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Hydrophilic Polyurethanes: A Brief Review from the Synthesis to Biomedical Applications

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ABSTRACT

In this work we present a brief-review on the state of the art of hydrophilic or waterborne polyurethanes from their synthesis to their applications in biomedicine. The fundamentals of the synthesis are analyzed starting with the chemistry of isocyanates, structure-property relationship, most common commercially available reagents, and the isocyanate blocking reactions. Then, the applicability of polyurethanes in biomaterials is studied focusing on the formulation of hydrogels for wound healing and tissue engineering, as well as drug delivery applications.

Keywords: Waterborne polyurethanes; Isocyanates; Drug release; Hydrogels; Biomedicine.

1. Introduction

Polyurethane is one of the most popular synthetic polymers and widely employed in biomedical fields owing to the excellent biocompatibility, hemocompatibility, controlled degradation and mechanical stability. Polyurethanes are easily prepared and their mechanical properties such as durability, elasticity, elastomer-like character, fatigue resistance, compliance, or tolerance in the body during the healing, they can be mediated by modifying the chemical structure [1]. Waterborne polyurethane is rapid growing segment of the polyurethane (PU) industry due to the increasing worldwide concern about the environmental conditions caused by the volatile organic compound content in traditional polyurethane coatings [2]. As we can see, these polyurethane formulations were developed initially as a greener alternative for coatings technologies. However, their characteristics such as the absence of toxic organic solvents and hazardous chemical make possible to apply them for biomaterials design and preparation.

The stability of aqueous polyurethane dispersions is achieved by introducing internal emulsifiers and employing water as dispersant. Internal emulsifiers are diols with ionic groups, including carboxylate, sulfonate, or quaternary ammonium salt, or non-ionic groups like poly ethers. These groups provide hydrophilic character, and they play an important role in the surface properties of polyurethanes [3-4].

Considering the current relevance of waterborne polyurethanes in the field of biomaterials and tissue engineering, in this work we present a brief review of the state of art of hydrophilic polyurethanes starting from the fundamentals for polyurethane synthesis as well as their recent applications for biomaterials design, particularly hydrogels for wound healing and drug release applications.

2. The chemistry of isocyanates

2.1. Materials

Isocyanate is the functional group –N=C=O which is an isomer of cyanate group (–O–C≡N). Any organic compound which contains an isocyanate group could also be referred as an isocyanate and those ones that contain

two isocyanate groups are called diisocyanates. The industrial synthesis of isocyanates is carried out by the phosgenation of primary amines. There are other applicable methods to the synthesis of isocyanates, but they are useful only at laboratory scale. Figure 1 shows the reaction between a primary amine and phosgene to yield an isocyanate with the elimination of two molecules of HCl.

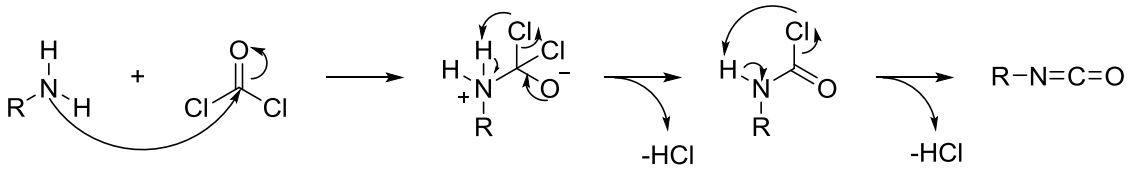

Figure 1. Phosgenation reaction of amines to generate isocyanates

The isocyanate group has a linear geometry, and the carbon atom has a *sp* hybridization forming two σ bonds with the nitrogen and oxygen atoms, and two π bonds with the same atoms, respectively. Due to the carbon atom's low electron density, this atom has an electrophilic character. The isocyanate group is very reactive and is attacked by nucleophiles such as alcohols, amines, and water.

