymer complexes, which contain different chain segments responsive to various stimuli. The permeability response of some of the membranes has been investigated.

Glucose permeation through random copolymer hydrogels of methacrylic acid and N-isopropylacrylamide was studied by the Siegel research group [Baker 1996]. At a fixed temperature (37°C), lowering the pH in one side of the cell induced hydrogel volume collapse and strongly attenuated glucose permeation across the membrane. However, the temperature response was not investigated.

Kubota et al. studied graft copolymer membranes of PAA-g-PNIPAAm hydrogels [Kubota 1998]. The light transparency of the membrane was measured as a function of temperature and pH. At pH < 4, the membrane was always turbid regardless of temperature, which was not explained. At pH > 4.5, the membrane changed from transparent to opaque as the temperature was raised above 31-33°C, due to collapse of PNIPAAm grafts. The transition temperature was almost the same as that of PNIPAAm and independent of PAA content.
Permeability of theophylline through the membrane was measured at pH 7.4 at 30°C and 40°C. It was found that the permeability was lower at 30°C than at 40°C, which was opposite to that of PNIPAAm hydrogel membranes. At pH 7.4, the PAA network was swollen. As a result, the conformation of the PNIPAAm grafted on the network would affect the permeability. At 30°C, the PNIPAAm chains expanded to close the network, in comparison with the collapsed PNIPAAm, leaving the network open at 40°C. However, the temperature effect on the permeability in low pH (i.e. pH < 4) was not reported.

Both temperature- and pH-responsiveness were also achieved by IPNs of PNIPAAm and PMAA [Zhang 1998]. The equilibrium and dynamic swelling of the membrane greatly changed with temperature between 22°C and 37°C as well with pH between 7.4 and 4.0. The permeability of oxprenolol HCl and vitamin B₁₂ across the membrane was measured at pH 7.4 and at both 27°C and 37°C. Lower permeability was observed at 27°C than at 37°C. The result is similar to the above PAA-g-PNIPAAm membrane, and may be due to the same mechanism. In addition, the temperature-responsive permeability was also not measured at pH 4.0.

Microcapsules based on a crosslinked poly(acrylic acid)-polyethylenimine complex containing photosensitive triphenylmethane leucohydroxide residues may exhibit both photo- and pH-responsive permeabilities [Kono 1995, 1993]. Permeation of p-toluenesulfonate through the capsule membrane was increased significantly by photoirradiation after several minutes at pH 8 and 30°C. The increase in permeability was attributed to the dissociation of the triphenylmethane derivative into an ion pair under ultraviolet light irradiation. The photo-induced increase in permeability was also pH-dependent. The difference between the permeability in the dark and that under irradiation reached a maximum near pH 8. Above and below this pH value, the effect of light on the permeability became less remarkable.
Microcapsule membranes prepared from PNIPAAm-grafted polyallylamine hydrochloride were expected to possess not only a thermal response but also pH sensitivity [Li 1995]. The pH-responsive release of phenobarbital natrium from the microcapsules was examined, indicating that in neutral pH, the release rate was slowest.

2.8 Summary

Permeability changes of a polymer membrane may be triggered via different mechanisms: swelling-deswelling transitions of the responsive polymers and hydrogels, phase transitions of liquid crystals and crystals, and oxidation-redox state transitions of the conductive polymers. It should be noted that the permeability is a function of both transport and thermodynamic properties, a product of diffusivity and partition coefficient, and that these parameters can be evaluated separately. Therefore, permeation characteristics of membranes depend on the sorption mechanism of permeants on the membrane surface and the diffusion mechanism within the membrane. As a result, permeability changes could be due to either or both mechanisms, and this was not clearly elucidated in the literature.

Each type of membrane has advantages and disadvantages. Hydrogel membranes may be the most extensively studied, both theoretically and experimentally. A number of theoretical models have been developed to predict the degree of swelling of hydrogels as a function of temperature [Harsh 1993, Peppas 1990], pH and ionic strength [Schroder 1996, Oppermann 1992, Brannon-Peppas 1990]. A number of theories and models have also been presented to describe permeability as a function of the degree of hydrogel swelling [Gehrke 1997, Peppas 1983] and attempts have been made to predict permeability in response to stimuli [Grassi 1999, Sassi 1996, Palasis 1992]. Experimentally, the hydrogel membranes with various structures have
been prepared in forms of homogeneous, heterogeneous bulk membranes and microcapsules. From a practical point of view, quick membrane response is required in most cases. Since the rate of response is inversely proportional to the square of hydrogel size [Yi 1998] the microcapsules would respond faster than the bulk membrane due to the much smaller size (micrometer versus millimeter). In addition, for drug delivery application, the microcapsule offers advantages over discs and slabs in the design of implantable formulations as it is possible to insert the microcapsules into target sites without surgery. On the other hand, there are several methods to increase the response rate of the bulk hydrogels. One is to graft PNIPAAm or poly(ethylene glycol) to PNIPAAm hydrogel networks [Kaneko 1998, Yoshida 1995]. The other is to make porous hydrogels, and this has been achieved using different techniques [Chen 1999, Sun 1999, Yan 1995].

In comparison with hydrogels, theoretical and experimental work on other types of membranes is limited. For example, the response rate and reversibility of the liquid crystalline polymers to electric fields have not been well investigated. The restricted mobility of the liquid crystalline side chains within a polymer network would hinder their arrangement. This may affect the response rate and reversibility. On the other hand, the membranes containing responsive small molecules, such as low-molecular-weight liquid crystals and crystals could show sharper and faster responsiveness than the responsive polymers. Nevertheless, since these small molecules were physically incorporated into the polymer membrane, they might partition out of the membrane matrix with time. This may cause unwanted side effects on the body if the membrane is used for drug release.

Responsive polymer-grafted porous membranes have been extensively studied as well. Such membranes may show the potential advantages over hydrogels in terms of mechanical
strength, dimensional stability and response rate. In addition, polymer-grafted membranes can be prepared much thinner than hydrogel membranes if required.

Although it was well reported that the responsive permeability membranes are promising for controlled release, few such delivery systems have been tested in clinics to demonstrate that the responsive release is truly advantageous over the conventional controlled release. One main reason may be that the human body can tolerate only small fluctuations from the norm, and the disease signals or external stimuli would normally be small in magnitude. This requires the membrane to respond to a slight fluctuation from norm, yet be able to achieve fast and on-demand release of drugs. Most responsive membranes have not met these requirements. In addition, an easy-to-use device is needed to provide the external stimuli for some types of release systems. On the other hand, the pH range of fluids in the gastrointestinal tract is wide. This may provide environmental stimuli suitable for responsive release using pH-sensitive membranes.

It has been claimed that novel applications could be developed using multi-stimuli responsive membranes. For example, it was stated that a hydrogel, showing responsive swelling to both pH and temperature, could be used in a condition where both phenomena are coupled, such as the site of a blood clot [Brazel 1995], a tumor [Ferraretto 1996] or inflammation [Park 1992]. A pulsatile local delivery system, based on pH- and temperature-sensitive hydrogels, was proposed and might be applied for treatment of coronary thrombosis or stroke patients [Brazel 1996]. The hydrogels were crosslinked poly(N-isopropylacrylamide-co-methacrylic acid) and were capable of pulsatile release of thrombolytic agents such as streptokinase. Although their clinical advantages over single-stimulus responsive membrane have not yet been clearly demonstrated, multi-stimuli responsive membranes offer intriguing possibilities for future applications.
2.9 Rationale for the Thesis

The discussion on the responsive-polymer grafted porous membrane demonstrates that graft parameters have a strong effect on both hydraulic and diffusional permeability response. However, different or even conflicting results have been reported. This may be because of discrepancies in substrate membrane properties (e.g., hydrophobic versus hydrophilic, initial pore size of the membrane ranging from 1 nm to 5 μm) and graft parameters (e.g., graft location, graft yield with different range, graft methods), which make it difficult to compare the reported results. A more systematic study is needed to understand the effects of graft yield and location on the permeability response, which may reconcile the conflicting reports.

Although multi-stimuli responsive hydrogel membranes have been reported, their permeability changes in response to multiple stimuli have not been well characterized. In addition, the mechanical strength and dimensional stability of the membranes are not desirable due to significant swelling of the hydrogels. Further studies may allow us to demonstrate more sophisticated permeability response using a multi-stimuli responsive membrane with good mechanical strength and dimensional stability. The multi-stimuli responsive permeability would give rise to more selective release of drugs in response to external signals or diseased states of the body.

With the data in mind, a photochemical graft polymerization method has been used to prepare responsive polymer-grafted porous membranes. The photochemical initiation would give rise to a wide range of graft yields and cause grafting to take place selectively on the membrane surface and/or inside the membrane pores. This will allow us to elucidate the effect of the graft yield and location on the permeability response. Moreover, a sequential co-grafting method has been developed to prepare porous membranes that contain multi-stimuli responsive
block copolymers with a wide range of compositions. The membranes would show good mechanical strength and dimensional stability and enable us to characterize their sophisticated permeation response to environmental changes.

Based on the above knowledge and techniques, an intelligent controlled release system may be constructed. For example, a controlled release chip may be fabricated from a polymer base material using photo-lithography etching techniques to create a number of separate reservoirs with pores [Kaetsu 1999]. For each reservoir, various kinds of responsive polymers can be grafted inside the pores and different drugs may be loaded. Independent release of multiple drugs could be obtained from this single device in response to multi-stimuli signals from the body or an external resource, creating a possibility for achieving many complex release patterns [Santini 1999].

Other potential applications of the responsive polymer grafted porous membrane include membrane separation and membrane bioreaction. Solutes of different molecular size may be separated by the membrane. Since the pore size of the membrane can be regulated in-situ by the surroundings, more selective solute permeation, especially through multi-stimuli responsive membranes, may be achieved, leading to various membrane processes including microfiltration and ultrafiltration by the same membrane [Liang 1999]. In addition, using a PNIPAAm and PMAA co-grafted membrane, a membrane bioreactor may be designed. Enzymes, such as amylase, can be immobilized on the membrane by covalent binding with MAA segments [Hoshino 1994]. Bioreactions, such as starch hydrolysis, and separation of products from substrates may be carried out simultaneously by cycling temperature below and above the transition temperature of PNIPAAm, resulting in high operation efficiency [Chen 1998].
2.10 References


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3.1 Materials

Low density polyethylene (PE) porous membranes produced via thermally induced phase separation were provided by 3M Company (St. Paul, MN, USA). The PE membranes are flat sheets with 50.5-μm thickness, 70.5% porosity and an average pore diameter of 0.19 μm as specified by the manufacturer. Methacrylic acid (MAA) monomer, purchased from Polyscience Co. (Warrington, PA, USA), was purified by distillation under vacuum. N-isopropylacrylamide (NIPAAm) monomer and photoinitiator xanthone, purchased from Sigma-Aldrich Canada Ltd. (Oakville, ON, Canada), were used as received. Other chemicals are ACS reagents.

3.2 Membrane Preparation

![Diagram](image)

Figure 3.1 Reactor for graft polymerization.

The PE substrate membrane was cut into 7 cm ×10.5 cm rectangular pieces, washed by acetone extraction for 24 hours, vacuum dried at room temperature, and weighed. The membrane was then soaked in acetone solution containing 0.3 wt% xanthone for 24 hours,
removed from solution and dried under vacuum at room temperature to prepare a xanthone-adsorbed film. Since the pores of the substrate are readily wetted by acetone, it was expected that xanthone would be adsorbed onto both membrane external surfaces and pore surfaces. A Pyrex glass reactor shown in Figure 3.1 was used for the graft polymerization.

3.2.1 PNIPAAm-g-PE

An aqueous NIPAAm solution of known concentration (ranging between 0.11M and 0.33M) was introduced into the reactor and purged with nitrogen for 20 minutes. The xanthone-adsorbed polyethylene film, fixed on the surface of the reactor’s inner tube, was then immersed in the monomer solution. The graft polymerization was initiated by UV irradiation provided by four 300 nm ultraviolet lamps (3.9 watts each) and four 350 nm ultraviolet lamps (4.5 watts each), mounted alternately in a Rayonet photochemical mini-reactor Model RMR-600 (Southern New England Ultraviolet. Branford. CT. USA). Reaction then proceeded under a nitrogen atmosphere for specified amounts of time ranging from 20 to 240 minutes. The reacted membrane was washed with 2 L of deionized water at room temperature for at least 24 hours, while the water was changed every 8 hours. The membrane was then dried under vacuum. The washing procedure was repeated until a stable dry membrane weight was obtained. Graft yield was then calculated as \((W_g-W_u)/W_u\) where \(W_u\) and \(W_g\) are the dry weights of the membrane before and after grafting, respectively.

3.2.2 PMAA-g-PE

The procedure and experimental set-up are the same as those used in the preparation of PNIPAAm-g-PE. 135 ml of MAA solution in deionized water or methanol/water mixtures in
concentration between 0.22M and 0.66M was introduced into the reactor and purged with nitrogen for 20 minutes. The xanthone-adsorbed polyethylene film was fixed on the surface of the reactor’s inner tube, then immersed in the monomer solution. The graft polymerization was initiated by UV irradiation provided by the Rayonet photochemical mini-reactor Model RMR-600. Reaction then proceeded under nitrogen atmosphere for specified amounts of time ranging from 20 to 360 minutes. The reacted membrane was washed with 60°C water for 24 hours and then dried under vacuum. The washing procedure was repeated until a stable dry membrane weight was obtained. Graft yield was then calculated as \( \frac{W_g - W_u}{W_u} \), where \( W_u \) and \( W_g \) are the dry weights of the ungrafted and grafted membrane, respectively.

### 3.2.3 PNIPAAm and PMAA Co-grafted PE Prepared by a Sequential Grafting Method

PNIPAAm-g-PE membranes with a wide range of graft yields were prepared by varying grafting time at a fixed monomer concentration of 0.22M using the same grafting process and apparatus applied for the preparation of PNIPAAm-g-PE and PMAA-g-PE membranes. To remove ungrafted homopolymers and residual photoinitiators, the membrane was washed in water at room temperature, and soxhlet extracted with methanol, then dried under vacuum. The process was repeated until a constant weight was achieved. The membrane was then soaked in methanol for 8 hours to completely wet it, and then in MAA monomer aqueous solution with a concentration of 0.22M. The graft polymerization was conducted using the same procedure and apparatus as above. The membrane was again subjected to the repeated washing and drying process until the constant dry weight was achieved. To obtain different PMAA graft yields, the PMAA grafting process, including soaking in methanol, UV irradiation of the membrane in MAA aqueous solution, repeated washing and drying, was cycled 2-3 times. The total graft yield
was then calculated as \((W_{\text{coag}} - W_u)/W_u\) where \(W_u\) and \(W_{\text{coag}}\) are the dry weights of the membrane before and after the co-grafting, respectively. The co-graft composition was calculated as the ratio between the dry weight of the PMAA graft and the total PNIPAAm and PMAA co-graft.

3.3 Membrane Characterization

3.3.1 X-ray Photoelectron Spectroscopy (XPS)

PNIPAAm-g-PE membranes were analyzed with an X-ray photoelectron spectrometer (XPS, Mau 200) with a Mg Kα X-ray radiation source at a pressure of \(10^{-5} \text{ Nm}^{-2}\) and an electron takeoff angle of \(90^\circ\). The binding energies of the electrons were referenced to carbon at 285 eV. Surface atomic ratios were calculated from peak areas using sensitivity factors for the instrument configuration.

3.3.2 Scanning Electron Microscopy (SEM)

The morphology of the PNIPAAm and PMAA grafted PE membrane cross-sections was visualized by a scanning electron microscope (Hitachi S2500 and X650). Samples were first freeze fractured under liquid nitrogen before further processing. Carbon paint was used to connect the samples to SEM stubs. All the samples were then vapor coated with gold in a sputter coating system.

3.3.3 Differential Scanning Calorimetry (DSC)

The PNIPAAm and PMAA co-grafted membranes with total co-graft yields of 410-472% and different compositions were cut into small pieces, wetted in methanol, and then equilibrated at pH 4.4 and 7.4 buffer solution at room temperature for two days. Membranes containing
approximately same amount of grafted PNIPAAm (4 mg) were sealed in DSC pans in a Perkin-Elmer model 7 differential scanning calorimeter. The sample was heated at 5°C/minute, the same heating rate that Liu et al. used [Liu 1999], from 0°C to 60°C under nitrogen in reference to an empty pan. Moreover, Baltes et al. verified that the heating rate within the range from 1°C/minute to 20°C/minute would not influence the LCST and calorimetric enthalpy measurements [Baltes 1999]. The temperature at the peak of a DSC thermogram was defined as the LCST [Liu 1999, Nonaka 1997]. The DSC instrument was calibrated using indium and cyclohexane as standards.

3.3.4 Membrane Thickness and Swelling Measurement

After permeation experiments, the PNIPAAm-g-PE membranes were put in the pH 7.4 buffer at different temperatures and their thicknesses were measured by a micrometer with an accuracy of 0.01 mm after excess surface water was eliminated with Kimwipes®. The equilibrium state was reached when there was no thickness change after 12 hours.

To determine the swelling and thickness of the PMAA grafted membranes, each membrane was placed in various pH buffer solutions with ionic strength of 0.01M at 37°C. At specified time intervals, the membrane was removed and excess surface water was eliminated with Kimwipes®. Membrane weight and thickness were measured by a balance with an accuracy of 0.0001 g and a micrometer with an accuracy of 0.01 mm. The procedure was repeated until equilibration. The equilibrium swelling ratio was calculated as (W_s - W_e)/W_e where W_s and W_e are the weights of the dry grafted membrane and the swollen membrane, respectively. The relative membrane thickness is calculated as the ratio of the thickness at pH 7.4 ± 0.05 relative to that at pH 4.4 ± 0.05.
The thickness of the PNIPAAm and PMAA co-grafted membranes was measured at 4 temperature and pH conditions (i.e. 37°C, pH 4.4, and 30°C 7.4, and 37°C, 7.4, and 30°C, pH 4.4) using the same method and instruments as above. The relative membrane thickness was calculated as the ratio of the thickness at pH 7.4, 30°C to the thickness at pH 4.4, 37°C.

3.4 Permeation Experiment

![Permeation apparatus](image)

Figure 3.2 Permeation apparatus: (1) magnetic agitation bar, (2) receptor cell, (3) poly(ethylene vinylacetate) ring, (4) donor cell, (5) test membrane, (6) station synchronous magnetic stirrer. The juncture of the membrane with the two cells was wrapped with Parafilm®.

Permeation experiments were carried out using standard side by side diffusion cells, as shown in Figure 3.2. The grafted membranes were cut into discs and soaked first in methanol to wet the membrane, then in pH 7.4 and 4.4 buffer solution with an ionic strength of 0.01M. Each test membrane was immersed in the buffer at the appropriate temperature for more than 12 hours prior to initiating permeation experiments. After checking for leakage, 25 ml of pH 7.4 phosphate buffer solution with ionic strength of 0.01M, and permeant solution in the same buffer were added simultaneously to the receptor and donor cells, respectively, and stirred with a pair of magnetic bars. 0.2 ml of solution was removed from the receptor cell at periodic time intervals, and solute concentration was determined by UV (Hewlett-Packard 8452Win Diode-array UV
spectrophotometer) and fluorescence (Shimadzu RF-535 fluorometer). The sample was replaced with 0.2 ml blank buffer. Permeability was calculated by the following equation, which was derived elsewhere based on Fick's first law [Flynn 1974]:

\[
\ln \left(1 - \frac{C_r}{C_0}\right) = -2 \frac{P A t}{(LV)} \quad (3.1)
\]

where \(C_r\) is the concentration in the receptor cell at time \(t\), and \(C_0\), \(P\), \(A\), \(L\), and \(V\) are the initial solute concentration in the donor compartment, permeability, effective diffusion area, thickness of the membrane and volume of the compartment. The permeability coefficient \(P\) can be calculated from the slope of the \(\ln(1-2C_r/C_0)\) versus \(t\) curve, determined by linear regression. Equation 3.1 was derived based on the following assumptions: (1) a pseudo-steady state is reached within the membrane, (2) the resistance to transport between the cells is controlled exclusively by the membrane, (3) the amount of permeant in the membrane is negligible, (4) the dilution effect of the replacing blank is negligible due to its small volume relative to the volume of the compartment (0.2 ml vs. 25 ml). Typical figures are included in Appendix 1.1. 95% confidence intervals on permeability calculated this way are typically within 7%.

