Chapter 1
Introduction

1.1 BACKGROUND AND LITERATURE REVIEW

Biocompatible polymers have emerged as biomaterials in contemporary times. The research in the field is approaching to most challenging level as they can transform the living standard of human beings a step forward. The popularity of polymers is due to their special structural design leading to flexibility, adaptability and lower manufacturing cost. The widespread applications of such biopolymers in biomedical field involves artificial organs, transdermal patches, implantable devices, wound dressings, tissue engineering, prostheses, ophthalmology, vaginal rings, dentistry and drug delivery systems [1]. The prerequisite for a polymeric material to be applicable as an ideal biomaterial is biocompatibility which in turn depends on several other factors, including the mechanical properties, morphology, thermal properties, magnetic properties, biodegradability as well as toxicity [2].

Polyurethanes (PUs) are one of the most versatile families of polymers. PUs pave a way to create the prospective for high performance materials due to their significant physical and mechanical properties and good biocompatibility [3,4]. PUs are characterized with the properties like high tensile strength, elasticity, durability, fatigue resistance, compliance, and acceptance or tolerance in the body during the drug release or healing. Furthermore, preference for bulk and surface modification via hard/soft segment balance or by attachments of biologically active species such as anticoagulants or bio-recognizable groups are possible via chemical groups typical for polyurethane structure. This possibility of variation in structure makes PUs adaptable for biomedical applications as well as enhances the acceptance of the device or implant [5,6].

1.1.1 CONTROLLED DRUG DELIVERY: USE OF POLYMERS

1.1.1.1 IMPORTANCE OF CONTROLLED DRUG DELIVERY

Controlled drug delivery is a term used by the biomedical researchers in order to define the advanced type of drug release systems as compared to classical drug delivery. The controlled drug delivery is defined as "Delivering the drug at the right place, at the right concentration for the right period of time" [7]. In classical drug delivery, for most of the pharmaceutical industries, existing drug delivery induces simple, fast-acting responses via oral or injection routes. However the classical drug delivery route faces some problems. This includes reduced potencies because of partial degradation. For example, there are some drugs which are partially degraded after administration and cannot affect potentially. Also, classical drug delivery systems may administrate toxic level of drug during dosage, resulting into serious side effects and wastage of excess drug. There is also a trauma of compliance issue due to pain induced during course of administration by injections.

Fig. 1.1 shows a graph of drug in the organism verses desired time of action. There are three levels for absorption of drug. First is "ineffective level", in which the drug concentration is not enough to give its effect. Second is "therapeutic level" which includes drug concentration desired for proper action of drug. Third is "toxic level" which describes drug concentration which can be toxic for the patient. In case of classical drug delivery by injection, the drug concentration starts from ineffective level, reaches to desired level and crosses to toxic level, again returning back to therapeutic level. To get rid of this problem of toxic level, repeated doses are administered so that the desired level of drug concentration can be achieved. But interestingly, in case of

controlled drug delivery, constant predictable release can be obtained within therapeutic level for longer period of time in a single dose!

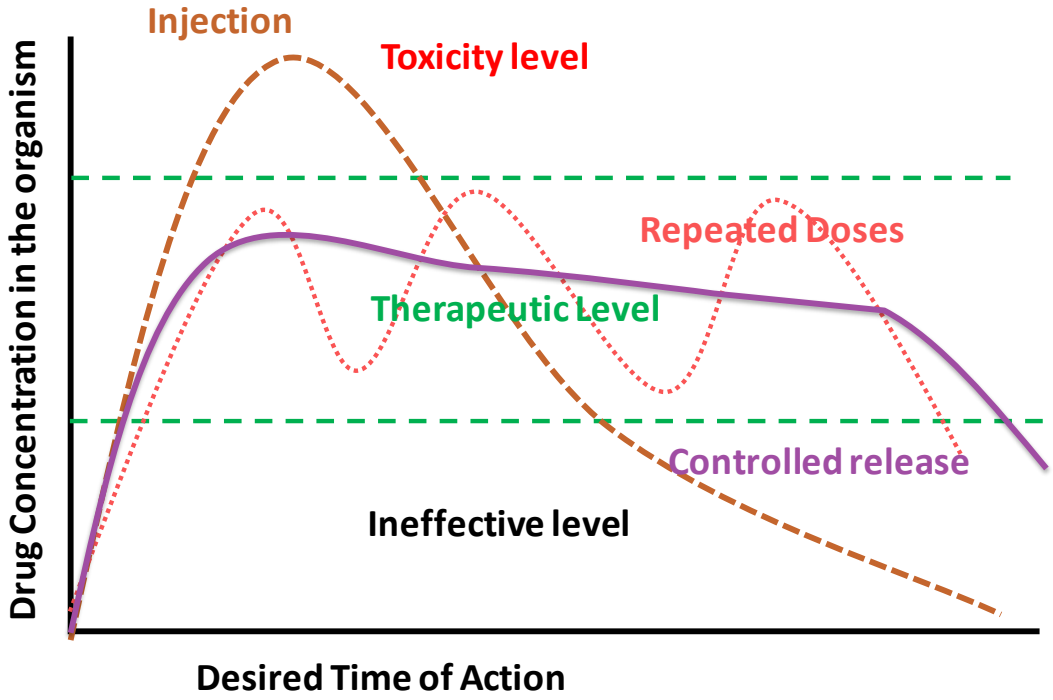


Figure 1.1 A schematic drawing illustrating controlled drug release *(Reproduced from Bajpai et al)*[8]

The importance of the controlled drug delivery comes from the fact that it can be utilized to achieve several advantages as listed below [8].

(1) Sustained constant concentration of drugs in the blood with least fluctuations.

(2) Predictable release rates with high rate of reproducibility over a long period of time.

(3) Protection of bioactive compounds having a very short half-life.

(4) Reduction of frequency of doses and elimination of side-effects.

(5) Optimized therapy and superior patient compliance.

(6) Solution to the drug stability problem and drug wastage.

1.1.1.2 POLYMERIC SYSTEMS AS CONTROLLED DRUG DELIVERY DEVICES

The biocompatible polymers are used in a variety of biomedical applications such as implants, scaffolds for tissue engineering, transdermal patches, catheters, and cavity liners [9]. For a polymer to be useful as a drug delivery device, besides its biocompatibility, biodegradability is an important property. This is because the fate of polymer after drug release decides the mechanism of the drug release. The polymers that can be excreted from the body by its natural excretion process such as via kidneys, are desirable for this type of applications [10,11]. Looking from the perspective of the chemistry of polymers, it is observed that depending on the type of raw materials, structure of polymers and degradability rate, the rate of drug release and its mechanism is largely affected. This shall be discussed in the next section. The following table describes the commonly used polymers in the biomedical applications [12].

Table 1.1 List of commonly used polymers in the biomedical applications [12]

Polymer	Specific Properties	Biomedical uses
Polyethylene	Low cost, excellent electrical insulation properties, excellent chemical resistance, toughness and flexibility even at low temperatures	Tubes for various catheters, hip joint, knee joint prostheses
Polypropylene	Excellent chemical resistance, weak permeability to water vapours, good transparency and surface reflection	Yarn for surgery, suture
Tetrafluoroethylene	Chemical inertness, exceptional weathering and heat resistance, non-adhesive property, very low coefficient of friction	Vascular and auditory prostheses, catheters tubes

Polyvinylchloride	Excellent resistance to abrasion, good dimensional stability, high chemical resistance to acids, alkalis, oils, fats, alcohols, and aliphatic hydrocarbons	Flexible or semi-flexible medical tubes, catheter, inner tubes components of dialysis installation and temporary blood storage devices
Polyacetals	Stiffness, fatigue endurance, resistance to creep, excellent resistance to action of humidity gas and solvents	Hard tissue replacement
Polycarbonate	Rigidity and toughness upto 1400°C, transparency, good Electrical insulator, physiological inertness	Syringes, arterial tubules, hard tissue replacement
Polyethylene terephthalate	Transparency, good resistance to traction and tearing, resistance to oils, fats, organic solvents	Vascular, laryngeal, oesophageal prostheses, surgical sutures, knitted vascular prostheses
Polyamide	Very good mechanical properties, resistance to abrasion and breaking, stability to shock and fatigue, low friction coefficient, good thermal properties	PA 6 tunes for intra cardiac catheters, urethral sound; surgical suture, films for packages, dialysis devices components

1.1.1.3 MECHANISMS OF DRUG DELIVERY SYSTEMS FROM POLYMER NETWORK

Drug delivery systems can be classified according to the mechanism controlling the drug release as follows [13].

(1) Diffusion-controlled systems

a. Reservoir (membrane systems)

b. Matrix (monolithic systems)

(2) Chemically controlled systems

a. Bioerodible and biodegradable systems

b. Pendent chain systems

(3) Solvent-activated systems

a. Osmotically controlled systems

b. Swelling-controlled systems

(4) Modulated-release systems

Each type of the mechanism stated above can give different type of drug release depending on mode of mechanism, type of polymer and type of drugs [8]. We have focused on the swelling controlled systems and we prepared the polymers that follow this type of mechanism. The mechanism based on swelling controlled drug release is described below.

The crosslinked polymers are characterized with the presence of tangled mesh structure which provides the matrix for the drug entrapment. When such polymers come in contact with thermodynamically compatible solvent, the polymer chains relax. This results into the entrapment of solvent molecules inside the polymer matrix, resulting into the swelling of polymer. If the polymer is kept in the saturated drug solution of such solvent, the entrapment of drug molecules together with the solvent molecules takes place (Fig. 1.2). After evaporation of solvent, the polymer is left with the entrapped drug molecules. When the release study is desired, the drug loaded polymer is kept in the release media in order to allow the polymer to swell in that release media. This results into the swelling of the polymer again, leading to the release of the drug depending on the swelling characteristics of the polymer in the release media.

The structure of polymer determines the rate of drug release due to the effect of glass transition temperature (T_g) of the polymer. For example, if the T_g of the polymer is below the experimental temperature, the polymer will remain in the rubbery state, providing high mobility to the polymer chains. This results into the easier penetration of the solvent molecules inside the polymer

matrix. This ultimately results in high drug loading and high rate of subsequent drug release. This type of drug release is characterized as Fickian diffusion (CASE-1) in which the solvent (or drug) diffusion rate is slower than the polymer chain relaxation rate [14].

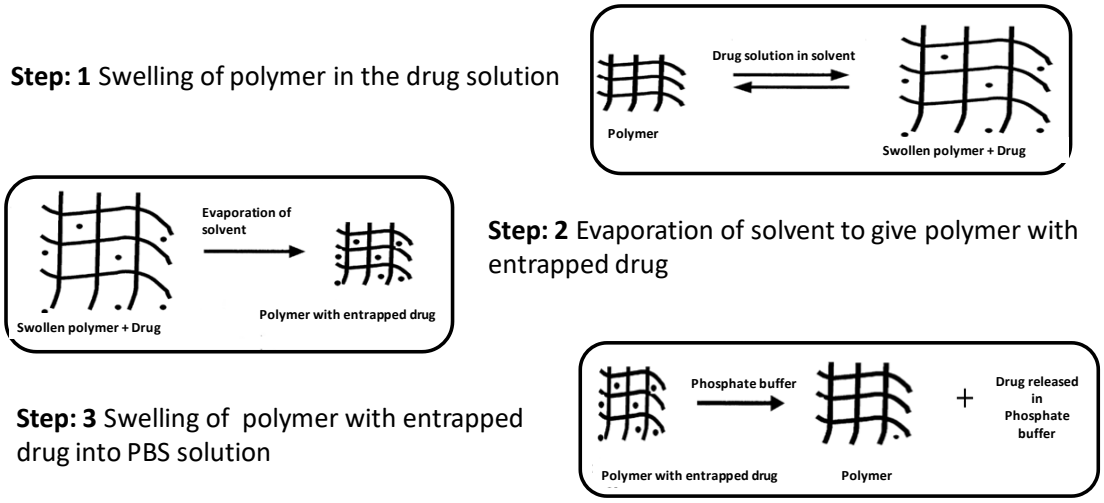


Figure 1.2 Mechanism of drug delivery by swelling

On the other hand, if the polymer is above its T_g then the polymer chains will be less flexible and the drug entrapment shall be difficult. This ultimately results in the slower rate of release of drug. This kind of release follows non-Fickian diffusion process which includes CASE-2 and anomalous diffusion, in which solvent (or drug) diffusion rate is faster or equal to the polymer chain relaxation rate respectively.

