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**ENZYMATIC SYNTHESIS OF ALLYL-(METH)ACRYLATE MONOMERS FOR
THIOL-ENE BIODEGRADABLE POLYMERS**

Florianópolis

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João Vitor Chiella Santin

**ENZYMATIC SYNTHESIS OF ALLYL-(METH)ACRYLATE MONOMERS FOR
THIOL-ENE BIODEGRADABLE POLYMERS**

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O presente trabalho em nível de mestrado foi avaliado e aprovado por banca examinadora composta pelos seguintes membros:

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Orientadora

Florianópolis, 2023.

Este trabalho é dedicado aos meus pais.

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“The etched letters over the top proclaimed, in High Imperial, **Wasing the Always of Wanting of Knowing**. Deep words. He’d heard them interpreted as, ‘The eternal desire of a hungry soul is knowledge.’”

(SANDERSON, 2015)

RESUMO EXPANDIDO

Introdução

O uso de polímeros derivados do petróleo é muito difundido na sociedade moderna devido a alta disponibilidade e baixo custo tanto da matéria-prima quanto do produto final. No entanto, esses materiais são caracteristicamente um recurso não-renovável e seus polímeros raramente são recicláveis ou degradáveis. Uso de óleos vegetais em polimerização e síntese de monômeros é aplicado no intuito de criar materiais renováveis, e a esterificação desses óleos pode ser utilizada como um caminho fácil para resolver o problema da degradabilidade, já que polímeros com grupos éster podem sofrer degradação por hidrólise, seja ácida, básica ou enzimática, quebrando partes da cadeia na presença de água. Em particular, esterificação com um álcool (meta)acrilato pode ser realizada, adicionando propriedades mecânicas interessantes ao material. Polímeros acrílicos são muito utilizados para a produção de plásticos, adesivos, e materiais odontológicos, sendo altamente reativos, com tempo de cura curto mesmo sem a presença de um iniciador. Tanto a síntese do monômero quanto a sua polimerização podem ser feitas por caminhos de química verde, utilizando enzimas como catalisador para a esterificação e posteriormente para a degradação do polímero, e com a adição tiol-eno como o mecanismo de polimerização foto iniciado desses monômeros. Reações de adição tiol-eno são classificadas como *click-chemistry*, por ocorrerem em condições brandas, de forma rápida e com produtos e subprodutos geralmente inofensivos. Essa adição pode ser utilizada como polimerização se monômeros multifuncionais forem utilizados, ocorrendo por crescimento em etapas, onde cada monômero tende a reagir com outro, finalizando sua cadeia temporariamente, até que outro monômero ou oligômero possuindo um radical reaja com ela novamente. O nome crescimento em etapas é utilizado como uma classificação desse comportamento, separando-o de outro mecanismo de crescimento conhecido como reação em cadeia, como é o caso da polimerização por radicais livres. Sistemas binário tiol-acrilato e ternário tiol-eno-acrilato já foram estudados na literatura, devido a ambos mecanismos tiol-eno e polimerização por radicais livres acontecem simultaneamente em tais sistemas, mas misturas binárias tiol-eno-(meta)acrilato utilizando um monômero assimétrico não foram, com exceção do acrilato de vinila que possui uma cadeia substituída curta, especialmente no que diz respeito a diferença no mecanismo entre os grupos acrilato e metacrilato em tais condições. Acrilato e metacrilato possuem diferentes constantes cinéticas de propagação e transferência de cadeia, tanto em relação a sua homopolimerização quanto a polimerização tiol-eno, com ambas constantes sendo mais altas para o acrilato e com a transferência de cadeia sendo proporcionalmente mais provável para este. No caso de reações tiol-acrilato e tiol-metacrilato, o primeiro reage pelo mecanismo tiol-eno e por radicais livres de maneira simultânea, enquanto a polimerização do segundo ocorre em dois tempos, iniciando com uma alta conversão de metacrilato por propagação, e depois com o tiol sendo consumido junto com a outra olefina.

Objetivo

O objetivo desse trabalho é a síntese de um monômero derivado de fontes renováveis através de esterificação enzimática, especificamente entre o ácido undec-10-enoico, derivado do óleo de rícino, e ambos acrilato de 2-hidroxietila (HEA) e metacrilato de 2-hidroxietila (HEMA), produzindo um dieno terminal assimétrico com dois grupos éster. A polimerização tiol-eno desses monômeros permite a observação da diferença no mecanismo de reação entre os

grupos acrilato e metacrilato, e a presença dos grupos éster permite a biodegradação por hidrólise enzimática do polímero.

Métodos

A síntese dos monômeros é realizada pela esterificação enzimática do ácido undec-10-enoico com HEA, no caso do monômero acrílico AEU, ou HEMA, no caso do monômero metacrílico MEU. A enzima utilizada foi a Novozym 435, e a reação procedeu sem o uso de solventes devido à miscibilidade dos reagentes, mantendo temperatura de 50 °C por 4 horas, com purificação por filtração sobre um leito de sílica gel. Pureza foi verificada por RMN de hidrogênio, e ambos monômeros foram polimerizados pelo mecanismo tiol-eno foto iniciada, utilizando DMPA como iniciador, e diferentes concentrações de monômeros tióis EDDET ou PETMP. Os oligômeros foram analisados por FTIR para observar o consumo de grupos funcionais, DSC para avaliar a possível cristalinidade dos materiais, análise de teor de gel e grau de intumescimento para estudar a matriz de reticulação, e testes de hidrólise enzimática foram aplicados para provar a hipótese de degradação dos polímeros pelo grupo éster.

Resultados e discussão

A síntese de ambos monômeros foi realizada e verificada por RMN, com o mesmo método descrito anteriormente para o monômero MEU alcançando o novo produto AEU. A fotopolimerização em massa dos dois monômeros produziu polímeros reticulados sólidos, com teor de gel entre 12% e 92%, com reticulação acontecendo até mesmo em amostras dieno-ditiol, que sem a ocorrência de propagação dos grupos acrilato ou metacrilato, deveriam produzir polímeros lineares. Análises de DSC indicaram uma estrutura semicristalina no caso de polímeros com o ditiol EDDET, enquanto que polímeros com tetratiol PETMP ou homopolímeros sem tiol possuem estrutura quase completamente amorfa. Análise de FTIR verificou a completa conversão de duplas ligações em 10 minutos de reação, e demonstrou grupos tióis não reagidos em amostras com MEU e proporção estequiométrica 1:1 de grupos funcionais tiol e dupla ligação, indicando a prevalência da propagação do metacrilato nestes sistemas, enquanto amostras com acrilato provavelmente tinham transferência de cadeia para o tiol e autopropagação do acrilato ocorrendo simultaneamente, em um processo misto de crescimento em cadeia e em etapa. A biodegradabilidade em meio enzimático, utilizando a lipase B de *Candida antarctica*, foi verificada pela perda de massa das amostras sólidas durante 28 dias, com resultados entre 10% e 70% de perda de massa, com a estrutura semicristalina, o alto teor de reticulação, e as condições brandas de incubação dos ensaios impedindo uma degradação ainda mais acentuada.

Conclusão

A síntese de monômeros parcialmente derivados de fontes renováveis foi alcançada e polimerização rápida e sem solventes destes obteve materiais poliméricos sólidos. Resultados indicam que a polimerização de sistemas tiol-eno-metacrilato realmente ocorre em duas etapas, com a adição do tiol sendo seletiva em direção a dupla alílica, enquanto que os sistemas com acrilato demonstram processos concomitantes e uma menor seletividade. Presença de grupos éster na estrutura do polímero permitem a degradação dos mesmos, porém a estrutura semicristalina e altamente reticulada dificulta a perda de massa.

Palavras-chave: Síntese enzimática. Polimerização tiol-eno. Sistemas tiol-eno-(meta)acrilato. Biodegradação de polímeros

RESUMO

O uso de polímeros derivados do petróleo é muito difundido na sociedade moderna devido à atual alta disponibilidade e baixo custo tanto da matéria-prima quanto do produto final. No entanto, esses materiais são caracteristicamente um recurso não-renovável e seus polímeros raramente são recicláveis ou degradáveis. Uso de óleos vegetais em polimerização e síntese de monômeros é aplicado no intuito de criar materiais renováveis, e a esterificação desses óleos pode ser utilizada como um caminho fácil para resolver o problema da degradabilidade. Em particular, esterificação com um álcool (meta)acrilato pode ser realizada, adicionando propriedades mecânicas interessantes ao material. Tanto a síntese do monômero quanto a sua polimerização podem ser feitas por caminhos de química verde, utilizando enzimas como catalisador para a esterificação e posteriormente para a degradação do polímero, e com o mecanismo de polimerização tiol-eno fotoiniciado. Sistemas tiol-acrilato e ternário tiol-eno-acrilato já foram estudados na literatura, devido a ambos mecanismos tiol-eno e polimerização por radicais livres acontecem simultaneamente em tais sistemas, mas misturas binárias tiol-eno-(meta)acrilato utilizando um monômero assimétrico não foram, especialmente no que diz respeito a diferença no mecanismo entre os grupos acrilato e metacrilato em tais condições. O presente estudo realiza a esterificação enzimática do ácido undec-10-enoico, derivado do óleo de rícino, com ambos acrilato de 2-hidroxietila (HEA) e metacrilato de 2-hidroxietila (HEMA) para produzir dois monômeros diênicos assimétricos em um sistema livre de solventes a 50 °C. Fotopolimerização em massa dos dois monômeros produziu polímeros reticulados sólidos, com teor de gel entre 12% e 92%, com diferentes propriedades mecânicas e cristalinidades. Análise de FTIR demonstrou grupos tióis não reagidos em amostras com metacrilato e proporção estequiométrica 1:1 de grupos funcionais tiol e dupla ligação, indicando a prevalência da propagação do metacrilato nestes sistemas, enquanto amostras com acrilato provavelmente tinham transferência de cadeia para o tiol e autopropagação do acrilato ocorrendo simultaneamente, em um processo misto de crescimento em cadeia e em etapa. Biodegradabilidade em meio enzimático foi verificada pela perda de massa das amostras sólidas durante 28 dias. A síntese de monômeros parcialmente derivada de fontes renováveis foi alcançada e polimerização rápida e sem solventes destes obteve materiais poliméricos sólidos. Resultados indicam que a polimerização de sistemas tiol-eno-metacrilato realmente ocorre em duas etapas, com a adição do tiol sendo seletiva em direção a dupla alílica, enquanto que os sistemas com acrilato demonstram processos concomitantes e uma menor seletividade. Presença de grupos éster na estrutura do polímero permitem a degradação dos mesmos, porém a estrutura semicristalina e altamente reticulada dificulta a perda de massa.

Palavras-chave: Síntese enzimática. Polimerização tiol-eno. Sistemas tiol-eno-(meta)acrilato.

Biodegradação de polímeros

ABSTRACT

The use of oil derived polymers is widespread in modern society due to the current high availability and low cost of both the source material and final product. However, these materials are characteristically non-renewable resources and the resulting polymers are very rarely recyclable or degradable. Use of vegetable oils in polymerization and monomer synthesis is employed in order to create renewable materials, and esterification of these oils can be used as an easy path to solve degradability. In particular, esterification with a (meth)acrylate alcohol can be performed, adding interesting mechanical properties to the material. Monomer synthesis and polymerization can be done through green pathways, using enzymes as a catalyst for esterification and later polymer degradation, and photoinitiated thiol-ene addition as the polymerization mechanism. Thiol-acrylate and thiol-ene-acrylate ternary systems have been studied in the literature, as both free radical and thiol-ene polymerization mechanisms occur simultaneously in such systems, but thiol-ene-(meth)acrylate binary mixtures using an asymmetric monomer have not, especially with regard to the difference in mechanism between acrylate and methacrylate groups in such conditions. This study uses enzymatic esterification of undec-10-enoic acid, derived from castor oil, with both 2-hydroxyethyl acrylate (HEA) and 2-hydroxyethyl methacrylate (HEMA) to produce two asymmetric diene monomers in a solvent free system at 50 °C. Bulk thiol-ene photopolymerization of both monomers with a dithiol or a tetrathiol, as well as free radical homopolymerization, yielded solid cross-linked polymers, ranging between 12% and 92% gel content, with different mechanical properties and crystallinity. FTIR analysis showed leftover thiol groups in methacrylate samples that had 1:1 stoichiometric proportion of thiol to double bond functional groups, indicating the prevalence of methacrylate propagation in such systems, while acrylate samples likely had both chain transfer to thiol and acrylate self-propagation occurring concurrently, in a mixed step-chain growth process. Biodegradability in enzymatic medium was verified by sample mass loss over 28 days. Partially derived from renewable sources monomer synthesis was achieved and quick and solvent free polymerization yielded solid materials. Results indicate that polymerization of thiol-ene-methacrylate systems does occur in two stages, and thiol addition is likely selective towards the allylic double bond, while acrylate systems show concurrent process and lower selectivity. Presence of ester groups in the polymer backbone allows for polymer biodegradation, though semicrystalline structure and a highly cross-linked matrix hinders mass loss.

Keywords: Enzymatic synthesis. Thiol-ene polymerization. Thiol-ene-(meth)acrylate systems. Polymer biodegradation.

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LIST OF ABBREVIATIONS AND ACRONYMS

- AEU – 2-(Acryloyloxy)ethyl undec-10-enoate
AIBN – Azobisisobutyronitrile
ATR – Attenuated total reflection
CALB – *Candida antarctica* lipase B
CDCl₃ – Deuterated chloroform
DMA – Dynamic mechanical analysis
DMPA – 2,2-Dimethoxy-2-phenylacetophenone
DSC – Differential scanning calorimetry
EDDET – 2,2'-(Ethylenedioxy)diethanethiol
FTIR – Fourier transform infrared spectroscopy
HEA – 2-Hydroxyethyl acrylate
HEMA – 2-Hydroxyethyl methacrylate
MEU – 2-(Methacryloyloxy)ethyl undec-10-enoate
N435 – Novozym 435
PETMP – Pentaerythritol tetrakis(3-mercaptopropionate)
UV – Ultraviolet

LIST OF SYMBOLS

k_p	Kinetic constant of propagation
k_{CTM}	Kinetic constant of chain transfer to monomer
k_{CTP}	Kinetic constant of chain transfer to polymer chain
Wt%	Percentage in relation to reagent weight
°C	Degrees Celsius

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1 INTRODUCTION

Synthesis of monomers derived from petroleum has allowed for the spread of plastics as very light as well as cheap alternatives for products that were once manufactured from metal, wood or fabric. However, when compared particularly to these last two, plastics are characteristically not as easily degradable and have non-renewable origins.

