Inês Marques Lopes

DEVELOPMENT OF UNSATURATED POLYESTERS FROM RENEWABLE SOURCES

Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Biomedical Engineering at the Faculty of Sciences and Technology of the University of Coimbra. Supervised by Professor Arménio Coimbra Serra, Professor Jorge Fernando Coelho and Doctor Ana Clotilde Fonseca.

September 2013

UNIVERSIDADE DE COIMBRA

Inês Marques Lopes

DEVELOPMENT OF UNSATURATED POLYESTERS FROM RENEWABLE SOURCES

Thesis submitted in partial fulfilment of the requirements for the degree of Master of Science in Biomedical Engineering at the Faculty of Sciences and Technology of the University of Coimbra. Supervised by Professor Arménio Coimbra Serra, Professor Jorge Fernando Coelho and Doctor Ana Clotilde Fonseca.

September 2013

· U C ·

UNIVERSIDADE DE COIMBRA

Only the one who does not question is safe from making a mistake.

Albert Einstein, 1945

ACKNOWLEDGEMENTS

Firstly, I would like to express my gratitude to Professor Arménio Serra and Professor Jorge Coelho, my supervisors, for the opportunity to work with them, for their wise guidance and constructive suggestions during this research project. I am particularly grateful for the assistance given by Doctor Ana Clotilde da Fonseca. Her unlimited willingness to give her time, understanding and knowledge so generously has been so deeply appreciated.

I would also like to extend my thanks to the colleagues of the Polymer Research Group of the Chemical Engineering Department, particularly to Inês Barata, Célia Frias, Bianca Viola, Pedro Cardoso, Filipa Dinis and Cátia Costa, for their welcome, joy and goodwill to help in so many ways.

Finally, I wish to thank my family and friends, in particular, my parents and sister, for their love and faith in me; Marta, for her daily support; Miriam and Inês, for their worry and fearless honesty; and all colleagues from SDDH/AAC group and futsal team, for the moments of inspiration and amusement. Although their contributions are not directly related to this research project, they were crucial to my performance during its development.

ABSTRACT

In last decade, unsaturated polyester resins (UPRs) have becoming important materials in the biomedical area. Such resins present excellent mechanical properties and an intrinsic capacity of biodegradation, but they are usually made of non-biocompatible monomers and crosslinking agents, which may compromise their applicability in healthcare products, such as tissue implants or adhesives, scaffolds and controlled drug delivery systems.

This thesis intends to develop UPRs more suitable to biomedical applications. In order to do that, monomers from renewable sources were used to produce the unsaturated polyester (UPs), in an attempt to increase their biocompatibility without compromising their mechanical properties. Therefore, the UPs were crosslinked with 2-hydroxyethylmethacrylate (HEMA), which is widely used in medical fields, such as ophthalmology and tissue engineering.

The synthesized UPs were characterized by FTIR, ^{1}H NMR (chemical composition), SEC (molecular weight), SDT and DMTA (thermo-mechanical properties). The crosslinked networks obtained from the thermal and photo crosslinking were firstly characterized in terms of their gel content. Then, the thermal crosslinked samples were analyzed by SDT and DMTA (thermo-mechanical properties), and their swelling capacity and *in vitro* hydrolytic behavior were also evaluated.

The results showed the success of the preparation of UPs and UPRs based on monomers from renewable sources, as well the observation of interesting and useful behaviors regarding their properties, which is an important starting point towards the further optimization of the systems and/or their application in biomedical field.

RESUMO

Na última década, as resinas de poliéster insaturado (UPRs) têm vindo a tornar-se um material importante na área Biomédica. Estas resinas apresentam excelentes propriedades mecânicas e uma capacidade intrínseca de biodegradação, contudo são constituídas normalmente por monómeros ou agentes de reticulação/monómeros reativos que não são biocompatíveis, o que pode comprometer a sua aplicabilidade em produtos da área da Saúde, como implantes e adesivos, *scaffolds* e sistemas de libertação controlada de fármacos.

Esta tese pretende desenvolver UPRs mais adequados para aplicações biomédicas. Para isso, são usados monómeros de origem renovável na produção dos poliésteres insaturados (UPs), na tentativa de aumentar a sua biocompatibilidade sem comprometer as suas propriedades mecânicas. Para isso, os UPs foram reticulados com 2-hidroxietil metacrilato (HEMA), pois é bastante usado em áreas médicas, como a Oftalmologia e a Engenharia de Tecidos.

Os UPs sintetizados foram caracterizados pelas técnicas de FTIR, ^{1}H NMR (composição química), SEC (peso molecular), SDT e DMTA (propriedades termo-mecânicas). As UPRs obtidas através de reticulação térmica e fotoreticulação foram primeiramente analisadas relativamente ao seu teor de gel. Seguidamente, as amostras reticuladas termicamente foram analisadas pelas técnicas SDT e DMTA (propriedades termo-mecânicas), e as suas capacidades de absorção e degradação hidrolítica *in vitro* também foram avaliadas.

Os resultados revelaram sucesso na preparação dos UPs e UPRs compostos por monómeros de fonte renovável, assim como a observação de efeitos interessantes nas suas propriedades, constituindo pontos de partida importantes para a futura otimização dos sistemas e respectiva aplicação no campo biomédico.

GOALS

The intent of this thesis is to synthesize UPs using monomers from renewable sources and to produce URPs using not toxic reactive solvents in order to increase their biocompatibility and biodegradability for further application in biomedical area (e.g., tissue engineering, drug delivery systems, coatings, etc). The goal is to develop new formulations in order to substitute the petrochemicals monomers used so far in UPs synthesis for others with a renewable and natural origin, as well as to substitute the styrene, the most reactive solvent used in UPRs production, for other less toxic and more biocompatible. Finally, the UPs will be characterized in terms of their chemical and thermal properties by proton nuclear magnetic resonance (^{1}H NMR), Fourier transform infrared spectroscopy (FTIR) and size-exclusion chromatography (SEC), and simultaneous thermal analysis (SDT), respectively. Regarding the UPRs, their thermo-mechanical properties will be evaluated by SDT and dynamic mechanical thermal analysis (DMTA) as well as their gel content, swelling capacity and *in vitro* hydrolytic behavior.

NOMENCLATURE

T_{on}	Extrapolated onset temperatures, in Celsius degrees (ºC)
$T_{5\%}$	Temperature corresponding to 5% of mass loss, in Celsius degrees (ºC)
$T_{10\%}$	Temperature corresponding to 10% of mass loss, in Celsius degrees (ºC)
T_p	Peak temperature, in Celsius degrees (ºC)
T_{deg}	Degradation temperature, in Celsius degrees (ºC)
T_g	Glass transition temperature, in Celsius degrees (ºC)
V_s	Volume of the sample, in millilitres (mL)
V_b	Volume of the blank, in millilitres (mL)
W_o	Initial weight of the sample, in grams (g)
W_e	Weight of the sample after being extracted, in grams (g)
W_d	Weight of the dry samples before immersion, in grams (g)
W_s	Weight of the swollen samples, in grams (g)
W_t	Weight of the dry samples after incubation for days, in grams (g)

LIST OF ACRONYMS

AV	Acid value
BPO	Benzoyl peroxide
C	Calculated relative molar percentage of monomer present in each UP
d_8-THF	Deuterated tetrahydrofuran
DAH	Dianhydrohexitol
DG	Diethylene glycol
DMTA	Dynamic mechanical thermal analysis
DV	Differential viscometer
DSC	Differential scanning calorimetry
DTGA	Derivative of thermogravimetric analysis
EtOH	Ethanol
F	Relative molar percentage of monomer used in the feed
FA	Fumaric acid
FCDA	2,5-furancarboxydialdehyde
FDCA	2,5-furandicarboxylic acid
FTIR	Fourier transform infrared spectroscopy
HEMA	2-Hydroxyethylmethacrylate
HQ	Hydroquinone
HMF	Hydroxymethylfurfural
HPSEC	High-performance gel permeation chromatography
^{1}H NMR	Proton nuclear magnetic resonance
IA	Itaconic acid
IB	Isosorbide
Ir-2959	Irgacure 2959
KOH	Potassium Hydroxide
LALLS	Low-angle laser-light scattering
M_s	Mass of the sample
M_n	Number average molecular weight
M_W	Molecular weight
NaN_3	Sodium azide
PBS	Phosphate buffered saline
PCL	Polycaprolactone
PC	Polycondensation
PDI	Polydispersity index
PDO	1,3 Propanediol

PE	Polyethylene
PET	Polyethylene terephthalate
PG	Propylene Glycol
PGA	Polyglycolic acid
PHA	Polyhydroxyalkanoate
PHB	Poly(3-hydroxybutyrate)
PLA	Polylactide
PP	Polypropylene
PS	Polystyrene
PTFE	Polytetrafluoroethylene
PVC	Polyvinylchloride
RALLS	Right-angle laser-light scattering
$R_d/_d$	Ratio between diols and diacids
RI	Refractive-index
ROP	Ring-opening polymerization
RS	Reactive solvent
SA	Sebacic acid
SEC	Size-exclusion chromatography
SDT	Simultaneous thermal analysis
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TGA	Thermogravimetric analysis
UP	Unsaturated polyester
UPR	Unsaturated polyester resin

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER I. INTRODUCTION

1.1. Motivation

Over the last century, the exponential progress of technology, the fast and easy widespread of knowledge and the success of interdisciplinary cooperation have encouraged the establishment of closest relationships between several areas, such as Engineering and Medicine. The increase of the interconnection of these two disciplines has led the scientific, industrial and medical communities to break classic barriers and work together in common problems and challenges. As a result, achievements which were very unlikely decades ago are now a reality, such as macro, micro and nano electronic devices incorporated in living tissue/organs [1-3]; complete or partial artificial tissues and/or organs [4, 5]; super lightweight and sensitive prostheses [5, 6, 7]; very efficient drug delivery systems [8, 9]; real-time diagnostic imaging and non-imaging techniques [1, 10]; wireless vital signals monitoring services/software/devices [1, 11]; long-lasting implants and transplants [1, 5, 6]; highly specific biosensors [12, 13]; and sophisticated and improved surgery equipment [1, 14], among others. However, in this interface, where the organic and inorganic components have to merge and work together, remains one of the biggest challenges to fully overcome – an effective biocompatibility in biomedical applications.

According to Williams (2008), *biocompatibility* should be defined as 'the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy.' [15]. A biocompatible material is no longer only a safe and stable material which does not harm the living tissue, in other words, which is not toxic, thrombogenic, carcinogenic, irritant or a trigger to inflammatory responses [15]. Nowadays, its ability to not release toxic substances/by-products (bioinertness), or to release them, but in harmless concentrations (biotolerance), is not enough [16]. It is required that "the third generation of biomaterials", as some call it [17], be bioactive, which means that they should be capable of performing positives interactions "with differentiation of tissue that leads to a close adhesion and interconnection along the interface of implant and tissue" [16], and it depends not only on the material, but on many others variables, such as application specific goals, biological conditions of operation, kind of target tissue, local of implementation, patient physical condition, etc [15].

Along with this change of the paradigm, the concept of biodegradation has also gained a new value and relevance in biomaterials due to the establishment of the idea of producing an implantable device or prosthesis as an integrant part of the body - not only as a temporary substitute. This led to the development of long-lasting applications or applications that "destroy" themselves when they are no longer

needed - thereby avoiding more surgery or invasive proceedings to the patient – particularly, in areas like as tissue engineering and drug delivery systems [18-20].

It is also important to realize that the degradation/decomposing phenomenon is complex and non-consensual. Some authors define *biodegradable* materials as "those that degrade both *in vivo* and *in vitro* into products that are either normal metabolites in the human body or that could be eliminated from the body with or without further metabolic transformations" [21]. Others consider that there are two different phenomena with different terminology regarding this matter - the biodegradability and the bioresorbability. Although they are usually used indistinctly, the first one refers to the materials ability of "decompose in the living body", where its degradation products "remain in long-term", while the second one can be defined as the materials ability of "degrade after implantation into non-toxic products, which are eliminated from the body" [18]. However, it is agreeable that the capacity to perform their role and disintegrate *in vivo* without harming the body, are two essential properties of biodegradable materials.

Polymers have been proving to be the most promising class of materials regarding these two issues - biocompatibility and biodegradability - according to clinical experience over the last century [22]. Comparatively to the others classes of materials, polymers do not have the high strength, ductility and resistance to wear of metals or the high resistance to corrosion, temperature and compression of ceramics. However, they are much more versatile and overcome the main metals and ceramics drawbacks, such as high stiffness and density (compared to living tissues), corrosion and low biocompatibility/the release of toxic ions (metals); and brittleness, high density, low fracture strength, low mechanical reliability and difficult processing (ceramics), respectively [22]. The ability of polymeric materials to be easily modified to achieve diverse structures (shape and form) and properties (chemical composition) that are present in the tissues of the body (Table 1), their large number and variety available (Table 2), and their capacity to respond to stimulus (e.g., to absorb liquids/to swell, to change shape, to degrade, etc.) are the main reasons for their widespread use [21, 22].

Table 1. Examples of different polymeric materials and their biomedical applications. Adapted from [16].

Polymer	Application
Polyethylene	Orthopaedic joint implants, syringes
Polypropylene	Heart valves, sutures, syringes
Polydimethylsiloxane	Breast implants contact lenses, heart valves, artificial hearts
Polyethyleneterephthalate	Vascular grafts, sutures, blood vessels
Polymethylmethacrylate	Bone cements, intraocular contact lenses, dental implants
Polyethyleneglycol	Pharmaceutical fillers, wound dressings
Poly-2-hydroxylethylmethacrylate	Contact lenses, urinary bladder catheter
Polytetafluoroethylene	Vascular grafts, sutures
Polylactic-co-glycolic acid	Resorbable meshes and sutures
Poly-ε-caprolactone	Drug delivery devices, sutures
Polyvinylchloride	Blood bags, blood tubes
Polyisoprene	Gloves
Collagen	Orthopedic and nerve repair matrices, tissue engineering matrices
Hyaluronic acid	Orthopedic repair matrices
Glycosaminoglycan	Orthopedic repair matrices
Elastin	Skin repair matrices
Fibrin	Hemostatic products, tissue sealants
Chitosan	Wound dressing
Alginate	Wound dressing

Polymers can be divided into natural and synthetic, depending on their origin (Table 2). Regarding biocompatibility and biodegradability, natural polymers seem to be the most adequate to bio-applications due to their chemical structure, which is very similar to the one present in all living organisms (cellular-based structure), and their inherent capacity to degrade by enzymatic or hydrolytic mechanisms, that are the most common phenomena of degradation in the body. However, the low versatility in what concerns their synthesis/production methods (it is only possible to extract them and perform some modifications in their structure); their associated health risks, as the possibility of carrying viral or bacterial infections and immune problems; the randomness and instability of their properties, which depends on their extraction and processing conditions; and, sometimes, the difficulty and high costs related to their extraction/collection, have led the current research and investment towards synthetic polymers. Besides the overcome of these drawbacks, polymers synthesized in laboratories also allow the combination of a large range of formulations and the induction/manipulation of specific and important properties (e.g., hydrophobicity/hydrophilicity, crystallinity, solubility, glass transition temperature and melting temperature), the monitoring and fine-control of the synthesis conditions/parameters, and a reliable reproducibility of their synthesis process. However, the simultaneous improvement of mechanical properties, effective biodegradability and long-lasting biocompatibility of several synthetic polymers remains an issue to overcome [21, 23].

Table 2. Some examples of synthetic (a) and natural (b) polymers, including the five most used families of synthetic polymers nowadays - polyethylene (PE), polypropylene (PP), polyvinylchloride (PVC), polystyrene (PS) and polyethylene terephthalate (PET). Adapted from [24, 25].

Origin	Type	Examples	ISO[1] Abbreviation
Synthetic	Homopolymers	Polyethylene	PE
		Polypropylene	PP
		Polystyrene	PS
		Polybutylene	PB
		Poly(methyl methacrylate)	PMM
		Polytetrafluoroethylene	PTF
		Poly(vinyl fluoride)	PVF
		Poly(vinylidene fluoride)	PVDF
		Poly(vinyl chloride)	PV
		Poly(vinylidene chloride)	PVDC
		Poly(vinyl acetate)	PVAC
		Poly(vinyl butyral)	PVB
		Poly(ethylene terephthalate)	PET
		Polyetheretherketone	PEEK
		Polyacrylonitrile	PAN
		Polyethersulphone	PESU
		Polycarbonate	PC
		Poly(butylene terephthalate)	PBTP
		Polyoxymethylene	POM
		Polyamide	PA
		Polyacrylamide	-
		Poly(phenylene oxide)	PPO
		Poly(phenylene sulphide)	PPS
		Epoxy	EP
		Polyurethane	PUR
		Polyisoprene rubber	IR
		Polychloroprene rubber	CR
		Silicone polymers	SI
	Copolymers and Hybrids	Acrylonitrile-butadiene-styrene	ABS
		Melamine-formaldehyde	MF
		Phenol-formaldehyde	PF
		Urea-formaldehyde	UF
		Unsaturated polyester	UP
		Styrene-acrylonitrile	SAN
Natural	Polysaccharides	Cellulose	-
		Amyloses, amylopectins	-
		Gums, mucopolysaccharides	-
	Proteins	Gelatin, enzymes, muscle, collagen, silk	-
	Polynucleotides	Deoxyribonucleic acid, ribonucleic acid	DNA, RNA
	Polyisoprenes	Natural rubber, gutta-percha	-
	Polyesters	Poly(3-hydroxybutyrate), cork	PHB, -
	Lignins	Cell walls, binder (for cellulose fibers)	-

Along with these scientific challenges, society's concerns about health care and environmental sustainability have also increased, claiming their importance in the future and, thereby, beginning to have a serious effect on industrial and economic fields [26-28]. In Europe, for example, an investment of €220

[1] *International Organization for Standardization*.

million is being estimated between 2007 and 2013 in biomedical areas, including "implanted biomaterials/tissue engineering" [29]. Moreover, there are in motion political programs (such as Sustainable Process Industry through Resource and Energy Efficiency (SPIRE) or Horizon 2020) and the creation of association/groups (such as European Renewable Resources and Materials Association (ERRMA) or Cleantech Group) which supports and promote "the deployment of innovative technologies and solutions required to reach long term sustainability for Europe and its process industries in terms of global competitiveness, ecology and employment." [30-32].

In conclusion, these are the main reasons that compose the motto of this thesis – the improvement of biocompatibility and biodegradability in biomedical applications by using "green" biomaterials and innovative technology and thereby following the recent trends of the investment in health care.

1.2. State of the art

1.2.1. Polyesters

Polyesters are the class of polymers most developed over the last two decades, due to their immense diversity and versatility (Table 3) [23, 33].

Table 3. The main family of polyesters currently used in industry and scientific research and some of its main properties and applications. Adapted from [34, 35].

Polyester family	Main chain composition	Origin	Current applications
Polylactide (PLA)	aliphatic	synthetic (bio/agro-resources)	packaging, agriculture, biomedicine
Polycaprolactone (PCL)	aliphatic	synthetic (fossil resources)	modeling, prototyping, biomedicine
Polyhydroxyalkanoate (PHA)	aliphatic	naturally produced (microbial production)	food, packaging, pharmaceutics, biomedicine
Polyglycolic acid (PGA)	aliphatic	synthetic (bio/agro-resources)	food packaging, biomedicine
Polyethylene terephthalate (PET)	aromatic	synthetic (fossil resources)	modeling, prototyping, packaging, electronics

The most used group of polymers to produce biodegradable materials nowadays (in both areas of medicine and environment) is aliphatic polyesters, because their ester linkages are inherently biodegradable (Figure 1) [26, 33, 36].

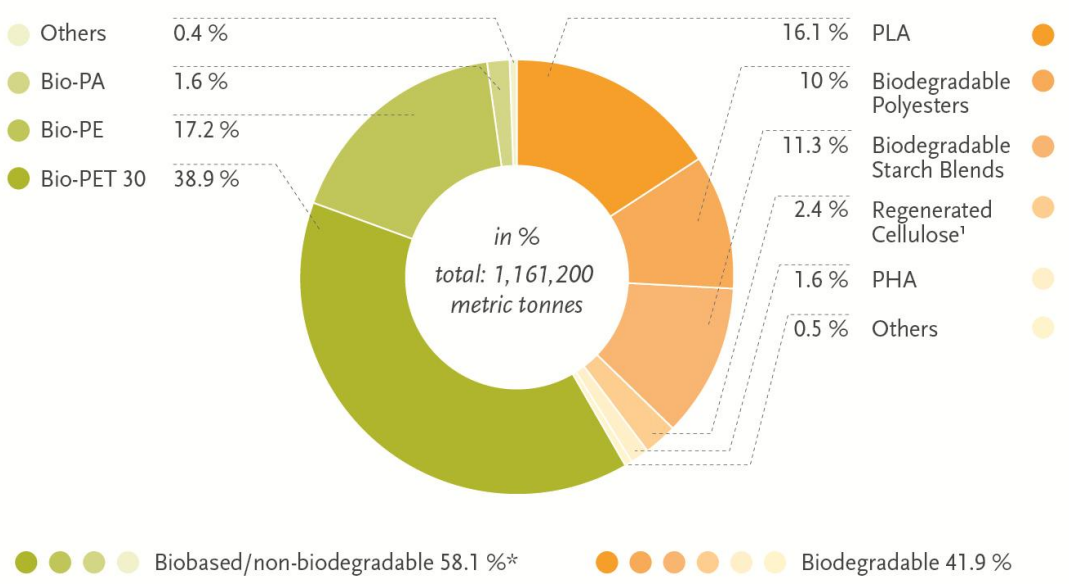


Figure 1. Bioplastics production capacity in 2011, according to *European Bioplastics* [37].

In addition, they also present high biocompatibility while used in biomedical applications, which have been turning it into the most promising type of synthetic biodegradable polymers in this field [38]. However, usually polyesters with good biodegradability and biocompatibility show a lack of others important properties (e.g., poor mechanical and thermal properties) or high costs, and vice versa. Two good examples of this contrasting phenomenon are PHAs and PETs: the first one is generally expensive and has low resistance to fracture and thermal degradation, but is also very elastomeric and has been recognized as biocompatible and biodegradable; the second one is widely used in several areas of industry and shows high thermal stability and very good physico-mechanical performance (due to its aromatic rings), but is not promising when used in biomedical applications, due to its insensitivity to biodegradation and weak performance in cellular adhesion and proliferation [26, 39].

The current challenge is to modify these polyesters in order to improve and adapt their properties, such as biological, mechanical, thermal and chemical ones, towards the needs and targets of each biomedical application in which they are involved [40, 41]. There are three main strategies followed nowadays in order to achieve that: the combination of polyesters with others different materials; the adoption of more advantageous and efficient synthesis methods; and the use of additives after polyester synthesis. Sometimes, the combination of two or three of these strategies is carried out, but it is not always a current practice because their operational conditions are often not compatible/well-matched or the associated costs are higher [33, 42, 43].

Regarding the first one, many approaches have been tried, such as (i) the use of more than one type of monomers (copolymers production) [34], (ii) the combination of different polyesters families or/and its derivatives, or even, other additives (e.g., processing additives, such as erucamide, silicon dioxide and

calcium carbonate) [44], (iii) the mixture with others classes of synthetic polymers (e.g., polyurethanes or polyamides) or natural polymers (e.g., chitosan) [42, 45], (iv) the blend with metallic or ceramic materials (composites production) [22], and (v) the insertion of nanomaterials in the polyester matrix or the production of polyester nanomaterials [20, 27]. In all these cases, the idea is to combine the desirable properties those materials offer with the original polyester, controlling their percentages in the formulation, according to the attributes required for the final application. For example, it is known that amide groups have strong hydrogen-bonding interactions between themselves and also that any material can achieve unique properties (e.g., stiffness, permeability, crystallinity, thermal stability) when produced in nano scale. Thus, if a weak polymer (as aliphatic polyesters) can be synthesized successfully holding ester and amide groups (poly(ester amide)) or nano-sized particles/fillers, it will probably present improved thermo-mechanical properties [27, 42]. Another example is the incorporation of functional groups into polymers during their synthesis – *functionalization*. If a polyester/copolyester is prepared as a functional material[2], its properties, such as crystallinity, hydrophilicity and solubility, will be modified. It has been demonstrated that a decrease in crystallinity and an increase in hydrophilicity and solubility are the key to improve biological properties such as biodegradation, biocompatibility and/or cell adhesion and proliferation [40, 41]. Moreover, functionalization also seems to enhance the possibility of crosslinking, due to the presence of more 'exposed' and reactive chemical groups [40, 46]. Thus, successfully functionalized-polyesters (e.g., hydroxyl-terminated aliphatic polyesters) could present improved biological and chemical properties, which have also already been accomplished [40, 41, 46]. It is also important to mention that unsaturated polyesters (UPs) are the most used polyesters in this approach, among others, due to their carbon-carbon double bonds [41, 46], as it will be further discussed in the following section.

About the second strategy, polyesters are usually synthesized by (i) a polycondensation reaction (PC) (reversible step-growth polymerization process), i.e., polyesterification of hydroxyacids or diols and diacids (or diacid derivatives), in this case; or by a ring-opening polymerization reaction (ROP) (opening cyclic monomers process) of lactones, glycolides or lactides (Figure 2) [21, 23]. However, according to recently literature [23, 49], the ROP seems to be the only method which allows the synthesis of polyesters with high molecular weight, an inherent variable/characteristic which improve thermo-mechanical properties [34]. Polymers with high molecular weights can only be obtained at very high conversions rates (98–99%) in polymerization reactions, which is very difficult to achieve in PC due to its side-reactions and deficient water removal [23, 34]. These two phenomena are difficult to avoid completely and impairs the precise stoichiometric equilibrium required between the reactants (acid and hydroxyl groups) to achieve a high degree of polymerization [34]. Furthermore, PC reactions require high temperature (100 to 200ºC), long reaction times (10 to 20 hours) and an efficient and continuous removal of reaction by-products (to guarantee that reaction occurs only in the forward orientation) to obtain polymers with useful

[2] Monomer with very reactive functional groups - due to their stereochemical locations [69].

characteristics [34, 49]. On the contrary, ROP allows the production of high-molecular weight aliphatic homo and co-polyesters without the removal of any reaction by-products. Nevertheless, ROP has some drawbacks, namely, the requirement of monomers with high purity, which are oftentimes difficult to prepare or very expensive [46, 50, 51]. In both methods, the presence of initiators and catalysts is usual, which improve the control over the reaction and others parameters such as molecular weight distribution of the polymer [33, 34]. Thus, regarding each methods specifications and characteristics, it is possible to manage bulk properties such as molecular weight, crystallinity, solubility, and glass transition temperature, among others, regarding the polymer final purpose [23].

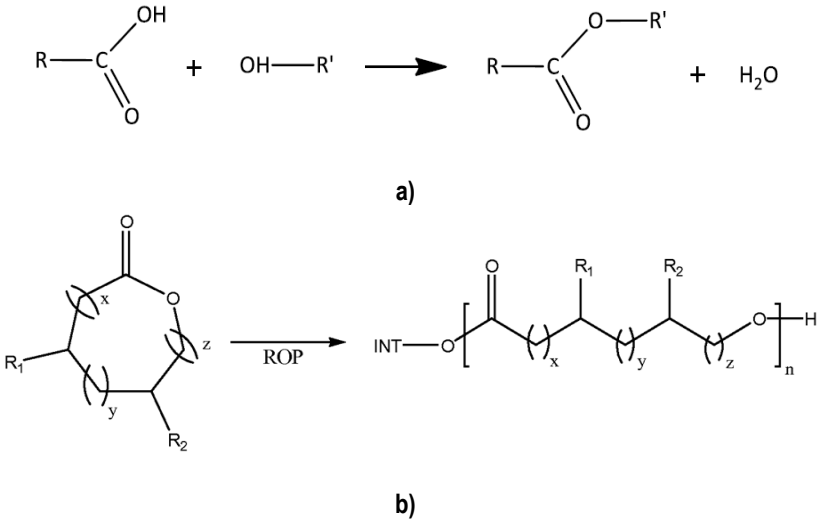


Figure 2. Schematic illustration of polycondensation (PC) (a) and ring-opening polymerization (ROP) (b) reactions. Adapted from [47, 48].

Finally, concerning the third strategy, many substances have been added to polymers after synthesis in order to protect, improve or simply change their characteristics, without alter their original structure or increase to much their cost. Those substances can be (i) plasticizers, if the goal is the increase of material plasticity or fluidity; (ii) stabilizers, if the challenge is the prevention of unwanted chemical modifications; (iii) surfactants, if the purpose is to decrease the surface tension; (iv) property modifiers, if the aim is to improve some mechanical and/or chemical properties; (v) pigments, if the color or texture must change; (vi) additives with bioactivity purpose, if the need is the improvement of biocompatibility or cell adhesion; or (vii) curing agents, if the intention is to enhance dimensional stability, processability and physical properties [52-54]. Despite all the options and considering the class of polyesters, the curing monomers have been one of the most used additives and have shown very efficient results in several industrial and scientific fields. Therefore, they will be deeper discussed in the following section.

1.2.2. Unsaturated polyesters resins (UPRs)

Since the beginning of this century, polymer industry has been produced thermosetting resins (viscous liquids with ability to hardening permanently) due to their excellent chemical, thermo and mechanical properties along with its easy, controllable, inexpensive fast molding and production [47, 55]. More specifically, these thermosets are very elastic (very ductile[3]), strong[4] (enough stiff[5], but quite tough[6]), dimensionally stable, resistant to heat and corrosion agents – which are all important requirements, regarding the final product and its fabrication or processing, in several industry fields, such as automobile and marine transportation (e.g., protective coatings, hulls and auto bodywork compounds) and civil infrastructure construction (e.g., covers, bathroom components and fixtures, pipes, tanks and fitting) [36, 56]. These properties are the result of a highly crosslinked network composed by polymer chains and an additionally monomer (solvent), which is very reactive [36, 56]. In order to obtain this highly stable and strong network, it is necessary the formation of covalent bonds between the polymer chains and the solvent monomers, which are only possible if they comprise functional groups that could react with each other, such as alkene groups (due to its carbon-carbon double bonds) [47, 57]. To accomplish that reaction between the functional groups, it is also necessary the presence of an ion or a radical, which are obtained by heating, heating and compression, or light irradiation of chemical compounds called initiators (Table 4) [47, 56, 57]. The ions or radicals work like a trigger by breaking some double bonds, which it will generate other reactive free ions or radicals. These would be able to "attack" the other double bonds along the chains and, as a result, a copolymerization occurs between the initial polymer and the solvent, producing the final resin [58].

Table 4. The most used initiators in UPRs curing reaction - peroxides [58].

Peroxide type	Examples
Ketone Peroxides	methylethylketone peroxide acetylacetone peroxide
Hydroperoxides	cumene hydroperoxide
Diacyl peroxides	dibenzoyl peroxide
Dialkyl peroxides	dicumyl peroxide tert-Butylcumyl peroxide
Alkyl peresters	tert-Butylperoxy-2-ethylhexanoate tert-Butylperoxybenzoate tert-Amylperoxybenzoate tert-Hexylperoxybenzoate
Percarbonates	bis(4-tert-butylcyclohexyl)peroxydicarbonate

[3] Ductility is the ability to deform (not permanently - elastic deformation) under tensile stress without fracture [78].

[4] Strength has several definitions depending on the material type and application. In this case, it means the material ability to resist enough to deformation (without losing its ductility) but do not fracture easily [78].

[5] Stiffness is the ability to resist deformation in response to an applied force [78].

[6] Toughness describes a material's resistance to fracture - amount of energy it can absorb before fracture [78].

This whole process is also known as *curing reaction* and it is not as simple as it seems. It comprises two solidification phases – *gelation* and *vitrification* – and two more sub-reactions – polymer and solvent homopolymerization – which are worth to be considered (Figure 3).

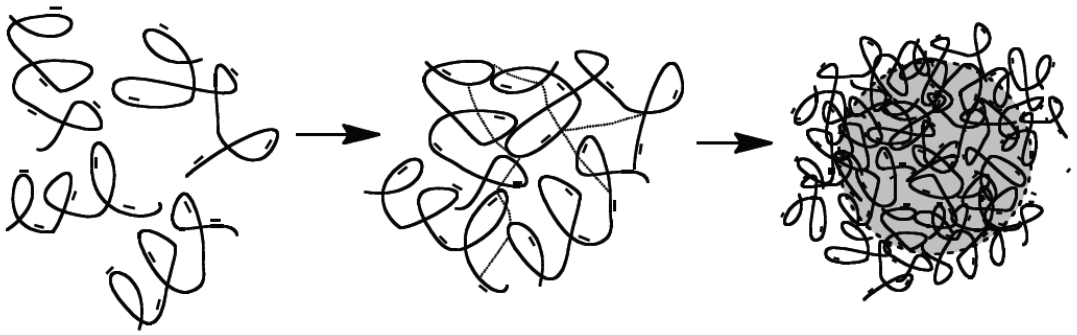


Figure 3. Schematic illustration of a curing reaction and its steps – from unlinked chains to gel formation. Adapted from [57, 59].

The gelation consists in a liquid (sol phase[7]) to rubber (gel phase[8]) transition controlled by the kinetics of the reaction, in which the resin molecular weight and viscosity increases considerably. After gelation, chains begin to lose their mobility (due to the increase of cross-linked network density) and a diffusion-controlled rubber-glass transition occurs – vitrification. This is an important stage since it determines the rate and degree of the reaction conversion and enables some modifications on the structure and properties of final resin [47, 57].

Regarding the sub-reactions, it is also relevant to notice that, besides the copolymerization between the polymer and the solvent, covalent bonds are also created within polymer chains or between the solvent monomer (Figure 4). These homopolymerization reactions have different kinetics and affect in different ways the macro and micro structure of the final crosslinked network [47].

[7] The phase in which the material is a fluid solution [79].

[8] The phase in which the material is a jelly-like diphasic system or network - with both liquid and solid phases – highly viscous [79].

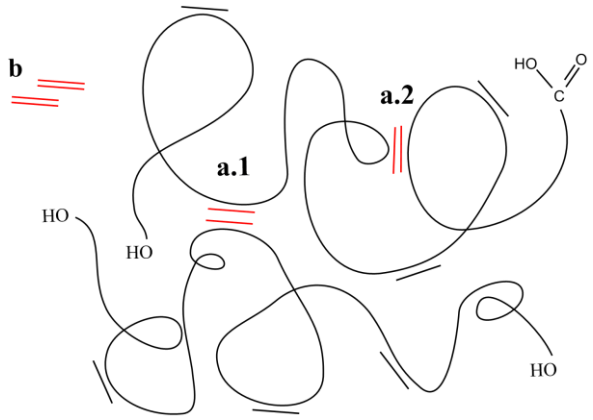


Figure 4. Schematic illustration of inter (a.1) and intra (a.2) polymer homopolymerization and solvent monomer homopolymerization (b). Adapted from [47, 59].

The UPs have been extensively used in biomedical and environmental areas. Due to their inherent biodegradability (ester linkages), biocompatibility and crosslinking ability (carbon-carbon double bonds) they had become the most suitable and promising candidate to produce resins which demands not only excellent physico-chemical properties but also good biological properties. Usually, UPs comprise glycols, saturated and unsaturated acids as monomers. The types and amounts of monomers used define the composition and the properties of the UP: the glycols and the saturated acids are responsible for the UPs strength and thermo-chemical resistance; and the unsaturated acids allows the crosslinking of UPs in curing reaction, due to their double bonds, as already mentioned [47, 57]. The most used monomers and reactive solvents are summarized in Table 5.

Table 5. The main petrochemical-based monomers used in UP synthesis and UPR curing reaction [36, 47, 58].

Compound	Examples
Glycols	ethylene glycol diethylene glycol propylene glycol dipropylene glycol methylpropane diol neopentyl glycol trimethylol propane glycerol
Saturated acids	phthalic anhydride isophthalic acid terephthalic acid chlorendic acid tetrabromophthalic anhydride adipic acid
Unsaturated acids	maleic acid
Solvent monomer	styrene methylstyrene p-vinyltoluene diallyl phthalate triallyl cyanurate

Despite its easy extraction and low cost, the majority of these monomers are toxic or very toxic [47]. At the beginning, that was an irrelevant fact, since their applications were related to construction and transportation industries, where biocompatibility and biodegradability were uninteresting properties. However, in the last years biodegradability started to be a concern due to the social and economical sustainability and biocompatibility become an essential subject in current medical applications. These issues encouraged industry community to begin investing and exploring other type of solutions – more "bio" and "green" ones [60-62].

