Technical White Paper

Absorbable Polyurethanes

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Polyurethanes represent a diverse family of materials with the versatility of being rigid, semi-rigid and flexible. First developed by Professor Otto Bayer in 1937, they can be either thermoplastics or thermosets. They are used in a wide variety of applications including automotive, apparel, seals, rigid foams, bushings, packaging, bedding, carpet padding and coatings. In addition, polyurethanes have also demonstrated excellent blood compatibility, outstanding hydrolytic stability, superior abrasion resistance, excellent physical strength, high flexural endurance and ease of processability. This has resulted in polyurethanes being used in a number of biomedical applications, including short-term medical devices (catheters, endotracheal tubes, cannulas), long-term implantable devices (vascular prostheses, intra-aortic balloons), tissue engineering scaffolds, infusion pumps and cardiac pacemakers. Such versatility and multitude of properties that can be obtained with polyurethanes result from the wide range of molecular variations that can be joined together via the urethane bond.

This white paper is intended to provide the readers with an overview of polyurethane chemistry, commercially available medical grade polyurethanes, novel absorbable isocyanates, absorbable amines and absorbable polyurethanes developed by our company. In addition, the present paper will also touch on some of the potential biomedical applications of our novel absorbable polyurethanes.

1.0 *Polyurethane Chemistry*

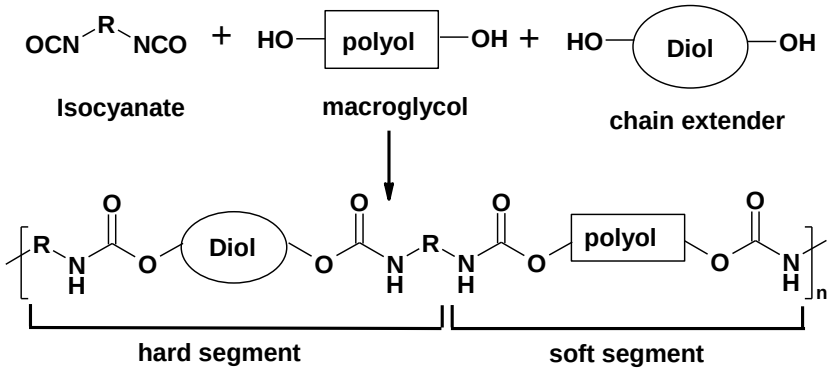


Figure 1. Polyurethane synthesis.

Polyurethanes are segmented block copolymers containing blocks of low molecular weight polyesters or polyethers linked together via a urethane group. Depending on their

composition and structure, they can exist in linear form (thermoplastic polyurethanes), cross-linked (thermosetting polyurethanes) and expanded (urethane foams).

Polyurethanes are prepared via reaction between three monomers: a) an isocyanate, b) a macroglycol or polyol and 3) a chain extender or curative. The reaction advances with the nucleophilic attack on the carbon atom of the isocyanate group by a nucleophilic group (OH, NH_2) present in various compounds such as alcohols and amines. Attack by an alcohol results in the formation of a urethane group (-NH-CO-O-). In the case of amines, urea (-NH-CO-NH-) bonds are formed and poly (urea-urethanes) are obtained.

As shown in **Figure 1**, thermoplastic polyurethane comprises of two segments: a) *hard segment* formed by the reaction between isocyanate and chain extender and b) a *soft segment* formed by the reaction between isocyanate and a macroglycol. Segmented polyurethanes can be prepared in two different ways: a) in a one step process wherein the isocyanate, chain extender and macroglycol are mixed together in one step, or b) in a two step process in which prepolymers are first synthesized by reacting isocyanates with macroglycol and then this prepolymer is reacted with a chain extender to form high molecular weight polyurethane. The two step process is used more in the preparation of medical grade segmented polyurethanes.

