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Isocyanates as Precursors to Biomedical Polyurethanes

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This work is a review of the main chemical properties of aliphatic and aromatic isocyanates and their advantages and disadvantages when used as precursors for polyurethane (PU) synthesis, to be applied as biomedical polyurethanes. Isocyanates react quantitatively with primary hydroxyl groups producing urethane groups. The presence of urethane groups can promote the restoration of living tissues. Molecules with two or more hydroxyl groups reacting with molecules containing two or more isocyanate groups results in PU, therefore PU is biocompatible, with the condition they have no remaining isocyanate groups and if all the precursor molecules from PU do not have damaging groups. Furthermore, this report describes the synthesis reactions of isocyanates used industrially and their advantages and disadvantages, alternative process as well as alternative compounds discussed in current articles, as isonitriles, carbamates, and new routes as transcarbamylase, blocked isocyanates, non-isocyanates, in order to suit the environmental and safety standards.

1. Isocyanates

Isocyanates are chemical compounds from the isocyanic acid having NCO groups in its structure. Due to the molecular orbital theory, the isocyanic group represents a linear structure with double bonds between C = N and C = O on the same axis with the respective π electrons double bands situated in different perpendicular planes. The reaction occurs when a nucleophilic compound containing an active hydrogen atom attacks the carbon atom from NCO, the hydrogen atom is added to the nitrogen, thus leading to a breaking of the double bond, and the reactivity is based on the high electronegativity of the atoms of nitrogen and oxygen, which displace the electron density of the molecule. In the polymerization process of the polyurethane, isocyanates containing at least two functional groups in its structure are required.
In general, aromatic isocyanates are more reactive than aliphatic ones, and this choice will change the final properties of the polyurethanes (Cherng et al., 2013). For example, if R is an aromatic group, the negative charge shifts in the R direction, so aromatic isocyanates are more reactive than aliphatic or cycloaliphatic. In the case of aromatic isocyanates, the nature of the substituent also determine the reactivity, an electron which attract substituents in the ortho position increase the reactivity, and substituents electron donors reduce the reactivity of the isocyanate group.
The reactivity of diisocyanates is still more complex. Symmetrical diisocyanates have the same reactivity ($k_1 = k_2 = k$) and assymmetric diisocyanates exhibit different reactivities (k_1 and k_2) (Delebecq et al., 2012), furthermore, it is necessary to consider the steric factors. Aromatic substituents in para position are more reactive than ortho substituents due to steric effects.
All of the isocyanates commercially available have two or more functional groups. The use of a diisocyanate is directly proportional to the amine cost and commercial availability. Aliphatic amines do not exhibit favorable costs and are difficult to be commercialized as 1,6-hexamethylene diisocyanate (HDI) and 1,4-butane diisocyanate (BDI). Aromatic amines are commercially available and at a low-cost, due to these factors, 95% of commercial diisocyanates are based on toluene diisocyanate (TDI) and methylene diphenyl diisocyanate (MDI) and its derivatives, as shown in figure 1.

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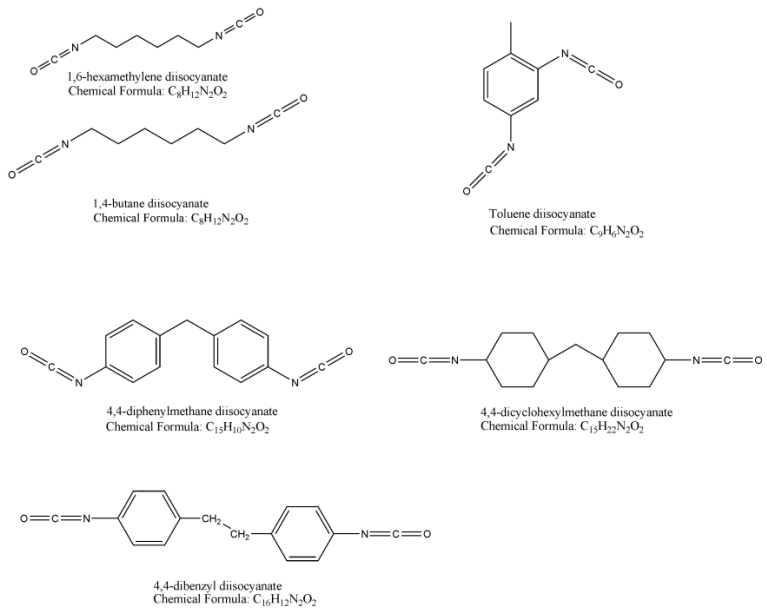


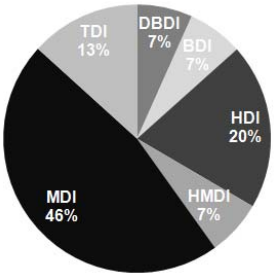
Figure 1: Example of diisocyanates currently used.

