Synthesis of sugar-based polymerizable materials for hydrogel preparation

Thesis for M.Sc. in Chemical and Process Engineering

by

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Abstract

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To match the growing need for biodegradable, biocompatible and biobased materials, this thesis explored the possibilities of the synthesis of bio-based (photo)polymerizable materials from sugars and sugar alcohols and the preparation of hydrogels from the obtained materials.

The (photo)polymerizable monomers were synthesized via two different routes: oxirane ring opening reactions or esterification reactions. Xylitol was chosen as the carbohydrate and it was reacted with excess methacrylate agent (glycidyl methacrylate, methacrylic anhydride, methacryloyl chloride or methyl methacrylate) to yield a water-soluble monomer product with, on average, more than one double bond per hydroxyl group. The double bonds were expected to be statistically distributed between the hydroxyl groups. The monomers were characterized with nuclear magnetic resonance spectroscopy (NMR).

The hydrogels were prepared by dissolving obtained monomers and initiator (redox or photo) in water. The multifunctional monomers functioned as cross-linkers in the polymerization process. Rheological measurements and swelling measurements were utilized for the characterization of the hydrogels.

The obtained gel materials had promising mechanical properties and could absorb up to 10,000 % water compared to their own weight. According to the results, a new approach to sugar derivatization has been discovered. Some possible applications of the materials prepared with this approach are thickening agents in cosmetics and pharmaceuticals, printable cell culture materials, injectable drug release materials and biodegradable absorbents.

Keywords: biopolymers, sugar, epoxy ring opening, esterification, photopolymerization, hydrogel

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Abbreviations

APS – Ammonium persulfate

BHT – Butylated hydroxytoluene

DBU – 1,8-diazabicyclo [5.4.0] undec-7-ene

DCM – Dichloromethane

DMA – Dimethylacrylamide

DMAc – Dimethylacetamide

DMSO – Dimethyl sulfoxide

DS – Degree of substitution

DSC – Differential scanning calorimetry

GMA – Glycidyl methacrylate

KPS – Potassium persulfate

LAP – Lithium phenyl (2,4,6-trimethylbenzoyl) phosphinate

MAA – Methacrylic anhydride

MAC – Methacryloyl chloride

MBA – N, N'–methylene-bis-acrylamide

MEK – Methyl ketone

MMA – Methyl methacrylate

NEt_3 – Triethylamine

NMR – Nuclear magnetic spectroscopy

TEMED – Tetramethylethylenediamine

UV – Ultraviolet

4-DMAP – 4- (N, N-Dimethylamino) pyridine

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1 Introduction

There is a growing need for replacing the petroleum-based plastics with more sustainable alternatives. Biodegradable polymers originated from natural sources are one of the solutions being investigated. (DeSimone, 2000)

Carbohydrates, such as sugars and sugar alcohols, are potential candidates for building blocks for the synthesis of sustainable polymers, since they come from natural renewable sources (approximately 75% of biomass consists of carbohydrates (Desport et al, 2016)), are biodegradable, easily available and inexpensive and have wide stereochemical diversity. Important for biomedical applications, they also are inherently biocompatible. Challenges which must be addressed when utilizing carbohydrates in polymer synthesis are the multifunctionality of the derived monomers, obtaining stereoregular and regioregular polymers. The multifunctionality usually requires the use of protecting groups in order to prevent undesired side reactions. Obtaining stereoregular and regioregular polymers requires strict control of the stereochemical course of the polymerization. (Galbis et al, 2016)

The object of this thesis was to study the synthesis of a sugar-based monomer derivatized with polymerizable double bonds and to prepare hydrogels thereof. Xylitol was chosen as the sugar alcohol for the monomer synthesis and to our knowledge, no prior studies have examined the same route and starting material for hydrogel preparation. Although the approach presented herein is demonstrated with xylitol, it is feasible for other polyols as well.

Xylitol is a naturally occurring sugar alcohol which has five carbon atoms and five hydroxyl functional groups. The main applications of xylitol have been in hygiene products, food industry and pharmaceutical industry. (Rafiqul and Mimi Sakinah, 2013) Industrially xylitol can be produced by chemically hydrogenating D-xylose into xylitol but alternative biotechnological production methods have been studied as well. (Granström et al, 2007)

The aim was to derivatize xylitol with methacrylate groups (using compounds such as glycidyl methacrylate and methacrylic anhydride) which would lead to monomers with built-in cross-linkers. Using a stoichiometric excess of the methacrylic donor would yield, on average, more than one double bond per hydroxyl group (fig. 1). Instead of synthesizing pure compounds the aim was to obtain mixtures of compounds with known average degrees of substitution (DS).

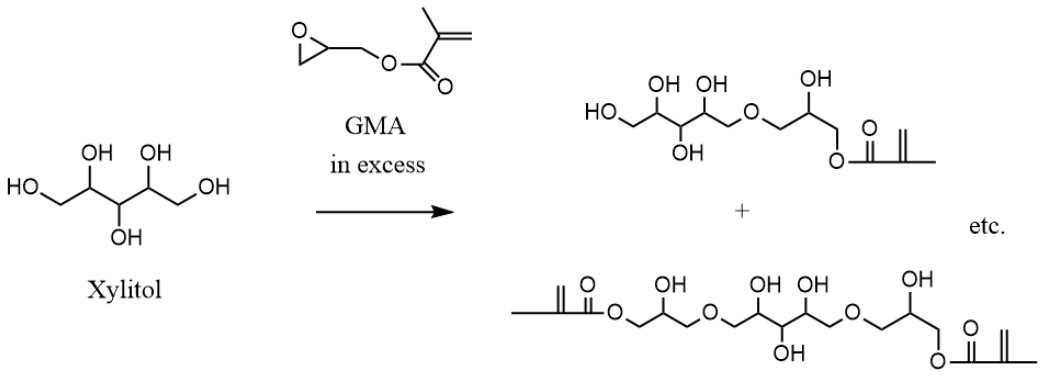

Figure 1. Reaction scheme for the reaction of xylitol with excess glycidyl methacrylate (GMA).

Hydrogels were prepared from (fig. 2), the aqueous solution of xylitol derivatives by free-radical polymerization mechanism by utilizing redox or photoinitiators.

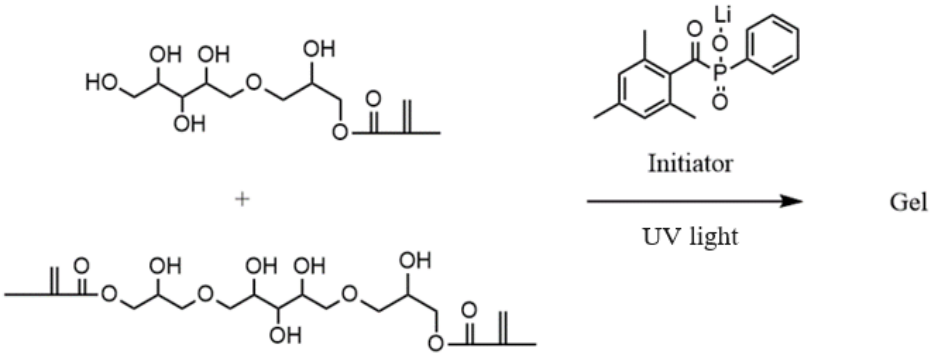

Figure 2. Principle of hydrogel preparation from sugar derivatives by photoinitiated radical polymerization.

Free-radical polymerization are classic chain polymerization reactions which produce either polymers or oligomers. (Ciuciu, 2014)
For the monomers to be able to react with the functional groups of other monomers in chain polymerization, an initiator, such as a free-radical initiator or an anionic or cationic initiator, is usually required. The interaction between monomers leads to formation of monomer chains and the main chains continue growing until other reactive groups terminate them. Activation of free radical chain polymerization can be done in different ways, for example utilizing voltage, redox reactions, heat, light or mechanical force. (Wu, 2018) Chain polymerization is a rapid process and it is particularly interesting in commercial purposes, since it can be applied to a broad range of monomers and since the required reaction conditions are quite unlimited. (Braun, 2009)

Photopolymerization is an advantageous polymerization method in many fields of engineering, since it has high energy efficiency, rapid reaction rate and it is usually free of solvents. Photopolymerization is utilized in a broad range of applications such as 3D printing, dental restoration, and coatings. (Andrzejewska, 2001). The fact that the polymerization process in photopolymerization is rapid makes it very attractive for 3D printing which

explains why photopolymers are the most utilized 3D printing materials. (Wohlers and Caffrey, 2016)

2 Literature review

2.1 Introduction of the (meth)acrylate containing moieties via esterification or oxirane ring opening

The synthesis of methacrylated sugar-based monomers can utilize for example esterification reactions or oxirane ring opening reactions (fig. 3).

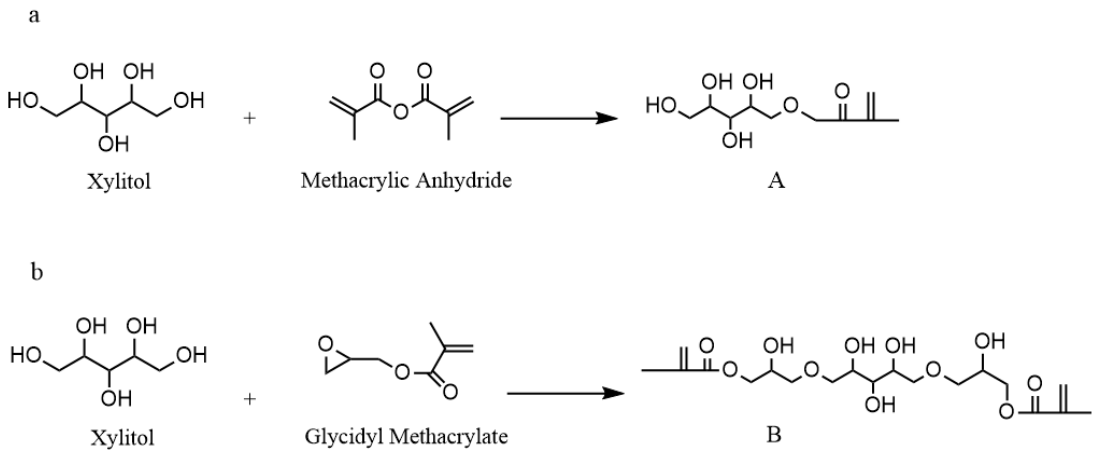

Figure 3. The two possible reaction routes for the monomer synthesis a) esterification and b) opening of the oxirane ring and the resulting products A and B.

Glycidyl methacrylate (GMA) is often utilized as the methacrylic donor in the oxirane ring route. GMA is an ester of methacrylic acid and glycidol and contains an oxirane ring. In aqueous media the reaction of GMA with hydroxyl groups depends strongly on the pH and results in either oxirane ring opening reactions or transesterification reaction. When utilizing organic solvents, the predominating reaction mechanism appears to be transesterification. The two different mechanisms

lead to a product which consists of a mixture of two different chemical compounds with a predominance of the esterification product. (Desport, 2016)

Methacrylic agents which may be utilized in the esterification route (fig. 3) include methacryloyl chloride, methyl methacrylate and methacrylic anhydride. One hydroxyl group is always lost in the esterification reaction which affects the product properties and makes the epoxidation route preferable.

The following sections provide a review of the studies based on synthesizing sugar-based methacrylated monomers.

2.1.1 Polyols

The work of Bruggeman et al. (2008) presents the synthesis of two xylitol-based biopolymers. Xylitol was reacted with water-soluble citric acid through polycondensation resulting in a water-soluble and biodegradable polymer which was then acrylated into an elastomeric photocross-linkable hydrogel. Alternatively, xylitol was reacted with water-insoluble sebacic acid to produce tough, biodegradable elastomers.

Narain & Armes (2002) have synthesized sugar methacrylate monomers from D-gluconolactone polyol utilizing a ring-opening reaction of 2-aminoethyl methacrylate. The reaction was performed without protecting groups under mild reaction conditions.

2.1.2 Monosaccharides and disaccharides

Desport et al. (2016) reported the synthesis of two regiospecific methacrylate monomers that were based on galactose. The two alternative routes both use the epoxy-ring opening reaction of GMA. In the first route, the reactivity of galactose is enhanced by oxidizing to an acid. In the second route, an identical analogue of the ring-opening product of GMA was produced by treating the galactose with epichlorohydrin with subsequent reactions with methacrylic acid.

Koruyucu et al (2016) have prepared sugar based methacrylates from diacetone derivatives (diacetone-glucose/mannose/galactose/fructose). The protected derivatives were synthesized first and then the remaining free hydroxyl groups were reacted with epichlorohydrin to create ether derivatives. The sugar methacrylates were produced by opening the epoxy rings of the ether derivatives and reacting them with methacrylic acid.

Sucrose-based methacrylates have been widely researched (Ferreira et al, 2000, Chen and Park, 2000, Pastoriza and Bertorello, 1986, Castellano and Martinez de Bertorello, 1989, Gruber and Greber, 1990). In the work of Ferreira et al. sucrose was non-selectively modified by the introduction of vinyl groups. The reaction of sucrose with GMA was proposed to occur via transesterification mechanism instead of the epoxide ring and the yield was reported to be lower than in similar reactions involving polysaccharides. Chen and Park combined sucrose with glycidyl acrylate to obtain a monomer which could be polymerized into a superporous hydrogel network.