The most important application of diisocyanates is the synthesis of polyurethanes and polyureas. Diisocyanates react with polyols (compounds with two or more -OH groups) and polyamines (compounds with two or more primary amine groups -NH_2) under mild conditions yielding prepolymers like polyurethanes or polyureas, respectively. These prepolymers can be extended by an amine or alcohol of larger hydrocarbon chain to form the terminal polyurethane/polyurea. The formation of urethane and urea groups takes place by a two-step mechanism consisting of a nucleophilic addition followed by a transposition (Figure 2).

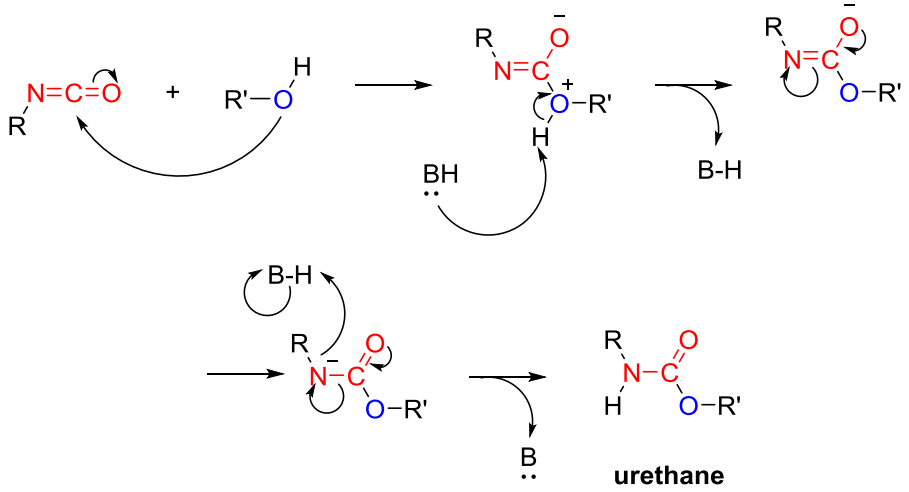

Figure 2. Mechanism for the reaction between an isocyanate and an alcohol to yield a urethane (in the presence of a base as a catalyst)

Commonly, a base such as a tertiary amine or organotin compounds are used as catalysts to carry out this reaction. From the point of view of the polymer chemistry, this reaction follows a step polymerization mechanism where the molecular weight of the polymer increases step by step. A polyurethane chain is considered a block copolymer. Where there are flexible segments (associated with the polyol) and hard segments (associated with the diisocyanate). During the copolymerization reaction, the architecture of the final polyurethane can be adapted by

modifying the molar ratio of the monomers used as well as their addition times; other methodologies involve using monomers with active functional groups to graft and have a diversity of chemical structures of polyurethanes.

3. Design of polyurethanes, structure-property relationship

3.1. Diisocyanates

Commercially available diisocyanates can be classified as aromatics and aliphatics. Further, those diisocyanates containing aliphatic but cyclic moieties are named alicyclic. The correct selection of the diisocyanate precursor is essential to obtain the desired properties in the final product. Figure 3 shows the structures of some common commercially available diisocyanates. Since chain stiffness is decisive for the mechanical properties of polymers, aromatic rings in hard segments leads to an increase in the rigidity of polymeric chains [5].