Dynamic permeation experiments were performed by transferring the permeation system between two water baths with temperatures of 37°C and 30°C (for the PNIPAAm-g-PE membranes) or by changing pH buffer solutions in both permeation cells simultaneously (for the PMAA-g-PE membranes), or by changing both temperature and pH (for the PNIPAAm and PMAA co-grafted membranes) at certain time intervals. A number of cycles were repeated. Precautions were taken to prevent pressure-driven flow. The permeability under each condition in the cycle was calculated using equation 3.1.
3.5 References


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Chapter 4  Temperature-Responsive Permeability of PNIPAAm-g-PE Porous Membranes

Abstract

Grafting a temperature-responsive polymer, poly(N-isopropylacrylamide) (PNIPAAm), onto porous polyethylene (PE) membranes by UV irradiation was investigated. A wide range of graft yields (5% - 449%) was achieved by varying irradiation time (20 - 240 minutes) and monomer concentration (0.11 - 0.33M). Characterization by XPS and SEM shows that the grafted polymers are located both on the external surfaces as well as inside the pores of the membranes. Diffusional permeation experiments show that two distinct types of temperature response were observed depending on the graft yield; permeability increases with temperature in low graft yield membranes while permeability decreases with temperature in high graft yield membranes. The different temperature responses are explained by the fact that at low graft yields, PNIPAAm is mainly inside the pores, resulting in a lower permeability in the expanded state than in the collapsed state, while at high graft yields, PNIPAAm forms a surface layer, leading to a higher permeability in the expanded state than in the collapsed state. It was also observed that the permeability response exhibits a maximum with respect to permeant molecular weight due to size exclusion effect. The permeability response is reversible as well.
4.1 Introduction

4.1.1 PNIPAAm and Its Hydrogels

PNIPAAm is a temperature-responsive polymer which exhibits a lower critical solution temperature (LCST) of around 31–33°C in aqueous solutions [Heskins 1968, Hoffman 1986]. The phase transition at the LCST has been variously described as expanded coil-collapsed globular conformation transition, soluble-insoluble transition, and hydrophilic-hydrophobic [Wu 1995, Takei 1994]. In the case of PNIPAAm hydrogels, hydration (swelling)-dehydration (deswelling) change and volume phase transition were used as a reflection of the LCST phenomenon [Wu 1997].

Because it has one of the sharpest transitions among many LCST polymers [Inoue 1997] and its LCST is near the body temperature, PNIPAAm has drawn much attention in the past decade for both scientific and practical significance [Schild 1992]. Although it is widely accepted that the LCST of PNIPAAm/H₂O system is due to temperature-dependent polymer-water interactions the theoretical and quantitative explanation for the phase transition at the molecular level is not yet conclusive. On the one hand, it has been suggested that the LCST behavior is due to a balance between hydrophilic interactions (i.e., hydrogen bonding between amide groups and water molecules) and hydrophobic interactions among isopropyl groups. Specifically, the hydrophobic interaction between the isopropyl groups is enhanced as temperature is raised due to the dissociation of hydrogen bonds between the amide groups and water at the elevated temperature, resulting in the LCST phenomenon [Feil 1993]. This argument is supported by quantitative study of the PNIPAAm-water interactions using thermo micro ATR/FT-IR, showing significant changes in both hydrogen bonding between the amide groups and water and hydrophobic interaction among the isopropyl groups [Lin 1999].
other hand, it has been suggested that the LCST behavior is due to the hydrophobic interaction between the isopropyl groups. Water molecules surrounding the isopropyl groups are highly hydrogen bonded and form ice-like ordered structures called water ‘cages’ [Shibayama 1993, Hirokawa 1984]. As temperature increases the water ‘cages’ are broken down, leading to association of the isopropyl groups and collapse of PNIPAAm [Subotic 1997].

A number of theories and models have been also developed to predict the transition phenomena in the polymer solution and hydrogels [Shirotta 1998, Oh 1998, Hino 1998, Hirotsu 1993]. However, either quantitative agreement has not been obtained or a large number of parameters without clear physical meaning are required in the model to fit the experimental data.

With respect to experimental studies, different, even conflicting reports on the phase transition temperatures of PNIPAAm and its hydrogels exist and cannot be reconciled. For example, it was reported that the transition temperature of the PNIPAAm hydrogel was unaffected by crosslinking density [Huglin 1997]. On the other hand, another research group found that the transition temperature shifted to higher values with an increase in the crosslinking density [Oh 1998]. Another example is the effect of molecular weight on the LCST of PNIPAAm in solution. It was stated without any theoretical and experimental support that three NIPAAm repeating units were long enough to show the LCST [Topp 1997]. Moreover, Wu found that the LCST decreased with an increase in the molecular weight [Wu 1998], while other researchers stated that the LCST was insensitive to the molecular weight when it was sufficiently high [Hino 1998], without defining the value of the ‘sufficiently high’ molecular weight.

From practical points of view, PNIPAAm based devices have potential applications in a variety of fields, especially in controlled release, biotechnology, medical diagnosis [Hoffman 1995, 1987], cell culture [Yamazaki 1995], and separations [Hoffman 1986].
4.1.2 Grafting of PNIPAAm

It is believed that grafted PNIPAAm chains at solid/liquid interfaces would retain temperature responsiveness [Kikuchi 1998, Zhu 1996]. Therefore, by grafting the polymer onto a polymer surface, the surface properties and morphologies can be regulated in response to temperature.

There are different ways to induce graft polymerization of NIPAAm onto a polymer surface. Table 4.1 summarizes the methods together with properties and potential applications of PNIPAAm-grafted surfaces.

Each method has advantages and disadvantages. For example, coupling reactions may give a well-defined chain length of grafted polymers; however, graft density is not as high as for monomer graft polymerization. The selection criteria of the method may depend on properties required for the grafted surfaces and difficulties in using the process. Exact initiation mechanisms for some methods, such as plasma treatment and electron beam irradiation, are not clear because of various reactive species generated [Inagaki 1996]. On the other hand, UV irradiation mechanisms in the presence of photoinitiators have been widely studied [Bellobono 1989].

A common problem with graft polymerization is the accompanying unwanted homopolymerization. The extent of homopolymerization is dependent on various factors, including grafting method, monomer concentration and structure, grafting time, temperature and solvent. Homopolymerization may be reduced but normally can not be eliminated. Another problem in graft polymerization is that no proper analytical methods are available to confirm the grafting. As a result, grafted polymers and adsorbed homopolymers can not be distinguished. It is generally assumed that a polymer is grafted if it can not be removed from a substrate membrane by a repeated washing process where a solvent for the polymer is used. However, it
was shown that this is not always true [Xue 1995]. By using proper solvents to dissolve membrane substrates and to separate the substrate and presumably grafted polymers, it was found that instead of being grafted onto a poly(ethylene terephthalate) membrane, the polymer formed a semi-interpenetrating network with the membrane due to homopolymerization of monomers within the membrane. As a result, the polymer could not be washed out because of entanglement of the two polymers. Xue’s study may provide an approach to confirming the grafting - or at least rule out strong physical entanglements.


Table 4.1 also shows that numerous experimental studies on the PNIPAAm grafted onto surfaces with different morphologies, flat versus curved, and non-porous versus porous have been accomplished but there are limited theoretical studies and models on the phase transition of the grafted PNIPAAm. For non-porous surfaces, their temperature-responsive properties are generally related to hydration-dehydration transitions of the PNIPAAm graft at the temperature below and above the LCST. The changes were characterized by different methods, such as water contact angle and swelling degree. For porous surfaces, temperature-responsive permeability
Table 4.1 PNIPAAm grafted surfaces

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Grafting Methods</th>
<th>Properties studied</th>
<th>Potential applications</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminated glass plate and beads</td>
<td>Coupling reaction</td>
<td>Temperature-dependent water contact angle</td>
<td>Cell culture</td>
<td>Takei 1994</td>
</tr>
<tr>
<td>Aminated glass plate and beads</td>
<td>Coupling reaction</td>
<td>Temperature-dependent water contact angle</td>
<td>Cell culture</td>
<td>Yakushiji 1998</td>
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<tr>
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<td>Coupling reaction</td>
<td>Protein adsorption/desorption</td>
<td></td>
<td>Yoshioka 1995</td>
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<td>Poly(chloromethyl styrene) nanoparticles</td>
<td>Coupling reaction</td>
<td>Temperature-dependent mucoadhesion</td>
<td>Drug delivery</td>
<td>Sakuma 1995</td>
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<td>Polystyrene latices</td>
<td>Free radical initiation</td>
<td>Temperature-responsive volume transition</td>
<td>Cell culture and drug delivery</td>
<td>Dingenouts 1998</td>
</tr>
<tr>
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<td>Coupling reaction</td>
<td>Temperature-dependent activation of blood platelets and lymphocytes</td>
<td>Cell culture and drug delivery</td>
<td>Takei 1995</td>
</tr>
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<td>Polystyrene latices</td>
<td>Electron beam irradiation</td>
<td>Activation/inactivation of blood platelets and lymphocytes</td>
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<td>Takei 1995</td>
</tr>
<tr>
<td>Polystyrene dishes</td>
<td>Electron beam irradiation</td>
<td>Temperature-dependent protein release</td>
<td>Controlled release for tissue engineering</td>
<td>Recum 1998</td>
</tr>
<tr>
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<td>Electron beam irradiation</td>
<td>Temperature-dependent cell adhesion and growth</td>
<td>Cell culture (bovine aortic endothelial cells)</td>
<td>Yamato 1999</td>
</tr>
<tr>
<td>Polystyrene dishes</td>
<td>UV irradiation + photoinitiator</td>
<td>Temperature-dependent cell adhesion and growth</td>
<td>Cell culture (mouse fibroblast cells)</td>
<td>Morra 1997</td>
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<tr>
<td>Polystyrene plate</td>
<td>Glow discharge</td>
<td>Temperature-dependent cell attachment and growth</td>
<td>Cell culture (mouse fibroblast cells)</td>
<td>Chen 1997</td>
</tr>
<tr>
<td>Polystyrene plate</td>
<td>UV irradiation</td>
<td>Temperature-dependent cell adhesion and growth</td>
<td>Cell culture (mouse fibroblast cells)</td>
<td>Chen 1998</td>
</tr>
<tr>
<td>Polystyrene plate</td>
<td>UV irradiation</td>
<td>Temperature-dependent cell adhesion and growth</td>
<td>Cell culture (mouse fibroblast cells)</td>
<td>Ito 1997</td>
</tr>
<tr>
<td>Material</td>
<td>Treatment Method</td>
<td>Property Description</td>
<td>Technique</td>
<td>Reference</td>
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<td>---------------------------------------------------------------------------------------</td>
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<td>-----------------</td>
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<tr>
<td>Polyurethane membrane</td>
<td>Ozone treatment + UV irradiation</td>
<td>Temperature-dependent friction coefficient</td>
<td>Friction control</td>
<td>Ikeuchi 1996</td>
</tr>
<tr>
<td>Poly(ethyl-vinyl acetate)膜</td>
<td>Electron beam irradiation</td>
<td>Temperature-dependent swelling</td>
<td>Immobilization and extraction</td>
<td>Pu 1996</td>
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<td>Cellulose powders</td>
<td>Photoinitiator + UV irradiation</td>
<td>Temperature-dependent swelling</td>
<td>Absorbents</td>
<td>Kubota 1998</td>
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<td>Corona discharge</td>
<td>Temperature-dependent water contact angle, water absorption</td>
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<td>Seto 1998</td>
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<td>Polyethylene membrane</td>
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<td>Temperature-dependent dimension</td>
<td></td>
<td>Kubota 1994</td>
</tr>
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<td>Polyethylene membrane</td>
<td>Photoinitiator + UV irradiation</td>
<td>Temperature-responsive permeability</td>
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<td>Yamada 1994</td>
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<td>Polytetrafluoroethylene</td>
<td>Oxygen plasma treatment + UV irradiation</td>
<td>Temperature-dependent water contact angle</td>
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<td>Photoinitiator attached glass plate</td>
<td>UV irradiation</td>
<td>Temperature-dependent water contact angle, capillary action</td>
<td>Membrane separation</td>
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<td>Polyester membrane with vinyl groups</td>
<td>Free radical initiation + crosslinking</td>
<td>Temperature-dependent swelling</td>
<td>Extraction separation</td>
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<td>Organosilane attached glass plate or silicone membrane</td>
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<td>Temperature-dependent swelling, water contact angle and surface tension</td>
<td>Controlled release</td>
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<td>Cellophane membrane</td>
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<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
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<td>Aminated porous glass beads</td>
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<td>Temperature-dependent size exclusion</td>
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<td>Porous glass particles chemically coated by a polymer</td>
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<td>Temperature-dependent protein adsorption</td>
<td>Chromatography</td>
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<td>Nylon capsule porous membrane</td>
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<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
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<td>Porous glass plate bound with vinyl groups</td>
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<td>Temperature-responsive permeability</td>
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<td>Porous polycarbonate membrane</td>
<td>UV irradiation</td>
<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
<td>Park 1998</td>
</tr>
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<td>Porous poly(vinylidene fluofide) membrane</td>
<td>Electron beam irradiation</td>
<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
<td>Akerman 1998</td>
</tr>
<tr>
<td>Porous poly(vinylidene fluofide) membrane</td>
<td>Glow discharge + UV irradiation</td>
<td>Temperature-responsive permeability</td>
<td>Ultrafiltration</td>
<td>Iwata 1991</td>
</tr>
<tr>
<td>Porous poly(ethylene terephthalate) membrane</td>
<td>γ-ray irradiation</td>
<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
<td>Spohr 1998</td>
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<td>Porous poly(ethylene terephthalate) membrane</td>
<td>γ-ray irradiation</td>
<td>Temperature-dependent pore size</td>
<td>Controlled release</td>
<td>Reber 1998</td>
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<tr>
<td>Porous polyamide membrane</td>
<td>Plasma treatment</td>
<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
<td>Lee 1997</td>
</tr>
<tr>
<td>Porous polyamide membrane</td>
<td>Plasma treatment or photoinitiator + UV irradiation</td>
<td>Temperature-responsive permeability</td>
<td>Controlled release</td>
<td>Lee 1995</td>
</tr>
</tbody>
</table>
was due to the conformational transition between an expanded state and collapsed state in response to the temperature as discussed in Chapter 2.

4.1.3 Responsive Properties of Grafted PNIPAAm

Although the temperature-responsive properties of the grafted PNIPAAm are related to that of PNIPAAm in solution, the predictive ability of such observations is limited and does not extend beyond qualitative guidelines. There would be quantitative differences between the two types of PNIPAAm architectures. However, the difference has not been widely investigated. Small angle X-ray scattering studies on particles composed of a polystyrene core and a crosslinked PNIPAAm shell affixed to the core indicated that the volume change of the PNIPAAm shell was about four times smaller than PNIPAAm hydrogels with a similar degree of crosslinking [Dingenouts 1998]. The difference was due to geometrical constraints from the polystyrene core to which the PNIPAAm shell was subjected. It was reported that graft architectures affect the thermoresponsive response [Yakushiji 1998]. For example, it was found that terminally grafted PNIPAAm showed larger and more rapid temperature responsiveness in terms of hydrophilic/hydrophobic changes than multipoint grafted and crosslinked PNIPAAm. In addition, the terminally grafted PNIPAAm showed a lower transition temperature and narrower breadth of the transition than the multipoint grafted PNIPAAm. The above observations were ascribed to more conformational freedom for the terminally grafted PNIPAAm [Takei 1994]. Moreover, Takei et al. prepared more sophisticated graft architectures: terminally grafted PNIPAAm, multipoint grafted or looped PNIPAAm and PNIPAAm terminally grafted onto the looped PNIPAAm [Yakushiji 1998]. They observed again that temperature-responsive wettability changes were strongly influenced by the graft architectures. The
PNIPAAm terminally grafted onto the looped PNIPAAm showed the largest wettability changes. PNIPAAm terminally grafted either directly to the surface or to the looped PNIPAAm had a transition temperature (32-35°C) which was about the same as the LCST of PNIPAAm in solution. In contrast, the looped PNIPAAm showed a lower transition temperature (27°C). The above findings were attributed to the PNIPAAm mobility, which was considered to be highest for the PNIPAAm grafted to the looped PNIPAAm.

The more mobile nature of the terminally grafted PNIPAAm was also confirmed by a deswelling study on a comb-type hydrogel [Yoshida 1995]. The hydrogel was composed of crosslinked PNIPAAm networks and PNIPAAm side chains terminally grafted onto the networks. It was shown that the grafted PNIPAAm collapsed before the crosslinked PNIPAAm began to collapse. The faster response of the grafted PNIPAAm relative to the crosslinked PNIPAAm implies that the PNIPAAm grafted membrane would respond faster than conventional PNIPAAm hydrogel membranes (i.e., crosslinked PNIPAAm without the grafted side chains).

4.1.4 Rationale for the Study of PNIPAAm-Grafted Porous Polyethylene Membranes

We are interested in developing permeability-variable membranes for drug release using the temperature responsiveness of PNIPAAm. One approach is graft polymerization of NIPAAm onto the surface of a porous membrane.

As discussed in Chapter 2, even though a great deal of work has been done on this type of membrane, a systematic study is needed to understand the effects of graft yield and location on the membrane permeability. This study may reconcile the conflicting reports in the literature and provide information for further development of multi-stimuli responsive membranes.
As the first stage of the project, we investigated PNIPAAm-grafted porous membranes. The membrane was prepared by graft polymerization of NIPAAm onto porous polyethylene membranes. In our work, we selected the photochemical graft polymerization (i.e., UV irradiation plus photoinitiator) method to prepare the membrane based on the following consideration: the method can induce graft polymerization on membrane surfaces as well as inside membrane pores. Compared with the electron beam or γ-ray irradiation and plasma treatment, the photochemical method is relatively simple and inexpensive, and the initiation mechanism is better determined. In addition, UV penetration and damage to the membrane are far less than for electron beam and γ-ray initiation methods [Ogiwara 1985, Ratner 1976]. As a result, the UV initiation method would induce surface graft polymerization without changing bulk properties of the membrane, such as mechanical strength. In comparison with free radical initiation, the photochemical method can generate grafting sites directly onto the membrane. In contrast, in the free radical method, the grafting sites are indirectly formed by attack on the membrane by primary radicals from initiators or by chain transfer between propagating radicals and the membrane. As a result, the photochemical method would be more efficient due to less homopolymerization. Finally, by using proper photoinitiators, it may be possible to design graft architectures by sequential graft polymerization of different monomers, as shown in the current work. Porous low density polyethylene membranes were used because they are easily grafted by the photochemical method and they do not absorb UV light at the wavelength involved (> 290nm).
4.2 Results and Discussion

4.2.1 Photochemical Grafting of NIPAAm onto Porous PE

It was found that NIPAAm was easily grafted onto porous polyolefins, especially low density polyethylene. Table 4.2 shows that graft yield increases with increasing monomer concentration and irradiation time. Graft yield increases may be ascribed to either increasing chain length or increasing density of the graft polymer; however, no further characterization was done in this study to distinguish between these two possibilities. PNIPAAm-g-PE porous membranes with a wide range of graft yields were prepared by varying graft yield and irradiation time, and used in subsequent studies.