In order to keep its advantages, such as strength, resistance and cost, scientists have attempted to produce new plastics using renewable or renewable source derived materials that are also biodegradable. Although this has been achieved in some instances (JIANG *et al.*, 2015; MEIER; METZGER; SCHUBERT, 2007) not all qualities are maintained, as these new materials often lack similar mechanical properties and/or are too costly to produce in higher scale.

The use of vegetable oils in polymerization and monomer synthesis has been studied (SENIHA GÜNER; YAĞCI; TUNCER ERCIYES, 2006) due to the low cost of these precursors and their low cytotoxicity, with monomer synthesis being a particular field of interest, as the direct polymerization of oils is unsuccessful in producing materials with desirable mechanical properties (ROMERA *et al.*, 2015).

With the intent to produce a more sustainable product, it is also important to apply green chemistry techniques, lowering the carbon footprint of the entire process. Romera (2018) achieved this by using enzymatic esterification as a tool of monomer synthesis using a renewable source derived reagent, which achieved a product that was much easier to purify due to the enzyme's selectivity, and using milder conditions as to others often applied with esterification techniques such as Steglich and Fischer esterification.

Monomers with ester groups are looked upon due to this bond being subject to hydrolysis under specific conditions, characteristic that can be carried over to the final polymer, adding a possible pathway to biodegradability. Ester hydrolysis can be both acid or base catalyzed, as well as catalyzed by enzymes such as lipases (ALEJANDRA; MARGARITA; MARÍA SOLEDAD, 2012).

In order to continue the trend of using green chemistry reagents and processes, polymerization through the thiol-ene mechanism is often employed. The thiol-ene addition reaction is often classified as click chemistry, due to occurring under mild conditions, achieving high yields, and producing inoffensive by-products (HOYLE; BOWMAN, 2010).

Its use in the production of polymers has been studied since the 1930s as an alternative to free radical polymerization of dienes, inserting a heteroatom into the main carbon chain and easily producing either linear or cross-linked polymers through the choice between bifunctional or multifunctional monomers.

While thiol-ene polymerization follows a step-growth mechanism, free radical polymerization of olefins is classified as a chain-growth mechanism, and is the pathway that acrylic monomers follow in their homopolymerization. Acrylic materials are very commonly used in coatings, paints, plastics and particularly dental materials, and more recently have been used in the modification of renewable precursors (LU; LAROCK, 2007) to improve their mechanical properties.

Despite being very similar, derivatives from methacrylic acid and acrylic acid produce polymers with different properties, due to the methyl group increasing the stability of the carbonyl radical and occupying additional space in the final polymer chain, causing a difference in the intermolecular interaction. In the case of the polymerization of methyl methacrylate and methyl acrylate, a huge difference in glass transition temperature and tensile strength is observed (CORSARO *et al.*, 2022).

In order to build upon available knowledge, this work aims to explore the effects of the different kinetics inherent to acrylate and methacrylate groups, while producing a polymer that is partially derived from renewable sources and can be biodegradable. Using Romera's (2018) work as a foundation, the synthesis of a diene allyl-methacrylate monomer from 10-undecenoic acid and 2-hydroxyethyl methacrylate was reproduced, and then an allyl-acrylate monomer, using the same acid but 2-hydroxyethyl acrylate as the alcohol was attempted via enzymatic esterification, followed by their thiol-ene photopolymerization. The use of solvents and high temperatures was avoided when possible, and the use of enzymes as catalysts and thiol-ene click reactions was applied to pursue green chemistry in both product and process.

1.1 OBJECTIVES

1.1.1 General Objectives

This study intends to synthesize a previously reported as well as a new diene ester monomer that are partially derived from renewable sources, and polymerize them via

photoinitiated thiol-ene addition in order to analyze their selectivity towards thiol addition, chain transfer or propagation, producing thin cross-linked polymers that can be hydrolyzed.

1.1.2 Specific Objectives

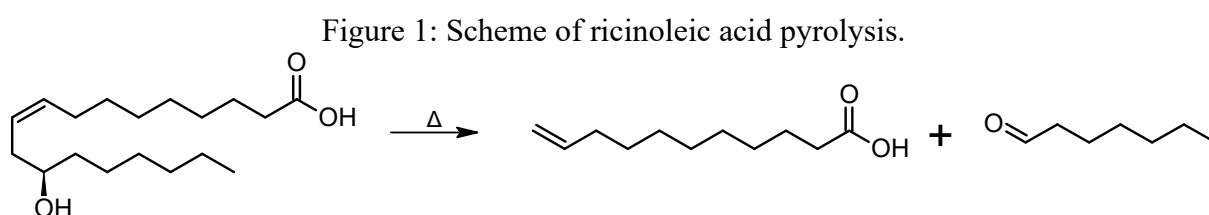
- 1- Synthesis and characterization of partially renewable allyl-(meth)acrylate ester monomers.
- 2- Synthesis and characterization of cross-linked polymeric materials via a mixed free radical/thiol-ene polymerization using synthesized diene monomers.
- 3- Analyze differences in polymer structure caused by differences in reaction conditions and functional group ratios.
- 4- Infer preferred mechanism of polymerization for (meth)acrylate groups by checking thiol group consumption.
- 5- Evaluate thermal characteristics and potential crystallinity of polymers.
- 6- Compare gel content in samples based on reaction conditions and monomer proportions.
- 7- Verify biodegradability through enzymatic hydrolysis.

2 LITERATURE REVIEW

2.1 MONOMERS DERIVED FROM PLANT OILS

With the intention of substituting petroleum derivatives in polymers, many researchers have looked towards plant oils in the production of new monomers. These oils come with excellent properties such as biodegradability, low price and low toxicity, along with chemically interesting structures, straight carbon chains, unsaturations and functional groups such as hydroxy or epoxy near the double bonds (VERHÉ, 2004).

Examples of plant oils with such desirable properties are linseed oil, corn oil, palm oil and castor oil. Specifically, this last one has been chosen previously (ACHAYA, 1971; MUTLU, 2012) for its high content of ricinoleic acid, which can be pyrolyzed into undecylenic acid (undec-10-enoic acid), as seen in Figure 1, product that possesses a very interesting terminal olefin.



Source: Author.

This type of pre-processing of plant oils is not inherently necessary, and direct polymerization of oils has been reported, however the results fail to achieve the necessary qualities to supplant the already established petrol derivatives (ESEN; KÜSEFOĞLU; WOOL, 2007; LI; LAROCK, 2000; ROMERA *et al.*, 2015; RYBAK; FOKOU; MEIER, 2008). Copolymerization of raw vegetable oils with non-renewable monomers is often tried to achieve the desired properties, although modification of the vegetable oils allows for a fully renewable or renewable-derived monomer.

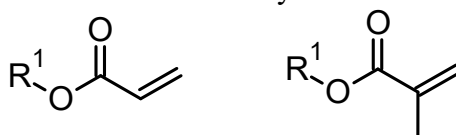
In the case of ricinoleic acid pyrolysis, examples of further modification are methyl-10-undecenoate, 10-undecenol and 10-undecenoyl chloride (ESPINOSA; MEIER (2011)), and more recently the development of diene monomers via esterification with 1,3-propanediol (CARDOSO, 2016; FOKOU; MEIER, 2010), isosorbide (MACHADO, 2015), and

(hydroxyethyl)methacrylate (ROMERA, 2019). The intention is usually to produce a diene that can be polymerized through free-radical, thiol-ene or olefin metathesis mechanisms.

2.2 ACRYLIC MONOMERS

Acrylates are a group of compounds that are derived from acrylic acid, characterized by the presence of a vinyl group bonded to a carboxyl group, as seen in Figure 2. These monomers are known to readily react in the absence of a stabilizer and their polymers are widely used for coatings, adhesives and plastics.

Figure 2: Generic structure of substituted acrylates and methacrylates, respectively.



Source: Author.

High reactivity of the double bond granted by the electron-drawing carbonyl allows the rapid curing of acrylic monomers into cross-linked polymer networks, with the incidence of UV light being a common method for initiation (GRUBER, 1992; LEE *et al.*, 2003). However, the reaction might be too fast, heavily impairing the ability to control the properties of the final product. This led to the use of methacrylate monomers, which can achieve materials that have similar mechanical properties with slower curing rates due to their lower kinetic constants (KUCHTA; VAN HERK; GERMAN, 2000), facilitating reaction control.

Methacrylate groups can have reactivities several degrees of magnitude lower than acrylates, specifically with relation to the propagation and termination kinetic constants (ANSETH; WANG; BOWMAN, 1994), not only influencing in curing times for polymers but also in its ability to undergo modifications such as a Michael addition, with acrylates being a much better Michael acceptor than methacrylates, due to the difference in nucleophilicity (MATHER *et al.*, 2006).

The presence of other functional groups inserted into the acrylate must also be taken into consideration, as even in a free radical homopolymerization the additional groups heavily affect the properties of the synthesized polymer. One very common example is the presence

of the hydroxy functionality, as it allows for intermolecular hydrogen bonding to improve the overall structure. This is usually achieved with the use of 2-hydroxyethyl acrylate (HEA) and 2-hydroxyethyl methacrylate (HEMA), with higher propagation rate coefficients compared to those of their alkyl-substituted counter parts (BUBACK; KURZ, 1998).

Despite being classically petrol-derived, both acrylic and methacrylic acid can be produced through biological pathways (AVASTHI *et al.*, 2020), however achieving a high degree of purity with the use of biobased feedstock is significantly harder than the already established non-renewable process, and the presence of impurities is known to reduce the rate of polymerization (HUO *et al.*, 1988).

2.3 ENZYMES AS CATALYSTS

Enzymes are often used as a substitute to chemical catalysts due to their versatility, selectivity and mild reaction conditions (VOULGARIS *et al.*, 2015), both in aqueous and in organic environments.

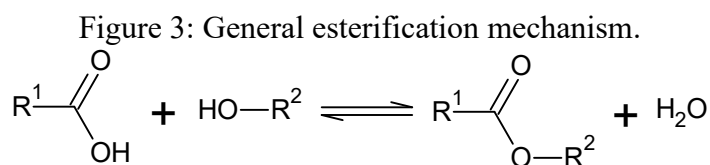
Despite having a higher cost than non-biological catalysts, the development of new recombinant DNA technologies should allow enzymes to be produced on a large scale and gradually lower their cost. By paying special attention to reaction conditions and enzyme activity, one can achieve much higher reaction rates and product specificity over the use of non-biological catalysts (KOELLER; WONG, 2001), and immobilized enzymes can be recuperated and reutilized (ROMERA, 2018).

Examples of syntheses using enzymes reported are chiral alcohol synthesis (ZHENG *et al.*, 2017), chiral amines (KOHLS; STEFFEN-MUNSBURG; HÖHNE, 2014), carboxylic acids via hydrolysis of nitriles (MARTINEZ *et al.*, 2008) or hydrolysis of esters (SCHÜLÉ *et al.*, 2016), and esterification (ROMERA, 2018).

2.3.1 Esterification for monomer synthesis

Enzymatic esterification has been studied (ROMERA, 2018) as a greener alternative to regular pathways for the synthesis of esters, in particular diene esters, such as the more common Fischer process, which involves a high temperature and the use of toluene for removal of produced water. In an enzymatic reaction, temperatures can be much milder,

solvents are not required in case reagents are miscible, and producing fewer by-products. Figure 3 presents the mechanism for esterification reactions.



Source: Author.

The esterification mechanism catalyzed by enzyme *Candida antarctica* lipase B (CALB) has been reported (ANDERSON; LARSSON; KIRK, 1998) with a Ser-His-Asp amino acid triad being responsible for the catalysis. Acid initially reacts with the serine active site, forming an acyl-enzyme, which can then be deacylated by an alcohol, regenerating the enzyme and producing the ester and water.

The same mechanism occurs if the initial acylation is done by an ester, producing the alcohol while in the presence of water. As such, the amount of water in the system is very relevant in the mechanism, as lipases are designed to perform hydrolysis in aqueous systems while also having much higher activity towards esterification if very small amounts of water are present as opposed to none at all.

It is also important to work within the boundaries of the selected enzyme, especially with regards to pH and pKa of reagents, as a highly acid medium deactivates the enzyme, specifically in the case of Novozym 435 much higher values of activity were found when the acid pKa was above 4.8 (HOLLMANN *et al.*, 2009; NORDBLAD; ADLERCREUTZ, 2008). When it comes to reaction temperature, the use of extreme conditions can cause enzyme denaturation, while milder temperatures, from 40 up to 60 °C, are where the enzymes are usually most efficient (ANDERSON; LARSSON; KIRK, 1998; LEE; WIDJAJA; JU, 2006). This turns out to be a quality, particularly useful in cases where the substrate would also deteriorate or even polymerize at higher temperatures.

Development of immobilized enzymes has also allowed for very simple purification steps and catalyst reuse, as the solid supports can be easily filtered once the reaction is complete, and then washed with solvent. In his synthesis work, Romera (2018) reported up to 90% conversion even after 10 reuse cycles of the same enzyme.

As such, an enzymatic process allows for a cleaner reaction and easier purification process, but is not as broad in scope as other catalysts, and is often more expensive.

2.3.2 Hydrolysis of polymers

In the same way enzymes can catalyze the production of an ester, while in the presence of water the reverse path may occur, hydrolyzing the ester into its constituent alcohol and acid, as shown in Figure 3. In the case of lipases, they are characterized as hydrolases, as this process is their original intent, and the reverse path, esterification in particular, is a secondary process that may occur under the right conditions.

This process allows ester-based materials to be biodegradable, as the ester bond can be easily cleaved under water abundant conditions, as long as there is enough contact between the enzyme and substrate, which is not a trivial condition when the ester moieties in question are trapped in a highly cross-linked polymer matrix.

Laycock and colleagues (2017) thoroughly described the mechanisms and kinetic control of the hydrolytic biodegradation of polymers such as polysaccharides, polyesters and polyamides. The authors describe two main mechanisms called bulk degradation and surface degradation, in the first the enzymes are able to diffuse through the matrix and the polymer loses mass uniformly through the film's thickness, and the second has negligible diffusion and the reaction occurs on the surface, slowly decreasing the thickness of the film.

As such, the rate of diffusion in the material, which itself is controlled by material hydrophilicity and cross-link density, and the original film thickness control the degradation rate. In the case of enzymatic degradation, it is considered that only surface degradation occurs, as the enzymes often are not able to penetrate the polymeric matrix, and so only diffusion in the overall medium and in the polymer surface need to be considered.

