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Design of Non-Toxic Biodegradable Polyurethanes for Biomedical Applications.

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Dedications

We would like to dedicate our Master-thesis:

- To our family especially our parents whose unbelievable endurance, unconditional love, and untouchable devotion have been monumental;

-To all our brothers and sisters;

-To those who will be happy with this new goal in our study career;

-To all our best friends;

- To anyone who has ever taught us anything.

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Contents

Table of contents

Chapter III
Biobased Polyurethanes for
Biomedical Applications

List of Figures

List of Figures

List of Figures **Page**

Chapter I Theoretical Background

Chapter III Biobased Polyurethanes for Biomedical Applications

List of Figures

List of Tables

List of Tables

Chapter I Theoretical Background

Chapter III **Biobased Polyurethanes for Biomedical Applications**

List Of Notations And Abbreviations

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Abbreviations	Description
AAc	ascorbic acid
AB	acryloylbenzothiazole
AFM	Atomic Force microscopy
ATR-FTIR	Attenuated total re ection Fourier transform infrared
AZO	4,4'-dihydrox-yazobenzene-3,3'-dicarboxylic acid
BD	1,4-Butanediol
BDA	1,4 Butanedia-mine
BDI	Butane diisocyanate
1, 4-BDI	1, 4 Butane diisocyanate
BES	N,N-bis (2-hydorxyethyl)-2-aminoethane-sulfonic acid
BHECA	N,N-bis(2-hydroxyethyl) cinnamamide
BioEPUR	Biodegradable polyurethane elastomers
CCHME	L-cystine dihy-drochloride methyl esters
CHIT	chitosan
CIP	ciprofloxacin
CL	ε-caprolactone
CNFs	carbon nano-fibres
CNTs	carbon nanotubes
DABCO	1,4-Diazabicyclo-[2.2.2]-octan
DBTDL	Dibutyltin dilaurate
DBTDO	Dibutyltin dioctanate
DD	1,10- decanediol
DMA	Dynamic mechanical analysis
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DOX	Doxorubicin
DSC	Differential scanning calorimetry
E_b	Elongation at break

List of Notations and Abbreviations

EO	Ethylene oxide
1, 2-EDO	1, 2- ethane diol
FTIR	Fourier transform infrared spectroscopy
HD	1, 6-hexanediol
HDI	Hexamethylene diisocyanate
1, 6-HDI	1,6 Hex methylene diisocyanate
HGF	Hepatocyte growth factor
HMDI	hydrogenated MDI
1H NMR	Proton nuclear magnetic resonance spectroscopy
HS	Hard segment
HTPB	Hydroxy terminated polybutadiene
IPDI	Isophorone diisocyanate
GLI	glycolide
LDI	L-Lysine methyl ester diisocyanate
LEE	Lysine ethyl ester
LLA	L-Lactide
M_n	number-average molecular weight of polymer [g/mol]
M_w	Molecular weight
MDI	Diphenylmethane diisocyanate
MIDE	2,2-(methylimino)diethanol
MW	Molecular weight (s)
NMR	Nuclear magnetic resonance spectroscopy
OD	1,8-octanediol
OEAD	Oligo (ethylene adipate)
PBA	poly(1,4-butylene adipate)
PBS	phosphate-buffered saline
PCL	Poly (ε-caprolactone)
PDMEA	poly(1,2-dimethylethylene adipate)
PDI	phenylene diisocyanate
PEG	Polyethylene glycol(s)

List of Notations and Abbreviations

PEUs	poly-ester-urethanes
PEUUs	poly-ester-urea-urethanes
PHA	Polyhydroxyalkanoate(s)
PHB	poly [(R,S)-3-hydroxybutyrate]
PHBHH	poly(3-hydroxybutyrate-co-3- hydroxyhexanoate)
PHC	poly(1,6-hexamethylene carbonate)
PHECA	N,N-Bis(2-hydroxyethyl) cinnamamide
PGs	Propylene glycols
PLA	Polylactic acid
PLAPBAPLA	polylactide-block-poly(butylene adipate)-block-polylactide
PPA	poly(1,3-propylene adipate)
PPG	Polypropylene ether glycol
PU	Polyurethane
PTMC	Polytrimethylene carbonate
PTMO	poly (oxytetramethylene) glycol
PURDDS	Polyurethane drug delivery systems
PVLCL	poly (δ-valerolactone-co-ε-caprolactone)
TEM	Transmission electron microscopy
TG	Glass transition temperature
TGA	Themogravimetric analysis
TDI	Toluene diisocyanate
TMA	Thermo-Mechanical Analysis
TMC	Trimethylene carbonate
TPUS	Thermoplastic polyurethanes
RAC-LA	RAC-Lactide
ROP	Ring-opening polymerization
SAXS	Small angles X-ray scattering
SEM	Scanning electron microscopy spectroscopy
SMPs	Shape memory polymers
SMPUs	Shape memory polyurethane

List of Notations and Abbreviations

SS	Soft segment
T_g	glass transition temperature
T_m	melting point
UV	ultraviolet radiation
XRD	X-ray diffraction
XRF	x-ray fluorescence
S_e	values of fail stress
$SnOct_2$	Tin(II) 2-ethylhexanoate

General Introduction

I. Introduction General

Polyurethane is a kind of polymer that contains repeating urethane groups. With an enormous diversity of chemical compositions and properties, it has found wide applications in a number of technological areas in our daily life, such as automotive parts, footwear, furnishings, construction ,coatings, etc. **[1]**. In the last few decades biomaterials used for prosthesis and medical devices have seen a rapid development and, due to advances in tissue engineering, polyurethane, as one of the most important biomaterials, finds a niche in this field because of its widely variable mechanical properties and excellent biocompatibility. Polyurethane materials were first introduced in biomedical applications in the late 1950s. In 1958, Pangman described composite breast prostheses covered with polyester urethane foam. Later that year, Mandarino and Salvatore **[2]** used a rigid polyurethane foam called Ostamer TM for in situ bone fixation. Since then, polyurethane, as a biomaterial, has been widely used in medical devices, and a series of biomedical grade polyurethanes were designed and developed.

Based on their excellent mechanical properties and biocompatibility, polyurethanes have been widely used in the preparation of all kinds of medical devices, including wound dressings, artificial organs, vascular stents, and so on. Many scientists worldwide are working in this area, to broaden the applications of polyurethane or to optimize its properties to meet the requirements of specific applications, and many papers and research results are published every year. Some very good reviews and books on the biomedical application of polyurethane have been published, which will give readers a comprehensive understanding of the progress of polyurethane in medical devices. **[3-20]**.

Overall; This Master-Thesis is composed of three chapters. The first presents a theoretical background of Polyurethane; their properties and various applications in biomedical fields the second chapter presents a brief presentation of some of the works that have been published and which covered different aspects of the subject. The third chapter illustrates Biobased polyurethanes for biomedical applications.

The overall conclusion of this bibliographic research is discussed in the last part.

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Chapter I
Theoretical Background

I.1 Introduction

Polyurethane is a versatile polymer that is formed by the reaction between an isocyanate and a polyol. It can be produced in a wide range of hardness, density, and chemical properties to suit various applications. Polyurethane has a wide range of applications and is used in many different industries, such as construction, automotive, furniture, electronics, and medical equipment. It has many desirable properties, including high strength, toughness, durability, and resistance to abrasion, chemicals, and weathering. It is also highly flexible and can be molded into various shapes and forms. These properties make it an attractive material for many different applications.

Thermosetting polyurethanes, on the other hand, are rigid and inflexible materials that are used in applications such as foams, elastomers, and coatings. They are formed through a chemical reaction that creates a three-dimensional network structure, which cannot be melted or reshaped without losing their mechanical properties.

While polyurethane has many benefits, it is important to be aware of its potential environmental impact. Improper disposal of polyurethane products can release harmful chemicals into the environment, and the production of polyurethane can also be energy-intensive. As such, it is important to use and dispose of polyurethane products responsibly **[1].**

I.2.Synthesis methods and chemical structure of polyurethane

In 1929, Carothers suggested a classification system based on the nature of the chemical reactions employed in the polymerization, called condensation and addition polymers; P.J. Flory has changed this classification for step reactions and chain reactions, which are similar, but not equal, to the first system. There is a particular difference in the case of synthesis of polyurethanes. This polymer is based on the reaction of isocyanates with hydroxyl compounds, but there is no elimination of small molecule, as the condensation polymers from Carothers's system had described. This mechanism usually involves unsaturated monomers, which are formed by free radical (can be also anions or cations). Since free radical generate a rapid formation of high molar mass polymers due to its high reactivity, the chain polymerization is the most important mechanism of polymers. The method follows three phases: initiation, propagation and termination. On the other hand, step's mechanism involves functionally substituted monomers, by condensation reactions. Usually it uses bifunctional reactants to form high molar mass and monofunctional reactants to control the reaction. Trifunctional compounds can be also used to form branched or cross-linked polymers**[2].**

PU's are an important class of thermoplastic and thermoset polymers obtained by polycondensation reactions among different polyols, isocyanates and chain extender compounds, leading to diverse polymers with many different properties and possibilities of application; their mechanical, thermal and chemical properties can be designed by the reaction between polyisocyanates and hydroxyl groups, generating urethane groups, being also possible the generation of ramifications by adding previously-produced urethane groups, which leads to alofonate formation as presented below.

The functionality of the hydroxyl compound as well as the isocyanate can increase to three or more in order to form branched or cross-linked polymers. Other structural changes can also be made at which the nature of monomers might be altered by changing its molecular weight and type. For this reasons, the cross-linking and chain flexibility properties of PU's and its intermolecular forces can be varied widely and independently **[3,4].**

Different kinds of isocyanates, with different chemical reactivities, can be exploited in polyurethane synthesis. In general, aromatic diisocyanates are more reactive than aliphatic ones, thus, aliphatic diisocyanates are applied only if their reactivities match the specific polymer reaction and special properties desired in the final product. Polyurethane coating from aliphatic

isocyanates are often light stable while polyurethanes from aromatic iocyanates will undergo photodegradation.

PU's are segmented polymers comprising of alternating sequences of soft and hard segments, ions can be introduced into both hard and soft segments producing, this way, many different kinds of polyurethane ionomers with a wide range of properties. The soft segments used in polyurethane elastomers are dihydroxy terminated long chain macroglycols with low molecular weight such as polyethers, polyesters, polydienes and polyolefins. Polyester-based urethanes are very sensitive to hydrolytic cleavage of the ester linkage when compared to those reached by using polyether-based urethanes. Polyurethane based on polyether or polyester soft segments and diisocyanate-based hard segments are well-known tough materials and are usually applied as additive to enhance toughness of brittle materials as well as their thermal properties.

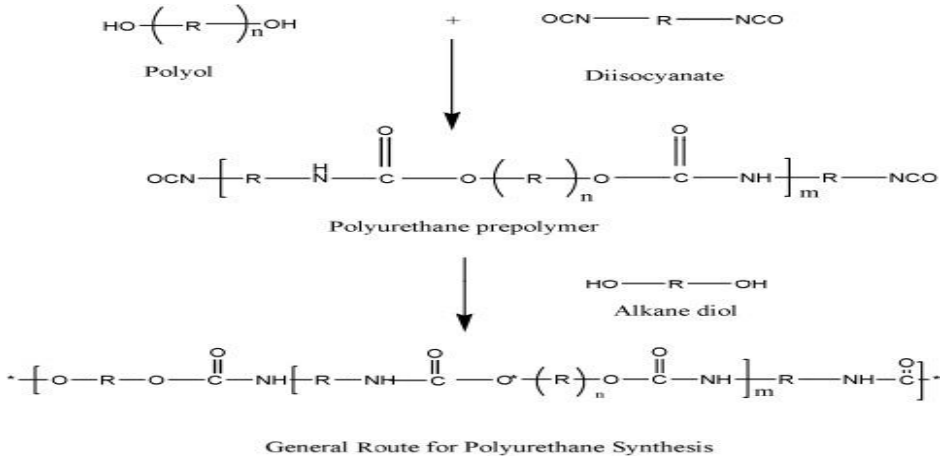
excellent mechanical properties of polyurethane can be reached by introduction of a suitable chain extender to increase the hard segment length, allowing, this way, microphase separation and consequently increase the modulus and glassy transition temperature of the product. Such chain extender can be group into two categories: aromatic diol and diamine, and the corresponding aliphatic diol and diamine. in general a softer product is reached when aliphatic diols or diamines are applied as chain extenders.

Due to the incompatibility between the hard and the soft segments, thermoplastic polyurethanes undergo microphase separation resulting in a hard-segment domain, soft segment matrix, and urethane-bonded interphase. The hard-segment domains act as physical cross-links in the soft-segment matrix. The primary driving force for phase separation is the strong intermolecular interaction of the urethane units, capable of forming intermolecular hydrogen bounds. Owing to such interactions, interconnected or isolated hard segments remain distributed in the soft-segment matrix, thought the soft domain may contain some hard segments dissolved in it, which is evident from the hydrogen bonding of the urethane -NH groups with the oxygen of the ether or ester linkages **[5].**

The synthesis of polyurethanes can be carried out 'by a variety of methods **[6]**, such as prepolymer technique, quasiprepolymer technique and 'one shot' technique.

I.2.1Prepolymer Technique

A polyurethane elastomer was formulated by the condensation polymerization of macrodiol, diisocyanate, and extended with chain extender via the prepolymer methodology following Barikani & Hepburn (1986, 1987). The reaction was carried out in a four-necked reaction kettle equipped with a mechanical stirrer, a reflux condenser, dropping funnel and a N2 inlet, outlet and heating oil bath. Polyol was placed (e.g., HTPB: 21.72g; 0.0072 mole) in the reaction kettle and heated to 60°C. Subsequently, tolylene diisocyanate (e.g., TDI: 3.78g; 0.0217 moles) was added and the temperature was raised to 100°C under a blanket of dry N2. A small portion of the reaction mixture was used to ensure the completion of the prepolymer synthesis by FTIR spectroscopy. NCO terminated PU prepolymer was obtained in 1 h at 100°C. Previously degassed chain extender (e.g., 1, 2-EDO: 0.88g; 0.0142 moles) was added during vigorous stirring of prepolymer to convert it into the final PU. When the reaction mixture was homogeneous and reflects the complete dispersion of the chain extender, subsequently the liquid polymer was cast into a Teflon plate to form a uniform sheet. The synthesized polymer samples were first placed under vacuum for 15 minutes to ensure the removal of air bubbles before casting and then cured for 24 hours in a hot air circulating oven at 100˚C. The cured sample sheets were then stored for one week at ambient temperature (25°C) and 40% relative humidity before testing. A schematic illustration for the synthesis of polyurethanes is shown in **Scheme I.1 [7].**



Scheme I.1: General scheme for the synthesis of polyurethane (PU).

In the special case of monocomponent PU, the single partner of the reaction is the prepolymer. The prepolymer is extended to a high-MW polymer by reaction with water present in the atmosphere. Water, is in fact, a chain extender and the resulting high-MW polymer has both bonds: urethane and urea bonds If a prepolymer derived from an oligo-triol or an oligo-polyol, having 3 or more terminal -NCO groups is used, if it is in contact with atmospheric humidity, cross-linked PU are obtained.

I.2.2Quasi prepolymer Technique

Quasiprepolymers are obtained in a similar way to the prepolymers, with the difference that the reaction between oligo-polyol and the isocyanates is developed in the presence of a large excess of isocyanate. Quasi prepolymers are a mixture of prepolymers and free isocyanates (around 16–32% free isocyanates),Quasi prepolymers are frequently used to transform a solid isocyanate, (e.g., pure MDI), into a liquid, and are used in flexible PU foams, in microcellular elastomers and in other PU applications**.**

I.2.3One-Shot Technique

One of the most used techniques to obtain PU is the one-shot technique, which consists of the very efficient mixing, in one step only, in a short time, of all the raw materials involved in PU fabrication: isocyanate, oligo-polyol, chain extenders or cross linkers, silicon emulsifiers, blowing agents, catalysts, such as tertiary amines and tin or stannous catalysts and other auxiliary raw materials (flame retardants, fillers). The ‘key’ to the ‘one-shot’ technique is extremely efficient mixing, in a very short time. At this initial stage, the reactions between isocyanates and active hydrogen compounds are insignificant and the reaction mixture is liquid.

In order to simplify the procedure of using too many components, a ‘master batch’, that is a mixture of the components that do not react with each other, (e.g., oligopolyol, water, chain extender, catalysts and so on), is made before foaming. Then it is possible to use only two components: one is the polyolic component (called component A or formulated polyol, containing a mixture of all raw materials except for the isocyanate, in the proportions needed) and the second component is the isocyanate (called component B or isocyanate component). The PU that results is a consequence of the very efficient contact between the isocyanate component and the polyolic component. Usually, in rigid PU foams only two components are used. In flexible foams, the polyolic

component is divided into two components, especially in order to avoid the contact of some hydrolysable component with water, (e.g., stannous octoate). The gravimetric ratio between the components is verified before the foaming process and if necessary, it is corrected.

Modern foaming machines permit a simultaneous dosing of many components, (e.g., seven components, three different oligo-polyols). The correct ratio between the components is assured by the perfectly controlled flow of each component. In this manner, it is possible to use a large range of formulations by simply changing the component flow. This facility assures a high flexibility in the foaming process.