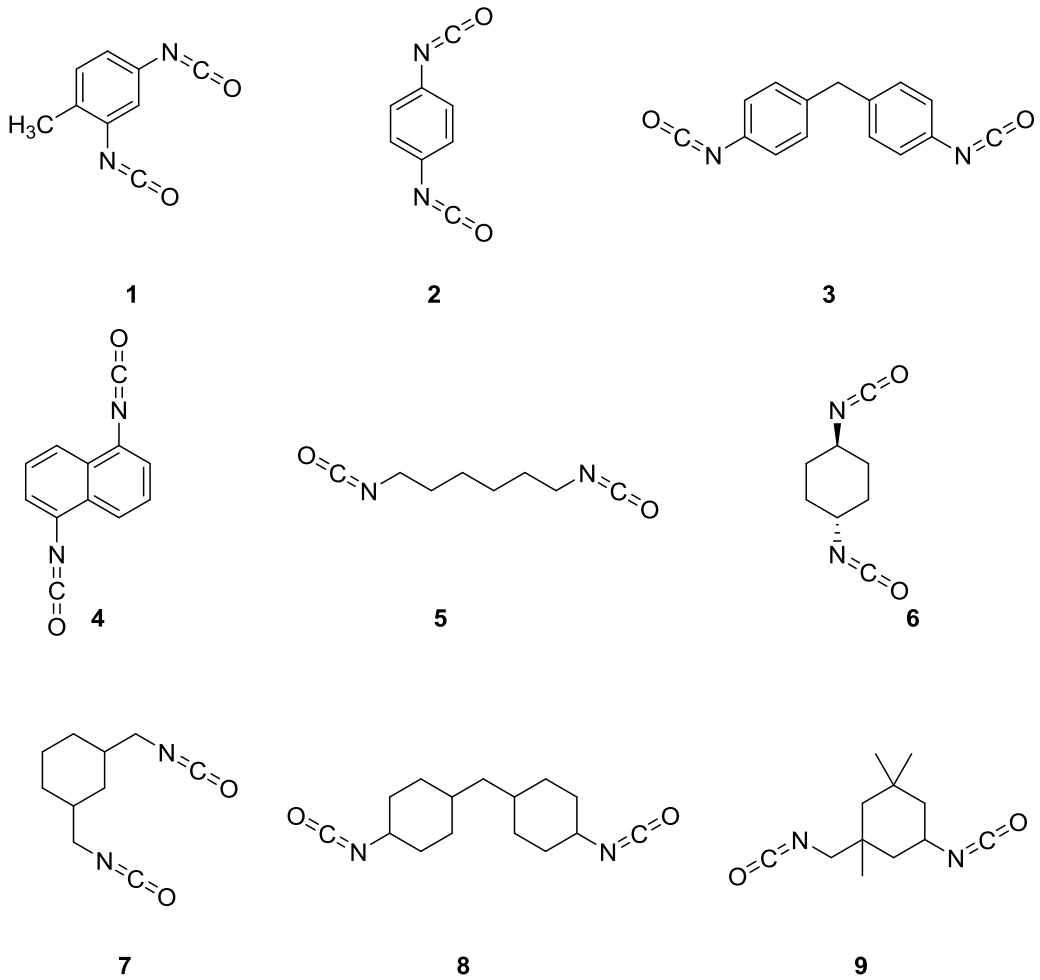

Figure 3. Commercially available diisocyanates for synthesis of polyurethanes

Further, aromatic isocyanates are more reactive toward -OH (from polyols) groups than the aliphatic species. Aromatic polyurethanes are synthesized from aromatic diisocyanates such as 2,4-diisocyanatotoluene (**1**), 1,4-diisocyanatobenzene (**2**), bis(4-isocyanatophenyl)methane (**3**), or 1,5-diisocyanatonaphthalene (**4**). Nowadays, aromatic diisocyanates are practically uniquely used for polyurethane foams production, since the mechanical properties of aromatic isocyanate-based polyurethanes are generally better than aliphatic isocyanate-based polyurethane foams [6].

Aliphatic diisocyanates increase the mobility of chains of the resulting polyurethane as well as the permeability [5]. The most flexible diisocyanate commercially available is 1,6-diisocyanatehexamethylene (**5**). Further, polyurethanes made from aliphatic diisocyanates are more resistant to ultraviolet radiation, whereas those made from aromatic diisocyanates undergo photodegradation. Also, polyurethanes based on aromatic diisocyanates have shown less biocompatibility than those synthesized from aliphatic diisocyanates, caused by toxic degradation products (aromatic amines) [7].

Polyurethanes based on alicyclic diisocyanate show better mechanical performance than the less rigid and completely linear aliphatic polyurethanes. Alicyclic diisocyanates **6** y **7** are structurally related with **2**; while diisocyanate **8** is a completely hydrogenated analogue of **3**. The decreased chain flexibility of alicyclic diisocyanates compared to linear aliphatic ones was proposed to increase modulus and tensile strength [8].