It is also important to note that mass loss might not be an immediate effect, particularly in bulk erosion, as some bonds might be broken without creating small enough oligomers that can diffuse out of the matrix, and swelling by osmosis might occur if the polymer is hydrophilic enough, increasing the overall mass.

Hoelscher *et al.* (2018) have reported the degradation of poly (thioether-ester) nanoparticles by evaluating particle swelling, change in morphology and decrease in molar mass. Results showed 90% molar mass reduction in 10 days in a CALB solution, while a pH

2.8 hydrochloric acid solution only achieved 37% reduction over three months of incubation, both tests being done at 37 °C and compared to a pH 7.4 phosphate buffer as a control, which showed no degradation. The semicrystalline character of the reported polymer likely hindered degradation, particularly in the acidic test, but the lack of cross-linked fractions facilitated the decrease in molar mass and propitiated the swelling behavior of particles once degradation started. In a second work (HOELSCHER *et al.*, 2021), the authors found even faster degradation rates of a similar poly (thioether-ester) material, though with a higher hydrophilic character.

2.4 POLYMERIZATION MECHANISMS

Polymerization is a type of chemical reaction characterized by the addition of repetitive small molecules, called monomers, to form long chains called polymers. Polymers are often associated with plastics in modern society, but they are also the very building blocks of life, as proteins are polymers of amino acids and both starch and cellulose are polymers made of sugar monomers.

Polymerization reactions can occur through several mechanisms, such as free radical polymerization, cationic and anionic polymerization, ring-opening polymerization and condensation polymerization, among others. In order to better organize these mechanisms and many others that have been reported, a classification arose separating them into step-growth polymerization and chain-growth polymerization.

Chain-growth polymerization is characterized by proceeding by a reaction between the monomer and the active site on the polymer chain, regenerating the active site at the end of each step, process that is also known as a propagation chain. This way, a chain quickly increases in size as soon as it is formed, reaching high molar masses even at low monomer conversion.

Step-growth polymerization occurs with several active sites, and monomer molecules tend to react to form several dimers, then trimers, oligomers, and eventually long chains, with very high molar masses only being observed once very high conversion values are reached.

Two main mechanisms were subject of this study: thiol-ene polymerization, an example of step-growth; and free radical polymerization, being characterized as a chain-growth mechanism.

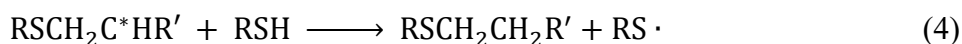
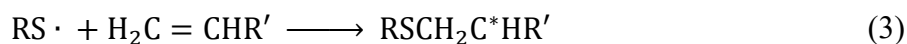
2.4.1 Thiol-ene

The thiol-ene addition mechanism was first reported by Posner in 1905, who achieved thiol coupling to several different olefins, with the structure of the unsaturation strongly influencing the anti-Markovnikov reaction. Later, in 1926, Braun and Murjahn obtained a gel by heating an allyl mercaptan. This was the first instance of a thiol-ene polymerization, mechanism that was later elucidated by Kharasch *et al.* (1938) as a free-radical process. For a thiol-ene polymerization to occur, multifunctional monomers have to be used, such as a dithiol reacting with a diene, or in the case of Braun and Murjahn, a single monomer with at least one double bond and one thiol group. This way, for every thiol or olefin consumed, a new molecule is added to the chain, with another functional group available.

Since then, extensive work had been performed in the study of materials synthesized through this mechanism, being eventually characterized as a click-chemistry reaction due to the mild conditions required, a high yield and generally inoffensive by-products.

The mechanism for free-radical thiol-ene polymerization is shown in Table 1. First step is initiation, where the decomposition of an initiator creates the first radicals through the incidence of light or heat, although in some cases neither may be necessary. In the second step, the initial radical reacts with a thiol group, removing a hydrogen and producing a thiyl radical, which is added to an ene double bond in step 3, the propagation step, leaving a carbonyl radical behind. Finally, this carbonyl radical undergoes a chain transfer reaction, removing a hydrogen from another thiol group, creating a new thiyl radical to restart the cycle, in step 4. Termination may occur if two carbonyl or thiyl radicals encounter each other, ending the reaction for both molecules.

Table 1: Thiol-ene polymerization mechanism.



Source: Adapted from Romera (2018).

Due to this propagation to chain transfer cycle, the thiol-ene mechanism is characterized as step-growth polymerization, and it heavily depends on the stoichiometric proportions of each functional group. Disproportional formulations tend to achieve much smaller molar masses (MACHADO, 2015).

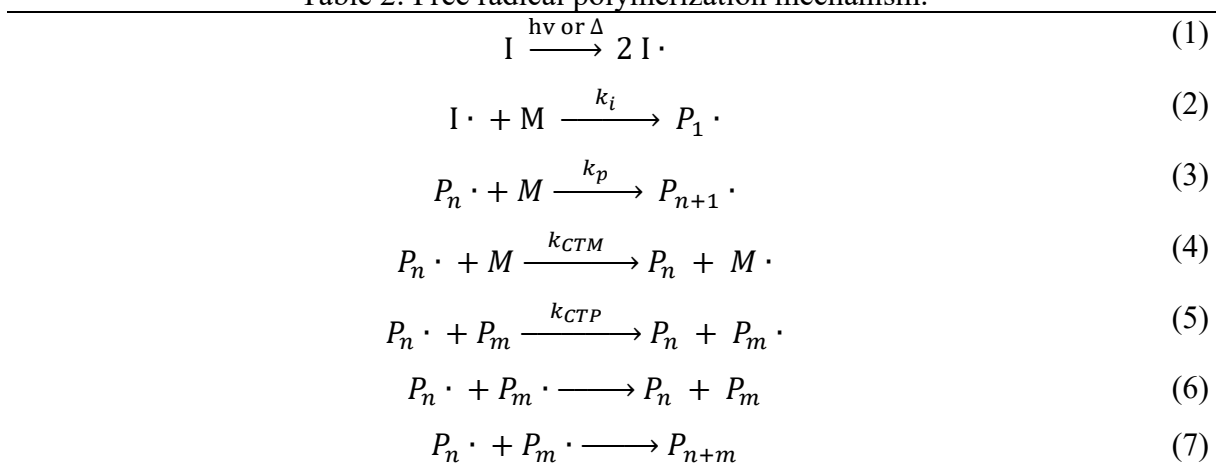
According to Cramer *et al.* (2002), reaction rates and functional group consumption can be modeled by the ratio of propagation to chain transfer kinetic parameters, which themselves depend on the electron density of the double bonds and the stability of the carbonyl radical formed. If the original diene produces a very stable carbonyl radical, the propagation constant is much higher than the chain transfer constant, and this last step might be skipped. This is not an ideal scenario, as the product would not be as uniform and the overall ratio of functional groups would become unbalanced. In such scenario, one might start the reaction with an already unbalanced stoichiometric ratio, predicting the additional propagation behavior and ensuring full conversion of both functional groups.

2.4.2 Free Radical

Despite the thiol-ene mechanism being mediated by free radicals, it behaves differently from the mechanism called free radical polymerization, that alkenes undergo without the presence of a multifunctional thiol. It is important to study both these mechanisms when analyzing thiol-(meth)acrylate polymerization systems, as both acrylate and methacrylate have very high propagation constants, such as 2560 and 9221 L mol⁻¹ s⁻¹ at 50 °C in the case of hydroxyethyl methacrylate (VAN HERK, 2000) and hydroxyethyl acrylate (DOSSI; STORTI; MOSCATELLI, 2011) respectively, and thiol-ene addition might not control the reaction, with both thiol-ene and free radical mechanisms occurring simultaneously or in different moments of the polymerization.

The mechanism is described in Table 2. Reactions 1 and 2 are initiation steps, with the formation of the radicals and reaction 3 is the propagation step, in which monomer molecules are repeatedly added to a polymer chain. Different monomers have different affinities towards propagation, characteristic that is denoted by the value of a kinetic propagation constant (k_p). Reactions 4 and 5 are chain transfer steps, which can be evaluated by a kinetic constant of chain transfer to monomer (k_{CTM} , simplified to k_{CT} in further mentions) or polymer (k_{CTP}), and reactions 6 and 7 are both termination steps, the former by chain disproportionation and the latter by combination, ending the reaction for both chains by extinguishing two radicals.

Table 2: Free radical polymerization mechanism.



Source: Adapted from Romera (2018).

In free radical polymerization, differently from step-growth thiol-ene polymerization, a propagation step is not very often followed by a chain transfer step. If the ratio between the propagation constant and chain transfer constant k_p/k_{CT} is equal to unity, it is said that both steps are equally as likely to occur, but is still not an indication that one step always follows the other.

In most cases, the propagation constant can be several orders of magnitude higher than the chain transfer to monomer constant, as is the case for methyl methacrylate, with a 10^5 ratio at 50 °C (O'BRIEN; GORNICK, 1955) and a 10^4 ratio for methyl acrylate (FEHÉERVÁRI *et al.*, 1982).

Even if the propagation constant is much higher, chain transfer does still occur, but it highly depends on the nature of the double bond and the stability of the carbonyl radical. In

order to stop chain growth in the polymerization of monomers with high k_p , a small quantity of a chain transfer agent might be used, inducing chains to stop propagation and lowering overall molar mass (WOODS, 1992).

2.4.3 Photoinitiation

In order to start a free-radical polymerization reaction a substance known as an initiator is often used. These molecules can be cleaved producing two radicals per molecule, with the cleaving being done by either the presence of heat, in the case of a thermal initiator, such as α,α' -azoisobutyronitrile (AIBN), or by the incidence of ultraviolet light, as is the case of 2,2-dimethoxy-2-phenylacetophenone (DMPA). When the latter is used, the reaction is characterized as photoinitiated. Although some polymerization reactions can occur spontaneously or in the dark, the use of an initiator allows for better control over the reaction kinetics, curing time, and overall process dynamics.

Photoinitiation has been thoroughly studied having considerable advantages over its thermal counterpart (GRUBER, 1992). In thiol-ene reactions, for example, photopolymerization has been known to suffer very little oxygen inhibition, while thermally initiated reactions have to be done under inert atmosphere in order to achieve comparable molar masses. There is also no need to spend energy increasing the temperature of the system beyond what the lamp's resistance and the reaction itself produce, and the reaction can be completed much faster, with the main disadvantage being the need for a specific equipment setup in order to apply the radiation, and ruling out the incorporation of light-sensitive drugs, for example.

2.5 THIOL-(METH)ACRYLATE POLYMERS

Despite acrylic monomers having widespread use via free radical polymerization, both in research and commercially, the intent to change the mechanical properties of its polymers has led to research using thiol-ene polymerization. Cramer and Bowman (2001) have synthesized and studied the kinetics of thiol-acrylate polymers, comparing them to thiol-allyl, thiol-vinyl ether and thiol-norbornene systems, using different ratios of functional groups. They furthered their study in 2003 looking more specifically which mechanism and

steps were rate limiting in the polymerization of the same monomer systems. Reddy *et al.* (2006) studied the same monomers used in a ternary system, and found a mixed step-chain growth mechanism in thiol-ene-acrylate systems, with the conversion of each monomer being related to both propagation and chain transfer kinetic parameters. The propagation and chain transfer parameters for a thiol-vinyl ether-acrylate system, specifically pentaerythritol tetra(3-mercaptopropionate) (PETMP), triethylene glycol divinyl ether, and hexyl acrylate, that were fitted to experimental data are shown in Table 3. These values are intended for order of magnitude analysis, and depend on temperature and chain length, particularly in the case of the alkyl (meth)acrylates, as described by Haehnel *et al.* (2014).

Table 3: Propagation and chain transfer parameters for a ternary thiol-vinyl ether-acrylate system. S stands for thiol, 1 for vinyl ether and 2 for acrylate.

k_{CTS1}	$2.1 \times 10^6 \text{ L mol}^{-1}\text{s}^{-1}$	k_{CTS2}	$0.8 \times 10^5 \text{ L mol}^{-1}\text{s}^{-1}$
k_{pS1}	$2.6 \times 10^6 \text{ L mol}^{-1}\text{s}^{-1}$	k_{pS1}	$1.2 \times 10^6 \text{ L mol}^{-1}\text{s}^{-1}$
k_{p11}	negligible	k_{p22}	$1.1 \times 10^5 \text{ L mol}^{-1}\text{s}^{-1}$
k_{p12}	$1.0 \times 10^5 \text{ L mol}^{-1}\text{s}^{-1}$	k_{p21}	$0.3 \times 10^5 \text{ L mol}^{-1}\text{s}^{-1}$

Source: Adapted from Reddy *et al.* (2006).

From these results, it is possible to calculate k_p/k_{CT} , specifically for acrylate to acrylate propagation over acrylate chain transfer to thiol, of 1.4. Cramer and Bowman (2001) had previously reported a similar result, evaluating this ratio in mechanism to be 1.5.

Lee and colleagues (2007) have reported that ternary thiol-ene-methacrylate systems tend to behave very differently than thiol-ene-acrylate, because of the higher stability of the radical in a methacrylate group. The methacrylate case leads to polymerization occurring in two stages, starting with a high conversion of methacrylate through free radical propagation using thiol as a chain transfer agent, and ending with the conversion of thiol and ene groups through the step-growth addition mechanism. Reported kinetic parameters were $3.0 \times 10^4 \text{ L mol}^{-1}\text{s}^{-1}$ for methacrylate to methacrylate propagation, and $k_p/k_{CT} = 1.7$, which compared to acrylate systems, is reasonably higher especially considering that the overall reaction is slower.

Another point of influence is the cross-link density of the polymer. The use of a tetrafunctional thiol over a bifunctional one tends to lead to a tighter network structure which reduces the mobility of growing radicals, hindering termination and causing it to be controlled

by diffusion. As such, overall polymerization rate is increased (ANSETH; WANG; BOWMAN, 1994; BERCHTOLD *et al.*, 2001).

Senyurt (2007) studied the effect of the addition of acrylates on the mechanical properties of thiol-ene binary system polymers. Compared to the binary systems, ternary thiol-ene-acrylate polymer films showed an increase in T_g proportional to acrylate concentration, as well as a decrease in magnitude of the $\tan \delta$ curves obtained via DMA, with an increase in the rubbery moduli of samples. Looking through the opposite end of the spectrum, the addition of thiol/ene groups into an acrylic polymer lowers the range of transition in storage modulus, indicating that the step-growth contribution results in a more homogeneous structure. The authors explain that chain transfer to thiol incorporates thioether structures that provide flexibility and uniform free volume distribution, causing the dynamic modulus transition to occur over a much smaller temperature range.