Table 4.2 Graft yield of membranes prepared by UV irradiation under various conditions

<table>
<thead>
<tr>
<th>Monomer Concentration (mole/L)</th>
<th>Irradiation time (minutes)</th>
<th>Graft yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.11</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>0.22</td>
<td>60</td>
<td>153</td>
</tr>
<tr>
<td>0.33</td>
<td>60</td>
<td>320</td>
</tr>
<tr>
<td>0.33</td>
<td>180</td>
<td>532</td>
</tr>
<tr>
<td>0.22</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>0.22</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>0.22</td>
<td>45</td>
<td>123</td>
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<tr>
<td>0.22</td>
<td>75</td>
<td>233</td>
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<tr>
<td>0.22</td>
<td>90</td>
<td>257</td>
</tr>
<tr>
<td>0.22</td>
<td>120</td>
<td>282</td>
</tr>
<tr>
<td>0.22</td>
<td>180</td>
<td>394</td>
</tr>
<tr>
<td>0.22</td>
<td>240</td>
<td>449</td>
</tr>
</tbody>
</table>

4.2.2 Characterization of Graft Location: XPS, SEM and Thickness Measurements

The membrane surface compositions before and after grafting were analyzed by XPS. Figure 4.1 shows the high resolution XPS scan of the C1s peak for the initial porous PE
membrane (Fig. 4.1a) and the grafted membrane (Figures 4.1b and 4.1c)). For a carbon bonded with electron withdrawing groups such as the amide group from NIPAAm, a shoulder peak with a higher binding energy would appear beside the normal position at 285.0 eV of the carbon atom in polyethylene. This was observed for both the front UV facing side of the membrane as well as the rear side against the vessel wall. These XPS results are consistent with the presence of PNIPAAm on the membrane surfaces.

![Graph showing XPS scan of C1s peak for the non-graft PE (a) and grafted PE membrane (b: rear side against the vessel wall; c: front UV-facing side) with graft yield of 28%.](image)

Figure 4.1 High resolution XPS scan of C1s peak for the non-graft PE (a) and grafted PE membrane (b: rear side against the vessel wall; c: front UV-facing side) with graft yield of 28%.

The N/C atomic ratios on the surface of membranes with different graft yields were calculated from the sensitivity factor-corrected area under each peak. Figure 4.2 shows that the ratio increases with increasing graft yield, reaching a plateau of approximately 0.055 at graft yields above about 150%. This can be explained by the grafting process and condition. Our
membrane preparation procedure ensures the uniform distribution of photoinitiator throughout the pores at the start of grafting. However, since the pores are not readily wetted by aqueous NIPAAm solutions, little or no monomer is present in the pores at the start of grafting. Therefore, surface grafting would pre-dominate at early times, or low graft yields. This would give rise to increasing N/C ratios on the surface at low graft yields.

![Graph](image_url)

Figure 4.2 N/C atomic ratios of the surfaces of PNIPAAm-g-PE membranes with different graft yields. ◇ for front UV-facing side, ● for rear side against the vessel wall.

While surface grafting proceeds, grafted PNIPAAm near the mouth of pores would attract water into the pores, and cause progressively inward wetting of the pores by the NIPAAm solution, thus introducing the monomer into the pores and facilitating grafting inside the pores.
Once the pores are wetted, diffusion of NIPAAm into the pores would continually replace reacted monomer, and perpetuate grafting in the pores. Pore grafting can therefore begin well before the surface is covered. Graft yield can continue to increase with little further increase in the surface N/C ratio due to increased pore grafting and/or increased thickness of surface layer beyond the thickness detection limit of XPS. As a result, the surface N/C ratio reaches a plateau. In addition, due to much larger pore areas than external surface areas (~5 m² pore areas based on the assumption of straight pores vs. ~40 cm² external surface areas for a 7 cm x 10.5 cm rectangular PE membrane), pore grafting can dominate surface grafting even at low graft yields (below 150%).

Figure 4.2 also shows that more polymer was grafted on the front side of the membrane than on the rear side, especially at low graft yields. This can be attributed to the easier access of monomer and UV light to the front side of the membrane. At longer grafting times, or higher graft yields, the difference appears to diminish. More sample analyses are required to estimate statistic significance of the difference. The highest surface N/C atomic ratio of 0.06 measured for the membrane with 320% graft yield is lower than the theoretical value for the NIPAAm monomer (0.17 calculated from the number of nitrogen atoms divided by the number of carbon atoms in the monomer). This indicates that the surface was not covered completely by the grafted polymer in the dry state.

SEM pictures showing the cross-section morphologies of the original PE membrane and grafted membranes are presented in Figure 4.3. Different structures between original and grafted PE membranes are seen. The fibrils visible in the cross-section of the original PE membrane are covered by the grafted polymers throughout the entire membrane thickness. Coverage appears to be denser in the 320% graft yield membrane than the 233% graft yield membrane.
Figure 4.3 Cross-sections of non-grafted (a) and PNIPAAm-g-PE membranes with graft yield of 233% (b) and 320% (c).
The thickness of the membrane in pH 7.4 buffer solution at the temperature below and above the lower critical solution temperature (LCST) of PNIPAAm was measured to characterize dimensional changes. Figure 4.4 shows that membranes with a graft yield less than 150% have about the same thickness as the original membranes, and do not show

![Figure 4.4](image.png)

Figure 4.4 The membrane thickness as a function of the graft yield at the solution temperature below and above the LCST. Error bars are standard deviations (n=4 pieces of the membrane made from the same batch).
dimensional changes with temperature. In contrast, at graft yields above 150%, membranes become thicker than the nascent membrane, and the thickness varies in response to temperature. The results suggest that PNIPAAm at low graft yields has no effect on the dimensional change, while, as the pores become filled with increasing graft yield, grafted polymers would extend out of the membrane pores in the solution. As a result, the PE surface is covered by PNIPAAm resulting in the thickness change in response to the temperature variation.

In summary, XPS and SEM results suggest that PNIPAAm was grafted on the surface and throughout the pores of the PE substrate. The combined observations of the effect of graft yield on thickness and the effect of graft yield on surface N/C ratio suggest that at low graft yields, although the membrane surface is grafted by PNIPAAm at the very beginning of grafting, most grafting occurs inside the pores. At high graft yields, the surface PNIPAAm layer increases in thickness, either due to the elongation of surface graft chains, or the extension of pore graft chains out of the pores. This thickness increase is not accompanied by any observable increase in the surface N/C ratio. This can be due to either partial surface coverage or due to the dehydration required for XPS analysis.

### 4.2.3 Permeation Study

#### 4.2.3.1 Effect of the Graft Yield

The temperature-dependent permeability of vitamin B₁₂ through PNIPAAm-g-PE of graft yields 233% and 320% are shown in Figures 4.5 and 4.6, respectively. It is interesting to note that temperature has opposite effects on the permeability of the 233% and the 320% graft yield membranes, indicating that two distinct types of valve functions exist, depending on the graft yield.
Figure 4.5 Effect of temperature on the permeability of vitamin B_{12} across a PNIPAAm-g-PE porous membrane with graft yield of 233% in pH 7.4 (I=0.01) buffer solution. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).
Figure 4.6 Effect of temperature on the permeability of vitamin B12 across a PNIPAAm-g-PE porous membrane with graft yield of 320% in pH 7.4 (I=0.01) buffer solution. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).

The two types of valve function are further demonstrated in Figure 4.7, in which the log permeability of vitamin B12 at 37°C and 30°C is plotted as a function of graft yield. It is seen that at lower graft yields, the permeability at 37°C is higher than that at 30°C. At high graft
yields, the permeability response switches, and a new pattern of valve function is observed. The permeability now becomes lower at 37°C than at 30°C, opposite to the behavior seen in lower graft yield membranes. Moreover, within the range of experimental conditions tested, the permeability in the collapsed state decreases up to 3 orders of magnitude with increasing graft yield.

![Graph](image-url)

**Figure 4.7** Effect of graft yield on the permeability (P) of vitamin B₁₂ across PNIPAAm-g-PE porous membranes in pH 7.4 (I=0.01) buffer solution at 37°C (○) and 30°C (●). The curves were obtained by hand-drawing to indicate the trend at 37°C, and by fitting data points at 30°C to a cubic polynomial. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).
Thickness measurements (Figure 4.4) indicate an increasing surface layer as graft yield increases, implying that as graft yield increases, graft polymer fills the pores and extends out of the pores to form a surface layer of graft polymer. These observations suggest that in the lower graft yield membranes, permeability is controlled by pore-grafted PNIPAAm. The expanded conformation of the grafted polymers below the LCST gives rise to a reduced effective pore size in comparison with the collapsed state observed above the LCST. In the higher graft yield membranes, permeability is controlled by the thick surface layer of PNIPAAm. As the surface PNIPAAm layer shrinks with increasing temperature, the layer becomes more compact and more resistant to diffusion, resulting in decreased permeability. The permeability response of higher graft yield membranes, i.e., higher permeability below the LCST than above, is consistent with PNIPAAm-based hydrogel membranes [Feil 1991]. The two response mechanisms are illustrated schematically in Figure 4.8.

![Diagram](https://via.placeholder.com/150)

Figure 4.8 Explanation of the dual response mechanism.
4.2.3.2 Effect of Permeant Size

Figure 4.9 shows the effect of solute size on the permeability response of the membrane with graft yield of 233% and 449%. Non-ionic, hydrophilic solutes with different molecular weights were used for the permeation study. The permeability response is measured as the ratio of permeabilities at 37°C and 30°C for 233% graft yield or 30°C and 37°C for 449% graft yield, respectively. For both membranes, the response shows a maximum at an intermediate solute molecular weight.

![Figure 4.9 Effect of the molecular weight (M_w) of solutes on the permeability change of the PNIPAAm-g-PE membrane. The permeability change is defined as ON/OFF ratio of permeability between collapsed and expanded states.](image)
Figure 4.10 schematically illustrates a possible explanation for this observation. In the pore-graft controlled (low graft yield) membrane (Figure 4.10(a)), size exclusion occurs when the solute size is within an order of magnitude of the effective pore dimension of the membrane. The effective pore size of the membrane changes due to the swelling or collapse of the graft polymer. The smallest penetrants are not significantly affected by the changing pore size since

![Diagram of size exclusion effect](image)

Figure 4.10 Explanation of the size exclusion effect on the two types of permeability response. (a) polymer-grafted porous membranes with low graft yields, (b) graft layers on the surface of polymer-grafted porous membranes with high graft yields.
the effective pore size, even with swollen grafts, is much larger than the penetrant. The largest penetrants are not significantly affected by the changing pore size because the effective pore size, in both the swollen and collapsed states, is comparable to penetrant size, and significant size exclusion exists in both states. For the intermediate sized penetrants, the change in pore size due to graft collapse or swelling represents a significant change in the extent of size exclusion, giving rise to the largest permeability response. A similar explanation can be applied to the higher yield membranes in which surface PNIPAAm layers control the permeability behavior (Figure 4.10(b)). The response behavior is similar to that of PNIPAAm hydrogel membranes, and size exclusion occurs when the solute dimensions approach the effective mesh size within the surface PNIPAAm layer.

4.2.3.3 Dynamic Permeability Response

The dynamic responsiveness of the membrane with graft yield of 449% was investigated using vitamin B\textsubscript{12} as a solute. The result is presented in Figure 4.11, which reveals that the membrane permeability can be regulated by changing solution temperature. Permeability at 30°C (i.e., ON state) is about 70 times higher than at 37°C (i.e., OFF state). The membrane shows good responsive reversibility and durability even after more than 10 cycles. This implies that the membrane has good mechanical strength and that PNIPAAm on the porous PE membrane is so stable that it is a grafted polymer.
Figure 4.1 Permeability of vitamin B₁₂ across PNIPAAm-g-PE membrane with graft yield of 44.9% in response to step-wise temperature changes between 37°C (●) and 30°C (○) in pH 7.4 (I=0.01) buffer solution. Symbols represent averaged permeability in each state. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).

The dynamic permeation experimental results suggest that reversible ON-OFF permeability response can be achieved. The membrane displays the potential for the design of temperature-responsive drug delivery systems. The system may be applied for topical drug delivery to the skin, or for localized delivery of drugs within the body using optical-fibre catheters to regulate the drug release. Moreover, utilizing the two types of permeability response, the drug can be either delivered or not delivered at body temperature, i.e., according to graft yield.
4.3 Conclusions

1. Poly(N-isopropylacrylamide)-filled porous polyethylene membranes with a wide range of graft yields can be prepared by photochemical graft polymerization. The graft polymer is located on both sides of the external surface and inside the pores of the membrane.

2. PNIPAAm grafts are predominantly located within the pores in low graft yield membranes. These membranes exhibit little change in thickness with solution temperature, and the membrane permeability increases when temperature increases above the LCST.

3. In high graft yield membranes, the membrane pores are filled with the graft polymer and the membrane surface may be covered by graft layers. As a result, the membrane thickness increases with graft yield and becomes sensitive to the solution temperature. Moreover, the membrane shows abruptly decreased permeabilities as the temperature is raised through the LCST.

4. The permeability response exhibits a maximum at an intermediate solute size.

5. The membrane shows reversible temperature-responsive permeability.
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Chapter 5  pH-Responsive Permeability of PMAA-g-PE Porous Membranes

Abstract

Poly(methacrylic acid) (PMAA) grafted porous PE membranes (PMAA-g-PE) were studied. It was found that: 1) a wide range of graft yields can be achieved by varying irradiation time (20 - 360 minutes) and monomer concentration (0.22 - 0.66M), 2) the grafted membrane exhibits reversible permeability response, 3) the membrane shows a maximum permeability response at an intermediate permeant molecular weight due to size exclusion effect, 4) depending on the graft yield, two types of permeability response can be obtained. These observations are consistent with our earlier study on poly(N-isopropylacrylamide) (PNIPAAm) grafted porous polyethylene membranes.

In addition, it was observed that the solvent used during grafting may influence the graft location - presumably due to variations in pore wetting. Specifically, it was found that methanol can increase grafting inside membrane pores in comparison with water solvent, which was inferred from membrane swelling, thickness measurement and SEM characterization. Moreover, preferential grafting inside the membrane pores, as controlled by increasing methanol content in the grafting solvent, results in lower membrane permeability and greater pore graft-controlled permeability response.
5.1 Introduction

To further generalize the conclusions from the work on PNIPAAm-g-PE membranes, a pH-responsive polymer, poly(methacrylic acid) (PMAA), grafted porous PE membrane was studied following the same method involved in the study on the PNIPAAm-g-PE membranes. In addition, different PMAA graft location (on the surface versus inside the pores) in the membrane was obtained by conducting the graft polymerization in non-pore wetting (water) and pore wetting (methanol) solvent. The permeability of these membranes, as a function of graft yield, solution pH and solute size, was investigated to understand the effect of graft location on membrane performance.

5.1.1 Conformation Transitions of PMAA

PMAA hydrogels have been studied since the 1950s [Katchalsky 1955, 1951]. It is well known that PMAA, a weak polyelectrolyte, shows pH-dependent conformations in aqueous solution due to its ionizable group: -COOH. In aqueous solution with the pH below the pK_a of the COOH groups, the -COOH groups are substantially protonated, which corresponds to PMAA with a compacted conformation. On the other hand, in aqueous solution with the pH above the pK_a of the COOH groups, the -COOH groups are substantially ionized to -COO' groups. PMAA becomes expanded due to electrostatic repulsion between the COO' groups.

Even though the pH-responsive conformational transition for PMAA has been confirmed by various techniques: viscosimetry, potentiometric titrations, fluorimetry, calorimetry [Bekturov 1981], and neutron and X-ray small-angle scattering method [Plestil 1986], many uncertainties remain regarding its behavior in aqueous solution [Heitz 1999]. In the literature, the compacted conformation has been variously described as a globular, hypercoiled or helicoidal structure,
which is grossly misleading [Yang 1999]. Recently, an X-ray scattering study on PMAA in aqueous solution suggested that uncharged PMAA had an overall dimension between that of a compact sphere without water molecules and that of a gaussian coil [Heitz 1999]. On the other hand, the expanded conformation was described as an extended coil [Heitz 1999] or a rod-like form [Leclercq 1999]. In addition to pH, the compacted and expanded conformations depend on ionic strength as well. The quantitative relationship between the conformation change and the degree of ionization is not clearly ascertained by the literature data.

The pH-responsive conformation transition of PMAA in solution has been extended to grafted PMAA on a solid surface. Theoretically, changes in the stretch-collapse transition of polyelectrolyte brushes (i.e. grafted polyelectrolytes whose radius of gyration is larger than grafting space) as solvent quality decreased has been predicted using different approaches, such as scaling arguments, self-consistent mean field approaches and Monte Carlo simulations [von Goeler 1996]. Though the solvent quality can be varied by changing solution pH or salt concentration, it is difficult to correlate the experimental conditions with the variables in the theoretical models. For example, it is hard to measure experimentally the graft density included in the theoretical prediction. The conformational transition of the grafted polyelectrolytes with pH has been confirmed as well by potentiometric and calorimetric studies on poly(acrylic acid) [Casolaro 1993] and poly(N-acryloy-glycine) [Barbucci 1991] grafted onto a porous membrane. On the other hand, it was found that longer time was required for the grafted polymers to reach equilibrium pH during titration than for free polymers, due to interactions between the grafted polymers and the membrane substrates (i.e. cellulose, polyurethane). However, it was reported that the titration curve for poly(acrylic acid) grafted on a polyethylene membrane was sharper than that for poly(acrylic acid) in solution. A significant difference in polarity between the non-
polar polyethylene surface and the polar aqueous solution might exaggerate the conformation transition of the polymer [Bergbreiter 1995]. In addition, the latest study on elasticity of a single PMAA graft chain by atomic force microscopy suggested a flexible conformation in an aqueous solution in which PMAA was considered partially ionized [Ortiz 1999]. This implies that the grafted PMAA in the ionized state may be an expanded coil.

5.1.2 Permeation through PMAA-Grafted Porous Membranes


As discussed before, we are interested in responsive polymer-grafted porous membranes for variable permeability. Depending on the responsive properties of the polymer grafted, the membrane permeability can be regulated by a variety of stimuli. Utilizing the pH induced conformation transition of PMAA, as discussed above, pH-responsive polymer grafted porous membranes were investigated.
Theoretical models on pH-responsive mass transport across polyelectrolyte grafted porous membranes have been developed [Akerman 1998, Kontturi 1996, Misra 1991]. The models described the hydraulic or diffusive permeability as a function of pH and ionic strength. Higher permeability was predicted if the polyelectrolyte was in the compacted or collapsed conformation, rather than in an expanded conformation. Moreover, a dramatic change in permeability occurred near the pH close to pKₐ value of the polyelectrolyte. However, the prediction of pH-responsive permeability was restricted to a membrane with low graft yield (<58%) and was based on the assumption that the polyelectrolyte was only located inside the membrane pores, probably true at low graft yields. Therefore, it is necessary to understand the pH-responsive permeability of high-graft-yield membranes and the effect of the graft location on the change in permeability with pH.

Experimental studies on PMAA-grafted porous polyethylene membranes showed that membrane porosity varied inversely with ionization degree as a function of solution pH [Islam 1992]. Both the porosity and ionization degree changed dramatically around pH 5. The result was consistent with the predicted effect of the conformational change on the permeability of grafted porous membranes. Below pH 5, the degree of ionization was low and the grafted PMAA was in the collapsed conformation, leaving the membrane pores open. Above pH 5, the ionization degree was high and the grafted PMAA was in the expanded conformation, closing the membrane pore. However, it should be noticed that the graft yield of the membrane studied was low: only 26%.

It can be seen that although theoretical and experimental work have been reported on the responsive polymer grafted porous membranes, effects of the graft yield and location on the permeability response have not been well understood.
With these data in mind, PMAA-g-PE porous membranes with a wide range of graft yields were prepared by UV irradiation, based on the previous study with poly(N-isopropylacrylamide) (PNIPAAm) grafted PE porous membranes. Methanol/water mixtures of varying composition were used as the solvent in the photografting procedure to control graft location, and thus, the permeability response. The photografted membranes were characterized by SEM, swelling and thickness measurements. The pH-dependent permeability response of the grafted membranes was studied as a function of the graft yield and permeant molecular weight. The dynamic permeability response to alternating pH changes was investigated as well.
5.2 Results and Discussion

5.2.1 Photochemical Grafting of MAA onto Porous PE

Photografting of MAA onto PE membranes has been investigated, and the effects of various graft conditions on graft yield are shown in Figure 5.1. As seen in Figure 5.1-a, graft yield increases with increasing monomer concentration for graft polymerization of MAA.