All the previous information regarding the general chemistry of PU and the structure of isocyanates have a role in the better understanding of how the oligo-polyols get chemically inserted in the high-MW PU structure and to understand the role played by the polyol structure in the properties of the resulting PU **[8].**

PU is a polymer consists of organic units, combined by carbamates (urethanes) links. PU can be produced by reacting isocyanates with polyol. Isocyanates will become a hard domain whereas polyol with diol or triol will become the soft domain in the polyurethane chain. **Figure I.1** shows the chemical structure of PU **[9].**

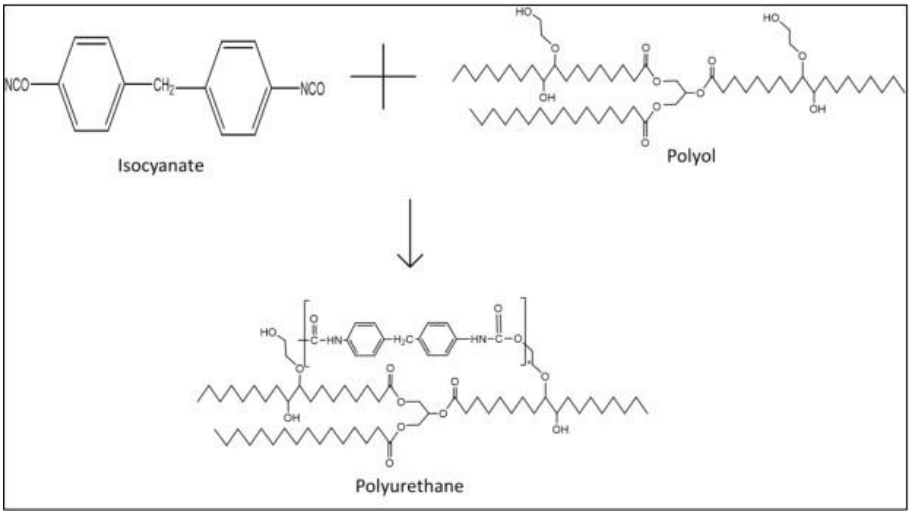
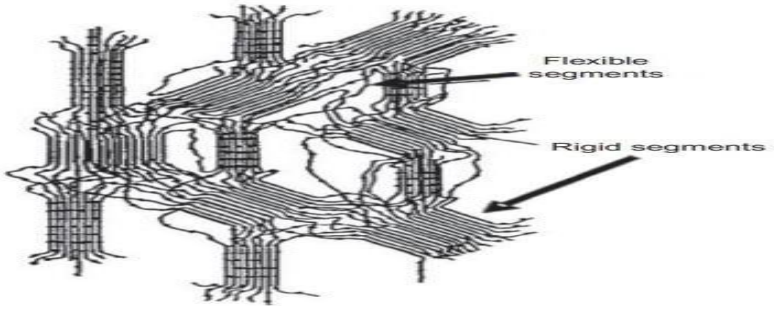


Figure I.1: Chemical structure of PU.

I.3 Structural Analysis of Polyurethanes

Thermoplastic polyurethanes have a segmented structure. Segmented polyurethanes are also considered as block copolymers of type (AB) n with alternating soft (A) and hard (B) segments. The specific segments have specific applications and properties. The detrimental factor in the PU applications are the length of each segment. The hard segments (HS) appear as dispersed in a matrix of soft segments (SS). A schematic representation of the segmented polyurethane is given in **Scheme I.2 [10].**



Scheme I.2: Segmented polyurethane.

The hard segments are normally aligned and induce crystallinity to the segmented PUs. Hence, some PUs are semi crystalline and have improved properties. The crystalline structure is observed at lower temperatures. At high temperatures, the crystallites melt and thus the structural changes with the application of temperature can be studied by Differential Scanning Calorimetric (DSC) and X-Ray diffraction (XRD) (**see Figure I.2**) **[11,12].**

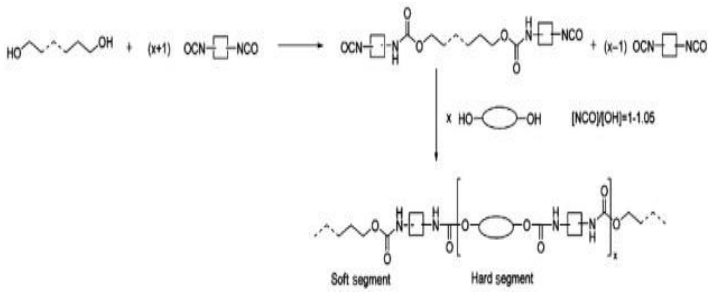


Figure I.2. The segmented structure of polyurethane.

I.4 Major advantages of polyurethanes

Polyurethanes offer a unique contribution to health care delivery. They comprise a broad family of polymers. On the one hand, this is a great advantage as it is possible to fabricate polyurethanes with diverse properties.

Because there is a large variety of different polyurethane materials that are excellent for specific applications, the right polyurethane for the particular application has to be selected. The type of polyurethane that is used has to be chemically stable and easy enough to process without giving large batch-to-batch variations that may cause service life problems. The application conditions may change greatly from those originally specified after several years of use, potentially causing changes to the service life.

I.4.1 Polyurethane's Role in the Materials Field

Polyurethanes have several advantages over competing material in the materials field. The major items of competition are metal, other plastics, and rubbers. Ceramics offer some competition to urethanes. Each of the above groups of materials, including polyurethanes, requires its own design adjustments for successful use in any application**.**

I.4.2 Comparison to Metals

The very much lower density of polyurethanes (1.0 to 1.2g/cm3) compared to the lightest of standard metals, namely aluminum (~2.7 g/cm3), gives it great weight advantages. The difference is magnified even more when compared to steel. Parts can be made so much lighter that they can be handled with ease.

The fabrication of polyurethanes into complex shapes is much easier than with metals. Large casting of up to 500 to 1,000 kg can be made from relatively simple molds and buckets, with minimal labor. The energy input into the production of a cast polyurethane part is low compared to the melting of a metal alloy. The actual molding costs are also lower.

Polyurethanes provide a large package of chemical resistance to metals within the operating temperature of the polymer. By careful selection, alloys can be used to provide the desired chemical resistance.

For smaller particle sizes (~1,000 microns), polyurethanes provide a superior erosive wear resistance to metals at most normal velocities of up to 20m/s. Outside these limits, the materials need to be evaluated in a manner that is as close to real conditions as possible. Polyurethanes can flex and deform to assist in any movement of parts. The elastic nature means that the polymer will return to close to its original shape after any minor deformation **[13].**

I.5 Drawbacks of polyurethanes

I.5.1Rationale

There are two major chemical areas of health concern in the polyurethane industry. The first is isocyanates, in their free form as a liquid or in the vapor form. The second is amines.

Even traces of isocyanate vapor in the atmosphere can cause bronchial troubles, either in the short or long term. Operators who have asthmatic problems are extremely sensitive to isocyanate vapors and must be kept clear of any exposure.

All chemicals used in the polyurethane industry can cause some harm and must be treated with both care and respect **[14].**

1.5.2 Work Environment

The overall work environment of a polyurethane workshop is prone to becoming untidy and hazardous due to the nature of the operations being carried out; e.g., there may be hot, slippery chemicals; hot molds; and curing ovens. The layout of the workflow must be under constant review as the emphasis of the product range changes.

I.5.3 Acute Exposure

Acute exposure generally refers to single-dose, high-concentration exposures over short periods. Some of the chemicals used in the polyurethane industry can cause acute health problems and have an immediate effect on the health of people exposed to it. The most prominent of the chemicals are the isocyanates. People with bronchial problems can have an immediate attack. It is often suggested that all employees be screened for lung function and for potential problems. Isocyanates also have the potential to sensitize people, and they can develop problems in the future**.**

If mercuric catalysts are used, they must be handled with great care. They can cause burns to the skin that will develop over the next 12 hours subsequent to handling [**15].**

I.6 Properties of Polyurethanes

Different types of polyurethanes are available according to their synthetic route and applications. Commonly available polyurethanes are PU foams.

Polyurethane foams may be low-density flexible foams or low-density rigid foams **[16]**. Low-density flexible foams are used for furniture, truck seating, and cushions. The properties required for the usage in such industries are the flexibility, resilience, high mechanical strength, and durability. Rigid foams have high mechanical strength, low heat conduction, low moisture absorption, and low density.

Another type is PU elastomers. They have low cost, resistance to high loads, high compression strength, and they can be easily formulated and colored. Polyurethane elastomers are considered as substitutes for plastics and rubbers. They have high abrasion resistance, resistance to solvents and chemicals, high impact strength, and low moisture uptake. These superior mechanical properties make them suitable for the manufacturing of packaging materials, in the health product industry, and the printing industry.

The most important class of polyurethanes are thermoplastic polyurethane. This type of material varies in its starting material and properties.

Thermoplastic polyurethanes can be synthesized according to the required properties. They are similar to plastics and they have good elasticity and transparency. Thermoplastic polyurethanes (TPUs) are segmented polyurethanes with alternating hard and soft blocks. The length of the soft and hard blocks can be controlled during the synthesis. TPUs have high abrasion strength, high chemical and solvent resistance, and resistance to oil and grease.

I.7 Phase Separation and Miscibility

The segmented polyurethanes are of importance due their special behavior of phase separation. The two segments, hard and soft, have high interphase adhesion, but they do not fail at the interphase. Polyurethanes will tend to phase separate because of the incompatibility between the soft and hard segments **[17, 18].** The hard segments normally act as crosslinks in the matrix. [**19].**

The enhanced properties of PUs are considered because of this phase separation. Petro Vic and Ferguson explained the phenomena of phase separation in polyurethanes and the thermodynamics of miscibility and phase separation. They considered the PU system to be similar to a polymer blend system, where the resultant blend is an average of the properties of the two polymers. In the case of PUs, the property of the material is the added sum of the hard segments and the soft segments **[20]**. Phase separation phenomena in segmented PUs depends mainly on the length of the hard and soft segments. If the soft segments are too long then they will phase separate and if they are too short, then the possibility of phase separation is decreased **[21]**. Phase separation process in PUs are affected by the hydrogen bonding interactions between urethane linkages, the reaction conditions during synthesis, the length of hard domains, and the temperature. The phase separation process is determined by the Differential Scanning Calorimetric **[22],** small angles X-ray scattering (SAXS) **[23]** and morphological analysis. Li and coworkers considered the phase separation in segmented polyurethanes with the help of the SAXS technique.

They concluded that the kinetics factor could control whether it was phase mixed or phase separated **[24, 25].** The DSC measurements are based on the fact that the two segments have different Tg and the variation in the glass transition temperature is useful in the study of phase separation in PUs. The hydrogen bonding interactions inside the polyurethane chains also plays a role in the phase separation process **[26]**. The variation in the temperature is a governing factor in the phase separation process. The separated structure at room temperature is extremely different from that at high temperature. A schematic representation of the separated structure at different temperatures is given in **Figure I.3.**

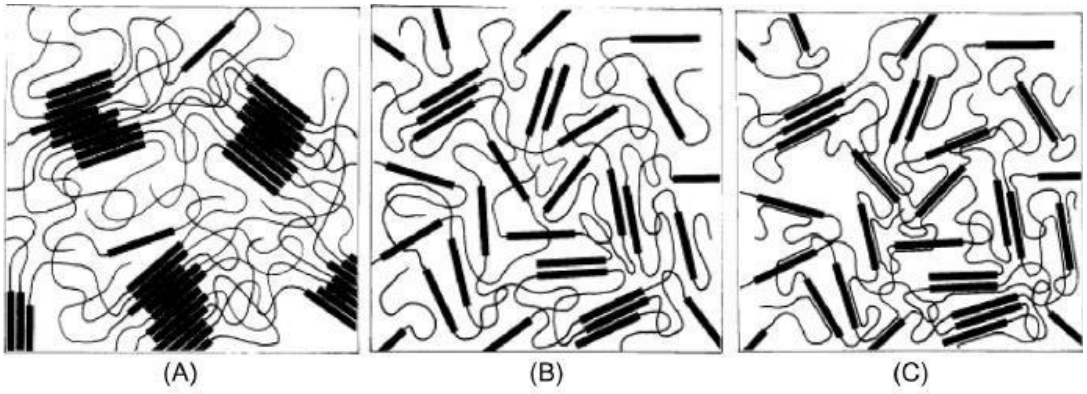


Figure I.3: Schematic representations of polyurethane structures at various temperatures: (A) room temperature phase-separated morphology; (B) most disassociated structures at high temperature; (C) dispersed phase "trapped" at extremely low temperature.

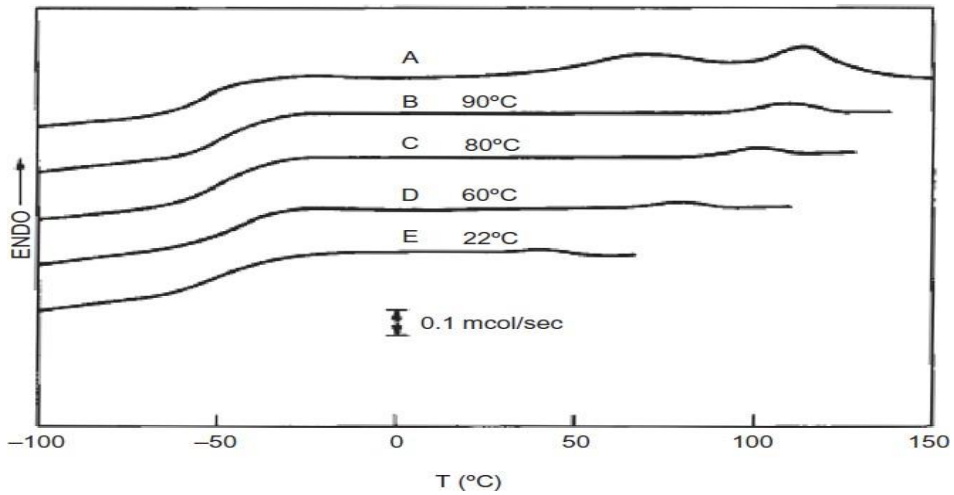


Figure I.4: DSC thermo grams of PU (A) as received and (B_E) annealed at 190°C for different time periods.

Hsu and coworkers studied the microstructure of polyurethane using FTIR technique **[27]**. They analyzed the variation in the absorbance peak of different functionalities and the extent of hydrogen bonding was studied quantitatively. From their studies, they proved that the spectroscopy data can be correlated to macroscopic structural properties, mainly the phase separation kinetics and the mixing process **[28]**. In another study, Key proposed that the glass transition temperature of the soft segment has a logarithmic variation during phase separation. He heated the polyurethane to 190°C at different time intervals to study the effect of phase separation on the Tg of soft segments **(see FigureI.4) [29].** The micro phase separation or segregation is more pronounced in the case of

polyether polyurethanes. When the temperature is too low and the length of the hard segments are enough then the formation of micro crystallites is possible.

Morphological analysis such as Atomic Force Microscopy (AFM) determines the type of phase separation occurring in the polyurethane chains. Petro Vic and coworkers suggested that the variation in soft and hard segments will vary the morphology of the end result. They chose thermoplastic PUs with 50% soft segment and 70% soft segment concentration.

The TPU with 50% soft segments showed a continuous structure whereas that with 70% SS showed globules of micro-sized domains Inside the matrix (**see Figure I.5**) **[30].**

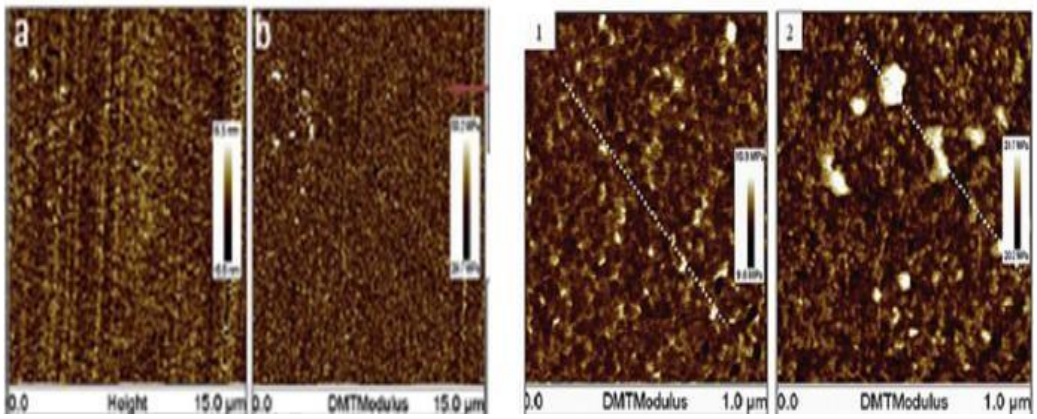


Figure I.5: AFM images of phase separated structure of TPU 50 (let) and TPU 70 (right).

I.8 Characterization techniques of polyurethanes

The polyurethane synthesis involves a change in functional groups. The OH groups and the NCO group react to form a NHCOO group. After the formation of the urethane prepolymer, polymerization takes place in the presence of a catalyst and chain extender. Spectroscopic techniques are useful in the detection of the products.