1.2.3. Polymers and monomers from renewable sources

The current energy crisis has been changing the social and industrial mindset. Since they became aware of the real unavailability of fossil resources in the near future and its contribution to the perpetuation of environmental problems (e.g., pollution, contamination, increasing emission of green house gases, etc.), alternatives solutions (e.g., nuclear, biomass, combustion, aeolian and geothermal sources) have been explored towards a more sustainable industrial and technological development. The constant increase of oil prices and the current "green" social trend have been the main triggers to overcome the massive use of petrochemical products, which lasts since the Second World War [61, 63]. Petrol, natural gas and coal have been not only the responsible for 90% of fuels produced and used nowadays, but also for the production of the vast majority of the synthetic polymers and organic chemicals. Despite the vast range of alternatives solutions and its recent improvements, biomass (i.e., renewable vegetable and animal counterparts) is the only valid substitute to the production of commodity polymers [61].

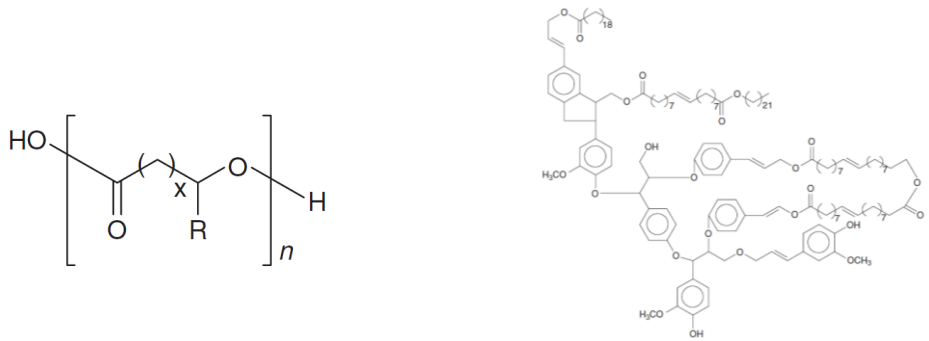
According to Belgacem and Gandini (2008), a *renewable resource* is "any animal or vegetable species which is exploited without endangering its survival and which is renewed by biological (short term) instead of geochemical (very long term) activities" and can be divided in three main groups based on its origin: vegetable, animal and bacterial. Regarding vegetable sources, they comprise (i) wood and its components (e.g., cellulose, lignin, hemicelluloses, tannins, rosins, and terpenes), and (ii) annual plants (e.g., starch, vegetable oils, hemicelluloses, mono and disaccharides and algae). They were indeed the renewable resources used to manufacture the first renewable-based plastics (e.g., natural rubber for tires, cellulose acetate and nitrate and plant-based dyes) at the beginning of the 20th century and are the most used class of renewable resource nowadays in sectors such as papermaking, cotton textiles, reinforcing agents, fuel, food additives, synthetic resins, adhesives, dyes, pharmaceuticals and cosmetics [60, 61]. About animal resources, chitin/chitosan, proteins and cellulose whiskers from mollusks are the most explored compounds and have been largely used in biomaterial and biomedical areas. Concerning bacterial sources, PHAs and bacterial cellulose have begun to be more exploited in the last years in polymer science and industry in order to be applied in almost every biotechnology area due its excellent biological

properties [61]. Although the drawbacks of natural polymers discussed before are still considered, the excellent biological properties of animal and bacterial sources have gained importance in several industries.

Thus, besides the key to the depletion of petrochemical feedstock, renewable resources present other interesting characteristics applicable in other areas, such as environment and biomedicine. Despites the abundance, variety, spontaneous origin and inexpensive extraction (comparing to the petrochemicals) of these natural compounds, their high potential biocompatibility and biodegradability have been the most valued properties nowadays, particularly regarding the specific case that has been discussed in this chapter – UPs and UPRs [55, 56, 63, 64]. Currently, it can be found (i) naturally occurring polyesters and also several (ii) monomers from renewable resources suitable to synthesize new polyesters (not necessarily from natural polyesters). Indeed, the actual novelty lies on the exploitation and use of these monomers and/or the monomeric compounds of the natural polyesters, since the latter, as a whole, are only capable of being modified (not used to synthesize new polymers) [61].

Naturally occurring polyesters

PHAs (Figure 5a) and suberin (Figure 5b) are the two main families of natural polyesters. The first one is produced by bacteria as an energy reserve and has very good biological (100% biodegradable), physical (mechanical strength and modulus) and chemical (high crystallinity, high melting temperature and good resistance to organic solvents) properties. However, its production rate is low and its production conditions are difficult to control - depending on the type of bacteria and its feeding, and the environmental conditions. The most common and simplest of the PHAs, PHB, was already used in food packing and plastic bags or bottles (due to its excellent barrier properties against gas permeation) and considered a potential substitute of PET in some applications. But its most recent exploitation has been made in the pharmaceutical and biomedical areas, in particularly, tissue engineering (e.g., scaffolds and bone repairs materials) and controlled drug delivery systems (due to biodegradability and biocompatibility) [61].



(a) **(b)**

Figure 5. The general formula of poly(hydroxyalkanoates) (a) and a schematic representation of the structure of suberin (b) – natural polyesters [61].

About suberin, it is an aromatic-aliphatic crosslinked polyester and the main component of cork. In contrast with PHAs, it is not much used as a whole polyester (due to its complex structure). Instead, its very long aliphatic moieties and interesting monomeric compounds are the most exploited issue in order to develop macromonomers useful in polymer synthesis, in particular, polyesters. Liquid polyols and dicarboxylic acids (and also ω,hydroxyfatty acids) - the two essential constituents of polyesters - are obtained by oxypropylation[9] of cork (Figure 6) and by depolymerization[10] of suberin, respectively [61].

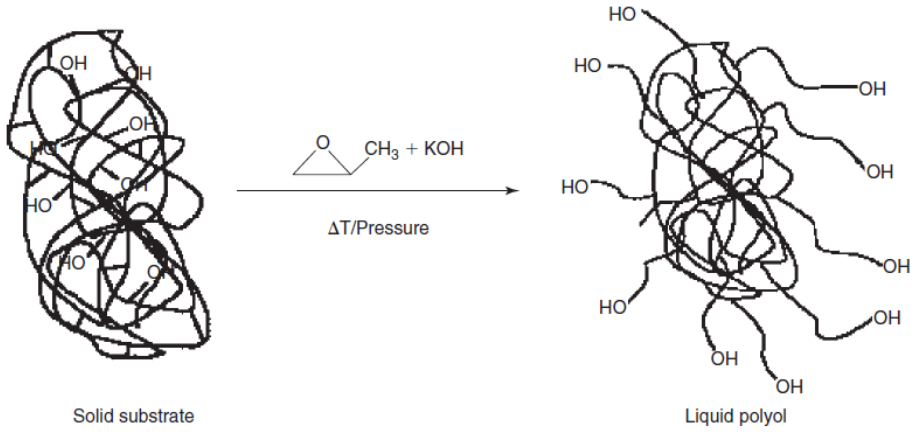


Figure 6. Schematic view of the oxypropilation of OH-bearing macromolecular materials [61].

Monomers from other renewable resources

Rosin, lignin and vegetable oils, along with monomers such as sugar-based monomers and furan-based monomers, have been extensively studied regarding polyester synthesis [61-63].

Rosin is the most common wood resin extracted from pine trees and it contains a several unsaturated polycyclic carboxylic acids, commonly known as resin acids, which are currently isolated and used to synthesize or functionalize new polymers, including polyesters [61]. Resins acids are diterpenic[11] mono-carboxylic acids derived from four main carbon skeletons, which differ in the position of their instaurations: abietane, pimarane, isopimarane labdane. The most commons are pimarane and abietane skeletons (Figure 7), which generate acids such as, respectively, pimaric, isopimaric and sandaracopimaric acids; and abietic, neoabietic, levopimaric, palustric and dehydroabietic acids. These acids are usually combined with other substances (e.g., maleic anhydride, fumaric acid, acrylonitrile, acrylic acid, vinyl acetate and

[9] Process in which the OH groups tied to the substrate are deprotonated by a nucleophilic catalyst, generating oxianions. These oxianions initiate the anionic polymerization of propylene oxides and, therefore, the respective stereochemical availability of the OH groups [61].

[10] Process of converting a polymer into a monomer or a mixture of monomers [61].

[11] Organic compound produced by plants and composed by four isoprene units [61].

formaldehyde) in order to form monomers which can be used as diacids in polyesters synthesis and UPRs production [61].

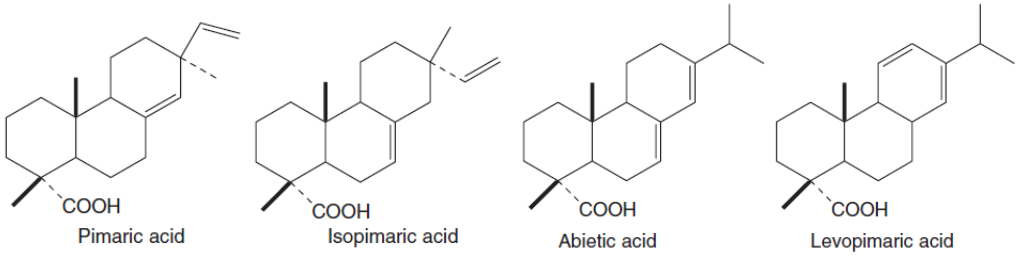


Figure 7. Structures of the some common pirame and abietane-type resin acids [61].

Lignin is an amorphous, irregular and complex organic molecule found in wood matrix and presents a high number of aliphatic and phenolic hydroxyl groups (Figure 8). Its oxypropilation originates liquid polyols, which are useful in polyesters synthesis, and several other chemical modifications leads to further blending with aliphatic polyesters in order to produced lignin with ether and ester moieties - macromonomers used in other polymer synthesis [61].

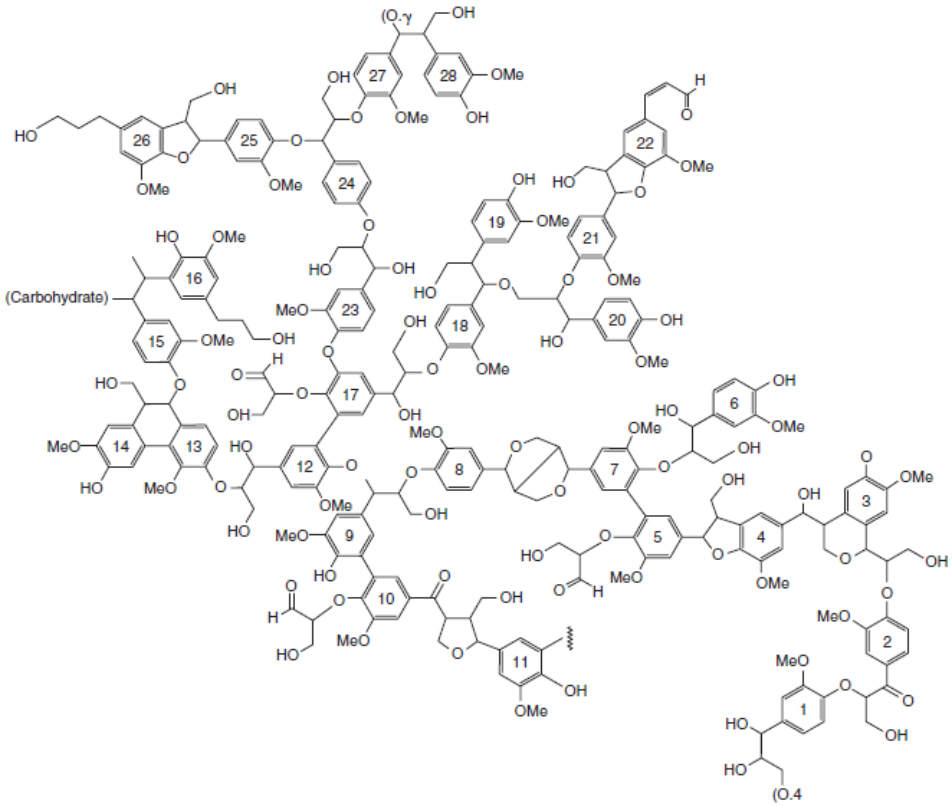


Figure 8. Lignin main moieties in a typical macromolecular assembly [61].

Vegetable oils are liquid triglycerides (at room temperature) produced by many kinds of plants and vegetables, such as soybean, palm, rapeseed/canola, sunflower, tallow, lard, butterfat, cottonseed, coconut, olive, corn, linseed, castor, among others [61, 65]. They are the most applied renewable resource nowadays in several different areas (e.g., coatings, inks, plasticizers, lubricants, alkyd resins and agrochemicals) and its major interest lies in their fatty acids [60]. The carboxylic group present in each fatty acid makes possible its esterification with a glycerol or other polyol, while the unsaturated carbon backbone, and its diversity, provides the chemical and mechanical properties required. Moreover, other bearing functional groups are found in fatty acids (e.g., epoxy rings, hydroxyl moieties, triple bonds and ether groups) and used to chemically modify and functionalize other materials [61]. However, in order to produce polyesters and UPRs, the type of fatty acid, its reactivity, the length of its carbon chains and the number and position of its unsaturations are the most relevant issues [60]. Myristic, palmitic, palmitoleic, stearic, oleic, linoleic, eleostearic, ricinoleic, vernolic and licanic acids are some of the most used fatty acids as macromonomers for the synthesis of vegetable oil-based polymers, in particular, the oleic and linoleic acids (Figure 9) in polyesters case [61].

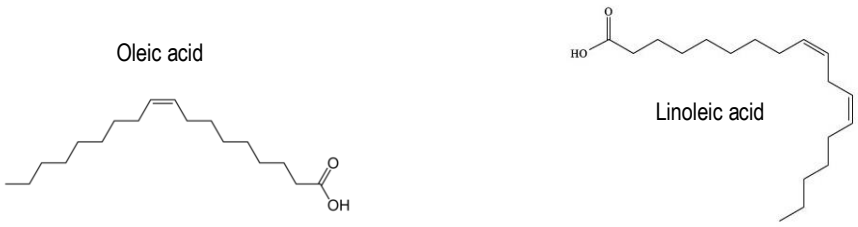


Figure 9. The structures of oleic and linoleic acids. Adapted from [61].

Sugar-based monomers derived from carbohydrates (e.g., starch) have becoming a representative source in the production of novel monomers, polymers and additives for biomedical applications, due to their high biocompatibility and biodegradability [56, 62]. Currently, 1,4:3,6-dianhydrohexitols (DAHs) are the most applied diols as monomers for the production of polymers due to the few number of hydroxyl groups they present, which are easy to control [62]. DAHs are made by dehydrating of hexitols, which are polyhydric alcohols derived from hexose sugars, mainly glucose, mannose and idose (Figure 10) [62]. Their three isomers, known as isosorbide, isomannide and isoidide (Figure 11), can be used as distinct monomers, because their reactivity is different (due to the stereochemical position of each hydroxyl group). The isomannide is the last reactive and isoidide is rare in natural and expensive, while isosorbide is the most abundant and economically viable [61, 62]. In addition, isosorbide also presents very good chemical properties, which explains their major incorporation as diol in thermoplastic polyesters (e.g., PET) and other thermoset materials (e.g., crosslinked epoxy resin) [56, 62].

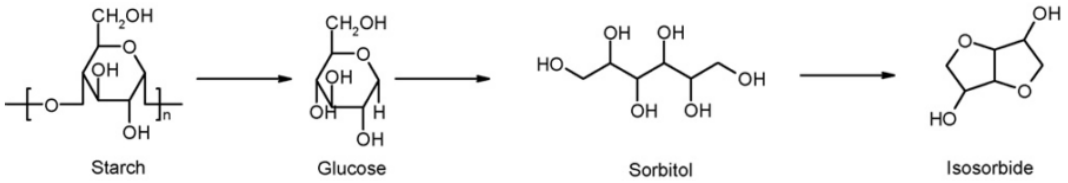


Figure 10. Conversion of starch into sorbitol and isosorbide [56].

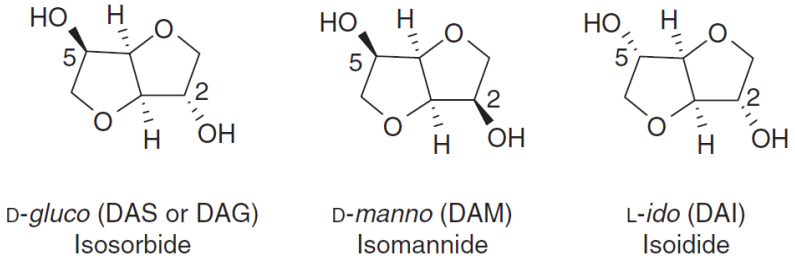


Figure 11. The structures of the three diastereoisomers of dianhydrohexitol [61].

Furan is an unsaturated heterocyclic family much studied in the last century in areas such as fine chemistry and polymer science and technology [61]. Although it cannot be found in nature as a single compound, it can be derived from precursors based on vegetable renewable sources. Furfural is one of these precursors, due to its high number of pentoses and low cost, and it is prepared from agriculture and forestry by-products and wastes (e.g., cobs, oat, rice hulls, cotton seeds, olive husks and wood chips) [61]. After the pentoses hydrolysis, followed by its progressive dehydration and final cyclization, the furan are achieved and prepared not only to be used as a commodity chemical, but also to be modified in order to become a viable monomer to apply in polymer synthesis [61]. Hydroxymethylfurfural (HMF) (Figure 12a) is an example of that. This is one of the most explored first generation furan derivative and it is converted in a dialdehyde (2,5-furancarboxydialdehyde, FCDA) or a diacid (2,5-furandicarboxylic acid, FDCA) due to its high sensitivity to resinification. Its diacid form (Figure 12b) is used as monomer to prepare resins and polyesters, among others polymers. The polyesters derived from FDCA have been considered a potential alternative to PET [61].

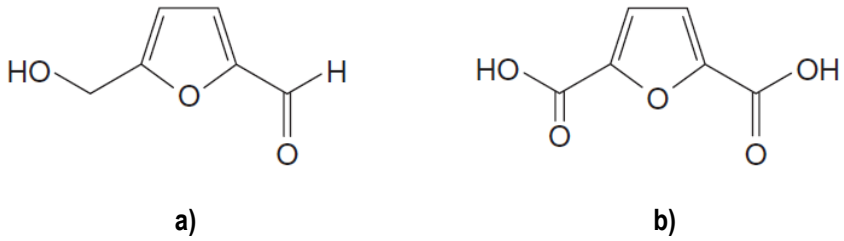


Figure 12. The structures of the hydroxymethylfurfural (a) and 2,5-furandicarboxylic acid (b) [61].

Although petro-based chemicals are still rooted in the major chemical production, the examples discussed have been demonstrating the promising viability of the known “green” and “bio-refining” concepts in the future of polymer science and industry. Particularly, in polymeric biomaterials sector, this seems to be an excellent opportunity to exploit a potential and significant improvement in the biocompatibility and biodegradability approaches of many biomedical applications.

CHAPTER II. MATERIALS AND METHODS

2.1. Materials

The reagents used to prepare, produce and characterize the UPs and UPRs are presented and divided based on their function in Table 6.

Table 6. The reagents used in UPs and UPRs production and characterization.

Function		Name	Abbr.	M.W.[1]	Purity	Source
UP Synthesis	Diacids	Fumaric acid	FA	116,07	99.0%	Sigma-Aldrich
		Itaconic acid	IA	130,10	99.0%	Acros Organics
		Sebacic acid	SA	202,25	94.5%	Sigma-Aldrich
	Diols	Isosorbide	IB	146,14	98.0%	Sigma-Aldrich
		Diethylene glycol	DG	106,12	99.0%	Sigma-Aldrich
		Propylene glycol	PG	76,09	99.0%	Sigma-Aldrich
		1,3 Propanediol	PDO	76,09	98.0%	TCI Europe
	Inhibitor	Hydroquinone	HQ	110,11	99.0%	AnalaR
Curing Reactions	Solvent	2-Hydroxyethylmethacrylate	HEMA	130,14	97.0%	Acros Organics
	Initiator (thermal)	Benzoyl peroxide	BPO	242,23	97.0%	Fluka Analytical
	Initiator (photo)	Irgacure 2959	Ir-2959	224,30	-	Ciba Specialty Chemicals
Acid Value Determination	Base	Potassium Hydroxide	KOH	56,10	85.0%	Sigma-Aldrich
	Solvent	Ethanol	EtOH	46,07	96.0%	Panreac
	Indicator	Phenolphthalein	-	318,32	-	RPE
Characterization	Solvent	Tetrahydrofuran	THF	72,11	99.0%	Fisher Chemical
	Solvent	Deuterated tetrahydrofuran	d8-THF	80,16	99.5%	Eurositop
	Buffer	Phosphate buffered saline tablets	PBS	-	-	Sigma (Aldrich)
	Buffer	Sodium azide	NaN_3	65,01	99.0%	Panreac

[1] Molecular weight.

2.2. Methods

2.2.1. UPs synthesis

The UPs were prepared by a bulk polycondensation reaction, performed in a four head reactor (250 mL) and equipped with a mechanical stirrer (700 rpm), a nitrogen inlet with constant flow, and a condenser attached to a round-bottom flask to collect the water (Figure 13).

The diacids, the diols (Figure 14) and the inhibitor (to prevent premature crosslinking) were put in the reactor and were heated up around 180 to 200ºC during 11 to 18 hours (depending on each formulation).

The reactions were stopped when the acid value[12] (AV) of the polyester was below 30 mgKOH/g.

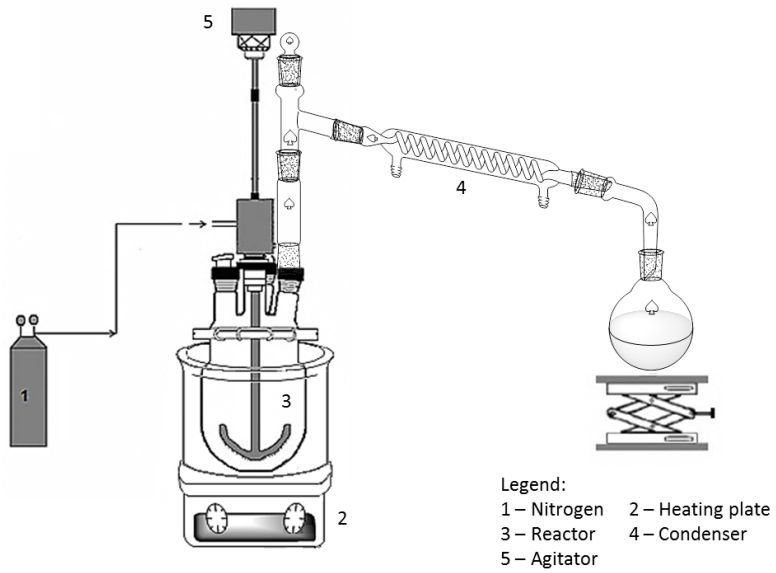


Figure 13. Schematic illustration of the reactor and its apparatus used to synthesize the UPs, kindly provided by Ana Cação.

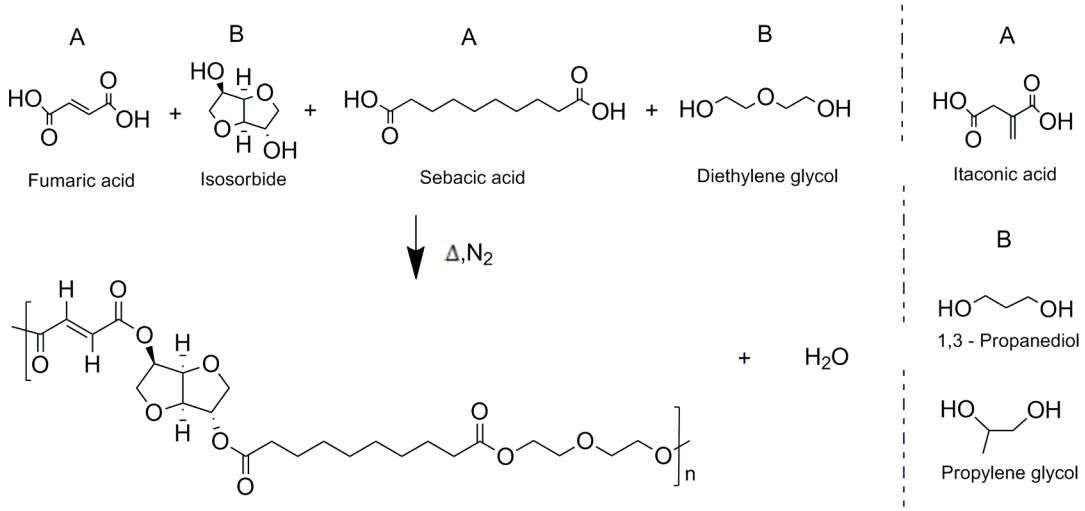


Figure 14. Schematic illustration of the UPs synthesis reaction occurred inside the reactor. The A represents the diacids and the B the glycols used.

[12] Important chemical parameter that indicates if the reaction is complete. It is obtained by an acid-base titration performed with a 1M (molar) KOH solution (known concentration - base) and a 50 mL ethanol solution with 1g of UP sample (unknown concentration - acid) and 1 mL of a color indicator (phenolphthalein solution, 1% (m/v)). Ethanol is used as blank (50 mL) and as solvent in all solutions. When the color of the solution changed from transparent to purple, the volume of the KOH solution used is registered and the acid value is calculated using the following equation:

$$AV\ (mg.KOH/g) = \frac{(V_s - V_b) \times 0{,}1 \times 56{,}01}{M_s}$$

where, V_s and V_b are the volumes of the UP sample and the blank, respectively; $0{,}1$ and $56{,}01$ are the values of KOH concentration and molar mass, respectively; and M_s are UP sample mass (~1g).

The formulations tested are described in Table 7 as well the conditions of each reaction in Table 8.

Table 7. The UPs formulations studied in this thesis.

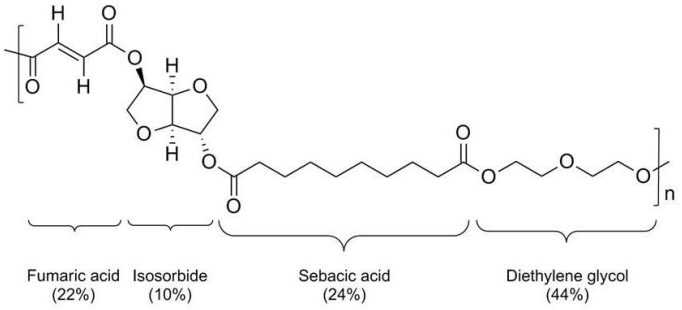
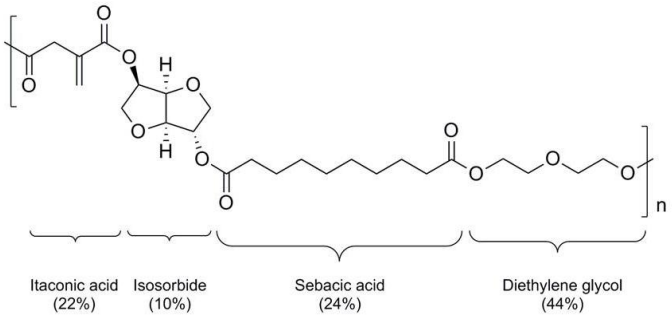
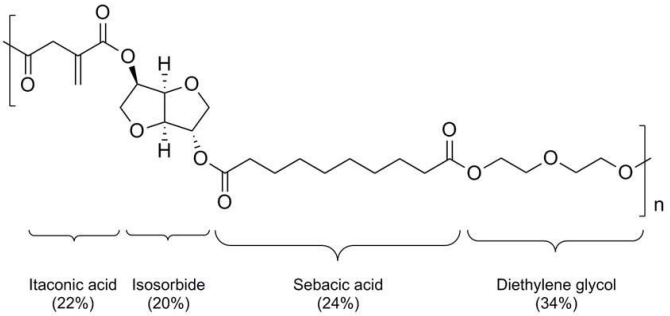
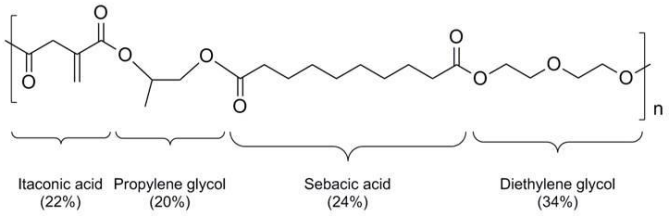
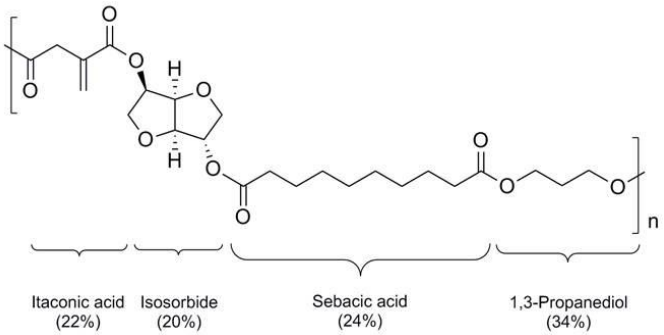
UP label	UP structure
UP 1	
UP 2	
UP 3	
UP 4	
UP 5	

Table 8. The compounds (diols and diacids) mass (m) used in each formulation and their reaction conditions (time (t) and temperature (T)).

UP	m_{diol1} (g)	m_{diol2} (g)	$m_{diacid1}$ (g)	$m_{diacid2}$ (g)	$m_{initiator}$ (g)	$t_{reaction}$ (h)	$T_{reaction}$ (ºC)
UP 1.0	(IB) 14,61	(DG) 46,69	(FA) 25,54	(SA) 48,54	(HQ) 0,03	*	*
UP 1.1	(IB) 14,61	(DG) 46,69	(FA) 25,54	(SA) 48,54	(HQ) 0,03	6,00 + 11,30	180, 190
UP 2.0	(IB) 14,61	(DG) 46,69	(IA) 28,62	(SA) 48,54	(HQ) 0,03	6,00 + 5,50	180, 190
UP 2.1	(IB) 14,61	(DG) 46,69	(IA) 28,62	(SA) 48,54	(HQ) 0,03	6,00 + 12,50	180, 190
UP 3.0	(IB) 29,23	(DG) 36,08	(IA) 28,62	(SA) 48,54	(HQ) 0,03	6,00 + 7,40	180, 190
UP 4.0	(PG) 15,22	(DG) 36,08	(IA) 28,62	(SA) 48,54	(HQ) 0,03	6,00 + 7,50	180, 190
UP 5.0	(IB) 29,23	(PDO) 19,40	(IA) 28,62	(SA) 48,54	(HQ) 0,03	6,00 + 9,00 + 7,00 + 5,50	180, 190, 200, 220
UP 5.1	(IB) 29,23	(PDO) 19,40	(IA) 28,62	(SA) 48,54	(HQ) 0,03	6,00 + 7,50	180, 190

* The sample degraded during the reaction.

2.2.2. Curing reactions

The UPs were crosslinked using HEMA as reactive solvent (RS), BPO as thermal initiator and Ir-2959 as photoinitiator. A predetermined amount of UP was dissolved in HEMA (Table 9) and then the initiator (3% w/w relatively to the amount of UP and RS) was added. After the total dissolution of the initiator, the samples were placed in teflon moulds and were cured at 80ºC for 3 hours or irradiated at 280 nm for 3 hours in a UV-irradiation chamber (Model BS-02, from Dr. Gröbel, UV-Electronik GmbH).

Table 9. The UPRs formulations and the percentage and masses of their compounds.

Formulation	UP	RS	m_{UP} (g)	m_{RS} (g)	$m_{initiator}$ (g)
UPR 1.0 (50RS/50UP)			2,50	2,50	0,15
UPR 1.1 (37RS/63UP)	1.1	HEMA	3,15	1,85	0,15
UPR 1.2 (25RS/75UP)			3,75	1,25	0,15
UPR 2.0 (50RS/50UP)			2,50	2,50	0,15
UPR 2.1 (37RS/63UP)	2.0	HEMA	3,15	1,85	0,15
UPR 2.2 (25RS/75UP)			3,75	1,25	0,15
UPR 3.0 (50RS/50UP)			2,50	2,50	0,15
UPR 3.1 (37RS/63UP)	3.0	HEMA	3,15	1,85	0,15
UPR 3.2 (25RS/75UP)			3,75	1,25	0,15
UPR 4.0 (50RS/50UP)			2,50	2,50	0,15
UPR 4.1 (37RS/63UP)	4.0	HEMA	3,15	1,85	0,15
UPR 4.2 (25RS/75UP)			3,75	1,25	0,15
UPR 5.0 (50RS/50UP)			2,50	2,50	0,15
UPR 5.1 (37RS/63UP)	2.1	HEMA	3,15	1,85	0,15
UPR 5.2 (25RS/75UP)			3,75	1,25	0,15
UPR 7.0 (50RS/50UP)			2,50	2,50	0,15
UPR 7.1 (37RS/63UP)	5.1	HEMA	3,15	1,85	0,15
UPR 7.2 (25RS/75UP)			3,75	1,25	0,15

2.2.3. Characterization techniques

Chemical structure identification

FTIR spectra were obtained in the range 4000−500 cm^{-1} at room temperature using a Jasco FT/IR-4200 spectrometer, equipped with a Golden Gate Single Reflection Diamond ATR. Data collection was performed with 4 cm^{-1} spectral resolution and 64 accumulations.

^{1}H NMR spectra of the UPs were obtained at 25ºC on a Varian Unity 600 MHz Spectrometer using a 3 mm broadband NMR probe in THF-d_8.Tetramethylsilane (TMS) was used as internal standard.

Molecular weight distribution

The molecular weight distribution of the samples was determined using high-performance gel permeation chromatography (HPSEC; Viscotek TDAmax) with a differential viscometer (DV); right-angle laser-light scattering (RALLS, Viscotek); low-angle laser-light scattering (LALLS, Viscotek) and refractive-index (RI) detectors. The column set consisted of a PL 10 mm guard column (50×7.5 mm^2) followed by one Viscotek T200 column (6 μm), one MIXED-E PLgel column (3 μm), and one MIXED-C PLgel column (5 μm). HPLC dual piston pump was set with a flow rate of 1 mL.min $^{-1}$. The eluent (THF) was previously filtered through a 0.2 μm filter. The system was also equipped with an on-line degasser. The tests were done at 30°C using an Elder CH-150 heater. Before the injection (100 μL), the samples were filtered through a polytetrafluoroethylene (PTFE) membrane with 0.2 μm pore. The system was calibrated with narrow polystyrene (PS) standards.

Thermal and mechanical properties

The thermal stability of the samples, both UPs and UPRs, was evaluated by simultaneous thermal analysis (heat-flux differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), using a TA Instruments SDT Q600 equipment (thermobalance sensitivity: 0.1 μg), which was previously calibrated in the range 25ºC to 1000ºC by running tin and lead as melting standards, at a heating rate (ϕ) of 10ºC.min^{-1}, using open alumina crucibles and a dry nitrogen purge flow of 100 mL.min^{-1}. Sample weights ranging from 8 to 10 mg were used.

DMTA was carried out using a Tritec 2000 DMA. The UPs were placed in stainless steel material pockets, and the test was run in single cantilever bending geometry. The UPRs were analyzed in tension mode. Both tests were carried out from −150ºC to 150ºC, in multifrequency mode, with a heating rate of 5ºC.min^{-1}.

Gel content

The UPRs were weighed, extracted with THF over night and dried under vacuum until constant weight. The gel content was determined from equation:

$$Gel\ content\ (\%) = \frac{W_e}{W_0} \times 100 \qquad (1)$$

where W_o is the initial weight of the sample and W_e is the weight of the sample after being extracted.

Swelling capacity

UPR with a known dry weight were immersed in PBS (pH 7.4, 0.01 M) at 37ºC for a period of time that allowed them to reach the swelling equilibrium. At predetermined times, the swollen samples were removed from the PBS solution and the surface water gently blotted by filter paper. The swollen samples were then weighted and the swelling capacity determined from equation:

$$Swelling\ capacity\ (\%) = \frac{(W_s - W_d)}{W_d} \times 100 \qquad (2)$$

where W_d is the weight of the dry samples before immersion, and W_s is the weight of the swollen samples. Two measurements were done for each UPR.