![Graph showing the effect of monomer concentration on graft yield.](image)

Figure 5.1-a Effect of monomer concentration on the graft yield.
in water or a 1:3 water/methanol solvent. Figure 5.1-b shows that graft yield increases with UV irradiation time, either in water or a water/methanol solvent. Moreover, within the range of irradiation times investigated, graft yield increases with time for all grafting solutions tested and appears to level off for graft polymerization in water at a high graft yield (~650%). Graft yield increases may be ascribed to either increasing chain length or increasing density of the graft polymer. Further investigations (beyond the scope of this study) are required to distinguish between these two possibilities and to explain the effects of the monomer concentration and UV

![Figure 5.1-b](image-url)

Figure 5.1-b Effect of UV irradiation time on graft yield. (●) grafted in water, [MAA]=0.66 M; (⊙) grafted in methanol/water (1:1 by volume), [MAA]=0.66 M; (□) grafted in methanol/water (1:3 by volume), [MAA]=0.22 M. The error bar is a standard deviation (n=3 replicates).
irradiation time on the graft yield.

Figure 5.1-c shows the effect of solvent composition on graft yield. A maximum in graft yield vs. volume fraction methanol is observed. At low methanol volume fractions, increasing methanol content promotes grafting and increases graft yield. A possible explanation is that methanol/water mixtures wet the pores of the hydrophobic PE membranes more readily than pure water, thus facilitating contact between MAA monomers and the pore surfaces. This would
result in increased polymer grafting inside the membrane pore. Supporting evidence for solvent-influenced graft location based on swelling, thickness and SEM characterization are discussed below. In contrast, at higher methanol volume fractions, further increases in the methanol content of the grafting solvent result in decreases in graft yield. Since the solubility of the photoinitiator, xanthone, in methanol/water increases with methanol content (solubility in 50\% methanol (0.21 mg/ml) is more than 40 times higher than that in water (< 0.005 mg/ml)), it is plausible that solvents of higher methanol content may dissolve and remove PE-adsorbed photoinitiator, leading to a reduction in graft polymerization. This is consistent with a control experiment, in which no graft polymerization took place after the membrane was immersed in methanol.

In summary, PMAA-g-PE porous membranes with a wide range of graft yields were prepared by varying monomer concentration and irradiation time using different grafting solvents.

5.2.2 Membrane Characterization: Graft Location and Morphology

Figure 5.2 shows the effect of graft yield and pH on membrane swelling for graft membranes prepared in either water or a 50/50 mixture of methanol/water. Swelling experiments were conducted in pH 4.4 or pH 7.4 buffer solutions, below and above the pKa of PMAA. It is seen that swelling increases with graft yield. In addition, at pH 7.4 when the grafted PMAA chains are in the expanded state, the effect of graft yield on swelling is more pronounced than at pH 4.4 when PMAA chains are in the collapsed state. Moreover, membranes grafted in water exhibit much larger swelling ratios than those prepared in methanol/water. This implies that methanol can increase grafting inside the membrane pores.
since the polymer chains grafted on the external surface would swell with less restriction than those inside the pores [Yamada 1992a, Yamaguchi 1997, 1991].

Figure 5.2 Effect of the graft yield on swelling ratio of membranes prepared in different solvents and at different pH: ▲ (water solvent, pH 7.4), ■ (water solvent, pH 4.4), △ (1:1 methanol/water, pH 7.4), □ (1:1 methanol/water, pH 4.4). Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).

The effect of graft yield and solution pH on the dimensions of the membrane is shown in Figure 5.3. The relative thickness (thickness at pH 7.4 / thickness at pH 4.4) increases with increasing graft yield, as expected. In addition, membranes grafted in water show more
pronounced pH-responsive changes in thickness than membranes prepared in methanol/water.

Figure 5.3 Thickness changes of the membrane grafted in water (○) or methanol/water with volume ratio of 1 (●) in response to pH changes between pH 4.4 and 7.4 as a function of the graft yield. The grafted membranes were prepared under a monomer concentration of 0.66M. Error bars are standard deviations (n=4 pieces of the membrane made from the same batch).

Since graft polymers located on the external membrane surface are expected to have a greater impact on the overall membrane thickness than those inside the membrane pores, these results suggest that polymers were primarily grafted inside the membrane pores when methanol/water is
used as the grafting solvent, but were mainly grafted on the external surface if water was the grafting solvent.

The graft location can be further confirmed by SEM pictures of the membrane cross-section. Figure 5.4 shows that grafted membranes (Fig. 5.4-b, 5.4-c) are thicker than the original substrate (Fig. 5.4-a); this observation can be attributed to the presence of graft polymers on the external membrane surface. In addition, it appears that the membrane grafted in methanol/water (Figure 5.4-c) shows a higher density bulk region than the membrane grafted in water (Figure 5.4-b). These observations are consistent with the swelling and thickness results presented earlier, which indicated that methanol/water promotes PMAA grafting inside the pores.
Figure 5.4 Cross-sections of ungrafted (a) and PMAA-g-PE membranes prepared in water with 278% graft yield (b) and prepared in methanol/water (1:1 by volume) with 313% graft yield (c).
5.2.3 Permeation Study

5.2.3.1 Effect of Grafting Solvent

In the above discussion, it has been shown that increasing the methanol content of the methanol/water mixture used as the photografting solvent results in preferential grafting of PMAA in the membrane pores. Figure 5.5 shows the permeability of vitamin B₁₂ at pH 7.4 through membranes grafted from methanol/water mixtures of varying methanol content. It shows

![Permeability vs. Graft Yield](image-url)

**Figure 5.5** Permeability of the PMAA-g-PE membrane prepared in water (●) and methanol/water (1:3 by volume: ▼ or 1:1 by volume: ▲) as a function of the graft yield in pH 7.4 buffer solution. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch). The curves were obtained by fitting the data points to a cubic polynomial - no physical significance should be attached to the curves.
that for all grafting solvents, as the graft yield increases, permeability decreases initially and then increases with further increases in the graft yield. This observation can be explained by viewing the membrane as a composite of two layers: a porous membrane layer and a surface graft layer which behaves similar to a hydrogel membrane. At low graft yields, the porous membrane layer dominates, and any graft polymer in the pores reduces the effective pore size, resulting in decreased overall permeability. Further increases in graft yield give rise to a more prominent surface graft layer, and the higher permeability of the surface layer relative to the porous membrane layer results in a higher overall membrane permeability -- calculated using the swollen thickness of the entire membrane. It has been reported that the swelling of surface grafted poly(4-vinylpyridine) in a porous polypropylene microfiltration membrane would result in an increase in its overall hydration, which becomes more significant with increasing graft yield [Mika 1997].

Figure 5.5 also shows that membrane permeability decreases with increasing methanol content in the grafting solvent. Using the two layer composite picture again, the preferential grafting in the pores as methanol content increases results in reduced permeability through the porous membrane layer, thus giving rise to a lower overall permeability. In addition, Figure 5.5 indicates that the graft yield at which minimum permeability is observed is higher for membranes grafted in the water/methanol mixture than in water due to the difference in the graft location.

5.2.3.2 Effect of Solution pH and Graft Location

Considering the value of \( pK_a = 5.8 \) for the grafted PMAA (see Appendix 3 for measurement of \( pK_a \)), a dramatic change in the degree of dissociation of the grafted PMAA
would take place in the pH range 4.4-7.4. Therefore, pH 4.4 and 7.4 were selected to induce collapsed and expanded conditions, respectively, in the following permeation study.

The pH-dependent permeability of vitamin B_{12} through the PMAA-g-PE with a wide range of graft yields is shown in Figure 5.6. There are two types of permeability response depending on the graft yield. At low graft yields, the membrane shows porous membrane

![Permeability of the PMAA-g-PE membrane prepared in water with different graft yields in pH 4.4 (○) and pH 7.4 (●) buffer solution. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch). The curves were obtained by fitting the data points to a cubic polynomial - no physical significance should be attached to the curves.](image-url)
responsive behavior, i.e., the collapse of the graft polymer would leave the membrane pore open compared with the expanded polymer. At high graft yields, the membrane may become more like a hydrogel membrane, showing lower permeability in the collapsed state. However, it should be noted that uncertainties about the two types of permeability response exist due to the overlap of the error bars. Figure 5.7 shows more evidence of the two types of permeability response.

Figure 5.7 shows the effect of graft location on the permeability response, described as the ratio of the permeabilities at pH 4.4 and 7.4. It can be seen that, compared with water as

![Graph showing permeability response](image)

Figure 5.7 Effect of grafting solvent on the permeability response. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).
grafting solvent, methanol/water solvent promotes the membrane response as a polymer grafted porous membrane where a pore-control mechanism is observed. In addition, the methanol/water grafted membrane may show a hydrogel-type of permeability response at a higher graft yield due to solvent reducing the relative formation of the hydrogel layer, especially for methanol/water solvent with 1:1 volume ratio. The result is consistent with those shown in Figures 5.5 and 5.6, and can be explained as follows: with more and more grafts located on the external membrane surface, a hydrogel layer would form on the porous substrate, switching the porous membrane responsive behavior to hydrogel responsive behavior. For the membrane with the polymer grafted inside the pores, the membrane permeability would be regulated by the conformational change of the grafts inside the pores. Higher graft yields are needed for the membrane with more grafts inside the pores to form the hydrogel layer which would regulate the membrane permeability by the swelling change of the surface layer.

Figure 5.8 illustrates the two response mechanisms based on the two layer picture described above. At low graft yields, the porous membrane layer dominates and the expanded conformation of the grafted polymer in the pores above its pKa gives rise to a reduced effective pore size in comparison with the collapsed state which exists below the pKa. This response mechanism was termed as the pore-control mechanism [Park 1997, Ito 1997]. On the other hand, the membrane shows a higher permeability above the pKa than below, as the graft yield increases above a transitional graft yield. The response behavior is similar to PMAA hydrogel membranes [Weiss 1986]. The second type of permeability response is attributed to the hydrogel layer formed on the membrane surface: with increasing graft yield, more PMAA was located on the external membrane surface, and the hydrogel layer becomes thicker and dominant in controlling permeability changes giving rise to the hydrogel-type of permeability response. In
addition, because more PMAA grafts are on the external surface of the water grafted membrane (Fig. 5.8-a) than the methanol/water grafted membrane (Fig. 5.8-b), the water grafted membrane switches to the second type of response at a lower graft yield.

Figure 5.8 Schematic illustration of two types of permeability response of PMAA grafted porous membranes prepared in water (a) and methanol/water (1:3 by volume) (b).

In summary, the permeability and response behavior of a responsive polymer-grafted porous membrane would be tailored by controlling the graft location, which may be achieved by varying the grafting solvent.

5.2.3.3 Effect of Permeant Size

Figure 5.9 shows the effect of solute size on the permeability response of the membrane grafted in water with a 387% graft yield. The permeability response is measured as the ratio of
permeabilities at pH 4.4 and pH 7.4. The permeability ratio shows a maximum at an intermediate solute molecular weight. The phenomenon and explanation are completely consistent with those demonstrated in the study of the PNIPAAm-g-PE membrane. Briefly, the effective pore size of the membrane changes due to the swelling or collapse of the graft polymer. Size exclusion occurs when the solute size is within an order of magnitude of the effective pore dimension of the membrane. The smallest permeant is not significantly affected by the changing pore size

Figure 5.9 Effect of permeant molecular weight ($M_w$) on the permeability response of the membrane grafted in water solvent. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch). The permeability response is defined as the ratio of the permeability at pH 4.4 vs. pH 7.4.

The permeability ratio shows a maximum at an intermediate solute molecular weight. The phenomenon and explanation are completely consistent with those demonstrated in the study of the PNIPAAm-g-PE membrane. Briefly, the effective pore size of

![Diagram of permeability ratio vs. molecular weight](image)
since the effective pore size, even with swollen grafts, is much larger than the permeant. The largest permeant is not significantly affected by the changing pore size either because the effective pore size, in both the swollen and collapsed states, is comparable to the permeant size, and significant size exclusion exists in both states. For the intermediate-sized permeant, the change in pore size due to graft collapse or swelling represents a significant change in the extent of size exclusion, giving rise to the largest permeability response.

5.2.3.4 Dynamic Permeability Response

The reversibility of the membrane response was examined by a dynamic permeability study using dextran with a molecular weight of 9400 as the permeant. The permeability in each cycle was calculated and presented in Figure 5.10, which shows the membrane permeability changes reversibly in response to solution pH alternating between pH 2 and pH 7.4. These results are consistent with the reversible response observed previously on PNIPAAm-g-PE membranes, and on poly(acrylic acid) grafted porous poly(propylene) membranes [Ulbricht 1996].
Figure 5.10 Dynamic permeability response of the membrane grafted in water to pH changes between 2 (○) and 7.4 (●). Symbols represent averaged permeability in each state. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).

5.3 Conclusions

1. Poly(methacrylic acid) grafted porous polyethylene membranes with a wide range of graft yields can be prepared by photochemical graft polymerization.

2. At appropriate an volume ratio of methanol to water, the presence of methanol in the grafting solvent can increase grafting inside the membrane pores, resulting in a significant decrease in pH-induced membrane swelling and thickness change in comparison with membranes prepared using water as the grafting solvent.
3. Membranes with low graft yields show decreased permeability with increasing graft yield followed by increased permeability with further increasing graft yield, i.e., permeability goes through a minimum with respect to the graft yield.

4. Depending on the graft yield and graft location, two types of permeability response can be obtained. Membranes with low graft yields show responsive behavior as a polymer grafted porous membrane, while membranes with high graft yields show permeability response as a hydrogel-like membrane. Membranes with more grafts on the external surface exhibit the hydrogel-type of permeability response at a relatively lower graft yield.

5. Membranes with graft polymers inside the pores show a greater pore graft-controlled type of permeability response than those with grafts on the membrane surface.

6. The permeability response exhibits a maximum with respect to solute molecular weight.

7. The membrane response is reversible.
5.4 References


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Chapter 6  Temperature- and pH-Responsive Permeability of PNIPAAm-block-PMAA Grafted PE Porous Membranes

Abstract

PNIPAAm and PMAA co-grafted PE porous membranes with a wide range of total co-graft yields and co-graft compositions were prepared by a sequential photografting method, which involved first the graft polymerization of NIPAAm, followed by the graft polymerization of MAA. The co-graft architectures are proposed to be di-block in nature based on the grafting procedure, evidence from DSC studies, and permeation results obtained at different temperature and pH conditions. At pH 7.4, when the MAA components of grafted copolymers are ionized, the copolymers with PMAA content ranging from 7.6% to 67% exhibit LCSTs close to that of PNIPAAm. At pH 4.4, when the MAA components are deionized, the grafted copolymers with the PMAA content above 22% show no LCST in the temperature range of 0 to 60°C, suggesting that complexes between PNIPAAm and PMAA were formed under these conditions.

Using membranes with a constant 1:1 mass ratio of grafted PNIPAAm to PMAA but varying total co-graft yields from 0 to 658%, it was found that permeability of vitamin B₁₂ shows a minimum at an intermediate graft yield of around 400%. In this range of graft yields, permeability at 37°C and pH 4.4 was always higher than at 30°C and pH 7.4. The difference in permeability increases with increasing graft yield below the intermediate graft yield, but decreases with increasing graft yield above the intermediate graft yield.

For membranes with total co-graft yield of around 240%, in which the grafted polymers are mainly inside membrane pores, the permeability increased with increasing PMAA content, with a higher permeability at 37°C, pH 4.4 than at 30°C, pH 7.4, regardless of the PMAA
content, implying a pore control mechanism.

For membranes with total co-graft yields of around 450%, permeability increases with increasing PMAA content as well. However, a crossover PMAA content, above which the block copolymers show no LCST, is observed. Below the crossover MAA content, the permeability at 37°C, pH 4.4 is lower than that at 30°C, pH 7.4, suggesting a surface control mechanism.

A two-layer model is proposed to describe the two control mechanisms. The polymers grafted inside the membrane pores act as a permeation valve to open and close the pores by extension and contraction of the graft chain. In contrast, the polymers grafted on the membrane surface act as a hydrogel layer to increase and decrease the permeability by swelling and deswelling changes. Due to a more significant effect of the collapsed PNIPAAm surface layer on permeability reduction than PMAA, a 100% PNIPAAm grafted membrane shows a surface control mechanism, while a 100% PMAA grafted membrane does not, at a graft yield of around 450%. Moreover, the complexation prevents the collapse of PNIPAAm blocks, reducing the effect of the surface layer on the permeability reduction. As a result, the co-graft membrane switches from surface control to pore control at a PMAA content of around 20%, above which the complexation occurs.

Finally, by imposing various combinations of temperature and pH, these multi-stimuli responsive membranes can be manipulated to exhibit more sophisticated permeability response than membranes that contain singly grafted PNIPAAm or PMAA.
6.1 Introduction

In Chapters 4 and 5, studies on PNIPAAm and PMAA grafted porous PE membranes were presented. These studies elucidated the effects of graft yield and location on membrane permeability and its response to either temperature or pH. Briefly, two types of permeability response were found, depending on the graft yield and location. At low graft yields, grafts are predominantly located in pores, and the expanded conformation of the grafted polymers gives rise to reduced effective pore size, and consequently, decreased permeability in comparison with the collapsed state. The permeability response thus exhibits a pore control mechanism. At high graft yields, pores are filled, and surface-graft layers are formed. The collapsed surface layer is more resistant to permeation than the expanded layer. With increasing graft yield, the surface layer becomes thicker, and controls permeability changes. The graft yield at which the mechanism switches from pore control to surface control depends on the graft location. It was also shown that graft location can be affected by the pore-wetting ability of grafting solvent: a pore-wetting grafting solvent results in more grafting inside the membrane pores. Thus, permeation shifts from pore- to surface-controlled, at higher graft yields.

6.1.1 Multi-stimuli Responsive Polymers/Membranes

The membranes studied in Chapters 4 and 5 are responsive to only one stimulus. The significance of multi-stimuli responsive polymers that respond to more than one environmental stimulus has been claimed [Brazel 1995, Chen 1995, Hoffman 1995, Kurisawa 1995]. These polymers are expected to provide more sophisticated responsiveness than those that respond to only one stimulus, and this may lead to novel applications. For example, it has been stated that a hydrogel exhibiting swelling response to both pH and temperature could be used for drug
delivery in conditions where the pH and temperature are different from physiologic norms, such as blood clots [Brazel 1996]. In addition, synthetic and biologically responsive polymers have been combined with a variety of biomolecules, such as enzymes, peptides and antibodies, leading to another new type of material called hybrid responsive polymers; these hybrids may be used in bioreactions, diagnostics, separations, cell culture, and drug delivery [Stayton 1995, Chen 1995, Hoffman 1995]. It is possible that the hybrid polymers would be responsive to both physicochemical stimuli and biological stimuli. However, this has not been demonstrated.

Multi-stimuli responsive polymers have been prepared by copolymerization of different responsive monomers or by formation of interpenetrating polymer networks (IPN) containing different responsive components. Random, graft, or block copolymers may be synthesized, giving rise to different responsive properties that will be discussed in the following sections.

6.1.2 Random Copolymers

A great deal of work has been reported on random copolymers and hydrogels composed of thermo-responsive NIPAAm and pH-responsive units; these reports are summarized in Appendix 3. A large number of these references deal specifically with random copolymers of NIPAAm and MAA. It has been found that with increasing MAA content, especially as MAA units are ionized at pH > pKₐ, the lower critical solution temperature (LCST) of the thermoresponsive component is either eliminated or becomes so high that it is out of the range of interest. This phenomenon is attributed to increased overall hydrophilicity of the copolymers [Feil 1993], which disrupts the balance between the hydrophilic and hydrophobic interactions that underlie the LCST transition. Figure 6.1 summarizes these findings in graphical form; the existence or lack of a detectable LCST as a function of pH and MAA content is shown. The
overlapping regions may be ascribed to different methods used to prepare the copolymer/hydrogel, resulting in variations in molecular weight, hydrogel shape, size and crosslinking density. The same trend was observed for other random copolymers, such as poly(NIPAAm-co-acrylic acid). For example, Chen et al. reported that at pH 7.4, as the acrylic acid content increased to 10 mol%, NIPAAm/AA random copolymers lost their temperature sensitivity [Chen 1995]. Recently, both pH- and temperature-responsive hydrogels prepared by

Figure 6.1 Graphical summary of literature reports on the LCSTs of random copolymers/hydrogels at different solution pHs. The material is composed of NIPAAm and MAA units with different compositions. (●) means that the LCST was observed in the range of 0-60°C, while (O) means that the LCST was not observed in this temperature range. Refer to Appendix 4 for the LCST values and references.
random copolymerization of N,N-dimethylaminoethyl methacrylate and ethylacrylamide were incorporated with insulin and glucose oxidase to achieve a glucose-responsive insulin release matrix [Yuk 1997].