In contrast to the soft segment, which is elastic, the hard segment has a rigid nature, either glass or semi-crystalline. Due to incompatibility between the two segments, these materials are characterized by a separation of phases in the solid state; the resulting two phase structure is formed by aggregates or domains of hard segments dispersed in the elastomeric matrix of the soft segment. Hard segments, dispersed in a matrix of soft segments, act as reinforcing particles and behave as physical cross-linking sites, which are reversible at high temperatures, giving the material elastomeric characteristics. Furthermore, these materials can undergo typical processing of the polymeric materials and once cooled, they behave again as chemically crosslinked rubber.

The driving force for the segregation in domains is the chemical incompatibility between the soft and hard segments. Factors affecting the phase separation include intermolecular hydrogen bond, copolymer composition, solubility of hard segments with respect to soft segments, crystallizability of each of the two segments, manufacturing method, and thermal and mechanical history.

During the polymerization, unwanted side reactions can occur, also. These include: a) reaction between diisocyanate and water leading to the formation of an amine with the release of carbon dioxide, b) reaction between diisocyanate and urethane groups leading to the formation of allophanates, c) reaction between diisocyanate and urea groups to form biurets, or d) dimerization or trimerization of aromatic diisocyanates. The formation of allophanates and biurets occur only at high temperatures.

In some cases, catalysts are required to facilitate polyurethane formation. This is required in instances where the size of the substituent on the polyol is large. Although, tertiary amines such as DABCO (tri-ethylene diamine 1,4-diazo (2,2,2,) bicyclooctane) and

organotin compounds are the most commonly used catalysts, organotin catalysts specifically catalyze the reaction between the hydroxyl and isocyanate groups to form urethane linkage and should be preferred over amines for the production of polyurethane elastomers.

1.1 *Isocyanates*

Figure 2 displays the structures and names of some common commercially important isocyanates used in polyurethane production. As shown, they can be aromatic or aliphatic. 4,4′-methylenebis(phenylisocyanate) (MDI) is the most commonly used aromatic isocyanate used in the polyurethane industry. It is a highly reactive isocyanate, in fact, so reactive that in many cases, a catalyst is not required for polyurethane synthesis.

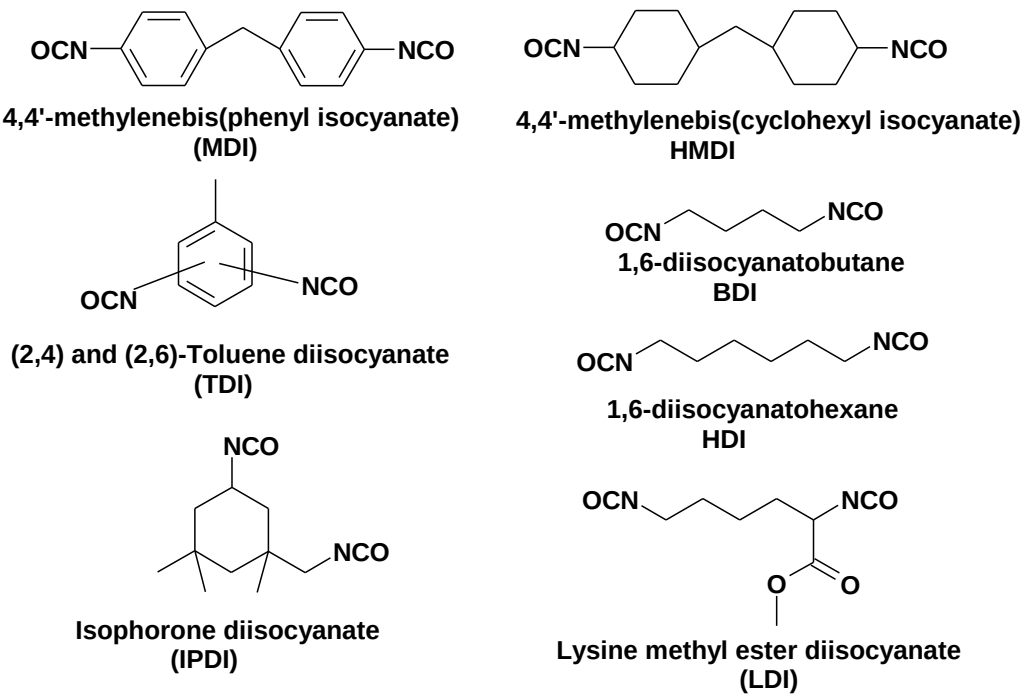


Figure 2. Examples of isocyanates of commercial importance.

