UNIVERSITY OF OTTAWA
Department of Chemical and Biological Engineering

SYNTHESIS OF STIMULI-RESPONSIVE HYDROGELS FROM GLYCEROL

By

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A thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Chemical Engineering

Statement of Contributions of Collaborators

I hereby declare that I am the sole author of this thesis. I performed all polymerization and hydrogel synthesis experiments, polymer and hydrogel characterization and data analysis for papers I, III and IV. For paper II, the initial screening study of the hydrogel formation using different cross-linkers was performed by Christopher Zuliani under my co-supervision. I trained him in the laboratory techniques and directly supervised his work in the laboratory. All polymerizations, swelling behaviour study and ATR-FTIR data analyses were done by me. The acquisition of the NMR spectroscopy data was contracted to the Department of Chemistry at the University of Ottawa. It should also be noted that Mr. Abebe Essayas assisted in the preparation of the manuscript found in the appendix.

The scientific guidance throughout the project and editorial comments of the written work were provided by my thesis supervisor Dr. Marc A. Dubé of the Department of Chemical and Biological Engineering at the University of Ottawa.

Somaieh Salehpour

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ABSTRACT

Due to an increased environmental awareness and thus, concerns over the use of fossil-based monomer for polymer production, there is an ongoing effort to find alternatives to non-renewable traditional monomers. This has ushered in the rapid growth in the development of bio-based materials such as green monomers and biodegradable polymers from vegetable and animal resources. Glycerol, as a renewable bio-based monomer, is an interesting candidate for sustainable polymer production. Glycerol is a renewable material that is a by-product of the transesterification of vegetable oils to biodiesel. Utilization of the excess glycerol derived from the growing biodiesel industry is important to oleochemical industries. The main objective of this thesis was to produce high molecular weight polyglycerol from glycerol and synthesize stimuli-responsive polyglycerol hydrogels**.** The work began with an investigation of the step-growth polymerization of glycerol to relatively high molecular weight polyglycerol using several catalysts. The catalytic reaction mechanisms were compared and the polymer products were fully analyzed. High molecular weight partially branched polyglycerol with multimodal molecular weight distributions was obtained. The polymerization of glycerol proceeded fastest with sulphuric acid as catalyst as indicated by the highest observed conversion of monomer along with the highest molecular weights. Theoretical models were used to predict the gel point and to calculate monomer functionality. High molecular weight polyglycerol was used to synthesize novel stimuli-responsive hydrogels. Real-time monitoring of step-growth polymerization of glycerol was investigated using in-line and off-line Attenuated Total Reflectance/Fourier Transform infrared (ATR-FTIR) technique.

RÉSUMÉ

Due aux inquiétudes sur l'utilisation de monomères à base de pétrole pour la production de polymères, il y a un effort en cours pour trouver des alternatifs aux monomères traditionnels non-renouvelables. Cela a introduit la croissance rapide dans le développement des biomatériaux comme les monomères verts et les polymères biodégradables provenant des ressources animal et légumes. Le glycérol, comme monomère bio-renouvelable, est un candidat intéressant pour la production des polymères durables. Le glycérol est une matière renouvelable qui est un dérivé de la transestérification d'huiles végétales au biodiésel. L'utilisation du glycérol en excès due à la croissance de la production mondiale du biodiésel est importante pour les industries oléochimiques. L'objectif principal de cette thèse était de produire le polyglycérol de poids moléculaire élevé du glycérol et de synthétiser des hydrogels de polyglycérol. Le travail a commencé par une enquête de la polymérisation du glycérol au polyglycérol de poids moléculaire élevé en utilisant plusieurs catalyseurs. Les mécanismes de réaction catalytiques ont été comparés et les produits ont été complètement analysés. Le polyglycérol branché au poids moléculaire élevé avec une distribution de poids moléculaire multimodale a été obtenu. La polymérisation du glycérol a procédé le plus rapidement avec l'acide sulfurique comme catalyseur. Les modèles théoriques ont été utilisés pour prédire le point de gel et pour calculer la fonctionnalité du monomère. Le polyglycérol de poids moléculaire élevé a été utilisé pour synthétiser des hydrogels sensibles aux stimuli. La mesure en temps réel de la polymérisation du glycérol a été enquêté en utilisant la technique ATR-FTIR (Réflexion Atténuée Totale-Infrarouge par Transforme Fourier).

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Nomenclature

C = Concentration, [mol L^{-1}]
f = average number of functional groups per molecule, [mol]
M = Monomer concentration, [mol L^{-1}]
M_c = Molecular weight between crosslink points, [g mol^{-1}]
M_e = Molecular weight between entanglements, [g mol^{-1}]
M_n = Number average molecular weight, [g mol^{-1}]
M_w = Weight average molecular weight, [g mol^{-1}]
M_t = Total amount of diffusing substance at time *t* ,[g]
M_∞=Total amount of diffusing substance after equilibrium ($t=\infty$), [g]
M_0 = Molecular weight of the monomer, [g mol^{-1}]
N_A = Avogadro's number, [mol^{-1}]
N_0 = total number of monomer molecules initially present
N = total number of monomer molecules present at time *t*
phm = parts per hundred parts of monomer
R = Universal ideal gas constant, [cm^3 bar mol^{-1} K^{-1}]
r_i = Reactivity ratio
R_p = Rate of polymerization, [mol L^{-1}]
T = Temperature, [K]
T_g = Glass transition temperature, [°C]
p= extent of reaction,
p_c = Critical extent of reaction
W_d = Weight of dry hydrogel, [g]
W_s = Weight of swollen hydrogel, [g]
$\overline{X}_n$ = number-average degree of polymerization

List of Abbreviations

^{1}H-NMR = Proton Nuclear Magnetic Resonance

^{13}C-NMR = Carbon Nuclear Magnetic Resonance

ATR-FTIR = Attenuated Total Reflectance/Fourier Transform infrared

GPC = Gel Permeation Chromatography

MWD = Molecular weight distribution

PDI = Polydispersity index

PVOH = Polyvinyl alcohol

PEG = Polyethylene glycol

PEGDE= poly(ethylene glycol) diglycidyl ether

VOC = volatile organic compounds

PTSA = *p*-toluene sulfonic acid

COSY= heteronuclear two-dimensional correlation spectroscopy

Acknowledgments

Finding suitable words to acknowledge everyone who helped in enriching my thoughts and guiding my ideas is not less difficult than the research process itself. The following few words are symbolic of my indebtedness to a few of the many who have refined my path.

The most important landmark on my journey is my intellectual supervisor and academic father, Dr. Marc A. Dubé. The various discussions with him opened new doors for my mind besides enriching many of my perceptions. His consistent support, both moral and substantial, enabled me to transcend many of the obstacles faced in my journey. I would not be here today without his support and guidance over these years. I also want to thank him for allowing me to participate in many international conferences. All has been an invaluable experience and I am truly indebted to him.

Also, I am indebted to the professors, staff and my colleagues at the Department of Chemical and Biological Engineering, who provided me with all the knowledge and help I required through all the different stages of my research, especially Dr. Xudong Cao and his research group, for helpful discussions regarding hydrogels.

I should express my boundless gratitude and thanks to my family: to my loving mother, whose encouragement and support enabled me to be here; my caring father, whose support never reached a limit; and my younger brothers who tried to help me by all means possible.

Special thanks go to my husband, Mohammad, who has been and will undoubtedly continue to be in the future, a perpetual source of inspiration and love.

Chapter 1. Introduction

Polymers are macromolecules made up of much smaller repeating units called monomers. They are used in a wide range of applications such as adhesives, packaging, construction materials, and coatings, to name just a few. Polymers are found in just about every manufactured product in the world; they are highly versatile due to the unique properties they exhibit compared to small molecules. They can be tailored to suit particular needs by choosing proper monomer(s) and reaction conditions that will result in desired physical and chemical properties.

In the past several decades, polymer scientists and engineers have been working towards the development of more sustainable polymer processes and products. The principles of green chemistry (Anastas and Warner, 2000) provide a practical framework for scientists and engineers to use when designing new materials, products, processes, and systems (see Appendix A). Significant contributions in the drive toward sustainability for the benefit of the environment and society are possible by applying these principles. The 4th of the well known "green chemistry principles" states that one should "use renewable feedstocks" (Anastas and Warner, 2000).

Growing interest in the use of renewable feedstocks derived from vegetable and animal sources has led to increased interest in the development of bio-based materials such as green monomers and biodegradable polymers. In parallel, we are witness to rapid growth in the production of bio-based transportation fuels such as biodiesel. Biodiesel, an environmentally friendly alternative to petro-diesel, is produced via transesterification of lipid feedstocks with an alcohol; the reaction scheme is shown in Figure 1.1. A major by-product of this process is glycerol, which is 10 wt.% of the total product mass. According to a recent biodiesel market analysis, biodiesel production increased from 959 to 15,760

million litres from 2001 to 2009 and the global glycerol production reached 1.2 million tons per year in 2010 (Global Biodiesel Market Analysis 2010). Due to substantial worldwide growth in the biodiesel industry, a large glycerol glut now exists at record-low prices in the neighborhood of $US 0.05/lb (Johnson and Taconi, 2007; Pagliaro et al., 2007). Therefore, considering the ongoing worldwide push towards increased biodiesel production, there is great interest in finding economic ways to use the emerging glycerol surplus. According to a US Department of Energy (DOE) 2010 "top 10" report, the use of glycerol is one of the top chemical opportunities from biorefinery carbohydrates (Bozell and Petersen, 2010).

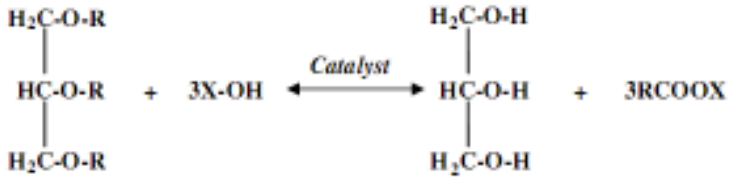


Figure 1.1 Elementary reaction scheme for transesterification of triglyceride.

Glycerol is a molecule rich in functionalities and significant research has been focused recently on its conversion to value-added chemicals its usage as a platform chemical to replace mainstream petroleum derived chemicals (Kenar, 2007; Pagliaro and Rossi, 2010). The polymerization of glycerol has been done traditionally for the production of several types of biodegradable surfactants, lubricants, cosmetics, and food additives which are available commercially (Pagliaro and Rossi, 2010). The polymer production from the excess glycerol derived from the growing biodiesel industry is not only important to oleochemical industries but also improves the sustainability of biodiesel production by using the side product of this process.

As shown in Figure 1.2, etherification reactions can be used to convert glycerol into polyglycerol (PG). However, until now, only oligomers were synthesized directly from glycerol as feedstocks and high molecular weight polyglycerols such as hyperbranched polyglycerol have been produced from toxic monomers such as glycidol, a carcinogenic monomer, via other polymerization methods (Sunder et al., 1999; Melnick, 2002; Steinhilber et al., 2011).

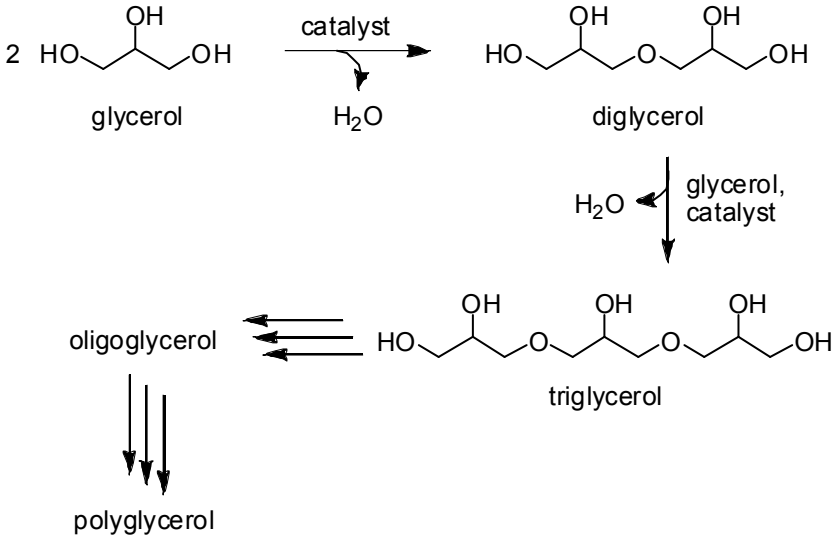
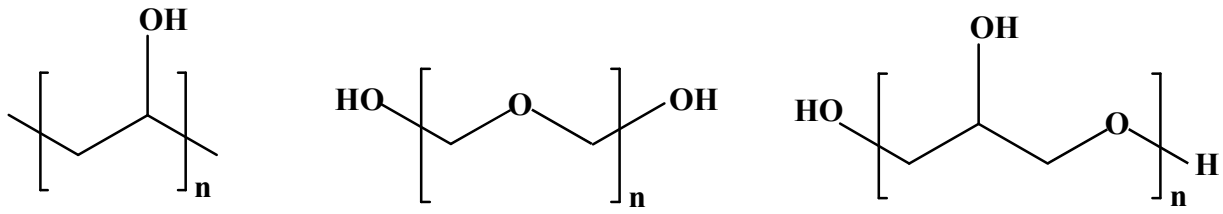


Figure 1.2. Schematic representation of the etherification of glycerol to polyglycerol

Polyglycerol is a biocompatible, biodegradable polymer (Daniel et al., 2010), which consists of an inert polyether backbone with an abundant number of functional hydroxyl side groups. As shown in Figure 1.3, the structural characteristics of the polyglycerol backbone resemble the well-known poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVOH). These two polymers, which are traditionally produced from fossil-based monomers, are biocompatible, non-toxic, and biodegradable. They are widely used for biomedical and pharmaceutical applications such as in hydrogels for drug delivery, wound

dressing and contact lenses (Hassan and Peppas, 2000; Peppas et al., 2000; Lin and Anseth, 2009). In consideration of the above-mentioned structural similarities polyglycerol, synthesized from a renewable source, has the potential to be a substitute for petroleum-derived PEG and PVOH.



PVOH PEG Polyglycerol

Figure 1.3. Poly(ethylene glycol), poly(vinyl alcohol) and polyglycerol chemical structure.

Considering polyglycerol hydrophilicity and functionality, it is a good candidate as a starting material for hydrogel formation and can find application where PEG and PVOH hydrogels are used. Hydrogels are three-dimensional polymer networks endowed with the ability to swell in water or aqueous solvents and absorb from 10% up to a thousand times their dry weight (Hoffman, 2002). They resemble natural living tissues and they were the first biomaterials designed to be used in the human body (Barbucci, 2009).

In this project, based on these considerations, the synthesis of high molecular weight polyglycerol using glycerol as a renewable monomer was studied (Salehpour and Dubé, 2011b). Comparison was made between polymerization of glycerol using different catalysts. Theoretical models were used to predict the gel point and functionality of the monomer. The high molecular weight polyglycerol was then used for production of stimuli-responsive hydrogels (Salehpour et al., 2011). Chemical and physical properties of

the hydrogels were fully investigated (Salehpour and Dubé, 2011a). Lastly, an exploratory study on the use of an in-line monitoring device was conducted and the results were compared to two other monitoring techniques to evaluate the different reaction monitoring methods for glycerol polymerization.

1.1. Objectives of the research

We hypothesized that high molecular weight polyglycerol can be produced from glycerol and can be used for the synthesis of stimuli-responsive hydrogels. In order to test these hypotheses, the following objectives were established:

Part 1: Sustainable production of high molecular weight polyglycerol from glycerol feedstock.

To achieve our primary objective, a screening study on glycerol step-growth polymerization was conducted. The catalytic polymerizations of glycerol were performed using different catalysts at different experimental conditions. The knowledge obtained serves as a guide for production of higher molecular weight polyglycerol. Synthesis of polyglycerol with high molecular weight from a green monomer has never been done before.

Part 2: Production of cross-linked polyglycerol.

Synthesis of cross-linked polyglycerol with different degrees of cross-linking was studied using polyglycerol from *part 1* and several epoxide-based cross-linkers. The results were used to produce pH and temperature-responsive polyglycerol.

Part 3: Study the application properties of stimuli-responsive polyglycerol hydrogels

Swelling kinetics and the diffusion process of stimuli-responsive hydrogels obtained from *part 2* were studied. Compressive mechanical properties of the hydrogels

were evaluated and the degradability of hydrogels was tested. These measurements provided information about the application properties of the hydrogels.

Part 4: Real-time monitoring of glycerol polymerization

The use of in-line and off-line monitoring of the reaction using attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy was investigated. The results were compared to conversion data from water production monitoring and a traditional wet chemistry method.

1.2. Thesis structure

This research project was accomplished to achieve the main goal of synthesis of stimuli-responsive hydrogels from glycerol. The research was divided into several sections. Each section was designed to fulfill one of the objectives outlined above.

The thesis is subsequently divided into four chapters. Since this thesis is prepared in a journal article format, each chapter corresponds to an independent publication that has been submitted to a refereed scientific journal. With this in mind, the reader can expect to find similar information in the introductory and methodological sections of the various chapters. The chapters are:

Chapter 2. Towards the Sustainable Production of Higher Molecular Weight Polyglycerol, Salehpour, S., Dubé M. A., Macromolecular Chemistry and Physics, 212(12): 1284-1293, 2011.

This chapter presents the results of the step-growth polymerization of glycerol to relatively high molecular weight polyglycerol. A screening study was performed to compare the polymerization of glycerol using different soluble catalysts. The reaction mechanisms were compared and their effect on polymer molecular weight and

microstructure was investigated. Theoretical models were used to predict the gel point and to calculate monomer functionality.

Chapter 3. Synthesis of Novel Stimuli-responsive Polyglycerol-based Hydrogels, Salehpour, S., Zuliani, C., Dubé, M. A., European Journal of Lipid Science and Technology, in press, 2011.

Temperature and pH-responsive polyglycerol-based hydrogels were successfully synthesized and characterized. Cross-linking of polyglycerol by multifunctional electrophilic epoxide-containing compounds was investigated to achieve increase in molecular weight of the polyglycerol and polyglycerol network. Novel temperature and pH-responsive polyglycerol-based hydrogel were successfully synthesized and characterized. The chemical structure of hydrogels and mechanism of cross-linking was studied by ATR-FTIR spectroscopy.

Chapter 4. Application properties of novel polyglycerol-based hydrogels, Salehpour, S., Dubé, M. A., Journal of Macromolecular Science. Part A Pure Applied Chemistry, in press, 2011.

Swelling kinetics and transient state swelling behavior of pH and temperature-responsive polyglycerol hydrogels were studied. A compressive mechanical property (i.e., Young's modulus) of the dry and swollen hydrogels was measured and the average molecular weight between cross-links was calculated. The degradability of these hydrogels was studied by monitoring the mass loss in phosphate buffered saline (PBS) solution over a period of 30 days.

Chapter 5. Reaction monitoring of glycerol step-growth polymerization using ATR-FTIR spectroscopy, Salehpour, S., Dubé, M. A., submitted to Macromolecular Reaction Engineering, 2011.

An exploratory study of the use of an ATR-FTIR spectroscopic probe for monitoring the step-growth polymerization of glycerol was carried out. The concentration of hydroxyl groups was monitored to provide real-time conversion data using a univariate method. The in-line and off-line ATR-FTIR spectroscopy data were compared to traditional off-line techniques, i.e., hydroxyl value calculation and water production monitoring. Fouling of the probe was investigated for in-line monitoring of the reaction. Paired comparisons of the differences between the conversions obtained from the different methods were carried out and the 95% confidence intervals were calculated.

Appendix A. Green pathways to polymer production: A critical review, Salehpour, S., Dubé, M. A., Essayas, A., to be submitted, 2011.

In this appendix, methods for sustainable production of polymers were discussed in light of the twelve principles of green chemistry. A number of these principles were employed toward sustainable polymerization of glycerol for hydrogel applications.

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Chapter 2. Towards the Sustainable Production of Higher Molecular Weight Polyglycerol

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Salehpour, S., Dubé M. A., Macromolecular Chemistry and Physics, 212(12): 1284-1293, 2011.

Towards the Sustainable Production of Higher Molecular Weight Polyglycerol

Somaieh Salehpour, Marc A. Dubé

Abstract

Glycerol is a renewable material that can be derived from the transesterification of vegetable oils to biodiesel. The step-growth polymerization of glycerol to relatively high molecular weight polyglycerol was investigated. Several soluble catalysts and their reaction mechanisms were compared and their effect on polymer molecular weight and microstructure was measured. High molecular weight polyglycerol with multimodal molecular weight distributions was observed using gel permeation chromatography. Partial branching was identified using ^{13}C-NMR spectroscopy. Theoretical models were used to predict the gel point and to calculate monomer functionality.

2.1. Introduction

In recent years, the interest in the use of bio-based polymers has grown tremendously. These types of polymers have a lower environmental burden and are ideal alternatives to conventional polymers made from petroleum, which is a limited natural resource. Glycerol as a bio-based monomer is an interesting candidate for a sustainable or "green" polymer production. During the last years, new opportunities for the conversion of glycerol into value-added chemicals have emerged due to the unique structure and properties of glycerol, its biocompatibility and biodegradability (Pagliaro and Rossi, 2010). According to US Department of Energy (DOE) 2010 "top 10" report, glycerol is one of the top chemical opportunities from biorefinery carbohydrates (Bozell and Petersen, 2010). Recent research has focused on using glycerol as a platform chemical to replace mainstream petroleum derived chemicals (Kenar, 2007; Behr and Gomes, 2010). Following the discovery of synthetic surfactants in the late 1940s and tens of new applications (see Figure 2.1), glycerol has been produced from epichlorohydrin obtained from propylene, as large chemical companies initiated its synthetic production and forecasted a glycerol shortage.

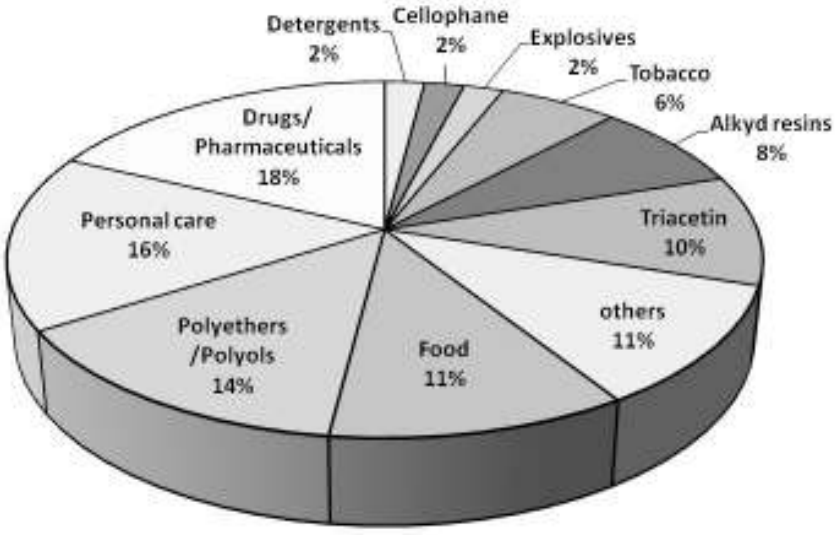


Figure 2.1. The market for glycerol (Pagliaro et al., 2007).

Nowadays, due to a significant glut in the glycerol market because of increasing biodiesel production, glycerol production plants are being shut down and new plants are being built for using glycerol as the raw material (Pagliaro et al., 2007). According to a recent biodiesel market analysis,(Global Biodiesel Market Analysis and Forecasts to 2020, 2010) biodiesel production increased from 959 to 15,760 million litres from 2001 to 2009. Considering government policies to spur the use of renewable energy and to satisfy the rising energy demand, the biodiesel market is expected to reach 45,291 million litres of biodiesel production in 2020.(Global Biodiesel Market Analysis and Forecasts to 2020, 2010; Global biodiesel market almost doubles every year between 2001 and 2009, 2010) In general, in manufacturing biodiesel fuel by transesterification, glycerol is normally generated at the rate of 1 mol of glycerol for every 3 mol of methyl esters synthesized;

therefore, approximately 10 wt.-% of total product is crude glycerol and utilization of excess glycerol derived from the growing biodiesel industry is important to oleochemical industries (Dube et al., 2007). The reaction scheme is shown in Figure 2.

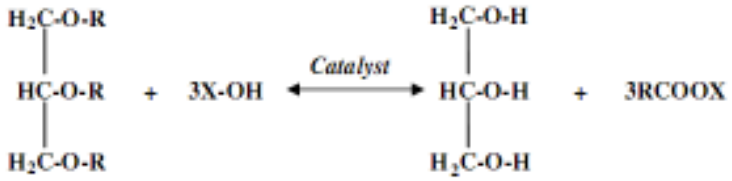


Figure 2.2. General reaction of the transesterification of triglyceride.

Glycerol, historically valued at $0.60-$0.90/lb, was economically unattractive as a feedstock chemical and commercial development of alternative processes for glycerol utilization has been limited (Johnson and Taconi, 2007). Recently, the price of crude glycerol has fallen to about $0.05/lb (Kelzer, 2010) and the production of glycerol has nearly doubled since the turn of millennium mainly due to biodiesel production. In Figure 2.3, global glycerol production estimates until 2010 are shown (Zhou et al., 2008).

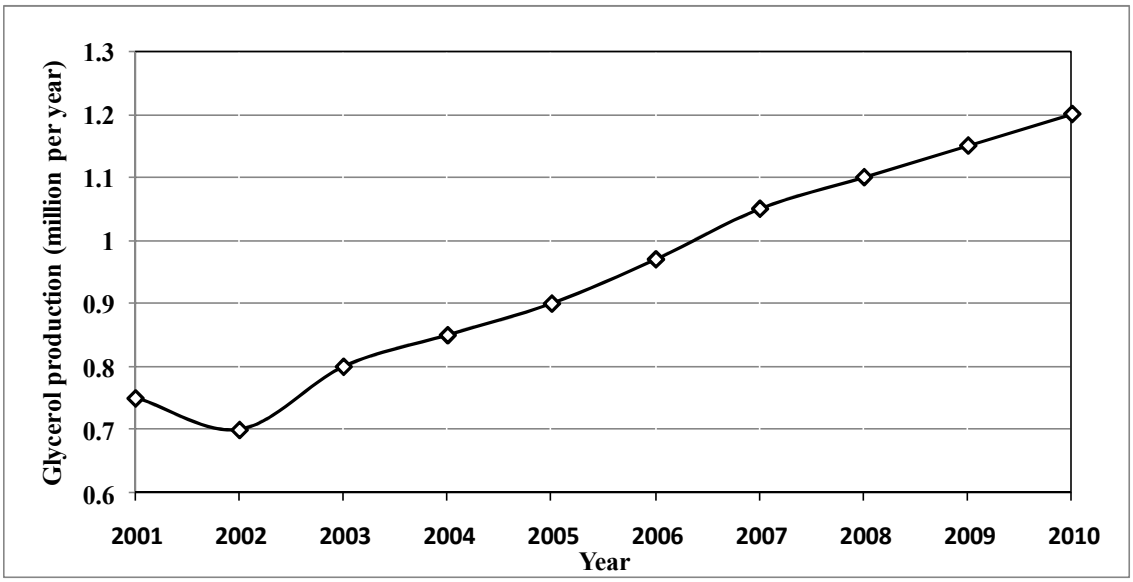


Figure 2.3. Global glycerol production estimates to 2010 (Zhou et al., 2008).

One approach to use glycerol surplus is to polymerize it. Glycerol is excellently suited for condensation polymerization. Polymerization of glycerol has been done traditionally for the production of several types of biodegradable surfactants, lubricants, cosmetics, and food additives which are available commercially (Clacens et al., 2002). However, for these applications, oligoglycerols were desirable and used. Etherification reactions can convert glycerol into polyglycerol (PG) as shown in Figure 2.4. Until now, only oligomers have been synthesized directly from glycerol as feedstocks and high molecular weight polyglycerols such as hyperbranched polyglycerol have been produced from toxic monomers, which are environmentally hazardous (e.g., glycidol) (Sunder et al., 1999). Within the last decade, hyperbranched and polyfunctional polyethers such as polyglycerol with high end-group functionality, have obtained increasing academic and industrial attention (Wilms et al., 2009). One of the most important reasons for the

increasing interest in polyglycerol chemistry is the inherent biocompatibility of the polymer and a variety of its derivatives (Kainthan et al., 2006). Polyglycerol is also known as an environmentally friendly material. Due to the presence of the ether group in the backbone of polymer chains, it is very sensitive to photochemical oxidation which causes chain scissions (Yang and Liu, 2009). Moreover, The structural similarity of polyglycerol to the well-studied poly(ethylene glycol) (PEG), makes it an interesting substitute for PEG in several biomedical and pharmaceutical applications such as drug conjugation and for the suppression of protein adsorption to blood-contacting surfaces (Wilms et al., 2010).

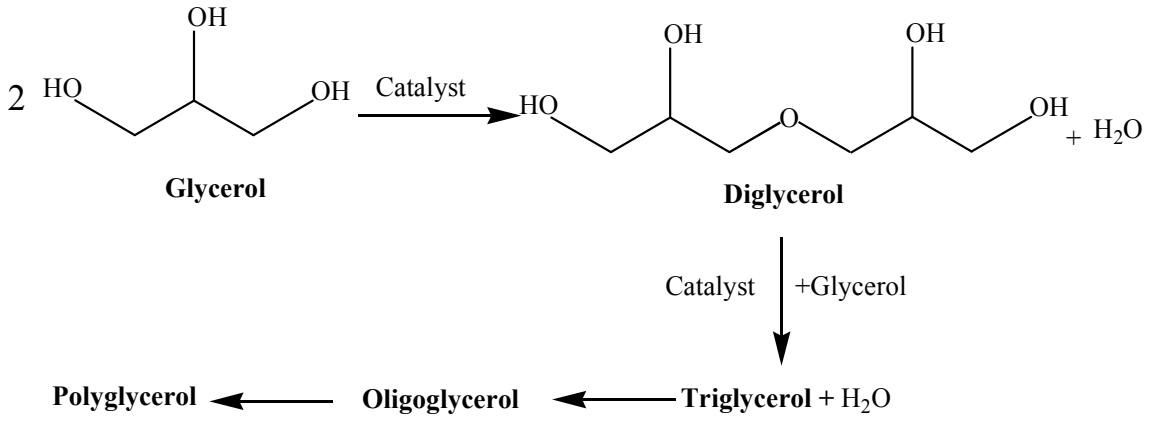


Figure 2.4. Schematic representation of the etherification of glycerol to polyglycerol

While short-chain oligoglycerols are often produced using homogeneous catalysis, the use of heterogeneously catalyzed processes has also been investigated (Behr et al., 2008). Heterogeneous catalysis has some advantages such as ease of catalyst removal and higher selectivity. However, slower reaction rates and significantly lower conversion levels have been reported for the use of heterogeneous catalysts in polyglycerol production and as a result, it is usually used for the formation of very low molecular weight oligomers (Behr et al., 2008). According to the studies on low molecular weight glycerol and glycerol

polymerization as emulsifiers, acid-catalyzed reactions have been claimed to yield oligoglycerols of higher degree of polymerization with low color values. However, production of branched- and cyclic glycerol has been also reported (Ebdo and Omori, 2008). On the other hand, it has been found that calcium containing hydroxide (e.g., calcium hydroxide) will greatly reduce the formation of cyclic oligoglycerol in the low molecular weight polymerization of glycerol (Lemoke, 2003). Moreover, it has been found that carbonates are more active than hydroxides and this has been attributed to the better solubility of carbonates in the glycerol and in the polymeric product at elevated temperatures (Marquez-Alvarez et al., 2004).

Modeling and study of non-linear step-growth polymerizations is a complicated process. Several methods have been illustrated and alternative approaches have been taken for calculation of molecular weights and gel point in a wide variety of multifunctional polymerizations. Flory and Stockmayer were the first who laid out the basic relations between the extent of reaction, number-average and weight-average molecular weights and gel point in non-linear multifunctional systems, using statistical approaches (Flory, 1941; Stockmayer, 1943). Gordon and coworkers approached the problem using the theory of stochastic branching process, also know as cascade theory (Gordon and Temple, 1970; Gordon and Judd, 1971). Although the method is fairly general and calculates the average properties directly, it is very complex and involves abstract mathematics. Macosko and Miller used an easier approach to predict the gel point and to calculate the average properties as a function of the extent of reaction (Macosko and Miller, 1976). In this method modification to analysis was performed for polymerizations involving

condensations. Moreover, several theoretical studies have been performed to model the intramolecular reactions and cyclizations (Kumar et al., 1986; Rankin et al., 2000).

To our knowledge, there is no comprehensive report on the production of polyglycerol from glycerol up to the gel point and also no comparison of polyglycerol synthesis using different soluble catalysis at elevated temperature. In this study, polymerization of glycerol using different catalysts was investigated. In addition, we illustrate the synthesis of polyglycerol with relatively high molecular weights from glycerol feedstock using a step-growth polymerization method along with the model predictions for gels points.

2.2. Experimental Section

2.2.1. Materials and Methods

All chemicals were purchased from Sigma-Aldrich Canada Ltd. (Oakville, ON) and used without further purification. Polymerizations were carried out in a 1 L glass reactor equipped with a distillation trap topped with a condenser, nitrogen inlet, catalyst feeding and sampling port, temperature probe, and a mechanical stirrer. The stirring speed (250 rpm) and the temperature were controlled by separate controllers. Polyglycerol was synthesized by glycerol etherification at 414 K in the presence of various catalysts. Since glycerol polymerization at atmospheric pressure tends to be too slow, a vacuum pump was attached to the reactor through the condenser and the condensation reaction was carried out at pressures below 200 mm Hg absolute. A Dean-stark trap topped by a condenser was attached to the reactor to continuously remove water from the reaction mixture. The reaction progress was determined by monitoring the water formation in the distillation trap. We assumed that the glycerol polymerization proceeded directly to completion; that is, the reaction did not assume some intermediate equilibrium state. Complete reaction will be favoured in this experiment by removing the volatile by-product, water.

Nitrogen was bubbled through the reaction mixture to permit the reactants to be blanketed with a stream of inert gas throughout the polymerization. In order to remove the catalyst, after the end product was cooled, an equal amount of deionised water can be added to the reaction mixture to dilute the viscous product. The diluted product can then be passed through an ion exchange column to remove the dissolved catalyst.

2.2.2. Characterization

A Waters Gel Permeation Chromatography (GPC) was utilized for the measurement of the polymer molecular weight and its distribution. The GPC system consists of a Waters 501 HPLC pump, a Waters R401 differential refractometer, and a VARIAN **PL aquagel-OH** column. Mobile phase, water, was running at 1 mL min^{-1}. The injection volume was 20 mL for each sample and all samples were dissolved in water and filtered through 0.45 mm membrane filter (Millipore) prior to injection. Polyethylene glycol (PEG) standards (VARIAN Inc.) were used to construct the calibration curve. The data were processed using Breeze software provided by Waters.

It should be noted that no experimental Mark-Houwink parameters, *K* and *a*, were available for polyglycerol at relatively high molecular weights. The Mark–Houwink equation gives a relation between the molecular weight of polymer and the intrinsic viscosity *[η]* as follows,

$$[\eta] = KM^a \tag{1}$$

In general, for most flexible polymers, the value of *a* varies from 0.5 in a poor solvent to 0.8 in a good solvent. In GPC analysis, the intrinsic viscosity of a polymer is directly related to the elution time which is associated with the hydrodynamic volume of the polymer chain (Hiemenz and Lodge, 2007). Hydrodynamic volume of branched polyglycerol with large number of functional groups is a function of degree of branching, degree of the polymerization and possible GPC column/polymer and solvent/polymer interactions. Therefore, using PEG Mark-Houwink parameters may over-represent the molecular weights due to a different hydrodynamic volume of polyglycerol and the utilized PEG standards. In order to estimate the appropriate *K* and *a*, glycerol and low molecular

weight polyglycerol samples from Solvay Chemicals with known molecular weights and narrow molecular weight distributions were used and Mark-Houwink values of a=0.75 and K= 0.0002 $cm^3 \cdot g^{-1} \cdot mol^{-1}$ were calculated. However, these values are not definitive and may be different for high molecular weight region but are adequate for purpose of comparisons.

NMR spectra were recorded on a Bruker Avance 500 MHz NMR spectrometer. The analyses were carried out in deuterated dimethylsulfoxide (with TMS) solutions at a concentration of approximately 2% w/v. This solvent was used as both the solvent and the reference.

Gel content was determined by the membrane gel partitioning method (Koehler et al., 1982). In this method, about 600 to 800 mg of 100 percent solid polymer is weighed onto a PVDF Millipore membrane disk of 5 mm porosity. The disk is heat sealed and transferred to a scintillation vial. About 20 mL of water is added to the vial and the vial is rotated on a shaker for 16 to 24 hours. The sealed disk is then removed, washed with water, and dried first by placing it on a Whatman No. 1 filter paper. The dried disk is weighed and the insoluble portion of the polymer determined by the following equation:

$$\text{percent insoluble} = \frac{(b-c)}{a} \times 100 = \%\text{gel} \qquad (2)$$

where a is the total weight of 100 percent solids polymer, b is the weight of the polymer plus membrane before water treatment and c is the polymer plus membrane remaining after water treatment.

2.3. Results and Discussion

Commonly, the step-growth polymerization of glycerol for oligomer production is carried out at temperatures above 200°C under alkaline conditions (Marquez-Alvarez et al., 2004). The condensation reaction mainly involves the terminal hydroxyl groups of glycerol molecules as they are more reactive than the 2-hydroxy groups. Some branched and even cyclic by-products are also formed (Ebdo and Omori, 2008). In this study, the reaction temperature was kept as low as possible to avoid boiling the glycerol monomer (b.p. = 290°C), degradation of the polymer product, as well as any undesired side reactions such as acrolein production (Behr et al., 2008). We carried out several polymerizations at temperatures starting from 100 ranging to 180°C. Heating the reaction mixture to a temperature below ~120°C resulted in some glycerol polymerization; however, the reaction rate was impractically slow (e.g., at 120°C, conversion of OH groups = 30 mol-% in 600 min using 1.2 wt.-% acid catalyst). Polymerizations were thus performed at 140°C under continuous sparging of nitrogen through the reaction mixture to prevent oxidation of glycerol.

2.3.1. Effect of Catalyst

Several materials have been tested as catalysts before, including acids, hydroxides, carbonates and oxides of several metals (Marquez-Alvarez et al., 2004). It has been found that the carbonates are more active than hydroxides, despite the weaker base character of the former. This has been attributed to the better solubility of carbonates in the glycerol and in the polymer product at high temperatures. (Marquez-Alvarez et al., 2004) Oxides like

MgO, CaO and ZnO are less active because of lack of solubility (Marquez-Alvarez et al., 2004).

In the current project, the polymerization of glycerol was investigated using mineral and organic acids, base and salt as catalysts at different concentrations. In Table 2.1, these reaction conditions are shown along with conversion and average molecular weight results for each run. The catalysts were chosen on the basis of their high activity at elevated temperatures and their good thermal stability. Both the high activity and good thermal stability are particularly advantageous for highly viscous bulk polymerizations at elevated temperatures.

Table 2.1. Conversion and molecular weight data for polymerization of glycerol at 140°C using different types and concentrations of catalysts.

Catalyst type	Catalyst Concentration [wt.-%]	Time [min]	Conversion of OH groups [mol-%]	M_w	M_n
$Ca(OH)_2$	1.2	400	10	113	100
$Ca(OH)_2$	2.4	360	12	124	106
$CaCO_3$	2.4	400	11	104	95
$CaCO_3$	1.2	420	7	100	93
H_2SO_4	1.2	445	40	720	160
H_2SO_4	3.6	360	71	95600	2700
H_2SO_4	4.8	240	72	111400	3600
PTSA	1.2	580	40	160	140

As seen in Table 2.1, the conversion of hydroxyl groups and the molecular weight of the polyglycerol were greatly influenced by the type of catalyst employed. The polymerization of glycerol proceeded fastest with sulphuric acid as catalyst as indicated by the highest observed conversion of monomer along with highest molecular weights. Comparison of polymerization rate using different concentrations sulphuric acid catalyst is shown in Figure 2.5. Faster conversions of hydroxyl groups were observed using higher concentrations of sulphuric acid. Results showed that concentration of catalyst had no significant effect on properties and structure of polymer samples which were taken at the same conversions of hydroxyl group.