In vitro hydrolytic degradation

In vitro hydrolytic degradation tests were done using a PBS solution (pH 7.4, 0.01 M) at 37ºC during 50 days. At predetermined periods of time, the samples were removed from PBS and washed with distilled water. Then, the UPR were dried under vacuum until no weight change was observed. The degree of degradation was estimated from the weight loss of the gels according to the equation:

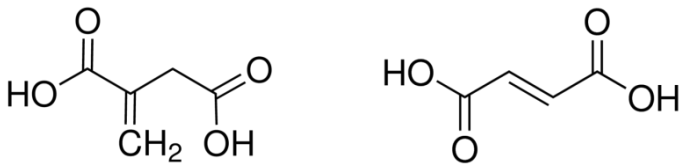
$$Weight\ loss\ (\%) = \frac{(W_d - W_t)}{W_d} \times 100 \qquad (3)$$

where W_d is the weight of the dry samples before immersion, and W_t is the dry samples weight after incubation for *t* days. Two measurements were done for each UPR.

CHAPTER III. RESULTS AND DISCUSSION

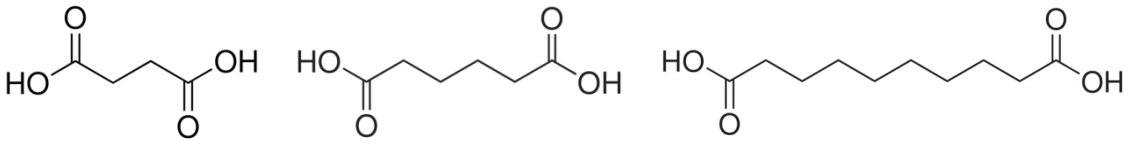
3.1. UPs synthesis and characterization

As already mentioned before, the synthesis of the new UPRs was done using monomers from renewable sources instead of petrochemical-based ones. Beginning with diacids, IA was chosen due to its pending double bonds, which make it a highly reactive compound [58] and, therefore, a promising candidate to substitute, for example, FA, which has been very used in the preparation of UPs [47, 58, 61] (Figure 15). Moreover, IA is derived from renewable resources and has not been extensively tested yet in polyester resins production [61, 66, 67], which could be an advantageous and innovator factor in this study. SA presents a longer carbon-carbon chain than others unsaturated diacids tested [47, 57, 61], such as, succinic or adipic acids (Figure 16). This long carbon-carbon chain provides a high flexibility to the UP, which is useful during the construction of crosslinked network in curing reaction [68, 69]. This is the main reason for its use, besides its natural/renewable origin and endogenous nature.



a) b)

Figure 15. Chemical structures of IA (a) and FA (b).

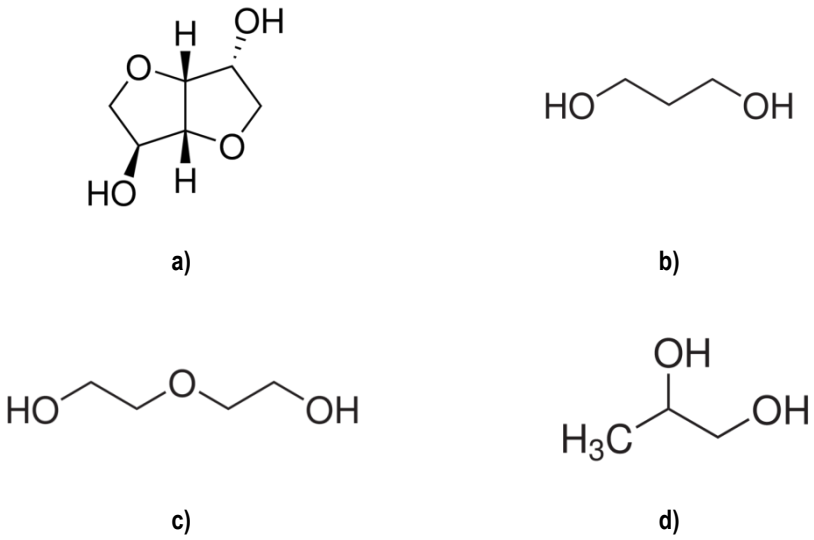


a) b) c)

Figure 16. Chemical structures of succinic acid (a), adipic acid (b) and SA (c).

Regarding the diols, IB and PDO were chosen due their natural/renewable origin. As stated before, IB is biocompatible, abundant and inexpensive, and therefore, it is already commercialized and used in polyester synthesis or resins production, among others products for biomedical area [62, 70]. Also, its ring structure (Figure 17a) can be useful to improve the mechanical properties of the final polyester, if the application demands it. PDO has began to be commercialized recently as a renewable source in the synthesis of polymers [71, 72], becoming an excellent potential substitute to PG. PG, along with DG, have

been the most used diols in UPs and UPRs production [47, 58, 73], and that is why they continue to be included in several formulations, although they do not have a natural/renewable origin. Particularly, DG is important due to its ether group (Figure 17c). It provides some flexibility to the chains [73], which can be useful in curing reaction or in specific applications.



a) **b)**

c) **d)**

Figure 17. IB (a), PDO (b), DG (c) and PG (d).

The formulations presented in Table 7 were designed without any previous specification, i.e., regarding no predetermined application. They constitute attempts to study the influence of different monomers and their combinations in the final properties of the resins. This type of study allows the choice of the most promising systems to further optimization and reproduction.

Considering the reactions, Table 10 summarizes the reaction times, temperatures and AVs in order to provide a general and comparative view over the UPs synthesis.

Table 10. Total time of reaction (t), final temperature (T) and acid value (AV) measured for each formulation.

Formulation	t_{total} (h)	T_{final} (°C)	AV (mgKOH/g)
UP 1.0	*	*	*
UP 1.1	17,30	190	25,59
UP 2.0	11,50	190	23,46
UP 2.1	18,50	190	9,00
UP 3.0	13,40	190	18,64
UP 4.0	13,50	190	16,51
UP 5.0	27,50	220	23,60
UP 5.1	15,50	190	15,22

* The sample degraded during the reaction.

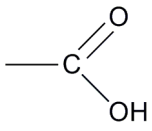
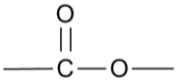
The UP 1.0 and 5.0 presented unexpected events: the first degraded during the reaction and the second last around twice the hours estimated and it needed higher temperatures. The UP 2.0 showed the presence of some unreacted monomers, although its synthesis seemed to occur as predicted. The formulation UP 1.0, 2.0 and 5.0 were synthesized again and only the UP 2.0 was still considered to further resin production. The new versions, UP 1.1, 2.1 and 5.1, achieved the required AV (<30 mgKOH/g - the reference value for the reaction end) at expected temperatures (180 to 200ºC) and reaction times (10 to 20 hours) (Table 10) [47, 57]. The lower AV, correspondent to UP 2.1, is explained by the extension of the time of reaction. Based on the unreacted monomer found in UP 2.0, it was decided to prolong the reaction in order to guarantee the complete monomer interaction. Nevertheless, the AV value indicates that the theoretically end of the reaction occurred earlier.

3.1.1. Chemical structure identification

FTIR

The FTIR spectra of the monomers have confirmed the presence of the main required functional groups, such as carboxyl groups in diacids (around 1700 cm^{-1} peak) and hydroxyl group in diols (around 3300 cm^{-1} peak). The FTIR spectrum of each monomer can be consulted in detail in Appendix A. Table 11 shows the wavenumbers and chemical structures of the chemical groups of interest present in the monomers and UPs.

Table 11. FTIR wavenumber and structure of the main functional groups present in the monomers and UPs. Adapted from [47, 74].

Monomer/UP	Functional Group		Wavenumber (cm^{-1})
	Group	Structure	
FA, SA, IA, IB, DG, PG, PDO	Hydroxyl	—OH	3570-3200
FA,IA UP 1.1, UP 2.0, UP 2.1, UP 3.0, UP 4.0, UP 5.0, UP 5.1	Alkenyl	—C=C—	1680-1620
SA, IB, DG, PG, PDO UP 1.1, UP 2.0, UP 2.1, UP 3.0, UP 4.0, UP 5.0, UP 5.1	Alkyl	— CH_2 —	2935–2915 2865–2845
FA, SA, IA	Carboxyl		1725–1700
UP 1.1, UP 2.0, UP 2.1, UP 3.0, UP 4.0, UP 5.0, UP 5.1	Ester		1750–1725
IB, DG UP 1.1, UP 2.0, UP 2.1, UP 3.0, UP 4.0, UP 5.0, UP 5.1	Ether	—O—	1150–1050

Regarding the UPs, all presented the bands corresponding to the ester group (a), around 1750 cm^{-1}, and also those corresponding to the double bonds (b), at 1680 cm^{-1}, which indicates that the UPs were successfully synthesized. These peaks can be detected in FTIR spectrum of UP 1.1 presented in Figure 18, as well in the other UPs spectra (see Appendix A).

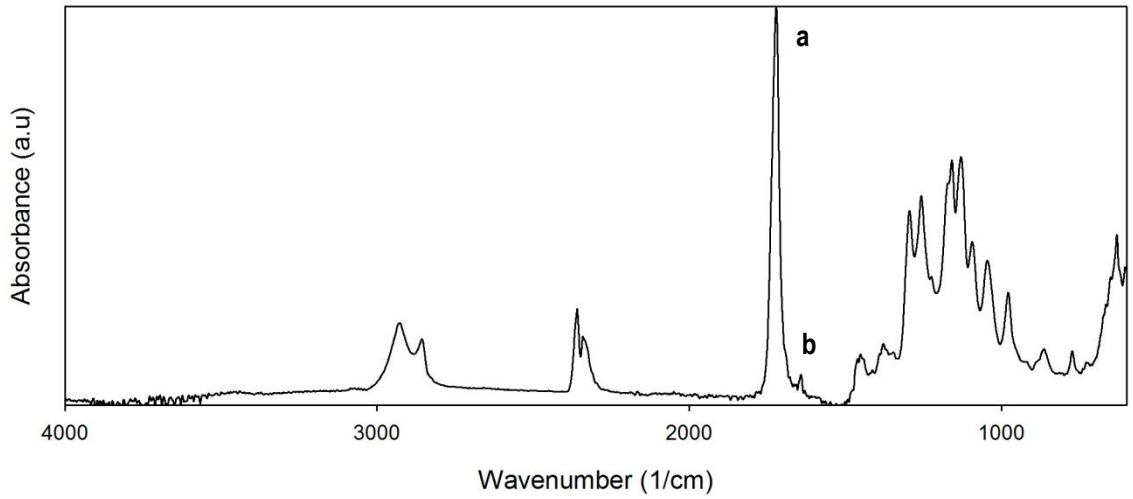


Figure 18. FTIR spectrum of UP 1.1 and the identification of the ester group (a) and the double bonds (b).

^{1}H NMR

Figure 19 presents the ^{1}H NMR spectrum of UP 1.1 and respective assignments. It is possible to see the proton resonances in accordance with the anticipated chemical structure, indicating the success of the reaction.

The UP 2.0 spectrum (Figure 20) showed unpredicted peaks at 6.18, 5.65, 3.50 e 3.20 ppm. The third value corresponds to unreacted DG, while the rest represent unreacted IA. The same formulation was polymerized again, but the UP 2.1 spectrum also showed some unreacted monomer.

Also UP 3.0 and 4.0 spectra seem to comprise some unreacted DG, although with less significance. As UP 1.1, also UP 5.1 did not present unreacted monomers (see Appendix B for the ^{1}H NMR spectra of UP 2.1, 3.0, 4.0 and 5.1).

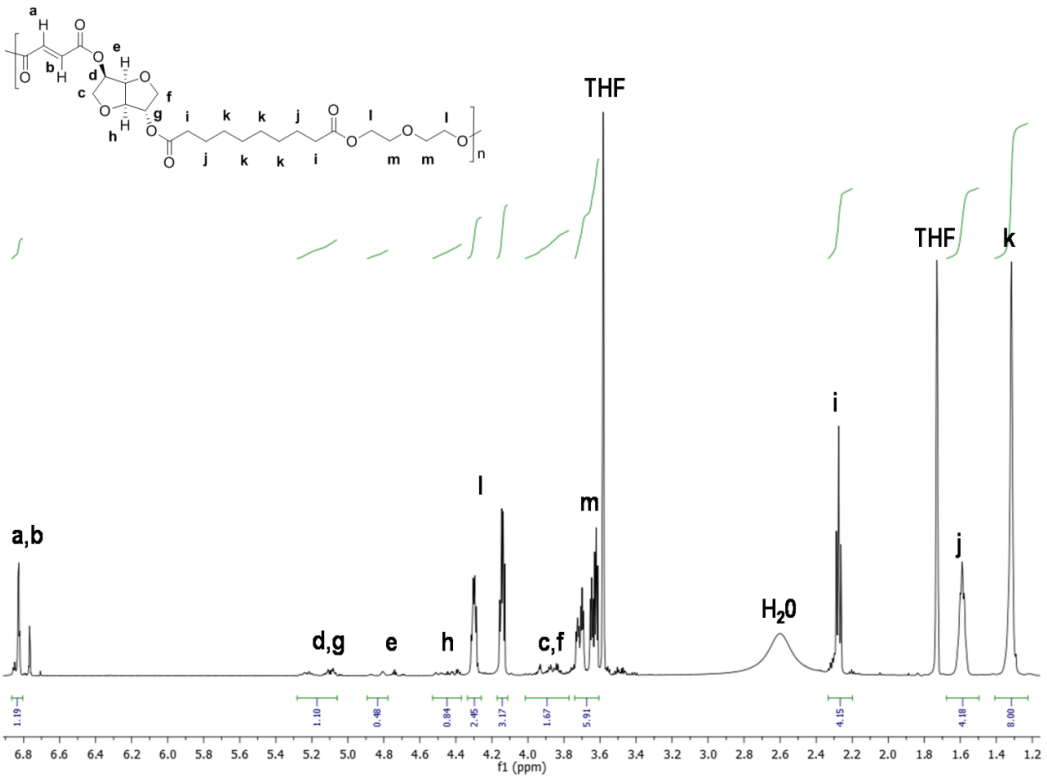


Figure 19. The ^{1}H NMR spectrum of UP 1.1 and the identification of the protons present in its chemical structure.

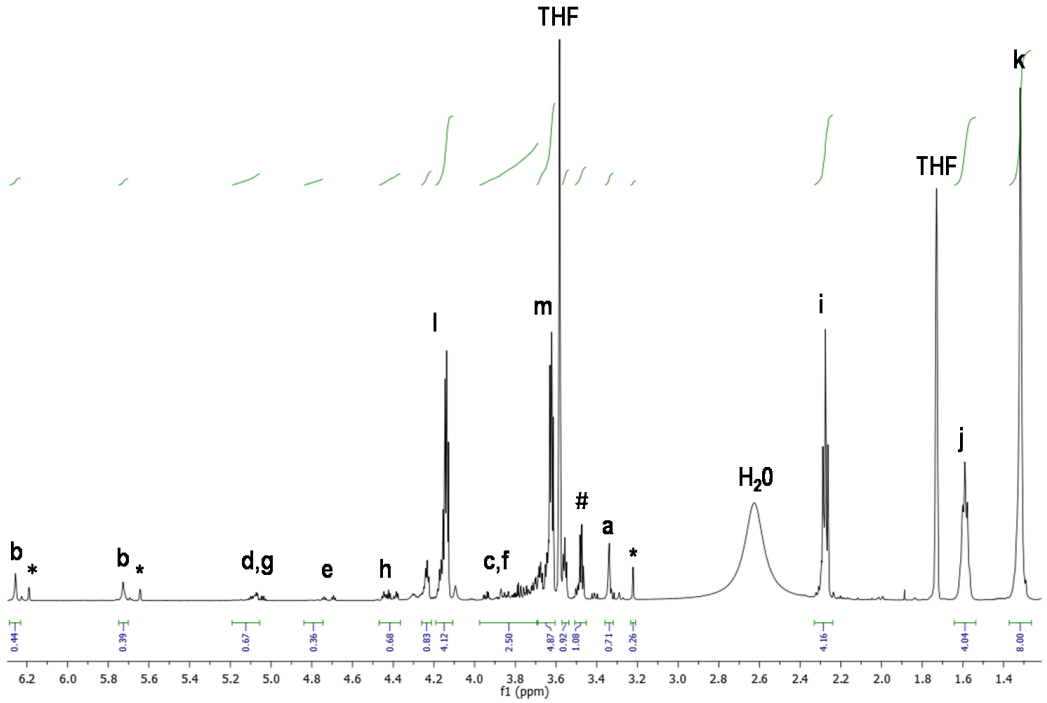


Figure 20. ^{1}H NMR spectrum of UP 2.0. The # and * symbols correspond to the unreacted diethylene glycol and itaconic acid, respectively.

The chemical composition of the UPs (calculated (C) from the ^{1}H NMR spectrum) is presented in Table 12 and compared to that used in the feed (F).

Table 12. Relative molar percentage of monomer used in the feed (F), calculated relative molar percentage of monomer present in each UP after synthesis (C) and the respective ratio between diols and diacids ($R_d/_d$).

UP	FA (%)		IA (%)		SA (%)		IB (%)		DG (%)		PG (%)		PDO (%)		$R_{d/d}$
	F	C	F	C	F	C	F	C	F	C	F	C	F	C	(%)
1.1	22,0	16,4		-	24,0	27,6	10,0	15,2	44,0	40,8	-	-	-	-	1,27
2.0	-	-	22,0	14,9	24,0	33,0	10,0	11,1	44,0	40,9	-	-	-	-	1,08
2.1	-	-	22,0	11,3	24,0	34,8	10,0	8,5	44,0	45,3	-	-	-	-	1,17
3.0	-	-	22,0	13,8	24,0	37,3	20,0	12,0	34,0	37,0	-	-	-	-	0,96
4.0	-	-	22,0	20,0	24,0	35,1	-	-	34,0	32,6	20,0	12,3	-	-	0,81
5.1	-	-	22,0	15,5	24,0	38,3	20,0	17,2	-	-	-	-	34,0	28,9	0,86

Looking to the Table 12, it is possible to see some differences between the values of molar percentages of the different monomers in the feed and in the final UP. The differences can be caused by the evaporation of some monomer during the reaction, loss of monomer during water distillation and errors inherent to the quantification by NMR. Also the fact that IB has two –OH groups (*endo* and *exo* positions) with different reactivities can contribute to the 'imbalance' of molar ratios in the final UP. It is interesting to note that SA has the highest value of molar percentage in the UP, which can be due to its high reactivity; and that DG is the one who has the most similar molar relative percentage values, although it was also the only one which presented unreacted amount most successively in UPs. This is an incoherency difficult to explain.

3.1.2. Molecular weight distribution

SEC

The molecular weight distribution was measured by SEC (conventional calibration). Figure 21 presents the RI normalized signal of the different UPs.

It is possible to see that all the UPs present a broad molecular weight distribution. The UP 2.0, UP 2.1, UP 3.0, UP 5.1 present additional shoulders, which indicates the presence of fractions of UP oligomers with very low molecular weight. UP 1.1 and UP 4.0 show the lowest values of retention time, meaning that these UPs have a higher molecular weight compared to UP 2.1, UP 5.1, UP 2.0 and UP 3.0.

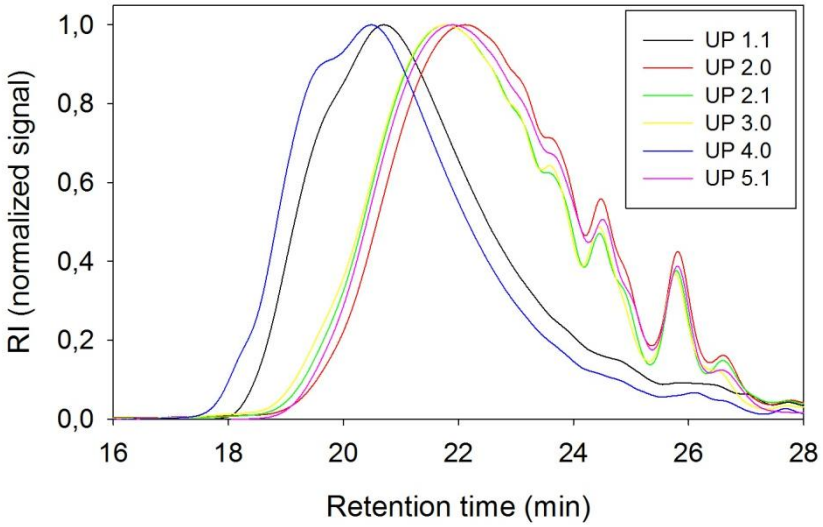


Figure 21. Molecular weight distribution of the UPs.

Table 13 presents the values of molecular weight and polydispersity index (PDI) of the UPs. The values were obtained from the conventional calibration.

Table 13. Number average molecular weight (M_n) of each UPs and their polydispersity index (PDI), according to conventional calibration.

UP	Formulation	M_n (g.mol^{-1})	PDI
UP 1.1	0.22 FA/0.24 SA/0.10 IB/0,44 DEG	3933	1,99
UP 2.0	0.22 IA/0.24 SA/0.10 IB/0.44 DEG	688	4,47
UP 2.1	0.22 IA/0.24 SA/0.10 IB/0.44 DEG	600	6,02
UP 3.0	0.22 IA/0.24 SA/0.20 IB/0.34 DEG	920	4,12
UP 4.0	0.22 IA/0.24 SA/0.20 PG/0.34 DEG	2020	5,05
UP 5.1	0.22 IA/0.24 SA/0.20 IB/0.34 PD	626	5,32

As can be seen from Table 13, UPR 1.1 and UPR 4.0 show the highest values of molecular weight, whereas the other UPs present a significantly lower value of molecular weight. This can be tentatively assigned to some differences in reactivity of the different monomers. The UPs show high values of PDI, which was expected since all the UPs were prepared from polycondensation reactions. Such reactions are known to provide polymers with broad molecular weight distributions.

3.1.3. Thermal and mechanical properties

SDT

The thermal stability and thermal events of the UPs were evaluated by simultaneous thermal analysis (TGA/DSC) in a 25-600ºC range. Figure 22 gives a global view of the thermal behavior of UP 1.1.

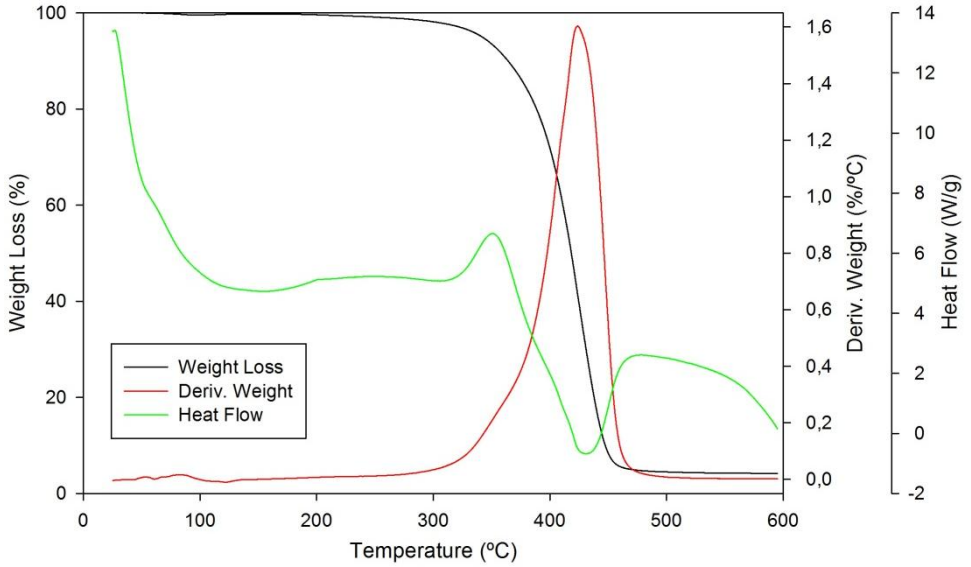


Figure 22. Simultaneous (DSC and TGA) thermoanalytical curves of UP 1.1.

It is possible to see that UP1.1 degrades in a single stage and presents an amorphous nature, since no transitions below the degradation temperature are detected in the heat flow curve. The remaining UPs present a similar profile (see Appendix C, for the thermoanalytical curves). Table 14 summarizes the relevant temperatures taken from the thermoanalytical curves.

Table 14. Characteristic quantities (average and standard deviation) obtained from TGA, DTGA and DSC data. T_{on}: extrapolated onset temperatures (TGA); $T_{5\%}$: temperature corresponding to 5% of mass loss; $T_{10\%}$: temperature corresponding to 10% of mass loss; T_p: peak temperature (DTGA); T_{deg}: degradation temperature of the UPs (DSC).

UP	Formulation	T_{on} (ºC)	$T_{5\%}$ (ºC)	$T_{10\%}$ (ºC)	T_{peak} (ºC)	T_{deg} (ºC)
1.1	0.22 FA/0.24 SA/0.10 IB/0,44 DG	386,9±1,9	344,5±3,5	364,9±1,0	425,1±0,8	434,4±3,6
2.0	0.22 IA/0.24 SA/0.10 IB/0.44 DG	394,2±1,9	308,3±6,3	233,6±17,7	430,5±0,4	436,4±0,8
2.1	0.22 IA/0.24 SA/0.10 IB/0.44 DG	388,6±1,9	250,8±6,8	320,5±10,8	431,0±0,4	439,0±2,8
3.0	0.22 IA/0.24 SA/0.20 IB/0.34 DG	390,3±3,0	279,0±3,9	337,4±3,3	430,5±2,0	435,8±0,0
4.0	0.22 IA/0.24 SA/0.20 PG/0.34 DG	382,0±2,3	331,2±8,3	361,2±4,7	430,7±0,8	443,7±4,8
5.1	0.22 IA/0.24 SA/0.20 IB/0.34 PDO	381,4±1,4	249,1±20,0	330,0±7,1	415,4±0,8	416,6±1,6

All the UPs are thermally stable until *ca.* 390ºC (T_{on} values) and degrade in a temperature range of 420-440ºC (T_{deg}). UP 1.1 and UP 4.0 show the highest values of T_{on}, $T_{5\%}$, $T_{10\%}$ and T_{deg}, indicating their higher thermal stability, which can be related to their higher molecular weight (see Table 13) relatively to the remaining UPs. UP 2.0, UP 2.1, UP 3.0 and UP 5.1 present $T_{5\%}$ and $T_{10\%}$ significantly lower than those of UP 1.1 and UP 4.0, which can be related to the evaporation of residual monomer present within the UPs. Nevertheless, if one takes only the T_{on} as the index of thermal stability no significant differences are seen. This suggests that changes in the 'core' composition of the UPs do not change significantly their thermal stability.

DMTA

The DMTA results show that all UPs experience a glass transition (see Appendix D for DMTA traces) between -30ºC and -22ºC (Table 15).

Table 15. Glass transition temperature (T_g) of the UPs.

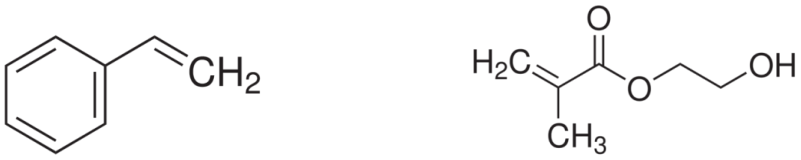
UP	Formulation	T_g (ºC)
UP 1.1	0.22 FA/0.24 SA/0.10 IB/0,44 DG	-21,7
UP 2.0	0.22 IA/0.24 SA/0.10 IB/0.44 DG	-37,3 | -12,1
UP 2.1	0.22 IA/0.24 SA/0.10 IB/0.44 DG	-37,4 | -13,0
UP 3.0	0.22 IA/0.24 SA/0.20 IB/0.34 DG	-30,0
UP 4.0	0.22 IA/0.24 SA/0.20 PG/0.34 DG	-32,5
UP 5.1	0.22 IA/0.24 SA/0.20 IB/0.34 PDO	-28,0

UP 1.1 presents the highest value of T_g, which can be related with its high molecular weight. Nevertheless, one should have in mind that this UP has embedded double bonds along the structure, which increases the stiffness of the polymeric chain and consequently the T_g. UP 2.0, UP 2.1 and UP 5.1, which have similar molecular weights, show some differences in their T_g values; UP 5.1 shows a T_g 10ºC higher than that of UP 2.0 and UP 2.1. This can be attributed to the absence of DG and consequently to the higher flexible ether linkages, in the structure of UP 5.1. Regarding the influence of the amount of IB in the UP, it is possible to see that UP 3.0 has a higher T_g (*ca.* 8ºC higher than UP 2.0 and UP 2.1). The increase in the IB amount, due to its rigid cyclic structure, increases the stiffness of the UP, with a concomitant increase in the T_g value. However, the fact that UP 3.0 has a molecular weight higher than UP 2.0 and UP 2.1 cannot be neglected, and can also have influence in the T_g values. Interesting to note that UP 4.0, whose molecular weight is substantially higher than that of UP 3.0, has a T_g lower than UP4.0. This fact can be attributed to the presence of IB in the structure of UP 3.0, whose cyclic structure provides additional stiffness to the UP.

The two transitions observed for UP 2.0 and UP 2.1 are unexpected and no valid reason was found for such behavior.

3.2. UPRs production and characterization

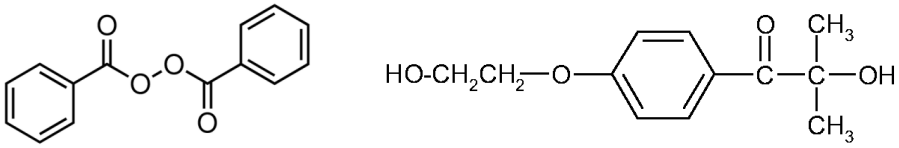
Styrene (Figure 23a) is the reactive solvent most used in UPRs production, as mentioned before. However, regarding its toxicity and the lack of biocompatibility, it had to be substituted. HEMA (Figure 23b) was the chosen solvent. Although it is not from renewable sources, HEMA is widely used in biomedical applications, such as contact lenses, dressings, drug delivery and tissue engineering, and has proven its potential as a very biocompatible monomer [75]. Samples with different amounts of HEMA were prepared in order to study its influence in the final properties of the resins (see Table 9 of *Materials and Methods*).



a) b)

Figure 23. Chemical structures of styrene (a) and HEMA (b).

Samples were cured by two different methods - thermal crosslinking and photocrosslinking – in order to compare their behavior and analyze their impact in resins final properties. Regarding the thermal crosslinking reaction, the most common initiators are peroxides [73], including BPO. Although it is non-biocompatible, BPO (Figure 24) it highly reactive and has low activation energy [68] – reason why it is widely used. Considering photo curing reaction, Ir-2959 (Figure 24b) was the selected, from a group of others photoinitiators previously tested [47]. It seems to be more biocompatible [47], since it has been use in food packing [76], very reactive and already used in UP functionalization [76]. The amount of initiator was kept constant (3% w/w).



a) b)

Figure 24. Chemical structures of BPO (a) and Ir-2959 (b).

3.2.1. Gel content

Table 16 and Figure 25 compare the gel content of the different formulations tested, both by thermal crosslinking and photocrosslinking.

Table 16. Gel content percentages of all thermal (T) and photocrosslinked (P) UPRs.

	1.0	**1.1**	**1.2**	**2.0**	**2.1**	**2.2**	**3.0**	**3.1**	**3.2**
T (%)	99,9	97,5	95,8	74,5	75,4	73,1	80,7	75,7	71,1
P (%)	91,5	82,0	80,7	82,8	76,8	72,5	68,7	73,4	69,6

	4.0	**4.1**	**4.2**	**5.0**	**5.1**	**5.2**	**7.0**	**7.1**	**7.2**
T (%)	95,3	93,3	92,7	83,4	78,0	75,1	87,9	82,7	77,2
P (%)	84,5	91,2	89,1	84,6	76,5	71,8	84,0	77,1	77,8

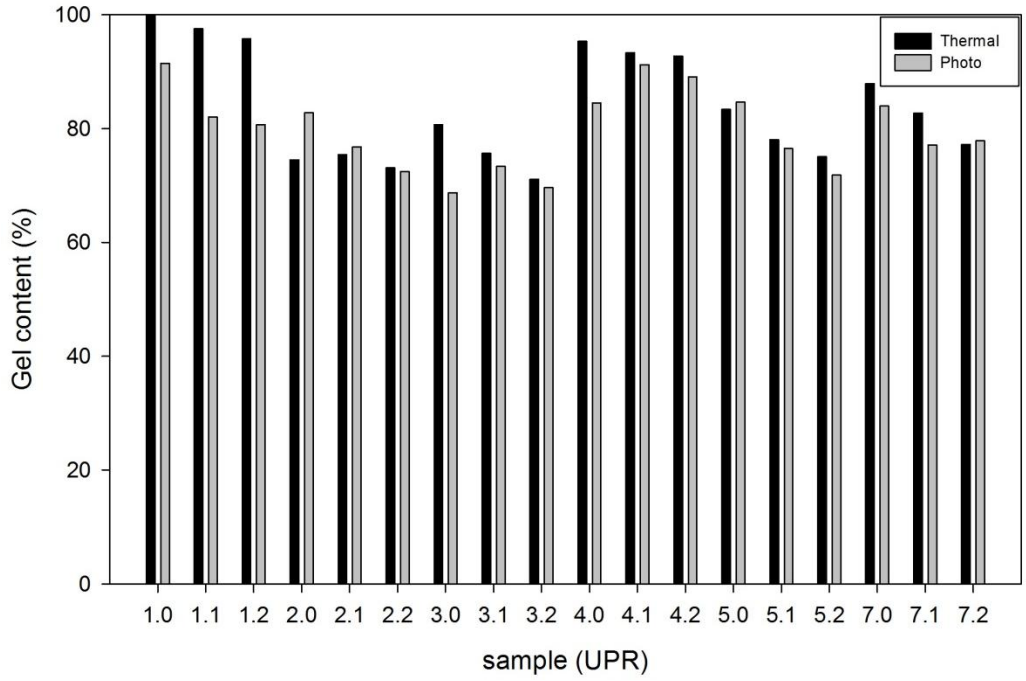


Figure 25. Gel content of all UPRs samples.

In general, the UPR 1 samples presented the higher gel content (≥95%), meaning that those samples present highly crosslinked networks, i.e., with less uncrosslinked monomer and UP. The UPR 1 series were obtained from the UPs 1.1, whose double bonds were embedded in the structure. For that reason, they were more sterically hindered and less reactive, when compared to the double bond of IA, present in the remaining formulations. Thus, it was expected that UPR 1 series presented the formulations with lower gel content but, surprisingly, this did not occur. It is not possible to explain such phenomenon due to the lack of information about the performance of these two unsaturated diacids in crosslinking reactions of UPRs.

The results also demonstrate that the crosslinked networks (UPR 1 and UPR 4) obtained from the UPs with the highest molecular weight (UP 1.1 and UP 4.0) presented high values of gel content. This can be ascribed to the higher amount of double bonds present in the polymeric chain, which in turn leads to a higher amount of crosslinking points.

The series UPR 2, UPR 3, UPR 5 and UPR 7 presented percentages around 70 to 85% of gel content. Such crosslinked networks were prepared from UPs (UP 2.0, UP 3.0, UP 2.1 and UP 5.1, respectively) that had very similar composition; the differences lie on the diol used in UP 5.1 (PDO instead of DG) and the diols percentages tried in each formulation. No information in the literature was found regarding the diols effect in the gel content of UPRs, and because of that, it is not possible to justify the gel content results of the above mentioned UPRs.

Analyzing the differences between series, a decrease in the gel content when the amount of HEMA also diminishes is noticed in almost all UPRs samples. This reveals the importance of the reactive monomer role in the crosslinking reactions of UPs.

Regarding the type of curing reaction, it is clear that the majority of thermally cured UPRs samples presented higher gel content percentages when compared to photo cured ones. Only the UPR 2 and UPR 5 seemed to diverge, in particular, in series 0. The fact that radiation can be less effective reaching all areas of the samples, internal and superficial, could be the justification for this outcome.