As such, a basis of knowledge in how thiol-ene-(meth)acrylate ternary systems behave already exists, though binary systems are less studied. Addition of a thiol comonomer in acrylate systems, or conversely addition of acrylic monomers in thiol-ene systems has been shown to be an appropriate pathway for fine-tuning mechanical properties in the polymer matrix.

The present work intends to build upon this knowledge through the enzymatic synthesis of asymmetric monomers that are allyl-acrylate and allyl-methacrylate, using a plant oil derivative, then polymerizing them through the thiol-ene mechanism in order to observe the prevalence of free radical polymerization over thiol-ene, and how acrylate and methacrylate systems differ in this regard. Since the polymer matrixes contain ester moieties in their backbone, these can suffer enzymatic hydrolysis rendering the material biodegradable.

3 SYNTHESIS AND POLYMERIZATION OF ALLYL-(METH)ACRYLATE MONOMERS

3.1 EXPERIMENTAL PROCEDURE

3.1.1 Materials

10-Undecenoic acid (Sigma-Aldrich, 98%), 2-Hydroxyethyl methacrylate (HEMA, Sigma-Aldrich, 97%), 2-Hydroxyethyl acrylate (HEA, Sigma-Aldrich, 96%) and lipase Novozym 435 (N435, Donated by Novozymes®, from *Candida antarctica*, $44.9 \pm 1.9 \text{ U} \cdot \text{g}^{-1}$ (ROMERA, 2018)) were used in the monomer synthesis.

For purification, *n*-hexane (P.A., Vetec) and ethyl acetate (P.A., Vetec) were used as eluents, as well as silica gel for column chromatography (Aldrich, 70-230 mesh) and aluminum oxide (Aldrich, 100%).

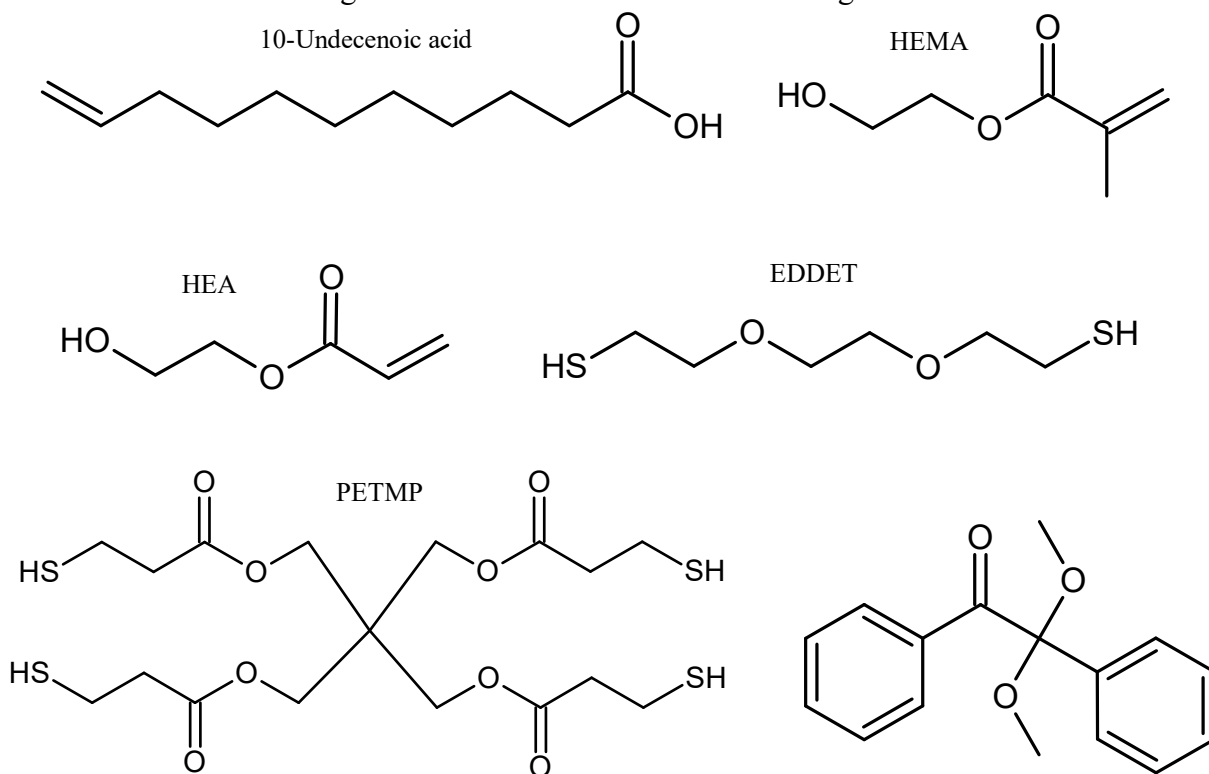
2,2'-(Ethylenedioxy)diethanethiol (EDDET, Sigma-Aldrich, 95%), Pentaerythritol tetrakis(3-mercaptopropionate) (PETMP, Aldrich, 95%) and 2,2-Dimethoxy-2-phenylacetophenone (DMPA, iGM Resins) were used in the photopolymerization of the synthesized monomers.

Phosphate buffer solution (pH 7, Neon Comercial) was used in the degradation tests, as well as a *Candida antarctica* lipase B free enzyme solution (Lipozyme CALB L, Novozymes). Toluene (P.A., Vetec) was used in polymer swelling tests and Chloroform (P.A., Vetec) in extraction to evaluate gel content.

^1H NMR samples were dissolved in deuterated chloroform (CDCl_3 , Sigma-Aldrich).

All materials were used as received, molecular structure for polymerization and monomer synthesis reagents are shown in Figure 4.

Figure 4: Molecular structure of used reagents.



Source: Author.

3.1.2 MEU/AEU synthesis via enzymatic esterification

21 mmol (3.8698 g) of 10-undecenoic acid were added to a round bottom flask, along with 25 mmol of either HEMA (3.2796 g) or HEA (2.9029 g) and N435 lipase, 0.1430 g and 0.1348 g respectively (2 wt% with relation to the mass of reagents). Reaction was carried during 3 h, at a temperature of 50 °C, maintained by a water bath with temperature control (IKA C-MAG HS 7), and under gentle magnetic stirring.

The enzyme was separated by filtration through a nylon cloth, and the filtrate was diluted with a mixture of hexane and ethyl acetate. This solution is filtered through a short pad of aluminum oxide followed by a short pad of silica gel, and the solvents are later removed under reduced pressure.

3.1.3 Photopolymerization

Photopolymerization reactions were performed inside a box with two UV lamps. The reagents were added and mixed on a watch glass that is placed under one of the UV lamps, using different proportions and combinations of the synthesized dienes (MEU/AEU) and thiols (EDDET and/or PETMP), applying DMPA as the photoinitiator. Different concentrations, reaction times and light intensities are shown in Table 4 and Table 5. The box is then closed, and a temperature of 40 °C is maintained inside by the lamps.

Thiol-ene reactions tend to be very reliant on the stoichiometric proportion of the reacting groups, with the higher molar masses being achieved using a 1:1 proportion of functional groups. This however cannot be stated for certain when one of the double bonds is a very reactive acrylate, leading to tests with both 1:1 and 2:1 proportions of double bond to thiol, where in the latter case it is assumed that the acrylates will only polymerize by free radical propagation, and the thiol groups will react with the undecenoic acid olefin. Samples 08, 09 and 10 were prepared in order to test this.

Table 4: Formulations of AEU polymers, molar ratio with respect to AEU. * Entries are duplicates.

Entry	EDDET (molar ratio)	PETMP (molar ratio)	DMPA (% diene mass)	Time	Light intensity (mW/cm ²)
PA01	1	-	1	2h	2.92
PA02	-	0.5	1	2h	2.92
PA03	0.33	0.33	1	2h	2.92
PA04	-	0.5	10	10 min	4.13
PA05	-	0.5	4	10 min	4.13
PA06	1	-	4	10 min	4.13
PA07	-	-	4	10 min	4.13
PA08*	0.5	-	4	10 min	4.13
PA09*	0.5	-	4	10 min	4.13
PA10	-	0.25	4	10 min	4.13

Source: Author.

Table 5: Formulations of MEU polymers, molar ratio with respect to MEU. * Entries are duplicates.

Entry	EDDET (molar ratio)	PETMP (molar ratio)	DMPA (% diene mass)	Time	Light intensity (mW/cm ²)
PM01	1	-	1	2h	2.92
PM02	-	0.5	1	2h	2.92
PM03	0.33	0.33	1	2h	2.92
PM04	-	0.5	10	10 min	4.13
PM05	-	0.5	4	10 min	4.13
PM06	1	-	4	10 min	4.13
PM07	-	-	4	10 min	4.13
PM08*	0.5	-	4	10 min	4.13
PM09*	0.5	-	4	10 min	4.13
PM10	-	0.25	4	10 min	4.13

Source: Author.

3.1.4 Proton Nuclear Magnetic Resonance (¹H NMR)

¹H NMR analyses were performed in deuterated chloroform, CDCl₃, using a Bruker Ascend 600 spectrometer at 200 MHz. Chemical shifts (δ) are reported in parts per million related to the internal standard tetramethylsilane ($\delta = 0.00$ ppm).

3.1.5 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR of the solid materials were performed on a Cary 660 FTIR equipment from Agilent Technologies, using the ATR accessory (ZnSe plate), in the 4000-700 cm⁻¹ range. Analyses were performed in the *Central de Análises* at the Department of Chemical Engineering and Food Engineering of the Federal University of Santa Catarina (CAEQA-UFSC).

3.1.6 Differential Scanning Calorimetry (DSC)

Polymer samples of 5 mg were dried, then analyzed using a Jade-DSC equipment from Perkin Elmer, under flow of nitrogen (10 mL/min), from -50 to 150 °C at a heating rate of 10 °C/min. The thermal history was then removed and a second run under the same conditions was performed, with a cooling rate of 10 °C/min. Analyses were also performed in the *Central de Análises* at the Department of Chemical and Food Engineering of the Federal University of Santa Catarina (CAEQA-UFSC).

3.1.7 Gel content

A sample of 200-400 mg of each polymer was placed in chloroform for extraction during 48 h, and then filtered using a nylon filter (0.45 µm), with the gel being retained either on the filter or in a beaker. Both beaker and filter were allowed to dry in a forced convection oven maintained at 60 °C, and then weighed. The gel content was determined by comparing the final dry mass to the original sample mass.

3.1.8 Polymer swelling

Polymer samples were weighed and placed in an Eppendorf vial along with 2 mL of toluene. After 24 h, excess surface moisture was absorbed by a paper towel, and swollen samples were weighed again.

3.1.9 Enzymatic degradation

The enzymatic degradation of polymer samples was carried out at room temperature in a pH 7 phosphate buffer solution. Samples were 5 x 5 x 1 mm polymer squares, with 10-20 mg initial weight. 2 mL of solution were added to each piece, along with 26 mg of N435 lipase, for a total 0.63 U per mL of solution. After 24 h, the samples were washed with distilled water, vacuum dried and weighed, following which these were added again to the solution for further degradation. Additional tests were done with enzyme CALB in solution, using 100 µL of solution in 2 mL of the same buffer solution.

3.2 RESULTS AND DISCUSSION

3.2.1 Synthesis and characterization of semi-renewable allyl-acrylate monomers

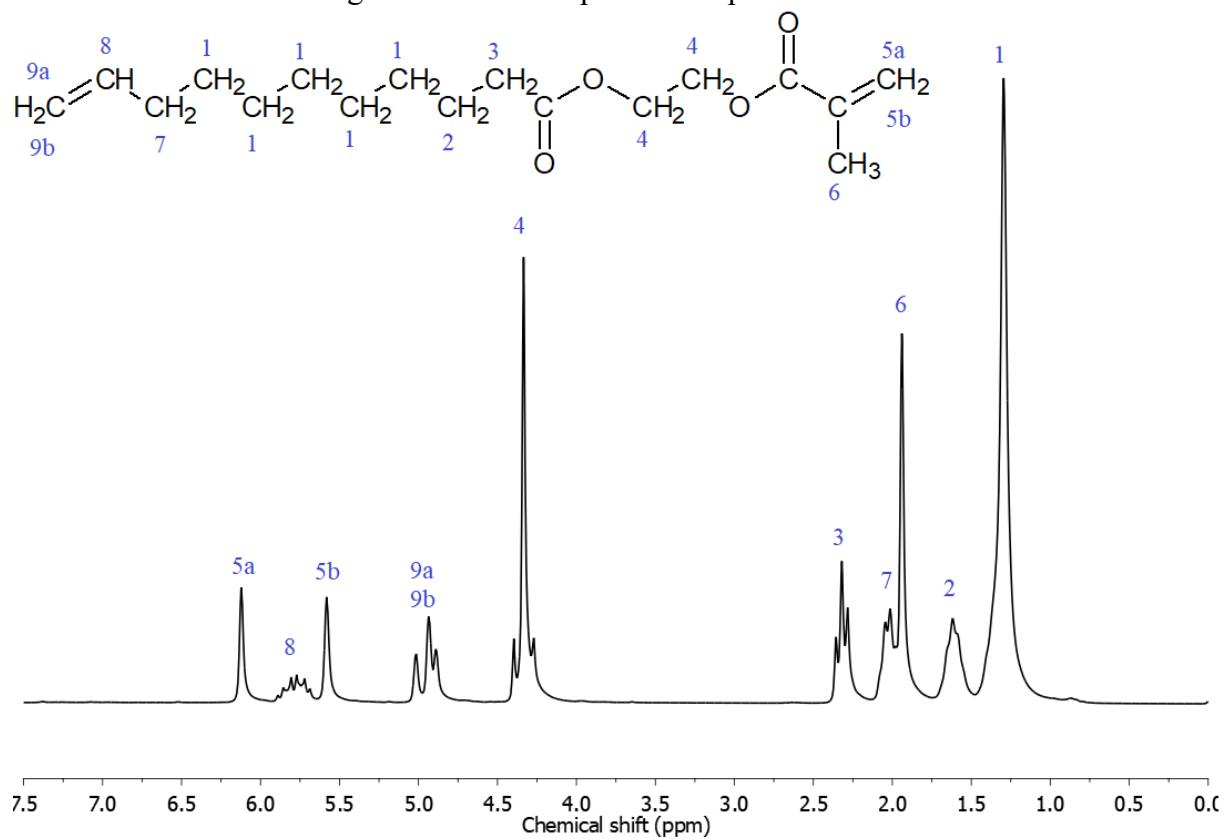
The use of 10-undecenoic acid in the production of an ester monomer alongside HEMA allows for a monomer with more flexible properties than each of the original monomers, as well as an easily breakable ester bond on the final product, which can be degraded by enzymes in the presence of water. This synthesis was proposed, studied and reported by Romera (2019), the product being named 2-(methacryloyloxy)ethyl undec-10-enoate (MEU, originally 2-(10-undecenoyloxy)ethyl methacrylate or MHU), which was polymerized in bulk and in miniemulsion.