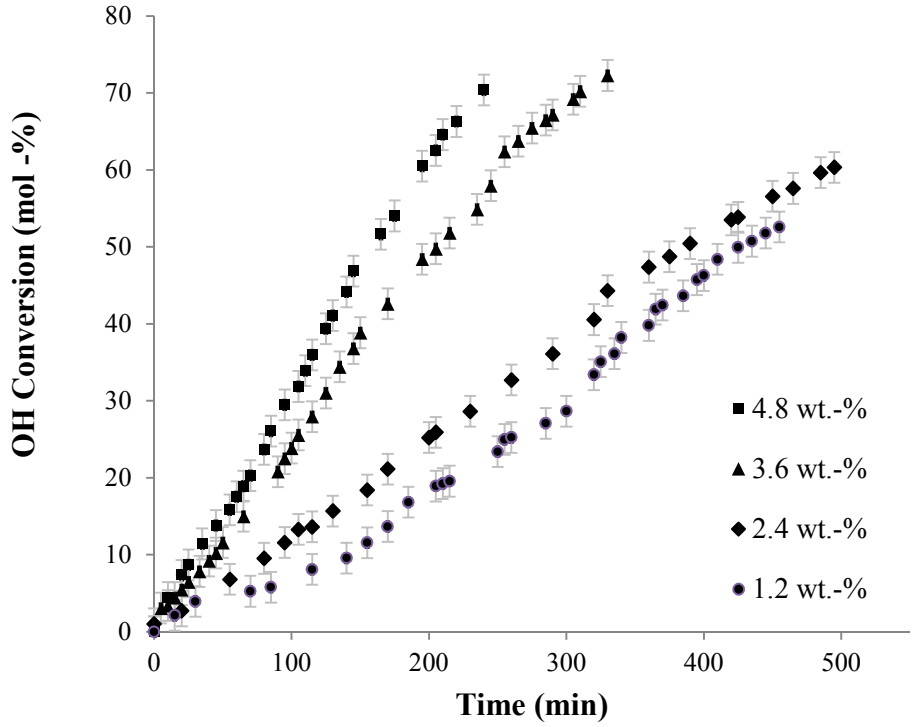


Figure 2.5. Conversion of hydroxyl groups vs. time for polymerization of glycerol using different concentrations of sulphuric acid catalyst.

The efficiency of catalysts based on the rates of polymerizations were observed to be as follows respectively, sulphuric acid> *p*-toluene sulfonic acid (PTSA) > calcium hydroxide > calcium carbonate. The difference between the polymerization rates can be explained by different catalytic reaction mechanisms which have been discussed as follows.

Acidic catalysis: sulphuric acid and PTSA are strong acids and act by protonating the primary alcohol of glycerol turning it into a good leaving group (see Figure 6). The reaction can proceed by a mixture of two path ways; Sn_1, where the H_2O leaves before the attack occurs and Sn_2, where the $^{+}H_2O$-C bond is still intact. Determining which reaction

occurs in preference would require some physical organic experiments which were beyond the scope of the project.

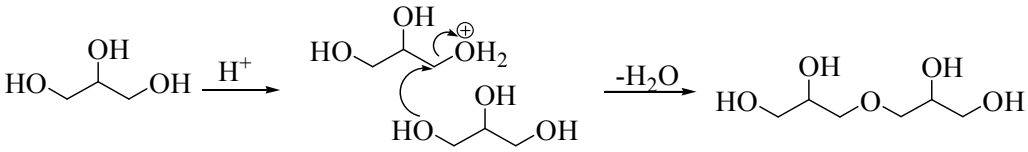


Figure 2.6. Acid-catalyzed reaction mechanism, Sn_2.

Moreover, carrying out the reaction at elevated temperatures favors the formation of glycidol, a reactive epoxide which can further react with glycerol after activation. However, the acid catalyzed opening of epoxide takes place at the most substituted carbon. The proposed mechanism is shown in Figure 2.7. Presence of tertiary carbons was confirmed by ^{13}C-NMR spectroscopy (see Figure 2.13).

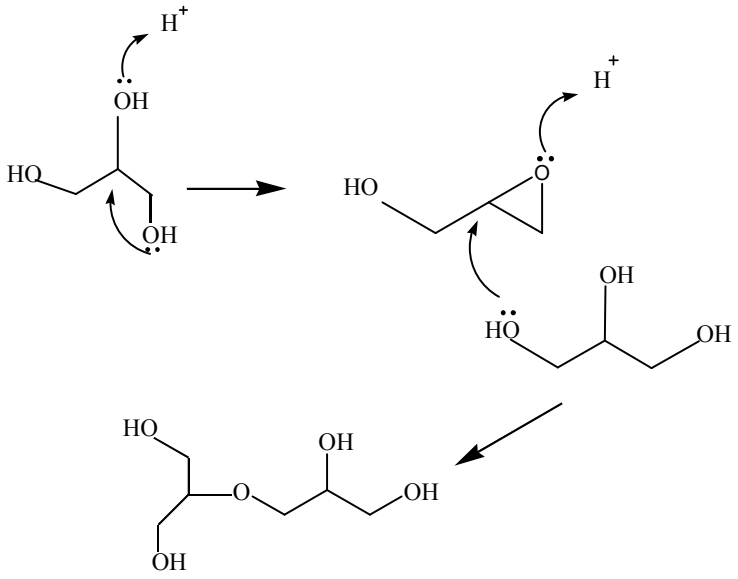


Figure 2.7. Acid-catalyzed reaction mechanism with epoxide intermediate compound.

Basic catalysis: $Ca(OH)_2$ can catalyze the reaction by first deprotonating the alcohol to form an alkoxide. In this case the alcohol was transformed into a better nucleophile. The alkoxide then can attack a second molecule of glycerol, the electrophile, on the back side of

one of the primary alcohols (see Figure 2.8.). In this reaction the glycerol is a much weaker electrophile than in the acid-catalyzed pathway. The improved nucleophile compensates for this to a certain extent, but the rate of reaction is still slower. This is a consequence of the higher energy barrier associated with the C-O bond breaking step. Therefore, in order to achieve higher rates of reaction, polymerizations should be carried out higher temperatures (Dolhaine et al., 1984).

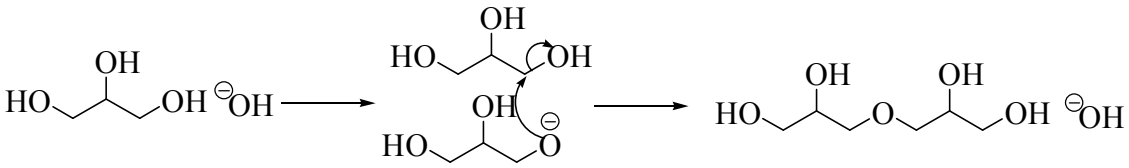
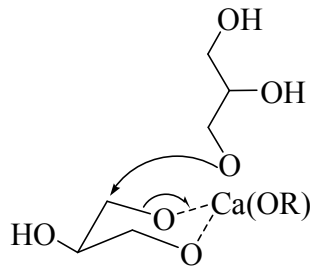


Figure 2.8. Base-catalyzed reaction mechanism.

The calcium can also participate through the reaction. It is well understood that calcium and magnesium^{2+} ions coordinate to the oxygen atoms of alcohols. This coordination, a pseudo-bond of sorts, would cause the carbon oxygen of a glycerol molecule to lengthen and thus lower the energy of the transition state complex (Bruice, 2001). Furthermore, the calcium-coordinated glycerol molecule, when drawn, forms a six-membered ring which is a very favorable bonding structure with organic molecules. Most small organic molecules form six-membered rings if they can and a lot of reaction path that ways go through six-membered rings give very useful, highly stereo selective results (see Figure 2.9).



OR= O-CH(OH)-CH_2OH or OH

Figure 2.9. Participation of calcium in polymerization reaction

Another probable pathway in this reaction is the formation of the above mentioned glycidol intermediate. The epoxide is formed by an intermolecular attack of alkoxide on the neighboring hydroxyl. This pathway can only occur at high temperatures (Dolhaine et al., 1984), nonetheless, the multiple processes lead to the same product (see Figure 2.10).

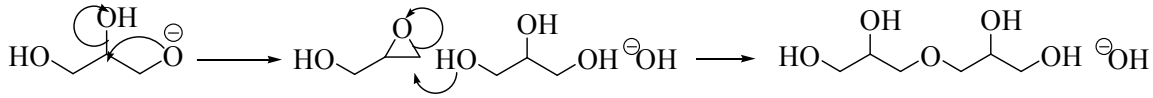


Figure 2.10. Base-catalyzed reaction mechanism with epoxide intermediate compound

For base-catalyzed formation of the epoxide, the alcohol of glycerol will favor attack to the less hinder side of the epoxide ring and the reaction will take place on the least substituted carbon leading to the product. This is contrary to reaction of epoxide in an acidic condition; when it reacts with the most substituted carbon, i.e., the secondary one. An interesting point that is worth noting is that the base-catalyzed pathway does not provide the conditions for the formation of acrolein as a by-product.

Calcium carbonate: the reaction can proceed by same mechanism as the calcium hydroxide but it would start out somewhat differently. The carbonate can deprotonate the primary hydroxyl of the glycerol. The generated bicarbonate ion from the first reaction would quickly decompose into carbon dioxide and hydroxide at elevated temperatures.

Thus, the carbonate is not recovered and the reaction is actually catalyzed by calcium hydroxide. Different steps are shown in Figure 2.11. The use of calcium carbonate as an alternative to calcium hydroxide would be only appealing at higher temperatures, when the rate of reaction is of practical interest and solubility of the catalyst is an issue. However, as mentioned before, at higher temperatures polymer decomposition will take place and only low molecular weight oligomers can be produced.

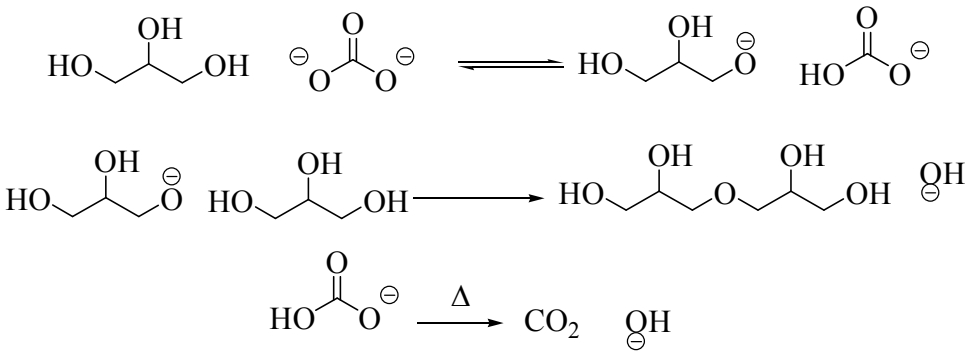


Figure 2.11. Salt-catalyzed reaction mechanism.

Polyglycerol obtained by self-condensation of glycerol in the presence of sulphuric acid is a mixture of polyols with linear, branched and cyclic structures of different degrees of polymerization with high functionality. The predominant species are polyglycerol with linear structure followed by branched structures as it was confirmed by ^{13}C-NMR (see Figure 2.13). Branched polymer can be formed according to proposed epoxide reaction mechanism or reactions with secondary hydroxyl group and cyclic products can result from intra-molecular ring closure reactions. The content of branched and cyclic structures in composition of polyglycerol became more important at higher extent of polymerization. However, these structures are all highly functional polyols and for some applications the presence of non-linear compounds are not detrimental. For example, polyglycerol mixture

was used as a starting material, where alkoxylation of mixture results in high functionality polyether polyol having ideal structure for rigid polyurethane (Ionescu and Petrovic, 2010).

2.3.2. Predicting the Point of Gelation

Polymerization of monomers like glycerol with average functionality (*f*) greater than two can lead not only to branching but also to a cross-linked polymer structure. In bulk polymerization of glycerol, cross-linking can eventually lead to gelation. At the moment when an infinite polymer network first appears, i.e., at the gel point, the polymerization system loses its fluidity which can be identified by the failure of nitrogen bubbles to rise through the reaction mixture. From a practical point of view, it is very important to predict the extent of reaction at the gel point in order to stop the polymerization prior to that point and avoid gelation for straightforward removal from the reaction vessel. Of course, there may be applications where gelation is required.

In step-growth polymerization, the reaction proceeds in a stepwise manner with the molecular weight of the polymer increasing continuously. The number-average degree of polymerization of the reaction mixture, $\overline{X}_n$, is defined as the total number of monomer molecules initially present (N_0) divided by the total number of monomer molecules present at time *t* (N):

$$\overline{X}_n = \frac{N_0}{N} \tag{3}$$

Every time a new linkage is formed, the reaction mixture will contain one less molecule. The number of linkages formed at extent of reaction, *p*, is equal to N_0-N. Since it takes two functional groups to form a linkage, moles of functional groups lost in forming N_0 - N

moles of linkages is equal to $2(N_0-N)$. Consequently, conversion, p, can be shown as (Chanda, 2000).

$$p = \frac{2(N_0 - N)}{N_0 f_{av}} \tag{4}$$

where f_{av} represents the average number of functional groups per molecule in the reaction mixture. Where

$$N = \frac{1}{2}(2N_0 - N_0 p f_{av}) \tag{5}$$

Therefore, from Equation (2):

$$\overline{X}_n = \frac{N_0}{N} = \frac{N_0}{(2N_0 - N_0 p f_{av})/2} = \frac{2}{2 - p f_{av}} \tag{6}$$

Equation (5) can be rearranged to Equation (6), which is often referred to as the *Carothers equation* (Odian, 2004).

$$p = \frac{2}{f_{av}} - \frac{2}{\overline{X}_n f_{av}} \tag{7}$$

The critical extent of reaction, p_c, will be reached at the gel point when the number-average degree of polymerization becomes infinite. Thus, at the gel point, the *Carothers equation* can be used to calculate the conversion of functional groups required to reach the onset of gelation (Flory, 1941; Odian, 2004):

$$p_c = \frac{2}{f_{av}} \tag{8}$$

Thus, for a homopolymerization of a trifunctional monomer, the calculated critical extent of reaction is 0.67.

Another approach for predicting conversion at the gel point is random the branching theory which uses statistical arguments. This method, which was first developed Flory and

Stockmayer, considers gelation to occur when the weight-average degree of polymerization, $\overline{X}_w$, reaches infinity. In some cases, the statistical method is preferred, since in a polymerization system polymer molecules larger than $\overline{X}_n$ are present and will reach the gel point earlier than those of size $\overline{X}_n$; the statistical treatment overcomes this error (Odian, 2004).

In the bulk homopolymerization of a multifunctional monomer, $\overline{X}_w$ can be predicted using the statistical approach (Odian, 2004).

$$\overline{X}_w = \frac{(1+p)}{1-p(f-1)} \tag{9}$$

the solution to Equation (8) exist only when *1> p(f-1)*. Thus, critical extent of reaction is (Odian, 2004):

$$p_c = \frac{1}{1-f} \tag{10}$$

where *f* is the functionality of the branch unit, which is equal to 3 for glycerol, yielding p_c = 0.50.

Samples collected during the polymerization were analyzed for gel content using the membrane gel partitioning method (Koehler et al., 1982). No gel was detected up to a conversion of 72 ± 3 % of the functional groups. The difference observed between the experimental p_c values and those calculated from Equations (8) and (10) can be ascribed to a failure of a number assumptions made during their theoretical derivation. Both approaches assume that the reactivity of all functional groups is the same for each monomer and is independent of the chain structure (i.e., degree of branching, degree of polymerization and presence of isomers). The difference between calculated and observed

values of p_c would decrease if the unequal reactivity of glycerol hydroxyl groups was considered and the calculations were corrected for the lower reactivity of the secondary hydroxyl group. Furthermore, they assume that there are no intramolecular reactions between functional groups on the same molecule. During polygycerol polymerization, intramolecular cyclization reactions would be expected to take place. These reactions would consume the functional groups normally expected to generate cross-links and polymerization would need to be carried out to a greater extent to reach the gel point. Some theoretical evaluations and modeling of intramolecular reactions in the step-growth polymerization of multifunctional monomers have been reported (Kumar et al., 1986). The main conclusion, confirmed by numerical computation and experiment, was that as the gel point is approached; reactant concentrations decrease and larger polymer chains are formed, which have a higher tendency to react intramolecularly. Nevertheless, the average number of rings per polymer chain remains small even at high conversions. Therefore, even after correcting for unequal reactivity of functional groups in glycerol, one can expect the actual extent of reaction to be higher than the calculated theoretical value.

Multimodal molecular weight distributions were observed for all samples. Both number-average molecular weight ($\overline{M}_n$) weight-average molecular weights ($\overline{M}_w$) showed an increase with reaction time. GPC overlay of polyglycerol samples obtained a run with 4.8 wt.-% sulphuric acid catalyst is shown in Figure 2.12. The increase in the width of the curves indicates that the polydispersity gets higher as the reaction progresses. However, calculating a single value of polydispersity is not valid for multimodal molecular weight distributions. It can also be seen from the shift to the left that larger molecules form as the reaction time increases.

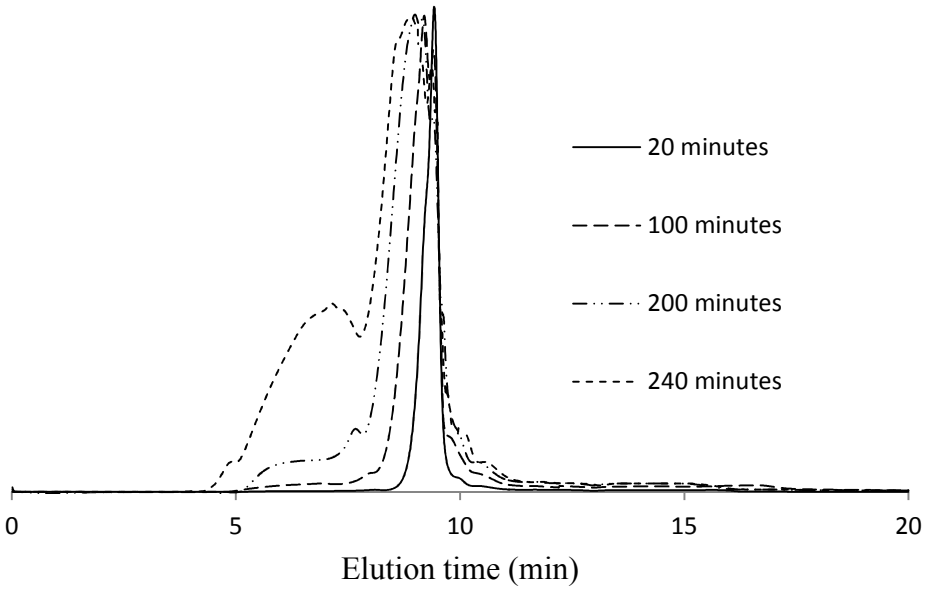


Figure 2.12. GPC elution curves of polyglycerol produced with 4.8 wt.-% of sulphuric acid catalyst.

In order to calculate the average molecular weight for each sample, multimodal peaks were deconvoluted using the GPC software. We should mention that GPC peak deconvolution is prone to errors. However, the general findings presented in this article will be unaffected by small errors in the numerical values reported for the average molecular weights. Average molecular weights can be predicted using the equations that were proposed by Macosko and coworkers (Macosko and Miller, 1976).

In general, their results are in good agreement with those obtained from Flory's and Stockmayer's statistical approach and they both use similar aforementioned simplifying assumptions (Flory, 1941; Stockmayer, 1943). Moreover, they both predict the same critical gel point. However, in derivations of average molecular weights, Flory's statistical approach do not account for condensation product weight and unreacted ends. In

the case of polymerizations involving condensation products $\overline{M}_w$ and $\overline{M}_n$ can be calculated using following equations proposed by Macosko and Miller (Macosko and Miller, 1976).

$$\overline{M}_w = \frac{(1+p)}{1-p(f-1)}(M_0 - \frac{fM_C}{2}) + \frac{(1-p)fM_C/2}{1-p(f-1)}\left[1 - p\frac{(M_0 - M_C}{M_0 - fM_C/2}\right] \qquad (11)$$

$$\overline{M}_n = (M_0 - \frac{fp}{2}M_C)/(1-fp/2) \qquad (12)$$

where M_0 is the molecular weight of the monomer and M_c is the molecular weight of the condensate. In polyetherification of glycerol M_0 = 92 and M_c = 18. In order to predict the average molecular weights by this model, appropriate *f* value should be determined. Since the experimental gel point and high molecular weights were observed at 74 ±3 mol-% conversion, it is obvious that average functionality is lower than 3 for this system. To calculate the functionality for our system, weight-average molecular weights, which were obtained by GPC, were used. Functionality was then calculated using Equation (10) for high molecular weight samples that were collected before the gel point and it was approximately 2.4 for all high molecular weight samples (see Table 2.2). Interestingly, using the statistical method and the estimated *f* value of 2.4, the gel point can be predicted to be at about 71 mol-% and functionality of conversion, which is fairly close to observed experimental critical conversion. Equations (11) and (12) can effectively predict $\overline{M}_w$ and $\overline{M}_n$ at low conversions but they fail to predict the average molecular weights in the middle of the reaction. This model also predicts much smaller $\overline{M}_n$ for high molecular samples which were collected close to gel point. These discrepancies between the model prediction and experimental data can be due to simplifying assumptions that were mentioned. As can be seen from the GPC elution curves (see Figure 2.12) polymer chains are growing during

the reaction and long chains are not only formed close to the gel point as the model foresees. Nonetheless, chain growth is very fast close to the critical point and it is very important to stop the reaction at the right time.

Table 2.2. Experimental results and model predictions from reactions using sulphuric acid catalyst

Reactions using sulphuric acid catalyst			
Catalyst concentration (wt.-%)	**1.2**	**3.6**	**4.8**
Conversion of OH groups (mol-%)	73	71	72
$\overline{M}_w$	58000	95600	111400
$\overline{M}_n$	2000	2700	3600
Predicted functionality (*f*)	2.37	2.40	2.39
Predicted critical conversion (mol-%)	72.9	71.4	71.9
Observed critical conversion (mol-%)	77	76	74
Predicted $\overline{M}_n$	560	520	550

^{1}H-NMR and ^{13}C-NMR spectra of a polyglycerol sample are shown in Figures 2.13 and 2.14. A detailed characterization of linear, branched and cyclic oligomers of glycerol (Cassel et al., 2001) and also hyperbranched polyglycerol (Sunder et al., 1999) by NMR spectroscopy has been described before. The chemical shifts of the carbon and hydrogen atoms were established based on the oligoglycerol standards (Cassel et al., 2001) and previous assignments for hyperbranched polyglycerol. Using information obtained from spectra, all signals can be assigned as they are shown in Figures 2.13 and 2.14. In ^{1}H-NMR spectrum, the methylene and methane protons of polyether appeared as a broad resonance pattern between 3.2 and 4.1 ppm and hydroxyl proton signals were observed around 5 ppm. In ^{13}C-NMR spectrum, signals in different regions can be assigned as follows, -CH_2OH carbons of end groups in 60 to 64 ppm, -CHOH- carbons in 68 to 73 ppm, -CH_2-O- carbons at 72 to 75 ppm and –CH-O carbons at 79 to 82 ppm region. Presence of branched structure is supported by NMR spectra as observed by repeating ^{1}C resonances in 79 to 82 ppm region. Detailed ^{13}C-NMR spectroscopic studies using well resolved peak regions were reported for polyglycerol using inverse gated (IG) and DEPT NMR spectra (Sunder et al., 1999) (Tokar et al., 1994). Additionally, an appearance of some weak signals was observed in the 0.75 to 2.5 ppm region in ^{1}H-NMR and in the 15 to 20 ppm region in ^{13}C-NMR spectra. In order to investigate the connectivity of different regions, heteronuclear two-dimensional correlation spectroscopy (COSY) experiments were performed, in which the two axes correspond to different isotopes (i.e., ^{13}C and ^{1}H). Assignment of the carbon nuclei with protons attached was made and the results indicate that above mentioned weak proton signals correlates to weak up field carbon signals. These signals were observed in samples from higher conversions of monomer and can be assigned to CH_2 and CH_3 groups

in different cyclic products which proposed for oligoglycerol before (Dolhaine et al., 1984).

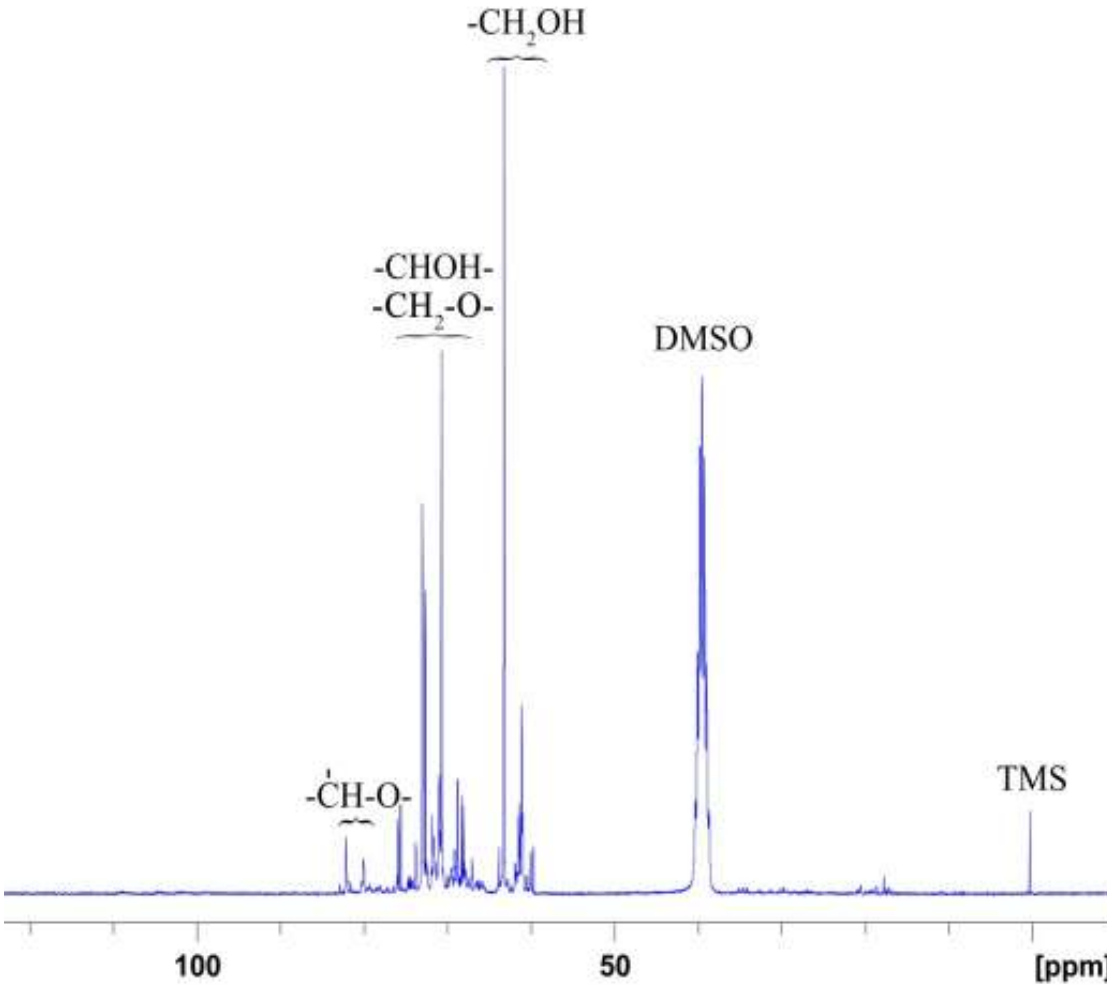


Figure 2.13. ^{13}C-NMR spectrum (DMSO-d_6) of polyglycerol

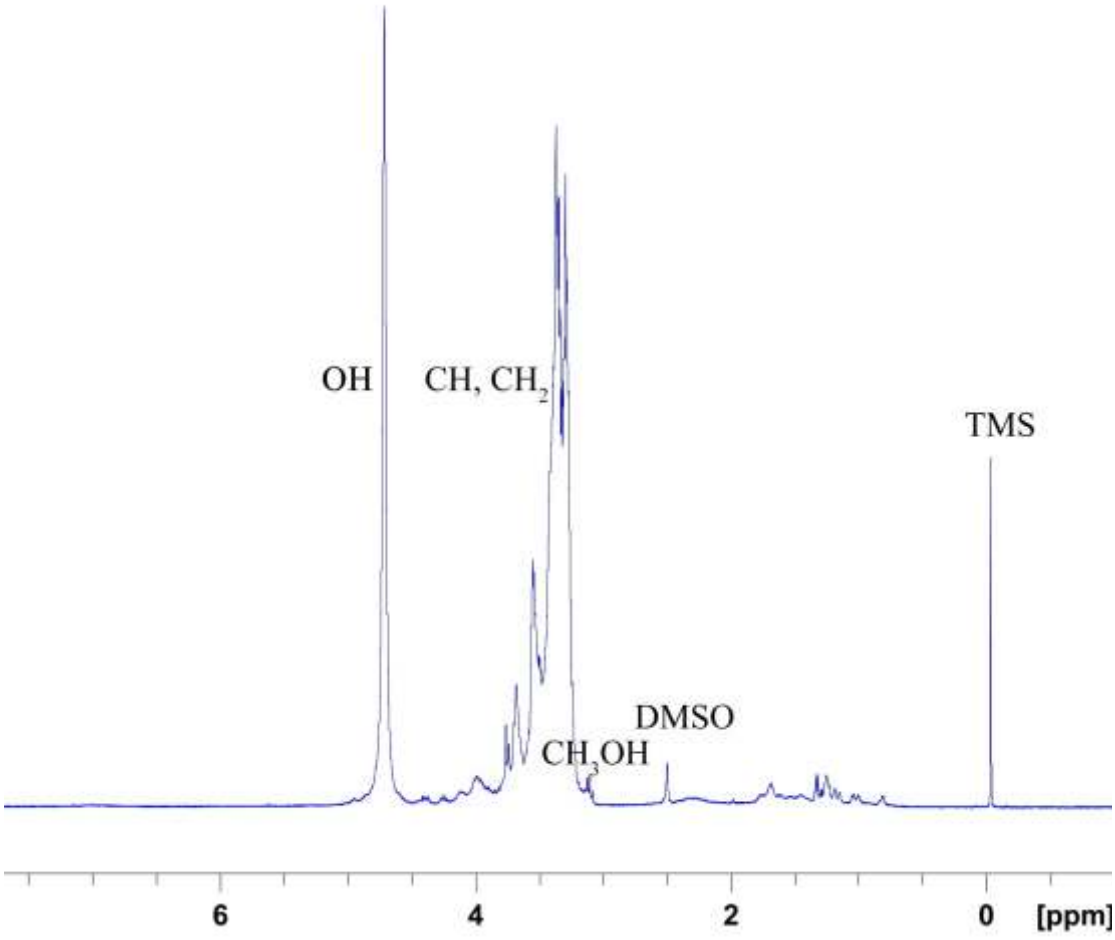


Figure 2.14. ^{13}H-NMR spectrum (DMSO-d_6) of polyglycerol

2.4. Conclusion

Using a step-growth polymerization at 140^{o}C, polyglycerol of relatively high molecular weights were produced. Comparison was made between polymerization of glycerol using different catalysts. The most effective catalyst for this process at the tested conditions was found to be sulphuric acid. Theoretical models were used to predict the gel point and functionality of monomer. Using the calculated functionality, critical extent of reaction can be predicted which is fairly close to the observed experimental data. NMR spectroscopic study was performed to characterize the polymer structure. It was found that branched polymer has been formed and concentration of catalyst has no obvious impact on the structure.

The biodegradability of polyglycerol and its synthesis from renewable sources make it an ideal polymer in the support of sustainable industrial practices. This polymer, with good biocompatibility properties and large number of derivatizable hydroxyl groups, may find applications in pharmaceutical and biomedical industry. In addition, its attractive properties and low raw material cost allow it to compete with polyethylene glycol or in new applications as a "green" polymer. These applications will be discussed in forthcoming publications.

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Chapter 3. Synthesis of novel stimuli-responsive polyglycerol-based hydrogels

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Synthesis of novel stimuli-responsive polyglycerol-based hydrogels

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Abstract

Temperature and pH-responsive polyglycerol-based hydrogels were successfully synthesized and characterized. An increase in polyglycerol molecular weight was achieved by cross-linking polyglycerol using multifunctional electrophilic epoxide-containing compounds. The chemical structure of polyglycerol-based hydrogels was determined by FTIR spectroscopy. The temperature-dependent swelling behavior of the hydrogels was studied at 293, 310, 333 and 353K and a negative temperature-sensitive system was observed. The hydrogels exhibited pH sensitivity at pH 4, 7 and 10. The hydrophilicity and biocompatibility of these hydrogels make them suitable for pharmaceutical, biomedical and biotechnological applications. They could potentially serve as a replacement for fossil-based poly(ethylene glycol) and poly(vinyl alcohol) hydrogels.

3.1. Introduction

Increases in petroleum prices combined with the limited oil resources and environmental issues associated with greenhouse gas emissions have resulted in enormous interest in the development of bio-based materials such as "green monomers". This has also ushered in the rapid growth of biodiesel production. Biodiesel, an environmentally friendly alternative to petro-diesel, is produced via transesterification of lipid feedstocks with an alcohol. A major by-product of this process is glycerol. Due to substantial worldwide growth in the biodiesel industry, a large surplus of glycerol now exists at record-low price of $US 0.05/lb (Johnson and Taconi, 2007; Pagliaro et al., 2007). Biodiesel production has increased from 959 to 15,760 million litres from 2001 to 2009 (Global Biodiesel Market Analysis and Forecasts to 2020, 2010) and considering the ongoing worldwide push towards biodiesel production, it is expected to reach 45,291 million litres per year by 2020 (Global Biodiesel Market Analysis and Forecasts to 2020, 2010). Finding new applications for excess glycerol derived from the growing biodiesel industry is a challenge to scientists since 10 wt.-% of total product of this process is crude glycerol (Kenar, 2007).

One approarch to make use of this surplus is the sustainable polymerization of glycerol (Salehpour and Dubé, 2011). Polyglycerol, with both pendant hydroxyl groups and ether linkages, has excellent hydrophilic characteristics. Additionally, it is biocompatible, biodegradable (Pagliaro and Rossi, 2010) and can be produced from abundant renewable sources. Moreover, it has available sites for cross-linking that make it a good starting material for the synthesis of relatively non-toxic hydrogels.

Hydrogels can be described as hydrophilic polymer networks which swell when placed in water or other biological fluids and absorb from 10-20 % up to a thousand times of their dry weight (Hoffman, 2002). Pioneering research on hydrogels was performed in

the 1960s by Wichterle and Lim on cross-linked hydroxyethyl methacrylate (HEMA) hydrogels (Wichterle and Lim, 1960). Ever since, hydrogels have been of great interest to materials scientists and have been used in a variety of applications (Peppas et al., 2004; Traitel et al., 2008).

From a structural point of view, the solid portion of a hydrogel is a three-dimensional hydrophilic polymer network with the interstitial space filled with fluid. The cross-linked polymer network can be formed by chemical or physical bonds, for instance, by covalent bonding, ionic bonding, hydrogen bonding, van der Waals interactions between chains and physical entanglements as well as forces that arise due to crystallization and electrostatic interactions (Li, 2009).

Hydrogels can be synthesized to be neutral, anionic, or cationic networks. The chemical characteristics of the polymer backbone and pendant fixed groups can affect the swelling behavior of hydrogels to a great extent. The volume transition of hydrogels is governed by a balance between the thermodynamic polymer-solvent Gibbs free energy of mixing, retractive elastic forces and by hydrophilic, hydrophobic and electrostatic interactions between polymer chains and the solvent (Bashir and Bhatia, 2006). From the thermodynamic point of view, when the solvent inside the network is in thermodynamic equilibrium with the solvent outside, an equilibrium state is reached. This can be characterized in terms of the osmotic pressure, the free energy and the chemical potential (Li, 2009).

These three-dimensional networks are able to imbibe large amounts of water or biological fluids, thus they resemble biological tissues. Their hydrophilic properties and the potential to be biocompatible are the main reasons that they have gained importance in

biomedical and pharmaceutical applications (Peppas et al., 2000; Hoffman, 2002; Deligkaris et al., 2010).

Many studies were carried out to control the swelling behaviour of hydrogels through external environmental conditions. These resulted in syntheses of "smart" or so called stimuli-responsive hydrogels (Li, 2009). Smart hydrogels can undergo continuous or discrete volume phase transitions or volume transformations in response to external environmental stimuli such as temperature, pH of solution, solvent composition, ionic strength, electric field and pressure (Li, 2009). In most cases, depending on the application, a stimuli-responsive hydrogel is designed to demonstrate reversible volume change. Among all stimuli-responsive hydrogels, temperature-sensitive and pH-sensitive hydrogels have gained significant attention. These two stimuli are the most relevant factors in biological systems including the human body (Lee et al., 1996). For example, a pH-sensitive hydrogel as a drug carrier can maximize the drug release in the neutral environment of the intestine, and minimize its release in the acidic condition of the stomach (Yang and Liu, 2009).

Polyglycerol has good potential as a starting material for hydrogel formation and is a polymer which has received significant attention for applications in the biomedical and pharmaceutical fields. This increasing interest in polyglycerol-based products is mainly due to the inherent biocompatibility of the polymer and a variety of its derivatives (Wilms et al., 2010). Polyglycerol consists of a polyether backbone with pendant hydroxyl groups. Due to the presence of the ether group in the backbone of the polymer chains, polyglycerol is very sensitive to photochemical oxidation, which results in chain scission and degradation (Yang and Liu, 2009).

The structural characteristics of the polyglycerol backbone resemble the well-studied poly(ethylene glycol) (PEG). PEG is widely employed in various biomedical applications such as in hydrogels for controlled release of biomolecules and scaffolds for regenerative medicine (Lin and Anseth, 2009). In addition, the high functionality and abundant number of hydroxyl groups of polyglycerol is comparable to another well-known polymer, poly(vinyl alcohol) (PVOH). PVOH is widely used in the biomedical and pharmaceutical industry as it is biocompatible, non-toxic, and exhibits minimal cell adhesion and protein absorption. Moreover, it has long-term temperature and pH stability (Byun et al., 2008). PVOH is also a versatile hydrophilic polymer as a precursor to hydrogels and can be modified by simple chemical reactions. PVOH gels have been used in a variety of applications such as in drug delivery, contact lenses and the lining for artificial hearts (Hassan and Peppas, 2000). It is noteworthy that both PVOH and PEG are polymers which are traditionally produced from fossil-based monomers.

In view of the above-mentioned structural similarities to PEG and PVOH, polyglycerol has the potential to be a great candidate for use as a hydrogel. There are reports on the production of polyglycerol-based hydrogels but these employed glycidol as opposed to glycerol as the starting material (Oudshoorn et al., 2006; Yang and Liu, 2009; Steinhilber et al., 2010a; Steinhilber et al.; Steinhilber et al., 2011). Where glycidol was found to be a carcinogenic monomer (Melnick, 2002). Therefore, one anticipated advantage of using polyglycerol from glycerol over PEG, PVOH or existing polyglycerol hydrogels is that polyglycerol is synthesized from a renewable and non-toxic source, glycerol.

Toxicity problems can be associated with hydrogels mostly due to the release of un-reacted compounds during application. Many of the commonly used cross-linking agents or components associated with chemical cross-linking such as chain extenders, initiators, un-reacted monomers and chain transfer agents, can be highly toxic. If these residues are not removed, they may leach out and show obvious undesirable effects. For example, diisocyanate compounds, which are widely used in the synthesis of PEG-based hydrogels (Graham and Zulfiqar, 1989; Rakovsky et al., 2009) are carcinogens and can cause immediate and serious toxic effect by inhalation (Pauluhn, 2008). Another example is glutaraldehyde, a common cross-linking agent for PVOH hydrogel when the gel is used as a carrier in drug delivery. Un-reacted glutaraldehyde could degrade the active agent being released or alter the biological activity of the agent (Hassan and Peppas, 2000). Regarding the reported polyglycerol hydrogels from glycidol, release of any un-reacted glycidol monomer can have serious carcinogenic effects on the biological system. Besides all the environmental and toxic effects mentioned, time and energy-consuming extraction procedures are not desirable, particularly at the industrial scale.

In order to decrease the toxicity risks, other methods of chemical cross-linking such as beam or γ-radiation or physical cross-linking can be used, which do not leave behind elutable agents (Hassan and Peppas, 2000). However, the same end-product properties may not be achieved using these different cross-linking methods.

Another approach to reduce health risks and extensive purification processes is to use non-toxic reagents such as benign neutral monomers such as glycerol. According to the US Department of Energy (DOE) 2010 “top 10” report, glycerol is one of the top chemical opportunities from biorefinery carbohydrates (Bozell and Petersen, 2010) and it is very

important to the oleochemical industry to find new applications for this abundant feedstock. Therefore, polyglycerol may be a cost-effective replacement for current fossil-based hydrogels such as PEG and PVOH. To our knowledge, there is no comprehensive report on the production of polyglycerol-based hydrogels from glycerol. The step-growth polymerization of glycerol to relatively high molecular weight polyglycerol was reported in our recent research paper (Salehpour and Dubé, 2011). In this study, a new application of glycerol in the area of hydrogels is described and more sustainable synthesis of polyglycerol-based hydrogels using less toxic cross-linkers is investigated.