Pastoriza and Bertorello (1986), prepared Sucro-Gel H-70, a hydrogel polyester of sucrose methacrylate, by transesterification. In the study of Castellano and Martinez de Bertorello (1989), methacrylic esters of sucrose and 2-hydroxy-N-(3,4dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine were prepared and copolymerized. The latter exhibits trypanocidal activity against T. cruzi and the prepared copolymer was designed to function as a prodrug. Gruber and Greber (1990) synthesized novel sucrose derivatives with different potential applications including: methacrylic esters of sucrose and derivatives containing photoactive, hydrophilic, biologically active or surface-active groups.

2.1.3 Glucose

Shin et al. (2011) report the synthesis of a hydrophilic biodegradable methacrylated polymer based on glucose acid and malic acid. Poly(glucose malate) was prepared with polycondensation and the remaining free hydroxyl groups were methacrylated by reacting them with methacrylic anhydride.

2.1.4 Fructose

Desport, Moreno and Barandiaran (2018) report the synthesis of radically polymerizable methacrylated fructose-based monomer via esterification reactions. The fructose-based monosaccharide included acetonide protecting groups and was selected, since it has a primary alcohol in an anomeric position which is beneficial due to its high selectivity and reactivity. Methacrylic anhydride was utilized in the incorporation of the methacrylate group.

In the work of Perin and Felisberti (2014), the synthesis of fructose-based methacrylated monomer was investigated. The monomer was synthesized by transesterification of D-fructose with trifluoroethylmethacrylate and the reaction was enzymatically catalyzed. Perin and Felisberti (2018) have also studied the synthesis of fructose methacrylate, glucose methacrylate, fructose dimethacrylate and glucose dimethacrylate by transesterification. The reaction was catalyzed enzymatically and vinyl methacrylate, methacrylic and 2,2,2-trifluoroethyl methacrylate were utilized as the methacrylic donors.

2.1.5 Polysaccharides

In the work of De Smedt et al. (1995) the synthesis of dextran-based methacrylated monomer and the hydrogel properties of the monomer were studied. Dextran was methacrylated with glycidyl methacrylate in the presence of 4-(dimethylamino)pyridine and using dimethylsulfoxide as a solvent. Van Dijk-Wolthuis et al. studied the same reaction twice (1995 & 1997) and noticed in the more recent study that the reaction mechanism is transesterification instead of the earlier assumed epoxide reactions. The group of Wang et al. (2014) utilized the same reaction to produce photopolymerizable methacrylated dextran-based monomers and controlled the mechanical properties through adjusting the degree of substitution. Kim and Chu (2000) created a methacrylated photopolymerizable monomer by reacting dextran with methacrylic anhydride in the presence of triethylamine. The monomer was used for hydrogel preparation.

Lepistö et al. (1983) prepared derivatized polysaccharides by reacting aqueous alkaline solutions of dextran, glycogen, hydroxyethyl starch and maltodextrin with acrylic acid glycidyl ester and studied the derivatization degree of the produced acryloylated polysaccharides with Fourier transform proton NMR spectroscopy.

The synthesis of inulin-based methacrylated monomer for the preparation of inulin hydrogels was studied by Vervoort et al. (1997). Inulin was reacted with glycidyl methacrylate and N, N-dimethylformamide was utilized as the solvent and 4-dimethylaminopyridine as the catalyst.

2.1.6 Cellulose

Synthesis of methacrylated hemicellulose derivative was studied by Peng et al. (2012). The xylan-rich hemicelluloses were reacted with glycidyl methacrylate in the presence of DMSO and according to the results, the reaction mechanism was transesterification.

Ultrafine fibrous cellulose membranes were created from cellulose acetate by electrospinning and then reacted with methacrylate chloride to produce activated surfaces in the work of Liu and Hsieh (2003). The methacrylated cellulose could be further copolymerized to three-dimensional networks or linear grafts by reacting with vinyl monomers.

2.1.7 Starch

The synthesis of methacrylated starch and its utilization as a precursor in the preparation of hydrogels has been investigated in several studies. Hedin, Östlund and Nydén (2010) reacted corn starch with glycidyl methacrylate in DMSO and in the presence of potassium-*tert*-butoxide.
Noè et al. (2020) synthesized methacrylated maize starch for hydrogel preparation. Starch was reacted with methacrylic anhydride to yield a photopolymerizable

monomer. A year later the group of Noè et al. (2021) continued their work by studying the coating possibilities of the prepared cross-linked starch.

Jantas (1997) utilized Schotten-Bauman's esterification in the preparation of acryloyloxyamylose, a derivatized starch monomer. In the reaction, amylose was reacted with acryloyl chloride.

2.2 Initiator classes – cross-linking on demand

2.2.1 Redox Initiators

In the beginning of the discovery of redox initiators the effect of oxygen on polymerization rates was unclear. Under some conditions, oxygen seemed to accelerate the polymerization and under others inhibit it. Later it was concluded that a redox process, reaction of oxidizing and reducing agents, caused the effect. (Braun, 2009)

In a redox reaction, an oxidizing agent forms a complex when it reacts with organic molecules which then decompose unimolecularly into free radicals which initiate the polymerization (Ozturk and Kacmac, 2007). Some examples of redox initiators are persulfate, peroxide, peroxomonosulfate, peroxidiphosphate and metal ion redox systems (Sarac, 1999).

Advantages in redox initiators include the ability to produce radicals at reasonable rates over a broad range of temperatures which is due to their relatively low activation energy (Odian, 2004). This is important in the industry and is utilized for example in low-temperature emulsion polymerizations (Vanderhoft, 1969). Additionally, redox initiators enable attaching functional groups at the ends of the formed polymer chains (Sarac, 1999).

2.2.2 Type I and II photoinitiators

Photoinitiators are utilized in converting light energy into chemical energy. Most industrial photoinitiators respond to energy provided by the near-visible and UV

range (200 to 450 nm). The energy conversion is done in the form of reactive intermediates, either cationic species or free radicals which are able to initiate a polymerization reaction. The wavelength of the supplied light and absorbance of the photoinitiator must be compatible for the process for the photoinitiator to reach an electronically excited state. (Green, 2010)

Photoinitiators may be classified into Norrish type I and type II based on the mechanism in which the active species are formed (Koleske, 2002). Both types include the photoexcitation of a carbonyl compound (Marchetti et al., 2019). Photoinitiators which produce initiating radicals through cleaving upon light excitation are called type I photoinitiators (Dumur& Noirbent, 2021). Most type I photoinitiators are aromatic carbonyl compounds which contain suitable substituents which may facilitate direct photofragmentation (Gruber, 1992). Some examples of type I photoinitiators are: benzyl derivatives, benzoin derivatives, hydroxyalkylphenones, dialkoxyacetophenones, organic peroxides and halogenated ketones.

In type II photoinitiators, the radicals or radical ions are produced by bringing the initiator molecule into an excited state and then allowing it to react with the appropriate co-initiator, which usually is a hydrogen donor or an electron acceptor or donor. (Tomal, 2020). Most type II photoinitiators are systems consisting of an excitable aromatic ketone and a compound which is capable of reacting as a coinitiator for the ketone, such as amines, alcohols, thiols and ethers. Of these, amines are the most efficient coinitiators. Other type II systems include benzophenone/amine and thioxanthone/amine systems, where the amine also acts as a coinitiator and a benzophenone or a thioxanthone is the excitable compound. (Gruber, 1992)
Both photoinitiator types are broadly utilized in different industrial applications. (Dumur & Noirbent, 2021)

2.2.3 Advancements in photoinitiators

Though photoinitiators are important to photopolymerization technology, they are not completely consumed in photopolymerization processes and may also easily

migrate from the cured surface which is why they are considered as potential environmental pollutants and toxic substances (Liu & Mabury, 2019; Kandirmaz et al., 2019; Kreutzer et al., 2017; Wu et al., 2017; Kandirmaz et al., 2018). This is why low toxicity is an important aspect in the development of new photoinitiators. Two possible ways for reaching low toxicity are utilizing the skeleton structure of small natural product molecules to produce highly efficient photoinitiators and designing macromolecular photoinitiators to reduce migration. (Zhao et al., 2015, Al Mousawi et al., 2018)

According to Dietliker et al. (1991), three important features in photoinitiators are: 1) the ability to provide high photosensitivity to black formulations, 2) compounds with low volatility and migration properties and 3) photolatent bases which enable the curing of new formulations.

2.3 Synthesis of hydrogels, characterization, and applications thereof

2.3.1 Synthesis of hydrogels

Hydrogels can be defined in several ways. At their simplest form, they can be described as polymeric materials that have the ability to swell and retain significant amounts of water within their structure but will not dissolve in water. The excellent water-absorbing ability is caused by the hydrophilic functional groups, which can be found in the polymeric backbone, whereas the cross-linking of the polymer network chains explains the resistance to dissolution.

Materials of both synthetic and natural origin fit in the definition of hydrogels. Natural polymers, which can form hydrogels include polysaccharides such as alginate and starch and proteins such as gelatin and collagen. Preparation of hydrogel-forming synthetic polymers is performed utilizing traditional chemical polymerization techniques. (Ahmed, 2015)

The synthesis of hydrogels can be performed in a number of methods, ranging from one-step procedures where the polymerization and cross-linking of multifunctional

monomers occur simultaneously to multiple step procedures, which include the synthesis of polymer molecules containing reactive groups and their subsequent cross-linking (Ahmed, 2015). Both the hydrogel structure and properties such as mechanical strength, biological and chemical response to stimuli and biodegradation can be controlled on a molecular level during the synthesis process (Burkert, 2007).

The polymeric composition of hydrogels can vary and they may be categorized as homopolymers, copolymers and multipolymeric interpenetrating polymeric networks (IPNs). A homopolymeric network contains only one type of monomer while copolymeric hydrogels are derived from two or more different monomer species of which at least one contains a hydrophilic component (Iizawa et al., 2007; Yang et al. 2002). Multipolymeric interpenetrating polymeric hydrogel networks consist of two independent cross-linked polymer components, which can be natural and/or synthetic compounds (Maolin et al., 2000).

Based on the cross-link junctions in polymer networks hydrogels can be divided into chemically cross-linked and physically cross-linked networks (Ahmed, 2015). While in the chemically cross-linked networks the junctions are permanent, the physically cross-linked networks have transient junctions, which are formed due to either physical interactions such as hydrophobic interactions, ionic interactions and hydrogen bonds or polymer chain entanglements (Ahmed, 2015, Hacker & Mikos, 2011).

Hydrogels may also be categorized based on properties such as configuration, physical appearance and network electrical charge. The configuration of a hydrogel depends on their chemical composition and physical structure. The three configurations of hydrogels are amorphous, crystalline and semicrystalline. The technique utilized in the polymerization process affects the physical appearance of hydrogels and results in either films, matrices or microspheres. Hydrogels may be ionic, nonionic, amphoteric or zwitterionic based on whether there is an electrical charge in the cross-linked chains. (Ahmed, 2015)

An additional feature of hydrogels is their ability to perform volume transitions in response to a range of chemical and physical stimuli such as magnetic or electric

field, temperature, sound, pressure, pH, light and ionic strength. This feature can be controlled and is utilized in several applications. (Ahmed, 2015)

Since hydrogels are hydrophilic polymer networks, which have been cross-linked to some extent there are many options for the preparation process and most of the techniques which produce a cross-linked polymer are suitable. Common methods are cross-linking with free radical polymerization and copolymerization, where the hydrophilic monomer reacts with a multifunctional cross-linker. (Ahmed, 2015)

2.3.2 Characterization techniques

2.3.2.1 Rheology

Rheology can be utilized for characterization of the mechanical properties of hydrogels. With rheological measurements, information about properties such as molecular weight, degree of cross-linking, structural heterogeneity/homogeneity and proximity of glass transition can be obtained. Rheological measurements are sensitive, rapid and require only a small amount of sample. (Zuidema et al., 2014)
The rheology of different types of hydrogels has been studied broadly (Picout et al., 2003; Van Den Bulcke et al.; 2000, Yan & Pochan, 2010)

Small deformation tests are typical methods for studying the rheology of hydrogels. The tests are performed within a linear viscoelastic region of the sample material, which ensures that the measured properties are independent of the magnitude of the imposed stress or strain. Small amplitude oscillatory shear (SAOS) measurements and creep and creep recovery tests are the main small deformation methods for hydrogels. (Macosko, 1994, Mezger 2006)
In the SAOS method, the sample is placed between either a cone and a plate or two parallel plates and small amplitude torsional oscillation is used to create a shear flow in the sample. (Morrison, 2001)

The properties measured as a function of time, strain and frequency are the shear storage modulus G', the loss modulus G'' and the loss factor tan δ. G' measures the

deformation energy stored during a shear process of a sample material, which can also be described as the stiffness of the sample material. G'' describes the energy dissipated during shear, which equals to the liquid-like or flow response of the sample material. For a viscoelastic liquid sample $G'' > G'$ and tan $\delta > 1$ and for a viscoelastic solid $G' > G''$ and tan $\delta < 1$. (Macosko, 1994, Mezger, 2006)

An applied sinusoidal strain can be described as

$$g = g \exp(iwt) \quad (1)$$

and the complex modulus of the sample material is

$$G*(w) = G' + iG'' \quad (2)$$

where $s*$ and $g*$ are G' and G'' are the real (in phase or elastic) and imaginary (loss or out of phase or viscous) components of $G*$, respectively. Tan δ, the loss factor, can be defined as G''/G'. (Macosko, 1994, Mezger, 2006)

When the evolution of G' and G'' is monitored as a function of time, gelation can be actively observed. The linear viscoelastic region where G' and G'' are independent of the shear strain can be determined by monitoring the moduli as a function of strain. Moduli vs. frequency measurements reveal the behavior of a hydrogel at different time scales. An important characteristic to observe is the frequency dependence of the moduli, since a sample material may seem liquid-like at low frequency (long time scales) but also be more solid-like at higher frequencies (and faster timescales). (Yan & Pochan, 2010)

Ross-Murphy (1987) classified the rheological behavior of polymer solutions and the frequency-dependence into four categories:

a) *weak gel behavior or structured liquid behavior*, where the G" is slightly smaller than G’ and both moduli are only slightly dependent on the frequency
b) *strong gel behavior or true gel behavior*, where G’ is greatly larger than G" and both moduli are independent of the frequency

c) *entangled polymer solution behavior*, where the G" is larger than G' at low frequencies but at higher frequencies both moduli increase and after a crossover G' finally becomes larger than G"
d) *non-entangled polymer solution behavior*, where both moduli are frequency-dependent and G" is larger than G' at all frequencies.