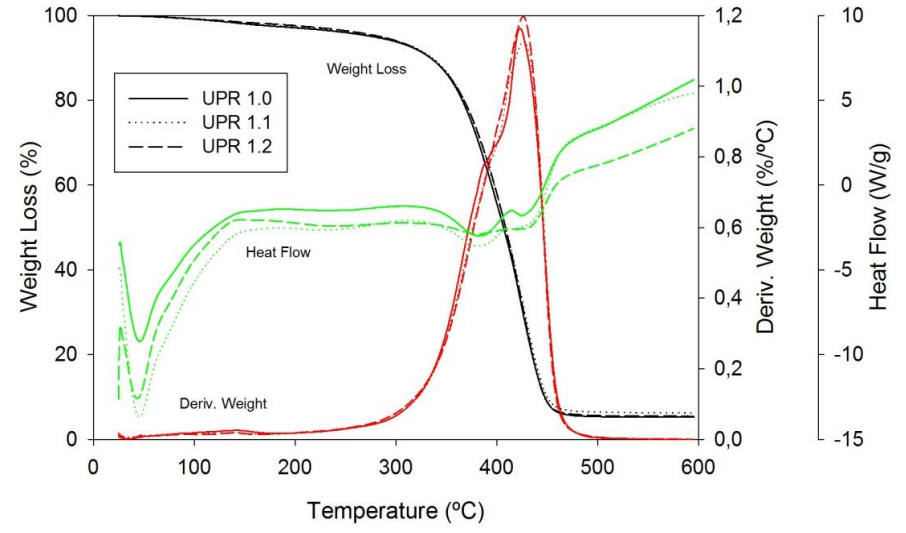
Thus, it can be assumed that a higher amount of HEMA and the thermal curing method are key parameters in what concerns the gel content of the UPRs. However, the chemical composition of the UPs is another parameter that has also a significant influence in the gel content.

Taking into account that the best results were obtained by thermal crosslinking, only the thermally crosslinked networks were further analyzed.

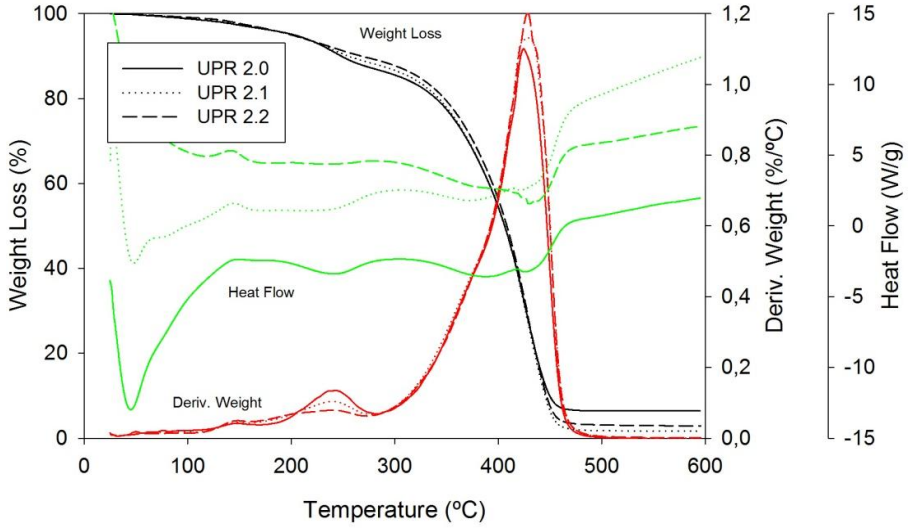
3.2.2. Thermal and mechanical properties

SDT

The thermal stability and thermal events of the UPRs were evaluated by simultaneous thermal analysis (TGA/DSC) in a 25-600ºC range. Figure 26 gives a global view of the thermal behavior of UPR 1 (Figure 26a) and UPR 2 (Figure 26b).



a)



b)

Figure 26. Simultaneous (DSC and TGA) thermoanalytical curves of UPR 1 (a) and UPR 2 (b).

The thermoanalytical curves of UPR 1 shows a main stage of weight loss with a very small shoulder between 100 ºC and 200ºC, and a similar profile was found in the UPR 4 and UPR 7 series (see Appendix C). In turn, UPR 2 presents two stages of weight loss and a similar behavior was found for the series UPR 3 and UPR 5. It is interesting to note that the UPRs that exhibit one main stage of weight loss were those that presented higher values of gel content. Since the crosslinked network is 'tighter' in this case, the existence of small molecules or oligomers of very low molecular weight is more unlikely. For that reason, all the 'components' in the crosslinked network will be degraded nearly at the same time. In the case of UPR 2, UPR 3 and UPR 5, the formation of small oligomers that are not embedded in the crosslinked

network can occur, since they have lower values of gel content when compared with the UPRs mentioned above. These small oligomers can be degraded in an early stage of the test, justifying this way the results.

Regarding the heat flow curves, it is possible to see that no thermal event occurs besides thermal degradation, meaning that the crosslinked networks have an amorphous nature, as expected.

Table 17 summarizes the relevant temperatures taken from the thermoanalytical curves.

Table 17. Characteristic quantities (average and standard deviation) obtained from TGA, DTGA and DSC data. T_{on}: extrapolated onset temperatures (TGA); $T_{5\%}$: temperature corresponding to 5% of mass loss; $T_{10\%}$: temperature corresponding to 10% of mass loss; T_p: peak temperature (DTGA); T_{deg}: degradation temperature of the UPRs (DSC).

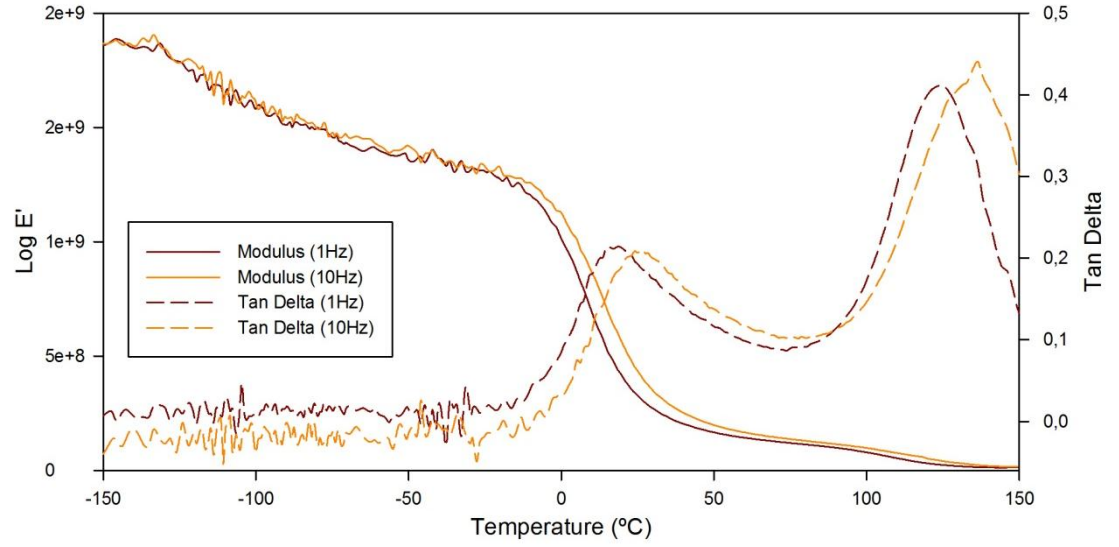
UPR	$T_{on\ I}$ (ºC)	$T_{on\ II}$ (ºC)	$T_{5\%}$ (ºC)	$T_{10\%}$ (ºC)	$T_{peak\ I}$ (ºC)	$T_{peak\ II}$ (ºC)	$T_{deg\ I}$ (ºC)	$T_{deg\ II}$ (ºC)
1.0	-	351,3±0,4	278,6±1,3	335,5±1,2	392,5±3,6	423,7±0,4	-	385,7±1,3
1.1	-	349,3±1,2	296,6±20,2	340,4±6,6	390,8±1,2	425,9±1,2	-	384,6±1,0
1.2	-	368,5±2,4	284,9±3,0	332,8±3,1	-	424,2±4,4	-	414,9±2,4
2.0	196,0±0,7	381,2±0,1	203,5±2,1	251,2±1,2	241,6±0,4	425,1±1,6	240,7±0,8	388,8±4,8
2.1	181,3±0,5	380,5±1,6	197,8±5,2	247,9±11,5	236,8±5,6	429,0±0,0	213,8±2,8	363,5±11,6
2.1	153,2±9,9	380,0±2,3	191,4±12,7	257,4±15,6	233,9±4,8	427,3±1,6	-	431,0±1,2
3.0	197,1±5,2	382,2±1,2	218,4±11,9	268,6±15,1	245,3±3,2	427,1±0,4	246,1±3,6	430,0±2,0
3.1	190,0±12,1	384,2±1,0	213,75±2,6	285,1±5,5	237,3±0,8	432,1±1,2	224,0±5,2	435,6±1,2
3.2	181,1±14,8	387,19±4,6	218,0±9,2	294,9±7,0	237,0±4,4	428,8±3,6	232,8±3,2	430,5±2,8
4.0	-	343,4±1,5	238,1±4,3	318,7±2,7	388,2±0,8	426,2±0,8	-	381,4±0,8
4.1	-	368,2±3,2	268,0±17,0	326,4±3,0	145,5±1,6	428,5±0,8	-	381,1±0,4
4.2	-	371,6±0,1	280,4±5,4	334,8±3,2	145,7±0,4	430,7±1,6	-	381,4±1,6
5.0	186,0±1,8	376,2±0,6	205,7±3,4	264,4±0,6	242,7±1,2	428,5±5,6	-	383,2±2,4
5.1	127,2±2,5	380,3±1,4	205,5±5,7	267,2±3,9	240,2±0,0	427,3±2,4	-	398,7±5,2
5.2	151,1±14,6	381,3±0,2	207,6±2,2	288,8±3,9	147,2±1,6	426,5±4,4	-	433,0±0,8
7.0	-	374,3±0,3	181,4±3,5	285,4±0,6	247,5±1,6	419,7±0,4	-	393,3±2,4
7.1	-	371,6±0,3	194,7±4,6	289,8±4,3	245,6±2,0	420,0±3,2	-	400,4±2,0
7.2	-	373,8±0,5	213,3±16,6	302,5±10,6	246,4±2,4	418,5±1,2	-	406,9±2,4

UPR 1, UPR 4 and UPR 7 are thermally stable until *ca.* 350ºC ($T_{on\ II}$), whereas UPR 2, UPR 3 and UPR 5 start to degrade at *ca.* 150-190ºC ($T_{on\ I}$). The reason for such behavior was previously discussed. It is interesting to observe that the main stage of weight loss in UPRs occurs at temperatures lower than those observed in the respective UPs. This seems somewhat contradictory, since the expected was to find a higher thermal stability in crosslinked network analysis compared to its uncrosslinked counterpart. However, in this case, it should not be forgotten that a reactive solvent was added and low molecular weight oligomers can be formed. Moreover, these oligomers can be one side bonded to the 3D network, starting to degrade earlier. This behavior is consistent with some studies reported in literature [47, 68, 77].

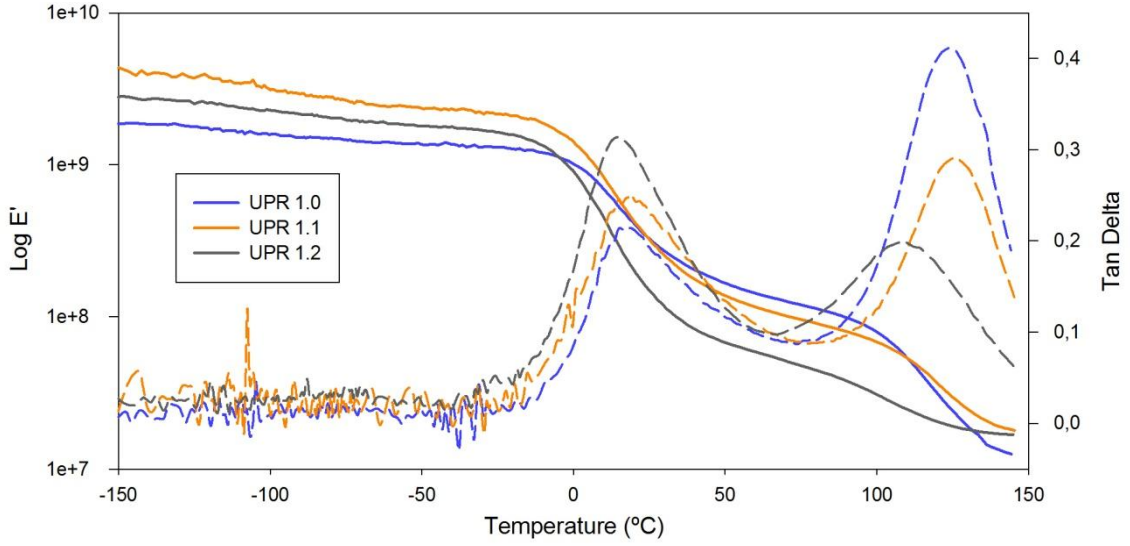
DMTA

Figure 27 presents the DMTA traces of the UPR prepared from the crosslinking reaction of UP 1.1 with different amounts of HEMA (the DMTA traces of the remaining UPRs are shown in Appendix D). Table 18

presents the values of T_g of all the UPRs, along with the values of elastic modulus (E') at different temperatures.



a)



b)

Figure 27. DMTA traces of UPR 1.0 at different frequency (1 and 10Hz) (a) and DMTA traces of UPR 1 with different amounts of HEMA at 1Hz (b).

Figure 27 demonstrates that the UPR 1.0, UPR 1.1 and UPR 1.2 present two distinct T_g, which indicates the presence of two different crosslinked phases. In Table 18, it is possible to observe a decrease in the higher T_g value as the amount of HEMA decreases in the formulation. Regarding the E' values, it is difficult to find a tendency between the E' value and the type of formulation or amount of HEMA at -50ºC. However, at temperatures above 0ºC it is possible to establish a relationship between E' value and the HEMA amount: E' value decreases when the HEMA amount also decreases in the formulation, which

indicates that the formulations with less amount of HEMA are less rigid. Concerning the effect of the type of UP, it is possible to see that the UPR 1, UPR 4, and UPR 7 have the highest values of E', showing a more rigid character. This can be related with their high values of gel content.

Table 18. Main values obtained from DMTA data. T_g: glass transition temperature; $E'_{-50°C:}$ modulus at -50ºC; $E'_{0°C:}$ modulus at 0ºC; $E'_{37°C:}$ modulus at 37ºC; $E'_{50°C:}$ modulus at 50ºC.

Formulation	T_g (ºC)	$E'_{-50°C}$ (MPa)	$E'_{0°C}$ (MPa)	$E'_{37°C}$ (MPa)	$E'_{50°C}$ (MPa)
UPR1.0 (50 IL1/50HEMA)	14,6 | 120,0	1361,0	1014,0	219,4	166,7
UPR1.1 (63IL1/37HEMA)	15,0 | 122,4	2353,6	1422,0	193,4	138,1
UPR1.2 (75IL1/25HEMA)	12,6 | 110,3	1795,9	908,9	90,5	67,9
UPR2.0 (50IL2/50HEMA)	-4,8 | 83,6	1163,1	297,0	86,0	51,4
UPR2.1 (63IL2/37HEMA)	-8,5 | 55,6	1043,8	172,5	35,5	19,7
UPR2.2 (75IL2/25HEMA)	-2,8 | 22,0	1477,7	71,1	9,7	5,3
UPR3.0 (50IL3/50HEMA)	-10,3 | 96,8	916,0	231,8	75,6	55,0
UPR3.1 (63IL3/37HEMA)	-6,7 | 78,9	1129,4	178,7	43,3	27,9
UPR3.2 (75IL3/25HEMA)	-6,7 | 59,1	1701,0	77,4	13,5	8,3
UPR4.0 (50IL4/50HEMA)	-8,3 | 112,5	1114,0	356,3	172,8	137,9
UPR4.1 (63IL4/37HEMA)	-11,9 | 98,7	1828,5	282,3	87,0	63,0
UPR4.2 (75IL4/25HEMA)	-11,0 | 57,9	1976,0	215,3	42,4	29,0
UPR5.0 (50IL2.1/50HEMA)	-18,3 | 91,9	985,8	280,6	104,8	72,1
UPR5.1 (63IL2.1/37HEMA)	-12,9 | 85,5	890,9	130,8	38,1	23,7
UPR5.2 (75IL2.1/25HEMA)	-13,8 | 44,5	1900,5	77,5	11,1	6,7
UPR7.0 (50IL5.1/50HEMA)	-1,3 | 96,8	1018,8	361,5	111,2	83,0
UPR7.1 (63IL5.1/37HEMA)	-1,7 | 80,7	1900,0	461,5	81,7	49,6
UPR7.2 (75IL5.1/25HEMA)	-4,4 | 33,0	1595,1	170,0	15,6	7,8

3.2.3. Swelling capacity

The swelling capacity of all UPRs was evaluated in PBS (pH 7.4) at 37ºC. In general, the UPR 1 was the group of samples which swelled less ($\leq$15%), while UPR 3 was the one which swelled more ($>$18%). UPR 2, UPR 7, UPR 4 and UPR 5 followed the UPR 3, respectively, showing intermediate values of swelling capacity (15-18%), as it can be verified in Appendix E. The amount of HEMA and the combination of monomers and their hydrophilicity are the explanation for these different outcomes, as discussed further on. It should be pointed out that the low values of swelling capacity that are observed indicate a highly hydrophobic nature of the UPRs.

The increase of HEMA amount in the formulations affected significantly the swelling capacity of all UPRs. In Figure 28, it can be seen the absorption percentage of UPR 1 rising faster in sample 0 (50% HEMA) in comparison to samples 1 (37% HEMA) and 2 (25% HEMA). The others UPRs showed the same trend and this behavior can be justified by the increased amount of HEMA. Being a highly hydrophilic molecule, an increase in its content turns the UPR more hydrophilic, and therefore, more able to swell.

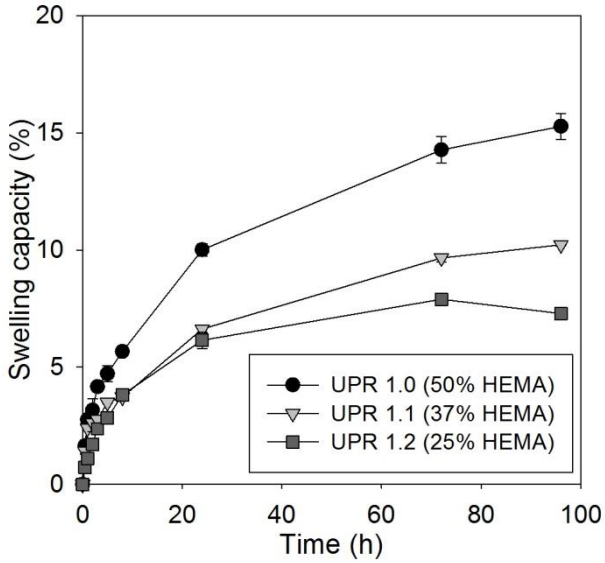


Figure 28. Swelling capacity of UPRs 1.0, 1.1 and 1.2 (HEMA amount effect).

The different amounts of IB used in UPs 2.0, 2.1 and 3.0 seemed to not affect significantly the performance of their respectively UPRs 2, 5 and 3, at least considering a 10% difference in the amount used. As the Figure 29 shows, there are no clear and standardized differences in the group of samples 0, 1 or 2.

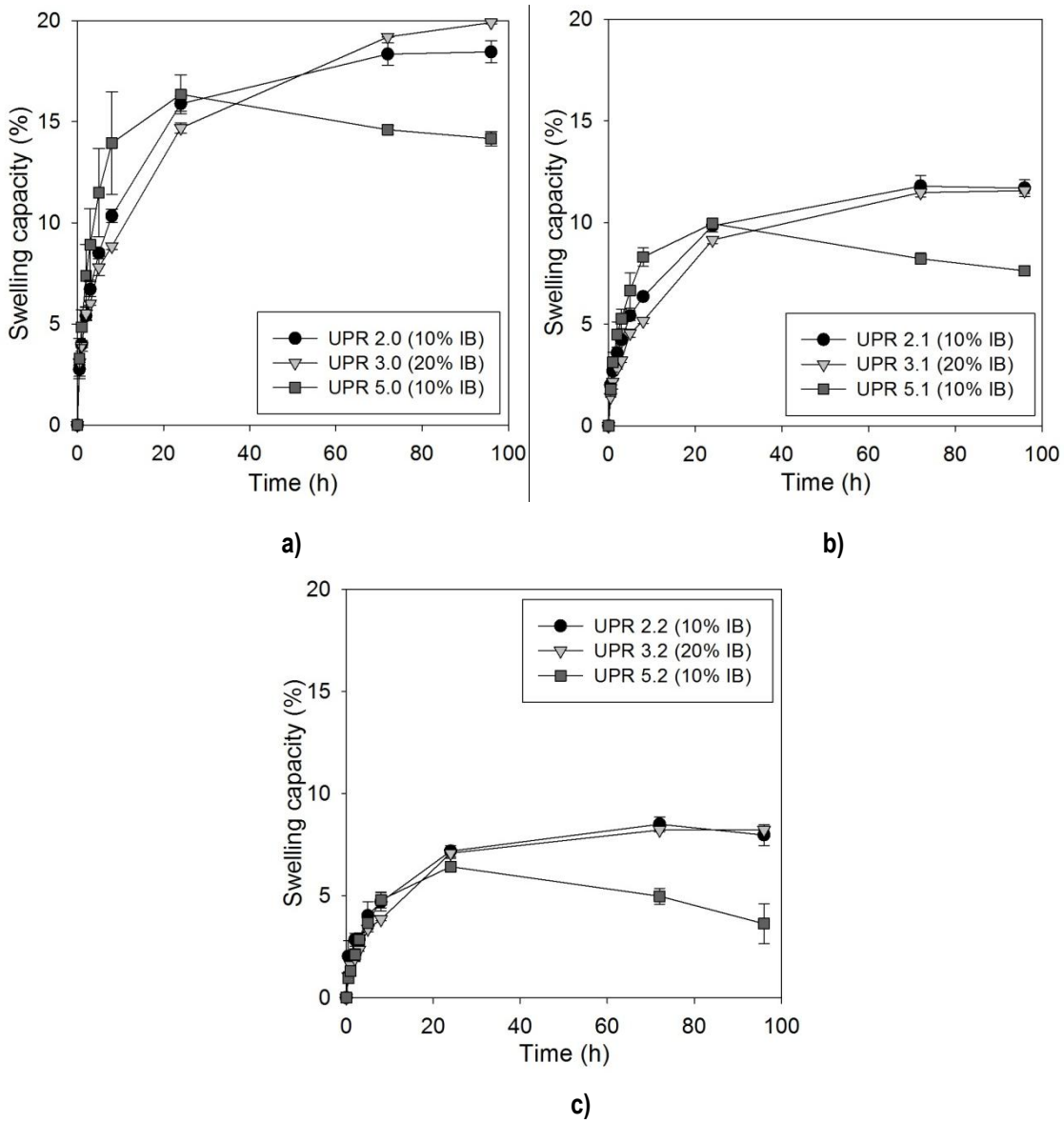


Figure 29. Swelling capacity of samples 0 (a), 1 (b) and 2 (c) from UPRs 2, 3 and 5 (IB amount effect).

In order to analyze the influence of the unsaturated diacids in the swelling capacity, a comparison between the series UPR 1, 2 and 5 was performed. Due to the unexpected behavior of UPR 5[13], only the series UPR 1 and UPR 2 will be compared. As it can be seen in Figure 30, UPR 1 presents a lower swelling capacity in all the tested HEMA percentages, which can be directly related to the higher gel content of UPR 1 series. This leads to the idea that the 'tighter' crosslinked networks have less ability to swell.

[13] The samples of UPR 5 are submitted to the swelling capacity test four times, due to the very incoherent profiles and values recorded each time. The profile presented was the most viable group of data, although it has become clear its insufficient reliability in order to formulate conclusions, compared to the other UPRs.

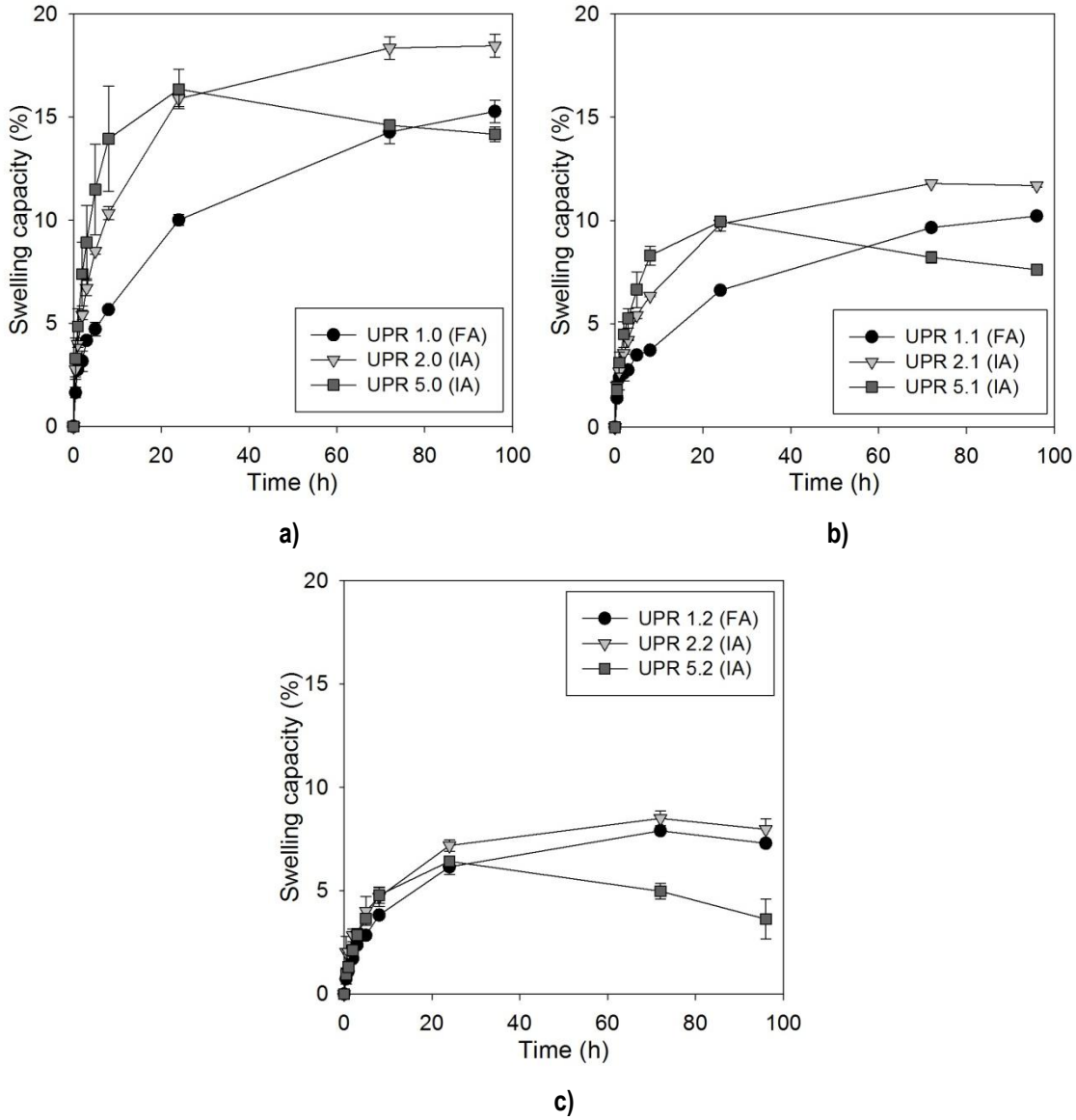


Figure 30. Swelling capacity of samples 0 (a), 1 (b) and 2 (c) from UPRs 1, 2 and 5 (diacids effect).

The diols seem to have little influence the swelling capacity of the resin, because only marginal variations were observed (Figure 31). Nevertheless, such differences will be tentatively explained. Regarding the series 0 (Figure 31a), it is possible to see that UPR 3.0 has the highest swelling capacity followed by UPRs 4.0 and 7.0. In this series, it is possible to infer the influence of the presence of different diols in UPR 4.0 and UPR 7.0. Taking into account the gel content values (Figure 25), it is expected that UPR 4.0 presents a lower swelling capacity compared to UPR 7.0, but this fact is not verified. Thus, this difference in the swelling capacity might be explained by the different diols used in the UP formulation, from which the UPRs were obtained. UPR 4.0 was obtained from the crosslinking of UP 4.0, which contains PG (20% molar) and DG (34% molar) as diols, whereas UPR 7.0 was obtained from the crosslinking of UP 5.1, which comprises IB (20% molar) and PDO (34 % molar). Since the amount of hydrophilic diol (DG) in UPR

4.0 is higher than in UPR 7.0 (IB), the former should be more hydrophilic than the latter, and therefore, its swelling capacity higher than that of series UPR 7.0. Concerning the series 1 and 2, attention will be focused on UPR 7 and UPR 3. The series UPR 3 present a gel content lower than that of series UPR 7, and therefore, it is expected that the former shows a swelling capacity higher than the latter. However this is not verified and can be a consequence of the different diols used in the synthesis of the UPs. In the series UPR 7, besides IB, PDO is used. In turn, in the series UPR 3, besides IB, DG is used. Taking into account the obtained results, it can be said that PDO turned UPR 7 series more hydrophilic, increasing their swelling capacity.

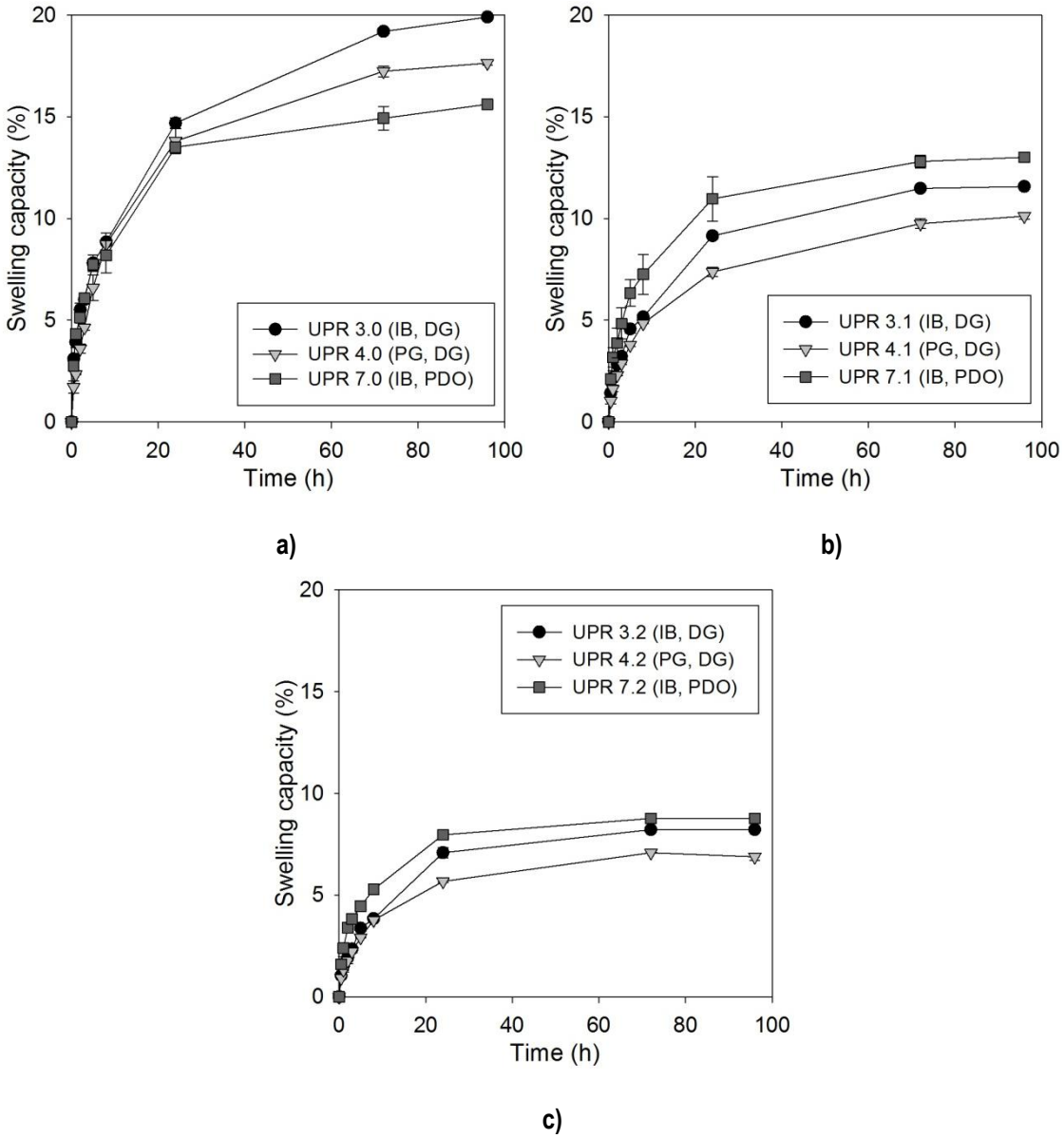


Figure 31. Swelling capacity of samples 0 (a), 1 (b) and 2 (c) from UPRs 1, 2 and 5 (diols effect).

3.2.4. In vitro hydrolytic degradation

The *in vitro* hydrolytic degradation behavior of the UPRs was evaluated in PBS (pH 7.4) at 37 ºC, for 50 days. In general, UPR 1 series was the one that presented lower values of weight loss ($\leq$ 2%), followed by UPR 4 (2-3%). The remaining UPRs lost around 6% to 9% of their masses. UPR 3 was the only one which had a profile more divergent and unclear, while UPR 2, 5 and 7 presented more regular and similar values (6-9%). The lower values of weight loss in aqueous medium are intimately related to the low swelling capacity of the UPRs, since degradation is hydrolytic. The less UPR can absorb/swell, the lower is the number of linkages liable to degrade (i.e., the area and weight to be lost), because the penetration of the medium within the network is more difficult.

Figure 32 presents the weight loss profile of UPR 1 series. The weight loss profiles of the remaining UPRs are shown in Appendix F.

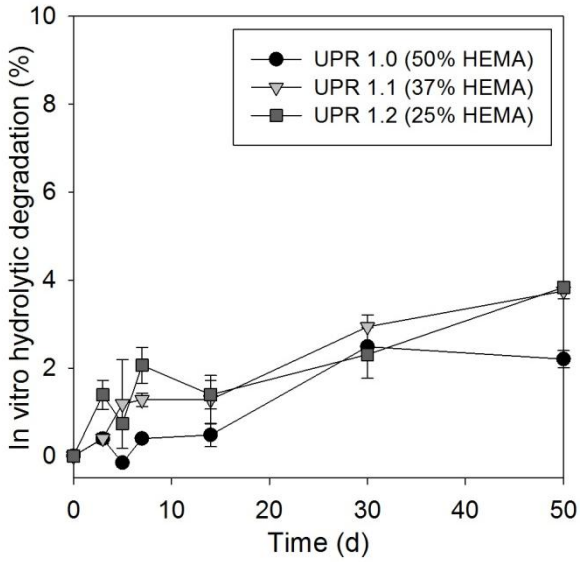


Figure 32. *In vitro* hydrolytic degradation analysis of the UPR 1 (HEMA amount effect).

It is possible to notice that the UPR containing the higher amount of HEMA in the formulation (UPR 1.0, 50% HEMA) has the lowest value of i*n vitro* hydrolytic degradation. In this case, the linkages (ester linkages belonging to the UP segments) are stronger and less available to be degraded, and therefore, the overall weight loss of the UPR is kept in very low values. It should be also pointed out that the segments of poly(HEMA) formed during the crosslinking reaction do not degrade in the conditions used to perform the *in vitro* hydrolytic degradation test.

The different diacids and diols have a pronounced effect in UPRs degradation behavior. There is an evident gap of 4%, approximately, between their profiles. The FA containing UPRs (UPR 1) degrade less, when compared to the other formulations (Figure 33), which can be directly related to their lower swelling

capacity. In the formulations containing IA, the most resistant to *in vitro* hydrolytic degradation are UPR 4 series (Appendix F), which once again can be related to their high gel content and low swelling capacity when compared to the other UPRs.