Aromatic isocyanates are generally more reactive than aliphatic isocyanates and yield polyurethanes with mechanical properties superior to those of aliphatic polyurethanes. This is attributed to the ability of aromatic polyurethanes to form much stronger intermolecular bonds than aliphatic polyurethanes. The hard segments in aromatic polyurethanes tend to be semicrystalline or crystalline in nature. Contrary to this, hard segments containing aliphatic isocyanates do not have the ability to crystallize. Since more crystalline hard segments help more phase separation in the copolymer, mechanical properties of aromatic polyurethanes are better than those of aliphatic polyurethanes.

However, aromatic polyurethanes turn yellow upon exposure to ultraviolet radiation. This is attributed to the formation of diquinone-imide structure, as shown in **Figure 3**, a chromophoric group that absorbs all colors except yellow. Although, yellowing does not cause any change in the physical properties and biocompatibility of polyurethanes, it is objectionable under certain circumstances. Another disadvantage of aromatic polyurethanes is the possibility of the formation of highly toxic aromatic aniline during improper thermal processing or excessive steam sterilization. This is attributed either to the thermal degradation or thermo hydrolytic degradation of the aromatic polyurethane under such conditions. **Figure 4** depicts the mechanism. It is for this reason that aromatic polyurethane pellets should be well dried prior to thermal processing and the finished product should not be subjected to prolonged steam sterilization cycles.

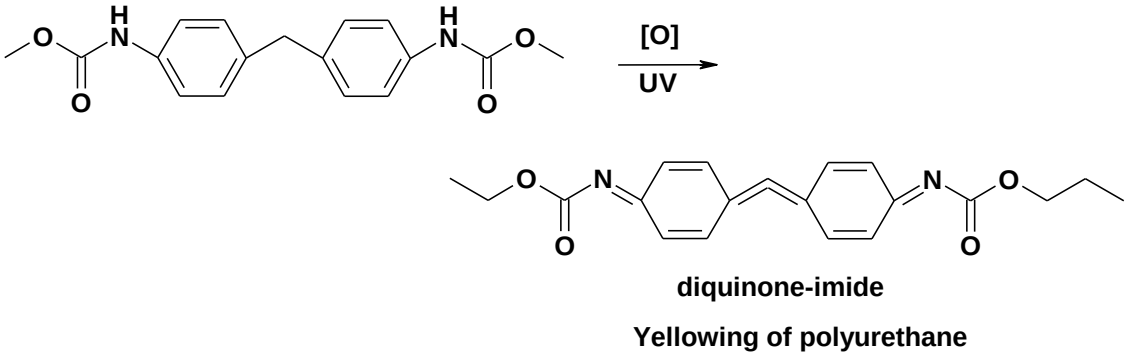


Figure 3. Formation of the diquinone-imide structure responsible for yellowing of polyurethane in the presence of ultraviolet light.