1.1.1.4 EXAMPLES OF CLASSICAL AND CONTROLLED DRUG DELIVERY SYSTEMS

1.1.1.4.1 ORAL DRUG DELIVERY

The oral drug delivery belongs to the classical drug delivery system (Fig. 1.3). The absorption of drug is through walls of gastro intestinal tract (GIT) [15]. Advantages involved in such type of drug delivery are easy portability, safe administration without pain and easy to take. However,

there are several disadvantages such as poor efficacy of drug, as only a part of the dose may be absorbed by GIT [16]. Also, unconscious patients are unable to swallow solid dosage.

Figure 1.3 Oral drug delivery

1.1.1.4.2 OCULAR DRUG DELIVERY

This type of drug delivery belongs to the controlled drug delivery type of drug release. The ophthalmic preparations that have been used commonly include the eye drops and ointments. However, these types of medications have some limitations like loss of drug due to draining from the ocular cavity because of tear flow and lachrymal nasal drainage. Frequent dosing is essential in order to maintain therapeutic level of drug inside the eye. These limitations can be addressed by using concept of controlled drug delivery approach such as in-situ gel, nanoparticles, liposome, nano-suspension, micro-emulsion, intophoresis and ocular inserts [17].

The most commonly used polymers in ocular drug delivery are hydrogels as shown in Fig. 1.4. This is for its advantages such as easier delivery to the ocular surface without extensive serological screening, favorable refractive index and high oxygen permeability [18]. The hydrogel containing dissolved drug is introduced into the cornea and the drug is introduced into

the eye when the eyelid movements occur.

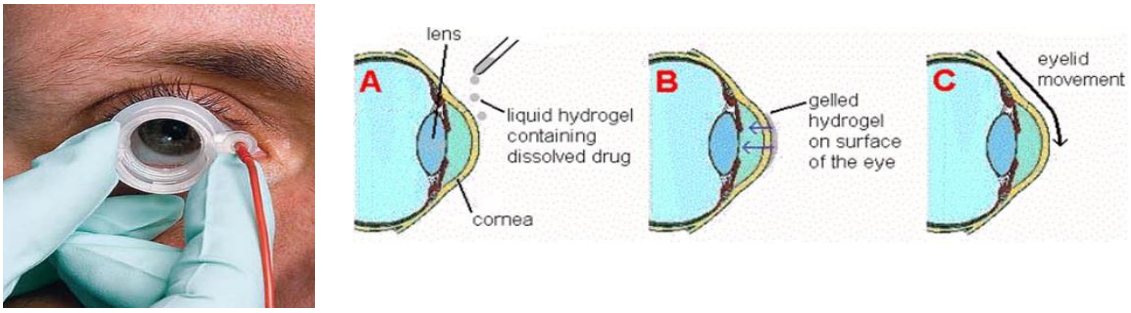


Figure 1.4 Ocular drug delivery

1.1.1.4.3 TRANS-DERMAL DRUG DELIVERY

The transdermal drug delivery (Fig. 1.5) uses the method of delivering drug inside skin through dermal layers. It represents an alternative to oral drug delivery and is poised to provide a substitute to hypodermic injections too [19]. In transdermal drug delivery, the drug is entrapped in to the polymer and is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream.

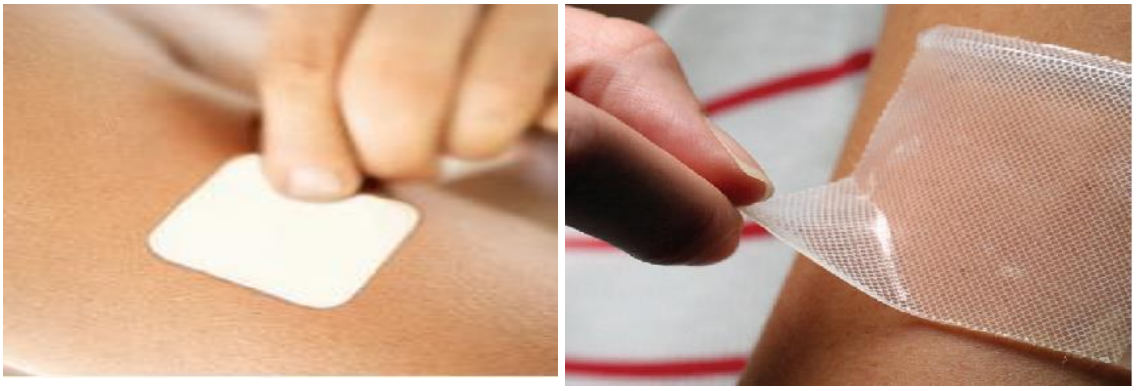


Figure 1.5 Transdermal drug delivery

An advantage of a transdermal drug delivery route over other types of medication is that the patch provides a controlled release of the medication. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only

medications whose molecules are small enough to penetrate the skin can be delivered by this method.

1.1.2 POLYURETHANE CHEMISTRY: A BRIEF OVERVIEW

The origin of polyurethanes (PUs) began in 1937 at I.G. Farbenindutrie when Otto Bayer, also called "father" of polyurethanes, and his coworkers performed the addition polymerization reaction between diisocyanates and diols. Since their discovery, the demand in PUs has continued to increase and is expected to attain a production of 18 million tons in 2016 [20–23].

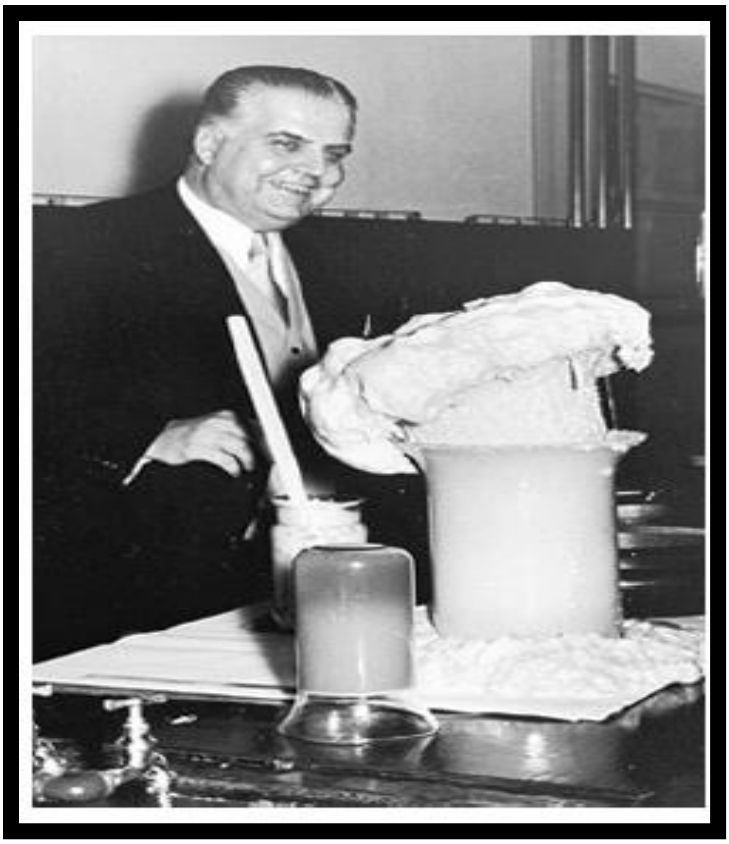


Figure 1.6 Picture of Otto Bayer

The term "polyurethane" is confusing since the name may mean that PUs are either polymers obtained by polymerization of ethane or these are polymers containing urethane compounds as

monomers; neither of the meaning is true! The PUs are the polymers with the plurality of urethane groups in the molecular backbone, regardless of the chemical composition of the rest of the chain. Thus a typical PU, in addition to urethane, may contain aliphatic and aromatic hydrocarbons, esters, ethers, amides, urea and isocyanurate functional groups.

The chemistry of PUs involves reactions between organic isocyanates and polyols i.e. compounds containing active hydrogen at proper ratio in presence of suitable catalyst (Fig. 1.7). The reaction is exothermic and leads to the formation of prepolymer. If the initial concentration of isocyanate is higher than polyol, the prepolymer obtained by reaction between them is said to be NCO-terminated prepolymer which can further react with other crosslinker/chain extender or other chemicals that are prone to react with NCO functional groups.

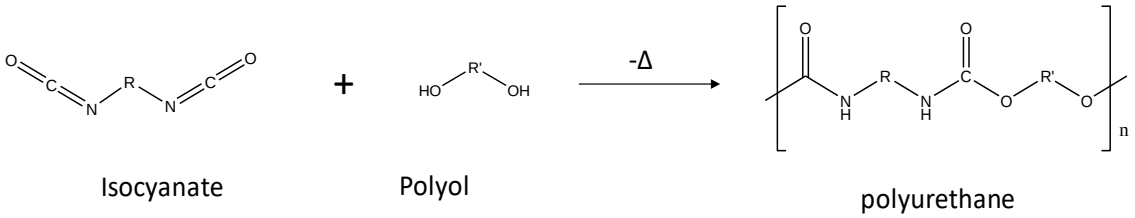
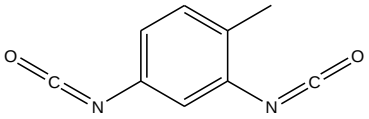
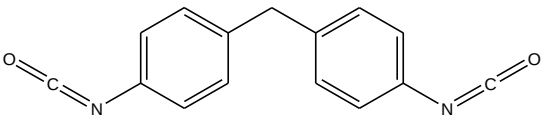
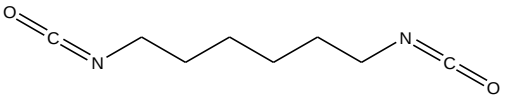


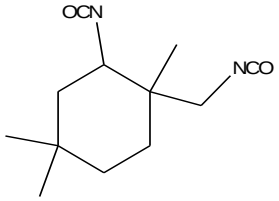
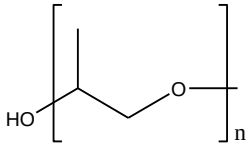
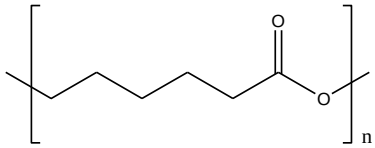
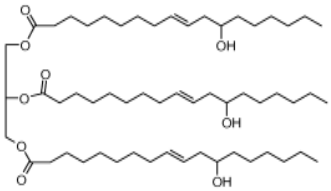
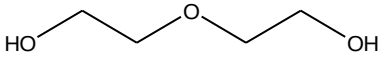
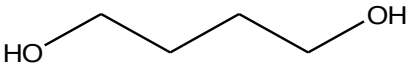
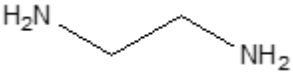
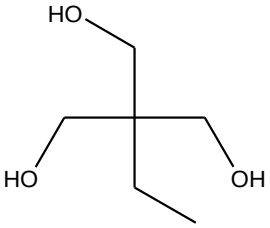
Figure 1.7 Chemical reaction of Polyurethane formation [24,25]**.**