The final proposed process is an enzymatic esterification, which may be performed in solvents or in bulk, since both reagents are liquid and miscible. In the same work, the author produces a further modified monomer, by doing a Michael addition of a diamine on the methacrylate center, ending with a symmetric diene. This reaction was performed during 72 hours to achieve 80% conversion, most likely due to the considerably lower reactivity towards Michael addition of methacrylate compared to an acrylate.

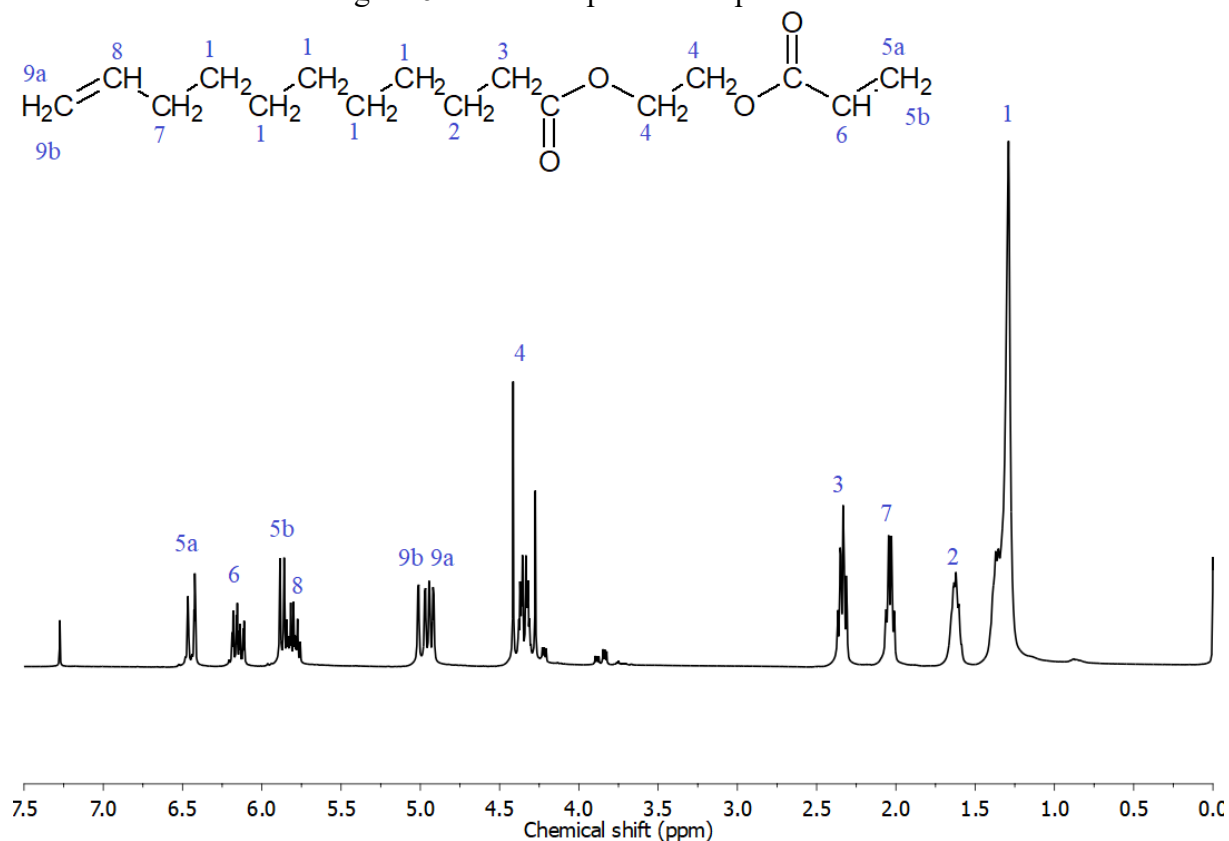
This work reproduced the enzymatic process and attempted a new synthesis, using HEA instead of HEMA as the alcohol, in order to investigate the reactivity and effects of the different acrylate groups. As both alcohols are very similar, the same procedure used to produce MEU was able to arrive at the new product, named 2-(acryloyloxy)ethyl undec-10-enoate (AEU).

After purification steps both products were achieved with at least 50% yield, being colorless liquids that are capable of autopolymerization at room temperature, and therefore had to be refrigerated or frozen.

Figure 5 and Figure 6 show the characteristic ^1H NMR spectrum of MEU and AEU respectively.

Figure 5: ^1H NMR spectrum of purified MEU.

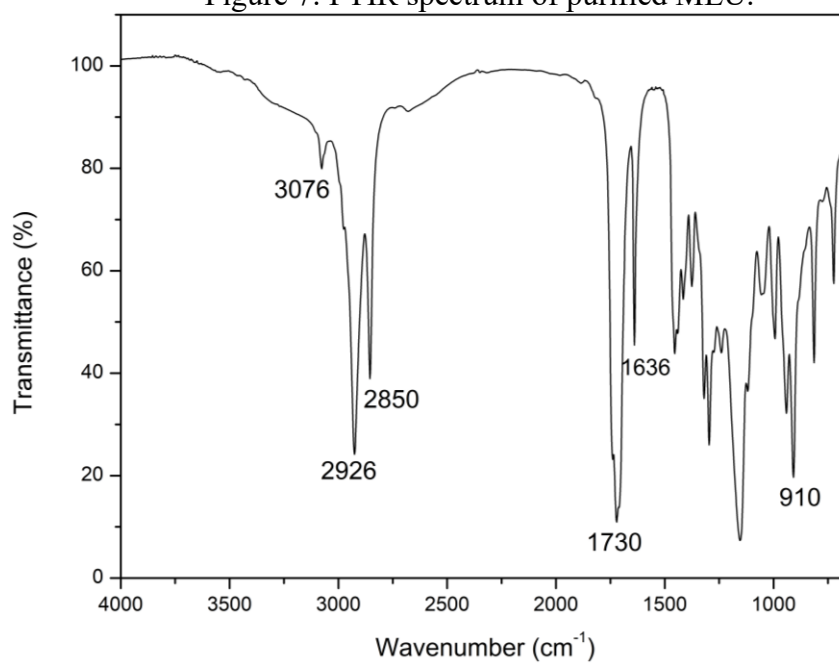
Source: Author.

Figure 6: ^1H NMR spectrum of purified AEU

Source: Author.

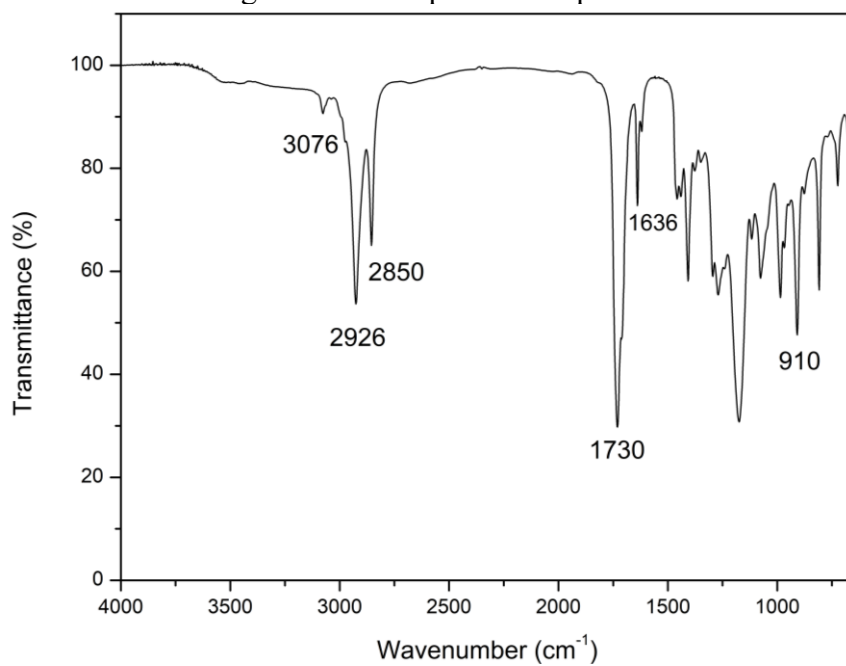
Figure 7 and Figure 8 show the ATR-FTIR spectra of purified MEU and AEU, respectively. Notable points of interest are at 3076 cm^{-1} , 910 cm^{-1} and 1636 cm^{-1} , representing the $=\text{C}-\text{H}$ stretch, CH_2 out of plane wag from $\text{C}=\text{CH}_2$ group in vinyl compounds, and $\text{C}=\text{C}$ stretch, stronger due to the presence of an acrylate olefin as well as the allyl. At 2926 cm^{-1} there is the CH antisymmetric and symmetric stretching in $-\text{CH}_3$ and $-\text{CH}_2-$ aliphatic groups, and 2850 cm^{-1} is the CH stretching modes in $-\text{CH}_3$ attached to oxygen. Finally, at 1730 cm^{-1} there is a very strong stretching peak of $\text{C}=\text{O}$ groups in esters.

Figure 7: FTIR spectrum of purified MEU.



Source: Author.

Figure 8: FTIR spectrum of purified AEU.



Source: Author.

3.2.2 Thiol-ene and free radical polymerization of MEU and AEU

As the synthesized monomers both have allyl and acrylate moieties, they can be polymerized via thiol-ene and free radical mechanisms, though the main mechanism for each double bond type remains a subject of debate. Reddy *et al.* (2006) found in ternary thiol-allyl-acrylate systems that the acrylate group tends to exclusively polymerize through free radical chain growth, while the allyl and thiol groups exclusively react via thiol-ene. In addition, the acrylate tends to react faster, reaching 100% conversion before the thiol is fully consumed.

Cramer and Bowman (2001) as well as Senyurt (2007) have found that the presence of a thiol copolymer changes physical properties of the acrylic polymers, decreasing their glass transition temperature and rubbery modulus.

Furthermore, the use of either a dithiol or a tetrathiol yields very different cross-linked matrixes, with either the acrylate function being the only cross-linker or with the help of another cross-linking agent. Gel content analysis and degree of swelling was used to analyze this effect, considering that the cross-linked fractions of polymers are insoluble, and should also reduce the enzymatic degradation of these polymers.

The effect of each mechanism and the difference between the methacrylate and acrylate groups was evaluated using different formulations of thiol and diene monomers and different reaction conditions. Due to the difference in the carbonyl radical stability, acrylate and methacrylate have very different ratios of k_p/k_{CT} and changes in reaction times and light intensity should lead to differences in kinetics between each suspected mechanism, while different thiol concentrations should help visualize the preference of the (meth)acrylic group of each monomer for thiol-ene or free radical mechanism through thiol group consumption, thermal properties and degree of cross-linking.

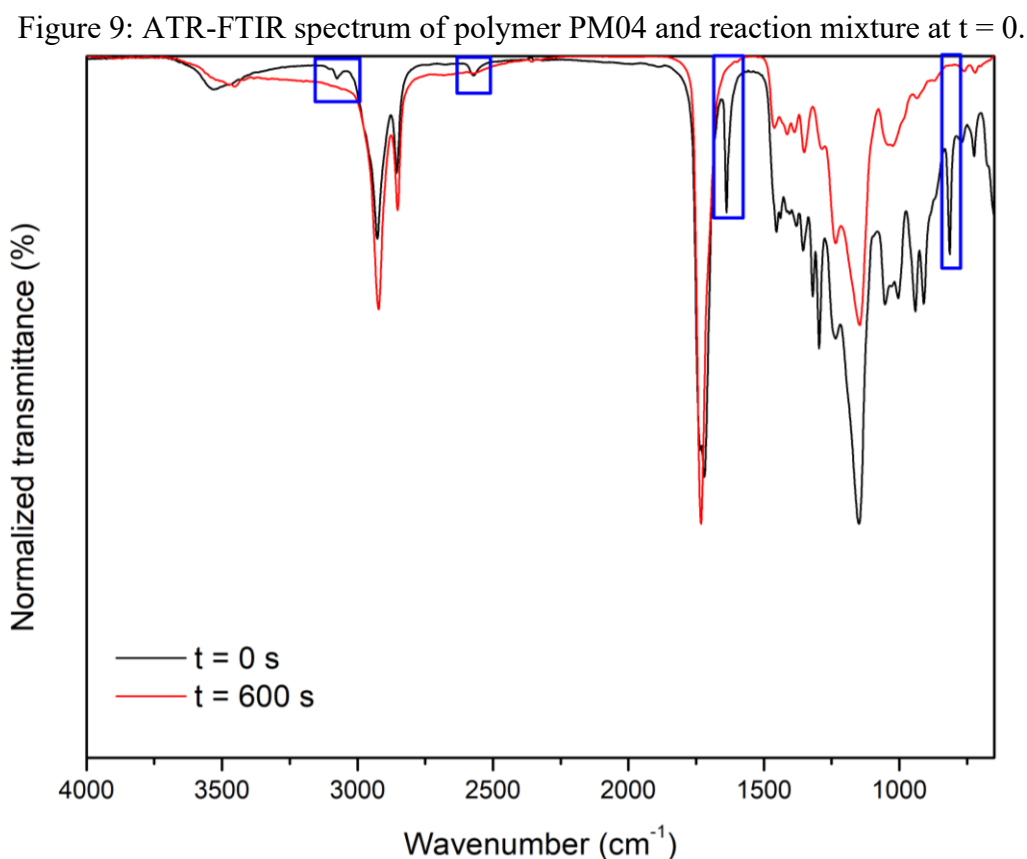
Photopolymerization was chosen as the initiation method for these reactions due to its low energy requirement, low inhibition by oxygen and lower termination kinetics, due to the lower overall temperature. Reaction was performed in a watch glass placed under a UV lamp with the distance between the two being directly related to the intensity of the light. According to radiometric tests of the lamps and chamber system, irradiance flux density at 4 cm and 2 cm were 2.92 mW/cm² and 4.13 mW/cm² respectively.