In general, diisocyanate chain symmetry is an important factor for the hard segment structure of polyurethanes [9]. Alicyclic diisocyanates **7** y **8** are completely symmetrical, while isophorone diisocyanate (**9**) is asymmetric. Also, methyl groups of **9** increase the steric hindrance and decreases the flexibility of the polymer chains. Polymers with two symmetrical diisocyanate moieties in the hard segment (**8**), regardless of aromatic or aliphatic origin, display higher crystallinity and hence higher strength [10]. Thus, polyurethanes synthesized from **8** have higher tensile strengths compared to polymers derived from **5** or **9** with the same hard segment content [11].

3.2. Polyols

Polyols used in polyurethane manufacture are divided in low molecular weight polyols and oligo-polyols (Figure 4). The first group include those compounds with two or more hydroxyl groups with low and monodisperse molecular weight, they are studied commonly in organic chemistry. Some examples include ethylene glycol (**10**), propylene glycol (**11**), diethylene glycol (**12**), dipropylene glycol (**13**), butane-1,4-diol (**14**), neopentylglycol (**15**), triethanolamine (**16**), glycerol (**17**), and isosorbide (**18**).

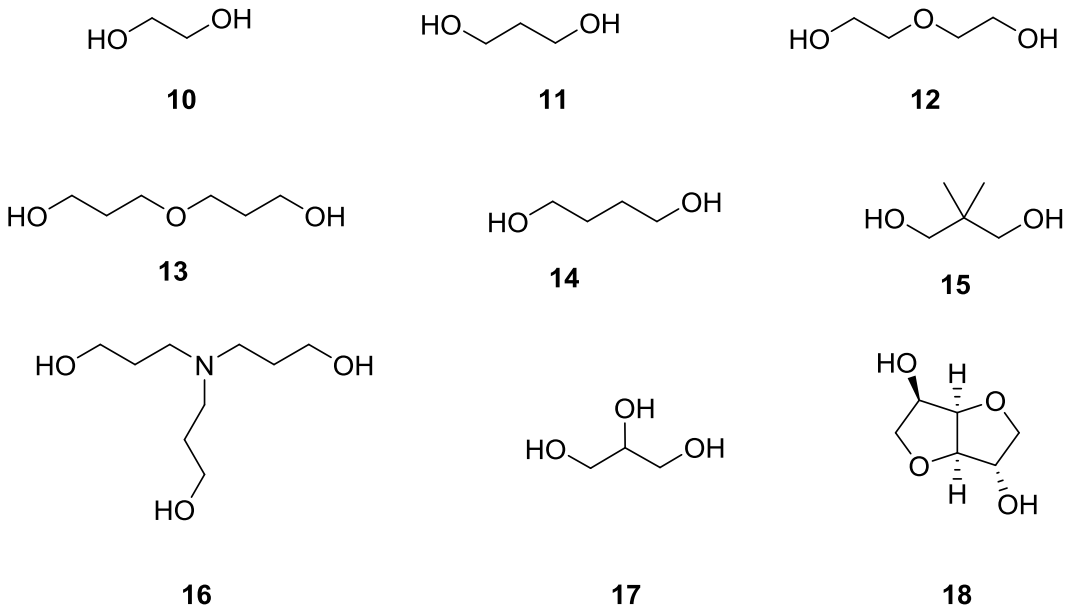

Figure 4. Commercially available low molecular weight polyols

Oligo-polyols are those polyols which are low molecular weight polymers (maximum 10 kDa) with terminal hydroxyl groups (**Figure 5**). Typical examples include the polymerization products of ethylene oxide and propylene oxide named poly(ethylene glycol) (PEG, **19**) and poly(propylene glycol) (PPG, **20**), respectively. Also, the product from the reaction of glycerol with ethylene oxide, glycerol ethoxylate (**21**) is another polyol suitable for polyurethane synthesis.