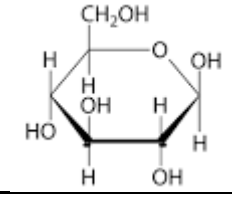
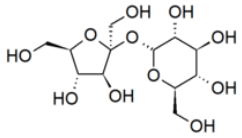
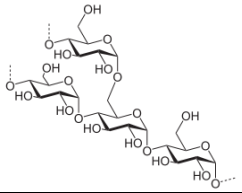
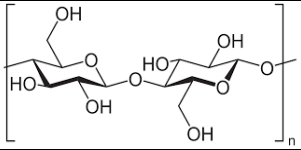
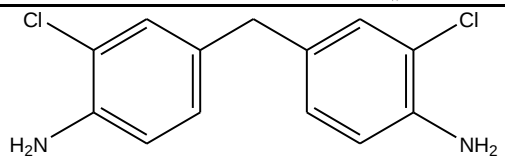
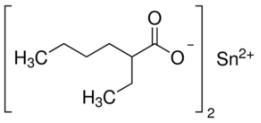
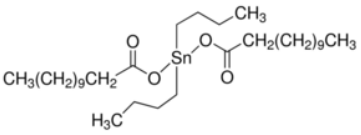
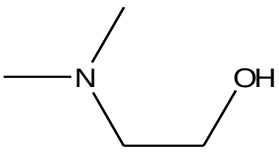
PUs are important versatile polymers varying from flexible thermoplastics to rigid thermosets. PUs are obtained by step growth polymerization between diisocyanate/polyisocyanate with isocyanate (-NCO) functional group and hydroxyl terminated oligomer (polyol) having at least two reactive hydrogen atoms [26]. PUs can be either thermoplastic or irreversibly thermoset depending upon its structure. For example, the PUs synthesized from diisocyanate and a bi-functional polyol results in thermoplastic PU, whereas introduction of crosslinkers with more than two functional groups will yield thermoset PUs with three dimensional crosslinking [27] The common components used in PU synthesis are listed in Table 1.2

The synthesis of PUs requires two essential ingredients: isocyanate (typically diisocyanate) and a bi- or multi-functional polyol with two hydroxyl (OH) terminal groups [28]. The step-growth polymerization reaction between these two reactants yields the polyurethane polymer. Polyols are generally di-hydroxyl terminated polymers viz. polyethers, polyesters of polycarbonates. The type, chain length, functionality and molecular weight of polyols have significant effect on the structural and physical properties of PUs. For example, relative cohesive energy of oligo-polyols increases as we move from polyester polyol to polyether polyols. Since a stronger cohesive energy leads to higher physico-chemical properties, the PUs based on polyester polyols impart better properties than those based on polyether polyols [25].

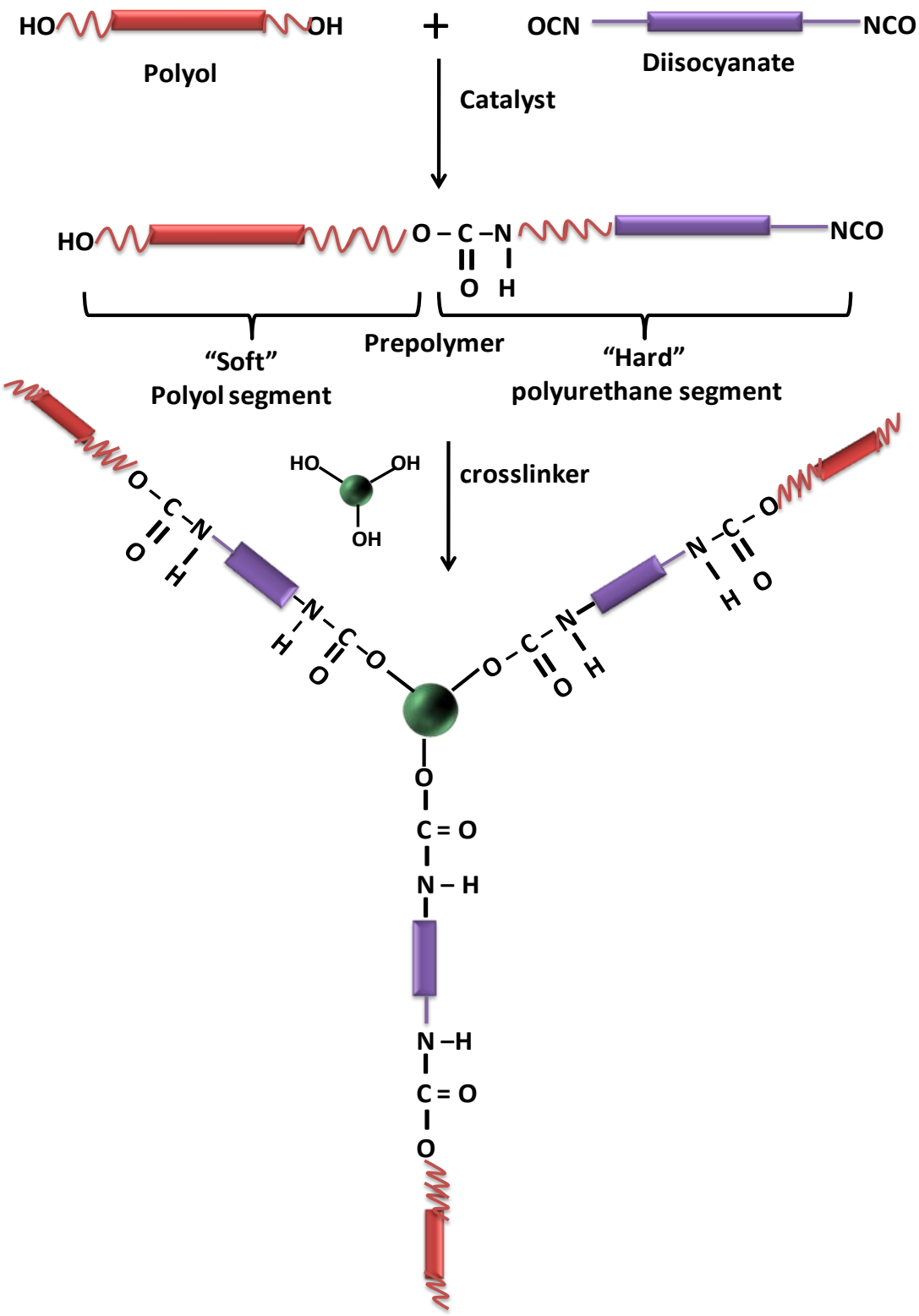
Table 1.2 List and details of common components in PUs

Component	Type	Examples	Structure
Diisocyanate	Aromatic	Toluene-2,4-diisocyanate (TDI)	
		4,4'- methylene-bis(phenylisocyanate)(MDI)	
	Aliphatic	Hexamethylene diisocyanate (HMDI) /1,6-diisocyanatohexane	

	Alicyclic	Isophorone diisocyanate (IPDI)	
Polyols	Polyether	Polypropylene glycols	
	Polyester	Polyester polyol of diacid and diol	
	Natural oils	Castor oil	
Chain extenders	Hydroxylated	Diethylene glycol	
		1,4-butane diol	
	Diamines	Ethylene diamine	
Crosslinkers	Hydroxylated	Trimethylol propane	
		Carbohydrates	

		Monosaccharide (Glucose)	
		Disaccharide (Sucrose)	
		Polysaccharide (Starch)	
		Polysaccharide (Cellulose)	
	Diamine	4,4'-methylene-bis-(2-chloroaniline)	
Catalysts	Organometalic	Stannous octoate	
		Dibutyl-tin-dilaurate	
	Amine	N,N-dimethylethanolamine	

Similarly, short chain polyol based PUs are having higher concentration of urethane and urea bonds leading to high cohesive interactions between these bonds which leads to rigid structure. On the contrary, long chain polyols leads to flexible PUs for the same reasons. If we compare functionalities of polyols, the high functionality polyol leads to high crosslinking in PU which ultimately results in enhanced rigidity, softening points and modulus of elasticity while reduced elongation and molecular mobility. On the other hand, low functionality polyols gives PUs with linear structure showing opposite trend of properties. Moreover, low molecular weight polyols yield hard PU, whereas high molecular weight polyols yields elastic, flexible PUs.



Crosslinked polyurethane elastomer

Figure 1.8 Synthesis of crosslinked PU elastomer

The PUs obtained through reaction between only bi-functional polyols and isocyanates is linear in nature and may show poor mechanical properties. The introduction of chain extenders/ crosslinkers (Table 1.2) into the PU network can yield PUs with improved physical properties. This is due to enhanced distinction of micro-phase separation between hard segments (composed of –NH-COO- and the chain extender/cross linker) and soft segments (the polyol part) as shown in Fig .1.8. The hard domains are responsible for mechanical strength while the soft domain provides flexibility [29,30]. The extent of hard and soft segment content influences directly the final properties of PUs. For example, PUs with hard segment content of 40-65% are reported to be tough elastomeric materials while those with hard segment contents of 15-40 wt% are rather soft and rubbery elastomers [31].

The electro positive character of the C atom of isocyanate group makes its affinity higher to react with nucleophilic reagents such as alocohols or amines leading to the formation of urethane or urea bond respectively. In addition to this, an isocyanate group can react with another isocyanate to yield dimer/trimer, biuret, carbodiimide or allophanate groups [32]. The reactions of isocyanate with other functional groups have been illustrated in Fig. 1.9.

The reaction of isocyanate with primary amine is very rapid and goes on without use of any catalyst. The tendency of isocyanate to react with primary alcohol is greater than secondary alcohols while for tertiary alcohols and phenols the reactions are very slow. The reaction needs a catalyst like dibutyl tin dilaurate (DBTDL). A diisocyanate can easily react with water to form amine and carbon dioxide, which is the main advantage of reaction for synthesis of PU foams, since the carbon dioxide gas can act as a blowing agent. The said reaction is so spontaneous that isocyanate can readily react with a small amount of moisture present in the air. This is the reason

why bottles of isocyanates shall be kept well protected from moisture. The amine formed in the above reaction can also react with other isocyanate molecules to give urea bond formation. Allophanates are formed when isocyanate reacts with urethane group. The reaction of isocyanate with carboxylic acid gives anhydride which subsequently gets converted to amide.