The loss of temperature sensitivity with increasing content of the pH-responsive component is a major drawback of multi-stimuli responsive random copolymers. It is believed that a long NIPAAm sequence is required to maintain the temperature responsiveness, however the required sequence length has not been defined [Vakkalanka 1996, Chen 1995, Yoshioka 1994]. In contrast to random copolymers, long continuous NIPAAm segments can be achieved in IPN and block or graft copolymers because of the polymeric nature of each component. Moreover, different domains or microphases may be obtained in IPN and block or graft copolymers and each domain or microphase may be composed of a single type of responsive component. As a result, the response of IPNs and block or graft copolymers would be independently activated by stimuli. Furthermore, hierarchical structures may be formed in block copolymers, resulting in sophisticated responsiveness [Ikkala 1999, Ruokolainen 1998].

6.1.3 IPN

It is known that IPN morphologies, e.g., phase continuity and domain size, depend on synthetic methods, miscibility and compositions of network constituents [Sperling 1981, Frisch 1998]. Therefore, it is expected that multi-stimuli responsiveness achieved by the IPN approach would be controlled by these factors. Both temperature- and pH-responsive IPN hydrogels composed of NIPAAm and other polymers, such as poly(acrylic acid) [Shin 1998, Lim 1997], poly(methacrylic acid) [Zhang 1998] have been investigated. It was found that temperature-
responsive swelling was affected by molecular interactions, such as hydrogen bonding between PNIPAAm and PAA in the network [Shin 1998]. In addition, the IPNs with more than 80 mol% PMAA showed no significant temperature responsiveness [Zhang 1998]; however, no explanation was given. IPNs composed of enzymatically degradable components have also been prepared; these showed biodegradation only in the presence of each of the two enzymes that hydrolyze each IPN component [Kurisawa 1998a, 1998b, Yamamoto 1996]. Such an IPN may be useful for preventing problems in drug release caused by a single enzyme [Kurisawa 1998a, 1998b].

6.1.4 Block or Graft Copolymers

A long NIPAAm sequence may also be achieved in block or graft copolymers, and thus maintain the LCST of PNIPAAm [Vakkalanka 1996, Chen 1995]. Since the copolymer regions whose structures are sensitive to different interactions (e.g., electrostatic, hydrophobic interactions and hydrogen bonding) are separated on a mesoscopic scale [Mikosch 1998], block or graft copolymers would independently exhibit phase transitions triggered by each stimulus. A variety of domain structures of block copolymers may be obtained by controlling overall molecular weight, composition and block-block interactions [Muthukumar 1997, Bates 1991]. PAA-g-PNIPAAm copolymers show temperature sensitivity over a wide range of acrylic acid content and their LCSTs are independent of the acrylic acid content [Chen 1995]. Appendix 5 summarizes more experimental evidence that the LCST of block and graft copolymers remains, even in the presence of a high content of other components, although slight shifts from the LCST of PNIPAAm may be observed.
6.2 Block Copolymer Grafted Porous Membranes

We are interested in multi-stimuli variable permeability membranes, i.e., polymer membranes whose permeability can be controlled by more than one factor because more control over the membrane permeability would be possible. For example, a single stimulus-responsive membrane shows permeability changes in response to two conditions below and above the critical temperature or pH, while a dual stimuli-responsive membrane may show permeability changes in response to coupled conditions, thus giving four permeability 'set points'. Controlled release systems with complex pulsatile release patterns may be designed using the membrane.

By grafting the multi-stimuli responsive block polymers onto a porous membrane, multi-stimuli responsive membranes are expected. Multiple architectures of the grafted chains can be designed, leading to sophisticated permeability response. In addition, depending on interactions between different blocks in response to solution conditions, the conformations may be tailored to regulate the membrane permeability.

Theoretical treatments and computer simulations to identify the structure of the grafted block copolymers under various solvent qualities have been attempted [Balazs 1997]. These studies predict that at relatively low grafting densities and in poor solvents (i.e., Flory-Huggins interaction parameter $\chi > 0.5$) for each block component, the grafted copolymers self-assemble into an ordered layer of pinned micelles. Depending on polymer-polymer and polymer-solvent interactions, "onion"-, "garlic"-, or "dumbbell"-like micelle structures were predicted [Zhulina 1996a]. As the solvent became a theta (i.e., Flory-Huggins interaction parameter $\chi = 0.5$) or marginally good solvent (i.e., $\chi < 0.5$) for the block at the free end of the graft and remained a poor solvent for the block at the fixed end, a "flowerlike" layer structure was predicted in which the solvophobic block formed the core of the "flower", and the soluble block formed the outer
corona of “petals” [Zhulina 1996b]. In another system composed of an inflexible rod-like block and a flexible coil block terminally grafted to the flat surface, separate globules and micellar structures analogous to “turnip” and “jellyfish” were predicted with increasing graft densities for the grafted copolymers in a poor solvent [Sevick 1997].

These theoretical studies indicate that block copolymers grafted on a surface form micellar structures. The structures are affected by surface restrictions, graft density, solvent quality, flexibility of each block and interactions between the blocks. However, it is difficult to experimentally prove the predicted structure because of the difficulty in preparing the model graft chains with uniform graft density and molecular weight distribution, and also because of limited analytical methods to characterize the grafted chains in solvents [Uyama 1998]. As an alternative, block copolymers adsorbed onto the surface were experimentally characterized due to easily controlled graft density and a well-defined molecular weight [Fytas 1996]. However, a high graft density is difficult to obtain by the polymer adsorption method since the crowding of adsorbed chains hinders further adsorption.

Recently, a number of studies on living free radical graft polymerization have been reported, which may provide new possibilities for preparing model block grafts with well controlled graft chain length [Higashi 1999, Husseman 1999, Huang 1999, Ejaz 1998]. For example, by the combined use of Langmuir-Blodgett and atom transfer radical polymerization techniques, block copolymers grafted onto a membrane with precisely controlled architectures and densities have been obtained [Ejaz 1998]. On the other hand, although atomic force microscopy has been successfully applied to characterize a variety of grafted polymers under conditions of good and poor solvents [Jimenez 1998, Uchida 1997, Koutsos 1997, Duchet 1997, Overney 1996], experimental studies on the structures of grafted block copolymers are lacking.
It is expected that the structure of the block copolymers grafted into membrane pores would be more complicated due to the restricted geometries [Gross 1996] and irregular surface topology [Sevick 1996, Murat 1991], and that atomic force microscopy may not be able to identify the structures of the block copolymers grafted inside the pores. Moreover, the assumptions for the theoretical treatment, such as uniform graft density, uniform molecular weight distribution and smooth surfaces, are not valid for the polymers grafted onto the porous membrane. Therefore, the theoretical models that have been developed can not be linked to the experimental results, and may not be able to describe the more complicated structures of the block copolymers grafted on the porous membrane.

Based on the knowledge gained in our previous studies [Peng 1998, 1999], the photochemical co-graft polymerization method was used to incorporate temperature and pH responsive polymers onto a porous membrane. To obtain the desired block structure, a sequential photografting procedure was devised based on a living free radical polymerization mechanism, which involves a reversible combination of growing polymer chains with stable free radicals. Living free radical polymerization has been widely investigated using different initiators named as iniferters (derived from initiator-transfer agent-terminator) [Sebenik 1998, Otsu 1998, Columbani 1997]. One class of iniferters is photoiniferters, which initiate living free radical polymerization under UV irradiation. Photoiniferters have been used to graft block copolymers onto a membrane [Higashi 1999, Nakayama 1996, Yang 1996]. The photoiniferter used in the graft polymerization was either immobilized on the membrane or dissolved in monomer solution. The initiators would generate surface-bound free radicals that could retain initiation ability and grow away from the surface, resulting in living ends of the graft chains as the living graft polymerization proceeded.
In this study, the desired block copolymer grafted porous membranes were prepared by a sequential grafting procedure using a photochemical technique. The sequential photografting was started with PNIPAAm-g-PE membranes, followed by grafting PMAA. The co-graft yield and co-graft composition were controlled by grafting time. Their effects on the membrane permeability were studied.
6.2 Results and Discussion

6.2.1 Co-graft Structure and Membrane Architecture

The structure of PNIPAAm and PMAA co-grafts on porous PE membranes is of primary importance in determining the permeation response of these membranes. In the following sections, the primary and secondary structures of the co-grafts under different environmental conditions are discussed. The conclusions of section 6.2.1 will serve as the basis for the discussion of permeation results in section 6.2.2.

6.2.1.1 Primary Structure of PNIPAAm-co-PMAA-g-PE: Living Radial Graft Polymerization

The co-graft membranes in this study were prepared by a sequential grafting procedure described in detail in Section 3.2.3. Briefly, PNIPAAm is first grafted onto porous PE with physically adsorbed xanthone photoinitiator. PNIPAAm graft yield is controlled by varying the PNIPAAm grafting time. Then the membrane is soxhlet-extracted with methanol in an attempt to remove any residual adsorbed photoinitiator. Finally, PMAA is grafted without adding more photoinitiator. Figure 6.2 shows the graft yield of PMAA as a function of grafting time onto PE membranes that had previously been grafted with PNIPAAm to varying extents. The figure shows that co-grafting can be achieved by this procedure, and that PMAA graft yield varies in an approximately linear fashion with grafting time – in agreement with results shown in Chapters 4 and 5 for singly grafted membranes. It can also be seen in Figure 6.2 that at equal PMAA grafting times, PMAA graft yield appears to be higher on membranes with higher PNIPAAm graft yields. This observation will be discussed later in this section.
Figure 6.2 Sequential photografting PMAA onto PNIPAAm-g-PE membranes.

To infer the primary structure of the co-grafts, it is necessary to understand where the PMAA chains are grafted. It is clear that grafted PNIPAAm chains prepared by this procedure must be attached to PE surfaces. Grafted PMAA chains, however, may theoretically be positioned on either the PE surfaces – giving independently grafted PNIPAAm and PMAA chains, or at the free ends of grafted PNIPAAm chains – giving di-block grafts of PNIPAAm and PMAA. Clearly, the primary structure of the co-grafts would influence the permeability
response of the membrane. The grafting procedure used in this study was devised in an attempt to create the di-block structure. As discussed in the introduction of this chapter, the block copolymer would show more desirable multi-stimuli responsiveness than the random-copolymer. It was reasoned that since NIPAAm or MAA photo-polymerization in solution requires photoinitiators [Kubota 1997], removal of the photoinitiator from the PE surface before PMAA grafting should prevent direct PMAA grafting onto the PE surface. Since xanthone is soluble in methanol (solubility = 4.9 mg/ml), the methanol extraction step after PNIPAAm grafting should remove any residual photoinitiator adsorbed on PE surfaces. Although no direct proof of complete xanthone removal was obtained due to the difficulty of identifying trace residual xanthone, supplementary experimental evidence described below strongly suggests that xanthone was effectively removed. If a PE membrane is first coated with xanthone, then soxhlet extracted with methanol, neither PNIPAAm nor PMAA can be grafted using water as a grafting solvent. This suggests that the methanol soxhlet extraction procedure is adequate for dissolving and removing xanthone adsorbed on PE surfaces. Thus, no hydrogen abstraction from PE can occur, and consequently, no grafting occurs. In addition, PNIPAAm and PMAA grafting experiments using pure methanol showed that very limited grafting (<5%) occurs under the same monomer concentration and UV irradiation time [refer to Figure 5.1-c]. This suggests that simply wetting the pores with pure methanol can dissolve and remove PE-adsorbed xanthone, further supporting the notion that methanol soxhlet extraction effectively removes PE-adsorbed xanthone. Therefore, it can be concluded that in the co-graft membranes prepared, PMAA was not grafted onto PE surfaces.

Having concluded that PMAA does not graft onto PE surfaces, it is still necessary to reason that PMAA was grafted onto the free ends of grafted PNIPAAm chains by living radical
polymerization before the di-block structure can be accepted. Extensive research on living free radical polymerization has provided a variety of techniques for synthesizing block copolymers [Kim 1999, Kitano 1999, Sebenik 1998, Sivaram 1997]. One approach is to use photoiniferters [Otsu 1998, Tasis 1998]. Yang et al. [Yang 1996] have reported living radical polymerization of PMAA on PE using xanthone as a photoiniferter. Although they could not show a linear relationship between monomer conversion and molecular weight with narrow distribution as a main criterion for living polymerization [Webster 1991], it was reasoned that an end group with re-initiating ability was obtained by the xanthone-induced photograft polymerization. It was proposed that under UV irradiation, xanthone is excited and turns into xanthone ketyl radical after abstracting a hydrogen atom. The radical is too bulky and stable to initiate polymerization. It participates mainly in a termination process, resulting in grafted PMAA chains with terminal xanthone ketyl groups. The termination is reversible, so that the end groups, under UV irradiation, decompose to form free radicals, leading to further PMAA grafting. A similar mechanism may apply for PNIPAAm grafting and subsequent PMAA grafting, as shown in Figure 6.3. This reversible combination of growing radicals with stable free radicals to retain the capacity for chain growth has been widely used as a main criterion for living free radical polymerization [Otsu 1998, Sebenik 1998, Yang 1996]. In addition, due to the covalent

![Figure 6.3 Schematic illustration of the sequential grafting mechanism.](image-url)
bond between the end groups and grafted chains, the methanol wash step would not remove the end groups. Therefore, although there is no direct proof of the chemical linkage between PNIPAAm and PMAA and of a linear relationship between monomer conversion and molecular weight, the known living radical polymerization mechanism suggests that it is highly plausible that a living radical at the end of PNIPAAm chains exists to initiate MAA grafting. This mechanism would result in the formation of a di-block grafted PNIPAAm-PMAA copolymer.

Having argued that a di-block primary structure of the co-grafts is likely obtained using the sequential procedure devised for this study, the results shown in Figure 6.2 may be discussed further. The observation that, at equal PMAA grafting times, the PMAA graft yield appears to be higher on membranes with higher PNIPAAm graft yields may be explained as follows. An increase in graft yield by a longer UV irradiation time (increasing number of initiating events) may be attributed to an increase in graft density. Therefore, it is plausible to assume that with the higher PNIPAAm graft yields, which were obtained by a longer grafting time (UV irradiation time is synonymous with grafting time), there should be a higher number of grafted chains, and therefore more radicals at the end of chains. In addition, for living free radical graft polymerization, a longer grafting time also gives rise to a longer graft chain, and the graft becomes more accessible to monomers. Then there should be a faster rate of PMAA grafting for the membrane with higher PNIPAAm graft yields. Because of the above reasons, the PMAA graft yield increase should be greater on membranes with greater initial PNIPAAm graft yields.

6.2.1.2 Secondary Structure of PNIPAAm-co-PMAA-g-PE: Complexation

It was argued in section 6.2.1.1 that grafted membranes with di-block co-grafts of PNIPAAm and PMAA have been prepared. The LCST of these membranes was measured by
DSC, as described in Section 3.3.3, in order to determine the transitional temperatures of these co-grafts, as well as to probe their secondary conformational structures. The LCST values of membranes with varying PMAA content at pH 4.4 and 7.4 are summarized in Table 6.1. Typical DSC thermograms are included in Appendix 6.

Table 6.1  LCST of PNIPAAm and PMAA co-grafted membranes with different PMAA content at pH 4.4 and pH 7.4

<table>
<thead>
<tr>
<th>PMAA wt%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>0%</th>
<th>7.6%</th>
<th>22.0%</th>
<th>47.5%</th>
<th>67.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.4</td>
<td>32.3°C</td>
<td>33.8°C</td>
<td>31.3°C</td>
<td>31.1°C</td>
<td>30.6°C</td>
</tr>
<tr>
<td>pH 4.4</td>
<td>33.5°C</td>
<td>34.8°C</td>
<td>N.D.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N.D.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N.D.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The wt% is based on the total mass of grafted PMAA and PNIPAAm on each membrane. The membranes measured had total graft yields of 410-472%;

<sup>b</sup>Not detectable in the range of 0 to 60°C.

The table shows that at pH 7.4, a thermal transition occurs for membranes of all co-graft compositions at a temperature near the LCST of pure PNIPAAm. This observation further supports the idea that the co-grafts are di-block in structure, such that the PNIPAAm segments can undergo LCST transitions in much the same way that homopolymers of NIPAAm do. At pH 4.4, however, no LCST was detected within the temperature range of 0 to 60 °C for membranes with a PMAA content of 22% or higher. A possible explanation for the disappearance of the LCST under these conditions is that complexes between PNIPAAm and PMAA can be formed at pH 4.4 via hydrogen bonding between amide groups on PNIPAAm and un-ionized carboxyl groups on PMAA (Figure 6.4). The LCST for PNIPAAm is a consequence of temperature-dependent changes in the balance between hydrophilic interactions in the form of hydrogen bonding between amide groups and water, and hydrophobic interactions among isopropyl groups. The shift in balance between these interactions results in a coil to globule conformational change in PNIPAAm chains [Lin 1999, Wu 1998].
Figure 6.4 Schematic illustration of reversible complexation between PNIPAAm and PMAA.

The presence of a complex between PNIPAAm and PMAA may result in the loss of thermal transition because: (1) The amide groups of PNIPAAm are less accessible to water because of the hydrogen bonding with carboxylic acid groups – thus disrupting the balance between hydrophilic and hydrophobic interactions, and/or (2) the coil to globule conformation change of the PNIPAAm blocks is inhibited due to the more rigid structure of the complex. At pH 7.4, when the carboxyl groups on PMAA are dissociated, no complexes are formed, and PNIPAAm thermal transition occurs across the entire compositional range.

It should be noted that the effect of MAA content on the temperature-responsive behavior of PNIPAAm in block copolymers is different from that in random copolymers. Figure 6.1 shows that the random copolymers do not show temperature responsiveness up to 60°C as MAA content increases above 35 wt% at pH < pKₐ and 15 wt% at pH > pKₐ, respectively. The phenomenon is attributed to increased overall hydrophilicity of the copolymers, especially at a pH > pKₐ, where MAA is ionized [Feil 1993]. In contrast, the block copolymers with an MAA content up to 67 wt% still show a temperature responsiveness similar to homopolymers of PNIPAAm at pH 7.4 (i.e. pH > pKₐ). However, the block copolymers lose the temperature responsiveness with increasing MAA content up to 22 wt% at pH 4.4 (i.e., pH < pKₐ), due to the
complexation between PNIPAAm and PMAA blocks, as discussed above. The temperature responsive behavior is consistent with the report that PAA-g-PNIPAAm shows LCSTs close to that of PNIPAAm at pH 7.4 over a wide range of PAA compositions due to long NIPAAm segments, while LCSTs are decreased at pH 4 due to complexation between the PAA backbone and the PNIPAAm graft [Chen 1995a, c]. As further discussed below, the complexation may reduce the LCST below 0°C. In other words, block or graft copolymers would lose their LCSTs in water.

The possible existence of PNIPAAm/PMAA complexes is supported by a number of literature reports [Garay 1997, Staikos 1997, 1996, Chen 1995a, c]. Chen et al. reported that intramolecular hydrogen bonding between a PNIPAAm graft and PAA backbone in PAA-g-PNIPAAm copolymers occurs at pH 4 [Chen 1995a, c]. Garay et al. reported that intermolecular hydrogen bonding between PNIPAAm and poly(carboxylic acids), i.e., PMAA and PAA, in acidic solutions (i.e. pH < pK_a) occurs, and that the hydrogen bonding results in a lower LCST of PAA-g-PNIPAAm. solution precipitation or reduced intrinsic viscosity, as summarized in Appendix 6. Moreover, based on viscosity measurements, it was inferred the NIPAAm/MAA molar ratio in the complex is 1 [Garay 1997]. The complexation was reported to be reversible as well as pH-sensitive, occurring only in solutions with a pH below the pK_a of the carboxylic acid. The compactness increases with temperature due to increased hydrophobic interaction between isopropylacrylamide groups of PNIPAAm and methyl groups of PMAA [Koussathana 1997, Staikos 1997].