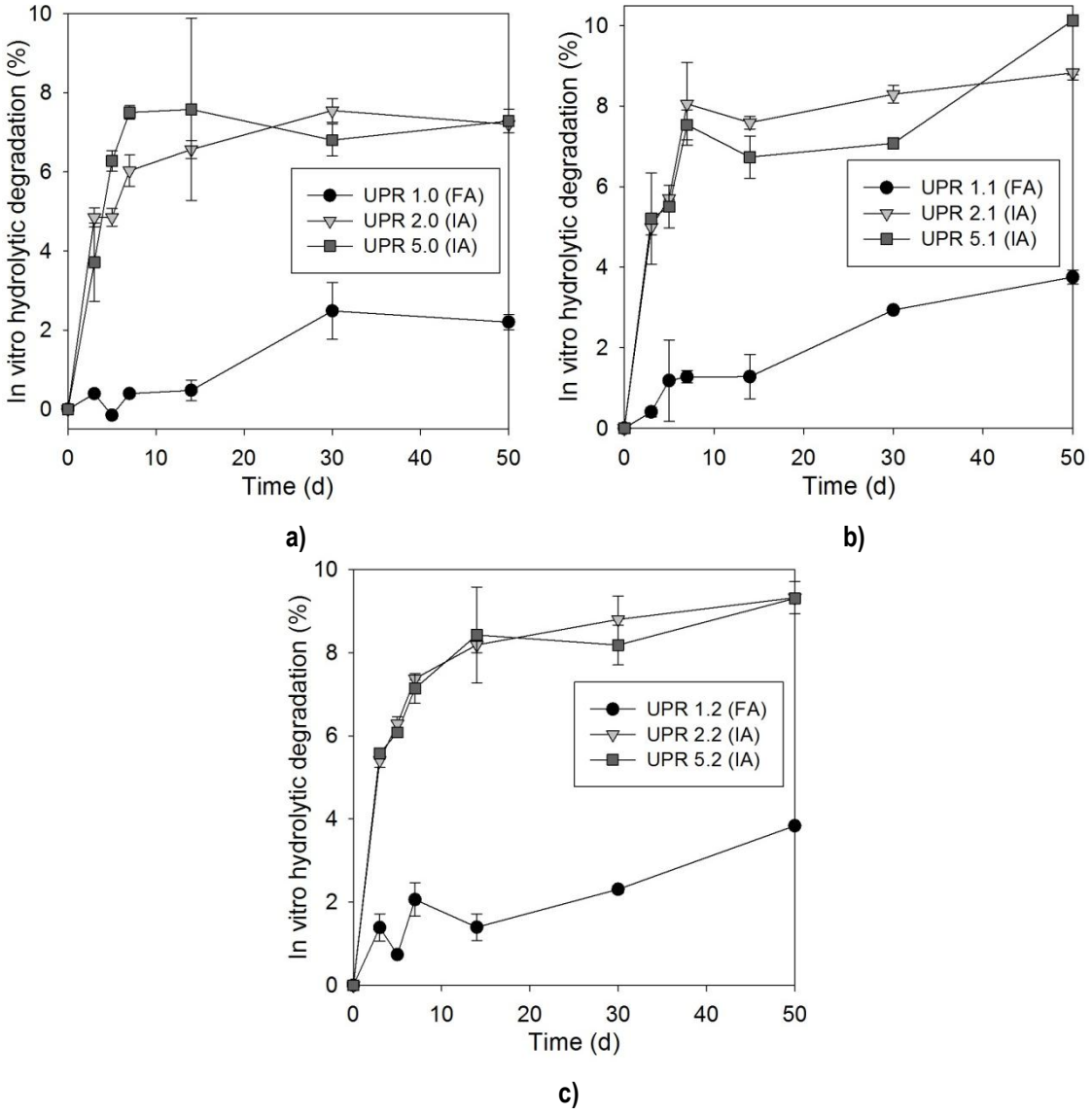


Figure 33. *In vitro* hydrolytic degradation analysis of samples 0 (a), 1 (b) and 2 (c) from UPRs 1, 2 and 5 (diacids effect).

Regarding the effect of the diols, conclusions about the way how they can tune the degradability of the UPRs is hard to be taken from the obtained results. Nevertheless, when UPR 3 and UPR 7 series are compared (Figure 34), it is possible to observe that the former is more susceptible to degradation than the latter (this event is more evident in the formulations containing higher amounts of UP). One could think that the presence of DG in the structure of UPR 3 turned the crosslinked network more hydrophilic and, consequently, with more affinity to the degradation medium. However, the swelling capacity showed an

opposite trend: UPR 7 has a higher swelling capacity than UPR 3. Thus, the reasons behind these behaviors remain unclear at this point.

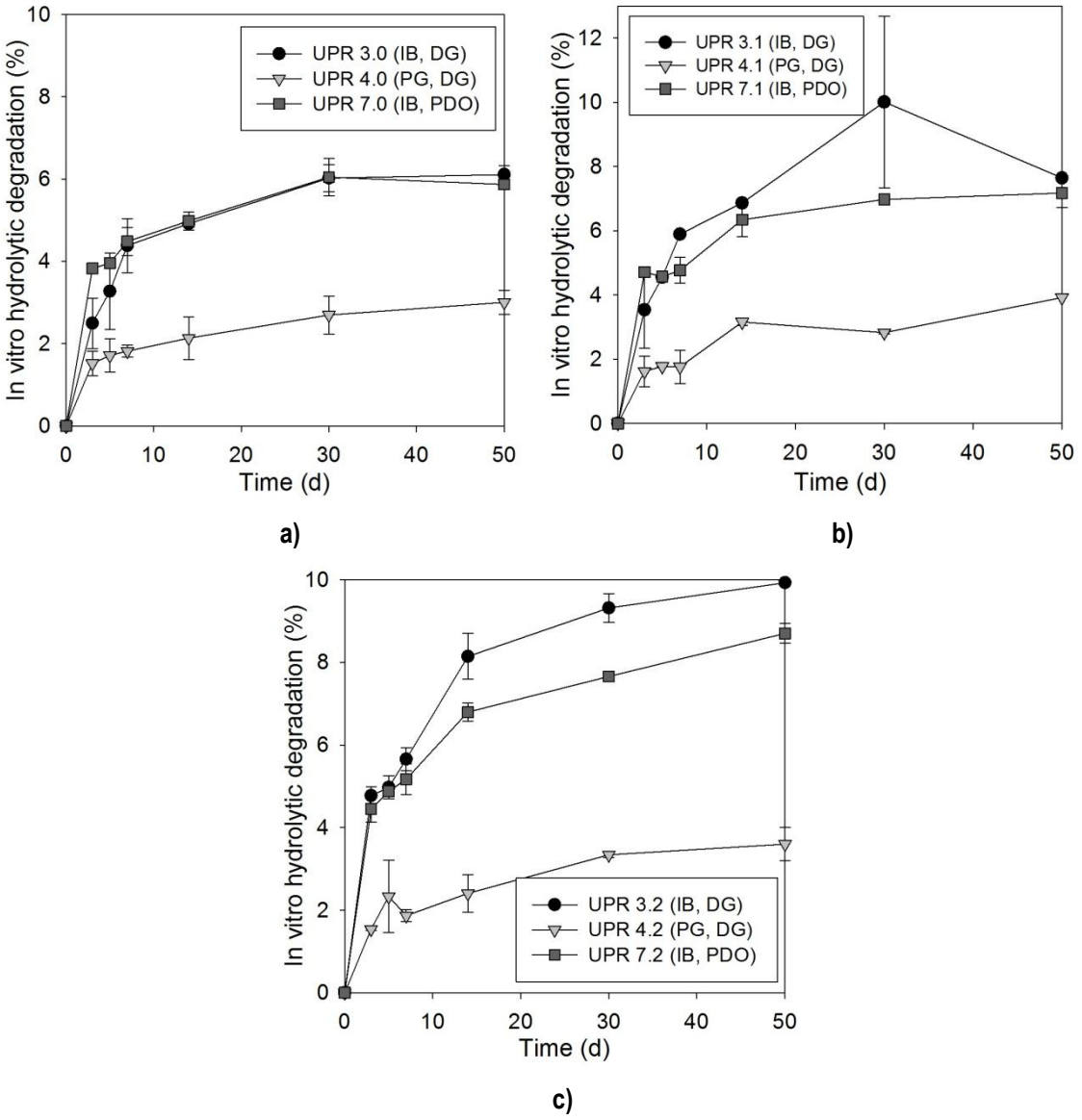


Figure 34. *In vitro* hydrolytic degradation analysis of samples 0 (a), 1 (b) and 2 (c) from UPRs 3, 4 and 7 (diols effect).

CHAPTER IV. CONCLUSION AND FUTURE WORK

Conclusion

The main objectives of this work were the synthesis of UPs using monomers from renewable resources and the preparation of their respective resins using biocompatible reactive solvents.

The spectroscopic analysis (FTIR and ^{1}H NMR) indicate that the UPs were successfully synthesized. However, some optimization is still required, since the presence of unreacted monomers was detected in some formulations. Additionally, some differences between the molar ratios in the feed and those calculated by ^{1}H NMR were also observed. The SEC analysis revealed that the UPs presented broad molecular weight distributions, which is characteristic of products resultant from polycondensation reactions. Some differences were noticed in the molecular weight values between the UPs, fact that can be related with the different reactivities of the monomers used. Concerning the thermal stability, the SDT results showed that all UPs degraded in a single stage, were stable until 390ºC and had an amorphous nature. In some cases, an initial weight loss was observed, which can be related to the evaporation of residual monomers. The DMTA analysis showed that all UPs experience a glass transition between -30ºC and -22ºC. The differences in the values can be attributed to the polyester molecular weight and/or chemical composition.

Regarding the UPRs, the first characteristic to be evaluated was their gel content. The results indicated that, in general, the thermally crosslinked network had higher gel content than the photocrosslinked networks. It was also shown that the HEMA amount and molecular weight of the UPs had important impact in the gel content. The presence or absence of a specific diacid or diol in the UPs structure seems to influence also gel content values, but the reasons behind these results remain unaddressed at this moment and require further studies. The SDT analysis has shown that the UPRs with higher gel content presented higher thermal stability and a single stage of weight loss, whereas the UPRs with lower gel contents presented an initial stage of weight loss and less thermal stability. This fact can be related to the presence of small oligomers or unreacted precursors in the former group of UPRs. It also should be pointed out that the UPRs had a slightly lower thermal stability than the UPs, which can be related to the presence of small oligo(HEMA) segments that are bonded in the side of the 3D network and degrade earlier. The DMTA analysis revealed the existence of two T_g in all formulations, which can be ascribed to the existence of two different crosslinked phases. The values of E' have shown to be dependent on both HEMA amount and type of formulation, but only at temperatures above 0ºC.

The swelling tests demonstrated that UPR 1 was the group of samples which swelled less. UPR 3 was the one which swelled more, followed by UPR 2, UPR 7, UPR 4 and UPR 5, respectively. The low values of swelling capacity obtained are indicative of crosslinked networks with a high hydrophobic nature. The

results showed that the swelling capacity of the UPRs enhances with the increase in the amount of HEMA, which can be justified by the HEMA hydrophilic nature. It was also found that the swelling capacity was highly dependent on the gel content. On the contrary, the different diacids and diols seemed to have little influence in this parameter, although some structure/swelling capacity relationships were inferred from the results. The *in vitro* hydrolytic degradation tests showed that UPRs were hardly degraded under the conditions tested. This result can be a consequence of the high hydrophobic nature of the crosslinked networks. The UPRs containing higher amounts of HEMA showed lower values of weight loss, since poly(HEMA) segments are not degraded under the conditions tested. The diols showed to have little impact in the degradation behavior of the UPRs.

To sum up, the main goals of this study were achieved, i.e., the successfully preparation of UPs and UPRs based on monomers from renewable sources. The results obtained can be seen as important starting point towards the further optimization of these systems and/or their application in biomedical field.

Future Work

Despite the promising results, there are some issues worth of optimization or/and further analysis.

Regarding the UP's formulations, the presence of unreacted monomer is an issue that deserves further attention. In order to deepen the study about UPs formulations, new monomers could be tested, such as diols derived from L-lactic acid; and also the relative molar ratios of the monomers could be changed.

Considering the reactive solvent, alternatives to HEMA should be considered, since UPRs prepared with it are not easily degradable in physiological medium. The use of degradable crosslinkers like diacrylates derived from L-lactic acid would be of interest.

Finally, the biocompatibility of the UPRs should be further analyzed. Although some of the monomers have a natural origin and poly(HEMA) is biocompatible, citotoxicity tests would confirm and analyse more precisely the biocompatibility of these UPRs.

REFERENCES

[1] K.-P. H. Rüdiger Kramme and R. S. Pozos, Eds., *Springer Handbook of Medical Technology*. Berlin, Germany: Springer-Verlag, 2011.

[2] D. G. Peter J. Groen, Marc Wine, "Implantable Medical Devices and EHR Systems," *Virtual Medical Worls*, 2007. [Online]. Available: http://www.hoise.com/vmw/07/articles/vmw/LV-VM-06-07-5.html.

[3] K. Bazaka and M. Jacob, "Implantable Devices: Issues and Challenges," *Electronics*, vol. 2, no. 1, pp. 1–34, Dec. 2012.

[4] P. S. Malchesky, "Artificial Organs 2012: a year in review," *Artificial organs*, vol. 37, no. 3, pp. 324–49, Mar. 2013.

[5] R. M. N. Fisher, John P., Antonios G. Mikos, Pierre M. Galletti, "Tissue Engineering, Prostheses and Artificial Organs," in in *The Biomedical Engineering Handbook: Tissue Engineering and Artificial Organs*, 3ª ed., J. D. Bronzino, Ed. Taylor & Francis Group, LLC, 2006.

[6] M. Brown, "Special Report: Biomaterials revolution," *Royal Society of Chemistry*, 2010. [Online]. Available: http://www.rsc.org/chemistryworld/Issues/2010/July/BiomaterialsRevolution.asp.

[7] M. Poussier, E. Denève, P. Blanc, E. Boulay, M. Bertrand, M. Nedelcu, a Herrero, J.-M. Fabre, and D. Nocca, "A review of available prosthetic material for abdominal wall repair.," *Journal of visceral surgery*, vol. 150, no. 1, pp. 52–9, Feb. 2013.

[8] S. Ritika, S. Arjun, K. Sunil, and J. Faraz, "Pulsatile drug delivery system: a review," *International Research Journal of Pharmacy*, vol. 3, no. 1, pp. 934–41 ST – Pulsatile Drug Delivery System for Co, 2012.

[9] C. Kiparissides and O. Kammona, "Nanoscale carriers for targeted delivery of drugs and therapeutic biomolecules," *The Canadian Journal of Chemical Engineering*, vol. 91, no. 4, p. n/a–n/a, Apr. 2012.

[10] D. M. D. Ribeiro, M. F. M. Colunas, F. A. F. Marques, J. M. Fernandes, P. S. Cunha, and S. Member, "A real time, wearable ECG and continous blood pressure monitoring system for first responders," in *33rd Annual International Conference of the IEEE EMBS*, 2011, pp. 6894–6898.

[11] W. X. LIU and W. F. GAO, "Wireless optical pulsometer system for use in medical filed, has monitoring personal computer attaching monitoring software to display user's pulse rate, positional information, body temperature or blood pressure," JP3167116-U.

[12] D. W. G. Morrison, M. R. Dokmeci, and U. Demirci, "Clinical Applications of Micro- and Nanoscale Biosensors," in in *Biomedical Nanostructures*, no. 1, K. E. Gonsalves, C. L. Laurencin, C. R. Halberstadt, and L. S. Nair, Eds. John Wiley & Sons, Inc., 2008, pp. 433–455.

[13] T. Vo-Dinh and B. Cullum, "Biosensors and biochips: advances in biological and medical diagnostics.," *Fresenius Journal Of Analytical Chemistry*, vol. 366, no. 6–7, pp. 540–551, 2000.

[14] J. Kirkup, *The History and Evolution of Surgical Instruments*, vol. 30, no. 3. California, USA: historyofscience.com, 2006.

[15] D. F. Williams, “On the mechanisms of biocompatibility,” *Biomaterials*, vol. 29, no. 20, pp. 2941–2953, Jul. 2008.

[16] S. Bauer, P. Schmuki, K. von der Mark, and J. Park, “Engineering biocompatible implant surfaces. Part I: Materials and surfaces,” *Progress in Materials Science*, vol. 58, no. 3, pp. 261–326, Apr. 2013.

[17] L. L. Hench and I. Thompson, “Twenty-first century challenges for biomaterials,” *Journal of the Royal Society Interface the Royal Society*, vol. 7 Suppl 4, pp. S379–91, Aug. 2010.

[18] M. E. Gomes and R. L. Reis, “Biodegradable polymers and composites in biomedical applocations: from catgut to tissue engineering,” *International Materials Reviews*, vol. 495, pp. 261–273, 2004.

[19] A. C. Vieira, R. M. Guedes, and A. T. Marques, “Development of ligament tissue biodegradable devices: a review,” *Journal of biomechanics*, vol. 42, no. 15, pp. 2421–30, Nov. 2009.

[20] G. Gaucher, R. H. Marchessault, and J.-C. Leroux, “Polyester-based micelles and nanoparticles for the parenteral delivery of taxanes,” *Journal of Controlled Release*, vol. 143, no. 1, pp. 2–12, Apr. 2010.

[21] L. Nair and C. Laurencin, “Polymers as biomaterials for tissue engineering and controlled drug delivery,” in in *Advances in Biochemical Engineering/Biotechnology*, vol. 102, K. Lee and D. Kaplan, Eds. Springer-Verlag, 2006, pp. 47–90.

[22] S. Ramakrishna, J. Mayer, E. Wintermantel, and K. W. Leong, “Biomedical applications of polymer-composite materials: a review,” *Composites Science and Technology*, vol. 61, no. 9, pp. 1189–1224, 2001.

[23] O. Coulembier, P. Degée, J. L. Hedrick, and P. Dubois, “From controlled ring-opening polymerization to biodegradable aliphatic polyester: Especially poly(β-malic acid) derivatives,” *Progress in Polymer Science*, vol. 31, no. 8, pp. 723–747, Aug. 2006.

[24] V. Koutsos, “Polymeric materials: an introduction,” in in *ICE Manual of Construction Materials*, London, UK: Institution of Civil Engineers, 2009, pp. 571–577.

[25] E. A. Rietman, “They’re everywhere!,” in in *Polymer chemistry: introduction to an indispensable science*, Virginia, USA: National Science Teachers Association Press, 2004, pp. 3–12.

[26] S. Sullalti, “New eco-friendly polyesters from renewable sources”, MSc thesis, Bologna University, 2012.

[27] P. Bordes, E. Pollet, and L. Averous, “Nano-biocomposites: biodegradable polyester/nanoclay systems,” *Progress in Polymer Science*, vol. 34, no. 2, pp. 125–155, Feb. 2009.

[28] “Health Research,” *European Comission Website*, 2012. [Online]. Available: http://ec.europa.eu/research/health/index_en.html.

[29] “Biomedical technologies,” *European Comission Website*, 2012. [Online]. Available: http://ec.europa.eu/research/health/biotechnology/biomedical-technologies/index_en.html.

[30] "A.SPIRE – supporting and implementing SPIRE PPP," *Sustainable Process Industry through Resource and Energy Efficiency Website*, 2012. [Online]. Available: http://www.spire2030.eu/about-spire.

[31] "European Renewable Resources and Materials Association," *National Non-Food Crops Centre Website*, 2002. [Online]. Available: http://www.errma.com.

[32] "Excellent Science: Horizon 2020," *European Comission Website*, 2011. [Online]. Available: http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=excellent-science.

[33] U. Edlund and A. C. Albertsson, "Polyesters based on diacid monomers," *Advanced drug delivery reviews*, vol. 55, no. 4, pp. 585–609, Apr. 2003.

[34] A. Albertsson and I. K. Varma, "Aliphatic Polyesters: Synthesis, Properties and Applications," in in *Advances in Polymer Science*, vol. 157, Springer-Verlag, 2002, pp. 1–40.

[35] "Lists of acceptable polymers for use in food packaging applications," *Health Canada*, 2009. [Online]. Available: http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/polymers_tc-polymere_tm-eng.php.

[36] K. Jonhson and L. Yang, "Preparation, Properties and Applications of Unsaturated Polyesters," in in *Modern Polyesters: Chemistry and Technology of Polyesters and Copolyesters*, J. Scheirs and T. Long, Eds. West Sussex, UK: John Wiley & Sons, Inc., 2003, pp. 699–712.

[37] "Labelling, logos, charts," *European Bioplastics*, 2013. [Online]. Available: http://en.european-bioplastics.org/press/press-pictures/labelling-logos-charts.

[38] P. Pan and Y. Inoue, "Polymorphism and isomorphism in biodegradable polyesters," *Progress in Polymer Science*, vol. 34, no. 7, pp. 605–640, Jul. 2009.

[39] R. J. Müller, I. Kleeberg, and W. D. Deckwer, "Biodegradation of polyesters containing aromatic constituents.," *Journal of biotechnology*, vol. 86, no. 2, pp. 87–95, Mar. 2001.

[40] H. Seyednejad, A. H. Ghassemi, C. F. van Nostrum, T. Vermonden, and W. E. Hennink, "Functional aliphatic polyesters for biomedical and pharmaceutical applications," *Journal of controlled release: official journal of the Controlled Release Society*, vol. 152, no. 1, pp. 168–76, May 2011.

[41] A. Finne and A. Albertsson, "New Functionalized Polyesters to Achieve Controlled," *Journal of Polymer Science: Part A: Polymer Chemistry*, vol. 42, pp. 444–452, 2003.

[42] A. Rodriguez-Galan, L. Franco, and J. Puiggali, "Degradable Poly(ester amide)s for Biomedical Applications," *Polymers*, vol. 3, no. 1, pp. 65–99, Dec. 2010.

[43] Q. Liu, L. Jiang, R. Shi, and L. Zhang, "Synthesis, preparation, in vitro degradation, and application of novel degradable bioelastomers - A review," *Progress in Polymer Science*, vol. 37, no. 5, pp. 715–765, May 2012.

[44] M. Hakkarainen, "Aliphatic Polyesters: Abiotic and Biotic Degradation and Degradation Products," in in *Advances in Polymer Science*, vol. 157, Springer-Verlag, 2002.

[45] T. A. Akopova, T. S. Demina, A. N. Shchegolikhin, T. S. Kurkin, C. Grandfils, N. S. Perov, A. S. Kechekyan, and A. N. Zelenetskii, “A Novel Approach to Design Chitosan-Polyester Materials for Biomedical Applications,” *International Journal of Polymer Science*, vol. 2012, pp. 1–10, 2012.

[46] S. Malberg, P. Plikk, A. Finne-Wistrand, and A.-C. Albertsson, “Design of Elastomeric Homo- and Copolymer Networks of Functional Aliphatic Polyester for Use in Biomedical Applications,” *Chemistry of Materials*, vol. 22, no. 9, pp. 3009–3014, May 2010.

[47] I. Fabela, “Photopolymerization and Characterization of Unsaturated Polyesters Resins,” MSc thesis, University of Coimbra, 2012.

[48] M. O. Trollsas, “Substituted polycaprolactone for coating,” EP2162503A1, US200802991642010.

[49] A. Löfgren, A.-C. Albertsson, P. Dubois, and R. Jérôme, “Recent Advances in Ring-Opening Polymerization of Lactones and Related Compounds,” *Journal of Macromolecular Science, Part C: Polymer Reviews*, vol. 35, no. 3, pp. 379–418, Aug. 1995.

[50] A. J. R. Lasprilla, G. a R. Martinez, B. H. Lunelli, A. L. Jardini, and R. M. Filho, “Poly-lactic acid synthesis for application in biomedical devices - a review,” *Biotechnology advances*, vol. 30, no. 1, pp. 321–328, 2012.

[51] L. Xiao, B. Wang, G. Yang, and M. Gauthier, “Poly(Lactic Acid)-Based Biomaterials: Synthesis, Modification and Applications,” in in *Biomedical Science, Engineering and Technology*, D. N. Ghista, Ed. InTech, 2012, pp. 247–282.

[52] Sigma-Aldrich, “Polymer Additives,” *Sigma-Aldrich Website*, 2013. [Online]. Available: http://www.sigmaaldrich.com/materials-science/material-science-products.html?TablePage=16371222.

[53] H. Muller and R. Gachter, *Plastics Additives Handbook: Stabilizers, Processing AIDS, Plasticizers, Fillers, Reinforcements, Colorants for Thermoplastics*, 4ª ed. Hanser Gardner Pubns, 1993.

[54] C. Wolf-Brandstetter, S. Roessler, S. Storch, U. Hempel, U. Gbureck, B. Nies, S. Bierbaum, and D. Scharnweber, “Physicochemical and cell biological characterization of PMMA bone cements modified with additives to increase bioactivity,” *Journal of biomedical materials research. Part B, Applied biomaterials*, vol. 101, no. 4, pp. 599–609, May 2013.

[55] D. Andjelkovic, D. Culkin, and R. Loza, “Unsaturated Polyester Resins Derived from Renewable Resources,” in *COMPOSITES & POLYCON*, 2009, pp. 1–6.

[56] J.-M. Raquez, M. Deléglise, M.-F. Lacrampe, and P. Krawczak, “Thermosetting (bio)materials derived from renewable resources: A critical review,” *Progress in Polymer Science*, vol. 35, no. 4, pp. 487–509, Apr. 2010.

[57] C. Costa, “Síntese e Caracterização de Poliésteres Insaturados - Influência da Estrutura nas Propriedades da Resina”, MSc thesis, University of Coimbra, 2011.

[58] J. K. Fink, *Reactive Polymers Fundamentals and Applications: a Concise Guide to Industrial Polymers*. New York, USA: William Andrew Publishing, 2005.

[59] Y. Yang and L. Lee, “Microstructure formation in the cure of unsaturated polyester resins,” *Polymer*, vol. 29, no. 10, pp. 1793–1800, Oct. 1988.

[60] M. a. R. Meier, J. O. Metzger, and U. S. Schubert, “Plant oil renewable resources as green alternatives in polymer science,” *Chemical Society Reviews*, vol. 36, no. 11, p. 1788, 2007.

[61] M. N. Belgacem and A. Gandini, Eds., *Monomers, Polymers and Composites from Renewable Resources*, 1ª ed. UK: Elsevier, 2008.

[62] X. Feng, A. J. East, W. Hammond, M. Jaffe, and L. Street, “Sugar-Based Chemicals for Environmentally Sustainable Applications,” in in *ACS Symposium Series: In Contemporary Science of Polymeric Materials*, no. 5, L. Korugic-Karasz, Ed. Washington, USA: Amarican Chemical Society, 2010, pp. 3–27.

[63] S. Dworakowska, W. Kasprzyk, S. Bednarz, and D. Bogdał, “Polyesters from renewable sources,” in *15th International Electronic Conference on Synthetic Organic Chemistry*, 2011.

[64] P. Bloom and P. Venkitasubramanian, “Monomers and polymers from bioderived carbon,” US 2009/0018300 A12009.

[65] P. S. Sathiskumar and G. Madras, “Synthesis, characterization, degradation of biodegradable castor oil based polyesters,” *Polymer Degradation and Stability*, vol. 96, no. 9, pp. 1695–1704, Sep. 2011.

[66] J. Retuert, M. Pedram, F. Martínez, and M. Jeria, “Soluble itaconic acid-ethylene glycol polyesters,” *Bulletin of the Chemical Society of Japan*, vol. 66, pp. 1707–1708, 1993.

[67] S. Ma, X. Liu, Y. Jiang, Z. Tang, C. Zhang, and J. Zhu, “Bio-based epoxy resin from itaconic acid and its thermosets cured with anhydride and comonomers,” *Green Chemistry*, vol. 15, no. 1, p. 245, 2013.

[68] M. Worzakowska, “Curing reaction of unsaturated (epoxy) polyesters based on different aliphatic glycols,” *Journal of Thermal Analysis and Calorimetry*, vol. 102, no. 2, pp. 745–750, Dec. 2009.

[69] N. Mohammad, “Synthesis, characterization and properties of the new unsaturated polyester resins for composite applications,” MARA University of Technology, 2007.

[70] F. Fenouillot, a. Rousseau, G. Colomines, R. Saint-Loup, and J.-P. Pascault, “Polymers from renewable 1,4:3,6-dianhydrohexitols (isosorbide, isomannide and isoidide): A review,” *Progress in Polymer Science*, vol. 35, no. 5, pp. 578–622, May 2010.

[71] “Bio-based, petroleum-free ingredients formulated for higher performance,” *DuPont Website*, 2011. [Online]. Available: http://www2.dupont.com/Bio-based_Propanediol/en_CN.

[72] S. S. Umare, a. S. Chandure, and R. a. Pandey, “Synthesis, characterization and biodegradable studies of 1,3-propanediol based polyesters,” *Polymer Degradation and Stability*, vol. 92, no. 3, pp. 464–479, Mar. 2007.

[73] J. Kroschwitz and F. M. Herman, *Encyclopedia of Polymer Science and Techonology*, 3ª ed. John Wiley & Sons, 2003.

[74] J. Coates, “Interpretation of Infrared Spectra, A Practical Approach,” *Encyclopedia of Analytical Chemistry*. John Wiley& Sons, pp. 10815–10837, 2000.

[75] I. Gibas and H. Janik, “Review: Synthetic Polymer Hydrogels for Biomedical Applications,” *Chemical & Chemical Technology*, vol. 4, no. 4, pp. 297–304, 2010.

[76] “Ciba IRGACURE 2959,” Ciba Specialty Chemicals, pp. 1–3, 1998.

[77] L. Jasinska and C. E. Koning, “Unsaturated, biobased polyesters and their cross-linking via radical copolymerization,” *Journal of Polymer Science Part A: Polymer Chemistry*, vol. 48, no. 13, pp. 2885–2895, Jul. 2010.

[78] “Mechanical Properties,” *EngineersHandbook.com*. [Online]. Available: http://www.engineershandbook.com/Materials/mechanical.htm.

[79] L. L. Hench and J. K. West, “The sol-gel process,” *Chemical Reviews*, vol. 90, no. 1, pp. 33–72, Jan. 1990.

APPENDICES

A. FTIR

- *Monomers*

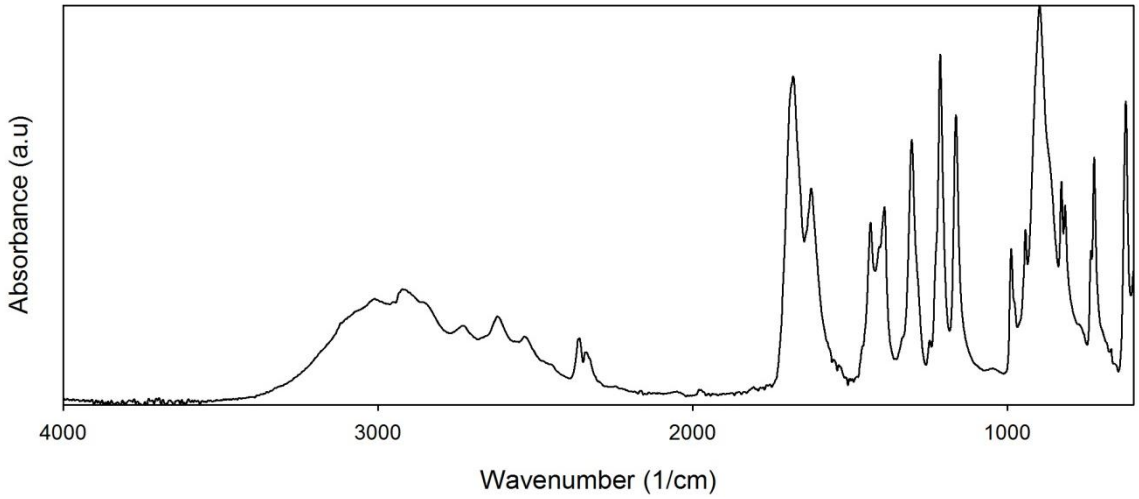


Figure A1. FITR spectrum of IA.

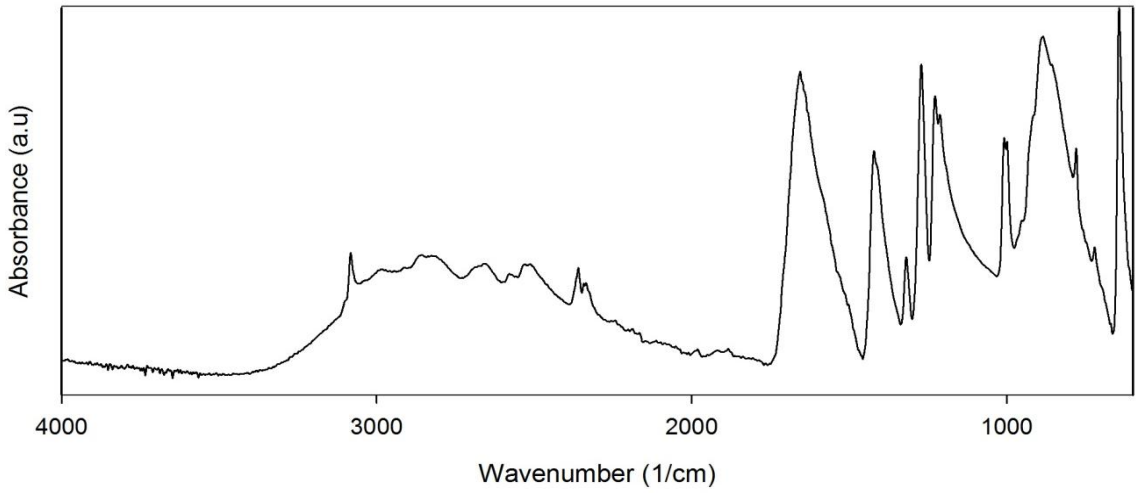


Figure A2. FITR spectrum of FA.

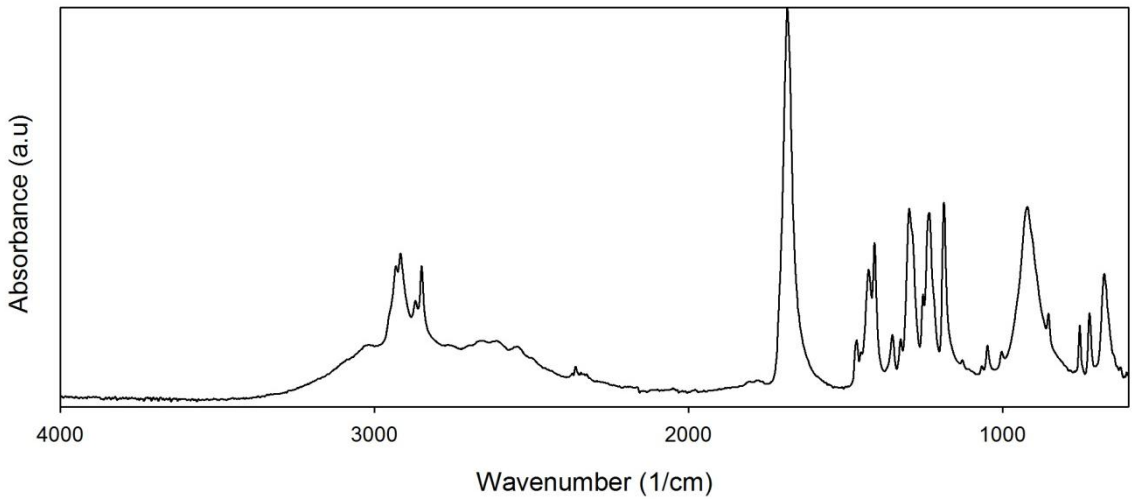


Figure A3. FITR spectrum of SA.