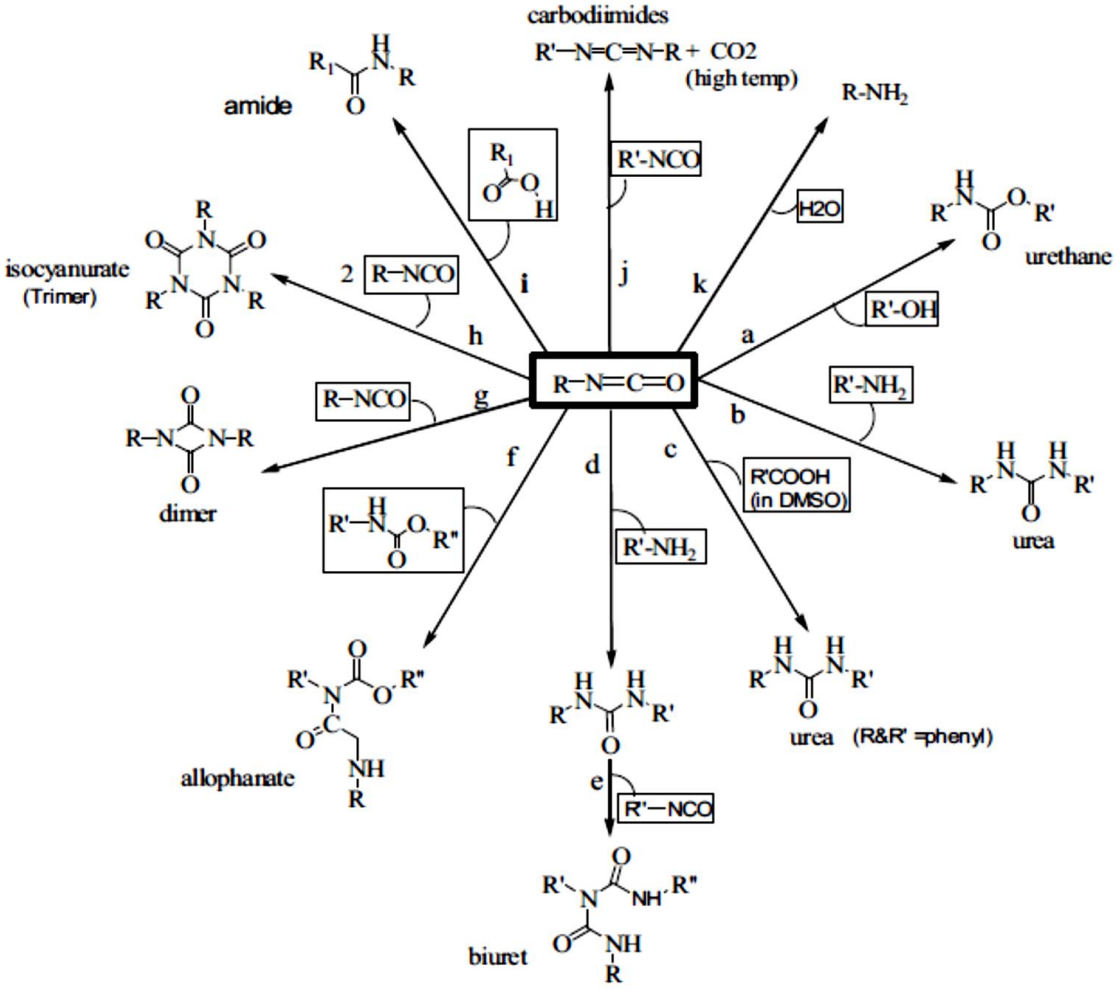


Figure 1.9 Reactions of isocyanate functional group with various reactants *(Reproduced from Levchik et al)*[33]

Thus a complex chemistry of polyurethane is made due to diverse affinity of isocyanate group to react with variety of functional groups. The ideal characteristic of PU that makes it a distinct polymer from other common polymers is the presence of phase segregation as shown in Fig.1.10.

This feature of PUs is attributed to difference in polarity between hard segment and soft segment. The hard segment is formed by isocyanate part, which consists of rigid aromatic moieties having strong tendency to stack via π-bonding of the benzene rings. In addition to this, hydrogen bonding may also be present between isocyanate derived urethane and urea groups.

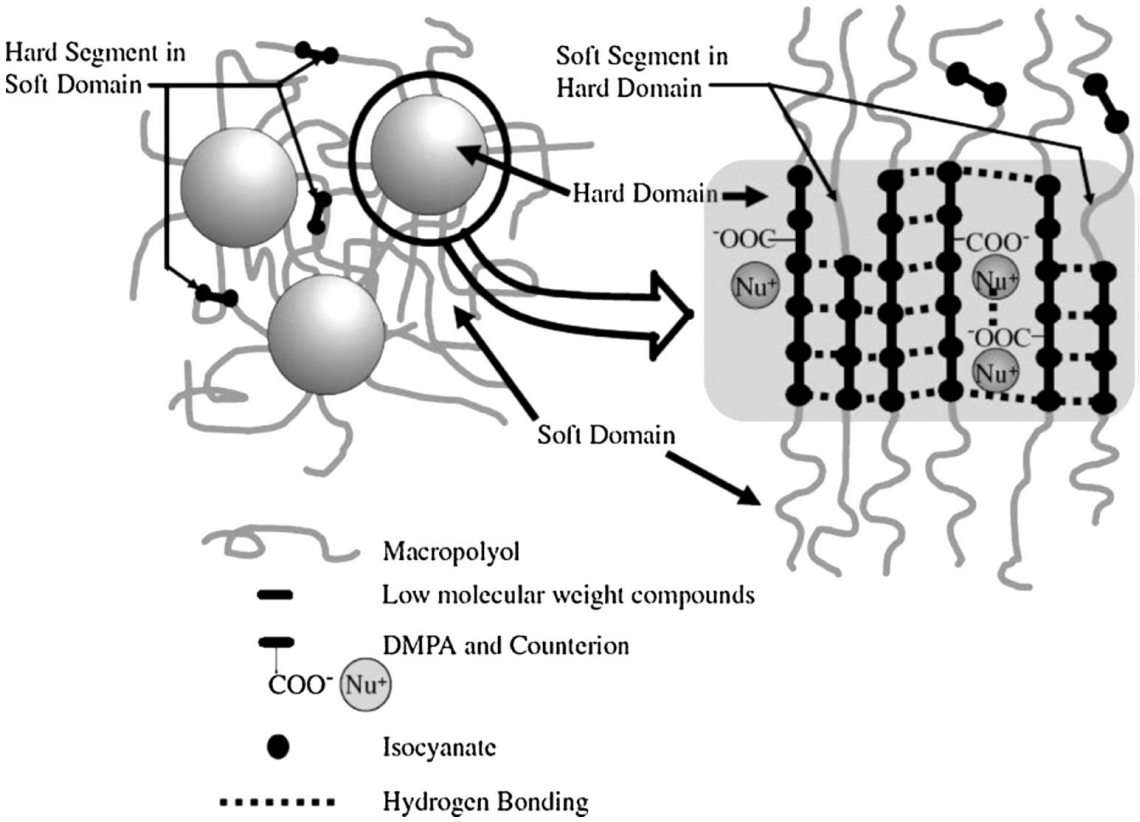


Figure 1.10 Representation of phase segregation in PU *(Reproduced from Tawa et al)* [34]**.**

On the other hand the soft segment consists of polyol segment which is amorphous and elastomeric in nature. Due to the difference in the hard and soft segment crystallinity, the PUs are reported to show several thermal transition temperatures. Depending on the hard segment content, the hard phase shows several melting transitions while soft phase shows glass and melting transition (if semi-crystalline) as it is responsible for the properties at low temperatures

[35]. Thus PU consists of discontinuously dispersed soft amorphous segments of long chain polyols and hard segments of diisocyanate and crosslinker/chain extender sections. PUs have found a vast diversity of industrial and engineering applications becoming a business area involving billions of dollars throughout the world (Fig. 1.11).

1.1.3 POLYURETHANES: BIOCOMPATIBILITY AND DRUG DELIVERY APPLICATIONS

Biocompatibility is defined as the ability of a material to perform with an appropriate host response in a specific application [36]. The biocompatible materials are thus having ability to perform their desired functions without eliciting any deleterious local or systematic effects. One of the main advantages of polyurethanes in biomedical applications is their flexible chemical structure. A simple modification in stoichiometry and/or raw materials used for synthesis of PU can result in a considerable change in the final polymer properties in order to produce polymers with a broad spectrum of properties ranging from thermoplastic elastic material to rigid thermoset polymer. In addition to that, PUs possess advantages such as adaptability to many different processing conditions, excellent mechanical properties, bio-stability, biocompatibility and biodegradability.

Polyurethanes (PU) are considered one of the most promising materials in biomedical applications due to their structure/property diversity. The PUs are characterized with unique combination of diverse mechanical properties and flexibility. PU's properties such as abrasion resistance, affordable manufacturing, chemical stability, durability, elasticity and haemocompatibility are fundamental for their extended applications in the biomedical field. Owing these properties, PUs have been successfully utilized for constructing variety of biomedical materials like blood bags, bladders, artificial heart, vascular grafts, neural conduits and bone cement for fracture.

Figure 1.11 Diversity of applications of PUs

1.1.3.1 EVALUATION OF PUS FOR CYTOTOXICITY IN-VITRO

In order to evaluate biocompatibility of PUs, the first step is to check its cytotoxicity in-vitro. The effect of PUs on cell viability, cell proliferation and cell adhesion are determined by using

appropriate cell line. MTT (3-[4,5-Dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay has been used for assessment of cell metabolic activity [37]. NAD(P)H-dependent cellular oxidoreductase enzymes may, under defined conditions, reflect the number of viable cells present. These enzymes are capable of reducing the tetrazolium dye MTT to its insoluble formazan, which has a purple color. Only living cells can produce such enzyme leading to the purple color formation. The absorbance of the colored solution can be determined by using UV-spectrophotometer by constructing the calibration plot. The variation in absorbance can be related to cell viability.

The commonly used cell lines for this purpose are fibroblasts and endothelial cells [38]. Some specific types of leukocytes, human osteosarcoma cell line MG63 [2,39], human cervical carcinoma cell line (HeLa cells), human breast adenocarcinoma cell line (MCF-7 cell) [40], and epithelial cells have also been used for evaluation of cytotoxicity of PUs intended for the application of implants [41,42].

1.1.3.2 CONTINGENCY OF PU STRUCTURE ON BIOCOMPATIBILITY

Structurally speaking, the biocompatibility of PUs depends on the type of ingredients used in the PU synthesis. PUs derived from aromatic isocyanate are more toxic as compared to PUs derived from aliphatic isocyanate. This is due to the fact that the hard segments obtained from aromatic isocyanates when degrade, yields aromatic amines which are toxic in nature [43–45]. More specifically, PUs prepared with TDI and MDI underwent degradation to yield 2,4-toluene diamine (TDA) [46] and 4,4-methylenedianiline (MDA) respectively, both of the products are toxic in nature [47]. However, many medical grade PUs are prepared from aromatic diisocyanates. These PUs may degrade in vivo to carcinogenic aromatic diamines. Although the

question of whether the concentrations of these harmful degradation products attain physiologically relevant levels is currently unresolved and strongly debated. In short, the aromatic isocyanates have been utilized to prepare PUs in biomedical application where degradation is not desired. Therefore, aromatic isocyanates based PUs are used in applications such as pacemaker lead coverings, catheters, and wound dressings. Such applications do not involve degradation of material and hence there is no trauma of toxic products and its associated side effects. The PUs with aliphatic isocyanates are more preferred for in-vivo biomedical applications due to its non-toxic degradation products. For example, Lysine diisocyanate is derived from amino acid (lysine), hence the products obtained after its in-vivo degradation are non-toxic and can be used for biomedical implants [2]. Segmented polyurethane urea synthesized by using lysine diisocyanate showed no toxicity when analyzed by using NIH3T3 fibroblasts and endothelial cells [48]. Porous polyurethane scaffolds based on Lysine diisocyanate, glucose, and poly(ethylene glycol) (PEG) supported the attachment, proliferation, and differentiation of rabbit bone marrow stromal cells and degraded to non-toxic decomposition products (e.g., lysine and glucose) in vitro [49], Isophorone diisocyanate [50] and Hexamethylene diisocyanate are also of interest for synthesis of biocompatible PUs [51].