2.3.2.2 Swelling

Swelling, when combined with a thermodynamically compatible solvent is a desired property for hydrogels. (Ganji et al., 2010)
A dehydrated hydrogel is in a glassy phase and when it swells, it develops into a rubbery phase (Lee, 1984). In the swelling process, the hydrogel surface is attacked by solvent molecules, which then penetrate into the polymeric network. Between the unsolvated glassy phase and the rubbery hydrogel phase is a moving boundary. When the meshes of the polymeric network in the rubbery phase start expanding more solvent molecules are allowed within the network. (Ganji et al., 2010)

The cross-linking degree is a property, which affects the swelling of hydrogels greatly, since it influences the area, which allows the diffusion to happen across the hydrogel network. It can be defined as the ratio of moles of cross-linking agent to the moles of the repeating units of the polymer. A high ratio means that the hydrogel structure contains plenty of crosslinking agent and that the structure is tight and immobile and thus will swell less than hydrogels with a lower cross-linking degree. (Peppas et al., 2000; Khan & Ranhja, 2014)

The swelling is affected by the chemical structure of the hydrogel. Hydrophilic groups in hydrogels cause the hydrogel to swell more than hydrogels with hydrophobic groups. The exposure to water molecules is minimized for hydrophobic groups due to their collapse in the presence of water. Swelling of hydrogels may also be affected by environmental stimuli. Some examples of these type of stimuli-responsive hydrogels are pH-sensitive, ionic strength-sensitive and temperature-sensitive hydrogels. (Peppas et al., 2000)

One important property of hydrogel swelling is the swelling rate. Several parameters affect the swelling rate, such as the type of porous structure and the extent of porosity. Based on these parameters, hydrogels can be classified as super-porous, macro-porous, micro-porous or non-porous. (Ganji et al., 2010)

According to literature (Edana & Inda, 2011), there is no standard protocol for measuring the swelling ratio but several different techniques have been presented. The reproducibility and repeatability of these techniques has been questioned (Mechtcherine et al., 2018). A typical procedure for studying the swelling behavior of hydrogels has been to allow the hydrogel samples to hydrate in excess distilled water at room temperature and weigh them before, during and after the swelling experiment. Basic information about the swelling properties can be obtained with the measured weights and the following equation:

$$Swelling = \frac{Ws - Wd}{Wd} \quad (3)$$

where W_s is the weight of the hydrogel at swelling state and W_d at dry state. (Thürmer et al., 2014; Chen et al., 1995; Yacob & Hashim, 2014; Holback et al., 2011)

2.3.2.3 Thermal properties (DSC)

Differential scanning calorimetry (DSC) is a thermal analytical method, which can provide quantitative information about energetic and physical properties of a substance. This information consists of endothermic, exothermic and heat capacity changes as a function of time and temperature, which describe purity, melting and glass transition temperature. (Clas et al., 1999)
DSC utilizes a two-pan configuration, where the sample is in one pan and the other pan is a reference pan. DSC measures energy differences between the two pans. (Turi et al., 1997)

DSC has been a widely utilized method for investigation of thermal properties of hydrogels (Yudianti et al., 2009, Reguieg et al., 2020, Ostrowska-Czubenko et al., 2011)

For hydrogels, DSC can provide interesting information about the phase transition of the bulk polymer, the sol-gel transition and the melting behavior. Other properties, such as the release of a substance from a hydrogel may also be studied (Castelli, 2008). Both the equilibrium water contents and state of the water in the gels affect these properties. Water may exist in several states (bound and unbound) in the polymer network. In the hydrophilic regions, the absorbed water molecules can be in three states: free water, freezable bound water and non-freezable bound water. Freezable bound water may have weak interactions with the hydrogel molecules while the non-freezable bound water has tight hydrogen bonds and an undetectable phase transition. Free water is not involved in the hydrogen bonding of the hydrogel. (Yudianti et al., 2009)

2.3.3 Applications

Hydrogels as polymers have special physical and chemical characteristics; they are self-supporting and hydrophilic three-dimensional viscoelastic networks to where cells and molecules can be diffused and attached (Cascone & Lamberti, 2020). Due to these characteristics and the rapid integration of 3D structures and easy customization with advanced synthesis methods hydrogels are an interesting subject of study for many fields (Sikdar et al., 2021).

To date, several applications of hydrogels have been presented and the medical field is one of the main target segments with applications such as biomedical applications (Stamatialis et al., 2017), diagnostics (Van der Linden et al., 2003), pharmaceuticals (Kashyap et al., 2005), wound dressing (Sikareepaisan et al., 2011), regenerative medicines (Saul & Williams, 2011), handling of cells and biomolecules (Wang et al., 2010), tissue engineering (Zhang et al., 2011), drug delivery systems (Singh et al., 2010) and barrier materials (Roy et al., 2010). Other applications include agriculture (Amulya, 2010), food industry (Chen et al., 1995), hygiene products (Singh et al., 2010), textiles (Wang et al., 2014), soft electronics (Keplinger et al., 2013), sealing

(Singh et al., 2010), actuators (Kim et al., 2012), sensors (Larson et al., 2016), pollutant removal (Khan & Lo, 2016) and coal dewatering (Sun et al., 2002).

The future prospects of hydrogels include improving the synthesis methods and meeting the specific requirements of the applications while maintaining the desired properties and eliminating limiting factors such as poor mechanical strength and toughness and difficulties in handling and sterilization (Sharma & Tiwari, 2020). The development of hydrophilic polymers of desirable functional groups and multifunctional structures (such as branched or grafted co-polymers and star polymers) could help in addressing several of the property-related issues (Parhi, 2017).

3 Experimental

3.1 Research objective

The objective of this thesis was to synthesize methacrylic xylitol-based monomers and utilize them in the preparation of hydrogels.

The monomers were synthesized via two different synthetic routes, the epoxy ring opening reactions (glycidyl methacrylate) and esterification reactions (methacrylated anhydride, methacryloyl chloride, methyl methacrylate).

Hydrogels were prepared from the obtained monomer products utilizing different initiators (photoinitiators, redox initiators) and mechanisms (UV light, heat).

3.2 Synthesis of (meth)acrylated sugars

3.2.1 Materials and methods

Materials

Butylated hydroxytoluene (BHT), triethylamine (NEt3), methacrylated anhydride (MAA) and dichloromethane (DCM) were obtained from Sigma-Aldrich. NaOH, dimethyl sulfoxide (DMSO) and dimethylacetamide (DMAc) were supplied by VWR. Methyl methacrylate (MMA), methacryloyl chloride (MAC), 4-(N, N-Dimethylamino) pyridine (4-DMAP) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) were obtained from Fluka, xylitol from TCI Chemicals and glycidyl methacrylate (GMA) from Acros Organics.

Methods

The monomer synthesis consisted of 52 experiments of which 30 were conducted using the glycidyl methacrylate route. Other routes, methacryloyl chloride, methyl methacrylate and methacrylic anhydride were used in 4, 3 and 15 experiments, respectively.
An example of each method with exact reagent amounts is provided in the following sections. The rest of the experiments were performed in the same manner as the examples.

Glycidyl Methacrylate Route

The first GMA route synthesis was based on the work of Ferreira et al. (2000). Xylitol (2.00 g, 13,1 mmol), glycidyl methacrylate (GMA) (3.74 g, 26.2 mmol) and 4-dimethylaminopyridine (DMAP) (or potassium tert-butoxide or 1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU)) (0.320 g, 2.62 mmol) along with dimethyl sulfoxide (DMSO) as a solvent (10 mL) and butylated hydroxytoluene (BHT) (0.1 g) as an inhibitor were weighed into a 50 ml round flask. The mixture was stirred with a magnetic stirrer under argon atmosphere for 15 minutes and then run at 80 °C for at least 20 hours. The product was precipitated in toluene and the solvents were evaporated with a rotary evaporator. The final product was stored in the freezer.

The second GMA synthesis route was based on the work of Ferreira et al. (2000) and Heinze et al. (2004). Xylitol (4.00 g, 26.2 mmol), glycidyl methacrylate (GMA) (10.5 mL, 78.9 mmol) along with dimethylacetamide (DMAc) as a solvent (35 mL) and butylated hydroxytoluene (BHT) as an inhibitor (0.1 g) were weighed into a 100

ml round flask. The mixture was stirred with a magnetic stirrer under argon atmosphere for 15 minutes and then heated to 80 °C. This was followed by the addition of sodium hydroxide (NaOH) (0.342 g, 7.89 mmol) dissolved in 1 mL water. The reaction was run at 80 °C for at least 20 hours. The product was precipitated in toluene/heptane/hexane. Excess sodium hydroxide was removed with a plug of silica using dichloromethane (DCM) as the solvent. Finally, butylated hydroxytoluene was added to inhibit polymerization during drying and the solvents were evaporated with a rotary evaporator. The final product was stored in the freezer.

The third GMA route was similar to the second route except that the reaction was done without solvent. Xylitol (8.00 g, 52.6 mmol) and butylated hydroxytoluene (BHT) (0.1 g) as an inhibitor were weighed into a 50 ml round flask. Sodium hydroxide (NaOH) (0.649 g, 15.8 mmol) was weighed and dissolved in 1 ml water and then combined with xylitol and BHT. The mixture heated to 80 °C and stirred with a magnetic stirrer until clear. Glycidyl methacrylate (GMA) (21 mL, 157 mmol) was added to the mixture dropwise under argon flow. The reaction was run in 80 °C for at least 17 hours. The product was precipitated in toluene and methanol was utilized as a solvent. The product was dissolved in a mixture of dichloromethane (DCM) and methanol and passed through a plug of silica to remove the NaOH particles. BHT (0.08 g) was added to inhibit further polymerization before evaporation of the solvents with a rotary evaporator. The final product was stored in the freezer.

Methacryloyl Chloride Route

The synthesis was based on the work of Jantas (1997). Xylitol (4.00 g, 26.2 mmol), aqueous potassium hydroxide (KOH) (3 mol/L) (8.73 mL, 26.2 mmol) and methyl ethyl ketone (MEK) (1.89 g, 26.2 mmol) were weighed into a 50 ml round flask and placed in an ice bath. Methacryloyl chloride (MAC) (3.84 mL, 39.3 mmol), methyl ethyl ketone (MEK) (2.08 g, 28.8 mmol) and toluene (0.482 g, 5.24 mmol) were mixed and added dropwise. The reaction was run and stirred for 40 minutes and then left for separation. Precipitation of the product was done with heptane and washed with chloroform. Finally, the solvents were evaporated with a rotary evaporator. The final product was stored in the freezer.

Methyl Methacrylate Route

The synthesis was based on the work of Ferreira et al. (2000) and was quite similar to the GMA route. Xylitol (4.00 g, 26.2 mmol), methyl methacrylate (MMA) (13.1 g, 131 mmol), 4-dimethylaminopyridine (DMAP) (2.56 g, 20.9 mmol) along with dimethyl sulfoxide (DMSO) as a solvent (25 mL) and butylated hydroxytoluene (BHT) (0.1 g) as an inhibitor were weighed into a 50 ml round flask. The mixture was stirred with a magnetic stirrer under argon atmosphere for 15 minutes and then at 80 °C for at least 15 hours. The product was washed several times with toluene (or diethyl ether) and the solvents were evaporated with a rotary evaporator. The final product was stored in the freezer.

Methacrylic Anhydride Route

The synthesis is based on the work of Desport et al. (2018). Xylitol (4.00 g, 26.2 mmol), 4-dimethylaminopyridine (DMAP) (0.967 g, 7.89 mmol), triethylamine (NEt_3) (1.1 mL, 7.89 mmol) along with butylated hydroxytoluene (BHT) (0.1 g) as an inhibitor and dimethyl sulfoxide (DMSO) as a solvent (20 mL) were weighed into a 100 ml round flask. The mixture was stirred with a magnetic stirrer for 15 minutes until clear. Methacrylic anhydride (MAA) (7.83 mL, 52.5 mmol) was added to the mixture dropwise. The reaction was run in room temperature for at least 18 hours. The product was precipitated in toluene (or diethyl ether/ hexane) and washed with heptane/hexane/ethyl acetate. The solvents were evaporated with a rotary evaporator. The final product was stored in the freezer.

3.2.2 Characterization

NMR

The monomer products were analyzed with proton nuclear magnetic resonance spectroscopy (1H NMR) and carbon nuclear magnetic resonance spectroscopy (13C NMR) utilizing a Bruker AVANCE III 500 MHz spectrometer and a

5 mm BBFO double resonance broad band optimized probe.