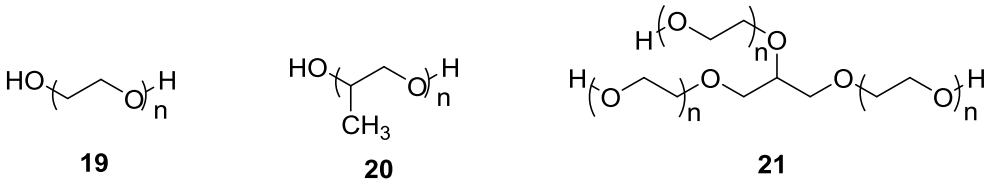

Figure 5. Commercially available polyols for synthesis of hydrophilic polyurethanes

Recently, vegetable oil-based polyols have been proposed to confer biodegradability and biocompatibility to polyurethanes, indispensable properties for medical and biomedical applications. However, they are often mixed with petrochemical-based polyols to improve the thermal and mechanical properties of polyurethane [12]. Palm and castor oil are the most common vegetable oils used for the synthesis of biocompatible polyurethanes. However, they are not employed as extracted, but they are chemically modified and functionalized by transesterification [13-14], epoxidation [12], silanization [15], etc.

From the physicochemical point of view, by increasing the flexible regions of the polyurethane (related to the polyol) and decreasing the rigid regions (related to the diisocyanate), polyurethanes are designed showing an elastomeric behavior, these polymers are characterized by a glass transition temperature (T_g); while if the rigid regions of the PU are increased (by increasing the diisocyanate content), polymeric chains with higher molecular order are formed, generating semi-crystalline structures with higher mechanical resistance, and these polymers are characterized by a specific melting temperature (Tm). In this way, by varying the molar composition of polyol/diisocyanate ratio, both the mechanical and thermal properties of the designed polyurethanes can be adapted.

4. Blocking urethane groups

A blocked isocyanate is the reaction product of a diisocyanate or isocyanate-terminated prepolymer in which the isocyanate functionality has been reacted with a 'blocking agent'. The general reaction for preparing blocked isocyanates is shown in **Figure 6**. Once 'blocked', the diisocyanate can be mixed with polyols or certain chain extenders, and these materials will not react at room temperature [16]. A formulation containing a blocked isocyanate have extended storage stability by minimizing moisture sensitivity of the system.

Table 1 shows some common blocking reagents for isocyanates with their respective deblocking temperatures (and the general reaction mechanism is presented in **Figure 7**). However, these values are reported for the self-condensation of polyurethane without any chain extensor. Sodium bisulfite is frequently used in waterborne coatings as the blocked product is water soluble, as well as being relatively cheap with no pollution [17]. Deblocking sulfite-blocked isocyanates is pH depending on and it is favorable at high pH values (or slightly

alkaline conditions) [18]. Thus, sulfite-blocked polyurethanes can react easily with polymers containing primary amine groups forming urea groups. This reaction follows the typical mechanism of an acyl nucleophilic substitution, and it can be carried out at low temperature (37 °C approximately).

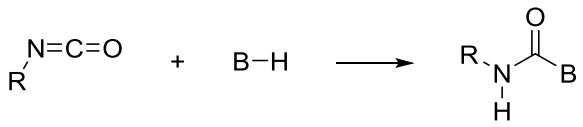

Figure 6. General reaction between an isocyanate with a hydrogen active blocking agent

Table 1. Selected blocking agents and their corresponding deblocking temperature ranges (modified from [19])

Blocking reagent	Examples	Deblocking temperature (°C)
Phenols	Phenol, *o*-cresol, *p*-chlorophenol	60-180
Amides	Acetanilide, *N*-methylacetamide	100-130
Imidazole and derivatives	Imidazole, 2-methylimidazole, 2-phenylimidazole	120-290
Cyclic amides	ε-caprolactam, pyrrolidone	70-170
Hydroxamic acid esters	*N*-(benzyloxy)methacrylamide	50
Other	Sodium bisulfite	40-160