Besides isocyanate, the type of polyol used in the synthesis of PU also plays an important role for PU to show biocompatibility. Natural oils like castor oil and other natural resources derived polyols can show better biological acceptance as compared to petroleum based polyols due to more adaptability to living organisms and better biocompatibility. For example, Polycaprolactone diol is finding increasing applications as a soft segment/polyol for synthesis of biocompatible polyurethanes due to its biocompatibility and biodegradability [52]. The biocompatibility of the Polycaprolactone diol is due to the fact that its degradation product is

lactic acid which can get easily metabolized. The biodegradability is attributed to affinity of its ester bonds to degrade under basic conditions. For this advantage, the Polycaprolactone diol based PUs have been reported for the intended applications like scaffolds for tissue engineering [53], cardiac tissue engineering [54] and biodegradable bone cement for healing of fractures [55]. Polycarbonate polyol has been successfully utilized for tissue-engineering [56–58] due to its biocompatibility. Polyethylene glycol is also widely used polyol for synthesis of biocompatible PUs [50,51].

The type of chain extender/ cross linkers used in synthesis of PU can also influence its biocompatibility. For instance, if naturally available biodegradable products are used as a crosslinker/chain extender, the resulting PU can give better biocompatibility. This is due to the fact that the degradation of hard segments of such PUs are expected to yield biodegradable and non-toxic byproducts. Amongst PUs based on petroleum derived chain extenders also, there can be difference in biocompatibility depending on the type of chain extenders. Zhang et al reported that while comparing N,N-bis (2-hydroxyethyl) -2-aminoethane-sulfonic acid (BES) and 2,2-(methylimino) diethanol (MIDE) chain extenders, PU containing MIDE showed better fibroblast cell attachment and proliferation than PU containing BES as a chain extender. The result was ascribed to higher interaction of chains in hard segment in BES based PU [59].

1.1.3.3 BIOMEDICAL APPLICATIONS OF PUS

PUs can be synthesized from a wide variety of materials exhibiting extremely different properties that can lead to a broad spectrum of biomedical application as illustrated in Fig.1.12.

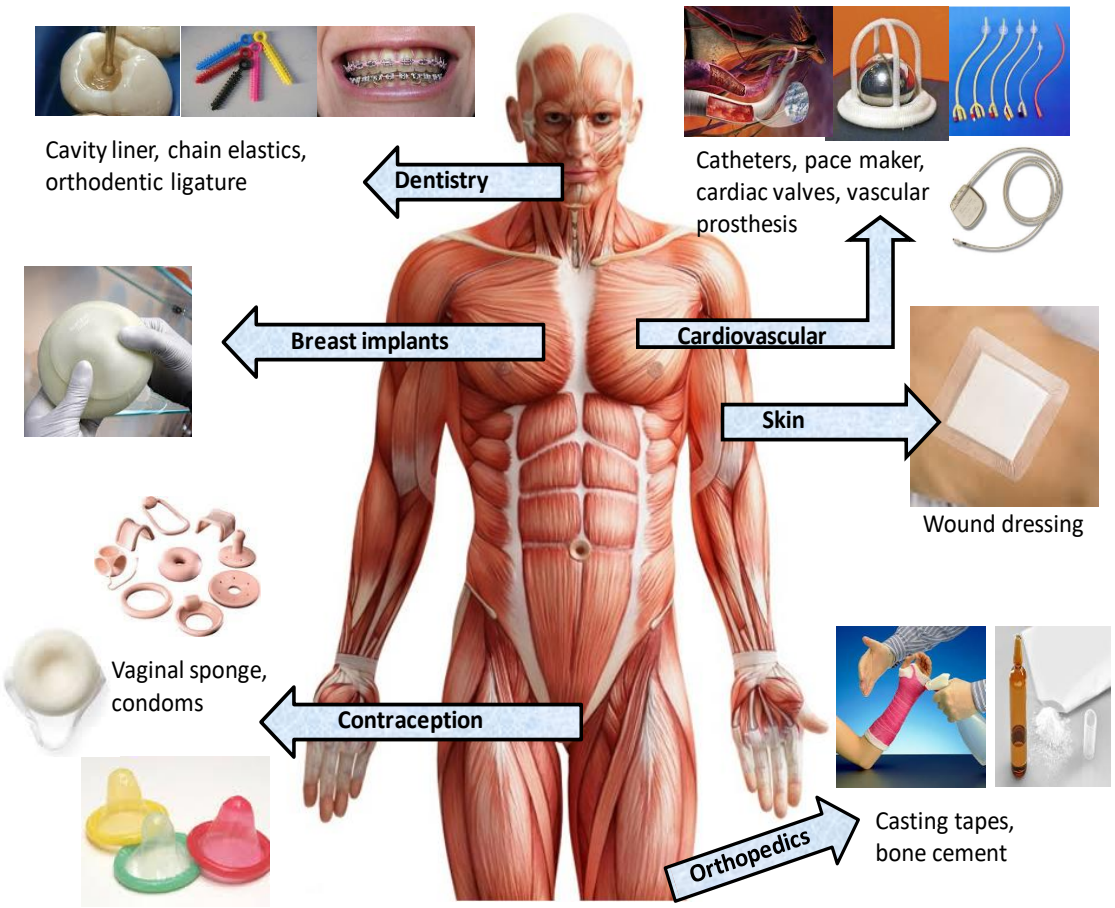


Figure 1.12 Applications of PUs in biomedical field

A broad spectrum of properties essential for biomedical applications can be duly achieved by maintaining the type and quantity of ingredients used for PU synthesis. The PUs are largely explored for various biomedical applications including drug delivery devices. Sivak et al reported catalyst dependent drug loading and controlled release of PU foams for implantable devices. The study revealed the role of catalyst selection in maintaining biocompatibility of medical-grade PU [60]. Biocompatible PU based on lysine diisocyanate was prepared and covalently bonded with 7-tert-butyldimethylsilyl-10-hydroxy-camptothecin (DB-67) for potential application in postoperative intracranial chemotherapy of cancers. The drug was released through

slow, passive hydrolysis of urethane bonds [61]. The commercially available biomedical grade PUs are listed in Table 1.3 [41].

Table 1.3 List of commercially available biomedical-grade PUs

Polyurethane	**Description (Possible Formulation)**	**Uses**
Biomer (Ethicon)	Family of polyurethane Ureas	Bladders, Chamber coatings
Biospan	MDI based Polyurethane	Artificial heart, drug eluting stents
Cardiothane 51	Mixture of polyetherurethane and polydimethylsioxane	Intra-aortic balloons, blood conduits
Corethane	Polycarbonate based PU	Cardiovascular applications
Techoflex	Aliphatic isocyanate based PU	Wound dressings
Bioclusive	Transparent PU film	Semi-occlusive/ occlusive
Enka PUR 817	Polyetherurethane	Vascular prosthesis
Viasorb	Polyester pad within PU sleeve	Composite dressing
Microthane	Polyester PU foam	Breast implant

1.1.3.4 IMPACT OF PU-CHEMISTRY ON DRUG DELIVERY PROFILES

As discussed in previous section, the PUs are characterized with phase segregation due to presence of hard and soft segments. This specific property is a boon for loading and release of drugs as shall be discussed in this section. The loading of drug in the PU matrix can be obtained due to three phenomenon (Fig. 1.13) as listed below [31].

(1) Drug entrapment inside crosslinked structure of PU (Fig. 1.13a).

(2) Incorporation of drug in soft segments (Fig. 1.13b).

(3) Covalent attachment of drug with the hard segment of PU (Fig. 1.13c).

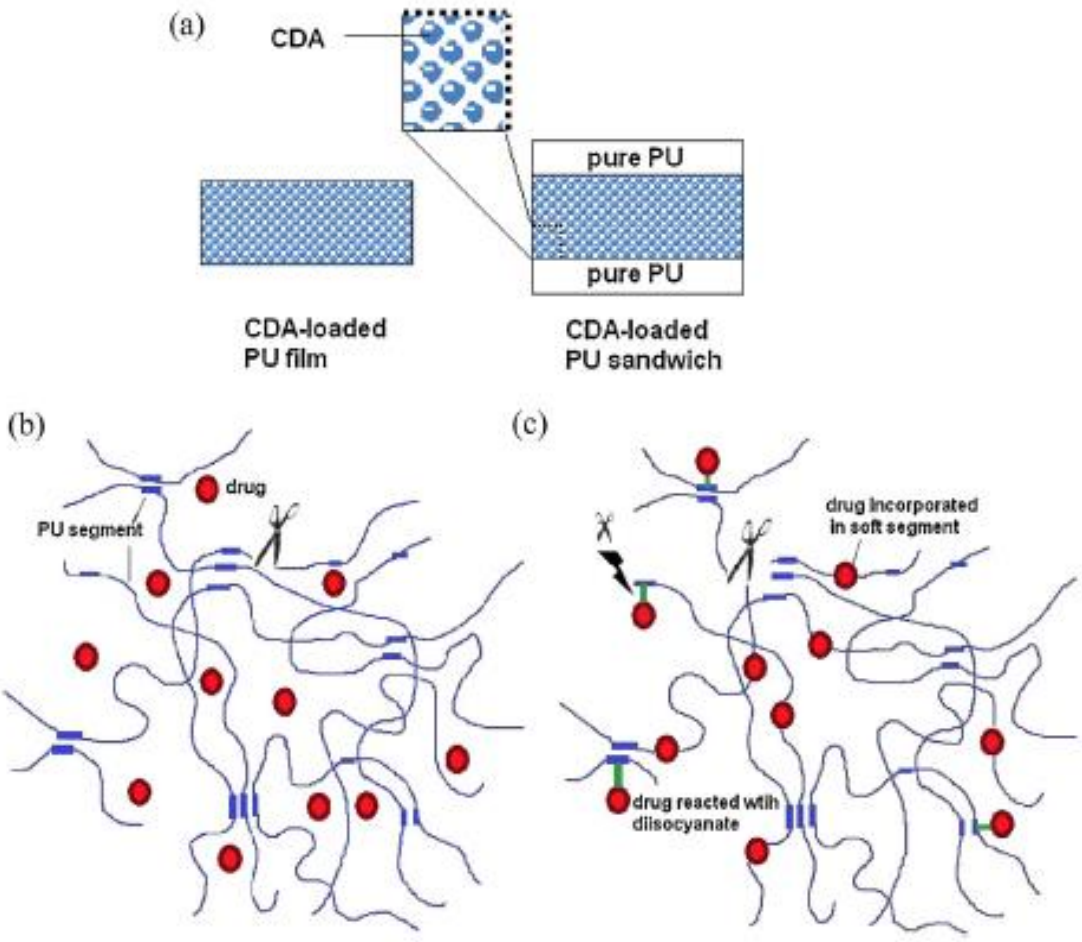


Fig. 1.13 Mechanism of drug loading in PU matrix (Reproduced from Cherng et al) [62].

