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Polyurethanes for Medical Use
Poliuretani za medicinsko uporabo

Scientific Review/*Pregledni znanstveni članek*
Received/*Prispelo* 10-2016 • Accepted/*Sprejeto* 06-2017

Abstract
Polyurethanes are synthetic copolymers containing urethane linkages in their complex chemical structure. They consist of three monomers: a diisocyanate, a polyol and a chain extender, which enables the synthesis of an endless number of polyurethanes with different physicochemical and mechanical properties. The physicochemical properties of various polyurethanes are largely dependent on the conformation of polyols, which may contain two or more different polyols, stabilisers, catalysts, liquids or solid additives and, in the case of foams, foaming agents. Depending on the structure of the polyols, i.e. the length of the chain, structure of the units (aliphatic or aromatic), ester or ether groups, or functionalisation by hydroxyl groups, polyurethanes may be flexible or rigid, and therefore suitable for various applications. In addition to the physical and chemical structure of polyurethanes, this review paper specifically addresses their use in medicine, particularly in wound dressings, tissue engineering scaffolds and drug delivery with nanoparticles and nanocapsules, and provides guidelines for the development of new biodegradable polyurethane materials.
Keywords: segmented polyurethanes, chemical structure, reactants, medical applications

Povzetek
Poliuretani so v svoji kompleksni kemijski zgradbi sintetični kopolimeri z uretansko vezjo. Njihova sestava iz treh različnih monomernih enot: diizocianatov, poliolov in podaljševalcev verig, omogoča sintezo neomejenega števila poliuretanov z različnimi fizikalno-kemijskimi in mehanskimi lastnostmi. Fizikalno-kemijske lastnosti različnih poliuretanov so odvisne predvsem od konformacije poliolov, ki lahko vsebujejo dva ali več različnih poliolov, stabilizatorjev, katalizatorjev, tekočih ali trdnih aditivov in pri penah tudi penilcev. Poliuretani so lahko fleksibilni ali togi in tako uporabni za različne namembnosti, kar je odvisno od dolžine molekul, alifatske ali aromatske strukture poliolov, prisotnosti estrskih ali eterskih skupin in funkcionalizacije poliolov s hidroksilnimi skupinami. Pregledni znanstveni članek poleg fizikalne in kemijske strukture poliuretanov posebej obravnava njihovo uporabo v medicini, zlasti pri obližih za rane, tekstilijah za tkivno inženirstvo, materialih s kontroliranim sproščanjem zdravilnih učinkovin, nanodelcih ali nanokapsulah, in podaja smernice za razvoj novih biološko razgradljivih poliuretanskih materialov.
Ključne besede: segmentirani poliuretani, kemijska struktura, reaktanti, medicinska uporaba

1 Introduction

For the most part, synthetic polymers have a relatively simple chemical structure, as they are synthesised from one or two monomers, which leads to the formation of homopolymers or copolymers, e.g. polyethylene terephthalate (PET), polytetrafluoroethylene (PTFE), polystyrene (PS), polyethylene (PE), polypropylene (PP), polybutadiene (PBA), etc. [1]. Polyurethanes (PU) differ from the aforementioned substances in that they have a more complex chemical structure, i.e. they contain three monomers: a diisocyanate, polyol and chain extender, which facilitates the synthesis of an infinite number of polyurethanes with different physicochemical and mechanical properties [2]. The density of polyurethanes

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*Tekstilec, 2017, **60**(3), 182-197*
DOI: 10.14502/Tekstilec2017.60.182-197