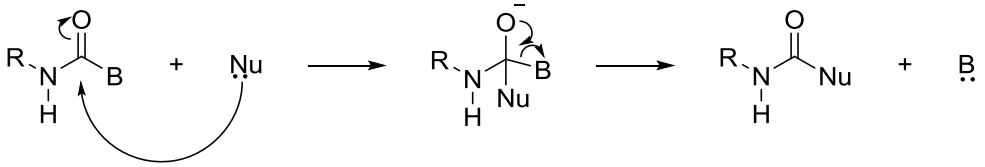

Figure 7. Deblocking reaction of a blocked-isocyanate

5. Biomedical applications of polyurethanes

5.1. Polyurethane hydrogels with biomedical applications

Until now, we have described the fundamentals for the synthesis and design of polyurethanes. Now we will describe how these polyurethanes are applied in biomedicine. Conventionally, fossil-based polyurethanes were applied in biomedicine such as non-implantable devices, long-term implants, and short-term implants generating vascular fillings, synthetic arteries, artificial respiration devices among others. Currently, biobased polyurethanes are used as non-implantable devices including wound dressings formed by foams, fibers of films; long-term implants such as scaffolds for hard and soft tissues; short-term implants useful for drug delivery and tissue adhesives [20]. Also, polyurethanes with antibacterial properties are employed for antibacterial catheters. These materials can prevent the growth of important pathogens such as Escherichia coli, Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa [21]. The applicability of polyurethanes in the

biomedical field is increasing due to the implementation of emerging processing techniques such as 3D-printing [22], where PU with low melting and/or softening temperatures are required for an optimal process, which is in constant development, and the design of polyurethanes with advanced properties like self-healing properties conferred by charge transfer interactions [23-24]. Considering that the human body is composed mainly of water (about 70% wt.) hydrogels are suitable for biomedical applications due to high water-absorption capacity of these materials. Some examples of polyurethane-based hydrogels and their applications in biomedicine are shown in Table 2.

Table 2. Polyurethane-based hydrogels for biomedical applications.

Isocyanate	**Polyol**	**Performance**	**Application**	**Reference**
L-lysine diisocyanate	Glycerol or poly(ε-caprolactone)	Considerable water uptake (~60%), strength above of 3 MPa, advisable modulus (0.9~1.7 MPa), high elasticity (above 700%), good biodegradability and biocompatibility. Hydrogen bonds served as reversible sacrificial bonds in the PU hydrogels endow them good toughness with partial hysteresis during deformation.	Antiadhesive membranes and catheters	[25]
Isophorone diisocyanate	Polycaprolactone-diol	The polyurethane shows dual stimuli response towards light and heat, representing a smart PU.	Bioprinting of soft tissues	[26]
1,6-hexamethylene diisocyanato	Poly(ethylene glycol) and polycaprolactone	The introduction of PEG into the polyurethane hydrogels improved the hydrophilicity. The hydrogels have a microstructure with interconnected porosity, and they are not cytotoxic.	Controlled release drug systems and tissue engineering scaffolds	[27]

1,6-hexamethylene diisocyanato	Poloxamer® 407, *N*-Boc diethanolamine	Hydrogels showed intrinsic antifungal and antibacterial activity against *C. albicans*, *S. aureus*, *E. coli*. They showed good injectability and capability to retain shape post-injection.	Multifunctional injectable delivery systems for mini-invasive wound treatment	[28]
1,6-hexamethylene diisocyanato	Poloxamer® 407, *N*-Boc diethanolamine	The polyurethane shows multi-responsive behavior and amphiphilic character. Changes in the dynamic micellar diameter were observed by changes in temperature, pH, and they are photoreactive.	Potentially, thermo-sensitive and photocurable bio-inks or post-injection cross-linkable thermo-sensitive systems or hydrogels with improved cell-adhesiveness	[29]

6. Polyurethane and biopolymers-based hydrogels

Polyurethanes for biomedical applications should have good biocompatibility and physical properties mimicking the tissues they are replacing. The chemical composition and topology of the polymer backbone alter the degradation properties. Regularity of the synthetic polymer chain creates crystalline regions, limiting the polymer chains to degradative agents [22]. Polyurethanes have found several applications in biomedicine, including antibacterial surfaces and catheters, drug delivery vehicles, stents, surgical dressings/pressure sensitive adhesives, tissue engineering scaffolds and electrospinning, nerve generation, cardiac patches, and PU coatings for breast implants [21].