It should be noted that the extent of the complexation effect on the LCST may depend on the compactness and rigidity of the complex. It was observed that PAA-g-PNIPAAm is soluble at pH 4 below its LCST of 16°C, but insoluble at pH 3 even at temperatures close to 0°C.
resulting in a disappearance of the LCST due to complexation [Chen 1995c]. Their random copolymers also show a decrease in the LCST with pH below 4 where the intra- and intermolecular hydrogen bonding complexes between acrylic acid and acrylamide groups are formed [Jones 1999]. However, the LCST of 3°C was still observed at pH 1. It is known that the graft copolymer containing long acrylic acid and isopropylacrylamide sequences shows greater extent of complexation than the random copolymer [Chen 1995a, c]. Moreover, the complexation between PMAA and PNIPAAm would be strengthened by the hydrophobic interaction between methyl groups of PMAA and isopropyl groups of PNIPAAm [Garay 1997], leading to a more significant effect on the LCST. The contribution of the hydrophobic interaction between methyl and methylene groups to the complexation was observed in PMAA and poly(ethylene oxide) complexes as well [Jiang 1999]. Therefore, it can be reasoned that the stronger complexation between PMAA and PNIPAAm blocks in the PMAA-b-PNIPAAm co-graft results in the disappearance of the LCST in comparison with a decrease in the LCST of the PAA-g-PNIPAAm copolymer. Furthermore, the complexation may occur not just between the two blocks of the same chain by intra-molecular hydrogen bonding between nonadjacent MAA and NIPAAm units after folding up the chain [Bokias 1994], but between blocks of different chains by intermolecular hydrogen bonding between MAA and NIPAAm sequences accessible to each other, which becomes more significant with increasing graft density [Tretinnikov 1997].

6.2.1.3 Summary

In summary, the PNIPAAm-block-PMAA co-grafted membrane was obtained by sequential photografting of NIPAAm and MAA onto porous PE membranes. Hydrogen bonding between PNIPAAm and PMAA results in the formation of a complex under acidic condition.
The complex structure results in the loss of the LCST for the PNIPAAm component. This implies that the complexation is a complication that reduces conformational changes of the co-grafts. The structure of the co-grafts, together with total graft yield, composition and graft location, will influence the permeability response of the membranes. Permeation results presented in section 6.2.2 will be discussed with the co-graft structures in mind.

6.2.2 Permeation Characteristics of Co-grafted Membranes

In this section, the effect of total co-graft yield and co-graft composition on the membrane permeation characteristics is examined. Membranes were prepared according to Section 3.2.3, and permeation experiments were conducted according to the procedures outlined in Section 3.4. Results are discussed in view of the co-graft structures discussed in the previous section, the membrane architecture that would result from those structures, as well as a two-layer membrane model. Finally, the possibility of multiple permeation set points is demonstrated.

6.2.2.1 Effect of Total Co-Graft Yield

Figure 6.5 shows the permeability of vitamin B₁₂ through co-grafted membranes with varying total graft yields and a constant mass ratio of 1:1 between grafted PNIPAAm and grafted PMAA. Permeation experiments were conducted under two conditions: the "expanded" condition corresponding to pH 7.4 and 30 °C when both the PNIPAAm and PMAA blocks of the co-grafts are expected to be in their expanded conformations, and the nominally "collapsed" condition corresponding to pH 4.4 and 37 °C when both the PNIPAAm and PMAA blocks are expected to be in collapsed conformations – recognizing that complexes are likely to exist that may inhibit the collapse of PNIPAAm blocks. The figure shows that (1) permeability in the
nominally collapsed state is always higher than in the expanded state, and (2) in both states, permeability first decreases with increasing co-graft yield, reaching a minimum, then increases as co-graft yield further increases.

Figure 6.5 Effect of total co-graft yield on vitamin B_{12} permeability through co-grafted membranes. All membranes contained 1:1 mass ratio of grafted PNIPAAm to grafted PMAA. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch). The "expanded" condition corresponds to pH 7.4 and 30 °C. and the nominally "collapsed" condition corresponds to pH 4.4 and 37 °C.

The observed experimental results can be explained in terms of a two layer model. The grafted membranes may be viewed as being composed of two layers: the porous membrane
layer which consists of polymers grafted in the pores of the PE substrate (pore grafts), and the surface layer which consists of polymers grafted on the external surfaces of the PE membrane (surface grafts) (Figure 6.6). The overall permeability of the membrane, $P$, is related to the total thickness $L$, the permeability $P_p$ and thickness $L_p$ of the porous layer, and the permeability $P_s$ and thickness $L_s$ of the surface layer in the following manner:

$$\frac{L}{P} = \frac{L_p}{P_p} + \frac{L_s}{P_s}$$

The thickness of the porous layer, $L_p$, is approximately constant and equal to the thickness of the native PE substrate, while the surface layer thickness $L_s$ increases with total graft yield. The permeability of the surface layer $P_s$ should be comparable to the permeability of a corresponding PNIPAAm/PMAA copolymer hydrogel membrane, while the pore layer permeability $P_p$ should decrease with increasing graft yield. The overall permeability may therefore be controlled by either the surface layer, the pore layer, or both layers, depending on the graft yield.

Due to the large pore surface area, it is expected that at low total graft yields, the co-
grafts would be primarily located inside the pores with only a small amount of grafting on the external surface \((L_S \approx 0)\); the porous layer should therefore be the rate-controlling layer. Under these circumstances, as graft yield increases, increasing blockage of the pores would result, giving rise to decreased permeability. This is consistent with the results shown in Figure 6.5. In addition, expanded graft conformations would lead to a greater obstruction of the pores, and thus lower permeabilities than collapsed conformations. Note that although complexation between PNIPAAm and PMAA blocks is expected at pH 4.4 and 37 °C, the complex should have a tighter, denser conformation than the expanded conformations at pH 7.4 and 30 °C, and would therefore provide less blockage of the pores than the expanded conformations. Figure 6.5 shows that at low yields, permeability in the nominally collapsed state is higher than in the expanded state: this is consistent with the expected conformations in the pore-layer controlled regime.

As graft yield increases, the pores would eventually become filled with grafts, and an increasingly significant surface layer would be formed; the overall permeability would then become increasingly influenced by the permeability of the surface layer. Since the permeability of the surface layer is higher than that of the porous layer, the overall permeability will begin to increase. This expected trend with respect to graft yield is observed in Figure 6.5 for both the expanded state and the nominally collapsed state. If at sufficient high graft yields, the surface layer becomes so thick that it is the rate-controlling layer, and the resistance of the porous layer becomes insignificant, then it would be expected that the overall permeability behavior would be the same as that of a hydrogel membrane. In this situation, the nominally collapsed conformation would present a denser barrier to diffusion than the expanded conformation, and a lower permeability would be expected for the collapsed state. In Figure 6.5, permeability in the
expanded state is always lower than in the collapsed state, suggesting that the surface layer-controlled limit is never reached within the range of experimental conditions tested. However, the difference in permeability between the two states appears to be getting smaller with increasing graft yield in the high graft yield range, suggesting that the surface layer-control limit would eventually be approached at higher graft yields.

6.2.2.2 Effect of Co-graft Composition

The effect of co-graft composition on permeability response was studied at two different ranges of total co-graft yields: 208-235% and 410-472%. Grafting times were used to control graft yields; since precise control is not possible by this procedure, ranges -- rather than precise values of graft yields were used. As described earlier, due to the significantly larger pore surfaces, grafting in the pores should dominate at low graft yields. The nominal porosity of the polyethylene substrate membranes is 0.705 by volume. An approximate calculation of the mass of grafts required to fill the pores, assuming equal density of PE and the grafts, and no grafting on the external membrane surface, gives 239% \((0.705/[1-0.705])\). Of course, grafts within the pores would be somewhat hydrated, with the extent of hydration partially influenced by the constricted volume, so that at 239% graft yield, some grafts would have to be on the surface. Nevertheless, it is expected that the grafts on membranes in the low graft yield range of 208-235% would primarily be located inside the pores. At 410-472% graft yields, the pores should be nearly completely filled, and a significant amount of graft should be located on the external surfaces, so that both pore and surface layers would influence permeation characteristics.

Figure 6.7 shows the relative thicknesses of the hydrated membranes, defined as the ratio of the membrane thicknesses in their expanded vs. nominally collapsed states and absolute
Co-graft yield: 208-235%

Figure 6.7 Relative membrane thickness (■) and absolute membrane thickness (○, □) as a function of PMAA content. Error bars are standard deviations (n=4 pieces of the membrane made from the same batch). The relative membrane thickness is defined as the ratio of the membrane thicknesses in their expanded vs. nominally collapsed states.

membrane thickness in their expanded vs. nominally collapsed states, as a function of PMAA content for the membranes with the lower graft yield range. The figure shows that the relative thickness is slightly higher than 1 and is approximately independent of PMAA content. A value of one for relative thickness would indicate that the grafts are located exclusively inside the pores. The values of greater than one suggest that some grafts are present on the external surface; the conformational changes of the surface grafts would lead to overall membrane
thickness changes. As discussed previously, although grafts are expected to be primarily located inside the pores in this low graft yield range, some amount of surface grafts are expected, which would result in the small thickness change seen. This is consistent with the larger absolute membrane thicknesses of grafted membranes than that of the non-grafted membrane (0.050 mm). Moreover, Figure 6.7 shows that the absolute membrane thickness increases with increasing PMAA content. This may indicate that increasing PMAA content would lead to a higher proportion of polymers located on the membrane surface, although the grafted polymers are mainly inside the pores, showing a constant relative membrane thickness.

Figure 6.8 shows the permeability of vitamin B$_{12}$ through co-grafted membranes within the lower graft yield range. Permeation experiments were conducted as a function of PMAA content, and at conditions that represent either fully expanded conformations (30°C, pH 7.4) or nominally collapsed conformations (37°C, pH 4.4). Permeability of the PMAA-grafted membrane prepared in water/methanol (1:1 by volume) is used for the membrane with 100% PMAA. The results show that: (1) permeability in the collapsed state is always higher than in the expanded state, and (2) permeability increases with PMAA content for both collapsed and expanded graft conformations. Since, in the graft yield range of 208-235%, grafted polymers are expected to be primarily located within pores, expanded polymers would be expected to obstruct the pores more than collapsed polymers, and would therefore lead to lower permeabilities. This is in agreement with the results shown in Figure 6.8.
Figure 6.8 Effect of co-graft composition on the permeability of the membrane with 208-235% total co-graft yields. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch). The "expanded" condition corresponds to pH 7.4 and 30°C, and the nominally “collapsed” condition corresponds to pH 4.4 and 37 °C.

The observed trend of increasing permeability with increasing PMAA content may be attributed to the preferential grafting of PMAA on the membrane surface. Due to the sequential photografting procedure, a higher PMAA content, or lower PNIPAAm content, means that surface adsorbed xanthone photoinitiator is removed from the pore surfaces at a lower partial graft yield, and therefore, a higher amount of polymer is subsequently attached onto the end of
previously grafted chains, according to the grafting mechanism shown in Figure 6.3. This situation would result in a higher proportion of grafted polymers on the membrane surface. Increasing PMAA content, therefore, would mean less polymers in the pores, leading to less obstruction in the pores, and therefore higher permeability. This is in agreement with the trend seen in Figure 6.8.

The effect of PMAA content on permeability can be further clarified by a comparison of permeability values between 100% PNIPAAm and 100% PMAA grafted membranes. The values are 1.1x10⁻⁷ cm²/s and 0.44x10⁻⁷ cm²/s for the PNIPAAm grafted membrane in collapsed and expanded states, respectively, while the corresponding values are 4.3x10⁻⁷ and 3.2x10⁻⁷ cm²/s for the PMAA grafted membrane in collapsed and expanded states, respectively. All the values are lower than permeability in non-grafted water-filled PE (5.5x10⁻⁷ cm²/s).

The different permeability values can be related to the graft location. The PNIPAAm-g-PE shows lower permeability than the PMAA-g-PE due to more PNIPAAm grafted inside the pores. The different graft location between PNIPAAm and PMAA will be discussed in section 7.1. In addition, at this graft yield range, grafts are mainly located inside the pores, leading to a decrease in membrane porosity. Therefore, the grafted membranes show a lower permeability than the non-grafted water-filled porous membrane. In addition, the PNIPAAm-g-PE membrane shows a larger permeability change due to more significant effect of collapsed PNIPAAm conformation on permeability. This is consistent with a larger permeability ratio between PMAA and PNIPAAm-grafted membranes in the collapsed state (~7.3) than in the expanded state (~3.9).

Figures 6.9 and 6.10 show the relative membrane thickness and absolute membrane thicknesses, and vitamin B₁₂ permeability, respectively, as a function of PMAA content for co-
grafted membranes with total graft yields of 410-472%. As explained earlier, at this graft yield, pores would be mostly or completely filled with grafts, and a significant graft layer should exist on the external surfaces of the membrane. The ratio of thicknesses between membranes with expanded vs. collapsed graft conformations and absolute membrane thicknesses in both expanded and collapsed states, should therefore be larger than those shown in Figure 6.7 for the pore graft-dominated membranes.

A comparison of Figures 6.7 and 6.9 confirms that the results are consistent with this explanation, and indicates that the difference increases with increasing PMAA content. Two possible factors may contribute to the dependence of relative thickness on PMAA content: (1) the relative thickness of PNIPAAm vs. PMAA external surface layers, and (2) the dependence of the amount of surface grafts on PMAA content. A comparison of literature data on PNIPAAm and PMAA grafted non-porous membranes with similar graft yields (223% PNIPAAm vs. 186% PMAA) shows that the dimensional change, defined as the ratio of membrane surface areas in their expanded vs. collapsed states, is about the same [Kondo 1998, Kubota 1994]. Swelling ratios of PNIPAAm and PMAA hydrogels of comparable crosslinking densities between their collapsed and expanded states are also similar [Brazel 1995, Quinn 1993, Hoffman 1986]. If dimensional changes of PMAA and PNIPAAm between their collapsed and expanded states are the same, then the PMAA content dependence of the relative membrane thickness seen in Figure 6.9 must be attributed to the second possible explanation: increasing surface grafts with increasing PMAA content. There are two possible reasons for this. First, due to the sequential grafting procedure, PMAA has to grow from the end of PNIPAAm chains, while PNIPAAm can also grow from the pore surfaces via pore surface-adsorbed xanthone, so PMAA will be more likely to be located on the surface while a larger proportion of PNIPAAm at the same graft
yield would be inside the pores. Second, PMAA is more likely than PNIPAAm to be grafted on the membrane surface. This phenomenon is consistent with the thickness measurement and SEM characterization that show more PMAA grafted on the membrane surface than PNIPAAm with comparable graft yields. Further discussion will be provided in section 7.1. Figure 6.9 also shows that the absolute membrane thickness increases with PMAA content; this result is also consistent with the preferential grafting of PMAA on the membrane surface.
Figure 6.10 shows the permeability of vitamin B$_{12}$ through co-grafted membranes with the higher range of co-graft yields. The permeation experiments were conducted under the same expanded and nominally collapsed conditions as the membranes with the lower co-graft yield range. Permeability of the PMAA grafted membrane with graft yield of 424% prepared in water/methanol (1:1 by volume) is used for the membrane with 100% PMAA. The following observations can be made: (1) in both expanded and collapsed states, permeability increases with PMAA content, and (2) at low PMAA content, permeability in the collapsed state is lower than in the expanded state, but the trend reverses as PMAA content increases.

![Figure 6.10](image_url)

Figure 6.10 Effect of PMAA content on the permeability of the co-grafted membrane with 410-472% total graft yields. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch). The “expanded” condition corresponds to pH 7.4 and 30 °C, and the nominally “collapsed” condition corresponds to pH 4.4 and 37 °C.
The first observation can be easily explained. In the graft yield range of 410 to 472%, it is expected that both the pore layer and the surface layer would influence the overall permeability. It may be argued that the permeability of the surface layer should be comparable to the permeability of a corresponding hydrogel membrane. Therefore, the permeability through the surface layer should increase with PMAA content due to higher permeability of PMAA membranes than PNIPAAm membranes in both expanded and collapsed states, as shown in Table 6.2. Within the porous layer, it has been reasoned that increasing PMAA content would result in a higher proportion of polymer grafted on the membrane surface, and thus a lower proportion of polymer in the pores. Less polymers in the pores mean less obstruction in the pores, and therefore, higher permeability. Therefore, the permeability of both surface and pore layers increases with increasing PMAA content, giving rise to an increased overall permeability, as shown in Figure 6.10 and Table 6.2.

### Table 6.2 Permeability through hydrogel membranes and co-grafted membranes composed of surface and pore layers

<table>
<thead>
<tr>
<th>Membrane/layer</th>
<th>PNIPAAm&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Surface layer</th>
<th>Pore layer</th>
<th>Overall</th>
<th>PMAA&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMAA content:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 wt%</td>
<td>-</td>
<td>increasing PMAA content</td>
<td>increasing surface grafts</td>
<td></td>
<td>100 wt%</td>
</tr>
<tr>
<td>Expanded state</td>
<td>&lt;2x10&lt;sup&gt;-9&lt;/sup&gt;cm&lt;sup&gt;2&lt;/sup&gt;/s</td>
<td>increasing</td>
<td>Increasing</td>
<td></td>
<td>2.1x10&lt;sup&gt;-9&lt;/sup&gt;cm&lt;sup&gt;2&lt;/sup&gt;/s</td>
</tr>
<tr>
<td>Collapsed state</td>
<td>&lt;1.8x10&lt;sup&gt;-9&lt;/sup&gt;cm&lt;sup&gt;2&lt;/sup&gt;/s</td>
<td>increasing</td>
<td>Increasing</td>
<td></td>
<td>1.1x10&lt;sup&gt;-9&lt;/sup&gt;cm&lt;sup&gt;2&lt;/sup&gt;/s</td>
</tr>
</tbody>
</table>

<sup>a</sup>Permeability was estimated from the diffusion coefficient of rhodamine B (water soluble solute like vitamin B<sub>12</sub> but lower molecular weight (479 vs. 1355) in the PNIPAAm hydrogel [Kato 1998] and the partition coefficient of vitamin B<sub>12</sub> between water and the hydrogel [Palasis 1992];

<sup>b</sup>taken from [Turner 1998].

To explain the second observation, it is necessary to compare the permeability through PNIPAAm and PMAA surface layers. It can be inferred from Table 6.2 that the permeability of the collapsed surface layer of PNIPAAm is much lower than that of PMAA (approximately three order of magnitude) and that of the pore-filled/little surface layer membranes shown in Figure...
6.8 (in the range of $10^{-7}$-$10^{-8}$ cm$^3$/s). Therefore, the collapsed PNIPAAm surface layer would result in a significant decrease in membrane permeability in comparison with the collapsed PMAA surface layer. On the other hand, the permeability of the expanded surface layer of PNIPAAm is close to that of the expanded PMAA surface layer. As a result, a 100% PNIPAAm grafted membrane shows a lower permeability in the collapsed state than in the expanded state, i.e., a surface control mechanism, while a 100% PMAA grafted membrane shows the opposite behavior, a higher permeability in the collapsed state, due to dominant effect of the pore layer on controlling overall permeability in this graft yield range.

As the PMAA content increases, the impact of PNIPAAm on the permeability through the co-grafted surface layer is reduced, which becomes dramatic when complexation occurs. It has been discussed that complexation prevents PNIPAAm blocks from collapsing. As a result, co-grafted polymers can not collapse like PNIPAAm alone to form a dense surface layer with a very low permeability in which surface control over permeability is dominant. Therefore, surface control is reduced with increasing PMAA content, and consequently, the pore layer becomes relatively more important. The argument is consistent with Figure 6.10 showing a crossover PMAA content which corresponds to the value above which the co-grafted membrane does not show a transition temperature in the normally collapsed state, due to complexation (see Table 6.1).

6.2.3 Responsive Membrane with Multiple Permeability Set Points

The dynamic permeability response of two co-grafted membranes was studied at four temperature and pH conditions: (30°C/pH 7.4), (37°C/pH 7.4), (30°C/pH 4.4), (37°C/pH 4.4). Permeation experiments were conducted according to the procedures outlined in Section 3.4.
Dextran with molecular weight of 4400 rather than vitamin B₁₂ was used as permeant since more dramatic permeability changes are expected based on studies of the effect of solute size on permeability response presented in Chapters 4 and 5.