Aromatic isocyanates are mainly represented by MDI and TDI, but they can undergo photodegradation. Aliphatic isocyanates, such as HDI and isophorone diisocyanate (IPDI) are more resistant to ultraviolet irradiation (UV). Moreover, in the medical field, PUs based on aromatic isocyanates are considered less biocompatible than PUs based on aliphatic isocyanates. This happens because the degradation products are toxic, such as aromatic amines from the rigid segments of polyurethanes. The process of photodegradation can be applied as biomaterials for the immobilization of cells and controlled release of drugs. UV irradiation can be applied to biomaterials for the process of situ polymerization, producing materials with desired elasticity and texture.

Table 1: Some isocyanates applied as monomers to biomedical polyurethanes.

Diisocyanate	Reference
1,4-Butane diisocyanate (BDI)	de Mulder et al. (2012)
4,4-Dibenzyl diisocyanate (DBDI)	Prisacariu and Scortanu (2010)
1,6-Hexamethylene diisocyanate (HDI)	Asefnejad et al. (2011) Caracciolo et al. (2013) Peponi et al. (2013)
4,4-Dicyclohexylmethane diisocyanate (HMDI)	Dulinska-Molak et al. (2013)
4,4-Diphenylmethane diisocyanate (MDI)	González-Paz et al. (2013) Hu et al. (2012) Kiran et al. (2012) Kuranska et al. (2013) Macocinschi et al. (2013) Mândru et al. (2013) Prisacariu and Scortanu (2010)
Toluene diisocyanate (TDI)	Das et al. (2013a) Das et al. (2013b)

Furthermore UV radiation is the most effective sterilization method for biomedical devices, but there are some restrictions as some sterilization techniques can react with functional groups of the polymer. Cherng et al. (2013) studied PU based on MDI in vivo and his results concluded that the aromatic amine diphenylmethane dianilines (MDA) were considered toxic due to the degradation of the hard segments of PU. Table 1 illustrates different types of aromatic and aliphatic isocyanates that are currently being applied as monomers to biomedical polyurethanes, and their authors. As previously mentioned, most applications use aromatic isocyanates. From this table it is possible to create the Graph 1, which shows the isocyanate and the corresponding percentage that it is being employed. The highest percentage, 46% belongs to the aromatic isocyanate MDI. Aliphatic isocyanates BDI and HDI represents together only 27%.



Graph 1: Graph created from Table 1 showing the percentage that some isocyanates has been applied in recent studies in the area of biomaterials.

2. Isocyanates synthesis

Isocyanate was first synthesized by Wurtz in 1848 by reacting diethyl sulfate and potassium cyanide (Scheme 1).

$$R_2SO_4 + KNCO \longrightarrow RNCO$$

Scheme 1: Reaction of Wurtz

The discovery of polyurethanes in 1937 by Otto Bayer and co-workers became one of the most produced chemical in the world. Otto Bayer discovered the polyurethane by the reaction from polyester diol and diisocyanate. From this discovery, several new routes for the production of isocyanates emerged.
A new linear structure terminated diisocyanate was synthesized from oleic acid via Curtis Rearrangement. The reaction started from oleic acid and dichloromethane with ozone. Then it was added copper chloride in methyl cyanide. It was added to this product triethylamine, obtaining the diisocyanate and it was characterized. The authors concluded that the synthesized diisocyanate has comparable properties to diisocyanates produced from petroleum. This new diisocyanate may prove to be a valuable substitute for comercial diisocyanate in several applications (Hojabri et al., 2009). In addition to this, new methods are currently being proposed.
Currently, the most important industrial synthesis of isocyanates is by phosgenation of primary amines. Phosgene is a highly toxic and flammable gas, which causes environmental hazards. This reaction occurs the formation of hydrochloric acid as a by-product, and the electric energy consumption is high. It is also possible to add alternative compounds as diphosgene and triphosgene. It is common to add alternative compounds such as nitrobenzene, which is highly explosive.
The classic process for obtaining TDI is by nitration of benzene, obtaining nitrobenzene. This is hydrogenated to form aniline. Through condensation of aniline with formaldehyde using sulfuric acid catalyst, is obtained MDA. After this step, the phosgenation of MDA is done, producing MDI. The process is also complex, nitrobenzene is a highly explosive compound, also occurs the presence of phosgene.
Another possibility of isocyanate synthesis is starting from carbamates, which are formal esters of carbamic acid. Therefore, carbamates are obtained from amines and alcohols with the addition of

phosgene or its derivatives (Kreye et al., 2013). Large parts of the amines are toxic and their addition should be avoided in the synthesis of biomaterials.
Another strategy is to obtain isocyanates via the oxidation of isonitriles (isocyanides). Isonitriles are characterized by an atom of Nitrogen and Carbon, linked by triple bond and connected to a radical, as Scheme 2. As described by Le and Ganem (2011), isocyanides was oxidized to isocyanate in the presence of dimethyl sulfoxide and trifluoroacetic anhydride, as a catalyst. The disadvantage of this method is certainly the absence of a sustainable route to isonitriles

Scheme 2. Oxidation of isonitriles to isocyanates.