Samples for NMR were collected from the monomer products mainly after solvent evaporation. Depending on the product, deuterated dimethyl sulfoxide (DMSO-d6), deuterium oxide (D2O), deuterated methanol (methanol-d4) or deuterated chloroform (chloroform-d) were used as NMR solvents. The samples were prepared by collecting some monomer product in a vial and adding 1 mL of suitable solvent to it.

In ^{13}C NMR samples, the amount of monomer product was 0,10 eq and the solvent amount was 1 mL. Chromium acetonate (17,5 mg/mL) was used as relaxation reagent and added to the solutions during preparation.

3.3 Hydrogel preparation via photoinduced cross-linking

3.3.1 Materials and methods

Lithium phenyl (2,4,6-trimethylbenzoyl) phosphinate (LAP), potassium persulphate (KPS) and tetramethylethylenediamine (TEMED) were purchased from Sigma-Aldrich. 2,2'-azobis[2-methylpropionamidine] dihydrochloride and N,N'–methylene-bis-acrylamide (MBA) were obtained from Acros Organics, ammonium persulfate (APS) from Fluka and dimethylacrylamide (DMA) from Thermo Fisher Scientific.

Photoinitiated Gel Preparation

Monomer 0.25 eq, initiator (lithium phenyl (2,4,6-trimethylbenzoyl) phosphinate) 0.02 eq (of monomer) and distilled water 0.75 eq were weighed into a sample flask and stirred. The mixture was poured on to a plastic Petri dish and covered with a

suitable glass lid and then carefully placed in the UV oven (fig. 4). After one hour, the gel sample was removed from the oven and allowed to cool for several hours.

Figure 4. An ultraviolet oven.

Redox-initiated Gel Preparation

Monomer 0.25 eq, initiator (ammonium persulfate, APS-TEMED) 0.02 eq (of monomer) and distilled water 0.75 eq were weighed into a sample flask. The mixture was stirred and poured on to a plastic Petri dish. Initiator (tetramethylethylenediamine, APS-TEMED) 0.02 eq (of monomer) was added directly to the Petri dish while the constantly stirring the mixture by hand. The Petri dish was covered with a plastic lid and left in room temperature for the minimum of 4 hours.

Thermal-initiated Gel Preparation

Monomer 0.25 eq, initiator (potassium persulfate/ 2,2'-azobis[2-methylpropionamidine] dihydrochloride) 0.02 eq (of monomer) and distilled water 0.75 eq were weighed into a sample flask. The mixture was stirred with a magnetic stirrer and an inert atmosphere was created with argon purging. The sample was then carefully placed in the oven. After 3-4 hours, the gel sample was removed from the oven and allowed to cool for several hours.

3.3.2 Characterization

Swelling

The gel samples were dried first in room temperature on a flat plate overnight and then in a vacuum oven at 50° for at least two hours. A pyramid-shaped polyethylene terephthalate tea bag (fig. 5) was utilized as an instrument in the swelling measurements. The store-bought tea bags were emptied by cutting a small hole in the bag close to the attachment point of the string (fig. 5a) and turning the bag inside out. The dried gel sample pieces were placed on the bottom of the tea bag and the samples and the tea bag were weighed both separately and together to obtain their initial weights.

For the swelling (fig. 6), the samples were allowed hydrate in excess distilled water for 105 minutes and weighed with certain time intervals to be able to follow the swelling process as a function of time. The samples (fig. 7) were weighed first every five minutes (until total time was 10 minutes), then every ten minutes (until total time was 65 minutes) and then every 20 minutes (until total time was 105 minutes). When weighing, the sample-containing tea bag was lifted from the beaker and hung above the beaker for a few seconds to remove excess water. Then, the tea bag was dried by tapping it gently with a tissue wiper and weighed on a glass Petri dish. The drying was always completed in 30 seconds and after measuring the weight the tea bag was returned to the water-containing beaker. The time was controlled in every phase to ensure enough swelling time for the samples.

An IR-35 Infrared Moisture Analyzer (Denver Instrument) (fig. 8) was utilized to measure the moisture percent of the sample. The swollen gel samples (fig. 9) from

the swelling measurement were exploited also in the moisture analyses. The samples were cut into small pieces to minimize trapping of moist under the sample and spread on to the measuring plate.

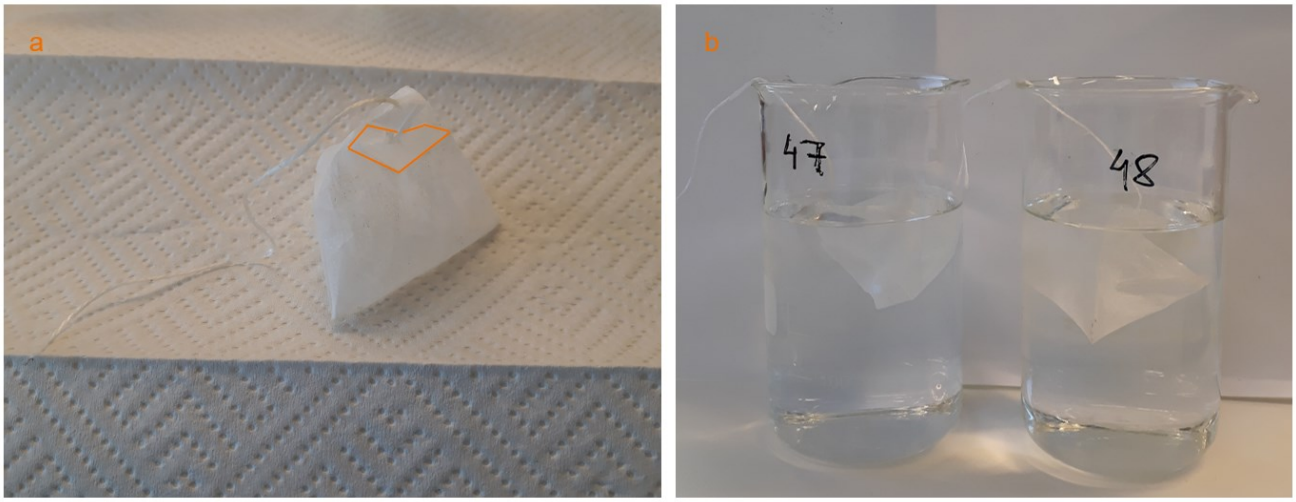

Figure 5. A tea bag (a) used in swelling measurements and two sample gels (b) swelling in excess water.

Figure 6. Set-up for swelling measurements.

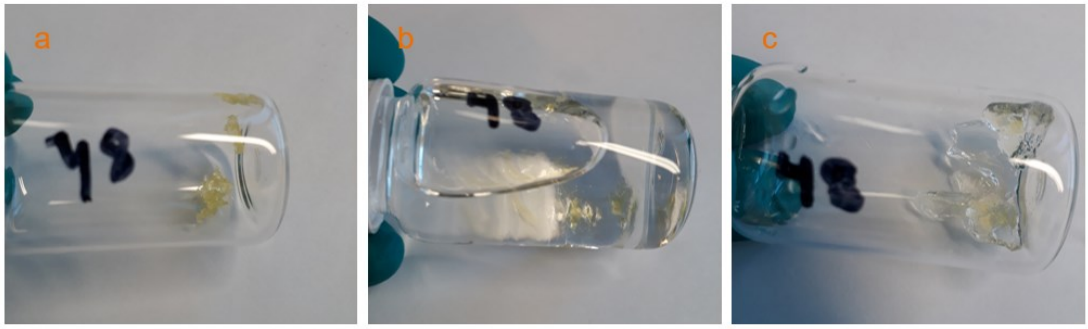

Figure 7. A dry gel (a), a partly swollen gel in water (b) and a swollen gel (c).

Figure 8. IR-35 Infrared Moisture Analyzer (Denver Instrument).

Figure 9. A gel sample before (left) and after (right) measuring the moisture content with IR-35 Infrared Moisture Analyzer (Denver Instrument).

Rheological measurements

Rheological measurements were done to swollen gel samples with a Physica MCR 301 rheometer (Anton Paar) (fig. 10). The gel samples were prepared as reported earlier in 3.3.1 and allowed to swell in excess water overnight. The water was changed at least once.

Frequency sweep and strain sweep were chosen as measurements and performed at 20,0 °C with a plate-plate geometry with serrated plates and a plate diameter of 25 mm. The samples for the rheometer were prepared by allowing a gel sample to swell in excess water in a plastic container overnight. The water was changed twice during the swelling process. The water was poured or pipetted out from the container and the sample was carefully transferred to the measuring plate with a wide spatula. Excess water from the swollen gel sample was dried with a tissue wiper and the gel was trimmed to fit the plate in situ (fig. 11). Before the onset of the reactions, the

normal force was fixed at 0,2 N and a solvent trap was used to reduce the evaporation during the measurements.

In the frequency sweep, a shear strain of 0,2% and an angular frequency of 1-300 rad/s were selected to ensure that the oscillatory deformation is within the linear regime. In the strain (amplitude) sweep, the shear strain was 0-75% and the angular frequency was 6,28 rad/s.

Figure 10. Anton Paar Physica MCR 301 rheometer.

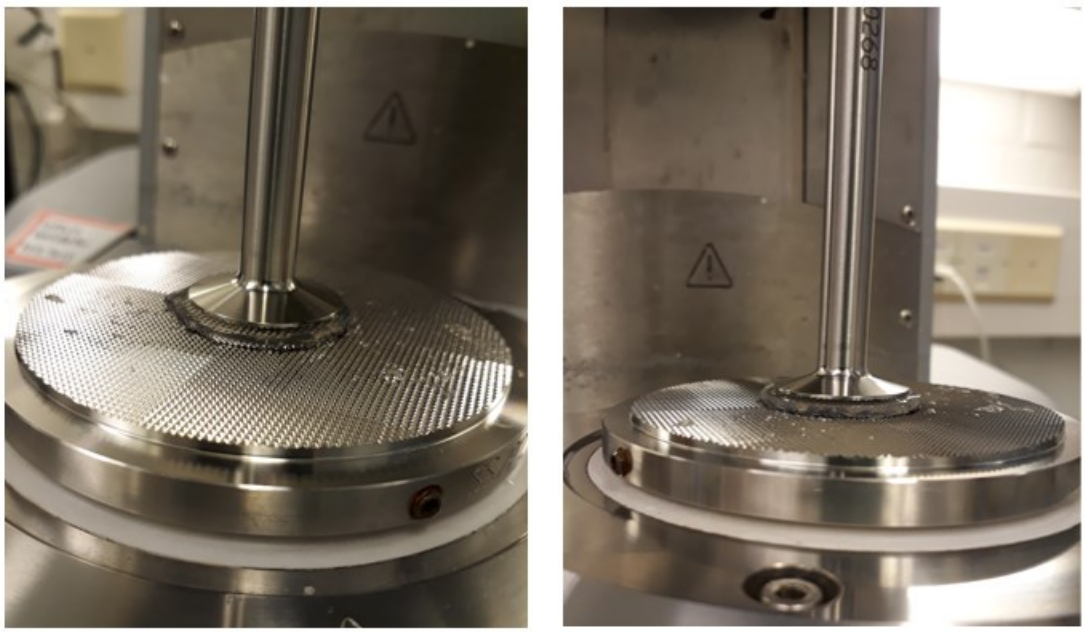

Figure 11. A gel sample in the rheometer.

4 Results and Discussion

4.1 Synthetic routes and characterization of photocross-linkable biobased monomers

Monomers were synthesized using four different methods, which differed from each other mainly in the type of base and solvents used. Since the aim of the synthesis was to prepare photopolymerizable and water-soluble monomers the key element to examine is the degree of substitution, which affects both. The degree of substitution (DS) is the average number of substituent groups attached per monomer unit. In the case of methacrylated xylitol, finding the right DS is a challenge, since a high DS leads to insolubility in water and a low DS leads to weak (photo)cross-linkability.

The main parameters studied in the monomer synthesis were the methacrylate donor type and per xylitol ratio, the usage of solvents and the base catalyst. Time and temperature were also studied in the initial experiments but kept constant towards the end of the experiments. An initial range for the methacrylate per xylitol ratio was found after few experiments to be between 1,5 and 3.

The first eight experiments were done with glycidyl methacrylate and resulted in a variety of products. The ones prepared with solvents were syrup-like viscous fluids with colours from different shades of brown to yellow (fig. 12). These products could be precipitated, dried and stored while products prepared without solvents were more viscous and often even solids and further handling of these products was not possible. According to the appearance and behaviour of these products they seemed to have polymerized further and/or their DS seemed to be high.

Figure 12. Monomer conversion products synthesized via the GMA route.

The next seven experiments utilized the esterification route with methacryloyl chloride and methyl methacrylate as the methacrylate containing reactants. The methacryloyl monomer conversion products consisted of two phases – an aqueous phase and an organic phase. The methyl methacrylate conversion products were either fluids or already solids. Further handling of both products was complicated mostly due to insolubility, which is why not many further experiments were conducted with methyl methacrylate and methacryloyl chloride.

In the next series of experiments the potential of methacrylic anhydride was investigated. Several experiments were conducted with different parameters and the after-reaction handling of the products was easier than for the previous products. The conversion products were mostly liquid or syrup-like. In the initial gelation tests the products showed minimal or no gelation. Some of the ungelated products were insoluble in water and some polymerized further into a hydrophobic polymer.