Aqueous isocyanate-blocked polyurethane dispersions have been successfully applied as crosslinking agents for collagen reacting with primary amine groups under mild reaction conditions (37 °C, neutral pH) forming urea groups (**Figure 8**) [30]. They were synthesized from poly(ethylene glycol) and 1,6-hexamethylene diisocyanate or isophorone diisocyanate, and sodium bisulfite as the blocking agent. However, recently polyurethanes obtained from glycerol ethoxylate and the same diisocyanates have been shown a high reticulation capacity modulating the chemical and mechanical stability, as well as the degradation rate, and conserving a high biocompatibility [31]. The reactivity of these waterborne polyurethanes has been applied for the collagen crosslinking forming hydrogels with high water absorption capacity (higher than 2000 %). This reaction is not affected by the presence of another polymer in the reaction mixture. This way is possible to obtain semi-interpenetrating networks (semi-IPN). The

collagen crosslinking reaction is compatible with several natural polymers such as guar gum [32], alginate [33], chitosan [34], and starch [35]; as well as synthetic polymers like polyacrylate [36]. Also, these formulations are versatile enough to incorporate inorganic materials like silicon oxide inside the polymer matrix [37].

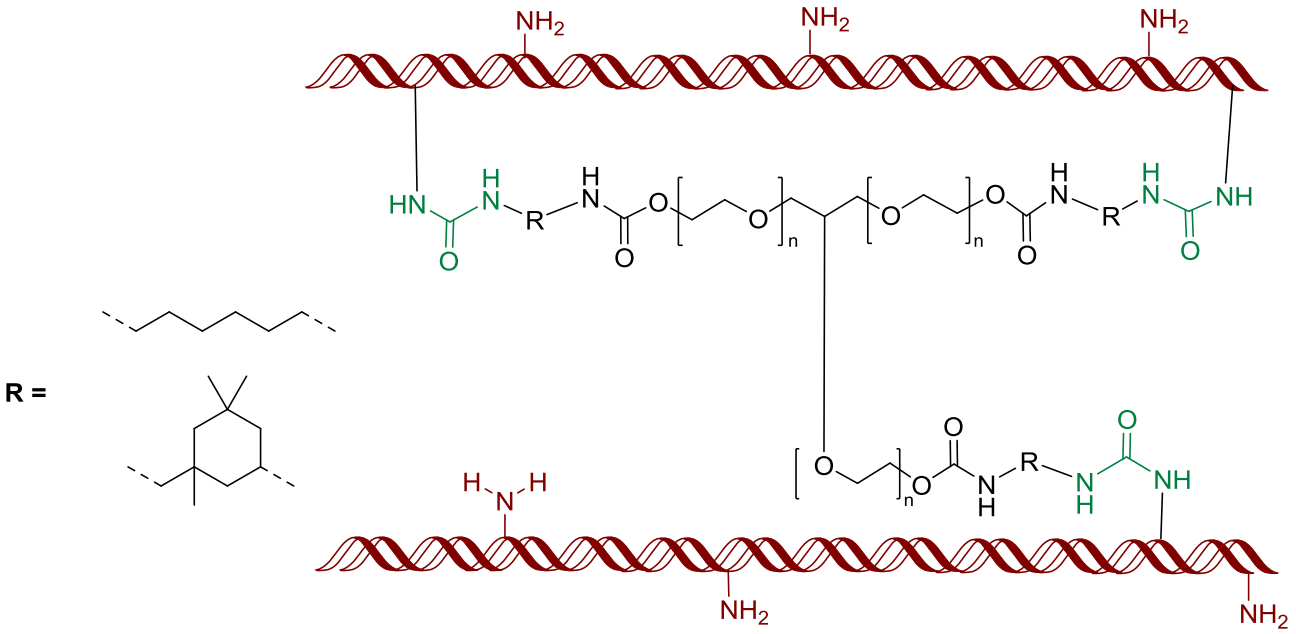

Figure 8. Schematic representation of collagen crosslinked by polyurethane

Further, this type of polyurethanes can react with carboxylate groups forming urea groups as it was observed in the alginate crosslinking [38]. The generation of these hydrogels based on biopolymers such as proteins and carbohydrates crosslinked with polyurethane allows to tailor the cellular metabolism for chronic wound healing strategies, thus designing smart hydrogels that could be used as healing wound dressings.