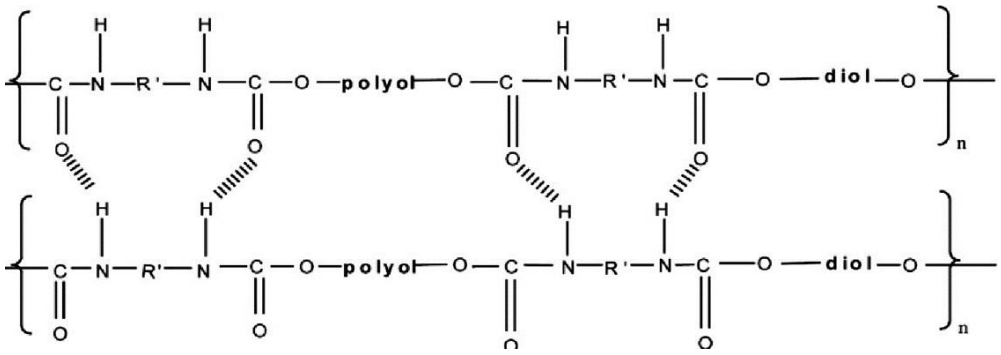
The side reactions and the byproducts can be identified using infrared and magnetic resonance spectroscopy. A clear pathway of the reaction is explained with the help of these techniques. The extent of hydrogen bonding between different groups in polyurethanes are normally studied

quantitatively using Fourier-transform infrared (FTIR). Possible formation of the hydrogen bonding in between the polyurethane chains is given in **Scheme I.3**.

In a polyurethane chain, both proton-donating groups like N_H and proton-accepting functionalities like C5O, C_O_C are present. Upon the formation of hydrogen bonds, these functionalities show a change in the fundamental frequency. This change is related to the strength of the hydrogen bond formed **[31].**

The most common functional frequencies in polyurethanes are given in **Table I.1**.

Polyurethanes contain an aromatic ring usually when derived from aromatic isocyanates such as MDI, and the important functionalities are _CH2, C5O (1700 cm21), _C_O_C (1329 cm21), NH (3328 cm21), _OH, _CH (2939 cm21), _C5C. The FTIR spectra of polyurethane **[32]** is represented in **Figure I.6.**



Scheme I.3: Formation of hydrogen bond in polyurethane.

Group	Mode	Frequency (cm^{-1})
N–H	Free	3445–3450
N–H	N–H. . .N–H	3315–3340
N–H	N–H. . .O (ether)	3260–3290
C = O (Urethane)	Free	1730–1740
C = O (Urethane)	C = O. . .H–N	1703–1710

Table I.1: Common functional frequencies in polyurethanes

Nuclear magnetic resonance (NMR) spectroscopy is also an important tool to identify reactions during PU synthesis and the quantification of the hydrogen bonding interactions. Both 1H NMR and 13C NMR techniques are well known for PU analysis **[31].** An example for the 1H NMR spectra is given in **Figure I.7.** Galbiati and coworkers synthesized polyurethane prepolymer from toluene diisocyanate and polypropylene glycol. They studied the important peaks and their variations. They found that at room temperature the chemical shifts of the groups are 7.78 ppm (_NH), 7.1_7.2 ppm (aromatic), 3.2_3.9 ppm (_CH), 1.1 ppm (CH3). The chemical shift values change according to the precursor materials **[33].**

X-ray diffraction analysis is useful in the case of samples that involve crystalline PUs **[34]**. The d-spacing is calculated from the XRD patterns using Bragg's equation. Trovati and coworkers analyzed the polyurethanes from MDI using FTIR, DSC, and XRD techniques. They considered three different types of PUs: rigid, semi-rigid, and soft PUs. The change in the crystalline structure with the type of PU is clear from the XRD pattern given in **Figure I.8.**

Rigid PUs are more crystalline when compared to soft and semi-rigid. The percentage crystallinity for rigid PUs was 37% while that of semi-rigid and soft were 29% and 24% respectively **[35].**

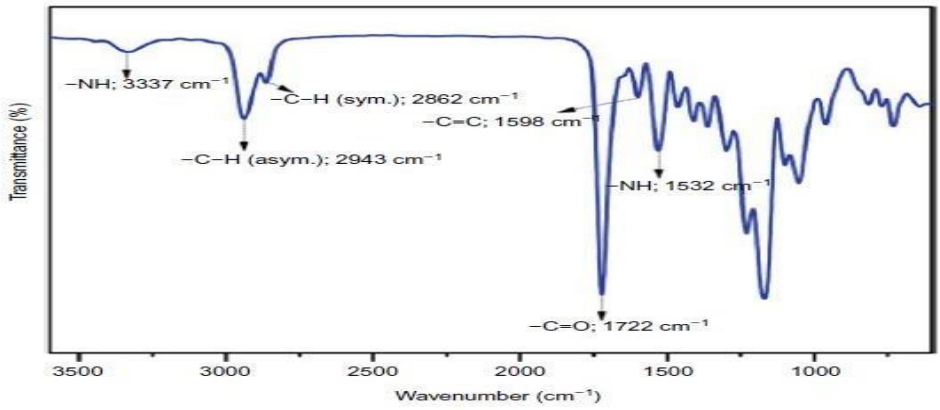


Figure I.6: FTIR spectra of a polyurethane model compound.

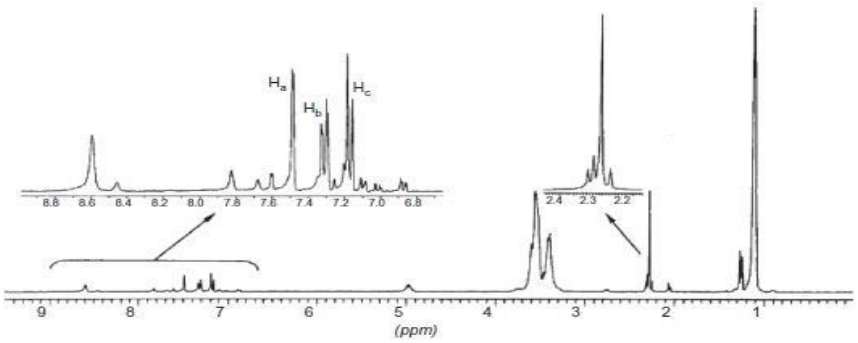


Figure I.7: 1H NMR spectra of polyurethane prepolymer derived from TDI and PPG.

Thermal properties of polyurethanes are measured using thermo gravimetric analysis and differential scanning calorimetric **[36, 37]**.

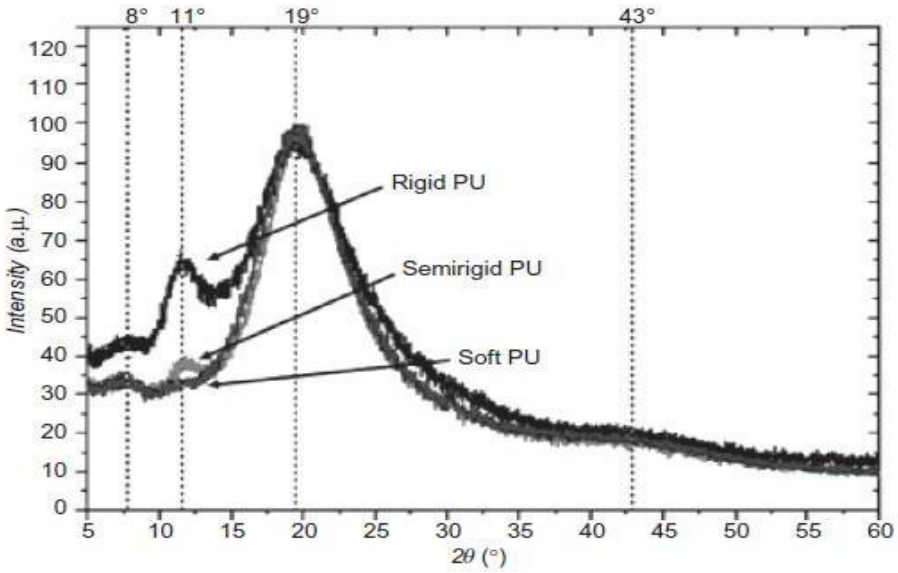


Figure I.8: XRD pattern of three types of polyurethanes.

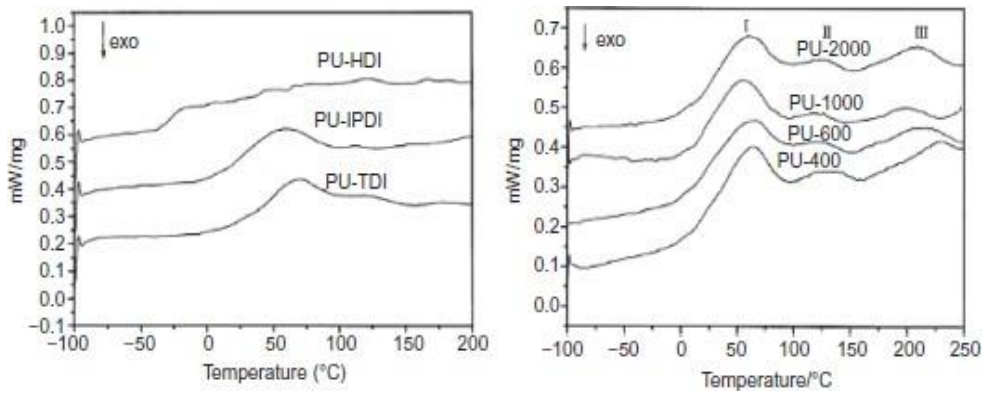


Figure I.9: DSC curves of PU derived from different isocyanates (left) and with different weight fractions of PEG (right).

The segmented polyurethanes have two glass transition temperatures. The Tg values are affected by the type of isocyanate and the amount used in the synthesis. Cheng et al investigated the thermal properties and the phase separation of polyurethane synthesized from different isocyantes and with different molecular weights. The no isothermal DSC curves of PUs synthesized from TDI, IPDI, and HDI under air atmosphere are given in **Figure I.9 [38].**

I.9 Applications of polyurethanes in medical fields

PUs are used in several medicine-related applications, including, but not limited to, general purpose tubing, surgical drapes, catheters, hospital bedding, wound dressing and several other injection-molded equipment. They are used for these applications due to their availability, good mechanical and physical properties and biocompatibility **[44, 45].** However, the most frequent use is in short-period implants. The incorporation of PUs in medicine-related application helps to offer cost effectiveness and provides adequate room for toughness and longevity of materials **[46].** This feature has allowed polymeric materials to replace the conventional materials, such as metals, ceramics and metal alloys. The global bio-based PU market was 1534 tons in 2012**[39]** Polyurethane hence obtained has a bio content ranging from 30% to 70%, depending largely on the type of bio-based feedstock employed for manufacturing the polyols. The global polyols market in 2015 reached almost USD 19.5 billion, with an annual growth of 8.5%. The bio-polyol market is currently worth USD 5.03 billion **[47].** The global bio based polyurethane market is expected to

reach USD 37.5 million by 2020, or less than 0.07% of the total PU market according to a new study by Grand View Researching **[48].** In one study, crystalline prepolymers were used to produce biodegradable PU, using water as a chain extender. Properties of the synthesized PU were compared with those obtained via a polyaddition reaction using ethylene glycol as a chain extender. It could be seen that there was an improvement in mechanical and degradation properties of the new material, which was also found to possess suitable application as an element for joint end prostheses **[57].** Full synthetic routes for the production of biodegradable PU using water and ethylene glycol as chain extenders, respectively. Also, due to the pH changes that one occur during sexual intercourse, special drug delivery systems, such as vaginal peccaries and microbicides, which could help to prevent the spread of sexually transmitted diseases, including HIV-AIDS, have been suggested **[49,50].** For this purpose, highly sensitive and smart PUs for vaginal drug delivery were synthesized **[51].** Moreover, PUs have been conveniently used for other purposes, such as drug delivery systems specially made for the colon **[52,53]** and as intra-vaginal rings**[54].** Recently, the suitability of carbohydrates as biomedical devices was investigated. Castor-oil-based biodegradable and biocompatible PUs were synthesized using polypropylene glycols (PGs) as the polyol and with different carbohydrates incorporated as cross-linkers **[42].** The properties of the produced PUs were investigated and it was found that the incorporation of carbohydrates nuanced the thermal, mechanical and degradation properties of the material due to the variety in carbohydrate structures **[50].** The characterizations performed revealed that the carbohydrates served as suitable components of biodegradable and biocompatible PUs. This strategy could therefore be used for developing certain biomedical devices **[42].** This report conforms to the observations reported by other researchers who reported that incorporating muddied starch and cellulose crystals into PUs could enhance their biocompatibility and biodegradability as well as their mechanical properties **[55, 56].** Other research studies on the applicability of PU for medical devices can also be found in the literature, including work reporting on the production of a low-cost biodegradable aliphatic PU, which had a high saline stability up to about 37 C without a sign cant decrease in mechanical strength **[41]** Furthermore, other medical-application-based studies were performed, including studies on a chitosan based PU for antibacterial properties**[42]** and biodegradable electro active PUs for cardiac tissue engineering **[40]** From these research studies on the medicinal applications of PUs, it was observed that some of the produced materials oen perform only at a moderate level, especially in terms of their resistance towards bacterial adhesion.

This is because most of them are susceptible to bacterial attack, thereby leading to the risk of infection. New strategies for producing antibacterial PUs have therefore become necessary. These could be achieved via the incorporation of certain surfaces that have the capability to resist or repel the attachment of bacterial to the material surface **[43].** These bacterial-resisting surfaces could be produced either through the incorporation of some antibacterial coatings or via some other surface medications that could enhance the antibacterial or anti-bio fouling properties of the materials.

- **Vascular Prostheses**

Several PU vascular prostheses have reached industrial production as substitutes for small diameter arteries. These include the Corvita, Thoratec, Pulse-Tec, Biomer, Mitrathane (which can be either hydrophilic or hydrophobic) and Vascugraft prostheses, each having its specific properties. Some of them deserve special attention. The Corvita Prosthesis is composed of polycarbonate-urethane and offers a compliant, low-stress fibrous structure with open communicating inter-fiber spaces. However, it must be sealed to prevent excess blood loss at implantation. The Thoratec prosthesis is made of polyether-urethane-urea, does not require sealing or percolating, and offers less space for tissue ingrowth. The pulse-Tec prosthesis has the fewest pores on its external surface. Thus, while it does not require percolating and may prove to be strong enough to resist kinking, its dense external surface may be responsible for delay in tissue ingrowth **[58].**

I.10 Conclusions

Polyurethanes are the most demanding type of polymers in the present era because of their versatility in properties and in the synthesis. The one-shot method of mixing and the prepolymer method are used in the production of polyurethane. As a large number of ingredients are available for the synthesis of PU. Polyurethanes are available as soft foams and hard tooling materials. Thermoplastic elastomers of polyurethanes are the most wanted materials in the industry. The generation from natural sources and recyclability are the attractive advantages of polyurethanes. Synthesized polyurethanes can be characterized via spectroscopy, calorimetry, and scattering techniques. They maintain the versatility in the results. There are particular features of this material, which offer substantial advantages over competitors such as polyethylene, polypropylene, and nylon. The main one of these is the composite nature of polyurethane systems, which allows materials to take on a range of different material properties, not the least of which is the ability to form elastomers. Recently polyurethane has also found its application in the bio-medical field as well. Polyurethanes can be prepared from a wide range of polyols and isocyanates; this helps in the fact that PU can be made in large array of products having different properties

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Chapter II

Literature Review

II.1 Literature Review

In this section and for the sake of illustration, a brief presentation of some of the works that have been published and which covered different aspects of the subject, will be made.

These studies are presented in a chronological order.

For Example; **Mehdi Barikani and Mohammad Barmar [1],** have studied the Synthesis method of the Thermoplastic Polyurethane Elastomers and their Effective in the Structural Parameters. From their study, two classes of polyols, a polyether and polyester, are used for synthesis of thermoplastic polyurethane elastomers. These elastomers are prepared by chain extension of polyol/toluene diisocyanate by prepolymer method and a variety of chain extenders. The effects of polyester and polyether polyols and chain extenders on the thermal stability have been investigated by means of thermogravimetric analysis (TGA). The dynamic mechanical thermal, as well as mechanical properties were also studied by means of DMA analysis, and tensile test; respectively. They results indicated that the polyester based PU elastomers are more stable than those of the polyether based PU elastomers. This could be attributed to the polar nature of esteric bonds. They have also found that the glass transition temperature of polyether based elastomer is 10°C lower than that of the polyester based elastomer. This is due to more flexibility of etheric band and higher phase separation in comparison with esteric bond. The mechanical results indicated that the polyester based TPUFs have higher tensile strength, tear strength compared to those of the polyether based elastomer.

In another study, **K. Sathiyalekshmi and S. Gopalakrishnan [2],** have investigated the synthesis methods and characterization of rigid polyurethanes based on hydroxyalkylated cardanol formaldehyde resin. The thermal and mechanical properties were also investigated by means of thermogravimetric analysis (TGA), as well as hardness test, respectively. They have found that the polyurethanes prepared from linear hydroxyalkylated cardanol formaldehyde resin have better thermal and mechanical properties than those of the polyurethanes prepared from branched hydroxyalkylated resins. This could be attributed to the lower molecular weight between crosslinks of these polyurethanes.

In another publication, synthesis method of polyurethane by cardanol was reported by **C.V.Mythili et al [3]**. The mechanical, thermal, and chemical properties were also investigated by means of tensile test, hardness, thermogravimetric analysis, and various solvents namely: hydrochloric acid (HCl), sodium hydroxide (NaOH), diethyl ether, ethanol,

toluene, sodium chloride (NaCl). From their results, the rigid polyurethane has the good tensile strength, hardness, thermal stability, as well as chemical resistance to reagents compared to those of tough polyurethane. This may be could be attributed to lower molecular weight between the cross links and higher cross link density of the rigid polyurethane.