3.2. Experimental

3.2.1. Materials

Glycerol (≥99%), trimethylolpropane triglycidyl ether, glycerol diglycidyl ether, poly(ethylene glycol) diglycidyl ether (number-average molecular weight (M_n)=526) and sodium hydroxide (>98%) were purchased from Sigma-Aldrich Canada Ltd. (Oakville, Canada) and were used without further purification.

3.2.2. Polyglycerol synthesis

Polymerization of glycerol was carried out using a method developed previously (Salehpour and Dubé, 2011). The polymerizations were performed in a 1 [L] glass reactor equipped with a nitrogen inlet, distillation trap topped with a condenser, sampling port, temperature probe and a mechanical stirrer. In order to form polyglycerol, glycerol etherification was carried out at 414 [K] in the presence of 4.8 wt.-% sulphuric acid catalyst. Nitrogen was bubbled through the reaction mixture to blanket the reactants with a stream of inert gas throughout the reaction. A vacuum pump was attached to the reactor

through the condenser and the polymerization was carried out at pressures below 26 [kPa]. Water was continuously removed from the reaction mixture by a Dean-stark trap which was attached to the condenser. The reaction conversion was calculated by monitoring the water formation in a Dean-stark trap.

3.2.3. Characterizations

A Waters Gel Permeation Chromatograph (GPC) was utilized for the measurement of the polyglycerol molecular weight and its distribution. More details are found elsewhere (Salehpour and Dubé, 2011). Attenuated total reflectance Fourier transforms infrared (ATR-FTIR) spectroscopy was performed using the REACTIR™ 1000 (Mettler Toledo) to characterize the presence of specific chemical groups in the hydrogel and to confirm the proposed cross-linking mechanism. Spectra were obtained within the range of 4000 to 400 cm^{-1}. Hydroxyl value determinations were completed according to the ASTM E 1899-08, standard test method.

3.2.4. Gel content measurement

A membrane gel partitioning method was used to measure the gel content of the samples (Koehler et al., 1982). The cross-linker efficiency was evaluated with the gel content experiment. In this method, about 600 to 800 [mg] of polymer samples were weighed on 5 [μm] porosity PVDF Millipore membrane disks. The heat-sealed disks were then transferred to scintillation vials, 20 [mL] of water were added to each vial and they were placed in a shaker for 16 to 24 h. The disks were then removed, washed with water, and dried by placing them on a Whatman No.1 filter paper. The dried disks were weighed and the gel content of the samples was determined using:

$$\%Gel = \frac{(b-c)}{a} \times 100 \qquad (1)$$

where *a* is the total weight of solid polymer, *b* is the weight of the polymer plus membrane before water treatment and *c* is the polymer plus membrane remaining after water treatment. Henceforth, the insoluble part of the polymer is referred to as gel and the fraction of the polymer soluble in water is referred to as sol fraction.

3.2.5. Polyglycerol-based hydrogel synthesis

A 2 M NaOH solution was added to an equal volume of polyglycerol. The solution was gently heated to 353 [K] and stirred until all the polyglycerol was dissolved. The cross-linker was then added to the reaction mixture drop-wise and the solution was heated to 393 [K]. The mixture was stirred vigorously until it became slightly gelatinous. The mixture was then poured into preheated Teflon moulds and then left to cure at 393 [K] for 6 h. Various molar compositions of cross-linkers were used to obtain different degrees of cross-linking. After curing in the oven, blocks of polymers were removed from the moulds then were immersed into distilled de-ionized water for 2 days at room temperature and the water was changed every 12 h to remove any impurities. The samples were dried at 323 [K] under vacuum, until constant weights were achieved, and were then stored in a dry atmosphere.

3.2.6. Measurement of equilibrium swelling ratio of hydrogels

Known weights of dry hydrogel samples were swollen in individual buffer solutions with pH between 4 and 10 to study the effect of pH on swelling behavior. Precise buffer solutions were prepared by dissolving the contents of pH buffer capsules (Cole-Parmer, Canada) in 100 [mL] distilled water. Buffer solutions were accurate to ±0.02 pH. The pH 4

capsules contained potassium biphthalate, the pH 7 capsules contained potassium phosphate monobasic and sodium phosphate dibasic and the ph 10 capsules contained carbonate and sodium bicarbonate. In addition, hydrogel samples were immersed into pH 7 buffer solutions at 293, 310, 333 and 353 [K] to investigate the effect of temperature on swelling behavior. At certain time intervals, the samples were removed from their solutions, blotted dry with absorbent paper to remove excess water and weighed immediately. The average values between three measurements were taken for each sample.

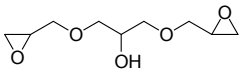
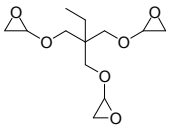
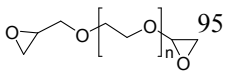
3.3. Results and Discussion

Cross-linking of polyglycerol was studied using different epoxide-containing compounds. A suitable cross-linker had to be hydrophilic, reactive towards alcohol functional groups and preferably biodegradable. Molecules containing nucleophiles including hydroxyls can be cross-linked using bi- or tri-functional cross-linkers containing epoxide groups on both ends. However, epoxide groups are only reactive at high alkaline pH values (i.e., in a range of pH 11-12) and are quite stable at neutral pH in aqueous environments (Hermanson, 1996). Cross-linking of polymers such as collagen has been previously reported using short-chain and long-chain polymeric epoxide-containing compounds (Murayama et al., 1988). In the current study, we have investigated the reactions of polyglycerol with short-chain bi-functional, tri-functional and long-chain PEG-based epoxide-containing cross-linkers (M_n = 526). As shown in Table 3.1, all cross-linkers contain ether bonds in their backbones which induce hydrophilicity and more importantly, degradability. In addition, ether bonds in both polyglycerol chains and cross-linkers are sensitive to photochemical oxidation which causes chain scission (Yang and Liu, 2009). Therefore, the product is expected to be an environmentally-friendly hydrogel. However,

only reaction with the long-chain cross-linker (PEGDE) resulted in hydrogel formation and reactions with trimethylolpropane triglycidyl ether and glycerol diglycidyl ether resulted mostly in extension of the polymer molecular weight. This can be due to the broad molecular weight distribution of the polyglycerol (Salehpour and Dubé, 2011) and the presence of small molecules (e.g., trimers, tetramers, etc.). Thus, treating the polymer with short chain cross-linkers have mostly resulted in increasing the number-average molecular weight of polyglycerol by connecting the polymer chains, which was originally M_n = 3600 g/mol. Chain extensions were confirmed by performing Gel Permeation Chromatography (GPC) analysis of the sol fraction (see Table 3.1). This is interesting because synthesis of high molecular weight polyglycerol from glycerol is quite challenging (Salehpour and Dubé, 2011)and one can use these cross-linkers to obtain higher molecular weight polyglycerols by a simple post-polymerization reaction.

Gel content results for systems with reagents having a hydroxyl to epoxide group molar ratio of 2 are presented in Table 3.1. Functionality of polyglycerol or moles of hydroxyl groups was calculated using known ASTM standard method for hydroxyl number determination. It should be mentioned that, although the method is designed for determination of hydroxyl groups attached to primary and secondary carbons of high solid polyols, the functionality of polyglycerol may be slightly under-represented. This can be due to steric limitations of the polymer chains and the high density of the hydroxyl groups, which can lead to incomplete conversion in the titration step of the procedure (Sunder et al., 2000). Nevertheless, hydroxyl number data for polyglycerol provides a reasonable estimate of functionality which is adequate for the purpose of comparison between cross-linkers.

Table 3.1. Studied cross-linkers for the preparation of polyglycerol-based hydrogels.

Cross-linker	Cross-linker structure	Gel content (wt.%)	Number-average molecular weight of sol fraction (M_n)	Weight-average molecular weight of sol fraction (M_w)
Glycerol Diglycidyl Ether (GDE)		3	35100	46000
Trimethylolpropane Triglycidyl Ether		6	19700	36000
Poly Ethylene Glycol Diglycidyl Ether (PEGDE)		95	400	1500

In order to form polyglycerol hydrogel, NaOH was used as a catalyst. The reaction proceeded first through deprotonation of the alcohol to form an alkoxide. In this step, polyglycerol was transformed into a better nucleophile. The alkoxide can then react with one end of the PEGDE cross-linker, the electrophile. The cross-linking reaction is likely to take place on the less hindered side of the epoxide ring and on the least substituted carbon

leading to formation of an ether linkage. The proposed reaction mechanism using PEGDE as a cross-linker is shown in Figure 3.1.

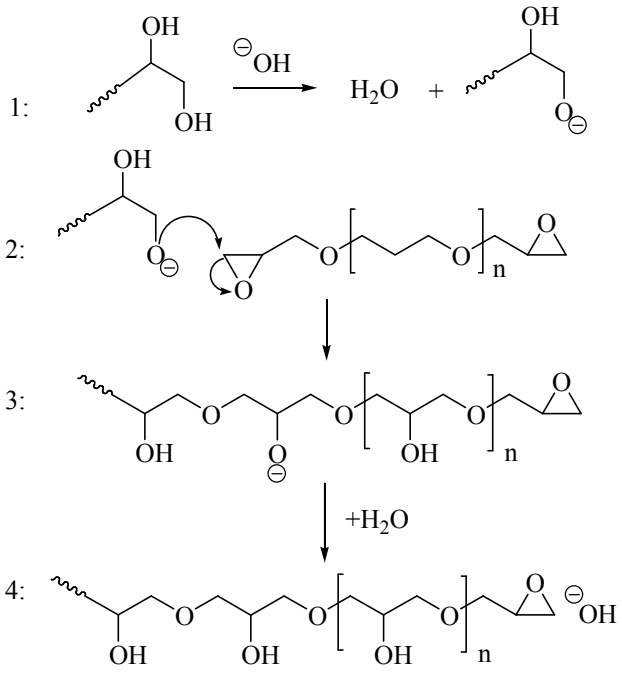


Figure 3.1: Mechanism of cross-linking reaction between hydroxyl group of polyglycerol and epoxide group of PEGDE

In order to confirm the presence of specific chemical groups in the polyglycerol hydrogel, ATR-FTIR spectroscopy was used. The proposed cross-linking mechanism of the polyglycerol using PEGDE and the effectiveness of the developed procedure were confirmed (see Figure 3.1).

The FTIR spectra of polyglycerol, PEGDE and polyglycerol hydrogel are shown in Figure 3.2. The main peaks associated with the polyglycerol structure and polyglycerol hydrogel are evident in spectrum a. Absorptions at 1000 to 1150 [cm^{-1}] are related to stretching of the ether groups, broad alkyl stretching bands were observed from 2750 to

3000 [cm^{-1}] and hydroxyl group bands were observed from 3000 to 3650 [cm^{-1}]. Regarding PEGDE, as shown in the FTIR spectrum b in Figure 3.2, the absorptions associated with the epoxide functional groups of PEDGE were observed at 853 [cm^{-1}] and at 760.4 [cm^{-1}] due to the three-member ring deformation. However, only weak absorptions were observed for these bands in the FTIR spectrum of the polyglycerol hydrogel. This, along with the broadening of the absorption peaks for the ether groups in the hydrogel indicate that the terminal epoxide groups in PEGDE were converted to ether groups by reaction with the hydroxyl groups of the polyglycerol.

One interesting aspect observed for the polyglycerol hydrogel is that although some of the alcohol groups in the polyglycerol reacted to form ether linkages, as seen in the loss of intensity of the peak at 3350 [cm^{-1}], there was still a considerable amount of hydrogen bonding occurring in the gel, whereas the FTIR spectrum c of the hydrogel shows a large broad adsorption at 3350 [cm^{-1}], which is indicative of hydrogen bonded alcohol groups. The typical non-bonded –OH stretching bands for free alcohol would have a sharper peak at ν= 3600-3650 [cm^{-1}] while hydrogel bonded bands appear at ν = 3200-3650 [cm^{-1}] (Mansur et al., 2004). This confirms the expected intramolecular and intermolecular hydrogen bonds in polyglycerol and polyglycerol hydrogel.

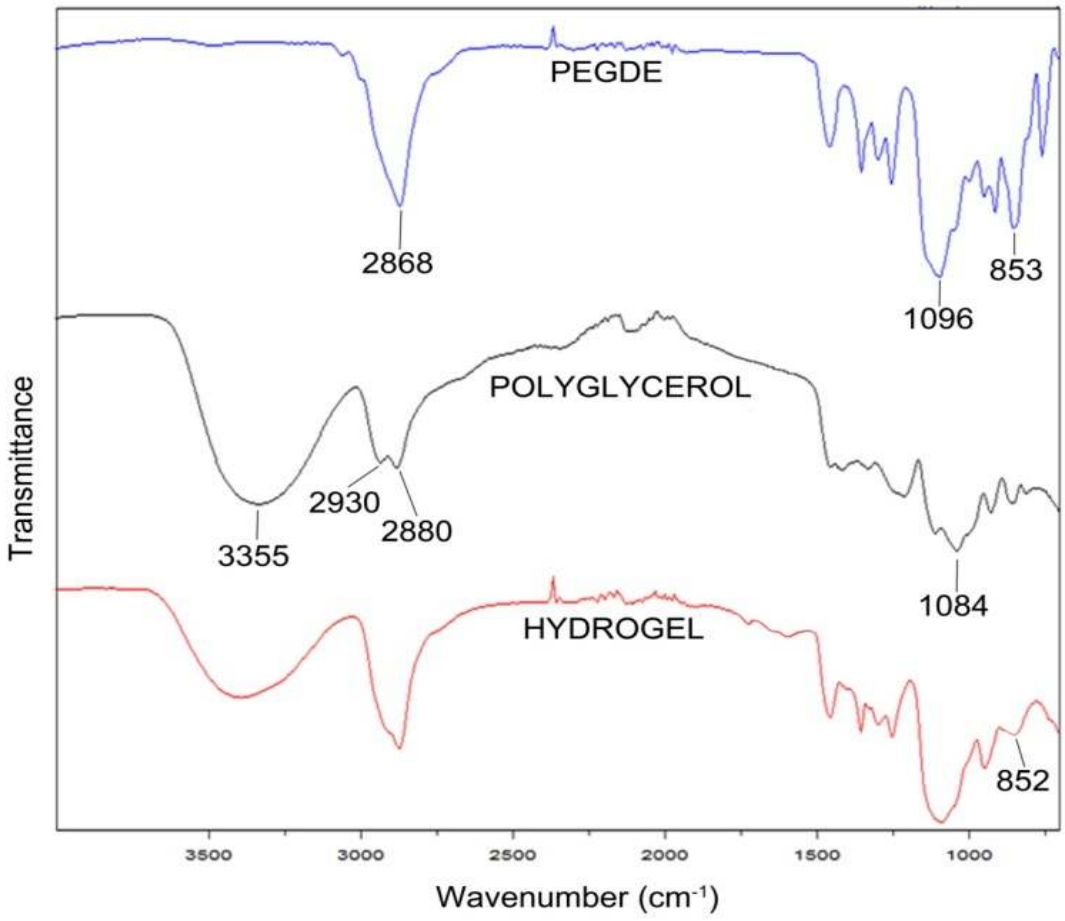


Figure 3.2: FTIR spectra of polyglycerol, PEGDE and polyglycerol hydrogel

The swelling behavior of a hydrogel is greatly affected by the structure and properties of its constituent monomer and cross-linker. Therefore, incorporating a hydrophilic, flexible, long-chain cross-linker like PEGDE should increase the volume transition of polyglycerol hydrogel. Another important factor is the degree of cross-linking, which controls the swelling ratio of the hydrogel and its mechanical properties (Li, 2009). In this study, the swelling behavior of two polyglycerol hydrogels was investigated. These hydrogels were differentiated on the basis of their hydroxyl to epoxide group molar ratios.

Thus, we henceforth refer to these hydrogels as “PG 2” and “PG 4”, with molar ratios of 2 and 4, respectively. The swelling ratio was calculated using the following equation:

$$swelling\ ratio = \frac{W_s - W_d}{W_d} \times 100 \tag{2}$$

where W_d is the weight of dry hydrogel and W_s is the weight of swollen hydrogel. The relation between swelling ratio and time at different temperatures for “PG 2” and “PG 4” is shown in Figure. 3.3 and 3.4. All equilibrium swelling ratios remained unchanged for at least 2 days, indicating a fairly stable hydrogel network for all samples.

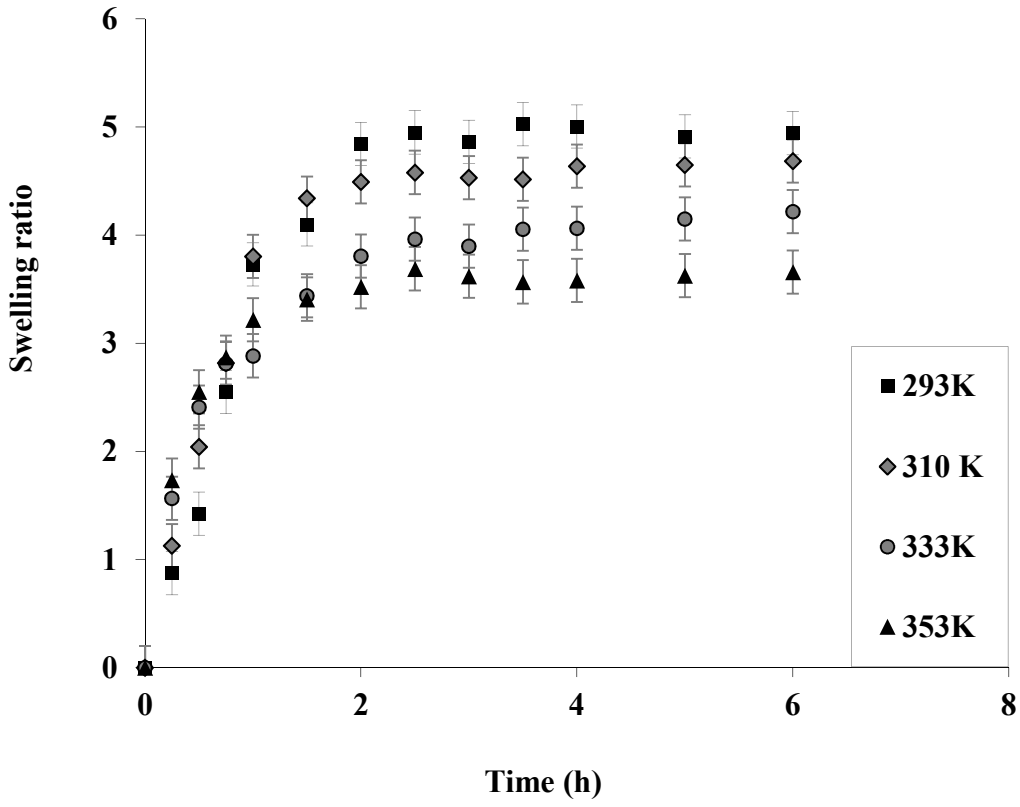


Figure 3.3: Temperature-dependent swelling behavior of PG 2 at pH 7

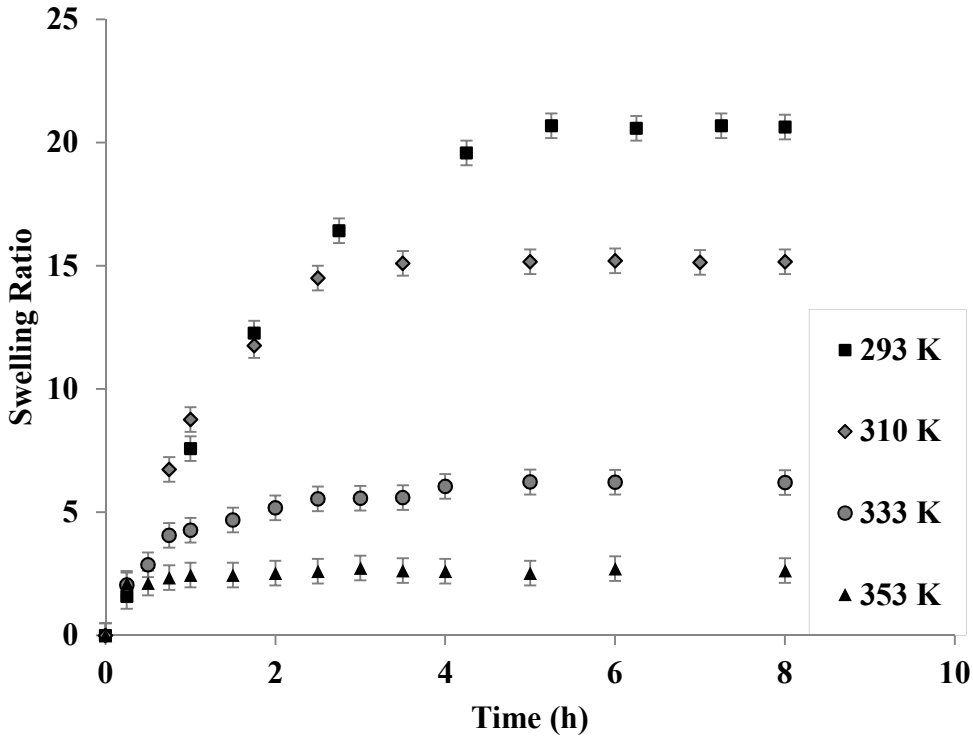


Figure 3.4: Temperature-dependent swelling behavior of PG 4 at pH 7

Comparing the swelling curves in Figures 3.3 and 3.4 at 293 [K], it was observed that water up-take of the polyglycerol hydrogel was significantly reduced by increasing the cross-linking density. Increasing the degree of cross-linking changed the swelling equilibrium by altering the composition and structure of the network (Graham and Zulfiqar, 1989). As the cross-linking density increased, the molecular weight between cross-links decreased, which resulted in a less elastic and denser hydrogel network. In addition, the weight percentage of polyglycerol in the hydrogel decreased as a result of increasing the cross-linking density. Thus, the functionality or number of hydroxyl groups of the network was reduced; therefore, the equilibrium swelling ratio was decreased.

The swelling of "PG 2" and "PG 4" in water at different temperatures was investigated to observe any temperature-dependent swelling behavior. As shown in Figures 3.3 and 3.4, equilibrium swelling ratios decreased with increasing temperature for both hydrogels, suggesting negative temperature sensitive systems. This behavior is similar to that of PEG-based (Graham et al., 1982) and PVOH-based hydrogels (Lee et al., 1996). As temperature increases, hydrogen bonding between the polymer chains and water molecules becomes less favorable thermodynamically compared to intermolecular interactions in hydrogel and water–water interactions. This results in lower equilibrium swelling ratios at higher temperatures (Bikram and West, 2008). Another interesting trend was exhibited in the swelling curves prior to equilibrium being reached. For both hydrogels, an increase in the rate of swelling with temperature was observed (see Figures 3.3 and 3.4). This was expected as this dynamic part of the swelling curve corresponds to the diffusion of water into the hydrogel where diffusion rates are expected to increase with temperature.

The pH-dependent swelling behavior of the hydrogels was investigated at 298 K. The swelling behavior in buffer solutions of pH 4, 7 and 10 are shown in Figures 3.5 and 3.6. Unlike PVOH and PEG hydrogels, polyglycerol hydrogels showed pH-sensitive swelling behavior. The swelling of PG 2 was less pH-sensitive compared to PG 4. This is attributable to higher concentrations of PEG-based cross-linker. The change in pH value of the solution can affect the internal osmotic pressure of the hydrogel. In addition, the presence of hydroxyl, ether and unreacted epoxide end groups, as well as unreacted anions (see Figure 3.1, step 3), can also affect the swelling behaviour. Observed higher equilibrium swelling ratios at lower pH might be attributed to the attraction of H^+ ions to the above mentioned groups, resulting in higher solution uptake. On the other hand, OH^-

ions are less attracted to these sites and their diffusion is less favorable. Moreover, protonation of the polymer chains in the hydrogel network might induce the ionic repulsion between the chains along with the dissociation of hydrogen bonds, which could result in the increase of free volume in the network and thus increase the swelling ratio.

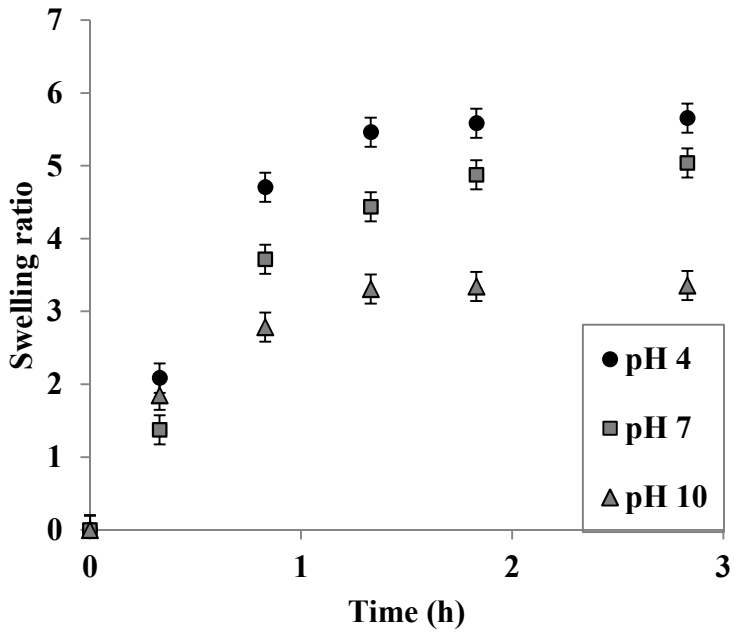


Figure 3.5: pH-dependent swelling behavior of PG 2 at 298K

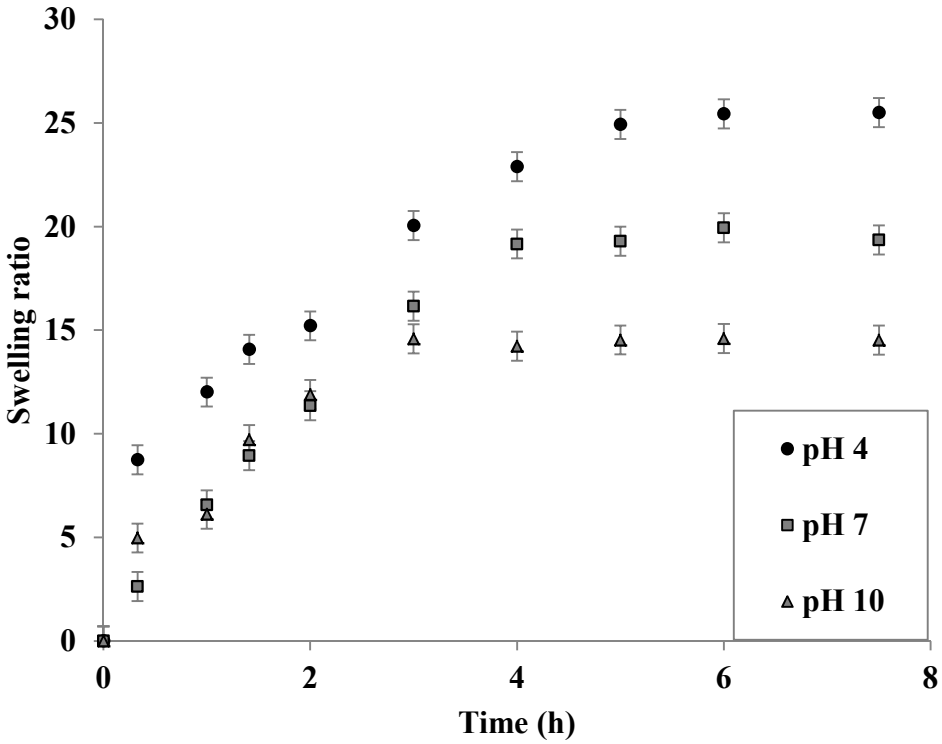


Figure 3.6: pH-dependent swelling behavior of PG 4 at 298 K

3.4. Conclusion

Novel pH/temperature-sensitive hydrogels were successfully synthesized by chemical cross-linking of polyglycerol. The chemical structure of the hydrogels and a proposed mechanism were confirmed by ATR-FTIR spectroscopy. Swelling behavior of the hydrogels can be modulated by changing the degree of cross-linking. Swelling behavior was studied at different temperatures and pH. The polyglycerol hydrogels exhibited a negative temperature sensitive behavior, which was attributed to the dissociation of hydrogen bonds. pH-dependent behavior was observed for the hydrogels, which was related to polymer-polymer and polymer-solvent interactions.

The polyglycerol employed in the synthesis of the hydrogels was produced from an abundant, renewable and non-toxic monomer, glycerol. Therefore, polyglycerol-based

hydrogels can be considered more environmentally-friendly than common fossil-based hydrogels such as PEG and PVOH. These pH/temperature-responsive polyglycerol-based hydrogels are strong candidates for biomedical applications such as drug delivery. Moreover, these hydrogels exhibited relatively high swelling ratios, which makes them suitable moisture absorbents and solvent dryers for a broad range of applications.

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Conflict of Interest: The authors have declared no conflict of interest.

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Chapter 4. Application properties of novel polyglycerol-based hydrogels

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Application Properties of Stimuli-Responsive Polyglycerol Hydrogels

Somaieh Salehpour, Marc A. Dubé

Abstract

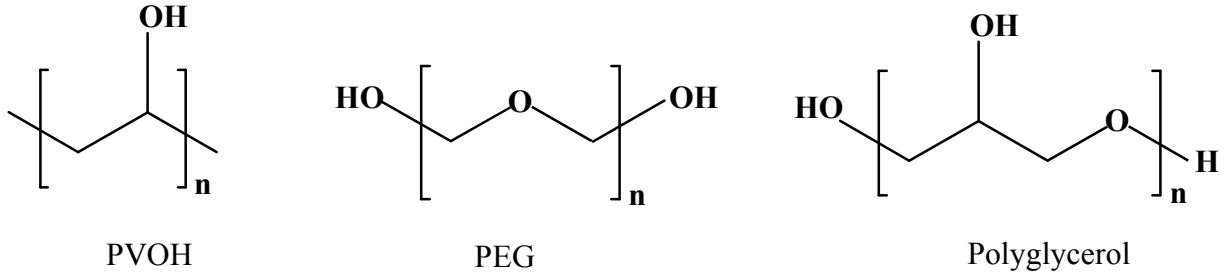
Transient state swelling behavior and swelling kinetics of novel stimuli-responsive polyglycerol hydrogels were studied at 293, 310 and 333 K. Depending on temperature, Fickian or anomalous diffusion behavior was observed. Mechanical properties of the hydrogels in the swollen and dry states were investigated and the average molecular weight between cross-links was calculated. To assess the potential for biodegradation of hydrogels, initial swelling behavior in phosphate buffered saline (PBS) solution and mass loss profiles as a function of degradation time were investigated over a period of 30 days. All swelling behavior, mechanical properties and degradations were clearly affected by the degree of cross-linking. The hydrophilicity and degradability of polyglycerol hydrogels make them suitable for pharmaceutical, biomedical and biotechnological applications. They could potentially serve as a substitute for common fossil-based hydrogels such as poly(ethylene glycol) and poly(vinyl alcohol) hydrogels.

4.1. Introduction

In recent years, environmental concerns combined with limited oil resources have led to growing interest in the use of renewable feedstocks derived from vegetable and animal sources. Development of bio-based materials such as bio-fuels, green monomers and biodegradable polymers has gained great importance. In addition, the sustainability of raw materials has become increasingly important to the chemical industry. This has also resulted in the rapid growth of biodiesel production, a greener alternative fuel to petro-diesel. Biodiesel production has increased from 959 to 15,760 million litres from 2001 to 2009 based on a recent market analysis (Global biodiesel market almost doubles every year between 2001 and 2009, 2010). Considering government policies to encourage the use of renewable energies, biodiesel production is expected to reach 45,291 million litres by 2020 (Global Biodiesel Market Analysis and Forecasts to 2020, 2010). In general, biodiesel fuel is manufactured via transesterification of lipid feedstocks with an alcohol (Cao et al., 2008). This process substantially produces glycerol, where it is normally generated at the rate of 1 mol of glycerol for every 3 mol of biodiesel synthesized. Since the turn of the millennium, glycerol production has nearly doubled mainly due to biodiesel production (Zhou et al., 2008) and a large surplus of glycerol now exists at a record-low price of $US 0.05/lb (Pagliaro and Rossi, 2010). According to the United States Department of Energy (US-DOE) 2010 “top 10” report, glycerol is one of the top chemical opportunities from biorefinery carbohydrates (Bozell and Petersen, 2010). Such low cost glycerol could become an important building block for the production of a variety of bio-based chemicals. In addition, utilization of excess glycerol derived from the growing biodiesel industry is important to oleochemical industries (Pagliaro et al., 2007). A considerable amount of

research has focused on using glycerol as a platform chemical to replace mainstream petroleum-derived chemicals (Behr et al., 2008a; Behr et al., 2008b).

One approach to making use of this surplus is the polymerization of glycerol (Martin and Richter; Salehpour and Dubé). Glycerol as a bio-based monomer is excellently suited for sustainable condensation polymerization. Traditionally, glycerol and oligoglycerols are used in different industries such as food, pharmaceutical, cosmetic, soap, toothpastes, fuel, paint, etc.; mostly as biodegradable additives (Pagliaro and Rossi, 2010). Polyglycerol is a biocompatible, biodegradable polymer (Daniel et al.), which consists of an inert polyether backbone with functional hydroxyl side groups that make it very suitable for the design of hydrogels. The structural characteristics of polyglycerol is comparable to poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVOH) as shown in Figure. 1.



PVOH PEG Polyglycerol

Figure.4.1: PVOH, PEG and polyglycerol chemical structure.

PEG and PVOH are biodegradable petroleum-derived polymers widely used in various biomedical and pharmaceutical applications. These biocompatible, non-toxic polymers exhibit minimal cell adhesion and protein absorption and show long-term temperature and pH stability (Byun et al., 2008). Considering their hydrophilic properties, they are also commonly employed as precursors to hydrogels for various applications such as in drug delivery, scaffolds for regenerative medicine and contact lenses (Hassan and Peppas, 2000).

In the last decade, polyglycerol with its inherent biocompatibility and variety of derivatives has received significant attention for applications in the biomedical and pharmaceutical fields (Wilms et al., 2010). Cost-effective polyglycerol with high functionality and an abundant number of hydroxyl groups is a viable candidate for hydrogel production. In addition, it has the potential to replace PEG and PVOH-based hydrogels which are produced from non-renewable sources.

Hydrogels are hydrophilic, three-dimensional polymer networks which swell when placed in water or other biological fluids and absorb from 10% up to a thousand times their dry weight (Hoffman, 2002). Since hydrogels have a soft consistency and are able to imbibe large amounts of water or biological fluids, to a great extent, they resemble natural living tissues (Peppas et al., 2000). Due to their hydrophilic properties and biocompatibility, hydrogels have been of great interest to material scientists, and in particular in the biomedical and pharmaceutical fields (Peppas et al., 2000; Hoffman, 2002; Deligkaris et al., 2010). In fact, they were the first biomaterials designed to be used in the human body (Barbucci, 2009).

Hydrogels can be synthesized by forming chemical or physical bonds between polymer chains, for instance, by covalent bonding, ionic bonding, hydrogen bonding, van der Waals interactions between chains and physical entanglements (Li, 2009). The chemical characteristics of the polymer backbone and the number and nature of side groups can greatly affect the swelling behavior of hydrogels. The cross-linked polymer network can be formed to be neutral, ionic networks (Li, 2009).

An interesting class of hydrogels are “smart” or so-called stimuli-responsive hydrogels (Li, 2009). The swelling behavior of these hydrogels is controlled by external

environmental conditions. They can undergo continuous or discrete volume transformations in response to external environmental stimuli such as solution pH, temperature, solvent composition and electric field (Li, 2009). The balance between the thermodynamic polymer-solvent energy of mixing, elastic forces, hydrophilic, hydrophobic and electrostatic interactions between polymer chains and the solvent governs the volume transition of hydrogels. Temperature and pH-sensitive hydrogels are the most popular networks, mainly in biomedical applications because these two stimuli are the most relevant factors in biological systems including the human body (Lee et al., 1996).

The kinetic process of swelling of stimuli-responsive hydrogels is complex and usually involves three consecutive steps: 1- the diffusion of solvent molecules into the polymer network; 2- the relaxation of the hydrated polymer chains; and 3- the expansion of the polymer network (Li, 2009). Many factors such as degree of cross-linking, solvent composition, hydrogen bonding, etc., can affect the swelling kinetics of the hydrogels. In order to design a hydrogel for particular applications (e.g., drug delivery), it is important to study the mass transport characteristics of these polymer networks. Measurement of the mechanical properties of the hydrogels is also important for evaluating the suitability of the product for application. For example, a drug delivery device designed to protect a sensitive agent, must be able to sustain its integrity in order to protect the drug until it is released (Peppas et al., 2000).

Besides assessing the swelling kinetics and the mechanical properties, it is essential for many applications that the degradability and degradation rate of the hydrogels be evaluated (Barbucci, 2009). Hydrogels could be non-biodegradable or biodegradable. Biodegradable hydrogels are usually fabricated from biodegradable polymer precursors and

do not show permanent foreign-body response inside the human body (Pang and Chu, 2010). For example, tuning the degradation profiles of hydrogels, which are attractive candidates for scaffolds in tissue engineering systems, is an important design parameter (Martens et al., 2003). Whereas, the degradation rate of the scaffold should mirror the rate of new tissue development or be adequate for the controlled release of molecules (Barbucci, 2009). Therefore, it is important to study the rate by which the hydrogel is degraded.

In previous studies, we reported on the step-growth polymerization of glycerol to relatively high molecular weight polyglycerol (Salehpour and Dubé, 2011b) and the production of novel temperature and pH-responsive hydrogels from polyglycerol (Salehpour and Dubé, 2011a). Other studies on the synthesis of polyglycerol-based hydrogels employed glycidol, a carcinogenic monomer (Melnick, 2002), as opposed to glycerol as the starting material (Oudshoorn et al., 2006; Yang and Liu, 2009; Steinhilber et al., 2010a; Steinhilber et al., 2010b; Steinhilber et al., 2011). To our knowledge, there is no comprehensive report on the swelling kinetics, mechanical properties and degradability of polyglycerol-based hydrogels from glycerol. In this work, the swelling behavior of hydrogels in the transient state, the compressive mechanical properties of polyglycerol hydrogels, and the degradability of hydrogels are reported.

4.2. Experimental

4.2.1. Materials

Glycerol (≥99%), phosphate buffered saline (PBS) solution, poly(ethylene glycol) diglycidyl ether (PEGDE, number-average molecular weight (M_n) = 526), sulphuric acid

and sodium hydroxide (>98%) were all purchased from Sigma-Aldrich Canada Ltd. (Oakville, Canada) and were used without further purification.

4.2.2. Polyglycerol and hydrogel synthesis

Polymerization of glycerol was carried out using a method developed previously (Salehpour and Dubé, 2011b). The polymerizations were performed in a 1 L glass reactor equipped with a nitrogen inlet, distillation trap topped with a condenser, sampling port, temperature probe and a mechanical stirrer. In order to synthesize polyglycerol, glycerol etherification was carried out at 414 K in the presence of 4.8 wt.-% sulphuric acid catalyst. Nitrogen was bubbled through the reaction mixture to blanket the reactants with a stream of inert gas throughout the reaction. A vacuum pump was attached to the reactor through the condenser and the polymerization was carried out at pressures below 26 kPa. Water was continuously removed from the reaction mixture by a Dean-Stark trap which was attached to the condenser. The reaction conversion was calculated by monitoring the water formation in the Dean-Stark trap. In order to avoid gelation, the reaction was stopped at 72 mol-% conversion of hydroxyl groups. Partially branched polyglycerol which was obtained from the reaction had a M_n of 3600 g/mol and a weight-average molecular weight (M_w) of 111,400 g/mol.