Products of the polymerizations performed with the dithiol and in the absence of the tetrathiol, entries PA01, PA06, PM01 and PM06, were gel-like for both dienes, while the rest

are solid thick films that go from very brittle, in the case of homopolymerization of both diene monomers (PA07 and PM07), to quite flexible, in formulations that use PETMP as a comonomer. Polymers were also translucent, sometimes showing a yellow tint, likely due to the use of DMPA as the initiator (GRUBER, 1992).

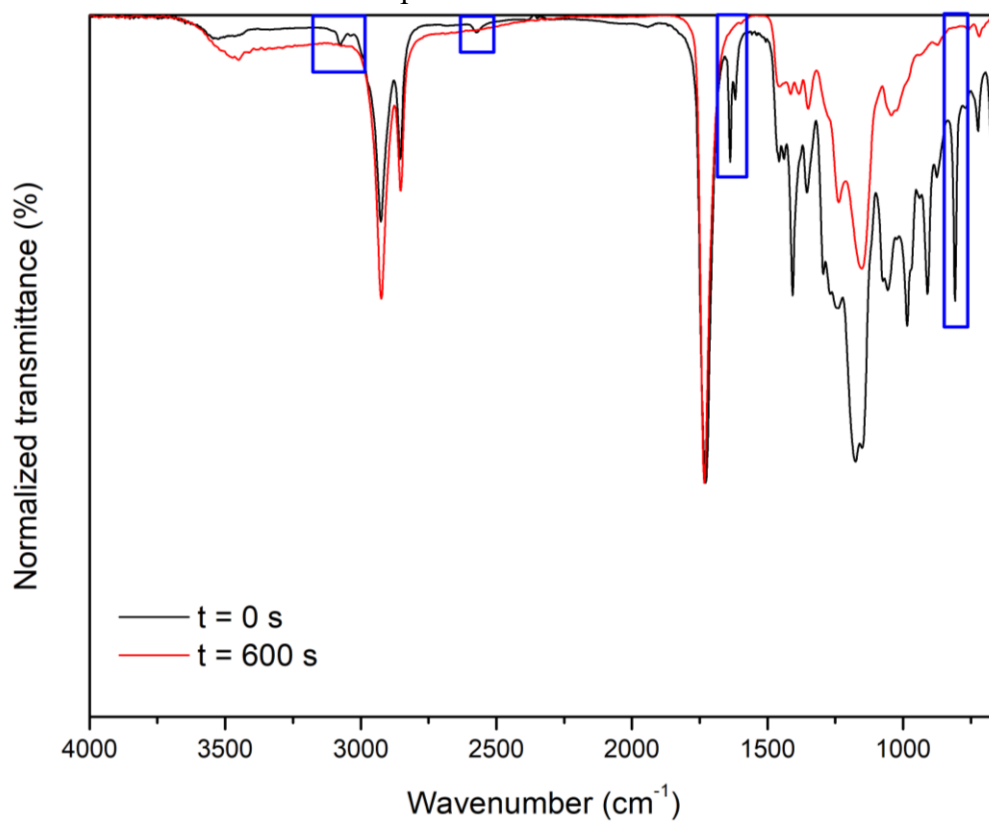
Attempts at reactions shorter than 10 min yielded polymers that were not fully cured for MEU, while AEU formed completely solid materials in reactions as short as 60 s.

Thiol and acrylate group consumption was verified through FTIR, where the carbon-carbon double bond adsorption peak at 1636 cm^{-1} , as well as the other two double bond related peaks at 3076 and 910 cm^{-1} , cannot be seen in the polymer analysis, but is present before the reaction, even in the proximity to the ester carbonyl stretch peak. At 2570 cm^{-1} , the thiol stretch is always present before polymerization, but after can be either partially or fully consumed, as seen in Figure 9 and Figure 10.



Source: Author.

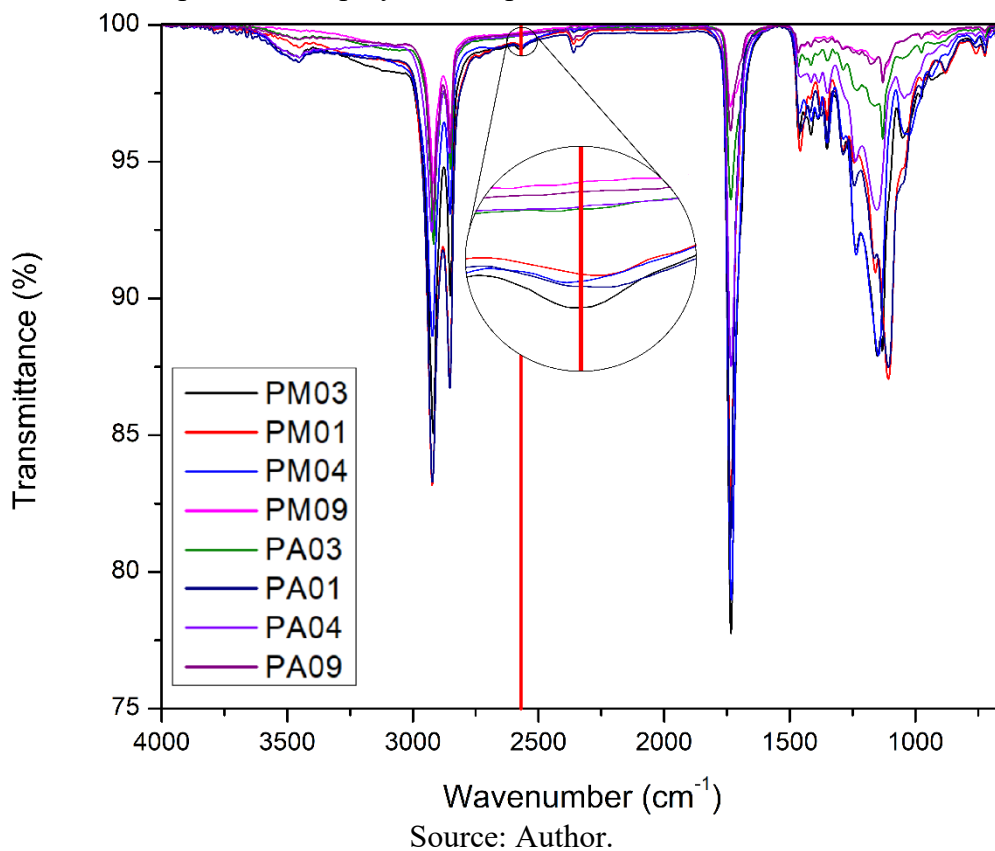
Figure 10: ATR-FTIR spectrum of polymer PA04 and reaction mixture at $t = 0$, here represented as A04.



Source: Author.

Figure 11 shows the presence or lack of the thiol stretch in tested samples, indicating the existence of unreacted thiol groups in the final polymer.

Figure 11: FTIR spectra of all polymer samples, with focus on the 2570 cm^{-1} thiol peak.



Polymer samples produced using MEU with 1:1 stoichiometric ratio of thiol:ene functional groups (PM01, PM03, PM04) still show the presence of thiol groups. This is likely due to the increased affinity of methacrylate groups to propagate over thiol addition, with an increased presence of thiol leading to further preference for propagation, as was reported by Lee *et al.* (2007), due to vitrification and increased cross-link density, this last one specifically lowering termination kinetics due to this process being diffusion controlled in high viscosity systems. In the case of sample PM09, the use of a non-stoichiometric ratio leads to full conversion of thiol groups.

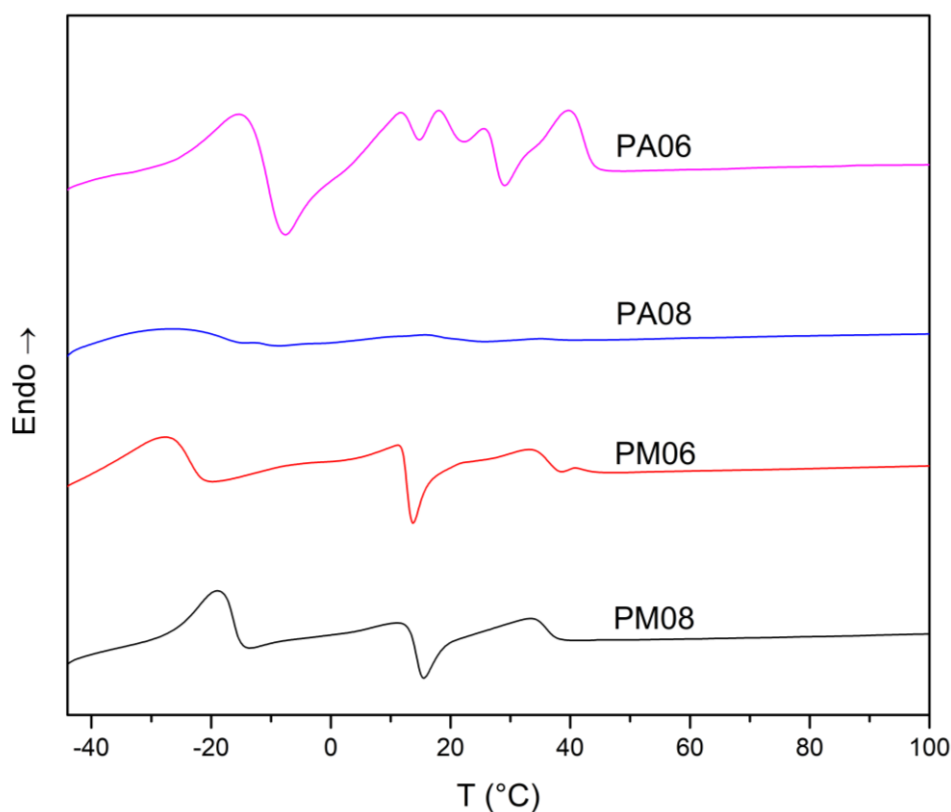
As for AEU samples, only PA01 shows leftover thiol, confirming the different behavior of acrylates (LEE *et al.*, 2004), with thiol addition and free radical propagation having similar likelihood and occurring simultaneously.

3.2.3 Thermal properties and crystallinity

DSC analysis shows the thermal behavior of the different thiol(meth)acrylate polymers. Senyurt *et al.* (2007) found that the increase of acrylate content in a thiol-ene system increases the T_g of polymers, up to the highest value with an acrylate homopolymer. In his work, Romera (2018) was not able to identify the glass transition of his samples, but did see a trend in the melting temperature T_m , with lower values being related to a higher dithiol to MEU ratio.

Figure 12 shows the DSC curves for polymer samples polymerized with EDDET.

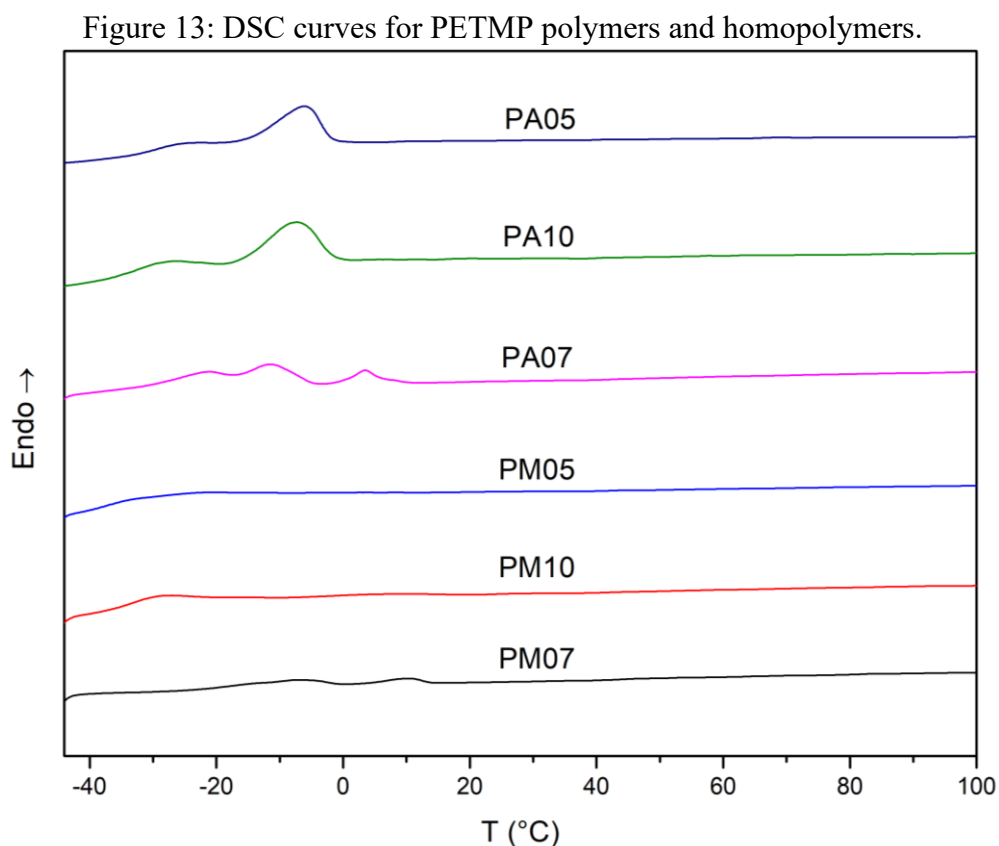
Figure 12: DSC curves of EDDET formulations.



Source: Author.

Multiple melting peaks can be seen in samples polymerized with EDDET, which have been previously reported in the literature (LOTTI *et al.*, 2006; TÜRÜNÇ; MEIER, 2010) being characteristic of thioethers, where there is a first partial melting, followed by continuous recrystallization and melting, and then a final melting of the organized structure.

Figure 13 shows DSC curves for both AEU/MEU homopolymers and PETMP polymer samples.



Source: Author.

Samples PM05 and PM10 show no thermal events and are therefore fully solid and amorphous in the analyzed temperature range. Both are PETMP formulations and have highly cross-linked structure with no methacrylate-thiol bonds. Their acrylate counterparts, PA05 and PA10, have a single very defined phase transition, indicating a fundamental difference between the polymer matrix in acrylates to methacrylates. As the melting occurs around -7°C , the material should be liquid at room temperature, but that was not the case, at least over a few months of shelf time. In the case of a duplicate of sample PA05 done at a higher scale, it did eventually melt at room temperature over the course of four months.