The first phenomenon is true for all polymers with cross-linked structure as for the PUs. What are special for PUs are last two phenomenons. It is therefore said that phase segregation can be a boon for drug delivery applications in case of PUs. The process of migration of drugs from their initial position inside the polymer matrix to the release medium is responsible for the release of drug from the polymeric matrix. The drug molecules might also have adsorbed onto the surface

of material that might get released immediately after it has been brought in contact with the release medium. PUs have been explored with increasing complexity and several functions in order to control release of drugs with respect to external factors like pH [63], temperature [39,64,65] and magnetic field [66]. Moreover, the surface of PU nanoparticles can be conjugated with targeting units to promote cellular recognition, binding and internalization [67].

Another interesting fact about structural dependency of drug release in case of PUs is that the drug release from the PU network is expected to follow different mechanisms depending on degradability of PUs. For example, the drug release in case of non-degradable PUs is mainly governed by diffusion and the rate of drug release is controlled by thickness and permeability of polymer network as well as the solubility of drug in the polymer matrix [68]. The non-degradable PUs find biomedical applications such as orthopedic implants [69] due to their good blood compatibility, durability and mechanical strength for long-term exposure. On the other hand, the drug release from degradable PU matrix is often discussed in relation to their composition, drug loading, swelling and rate of degradation. The pH of external media, presence of enzymes and temperature of release media also affect the rate of drug release. The major area of application for degradable PUs include nano particulate systems [70], membrane systems [64] and matrix/scaffolds [71,72].

Moreover, the stoichiometry of PUs does impact the drug release profiles. This is because by variation of stoichiometry of PU, the mechanical, thermal and morphological properties can be tuned [44,73–75]. Such tuning can lead to control over swelling properties of PUs thereby possible command over drug loading and release profiles of PUs. The variation in ratio of hard/soft segment content can have considerable effect on properties of PU. This characteristic of

PU can be implemented for essential modification of drug diffusion and release profiles. Hence, by altering the stoichiometry of PUs, desired drug payload and release rate can be established.

1.1.3.5 USE OF CARBOHYDRATES IN PU SYNTHESIS

Carbohydrates are amongst abundant and inexpensive renewable resources. Being multihydroxyl compounds they easily serve the purpose of a crosslinker due to reactivity of hydroxyl groups with isocyanate groups. Carbohydrates such as starch, cellulose, chitosan, carrageenan and alginate are finding increasing application as biomaterials, due to their properties like availability, biodegradability, sustainability, lower toxicity and biocompatibility. However, lack of thermal stability, poor solubility and difficult processability are serious limitations for these materials. The incorporation of carbohydrates in the structure of PU can result into synergistic polyurethane with enhanced mechanical properties, thermal stability and biodegradability. The multiple hydroxyl groups in the carbohydrate structure can be utilized in the synthesis of PUs to confer biomaterial qualities. Hence we decided to use multi hydroxyl carbohydrates as crosslinkers in PU system which is likely to offer following advantages.

1. Enhance both degradability and mechanical properties of polymer
2. Provide multifunctional sites to form randomly crosslinked networks
3. Nontoxic, inexpensive, readily available from renewable resources

Among carbohydrates, the use of starch and cellulose has been reported in the synthesis of PUs [74,76–78].

Starch is major carbohydrate reserve in plants. It is found in natural resources of plants like its leaves, fruits, flowers, seeds, stems and roots [79]. Chemically, starch consists of mainly two units' viz. several million amylopectin molecules and much larger number of smaller amylase molecules. The biochemical chain responsible for starch synthesis involves glucose molecules produced in plant cells by photosynthesis. Amylopectin consists of linear chains of glucose units linked by α-1, 4 glycosidic bonds. It is highly branched at the α-1, 6 positions by small glucose

chains at intervals of 10 nm along the molecule's axis. Amylopectin constitutes between 70 to 85% of common starch [80]. On the other hand, Amylose is essentially a linear chain of α-1, 4 glucans with limited branching points at the α-1, 6 positions. Amylose constitutes between 15-30% of common starch. Starch's structural units, amylose and amylopectin, are shown in Fig 1.14.

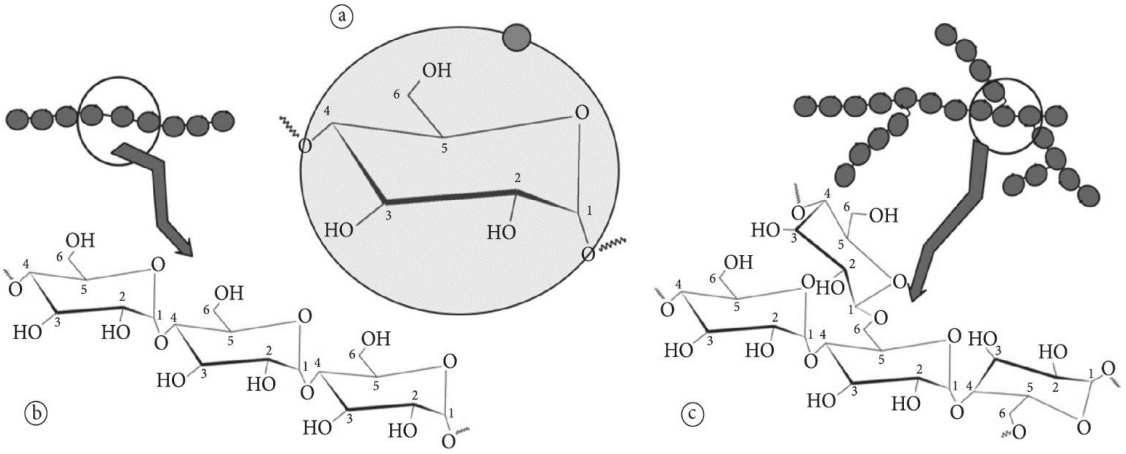


Figure 1.14 Chemical structures of (a) Starch, (b) Amylose and (c) Amylopectin

Plasticized starch has been reported for enhancement of mechanical properties, biodegradation and water resistance of poly(ε-caprolactone) based PUs [81]. For enhancement in mechanical properties, starch nanocrystals have been used as fillers to prepare nanocomposite materials by preparing its composites with PU [76].

Cellulose is found in plants as microfibrils [82,83] with dimension of around 2-20 nm diameter and length of 100 - 40 000 nm. The cellulose is responsible for the formation of strong framework in the cell walls. Structurally, cellulose is a linear polymer of β-(1 4)-D-glucopyranose units as shown in Fig 1.15. The fully equatorial conformation of β-linked

glucopyranose residues stabilizes the chair structure, minimizing its flexibility (for example, relative to the slightly more flexible α-linked glucopyranose residues in amylose).

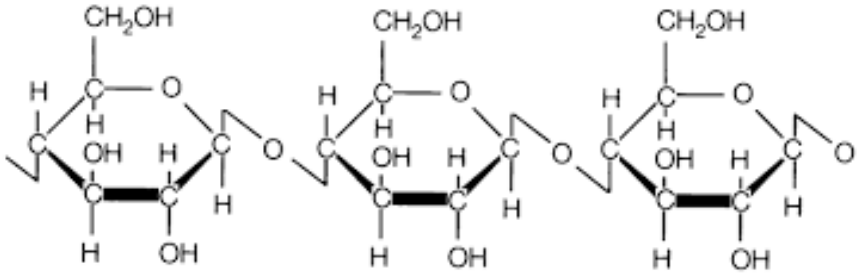


Figure 1.15 Chemical structure of Cellulose

Cellulose nanocrystals were loaded in low quantity as fillers in waterborne PU matrix in order to obtain reinforcement effect on resulting PU. The strong hydrogen bonding between PU matrix and cellulose nanocrystals as well as the rigid nature, hydrophilicity and high aspect ratio were considered as main factors contributing excellent reinforcement of properties [65,84]. Cellulose nanocrystals were dispersed in thermoplastic polyurethane as matrix. It was observed that the matrix formation can have significant effect on PU microstructure. The presence of high number of hydroxyl groups on the surface of cellulose nanocrystals were deemed responsible for interactions between soft segments and hard segment [35]. Moreover, the nanocomposites prepared from cellulose nanocrystals and PU have been reported for wool antifelting agents intended for application in textile field [4]. Cellulose acetate and PU were blended to prepare nano-fibrous scaffolds. The drug loading on PU scaffolds was carried out by electrospinning process for intended applications in burn, chronic and diabetic wound infections [85].

Incorporation of modified forms of starch and cellulose nanocrystals in PUs showed enhancement in mechanical strength, biodegradability as well as biocompatibility [84,86,87]. However a systematic investigation and comparison of performance of various carbohydrates as

crosslinkers of PUs is not available. Moreover the major concern is the thermal stability of the resulting PUs.

1.2 THESIS AIM AND HYPOTHESIS

This thesis aims to carry out studies on synthesis and characterization of novel carbohydrate crosslinked polyurethanes and to further explore the application of synthesized PUs as drug delivery devices. A variety of polyols ranging from synthetic polyols like polypropylene glycols of different molecular weights to the bio-based polyol like castor oil have been used to demonstrate effect of polyols on structure and properties of PUs. Similarly, a range of carbohydrates starting from monosaccharide such as glucose to disaccharide like sucrose and polysaccharides like starch and cellulose have been utilized as a crosslinkers into the PU network in order to observe the effect on PUs implied by carbohydrate crosslinkers. After establishing the structure-property relationships of PUs, a new set of carbohydrate crosslinked PUs with diethylene glycol as a chain extender has been prepared. The effect of variation of stoichiometry on drug release properties of such PUs has been studied. Furthermore, to prepare stimuli-sensitive polyurethanes, the so called "Smart polymers", were prepared by introduction of α-hydroxy acids into the PUs. This resulted into pH-responsive characteristic of synthesized PUs, with varying response to pH as a function of α-hydroxy acids-drug release modifiers. One more variety of stimuli-sensitive polyurethane i.e. magnetic responsive PUs were synthesized by conjugating PU on iron oxide nanoparticles. Additionally, β-Cyclodextrin was used in the backbone of PU for enhancing drug release. Of interest, is the application of these materials to accommodate and release a wide variety of drugs in response to the properties of external stimuli. The various types of drugs that have been used as model drugs include antiepileptic

(Lamotrigine and Felodipine) and anticancer (Dacarbazine) drugs. The overall objective of this research was to examine the potential of carbohydrate crosslinked PUs as controlled drug delivery systems and devise a guide for prediction of drug release profile based on the structure of PUs.

The main hypotheses driving this research were:

1. The carbohydrates can be promising crosslinkers for synthesis of polyurethanes.
2. With a combination of polyols and carbohydrates, a wide spectrum of significant mechanical properties can be achieved which can be further tuned by varying the NCO/OH ratio and polyol/crosslinker ratio.
3. Synthesis of PUs with carbohydrate crosslinkers can lead to a strategy for achieving high mechanical performance along with biodegradability and biocompatibility for potential applications as drug delivery systems.
4. Control of structural design of PUs can allow control of the drug release from the polyurethane matrix.
5. Introduction of α-hydroxy acids into the PU matrix can alter the properties of PU such that it behaves in response to pH, leading to synthesis of pH responsive PU.
6. A system with combination of β-Cyclodextrin and magnetic nanoparticles can be prepared by using PU as linking material. Such system can provide synergistic advantage of both enhanced bioavailability of drug and magnetic responsive transport.

1.3 REFERENCES

[1] L.S. Nair, C.T. Laurencin, Biodegradable polymers as biomaterials, Prog. Polym. Sci. 32 (2007) 762–798. doi:10.1016/j.progpolymsci.2007.05.017.