In order to form polyglycerol hydrogel, a 2 M NaOH solution was added to the polyglycerol. The mass ratio of NaOH to polyglycerol was kept constant: 1 g of NaOH/18 g of polyglycerol for all reactions. The solution was gently heated to 353 K and stirred until all the polyglycerol was dissolved. A PEGDE cross-linker was then added to the reaction mixture drop wise and the solution was heated to 393 K. The mixture was stirred vigorously until it became slightly gelatinous. It was then poured into preheated circular

Teflon molds (diameter = 8 cm) and allowed to cure at 393 K for 6 h. In order to obtain different degrees of cross-linking, two polyglycerol to cross-linker molar ratios were used. The final hydrogel products were differentiated on the basis of polyglycerol hydroxyl to PEGDE epoxide group molar ratios; henceforth, referred to as "PG2" and "PG4", with molar ratios of 2 and 4, respectively. After curing, the polymer blocks were removed from

the molds and were immersed in distilled de-ionized water for 2 days at room temperature; the water was changed every 12 h to remove any impurities. Attenuated total reflectance Fourier transforms infrared (ATR-FTIR) spectroscopy of the final wash solution did not reveal any significant amounts of residual epoxide. The samples were dried at 323 K under vacuum until constant weights were achieved, and were then stored in a dry atmosphere.

4.2.3. Characterizations

A Waters Gel Permeation Chromatograph (GPC) was utilized for the measurement of the polyglycerol molecular weight and its distribution. More details are found elsewhere (Salehpour and Dubé, 2011b). As reported in our previous study (Salehpour and Dubé, 2011a), ATR-FTIR spectroscopy was performed using a REACTIR™ 1000 (Mettler Toledo) to characterize the presence of specific chemical groups in the hydrogel and to confirm the proposed cross-linking mechanism. The value of Young's modulus, E, in both the dry and swollen states were obtained from uniaxial compression measurements using an Instron ElectroPuls mechanical tester, at a cross-head rate of 0.1 mm/s. Tests were performed on cylindrical samples of 30 mm diameter, with thicknesses of 10-30 mm.

Young's modulus was calculated as the slope of the initial linear portion of the stress-strain curve.

4.2.4. Swelling and mass loss measurement

Known weights of dry hydrogel samples were immersed in pH 7 buffer solutions at 293, 310, 333 and 353 K to investigate the effect of temperature on swelling behavior. Precise buffer solutions were prepared by dissolving the contents of pH 7 buffer capsules (Cole-Parmer, Canada) in 100 mL distilled water. Buffer solutions were accurate to ±0.02 pH. The buffer capsules contained potassium phosphate monobasic and sodium phosphate dibasic. At certain time intervals, the samples were removed from their solutions, blotted dry with absorbent paper to remove excess water and weighed immediately. The average values between three measurements were taken for each sample.

To study the degradability of the hydrogel, dry circular hydrogel samples (diameter = 3 cm, thickness = 2 mm) were weighed (m_d), immersed in PBS solution (0.01 M, pH=7.4), and incubated at 37ºC. The PBS medium was replaced daily with an equal volume of fresh solution. At different time intervals, the samples were removed from solution, rinsed thoroughly with PBS, freeze-dried, and re-weighed (m_f). The percentage weight loss was calculated using equation 1,

$$\%mass\ \ loss = \frac{(m_d - m_f)}{m_d} \times 100\% \quad (1)$$

The reported weight loss value at each time interval was an average of measurements for three samples.

4.3. Results and discussion

4.3.1. Temperature-dependent swelling and diffusion

The preparation method and the equilibrium swelling behavior of two polyglycerol-based hydrogels "PG2" and "PG4" at several pH and temperatures, were previously reported (Salehpour and Dubé, 2011b; Salehpour and Dubé, 2011a), where "PG2" and "PG4" hydrogels had hydroxyl to epoxide group molar ratios of 2 and 4, respectively. Besides evaluating swelling properties at equilibrium, it is important to obtain a thorough understanding of the transient swelling behavior in order to tailor the properties of the hydrogel for particular applications. In this study, the swelling behavior of hydrogels in the transient state was investigated at different temperatures. The swelling ratio was calculated using the following equation:

$$swelling\ \ ratio = \frac{W_s - W_d}{W_d} \tag{2}$$

where W_d is the weight of dry hydrogel and W_s is the weight of swollen hydrogel. At 293, 310 and 333 K, final equilibrium swelling ratios of 5, 4.6 and 4.2 for "PG2" hydrogel and 20.6, 15.1 and 6.2 for "PG4" hydrogel were calculated, respectively. Comparing the equilibrium swelling ratios of these two polyglycerol hydrogels at all temperatures, it was observed that water up-take of the hydrogel was significantly increased by decreasing the cross-link density. The composition and the structure of the network were changed by decreasing the degree of cross-linking. A more elastic and looser hydrogel network with higher molecular weight between cross-links was achieved by decreasing the cross-linking density; this allowed a higher absorption of water molecules. In addition, the functionality or number of hydroxyl groups of the network and consequently, the hydrophilicity of the

hydrogel, was increased by incorporating a higher fraction of polyglycerol and lower fraction of PEGDE cross-linker; the latter has no hydroxyl group. As a result, the equilibrium swelling ratio was increased. For both hydrogels, equilibrium swelling ratios decreased with increasing temperature, suggesting negative temperature sensitive systems. Similar behavior has been observed for PEG-based (Graham et al., 1982) and PVOH-based hydrogels (Lee et al., 1996). The decrease in swelling ratios at higher temperatures can be due to a lower chemical affinity of the hydrogel with water and the dissociation of hydrogen bonding between the polymer chains and water molecules (Bikram and West, 2008).

Although lower equilibrium swelling ratios were obtained at higher temperatures for both hydrogels, an increase in the initial swelling rate with temperature was observed in the transient state, where the transient or dynamic part of the swelling process corresponds to the initial gradual upward part of the swelling curve prior to equilibrium (see Figures. 4.2 and 4.3). This trend was also observed for polymers with similar chain structures such as PEG (Graham and Zulfiqar, 1989) and was expected as the diffusion rate of water molecules into the hydrogel network increases with temperature. The temperature dependence of swelling in a transient state is also predicted in most mathematical models [20].

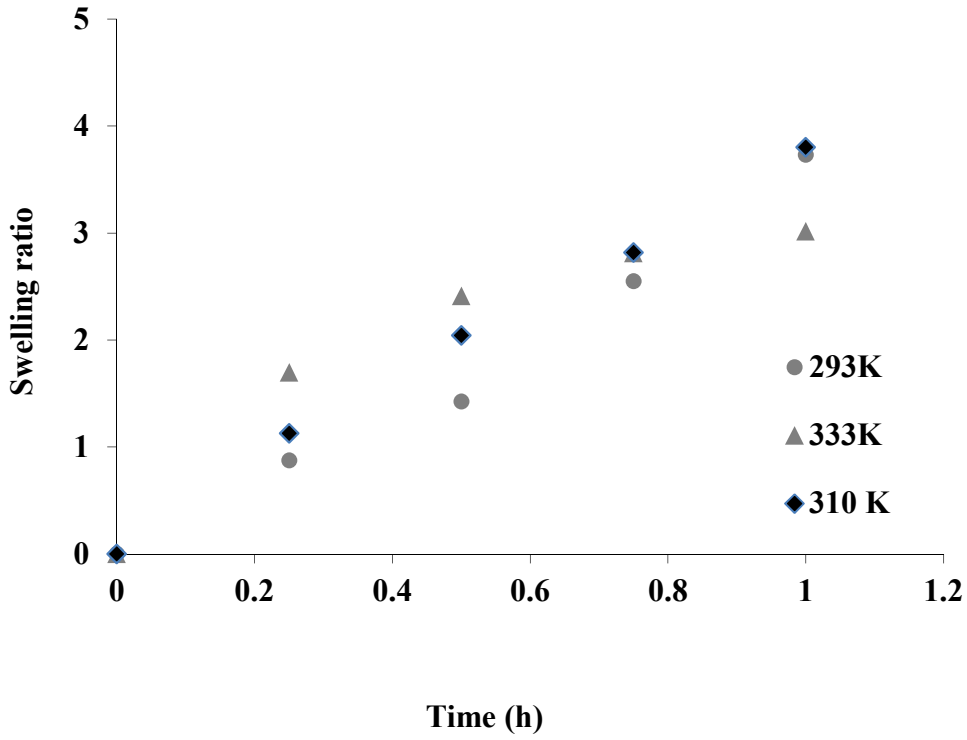


Figure. 4.2. Initial water-uptake of "PG4" hydrogels at 293, 310 and 333 K

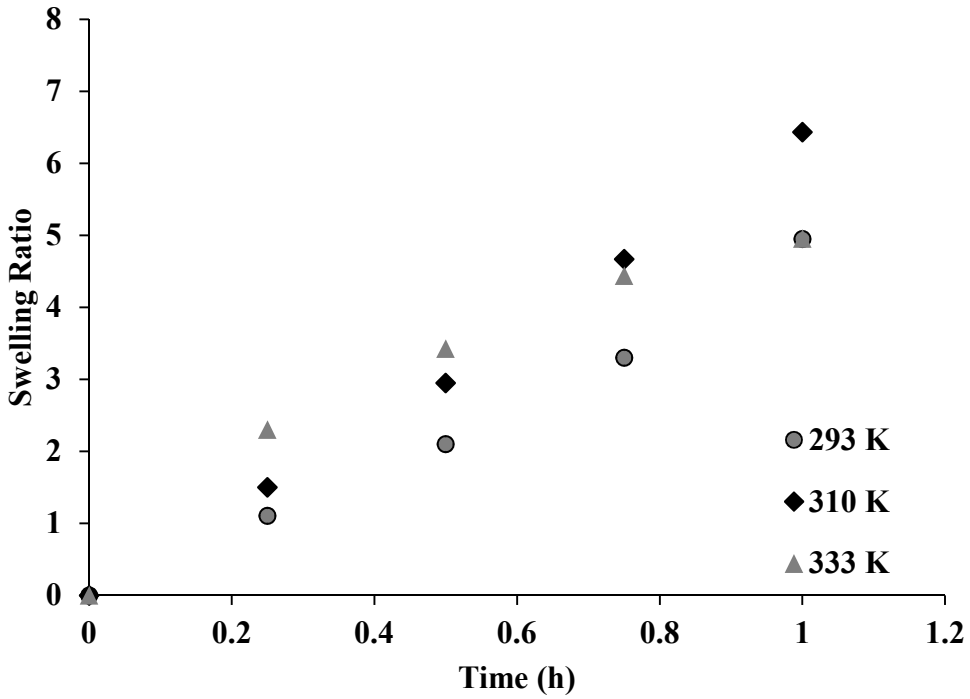


Figure. 4.3. Initial water-uptake of "PG2" hydrogels at 293, 310 and 333 K

Several transient models have been developed to evaluate the swelling kinetics and the diffusion of solvents into hydrogels with varying degrees of complexity (Ritger and Peppas, 1987; Peppas and Sahlin, 1989; Li, 2009). In general, in order to describe the diffusion of solvent into the polymer matrix, two processes are employed: the diffusion of solvent into the network and the advancement of the swollen-unswollen boundary due to polymer relaxation (Li, 2009). When the diffusion of the solvent is considerably faster than the advancement of the swollen-unswollen boundary, the process can be described by Fick's law of diffusion and the weight change of hydrogel slabs can be expressed by equation 2 (Crank, 1975).

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{l^2}\right)^{1/2} \times \left[\frac{1}{\pi^{1/2}} + 2\sum_{n=1}^{\infty}(-1)^2\, ierfc\left(\frac{nl}{2(Dt)^{1/2}}\right)\right] \qquad (2)$$

where M_t and M_∞ are the total amount of diffusing substance at time t and after equilibrium ($t=\infty$) and D and l are the diffusion constant of polymer network and final equilibrium thickness, respectively. Based on the amount of solvent uptake, i.e., the M_t/M_∞ value, equation 2 can be adapted as follows (Lee et al., 1996):

$$0 < \frac{M_t}{M_\infty} < 0.6 \qquad \frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi l^2}\right)^{1/2} \text{ or } \frac{M_t}{M_\infty} = kt^{1/2} \tag{3a}$$

$$\frac{M_t}{M_\infty} > 0.6 \qquad \frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\exp\left[\frac{-\pi^2 Dt}{l^2}\right] \tag{3b}$$

where k is a proportionality constant. According to equation 3a, if there is a linear relation between water uptake and time$^{1/2}$, the hydrogel is regarded to exhibit Fickian behavior. In Figures. 4.4 and 4.5, the relation between M_t/M_∞ and time$^{1/2}$ for "PG2" and "PG4" hydrogels at different temperatures are presented. As shown in Figure. 4.4, the relation between water uptake and time$^{1/2}$ for "PG2" hydrogel was linear at 333 K but the system demonstrated a non-linear sigmoidal diffusion pattern at lower temperatures. The same trend was observed for the "PG4" hydrogel (see Figure. 4.5) with a greater deviation from linearity. Therefore, it can be concluded that both hydrogels exhibited Fickian behavior at 333 K and anomalous non-Fickian diffusion at lower temperatures. An initial time lag was observed for the diffusion processes at 293 and 310 K for both hydrogels, while the sigmoidal shape of the dynamic swelling curve became more accentuated for diffusion at 293 K. This behavior suggests that the swelling mechanism might follow autocatalytic kinetics at lower temperatures, where hydrogen bonding has an influence on swelling behavior (Díez-Peña et al., 2002). The hydrogen bonds act to block the passage of the diffusing solvent through the polymer matrix. As mentioned before, diffusion of water in a hydrophilic network is a complex phenomenon, particularly when intramolecular and

intermolecular interactions due to hydrogen bonding are present. In an autocatalytic mechanism, the initial diffusion of water molecules will result in the dissociation of hydrogen bonds inside the hydrogel, thus, facilitating the diffusion process. The diffusion of the first water molecule assists the uptake of the next one by breaking down the hydrogen bonds at the blocked sites (Díez-Peña et al., 2002). At higher temperatures, this anomalous feature was not found in the swelling dynamics measurements because hydrogen bonds were already disrupted or were much weaker at those temperatures. The autocatalytic mechanism was more pronounced in the diffusions in "PG4" hydrogel with higher hydroxyl group contents and thus a higher number of hydrogen bonds in the network.

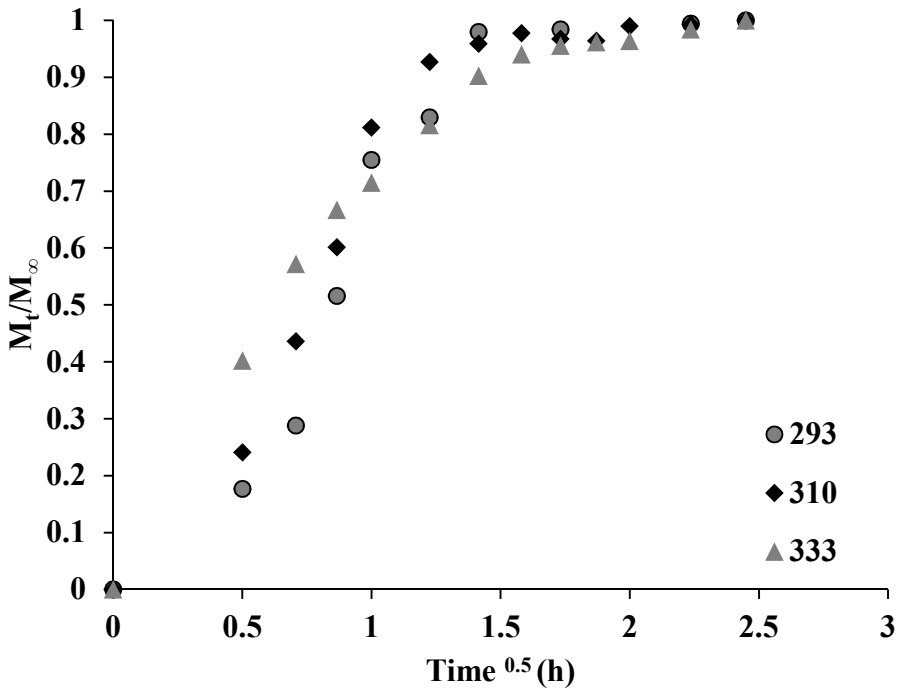


Figure. 4.4. Swelling kinetics of "PG2" hydrogel versus square root of time at 293, 310 and 333 K.

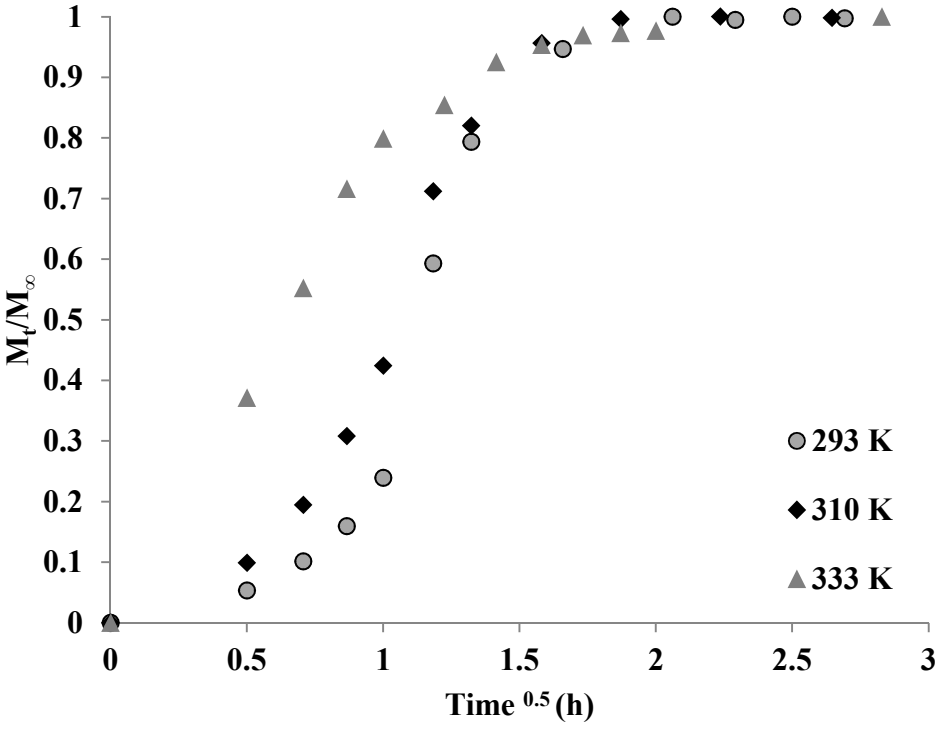


Figure.4.5. Swelling kinetics of "PG4" hydrogels versus square root of time at 293, 310 and 333 K.

4.3.2. Mechanical properties

The understanding of hydrogel mechanical properties is very important for evaluating the feasibility of the material for the specific applications. In addition, in order to tailor the hydrogel properties to meet the final product specification, knowledge of the structure-property relation is essential. Hydrogels in their swollen state can be considered as elastomers. Therefore, by using rubber elasticity theories to describe the mechanical behavior, it is possible to analyze the polymer structure and determine the effective

molecular weight between cross-links (Anseth et al., 1996). For the case of an affine deformation of the polymer network, the average molecular weight between cross-links (M_c) can be calculated using the following equation derived from rubber elasticity theory (Flory, 1978; Iza et al., 1998):

$$M_c = 3\frac{\rho RT}{E}.\varphi^{1/3} \quad (4)$$

where E is the Young's modulus, R is the gas constant, T is the absolute temperature, ρ is the polymer density which was equal for 1.126 g /cm^3 and φ is the equilibrium volume fraction of polymer in the swollen state. φ was approximated by the ratio of initial to final weight of polymer ($M_0/(\rho M_\infty)$). Mechanical tests were carried out at 293±2 ºC. The values of Young's modulus (E) for "PG2" and "PG4" hydrogel and xerogel (i.e., dry hydrogel) along with the calculated molecular weight between cross-links for swollen hydrogels are presented in Table 4.1.

Table 4.1: Young's modulus and molecular weight between cross-links for polyglycerol hydrogels

Polyglycerol	Xerogel E (kPa)	Hydrogel E (kPa)	M_c
PG2	550 ± 60	160 ± 25	3100
PG4	62 ± 10	8.5 ± 2	37000

It is noteworthy that for the model derivation an ideal network with isothermal and affine deformation was assumed despite the fact that the hydrogels may have contained structural imperfections such as cross-linking heterogeneity, entanglements, hydrogen bonding, etc. Hence, the calculated M_c of the networks should not be considered as an absolute measure but can be used for the sake of comparison within this study.

As expected, when the ratio of cross-linker to polyglycerol was doubled from "PG4" hydrogel to "PG2" hydrogel, the degree of cross-linking was increased, M_c was decreased and the modulus was increased. Once the mechanical properties of the hydrogels have been determined, it is often necessary to improve them in order to make the product suitable for the target application. There are several ways of controlling the mechanical properties such as altering the monomer composition and changing the cross-linking density. However, the mechanical strength of a hydrogel is often derived almost exclusively from the cross-links in the network; especially in the swollen state where physical entanglements are nearly non-existent (Anseth et al., 1996). The strength of the hydrogel can be increased dramatically with increasing cross-linking density. On the other hand, a higher degree of cross-linking will result in a brittle structure. Therefore, it is important to find an optimum degree of cross-linking to achieve a relatively strong and yet elastic hydrogel for the desired application (Peppas et al., 2000). It should also be mentioned that mechanical properties are highly dependent on environmental conditions (Anseth et al., 1996).

4.3.3. Swelling in PBS solution and Degradation

Biodegradable hydrogels have become increasingly important in biomedical applications because they can be degraded and eliminated from the biological system after use. They also provide design flexibility for many applications such as drug carriers. One example is in the design of delivery devices for large molecular weight drugs, such as pharmaceutically active proteins and polypeptides (Oudshoorn et al., 2006).

There are three major degradation mechanisms for hydrogels in biological systems: hydrolysis, enzymatic cleavage and dissolution (Barbucci, 2009), where degradation of

most of the synthetic hydrogels are through hydrolytic cleavage reactions. Polymers with a hydrolytic labile structure, especially those made by step-growth polymerization such as polyesters and polyether, have potential as biodegradable materials (Crommen et al., 1992). Hydrolysis reactions which can break down the ether bonds in polyglycerol are, in fact, the reverse of the glycerol polycondensation reaction. Hydrolytic degradation which occurs in aqueous solutions is usually catalyzed by a salt of a weak acid or a weak base (Barbucci, 2009).

The initial solvent uptakes of "PG2" and "PG4" hydrogels in PBS were illustrated in Figure. 4.6. While equilibrium swelling was reached in water after a few hours (Salehpour and Dubé, 2011a), the solvent uptake continued to increase in PBS solution. This indicates a loosening of the network structure and the initiation of degradation. "PG2" hydrogel with lower polyglycerol content showed lower initial solvent uptake in both PBS solution and water compare to "PG4" hydrogel, which was expected and was explained earlier.

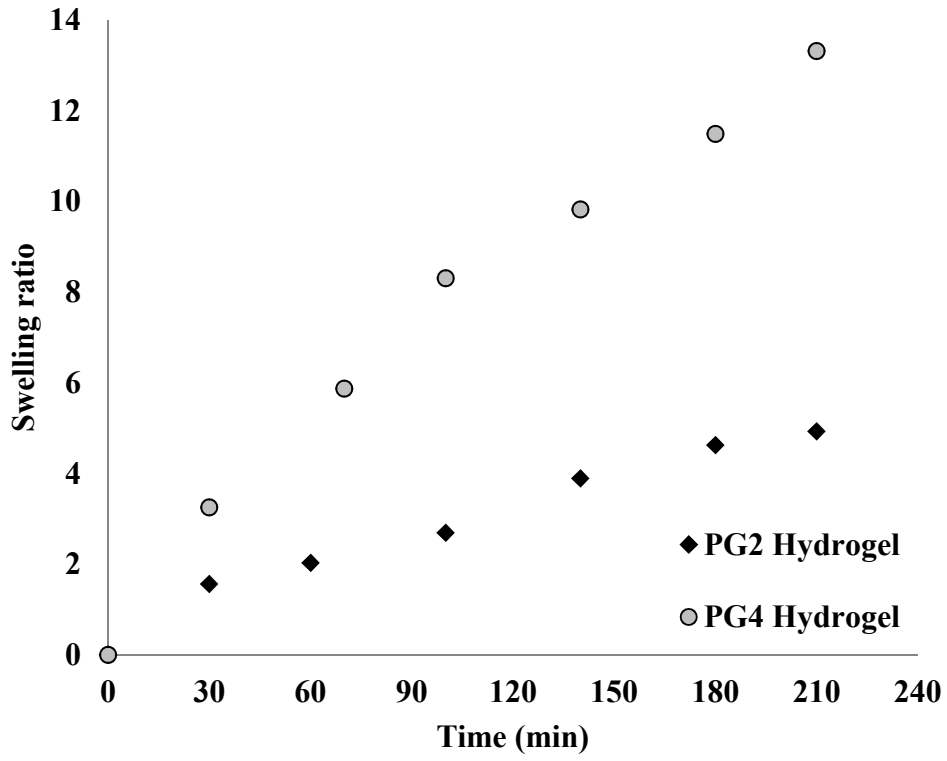


Figure. 4.6 Swelling behavior of "PG2" and "PG4" hydrogels in PBS at 310 K.

The dependence of the mass loss on the degradation time of "PG2" and "PG4" hydrogels in PBS is shown in Figure. 4.7. The initial difference in the degradation-induced mass loss of samples (see Figure. 4.7) was due to the difference in the structure and composition of the networks. Degradation proceeds at a higher rate in "PG4" hydrogels. The "PG4" network with a lower cross-linking density and higher hydrophilicity degraded faster because the PBS diffusion into the polymer hydrogel proceeded more readily. However, the "PG2" hydrogel exhibited lower solvent uptake only at the beginning of the degradation period and the difference between mass loss values was not significant after 15 days. The reason for this behavior is due to the higher numbers of ether bonds capable of

hydrolysis in "PG2" hydrogels compared to that in the "PG4" hydrogels. As previously mentioned, the molecular structure of polyglycerol is comparable to that of PVA and PEG. For the sake of comparison, degradation times of 34 days for PEG homopolymer gels and 28 days for PEG/PVA copolymer gel have been reported (Lum and Elisseeff, 2003).

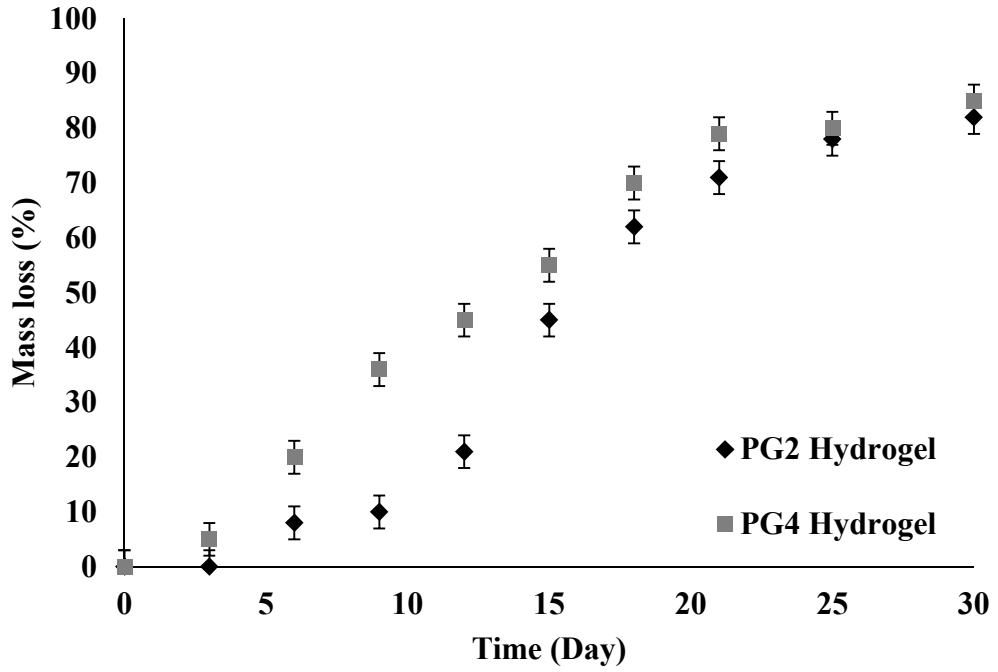


Figure. 4.7 Biodegradation behavior of "PG2" and "PG4" hydrogels with different degrees of cross-linking in PBS solutions at 310 K.

It is worth mentioning that in addition to degradation in PBS, polyglycerol hydrogel has the potential for aerobic biodegradation. Due to the presence of the ether group in the

backbone of the polymer chains, polyglycerol is very sensitive to photochemical oxidation, which results in chain scission and degradation (Yang and Liu, 2009).

4.4. Conclusion

Swelling kinetics and the diffusion process of two novel stimuli-responsive hydrogels,"PG2" and "PG4", synthesized by chemical cross-linking of polyglycerol were studied. The swelling behavior of the hydrogels can be modulated by changing the degree of cross-linking. The hydrogel systems exhibited Fickian diffusion at higher temperatures and non-Fickian sigmoidal diffusion at lower temperatures, which was attributed to the dissociation of hydrogen bonds at the higher temperatures. Young's moduli of xerogels and swollen hydrogels were calculated and were found to cover a broad range. Mechanical properties fell within the range of suitability for drug delivery matrices and tissue engineering applications (Martens et al., 2003). These mechanical properties were affected by the degree of cross-linking. A mass loss study of networks in PBS showed about 85% degradation within 30 days.

Polyglycerol-based hydrogels were produced from a renewable, non-toxic and abundant monomer, glycerol. Thus, these hydrogels can be considered more environmentally-friendly than common fossil-based hydrogels such as PEG and PVOH. Stimuli-responsive biodegradable polyglycerol-based hydrogels with good mechanical properties offer excellent opportunities for biomedical applications. In addition, these hydrogels exhibited relatively high swelling ratios, which make them suitable as moisture absorbents and solvent dryers for a broad range of applications.

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Chapter 5. Reaction monitoring of glycerol step-growth polymerization using ATR-FTIR spectroscopy

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Reaction Monitoring of Glycerol Step-growth Polymerization using ATR-FTIR Spectroscopy

Somaieh Salehpour, Marc A. Dubé

Abstract

The sustainable step-growth polymerization of glycerol was monitored in-line and off-line using an Attenuated Total Reflectance/Fourier Transform infrared (ATR-FTIR) spectroscopic probe. The concentration of hydroxyl groups was monitored to provide real-time conversion data using a univariate method. Traditional off-line techniques, i.e., hydroxyl value calculation and water production monitoring, were compared to the in-line and off-line ATR-FTIR spectroscopy method. Fouling of the probe was observed beyond 42 mol% conversion of hydroxyl groups. No statistically significant differences were found between the conversion data from off-line/in-line ATR-FTIR spectroscopy and two other methods at a 95% confidence level prior to fouling, and this confirms that ATR-FTIR spectroscopy is a reliable tool for monitoring conversion for production of oligoglycerols from a renewable feedstock, glycerol.

5.1. Introduction

The 11th of the well known "green chemistry principles" (Anastas and Warner, 2000) states that one should "analyze in real time to prevent pollution". This could result in improved process control and yield more "greener" processes by minimizing or eliminating the formation of waste and byproducts. Increasing interest in the sustainable synthesis of polymers with pre-specified properties combined with the need to improve process control procedures have spurred the investigation of real-time monitoring techniques. However, due to the physical nature of the polymerization reaction (i.e., high viscosity), in-line monitoring is not always possible and traditional, off-line methods are used. Off-line polymerization monitoring methods are usually performed by characterization of samples from the reaction mixture. A main disadvantage of common off-line characterization methods, such as NMR spectroscopy and wet chemical methods is the time lag between the result and sampling. Although these methods are accurate, they are often tedious, time consuming and not environmentally friendly (Roberge and Dubé, 2007). On the other hand most real-time methods are cost-effective, non-destructive and have no negative effect on our environment. In addition, in-line monitoring of the reactions has great impact on real-time process control/manipulation and prevention of waste (Fonseca et al., 2009). During the last two decades, there has been significant growth in sensor technologies for monitoring polymerizations (Fonseca et al., 2009). Depending on reaction conditions and polymer product properties, several on-line methods such as gas chromatography, densimetry, calorimetric and spectroscopic methods can be used to monitor polymerizations (Canegallo et al., 1993; Urretabizkaia et al., 1993; Hua and Dubé, 2002; Fonseca et al., 2009). Among all real-time reaction monitoring techniques, spectroscopic techniques such as near- and mid-infrared spectroscopy are particularly suitable due to the

low cost of modifying existing process equipment and the fast analysis time (Kammona et al., 1999). In addition, the necessity for sample preparation is eliminated using infrared probe. The Infrared spectroscopy is a popular analytical method for preparative and analytical chemistry which provides structural and kinetic information in a non-destructive and waste-free way (Smith, 2009). Compared to near-infrared (NIR), the mid-infrared (MIR) range, extending from 4000 to 400 cm^{-1}, is the preferred choice owing to the unmatched wealth of molecular information contained in the infrared portion of the electromagnetic spectrum (Fevotte et al., 1996). In addition, in this region, peaks are usually more distinctive and narrower, which make the identification of peaks and monitoring of peak changes easier during a reaction. In-situ Fourier Transform Infrared (FTIR) spectroscopy is a state-of-the-art monitoring technique that is well suited for obtaining real-time structural and kinetic information for polymerization processes. In addition, when using FTIR, reactions can be analyzed without complicated sampling methods and difficult experimental operation. With the rapid-scanning capability of FTIR spectroscopy, the time-dependent intensity changes of absorbance bands characteristic of polymerization reactants and reaction products can be monitored (Shaikh and Puskas, 2003). Over the last decade, robust and precise ATR–FTIR spectroscopy has been used for the monitoring of polymerizations, where conversion of reaction and composition were successfully analyzed (Roberge and Dubé, 2007; Fonseca et al., 2009; Dubé and Li; Patel et al., 2010).

In conventional mid-infrared spectroscopy and when water exists in the reaction mixture, the strong absorption of water overlaps with the majority of the peaks in a wide range of the spectra. This issue can make the collection of information on reaction

evolution very challenging. In order to resolve this problem for cases where water is involved in the reaction, internal reflection spectroscopy (often called Attenuated Total Reflectance or ATR) can be applied (Smith, 2009). Internal reflection spectroscopy is a non-destructive, widely used technique for the analysis of samples with low transmission. It is a contacting sampling method involving a crystal, used as an internal reflection element, with high refractive index and low IR absorption in the IR region of interest. When the IR beam enters the internal reflection element below an angle that exceeds the critical angle for total internal reflection, an evanescent wave is set up which penetrates a small distance beyond the crystal surface into space. A sample brought into contact with the crystal can interact with the evanescent wave, absorb infrared radiation, and have its infrared spectrum detected. The evanescent wave is attenuated by the sample's absorbance. Thus, intimate contact between the sample and crystal is critical to ensure the evanescent wave penetrates into the sample (Hua et al., 2004). The penetration depth of the evanescent wave is usually in the range of 1–10 mm and which makes it suitable for quantitative analysis of small samples. ATR spectroscopy is a powerful technique due to its insensitivity to strongly absorbing compounds (e.g., water) and sample thickness. The use of ATR-FTIR for monitoring emulsion polymerizations has been reported for a variety of systems such as butyl acrylate, methyl methacrylate, and vinyl acetate batch emulsion homopolymerizations and styrene/1,3-butadiene emulsion copolymerization (Hua and Dubé, 2002; Dubé and Li, 2010). However, very few comprehensive IR monitoring studies on step-growth polymerization systems have been reported (Sahre et al., 2006; Frauendorfer et al., 2010).

In previous studies, we reported on the sustainable production of polyglycerol via step-growth polymerization and synthesis of novel stimuli-responsive hydrogels from polyglycerol (Salehpour and Dubé, 2011b; Salehpour and Dubé, 2011a; Salehpour et al., 2011). These biodegradable polyglycerol and polyglycerol hydrogels were produced from a renewable, non-toxic and abundant monomer, glycerol. Sustainable production of polyglycerol satisfies seven of the twelve "green chemistry" principles via the production of an environmentally friendly, non-toxic product, by avoiding the use of toxic solvents and chemicals in the process, by using a renewable feedstock material (i.e., glycerol, a by-product of biodiesel production), among others. As noted above, in this study we apply another "green chemistry" principle, by monitoring the reaction in real time to prevent pollution. In our previous work, reaction progress and conversion of hydroxyl groups of glycerol into ether groups was determined by monitoring the water formation in a distillation trap throughout the course of polymerization (Salehpour and Dubé, 2011b; Salehpour and Dubé, 2011a; Salehpour et al., 2011). While this is a simple method at the laboratory scale, it may not be a practical monitoring technique at the industrial scale. There are other traditional methods for monitoring the conversion of hydroxyl groups in polyol syntheses such as acid or hydroxyl value calculations of monomer/polymer by wet chemical tests such as titration (Patel et al., 2010). Although these methods are accurate and precise they can take several hours to complete. In addition, they use highly toxic, irritating and corrosive chemicals such as pyridine and acetic anhydride, which are harmful to workers and the environment (Lee et al., 1990). Therefore, in order to reduce these process monitoring challenges and to make the synthesis of polyglycerol even more

environmentally friendly, it is logical to investigate the feasibility of other monitoring techniques such as ATR-FTIR spectroscopy.

In this work, a MIR spectroscopy technique was employed for monitoring step-growth glycerol polymerization and polyglycerol hydrogel formation. The ReactIR™1000 reaction analysis system (Mettler-Toledo) was used in-line and off-line to evaluate its potential to determine monomer conversions from characteristic peak changes. The collected kinetic results through the ATR-FTIR analysis were compared to data from water removal and the hydroxyl value wet chemistry method.

5.2. Experimental

5.2.1. Materials

Glycerol (≥99%), poly(ethylene glycol) diglycidyl ether (PEGDE, number-average molecular weight (M_n) = 526), sulphuric acid and sodium hydroxide (>98%) were all purchased from Sigma-Aldrich Canada Ltd. (Oakville, Canada) and were used without further purification.

5.2.2. Polyglycerol and hydrogel synthesis

Polymerization of glycerol was carried out using a method developed previously (Salehpour and Dubé, 2011b). The polymerizations were performed in a 1 L glass reactor equipped with a nitrogen inlet, distillation trap topped with a condenser, sampling port, temperature probe, IR probe and a mechanical stirrer. Glycerol etherification was carried out at 414 K in the presence of 4.8 wt.-% and 1.2 wt.-% sulphuric acid catalyst. Nitrogen was bubbled through the reaction mixture to blanket the reactants with a stream of inert gas throughout the reaction. The polymerization was performed at pressures below 26 kPa,

where a vacuum pump was attached to the reactor through the condenser. Water was continuously removed from the reaction mixture and collected in a Dean-Stark trap which was attached to the condenser. The reaction conversion was calculated by monitoring the water formation in the Dean-Stark trap. Hydroxyl value determinations were completed according to the ASTM E 1899-08, standard test method. For the latter method, the average values between three measurements were taken for each sample.

In order to form polyglycerol hydrogel, polyglycerol was added to a 2 M NaOH solution. The mass ratio of NaOH to polyglycerol was kept constant: 1 g of NaOH/18 g of polyglycerol. The solution was gently heated to 353 K and stirred until all the polyglycerol was dissolved. A PEGDE cross-linker was then added to the reaction mixture drop wise and the solution was heated to 393 K. The mixture was stirred vigorously until it became slightly gelatinous. It was then poured into preheated circular Teflon molds (diameter = 8 cm) and allowed to cure at 393 K for 6 h. Greater details about this polyglycerol hydrogel formation are found elsewhere (Salehpour and Dubé, 2011a).

5.2.3. Reaction monitoring

In order to monitor the glycerol polymerization, the reaction conversion was followed via in-line and off-line ATR-FTIR spectroscopy using the REACTIR™ 1000 (Mettler Toledo). The ReactIR™ 1000 reaction analysis system is equipped with a light conduit and DiComp (diamond composite) insertion probe to collect mid-FTIR spectra of the polymerization components. The term “in-line” in this context refers to measurements performed directly in the process stream using the insertion probe prior to fouling of the probe, whereas the term “off-line” refers to measurements carried out on samples taken from the reaction mixture.

For the hydrogel production study, infrared spectroscopy was performed on the glycerol polymer, the hydrogel and the cross-linker. Due to the solid nature of the hydrogel and the high viscosity of the polyglycerol during this stage, only the composition and the effectiveness of the cross-linking reaction were studied; no quantitative analyses were performed.

In all cases, the data comprised spectra collected from 128 scans, over the spectral ranges of 4000 – 700 cm^{-1}, with 4 cm^{-1} resolution. The spectra were further analyzed using the ReactIR™ software version 2.2 and were used to calculate monomer conversion and polymer gel composition, the latter in the case of hydrogel formation. The monomer conversion was estimated by calculating the ratio of the absorbance of the characteristics bands of the monomers (Jovanovic and Dubé, 2001; Jovanovic, 2004). The reported conversion for each sample was an average value taken from three measurements.