Polymers PA07 and PM07, produced in the reactions performed without any thiol show very small phase transition peaks, implying these polymers are almost completely amorphous.

3.2.4 Gel content and swelling ratio

Both homopolymers and thiol polymers can form cross-linked networks, as free radical polymerized dienes can have two new bonds in each olefin, and monomers with more than two thiol functionalities, such as PETMP with four, can connect two different polymer strands once the third or fourth thiol is consumed. Gel content analysis was employed to evaluate the degree of cross-linking achieved in each formulation.

Samples were grouped by which conditions were set constant, and organized in Table 6-Table 8.

Table 6 shows the difference in gel content for the same monomer composition, but different reaction conditions, namely light intensity, initiator concentration and reaction time.

Table 6: Gel content comparison of 01 and 06 polymers.

Entry	EDDET	PETMP	Light intensity (mW/cm ²)	Initiator (% diene mass)	Time	Gel Content
PA01	1	-	2.92	1	2h	31%
PM01	1	-	2.92	1	2h	44%
PA06	1	-	4.13	4	10 min	12%
PM06	1	-	4.13	4	10 min	24%

Source: Author.

Our first clear result comes from the fact that an insoluble fraction was formed in all these formulations with a bifunctional thiol, a direct proof that the thiol-ene mechanism is not the only reaction occurring, as the reaction between a diene and a dithiol should always produce linear polymers. Therefore, some acrylate free radical polymerization must be occurring and is creating cross-linked sections in the matrix.

Higher curing time was able to achieve a higher gel content, as both acrylates reacted quickly while the thiol-ene part of the curing was able to benefit from the additional time. MEU polymers also reached a higher gel content as the bifunctional EDDET doesn't act as a cross-linker, hindering the acrylate in the AEU case, while MEU preferentially propagates creating the cross-linked matrix.

Table 7: Gel content comparison of 02 and 04 polymers.

Entry	EDDET	PETMP	Light intensity (mW/cm ²)	Initiator (% diene mass)	Time	Gel Content
PA02	-	0.5	2.92	1	2h	68%
PM02	-	0.5	2.92	1	2h	85%
PA04	-	0.5	4.13	10	10 min	92%
PM04	-	0.5	4.13	10	10 min	79%

Source: Author.

With PETMP as a monomer, which does act as a cross-linker, an increased gel content can be achieved with a longer reaction time in the methacrylate case, as expected due to the nature of thiol-ene-methacrylate reactions, with the thiol-ene part happening after the methacrylate has been thoroughly consumed by free radical propagation. As for the acrylate polymers, a shorter time but higher light intensity and initiator concentration reached a higher gel content, which could be explained by an increased consumption of the plentiful thiol groups as was verified in the FTIR spectra on Figure 11.

Table 8: Gel content comparison of all 10 min reactions.

Entry	EDDET	PETMP	Light intensity (mW/cm ²)	Initiator (% diene mass)	Time	Gel Content
PA06	1	-	4.13	4	10 min	12%
PM06	1	-	4.13	4	10 min	24%
PA09	0.5	-	4.13	4	10 min	45%
PM09	0.5	-	4.13	4	10 min	58%
PA10	-	0.25	4.13	4	10 min	78%
PM10	-	0.25	4.13	4	10 min	79%

Source: Author.

While keeping reaction conditions constant and testing different thiol formulations, the usage of stoichiometric EDDT leads to very low gel content, as it only extends the chains without cross-linking, and ending the acrylate propagation. This effect is attenuated

with a lower concentration of the dithiol, leading to a higher gel content. Finally, the use of PETMP greatly increases the cross-linking in the material.

As such, the obtained gel content values agree with the theory of how each (meth)acrylate group reacts in the presence of a thiol group as well as a less reactive olefin, but in a binary system.

In order to attain some degree of understanding about the degree of cross-linking in the matrixes, swelling ratio of a few samples with high gel content was evaluated, and is displayed in Table 9.

Table 9: Swelling ratio of polymer samples. Values are reported as ratio of additional mass above initial sample mass.

Entry	EDDET	PETMP	Light intensity (mW/cm ²)	Initiator (% diene mass)	Time	Gel Content	Swelling
PA02	-	0.5	2.92	1	2h	68%	44%
PM02	-	0.5	2.92	1	2h	85%	33%
PA04	-	0.5	4.13	10	10 min	92%	39%
PM04	-	0.5	4.13	10	10 min	79%	43%
PA09	0.5	-	4.13	4	10 min	45%	-15%
PM09	0.5		4.13	4	10 min	58%	157%
PA10	-	0.25	4.13	4	10 min	78%	17%
PM10	-	0.25	4.13	4	10 min	79%	61%

Source: Author.

Sample PA09 had the lowest gel content, and so ended up losing mass by dissolution in toluene. Its pair PM09 likely also lost some soluble fraction, but the methacrylate matrix created by propagation allowed for a very high amount of swelling. PA10 had the lowest swelling, and therefore has the highest cross-link density, indicating that the non-stoichiometric ratio of functional groups along with the acrylate monomer creates a very tight matrix.

3.2.5 Enzymatic degradation

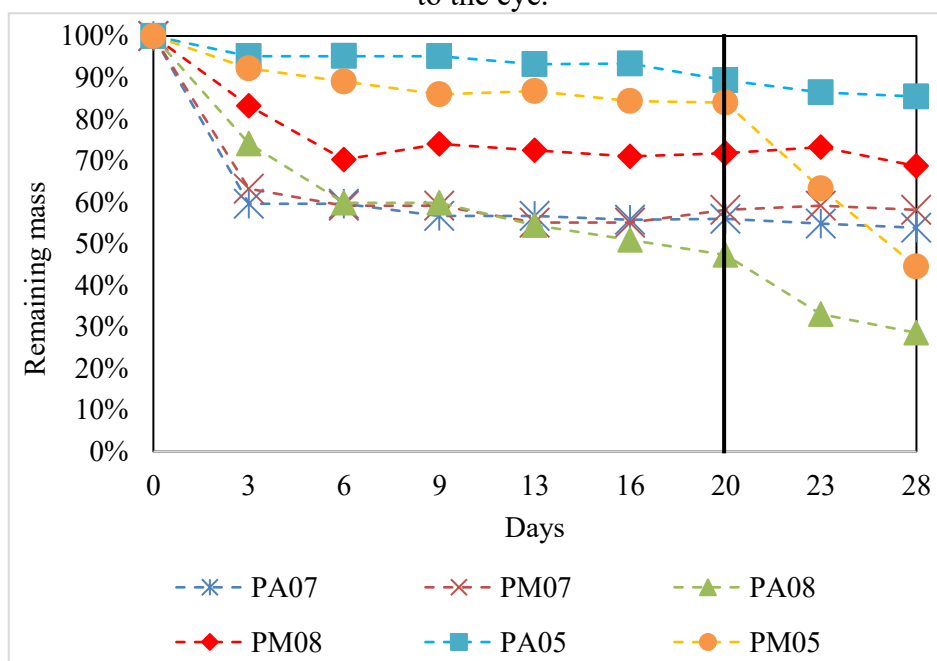
In the same way as the monomers are initially produced through an enzymatic process, the reverse reaction can be done to hydrolyze the polymer, degrading it into smaller fractions. This process is controlled by the reaction equilibrium, pH, temperature and the

degree of cross-linking of the polymer. There is also the matter of interfacial area where the reaction would occur, whether the polymer is solid or liquid, and the enzyme is immobilized or free in solution.

Both MEU and AEU have two ester moieties that are susceptible to hydrolysis, however both produce highly cross-linked polymers, as shown before in our gel content data. Alongside that, the polymers are not hydrophilic and do not exhibit swelling in the presence of water, which imply surface erosion to be the likely mechanism through which hydrolysis would occur in the absence of enzymes. Specifically in the case of enzymatic processes, surface erosion is reported to always be the case, as enzymes are too bulky to penetrate the polymer matrix (LAYCOCK *et al.*, 2017).

Samples were subjected to enzymatic degradation at room temperature and pH 7 buffer during 28 days, as shown in Figure 14.

Figure 14: Enzymatic degradation using immobilized lipase N435. Lines are merely a guide to the eye.



Source: Author.

Immobilized N435 lipase was used until day 20. This was initially attempted in order to use the same enzymes used in the monomer synthesis for the polymer's degradation, completing the cycle. However, as both enzyme and polymer are solid, a direct contact between both was necessary for degradation to occur. In a few samples, the immobilized

particles stuck to the surface of the polymer, while others ended up floating in the solution and not coming into contact with the material, and no agitation was employed in the incubation process.

Samples PA05 and PM05, both synthesized with tetrathiol PETMP had the lowest degradation rate, while samples with dithiol EDDET (PM/A08) or no thiol (PM/A07) had higher loss of mass, particularly during the first three days. After that, sample PA08 still presented some degradation, while minimal loss was observed for the remaining samples, and any variation recorded was likely due to measuring errors, and fell within a $\pm 5\%$ error.

On the 20th day samples were removed from the initial solution with immobilized enzymes and placed on a new solution of 100 μL CALB lipase solution dissolved in 2 mL of pH 7 phosphate buffer, to check if degradation was being halted by lack of contact surface for the reaction. Further degradation was observed in samples PM05, PA08, and PA05 to a smaller extent, but not in the remaining samples. This indicates that the difference in interfacial area did affect degradation, though it is likely that most easily available ester groups had already been degraded.

The semi-crystalline structure of EDDET samples likely hindered degradation, as the crystalline blocks reduce the rate of transport processes in the polymer matrix, particularly the diffusion of solvent and oligomers (LAYCOCK *et al.*, 2017). In the case of PETMP samples, high gel content is the suspect for the low degradation rate.

Use of a pH 7 buffer solution was deliberate with the intent of testing very simple and mild conditions, but as ester hydrolysis can be both acid and base catalyzed it likely hindered degradation, which could potentially have a faster rate and higher total mass loss if the intent was to use more aggressive conditions.

With the same idea, the incubation was done at room temperature, slowing down reaction kinetics. In their tests, Hoelscher *et al.* (2021) performed incubation at 37 °C, as the analyzed polymer particles were intended for drug delivery or other biomedical purposes. Our synthesis however was not focused on that approach, and so studied degradation that could be performed in nature, at room temperature.

In future tests, free enzyme should be tested from the start, and different pH and temperature condition could also be tried, although degradation at room temperature would be the most environmentally friendly process.

Results show that the hydrolysis of ester bonds is possible even in highly cross-linked samples and without the employment of heat. As well as that, the use of enzymes in solution can achieve higher mass loss than immobilized enzyme, though the latter does also work even with the lower efficiency due to lower surface of contact between both solids.

4 FINAL CONSIDERATIONS

4.1 CONCLUSIONS

One novel and one previously reported terminal diene monomers were synthesized via enzymatic esterification of 10-undecenoic acid and 2-hydroxyethyl acrylate or 2-hydroxyethyl methacrylate. These monomers, named AEU and MEU respectively, were then polymerized in bulk through thiol-ene photopolymerization, while testing different reaction conditions and ratios of olefin and thiol functional groups.

Both monomers were successfully synthesized and characterized via ^1H NMR and FTIR, and their bulk polymerization produced translucent polymers with varying degrees of flexibility and shear resistance. Consumption of thiol groups was verified through FTIR, with leftover thiol being found in samples produced with the methacrylate monomer when a stoichiometric ratio between thiol and double bonds was maintained. DSC analysis characterized polymer samples produced with dithiol EDDET to be semicrystalline, while samples with PETMP or homopolymerized were almost completely amorphous. All polymers showed some amount of cross-linked sections, with PETMP strongly acting as a cross-linking agent, though the synthesized monomers produced cross-linked matrixes even while using dithiol monomers, which would otherwise be completely linear. Presence of ester bonds allowed polymers to undergo enzymatic hydrolysis in aqueous conditions, even without a change in temperature or pH, and mass losses of up to 70% were reported over a period of 28 days, though lower values were more common particularly in highly cross-linked samples.

Methacrylate monomer MEU showed to undergo a process similar to what was reported by Lee (2007), with a high conversion of methacrylate occurring before thiol and other double bonds were able to react, as evident by the leftover thiol groups even after 10 min of reaction. AEU results also seem to agree with the literature, with a mixed step-chain growth mechanism occurring, achieving fully cured solids even after 60 s and with full conversion of thiol groups. Biodegradability of polymers was achieved, though the high degree of cross-linking heavily hindered this process.

4.2 SUGGESTIONS FOR FURTHER WORK

1. Analysis of the mechanical properties of polymer samples through DMA.
2. RTIR monitoring of functional group consumption to verify different mechanism preference by methacrylate and acrylate moieties.
3. Photorheology analysis to closely observe matrix gelation.
4. Enzymatic degradation tests under different pH and temperature conditions, as well as different free enzymes.
5. Michael addition modification of monomer AEU, resulting in a symmetric monomer, with no differences in reactivity and additional heteroatoms in the main chain.