[2] S. A. Guelcher, K.M. Gallagher, J.E. Didier, D.B. Klinedinst, J.S. Doctor, A.S. Goldstein, et al., Synthesis of biocompatible segmented polyurethanes from aliphatic diisocyanates and diurea diol chain extenders., Acta Biomater. 1 (2005) 471–84. doi:10.1016/j.actbio.2005.02.007.

[3] S. Dutta, N. Karak, J.P. Saikia, B.K. Konwar, Biocompatible epoxy modified bio-based polyurethane nanocomposites: mechanical property, cytotoxicity and biodegradation., Bioresour. Technol. 100 (2009) 6391–7. doi:10.1016/j.biortech.2009.06.029.

[4] Q. Zhao, G. Sun, K. Yan, A. Zhou, Y. Chen, Novel bio-antifelting agent based on waterborne polyurethane and cellulose nanocrystals., Carbohydr. Polym. 91 (2013) 169–74. doi:10.1016/j.carbpol.2012.08.020.

[5] D.M. Running, J.B. Ligon, I. Miskioglu, Biomedical applications of polyurethanes: a review of past promises, present realities, and a vibrant future., J. Compos. Mater. 33 (1999) 928–940. doi:0803973233.

[6] P.O. Polyurethanes, T.F. Garrison, M.R. Kessler, Plant Oil-Based Polyurethanes, in: Bio-Based Plant Oil Polym. Compos., 2016: pp. 37–54. doi:10.1016/B978-0-323-35833-0/00003-7.

[7] C.S.S.R. Kumar, F. Mohammad, Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery, Adv. Drug Deliv. Rev. 63 (2011) 789–808. doi:10.1016/j.addr.2011.03.008.

[8] A. K. Bajpai, S.K. Shukla, S. Bhanu, S. Kankane, Responsive polymers in controlled drug delivery, Prog. Polym. Sci. 33 (2008) 1088–1118. doi:10.1016/j.progpolymsci.2008.07.005.

[9] I. Gibas, H. Janik, Review : Synthetic Polymer Hydrogels for Biomedical, Chem. Technol. 4 (2010) 297–304.

[10] R. Langer, 1994 whitaker lecture: Polymers for drug delivery and tissue engineering, Ann. Biomed. Eng. 23 (1995) 101–111. doi:10.1007/BF02368317.

[11] J. Heller, J. Barr, S.Y. Ng, K.S. Abdellauoi, R. Gurny, Poly(ortho esters): Synthesis, characterization, properties and uses, Adv. Drug Deliv. Rev. 54 (2002) 1015–1039. doi:10.1016/S0169-409X(02)00055-8.

[12] B.D. Ulery, L.S. Nair, C.T. Laurencin, Biomedical applications of biodegradable polymers, J. Polym. Sci. Part B Polym. Phys. 49 (2011) 832–864. doi:10.1002/polb.22259.

[13] N.A. Peppas, A.R. Khare, Preparation, structure and diffusional behavior of hydrogels in

controlled release, Adv. Drug Deliv. Rev. 11 (1993) 1–35. doi:10.1016/0169-409X(93)90025-Y.

[14] R.A. Grinsted, L. Clark, J.L. Koenig, Study of cyclic sorption-desorption into poly(methyl methacrylate) rods using NMR imaging, Macromolecules. 25 (1992) 1235–1241. doi:10.1021/ma00030a006.

[15] S. Sajeesh, C.P. Sharma, Cyclodextrin-insulin complex encapsulated polymethacrylic acid based nanoparticles for oral insulin delivery., Int. J. Pharm. 325 (2006) 147–54. doi:10.1016/j.ijpharm.2006.06.019.

[16] L. Plapied, N. Duhem, A. des Rieux, V. Préat, Fate of polymeric nanocarriers for oral drug delivery, Curr. Opin. Colloid Interface Sci. 16 (2011) 228–237. doi:10.1016/j.cocis.2010.12.005.

[17] P. Tangri, S. Khurana, Basics of Ocular Drug Delivery Systems, Int. J. Res. Pharm. Biomed. Sci. 2 (2011) 1541–1552.

[18] B. Wright, S. Mi, C.J. Connon, Towards the use of hydrogels in the treatment of limbal stem cell deficiency, Drug Discov. Today. 18 (2013) 79–86. doi:10.1016/j.drudis.2012.07.012.

[19] M.A. Khanday, A. Rafiq, Variational finite element method to study the absorption rate of drug at various compartments through transdermal drug delivery system, Alexandria J. Med. (2014). doi:10.1016/j.ajme.2014.09.001.

[20] M. Melchiors, M. Sonntag, C. Kobusch, E. Jürgens, Recent developments in aqueous two-component polyurethane (2K-PUR) coatings, Prog. Org. Coatings. 40 (2000) 99–109. doi:10.1016/S0300-9440(00)00123-5.

[21] M. Szycher, A.M. Reed, Biostable polyurethane elastomers., Med. Device Technol. 3 (1992) 42–51.

[22] M. Szycher, Szycher's Handbook of Polyurethanes, Second Edition, 2013. doi:10.1038/142853a0.

[23] M.F. Sonnenschein, Polyurethanes: Science, Technology, Markets, and Trends, 2014. doi:10.1002/9781118901274.

[24] M.F. Sonnenschein, Introduction to Polyurethane Chemistry, Polyurethanes. (2014) 105–126. doi:10.1002/9781118901274.ch3.

[25] M. Ionescu, Chemistry and technology of polyols for polyurethanes. ., 2007. doi:10.1002/pi.2159.

[26] D.K. Chattopadhyay, K.V.S.N. Raju, Structural engineering of polyurethane coatings for high performance applications, Prog. Polym. Sci. 32 (2007) 352–418. doi:10.1016/j.progpolymsci.2006.05.003.

[27] M. Ilavsk, H.W. Ulmer, K. Te Nijenhuis, W.J. Mijs, Network formation in polyurethanes

based on triisocyanate and diethanolamine derivatives, Eur. Polym. J. 37 (2001) 887–896. doi:10.1016/S0014-3057(00)00217-2.

[28] P. Król, Synthesis methods, chemical structures and phase structures of linear polyurethanes. Properties and applications of linear polyurethanes in polyurethane elastomers, copolymers and ionomers, Prog. Mater. Sci. 52 (2007) 915–1015. doi:10.1016/j.pmatsci.2006.11.001.

[29] P. Ping, W. Wang, X. Chen, X. Jing, The Influence of Hard-Segments on Two-Phase Structure and Shape Memory Properties of PCL-Based Segmented Polyurethanes, (2006) 8–12. doi:10.1002/polb.

[30] P.C. Caracciolo, F. Buffa, G.A. Abraham, Effect of the hard segment chemistry and structure on the thermal and mechanical properties of novel biomedical segmented poly(esterurethanes), J. Mater. Sci. Mater. Med. 20 (2009) 145–155. doi:10.1007/s10856-008-3561-8.

[31] J.Y. Cherng, T.Y. Hou, M.F. Shih, H. Talsma, W.E. Hennink, Polyurethane-based drug delivery systems., Int. J. Pharm. 450 (2013) 145–62. doi:10.1016/j.ijpharm.2013.04.063.

[32] S. Levchik, E. Weil, Thermal decomposition, combustion and fire-retardanc of polyurethanes—a review of the recent literature, Polym. Int. 1610 (2004) 1585–1610. doi:10.1002/pi.1314.

[33] S. V Levchik, E.D. Weil, Thermal decomposition, combustion and fire-retardancy of polyurethanes—a review of the recent literature, Polym. Int. 53 (2004) 1585–1610. doi:10.1002/pi.1314.

[34] T. Tawa, S. Ito, The Role of Hard Segments of Aqueous Polyurethane-urea Dispersion in Determining the Colloidal Characteristics and Physical Properties, Polym. J. 38 (2006) 686–693. doi:10.1295/polymj.PJ2005193.

[35] L. Rueda-Larraz, B.F. d'Arlas, a. Tercjak, a. Ribes, I. Mondragon, a. Eceiza, Synthesis and microstructure–mechanical property relationships of segmented polyurethanes based on a PCL–PTHF–PCL block copolymer as soft segment, Eur. Polym. J. 45 (2009) 2096–2109. doi:10.1016/j.eurpolymj.2009.03.013.

[36] D.F. Williams, On the mechanisms of biocompatibility, Biomaterials. 29 (2008) 2941–2953. doi:10.1016/j.biomaterials.2008.04.023.

[37] I.A. Notes, Proliferation Assay MTT Protocol, Wallert Provast Lab. (2007) 1–2. doi:10.1007/978-1-61779-080-5_20.

[38] Q. Chen, S. Liang, G. A. Thouas, Elastomeric biomaterials for tissue engineering, Prog. Polym. Sci. 38 (2013) 584–671. doi:10.1016/j.progpolymsci.2012.05.003.

[39] D.N. Heo, D.H. Yang, H.-J. Moon, J.B. Lee, M.S. Bae, S.C. Lee, et al., Gold nanoparticles surface-functionalized with paclitaxel drug and biotin receptor as theranostic agents for cancer therapy., Biomaterials. 33 (2012) 856–66.

doi:10.1016/j.biomaterials.2011.09.064.

[40] A.Z.M. Badruddoza, M.T. Rahman, S. Ghosh, M.Z. Hossain, J. Shi, K. Hidajat, et al., β-Cyclodextrin conjugated magnetic, fluorescent silica core-shell nanoparticles for biomedical applications, Carbohydr. Polym. 95 (2013) 449–457. doi:10.1016/j.carbpol.2013.02.046.

[41] A. Burke, N. Hasirci, Polyurethanes in biomedical applications., Adv. Exp. Med. Biol. 553 (2004) 83–101.

[42] S.A. Guelcher, Biodegradable polyurethanes: synthesis and applications in regenerative medicine., Tissue Eng. Part B. Rev. 14 (2008) 3–17. doi:10.1089/teb.2007.0133.

[43] R.E. Marchant, Q. Zhao, J.M. Anderson, A. Hiltner, Degradation of a poly(ether urethane urea) elastomer: infra-red and XPS studies, Polymer (Guildf). 28 (1987) 2032–2039. doi:10.1016/0032-3861(87)90037-1.

[44] U. Ojha, P. Kulkarni, R. Faust, Syntheses and characterization of novel biostable polyisobutylene based thermoplastic polyurethanes, Polymer (Guildf). 50 (2009) 3448–3457. doi:10.1016/j.polymer.2009.05.025.

[45] D. Pinchuk, O. Pinchuk, K. Sirbiladze, O. Shugar, Clinical effectiveness of primary and secondary headache treatment by transcranial direct current stimulation, Front. Neurol. 4 MAR (2013). doi:10.3389/fneur.2013.00025.

[46] M. Szycher, A.A. Siciliano, An assessment of 2,4 TDA formation from Surgitek polyurethane foam under simulated physiological conditions., J. Biomater. Appl. 5 (1991) 323–36.

[47] H.M.D. Luu, J.C. Hutter, Pharmacokinetic modeling of 4,4'-methylenedianiline released from reused polyurethane dialyzer potting materials, J. Biomed. Mater. Res. 53 (2000) 276–286. doi:10.1002/(SICI)1097-4636(2000)53:3<276::AID-JBM13>3.0.CO;2-E.