In another article, **Piotr Kro´l [4]** has investigated and studied the synthesis methods, chemical structures and phase structures of linear polyurethanes. Properties and applications of linear polyurethanes in polyurethane elastomers, copolymers and ionomers. Chemical and super-molecular structures occurring in linear polyurethanes were presented and they were referred to the analysis of the reactions connected with the step-growth poly-addition process of diisocyanates and polyols. The applicability of such research methods such as TGA and DTG for the thermal analysis in the linear polyurethanes. Also, the influence of phase separation on thermal properties of the polyurethane products was reported. Thermogravimetric analysis as well as derivative thermogravimetric showed that the thermal decomposition of segmented PUs is a multi-stage process (i.e: the first degradation stage which concerned the hard segments meanwhile the second degradation represents the soft segments).

In another study, **Changhong Zhang et al [5]** have reported the synthesis and characterization of biodegradable elastomeric polyurethane using the inkjet technique. Biodegradable polyurethanes (PUs) were synthesized from methylene di-p-phenyl-diisocyanate (MDI), polycaprolactone diol (PCL-diol) and N,N-bis (2-hydorxyethyl)-2-aminoethane-sulfonic acid (BES), serving as a hard segment, soft segment and chain extender, respectively. MDI was chosen due to its reactivity and wide application in synthesis of biomedical polyurethanes due to its reactivity; PCL-diol was chosen because of its biodegradability; and BES was chosen because it allowed the introduction sulfonic acid groups onto the polymer chains. We evaluated the polyurethanes' degradation rate, mechanical properties, and ability to support fibroblast cell attachment and growth by comparing with polymers having a 2,2-(methylimino)diethanol (MIDE) chain extender. The degradation processes as well as the mechanical properties of the biodegradable polyurethane were also investigated by in vitro degradation and tensile test, respectively. Their results indicated that a successfully synthesized of a biodegradable polyurethane elastomer; in other words: a water-soluble polyurethane elastomer that showed a rapid phase change by incorporation of **PCL** and sulfonic acid into PU chains. The polymer proved to be degradable, possesses good anticoagulation properties. Mechanical testing demonstrated that the PU

containing BES has tensile strengths of about 17 MPa and elongations up to 400%, about three times the strength and four times the elongation compared to those of the MIDE based PUs.

Huibo Zhang et al [6] have studied the synthesis methods and characterization of Polyurethane Elastomers. Their study reports the synthesis and characterization of PU elastomers, with emphasis on the effect of different routes and order for raw materials feeding. First, a series of PU elastomers is synthesized using polyether glycol, toluene diisocyanate (TDI), and extender chain reagent. The mechanical behavior, thermal, and morphological properties were also investigated by means of tensile test, TGA, TEM micrographs, and solvent resistance. The results showed that after diisocyanate is dipped into the dried polyether, the elastomers synthesized using extender chain reagent exhibit the best properties. The subsequent characterization and measurements further showed that by an optimum synthetic method, considerable hard segments can be formed uniformly in the soft segments, and the extent of micro-phase separation is relatively perfect. Moreover, it is demonstrated that the relative molecular weight (Mw) of polyether glycol has an important effect on the mechanical properties of the synthesized PU elastomers. The more the relative molecular weight, the more soft segments are contained, and the smaller the tensile strength, rupture strength, and rigidity are noted. The thermal analysis showed that the thermal stability of elastomers was higher and the lowest decomposing temperature of elastomers prepared by different raw materials was 268°C. Microanalysis further confirms that the compatibility between soft and hard segments and stronger interaction helped to improve mechanical properties of elastomers. The measurements of water resistance indicated that the prepared polyether-type elastomers exhibited an excellent solvent resistance.

Cristian-Dragos Varganici et al [7] have investigated the Synthesis and Characterization of a New Thermoreversible Polyurethane Network. A new polyurethane network was synthesized by the Diels−Alder cross-linking reaction of polyurethane to bisfuryl monomer. Attenuated total reflectance in conjunction with Fourier transform infrared spectroscopy (ATR-FTIR) spectra of the network showed the disappearance of the absorption bands of maleimide and the appearance of new bands attributed to furan-maleimide cycloadduct. Chemical shifts characteristic to the cycloadduct appeared in the proton nuclear magnetic resonance spectra. ATR-FTIR and differential scanning calorimetry (DSC) demonstrated the thermal reversibility of the material by the reproduction of the retro-Diels−Alder and Diels−Alder processes upon heating and cooling. Global kinetic Nonisothermal

decomposition parameters in nitrogen were determined by the Flynn-Wall-Ozawa method. A three successive stage thermal decomposition mechanism depicted by **n** order reaction model for each stage was proposed. The validity of the chosen kinetic model and the values of the kinetic parameters of the individual decomposition stages were determined by the multivariate nonlinear regression method.

N J Sangeetha et al [8] have studied an advanced methods of polyurethane synthesis based on natural resources. Their study presents the recent methods and synthesis of polyurethanes derived from natural resources such as natural fibers, natural fillers, natural oils and other natural resources. Polyurethanes are one of the most various plastic materials obtained by the reaction of a polyol with an isocyanate or diisocyanate in the presence of suitable catalysts and certain additives. The properties were examined by spectroscopic methods, thermo-mechanical methods, scanning electron microscopy (SEM) and x-ray fluorescence (XRF). This leads to high-performance products for building, furniture, bedding, automotive, ligature and industry due to their enduringness, lightweight, strength, tractability and chemical resistance. The mechanical and morphological properties find wide range of applications. The incorporation of fillers and fibers into polyurethanes provides intermolecular interactions between them. The solid polyurethanes obtained from natural sources such as glucose and xylose draws increased transition temperature and stiffness due to the rigidity of the glucose unit increases hydrogen bonding and potential for cross linking.

Marcin Sobczak and coworkers [9] have reported the Biodegradable Polyurethane Elastomers for Biomedical Applications and study the Synthesis Methods and Properties. Biodegradable polyurethane elastomers (BioEPUR) are becoming increasingly important as biomaterials because they have excellent chemical, Physico-mechanical and biological properties. Their study presents the recent development son BioEPUR and their potential applications in the biomedical and pharmaceutical fields. The aim of their work is to present an overview of the various methods of synthesis and properties of biomedical BioEPUR. Polyurethanes-base daliphatic or cycloaliphatic diisocyanates and polyesters, poly(ester carbonate) so copolymers of heterocyclic monomers were discussed. This study highlights some recent developments in various aspects of BioEPUR synthesis, physicochemical and biological characterization. These elastomers seem to be an interesting and promising developmental direction for medicine, biomedicine and pharmacy due to their unique properties. BioEPURs are an emerging class of biomaterials with many potential clinical applications including implanted devices, tissue engineering and drug delivery systems.

Several elastomers have been proposed recently; however, the most prospectively useful type of elastomers appear to be multifunctional biomedical elastomers (used as implantable drug delivery systems, for example). Such BioEPURs should be useful for a broad range of clinically relevant applications, and in years to come, the number of BioEPUR applications will certainly increase.

Míriam Sáenz-Pérez et al [10], have studied the Synthesis and Characterization of Shape Memory Polyurethanes, Shape memory polymers (SMPs) have attracted extensive attention from basic and fundamental research to industrial and practical applications because they have emerged as a cheap and efficient alternative to well-known metallic shape-memory alloys. Among them, shape memory polyurethanes (SMPUs) own different applications such as the textile finishing, adhesives, coatings, automotive, furniture, construction, and thermal insulation and footwear industries, due to it can be synthesized with different types of molecular architectures by manipulating their composition and choosing properly the chemical structure of their components. In their study, the synthesis and characterization of shape memory polyurethanes, based on two-step polymerization, is reported. The hard segment of SMPU was composed of diisocyanate and a chain extender. On the other hand, the soft segment was prepared by polyols with different molecular weights. Depending on the structure of the synthetized polyurethanes, the materials presented different properties. Thermal characterization was performed by means of Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). Furthermore, mechanical properties and shape memory effect were also determined by Dynamic Mechanical Analysis (DMA) and Thermo-Mechanical Analysis (TMA).

John O. Akindoyo et al [11], have studied the polyurethane types, synthesis and applications. Polyurethanes (PUs) are a class of versatile materials with great potential for use in different applications, especially based on their structure–property relationships. Their specific mechanical, physical, biological, and chemical properties are attracting significant research attention to tailoring PUs for use in different applications. Enhancement of the properties and performance of PU-based materials may be achieved through changes to the production process or the raw materials used in their fabrication or via the use of advanced characterization techniques. Clearly, modification of the raw materials and production process through proper methods can produce PUs that is suitable for varied specific applications. This study aims to shed light on the chemistry, types, and synthesis of different kinds of PUs.

Some of the important research studies relating to PUs, including their synthesis method, characterization techniques, and research findings, are comprehensively discussed. Herein, recent advances in new types of PUs and their synthesis for various applications are also presented. Furthermore, information is provided on the environmental friendliness of the PUs, with a specific emphasis on their recyclability and recoverability. Polyurethanes (PUs) are some of the most common, versatile and researched materials in the world. They combine the durability and toughness of metals with the elasticity of rubber, making them suitable replacements for metals, plastics and rubber in several engineered products. They have been incorporated into many types of industrial equipment and for making numerous items, such as paints, liquid coatings, elastomers, rigid insulations, elastic, so flexible foams and even as integral skins. PUs may be produced from a wide range of diisocyanates, a variety of polyols and other chain extenders and cross-linking agents. This makes it possible to obtain a large range of tailored materials that can serve many specific applications. Initially, most of polyols used to prepare PUs were obtained from petroleum sources, but the high cost and energy demands as well as environmental concerns have increased the necessity for a more suitable and environmentally friendly substitute. This has recently drawn enormous commercial and academic attention to renewable sources, such as vegetable oils. The last decade has witnessed a clear majority of studies appearing in the literature on the use of vegetable oils as alternatives to petroleum-based materials for PU production. However, there are certain shortcomings associated with these kinds of materials, especially in terms of performance. The use of nanomaterials has been suggested to offer additional advantages for desirable performance. Hence, the incorporation of nanoparticles that can suitably replace the hard segments from isocyanate precursors has therefore been widely investigated. Thus, materials such as carbon nano-fibres (CNFs), carbon nanotubes (CNTs) and clays are attracting significant interest as important additions into PU products. With all this enormously diverse research on PU, recyclability of the product is very important. Fortunately, the recycling processes of PU have been reported to be economical and practical. Thus, PU could be considered to be environmentally non-hazardous and more economical compared to other conventional polymers, due to its good recycling and recoverable properties.

Sophie Wendels et al [12], have studied the Biobased polyurethanes for biomedical applications. Polyurethanes (PUs) are a major family of polymers displaying a wide spectrum of physico chemical, mechanical and structural properties for a large range of fields. They have shown suitable for biomedical applications and are used in this domain since

decades. The current variety of biomass available has extended the diversity of starting materials for the elaboration of new biobased macromolecular architectures, allowing the development of biobased PUs with advanced properties such as controlled biotic and abiotic degradation. In this frame, new tunable **biomedical** devices have been successfully designed. PU structures with precise tissue bio-mimicking can be obtained and are adequate for adhesion, proliferation and differentiation of many cell's types. Moreover, new smart shape-memory PUs with adjustable shape-recovery properties have demonstrated promising results for biomedical applications such as wound healing. The fossil-based starting materials substitution for biomedical implants is slowly improving; nonetheless better renewable contents need to be achieved for most PUs to obtain **biobased** certifications. After a presentation of some PU generalities and an understanding of a biomaterial structure-biocompatibility relationship, recent developments of biobased PUs for non-implantable devices as well as short- and long-term implants are described in detail in this review and compared to more conventional PU structures.

Dulce María González-García et al [13], have studied the Synthesis and In Vitro Cytocompatibility of Segmented Poly(Ester-Urethane)s and Poly(Ester-Urea-Urethane)s for Bone Tissue Engineering. Two series of segmented polyurethanes were obtained and their mechanical and thermal properties as well as their biodegradability and cytotoxicity were evaluated. The chemical nature of the polyurethanes was varied by using either 1,4 butanediol (poly-ester-urethanes, PEUs) or L-lysine ethyl ester dihydrochloride (poly-ester-urea-urethanes, PEUUs) as chain extenders. Results showed that varying the hard segment influenced the thermal and mechanical properties of the obtained polymers. PEUs showed strain and hardness values of about 10–20 MPa and 10–65 MPa, respectively. These values were higher than the obtained values for the PEUUs due to the phase segregation and the higher crystallinity observed for the polyester-urethanes (PEUs); phase segregation was also observed and analyzed by XRD and DSC. Moreover, both series of polymers showed hydrolytic degradation when they were submerged in PBS until 90 days with 20% of weight loss. In vitro tests using a Human Osteoplastic cell line (Hob) showed an average of 80% of cell viability and good adhesion for both series of polymers.

Marcos-Fernandez and coworkers [14] have reported the Synthesis and characterization of biodegradable non-toxic poly(ester-urethane-urea)s based on poly(3-caprolactone) and amino acid derivatives**.** Non-toxic biodegradable linear poly(ester-urethane-urea)s with different hydrophilic character were synthesized from poly(3-caprolactone) as macro-diol, L-lysine

diisocyanate (LDI) and ethyl ester L-lysine or L-ornithine as chain extenders. Linear segmented polymers were synthesized by the pre-polymer method with a tertiary amine playing a critical role in the chain extension in heterogeneous conditions. The prepared segmented polymers were fully chemically and physically characterized, including water uptake and hydrolytic stability measurements. Depending on the poly (3-caprolactone) length, the segmented polymers were amorphous or semicrystalline. The crystallinity degree strongly affected the mechanical properties and water uptake behaviour.

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Chapter III
Biobased Polyurethanes for Biomedical Applications

III.1 Introduction

Biomaterials have constituted a very important field in science during the last 30–40 years. They are classified into four groups: polymers, metals, ceramics and composites**[1–4]**.

Biomedical polymers include natural (e.g., albumins, alginate, caseins, cellulose, chitin, collagens, gelatins, hyaluronate, starch), synthetic (e.g., poly(ethylene glycol), poly(hydroxy acid), poly(vinyl alcohol), polyvinylpyrrolidone, aliphatic polyesters or polycarbonates, co- or terpolymers of hetero- cyclic monomers) and semisynthetic macromolecular com-pounds**[1-4]**. Biomedical applications of polymers contain main three categories **[3].** The first one are extracorporeal applications (e.g., artificial skin, catheters, dialysis membranes or artificial kidney, fluid lines, ocular devices, tubing, wound dressings). Permanently implanted devices (e.g., cardiovascular devices, dental devices, orthopedic devices, sensory devices) are the second of category of biomaterials. The third kind of biomaterials are temporary implants (e.g., degradable sutures, implantable drug delivery systems, polymeric scaffolds for cell or tissue transplants, temporary small bone fixation devices,

temporary vascular grafts and arterial stents) **[3–5].**

Biodegradable or bioresorbable polymers are one of the most interesting groups of biomedical materials because of their good biocompatibility and lack of toxicity. They are degraded in vivo by hydrolytic or enzymatic decomposition into mono- mers. Next, monomers become involved in the carboxylic acid cycle and are subsequently excreted as carbon dioxide and water **[6]**. Biodegradable or bioresorbable polymers are com- monly used as erodible matrices for controlled drug delivery systems, as erodible tissue engineering scaffolds, macromole- cular prodrugs, sutures, therapeutic systems, etc **[5–8]**.

One of family of biodegradable polymers are biomedical elastomers (**Table III. 1**). Degradable biomedical elastomers are defined as biodegradable elastic polymers used in human or veterinary medicine, by themselves or as parts of a complex system, to direct the course of any diagnostic or therapeutic procedure by the control of interactions with the components of living systems**[9]**. Generally, biomedical elastomers are classified in two categories: the materials suitable for long- term physiological contact or implantation and the biodegrad- able materials for medium- or short-term physiological contact or implantation **[10]**.

Biodegradable polyurethane elastomers (BioEPUR) are an important class of hydrolytically and enzymatically degradable polymers used in the medical, pharmaceutical or biomedical fields. BioEPUR are very interesting materials that characterize unique combination of biological, chemical and physical proper- ties. They have good physicomechanical properties, good antith-rombogenicity and biocompatibility **[11]**. There are known several commercial BioEPUR used in medicine or pharmacy (**Table III. 2**). Biodegradation process depends on different factors that include polymer characteristics (molecular weight or polydis- persity, crystallinity, tacticity, the kind of functional groups and substituents present in its structure, hydrophilic-hydrophobic properties) and type of microorganism or con- dition (pH, temperature, UV). BioEPUR with amorphous and hydrophilic soft segments usually degrade more quickly than those with semi- or crystalline and hydrophobic soft segments **[9,12]**. It is known, that ester linkages hydrolyze in vivo or in vitro, while urethane, carbonate and urea linkages only enzymatically degrade, and the composition of the poly- ols can control the *in vitro* degradation rate **[13].**

Biomedical PUR (biodegradable or non-biodegradable) have been used e.g.,in blood-contacting materials, catheters, heart assist devices, heart valves, infusion pumps, ligament and meniscus reconstruction, insulators for pacemaker leads, nerve guidance channels, restorative and preventative dental materials, soft tissue engineering and control drug delivery systems**[9,14-17]**.