5.3. Results and discussion

To evaluate the potential of ATR–FTIR spectroscopy for monitoring the step-growth polymerization of glycerol, a number of issues were investigated. These included effects of the use of an appropriate background spectrum, the signal-to-noise ratio, the assignment of appropriate spectral peaks, and probe fouling.

In order to facilitate the monitoring of reactions containing strongly absorbing substances (e.g., water) a background spectrum is usually collected and subtracted from the reaction spectra. In our bulk polymerization system, an air background was found to be sufficient to follow the reaction progress.

At all stages of the reaction, the signal-to-noise ratio was large enough to permit the identification of main peaks. A resolution of 4 cm^{-1} is usually sufficient for fine peak

resolution and high signal-to-noise ratio for most condensed phase samples. Applying a higher resolution would result in noisier spectra and an increase in the data acquisition time, while significant improvement in peak assignment and measurement accuracy would not be observed compared to lower resolution spectra (Hua and Dubé, 2002). A polyglycerol ATR-FTIR spectrum is shown in Figure 5.1.

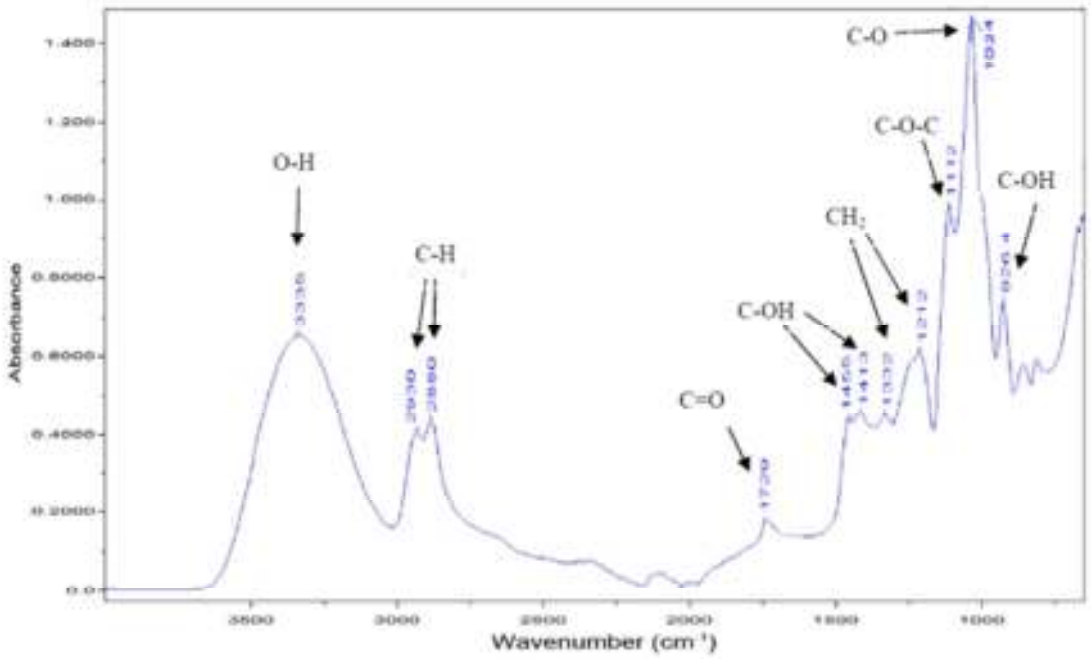

Figure 5.1. Single sample reaction spectrum for polyglycerol step-growth polymerization.

There were two major absorptions observed in the functional group region of the spectrum (4000 to 1500 cm^{-1}). The strong absorption around 3300 cm^{-1} was due to OH stretching of polyglycerol and the bimodal peak around 2900 cm^{-1} was due to CH stretching. A number of overlapping peaks were observed in the fingerprint region (1500-700 cm^{-1}). Absorptions in this region arise from complex deformations of the polymer and

monomer molecules. These peaks are usually due to molecular symmetry, or combination bands arising from multiple bonds deforming at the same time. Absorptions due to CH_2 bending (1500-1200 cm^{-1}), C-O stretching (1200-900 cm^{-1}) and C-O-C stretching (1290-1100 cm^{-1}) were observed in this region. A very weak absorption at 1729 cm^{-1} was absorbed toward the end of the reaction which can be associated with undesired side reaction products such as acrolein, which has a carbonyl bond. Peak assignment for infrared spectrum of polyglycerol is presented in Table 5.1. Although the fingerprint region in the spectrum revealed important information about the groups which are presented in the polymer, the overlapping peaks in this region were not suitable to monitor for quantitative analysis and conversion measurement. Therefore, the highly distinctive peak at ~3300 cm^{-1} in the functional group region (see Figure 5.1), which was assigned to the glycerol monomer hydroxyl group, was chosen for the purpose of reaction monitoring with ATR-FTIR spectroscopy.

Table 5.1. Polyglycerol infrared spectrum peak assignments(Ahmed et al., 2010).

Spectral region (cm^{-1})	**Absorbance assignment**
926	C-OH stretch
1034	C-O stretch
1112	C-O-C stretch and C-O stretch
1212-1332	CH_2 wagging
1413-1455	C-OH in-plane bending and CH_2 bending
1729	C=O stretch
2880 and 2930	C-H symmetric and asymmetric stretch
3335	O-H stretching

A univariate method was used to calculate the conversion of hydroxyl groups from the in-line and off-line monitoring data. Conversion monitoring was accomplished by following the change in the absorbance of the OH peaks (see wave number = 3335 cm^{-1} in Figures 5.1) in the infrared spectra throughout the course of polymerization. According to Beer's law (Smith, 2009), it could be assumed that the hydroxyl concentration was proportional to absorbance measured as the corresponding peak heights. The conversion, x, of hydroxyl groups was calculated using:

$$x(mol\%) = \left(1 - \frac{peak\ height\ at\ time\ t}{peak\ height\ at\ time\ t = 0}\right) \times 100 \quad (1)$$

Reaction spectra for a glycerol polymerization at 140ºC using 0.8 wt.% concentration of sulphuric acid are shown in Figure 5.2, while conversion vs. time data calculated from water removal monitoring and in-line spectroscopy are shown in Figure 5.3. For the in-line monitoring of the reactions, the hydroxyl group absorption (wavenumber = 3335 cm^{-1}) was monitored by way of its peak height, which decreased steadily with conversion up to the fouling point (see Figure 5.2). The probe fouling was observed for hydroxyl conversions above ~40 mol%. Beyond this point, the collected spectra remained unchanged, while off-line monitoring of the same reaction demonstrated the expected conversion trajectory. This effect was due to the production of higher molecular weight polymer which resulted in an increasingly high viscosity reaction mixture at hydroxyl conversions above ~40 mol%. A paired comparison of the difference between the water removal method and the in-line ATR-FTIR monitoring method prior to the fouling point was performed and the 95% confidence interval was found to be [-2.88, 0.56] mol%. Thus, it can be concluded that in-line monitoring of glycerol is only a suitable

method for production of widely used polyglycerol oligomers which are obtained at lower conversions. Synthesis of oligoglycerol has been commonly performed for the production of various types of biodegradable surfactants, lubricants, cosmetics, and food additives, which are available commercially. In-line monitoring of the reaction can have a significant impact on real-time process control for oligoglycerol production (Clacens et al., 2002).

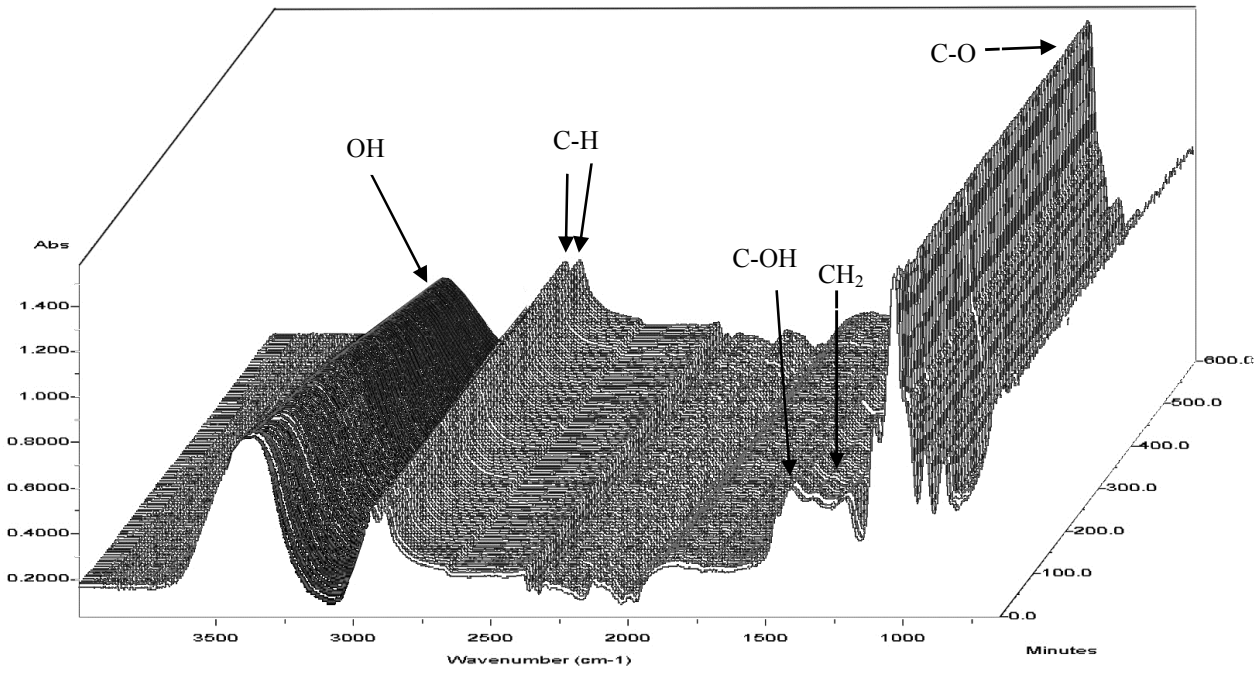

Figure 5.2: In-line monitoring reaction spectra for step-growth polymerization of glycerol.

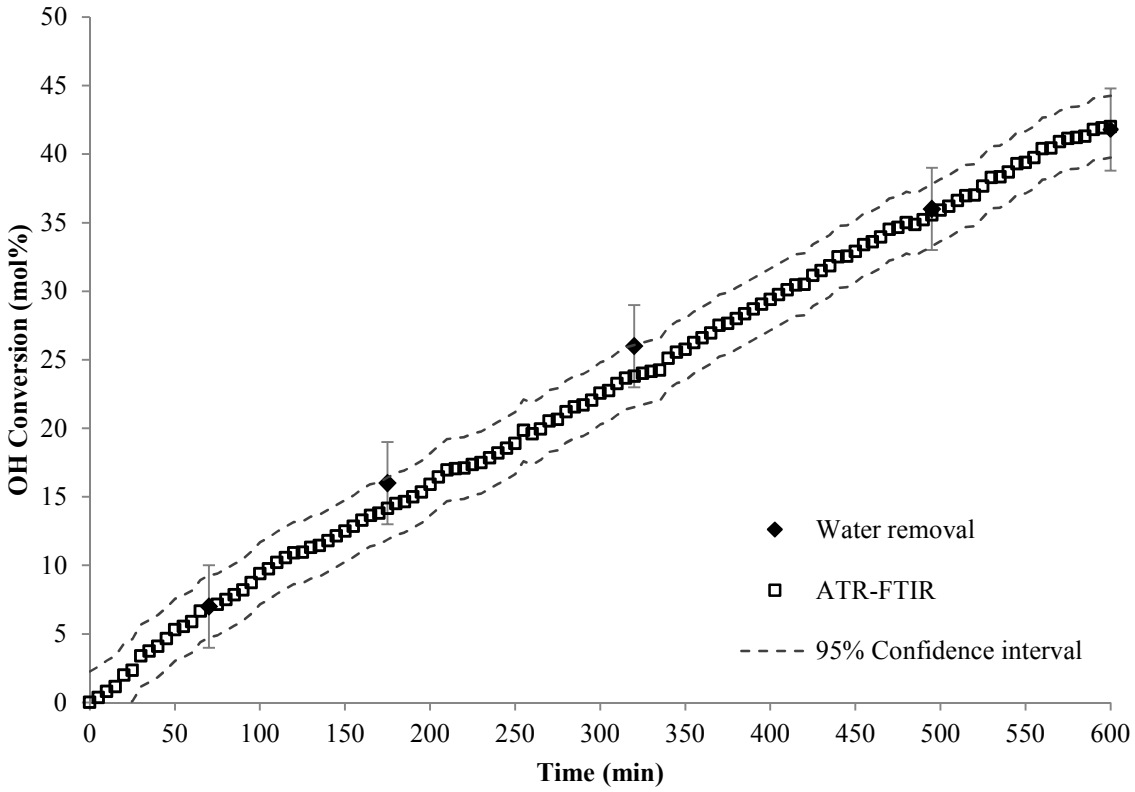

Figure 5.3: Conversion vs. time calculated via in-line monitoring of the reaction and water removal.

In a previous study (Salehpour and Dubé, 2011b), high molecular weight polyglycerol with a weight-average molecular weight (M_w) of 111,400 g/mol was produced and a 72 mol% hydroxyl conversion was achieved. This conversion is below the critical conversion (or gel point) of this system (i.e., 77 mol%). At the gel point, cross-linking of polymer chains occurs and the polymer no longer flows. From a practical point of view, it is very important to monitor the reaction before the gel point is reached in order to stop the polymerization and avoid gelation for straightforward removal from the reaction vessel. Since fouling did not permit in-line monitoring of the polymerization, off-line monitoring of polymerization was performed on the higher viscosity samples (see Figure 5.4).

Nonetheless, the off-line use of the ATR-FTIR probe was relatively fast and the monitoring results are certainly comparable to real-time monitoring of the reaction.

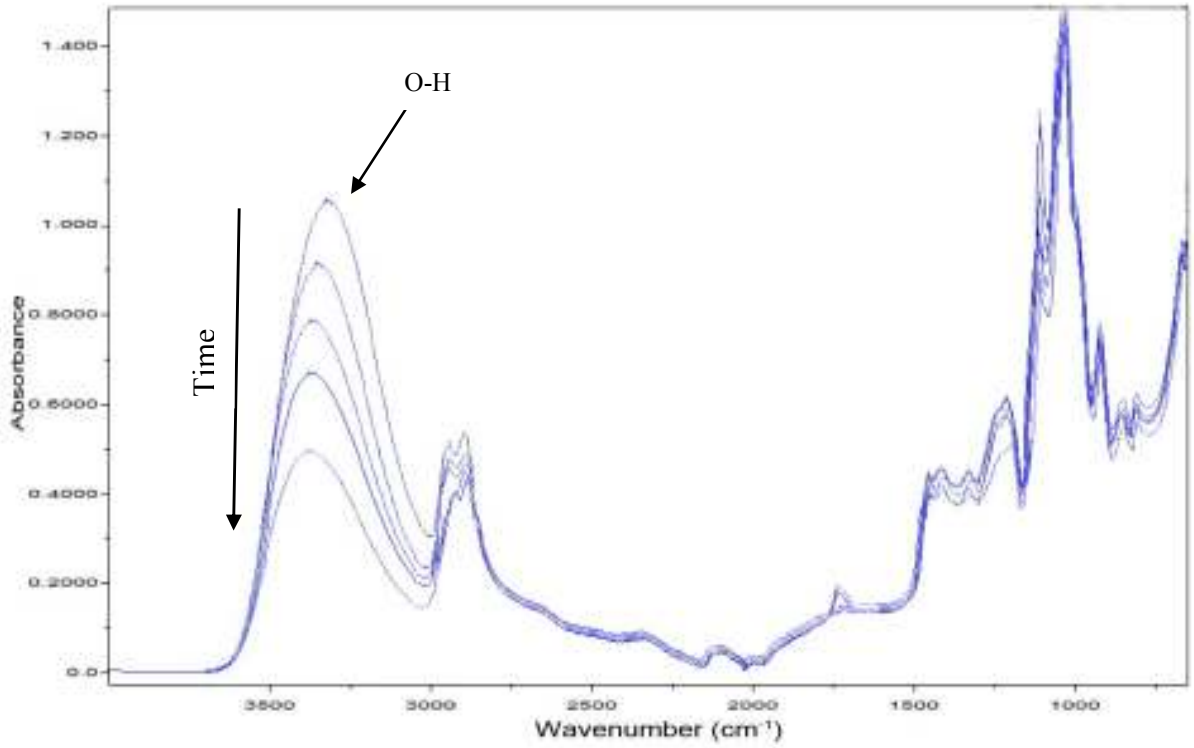

Figure 5.4: Polymerization reaction spectra obtained from off-line monitoring using ATR-FTIR spectroscopy.

As mentioned earlier, monitoring the amount of water produced as a by-product of the step-growth glycerol polymerization is the most straightforward method but this method may not be practical at the industrial scale. On the other hand, hydroxyl number measurement is a common method for characterization of functionality of polyether-polyols which does not require any modification to the reactor (Sunder et al., 2000). However, this method is time-consuming and does not allow the fast determination of

conversion required for prompt process control action. Hydroxyl number represents the milligrams of potassium hydroxide equivalent to the content of 1 g of material. This value is a measure of number of hydroxyl groups present in the sample. The conversion, *x*, of hydroxyl groups from the hydroxyl numbers can be calculated using:

$$x(mol\%) = \left(1 - \frac{hydroxyl\ number\ at\ time\ t}{hydroxyl\ number\ at\ time\ t = 0}\right) \times 100 \qquad (2)$$

where the initial reaction mixture (glycerol) had a hydroxyl number of 1826 mg KOH/g and the final product had a hydroxyl number of 400 mg KOH/g. It should be mentioned that, even though the method is designed for calculation of number of hydroxyl groups attached to primary and secondary carbons of polyols, the actual functionality of polyglycerol may be slightly different. This can be due to sensitivity of this method to water and other impurities, steric limitations of the polymer chains, and the high density of the hydroxyl groups, all of which can lead to incomplete conversion in the titration step of the procedure (Sunder et al., 2000). Nonetheless, hydroxyl value data for polyglycerol provided a reasonable estimate of conversion although this method expressed greater variability. In order to assess the potential of off-line ATR-FTIR monitoring for polyglycerol production, the results were compared to two off-line monitoring methods: water removal and hydroxyl value calculation via wet chemistry. Conversion vs. time data for the three different methods are presented in Figure 5.5. Conversion values obtained by ATR-FTIR monitoring of the reaction were slightly lower than the conversion value determined by water removal toward the end of the reaction, especially after the fouling of the probe point (i.e., beyond ~40 mol% conversion). This difference was due to the high viscosity of the reaction mixture which results in error in quantitative IR measurements at higher conversions. Three paired comparisons of the differences between the conversions

obtained from the three different off-line methods were carried out (see Figure 5.5). The 95% confidence intervals were found to be [-3.78, 4.78] mol% for the difference between the hydroxyl value method and the water removal monitoring method, [-1.05, 8.80] mol% for the difference between the hydroxyl value method and the ATR-FTIR monitoring and [-5.30,-1.44] mol% for the difference between the water removal method and that using ATR-FTIR monitoring. As mentioned before, a paired comparison of the differences between the water removal method and the in-line ATR-FTIR monitoring method prior to the fouling point showed that the 95% confidence interval was found to be [-2.88, 0.56] mol%. A similar confidence interval was obtained for the off-line ATR-FTIR monitoring of the reaction (i.e., [-3.00, 0.45]). Therefore, it can be concluded that there is no significant difference between conversion measured using the hydroxyl value method and the water removal method. On the other hand, the off-line ATR-FTIR monitoring was not suitable for predicting conversion toward the end of the polymerization due to the high viscosity of the reaction mixture. However, the ATR-FTIR was quite reliable for both in-line and off-line monitoring up to ~40 mol% conversion. The desirable OH conversions for the production of many common oligoglycerols are usually lower than 40 mol% (Zhou et al., 2008; Rahmat et al., 2010).

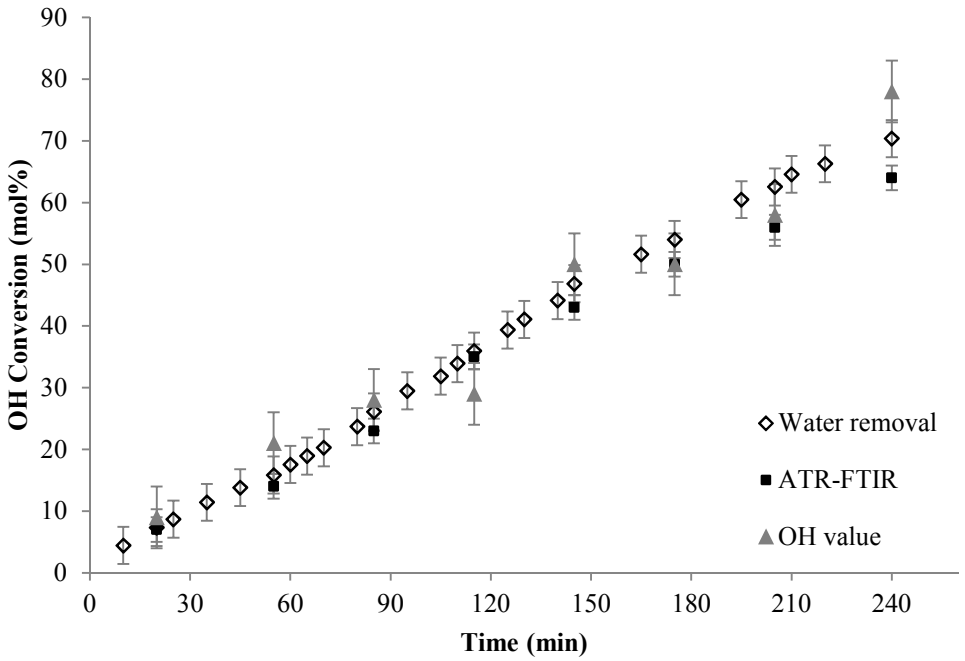

Figure 5.5: Conversion vs. time calculated using three different monitoring methods.

5.3.1. Monitoring hydrogel formation

Despite the solid state of our hydrogels, the use of the ATR-FTIR probe was tested to confirm the presence of specific chemical groups in the polyglycerol hydrogel and to evaluate the proposed cross-linking mechanism of the polyglycerol using PEGDE (Salehpour and Dubé, 2011a). The infrared spectra of polyglycerol, PEGDE and polyglycerol hydrogel are shown in Figure 5.6. The main peaks (i.e., OH and CH absorptions) associated with the polyglycerol structure and polyglycerol hydrogel are apparent in the spectra (see Table 5.1). As for PEGDE, the absorptions associated with the epoxide functional groups of PEDGE were observed at 853 [cm^{-1}] and at 760.4 [cm^{-1}] due to the three-member ring deformation. The spectra of the polyglycerol hydrogel showed

only weak absorptions at these wavenumbers. This implies that the epoxide groups in PEGDE were converted to ether groups by reacting with the hydroxyl groups of the polyglycerol.

One interesting observation for the polyglycerol hydrogel spectrum is that in addition to the loss of hydroxyl groups in the polyglycerol due to the cross-linking reactions and the formation of ether linkages, there was a considerable amount of hydrogen bonding occurring in the gel. A broad absorption at 3350 [cm^{-1}] with a shoulder was observed in the infrared spectrum of the hydrogel, which is indicative of hydrogen bonded hydroxyl groups. This confirms the expected intramolecular and intermolecular hydrogen bonding in the polyglycerol hydrogel at room temperature.

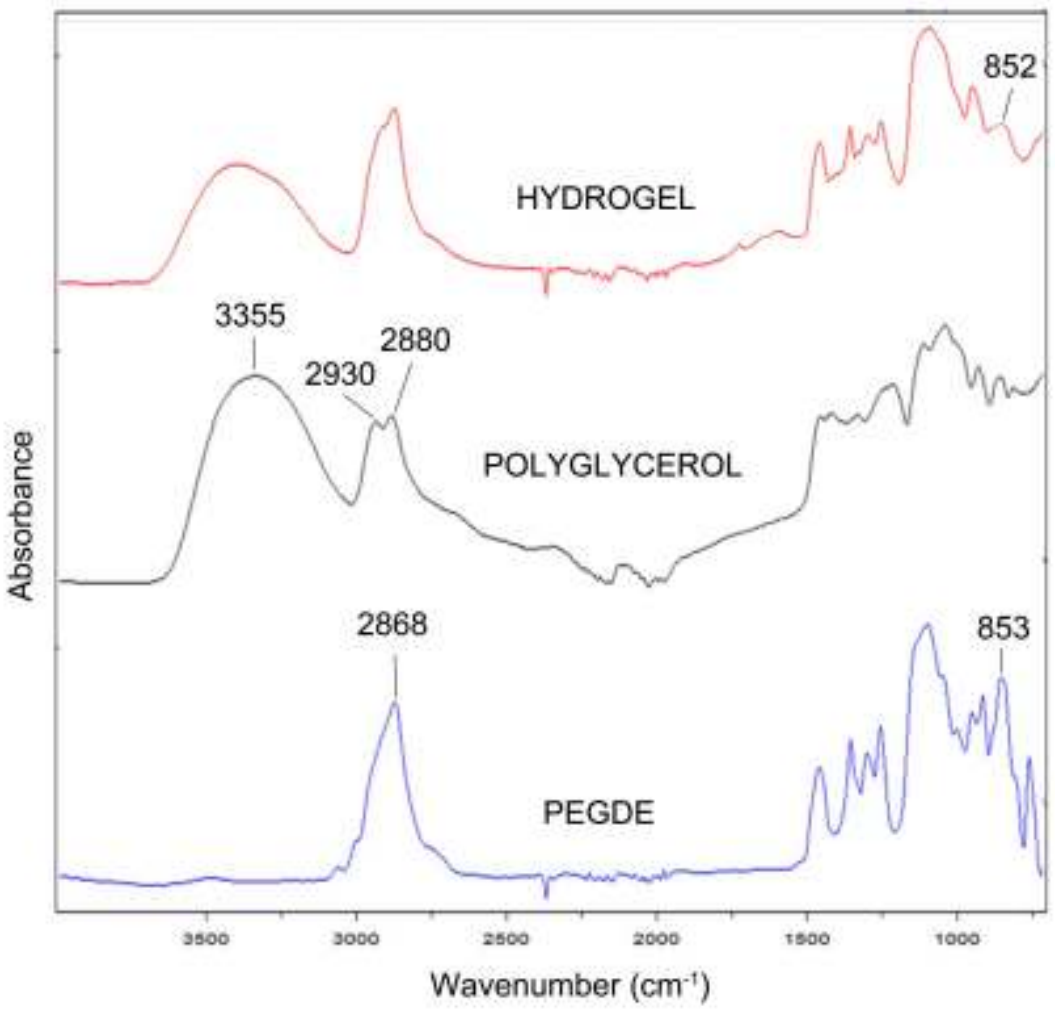

Figure 5.6: ATR-FTIR spectra of polyglycerol, PEGDE (cross-linker) and polyglycerol hydrogel.

5.4. Conclusion

The step-growth polymerization of glycerol was monitored off-line using a hydroxyl number calculation, water removal monitoring and ATR-FTIR spectroscopy. In addition, in-line ATR-FTIR monitoring of the reaction was performed successfully up to medium conversions (i.e., <42 mol% conversion). Paired comparison analyses between the different methods confirmed the validity of the hydroxyl value method and the water

removal monitoring technique. The ATR-FTIR spectroscopy method (in-line and off-line) was shown to be valid and consistent with the other off-line monitoring techniques at lower viscosities which corresponded to conversions below ~40 mol% conversion. Therefore, it can be concluded that ATR-FTIR spectroscopy is a reliable tool for monitoring of the production of oligoglycerols due to its wealth of qualitative and quantitative information.

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Chapter 6. General Discussion and Conclusions

6.1. General discussion

Our society's drive towards the greening of consumer products has given scientists and engineers the opportunity and environmental stewardship to produce products that have a lower impact on the planet. The research in this thesis on the step-growth polymerization of glycerol to high molecular weights is a step forward in the sustainable production of polymeric products.

The first part of this study was devoted to finding a suitable catalyst and reaction conditions for the synthesis of high molecular weight polyglycerol using step-growth polymerization (Salehpour and Dubé, 2011). Since the bulk polymerization was performed at an elevated temperature (i.e., 140^{o}C) and achieving a highly viscous reaction mixture was expected towards the end of the reaction, the catalysts were chosen on the basis of their solubility, thermal stability and high activity at elevated temperatures. Several catalysts were tested including a mineral acid (i.e., sulphuric acid) an organic acid (i.e., *p*-toluene sulfonic acid (PTSA)), a base (i.e., calcium hydroxide) and a salt (i.e., calcium carbonate). The efficiency of catalysts based on the rates of polymerizations was observed as, sulphuric acid > PTSA > calcium hydroxide > calcium carbonate, respectively, in order of decreasing efficiency. The difference between the polymerization rates was explained by different catalytic reaction mechanisms. The polymerization of glycerol using sulphuric acid catalyst resulted in significantly higher monomer conversions along with higher molecular weights compared to polymerizations using other catalysts, which only resulted in oligoglycerol (i.e., low molecular weight polymer) production. Polyglycerol with a weight-average molecular weight of 111,400 g/mol was synthesized in ~4 h. The rate of polymerization was controlled by manipulating the concentration of the sulphuric acid

catalyst. As shown in Figure 6.1, higher reaction rates were observed using higher concentrations of sulphuric acid.

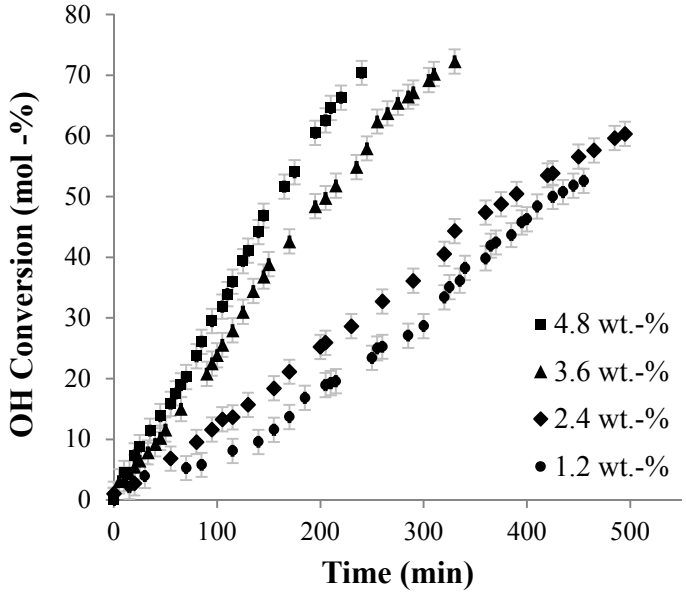

Figure 6.1. Conversion of hydroxyl groups vs. time data for polyglycerol synthesis using sulphuric acid catalyst.

The GPC analysis of high molecular weight polyglycerol samples showed multimodal molecular weight distributions, which is characteristic of most step-growth polymerization products. The chemical structure of the polyglycerol was investigated using ^{13}C-NMR and ^{1}H-NMR spectroscopy and the results indicated that the product was a mixture of polyglycerols with linear, branched and cyclic structures. The predominant species were linear polyglycerol followed by branched structures. Formation of branched polyglycerol can take place via an epoxide intermediate reaction pathway or reactions with secondary hydroxyl groups. In addition, a small amount of cyclic products could be formed via intra-molecular ring closure reactions. Nonetheless, the polyglycerol mixture had a high functionality and the presence of non-linear compounds is not typically detrimental for many applications.

The bulk polymerization of glycerol monomer with three functional groups can not only result in branching reactions, but also in cross-linking reactions, which can eventually lead to gelation. From a practical point of view, it is important to find the actual functionality of the monomer and the critical extent of reaction in a polymerization system to stop the reaction prior to the gel point to prevent waste. A functionality of 2.4 for the glycerol monomer was calculated using Macosko and Miller's theoretical model for step-growth polymerization (Macosko and Miller, 1976). Using the calculated functionality and the Flory and Stockmayer statistical approach (Odian, 2004), the critical extent of reaction was predicted to be about 71 mol% and it was fairly close to the observed experimental onset of gelation.

In the second part of this project cross-linking of polyglycerol was studied and the synthesis of stimuli-responsive polyglycerol hydrogels was the result (Salehpour and Dubé, 2011; Salehpour, Dubé et al., 2011). A general scheme for hydrogel formation is shown in Figure 6.2.

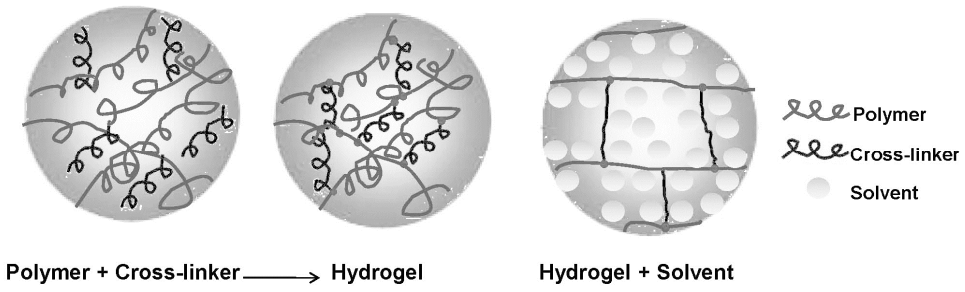

Figure 6.2. Hydrogel formation using long-chain cross-linker

Cross-linking reactions with short-chain bi-functional, tri-functional and long-chain PEG-based epoxide-containing biodegradable cross-linkers (M_n = 526) were studied. Due to the broad molecular weight distribution of the polyglycerol, reactions with long-chain cross-linker resulted in hydrogel production. The reactions with low molecular weight

cross-linkers mostly resulted in the extension of molecular weights and a small amount of gel. Therefore, small molecule cross-linkers can be used for applications where partial cross-linking or low gel content is required. The cross-linking reaction mechanism was studied using an ATR-FTIR spectroscopy technique. Then reaction mechanism is shown in Figure 6.3.

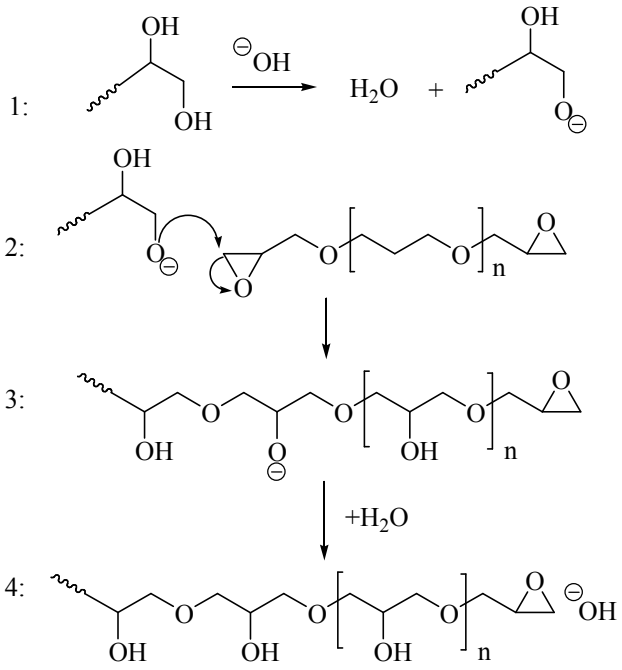

Figure 6.3. Mechanism of cross-linking reaction between hydroxyl group of polyglycerol and epoxide group of cross-linker.

In order to study the effect of the degree of cross-linking on hydrogel properties, two hydrogels with different hydroxyl to epoxide group molar ratios were synthesized and they were referred to as PG 2 and PG 4, with molar ratios of 2:1 and 4:1, respectively. The degree of cross-linking is an important factor, which controls the swelling ratio of the hydrogel and its mechanical properties (Fonseca, Dubé et al., 2009). The swelling behaviour of hydrogels was studied at different temperatures (i.e., 293, 310, 333 and 353 K) and buffer solutions of pH 4, 7 and 10. It was observed that the swelling ratios of the

polyglycerol hydrogels were significantly increased by decreasing the cross-linking density. Increasing the degree of cross-linking changed the swelling equilibrium by altering the composition and structure of the network (Graham and Zulfiqar, 1989). As the cross-linking density decreased, the molecular weight between cross-links increased, which resulted in a more elastic and less dense hydrogel network. In addition, the weight percentage of polyglycerol in the hydrogel increased as a result of decreasing the cross-linking density. Therefore, the functionality or number of hydroxyl groups of the network was increased; thus, the equilibrium swelling ratio was increased. The swelling behaviour of PG2 and PG4 hydrogels in water at 293 K and 310 K are presented in Figure 6.4.

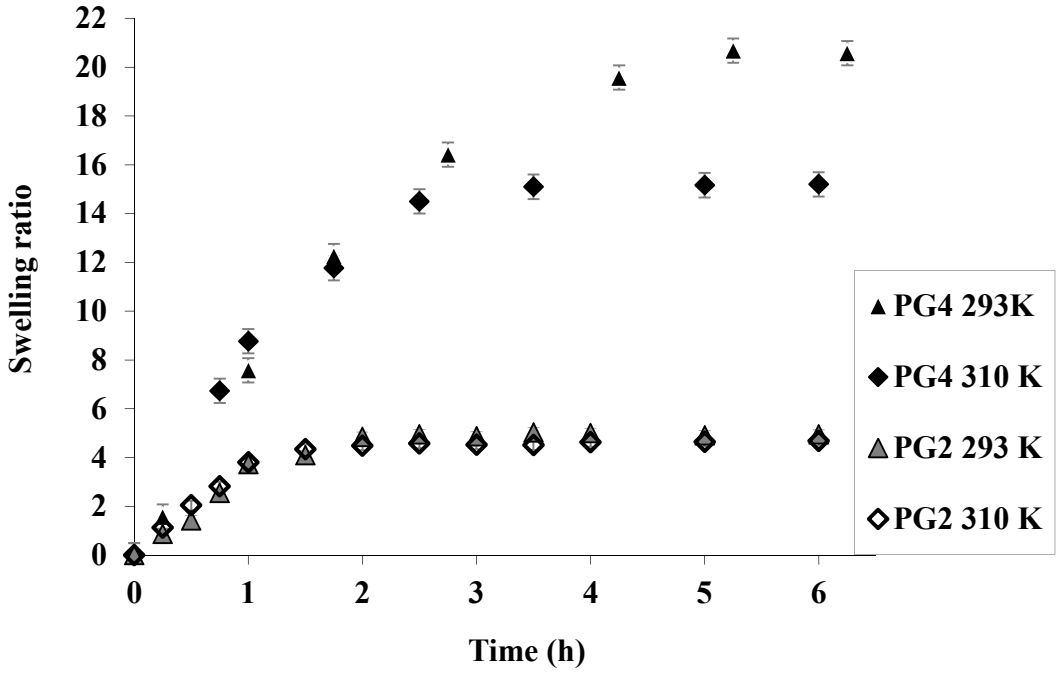

Figure 6.4. Swelling behaviour of PG2 and PG4 hydrogels at 293 K and 310 K

As shown in Figure 6.4 a negative temperature-sensitive swelling behaviour was observed for both hydrogels. The effect of temperature was less pronounced for the PG2 hydrogel due to its denser network structure and lower polyglycerol content compared to

the PG4 hydrogel. Similar behaviour was observed for PEG-based (Graham, Nwachuku et al., 1982) and PVOH-based hydrogels (Lee, Kim et al., 1996). This temperature dependence is due to the lower chemical affinity of the hydrogel to water and the dissociation of hydrogen bonds between water molecules and polymer chains at higher temperatures. As temperature increases, hydrogen bonding between the polymer chains and water molecules becomes less favorable thermodynamically compared to intermolecular interactions in hydrogel and water–water interactions (Bikram and West, 2008). Therefore, lower equilibrium swelling ratios at higher temperatures were obtained.

In addition to the temperature-dependent swelling behaviour, the hydrogels exhibited pH-dependent swelling behaviour. The pH-sensitivity of polyglycerol hydrogels is unlike PVOH and PEG hydrogels which are not pH-responsive. The swelling of PG2 hydrogels was less pH-sensitive compared to that of the PG4 hydrogel due to the presence of higher concentrations of PEG-based cross-linker.