Figure 6.11 shows the permeability response of the membrane with a total graft yield of 208% and a 1:1 PNIPAAm to PMAA mass ratio. As explained earlier, at this graft yield, grafted polymers are expected to be primarily located within pores. Figure 6.11 shows four set points of membrane permeability, corresponding to the four temperature and pH conditions. The
permeability can be ranked in order as $P(30^\circ C/\text{pH } 7.4) < P(37^\circ C/\text{pH } 7.4) < P(30^\circ C/\text{pH } 4.4) < P(37^\circ C/\text{pH } 4.4)$. Since the membrane was exposed to the four conditions in a random order, the figure shows that the membrane response is completely reversible. The response time of the membrane was not determined quantitatively. After changing the temperature and pH, the first sample of the permeation experiment was typically taken within 2 to 5 hours. Permeation results show that by the first time point, a steady state has been reached. Therefore, it can be estimated that the response time is less than two hours. Although it was reported that a much longer time (about a week) is needed for hydrogels to reach equilibrium [Yoshida 1995], it is impossible to make a comparison due to the much larger membrane thickness of hydrogels than of grafted membranes.

Figure 6.12 shows a similar responsive behavior of a membrane with a total graft yield of 438% and a 1:1 PNIPAAm to PMAA mass ratio. At this graft yield, pores would be mostly filled with grafted polymers, and a graft layer should exist on the membrane surface. As explained earlier, the effect of the surface layer on the permeability reduction in the normally collapsed state is significantly reduced due to the complexation which occurs at this PMAA content (~50 wt%). As a result, the membrane shows a pore control mechanism, which is consistent with the figure showing permeability ranked in order as $P(30^\circ C/\text{pH } 7.4) < P(37^\circ C/\text{pH } 7.4) < P(30^\circ C/\text{pH } 4.4) < P(37^\circ C/\text{pH } 4.4)$. 
Both Figures 6.11 and 6.12 demonstrate that a more sophisticated permeability response can be obtained by co-grafting responsive polymers onto a porous membrane in comparison with PNIPAAm or PMAA singly grafted membranes.

As shown in Table 6.3, a comparison of the permeability of the co-grafted membrane with 208% and 438% graft yield shows that increasing graft yield leads to a greater decrease in permeability at pH 7.4, 30°C and pH 7.4, 37°C than at pH 4.4 30°C, pH 4.4 37°C. This may be due to reduced effect of the grafted polymer on permeability resulting from the complexation
which prevents the co-graft from collapsing.

Table 6.3 Permeability (×10^8 cm²/s) of co-grafted membranes under different temperature and pH conditions, as shown in Figures 6.11 and 6.12

<table>
<thead>
<tr>
<th></th>
<th>pH 7.4 30°C</th>
<th>pH 7.4 37°C</th>
<th>pH 4.4 30°C</th>
<th>pH 4.4 37°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>208%</td>
<td>0.30, 0.24, 0.23</td>
<td>0.72, 0.73</td>
<td>5.0, 5.4</td>
<td>9.5, 9.8</td>
</tr>
<tr>
<td>Schematic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>illustration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>438%</td>
<td>0.015, 0.017</td>
<td>0.074, 0.080</td>
<td>2.3, 2.5</td>
<td>6.0, 5.7</td>
</tr>
<tr>
<td>Schematic</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>illustration</td>
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</tr>
</tbody>
</table>

The multiple set point permeability may be related to multiple co-graft architectures. The combined effect of the di-block covalent structure, the complexation between PNIPAAm and PMAA blocks, and conformations of each block can be illustrated in Figure 6.13.

![Figure 6.13](image)

Figure 6.13 Schematic illustration of co-graft architectures at combined temperature and pH conditions.
At 30°C, pH 7.4, no complex is formed. Both PNIPAAm and PMAA blocks are expanded, having the largest size of the co-graft. At 37°C, pH 7.4, PNIPAAm blocks collapse, showing the LCST, while PMAA blocks are expanded. The structure is similar to pinned block copolymer micelles [Zhulina 1996b]. The overall chain size decreases. At 30°C, pH 4.4, complexes are formed. The hydrophilic groups in the co-grafted polymer (i.e. amide and carboxylic acid groups) involved in the hydrogen bonding are no longer available for water molecules. The formed complex shows a hydrophobic, compact structure and tends to aggregate. The complex should have a tighter, denser conformation than the partially expanded conformation at 37°C and pH 7.4. At 37°C, pH 4.4, the complex becomes tighter due to increased hydrophobic interaction between methyl groups of PMAA and isopropyl groups of PNIPAAm with temperature, resulting in a more compact structure [Staikos 1997, Koussathama 1997]. The overall chain size, \( R \), of the grafted di-block polymer is ranked in order as:

\[
R_{(30^\circ C/pH \ 7.4)} > R_{(37^\circ C/pH \ 7.4)} > R_{(30^\circ C/pH \ 4.4)} > R_{(37^\circ C/pH \ 4.4)}
\]

This is consistent with the permeation results shown in Figures 6.11 and 6.12. The larger the chain is, the smaller the membrane permeability.

### 6.3 Conclusions

Membrane preparation, co-graft structure and membrane permeability have been studied with the following conclusions:

1. Both temperature and pH responsive membranes with a wide range of co-graft yield and composition can be prepared by the sequential photografting method. The process shows living radical polymerization characteristics leading to a di-block co-graft structure.

2. The co-grafted membrane with the PMAA content ranging from 7.6 to 67.1 wt% shows the
LCST at pH 7.4. In contrast, the co-grafted membrane with the PMAA content above 22 wt% shows no LCST at pH 4.4 due to complexation between PMAA and PNIPAAm blocks.

3. The permeability of the co-grafted membrane is controlled by the co-graft architecture which, in turn, is affected by the total co-graft yield and co-graft composition.

4. More sophisticated permeability changes are achieved in response to temperature and pH due to multiple co-graft architectures.
6.4 References


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Chapter 7  Overall Discussion

This chapter provides overall discussion of the experimental results presented in Chapters 4, 5, and 6. The discussion is focused on comparing PNIPAAm, PMAA singly grafted and co-grafted porous membranes in terms of graft yield, graft location, and membrane permeability. The two-layer model will be further discussed in terms of the graft yield and location.

7.1  Photochemical Graft Polymerization: Mechanism, Graft Yield and Location

The photochemical graft polymerization method has been widely used to modify polymer membranes. Depending on the photoinitiators used, there are two known grafting mechanisms. Photoinitiators that undergo unimolecular dissociation to generate free radicals show a photofragmentation grafting mechanism, while those which only generate free radicals through bimolecular hydrogen abstraction from a suitable hydrogen-donor show a hydrogen abstraction grafting mechanism [Bellobono 1989, Hageman 1989]. It has been reported that the hydrogen abstracting photoinitiator used in this work would be more desirable for the graft polymerization due to higher grafting efficiency than obtained with the photofragmenting initiator [Li 1997].

Polyethylene (PE) and monomers N-isopropylacrylamide (NIPAAm) and methacrylic acid (MAA) do not absorb UV at the wavelength involved in the grafting process ( > 290 nm). All of the following three elements are required to induce graft polymerization onto porous PE membranes: photoinitiator, monomer and UV irradiation. Xanthone was adsorbed onto both the external surface and pore surface by soaking the membrane in an acetone solution of the photoinitiator prior to the graft polymerization, which would give rise to higher grafting efficiency than graft polymerization induced by the photoinitiator in solution [Ulbricht 1995].

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This is consistent with the experimental result on the effect of grafting solvent on the graft yield of PMAA grafted membranes (see discussion of Figure 5.1-c). Since the swelling of bulk polyethylene in the acetone used to prepare the xanthone-adsorbed membrane is limited [Hegazy 1999], the photoinitiator should be mainly adsorbed on the membrane surface and pore surface, rather than distributed in the membrane matrix. Moreover, the swelling of polyethylene in the grafting solvents, e.g. water and methanol, is also limited, only 4 wt% and 10 wt%, respectively [Kaur 1997]. It is likely that the graft polymerization would be restricted on the membrane surface and inside the pores rather than in the matrix. In addition, due to the porous structure of the membrane, UV light will be scattered and reflected with limited transmission through the original membrane. However, as the membrane is wetted during the grafting process, UV light can pass through the membrane. This is consistent with the XPS analysis showing more grafting at the front (UV-facing) side than the rear side of the PNIPAAm-g-PE membrane with 28% graft yield, while the difference becomes smaller with increasing graft yield (see discussion of Figure 4.2).

For graft polymerization in water, the grafting may proceed as follows: grafting onto the external membrane surface of the front UV-facing side, wetting the membrane during the polymerization due to grafted polymers, grafting inside the pores and the other external membrane surface of the rear side, and at the same time, continuous grafting onto the external membrane surface of the front UV-facing side. The relative amount of polymers grafted on the membrane surface and pore surface depends on the relative grafting rate on the two surfaces which, in turn, is influenced by local monomer concentration, surface area and crowding of grafted chains. The first two factors would have a positive effect on the grafting rate, while the third factor would have a negative effect. However, a systematic study is needed to understand
the significance of each factor on the grafting rate. It is expected that due to much larger pore surface area than membrane surface area (more than 1000 times), grafting inside the pores would have a significant effect on the graft yield. In addition, as the pores are filled with grafted chains, continuous grafting onto the membrane surface would become preferential.

A great deal of work on the effects of photochemical grafting conditions, such as UV irradiation time, monomer and photoinitiator concentration, type of photoinitiators, grafting solvent and temperature on the graft yield, has been investigated [Li 1997, Kubota 1997a, Yang 1996, Bellobono 1989, Davis 1976]. We focused on controlling UV irradiation time and monomer concentration to obtain a wide range of graft yields. It is known that the graft yield would increase with respect to these two variables for the graft polymerization of NIPAAm and MAA onto PE membranes using xanthone as the photoinitiator [Kondo 1998, Kubota 1997b, Kubota 1994].

Table 7.1 compares the grafting rate of PNIPAAm, PMAA and their copolymers. The grafting rate, defined as a ratio between the graft yield and the grafting time, was calculated from the slope of the graft yield versus grafting time curve, which was determined by linear regression assuming zero order reaction kinetics with respect to the grafting time. The following observations can be made: (1) the grafting rate of PNIPAAm in water is much higher than that of PMAA under same conditions of monomer concentration (0.22M) and grafting solvent (water), (2) the grafting rate of PMAA in water is much lower than in the methanol/water mixture with 1:3 volume ratio under the same monomer concentration (0.22M); however, the grafting rate in water becomes higher than in the methanol/water mixture with 1:1 volume ratio under the same monomer concentration (0.66M), (3) the grafting rate in water increases dramatically as the monomer concentration is increased from 0.22M to 0.66M, (4) the grafting rate of PMAA on PE
in water is close to that of PMAA on PNIPAAm-g-PE with 67% and 233% graft yield (14.8 wt%/h vs. 14 and 18.7 wt%/h) under the same monomer concentration (0.22M); however, the grafting rate in methanol/water (1:3 by volume) is much higher than the grafting rate on the PNIPAAm-g-PE membrane in water.

Table 7.1 Reaction kinetics of graft polymerization of NIPAAm in water and MAA in water or methanol/water mixtures, and co-graft polymerization of NIPAAm and MAA

<table>
<thead>
<tr>
<th>Monomer Grafting solvent</th>
<th>NIPAAm</th>
<th>MAA</th>
<th>MAA</th>
<th>MAA</th>
<th>MAA</th>
<th>MAA</th>
<th>MAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grafting solvent</td>
<td>Water</td>
<td>Water</td>
<td>Methanol/ water (1:3 by volume)</td>
<td>Water</td>
<td>Methanol/ water (1:1 by volume)</td>
<td>Water</td>
<td>Water</td>
</tr>
<tr>
<td>Concentration (M)</td>
<td>0.22M</td>
<td>0.22M</td>
<td>0.22M</td>
<td>0.66M</td>
<td>0.66M</td>
<td>0.22M</td>
<td>0.22M</td>
</tr>
<tr>
<td>Membrane</td>
<td>PE</td>
<td>PE</td>
<td>PE</td>
<td>PE</td>
<td>PE</td>
<td>67% PNIPAAm-g-PE</td>
<td>233% PNIPAAm-g-PE</td>
</tr>
<tr>
<td>Grafting rate (wt%/h)</td>
<td>138</td>
<td>14.8</td>
<td>93.3</td>
<td>276</td>
<td>105</td>
<td>14</td>
<td>18.7</td>
</tr>
</tbody>
</table>

The first observation agrees qualitatively with the report on the graft polymerization of these two monomers onto non-porous PE membranes using the same photoinitiator [Kondo 1998, Kubota 1997b, Kubota 1994] and other photoinitiators [Kubota 1997a]. However, due to the pore structure of the PE membrane used, especially much larger pore surface areas relative to membrane surface areas, grafting onto pore surfaces plays an important role in determining the grafting rate. Since it was reported that the reactivity ratio for solution copolymerization of the two monomers was close (reported values: 0.891 for NIPAAm versus 1.128 for MAA) [Brazel 1995], the higher grafting rate of PNIPAAm may be due to more significant grafting of PNIPAAm inside the pores. This is consistent with membrane characterization by SEM presented in Figures 4.3 and 5.4, respectively, showing more PNIPAAm grafted inside the pores.
Figure 7.1 Relative thicknesses of PMAA-g-PE membranes prepared in water (○) or methanol/water with 1:1 volume ratio (■), and PNIPAAm-g-PE membranes (●) as a function of graft yield. The relative membrane thickness is defined as ratio between expanded vs. collapsed states. The expanded state corresponds to 30°C for PNIPAAm-g-PE, and pH 7.4 for PMAA-g-PE. The collapsed state corresponds to 37°C for PNIPAAm-g-PE, and pH 4.4 for PMAA-g-PE. Error bars are standard deviations (n=4 pieces of the membrane made from the same batch).

than PMAA. It is also consistent with a comparison of relative membrane thicknesses in Figure 7.1. As explained in section 6.2.2.2, larger relative membrane thicknesses mean more polymer grafted on the membrane surface. Therefore, the PMAA-g-PE membrane prepared in water shows largest thickness changes due to most grafting occurring on the membrane surface. In contrast, the PMAA-g-PE membrane prepared in the water/methanol mixture and the
PNIPAAm-g-PE membrane show a smaller relative membrane thickness due to more significant grafting inside the pores. In addition, the relative membrane thickness of the PMAA-g-PE membrane prepared in the water/methanol mixture is larger than that of the PNIPAAm-g-PE membrane prepared in water.

Considering the structural difference between the two monomers as shown in Figure 7.2, the differences in the reaction kinetics and graft location between grafting PNIPAAm and PMAA in water may be due to the following two reasons. The first is that the affinity of NIPAAm for the hydrophobic PE surface is higher than that of MAA due to more hydrophobic characteristics of NIPAAm resulting in higher grafting rate both on the membrane surface and inside the pore [Yang 1996, Yamada 1992]. The second reason may be that electrostatic repulsion between ionized MAA and grafted PMAA would retard diffusion of the ionized monomer into the pores resulting in less grafting inside the pores. This is consistent with my experimental result that grafting PMAA at pH 12, when the monomer and grafted polymer are completely ionized, gives a graft yield of only 23%. In contrast, grafting PMAA in water under the same monomer concentration and grafting time gives a higher graft yield of 187%. Since polymerization rates of MAA at pH 12 and in water are close (2.88×10⁻⁵ M/s vs. 2.3×10⁻⁵ M/s).

![Figure 7.2 Monomer structures of NIPAAm and MAA.](image)
[Shoaf 1991], the significant difference in the graft yield may be ascribed to the electrostatic repulsion between ionized MAA and grafted PMAA, which reduces grafting inside the pores. The result also supports the argument that grafting inside the pores would have a significant effect on the graft yield due to much a larger pore surface area than membrane surface area. This is consistent with the report that the graft yield is much higher for a porous membrane than for a non-porous membrane, observed during studies of electron-beam-induced graft polymerization of glycidyl methacrylate onto polyethylene [Lee 1996a]. It should be noted that the degree of ionization of MAA and its grafted polymer in water is lower than at pH 12, so the electrostatic repulsion effect would not be so significant.

The second observation in Table 7.1, i.e., the effect of grafting solvent on the grafting rate of PMAA, has been explained in Section 5.2.1 (see Figure 5.1-c). Briefly, methanol would wet the membrane pore surface, resulting in an increase in the amount of PMAA grafted inside the pores. Due to much larger pore surface area than membrane surface area, the increased grafting inside the pores gives rise to a significant increase in the grafting rate in the methanol/water mixture with 1:3 volume ratio. On the other hand, at a higher methanol content, i.e., 1:1 by volume, methanol can remove PE-adsorbed photoinitiators, leading to a reduction in the grafting rate.

The third observation, i.e., the grafting rate in water increases dramatically as the monomer concentration is increased from 0.22M to 0.66M, can be explained by effects of following factors on the grafting rate. First, the grafting rate order with respect to monomer concentration is normally larger than 1. As a result, the grafting rate shows a significant increase rather than linear or gradual increase in the grafting rate with increasing monomer concentration [Minko 1999]. Second, it was found that the grafting efficiency (ratio of grafted polymer to
homopolymer) increased dramatically as monomer concentration was increased above 0.7 M (close to 0.66M in this study) in the photograft polymerization of MAA onto non-porous PE membranes [Ogiwara 1988]. This may be due to the fact that the substrate macroradicals are immobile and their reaction with MAA monomers (i.e., the graft polymerization) would rely on the availability of MAA molecules in their vicinity. This may result in a higher monomer concentration required for the graft polymerization in comparison with the homopolymerization. As a result, the grafting rate would increase dramatically. Therefore, due to the above combined effects, the grafting rate increases dramatically.

The fourth observation may be explained in terms of differences in substrates and initiator concentration. One the one hand, the grafting rate on PE in water is expected to be lower than on PNIPAAm-g-PE due to the more hydrophobic nature of PE. On the other hand, the grafting rate on PE is expected to be higher due to a higher initial photoinitiator concentration. As a result of the two opposite effects, the grafting rate on the PE is close to that on the PNIPAAm-g-PE. However, the grafting rate on PE in the methanol/water mixture (1:3 by volume) is higher than the grafting rate on PNIPAAm-g-PE in water, since methanol can wet the PE. It should be noted that different initiation mechanisms (hydrogen abstraction vs. decomposition of living end groups) are involved in the two grafting processes.

Finally, Table 7.1 shows a higher grafting rate for the PNIPAAm-g-PE membranes with higher PNIPAAm graft yields. This has been explained in Section 6.2.1.1 (see discussion of Figure 6.2).

Figure 7.1 shows larger relative membrane thicknesses of the PMAA-g-PE prepared in the methanol/water mixture (1:1 by volume) than those of PNIPAAm-g-PE, especially at higher graft yields, due to more grafting of PNIPAAm inside the pores than of PMAA. This is
consistent with a comparison of SEM characterization of the PNIPAAm-g-PE and PMAA-g-PE membranes prepared in the water/methanol mixture with a similar graft yield (Figure 4.3-c vs. Figure 5.4-c). The thickness of the PNIPAAm-g-PE membrane is smaller than that of the PMAA-g-PE membrane (0.05 mm vs. 0.06 mm in the dry state). More significant grafting of PNIPAAm inside the pores than of PMAA may be due to two reasons. One reason is the electrostatic repulsion between ionized MAA and its grafted polymers, as discussed above. It is known that the degree of ionization decreases with the addition of methanol. On the other hand, the dielectric constant also decreases with the addition of methanol. Since the electrostatic repulsion force is proportional to the number of ionized groups and the inverse dielectric constant of solvent, the two opposite effects may cancel out [Islam 1992]. Therefore, the repulsion force effect on the graft location may be similar during grafting in water and in the methanol/water mixture. The other reason is the removal of photoinitiator from the membrane surface and pore surface. As discussed in Section 5.2.1 (see Figure 5.1-c), the solubility of the photoinitiator in grafting solvents increases with methanol content (solubility in 50 vol% methanol (0.21 mg/ml) is more than 40 times higher than that in water (< 0.005 mg/ml)). Thus, the water/methanol mixture may dissolve and remove PE-adsorbed photoinitiator, leading to a reduction in grafting on the external membrane surface and inside the pores. Moreover, the grafting process inside the pores in the methanol/water mixture includes three steps: wetting the pores, diffusion of monomers into the pores, and then reaction of the monomers with free radicals. If the monomer diffusion is slow relative to other steps, some photoinitiators may be removed by the grafting solvent before reaction with the monomer. The diffusion effect on the grafting onto the external membrane surface is less significant. As a result, the reduction in grafting inside the pores may be more significant than that onto the membrane surface.
In summary, the graft yield and location of the membrane prepared in the methanol/water mixture depend on the balance between the two effects, the effect of the grafting solvent on wetting the pores and the effect of the grafting solvent on removing the photoinitiator.