TABLE III.1: Biodegradable biomedical elastomers

Type of biodegradable elastomers	**Examples**
Double-bond-cured bioelastomers	Poly(1,8-octanediolcitrate), poly (ethylene glycol multimer hydromuconoate)
Diol/polybasic acid-based biomedical elastomers	Poly(ε-caprolactone) diol/polybasic acid, polycarbonate diol/ polybasic acid, poly (diol citrate), poly (ethylene glycol citrate), poly(1,8-octanediolcitrate), poly(1,8-octanediol-citrate-sebacate), poly(1,2-

	propanediol-sebacate-citrate), urethane doped poly (1,8-octanediol citrate)
Polyol/dicarboxylic acid based biomedical elastomers	Poly (erythritol dicarboxylate), poly (glycerol dodecanoate), poly (1,12-dodecandiol malate), poly (glycerol sebacate), poly (glycerol-sebacate-lactic acid), poly (polyol sebacate), poly (triol α-ketoglutarate)
Polyol/polybasic acid-based biomedical elastomers	Poly(glycerol-sebacate-citrate)
Photo-cured degradable bioelastomers	Acryloyl chloride-based poly (1,3-trimethylene carbonate), acrylated poly (glycerol sebacate), fumaric acid monoethyl ester-based poly (1,3-trimethylene carbonate), poly (ε-caprolactone-adipate-4- hydroxycinnamate), pentaerythritol triacrylate based poly (1,3-trimethylene carbonate), poly(octamethylene-maleate-citrate),
Ring-opening polymerization-cured biomedical elastomers	Poly (ε-caprolactone-co-D, L-lactide),2,2-bis(ε-caprolactone-4-yl)- propane
Thermoplastic degradable biomedical elastomers	Poly (glycerol sebacate), segmented polyurethanes, poly (ether ester) s, poly (ester amide) s, block copolymers of cyclic esters and carbonates, bile acid based biomedical elastomers, blends of polyesters, polycarbonates and copolymers of cyclic esters and carbonates, Per lasticized starch based biomedical elastomers

TABLE III.2: Commercial BioEPUR

Name product	**Manufacturer/suppler**	**Type of biodegradable Polyurethane elastomers**	**Example of applications**
Actifit	Orteq, Netherlands	BDI/PCL/BD ; porous material	Meniscal repair
Artelon	Artimplant, Sweden	Polyurethane urea; fibres, scaffolds, films, granules	Ligament fixation, bone scaffolds (odontology)
ChronoFlexAL	AdvanSource Biomaterials, USA	USA HMDI/polycarbonate/BD	Various biomaterials
Degrapol	AB Medica Spa, Italy	Porous foam	Nerve and bone regeneration
Epidel	Interface Biologics, Canada	Polyurethane-co-drug, PCL based PU	Catheter cuffs, antimicrobial materials
Lacthane	Polyganics, Netherlands	BDI/polyethers/polyesters	Wound and nasal dressing, surgical sealant
Novosorb	PolyNovo Biomaterials, Australia	Injectable gel, X-linked polymer,prepolymers	Porous nonporous monoliths orthopaedic
SynBioSys	Octoplus, Netherlands	BDI/PLGA/PEG/PCL	stent coatings, drug eluting microspheres
Tecoflex	Thermedics Inc., USA	HMDI/PTMO/BD	Ttubing,blood pump diaphragms, adhesive, sheet, film fiber, catheters, wound dressings

III.2.Synthesis and properties of biodegradable biomedical polyurethane elastomers

BioEPUR can be obtained on the polyaddition processwhich involves diisocyanates and bi- or multi-functional poly-ols (e.g.,polyesters, polyethers, polycarbonates, poly(ester-carbonate)s, co- or terpolymers of cycle monomers), alcoholsor amines with hydroxyl terminal group (by one- or two-stepmethods). The catalytic activity in the reaction of isocyanatewith hydroxyl or amine groups is shown by organometalliccompounds (mainly Sn) or amines **[18,19]**. The BioEPUR areusually obtained in a two-step method. In the first step ofthe synthesis, polyols are continuously stirred with diisocya-nates, and then the obtained prepolymers are extended byusing chain extenders (such as diol or diamine) (**Figure III. 1**)**[18,19].**BioEPUR are built from soft segments (polyester, poly- ether, polycarbonate, poly(ester-carbonate) or siloxane seg-ments) and hard segments (the segments formed bydiisocyanates and chain extenders). Moreover, BioEPUR can microphase separate to form hard and soft domains. Structure and properties of them can be adjusted in a wide range by con-trolling the types of diisocyanate, polyol and chain extender. The soft segments determine low glass-transition temperature (T_g) or high elasticity of BioEPUR. The hard segments determine high T_g, melting point (T_m) or high strength ofBioEPUR**[9,18,19]**. It is known that chemical and physicomecha- nical properties of BioEPUR are very important with respectto biomedical applications; they are different and depend on structure, microstructure and morphology of polyurethane.

The values of fail stress (S_e) and elongation at break (E_b) are 5-230 MPa and 200–1300%, respectively **[18,19]**.

As isocyanate components are often used aliphatic or cycloaliphatic diisocyanate (e.g.,1,4-butane diisocyanate (1,4-BDI), 1,6-hexamethylene diisocyanate (1,6-HDI), iso- phorone diisocyanate (IPDI)), 4,4’-dicyklohexamethylene dii- socyanate (HMDI) and L-Lysine methyl ester diisocyanate (LDI) (**Figure III. 2**)**[18-23]**. It is commonly known that aromatic dii- socyanates should not be used in synthesis of BioEPUR, because the toxicity of the monomers and degradation productsposes medical problem **[9,19]**.

Poly(ε-caprolactone) (PCL), poly (ethylene glycol) (PEG), polyhydroxyalkanote (PHA), poly (lactic acid) (PLA) and co- or terpolymers of ε-caprolactone (CL), *rac*-lactide (*rac*-LA), L-lactide (LLA), trimethylene carbonate (TMC), neopentyl carbonate and ethylene oxide are usually used as a soft segment.They are biocompatible and readily hydrolytically or enzymatically biodegradable **[18–20]**. The polyols are usually prepared by ring-opening polymerization (ROP) of heterocyclic monomers(esters, ethers, carbonates) in the presence of alkaline, Lewis acids, enzymes and coordination catalysts **[24–27]**.

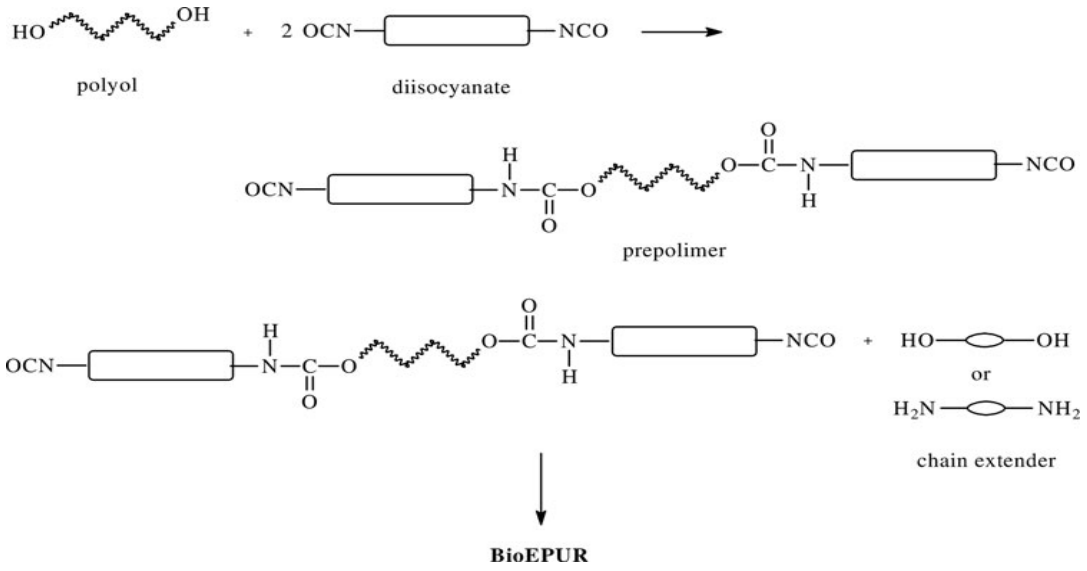

Figure III.1. Synthesis of BioEPUR in the two-step method.

Figure III.2. Diisocyanates used in the synthesis of BioEPUR.

1,4-Butanediol (BD) is most often used as the chain extender in preparation of BioEPUR **[18,19]**. A very popular amine catalyst is 1,4-diazabicyclo- [2.2.2]-octane (DABCO). The most widely used tin catalysts are dibutyltin dilaurate (DBTDL), dibutyltin dioctanate (DBTDO) and tin (II) 2-ethyl- hexanoate ($SnOct_2$) **[18]**. Non-catalyst methods of synthesis of BioEPUR are also known **[9,28]**.

A. Synthesis of BioEPUR Based on Aliphatic Diisocyanates

The two most commonly used diisocyanates in BioEPUR synthesis are 1,4-BDI and 1,6-HDI. Use 1,4-BDI is a good strategy because the degradation products (e.g.,1,4-butanedia-mine (BDA)) are non-toxic**[9,20–22]**. 1,6-HDI is seldomly usedto construct hard segments of BioEPURincomparisonwith1,4-BDI**[18,19]** Copolymers of CL and PEG are often used in the BioEPURsynthesis. For example, biomedical poly(ether-ester) urethane was prepared from triblock copolymers PCL-PEG-PCL (**Figure III. 3**) **[29]**. Polyols were obtained by using PEG (M_w 600 or 1000 g/mol) as macro-initiator of ROP of CL. The process ROP was carried out at 120°C for 24 h under a nitrogen atmos-phere in the presence of $SnOct_2$ as catalyst. Then, the polyols PCL-PEG-PCL were mixed with 1,4-BDI at 75°C for 3 h (in dimethylsulfoxide (DMSO) as solvent). $SnOct_2$ was used as polyaddition process catalyst. Finally, BDA was added intothe synthesized prepolymers to extend the chains to obtainthe BioEPUR. The molar ratio of the reaction was of 2: 1: 1 (1,4-BDI/PCL– PEG–PCL/BDA). BioEPUR exhibited low T_g and possessed S_e ranging from 8 to 20 MPa and E_b from 325 to 560%. The obtained BioEPUR was also modified by the immobilization of the cell adhesion peptide Arg- Gly-Asp-Ser to enhance endothelial cell adhesion and growth. The mass losses of received BioEPUR were below about 35% after 56 days of *in vitro* degradation in the presence of elastase **[29]**.

BioEPUR (as candidates for fabricating tissue engineering scaffolds) were obtained from noncrystalline poly (trimethy- lene carbonate) (PTMC) or poly (δ-valerolactone-co-ε-capro-lactone) (PVLCL) polyols of different molecular weights as soft segment, and 1,4-HDI and chain extended with 1,4-BDA **[30]**. The obtained BioEPUR showed large E_b (800– 1400%) and high S_e (30–60 MPa). Degradation studies in phosphate-buffered saline (PBS) containing 100 U/mL lipase showed significantly greater mass loss for the PCL-based BioEPUR in comparison to the PTMC-based BioEPUR and for PVLCL-based BioEPUR in comparison to PCL-based

BioEPUR. Basic cytocompatibility of synthesized materials was demonstrated with primary vascular smooth muscle cell culture **[30]**.

The use lysine ethyl ester (LEE) in synthesis of BioEPUR is very interesting due to biocompatibility of obtained materials. BioEPUR were synthesized from PCL diol, 1,4-BDI, and BDA or LEE in the presence of $SnOct_2$ as catalyst (**Figure III. 4)[31]**. The molar ratio of polyol: diisocyanate: diamine (LEE) was 1: 2 :1. The synthesized BioEPUR were highly flexible, with E_b of 650–900% and S_e from 9 to 29 MPa. Incubation of obtained BioEPUR (based on LEE) in PBS for 8 weeks resulted in mass loss above 50%, while the mass loss was above 10% when BDA was used as the chain extender. The obtained biodegradable materials demonstrate potential application as cell scaf- folds in cardiovascular tissue-engineering or+ demonstrate potential application as cell scaf- folds in cardiovascular tissue-engineering or other soft-tissue applications **[31]**. The degradation products of the synthesized BioEPUR showed no toxic effect to human umbilical vein endothelial cells. Moreover, the BioEPUR was coupled with peptide Arg-Gly-Asp-Ser by using radio-frequency glow dis- charge to encourage cell adhesion on the biomaterials**[32-34]**.

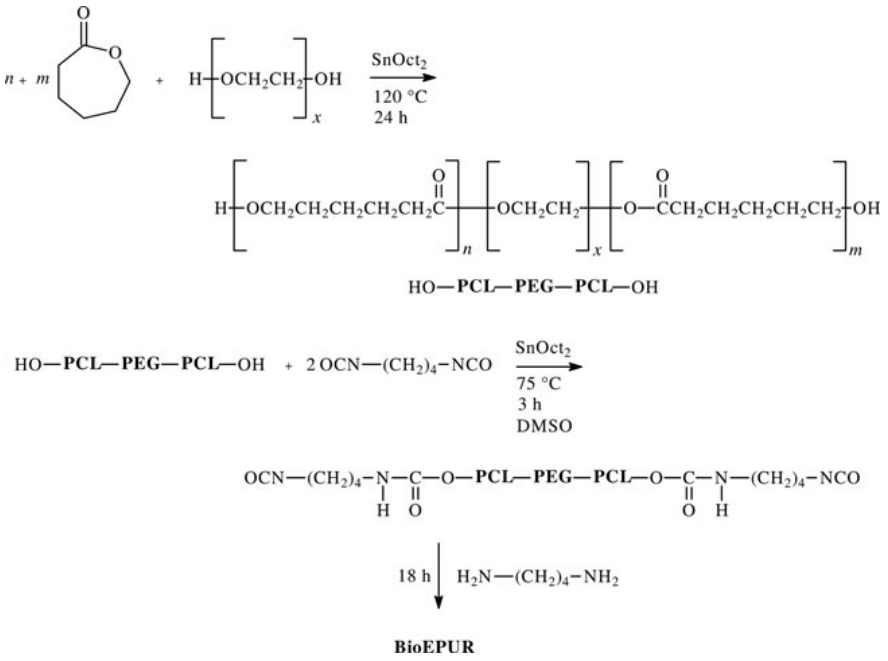

Figure III.3. Synthesis of BioEPUR from 1,4-BDI, PCL–PEG–PCL and BDA.

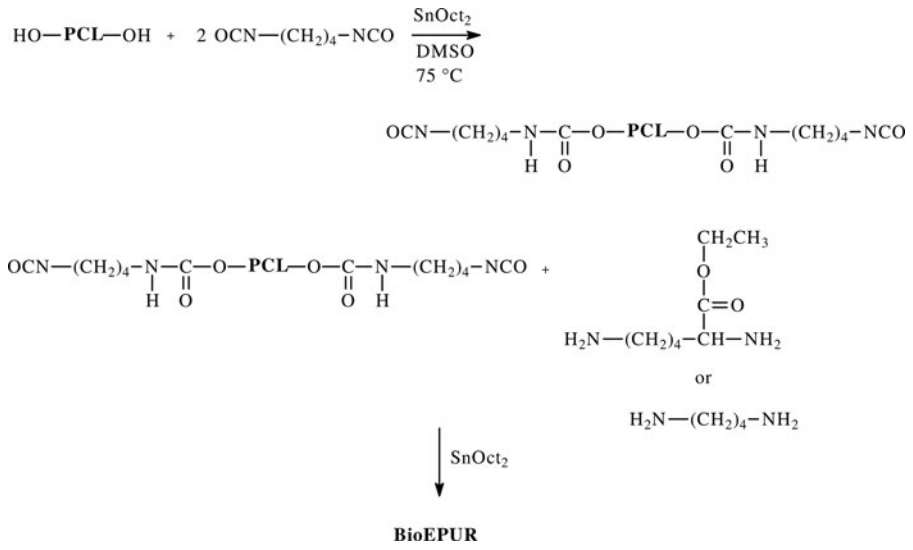

Figure III.4. Synthesis of BioEPUR from PCL diol, 1,4-BDI and BDA or LEE.

There are known some methods of obtaining of BioEPUR systems with drugs. BioEPUR with high elasticity, low throm- bogenicity and paclitaxel (PACL) loading (for vascular grafts and stents) were obtained**[35]**. A phosphorylcholine containing poly(ester urethane) urea was synthesized by grafting aminated phosphorylcholine onto backbone carboxyl groups of PUR (PUR-COOH). PUR-COOH were synthesized from a soft segment blend of PCL and dimethylolpropionic acid, and a hard segment of 1,4-BDI and BDA. The synthesized BioEPUR showed E_b above 600% and S_e in the 20–35 MPa range. PACL loaded in obtained PUR continued to release for 5 days after a burst release in a 10% ethanol/PBS solution. The ethanol/PBS solution was used to increase the solubility of the PACL**[35].**

The perspective group of chain extenders are peptides**[36]**. BioPUR were obtained from 1,4-BDI, PCL–PEG–PCL diol and Ala-Ala-Lys. The synthesized BioEPUR had high molecular weights and low T_g (< 54°C). The E_b and S_e of BioEPUR were 670–890% and 15–28 MPa, respectively. The Ala-Ala- Lys units endowed the BioEPUR with elastase sensitivity.

The mass losses of the obtained BioEPURs were below 20% after 56 days of in vitro degradation without elastase, while the mass losses with elastase reached about 35%. It was found that BioEPUR are characterized endothelial cell adhesion and growth (endothelial cell adhesion was > 140% of tissue culture polystyrene on BioEPUR surfaces; and > 200% on Arg-Gly- Asp-Ser-modified surfaces). It suggested that obtained materi- als had no cytotoxicity**[36]**.