Some authors have proposed alternative routes for the synthesis of isocyanates. Initial studies were proposed by Knolker in 1995 produced by the reaction of primary amines with di-tert-butyl dicarbonate (Boc_2O) and 4-dimethylaminopyridine (DMAP). This method is effective but using Boc_2O which is toxic and phosgene derivative, and does not follow the requirements of green chemistry (Kreye et al., 2013).
Coppola et al. (2013) studied a reaction process for bromobenzyl TosMIC in the presence of organolithium bases, that involves a six-membered ring heterocyclization reaction, followed by an isocyanide-cyanide rearrangement and subsequent formation of 2,3-dihydroindenimines, which are able to rearrange to cyano derivatives. The authors concluded that the isocyanide function can undergo alpha additions and acid alpha carbon atom and the sulfonyl group in the alpha position can increase the acidity of the alpha-carbon. This process may represent a new synthesis of aromatic nitriles by rearranging isocyanide-cyanide in the heterocyclization process.
Touchet et al. (2013) proposed a new route for the synthesis of α- isocyanate by sigmatropic rearrangement, from boron compounds. Initially, the authors synthesized carbamate from 3-butyn-2-ol, pinacolborane, potassium bisulfate, methanol and water. The carbamate was then converted to the isocyanate by reaction with carbon tetrabromide, triphenylphosphine and in methylene chloride. Until now alternative methods are not selective enough, at competitive cost for phosgene replacement, and that can be produced on a large scale.

3. New routes: Transcarbamylase, blocked isocyanates, non-isocyanates

In the polyurethane chemistry, having the isocyanate as one of the monomers is clearly the versatility of urethane and urea linkages in addition to the higher reactivity of the isocyanate. Due to the high toxicity of isocyanates, several studies have emerged in order to replace the isocyanate monomer in the polyurethane synthesis reaction to suit the environmental and safety standards.
A recent strategy is the transcarbamylase, aiming the synthesis of polyurethane using as the polyol monomer and a urethane diol.
The technology of blocked isocyanates is another strategy that enables the blocking of the isocyanate function in order to remove them from the formulation and then the isocyanate functional is regenerated by heating to high temperature. This presents some advantages like marked reduction of moisture and water sensitivity but due to this process, the reactivity of isocyanate groups is reduced. Ranjbar et al. (2010) used the technology of blocked isocyanates and prepared four blocked types of isocyanates, from HDI, MDI, IPDI and TDI using diethylene glycol monobutyl ether (DEGMBE). The deblocking process was obtained by temperature and it was found that aromatic diisocyanates were deblocked at lower temperatures than aliphatic diisocyanates.
Another strategy is to use the called polyurethane NIPUs, which obtains polyurethane by reaction between cyclic carbonates, which are non-toxics and biodegradables, and an amine or polyamine. It is necessary to add a catalyst to enhance the reaction rate and selectivity (Guan et al., 2011). The material presents no toxicity, but the reaction rate is slow, and the reactivity is reduced. Properties of chemical and mechanical resistance are affected compared to acidic and alkaline solutions. In addition, the thermal stability of the material must be improved. The isocyanates functions may reappear in the material, because the reversibility of urethane linkage by some later stage such as heat treatment. Bahr and Mulhaupt (2012) synthesized PUs based soy and linseed oil with carbon dioxide via NIPUs. Oils were cured with 1,2 ethanediamine (EDA), 1,4-butanediamine (BDA) and isophoronediamine (IPDA), and NIPUs were obtained. Thermal and mechanical properties were available and PUs presented dimensional stability and stiffness, and the route was considered interesting based on renewable resources and carbon dioxide.

The chemistry of polyurethanes making use of isocyanates is old but is most promising technique and proposes several challenges in the areas of chemistry and materials science. The strategies mentioned may be alternatives, but several other secondary reactions occur and unwanted by-products.

4. Conclusions

This review summarizes the major issue of isocyanates applied as monomers to biomedical polyurethanes, due to high toxicity of the isocyanate. The choice between aromatic and aliphatic isocyanates is also a determinant factor, due to cost and influence on the toxicity of the final PU. It is clear that alternative routes to produce isocyanate by replacing phosgene are necessary. Several existent techniques, as transcarbamylase, blocked isocyanates, and non-isocyanate polyurethanes are alternative routes, but there are still superficial and may be several secondary reactions and unwanted by-products, in addition to the change of the chemical and physical properties of polyurethanes. The polyurethane chemistry making use of the isocyanate is the most promising technique and proposes several challenges in the field of biomaterials.

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