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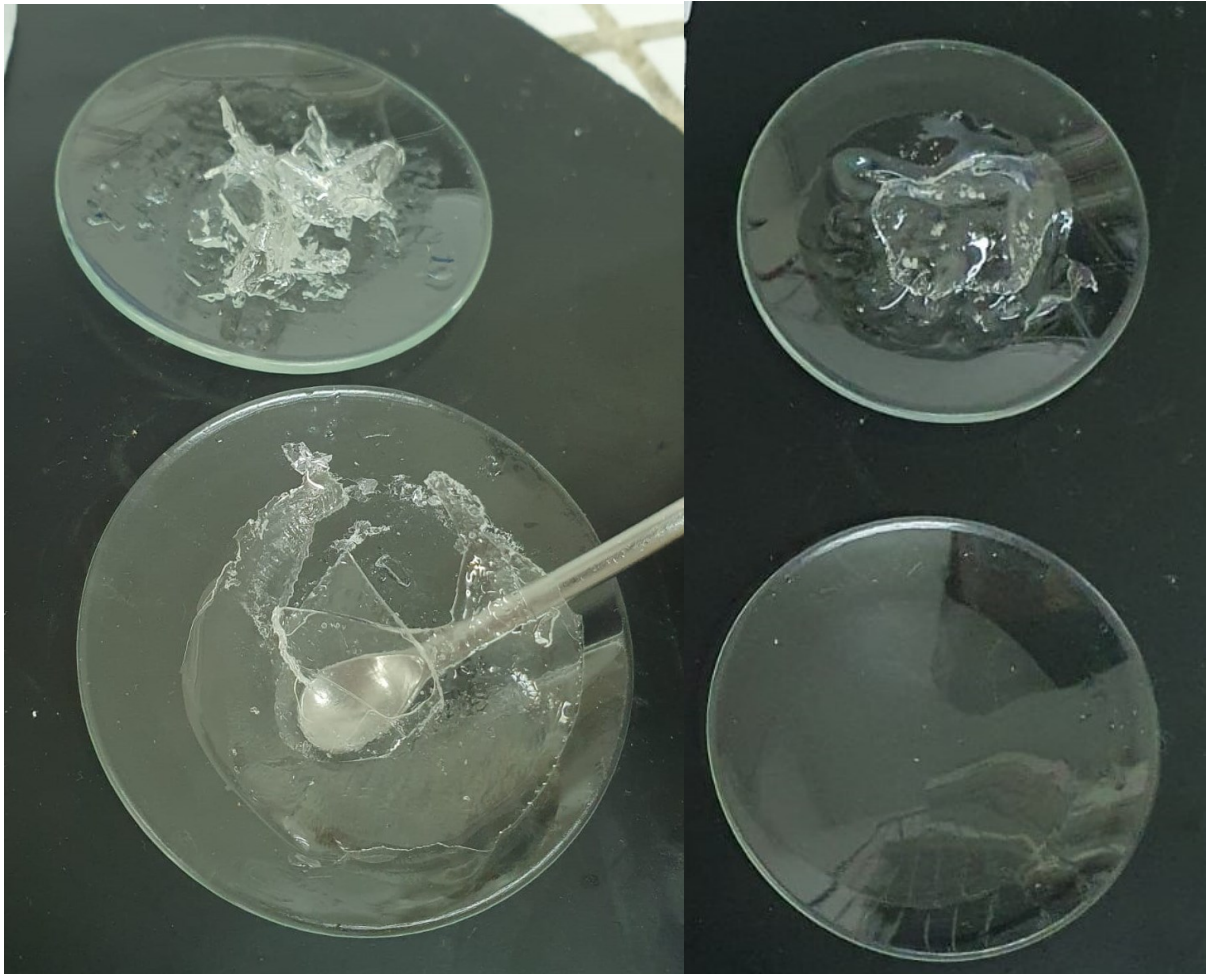
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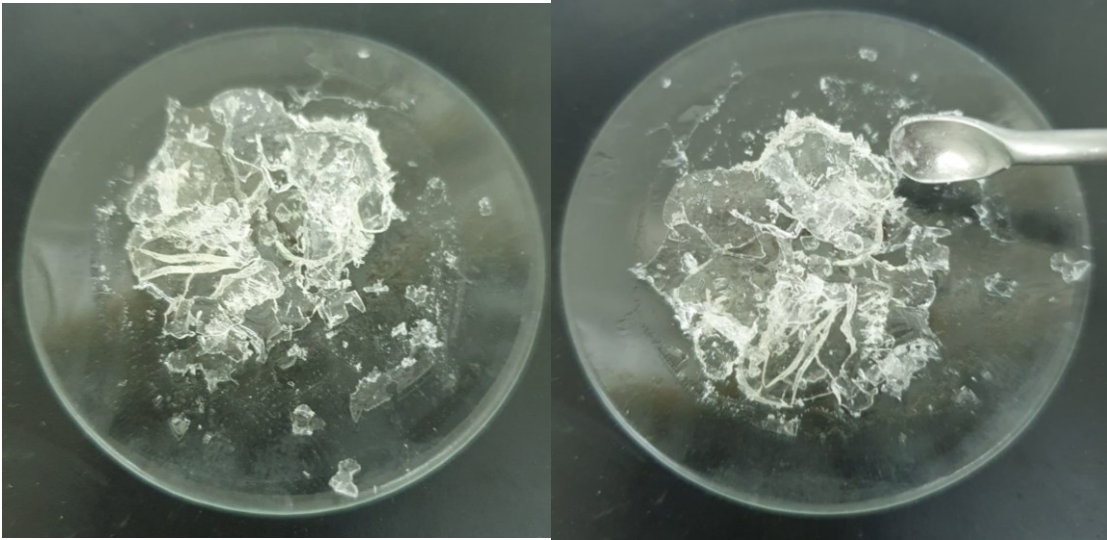
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APPENDIX**SAMPLE PICTURES**

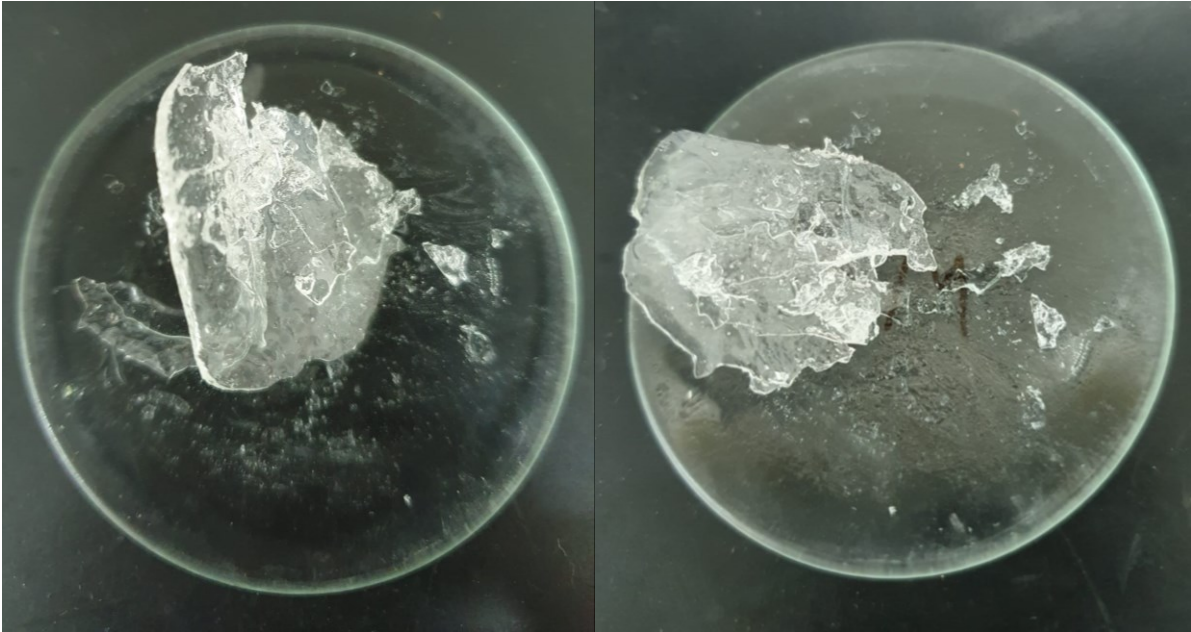
Samples PA02 (top) and PM02 (bottom).



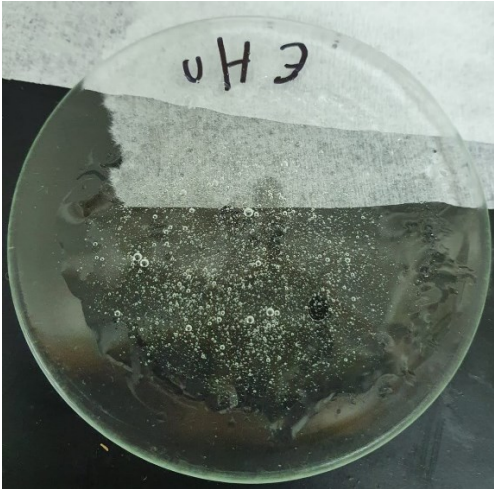
Sample PA03.



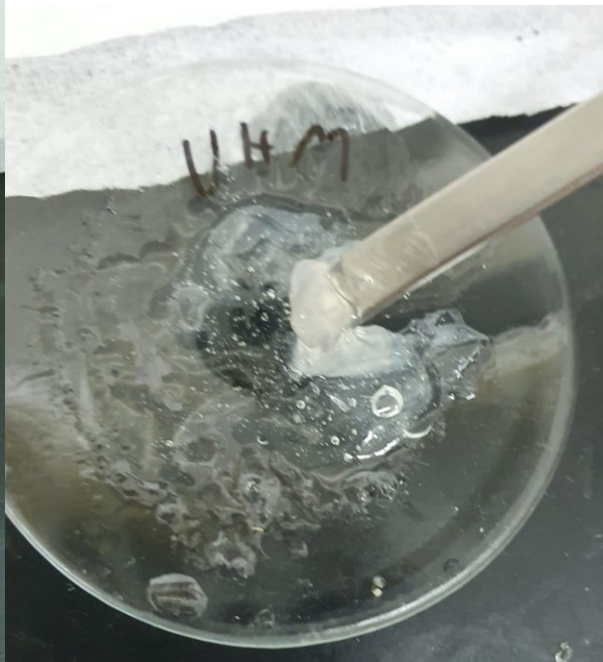
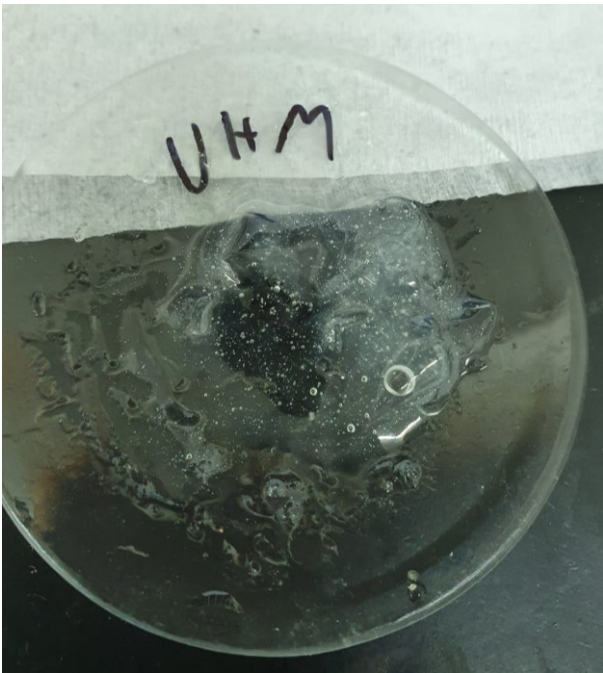
Sample PM03.



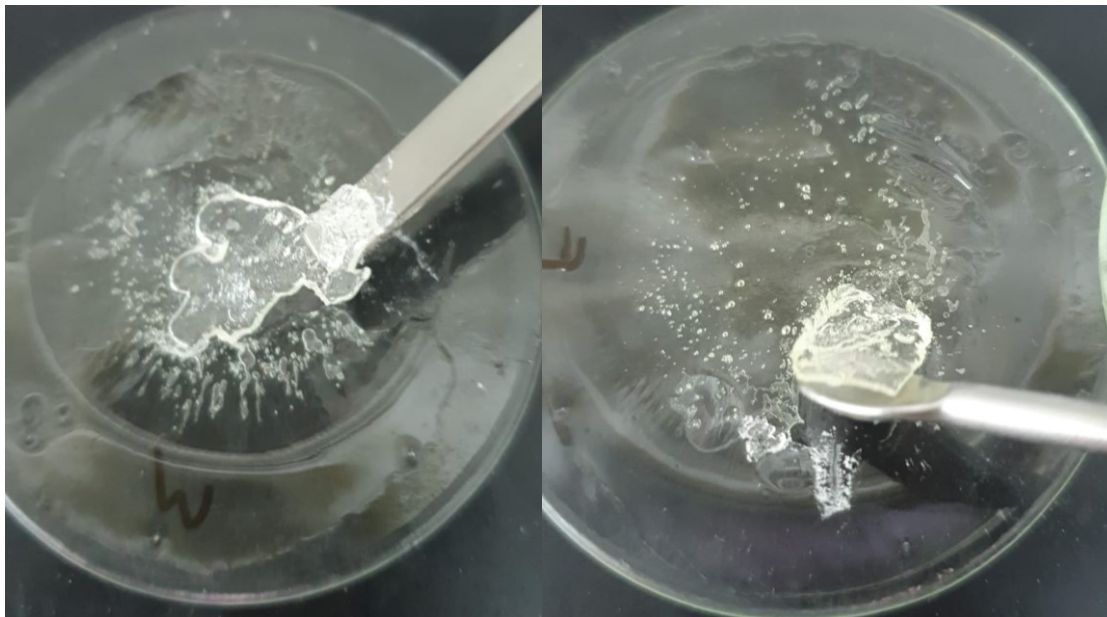
Sample PA01.



Sample PM01.



Samples PM04 (left) and PA04 (right).



ADDITIONAL WORK

Synthesis of MEU-HMD and AEU-HMD

According to the procedure by Romera (2018), both diene monomers were modified by Michael addition of a diamine, producing a symmetric monomer. Reaction was done at 50 °C, during 72h, in chloroform, and the product was not purified, with the result being a viscous caramel-like liquid.

Long reaction time is derived from Romera's conversion tests, likely due to low methacrylates reactivity towards Michael addition. Reaction with the acrylate monomer could be shorter, depending on conversion measures throughout the reaction, which were not performed in this work.

Unpurified modified monomers were polymerized in similar reaction conditions as to the original monomers, though the use of a more hydrophilic initiator, in this case Irgacure 2959 (1-[4-(2-Hydroxyethoxy)phenyl]-2-hydroxy-2-methyl-1-propan-1-one), is advised, as new monomers are more hydrophilic than the original AEU and MEU.

Polymers were liquid, maintaining the yellow/caramel character, though even more viscous. After cooling, they became closer to solid.

In a future work, we advise to start by doing a simple reaction kinetics to observe the different reactivities and likely faster reaction time for the acrylate monomer, and if that is the case, only this monomer should be tested, as both symmetric monomers should have no further differences between each other.

Synthesis of isosorbide dicrotonate

Another diene monomer synthesis was attempted, performing the esterification of crotonic acid and isosorbide. Both these reagents are derived from renewable sources.

Enzymatic esterification failed to reach the desired product, likely due to the high acidity of crotonic acid over undecenoic acid, namely a pKa of 4.69 for the former and 5.02 for the latter, with the enzyme used in the work, Novozym 435, having better results for acids with a pKa above 4.8.

The synthesis of this monomer was already reported by Goerz and Ritter (2014), who used Fischer esterification during 72h, and a simple 2x saturated sodium bicarbonate solution wash as purification. This method did yield the product, as a yellow powder, however the same yielded was not achieved and the product was still very impure even with additional purification through additional washes.

Due to these impurities, only a simple thermal polymerization was attempted and the product had very low molar mass.