BioEPUR incorporated by bioactive insulin-like growth factor-1 (IGF-1) and hepatocyte

growth factor (HGF) were obtained**[37]**. BioEPUR scaffolds were prepared with 1,4- BDI, PCL diol (M_w 2000 g/mol) and BDA. The stoichi- ometry of the reaction was 2 : 1 : 1 (diisocyanate : polyol : dia- mine). The two-step process was catalyzed by $SnOct_2$. BioEPUR scaffold degradation accelerated by lipase led to delivery of

above 90% proteins over 9 weeks. The IGF-1 and HGF bioactivity in the first 3 weeks was confirmed**[37]**.

In one reference**[38]**, a method of synthesis of BioEPUR from tyramine (T) (naturally occurring monoamine and trace amine derived from the amino acid tyrosine) was described. The T-1,4-BDI-T was used as chain extender to prepare BioE- PUR (**Figure III. 5**)**[38,39]**. In the first step, T-1,4-BDI-T were obtained in the noncatalyst reaction of amine with 1,4-BDI at 80°C for 24 h. Next, PCL diols (Mw 1100–2700 g/mol) were synthesized in the ROP of CL in the presence of BD as initiator and SnOct2 as catalyst. The ROP process was carried out at 135°C for 24 h under argon atmosphere. Finally, BioEPUR was obtained by prepolymer method (by reacting the PCL diol with 1,4-BDI at 80°C in N,N-dimethylformamide (DMF) as a solvent, and then by reacting the obtained prepoly- mer with T-1,4-BDI-T at 80°C). The Tm of obtained BioEPUR, increased from 21 to 61°C and Se increased from 52 to 278 MPa with increasing Mw of PCL diol. Bone marrow stromal cells were cultured on BioEPUR films under osteogenic conditions. The positive effect of obtained biomaterial scaffold modulus on bone tissue development was also established**[38]**.Polycarbonates are other kinds of biocompatible, biode- gradable and nontoxic polyols used in BioEPUR synthesis.

The polycarbonate-based BioEPUR were prepared from PCL diol (Mn 2000 g/mol), poly(1,6-hexamethylene carbonate) (PHC) diol (Mn 2000 g/mol), 1,4-BDI and BDA (**Figure III. 6**) **[40]**. First, the PCL diol and PHC diol (molar ratio of PCL/PHC was 100 : 0, 75 : 25, 50 : 50, 25 : 75, and 0 : 100) were reacted with 1,4-BDI.

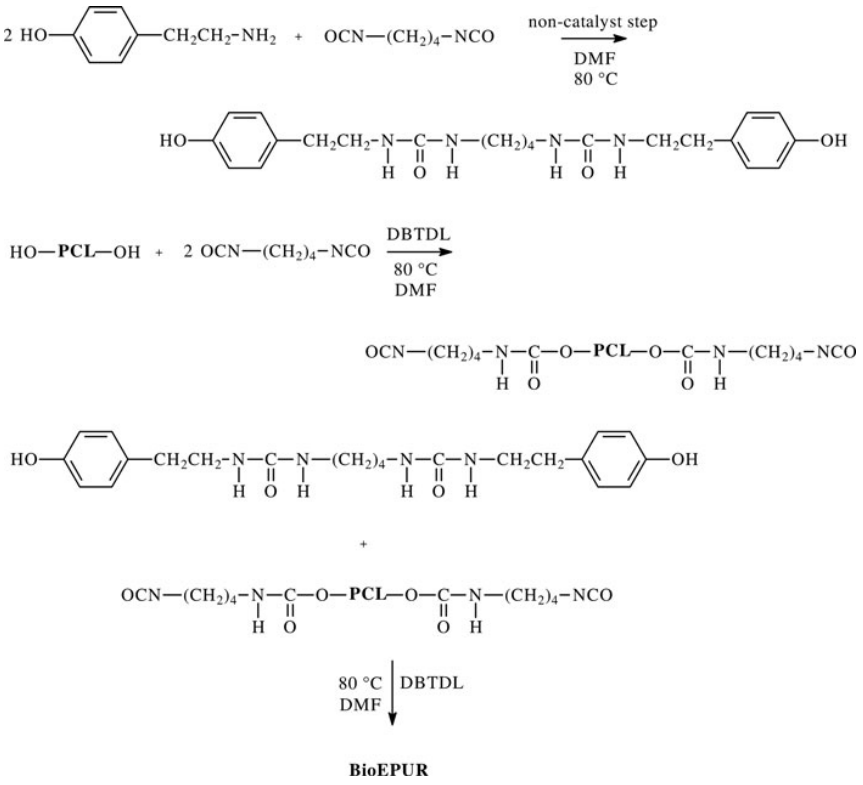

Figure III.5. Synthesis of BioEPUR from tyramine-1,4-BDI-tyramine and 1,6-HDI.

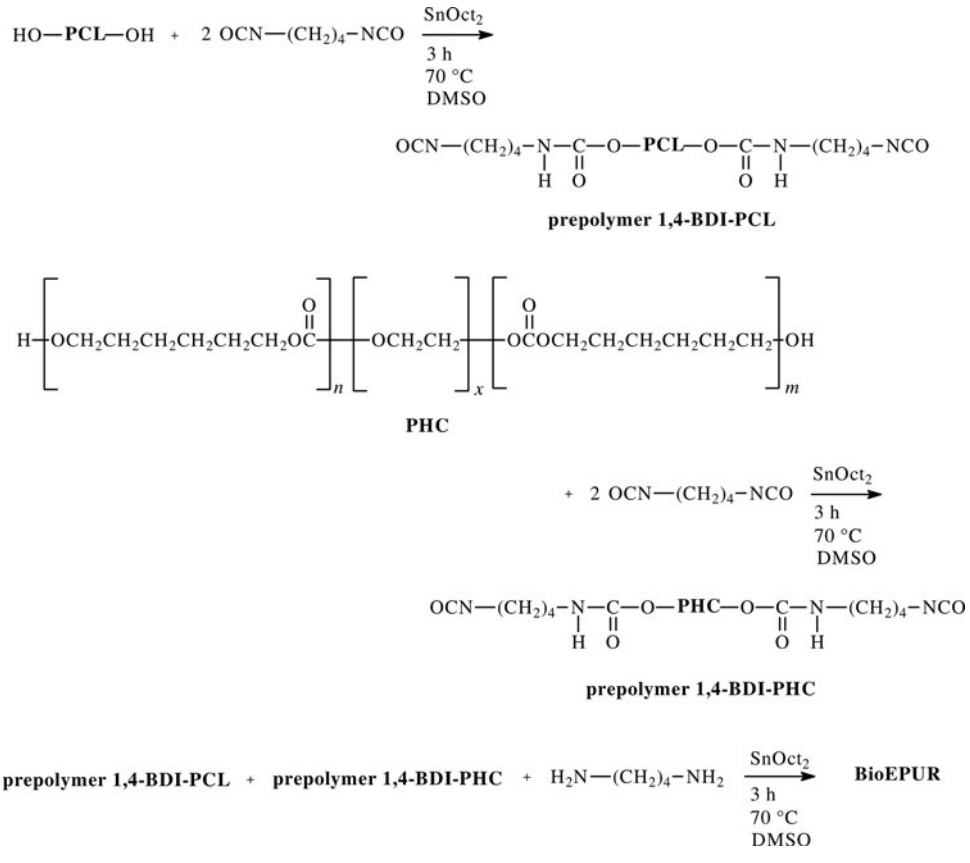

Figure III.6. Synthesis of BioEPUR from PCL diol, PHC, 1,4-BDI and BDA.

The two-step process was carried out for 3 h at 70°C by using SnOct2 as catalyst in DMSO.

The *Se* of BioEPUR varied from 14 to 34 MPa, *Eb* of 660– 875% and initial moduli of 8–24 MPa. It was found that the introduction of polycarbonate segments greatly decreased the degradation rate of the BioEPUR. The obtained BioEPUR without polycarbonate segments exhibited 9% mass loss, while the BioEPUR contained polycarbonate segments did not show any detectable mass loss after 8 weeks of in vitro degradation process (in PBS at 37°C). Moreover, the BioEPUR scaffolds (implanted in rats) obtained from PHC diol degraded much slower than those without polycarbonate segments**[40]**.

The non-catalyst methods are very promising in the syn- thesis of BioEPUR intended for biomedical applications. BioEPUR from PCL diol, BD, and 1,4-BDI were synthe- sized without any catalyst for the production of a degradable meniscus scaffold (**Figure III.7)[28]**.

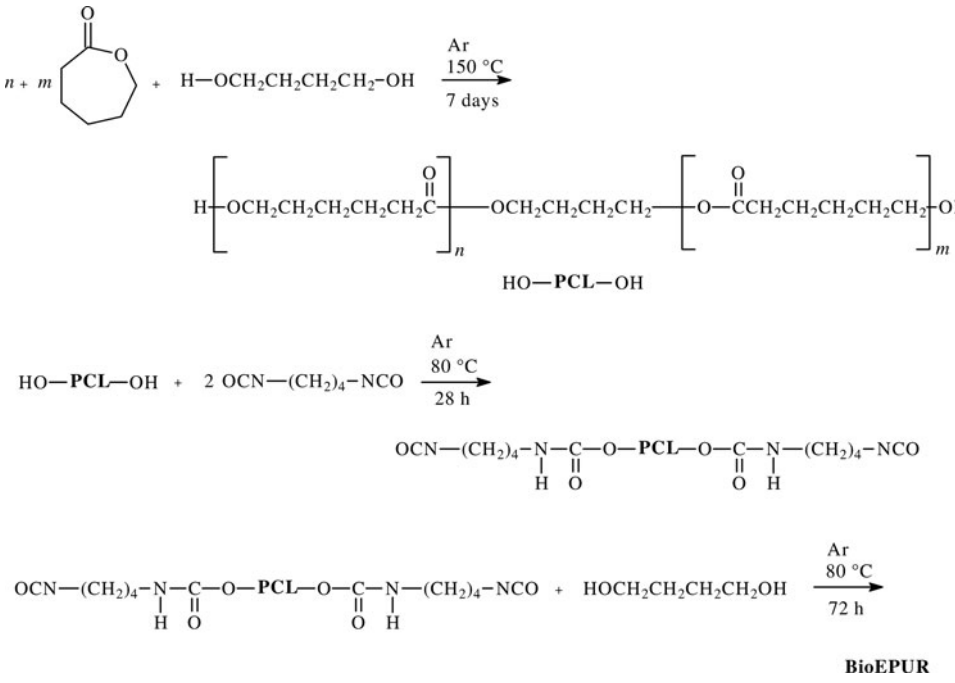

Figure III.7. Non-catalyst method of synthesis of BioEPUR.

In the first step, PCL diols (M_n 800–3200 g/mol) were prepared by the ROP of CL initiated by BD. The process was carried out for 7 days at 150°C. Next, the obtained polyols were reacted with 1,4- BDI in bulk (by the two-step method). The synthesized BioEPUR had molecular weights between 79000 and 164 000 g/mol. They were characterized very good mechanical properties. The *E* varied between 30 and 264 MPa. Moreover, the E_b varied

between 870 and 1200%. The obtained BioEPUR were characterized as having good biological properties and processed into meniscus reconstruction scaffolds**[28]**.

BioEPUR were also prepared with 1,6-HDI and varying ratios of isosorbide, and PCL diol *via* a simple one-step poly- merization without a catalyst (**Figure III. 8**)**[41]**. The degradation tests (performed at 37°C in PBS) showed a mass loss of about 5% after 12 weeks, except for the BioEPUR with the highest iso- sorbide content, which showed an initial rapid mass loss. It was found that the obtained BioEPUR were cytocompatible and biocompatible, and may be useful for various biomedical applications (bladder, cardiovascular and trachea applications)**[41]**. Copolymers of heterocyclic monomers are more and more often used in the BioEPUR synthesis. BioEPUR from a random poly(ε-caprolactone-lactide) diol (PCLA diol), 1,6-HDI and BD were prepared**[42]**. Polyols were first obtained by the ROP of CL and LLA initiated by BD and catalyzed by $SnOct_2$ (**Figure III. 9**). The obtained BioEPUR (M_w 280,000–570,000 g/mol) have potential for use in soft tissue engineering and artificial skin. The T_g of synthesized BioEPUR was below 8°C, and their soft domains became amorphous as the LA content increased. They are characterized excellent mechanical properties, such as the S_e as high as 38 MPa, and the E_b of 1300%.**[42]**

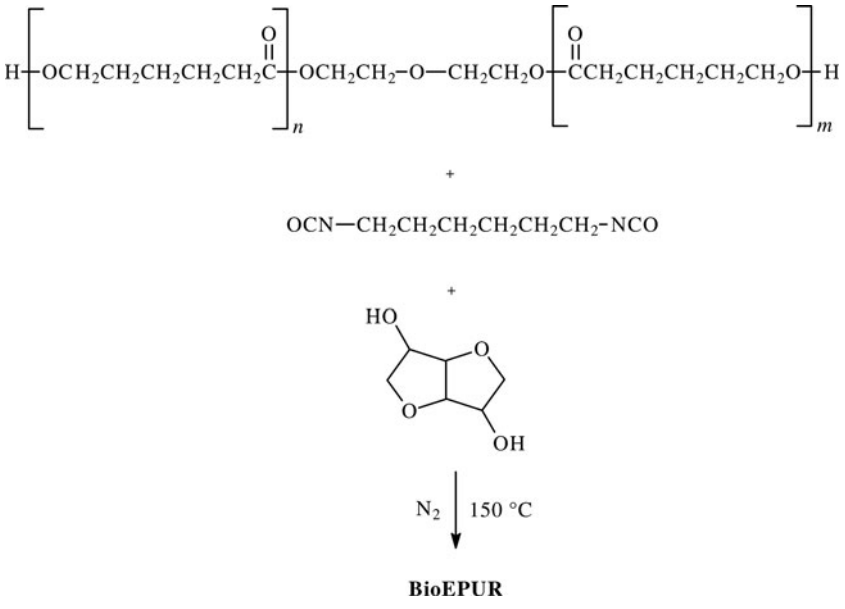

Figure III.8. Synthesis of BioEPUR from PCL diol, isosorbide and 1,6-HDI.

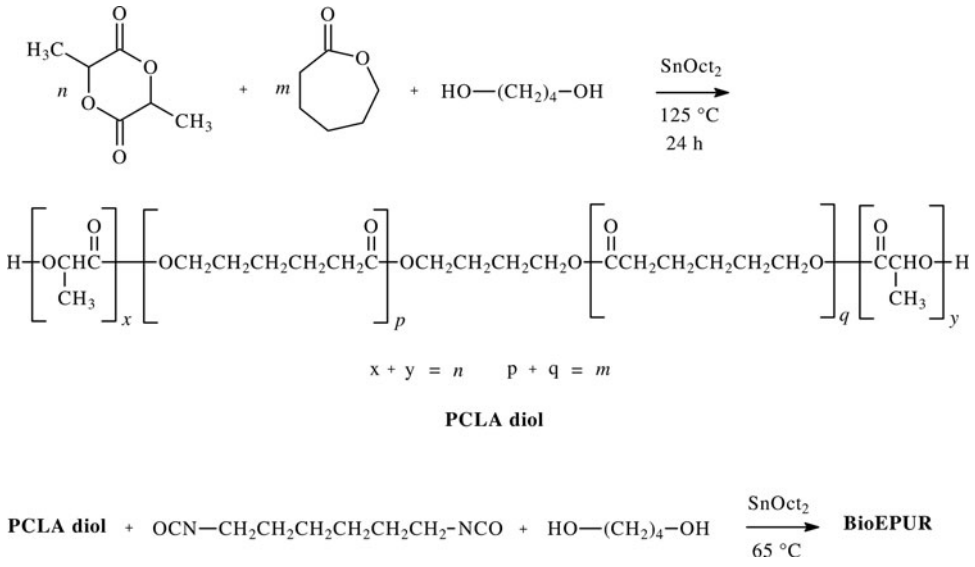

Figure III. 9.Synthesis of BioEPUR from PCLA diol, 1,6-HDI and BD.

The novel families BioEPUR from poly[(R,S)-3-hydroxy- butyrate] (PHB) diol, 1,6-HDI and various aliphatic diols ((BD, 1,6-hexanediol (HD), 1,8-octanediol (OD), 1,10-decanediol (DD)) were also obtained (**Figure III. 10**)**[43]**. The PHB diols were synthesized by the transesterification and conden- sation between ethyl(R,S)-3-hydroxybutyrate and the aliphatic

diols with dibutyltin oxide as catalyst. The process was carried out in bulk at 100°C for 8 h under argon atmosphere with grad- ual reduction of pressure to 0.5 mm Hg. Next, the BioEPUR were obtained by reacting 1,6-HDI with the PHB diol at 80° C with DBTDL as catalyst. Then 1,2-dichloroethane was used as a reaction medium**[43]**. BioEPUR were also synthesized from telechelic hydroxylated poly(3-hydroxybutyrate-co-3- hydroxyhexanoate) (PHBHH) and PEG *via* a melting polyaddition process using 1,6-HDI. Implantation of obtained biomaterials in mouse abdominal cavity indicated that tissue regeneration and tissue compatibility of BioEPUR was very high**[44]**.

Shape-memory polymers have attracted significant atten- tion from biomedical materials industry due to their useful and interesting functionality.