After several attempts with the esterification route, it was time to return to the glycidyl methacrylate route and modify the recipe slightly. The new recipe with sodium hydroxide as the base enabled a solvent-free reaction, which made the after-reaction handling simple. The conversion products were colourless syrup-like viscous fluids. The products were water-soluble and the gelation tests revealed good gelation potential. Based on visual examination, a GMA per xylitol ratio between 1,5 and 3 seemed to produce the most durable gels. The last experiments focused on preparing monomers and optimizing the process within this range.

Removing the solvents while inhibiting further polymerization was a challenge when drying the products throughout the experiments. The addition of an inhibitor and low

temperatures were used as methods to prevent further polymerization. Some of the products also kept polymerizing further in the freezer, where all the monomer product samples were stored.

NMR and DS

A 1H NMR spectrum for a methacrylated xylitol monomer is presented in figure 13. The monomer was prepared using the third GMA route. The methacrylate functional group is recognizable in the 1H NMR with signals for vinyl protons at 5.55 and 6.04 ppm and for methyl protons at 1.85 ppm. The presence of the xylitol protons is confirmed by the signals between 3.40 and 3.60 ppm. The protons of the opened epoxide ring structure can be found between 3.50 and 4.50 ppm.

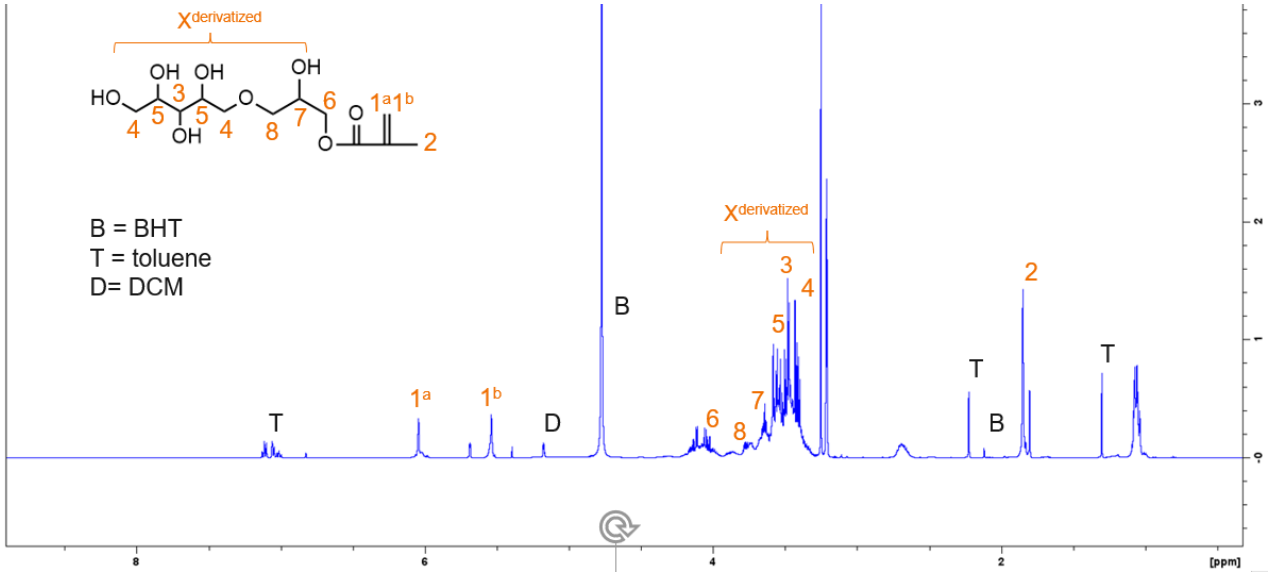

Figure 13. 1H NMR spectrum of a methacrylated xylitol monomer in methanol-d4. The monomer product was prepared using the third GMA route. The two protons of the double bond are marked separately (1^a and 1^b) as well as the xylitol backbone and its new structures ($X^{derivatized}$).

When comparing a H NMR reference spectrum of xylitol (fig. 14) with the sample spectrum (fig. 13), the signals for the xylitol protons can be found at the same ppm range and the formation of a new compound is confirmed with the new signals

appearing in the sample spectrum at a range between 3.5 and 4.5 ppm (fig.13, $X^{derivatized)}$.

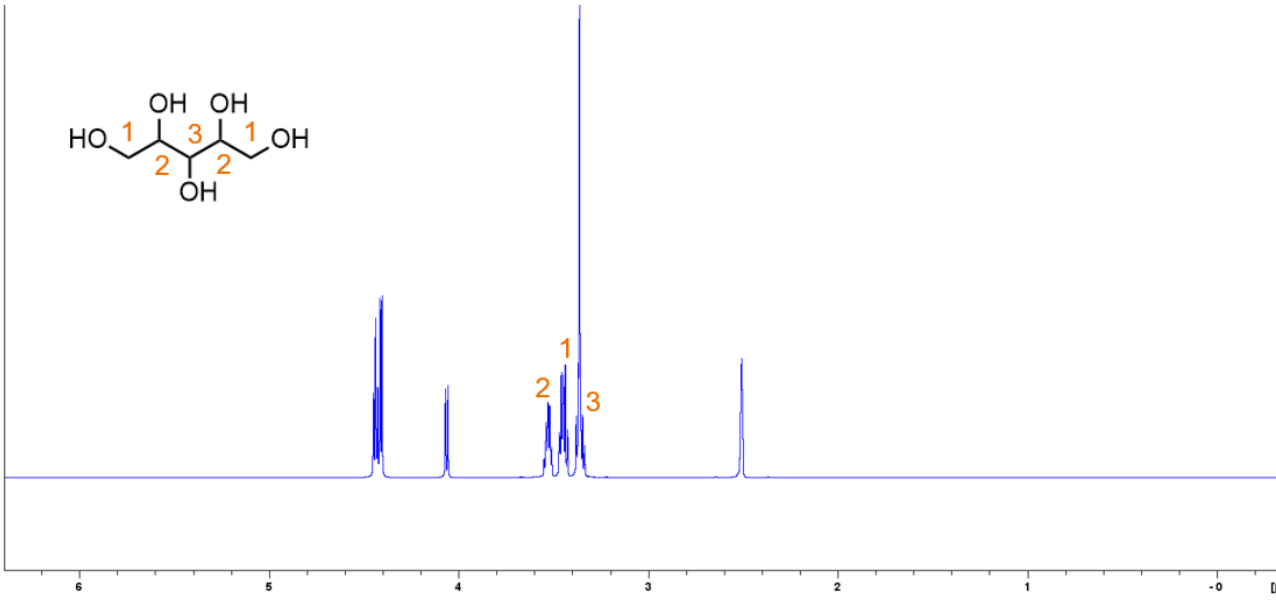

Figure 14. A 1H NMR reference spectrum of xylitol in dimethyl sulfoxide -d6.

The same groups can be found in the 13C NMR (fig. 15) spectrum at 125.2 and 136.4 ppm (vinyl), 18.6 ppm (methyl), 63.2, 71.1 and 72.6 ppm (xylitol) and 48.0 - 65.0 ppm (former epoxide ring structure).

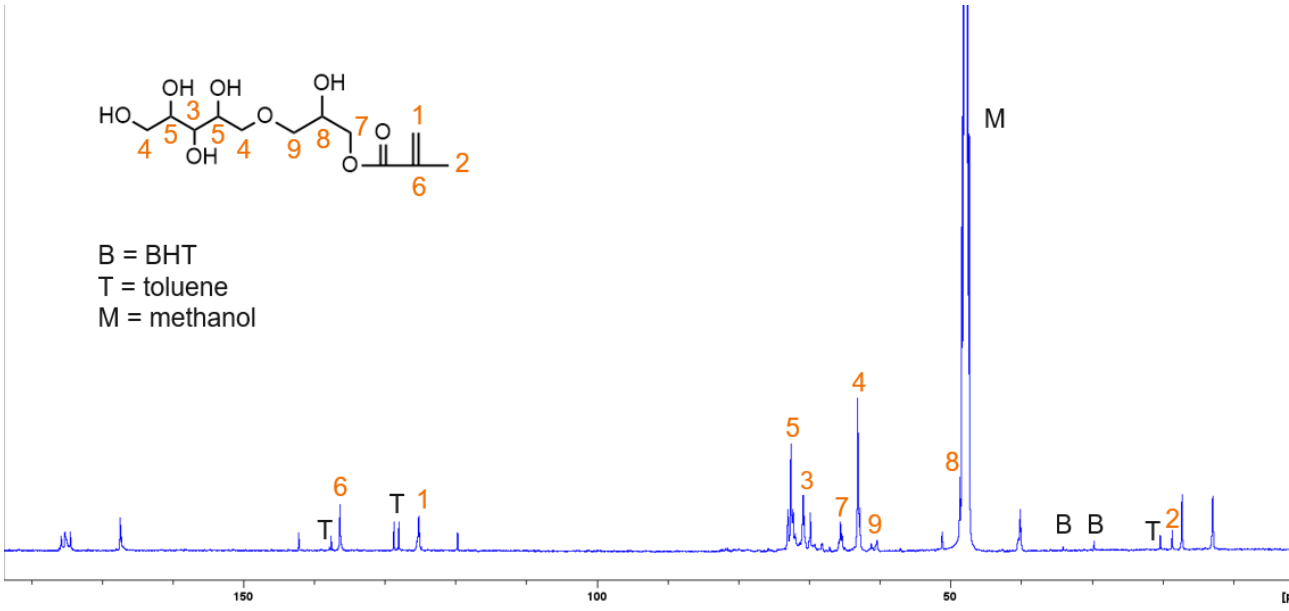

Figure 15. 13C NMR spectrum of a methacrylated xylitol monomer in methanol-d4. The monomer product was prepared using the third GMA route.

The calculated degrees of substitution for all samples are presented in figure 16. The two possible reaction routes for products prepared with GMA, epoxidation and transesterification, have been taken into account by calculating a DS range for these samples. The DS range consists of two values, which have been calculated assuming purely epoxidation reaction route or transesterification route. The reaction can be assumed to occur through both routes with a certain ratio but defining the exact ratio is beyond the scope of this study.

DS calculation methods for the epoxidation route (4) and the transesterification/esterification (5) route are presented below:

$$DS = \frac{amount\ of\ double\ bonds}{\frac{(amount\ of\ xylitol - 5)}{7}} \quad (4)$$

$$DS = \frac{amount\ of\ double\ bonds}{\frac{(amount\ of\ xylitol)}{7}} \quad (5)$$

where the amount of double bonds and the amount of xylitol come from the integrated sample spectrums. The division with seven regards the number of protons (7 protons) in the xylitol structure (excluding the protons in OH-groups). For the epoxidation route (4), the remaining protons of the GMA are regarded with the subtraction of 5 from the amount of xylitol.

According to the literature, the use of an aprotic solvent, such as DMSO or DMAc, favours the transesterification reaction and in a protic solvent the favoured reaction mechanism is epoxidation (Reis et al., 2008). In figure 16, the GMA products which have been prepared using an aprotic solvent have been marked with an asterisk. Assuming that the transesterification route is favoured, the blue column should be higher in these products. This is true for 4/8 of the samples. The rest of these samples had a clearly higher orange column, which indicates that the epoxidation route was favoured.

Monomers with a DS value around 1 are expected to have the most optimal gelation possibilities. According to figure 16, the products which are closest to 1 most often are the GMA products. MAA and MAC seem to be the second-best alternatives. The DS of MMA products remains clearly under 0,5. It seems clear that the samples with a DS value exceeding 5 have not occurred purely via the epoxidation route, because the maximum value for DS is 5.

When taking a closer look at the DS values of the GMA products, it becomes clear that the products prepared through the second and third GMA routes have generally higher DS values. These values have been compared with the GMA per xylitol ratio in figure 17. According to the results, the optimal DS value around 1 would be obtained with a GMA per xylitol ratio between 1 and 2.

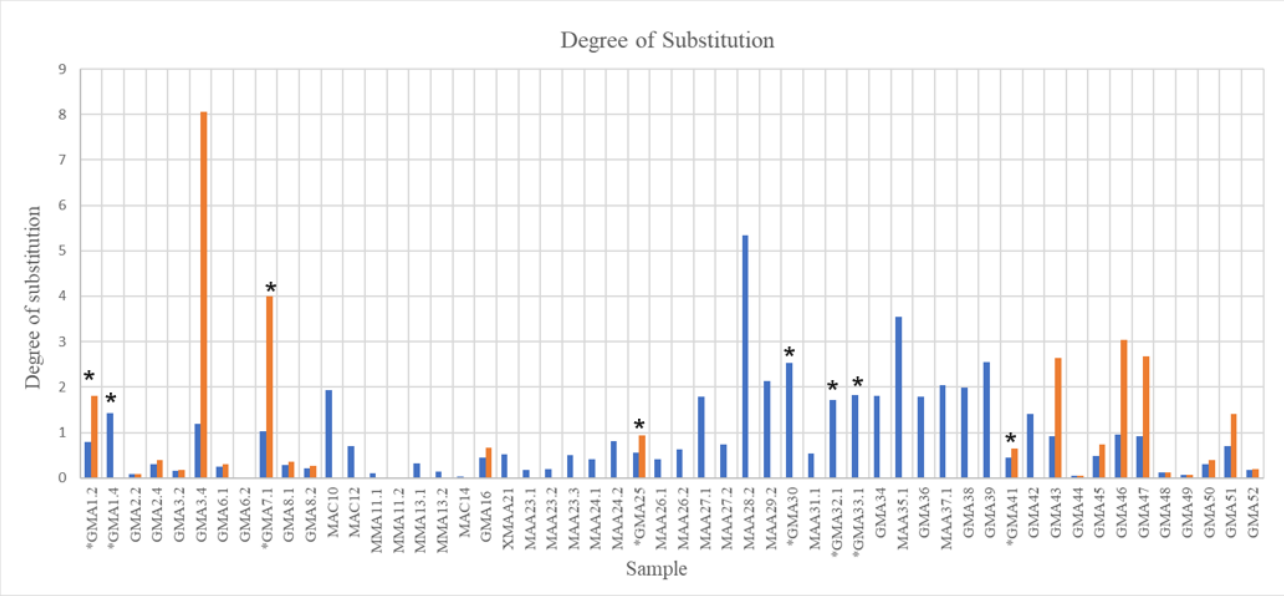

Figure 16. Degree of substitution of all the samples. For the GMA samples, the DS is marked with orange when the reaction is assumed to occur purely via the epoxidation route and with blue when assuming purely transesterification route. The GMA products, which have been prepared with an aprotic solvent have been marked with an asterisk.