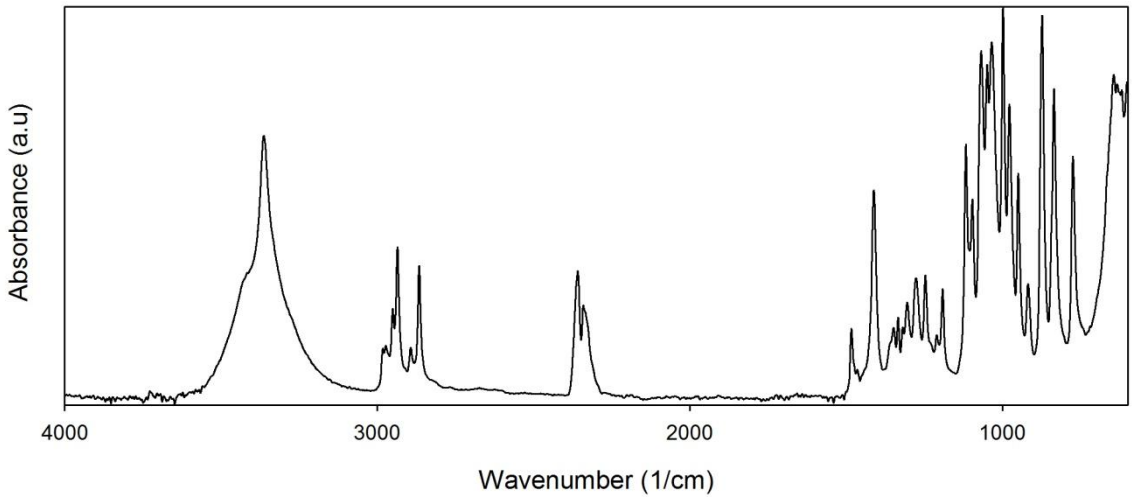


Figure A4. FITR spectrum of IB.

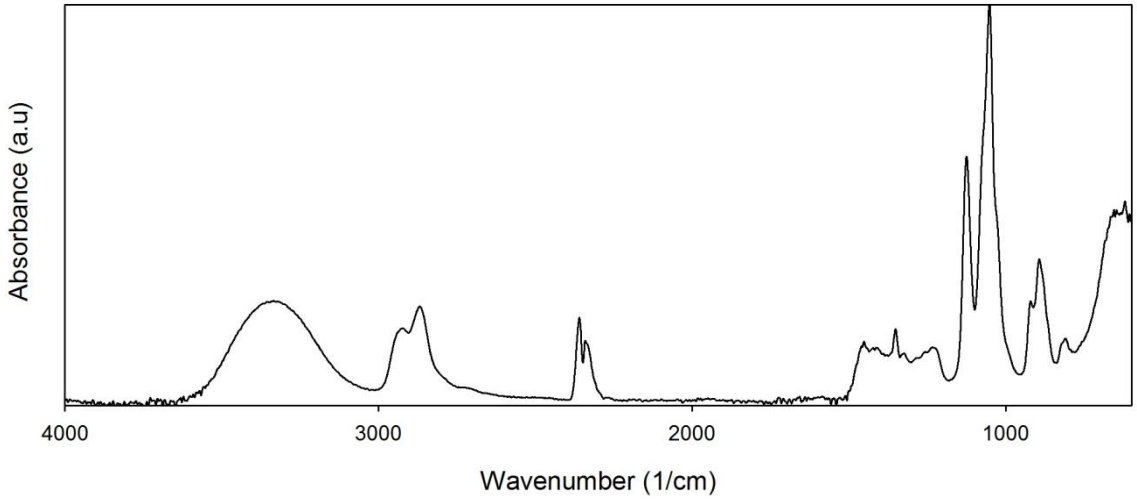


Figure A5. FITR spectrum of DG.

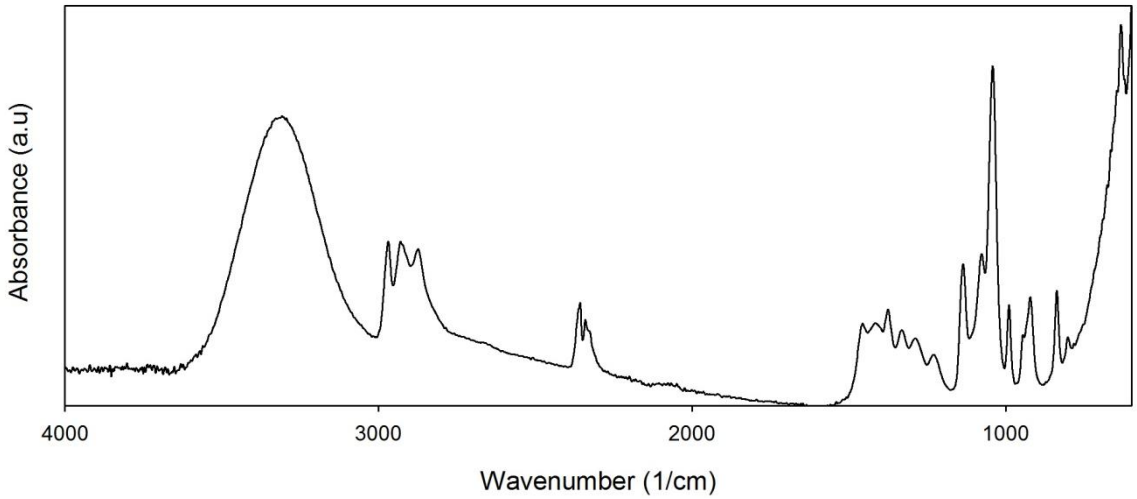


Figure A6. FITR spectrum of PG.

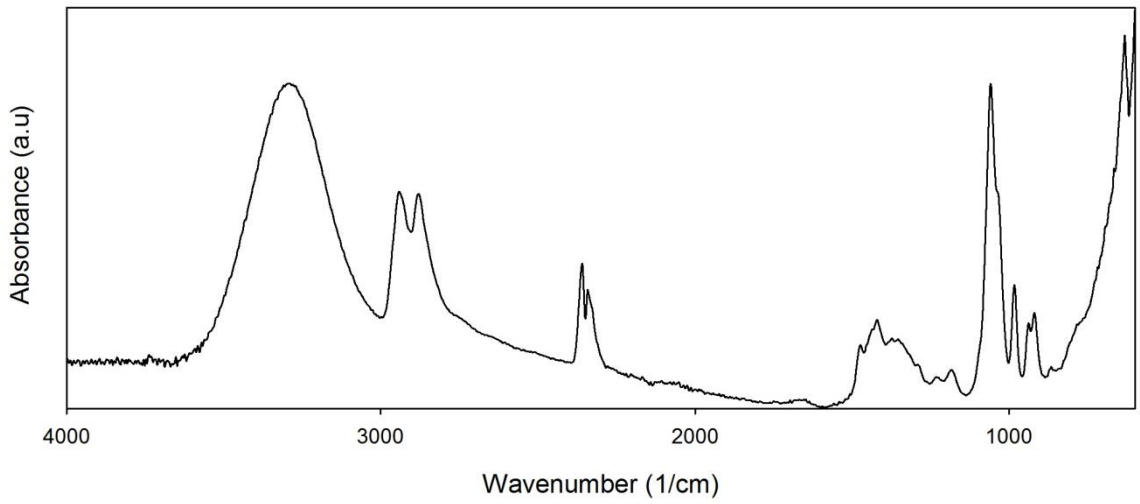


Figure A7. FITR spectrum of PDO.

- *UPs*

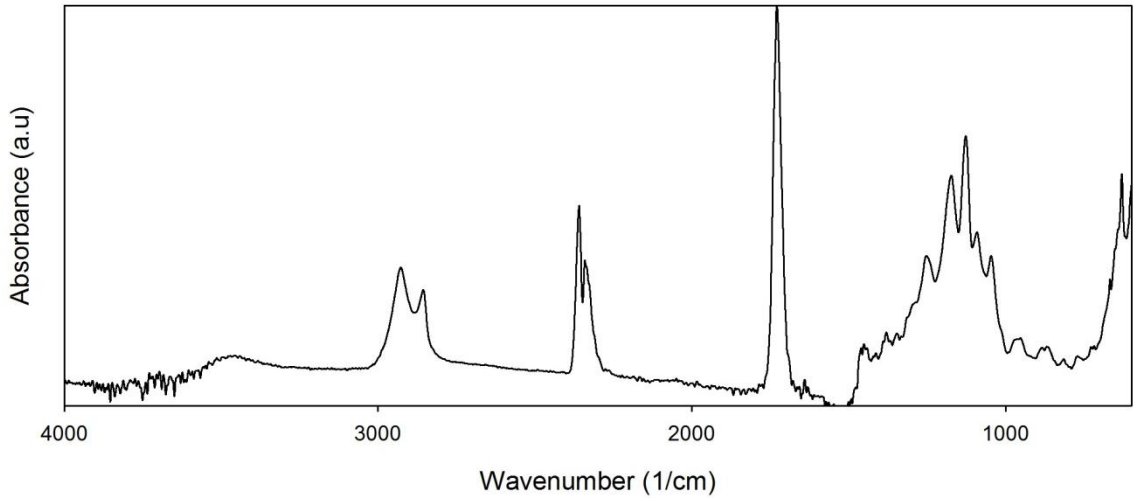


Figure A8. FITR spectrum of UP 2.0.

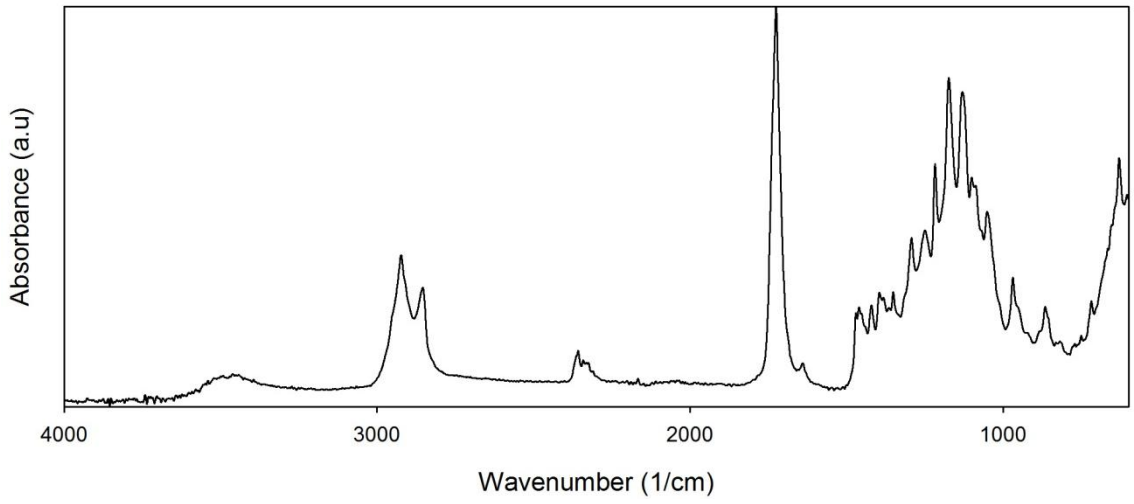


Figure A9. FITR spectrum of UP 2.1.

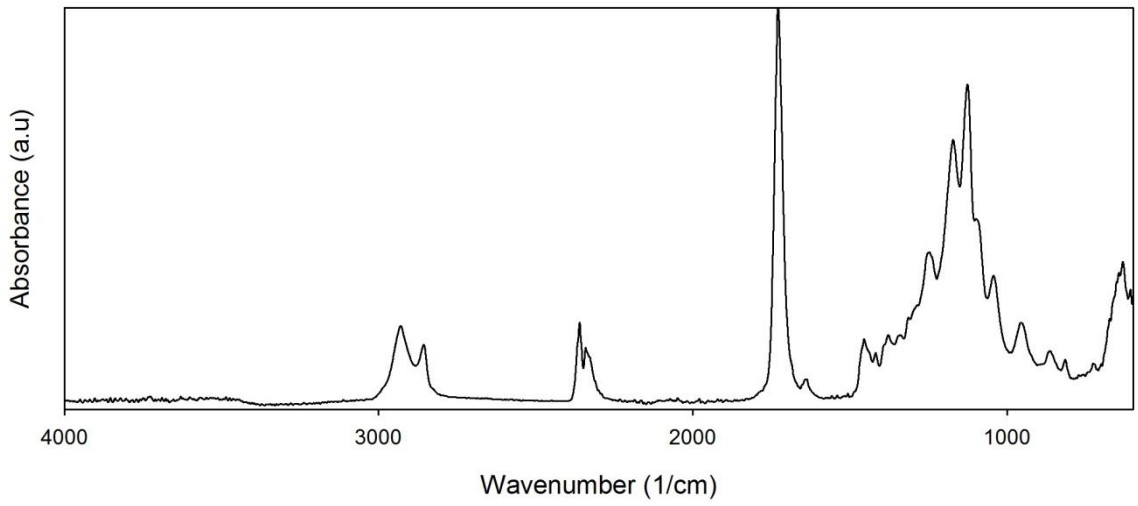


Figure A10. FITR spectrum of UP 3.0.

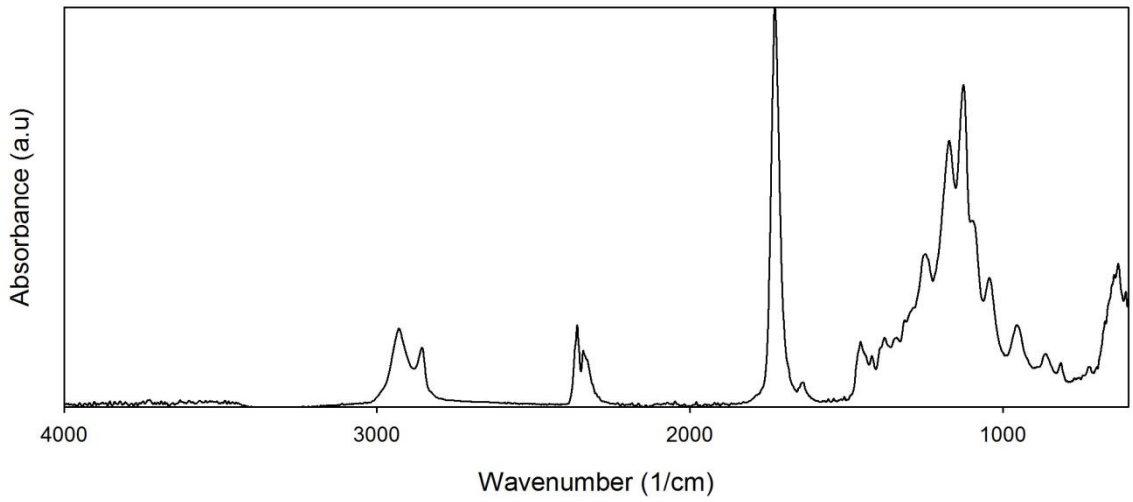


Figure A11. FITR spectrum of UP 4.0.

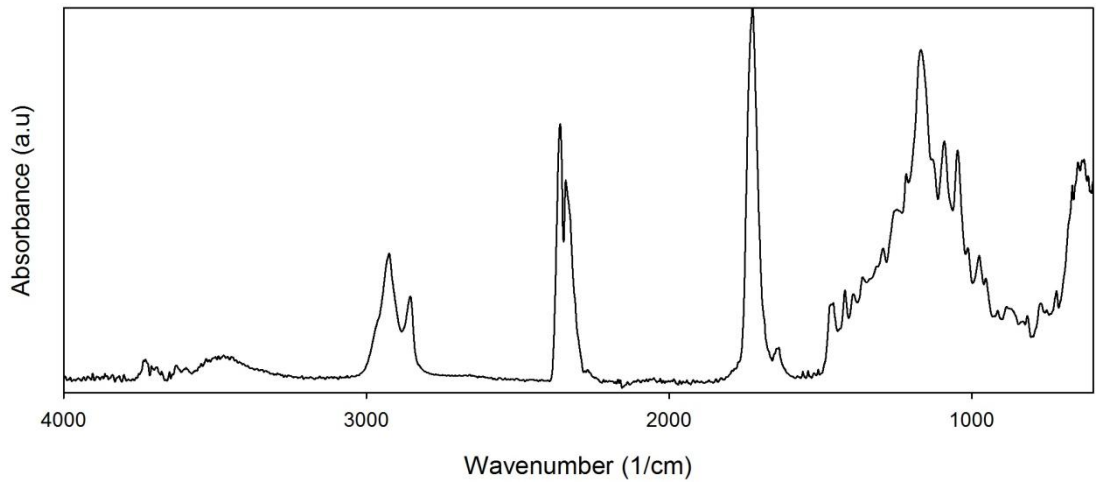


Figure A12. FITR spectrum of UP 5.1.

Although the FTIR spectra confirm the success of the UPs synthesis, they also show some evidences regarding the presence of unreacted monomer. The bands above 3000 cm^{-1} (that appear in UP 2.0, 2.1 and 5.1 spectra) correspond to the hydroxyl groups, which probably indicate the presence of some unreacted diols.

B. ^{1}H NMR

- *Monomers*

The chemical composition of monomers was confirmed by ^{1}H NMR spectra. The number and quantity of protons expected were identified in each spectrum. The peaks at 1.70 and 3.60 ppm represent the test solvent, THF, and the absence of OH groups peaks in some diacids is explained by the their continuous interaction and interchange with the water present in the test, which oftentimes hampers their detection. The peak around 2.50 ppm seen in diols spectra corresponds to the saturation point of the water, which is a consequence of the test procedure; and the absence of OH groups peaks in IB spectrum is related to their unique and complex structure. Nevertheless, this absence seems irrelevant before all the other peaks that are consistent with the predicted IB chemical composition.

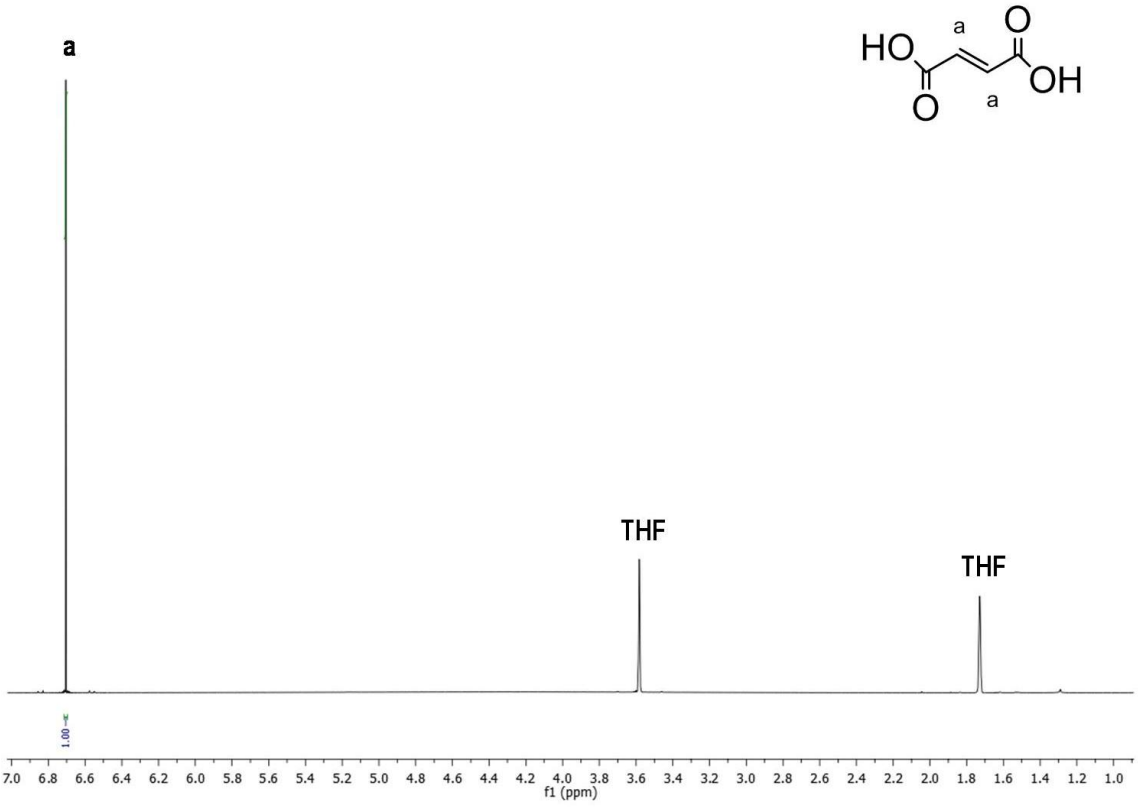


Figure B1. ^{1}H NMR spectrum of FA.

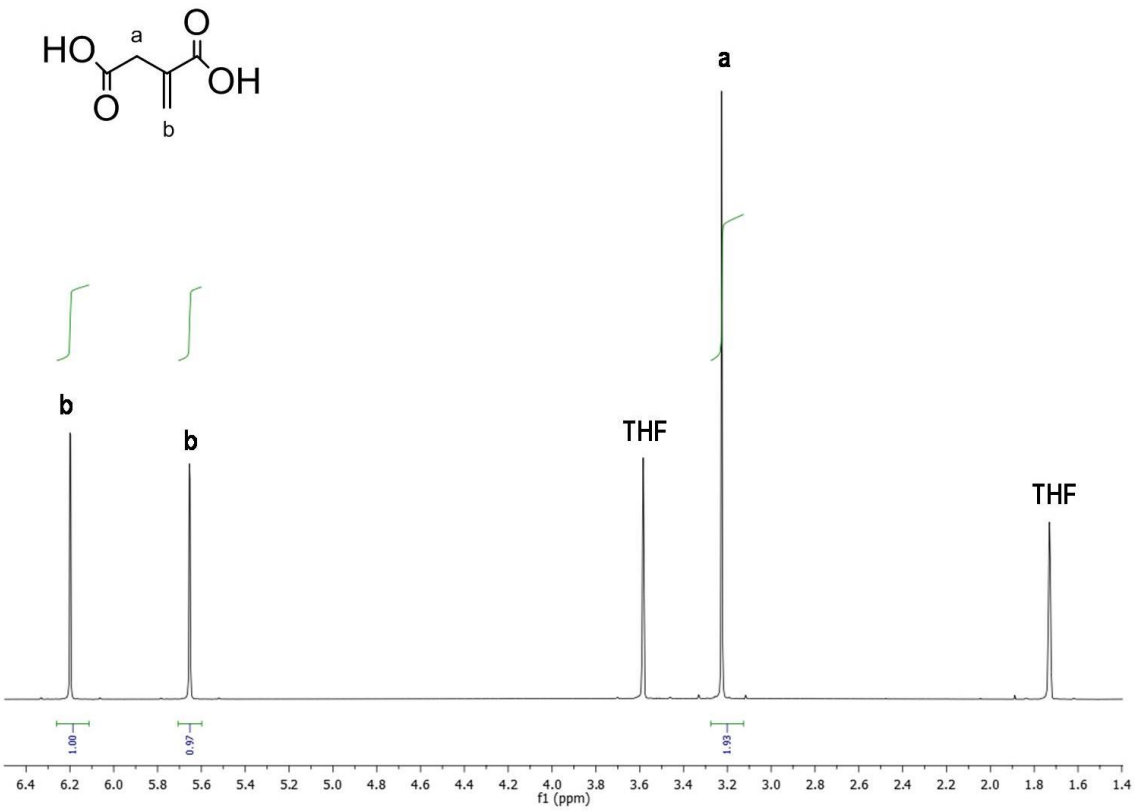


Figure B2. ^{1}H NMR spectrum of IA.

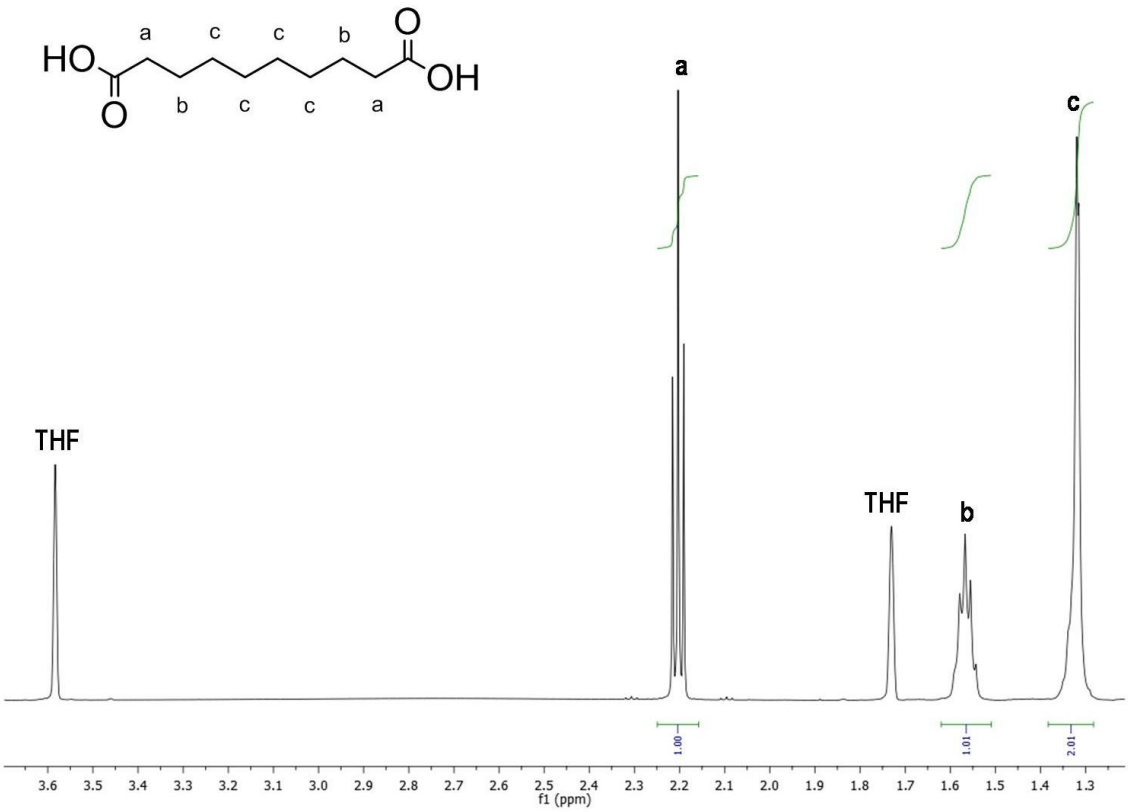


Figure B3. ^{1}H NMR spectrum of SA.

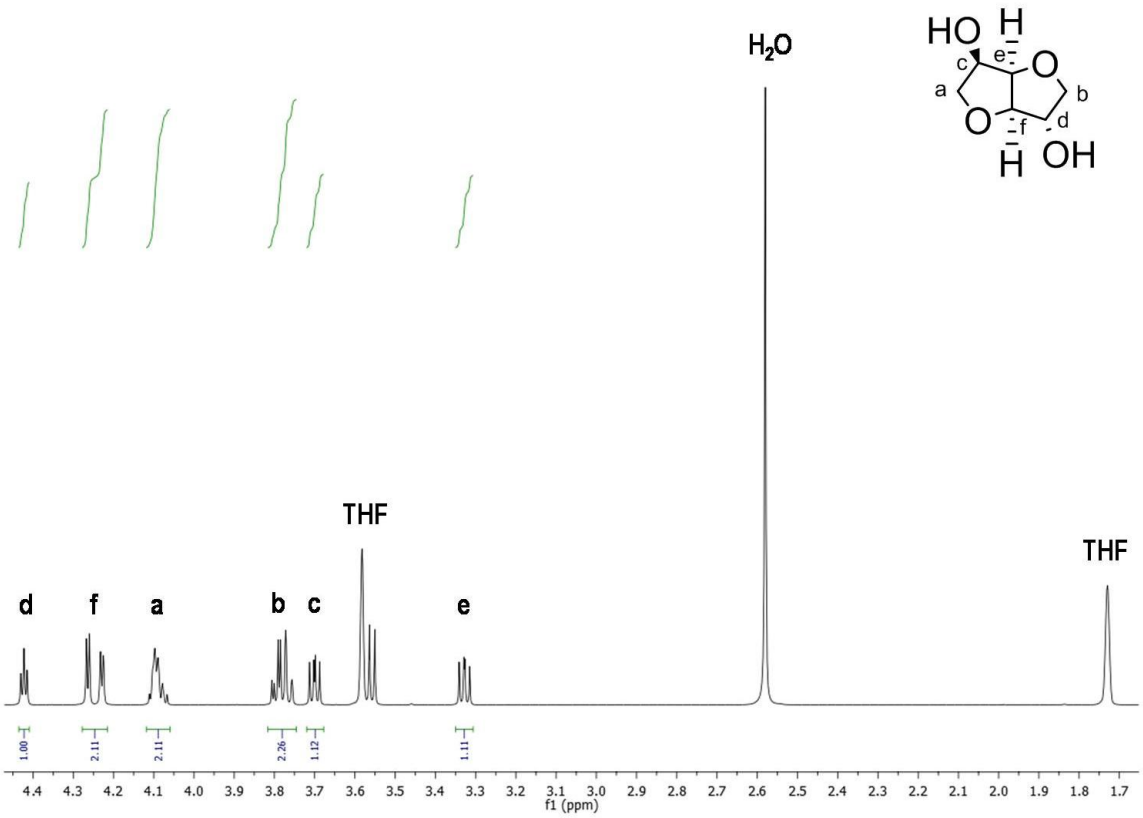


Figure B4. ^{1}H NMR spectrum of IB.

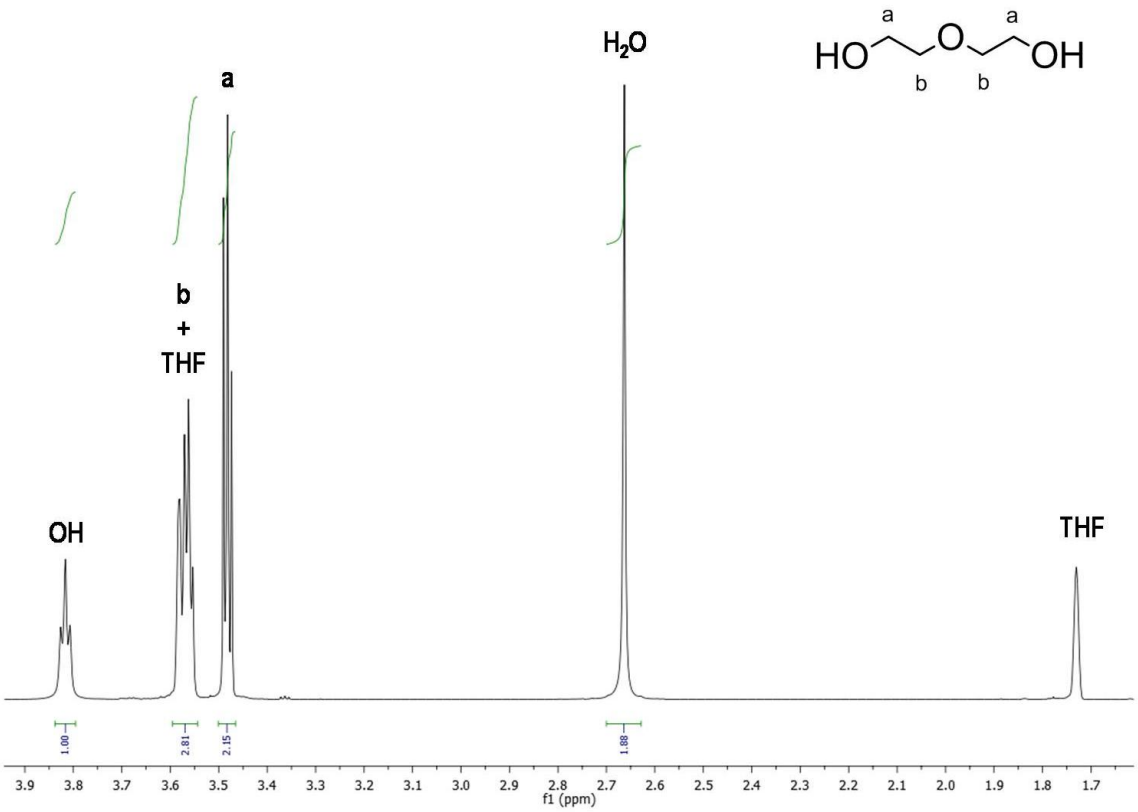


Figure B5. ^{1}H NMR spectrum of DG.

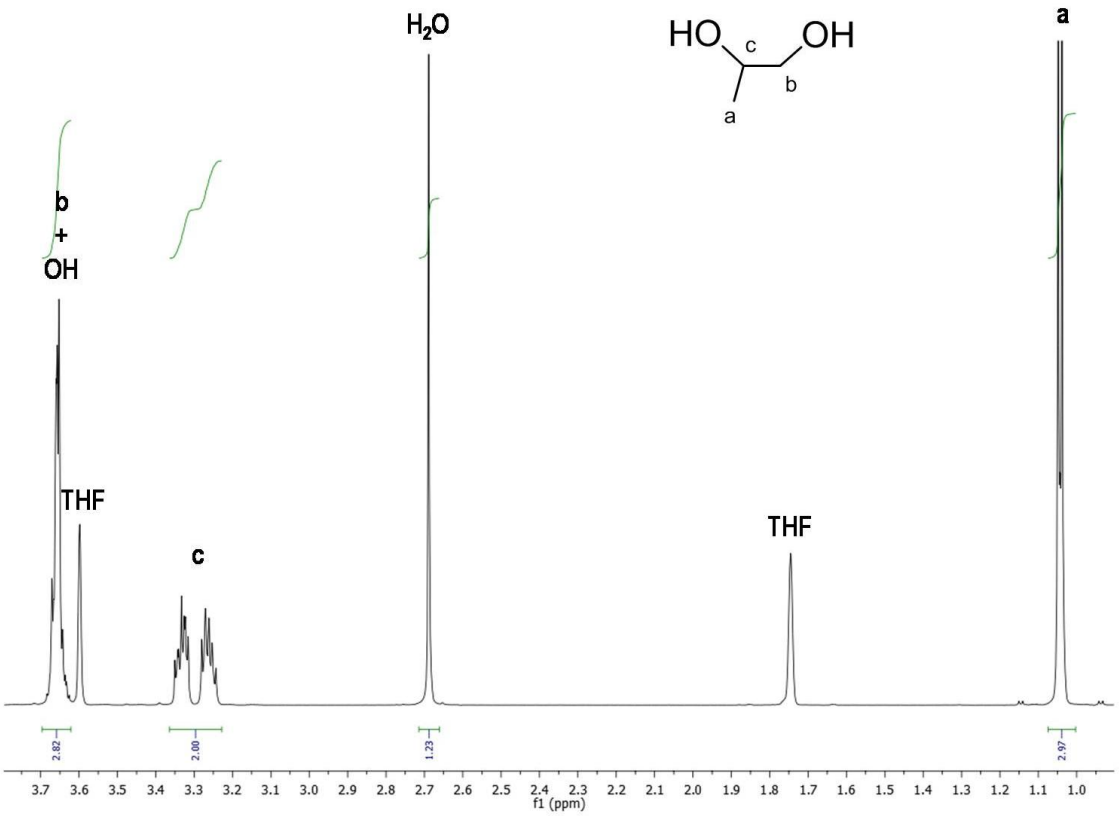


Figure B6. [1]H NMR spectrum of PG.

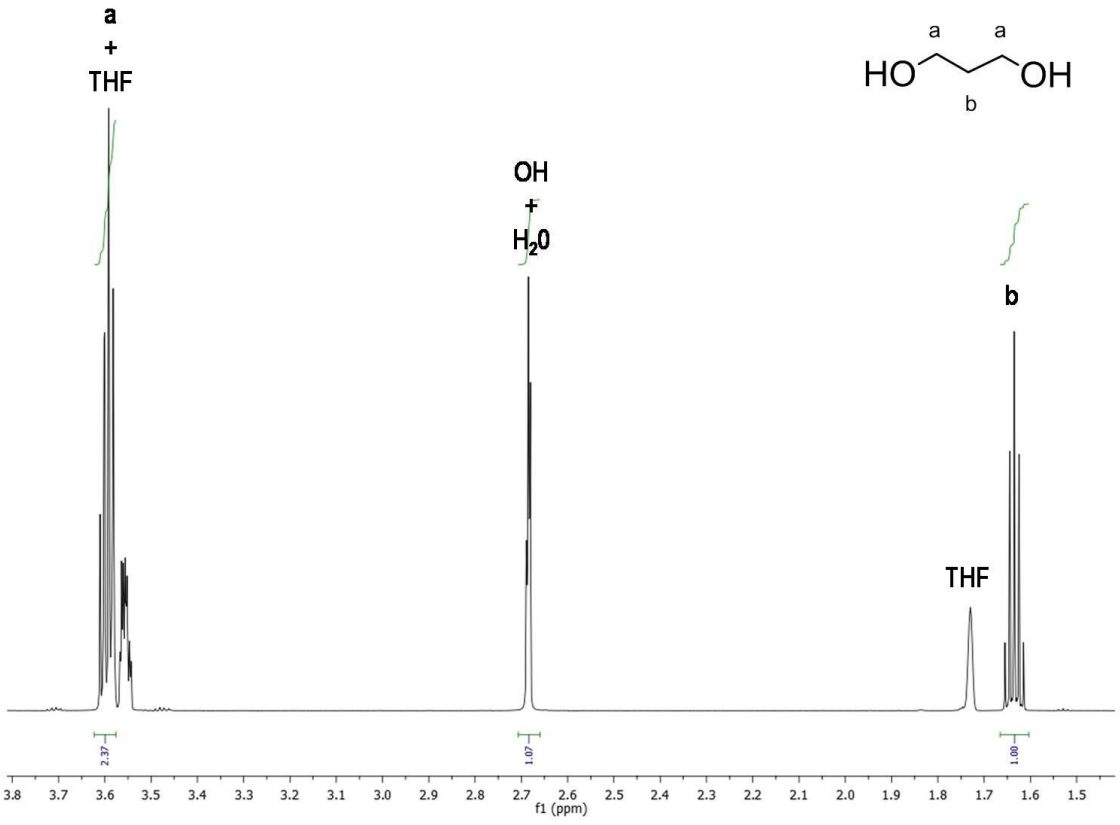


Figure B7. [1]H NMR spectrum of PDO.