BioEPUR exhibiting light-induced shape memory effect at room temperature was obtained by a two-step polyaddition process using N,N-bis(2-hydroxyethyl) cinnamamide (BHECA), PCL diol, PLLA diol and 1,6-HDI (**Figure III. 11**)**[45]**. The obtained biomaterials are very interesting, because BHECA is currently used in medicine as a muscle relaxant **[9,45]**. In the

first step, BHECA and PCL diol were reacted with 1,6-HDI. The process was carried out in the presence of $SnOct_2$ as catalyst, in 1,4-dioxane as a medium, for 3–3.5 h at 80–85°C under nitrogen. Then, the PLLA diol was added to the mixture reaction for 4–5 h. It was found that E_b of the BioEPUR clearly depended on the PCL content. The higher PCL content led to the higher E_b. The E of the BioEPUR seemed to be determined mainly by the PLLA content. However, their S_e did not show any clear dependence on the PLLA content**[45]**. The pendant cinnamamide groups of BioEPUR chains worked as photoresponsive molecular switches. They provided the BioEPUR with light-induced shape memory effect *via* revers-ible **[22]** cycloaddition cross-linking. The degradation tests showed BioEPUR lost 12–25% weight after 32 weeks in PBS**[9]**. Many other functional aliphatic polyesters are now also commonly used as precursors for the BioEPUR synthesis.

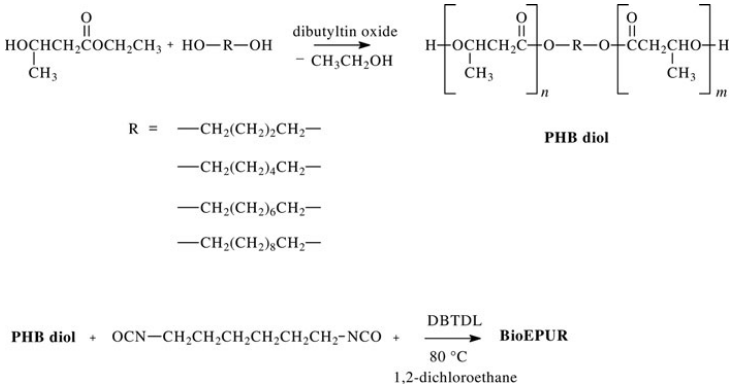

Figure III.10. Synthesis of BioEPUR from PHB, 1,6-HDI and aliphatic diols.

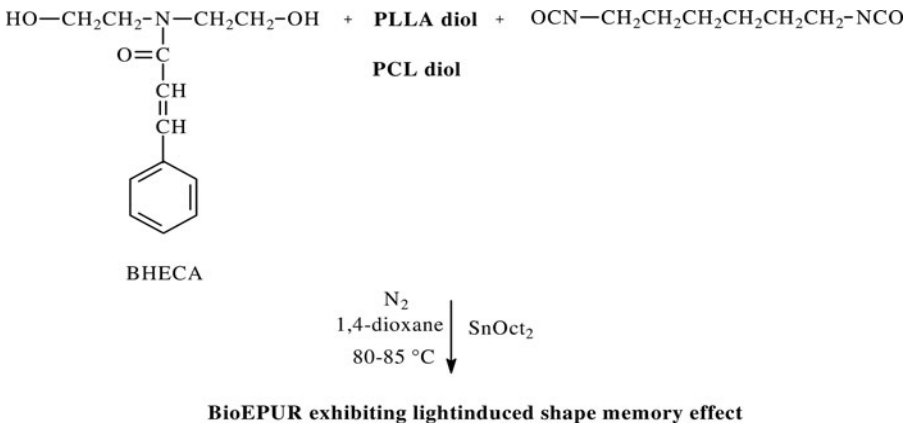

Figure III.11.BioEPUR exhibiting light-induced shape memory effect.

BioEPURs based on poly(1,3-propylene adipate) (PPA), poly(1,4-butylene adipate) (PBA), poly(1,12-dodecylene seba- cate) (PDS) and poly(1,2-dimethylethylene adipate) (PDMEA) were prepared[46,47]. For example, the BioEPUR were pre- pared by using PDMEA diols, hexamethylene diamine (HAD) and 1,6-HDI. PDMEA diols were synthesized by the reaction of 1,2-dimethylglycol with adipic acid in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene as a catalyst (**Figure III. 12**)**[46]**. The low *E* at room temperature and sufficiently high E_b of the obtained BioEPUR, make it suitable for use in cardiovascular applications.

The other example of biomaterial is the BioEPUR synthe- sized by using polylactide-block-poly(butylene adipate)-block- polylactide (PLAPBAPLA) diol and 1,6-HDI. PLAPBAPLA diols were first synthesized with LLA and PBA diol, and then the obtained polyols were melt chain extended by using 1,6- HDI in the presence of $SnOct_2$. The mechanical properties of the obtained biomaterials could be regulated by the length ratio of PLA block to PBA block and the molecular weight of the BioEPUR. The S_e and E_b of BioEPUR were from 6.6 to 24.4 MPa and the E_b was from 190% to 780%.**[47]** Synthesis of BioEPUR Based on LDI.

LDI is another good choice for obtaining hard segments because the degradation products are also noncytotoxic**[23]**.

BioEPUR from PCL diols, LDI and BD were synthesized in the presence of DBTDL as a catalyst (**Figure III. 13**)**[48]**. The prepo- lymers were first synthesized by the reaction of BD and LDI. The process was carried out at 40°C for 30 min. in toluene as a reaction medium. Next, the PCL diols were added to the pre- polymers (for 22 h). The resulting materials had good mechan- ical properties (Se of 33 MPa and Eb of 1000%). The synthesized BioEPUR could be potentially used as temporary orthopedic implant devices**[48]**.

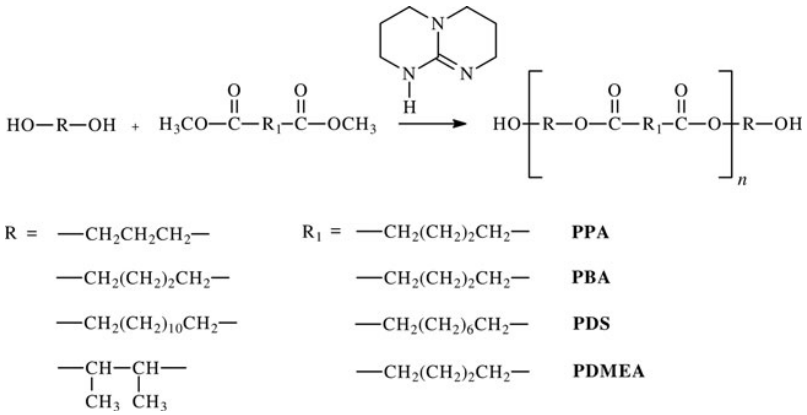

Figure III 12. Synthesis of polyols.

LDI was also used in the synthesis of cationic biodegrad- able polymers. Cationic BioEPUR was prepared through intro- ducing gemini quaternary ammonium side groups on hard segments (**Figure III. 14**)**[49]**. In the first step, L-lysine-derivatized diamines containing gemini quaternary ammonium side groups (GA) were obtained. Next, the prepolymers were prepared by reacting PCL diol and LDI at 60°C for 1 h (in N,N-dimethyla- cetamide, under a dry nitrogen atmosphere). The obtained pre- polymers were then extended by using BD and GA. The process was carried out in the presence of $SnOct_2$ as catalyst (at 60–70°C for 2 h).

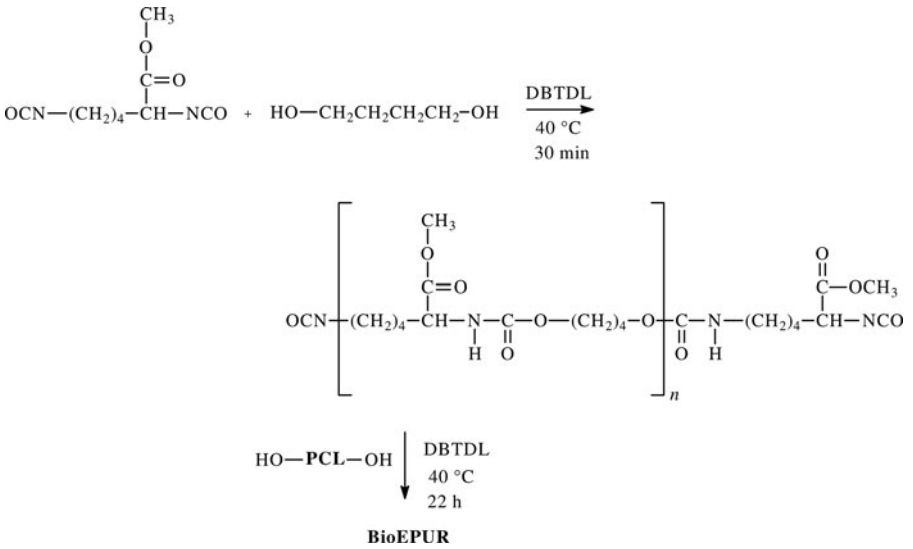

Figure III.13.Synthesis of BioEPUR from PCL diol, LDI and BD.

Next, methoxyl-PEG was added to mix- ture reaction with the extended prepolymers (at 60°C for 1 h). The in vitro enzymatic and hydrolytic degradation tests was carried out. It was found that the degradation rate increased with the increase of GA content in polymer chain. After 12 h of in vitro degradation process, the mass losses of the obtained BioEPUR was about 50% and 100% at GA molar contents of 70% and 100%, respectively**[49]**.

BioEPUR based on LDI, PCL diols (M_n 530, 1250 or 2000 g/mol) and BDA were synthesized in absence of cata- lyst**[50]**. The obtained biomaterials had high molecular weights, low T_g and high E_b. NIH3T3 fibroblasts have been used for cell-adhesion studies on BioEPUR to investigate the biocom- patibility. Moreover, sulfamethoxazole was loaded in obtained biomaterials. The kinetic of BioEPUR degradation and drug release (in alkaline solution and *in vitro* drug release in Ph 7.4 buffer) were investigated. The obtained biomaterials are the example of biodegradable matrices of sulfamethoxazole for fully controlled release**[50]**.

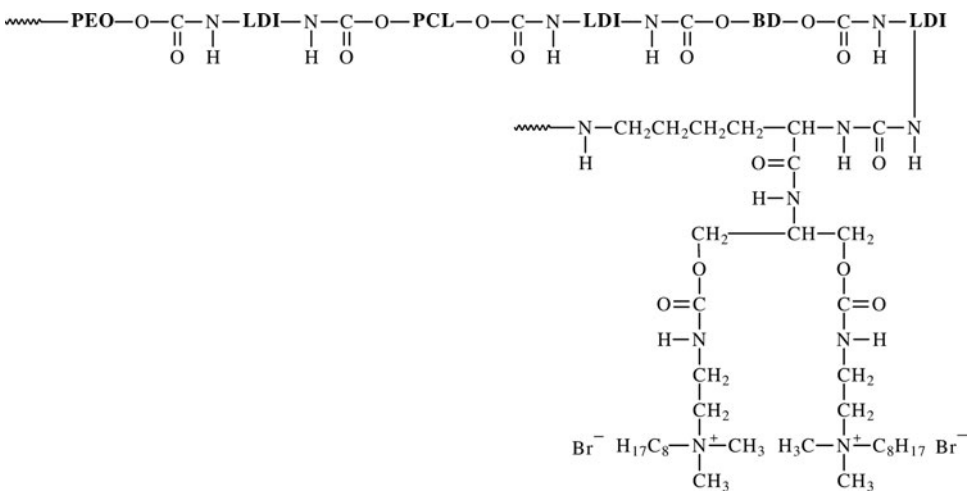

Figure III.14. Structure of cationic BioEPUR

B. Synthesis of BioEPUR Based on Cycloaliphatic Diisocyanates

Potential substrates for the production of BioEPUR are also cycloaliphatic diisocyanates.

BioEPUR based on cycloaliphatic diisocyanates with potential for biomedical applications were synthesized by the reaction of PCL and IPDI, extended with different mass ratio of chitosan (CHIT) and BD (**Figure III. 15**)**[51]**. Incorporation of CHIT contents into the BioPUR backbone caused improvement in thermal stability and degradation rate. It was found that hydrophilicity decreased and crystallinity increased with increasing CHIT content in BioEPUR back- bone**[51]**.

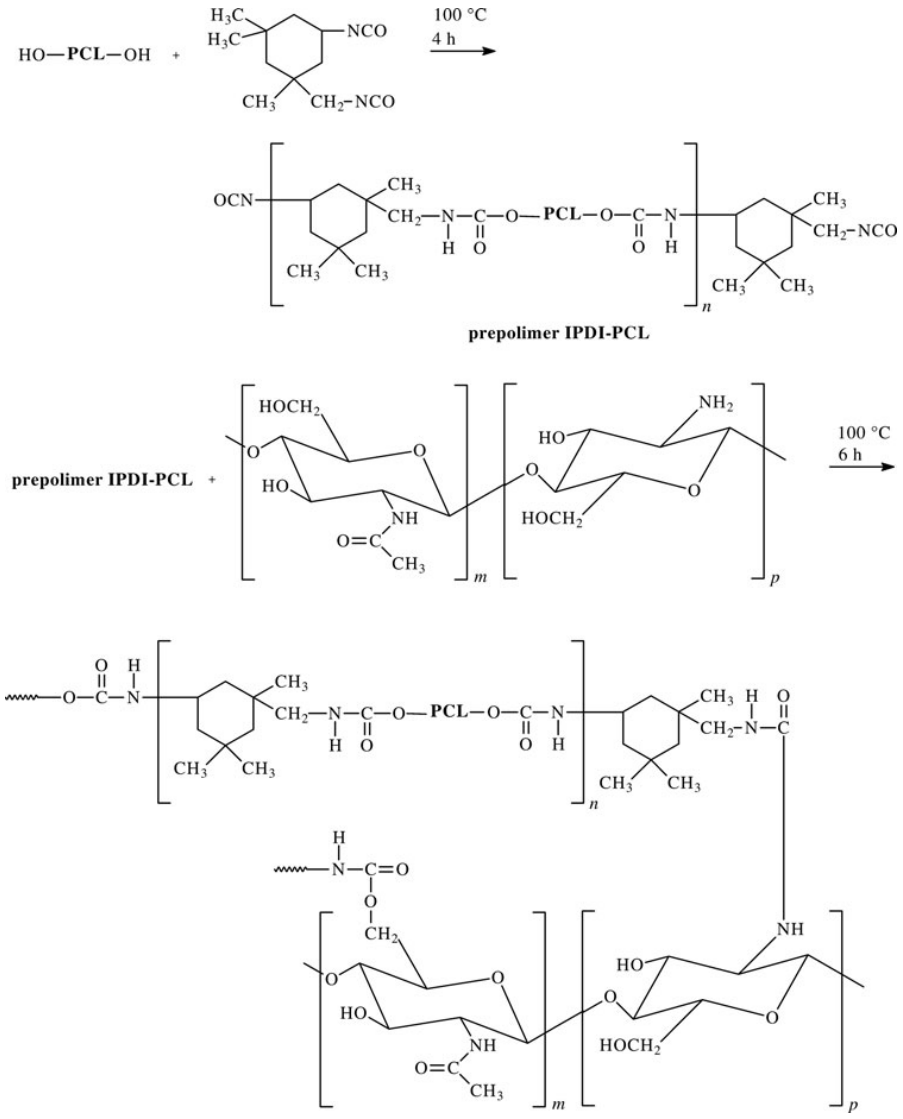

Figure III.15. Synthesis of BioEPUR from PCL, IPDI, CHIT and BD.

Novel BioEPUR from PCL, HMDI and L-cystine dihy- drochloride methyl esters (CChME) were synthesized by the two-step method (**Figure III. 16**)**[52]**. The process was carried out in the presence of DBTDL as a catalyst. The obtained BioEPUR are characterized by S_e 3–12 MPa and E_b 440– 850%. The influence of the materials on human umbilical vein endothelial cells was investigated by WST-1 assay. The results showed that the BioEPUR sustained much higher cell viability than the controls. The obtained biomaterials could be used as cell scaffolds, drug delivery systems and wound closure devices**[52]**.

BioEPUR (as promising materials for cardiovascular appli- cations) were prepared with PCL diols, HMDI and BD or dithioerythritol as chain extenders. Platelets adhesion on obtained biomaterials was tested. It was observed that relative viability was higher than 80% on human umbilical vein endo- thelial cells in contact with BioEPUR extracts after 1 week**[53]**. Another

biomaterials, which could be used in the design of vascular grafts for tissue engineering, were prepared from e.g., amino acids.

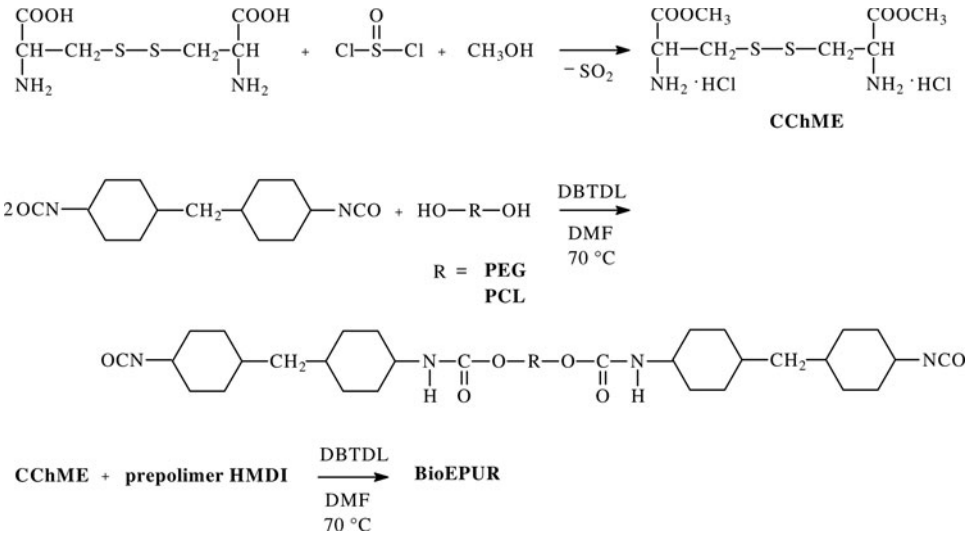

Figure III.16.Synthesis of BioEPUR from PCL, HMDI and CChME.