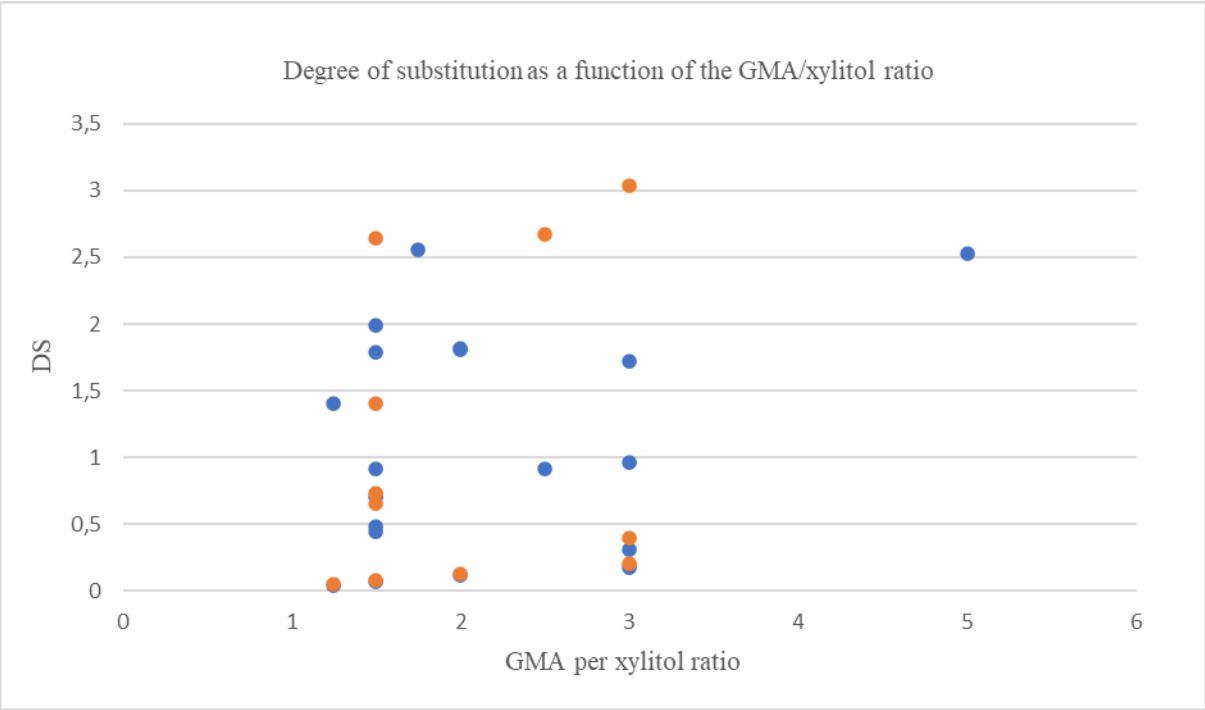

Figure 17. The degree of substitution as a function of the GMA per xylitol ratio in the GMA samples prepared with the second and third GMA method. The DS is marked with blue when assuming purely epoxidation reaction route and with orange when assuming purely transesterification reaction route.

4.2 Synthesis and characterization of hydrogels

Practical aspects

Gelation tests were performed to all the obtained monomer products. The initial tests were done in the oven with potassium persulfate or an azo initiator as the polymerization initiator and followed by gelation to films with redox initiators and photoinitiators. In the initial gelation tests, different monomer concentrations and initiator concentrations were tested to find a suitable recipe for the actual films.

Of all the monomer products, the GMA products prepared without solvents and with sodium hydroxide as the catalyst gave gels with the most optimal durability and homogeneity based on visual and manual examination. It must be emphasized that the other products may also have gelation potential but due to the time constrains of

this project it was decided that the further experimenting and analyses were continued with only the aforementioned gels.

A methacrylate per xylitol range of the GMA products with the most promising gelation results was determined based on visual examination and the properties of these gels were analyzed with rheological measurements and swelling measurements. The range was between 1,5 and 3 and the gels prepared from products with ratios within this range were fully or almost fully gelated and mechanically strong enough to be analyzed.

The gels chosen for the swelling measurements and rheological measurements were prepared with redox initiator concentration of 2 wt% (of the monomer concentration) and monomer concentration of 25 %. The same measurements were performed for four reference gels: a product gel made with a photoinitiator in an UV oven, gels made with redox initiator where some of the monomer was replaced with methylene bisacrylamide and a no-product gel where the monomer consisted of dimethylacrylamide and methylene bisacrylamide made with redox initiator. Gels based on methylene bisacrylamide and dimethyl acrylamide were chosen as reference gels, because methylene bisacrylamide, a water-soluble cross-linker (Kabiri & Zohuriaan-Mehr, 2003; Rosa et al., 2002), and dimethyl acrylamide, an easily polymerized and nonionic monomer, are one of the most common agents used in hydrogel preparation and they produce gels with good mechanical properties (Akhmetzhan et al., 2021).

All the gels utilized in the measurements are presented in table 1.
The names of the samples have been chosen as follows: chosen sample number – GMA per xylitol ratio of the sample – preparation method.

Table 1. Gel samples for rheological and swelling measurements.

Gel	GMA/xylitol ratio	Monomer concentration	Initiator, concentration	Preparation
Product gels				
1-1,5-r	1,5	25 wt%	[1]	[R]
2-2,0-r	2,0	25 wt%	[1]	[R]
3-2,5-r	2,5	25 wt%	[1]	[R]
4-3,0-r	3,0	25 wt%	[1]	[R]
Reference gels				
5-1,5-u (product, photoinitiator)	1,5	25 wt%	[2]	[U]
6-2,0-br (product+cross-linking agent)	2,0	25 wt% of which 2 wt% methylene bisacrylamide and the rest product	[1]	[R]
6-3,0-br (product+cross-linking agent)	3,0	25 wt% of which 2 wt% methylene bisacrylamide and the rest product	[1]	[R]
7-db-r (hydrophilic monomer+cross-linking agent)	-	25 wt%, of which 2 wt% methylene bisacrylamide and the rest dimethylacrylamide)	[1]	[R]

[1] Redox (APS-TEMED), 2wt%
[2] Photoinitiator (LAP), 2 wt%
[R] RT for at least 3 hours
[U] UV oven for 1 hour

The gel preparation included several factors which may affect the properties of the final gel films. In the gels prepared with APS-TEMED redox initiator system, the aqueous gel solution was poured to the Petri dish and the TEMED was added directly to the Petri dish and the mixture was stirred by hand, which may possibly lead to uneven distribution of the TEMED. Ensuring an even surface under the Petri dishes was also challenging inside the fume hood and this may have led to somewhat irregular thicknesses of the gels, which possibly may for example effect on the rheological measurements.

The rheological measurements also required a certain diameter (25 mm) and thickness (>3 mm) for the gels and this had to be considered already during the gel preparation, because the fragility of the gels limited the handling – the transferring and trimming. This meant that the diameter and thickness of the prepared gels had to be close to the ones required so that all additional handling of the gels could be

avoided. Reaction mixture volumes were tested to find a volume that would produce a gel film with the optimal dimensions. Transferring the gel films from the Petri dishes to the containers where the gels were washed was a challenge, since the films easily broke into pieces while detaching the film from the Petri dish.
Finding the optimal parameters and plate surface geometries for the measurements on the rheometer required several test runs, since the samples exhibited wall slipping, which is a common phenomenon when performing rheological measurements on gel samples (Walls et al., 2003). Serrated surface geometries and a sufficient normal force were utilized as methods for preventing the phenomenon, but some slippage was noticed towards the end of the amplitude sweeps in almost all samples.

The gel films which were used in the rheological measurements were also used in the swelling measurements. The gel films were cut to pieces and dried before the swelling process. Despite the efforts to cut the pieces of different gels to the same size, the uneven size distribution could possibly affect the results of the swelling measurements. Another issue in the swelling measurements was the drying of the tea bag which was used as a vessel for the gel pieces to swell in and to be transferred in. Although it was attempted to standardize the drying process the removal of excess inter-particle water and water absorbed by the tea bag before weighing may be incomplete and vary between measurements and samples. This and other issues have been previously identified in the literature (Zhang et al., 2020). According to the work of Zhang et al. the results obtained with the tea bag method always seemed to be significantly lower than with other methods. Pyramid-shaped tea bags seemed to be somewhat more accurate, but the results were still lower than with other methods.

The moisture content of the gel samples was measured after the swelling measurements. Though the swollen gel sample pieces were spread on the measuring plate evenly with a spatula, trapping of moist under the pieces may occur and affect the results.

Visual examination

The prepared gels were generally clear and colourless (fig. 18). In some of the gels prepared with photoinitiator, the colour shifted slightly towards yellow. The

photoinitiator, lithium phenyl (2,4,6-trimethylbenzoyl) phosphinate (LAP), seemed insoluble in some of the gel solutions and produced a turbid gel/liquid with small particles of LAP in them (fig. 19).

Most of the gel samples had a smooth surface (fig. 20) but in some of the photopolymerized gels the surface was uneven. This could possibly be due to the insolubility of the photoinitiator or the incomplete permeation of the UV radiation through the sample container lids.

Many of the samples broke into pieces during lifting and transferring. As expected, the DMA-bisacrylamide reference gels were the most durable. The gels with a higher GMA per xylitol ratio seemed generally stronger, which is potentially due to a higher degree of cross-linking.

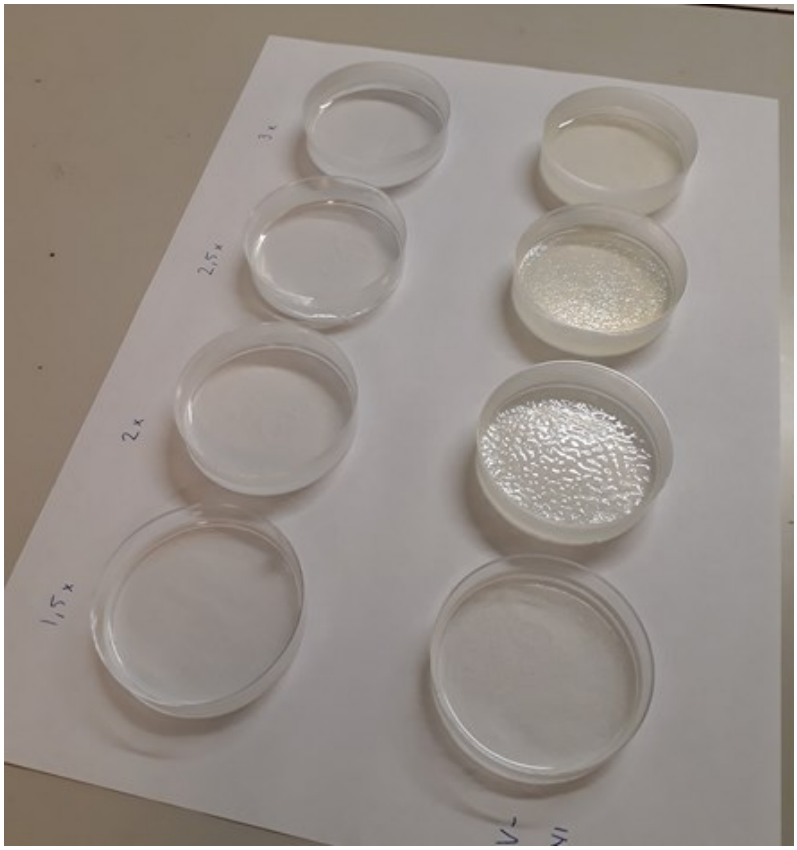

Figure 18. Gel samples prepared with photoinitiator or redox initiator.