[48] T.T. Reddy, A. Kano, A. Maruyama, A. Takahara, Synthesis, characterization and drug release of biocompatible/biodegradable non-toxic poly(urethane urea)s based on poly(epsilon-caprolactone)s and lysine-based diisocyanate., J. Biomater. Sci. Polym. Ed. 21 (2010) 1483–502. doi:10.1163/092050609X12518804794785.

[49] J.Y. Zhang, E.J. Beckman, N.P. Piesco, S. Agarwal, A new peptide-based urethane polymer: synthesis, biodegradation, and potential to support cell growth in vitro, Biomaterials. 21 (2000) 1247–1258. doi:10.1016/S0142-9612(00)00005-3.

[50] L. Rao, H. Zhou, T. Li, C. Li, Y.Y. Duan, Polyethylene glycol-containing polyurethane hydrogel coatings for improving the biocompatibility of neural electrodes., Acta Biomater. 8 (2012) 2233–42. doi:10.1016/j.actbio.2012.03.001.

[51] D. Park, W. Wu, Y. Wang, A functionalizable reverse thermal gel based on a polyurethane/PEG block copolymer., Biomaterials. 32 (2011) 777–86. doi:10.1016/j.biomaterials.2010.09.044.

[52] B. Bogdanov, V. Toncheva, E. Schacht, L. Finelli, B. Sarti, M. Scandola, Physical properties of poly(ester-urethanes) prepared from different molar mass polycaprolactone-diols, Polymer (Guildf). 40 (1999) 3171–3182. doi:http://dx.doi.org/10.1016/S0032-3861(98)00552-7.

[53] M. Bil, J. Ryszkowska, J. a Roether, O. Bretcanu, a R. Boccaccini, Bioactivity of polyurethane-based scaffolds coated with Bioglass., Biomed. Mater. 2 (2007) 93–101. doi:10.1088/1748-6041/2/2/006.

[54] D.N. Rockwood, R.E. Akins, I.C. Parrag, K.A. Woodhouse, J.F. Rabolt, Culture on electrospun polyurethane scaffolds decreases atrial natriuretic peptide expression by cardiomyocytes in vitro, Biomaterials. 29 (2008) 4783–4791. doi:10.1016/j.biomaterials.2008.08.034.

[55] S.A. Guelcher, A. Srinivasan, J.E. Dumas, J.E. Didier, S. McBride, J.O. Hollinger, Synthesis, mechanical properties, biocompatibility, and biodegradation of polyurethane networks from lysine polyisocyanates., Biomaterials. 29 (2008) 1762–75. doi:10.1016/j.biomaterials.2007.12.046.

[56] A.B. Mathur, T.O. Collier, W.J. Kao, M. Wiggins, M.A. Schubert, A. Hiltner, et al., In vivo biocompatibility and biostability of modified polyurethanes, J. Biomed. Mater. Res. 36 (1997) 246–257. doi:10.1002/(SICI)1097-4636(199708)36:2<246::AID-JBM14>3.0.CO;2-E.

[57] M. Yeganegi, R. a Kandel, J.P. Santerre, Characterization of a biodegradable electrospun polyurethane nanofiber scaffold: Mechanical properties and cytotoxicity., Acta Biomater. 6 (2010) 3847–55. doi:10.1016/j.actbio.2010.05.003.

[58] J.P. Santerre, K. Woodhouse, G. Laroche, R.S. Labow, Understanding the biodegradation of polyurethanes: from classical implants to tissue engineering materials., Biomaterials. 26 (2005) 7457–70. doi:10.1016/j.biomaterials.2005.05.079.

[59] C. Zhang, X. Wen, N.R. Vyavahare, T. Boland, Synthesis and characterization of biodegradable elastomeric polyurethane scaffolds fabricated by the inkjet technique, Biomaterials. 29 (2008) 3781–3791. doi:10.1016/j.biomaterials.2008.06.009.

[60] W.N. Sivak, I.F. Pollack, S. Petoud, W.C. Zamboni, J. Zhang, E.J. Beckman, Catalyst-dependent drug loading of LDI-glycerol polyurethane foams leads to differing controlled release profiles., Acta Biomater. 4 (2008) 1263–74. doi:10.1016/j.actbio.2008.01.008.

[61] W.N. Sivak, I.F. Pollack, S. Petoud, W.C. Zamboni, J. Zhang, E.J. Beckman, LDI-glycerol polyurethane implants exhibit controlled release of DB-67 and anti-tumor activity in vitro against malignant gliomas., Acta Biomater. 4 (2008) 852–62. doi:10.1016/j.actbio.2007.10.012.

[62] J.Y. Cherng, T.Y. Hou, M.F. Shih, H. Talsma, W.E. Hennink, Polyurethane-based drug delivery systems, Int. J. Pharm. 450 (2013) 145–162.

[63] L. Zhou, L. Yu, M. Ding, J. Li, H. Tan, Z. Wang, et al., Synthesis and Characterization of

pH-Sensitive Biodegradable Polyurethane for Potential Drug Delivery Applications, Macromolecules. 44 (2011) 857–864. doi:10.1021/ma102346a.

[64] Y. Chen, R. Wang, J. Zhou, H. Fan, B. Shi, On-demand drug delivery from temperature-responsive polyurethane membrane, React. Funct. Polym. 71 (2011) 525–535. doi:10.1016/j.reactfunctpolym.2011.01.010.

[65] G. Wu, J. Chen, S. Huo, G. Liu, Z. Kong, Thermoset nanocomposites from two-component waterborne polyurethanes and cellulose whiskers., Carbohydr. Polym. 105 (2014) 207–13. doi:10.1016/j.carbpol.2014.01.095.

[66] M. Yoonessi, J.A. Peck, J.L. Bail, R.B. Rogers, B. a Lerch, M. a Meador, Transparent large-strain thermoplastic polyurethane magnetoactive nanocomposites., ACS Appl. Mater. Interfaces. 3 (2011) 2686–93. doi:10.1021/am200468t.

[67] M. Ding, X. He, Z. Wang, J. Li, H. Tan, H. Deng, et al., Cellular uptake of polyurethane nanocarriers mediated by gemini quaternary ammonium., Biomaterials. 32 (2011) 9515–24. doi:10.1016/j.biomaterials.2011.08.074.

[68] A. Manuscript, D.R. Kinetics, D. Polymeric, D. Systems, Drug Release Kinetics and Transport Mechanisms of Non- degradable and Degradable Polymeric Delivery Systems, Expert Opin Drug Deliv. 7 (2010) 429–444. doi:10.1517/17425241003602259.Drug.

[69] R. Adhikari, P.A. Gunatillake, I. Griffiths, L. Tatai, M. Wickramaratna, S. Houshyar, et al., Biodegradable injectable polyurethanes: synthesis and evaluation for orthopaedic applications., Biomaterials. 29 (2008) 3762–70. doi:10.1016/j.biomaterials.2008.06.021.

[70] L. Yu, L. Zhou, M. Ding, J. Li, H. Tan, Q. Fu, et al., Synthesis and characterization of novel biodegradable folate conjugated polyurethanes., J. Colloid Interface Sci. 358 (2011) 376–83. doi:10.1016/j.jcis.2011.03.007.

[71] Y. Niu, K.C. Chen, T. He, W. Yu, S. Huang, K. Xu, Scaffolds from block polyurethanes based on poly(ε-caprolactone) (PCL) and poly(ethylene glycol) (PEG) for peripheral nerve regeneration., Biomaterials. 35 (2014) 4266–77. doi:10.1016/j.biomaterials.2014.02.013.

[72] P. Punnakitikashem, D. Truong, J.U. Menon, K.T. Nguyen, Y. Hong, Electrospun biodegradable elastic polyurethane scaffolds with dipyridamole release for small diameter vascular grafts., Acta Biomater. (2014). doi:10.1016/j.actbio.2014.07.031.

[73] D. Macocinschi, D. Filip, S. Vlad, M. Butnaru, L. Knieling, Evaluation of polyurethane based on cellulose derivative-ketoprofen biosystem for implant biomedical devices, Int. J. Biol. Macromol. 52 (2013) 32–37.

[74] R. Lalwani, S. Desai, Sorption behavior of biodegradable polyurethanes with carbohydrate crosslinkers, J. Appl. Polym. Sci. 115 (2010) 1296–1305. doi:10.1002/app.30214.

[75] A. Solanki, J. Mehta, S. Thakore, Structure-property relationships and biocompatibility of

carbohydrate crosslinked polyurethanes., Carbohydr. Polym. 110 (2014) 338–44. doi:10.1016/j.carbpol.2014.04.021.

[76] J. Zou, F. Zhang, J. Huang, P.R. Chang, Z. Su, J. Yu, Effects of starch nanocrystals on structure and properties of waterborne polyurethane-based composites, Carbohydr. Polym. 85 (2011) 824–831. doi:http://dx.doi.org/10.1016/j.carbpol.2011.04.006.

[77] H. Liu, S. Cui, S. Shang, D. Wang, J. Song, Properties of rosin-based waterborne polyurethanes/cellulose nanocrystals composites, Carbohydr. Polym. 96 (2013) 510–515.

[78] W. Han, M. Tu, R. Zeng, J. Zhao, C. Zhou, Preparation, characterization and cytocompatibility of polyurethane/cellulose based liquid crystal composite membranes., Carbohydr. Polym. 90 (2012) 1353–61. doi:10.1016/j.carbpol.2012.07.004.

[79] A. Buleon, P. Colonna, V. Planchot, S. Ball, Starch Granules: Structure and Biosynthesis, Int J Biol Macromol. 23 (1998) 85–112. doi:S0141-8130(98)00040-3 [pii].

[80] C.M. Durrani, A.M. Donald, Physical characterisation of amylopectin gels, Polym. Gels Networks. 3 (1995) 1–27. doi:10.1016/0966-7822(94)00005-R.

[81] X. Cao, P.R. Chang, M.A. Huneault, Preparation and properties of plasticized starch modified with poly(ε-caprolactone) based waterborne polyurethane, Carbohydr. Polym. 71 (2008) 119–125.

[82] R.M. Brown, Cellulose structure and biosynthesis, Pure Appl. Chem. 71 (1999) 767–775. doi:10.1351/pac199971050767.

[83] A. O'sullivan, Cellulose: the structure slowly unravels, Cellulose. 4 (1997) 173–207. doi:Chemistry and Materials Science.

[84] Z. Gao, J. Peng, T. Zhong, J. Sun, X. Wang, C. Yue, Biocompatible elastomer of waterborne polyurethane based on castor oil and polyethylene glycol with cellulose nanocrystals, Carbohydr. Polym. 87 (2012) 2068–2075. doi:10.1016/j.carbpol.2011.10.027.

[85] A.R. Unnithan, G. Gnanasekaran, Y. Sathishkumar, Y.S. Lee, C.S. Kim, Electrospun antibacterial polyurethane-cellulose acetate-zein composite mats for wound dressing., Carbohydr. Polym. 102 (2014) 884–92. doi:10.1016/j.carbpol.2013.10.070.

[86] F. Zia, K.M. Zia, M. Zuber, S. Kamal, N. Aslam, Starch based polyurethanes: A critical review updating recent literature, Carbohydr. Polym. 134 (2015) 784–798. doi:10.1016/j.carbpol.2015.08.034.

[87] H. Liu, S. Cui, S. Shang, D. Wang, J. Song, Properties of rosin-based waterborne polyurethanes/cellulose nanocrystals composites., Carbohydr. Polym. 96 (2013) 510–5. doi:10.1016/j.carbpol.2013.04.010.