In the third part of this project, the application properties of polyglycerol hydrogels such as the diffusion mechanism and the transient swelling behaviour at several temperatures, a key mechanical property and the degradability of the hydrogel, were investigated (Salehpour and Dubé, 2011). An interesting trend was exhibited in the swelling curves prior to equilibrium being reached or the so-called transient state. For both hydrogels, an increase in the initial rate of swelling with temperature was observed. This was expected as this dynamic part of the swelling curve corresponds to the diffusion of water into the hydrogel where diffusion rates are expected to increase with temperature. This trend was also observed for polymers with similar chain structures such as PEG (Graham and Zulfiqar, 1989). The temperature dependence of swelling in a transient state

is also predicted in most mathematical models (Fonseca, Dubé et al., 2009). The diffusion process can be described by Fick's law of diffusion (Crank, 1975). The diffusion behaviour was investigated by studying the relation between water uptake and time$^{1/2}$ in the transient state. For both PG2 and PG4 hydrogels, the relations were linear at 333 K but the system demonstrated a non-linear sigmoidal diffusion pattern at lower temperatures (see Figure 6.5 for PG4 hydrogel). Thus, it was concluded that both polyglycerol hydrogels exhibited Fickian behaviour at 333 K and anomalous non-Fickian diffusion at lower temperatures. For both hydrogels, an initial time lag was observed for the diffusion processes at 293 and 310 K, while the sigmoidal shape of the dynamic swelling curve became more accentuated for diffusion at 293 K (see Figure 6.5). This behaviour was due to autocatalytic kinetics of swelling mechanism at lower temperatures, where presence of hydrogen bonding in the hydrogel affects the initial swelling behaviour (Díez-Peña, Quijada-Garrido et al., 2002).

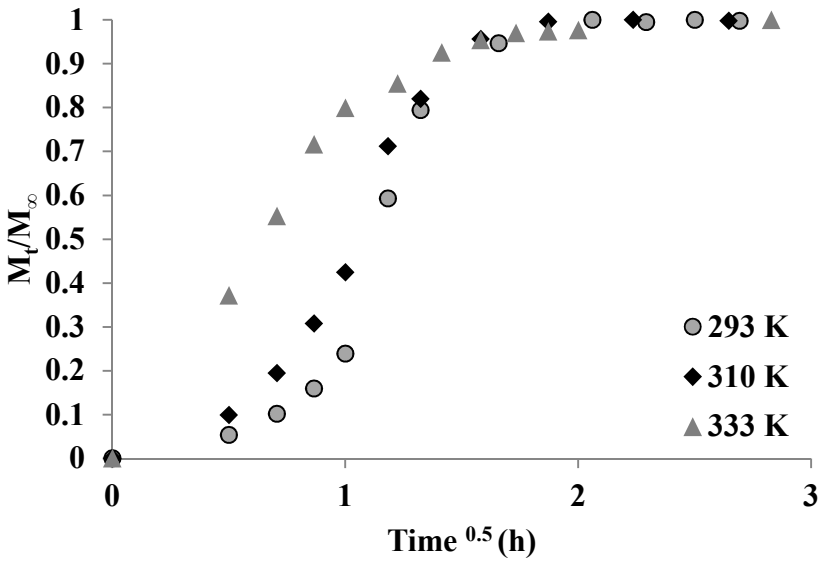

Figure 6.5. Swelling kinetics of PG4 hydrogels versus square root of time at 293, 310 and 333 K.

Since the knowledge of the mechanical properties and microstructure of the hydrogels is necessary in order to tailor the hydrogel properties to certain applications, a compressive mechanical property and the molecular weight between cross-links were measured for PG2 and PG4 hydrogels and dry gels (see Table 6.1). A higher Young's modus (E) was observed for PG2 hydrogel with a higher degree of cross-linking as mechanical strength of hydrogels are often derived almost exclusively from the cross-links in the network; particularly in the swollen state where physical entanglements are nearly non-existent (Anseth, Bowman et al., 1996).

Table 6.1. Young's modulus and molecular weight between cross-links for polyglycerol hydrogels

Polyglycerol	**Xerogel E (kPa)**	**Hydrogel E (kPa)**	**M_c**
PG2	550 ± 60	160 ± 25	3100
PG4	62 ± 10	8.5 ± 2	37000

The degradability of hydrogels was investigated by monitoring the mass loss of PG2 and PG4 hydrogels in PBS solution. The PG4 hydrogel with a looser network and higher hydrophilicity degraded faster at the beginning of the degradation period because the PBS diffusion into the polymer hydrogel proceeded more readily. Nonetheless, the difference between mass loss values of hydrogels was not significant after 15 days. Both hydrogels were completely degraded in about 42 days.

The final part of this study was devoted to the assessment of the potential for real-time monitoring of the glycerol polymerization using ATR-FTIR spectroscopy. All peaks

were identified and the change in hydroxyl group absorption, which represents the concentration of hydroxyl groups in the reaction mixture, was used to monitor the reaction. Real-time conversion data were obtained using a univariate method. Reaction spectra for in-line monitoring of the reaction is shown in Figure 6.6. During the in-line monitoring of the reaction, fouling of the probe was observed beyond 42 mol% conversion of hydroxyl groups.

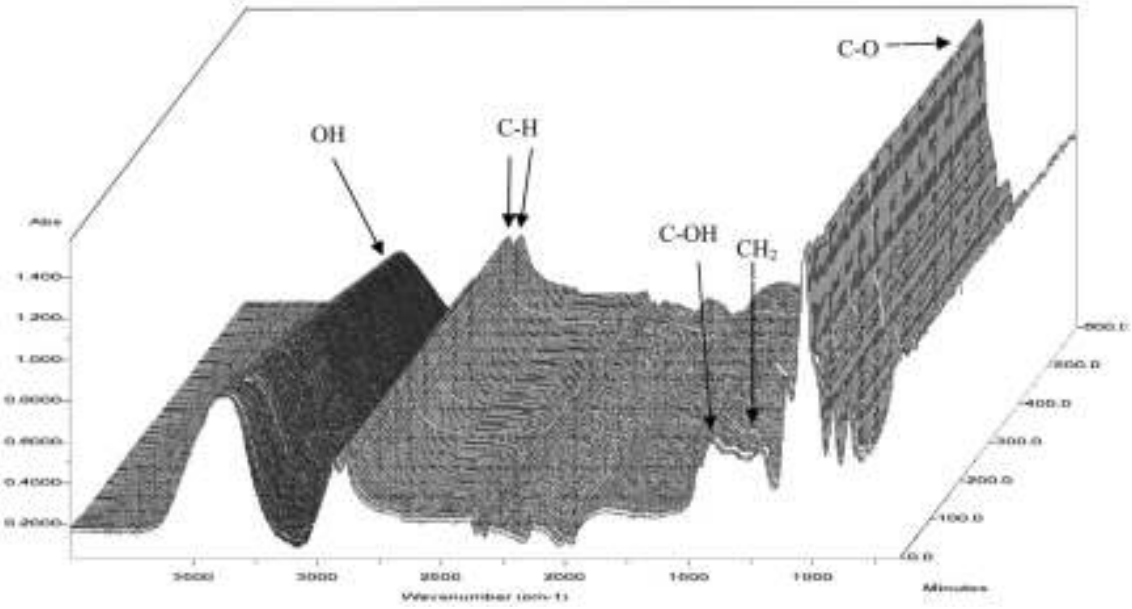

Figure 6.6. In-line monitoring reaction spectra for step-growth polymerization of glycerol.

In order to evaluate the real-time monitoring data, two off-line monitoring methods, hydroxyl number calculation and water removal monitoring, were used for calculation of conversion data. Paired comparisons of the differences between the conversions obtained from the different methods were carried out and the calculated results with 95% confidence intervals indicated that there was no significant difference between the conversion measured using the hydroxyl value method and the water removal method throughout the reaction and in-line and off-line ATR-FTIR monitoring prior to fouling. The in-line and

off-line ATR-FTIR monitoring techniques were suitable for predicting conversion at lower viscosities, which corresponded to conversions below ~40 mol%. Therefore, ATR-FTIR spectroscopy was found to be a reliable tool for monitoring conversion for the production of oligoglycerols from glycerol.

6.2. Concluding remarks and future recommendations

The summary of the findings, main impacts and contributions of this thesis along with future recommendations are briefly detailed below,

6.2.1. Part 1: The synthesis of polyglycerol from a renewable source makes it an ideal polymer in the support of sustainable industrial practices. There is no report of polymerization of glycerol to high molecular weight and we have filed a patent based on this work. This innovation opens the door to a broad range of new applications for polyglycerol; higher molecular weight implies more flexibility in the range of application properties. Polyglycerol consists of an inert polyether backbone with an abundant number of functional hydroxyl side groups, which makes it a suitable cost-effective candidate for the replacement of popular fossil-based PEG and PVOH with a comparable structure. This polymer, with good biocompatibility properties and a large number of derivatizable hydroxyl groups, can find application in the pharmaceutical and biomedical industries where modification of functional groups is often required. The following list offers various recommendations for future research:

a) Synthesis of higher molecular weight polyglycerols: This may be achieved by investigating other polymerization methods such as solution polymerization. The incorporation of a solvent into the polymerization system reduces the viscosity of the reaction mixture and may delay the

gelation point of the reaction. Of course, a non-toxic, renewable solvent would be preferred.

b) Trying other active catalysts for this system: The polymerization of glycerol using other strong acids such as hexafluorophosphoric acid, tetrafluoroboric acid and trifluoromethanesulfonic acids can be investigated. Reactions with these acids may enable different reaction mechanisms and result in less branched polyglycerol products or a higher gelation point.

c) Copolymerization of glycerol: In order to tailor the properties of polyglycerol such as hydrophilicity, molecular weight, melting point, glass transition temperature and mechanical properties, di-functional or multifunctional monomers can be used to produce copolymers with significantly different properties.

6.2.2. Parts 2 and 3: Novel stimuli-responsive polyglycerol hydrogels were synthesized for the first time using a long chain PEG-based cross-linker and application properties were investigated. The hydrogels exhibited a wide range of swelling ratios which were sensitive to pH and temperature of the diffusing solvent and were controllable by the degree of cross-linking. Diffusion kinetics were studied and can be used for the evaluation of hydrogels for specific applications such as drug delivery. A compressive mechanical property of the hydrogels, which can be controlled by the degree of cross-linking, was calculated and was found to cover a broad range. The mechanical property fell within the range of suitability for drug delivery matrices and tissue engineering applications (Martens, Bryant et al., 2003). Degradability of the hydrogels was studied and was comparable to that of PEG and PVOH hydrogels. The hydrophilicity and

biodegradability of polyglycerol hydrogels make them suitable for pharmaceutical, biomedical and biotechnological applications. They could potentially serve as a replacement for well-studied PEG and PVOH hydrogels. Polyglycerol with considerably high swelling ratios can also be used as moisture absorbents and solvent dryers for a broad range of applications. The following studies are recommended for future work:

a) Study the effects of other stimuli on swelling behaviour: Sensitivity and response of the hydrogels to other important stimuli such as biomolecules (e.g., glucose) and ionic strength of solvent can be investigated.
b) In vivo studies of the hydrogels: Comprehensive in vivo evaluation of the hydrogels is recommended such as in vivo biocompatibility and in vivo biodegradability.
c) Study of other cross-linking techniques: Evaluation of other cross-linking techniques such as thermal cross-linking and UV cross-linking of hydrogels is recommended to replace the current chemical cross-linking method.
d) Utilization of different cross-linkers: Study of reactions with other multi-functional cross-linkers with different degrees of polymerization such as PEGDE with M_n=2000 or cross-linkers with completely different chemical structures such as glutaraldehyde is interesting for the synthesis of polyglycerol hydrogels with new properties.
e) Study adhesive applications of hydrogel: Polyglycerol, with its abundant number of hydroxyl groups, is a suitable candidate for hydrogel adhesives or partially cross-linked adhesive applications.

f) Study the biodegradation products: It is important for most biomedical and pharmaceutical applications to identify the in vivo and in vitro biodegradation products.

6.3.3. Part 4: The step-growth polymerization of glycerol was monitored using three different techniques: water production monitoring, hydroxyl value calculation and ATR-FTIR spectroscopy. The ATR-FTIR monitoring of glycerol consumption was a real-time technique performed for the first time. In-line and off-line ATR-FTIR spectroscopy was a successful method for monitoring of the reaction up to medium conversions. It was also a reliable tool for monitoring the compositions in polyglycerol hydrogel production. The following future recommendations can be considered for improving the real-time monitoring of glycerol polymerization:

a) Use of an alternative probe: The ability to monitor the polymerization to higher conversions will be facilitated by the use of an alternate probe type which does not allow probe fouling.
b) Prevention of probe fouling: In-line monitoring of the reaction may be possible throughout the reaction by finding an alternative mixing method or continuous probe cleaning method.
c) Use of a solvent: Performing the polymerization in a solution state will keep the viscosity down and prevents the fouling of the probe.

In general, the project had the intention of contributing to green polymer reaction engineering (Anastas and Warner, 2000). Through this project, the following green chemistry principles (see Appendix A) were satisfied,

- Design safer chemicals and products: Production of environmentally friendly polyglycerol;
- Design less hazardous chemical syntheses: Glycerol bulk polymerization as opposed to solution polymerization using toxic solvents;
- Use renewable feedstock: Using glycerol as a monomer;
- Use catalysts: Sulphuric acid as the catalyst;
- Avoid chemical derivatives: Avoided the toxic glycidol as the monomer;
- Use safer solvents and reaction conditions: No solvents;
- Design chemicals and products to degrade after use: Synthesis of biodegradable polyglycerol;
- Analyze in real time to prevent pollution: ATR-FTIR spectroscopy monitoring technique.

It is worth mentioning that in addition to the above mentioned advantages, by utilization of the by-product of biodiesel production (i.e., glycerol) and converting it into a biodegradable polymer (i.e., polyglycerol), the biomass cycle of biodiesel was improved and waste production was reduced (see Figure 6.7).

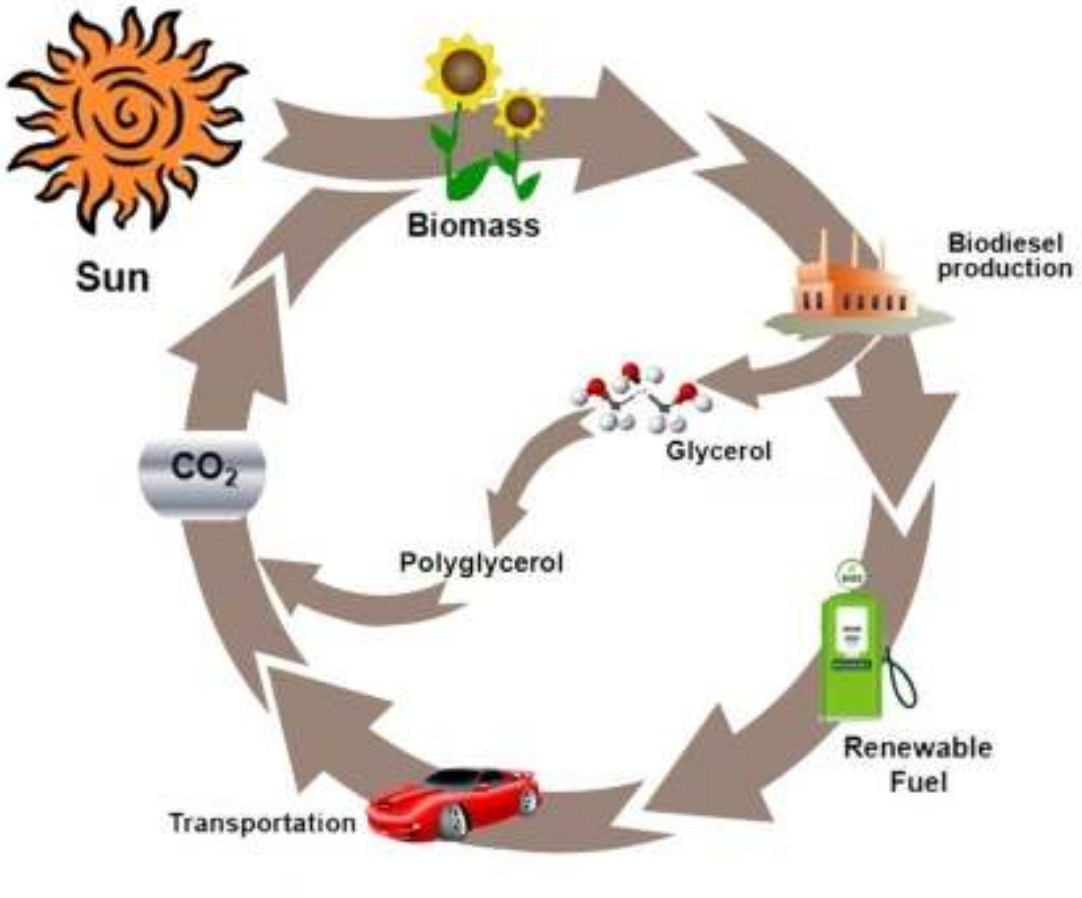

Figure 6.7. Biodiesel and glycerol production biomass cycle.

6.3. Publications and Patents

This research project contributed five peer-reviewed publications, where three of the papers have already been accepted, one submitted and one to be submitted shortly. They comprise the manuscripts presented herein and are listed below:

1. Salehpour, S., Dubé M. A. (2011) "Towards the Sustainable Production of Higher Molecular Weight Polyglycerol", Macromolecular Chemistry and Physics, 212(12): 1284-1293

2. Salehpour, S., Zuliani, C., Dubé, M. A. (2011) "Synthesis of Novel Stimuli-responsive Polyglycerol-based Hydrogels", European Journal of Lipid Science and Technology, in press
3. Salehpour, S., Dubé, M. A. (2011) "Application Properties of Novel Polyglycerol-based Hydrogels", Journal of Macromolecular Science, Part A Pure and Applied Chemistry, in press.
4. Salehpour, S., Dubé, M. A. (2011) "Reaction Monitoring of Glycerol Step-growth Polymerization using ATR-FTIR Spectroscopy", submitted to Macromolecular Reaction Engineering.
5. Salehpour, S., Dubé, M. A., Essayas, A., (2011) "Green Pathways to Polymer Production: A Critical Review", to be submitted.

In addition to the above mentioned papers, one patent application has been filed and a formal disclosure to an intellectual property receptor has been submitted based on this project.

1. Pending Patent: "Methods for Making Polyglycerol", Patent Application No. PCT/US2011/028871 (filed March 2011), Inventors: M. A. Dubé and S. Salehpour
2. Formal disclosure submitted: "Polyglycerol for Stimuli-responsive Hydrogel" (submitted August 2011), Inventors: M. A. Dubé and S. Salehpour

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Appendix A. Green pathways to polymer production: A critical review

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Salehpour, S., Dubé, M. A., Essayas, A., to be submitted, 2011.

Introduction

Living in an industrialized world, humankind is expressing great concern for sustainable development as they are entitled to a healthy and productive life in harmony with nature. The ability to meet current needs without putting in jeopardy the ability of future generations to meet their own needs, has been dealt with in several ways, one of which is the application of the principles of green chemistry. As a mature and versatile field, the polymer industry plays a significant role in our society as polymers have become ubiquitous.

Issues with the extensive use of fossil-based raw materials and large amounts of reagents that are of environmental concern, in addition to the accumulation of polymeric materials in the environment, has led scientists and engineers to re-examine the polymerization process in light of the twelve principles of green chemistry.

1. Prevent Waste: Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
2. Design safer chemicals and products: Design chemical products to be fully effective, yet have little or no toxicity.
3. Design less hazardous chemical syntheses: Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
4. Use renewable feedstock: Use raw materials and feedstock that are renewable, rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

5. Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are used in small amounts and carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. Avoid chemical derivatives: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
7. Maximize atom economy: design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
8. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals. If a solvent is necessary, water is a good medium as well as certain eco-friendly solvents that do not contribute to smog formation or destroy the ozone.
9. Increase energy efficiency: Run chemical reactions at ambient temperature and pressure whenever possible.
10. Design chemicals and products to degrade after use; design chemical products to break down into innocuous substances after use so that they do not accumulate in the environment.
11. Analyze in real time to prevent pollution: Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of by-products.

12. Minimize the potential for accidents; Design chemicals and their forms (solid, liquid or gas) to minimize the potential for chemical accidents including explosions, fire, and release to the environment

These principles as applied to carrying out polymerizations via a green pathway are described herein.

1. Prevent waste: Design chemical synthesis to prevent waste, leaving no waste to treat or clean up.

The generation of waste in polymerization processes primarily emanates from three main sources: residual monomers due to incomplete conversion, waste from compounds such as solvents and suspending agents used during the process but not consumed in the reaction, and off-spec material generated due to excursions from controlled conditions.

Residual monomers in particular are problematic due to their typically hazardous nature. Since most monomers exhibit significant toxicity to human health, reducing the residual monomer content is desired to prevent workplace exposure as well as exposure to the consumer. There are numerous industrial practices involving residual monomer reduction techniques. Residual monomer removal techniques can be classified into two categories; (i) chemical methods, in which the residual monomer is reacted to generate additional polymer (or being aggregated to existing ones), or to generate compounds which could either be easily removed, are non-toxic or less volatile than the initial monomer. (ii) A physical method which involves stripping of the residual monomer from the polymer by volatilization or by extraction with a solvent or with the aid of an ion-exchange resin (Arajuo, 2002).

Chemical methods include ramping the reaction temperature and using a finishing catalyst often referred to as a "chaser" (either additional amounts of the same catalyst or a more reactive one) towards the end of the reaction process to reduce residual monomer. Other techniques may occur immediately after the polymerization process and incur the additional cost of at least one more processing stage and may require further treatment of residual water and emissions. This includes techniques such as steam stripping, gas purging or other devolatilization techniques. These methods are questionable due to increasing workplace health and environmental requirements, in that these procedures may generate residual waters and VOC emissions. Of course, with appropriate recovery (and cost), these methods can be effective. Methods like post-polymerization and/or chemical monomer removal are often used in order to lower the monomer content prior to the use of devolatilization processes. This is but one example where several methods of residual catalyst removal are coupled. Other techniques of this type include post-catalysis procedures followed by spray-drying (Schul, 1998), and hydrolytic slitting of the monomers followed either by distillation (Noelken, 1994) or by the use of an oxidizing agent (Huth, 1995).

In contrast to the above methods, ways to ensure that the monomer is not occluded from the locus of reaction either by diffusional resistances or phase differences could be used. An example is the formation of polystyrene latex via ultrasonic initiation (Ooi, 2000). The presence of ultrasonic irradiation resulted in the speeding up of the polymerization rate and the resulting molecular weight of the polymer latex obtained was higher than the conventionally manufactured one, showing that monomer conversion to polymer was the

highest and the amount of residual monomer in the final polymer product was minimized (Ooi, 2000).

Choosing the best technique for the removal of residual monomers is very case specific as each polymerization type (homogeneous or heterogeneous) and monomer system has its own peculiarities. However, one major principle that governs the choice of residual monomer techniques is the point that the procedure used should not affect the properties of the polymer.

Solution polymerization is often employed rather than bulk polymerization due to viscosity and heat transfer issues . The obvious disadvantage of these types of polymerizations is the removal of the solvent from the polymer, which may require energy intensive methods such as distillation . Not all polymerizations can be practically carried out in a solvent-free environment, and many solution polymerization products possess superior properties. There are as a result, many efforts underway to replicate the properties in either alternative solvents or by other means (Salehpour, 2008; Fonseca, 2010; Salvini, 2010).

Finally, the issue of off-spec material is one that concerns many industries. In the polymer industry there are numerous sources for producing off-spec material. The viscous nature of high molecular weight polymers makes them prone to temperature excursions during their manufacture. These excursions can affect the polymer molecular weight and lead to branching, cross-linking and ultimately, the formation of gel. In many cases, the presence of cross-linked materials and gels is desired to impart certain performance properties. However, there are certainly many instances where these are not desired.

Ensuring adequate process control methods for reaction temperature is not easy but there are certainly many options to consider. This may include mixing considerations.

In addition to the above, off-spec materials can result from the presence of impurities found in the monomer feed stream. Impurities that scavenge radicals in free-radical polymerizations can have a profound effect on the final product (cite papers by me and Penlidis regarding impurities). One should also consider that bad batches are often blended with good ones (Schulz, 1959; Bamford, 1969; Stickler, 1984).

Recent advances in controlled radical polymerization have enabled tremendous microstructural control and have also served to suppress the formation of unwanted compounds.

As can be seen, there is not a single pot solution for the minimization of waste production in polymerization processes. Often, a combination of several steps is taken. These steps include measures taken in regards to the use of solvents, the implementation of catalysis to improve yield, and means to lower residual monomer. The use of alternatives to current solvent-based synthesis may play a significant role in reducing waste, but the maintenance of high quality final product properties is of concern. Hence, more study has to be done in improving the property of polymers produced under solvent-free conditions.

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2. Design safer chemicals and products: Design chemical products to be fully effective, yet have little or no toxicity.

In a relative way, polymer products tend to be inherently safer than their starting materials (e.g., monomers, solvents). In general, polymers are in and of themselves non-toxic. However, in the event that they are degraded or burned, their degraded components may present serious environmental effects. In addition, incomplete conversion of the starting materials may result in residual monomers in the product, which upon release can prove to be quite harmful. Moreover, in many instances a variety of additives are often used to modify a polymer's properties and these also can pose health and environmental risks. These additives may include plasticizers, solvents, fire retardants, oxygen scavengers, pigments, etc.

Solvents are a major input in the polymerization industry and are accountable for a significant fraction of the waste generated as well as a large portion of workplace hazards. A significant source of toxicity in polymer products occurs when solvents are used either as diluents or to enable the application of the polymer (e.g., as a paint or adhesive). Volatile organic compounds (VOCs), highly polar conventional solvents such as *N*-methylpyrrolidone, *N,N′*-dimethylacetamide, *N,N′*-dimethylformamide, pyridine, and chlorinated solvents, which are used in polycondensation polymerizations, result in increased air pollution, most of them being volatile and most of them toxic and flammable. These solvents are high on the list of harmful chemicals because they are used in significant volumes and are often volatile which makes them difficult to handle . Hence based on these, certain greener surrogates have been suggested for use. Among the suggested solvent alternatives are monoterpenes (MTs), ionic liquids (ILs) and supercritical

fluids (mainly supercritical carbon dioxide), to name but a few. These substituent solvents perform substantially at par with their conventional counterparts (fossil-fuel based solvents) and have an advantage in that they are environmentally benign (Welton, 1999; Benton et al., 2004; Xie, 2005). A more in depth discussion on solvent alternatives is covered in Section 8.

Most monomers exhibit significant toxicity to human health. Thus, reducing the residual monomer content is desired to prevent workplace exposure as well as exposure to the consumer. There are numerous industrial practices involving residual monomer reduction techniques. Residual monomer removal techniques can be classified into two categories; (i) chemical methods, in which the residual monomer is reacted either generating new polymer chains (or being aggregated to old ones), or generating new compounds which could be easily removed, nontoxic or even less volatile than the residual monomer itself. (ii) A physical method which involves stripping of the residual monomer from the polymer by volatilization or by extraction with a solvent or with the aid if an ion-exchange resin (Araujo, 2002).

Increasing reaction temperature and using finishing catalyst or a reactive monomer are common methods applied towards the end of reaction processes to reduce residual monomer. Other techniques employed for the removal of residual monomer occur immediately after the polymerization process which incur additional cost of at least one more stage and may require further treatment of residual water and emissions (e.g., devolatilization procedures).

Certain methods exist for avoiding the root cause of residual monomer formation at the design stage, but these may in turn interfere with the final product properties. One

example is the formation of polystyrene latex via ultrasonic initiation (Ooi and Biggs, 2000). The use of ultrasonic irradiation resulted in an increased rate of polymerization and the resulting molecular weight of the polymer latex obtained was higher than that using conventional methods. The amount of residual monomer was minimized by design (Ooi and Biggs, 2000).

Choosing the best technique for the removal of residual monomers is very case specific as each polymerization type (homogeneous or heterogeneous) and monomer system has its own peculiarities. However, one major principle that governs the choice of residual monomer techniques is the point that the procedure used should not affect the properties of the polymer. Techniques such as stripping, gas purging or other devolatilization techniques are no more adequate for reducing the residual monomer content due to increasing health and environmental requirements and to the even more strict laws concerning monomer emissions, in that these procedures may generate residual waters and VOC emissions. Hence, methods like post-polymerization and/or chemical monomer removal are used in order to lower the monomer content prior to the use of devolatilization processes. This is but one example where several methods of residual catalyst removal are coupled. Other techniques of this type are post-catalysis procedure followed by spray-drying (Schull, 1998), hydrolytic slitting of the monomers followed either by distillation (Noelken, 1994) or by the use of an oxidizing agent (Huth, 1995).

Many polymer products involve the use of several additives, in order to enhance the final properties of the polymer, among which plasticizers and stabilizers are examples. A plasticizer, by definition, is a substance incorporated into a material to increase its flexibility and workability (Cadogan and Howick, 2005). Phthalates, which are the diesters

of 1,2-benzenedicarboxylic acid (phthalic acid), are the most common class of plasticizers used in industry. One of the most widely used plastics for a multitude of applications is polyvinyl chloride (PVC). One of its applications is in the medical stream where this plasticized polymer is used to collect, store and collect blood or blood products, to infuse drug solutions into the veins, to collect urine. In order for PVC to be suitable for use in such applications, it has to be able to be processed in various sizes and shapes with a higher degree of flexibility and color. In turn, to have such properties and also to stabilize this relatively unstable polymer, it needs to have several additives put into it and pass through heat and pressure, which eventually presents potential toxicological problem. In comparison, polymers that have been used for prosthetic devices such as dentures and liners in the dental profession, since the requirements for such devices has focused much on rigid polymers (those that contain less material that could conceivably migrate from the plastic), generally fewer toxicological problems have been reported (Guess, 1968).

Some of other common additives used in plastic processing include Bisphenol A (BPA) and polybrominated diphenyl ethers (PBDEs). BPA is used in a variety of consumer products mostly as food cans lining (Kang, 2003) and also in polycarbonate plastics as used for baby bottles and other containers (Brede, 2003). PBDEs on the other hand are flame retardant chemicals used in textiles, thermoplastics used in electronics. Studies prove that exposure to these additives causes altered endocrine function, reproductive or developmental effects (Meeker and Sathyanarayana, Shanna H. Swan) and might also result in cancer in the case of higher percentage accumulation (Wang, 2011). Hence, more research is being undertaken by scientists in order to minimize the level of these additives and/or replace them with suitable surrogates that do not have adverse effect on the

environment and human health. One of the efforts being undertaken is the case of self-plasticizing polymers. Instead of using low molecular weight plasticizers such as diisooctyl phthalate and tritolyl phosphate, a rubbery polymer such as polyBA, grafted from PVC chains via ATRP, can serve as a plasticizer yielding a self-plasticized material in which leaching of the plasticizer is essentially eliminated (Tsarevsky and Matyjaszewski, 2007). It has also been reported that a typical esterification reaction between citric acid and 2-butoxyethanol has been used to successfully synthesize an enviro-friendly citrate electrolyte-based anti-static plasticizer (CEAP) having sodium thiocyanate-doped tris (2-butoxyethyl) citrate.

The persistent use of VOCs present as solvents, residual monomers and additives in the polymer industry poses many potential negative consequences to human health and the environment. A great many alternative methods to remove these threats without substantially affecting the quality and properties of the polymer products is an area of ongoing study. The use of alternative solvents as suggested in section 3 presents an area of significant impact. The presence of residual monomers while not as significant in quantity as other volatile components, nonetheless provides an important area for improvement especially in light of the increased use of polymers in medical applications. Polymer additives have only begun to be targeted by various concerned groups and their replacement with environmentally benign compounds is also at the forefront of several research efforts.

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3. Design less hazardous chemical synthesis: Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

The transformation of one or more monomers into a final polymer product usually includes a number of additional components to aid synthesis or to modify the final product properties. A large volume of solvents, often petroleum-based, as well as plasticizers, fire retardants, pigments, stabilizers, catalysts, and the like are used throughout the synthesis stage and these often pose serious toxicity concerns. In addition to the workplace hazards posed by these materials, their release to the environment during product use, under unexpected conditions (e.g., in a fire) and after disposal may also pose significant risks (see section 2). Hence, a greener polymer synthesis suggests the replacement of these toxic starting materials, processing aids and product modifiers, including monomers, with environmentally benign substances. Accordingly, the discussion that follows is focused on the use of green monomers, solvents, catalysts, and additives as possible surrogates for conventional components in polymer product synthesis, processing and modification.

It is widely accepted that many monomers pose serious health hazards but in a polymerized form, the hazard is no longer present or is significantly reduced. Of course, the hazard of exposure to monomers does exist during polymer synthesis in the workplace but may also exist in the product in the event of incomplete conversion where residual monomer remains. One also should not forget the case of epoxies where the curing of the polymer must take place. Eventually, depending on the usage and disposal methods, a polymer may revert to its original monomer components and once again, the toxicity of the monomer would become important. Although there are synthetic polymers that aren't bio-

sourced and still environmentally benign, a shift to the use of greener monomers often implies the use of starting materials from biomass.

Polymers derived from biomass, mostly from cellulose and ligno-cellulosic materials, were reported to present poorer performance compared to those derived from petroleum-based monomers, especially in terms of thermal processability (Yoshioka, 2005). The relative difficulty of converting biomass into plastics is due to cellulose's rigid backbone. This is a common refrain when it comes to replacing long-existing products with greener options. It is clear that work has to be done to improve the performance of bio-based materials but successes are indeed possible (Somaieh: Please cite your work on ``glycerol`` here). Below, we investigate in further detail, the numerous examples of greener monomers being successfully transformed to quality polymer products.

The most attractive materials with the greatest potential in terms of environmental compatibility include cellulose derivatives, among which nitrocellulose (NC) and cellulose acetates (CA) are the most common. NC was a pioneer of the present plastic industry, but recently more studies have focused towards CA, mainly because it is produced in large quantities. A method was developed for plasticizing CAs with dibasic acid anhydrides and monoepoxides during melt-processing (Yoshioka, 1996). This method of introducing an oligoester side chain into a CA molecule enhanced the thermo-plasticity of CA (internal plasticization), whilst homo-oligomers of the oligoester would be produced at the same time, acting as external plasticizers. Cellulose di-acetate (CDA), which has the greatest thermo-plasticity among cellulose acetates, lacked melt-processability, but when reacted with SA (succinic anhydride) and PGE (phenyl glycidyl ether) at 120^{o}C for 20 min, was converted into a thermoplastic material. It was also reported that grafting CAs with cyclic

esters, in which cyclic esters were made to react with CA (Yoshioka et al., 1999), also enhanced the thermoplastic properties of CDA and the products were moldable by hot pressing, without the addition of plasticizers.

Another class of biomass that can be processed into plastics is the lignocellulosics group, mainly wood. Since lignocellulosics are not thermally flowable materials; methods for processing them are limited. But if appropriate properties could be imparted on them, their easy processability can be attained. Simple reactions such as esterification and etherification were reported during the late 1970s and early 1980s to convert wood into a plastic material by chemical modification (Shiraishi et al., 1979), (Shiraishi, 1983). Such a conversion was mostly related to the internal plasticization of wood, and the degree of plasticization was found to be insufficient especially when small substituent groups and/or polar groups were used. Hence, there was a need for external plasticization to accompany the internal plasticization for achieving better properties. Benzylated wood (BzW), a mouldable material with excellent mechanical properties, is one of the most common externally plasticized lignocellulosics. . Tensile strengths of 42.7 MPa were reported, which compared well with polystyrene (PS) which had a tensile strength of 29.4 MPa under the same conditions (Yoshioka, 2005). Slight differences only exist in the temperature at which these two materials start to flow. PS undergoes flow at 153^{o}C while BzW starts to flow at 175^{o}C; still this temperature difference can be narrowed by blending polycaprolactone (PCL) with BzW (Yoshioka, 1992).

Poly(lactic acid)/poly(lactide) (PLA) is a highly biocompatible and bioresorbable polymer that is derived from lactic acid (2-hydroxy propionic acid) as a monomer, which is a natural product found in the body (Lipinsky and Sinclair, 1986; Ulrich, 1999; Albertson

and Varma, 2002; Mochizuki, 2002; Tsuji, 2002). Its original application was in the biomedical field for fracture fixation pins (Lipinsky and Sinclair, 1986; Ulrich, 1999; Albertson and Varma, 2002), but improvements in the synthesis of PLA over the past decade, especially from improved fermentation methodologies to convert corn starch into lactic acid, and the resulting lower costs have led to the study of PLA for a wider range of applications such as packaging materials, plastic bags, and thermoforms (Gruber et al., 2000; Auras et al., 2004).

Monoterpenes (MTs) have the potential to replace petroleum-based solvents as will be discussed later. However, MTs can equally be used as green monomers in producing polymers which possess similar qualities and properties as some conventional polymers. MTs of industrial significance are β-pinene, α-pinene and dipentene (d, limonene), which are readily derived from pine trees as mixtures known as terpentines. β-pinene comes first in the order of reactivity followed by dipentene and α-pinene. The polymerization of MTs proceeds through cationic means because these monomers are electron-rich and devoid of basic functionalities (Mathers and Lewis, 2011). The commercial production of terpenic resins has progressed in terms of efficiency through the years, but the main drawback to contemporary systems is the solubility of the co-initiators inside the reaction medium, making recycling difficult and resulting in higher material consumption and waste generation. As an example, $AlCl_3$ forms adducts with aromatic and olefinic compounds and can't be easily separated from the product, necessitating de-ashing steps that generate $Al(OH)_3$ and HCl (Olah, 1979). For a chemical system to be green and commercially viable, the co-initiator should have minimal solubility in the product, be of moderate to low cost, possess high activity under a wide range of process conditions, and be able to be

recycled. Few initiator systems have been developed recently to aid the green production of terpenic resins, which are heterogeneous systems based on strong Bronsted acids in conjuction with Lewis acids or ones consisting of strong Lewis acids in combination with weak Lewis acids (Chen, 1997a; Chen, 1997b). These combinations of initiators function as solid superacids where a proton derived from either the Bronsted acid or from adventitious moisture initiates polymerization. They also don't contaminate the product with Lewis acid and are compatible with continuous processes. Although advantageous in regards to product contamination, these initiator systems give rise to products with broad molecular weight distribution, limiting their utility, and are still questionable in terms of recyclability. But a novel system for the economic green production of polyisobutylene and butyl rubber may also be promising for the synthesis of terpenic resins in that the system uses heterogeneous co-initiators based on methylaluminoxane (MAO), the co-initiators are insoluble in the reaction medium and can be supported on a variety of substrates (Lewis, 2009; Mathers, 2010).

As mentioned earlier, biodegradable aliphatic polycarbonates obtained from the ROP of six-membered cyclic carbonates are an interesting class of polymers that can be employed to produce non-toxic thermoplastic elastomers. Because these polymers are of significance in the medical field, i.e., in the production of sutures, drug delivery systems, body and dental implants, and tissue engineering, which mostly end up in the body, the use of biocompatible and bioresorbable components in their manufacture is a main target (Smith and Hunneyball, 1986; Albertson and Eklund, 1994; Marler, 1998; Pencom, 1998; Pêgo, 2003a; Pêgo, 2003b). There have been several mechanisms studied with regards to the catalytic routes towards the formation of biodegradable aliphatic polycarbonates,

mainly via cationic, anionic, enzymatic, coordination-insertion, and organocatalytic ROP polymerizations. Biocompatible catalytic systems have recently been reported in the literature and include organic based and biocompatible metal based catalysts that contain calcium, zinc, potassium, and magnesium.

Satisfactory results were obtained in the use of these biocompatible catalysts and some notable observations were

- The melt polymerization of trimethylene carbonate (TMC) catalyzed by $BF_3.OEt_2$ yielded poly(TMC) with very high molecular weight within a temperature range of 353-373K. Ether linkages, that were a result of the unwanted decarboxylation side-process, were seen to be eliminated at lower temperature ranges, but the higher ends gave polymers that contained some ether linkages.
- First catalyst reported for use with the anionic pathway was K_2CO_3 by Carothers (Carothers and Van Natta, 1930). Afterwards alkoxide-, alkylithium and also alcoholate based catalysts were investigated, but the industrial use of the first two may be complicated by their instability and high reactivity (Rokicki, 2000). The main advantage of proceeding via this route is the fact that high molecular weight polycarbonates can be formed in the absence of ether units.
- Enzymatic catalysis seems to be a better alternative in that it requires milder conditions and enzyme catalysts are safe and can often be recycled (Bisht, 1997; Kobayashi et al., 1997; Matsumura et al., 1997; Al-Azemi et al., 2000; Matsumura et al., 2000; Matsumura et al., 2001; Feng et al., 2002; He, 2003; Tasaki et al., 2003) unlike metal based catalysis which often requires the use of pure monomers, anhydrous conditions and the need for catalyst removal from the final polymer.

Lipase derived from Candida Antarctica was demonstrated to catalyze the ROP of TMC in bulk, and results showed that the molecular weight of the final polymer decreased with an increase in temperature and could have been due to side reactions such as hydrolysis, increased chain initiation and depolymerization reactions. Higher water content also led to higher molecular weights and increased polymerization rates because of an increase in the propagating chain ends and enhancement in the enzymatic activity. Immobilizing the enzymes with silica micro-particles had a positive impact on the catalytic efficiency as a result of their thermal activation and stability (Feng et al., 2002; He, 2003).