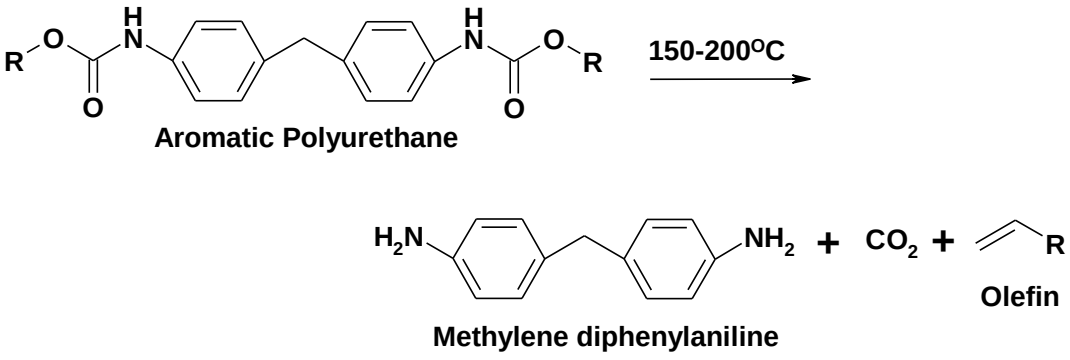


Figure 4. Thermal degradation of aromatic polyurethane, resulting in formation of toxic dimethylaniline.

In contrast to aromatic isocyanates, aliphatic isocyanates such as methylene bis (cyclohexyl diisocyanate) (HMDI) yields polyurethanes that are color stable. However, the physical properties of aliphatic polyurethane elastomers are somewhat inferior to their aromatic counterparts and are also more expensive. Furthermore, the lower reactivity of aliphatic isocyanates as compared to aromatic isocyanates results in a longer curing time as well as the needed presence of catalyst during the synthesis of aliphatic polyurethanes.

Although both aromatic and aliphatic polyurethanes are used in commercial biomedical-grade polyurethanes, as shown in **Table 1**, the majority of the medical grade polyurethanes are based on aromatic diisocyanate, MDI.

Table 1. Selected commercial medical grade polyurethanes

Manufacturer	Trade Name	Isocyanate	Chain Extender	Polyol
DSM PTG	Elasthane	MDI	1,4-Butanediol	PTMEG
DSM PTG	BioSpan	MDI	Diamine	Polyether
Thermedics	Tecoflex	HMDI	1,4-Butanediol	Polyether
DSM PTG	Bionate	MDI	Diamine	Polycarbonate
Pellethane	Dow Chemical	MDI	1,4-Butanediol	PTMEG

DSM PTG: DSM Polymer Technology Group, PTMEG: Poly (tetramethyelene ether) glycol

1.2 *Macroglycols*

Although isocyanate plays an important role, many of the properties associated with polyurethanes are determined by the macroglycol portion of the chain. Polyester and polyether diols are the most commonly used macroglycols for the synthesis of polyurethanes for biomedical applications, in particular, poly (tetramethylene ether) glycol (PTMEG). The necessity of using different macroglycols is determined by the fact that polyurethanes obtained from polyester diols are subjected to in-vivo degradation and the type of glycol determines this effect. Polyether based polyurethanes, particularly those based on PTMEG, are by far the most commonly used biostable polyurethanes in biomedical applications. Once implanted inside the body, however, the polyether soft segment is susceptible to oxidative degradation by the hydroperoxide radicals released by the macrophages. In order to increase the stability of the soft segment, polycarbonate diols are being increasingly used in place of PTMEG, as poly(carbonate urethanes) are reported to be the most biostable polyurethanes.

1.3 *Chain Extenders*

Chain extenders are used for the preparation of polyurethanes with a segmented structure and desirable physical properties. They are difunctional molecules containing amino or hydroxyl end groups. 1,4-butanediol is the universal choice of chain extender for the synthesis of thermoplastic polyurethanes. According to the literature, when the chain extender contains an even number of carbon atoms, the hard segment crystallizes easier than when the number of carbon atoms is odd. Ethylene diamine is also used as a chain

extender. It results in the formation of polyureaurethanes that are less soluble in common solvents and hence they are difficult to process in extrusion or moulding. This limits their application in the production of fibers and dip coating.

2.0 ***Absorbable Polyurethanes***

In spite of excellent mechanical properties, biostable polyurethanes cannot be used in biomedical applications where biodegradability of the polymer is a necessary prerequisite.