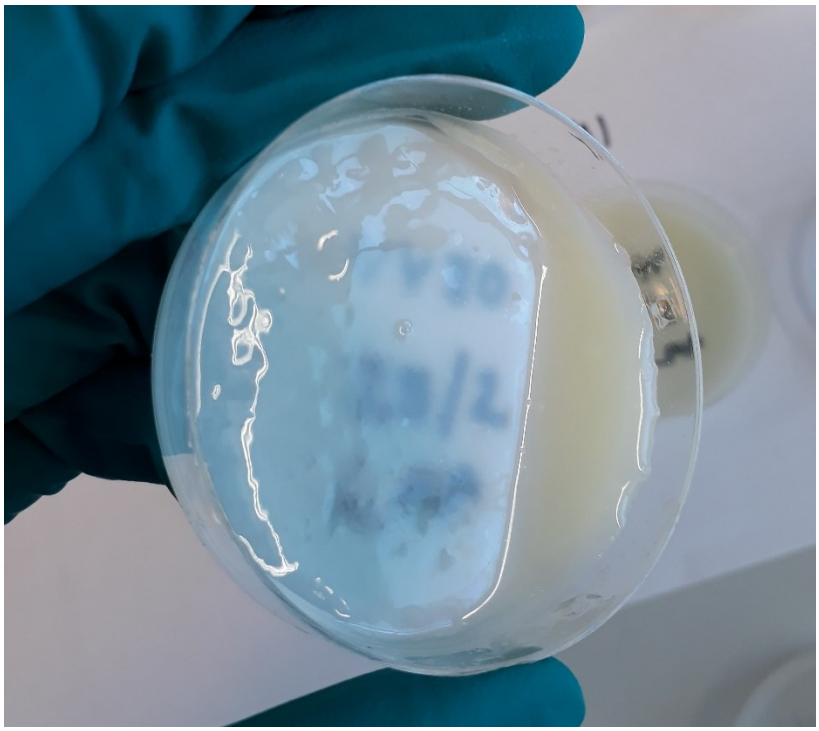

Figure 19. A turbid photopolymerized gel sample.

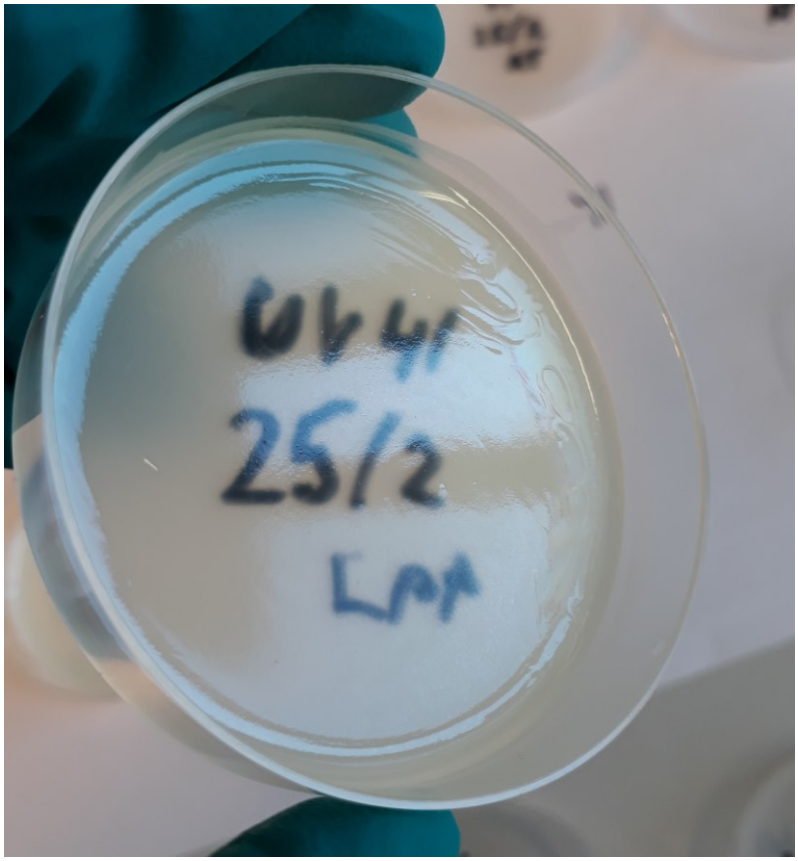

Figure 20. A gel sample prepared in the UV oven with LAP as the initiator.

Swelling measurements

The swelling ratios of all the gel samples are presented in figure 20. Generally, a lower GMA per xylitol ratio led to a higher swelling ratio. The monomer product containing gels had swelling ratios in approximately same range. According to the results, the photopolymerized reference gel had the highest swelling ratio. The two other reference gels, the bisacrylamide/dimethylacrylamide gel and the product/bisacrylamide gel, had the lowest swelling ratios which is most likely explained by higher degree of cross-linking (Zohuriaan-Mehr & Kabiri, 2008; Lee & Wu, 1996).

Comparison of the swelling ratios with the degrees of substitution from the monomer synthesis (fig. 16) reveals that the gels prepared from products with highest DS values had the lowest swelling ratios. This could be explained by the fact that a high DS leads to a higher amount of double bonds present in the structure and thus higher potential for the formation of cross-links, which reduce the swelling ability (Zohuriaan-Mehr & Kabiri, 2008).

The swelling ratios measured with the moisture analyzer (fig. 21) are generally lower than the values obtained from the swelling measurements.

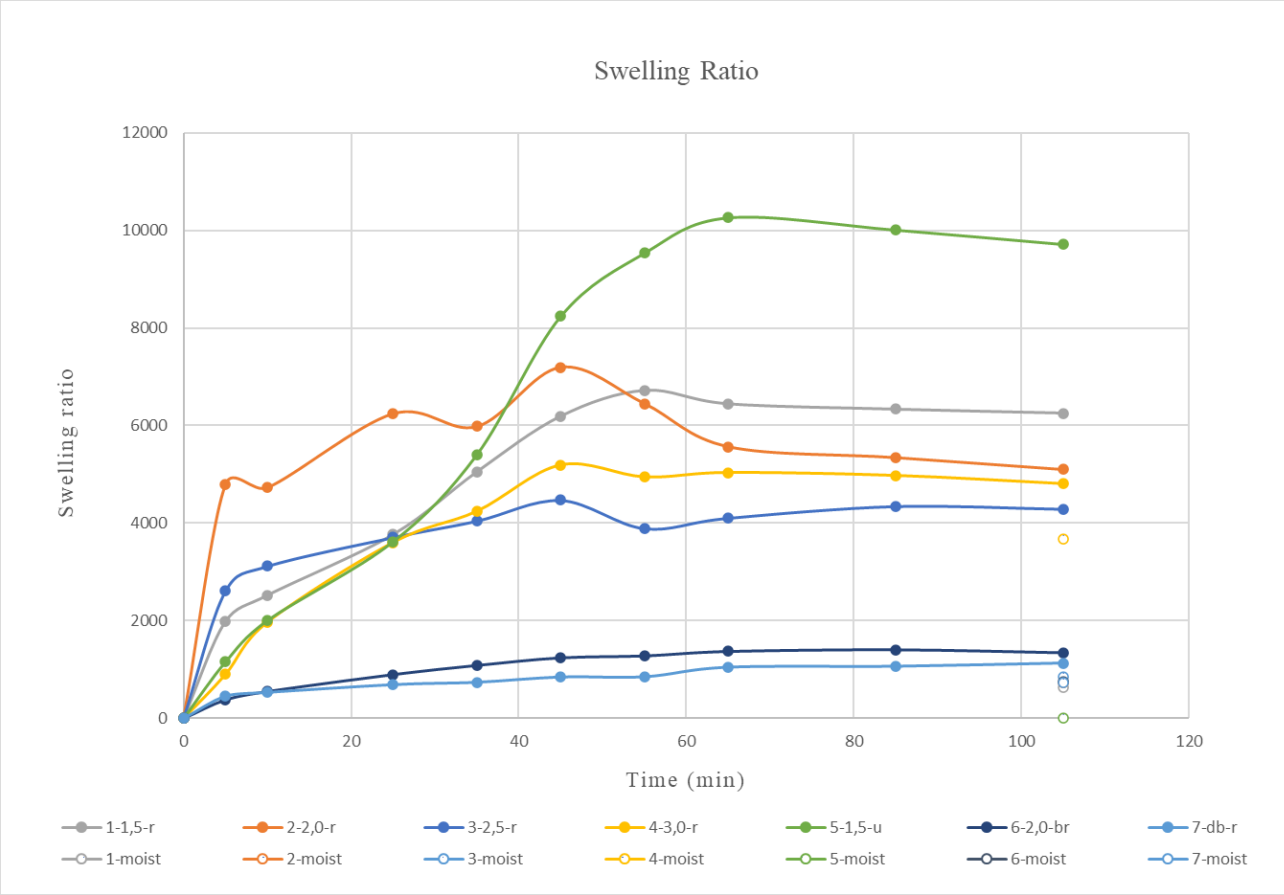

Figure 21. Swelling ratios of all samples with a closed marker expressing the swelling ratio measured with the tea bag method and an open marker expressing the swelling ratio measured with a moisture analyzer. The lines are to guide the eye.

Rheological measurements

The results of the frequency sweep measurements are presented in figure 22. According to the figure, G' > G" within the inspected frequency range for all the samples. This indicates that a well-developed network has formed in the gel samples.

When comparing the moduli of gel samples with different GMA per xylitol ratios, it can be seen from the figure that a higher ratio generally equals higher moduli values. Both moduli of the photopolymerized reference gel are significantly lower than the moduli of the gels prepared with redox initiator which is consistent with the previously mentioned high swelling ratio of the gel. This could potentially be due to a lower of number cross-links and a high number of unsubstituted hydrophilic hydroxyl groups present in the structure of the photopolymerized sample (Khan & Ranhja, 2014).

The results of the frequency sweep are not fully consistent with the swelling results when examining the connection between the DS values of the monomer product (fig. 16) and the gel properties. The gel prepared from a monomer product with the highest DS had the lowest moduli values of all four product gels and the product gel with the lowest DS had second highest moduli values. On the other hand, the product gel with the second highest DS had the highest moduli. The inconsistencies may be explained by the fact that only one sample per monomer was analyzed and there is the possibility that something has happened to the samples during the process (handling, storage, measurements).

According to the amplitude sweep (fig. 23), all the samples have G' > G" in the LVE region, and thus confirms that they have a gel-like structure. This result is in accordance with the frequency sweep results. The determined LVE region was used to measure the moduli in the frequency sweep.

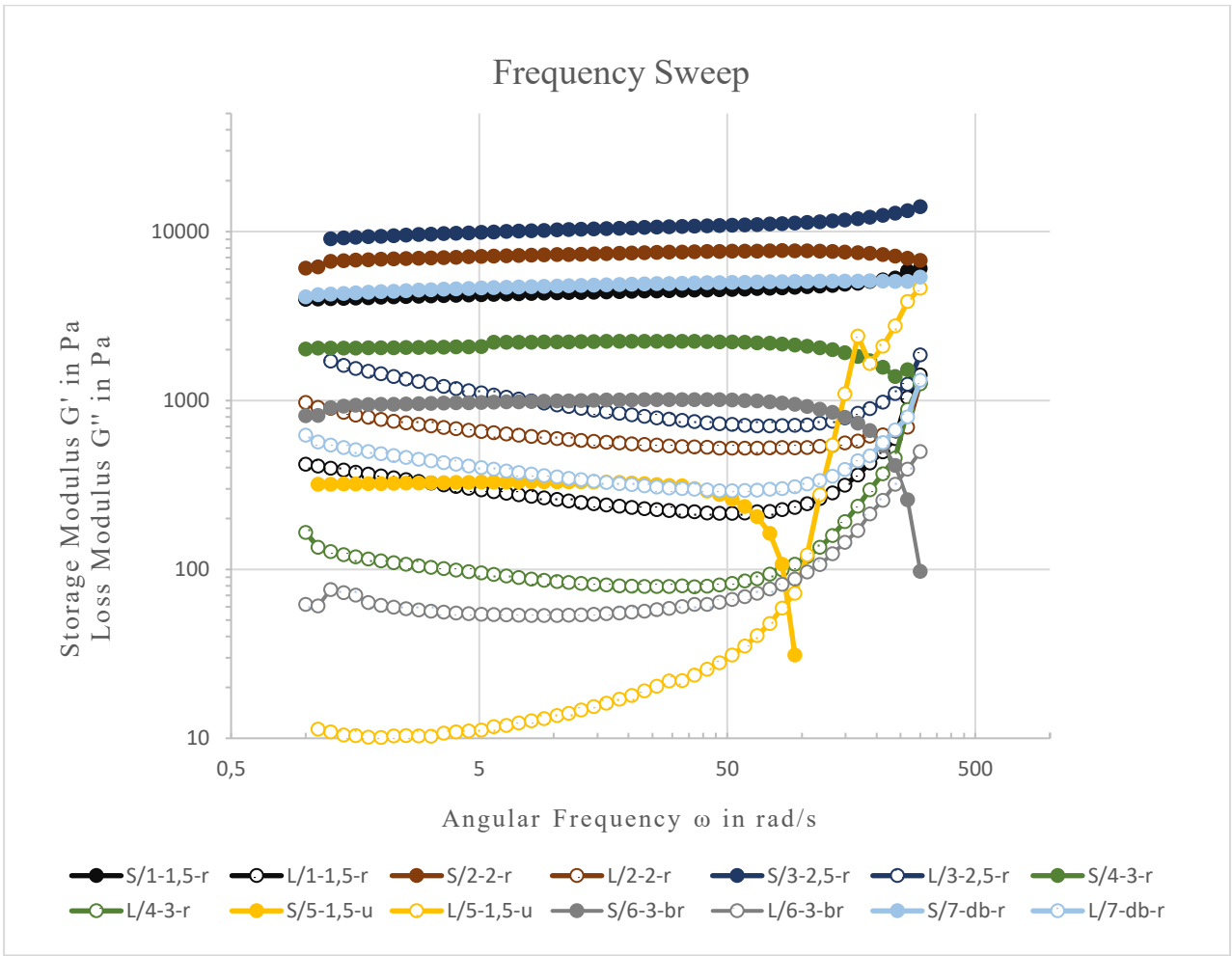

Figure 22. Frequency sweep results of all samples with a closed marker expressing the storage modulus and an open marker expressing the loss modulus.