- The insertion-coordination pathway is an alternative pathway which uses metal based catalysts and is advantageous for its improved control of the polymer molecular weight and the absence of ether linkages in the polycarbonates. The interesting route discovered in the coordination-insertion pathway was the catalyzed copolymerization of oxetone and carbon dioxide to give poly (TMC) and a preformed TMC as a by-product (Darensbourg et al., 2011). This in turn means that the TMC by-product can further be processed to poly (TMC) via ROP. Hence, this catalytic route is extremely important in ensuring that no waste is generated and any by-product is re-processed into products. The type of catalyst used was (salen)Cr(III)Cl complex in the presence of n-Bu_4NX (X=Cl, N_3) as a co-catalyst.

Several other green monomers exist either as naturally occurring compounds or through certain chemical transformations based on natural substances. It has been a common practice to convert starch (polysaccharides) into environmentally benign monomers via

catalytic reductions under acidic, basic, oxidative, reductive and hydrothermal conditions. To name a few, compounds such as polyols, organic acids (lactic and glycolic acid), 5-Hydroxymethylfurfural and levulinic acid have been formed as a result of the catalytic breakdown of starch (Verendel et al., 2011). As a by-product of biodiesel production, glycerol serves as a significant green source for the production of poly(glycerol). A very broad range of polyols or diols and in some instances, poly- or diisocyanates, can be obtained from vegetable oils. A wide variety of polyurethane materials ranging from flexible foams to ductile and rigid plastics have been able to be produced based on a wide range of vegetable oil-based monomers. These vegetable oil based polyurethanes have been evaluated and proved to be of comparable or even better in performance than the petroleum based counterparts (Pfister et al., 2011).

The topic on solvents has been covered extensively in the Section 8, hence only a brief summary will follow accordingly. Polymers in industry are mostly processed in solvents for use either as diluents or for enabling the use of the polymer (as in the case for paints and adhesives), and among the solvents used are mostly volatile organic compounds (VOCs). VOCs have been reported to be harmful in that they are toxic, flammable, volatile, which makes them difficult to handle, and might also be carcinogenic (Welton, 1999). Therefore, based on attempts to replace these environmentally harmful compounds have ILs, MTs, Supercritical fluids (mainly CO_2) come in place. These green solvents are well known to be environmentally benign and can be used for polymerization processes with good solvation properties for monomers, catalysts and also polymers. In addition to acting as solvents, certain fringe benefits have also been realized to arise from these solvents such as catalytic behaviour in the case of ILs and the minimization of the release of CO_2 as a

green house gas to the environment, in the use of supercritical carbon dioxide as a solvent. There are also certain drawbacks in the use of these solvents and also areas in which these solvents haven't been tested yet, therefore more research and scientific investigation is imminent.

Polymerization involves the use of several additives, in order to enhance the final properties of polymers, among which plasticizers, stabilizers, and flame retardants are the most common examples. A plasticizer, by definition, is a substance incorporated into a material to increase its flexibility, workability, or disintensibility (Cadogan and Howick, 2005). Phthalates, which are the diesters of 1,2-benzenedicarboxylic acid (phthalic acid), are the most common class of plasticizers used in industry. One of the most widely used plastics for a multitude of applications is polyvinyl chloride (PVC). One of its applications is in the medical stream where this plasticized polymer is used to collect, store and collect blood or blood products, to infuse drug solutions into the veins, to collect urine. In order for PVC to be suitable for use in such applications, it has to be able to be processed in various sizes and shapes with a higher degree of flexibility and color. In turn, to have such properties and also to stabilize this relatively unstable polymer, it needs to have several additives put into it and passed through heat and pressure, which may eventually present toxicological problems. In comparison, polymers that have been used for prosthetic devices such as dentures and liners in the dental profession, since the requirements for such devices has focused much on the rigid polymers (those that contain less material that could conceivably migrate from the plastic), generally fewer toxicological problems have been reported (Guess, 1968). Hence, efforts towards addressing this problem have been able to come up with some results:

(i) The typical esterification reaction between citric acid and 2-butoxyethanol, which has been used to successfully synthesize an enviro-friendly citrate electrolyte-based anti-static plasticizer (CEAP) having sodium thiocyanate-doped tris(2-butoxyethyl) citrate,

(ii) The substitution of ionic nonylphenol ethoxylates (NPEOs) with non-ionic alkyl phenol free emulsifiers having a more favourable ecological profile (Fernandez, 2005). NPEOs are widely used as surfactants for emulsion polymerization and for post adding stabilization in latex applications with formulations of high filler content. However, the use of NPEOs has been deemed as being an environmental concern in that alkyl-phenol residues are formed when these surfactants are released to the environment (Vandenberghe, 1998; Dodgson, 2003). Because of the aforementioned reason and also due to the fact that the NPEOs aren't as 'readily biodegradable' as their counterparts, fatty alcohol ethoxylates (FAEOs), more attention is being given to FAEOs as green surfactants. These surfactants, having an ethoxylation degree between 7 and 40, are clear, high solids at room temperature exhibiting excellent water miscibility and performance in emulsion polymerization (Fernandez, 2005). The hydrophobe in the surfactants is mostly made from natural renewable resources and the use of these non-ionic surfactants has proven to be successful when tested with different monomers such as all acrylic screening systems, styrene/butyl-acrylate and vinyl acetate/butyl acrylate systems (Baumann et al., 1996; Fernandez, 2005). There exists a very large list of environmentally benign emulsifiers, most of which are derived from natural sources. Some of these include surfactants based on mannuronate moieties derived

from alginates and fatty hydrocarbon chains derived from vegetable resources (Benvegnu and Sassi, 2010), Ionic liquids as surfactants (Smirnova and Safonova, 2010), surfactants based on lipo-peptides (Rondel, 2011)…

(iii) Flame retardants are common additives in the plastic industry used for reducing the flammability of plastics. A wide range of flame retardants are available in two broad categories: Organohalogen and organophosphorous compounds (Green, 1992; Weil, 1992; Gann, 1993; Davis, 1996; Weil, 1999; Lu, 2002). The organohalogenic compounds, particularly brominated aromatics, have been the most commonly used ones because of their effectiveness and low cost. On the other hand organophosphorous compounds, are green alternatives which have an equal effectiveness as the organohalogenic compounds, but come at a much more higher expense. Although widely used in industry, the bioaccumulation of organohalogenic compounds in the environment and the related health risks are forging polymer industry's direction towards alternative green flame retardants, which adapt certain properties as the organophosphorous compounds (Wheler, 1997; Alaee, 2002; Birnhaum, 2004; Pepich, 2005; de Wit, 2006; Law, 2006). A recent breakthrough has been the discovery of a green flame retardant that is derived from tartaric acid, which is a by-product of the wine industry. Tartaric acid can easily be converted to di-ethyl ether and the presence of two hydroxyl groups in this compound makes it easier for the incorporation of phosphorous containing moieties. In this specific case, the tartaric acid, as a di-ethyl ester, is treated with diphenyl phosphonic chloride (Howell and Carter, 2010). The result was diethyl 2,3-diphenylphosphinato- 1,4-butanedioate, which undergoes thermal

decomposition, most likely to liberate diphenylphosphonic acid to promote char formation, at the combustion temperature of most common polymers. Furthermore, it may also serve as one component of high-phosphorus content oligomers with flame retarding properties. Hence, it might serve as a base for developing a family of bio-based, environmentally friendly flame retardants for polymeric materials.

Catalysts, although used in very small amounts in polymerization reactions, have the potential to be causes for environmental concern. Catalysts are used both in monomer as well as polymer synthesis. Ring-opening polymerization (ROP) reactions of six-membered cyclic carbonates provide simplistic routes to the production of biodegradable polycarbonates (Smith and Hunneyball, 1986; Marler, 1998; Pencom, 1998; Pêgo, 2003a; Pêgo, 2003b). Trimethylene carbonate (TMC) or 1,3-dioxan-2-one is the most well studied cyclic carbonate monomer for this process and is synthesized by the transesterification of 1,3-propanediol and derivatives with various reagents. The study on finding a renewable source of 1,3-propanediol is mainly focused on glycerol due to its availability in abundance in the market, especially as a by-product from the bio-fuels industry. Heterogeneous catalysts aren't selective for the transformation of glycerol to 1,3-propanediol (Perosa and Tundo, 2005) and limited success has been enjoyed in using homogeneous catalysts (mainly cationic ruthenium complexes). Hence, most of the activity in relation to the production of 1,3-propanediol from renewable sources is centered on the use of biocatalysts. It's a well known fact that glycerol can be converted into 1,3-propanediol via anaerobic fermentation (Freund, 1881). Forsberg has reported the formation of 1,3-propanediol from glycerol as a major fermentation product using a number of bacteria, including various strains of Clostridium acetobutylicum (Forseberg,

1987), while the microbial production has been examined on an industrial scale by Henkel with an expected theoretical yield of 1,3-propanediol (Kretschmann, 1993).

Some major breakthroughs as well as undergoing research in an attempt to replace conventionally used compounds in polymerization (which have been of environmental concern) with environmentally benign counterparts that generate less waste, has been outlined and discussed. Most of the studies regarding green surrogates for polymerization have dated back since 1990, and the results obtained so far suggest that this is a fertile area for research with much more yet to come. As there isn't a complete knowledge of the characteristics and properties of these substituents, future research work needs to emphasize the improvement of their performance properties under different process conditions. More economically feasible and simpler techniques also need to be identified for the derivation of these green replacements from renewable raw materials.

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4. Use renewable feedstock: Use raw materials and feedstock that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

The relative importance of macromolecular materials based on renewable resources suffered a setback first with the rapid surge of coal-based chemistry starting in late 19th century and then with the petrochemical revolution of the 20th century (Gandini, 2008). However, in recent years, increasing concern towards environmental issues and the need for more versatile polymer-based materials has led to interest in polymers from renewable feedstocks. This includes the design and synthesis of renewable polymers with various macromolecular architectures and enhanced properties (Coates and Hillmyer, 2009). The consumption of fossil fuels in the production of plastics was reported to be about 7% of worldwide oil (Williams and Hillmyer, 2008b). Therefore, concerning the increasing oil price and its limited sources, it is necessary to develop new pathways to polymeric materials using renewable resources. Some interesting renewable sources are discussed below.

Lactic acid: Corn or sugar feedstocks can be processed to yield D-glucose that can then be fermented to yield lactic acid. The lactic acid is converted thermally and catalytically into its cyclic dimer and lactide. Using a suitable reactive catalyst, lactide will undergo ring-opening polymerization to yield polylactide (PLA) (Auras et al., 2004b). PLA has attracted significant attention as it is produced from plant derived sources, it also has suitable properties as a replacement material for polyolefins yet degrades to metabolites. The resultant plastic has properties related to polyolefins and polystyrene and can be

converted into various products mainly in packaging and fiber applications (Auras et al., 2004b).

Plant oils: Plant oils, such as soybean oil, palm oil, and rapeseed oil are some of the most important renewable raw materials for the chemical industry. They are extracted primarily from oilseed plants and have a wide variety of applications such as foods, fuels (biofuels), lubricants, paints, cosmetics, pharmaceuticals, plasticizers, and construction materials (Metzger and Bornscheuer, 2006). They are also attractive as monomers for polymer synthesis due to their natural abundance and reactive functionality. Plant oils have been used for decades in paint formulations, as flooring materials and for coating and resin applications. The best known application is linoleum flooring, which was industrially produced in 1864 (Meier et al., 2007). Linoleum's main component is linseed oil and it provides a durable and environmentally friendly alternative to PVC flooring. Plant oils consist of a varying composition of fatty acids (i.e., triglycerides) depending on the plant, the crop, the season, and the growing conditions. The word 'oil' refers to triglycerides which are liquid at room temperature. The most important parameters affecting the physical and chemical properties of such oils are the stereochemistry of the double bonds of the fatty acid chains, their degree of unsaturation, as well as the length of the carbon chain of the fatty acids.

In recent years, extensive studies have been carried out on the production of various polymers from plant oils (Seniha Güner et al., 2006; Montero De Espinosa and Meier, 2011; Öztürk and Küsefoğlu, 2011); their use as monomers presents challenges due to their heterogeneous and variable structures. It can be expensive to separate and extract

the different triglycerides because the oils are typically expressed in low concentrations and the composition of a particular oil can vary seasonally (Williams and Hillmyer, 2008b).

Carbon Dioxide: Carbon dioxide is an interesting synthetic feedstock since it is abundant, inexpensive, non-flammable and a waste product of many chemical processes. Although it is estimated that nature uses CO_2 to make over 200 billion tons of glucose by photosynthesis each year, synthetic chemists have had little success in developing efficient catalytic processes that exploit this attractive raw material (Williams and Hillmyer, 2008b). The applications of carbon dioxide are rather limited, for example in the organic synthesis arena only urea, salicylic acid, and some cyclic carbonates can be viably produced from CO_2 at this time. However, carbon dioxide can be copolymerized with heterocycles (e.g., epoxides, aziridines, episulfides) to yield a range of novel alternating copolymers. Carbon dioxide can be used as a feedstock for large scale polycarbonate synthesis (Sugimoto and Inoue, 2005). Polycarbonates represent a very promising class of materials; they are thermoplastic materials and can be produced with reasonable efficiency from CO_2 and epoxides.

Glycerol: Due to a significant glut in the glycerol market because of increasing biodiesel production, science and industry are showing interest in finding economic ways to utilize the emerging surplus of glycerol. Glycerol as a bio-based monomer with high functionality is an interesting candidate for sustainable step-growth polymerization. Recently, new opportunities for the conversion of glycerol to high molecular weight polymers have emerged (Salehpour and Dubé, 2011b). Polyglycerol produced from this cost-effective renewable monomer was used to produce hydrogels suitable for a wide range

of pharmaceutical and biomedical applications (Salehpour and Dubé, 2011a; Salehpour et al., 2011).

The field of renewable monomers is fairly new and interest in this area is increasing. While current limits to the feedstocks for renewable polymers imply that they are not expected to overtake the market for polyethylene or polypropylene in the near future, the use of renewable polymers in a wide range of specialty products is promising.

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5. Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are used in small amounts and carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

In many commercial polymerizations, catalytic agents are used to not only increase reaction rate but to manipulate the final product properties. In free radical polymerization, for example, a small amount of catalyst say, 10^{-9} to 10^{-3} M, results in the reaction of 0.1 to 10 M reactive groups. When it comes to the use of a catalyst, waste formation is minimized based on catalytic parameters such as activity, selectivity (chemo-, regio-, enantio- and diastereo-) and stability. While it may be possible in some cases to recover/recycle the catalyst after use, in the majority of cases, separating the catalysts from the resulting polymer matrix is not possible. This is not usually an issue as the catalysts are often used at very low concentrations and can be neutralized or thermally deactivated.

The types of catalysts used in polymerization are either homogeneous (i.e., the catalyst is soluble in the reaction medium) or heterogeneous (i.e., the catalyst exists within a phase distinct from the reaction medium). A majority of homogeneously catalyzed processes exist in the liquid phase and operate at moderate pressures (<20 atm) and temperatures (<150^{o}C). Homogeneous catalysis is advantageous in terms of increased activity but problems may arise due to corrosion of reaction vessels and difficult separation processes. On the other hand, the use of heterogeneous catalysts has proved to be an increasingly interesting alternative as solid catalysts are rarely corrosive, are capable of withstanding a wide range of temperatures and pressures without a significant impact on

their activity, and separation of the catalyst from the product may be straightforward (Lester, 1995).

The use of catalysts dates back to 1953, where some transition metal compounds, like $TiCL_4$, used in conjunction with aluminum alkyls were able to polymerize ethylene into linear poly-ethylene under mild reaction conditions of temperature and pressure, and later, used for the regio- and stereoselective polymerization of propylene. The massive expansion of the property envelope of polyolefins through years has led to the exponential growth of the use of Ziegler Natta polymerization in the polymer industry. By using Ziegler Natta catalysts, it has been possible to attain exceptional balance between properties such as fluidity, rigidity, impact strength, transparency… and starting from the initial few thousand tons, the production of polyolefins via Ziegler Natta polymerization is over 70 million tons on a global scale (Cecchin et al., 2000). After initial studies have been carried out on titanocenes (Breslow and Newburg, 1957), a class comprising homogeneous and single-site catalyst systems were developed, based on metallocenes (Gupta et al., 1994; Moehring and Coville, 1994; Brinzinger, 1995; Kaminsky and Arndt, 1997; Alt and Koeppl, 2000; Coates, 2000; Resconi, 2000) or late transition-metal complexes (Britovsek, 1999; Ittel et al., 2000) that in theory are superior over the conventional Ziegler-Natta systems. However, contrary to the aforementioned facts, heterogeneous Ziegler-Natta catalysts are still at the forefront of most of the industrial and also scientific arena, since they still account for the majority of the global polyolefin market share.

In addition to polymer product optimization and property enhancement, polymerization technologies were also improved to a greater extent in the evolution of Ziegler-Natta catalysts. Some of these are:

- Complete control of morphology over both the catalyst and polymer particles
- Very high mileage (chlorine content of less than approximately 50ppm, preferably <10ppm)
- Control of the most important polymer parameters such as molecular mass (MW), molecular weight distribution (MWD), and comonomer incorporation, whenever required

Most of all, post-polymerization deashing and extraction steps that were important in removing catalyst residues and the amorphous contents from the polymer, respectively, were able to be removed because of an increased isospecificity, leading to a more improved catalytic polymerization technique. The amount of catalysts used in reactions was also a major issue as more residual catalyst in the final polymer product could lead to an alteration of certain properties, especially when exposed to certain conditions. However, the advance in catalytic parameters such as activity, selectivity, specificity… had led to the use of extremely low amounts of catalysts yielding very high amounts of the desired product, minimizing the chance of formation of unwanted substances via side reactions. As an example, the typical productivities of catalysts for polyethylene, based on either $MgCl_2$ or its precursors, range from approximately 10kg Polymer/g Catalyst to 40 kg/g Catalyst (Cecchin et al., 2000).

Another class of catalysts worth mentioning in regards to catalytic polymerization, that has received more attention nowadays, are enzymes. “Enzymatic Polymerization” is defined as “chemical polymer synthesis *in vitro* (in test tubes) via nonbiosynthetic (nonmetabolic) pathways catalyzed by an isolated enzyme.” In most cases, enzymatic polymerization enables the production of polymers, which otherwise are difficult to prepare

and these groups of catalysts are advantageous over chemical catalysts as they result in much more accelerated reaction rates, operate in mild conditions and have high stereo-, regio- and chemoselectivities of reactions (Kobayashi, 2010). Table 1 shows the different types of polymers produced with their respective enzymes.

Table 1: Classification of Enzymes and In Vitro Production of Typical Polymers Catalyzed by Respective Enzymes (Kobayashi, 2010)

Enzymes	**Typical polymers**
Oxidoreductases	Polyphenols, polyanilines, vinyl polymers
Transferases	Polysaccharides, cyclic oligosaccharides, polyesters
Hydrolases	Polysaccharides, poly (amino acid)s, polyamides, polyesters, polycarbonates

Enzymatic polymerization is often a route that's environmentally benign, where the feed stocks and final products are within the natural material cycle, that's in compliance with "green polymer chemistry" (Kobayashi, 1993; Kobayashi, 1999).

Catalysis, in general, as the most evolved and most advanced sector in polymerization, serves a key role in the industry in accelerating reaction rates, minimizing waste and manipulating final polymer product properties. However, only certain polymerizations make use of catalysis, showing that their use hasn't been extended to a majority of the polymerization techniques present currently in industry. For instance, most step-growth polymerizations are deemed to proceed non-catalytically and the introduction

of catalysts to such systems will essentially result in the minimization of waste production (which used to result from impurities in monomers undergoing certain side reactions), and also reduce the energy expenditure for running the reaction (Hamielec and Tobita, 2000). Hence further research in areas of applying catalysis for different polymerization techniques should be dealt with a greater intensity so as widen the application of catalysts.

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6. Avoid chemical derivatives: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

During the course of transformation of a monomer to a polymer product, there may be instances in which the material under transformation must be modified either to make it compatible for further steps (e.g., temporary modification of polymer surfaces) or to impart certain characteristics vital to the polymer product performance. Such temporary or permanent modifications are sometimes effected by the use of blocking or protecting groups which in turn introduce additional reagents in the process that lead to the generation of waste. For example, poly (vinyl alcohol) (PVA), which has vast applications in imaging processes, is usually modified temporarily via t-butoxycarbonyl group (t-BOC) into Poly (vinyl-t-butyl carbonate) and then thermolyzed to get the final PVA. Such a modification is done in order to make PVA soluble in a wide variety of organic solvents, but in doing so, carbon dioxide and 2-methyl-propene are released, which are of concern to the environment and workplace safety (Jiang et al., 1987). Accordingly, a search for alternative means by which the desired product performance properties can be obtained without the use of additional reagents, is under study. Although this issue has not been of significant priority so far, some progress has been made and certain specific advances have been reported.

2-Hydroxyethyl methacrylate (HEMA) is an important functional monomer widely used in the manufacture of soft contact lenses (Montheard et al., 1992; Dumitriu, 1994). Although HEMA homopolymer is hydrophilic and has a high degree of hydration, it isn't water soluble. There have been several reports on the synthesis of controlled-structure

HEMA-based block copolymers via anionic polymerization, but this approach requires the protection of the alcohol functionality in the presence of additional reagents (Sogah, 1987; Nagasaki, 1995). Such syntheses, in addition to being harmful to the environment due to the release of wastes, involve at least three steps: synthesis of the protected monomer, its controlled polymerization and subsequent removal of the protecting groups, incurring additional costs for energy. Atom transfer radical polymerization (ATRP), since its discovery in 1995 (Kato, 1995; Wang and Matyjaszewski, 1995; Patten and Matyjaszewski, 1998) has been effective for hydrophilic monomers in aqueous media under mild conditions; however this wasn't the case when used for the production of HEMA in aqueous media. Although a quantitative yield was obtained within a short period of time at lower temperatures, it has been found that some degree of cross-linking has occurred, making it difficult to re-dissolve the HEMA homopolymer. However a switch of medium to a 50:50 methanol/water mixture led to excellent results and the use of a protecting group to aid in solvation was avoided. Not only was the use of a protecting agent overcome, but the reaction was carried out at 20^{o}C, which is a very energy efficient approach (Robinson, 2001).

Similar results were also obtained when ATRP was employed to form 3-sulfopropyl methacrylate (SPMA) homopolymers and amphiphilic block copolymers with methyl methacrylate (MMA) in a water/dimethylformamide (DMF) mixed solvent at 20^{o}C using Cu/bipyridine catalyst. The most interesting feature of the mixed solvent polymerization system is that it showed it is possible that hydrophobic monomers can also be block-polymerized in the same solvent allowing the direct synthesis of hydrophobic-hydrophilic

block copolymers without the application of protecting group chemistry or post-polymerization derivatization. However, despite the lack of protecting groups, there were some drawbacks. In particular, the small amount of residual SPMA monomer present during the initial stage of the MMA polymerization had a significant effect on the micellization properties (Masci, 2004).

The application of blocking and protecting groups for temporary modifications on polymeric substances is often applied via Controlled Radical Polymerization (CRP), but the outstanding property control afforded by these methods may present an intriguing dilemma. More frequently, however, one finds the application of blocking and protecting groups in the preparation of polymeric materials for biomedical applications. As a matter of fact, blocking and protecting groups are used extensively in the biomedical polymer industry and this is due to the need for bulk and surface modification to achieve a hydrophobic/hydrophilic balance or through attachments of biologically active species such as anticoagulants or biorecognizable groups, which is made possible via chemical groups (protecting/de-protecting). Such modifications are put in place to mediate and enhance the acceptance and healing of the synthetic device or medical implant. Many of the innovative processing technologies are used to produce functional devices, feeling and often behaving like natural tissues (Zdrahala and Zdrahala, 1999). Often, the synthetic materials fabricated for medical purposes need to be made compatible with reactions taking place in the body, via the incorporation of reagents as blocking or protecting groups. Although the generation of waste, that arises as a result of the introduction of further reagents, is undoubtedly an issue to be dealt with in designing a green and sustainable polymerization process, it is seen

that the related impacts aren't as serious as some of the other issues presented herein (Kulkarni, 1966; Gunatillake et al., 2003).

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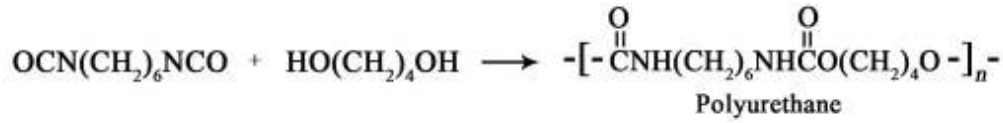
7. Maximize atom economy: design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

Synthetic efficiency is a key factor towards the attainment of green polymer synthesis; it should be addressed not only in terms of selectivity (chemo- (functional group differentiation), regio- (orientational control of two reacting partners), diastereo- (control of relative stereochemistry), and enantio- (control of absolute stereochemistry)), but also through the number of atoms in the reactants (monomers and other reagents) that are retained in the final product (polymer) (Trost, 1991). This feature is referred to as atom economy, and is calculated by dividing the molecular weight of the desired product/polymer by the sum of the molecular weights of all the substances produced in the stoichiometric equation. In ideal terms, a 100% atom efficient process signifies one in which the product would incorporate all of the atoms of the reactants and no waste is produced. The degree of atom economy is commonly defined by the E-Factor, the ratio of the amount of waste produced to the amount of product that results (kg of waste/kg of product) (Sheldon, 2007). Therefore, the lower the value of the E-Factor, the less waste is produced, the greener is the process, and vice versa. Accordingly, the major benefits derived from an atom economical process are most notably the effective use of scarce raw materials and decreased emissions as well as low waste disposal.

In the case of elementary reactions, atom efficiency can easily be enhanced by using catalysts. Using catalysts facilitates the pathway by which a desired product can be obtained via selectivity, activity and so forth, and by doing so the possible formation of unwanted by-products gets suppressed, ideally leading to a 100% atom economical process

(Sheldon, 2000). However, in the case of polymerization, there isn't any one-pot remedy to transform a less atom economical process towards a more atom efficient one as there are



multiple factors responsible for the production of unwanted by-products. Atom wastage in polymerization, in some instances, is inevitable – due to the nature of the process and the absence of alternative means to synthesize the polymer. The most common example of polymerization, in which by-products are most certainly produced, is the step-growth technique. There is generally only one type of chemical reaction which links molecules of all sizes and some of the typical chemical reactions that lie under this category are esterification, amidation, formation of urethanes, and aromatic substitution (Hamielec and Tobita, 2000). Due to limitations in the types of chemical reactions by which the polymerization of certain monomers can proceed using the step-growth technique, the polymer industry has been forced to follow such pathways even though unwanted by-products were continually being produced. For instance, Nylon 66 is reported to be produced via step-growth polymerization according (Hamielec and Tobita, 2000). There is always one mole of water produced as a by-product for every linkage produced. Hence, this reaction isn't completely atom efficient, with an atom efficiency of 91.26%. On the other hand, there are also 100% atom efficient polymerizations such as in the case of polyurethanes.

Unlike most step-growth polymerizations, which proceed via a single pathway, there are cases such as the formation of poly(ethylene terephthalate), which can proceed by several pathways. Based on this, one may decide to proceed with a pathway in view of the atom economy, but availability of the corresponding monomers, price, reaction conditions, energy consumption and safety should be considered as there is indeed a trade-off between these criteria and sustaining an atom economy (Hamielec and Tobita, 2000). A similar scenario can be witnessed in the production of poly(glycerol), which can be synthesized via two pathways, i.e., (i) using glycidol as a monomer via free radical polymerization, which has a higher atom economy and (ii) from glycerol via step-growth polymerization, which has a relatively lower atom economy.

Among the different step-growth polymerization techniques, it is the interfacial type that is referred to as the most atom economical process and for which higher molecular weight polymers are produced (Morgan, 1965; Millich et al., 1982). In interfacial polymerization, polymers are formed at or in the vicinity of a phase boundary of two immiscible monomer solutions. The lower temperatures used suppress the relative rates of side reactions, and, therefore the purity of monomers isn't as important as in most other step-growth polymerizations. Despite its high atom efficiency, interfacial polymerization hasn't been applied widely industrially due to the high cost of acquiring the reactive monomers and the large amount of solvent which must be removed at the end of the process and recovered (Hamielec and Tobita, 2000). However, in the case of many other step-growth polymerizations, monomer purity is of prime significance as it determines the possibility of formation of unwanted by-products through side reactions;

hence higher atom economy is to be expected only when highly pure monomers are employed.

Generally speaking, chain growth polymerizations are highly atom efficient. Typically, all atoms in the monomers find their way into the polymer product. Where a chain growth polymerization might be considered to lose atoms is strictly from the point of view of waste generation. As discussed in section 1, the generation of waste will be influenced by monomer purity and control on the reaction conditions (e.g., temperature, ingredient feed rates).

In conclusion, atom economy (or E-factor) is an important criterion to be accounted for, when considering green processes. Several methods to reduce waste formation in, for example, the fine chemical industry have been implemented and resulted in higher atom economy. Polymer processes, for the most part, tend to have an inherently high atom economy from the point-of-view of the reaction mechanism. Achieving an even higher atom economy may involve a trade-off among several other equally or more important factors that contribute towards the attainment of a green and environmentally benign process. Often, one would need to employ an alternative polymerization mechanism to obtain the same polymer and this may not always be possible.

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8. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals. If a solvent is necessary, water is a good medium as well as certain eco-friendly solvents that do not contribute to smog formation or destroy the ozone.

A number of polymer products have been traditionally been made using solution polymerization for over half a century to produce polymers with valuable properties. The use of a solvent as a polymerization media prevents increases in viscosity due to the generation of high molecular weight polymer chains by diluting the reaction mixture. This translates into improved heat transfer and prevention of thermal runaway by absorbing the heat of polymerization. Many polymer products have been developed over time, which present desirable molecular weight qualities and other final properties that cannot be met by other polymerization technologies (i.e., bulk or emulsion polymerization). However, with the growing need to create a cleaner environment along with strict regulations and concerns regarding volatile organic compounds (VOCs), alternatives to conventional solvents are being sought. Some important enviromentally-friendly alternative solvents are discussed below.

Monoterpenes: Monoterpenes (MTs) are a C_{10} subset of terpenes. Terpenes are a broad class of molecules found in trees, flowers, fruits and spices that are a function of C_5 isoprene variations, in which their structure may be cyclic or acyclic, containing alkenes or other functional groups such as alcohols, aldehydes, ketones, esters and carboxylic acids. MTs, although possessing several differences with petroleum solvents, also have several similarities. Based on available data for dielectric constants and densities (Mathers and Lewis, 2011), MTs have a greater resemblance to aromatic solvents, such as toluene and

xylene, than saturated hydrocarbons, such as heptanes. Despite the fact that MTs are less volatile and more viscous than petroleum based hydrocarbon solvents, they have the potential to act as solvents for a wide variety of monomers and catalysts. Due to this fact, MTs have the ability to replace petroleum based solvents as green and environmentally benign solvents in some polymerization processes. The replacement of petroleum-based solvents such as toluene and methylene chloride with MTs has been reported for ring-opening metathesis polymerization (ROMP) (Mathers, 2006), as well as for the preparation of a wide variety of polyesters, polyethers, polyamides and unsaturated polyolefins (McGrath, 1985; Grubbs, 2003; Hoff, 2009). Generally, the molecular weights obtained from polymerizations in MTs are lower than that in toluene and this can be attributed to the vinylidene or vinyl alkene substituents of MTs participating in ROMP by reacting with metathesis catalysts. Hence, the resulting chain transfer with these accessible alkenes results in lower weight-average molecular weight $\overline{M_w}$ values. However, if molecular weight control is not necessary, hydrogenated d-limonene is a viable alternative to obtain higher molecular weight values that are closer to polymerizations in toluene. As a function of time, $\overline{M_w}$ values show a gradual decrease in toluene due to secondary intramolecular and intermolecular metathesis reactions. This phenomenon is also seen in the case where MTs have been used.

MTs can also be integrated as renewable resources with hyperbranched polymers to synthesize one-pot procedures that provide an economic alternative to multi-step dendrimer synthesis (Mathers, 2009). The polymerization of dicyclopentadiene (DCPD) with ruthenium metathesis catalysts ring opens the norbornene and cyclopentene alkenes, the outcome being cross-linked to yield an insoluble heterogeneous network. However, in the

presence of MTs, chain transfer limits the formation of growing insoluble networks, hence a homogeneous phase occurs. From the standpoint of waste reduction/minimization, slow monomer introduction avoids the need for dilution and also controls the chain transfer rate relative to the rate of cross-linking. The resulting homogeneous poly (DCPD) possesses good physical properties (T_g = 158^{o}C) compared to that of the heterogeneous network produced in the presence of toluene (T_g = 158^{o}C). In addition to the good physical properties, these prepolymers have much better processability, have the potential of undergoing future cross-linking, and do not exhibit the bad odour associated with DCPD (Mathers and Lewis, 2011).

Another scenario in conjunction with the use of MTs as solvents is the case of metallocene polymerizations. The di- and tri-substituted alkenes in MTs are in most cases unable to enter into the active site of the metallocene-methylaluminoxane (MAO) catalyst system and homopolymerize, although they may coordinate to the active site. Based on this, MTs have the potential to act as innocuous chain transfer agents and solvent replacements in metallocene polymerizations. An important factor in the success of metallocene polymerizations using MTs is the interaction between the catalyst and the MT. In this regard, MTs with Lewis basic atoms would be harmful and standard solvent purification procedures would have to be employed to remove excess/non-essential water and avoid the deactivation of early-metal transition metal catalysts.

Ionic liquids: These novel, recyclable solvents are composed of ions in liquid form at or close to room temperature and are organic salts in nature (Laszlo, 2001). Compared to conventional media, ionic liquids (ILs) have great potential as non-volatile organic media for undertaking polymerizations and polymer processing because of their near-zero vapour

pressure, non-flammability, low cost and ease of production (Shadpour, 2010). The term "IL" also includes ionic fluid, molten salt, liquid organic salt, fused salt or neoteric solvent (Dupont, 2002; Fang, 2007; Mallakpour, 2007; Wang, 2009). Due to widespread interest in these compounds, ILs have been heralded as the green, high-tech media of the future (Liu, 2005; Yang, 2006; Rantwijk, 2007). However, their toxicity has not been thoroughly tested. The most important properties of ILs are as follows:

a) They are relatively non-volatile, meaning that they do not yield atmospheric VOCs and can be utilized in low pressure environments (Fraga-Dubreuil, 2002; Binnemans, 2005; Ding, 2005a; Jain, 2005)
b) They exhibit good thermal stability and tend not to decompose over a wide temperature range, thereby making them ideal for use at high temperatures (e.g., 800^{o}C) (Jain, 2005; Parvulescu, 2007; Greaves, 2008; Martins, 2008)
c) They show a higher potential for enantioselective reactions in which they have a significant impact on reactivity and selectivity due to their polar and non-coordinating properties. In addition, chiral ILs are often used to control stereoselectivity (Ding, 2005a; Bica, 2008).
d) They can be considered as both polar and non-coordinating solvents and are good solvents for a wide variety of chemical processes (Binnemans, 2005; Greaves, 2008).
e) They are versatile and complex solvents in that they have the ability to interact through hydrogen bonding, i.e., π-π, n-π, dispersive, dipolar, electrostatic, and hydrophobic interactions (Binnemans, 2005; Greaves, 2008; Martins, 2008).

f) They are known to serve as good media for solubilizing gases such as H_2, CO, O_2 and CO_2 (Huang, 2008).

g) Their highly ionic character enhances reaction rates to a greater extent in many reactions including microwave-assisted organic synthesis as well as polymerizations (Liao, 2006).

h) They can be stored without decomposition for a long period of time and have good miscibility with other organic solvents or monomers (Liao, 2007).

i) In addition, an unquestionable advantage in the use of ILs is their recyclability. Hence, ILs (frequently containing dissolved catalysts) can be repeatedly used in subsequent reaction cycles (Wu, 2009).

The use of ILs as a polymerization solvent has been reported for polycondensations, free-radical polymerizations and ionic (anionic and cationic) polymerizations. Polycondensation reactions are usually carried out at relatively high temperatures, thus, thermally stable ILs have been tested in this instance. The research has focused mainly on the synthesis of polyamides, polyimides and polyesters. Accordingly, when dicarboxylic acids (less toxic although less reactive than corresponding chlorides or anhydrides) were used in direct polycondensation with diamines, polyamides with relatively higher molecular weights were obtained in the absence of any added catalyst (Lozinskaya, 2004; Yoneyama, 2006). Hence, it was concluded that ILs not only act as solvents but also as catalysts. The catalytic behaviour of ILs was also noticed in other polycondensation processes namely, the polycondensation of phenol and formaldehyde (Ogoshi, 2008). Another major advantage of using ILs relates to enzyme deactivation, which usually occurs in many polar organic solvents such as methanol. This is typically not a concern when

using common ILs (Kubisa, 2009). Several studies have confirmed that when conventional free-radical polymerizations are conducted in an IL media, the molecular weights and reaction rates are higher than in polymerization in bulk or in organic solvents (Liao, 2006; Parvulescu, 2007; Bica, 2008; Greaves, 2008; Huang, 2008). The rate constants of propagation tend to be higher and the rates of termination lower than in bulk or conventional solution polymerization. This phenomenon has special significance for controlled radical polymerization (CRP), especially atom transfer radical polymerization (Tsarevsky, 2007). As its name implies, CRP is not living because termination isn`t eliminated. Hence, any factor that leads to an increase in the k_p/k_t ratio widens the window of polymerization conditions within which polymerization can be controlled. This is one of the advantages of carrying out CRPs in ILs. Another advantage is the solubility of several transition metal complexes that are used as atom transfer radical polymerization (ATRP) catalysts such as Cu salts with amine ligands. Accordingly, many of the polymerizations occur under homogeneous conditions and the catalysts can easily be separated from the polymer (Biedron, 2001). The catalyst solution can be recovered and reused (Ding, 2005b; Tsarevsky, 2006; Li, 2007). On the other hand, difficulties in obtaining higher molecular weight polymers due to the issue of solubility has been indicated in reports dealing with the synthesis of polyesters in ILs by polycondensation. It was reported that the solubility of polyesters was limited in ILs and mainly depended on the structure of the IL (i.e., the nature of the cation and anion) (Welton, 1999). Regarding ionic polymerization in ILs, ILs have yielded better results compared to supercritical CO_2 and organic solvents (e.g., CH_2Cl_2) in the cationic polymerization case but haven't been shown to be particularly

suitable for use in anionic polymerizations. This is because ILs aren't entirely stable under different process conditions (Kubisa, 2009).

Despite their numerous advantages, ILs do pose some technical challenges: they possess high viscosity, are often sensitive to moisture and are difficult to purify. In addition, their lack of toxicity has not been widely confirmed. As an example, for a variety of ILs, their viscosity has been reported to be in the range of 10-500 mPa/s at room temperature, which is one to three orders of magnitude higher than conventional solvents. Such a high viscosity, in turn, can affect transport properties such as diffusion and may be an issue (Welton, 1999; Imperato, 2007).

Supercritical fluids: Supercritical fluids and more specifically, supercritical CO_2, constitute a broader class of solvents that can be employed in polymerization reactions. Supercritical CO_2 has many attractive properties that have allowed it to emerge as the most extensively studied supercritical fluid suitable for polymerization reactions. Some of these important characteristics are its fluid properties, effects on polymers, and environmental advantages. Supercritical fluids are known to possess the best properties from both physical states: i.e., they can have gas-like diffusivities (important for reaction kinetics) while still having liquid-like densities that allow solvation of many compounds (Kendall, 1999). They also exhibit changes in solvent density as a result of small changes in temperature or pressure without a significant change in solvent composition. Additional advantages arise when carbon dioxide is used as a supercritical fluid. CO_2 occurs naturally and is abundant in reserves. In addition, it is known to be released in very large quantities, as a by-product, from electric power generation stations that burn fossil fuels and also from ammonia, hydrogen and ethanol plants. CO_2 has a critical point that can be easily reached with a T_c of

31.1°C and P_c of 73.8 bar. The fact that CO_2 is an ambient gas has two major advantages: polymers that are processed in it can be isolated from the reaction media by means of simple depressurization, which results in a dry polymer product and it can be recycled after use as a solvent to eliminate contributions leading to greenhouse effects. Both of these features eliminate the expenditure of high amounts of energy for reaching critical conditions as well as during drying procedures. Hence, in general, using supercritical CO_2 can be advantageous due to the fact that it is inexpensive, non-flammable and non-toxic (Kendall, 1999). Although supercritical CO_2 has a multitude of advantages, especially in regard to environmental impact in the processing of polymers, there are certain constraints for its use as a solvent in polymer synthesis. While CO_2 is a good solvent for most non-polar and some polar molecules of low molar mass (Hyatt, 1984), it is a poor solvent for most high molar mass polymers under mild conditions (i.e., <100°C and/or <350 bar). For example, poly (methyl acrylate) requires 2000 bar CO_2 and 100°C for a 10^5 g/mol polymer to dissolve in CO_2. Such elevated pressures are impractical and too costly for their widespread implementation in the polymer industry. The only polymers that show good solubility in CO_2 under mild operating conditions are amorphous fluoropolymers and silicones (Yilgor, 1984; Krukonis, 1985; DeSimone, 1992; Guan, 1993; Hoefling, 1993; McHugh, 1993).