Relatively little research has been done so far at developing absorbable polyurethanes for temporary implantation. Several papers were published in the early 1980's describing polyurethane/polylactide blends as degradable materials for skin substitutes, vascular prostheses and nerve regeneration guides. However, in these cases the polyurethane portion of the blend was non-degradable and served only to provide favorable mechanical properties. Subsequent work by Bruin et al. (PCT Publication WO 9526762A1) involved the synthesis of crosslinked polyurethane networks incorporating a lactide or glycolide, and an epsilon-caprolactone joined by a lysine-based diisocyanate. These polymers displayed good elastomeric properties and were found to degrade within 26 weeks in vitro and 12 weeks in vivo (subcutaneous implantation in guinea pigs).

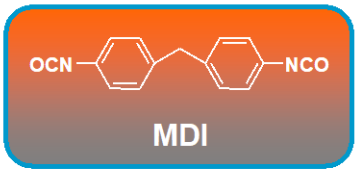
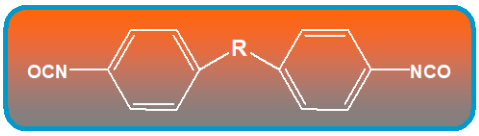
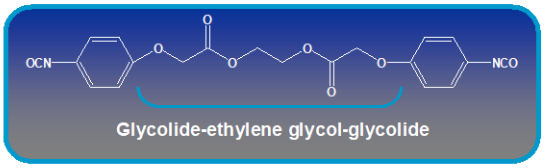
However, a drawback of this approach is that the highly crosslinked polymer may not be processed by standard techniques such as solution casting or melt processing, as is the case for typical linear, segmented polyurethanes. Furthermore, Cohn et al. (US Patent Application Publication No. 2007/0116666A1, US Patent No. 6579951) developed a series of elastomeric polyester-polyether-polyurethane block copolymers intended for use as surgical articles. Beckmann et al. (US Patent Application Publication No. 2004/0170597A1) developed polyurethane based biodegradable adhesive from multi-isocyanate functional molecules and multifunctional precursor molecules with terminal groups selected from hydroxyl and amino groups. Woodhouse et al. (US Patent No. 6221997) developed absorbable polyurethanes from lysine diisocyanate and lysine triisocyanate and polyols. Similarly, Fuller et al. (US Patent No. 4829099) developed absorbable polyurethanes based on biodegradable isocyanates from diols and nitrobenzoic acid.

However, all these absorbable polyurethanes suffered from the following drawbacks: a) the rate of formation of polyurethane is very slow, and this is attributed to the low reactivity of the isocyanates; and b) neither the biodegradable isocyanates nor the absorbable polyurethanes derived from them have tunable physical and mechanical properties, and controllable hydrolytic degradation profiles. Furthermore, the synthetic method used by Fuller et al. to prepare biodegradable isocyanates is quite cumbersome and highly uneconomical.

3.0 *Novel Absorbable isocyanates from Bezwada Biomedical*

In order to overcome the prior drawbacks and limitations, at Bezwada Biomedical we have developed highly reactive isocyanates that are similar to MDI but are biodegradable and have tunable hydrolytic degradation profiles. *What distinguishes our isocyanates from the commonly used isocyanate, MDI, is the presence of a degradable linkage bridging the aromatic rings instead of the non-degradable methylene group. Furthermore, the degradable linkage in our isocyanates is derived from safe and biocompatible glycolic acid, lactic acid, caprolactone, p-dioxanone and diols, examples of which are shown in* ***Figure 6***. A comparison between the prior art and our state-of-the-art is given below in **Table 2**.

Table 2. Comparison between Prior art and Our State-of-the-Art.