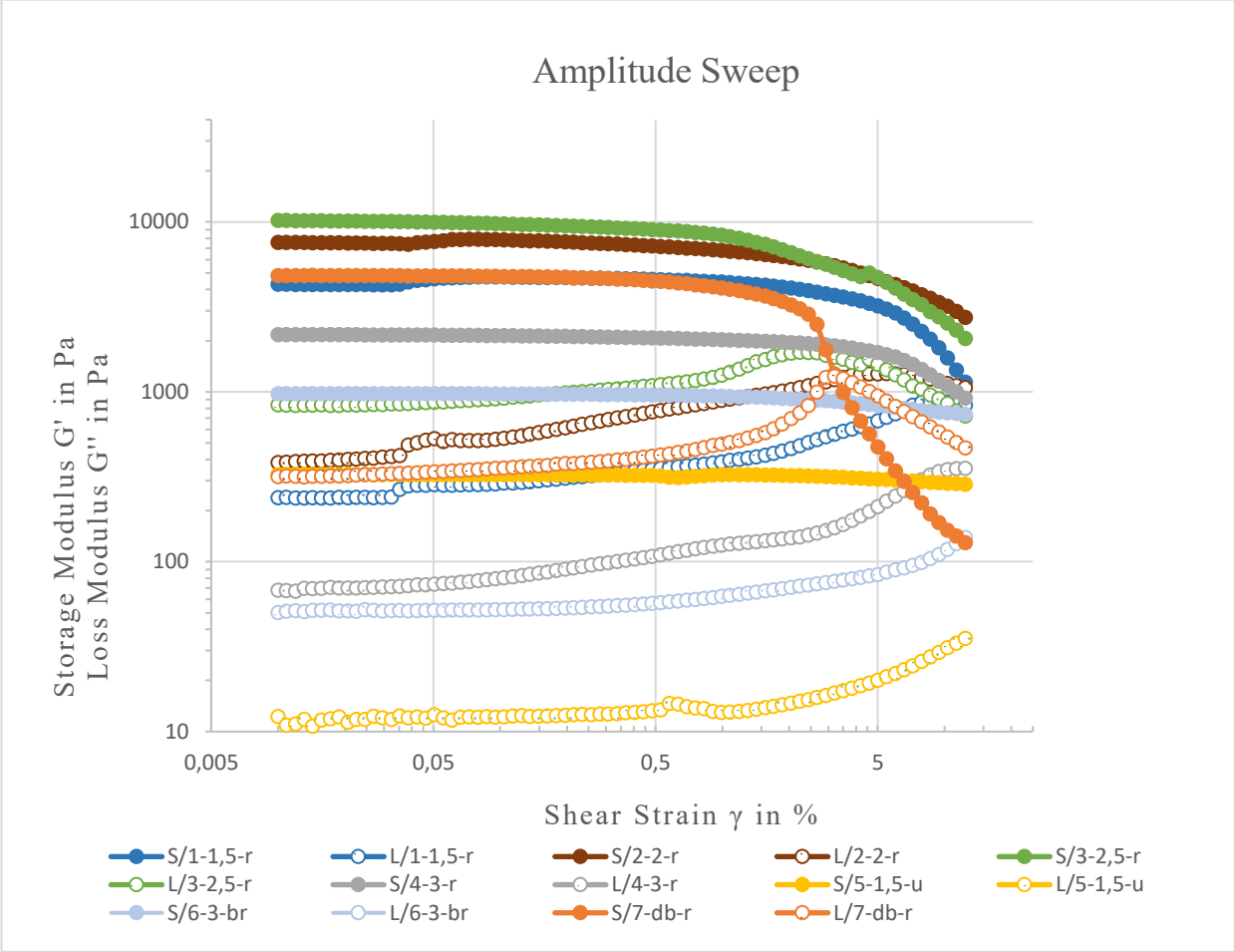

Figure 23. Amplitude sweep results of all samples with a closed marker expressing the storage modulus and an open marker expressing the loss modulus. The end parts of the plots in the higher strain area have been left out of the graph due to slippage of the samples.

4.3 Applicability in large-scale processes

The xylitol-based monomer synthesis and gel preparation are both fully applicable in large-scale processes. The utilized reactants are relatively inexpensive and readily available. The main raw material, xylitol, can be obtained in a sustainable manner from hydrolysis of hemicellulose xylan. Thus, the utilization of fossil feedstocks may be avoided for the most part. The sugar starting material may be diversified, since the approach is feasible for any sugar or sugar alcohol.

The reaction conditions are mild and no purification step is required, since the reaction and the consistency of the product mixture can be optimized. Due to the built-in cross-linkers, no other additives are required in the gel preparation. The gels may be formed by photopolymerization which enables 3D printing and printable applications such as cell culture or drug release materials. Polymerization into desired shapes is also possible. Other future applications could for example be soft contact lenses, thickening agents in cosmetics and pharmaceuticals and biodegradable absorbents.

5 Conclusion and Outlook

The aim of this thesis was to study the synthesis of photopolymerizable monomers from sugars and sugar alcohols. Monomers were prepared with four different methacrylate donors: glycidyl methacrylate, methacrylic anhydride, methacryloyl chloride and methyl methacrylate. The synthesis route of the monomers was either through epoxide ring opening reactions or esterification reactions and while this was confirmed with nuclear magnetic resonance analyses the exact reaction routes remain unclear and to be studied further. The synthesized monomers were water-soluble and photopolymerizable. The monomers prepared using a GMA route had the most optimal degree of substitution values for gelation purposes.

The monomer synthesis was followed by gel preparation. Different initiators were utilized in the gel preparation, including photoinitiators and redox initiators. An optimal GMA per xylitol ratio range for gelation was found and eight different gels were prepared within this range and then analyzed visually and for their rheological and swelling properties. According to the results, a high GMA per xylitol ratio led to higher mechanical strength but also to a lower swelling ratio. A photopolymerized reference gel had the highest swelling ratio.

In conclusion, it appears that the xylitol-based monomer synthesis and gel preparation are both fully applicable in large-scale processes. Future research should further develop and confirm these initial findings by optimizing the reaction and investigating the possibilities to extend the approach to other polyols, sugars, sugar alcohols, carboxylic acids and amines. A more detailed analysis of the reaction route and the monomer products is also desirable.

6 Swedish summary - Svensk sammanfattning

Syntes av sockerbaserade polymermaterial för framställning av hydrogel

I dagens läge finns det ett stort behov av hållbara lösningar, och bionedbrytbara, biokompatibla och biobaserade material är ett exempel på dessa. För polymerproduktion betyder stegen mot mera hållbara lösningar att oljebaserade råvaror som används i produktionen ersätts med något annat. I detta arbete undersöks möjligheterna att syntetisera nya kolhydratbaserade monomerer genom att derivatisera socker och sockeralkoholer. Kolhydrater är naturligt förekommande polymerer som är billiga och tillgängliga.

Xylitol, en polyol med fem kolatomer och fem hydroxylgrupper och som framställs ur sockerarten xylos, valdes som kolhydratmolekyl för monomersyntesen. Enligt litteraturen, har olika sockermolekylers användning i både derivatisering och hydrogelframställning undersökts men användningen av xylitol till dessa har inte studerats. De tidigare studerade sockermolekylerna har varit t.ex. stärkelse, polysackarider, monosackarider och polyoler.

I detta arbete sker derivatiseringen genom att sammanfoga en vinylgrupp (en kol-kol-dubbelbindning) till kolhydratstammen. Vinylgruppen kan sedan i polymeriseringsfasen bilda ett nätverk med andra molekyler. Derivatiseringen kan ske genom olika reaktioner. I detta fall var det hydroxylgruppens reaktion med antingen en epoxidring eller dess esterbildningsreaktioner. Meningen var att använda ett överskott av den reagensen med vinylgrupp, vilket skulle teoretiskt leda till i genomsnitt mer än en dubbelbindning per hydroxylgrupp. Därmed var målet inte att producera rena föreningar utan blandningar av föreningar med olika substitutionsgrader. Substitutionsgraden beskriver hur stor del av hydroxylgrupperna i xylitol har derivatiserats. Nukleärmagnetisk resonansspektroskopi (NMR) användes i definieringen av substitutionsgraden och i karakteriseringen av monomerprodukterna efter syntesen.

De vinylgruppinnehållande reagenserna som användes i denna avhandling var glycidylmetakrylat (GMA), metakrylsyraanhydrid (MAA), metakryloylklorid (MAC) och metylmetakrylat (MMA). Av dessa baseras glycidylmetakrylatens reaktion med hydroxylgruppen på en öppning av epoxidringen och transesterbildning och resten av reagenserna använder esterbildningsreaktionerna. Reaktionen med GMA föredrogs eftersom mängden hydroxylgrupper inte minskar i den, vilket förbättrar monomerproduktens egenskaper.

Ett mål för projektet var att använda de tillverkade derivatiserade monomererna i hydrogelframställning. Detta kräver att monomererna har en viss substitutionsgrad och att de är vattenlösliga. Förutom att tillverka polymeriserbart material, var ett mål att också tillverka material som kan fotopolymeriseras eftersom fotopolymeriseringsförmågan ökar produkternas tillämpningsmöjligheter. Potentiella tillämpningar för hydrogeler är t.ex. inom medicin och hygien- och kosmetikindustrin och i olika absorbentmaterial.

Det totala antalet experiment som utfördes i monomersyntesen var 52, varav 30 experiment var en reaktion mellan xylitol och GMA, 15 mellan xylitol och MAA, 4 mellan xylitol och MAC och 3 mellan xylitol och MMA. Experimenten med GMA utfördes med tre olika metoder varav den tredje kunde utföras helt utan lösningsmedel, vilket är gynnsamt med tanke på rening av produkten. Parametrar som varierades i experimenten var förhållandet av mängden vinylgruppinnehållande reagens per mängden xylitol, baskatalysator, temperatur, tid och användning av lösningsmedel (lösningsmedel/ icke-lösningsmedel. NMR-mätningarna bekräftade bildningen av nya föreningar och möjliggjorde beräkning av substitutionsgrader. Beräkningarna är dock bara uppskattningar och presenterades som en variationsbredd eftersom det visade sig att identifieringen av de exakta reaktionsmekanismerna som påverkar beräkningarna faller utanför detta arbetes räckvidd. Enligt beräkningarna (fig. 16), hade monomererna som gjordes med GMA och utan lösningsmedel högsta substitutionsgrader.

På basen av visuell och mekanisk examination av initiella gelprov valdes fyra monomerer till fortsatta analyser, där gelernas reologiska och svällningsegenskaper

undersöktes. De valda monomererna var gjorda med GMA och deras GMA per xylitol-förhållanden var inom ett visst område, mellan 1,5 och 3. Utöver dessa tillverkades fyra referensgelprov på tre olika sätt: 1) ett där 25 % av monomerinnehållet var monomerprodukt (GMA per xylitol -förhållande 2,0 eller 3,0) och resten metylbisakrylamid, 2) ett med UV-initiator i UV-ugn med monomeren gjord av 100% av produkt och 3) ett helt utan produkt med metylbisakrylamid och dimetylakrylamid. Dimetylakrylamid-metylbisakrylamid-gelerna är kända för sina goda mekaniska egenskaper. Alla valda produkt- och referensgeler förutom UV-referensgelen (2) gjordes med redoxinitiator.

De reologiska analyserna utfördes med en reometer och svällningen mättes med en sk. tea bag-metod och med en fukthaltsvåg. Centralt i analyserna av gelerna var att betrakta hur överskottet av den vinylgruppinnehållande reagensen, substitutionsgraden och tvärbindningspotentialen påverkar deras reologiska och svällningsegenskaper. Ett högt GMA per xylitol-förhållande borde leda till en hög substitutionsgrad och därmed hög tvärbindningspotential. En gel med hög tvärbindningsgrad har goda mekaniska egenskaper men dess svällningspotential är lägre.

Resultaten från svällningsmätningarna (fig, 21) visade att gelerna kunde svälla upp till 10 000 % och att gelen med högsta svällningsförmågan var den fotopolymeriserade referensgelen, varefter kom de monomerproduktinnehållande gelerna och de andra referensgelerna. De andra referensgelernas svaga svällningsförmåga kan möjligtvis förklaras med deras höga tvärbindningsgrad. Generellt ledde ett lågt GMA per xylitol-förhållande och en låg substitutionsgrad till en hög svällningsförmåga. Detta kunde dock inte bekräftas helt med resultaten från de reologiska mätningarna (fig. 22) eftersom enligt dem hade gelerna med höga GMA per xylitol-förhållanden visserligen goda mekaniska egenskaper men gelerna med höga substitutionsgrader däremot inte. De reologiska mätningarna bekräftade också att alla gelprov hade bildat ett välutvecklat nätverk.

Resultaten av denna studie visar att xylitol kan derivatiseras på ovan beskrivet sätt och den derivatiserade xylitolmonomeren kan användas i hydrogelframställning.

Hela processen kan upprepas i stor skala eftersom reaktanterna är relativt billiga och tillgängliga och reaktionsförhållandena är milda. Det krävs inte heller några särskilda reningsprocesser eftersom reaktionerna och produkterna kan optimeras. I framtiden rekommenderas ytterligare studier i detta ämne i form av att utveckla och bekräfta dessa upptäckter genom att optimera reaktionerna och undersöka möjligheten att utvidga metoden till andra kolhydrater.

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