7. Drug-release vehicles

Drug release from polyurethane-based vehicles can occur by several mechanisms such as solute diffusion, polymer swelling, polymer erosion, and polymer degradation. The release by solute diffusion takes place following the Fick's law of diffusion transporting drug molecules from a polymer matrix to the outer medium. The swelling mechanism depends on the chemical structure and mechanics of 3D network of the polyurethane, mainly on the number of electronegative atoms and the reticulation degree.

When the polymer matrix swells, the mobility of the polymer chains and drug molecules increases, improving the releasing rate. Erosion and degradation of the polymer matrix facilitate the drug release when the PU is subjected to hydrolytic or proteolytic conditions. The first consist in the progressive loss of mass, and the seconds consist in the cleavage of the polymer chains forming oligomers and monomers, involving the generation of polar sites that facilitate their rupture in presence of water [7].

Generally, the above-mentioned mechanisms do not occur independently, and they can be simultaneously. With the aim to modulate the drug release rate of polyurethane vehicles, several formulations have been designed. Some of they are shown in Table 3 including the encapsulated drug and the enhancement achieved.

Table 3. Polyurethane-based drug release vehicles

Isocyanate	Polyol	Encapsulated drug	Performance	Reference
L-lysine diisocyanate methyl esther	Chitosan, melamine-based Schiff base	5-fluorouracil	Higher loading and releasing performance compared with 1,6-hexamethylene diisocyanate and isophorone diisocyanate-based polyurethanes.	[39]
Hexamethylene diisocyanate	Poly(ethylene glycol), polycaprolactonetriol	Sodium diclofenac	Efficient and quick load of hydrophobic drugs. Loaded polyurethane swelling in acidic media promotes drug precipitation that minimizes its release, allowing a further selective delivery in neutral or basic pH media.	[40]
Prepolymer synthesized from poly(tetramethylene glycol) and hexamethylene diisocyanate	Dextrin	Dexamethasone	Real efficacy of the controlled drug release from the injectable hydrogel with significant melanoma suppression without any side effects.	[41]
4,4-diphenylmethylene diisocyanate	Gyrothane 639	Diclofenac	The contribution of the other mechanisms apart from diffusion	

			increases with the flow rate and as the percentage of drugs.	
Hexamethylene diisocyanate	Isopropyl ricinolate diol, Pluronic p-123, and phosphatidylcholine-based diol	Neomycin sulfate	The release profiles manifested a rapid diffusion and a polymer relaxation mechanism, which control the release of the drug.	[42]
Poly(azomethine urethane) (PAMU)	Poly(vinyl alcohol)	5-fluoroacil	5-fluoroacil loading and release performance of the hydrogel samples were increased with the increase of PAMU content in the hydrogel matrix. These results could be attributed to the higher swellability and more porous structure of PAMU containing in hydrogels.	[43]
Tecoflex EG 85 A	Dextran	Curcumin	Membranes exhibited pH-controlled drug release potency and synergistic antibacterial activity against *gram-positive* bacteria.	[44]

Tetramethylene glycol/bis(4-isocyanatephenyl) methane prepolymer	α-cyclodextrin	Paclitaxel	Functionalization with polyurethane alter the hydrophilicity of cyclodextrin ring. Sustained drug delivery is achieved using functionalized copolymer. A significant suppression of tumor volume using drug embedded in graft copolymer was observed.	[45]

8. Conclusion

The design and application of polyurethanes for biomedical hydrogels requires a suitable selection of diisocyanate and polyol monomers, preferring the non-aromatic diisocyanates and long-chain flexible polyols (like those containing polyether segments). The composition of polyurethanes must provide a good stability in water dispersion to be applicable as a crosslinking agent in the formulation of hydrogels. For this application, it is necessary to block the isocyanate end-groups of polyurethane prepolymer to avoid the spontaneous reaction of this with other molecules. Depending on the structure of polyurethanes the physicochemical properties could be tailored allowing to obtain specific characteristics for wound healing or drug release applications.

Declarations

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Competing Interests Statement

The authors have declared that no competing financial, professional or personal interests exist.

Consent for publication

All authors contributed to the manuscript and consented to the publication of this research work.

Availability of data and material

Not applicable.

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