Biodiesel: Recently, biodiesel (fatty acid methyl ester or FAME) produced from canola oil has been used as a green polymerization solvent, where solution polymerizations of four commercially important monomers (i.e., methyl methacrylate (MMA), styrene, butyl acrylate (BA) and vinyl acetate (VAc)) were studied at 60°C and 120°C using FAME produced from canola oil as a solvent (Salehpour and Dubé, 2008a; Salehpour and Dubé,

2008b; Salehpour et al., 2009). In the 1960s, the use of methyl oleate, a major component of biodiesel, as a polymerization solvent was explored (Jordan Jr and Artymyshyn, 1969). However, the high cost of the pure compound prevented its widespread application. The solvating ability of biodiesel has only recently started to be investigated (Hu et al., 2004). Biodiesel is more commonly known as an environmentally friendly alternative to petroleum diesel for use in combustion engines. It has the chemical structure of fatty acid alkyl esters (FAAE) and is produced by the transesterification of vegetable oils, animal fats or grease with an alcohol in the presence of a catalyst. Different types of alcohols can be used in the transesterification reaction such as methanol, ethanol, propanol, and butanol. Usually, the process is carried out with an alkaline catalyst (e.g., NaOH) dissolved in excess methanol under agitation, controlled temperature and atmospheric pressure (Cao et al., 2009). Biodiesel fulfills the requirements of a good polymerization solvent; it is environmentally benign and has low volatility, low viscosity and good solubility. In addition, biodiesel boils at temperatures beyond 300°C (326°C for canola-based biodiesel) (Salehpour and Dubé, 2008b). This means that it will not pose a hazard in the workplace due to evaporation and reactions can be carried out at elevated temperatures without fear of excessive pressure buildup aside from the contributions of the monomers. There has been mounting interest in carrying out polymerizations at elevated temperatures (McManus et al., 2004). Advantages of using high temperatures include:

- Decrease in concentration of chain transfer agents and initiators; this would reduce costs.
- Increase in the rate of reaction and therefore, an increase in productivity.
- Decrease in the polymer molecular weight without using chain transfer agents.

However, there are disadvantages inherent to running reactions at elevated temperatures such as increased energy consumption, safety considerations and possible undesired side reactions that may occur, i.e., intramolecular chain transfer and depropagation (Quan et al., 2005). A drawback of using biodiesel as a high-boiling solvent in solution polymerizations is the difficulties in solvent removal from the final products, whereas in polymerizations in traditional low-boiling solvents, the solvent can be easily removed from the polymer product by an evaporation process.

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9. Increase energy efficiency: Run chemical reactions at ambient temperature and pressure whenever possible.

Polymerization reactions often proceed under conditions of mass self-heating due to the exothermic nature of the chain propagation reaction (Stolin, 1979). If reaction heats are small, the temperature dependence of the reaction is reduced and the viscosity of the reacting mass during the initial stages of polymerization remains low and approximately isothermal conditions can be maintained. However, a measurable increase in the viscosity of the reaction media, low thermal conductivity and thermal self-acceleration due to strong temperature dependence of the reaction rate lead to continuous and often non-uniform temperature growth. The non-isothermicity of polymerization reactions has often been regarded as a negative factor that leads to non-uniform polymer properties and involves significant challenges in controlling the reaction temperature. However, in recent years, heat generation has been considered as a favourable factor in polymerization with key applications especially in regards to minimization in the expenditure of energy needed to run the reaction. These polymerization reactions can be made to proceed in an almost self-propagating mode and furthermore, the heat generated by the polymerization could be used to preheat various input streams. In other words, there is a case to be made for the use of adiabatic polymerization conditions.

To explain the effects of temperature on chain growth polymerization, for example, it is useful to consider the general polymerization rate equation:

$$R_p = \left(\frac{k_p}{k_t^{0.5}}\right)(2k_d f[I])^{0.5}[M] \quad (1)$$

where [I] = concentration of initiator or catalyst

[M] = total monomer concentration

f = initiator efficiency

k_p, k_t and k_d = propagation, termination and decomposition rate parameters

According to the polymerization rate equation (see Equation 1), the effect of an increase in temperature can be estimated by the change in the quantity $k_p(k_d/k_t)^{0.5}$. Based on the fact that the kinetic rate parameters obey the Arrhenius equation, the activation energy of the polymerization, E_R, which is a function of E_P (activation energy for propagation), E_d (activation energy for initiator decomposition) and E_t (activation energy for bimolecular termination), tends to be high at elevated temperatures largely due to the very high activation energy for initiator decomposition (Hamielec, 2000). This indicates that the rate of polymerization increases strongly with temperature. In bulk or solution chain growth polymerization, the average polymer chain length decreases significantly with increasing temperature when the initiation and bimolecular termination steps dominate over other molecular mass development steps (i.e., when most of the polymer chains are produced by bimolecular termination). When unimolecular termination (chain transfer to small molecules) dominates the molecular mass development, E_P is found to be less than E_f (activation energy for chain transfer reaction), implying that the molecular mass can decrease with an increase in temperature. Manipulating the chain transfer agents used or using a cocktail of initiators with different k_d values (each dissociating at specific temperature ranges) can help maintain a constant concentration of free radicals, which in turn helps maintain a constant polymerization rate, ultimately leading to a relatively uniform molecular weight distribution (Dubé, 1997). Thus, in the case of an adiabatic polymerization, one could potentially employ initiation and chain transfer agent

manipulation to compensate for the effect of increasing temperature and therefore control the polymer properties.

Photopolymerization reactions, since their use by the ancient Egyptians as a part of the mummification process, have significant capabilities compared to the more traditional polymerizations (Decker, 1987). One of their most notable characteristics is the ability of photopolymers to cure rapidly at ambient conditions (Anseth K.S., 1995; Berchtold 2004). With an intimate spatial and temporal control of the reaction rate (i.e., when and where the polymerization occurs), it has been possible to implement photopolymerization in a wide range of applications such as in dentistry (Lovell 2001; Stansbury 2008; Steinhilber, Seiffert et al. 2011), contact and other lenses (Wichterle 1960; Zwiers 1985; McMahon 2000), coatings (Ma 2000; Harant 2006; Khire 2006; Khire 2007), photolithography (Willson 2003; Hutchison 2004; Gates 2005; Khire 2008), tissue engineering matrices (Rydholm 2005; Rydholm 2007; Lin and Anseth 2009) and 3D prototyping (Neckers 1992; Young 1999). Despite the vast potential for energy efficient and solvent free reactions that are able to be undertaken under ambient conditions, the areas where photopolymerizations are utilized is still limited by a general lack of understanding of the polymerization process itself as well as a lack of solutions to problems related to volume shrinkage and stress (Kloosterboer 1988; Francis 2002; Braga 2005; Steinhilber, Seiffert et al. 2011), oxygen inhibition (Decker 1987; Kloosterboer 1988; Gou 2006; O'Brien 2006; O'Brien 2006; O'Brien 2006) and the presence of unreacted monomer (JG. 1988), (Bowman 1991; Cook 1992; Scranton 1992). This is mostly due to the fact that in nearly all practical photopolymerization reactions, the polymer formation step is simultaneously associated with a dramatic material property change (Bowman 2008). Although these materials are

initially liquids with low viscosity, they are rapidly (frequently in less than a second) converted into glassy, highly cross-linked materials. It is this dramatic evolution of the material properties that has significant consequences on the polymer behaviour, leading to complexities in the reaction system that include diffusion controlled reactions (Kloosterboer 1988), (Tulig 1981; Ballard M.J. 1986; Russell 1988; Anseth K.S. 1994; Buback 1994; O'Neil 1999; Lin and Anseth 2009). Thus, there is significant energy efficiency in photopolymerizations that can still be exploited.

Another area of potential energy efficiency lies in ambient temperature reactions. Reversible addition fragmentation chain transfer radical (RAFT) polymerization is a highly versatile form of controlled radical polymerization (Chiefari 1998; Mayadunne 2000; Barner-Kowollik 2006; Bussels 2006). This technique was extensively applied to the polymerization of a majority of monomers that were able to polymerize under conventional free radical polymerization conditions, providing remarkable control over their molecular weight, affording polymers with low molecular weight distributions, and allowing for the facile synthesis of polymers with complex architectures (Chong 1999; Mayadunne 2003; Liu 2005; Li 2006; Nguyen 2006). Ambient temperature RAFT polymerization is a rather straightforward technique. Recently, McCormick and coworkers (Luo 2002; Luo 2002; Luo 2003) reported some remarkable examples for the ambient temperature RAFT polymerization of acrylamide monomers. However, due to the retardation effect caused by either initialization period (Rydholm 2005; Lin and Anseth 2009) or slow fragmentation of the intermediate radicals (Rydholm 2007), adjusting the structure of the RAFT agent or chain transfer agent (CTA) is not solely sufficient to achieve a highly efficient and well controlled ambient RAFT polymerization of most commonly used monomers (YIN 2007).

Results from Pan and coworkers (DC. 1992) on the (dibenzyl trithiocarbonate)-mediated radical polymerization under UV radiation at ambient temperature demonstrated that longer reaction time was needed for these polymerizations to achieve moderate conversion levels and this in part was attributed to the fact that the CTA functionalities had undergone photolysis, causing permanent premature termination, thereby deteriorating the living character of the polymerization. CTAs and their corresponding growing-chain derivatives are strongly sensitive to the UV radiation that covers the CTA moieties characteristic maximum adsorption wavelength, and as a remedy, cutting off the CTA-sensitive shorter–wave radiation significantly suppressed the photolysis, thus improving the living behaviour of these polymerizations (YIN 2007).

The search for energy efficient and cost effective polymerization techniques has become more critical of late due to quickly escalating energy costs. Most of the techniques used for increasing the energy efficiency of polymerization reactions are either in terms of running polymerizations adiabatically or implementing photopolymerization, in which UV rays are used in initiating the reaction. The former has been dealt with for a longer period of time and is a mature technology, while the latter is relatively young and needs more research as it is a fertile ground with a higher possibility of development.

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10. Design chemicals and products to degrade after use; design chemical products to break down into innocuous substances after use so that they do not accumulate in the environment.

Polymers are employed in a vast multitude of applications in some cases due to their lower weight, flexibility, durability and lifespan, ease of processing and lower cost. In addition, the physical and mechanical properties of polymeric materials can often be easily manipulated. As a result, a great many polymeric materials have replaced much traditional paper-, metal- and wood-based materials. Despite their many advantages, most polymeric materials have extremely long persistence times which often go well beyond the intended practical lifespan of the material (e.g., packaging materials, disposable cutlery and cups). This can result either in limiting the lifetime of landfill sites or, in the case of incineration, the release of greenhouse gases into the environment. To further illustrate, polyolefins such as polyethylene and polypropylene are produced at a rate of 200,000,000 metric tonnes annually with polyethylene alone being produced in amounts exceeding 80,000,000 metric tonnes per year (A. Razavi, 2000). While the useful lifetime of polyethylene packaging is typically hours or days, it pervades the environment for decades without any significant decomposition of the polymer. Hence, there is an illustrated need for the production of biodegradable polymers.

It is worth noting some common confusion in terminology: biodegradable polymers are not necessarily biopolymers, which are made from renewable raw materials. Biodegradability does not imply anything about the raw materials used to produce the polymers. Instead, biodegradability refers to the polymer's ability to breakdown into energy and more elementary components such as carbon dioxide, methane, water through

the actions of microorganisms (MOs) such as fungi, bacteria, algae and yeasts within a given period of time (Bastiolo, 2006), (Steinbuchel, 2002). Biodegradation occurs either aerobically (i.e., organic matter is converted into CO_2, energy, water, etc., by MOs in the presence of oxygen) or anaerobically (i.e., organic matter is metabolized by MOs in the absence of oxygen) (Kleeberg, 1998). Thus, biodegradability depends on the chemical composition of the polymer and biodegradable polymers can be made from either renewable raw materials or fossil-fuel based feedstocks.

A second important issue revolves around the mechanism of polymer degradation. One may mechanically degrade a polymer whereas biodegradation is a certified performance characteristic (ISO 17088, EN 13432 in EU, ASTM D 6400 in North America, GreenPla in Japan). To be in compliance with, e.g., the EN 13432 norm, a polymer must be converted to CO_2 by over 90% within 180 days under defined conditions of humidity, temperature and oxygen level (Breulmann, Künkel et al., 2009).

Many commercially produced biodegradable polymers are insoluble in water[Polymers, biodegradable.pdf]. Due to their size, the polymers cannot penetrate the cellular membranes of the MOs and thus, prior to being absorbed, the polymers must undergo chain cleavage via enzymes (e.g., using lipases, esterases) secreted by the MOs in their natural environment (Kleeberg, 2005). Oligomers resulting from chain cleavage are then absorbed and metabolized by the MOs. The process of biodegradation not only depends on the activity of the enzyme, but also on factors such as temperature, humidity, nutrients, and gases (e.g., oxygen in aerobic biodegradation). Caution should be exercised to ensure that the products of polymer degradation also present no environmental and toxicological risks.

Biodegradable polymers can be obtained from both renewable as well as non-renewable (fossil-based) raw materials. Major fossil-based monomers leading to biodegradable polymers are: butanediol (BDO) and the dicarboxylic acids adipic acid, terephthalic acid, and succinic acid. BDO is produced in large quantities by different processes and feedstocks (acetylene by the Repe process, butane, butadiene), while succinic acid is produced on a smaller scale from maleic acid anhydride (MSA). Adipic acid is based on cyclohexane derived from benzene and terephthalic acid is based on p-xylol (Breulmann, Künkel et al., 2009). On the other hand, renewable raw materials may be used for monomer production (e.g., lactic acid via the fermentation of glucose obtained from the hydrolysis of starch), polymer production (e.g., polyhydroxyalkanoates, PHA) or structural materials (e.g., cellulose) and as a compound ingredient or filler (e.g., starch) for biodegradable polyesters.

Among the bio-sourced biodegradable polymers, poly(lactic acid) (PLA) is a major commercial success story. Derived from lactic acid (2-hydroxy propionic acid), this polymer is highly biocompatible and bioresorbable (Lipinsky and Sinclair, 1986; Kleeberg, 1998; Ulrich, 1999; Albetsson and Varma, 2002; Mochizukim, 2002; Steinbuchel, 2002; Tsuji, 2002; Kleeberg, 2005; Breulmann, Künkel et al., 2009). Over the past decade, improved fermentation methods to convert corn starch into lactic acid, and the resulting lower costs have led to the use of PLA for a wide range of applications including packaging materials for food and beverages, plastic bags, thin film coatings, and rigid thermoforms (Gruber, Drumright et al., 2000; Auras, Harte et al., 2004). Lactic acid can be generated from renewable sources such as corn, sugar beets, and almost any other carbohydrate containing feedstock (Kharas, Sanchez-Riera et al., 1994).

High molecular weight PLA (M_w ~100,000 $gmol^{-1}$) can be processed via direct condensation polymerization, azeotropic dehydration and ring opening polymerization (ROP) of lactide, the cyclic di-ester of lactic acid. The high energy requirements and difficulty in controlling polymer properties in both the azeotropic dehydration and direct polymerization have shifted the large scale industrial production of PLA to the ROP method. The most common way of synthesizing PLA via ROP at the large scale involves the prepolymerization of lactic acid to low molecular weight PLA, which can then be catalytically converted into a mixture of lactide stereoisomers by transesterification (Albetsson and Varma, 2002). The three stereoisomers of lactide, which are L-lactide (S,S), D-lactide (R,R) (commercially available in both enantiopure and as racemic mixture forms), and meso-lactide (R,S), can be synthesized using homochiral lactic acid or a racemic mixture, which will then be purified by distillation or recrystallization before being polymerized via ROP in the presence of a range of initiators and catalysts.

PLA has many desirable properties that make it an interesting material for commodity applications such as packaging. PLA possesses many physical and mechanical properties comparable to that of other major commodity polymers, namely that of poly(ethylene terephthalate) (PET) and poly(styrene) (PS). This makes it possible to introduce PLA in a wide range of packaging and fibre products (Tullo, 2002), as surrogates for PET components. The fibrous materials of PLA have low odour retention, very good moisture wicking properties (Tullo, 2000; Gross and Kalra, 2002), and films, bottles and thermoformed containers are resistant to oils and fats, and also tend to display the potential to 'block' flavours and 'aromas' (Anderson, Schreck et al., 2008).

Although several properties have been noted in regards to the advantages in the use of PLA, some drawbacks also exist which have limited the use of PLA to a certain extent. For instance, PLA's limited thermal performance as measured by the glass transition temperature, T_g, or melting temperature, T_m, brittleness/low impact strength and its poor barrier properties limit its application at high temperatures, or where mechanical strength or high elongation are needed (Tullo, 2002; Auras, Harte et al., 2004; Williams and Hillmyer, 2008). To a certain extent, these properties can be modified by adapting the material processing conditions, but several other methodologies are under investigation to address these problems; these include, most notably, reactive extrusion, blending, plasticization, and synthesis of new functional lactide-related cyclic esters or copolymers (Anderson, Schreck et al., 2008; Baker, Vogel et al., 2008). In addition, future research will focus on delivering improved fermentation techniques in order to synthesize lactic acid from an increasing variety of sources, as well as discovering more active and selective ROP catalysts.

Structurally related to PLA are the polyhydroxyalkanoates (PHA), a group of polyesters that originate from hydroxyalkanoic acids which differ in chain lengths and in the position of their hydroxyl groups. Poly(3-hydroxybutyrate) (P(3-HB)), poly(4-hydroxybutyrate) (P(4-HB)), poly(hydroxybutyrate-co-valerate) (PHBV), and poly(hydroxybutyrate-co-hexanoate) (PHBH) are the most common examples within this class of biodegradable polymers. Similar to PLA, PHAs are derived from renewable resources like sugars, starch, or fatty acids. Moreover, hydrocarbons like methane have been discovered to be used for the fermentative synthesis of PHB by methanotrophic bacteria (Wendlandt, 1998). The great structural variety of PHAs gives rise to a multitude

of manifold property profiles and different possible applications including injection-moulded articles for bioresorbable medical and nonmedical applications such as fishing nets, degradable films (Lee, 1996; Asrar and Gruys, 2002; Williams, Martin et al., 2002). Unlike the case in PLA production, no chemical transformation is needed for the production of PHA. PHA is made by MOs as a carbon and energy storing substance (Lee, 1996), in which the mass of the polymer can reach 90% of the dry weight of the cell mass. The composition of the carbon source which the MOs have fed on and the bacterial species are the two factors most responsible for the chemical structure of the resulting PHA (Steinbüchel and Valentin, 1995). Once fermentation and cell lysis has occurred, high purity PHA can be isolated by chemical extraction. As PHAs are direct metabolites of MOs, they serve as food sources by several abundant microbe species which break the polymer down by extracellular poly(hydroxyalkanoic acid) depolymerases (Jendrossek, 1998). Hence, for this reason both aerobic (e.g., composting) as well as anaerobic conditions (e.g., marine environments, landfills) are suitable for the biodegradation of PHA.

There is continued intense research on the optimization process, by developing genetically modified MOs, and most recently transgenic plants that produce PHAs within their cell membranes (Lee, 1996; Williams and Peoples, 1996). However, bacterial fermentation continues to be the most commercially viable way of producing PHAs at the industrial scale (Lee, 2003).

The first completely fossil-based polymers that combined the useful mechanical properties of modern plastics and the biodegradability of polymers were aliphatic polyesters. The two fundamental structures of synthetic polyesters are closely related to

fermentative PHAs, which are derived from hydroxyalkanoic acids and their intramolecular, cyclic condensates, lactones. Poly-ε-caprolactone, produced via the ROP of ε-carpolactone, is the most common derivative under this class (Löfgren and Albertson, 1995; Mercerreyes and Jerome, 1999). Synthetic polyesters are also based on the direct condensation reaction of aliphatic dicarboxylic acids and aliphatic glycols (Jenrossek, 1998), among which polycondensates from 1,2-ethylene glycol or 1,4-butanediol with succinic acid, adipic acid, or combinations of both, are the most important derivates in this category. Aliphatic polyesters are degraded with a combination of chemical and enzymatic hydrolysis and the fragments are eventually degraded to carbon dioxide and water in microbially active environments like soil and compost (Fujimaki, 1998).

The fact that aliphatic polyesters are prone to chemical hydrolysis, leading to chemical hydrolysis and poor shelf life, and also relatively lower mechanical properties, can to some extent be overcome by copolyesterification of aliphatic and aromatic monomers (Müller, 1998). This combination is made in an aim to couple the good biodegradability of aliphatic polyesters and good mechanical properties of aromatic monomers. Aliphatic/aromatic are synthesized in melt polycondensation process from aliphatic acids (typically adipic acid) and also aromatic dicarboxylic acids (typically terephthalic acid) with aliphatic glycols (typically 1, 4-butanediol).

Ecoflex, by BASF, is the best known polyester (Breulmann, Künkel et al., 2009). Ecoflex is designed to be strong and also flexible material with mechanical properties similar to PE (Yammamotom, 2002). Hence, Ecoflex can be melt-processed on standard polyolefin equipment for use in film applications like organic waste bags, mulch films, shopping bags, and cling films. Ecoflex is also used as a replacement for PE in paperboard coating, to yield

completely biodegradable products like paper cups, and also as an ”enabler” for renewable biopolymers like starch, PLA, PHAs, lignin, and cellulose. Copolyesters of aliphatic and aromatic monomers are completely biodegradable (in microbially active environments mainly by enzymatic hydrolysis followed by complete mineralization of the resulting fragments), given that the aromatic portion doesn't exceed a certain limit (Witt, Müller et al., 1995; Witt, Müller et al., 1996; Müller, 1998; Yammamotom, 2002), because pure aromatic polyesters like poly (butylenes terephthalate) aren't prone to microbial attack.

Native starch occurs as discrete particles (starch granules) in plants. Starch molecules are polysaccharide compounds composed of anhydroglucose units. Starch granules are composed of a multilayer structure from two polymers namely, amylase and amylopectin. Amylose is predominantly linear 1,4-α-D-anhydroglucose polymer, while amylopectin consists of anhydro-glucose units connected by 1,4-α-linkages, branched points being generated by 1,6-α-linkages at select sites. Pure starch can be successfully formulated only for a limited number of applications in the plastic industry such as foam, e.g., for loose fill. This is because pure starch films and sheets are brittle and moisture sensitive, which disintegrate in the presence of water. Additionally, the temperature limit for processing is very small, because of the limited temperature stability of natural starch of about 170-180^{o}C. Chemical modification of starch by partial substitution of hydroxyl groups (e.g., with esters or ethers) can significantly improve hydrophobicity and the rheological properties, while cross-linking of the starch chains improves stability against acids, heat treatment, and shear forces (Swinkles, 1999). However, the high requirements of film applications are not easily fulfilled by modified starch alone; hence compounds with biodegradable polyesters as “enablers” have been suggested to be the appropriate

solution. The demand for biodegradable polymer solutions by the market can be met by developing a combination of rigid polymers such as PLA and PHA and soft and impact-resistant synthetic biodegradable polymers like PBAT. Such a material responds precisely to the application requirements. Starch molecules with polyesters are used to enhance hydrophobicity as well as mechanical and thermal properties of compounded products. The crystalline structure of starch granules has to be disintegrated prior to its use in applications (e.g., production of thin films and bags) because starch granules, as large as the film thickness, reduce the mechanical properties. In addition, high shear forces, heat and/or plasticizers are used in a separate compounding step to turn granular starch into thermoplastic starch (Breulmann, Künkel et al., 2009).

Other polymers that are designed to be biodegradable include polyaspartate (synthesized by the polycondensation reaction of aspartic acid via polysuccinimide, followed by hydrolysis), polyethylene glycol (a water soluble and completely biodegradable polymer at lower molecular weights) (Fincher and Payne, 1962; Ogata, 1975; Kawai, 1977; Kawai, 2002), and poly(vinyl alcohol) (PVOH), which is produced by the hydrolysis of poly (vinyl acetate) and further processed into films by solution casting or thermoplastic melt processing (08 January 2009).

Extensive research continues to be performed on the development of degradable as well as biodegradable polymers. Nowadays, biodegradable polymers are largely regarded as specialty plastics for selected applications where biodegradability adds value. The market for biodegradable polymers (65 x 10^3 tons in 2007, excluding loose fill) represents a niche segment compared to the global market for polyethylene (PE) film (approximately 30,000 x 10^3 tons in 2007) or to the global polymer market (approximately 250,000 x 10^3

tons in 2007). Based on different driving factors (changing consumer behaviour, improved composting infrastructure, technology, application and capacity development), the expected growth of 25% per annum can be influenced significantly.

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11. Analyze in real time to prevent pollution: Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.

Real-time polymerization monitoring techniques are important for the synthesis of polymers with pre-specified properties and for the prevention of waste. These methods improve and/or enable process control procedures; prevent accidents such as runaway reactions, which ultimately serves to protect operators and equipment (see section 12). Most real-time methods are cost-effective, non-destructive and have little if any negative effect on the environment. During the last two decades, there has been significant growth in sensor technologies and methods for monitoring polymerizations (Fonseca, Dubé et al., 2009; Alig, Steinhoff et al., 2010; Frauendorfer, Wolf et al., 2010). The perfect reaction monitoring tool should be cost effective, easy-to-install, explosion proof, and preferably calibration and maintenance free. However, until now, only pressure and temperature sensors have come close to meeting these ideal conditions(Frauendorfer, Wolf et al., 2010). Nevertheless, these sensors only measure the state of the reactor and do not monitor the important ongoing reaction changes like composition of the reaction mixture. Some ommon monitoring techniques are described below:

Reaction Calorimetry: The heat generated due to the conversion of monomer to polymer can be measured to monitor the (co)polymerization(McKenna, Othman et al., 2000; BenAmor, Colombié et al., 2002; Alhamad, Gomes et al., 2006). Heat balance calorimetry, which measures the energy balance of the jacket cooling medium, is a well-known method for monitoring and control of polymerizations and has been used industrially for some time (Gesthuisen, Kramer et al., 2005). However, several factors can

affect the heat balance calculation which can compromise the results such as sampling from the reactor and feeding in semi-continuous reactors, heat loss by radiation and conduction, and heat dissipation as a result of mixing in reaction mediums with high viscosity. In addition to the above possible sources of error in the calorimetry method, this technique has shortcomings when it comes to multi-component and copolymerization systems. This is because it uses the sum of the heats of all reactions taking place during polymerization. Therefore, supplementary data about specific monomers are must be obtained via other methods.

Gas Chromatography (GC): This method is the most widely used on-line monitoring technique for chemical reactions in the petrochemical industry(Blomberg, Schoenmakers et al., 2002) and for organic syntheses(Beens and Brinkman, 2005) due to its wealth of qualitative and quantitative information (Tups, 2010). The sample from the reaction mixture should be fed into the GC instrument for analysis via a circulation loop or a transfer line. However, there is usually a time-lag between the sampling time and the analytical results. Therefore, in cases with long delays, this method can be considered an off-line monitoring tiik rather than a real-time one. Another drawback of this method for monitoring polymerizations is that the highly viscous or solid polymer product can clog transfer lines, valves and columns and may require additional dilution. Nonetheless, GC is a common method for monitoring residual monomer and volatile organic compounds in polymerization mixtures (Frauendorfer, Wolf et al., 2010).

Optical Spectroscopy: the composition of the reaction mixture and the progress of polymerizations can be monitored using different optical methods via in-line or fast off-line analysis. Spectroscopic techniques have many advantages over some other monitoring

techniques such as wet chemistry or GC as they usually do not require any additional chemicals or sample pre-processing (e.g., dilution). They are also non-destructive and prevent waste formation. Therefore, these robust techniques enable the fast real-time analysis of samples without the need to extract the samples from the reaction vessel. One concern about monitoring polymerizations with optical sensors is the formation of a polymer film on the optic probe which might be resolved by cleaning the sensor with by-passes, process feeds (e.g., solvents and monomers) or extraction fixtures (Frauendorfer, Wolf et al., 2010).

Monitoring high pressure polymerization systems is also a significant challenge. Reactors are often cleaned by means of high-pressure jets of cleaning solutions and a direct hit of a sensor probe by this jet might lead to permanent damage to the sensor (Frauendorfer, Wolf et al., 2010). Brief description of some common spectroscopic techniques are presented below. More details about on-line sensors can be found in a recent review paper (Fonseca, Dubé et al., 2009).

- Infrared (IR) Spectroscopy: IR spectroscopy is a popular analytical method for preparative and analytical chemistry which provides structural and kinetic information in a non-destructive and waste-free way (Smith, 2009). The IR band is divided into three regions: near-, mid- and far-IR. The near-infrared (NIR) spectrum extends from 13000 to 4000 cm^{-1} and it provides information on overtones or a combination of the fundamental stretching bands occurring from 3000 to 1700cm^{-1}. On the other hand, the mid-infrared (MIR) spectrum extending from 4000 to 400cm^{-1} gives information on fundamental molecular vibrations and usually is the preferred choice owing to the unmatched wealth of molecular information

contained in this portion of the electromagnetic spectrum (McKenna, Othman et al., 2000). In-situ Fourier Transform Infrared (FTIR) spectroscopy which simultaneously collects spectral data in a wide spectral range, is a modern polymerization monitoring technique that is well suited for obtaining real-time structural and kinetic information. The rapid-scanning capability of FTIR spectroscopy enables monitoring of the time-dependent intensity changes of absorbance of the molecules throughout the polymerization (Shaikh and Puskas, 2003). In order to monitor the water-rich reactions internal reflection spectroscopy (often called Attenuated Total Reflectance or ATR) can be used. Real-time monitoring of conversion of reaction and composition are possible using ATR-FTIR spectroscopy (Roberge and Dubé, 2007; Fonseca, Dubé et al., ; Patel, Bakeev et al., 2010).

- Raman spectroscopy: Similar to IR spectroscopy, the molecular structure and properties of reaction components can be analyzed using Raman spectroscopy based on their vibrational transitions. However, most Raman monitoring techniques use fiber-optic probes (Al-Khanbashi, Dhamdhere et al., 1998) which employ a single frequency of radiation to irradiate the sample, in contrast to IR spectroscopy which uses a range of frequencies (Schmitt and Popp, 2006). This method is suitable for monitoring high water content reactions such as emulsion and suspension polymerizations and is very suitable for monitoring the signal from carbon–carbon double and triple bonds (Frauendorfer, Wolf et al., 2010). It is worth mentioning that Raman spectroscopy can be strongly affected by properties of the medium such as turbidity (Van Den Brink, Hansen et al., 2001).

- UV/Vis Spectroscopy: UV spectroscopy is a well-known analytical technique which is quite fast and requires only a small amount of sample. Therefore, it is a suitable method for on-line monitoring. The UV-Vis part of the spectrum, extending from 200 to 800 nm, corresponds to the excitation of the outer electrons of a molecule (Fonseca, Dubé et al., 2009). However, only vinyl monomers show adsorption in this spectral range (Kim and Sung, 1995). Successful monitoring of methyl methacrylate (MMA) and styrene polymerization was performed via this technique.
- Ultrasound: Ultrasonic methods are cost-effective, non-invasive real-time monitoring techniques. Certain properties of a medium such as velocity, viscosity and elasticity can be measured utilizing ultrasonic waves (Bond, Morra et al., 2003). Using semi-empirical models, properties like sound velocity can be related to the conversion of polymerization (Canegallo, Apostolo et al., 1995).However, this technique has certain disadvantages, whereas acoustic properties of the material and accurate models are required in order to perform reliable data analysis (Hauptmann, Hoppe et al., 2002).

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12. Minimize the potential for accidents: Design chemicals and their forms (solid, liquid or gas) to minimize the potential for chemical accidents including explosions, fire, and release to the environment

The potential for accidents in the polymer industry is large due to the variety and volume of materials used as well as the presence of these materials in different states (i.e., gas, liquid or solid). As discussed earlier, many polymerizations are conducted under fairly aggressive conditions (i.e., elevated temperatures and pressures) and many are quite exothermic, posing the threat of thermal runaway. The potential for accidents can be considered from two perspectives: (i) during the synthesis and processing stages of polymer production and (ii) accidents occurring when using the final polymer product. The latter relates primarily to the release of hazardous materials in the event of a fire. It is often mitigated by the use of fire retardants and oxygen scavengers which serve to prevent degradation and release of harmful materials to the environment (Barton and Nolan, 1989; P., J. et al., 2000; J., 2004). The focus of the present discussion is on minimizing incidents during polymer synthesis and processing.

One major cause of accidents in polymer synthesis relates to the transport and handling of chemicals. These chemicals, particularly monomers and initiators, may have the potential to react, triggered by external factors, and cause damage to the environment as well as the workplace. One significant incident occurred in the Scottish seaport of Grangemouth, August 23rd, 2006 where 24,000 L of divinyl benzene (DVB) contained in a tanker exposed to sunlight on the docks self-polymerized. DVB is an aromatic monomer used mainly for cross-linking styrene in the production of ion exchange resins (Brown, June 2007). The tank fracture, due to its displacement, became the cause for the loss of

large amounts of DVB as a white and dense plume of vapour. Firefighters sealed off the area within a 500 m range and residents were forced to remain in their homes for 24 h because of the irritating characteristics of the substance to the skin and eyes. The seaport was also idle for 36 h, until the wind had completely dispersed the cloud of vapour; luckily, no injuries were reported (Casson and Maschio, 2011).

Time and conditions during the transport and storage of monomers (in particular the storage temperature) are very important factors that affect the self-polymerization aptitude of these substances. As a stabilization measure, usually 4-tert-butylcatechol (TBC) is added at a level of 900–1200 ppm by weight to act as an inhibitor to prevent the self-initiated auto-polymerization of the material. However, it was noted that the addition of TBC alone wasn't sufficient to stabilize DVB in the Grangemouth incident and that the level of oxygen in the tank also played a very important role in activating the inhibition mechanism. Hence it was storage temperature that played an important role in the auto-polymerization of DVB and oxygen that acted towards the inhibition of the compound. Accordingly, due to the low concentrations of TBC and oxygen it must be concluded that the probability of forming a peroxy radical in an encounter of a radical with an oxygen molecule is greater than that for a propagation reaction when a radical encounters a monomer. Obviously, each particular incident has its own peculiarities but temperature and the presence of radical scavengers play important roles (Casson and Maschio, 2011).

Polymerization reactions are exothermic in nature, and whenever cooling fails, a self-sustaining uncontrolled runaway reaction may occur, leading to increased temperatures and a potential chain of events leading to disaster. With these temperatures come increased vapour pressures and secondary reactions may occur, which further generate heat and/or

non-condensable gases. This in turn will generate pressure in sealed or inadequately vented reactors, possibly leading to a hazardous loss of containment of the reactor contents in the case where the design parameters or the reactor (temperature and pressure) are exceeded. Although fortunately not common, runaway polymerizations make up a large part of industrial incidents (Barton and Nolan, 1989). Hence it is of paramount importance to safeguard industrial polymerization reactors. Several methods exist on safeguarding reactors among which the most common is the use of pressure relief valves or rupture discs connected to the reaction vessel. Such mechanical safety devices will relieve the reactor pressure, but still the contents of the reactor must be released to a safe place (e.g., a containment tank). Unless this is done, the reactor contents could form an explosive cloud that could ignite, because of the monomers involved in the polymerization.

The highly exothermic nature of many polymerization reactions provides a large potential for thermal runaway reactions. In these cases, appropriate process control techniques should be implemented. This could include manipulating not only the heat transfer equipment but the inputs of the various reaction ingredients, and in particular the initiator.

In the end, it is important to consider the associated risks in the synthesis, processing and use of the polymer products from a "cradle to grave" perspective. A study combining the classical risk assessment methods developed by the life cycle assessment (LCA) community with statistics on technological disasters, accidents, and work related illnesses was carried out to assess the associated risks of certain polymers, namely polytrimethylene terephthalate (PTT), polyhydroxyalanoates (PHA), polyethylene

terephthalate (PET) and polyethylene (PE) (Roes and Patel, 2007). The total risk to human health throughout a chemical's life cycle was estimated by summing up the results of

- External risks (risks imposed on the public) due to the release of emissions from regular operation;
- External risks due to technological disasters
- Risks of work-related accidents; and
- Risks of work-related illnesses.

Based on this risk assessment strategy, estimates for the total number of years lost per unit of product throughout the process chain were obtained as can be seen in Table 1 for PTT, PHA, PET and PE. Interestingly, since both petrochemical and bio-based production routes exist for PTT, it was possible to compare the risks associated with the derivation of the polymer from two different sources. PHA is only produced with bio-based feedstocks, while PET and PE are petrochemical alternatives. Hence, bio-based PHA was compared to petrochemical PET and PE.

According to the results shown, the conventional risks of all bio-based products are lower than those of the petrochemical products. For example, the total risk of bio-based PTT is 12–25% lower than that of petrochemical PTT. The risk caused by the production of PHA by fermentation is 7–22% lower than that caused by the production of petrochemical PET and 39–49% lower than that of petrochemical PE. The risk caused by the production of ethanol by dry milling is 68–74% lower than its production from ethene (identical with ethylene).

Table 1. Results of the Risk Assessment for PTT, PHA, PET and PE (Roes and Patel, 2007)

Product	**Risk (YOLL/Ton Product)**
PTT	
- From ethylene oxide	0.003821
- From acrolein	0.0043031
- Via anaerobic fermentation of dextrose	0.003001
- Via anaerobic fermentation of glycerol	0.003227
- Via aerobic fermentation 1	0.003039
- Via aerobic fermentation 2	0.003381
PHA	
- Via fermentation 1	0.002501
- Via fermentation 2	0.002988
- **PET**	0.003211
- **PE**	0.004949

These results allowed a comparison of the distribution of risks over the risk categories and industrial activities. The following conclusions were drawn: (1) The largest difference between bio-based and petrochemical products relate to the regular release of emissions to the atmosphere. (2) Pulmonary health problems and fatal accidents tend to be more important in the production of bio-based polymers than petrochemical products, but these differences are far outweighed by the risks caused by the regular release of emissions to the atmosphere. (3) The breakdown of the total risk by sector shows that the chemical

industry is more important for the petrochemical products than for bio-based products. (4) Waste management is equal to or very similar for all production routes (petrochemical and bio-based) because it is based on the calorific value of the product (the production method had no influence). (5) Transport is equal for bio-based and petrochemical production because the same transport was assumed for all production routes (500 ton/km by 32-ton load-capacity trucks). (6) The agriculture sector is only relevant for bio-based production routes. The cultivation of crops yielded a "negative risk" in the agriculture sector because of the uptake by crops of CO_2 from the air (CO_2 uptake is valued as a negative impact by the EPS 2000 method). (7) The share of the extraction and refining of the fossil fuels sector tends to be slightly higher than for petrochemical production routes. (8) The power generation sector has a similar share in both the bio-based and petrochemical production of PTT. Compared to PET and PE, the share is higher for the production of PHA (Roes and Patel, 2007).

Accidents related to the polymerization process are largely due to the transport and handling of several feedstocks used in the process such as monomers, solvents, and initiators as well as the highly exothermic nature of the process. Adequate environmental controls need to be in place for workplace safety, while advanced process control leads the way in mitigating thermal and pressure runaways that can occur during the polymerization process.

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Conclusion

As an economically significant and technologically vast and interesting field, polymer reaction engineering is a prime target for transformation towards greater sustainability. There isn't a one-pot solution for the transformation of polymerization processes into greener ones, hence the coordination and optimization of multiple steps resulting in an environmentally friendly polymerization process. This transformation is being made possible via the twelve principles of green chemistry, which have been explored one by one in this report. Although all of the twelve principles of green chemistry are of importance when dealing with "greening" a process, a few principles from within the list tend to be much more significant. Designing less hazardous chemical syntheses, preventing waste and making polymers biodegradable (to make them easily degrade after use) are in our opinion the most relevant with a greater chance of significant impact for the future. The remaining principles cannot either be easily applied or are already well established in the process of polymerization.