Prior Art	Our State-of-the-Art
 • Non-degradable aromatic diisocyanates • Derived polyurethanes are biostable	 R= degradable linkages derived from glycolide,lactide, PDO and caprolactone monomers and ethylene glycol.  • Degradable Aromatic Diisocyanate similar to MDI • Derived from safe and biocompatible monomers • Degradation products: safe and biocompatible • Controlled degradation profile **Renders derived polyurethane hydrolysable/absorbable**

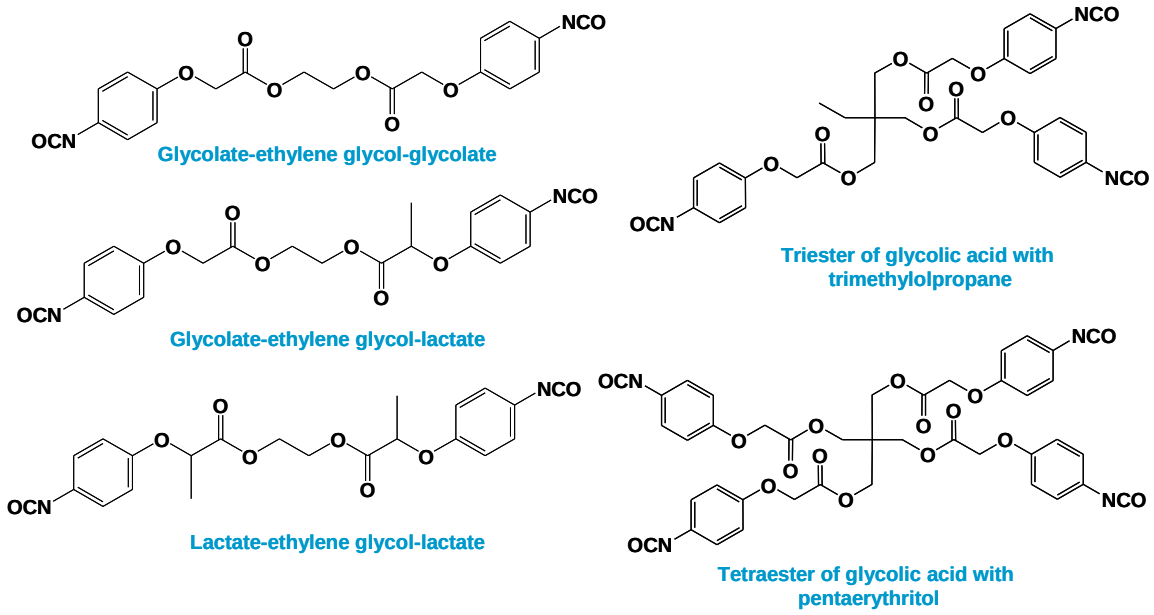


Figure 6. Selected examples of novel degradable aromatic isocyanates from Bezwada Biomedical.

As can be seen from **Figure 6**:

- At Bezwada Biomedical we have both di- as well as multi isocyanates with controlled degradation profiles.
- The degradation rate of these isocyanates is controlled by varying the chain length of the degradable linkage and by varying the safe and biocompatible molecule within the degradable linkage, i.e., replacing glycolide with lactide or p-dioxanone, and the like.
- Interestingly, the polyurethanes derived from these novel isocyanates and chain extender diols will be not only absorbable but will also possess, for the first time, degradable hard segments.
- The derived polyurethanes will have the toughness and mechanical properties of that of commercially available medical grade polyurethanes, and the absorbability of commercial biodegradable polymers.
- Upon hydrolysis, the derived absorbable polyurethanes will degrade into safe and biocompatible degradation products, unlike polyurethanes derived from MDI.

4.0 *Potential biomedical applications of absorbable polyurethanes derived from novel absorbable isocyanates from Bezwada Biomedical*

- Tissue adhesives and sealants
- Adhesion prevention barrier
- Absorbable scaffolds for tissue engineering
- Absorbable coatings
- Controlled release of drugs

For further information on how we can help you engineer your success, please contact us at rao@bezwadabiomedical.com or visit us at www.bezwadabiomedical.com

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