BioEPUR were synthesized by a two-step method using a molar ratio of 1 : 2.05 : 1 (PCL : HMDI : chain extender). Amino acids (L-arginine, glycine and L-aspartic acid) were used as chain extenders (**Figure III. 17**). The biodegradability and human umbilical vein endothelial cells proliferation on amino acid- based BioEPUR were tested. It was found that the obtained materials characterized good biological properties**[54]**.

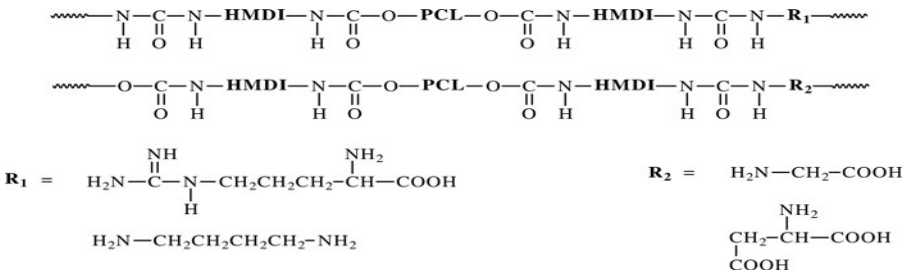

Figure III.17. Structure of BioEPUR based on amino acids.

III.3 BioEPUR as Multifunctional Biomaterials

BioEPUR are a very group of prospective biomaterials that could be used for the controlled release of drugs and (targeted) delivery of biotherapeutics (short or long-term types)**[55]**. They are known as BioEPURs, in which drug molecules are covalently bound to PUR segments.

Studies of the release of ascorbic acid from PUR systems was reported by Zhang et al**.[56]** Polyurethane drug delivery systems (PURDDS) were prepared by reacting hydroxyl groups of ascorbic acid (AAc) and

glycerol with LDI to form urethane linkages. It was found that the release rate of AAc from the PUR system was mainly dependent on the degra- dation rate of urethane bonds. Moreover, AAc released from PURDDS stimulated cell proliferation, collagen (type I) and alkaline phosphatase *in vitro* synthesis**[56]**.

Another biodegradable and biocompatible PURDDS for the controlled release of an anticancer agent 7-tertbutyldi- methylsilyl-10-hydroxy-camptothecin (DB-67) were obtained. The PURDDS were prepared form LDI-based PUR in the presence of DB-67, which was covalently incorporated into the LDI-glycerol *via* the formation of urethane linkages**[57]**. It was found that the *in vitro* release of DB-67 from the obtained PURDDS indicated that only a very small fraction of the drug was released in pH 7.4 at 37°C after 9 weeks. It was likely a result due to the hydrophobic milieu created by the presence of DB-67 in the PUR. Moreover, it was observed that cellular proliferation assays on the empty LDI-based PUR discs alone do not significantly alter the growth of malignant human glioma cell lines**[57]**.

The anticancer drug, doxorubicin (DOX), was covalently bound to PUR chains *via* a urethane or a urea linkage**[58].** As is known, the DOX molecule has four OH and one primary NH_2 for attachments. The long-term application systems were obtained. It was found that the synthesized PURDDS exhibited very slowly drug release (below 0.1%) at 37°C after 10 weeks.

Authors suggested that the reason for the slow DOX release is the very slow hydrolytic of the many chemical bonds between the drug molecules and the polymer chain **[58].**

PURDDS were also obtained from 1,6-HDI, 4,4’-dihydrox- yazobenzene-3,3’-dicarboxylic acid (AZO I) or 4,4’-dihy- droxy-3’-formyl azobenzene-3-carboxylic acid (AZO II) and 5-aminosalicylic acid (5-ASA). The azo compounds containing 5-ASA and AZO-I or 5-ASA and AZO-II were linked onto the PUR backbone **[59]**. AZO I was *in vitro* released gradually from the obtained PURDDS at pH 7 and 37°C for 10 days. Faster release of AZO I (70% released after 1 day) was observed at pH 9. It was found that the release of AZO II from PURDDS was similar to AZO I, which exhibited the pH-con- trollable release of the azo PURDDS**[59]**.

Recently, we found that aliphatic PUR is satisfactory car- riers for fluoroquinolones **[60,61]**.

The fluoroquinolones are a family of synthetic broad-spectrum antibacterial substances.

A series of linear PUR conjugates of norfloxacin (NOR) were prepared in our laboratory (**Figure III. 18**)**[60]**. First, polyols were obtained by the ROP of CL, LLA and *rac*-LA initiated by creatinine (breakdown product of creatine phosphate in mus- cle). Next, the PUR conjugates of NOR were obtained in the reactions of the PCL diols (M_n 2,400 or 2,600 g/mol), PLA diols (Mn 1,800 or 2,000 g/mol), commercial oligo (ethylene adipate) (OEAD) diol (M_n 1 000 g/mol) with 1,6-HDI and NOR. PURDDS were synthesized in one or two-step processes. $SnOct_2$ or DBTDL were used as the polyaddition catalysts. It was found that the rate of NOR release from PUR conjugates was generally depended on the structure of the polymer. It was observed that the order of hydrolytic degradation was as follows: PLA-PUR > OEA- PUR > PCL-PUR **[60]**.

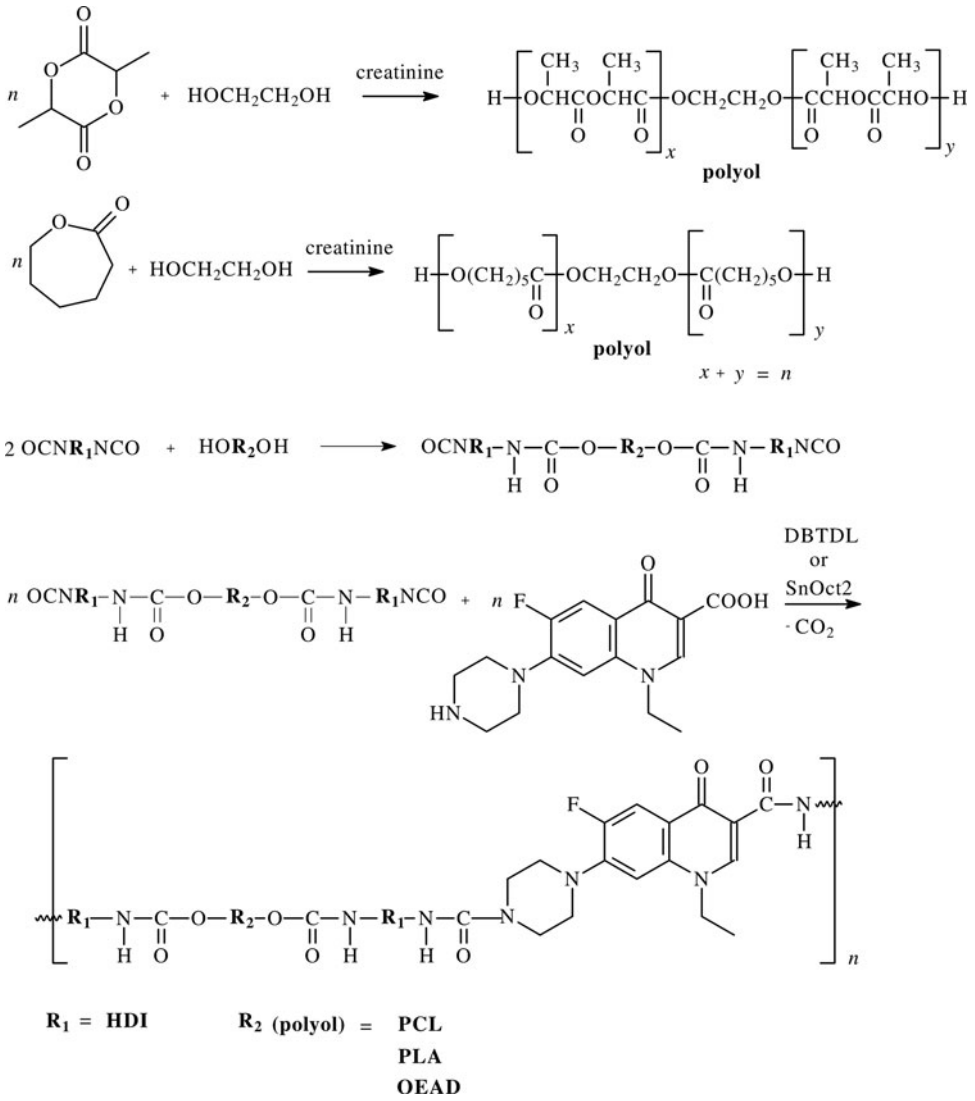

Figure III.18. Synthesis of PUR-fluoroquinolone conjugates.

PUR conjugates were also obtained in the polyadditon reac- tions between polyols (copolymers of rac-LA or glycolide (GLI)), ciprofloxacin (CIP) and 1,6-HDI[61]. PUR conjugates of CIP were synthesized in two-steps process. The polymeriza- tion reaction was carried out at the NCO/OH molar ratio of 1 in the presence of SnOct2 as a catalyst. Polyols were synthe- sized by the ROP of rac-LA and GLI (SnOct2 was used as catalyst). The preliminary studies on the release of CIP from the obtained PUR conjugates of CIP have been carried out. The hydrolytic stability of the prepared biomaterials was tested in the PBS in the presence of Cholesterol esterase. The per- centage of the released CIP from PURDDS was 15-30% after 6 weeks**[61]**. The obtained results demonstrated that the synthe- sized fluoroquinolones-PURDDS are interesting components of BioEPUR for the controlled release of antimicrobial substances.

PUR conjugates of drug (as components of elastomeric implants) were also prepared by the reaction between PCL or PLA diols, copolymers of CL and rac-LA, OEDA diol, 5-fluorouracil (5-FU) with 1,6-HDI (**Figure III. 19**)**[62]**. The release or biodegradation rates of the anticancer drug were shown to be directly dependent on the kind of the polyols used in PUR conjugates synthesis. The release rate of 5-FU was seen to be much faster from PUR conjugates made with PLA diol as compared to those made with PCL diol**[62].**

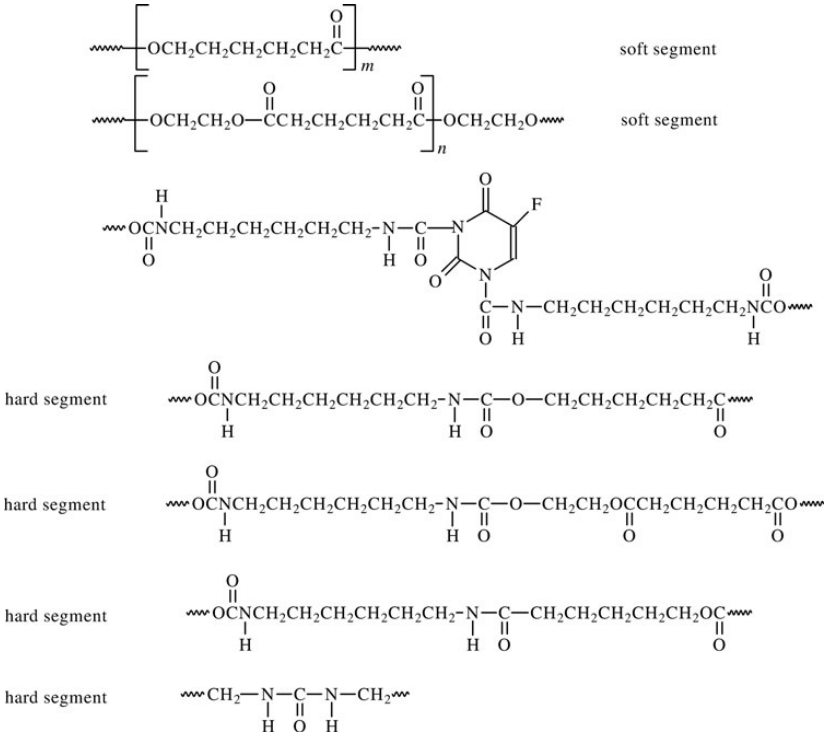

Figure III.19.Structure of PUR-5FU conjugates.

III.4. Conclusion

This review highlights some recent developments in various aspects of BioEPUR synthesis, physicochemical and biologi- cal characterization. These elastomers seem to be an interest- ing and promising developmental direction for medicine, biomedicine and pharmacy due to their unique properties. BioEPURs are an emerging class of biomaterials with many potential clinical applications including implanted devices, tissue engineering and drug delivery systems. Several elasto- mers have been proposed recently; however, the most prospec- tively useful type of elastomers appear to be multifunctional biomedical elastomers (used as implantable drug delivery sys- tems, for example). Such BioEPURs should be useful for a broad range of clinically relevant applications, and in years to come, the number of BioEPUR applications will certainly increase.

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Conclusion

Conclusion

Polyurethanes are the most commonly used materials in the production of blood contacting devices such as heart valves or artificial veins and arteries. They comprise a large family of materials with the only common characteristic of the presence of urethane linkages along the large molecular chains. In general urethane linkages form by the reaction of isocyanates and alcohols. During the preparation and the curing processes of polyurethanes, besides the formation of urethane linkages, many other reactions take place and lead to formation of various bonds such as allophanate, biuret, acylurea or isocyanurate and these bonds may lead to further branching or crosslinking affecting the whole physical, chemical and mechanical properties as well as the biocompatibilities of the resulting polymers.

In conclusion, Polyurethanes (PUs) are a major family of polymers displaying a wide spectrum of physico-chemical, mechanical and structural properties for a large range of fields. They have shown suitable for biomedical applications and are used in this domain since decades. The current variety of biomass available has extended the diversity of starting materials for the elaboration of new biobased macromolecular architectures, allowing the development of biobased PUs with advanced properties such as controlled biotic and abiotic degradation. In this frame, new tunable biomedical devices have been successfully designed. PU structures with precise tissue bio mimicking can be obtained and are adequate for adhesion, proliferation and differentiation of many cell's types. Moreover, new smart shape-memory PUs with adjustable shape-recovery properties have demonstrated promising results for biomedical applications such as wound healing. The fossil-based starting materials substitution for biomedical implants is slowly improving; nonetheless better renewable contents need to be achieved for most PUs to obtain biobased certifications.

Abstract

Polyurethanes (PUs), formed by the reaction of diisocyanates with polyols (or equivalent) in the presence of a catalyst, have a wide variety of industrial uses. Much recent attention has focused on their biomedical applications, owing to their biocompatibility, biodegradability and tailorable chemical and physical forms. Examples of such application areas include antibacterial surfaces and catheters, drug delivery vehicles, stents, surgical dressings/pressure sensitive adhesives, tissue engineering scaffolds and electrospinning, nerve generation, cardiac patches and PU coatings for breast implants.

Keywords:

Diisocyanates, Polyols, Polyurethanes, Biodegradability, Biomedical Applications.

Résumé

Les polyuréthanes (PU), formés par la réaction de diisocyanates avec des polyols (ou équivalent) en présence d'un catalyseur, ont une grande variété d'utilisations industrielles. Une grande attention récente s'est concentrée sur leurs applications biomédicales, en raison de leur biocompatibilité, de leur biodégradabilité et de leurs formes chimiques et physiques personnalisables. Des exemples de tels domaines d'application comprennent les surfaces antibactériennes et les cathéters, les véhicules d'administration de médicaments, les stents, les pansements chirurgicaux/adhésifs sensibles à la pression, les échafaudages d'ingénierie tissulaire et l'électrofilature, la génération de nerfs, les patchs cardiaques et les revêtements PU pour les implants mammaires.

Mots clés:

Diisocyanates, Polyols, Polyuréthanes, Biodégradabilité, Applications biomédicales.

ملخص

يتكون البولي يوريثان (PUs) من تفاعل ثنائي أيزوسيانات مع البوليوالت)أو ما يعادلها(في وجود محفز ، ولها مجموعة متنوعة من االستخدامات الصناعية. ركز الكثير من االهتمام مؤخ ًرا على تطبيقاتها الطبية الحيوية ، نظ ًرا لتوافقها الحيوي ، وقابليتها للتحلل البيولوجي ، وأشكالها الكيميائية والفيزيائية القابلة للتخصيص. تشمل ألمثلة على مجاالت التطبيق هذه ألسطح والقسطرات المضادة للبكتيريا ، ومركبات توصيل ألدوية ، والدعامات ، والضمادات الجراحية / المواد الالصقة الحساسة للضغط ، وسقاالت هندسة ألنسجة ، والغزل الكهربائي ، وتوليد ألعصاب ، والبقع القلبية ، وطالءات البولي

يوريثان لغرسات الثدي.

الكلمات المفتاحية:

ثنائي أيزوسيانات ، بوليوالت ، بولي يوريثان ، تحلل حيوي ، تطبيقات طبية حيوية