- *UPs*

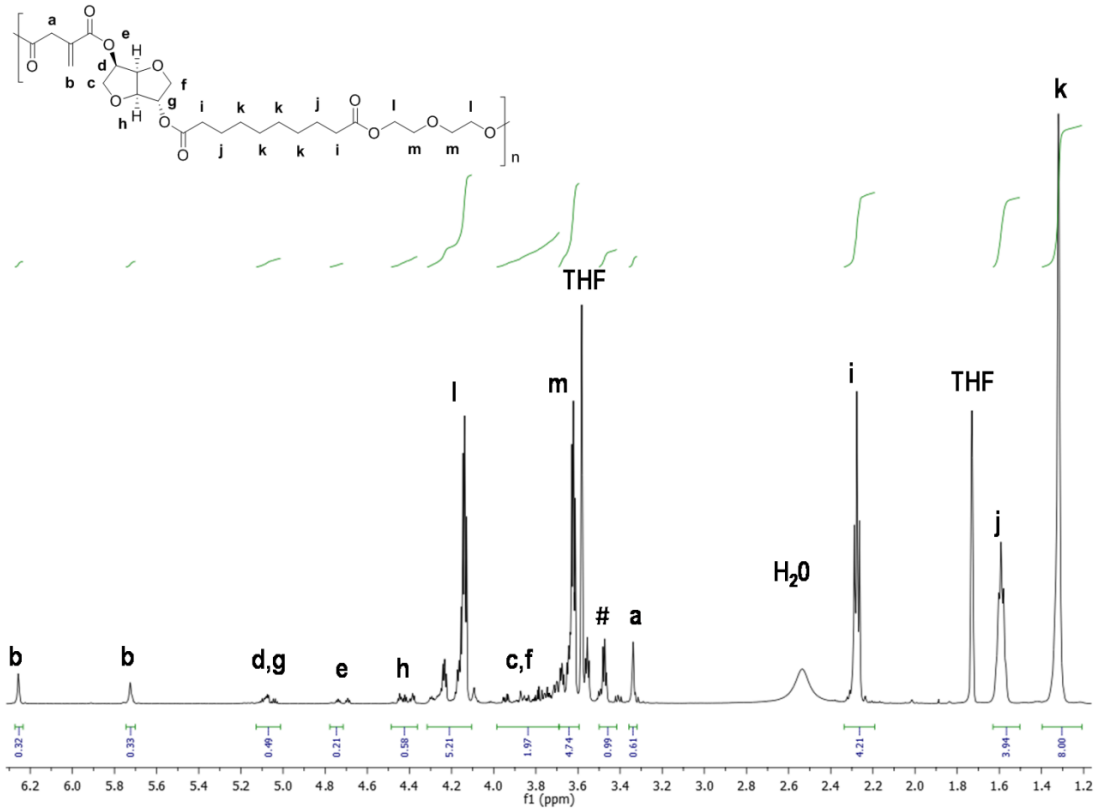


Figure B8. ^{1}H NMR spectrum of UP 2.1. The # symbol correspond to the unreacted diethylene glycol.

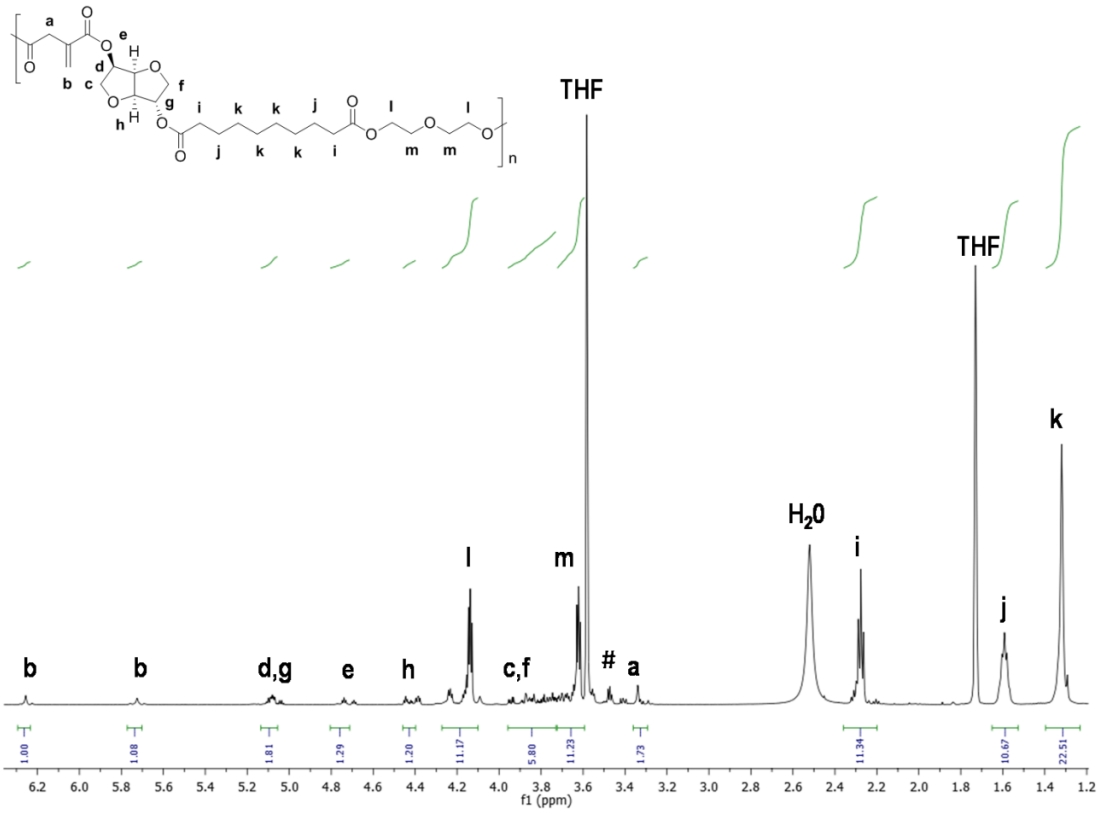


Figure B9. ^{1}H NMR spectrum of UP 3.0. The # symbol correspond to the unreacted diethylene glycol.

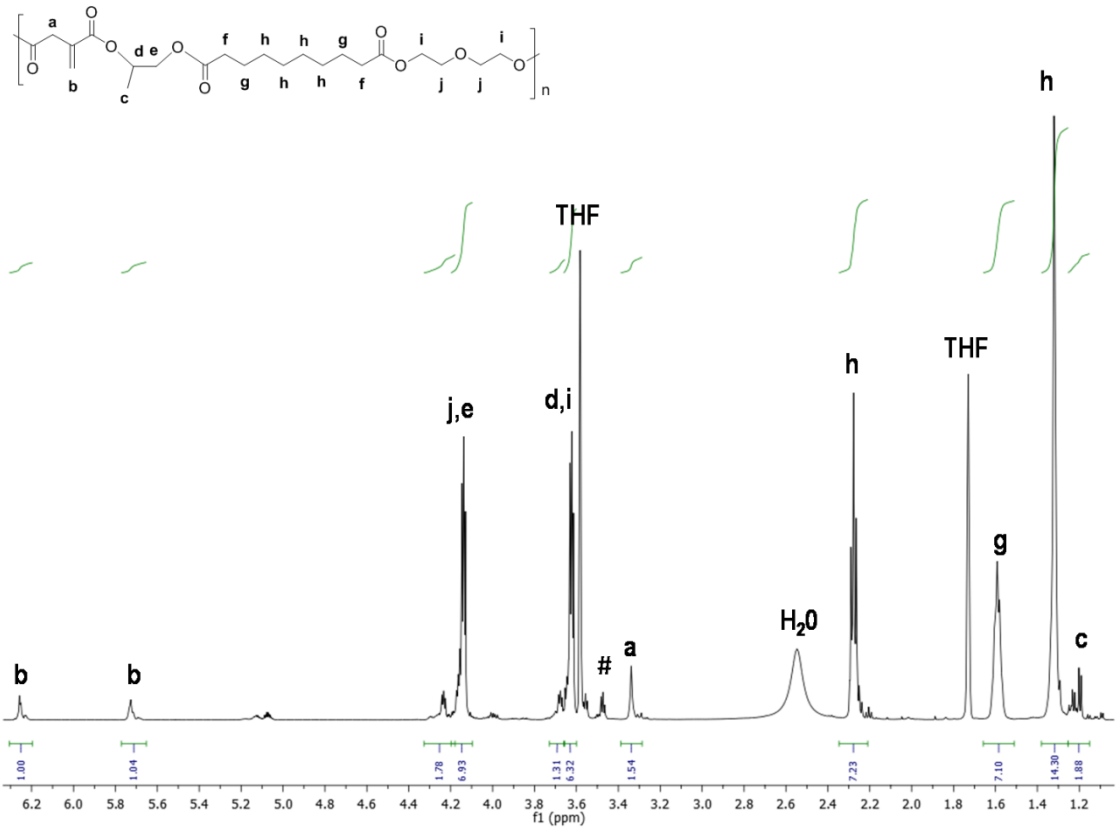


Figure B10. ^{1}H NMR spectrum of UP 4.0. The # symbol correspond to the unreacted diethylene glycol.

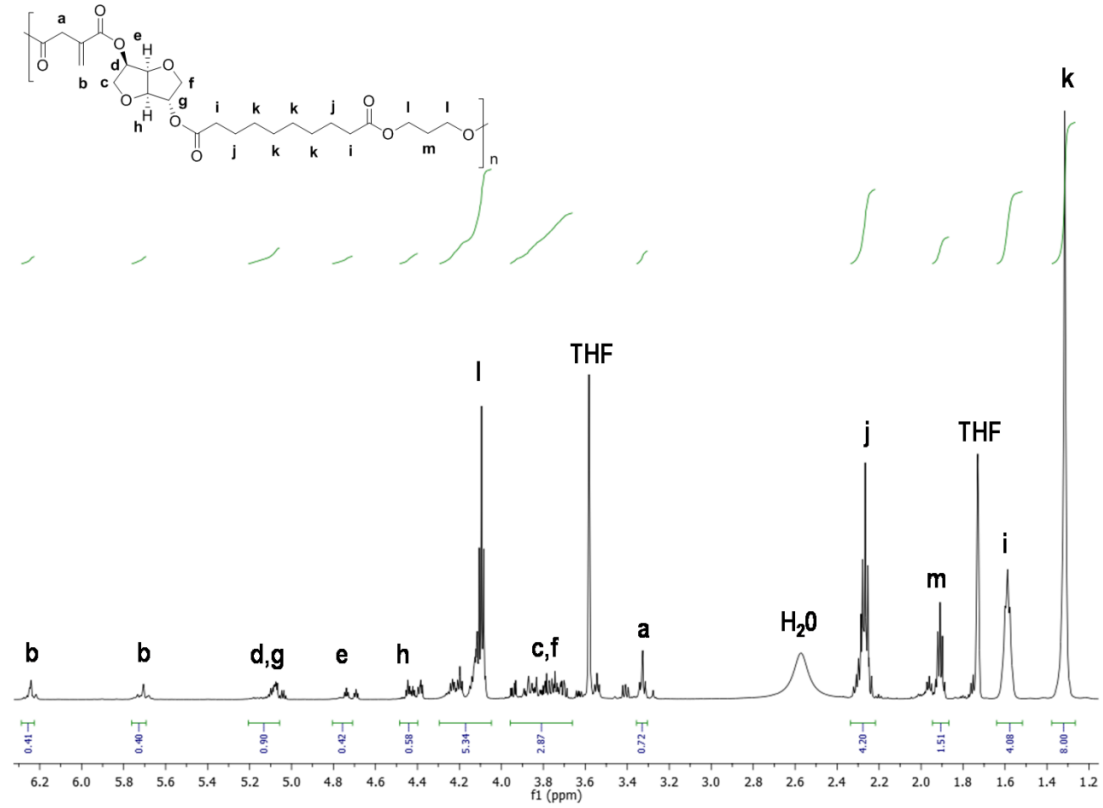


Figure B11. ^{1}H NMR spectrum of UP 5.1.

C. **SDT**

- *UPs*

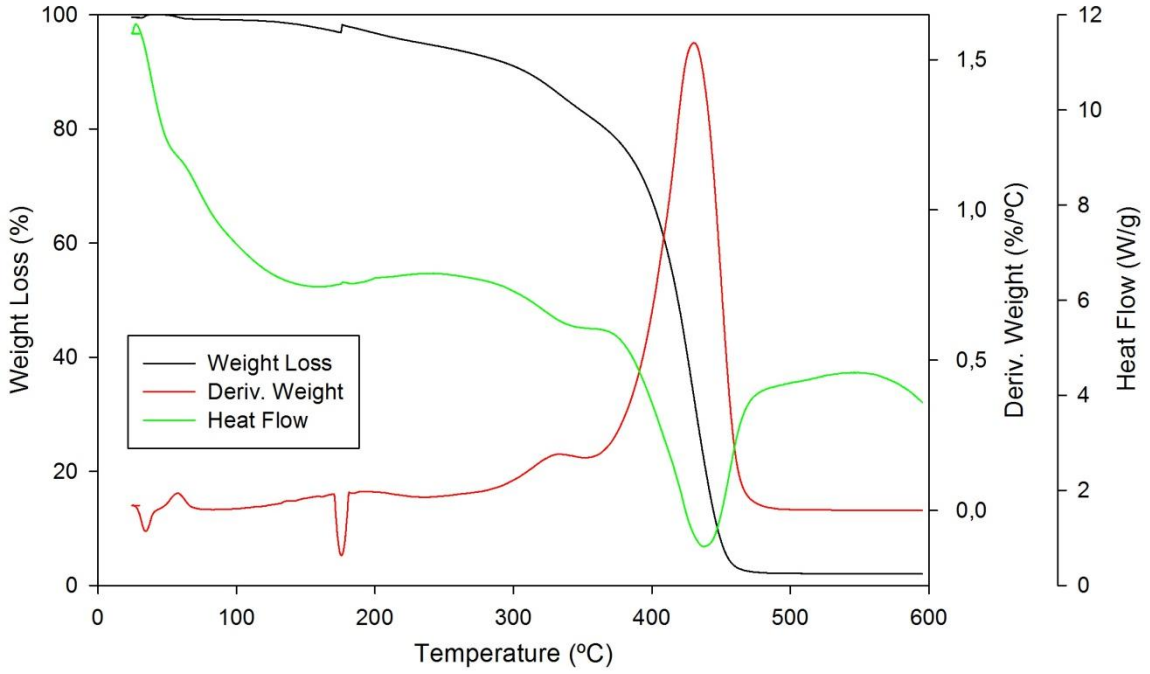


Figure C1. Simultaneous (DSC and TGA) thermoanalytical curves of UP 2.0.

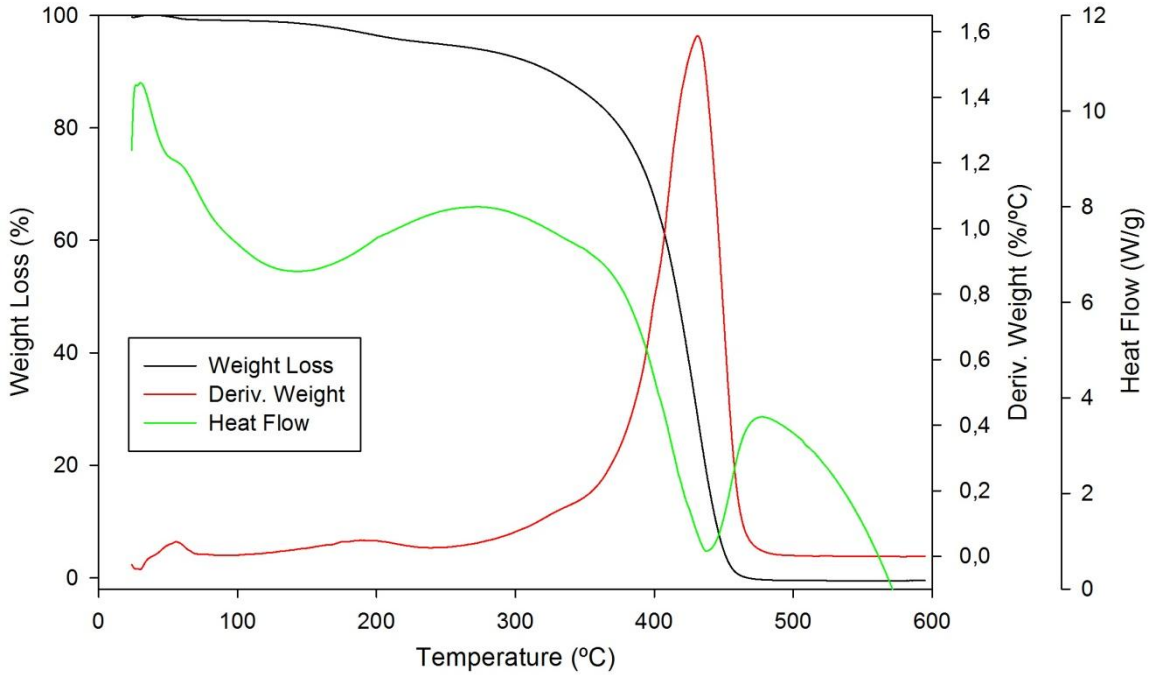


Figure C2. Simultaneous (DSC and TGA) thermoanalytical curves of UP 2.1.

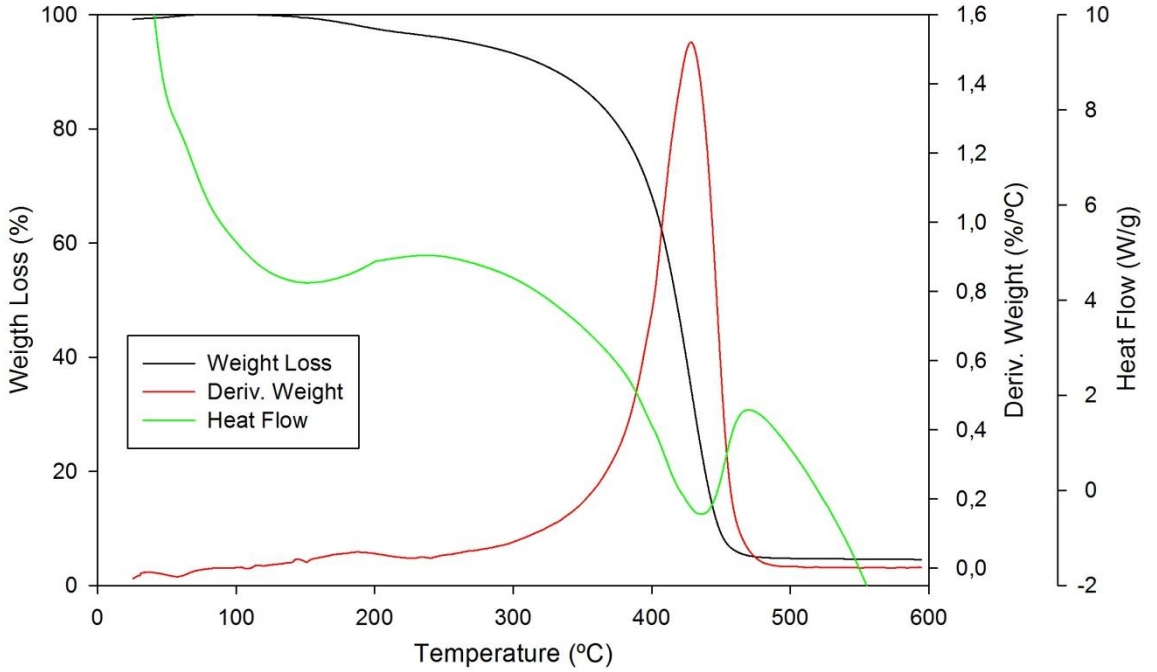


Figure C3. Simultaneous (DSC and TGA) thermoanalytical curves of UP 3.0.

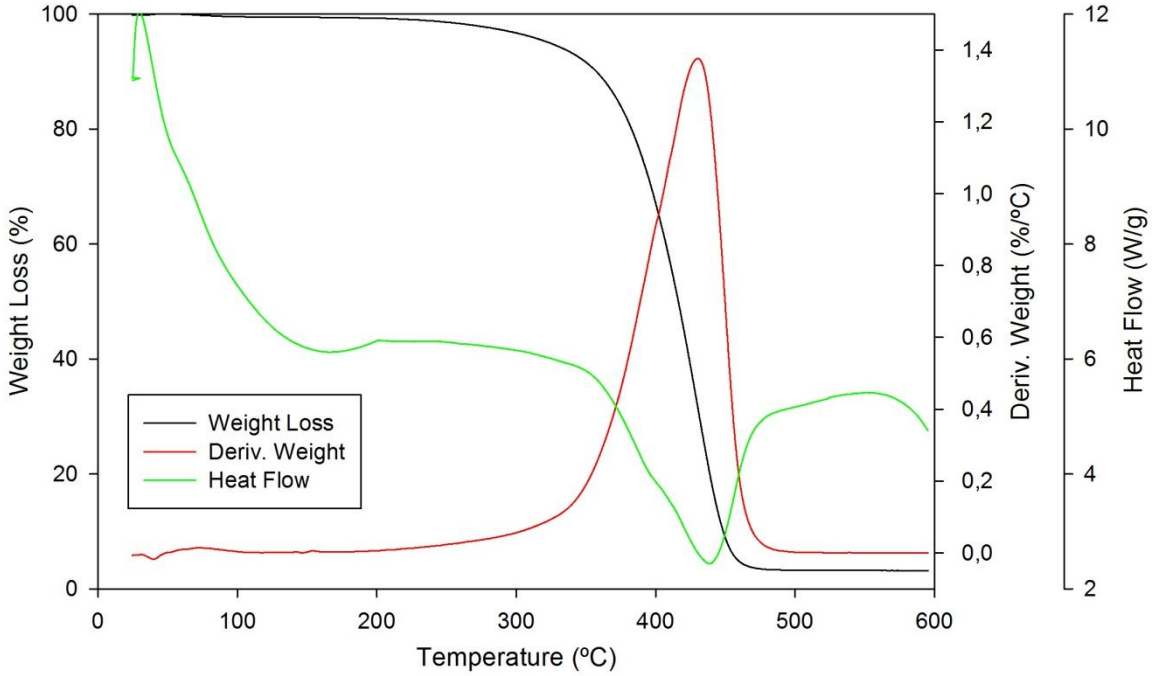


Figure C4. Simultaneous (DSC and TGA) thermoanalytical curves of UP 4.0.

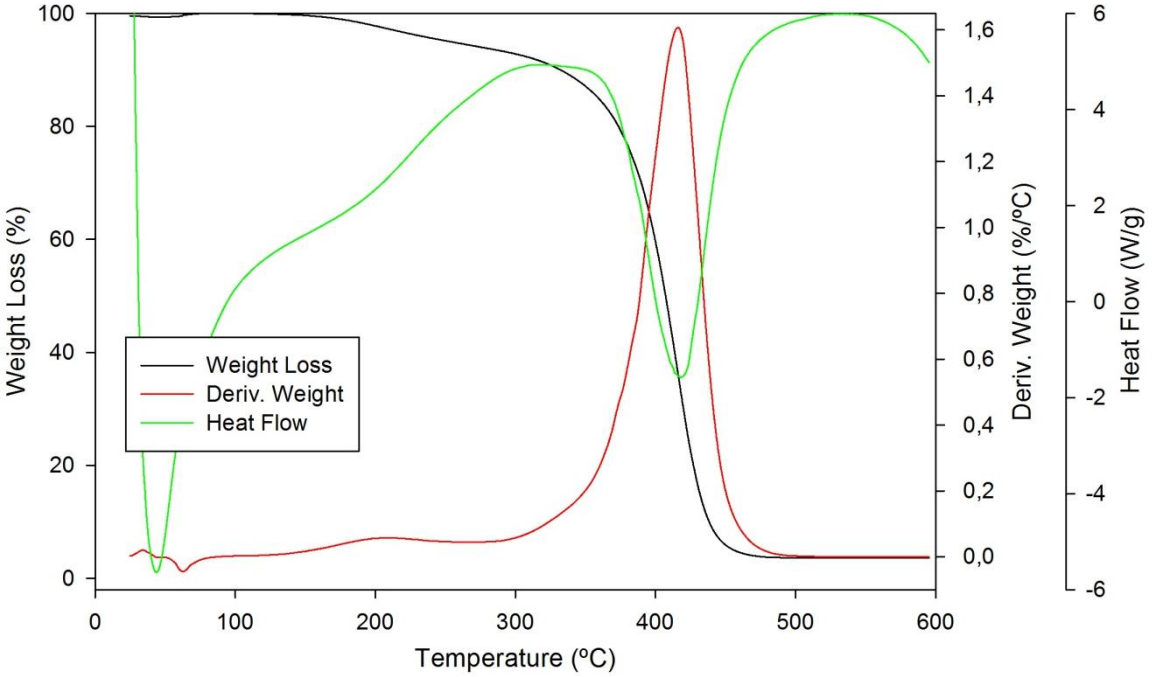


Figure C5. Simultaneous (DSC and TGA) thermoanalytical curves of UP 5.1.

- *UPRs*

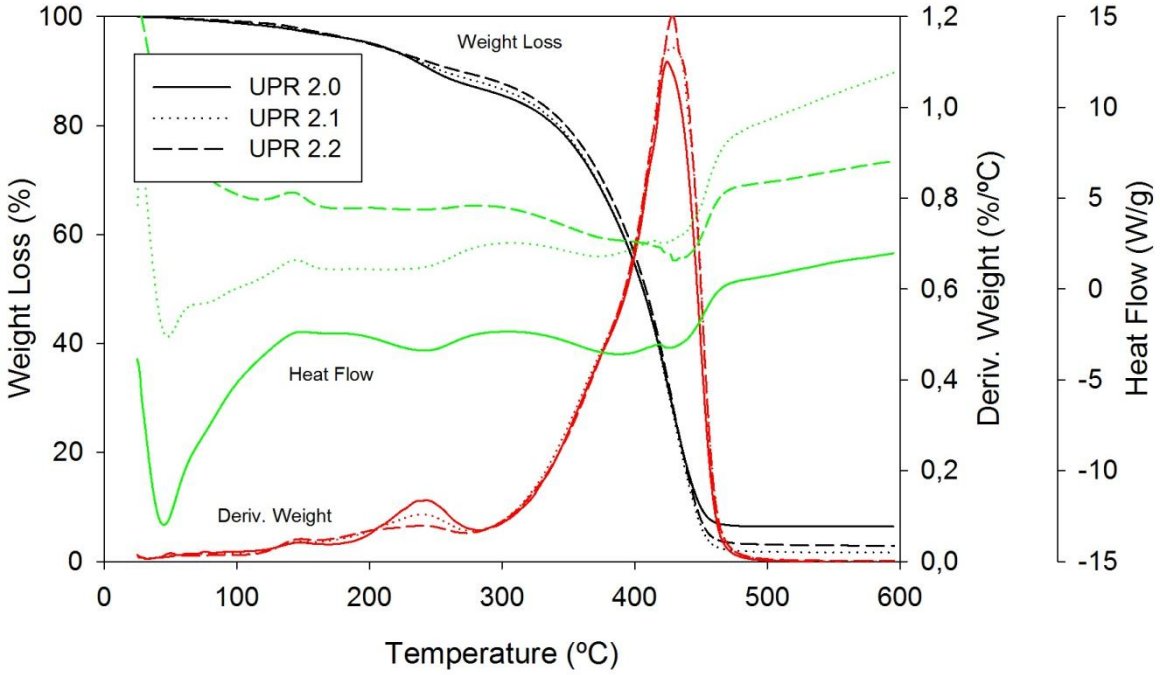


Figure C6. Simultaneous (DSC and TGA) thermoanalytical curves of UPR 2.

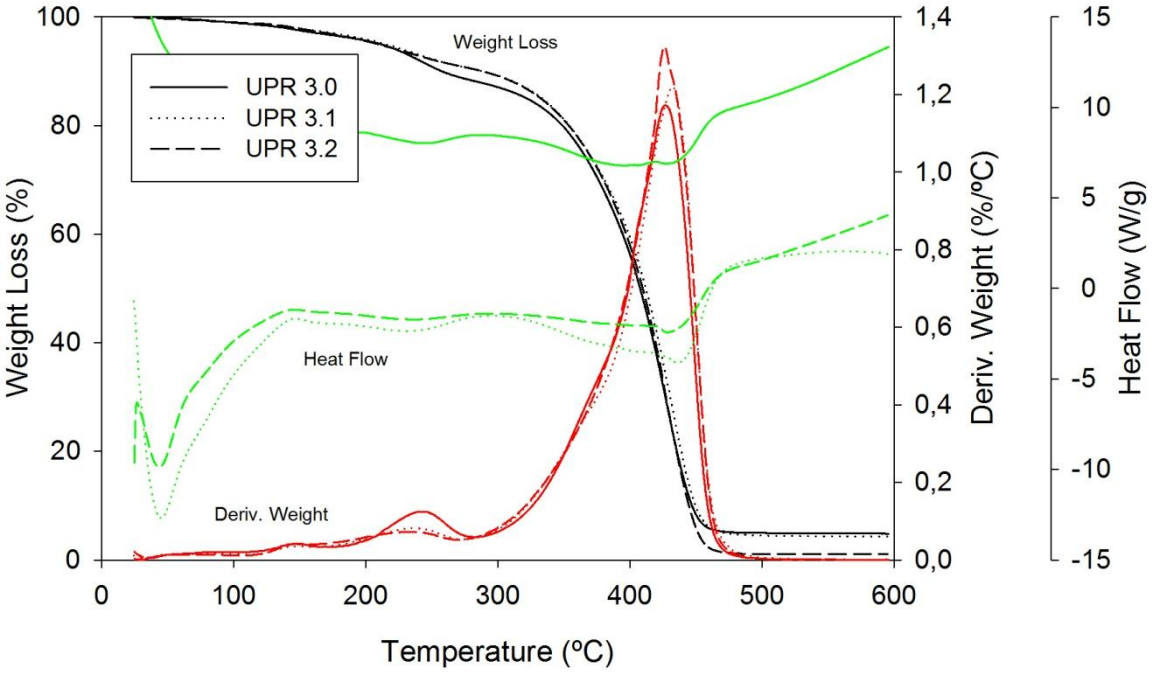


Figure C7. Simultaneous (DSC and TGA) thermoanalytical curves of UPR 3.

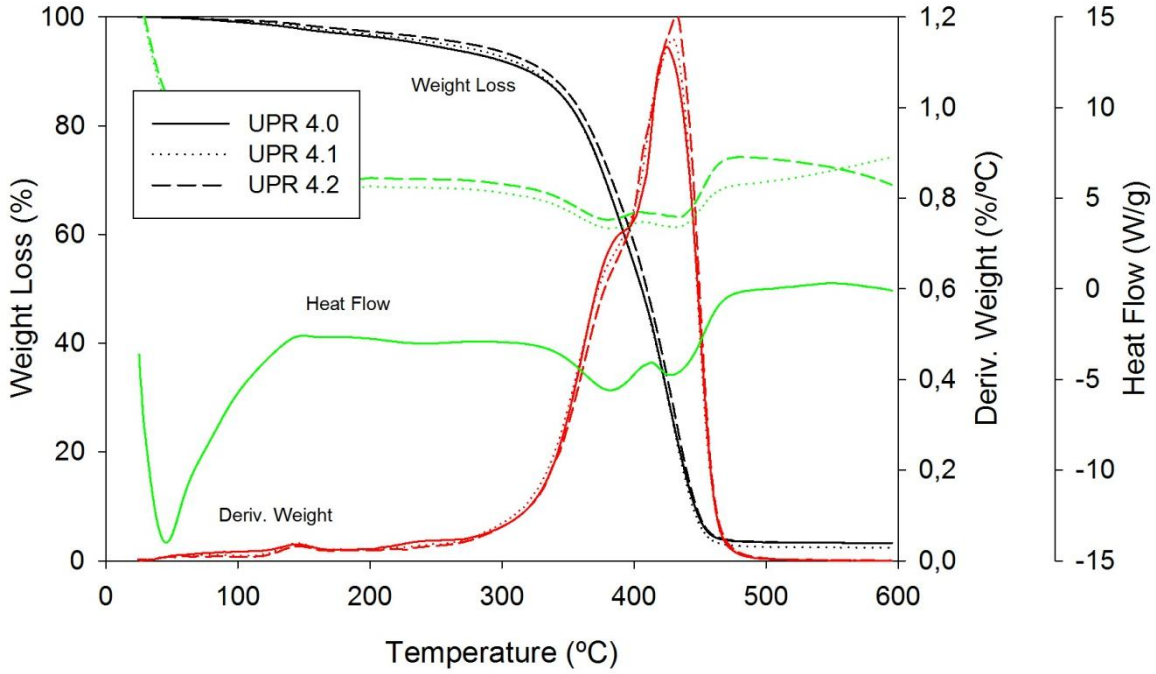


Figure C8. Simultaneous (DSC and TGA) thermoanalytical curves of UPR 4.

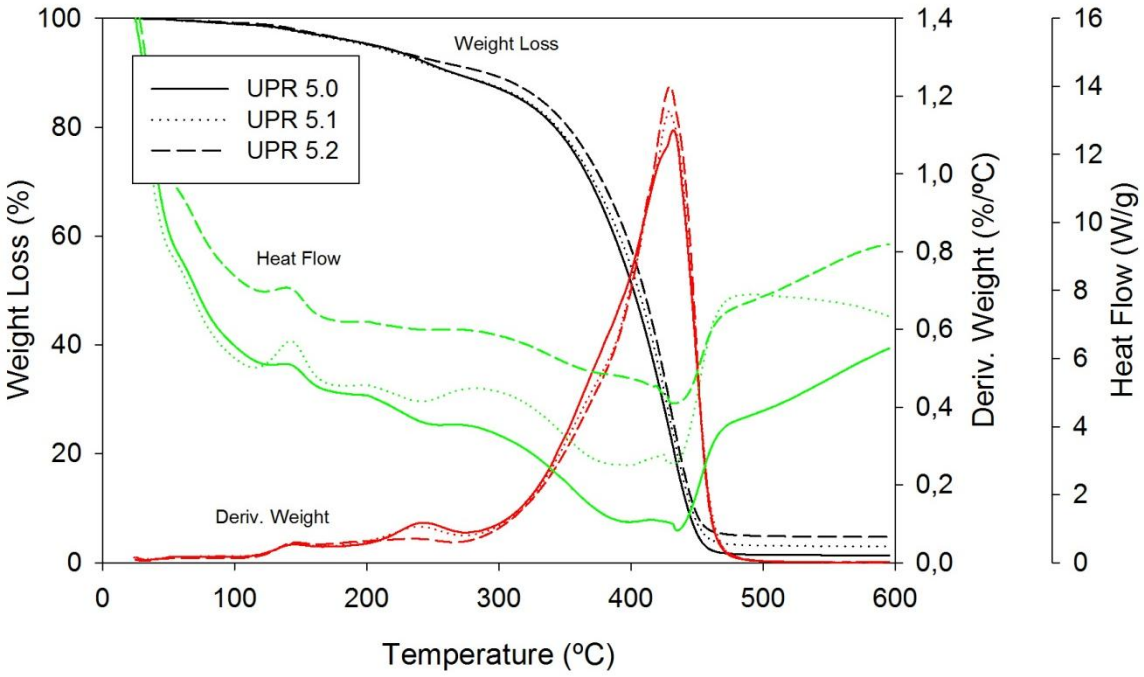


Figure C9. Simultaneous (DSC and TGA) thermoanalytical curves of UPR 5.