It should be noted that graft yield increases may be ascribed to either increasing molecular weight or increasing density of the grafted polymer; however, no further characterization was done in this work to distinguish between these two possibilities. It is quite difficult to directly determine the molecular weight of the polymer grafted on the substrate [Penn 1999]. It has been reported, without theoretical argument, that the molecular weight of the grafted chains could be related to that of homopolymers created during the graft polymerization [Ulbricht 1995, Uchida 1994]. The correlation is very doubtful since the initiation and termination mechanisms for the two processes are very different. It has recently been reported that grafted polymers have different molecular weight averages and distributions from homopolymers created during the graft polymerization [Prucker 1998]. Graft density was determined by assuming that each free radical generated during the initiation process would induce a grafted polymer [Ito 1990]. The amount of free radicals could be quantified with 1,1-diphenyl-2-picrylhydrazyl (DPPH) [Lee 1996b, Ito 1990].

7.2 Permeation through Polymer-Grafted Porous Membranes

For a porous membrane grafted with a polymer, the polymer would provide a secondary structure or fibrous network, through which solutes must pass. Therefore, its conformation determines the permeability of the grafted membrane. It has been known that conformations of the grafted chain significantly affect permeability [Castro 1993, Yamada 1996]. However, the effect of the polymer grafted at the membrane surface on the responsive permeability of the
membrane would be different from that of the polymer grafted inside the pores. We developed a simple two-graft-layer model that allows us to demonstrate the difference and describe the effect of graft yield and location on the permeability.

As discussed in the previous chapters, the model views the grafted membrane as two layers: surface layer and pore layer. The overall responsive permeability depends on the permeability and thickness of each layer.

Figure 7.3 shows that permeability dependence on the graft yield follows a similar trend for three types of polymer-grafted membranes in the expanded state. The permeability decreases with increasing graft yield, reaches a minimum, and then increases with increasing graft yield. The trend has been explained using the two-layer model. At low graft yields, polymers are mainly grafted inside the pores, and the pore size decreases with increasing graft yield, resulting in a decrease in permeability. With further increase in the graft yield, the pores would eventually become filled with grafted polymers, and an increasingly significant surface layer would be formed; the overall permeability would then become increasingly influenced by the permeability of the surface layer. Since the permeability of the surface layer is higher than that of the porous layer in the expanded state, the overall permeability will begin to increase, showing a minimum at an intermediate graft yield. However, the curve for the PMAA-g-PE membrane appears to be shallower than for the PNIPAAm-g-PE and co-grafted membranes. In addition, the co-grafted membrane shows a permeability in between that of the PNIPAAm and PMAA singly grafted membrane. The observation may be explained in terms of the graft location, i.e. surface grafts vs. pore grafts, and the effect of the surface layer on the permeability. As discussed earlier, PNIPAAm is more likely to be grafted inside the pores than PMAA, and membrane permeability in the expanded state increases with an increasing thickness of the surface layer.
Figure 7.3 Effect of the graft yield on the permeability of PNIPAAm (●), PMAA (■) and PNIPAAm-block-PMAA (▲) grafted porous PE membranes in the expanded state. PNIPAAm and PNIPAAm-block-PMAA were grafted in water. PMAA was grafted in methanol/water mixture (1:1 by volume). The expanded state corresponds to 30°C for the PNIPAAm-g-PE, pH 7.4 for the PMAA-g-PE and 30°C, pH 7.4 for the co-grafted PE. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).

More polymers grafted inside the pores mean more obstruction in the pores, and thus, lower permeability. Therefore, the PNIPAAm-g-PE membrane shows a lower minimum permeability than the PMAA-g-PE membrane. On the other hand, more polymer grafted inside the pores means that PNIPAAm would form a surface layer at a higher graft yield than PMAA. Moreover, the permeability through the PNIPAAm surface layer is lower than that through the PMAA
surface layer, as discussed in section 6.2.2.2. Therefore, the PNIPAAm-g-PE membrane shows an increase in permeability at a higher graft yield. For the co-grafted membrane, since it was prepared by grafting PNIPAAm first followed by grafting PMAA onto the end of the grafted PNIPAAm, the relative amount of surface grafts to pore grafts may be in between that of singly grafted PNIPAAm and PMAA. In addition, the permeability through the co-grafted surface layer is expected to be in between the permeability of PNIPAAm and PMAA surface layer. As a result, the co-grafted membrane shows the trend of permeability dependence on the graft yield in between that of the PNIPAAm and PMAA singly grafted membranes as shown in Figure 7.3.

Figure 7.4 compares the dependence of permeability on the graft yield of the three types of membranes in the collapsed state. At low graft yields, Figure 7.4 shows a similar trend to Figure 7.3. However, at higher graft yields, PNIPAAm-g-PE membranes show a dramatically different profile from the PMAA-g-PE and co-grafted PE membranes. The observation can be explained in terms of graft location and different permeabilities through surface layers using the two layer model. At the low graft yield range, grafts are mainly inside the pores resulting in obstruction in the pores, and therefore decreased permeability with increasing graft yield. At the high graft yield range, the surface layer would be formed. Depending on the permeability through the surface layer, the membrane shows different profiles. As discussed in section 6.2.2.2, the permeability through the PNIPAAm surface layer in the collapsed state is lower than that of the PMAA surface layer and the pore layer filled with grafted polymers. As a result, the collapsed PNIPAAm surface layer results in a significant decrease in membrane permeability. In contrast, the permeability through the collapsed PMAA surface layer is higher than that through the pore layer. Therefore, the membrane permeability would increase with increasing graft yield at the high graft yield range. It is expected that the permeability through the co-grafted surface
Figure 7.4 Effect of the graft yield on the permeability of PNIPAAm (○), PMAA (□) and PNIPAAm-block-PMAA (Δ) grafted porous PE membranes in the collapsed state. PNIPAAm and PNIPAAm-block-PMAA were grafted in water. PMAA was grafted in methanol/water mixture (1:1 by volume). The collapsed state corresponds to 37°C for the PNIPAAm-g-PE, pH 4.4 for the PMAA-g-PE and 37°C, pH 4.4 for the co-grafted PE. Error bars are standard deviations (n=3 pieces of the membrane made from the same batch).

Layer is in between the permeability through the PNIPAAm and PMAA layers. Moreover, it has been discussed that the complexation occurs at this PMAA content (~50 wt%), and complexation prevents the collapse of PNIPAAm blocks. In addition, the PNIPAAm blocks are mainly located inside the pores, since PNIPAAm is grafted first. The co-grafted surface layer is mainly composed of PMAA blocks. Because of the above reasons, the co-grafted polymer can not form as dense a surface layer as PNIPAAm alone, thus reducing the effect on membrane permeability.
Therefore, the co-grafted membrane does not show a significant decrease in the permeability with increasing graft yield, while showing a similar behavior to the PMAA-g-PE membrane.

In summary, the two-layer model can describe the permeation behavior of the responsive polymer grafted porous membranes with different graft yields and locations. The permeability dependence on the graft yield and location is greatly affected by the permeability through the surface layer.

7.3 Reference


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Chapter 8  Summary and Recommendations for Future Work

8.1 Summary

This thesis can be summarized in terms of graft yield, graft location, co-graft structure and their effects on the responsive permeability of the polymer grafted porous membranes:

1. A photochemical graft polymerization method was developed to prepare PNIPAAm and PMAA singly grafted and co-grafted porous polyethylene membranes.

2. A wide range of graft yields can be obtained by controlling grafting time and monomer concentration. The graft yield increases with increasing grafting time and monomer concentration. The graft location can be controlled by grafting solvent. A pore wetting solvent would increase grafting inside membrane pores in comparison with a non-pore wetting solvent.

3. A transitional graft yield is identified. Below the graft yield, the responsive polymer grafted inside the membrane pore (pore graft) acts as a permeation valve to close and open the pore by extension and contraction of the grafted chain, showing a pore control mechanism. Above the transitional graft yield, the responsive polymer grafted on the membrane surface (surface graft) would form a hydrogel surface layer to increase and decrease the permeability by swelling and de-swelling changes, showing a surface control mechanism. The value of the transitional graft yield depends on the graft location. Preferential grafting inside the pores gives rise to a greater pore-controlled type of permeability response and a higher graft yield to switch from the pore controlled to the surface controlled type of permeability response. A two-layer model can be used to describe the different effect between the pore graft and surface graft on the permeability changes.
4. A di-block co-graft structure can be obtained using the sequential photografting procedure. The secondary structure of the grafted di-block polymer depends on temperature, pH, block-block interactions and the co-graft composition.

5. The permeability of the co-grafted membrane depends on both co-graft yield and composition. At low graft yields, the membrane shows the pore control mechanism. At high graft yields, the membrane may show the surface control mechanism. The switch from the pore control to the surface control depends on the co-graft composition.

6. The permeability change of the grafted membranes is reversible and reaches a maximum with solute size due to the size exclusion effect. The PNIPAAm-block-PMAA grafted membranes show more sophisticated control over the membrane permeability than the PNIPAAm and PMAA singly grafted membranes.

8.2 Recommendations for Future Work

1. The differences in graft location and reaction kinetics of the graft polymerization onto porous polyethylene membranes between NIPAAm and MAA were observed. Further studies are required to clarify the cause of the differences.

2. Living free radical graft polymerization mechanism was confirmed based on the grafting procedure. Some analytical techniques may be able to provide further information on the grafting mechanism. For example, electron spin resonance may identify free radicals that induce the graft polymerization [Hawthorne 1999].

3. The significance of block-block interactions on the responsiveness of the co-grafted membrane, including the LCST phenomena, needs to be further investigated. pH-responsive blocks, showing no hydrogen bonding with PNIPAAm blocks, can be selected to synthesize
di-block polymer grafted membranes.

4. A clinical scenario in which complex controlled release in response to both temperature and pH is required, has to be identified to test potential clinical applications of the co-grafted membrane.

5. Permeation of solutes with different molecular sizes across the grafted membrane can be conducted to show the potential application of the membrane for separation by in-situ variation of pore size.

8.3 References

Permeation curves for a PNIPAAm-g-PE membrane with 233% graft yield at different temperatures: ● 27.5°C, □ 30.0°C, ▲ 32.5°C, ○ 35.0°C, □ 37.0°C, ▼ 40.0°C.

Calculated permeability (×10⁻⁸ cm²/s) of a PNIPAAm-g-PE membrane with 233% graft yield at different temperatures

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## Appendix 2  PMAA Grafted Surfaces

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Appendix 3 Measurement of the Apparent Dissociation Constant \( pK_a \) of Grafted Poly(methacrylic acid) (PMAA)

Experimental

The \( pK_a \) was determined by potentiometric titration according to reported method [Eichenbaum 1998, Jimbo 1998, Suzuki 1999]. All the following procedures were carried out under nitrogen. Boiled carbonate-free water was used to prepare NaOH and HCl standard solution. Small pieces of PMAA grafted polyethylene (PE) membrane with 532% graft yield were suspended in 10 ml 0.01 M NaOH solution with stirring to completely ionize carboxylic acid groups of PMAA. The titration was performed with 0.01025 M HCl using a burette with an accuracy of 0.01 ml. The pH was measured by a FisherScientific pH meter (model 15) equipped with a combination pH electrode made by Cole-Parmer Instrument Co. The pH meter and electrodes were calibrated by standard buffer solutions with pH of 4.0, 7.0 and 10.0. The degree of protonation, \( \alpha \) was calculated according to the following relation [Suzuki 1999, Porasso 1999]:

\[
\alpha = \frac{[C_{HCl} + (C_{OH^-} - C_{H^+})]}{C_{COOH}}
\]

where \( C_{HCl} \) is the molar concentration of HCl added, and \( C_{OH^-}, C_{H^+} \) are the molar concentrations of \( OH^- \) and \( H^+ \) ions, respectively. \( C_{COOH} \) is the total molar concentration of COOH. The \( pK_a \) was defined as the pH at which half of the carboxylic acid groups of PMAA were protonated and obtained by plotting the degree of protonation against solution pH. The value is 5.8 as shown in the figure.
Titration of PMAA-g-PE membrane with graft yield of 532% with 0.01 M HCl: degree of protonation vs. pH.
References


Porasso R.D., Benegas J.C., van den Hoop M.A.T., (1999), Chemical and electrostatic association of various metal ions by poly(acrylic acid) and poly(methacrylic acid) as studied by potentiometry, J. Phys. Chem., B, 103, 2361-2365

**Appendix 4**  
**Effect of pH-Responsive Components on the LCST of Random Copolymers/Hydrogels Composed of NIPAAm and pH-Sensitive Units**

<table>
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<th>pH-sensitive comonomer</th>
<th>Composition</th>
<th>Synthetic method</th>
<th>Solution pH</th>
<th>Transition temperature (°C)</th>
<th>Measurement method</th>
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<td>1 - 10 mol%</td>
<td>Solution</td>
<td>1</td>
<td>30-33</td>
<td>Swelling</td>
<td>Velada 1998</td>
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<tr>
<td></td>
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<td>5.7</td>
<td>32</td>
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<tr>
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MAA = methacrylic acid, AA = acrylic acid, DMAA = N,N-dimethylacrylamide, DEAEMA = N,N-dimethylaminoethylmethacrylate, MAPTAC = methacrylamidopropyltrimethylammonium chloride. pH of deionized/distilled water is presumably 6.
References


Yoshida R., Ichijo H., Hakuta T., and Yamaguchi T., (1995), Self-oscillating swelling and

## Appendix 5  LCST of PNIPAAm Block or Graft Copolymers and Hydrogels

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<th>Component B</th>
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<td>PNIPAAm graft</td>
<td>Poly(ethylene oxide) (PEO)</td>
<td>36</td>
<td>Bhalerao 1998</td>
</tr>
<tr>
<td>$M_w=6000$</td>
<td>$M_w=12000$</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>PNIPAAm backbone</td>
<td>PEO graft</td>
<td>31</td>
<td>Kaneko 1998</td>
</tr>
<tr>
<td>$M_n=5100 0%$</td>
<td></td>
<td>32.5</td>
<td></td>
</tr>
<tr>
<td>$M_n=5100 5%$</td>
<td></td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>$M_n=5100 10%$</td>
<td></td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>$M_n=5100 15%$</td>
<td></td>
<td>35.5</td>
<td></td>
</tr>
<tr>
<td>$M_n=5100 30%$</td>
<td></td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>$M_n=5100 50%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNIPAAm backbone</td>
<td>PEO graft</td>
<td>32</td>
<td>Qiu 1997</td>
</tr>
<tr>
<td>$M_w=7000-8000$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References


Cheon J.K., Jeong Y., Cho C.S., (1999). Effects of temperature on diblock copolymer micelle composed of poly(γ-benzyl L-glutamiate) and poly(N-isopropylacrylamide), Polym., 40, 2041-2050


Qiu X. and Wu C., (1997), Study of the core-shell nanoparticle formed through the coil-to-globule transition of poly(N-isopropylacrylamide) grafted with poly(ethylene oxide), Macromol., 30, 7921-7926

Topp M.D.C., Dijikstra P.J., Talsma H., and Feijen J., (1997), Thermosensitive micelle-forming block copolymers of poly(ethylene glycol) and poly(N-isopropylacrylamide), Macromol., 30, 8518-8520


Appendix 6  DSC Thermograms for the PNIPAAm and PMAA co-grafted PE membranes with different PMAA contents

| T | 30.783 °C |
| Tc | 35.850 °C |
| Peak | 33.814 °C |
| Area | 22.567 mJ |
| ΔH | 4.179 J/g |
| Height | 1.304 mW |
| Onset | 32.571 °C |

PNIPAAm/PMAA co-grafted PE membrane with 461% co-graft yield and 7.6 wt% PMAA at pH 7.4
PNIPAAm/PMAA co-grafted PE membrane with 461% co-graft yield and 7.6 wt% PMAA at pH 4.4
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### Appendix 7  
**PNIPAAm and PMAA or PAA Interpolymer Complexes**

<table>
<thead>
<tr>
<th>Polymer A</th>
<th>$M_w$</th>
<th>Solution pH</th>
<th>Polymer B</th>
<th>$M_w$</th>
<th>Solution pH</th>
<th>Mole ratio</th>
<th>Temperature (°C)</th>
<th>Complexation characterization</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNIPAAm graft</td>
<td></td>
<td>pH=7.4, pH=4</td>
<td>PAA backbone</td>
<td></td>
<td>pH=7.4, pH=4</td>
<td></td>
<td></td>
<td>Higher LCST at pH 7.4 than at pH 4</td>
<td>Chen 1995</td>
</tr>
<tr>
<td>PNIPAAm</td>
<td>76100</td>
<td>pH=6</td>
<td>PMAA</td>
<td>23000</td>
<td>pH=4.5</td>
<td>20/80 35/65 50/50 65/35 80/20</td>
<td>Room temperature</td>
<td>Precipitation</td>
<td>Garay 1997</td>
</tr>
<tr>
<td>PNIPAAm</td>
<td>76100</td>
<td>pH=6</td>
<td>PAA</td>
<td>50000</td>
<td>pH=4.5</td>
<td>20/80 35/65 50/50 65/35 80/20</td>
<td>Room temperature</td>
<td>Precipitation</td>
<td>Garay 1997</td>
</tr>
<tr>
<td>PNIPAAm</td>
<td>280000</td>
<td>pH=4.15</td>
<td>PAA</td>
<td>72000</td>
<td>pH=4.15</td>
<td>7 1 3</td>
<td>25</td>
<td>$\eta_{\text{mix}}/\eta_{\text{ave}}=0.25$ $\eta_{\text{mix}}/\eta_{\text{ave}}=0.12$ $\eta_{\text{mix}}/\eta_{\text{ave}}=0.6$</td>
<td>Staikos 1996</td>
</tr>
<tr>
<td>PNIPAAm</td>
<td>230000</td>
<td>pH=4.1</td>
<td>PAA</td>
<td>94000</td>
<td>pH=4.15</td>
<td>1 1 1 1 5 15 20 25</td>
<td></td>
<td>$\eta_{\text{mix}}/\eta_{\text{ave}}=0.9$ $\eta_{\text{mix}}/\eta_{\text{ave}}=0.55$ $\eta_{\text{mix}}/\eta_{\text{ave}}=0.45$ $\eta_{\text{mix}}/\eta_{\text{ave}}=0.1$</td>
<td>Staikos 1997</td>
</tr>
<tr>
<td>PNIPAAm</td>
<td></td>
<td>pH=4.4, pH=4, pH=7.4</td>
<td>PMAA</td>
<td></td>
<td>pH=4.4, pH=4, pH=7.4</td>
<td>25 37 25 37</td>
<td>Cloudy</td>
<td>Clear solution</td>
<td>Cloudy</td>
</tr>
</tbody>
</table>

PNIPAAm = poly(N-isopropylacrylamide), PMAA = poly(methacrylic acid), PAA = poly(acrylic acid), $\eta_{\text{mix}}/\eta_{\text{ave}}$ is viscosity ratio, where $\eta_{\text{mix}}$, $\eta_{\text{ave}}$ are intrinsic viscosity of the polymer mixture and the weight-average of the intrinsic viscosity of each pure component, respectively.
References


Garay M.T., Llamas M.C., and Iglesias E., (1997), Study of polymer-polymer complexes and blends of poly(N-isopropylacrylamide) with poly(carboxylic acid): 1. Poly(acrylic acid) and poly(methacrylic acid), Polym., 38, 5091-5096