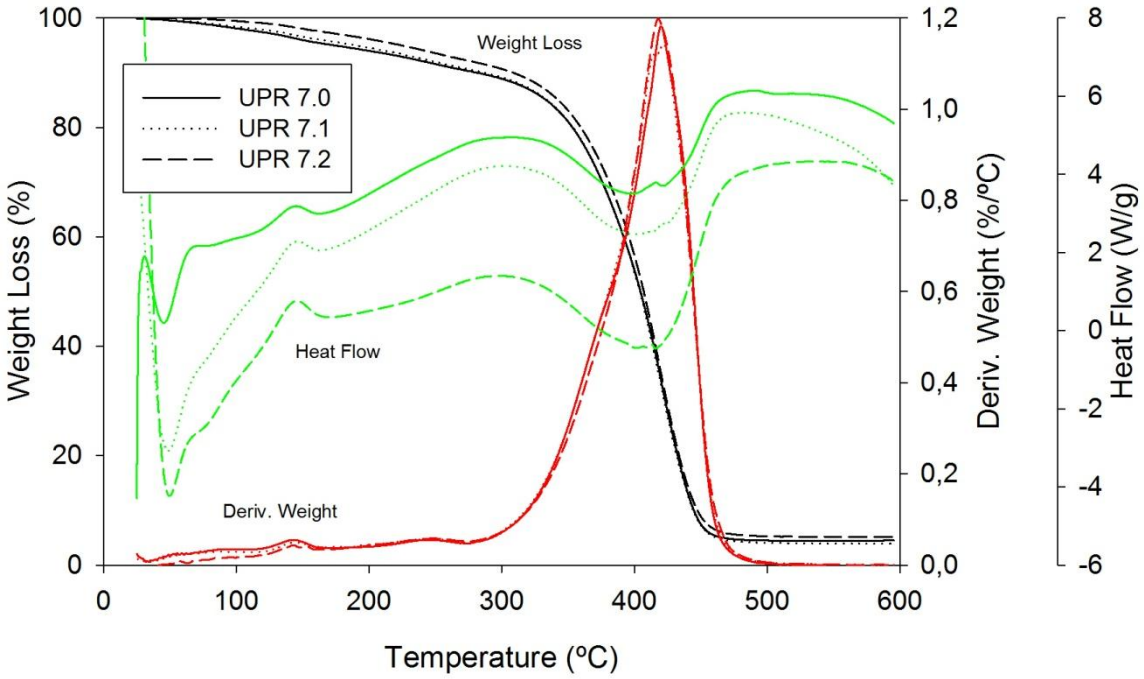


Figure C10. Simultaneous (DSC and TGA) thermoanalytical curves of UPR 7.

D. **DMTA**

- *UPs*

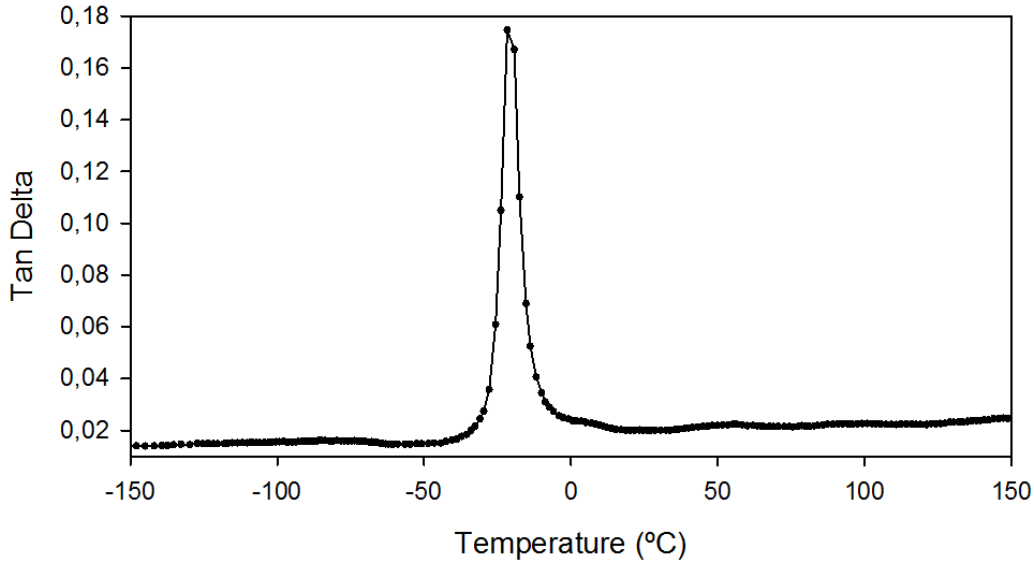


Figure D1. DMTA analysis of UP 1.1.

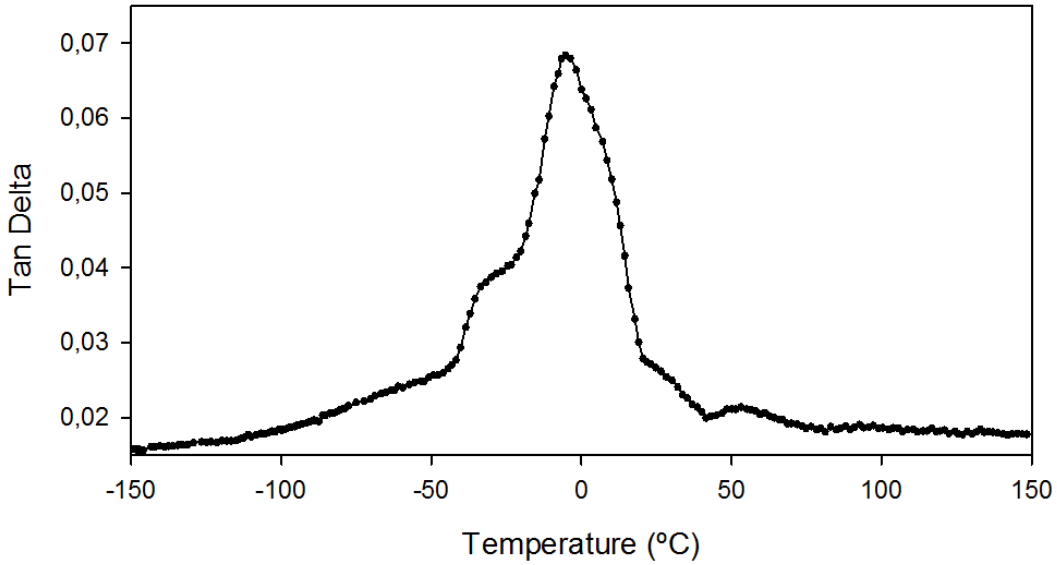


Figure D2. DMTA analysis of UP 2.0.

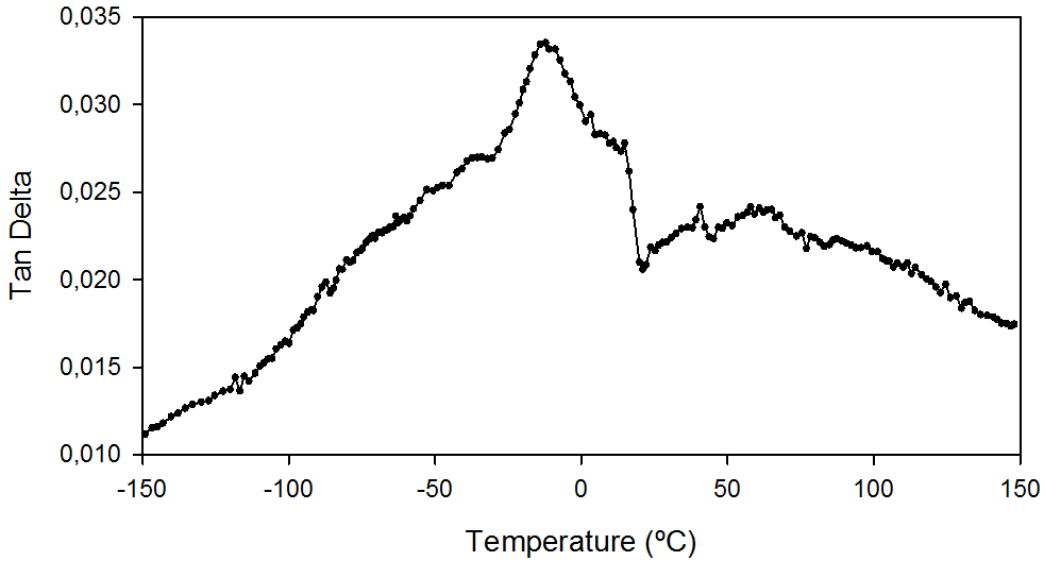


Figure D3. DMTA analysis of UP 2.1.

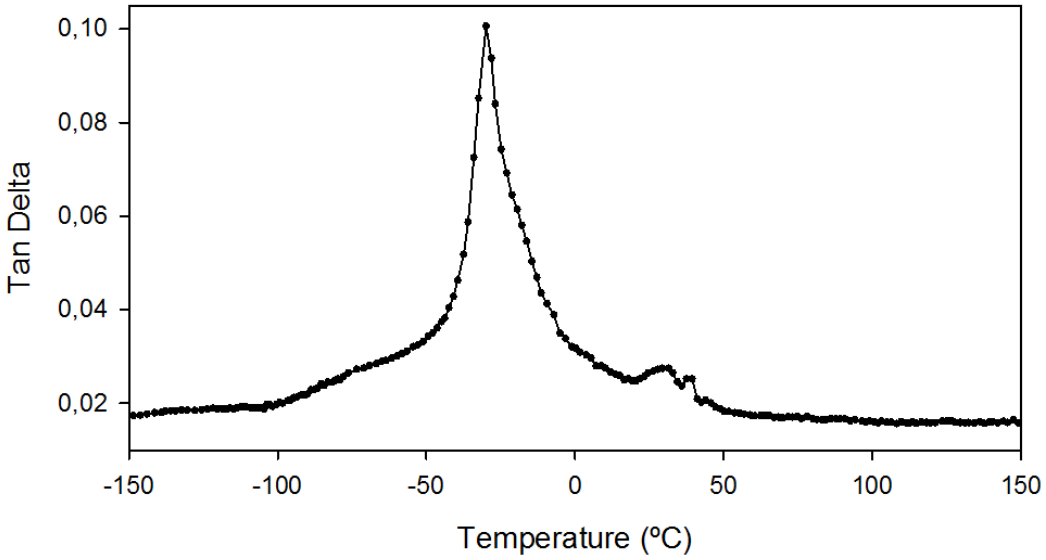


Figure D4. DMTA analysis of UP 3.0.

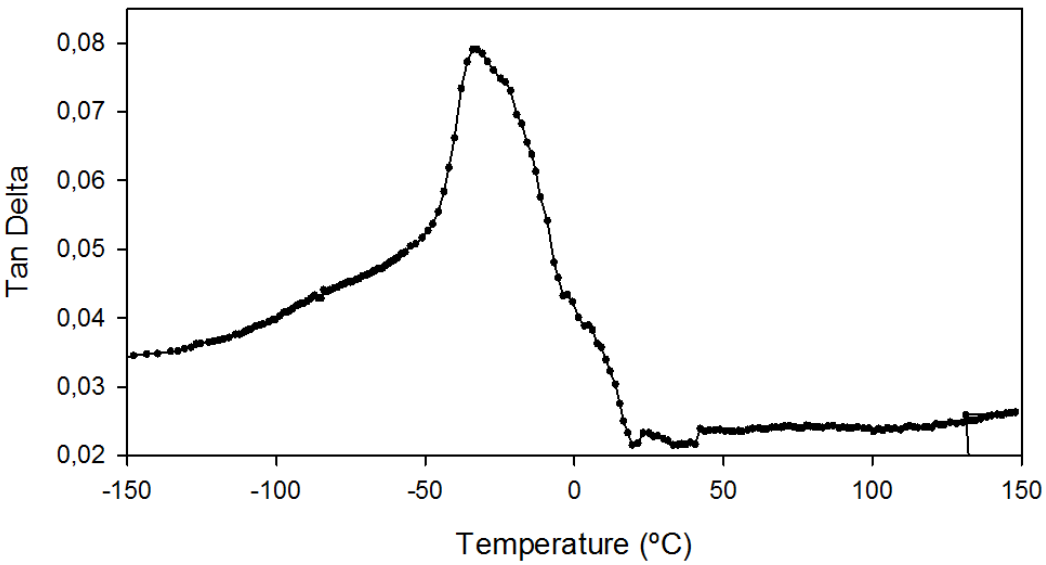


Figure D5. DMTA analysis of UP 4.0.

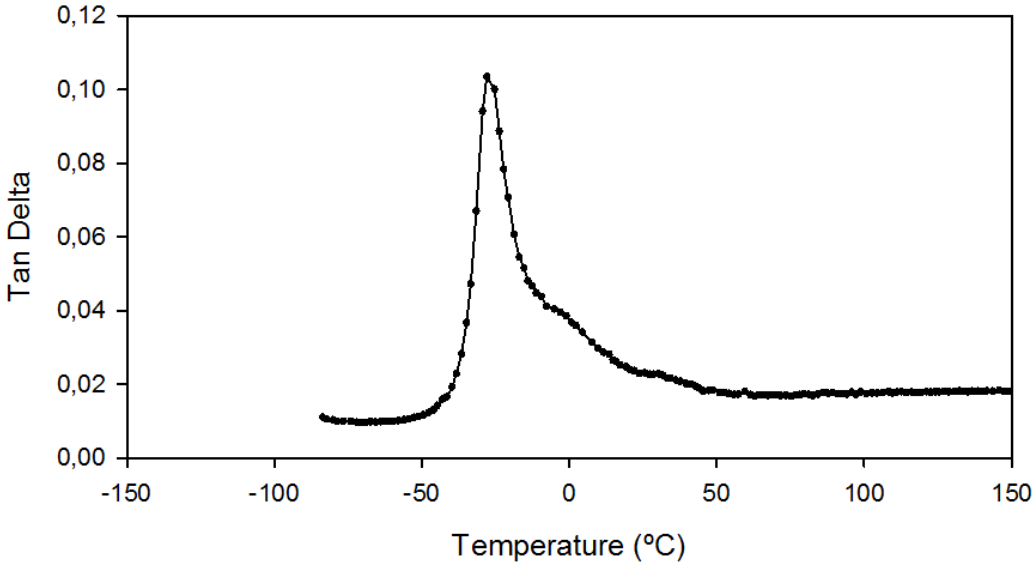


Figure D6. DMTA analysis of UP 5.1.

- *UPRs*

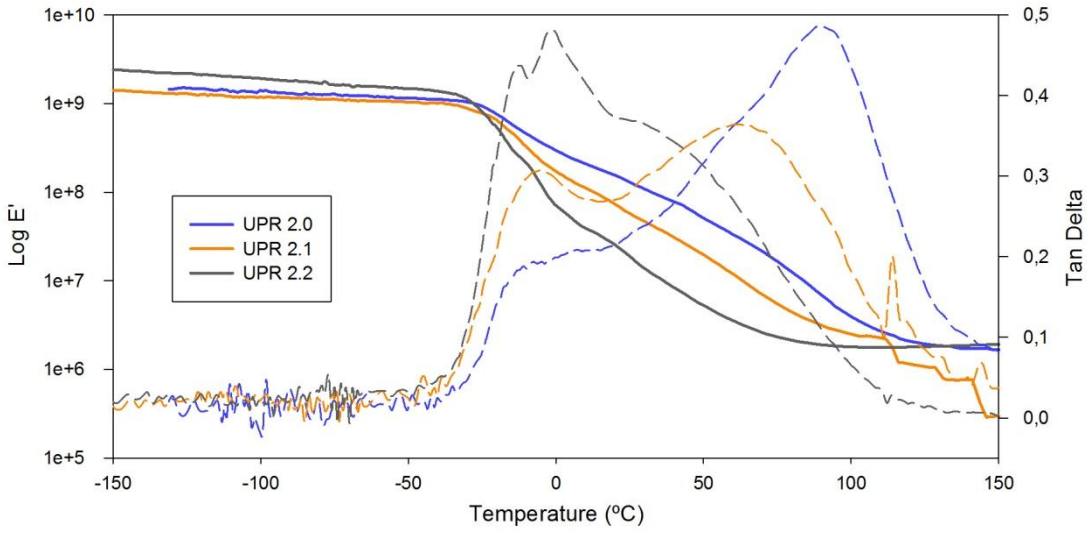


Figure D7. DMTA analysis of UPR 2.

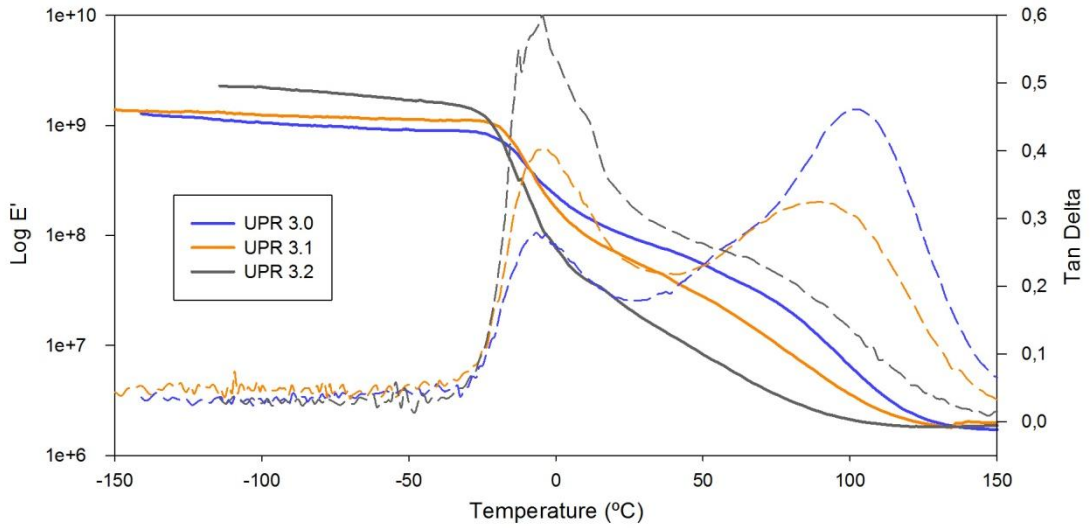


Figure D8. DMTA analysis of UPR 3.

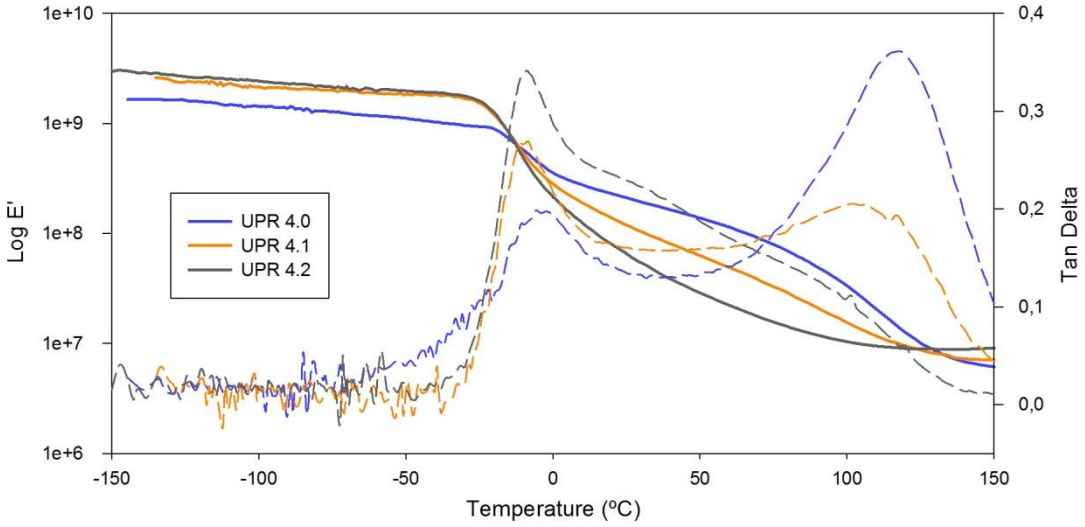


Figure D9. DMTA analysis of UPR 4.

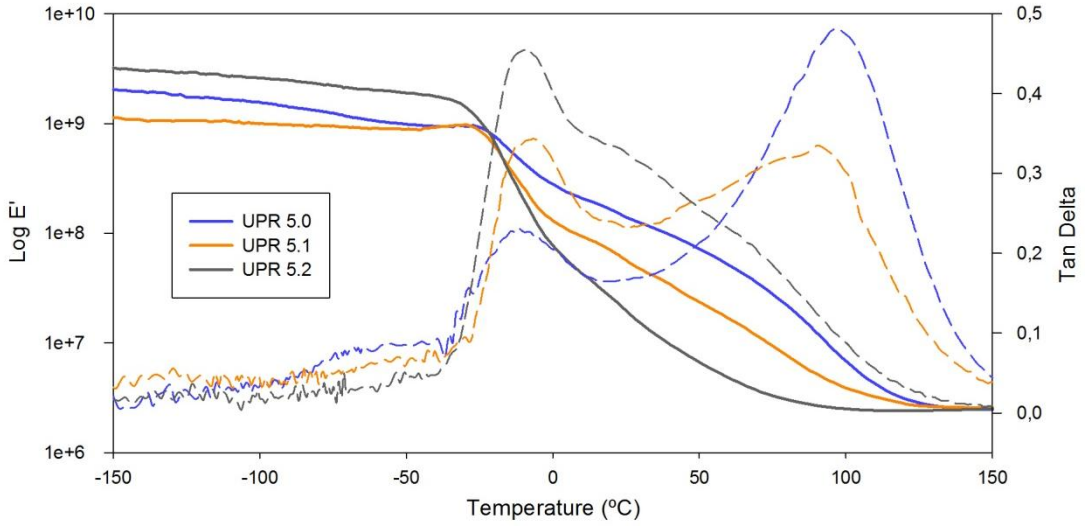


Figure D10. DMTA analysis of UPR 5.

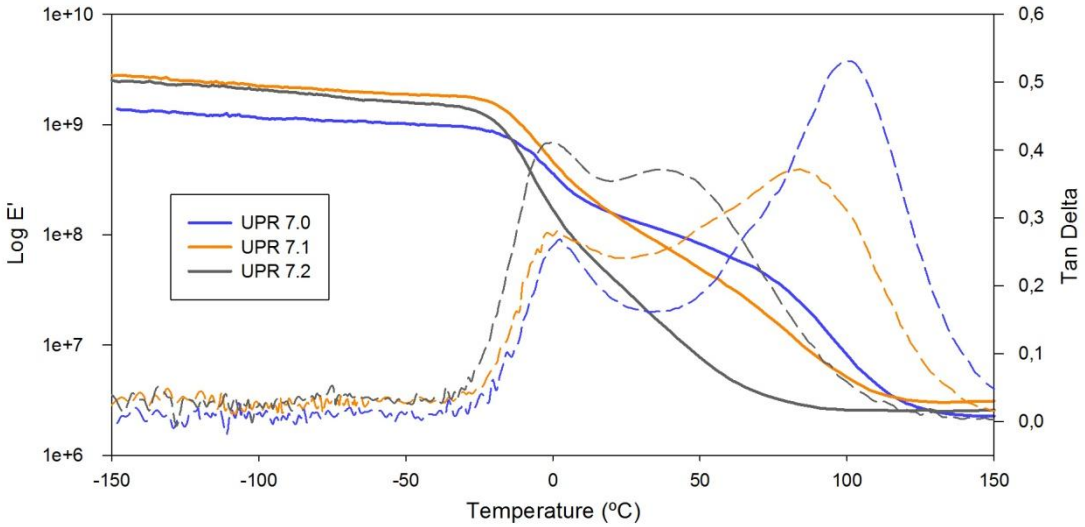


Figure D11. DMTA analysis of UPR 7.

E. **Swelling Capacity**

- *HEMA*

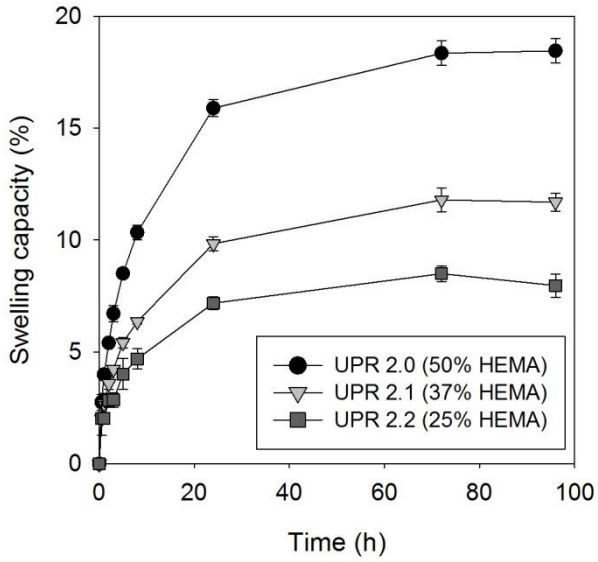


Figure E1. The swelling capacity of UPR 2.

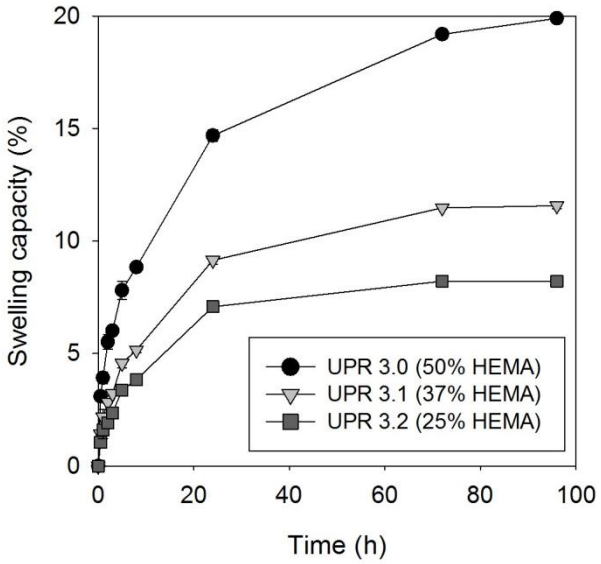


Figure E2. The swelling capacity of UPR 3.

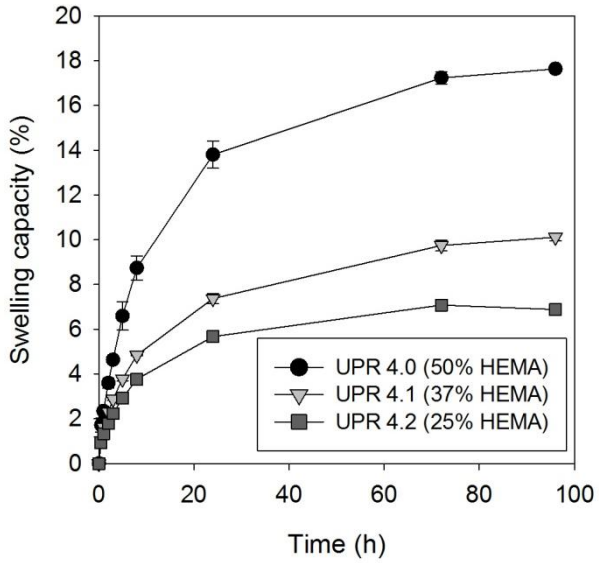


Figure E3. The swelling capacity of UPR 4.

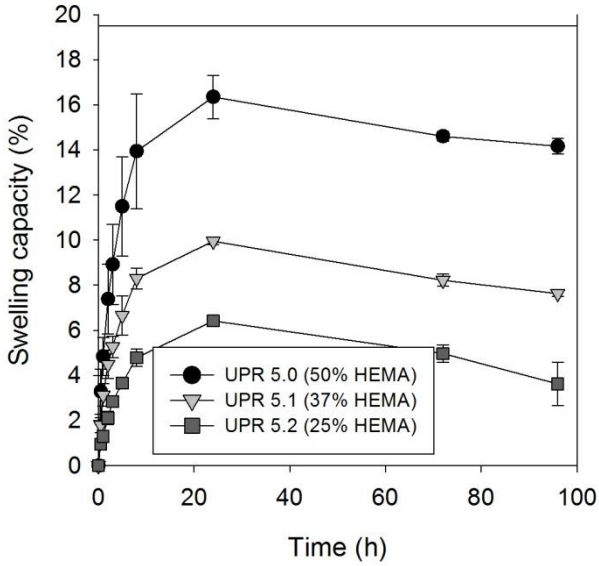


Figure E4. The swelling capacity of UPR 5.

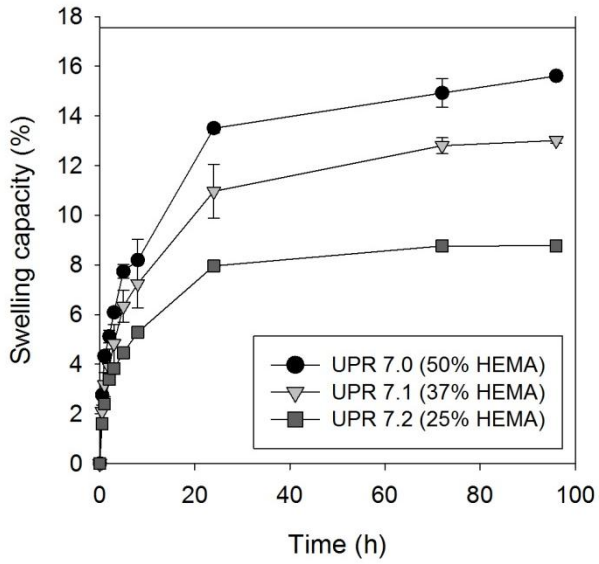


Figure E5. The swelling capacity of UPR 7.

F. *In vitro* hydrolytic degradation

- *HEMA*

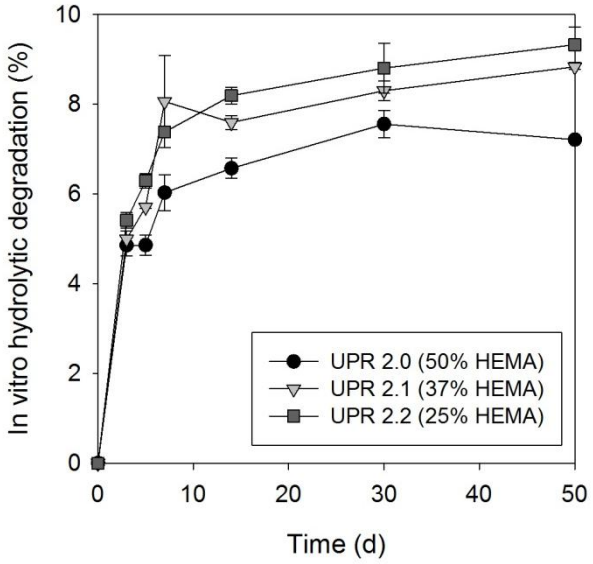


Figure F1. The *In vitro* hydrolytic degradation of UPR 2.

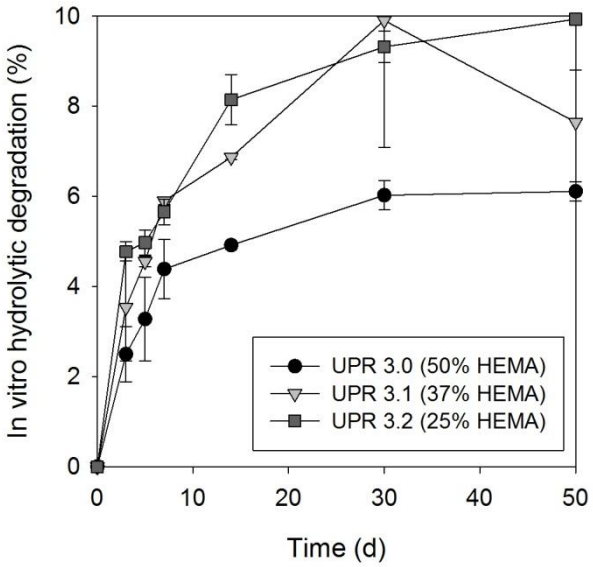


Figure F2. The *In vitro* hydrolytic degradation of UPR 3.

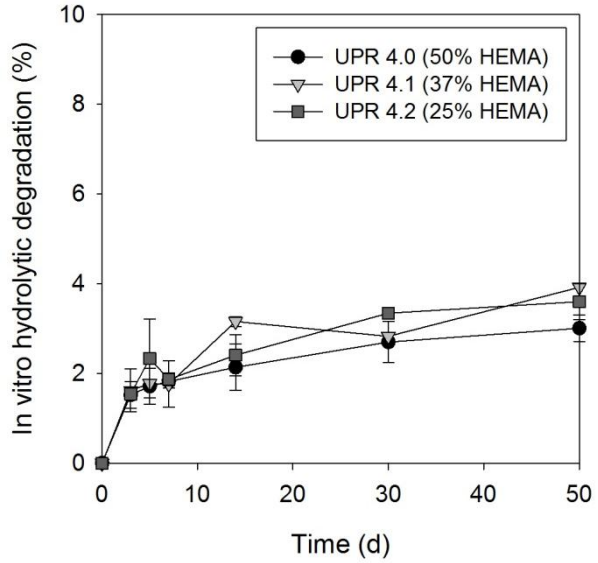


Figure F3. The *In vitro* hydrolytic degradation of UPR 4.

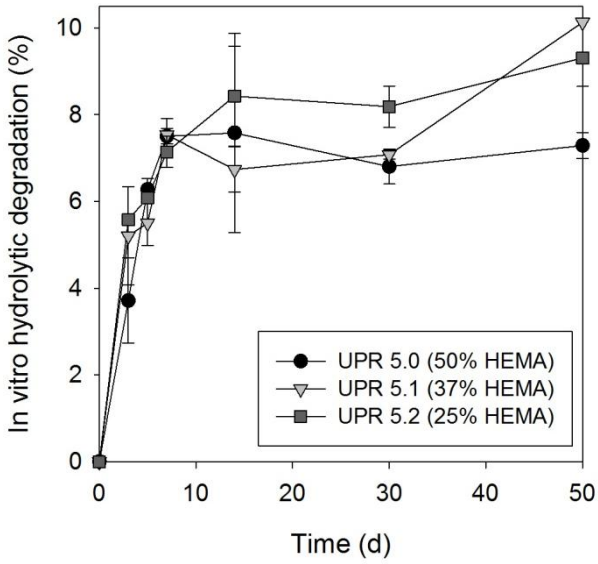


Figure F4. The *In vitro* hydrolytic degradation of UPR 5.

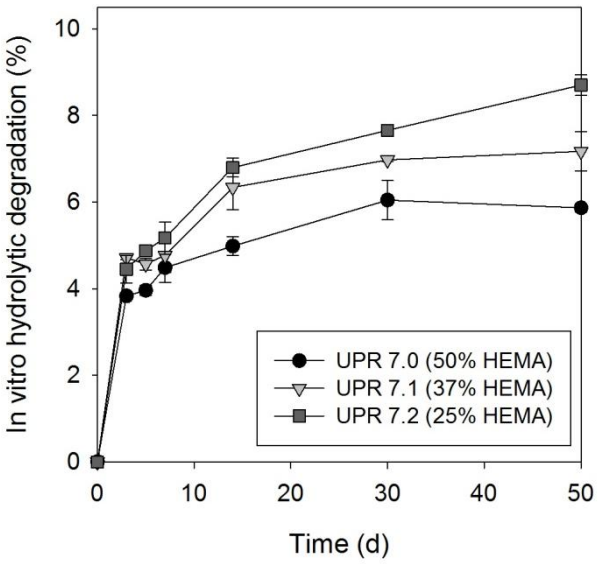


Figure F5. The *In vitro* hydrolytic degradation of UPR 7.