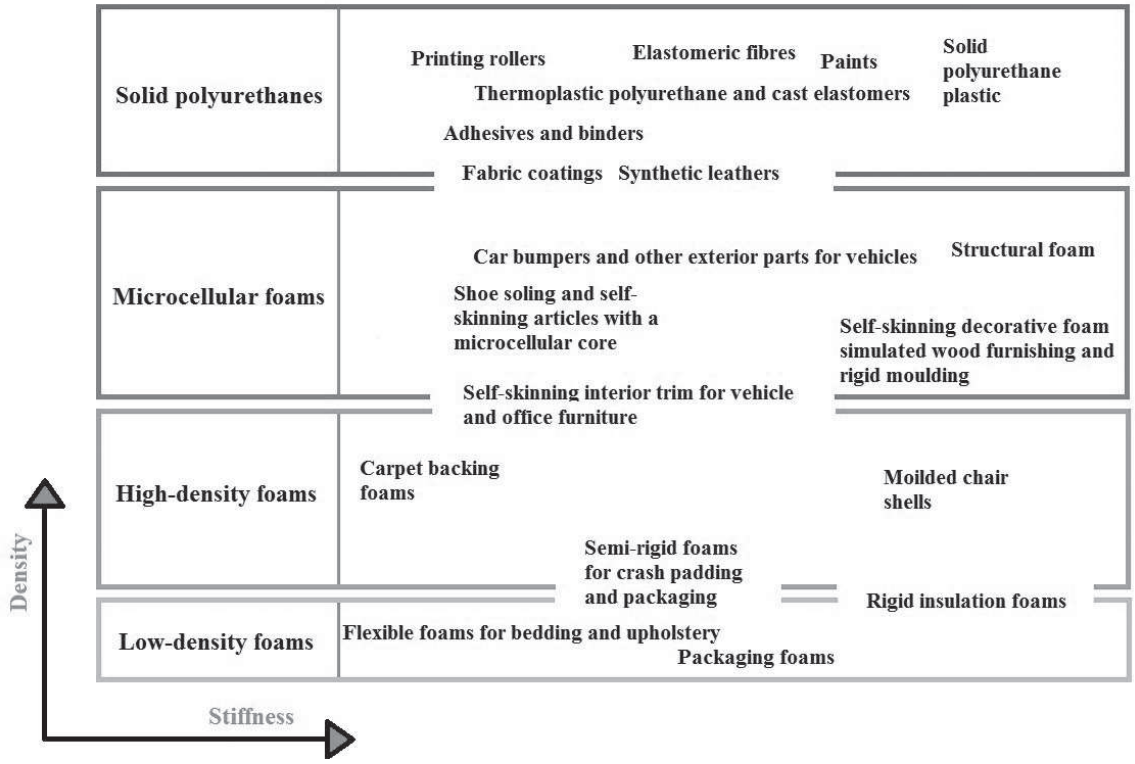

Figure 1: Spectrum of polyurethanes with regard to their density and stiffness

may range from 6 to 1220 kg/m^3, while their hardness ranges from 24 units (acc. to Shore A) to 80 units (acc. to Shore D), representing materials from extremely flexible elastomers to extremely rigid and hard plastics (Figure 1) [3–5].

The possible uses of polyurethanes are endless, while they are also the best choice of materials for certain specific applications. One of those applications is polyurethane packing foam for protection during transport or hard thermal insulation foam used for household appliances. With an excellent strength-to-weight ratio, good insulation properties, durability and versatility, polyurethane is a commonly used material in construction. In the manufacture of automobiles, polyurethanes reduce a car's weight and increase fuel economy, comfort, corrosion resistance, and thermal and acoustic insulation. They are used as liners or coatings in the manufacture of floor coverings, and in furniture production primarily in the form of flexible foams that ensure upholstered furniture is more durable, comfortable and supportive. Polyurethane foam is used in vessels for acoustic and thermal insulation, strength and increased carrying capacity with minimum weight. Polyurethane epoxy resins, which are used as coatings on vessels, also provide protection against water, weather conditions and corrosion, and have an impact on hydrodynamics [6].

Polyurethanes are also used extensively for the production of fibres [7, 8] and membrane materials, and for coatings on textiles. Polyurethane fibres are (i) highly crystalline fibres of linear structure [9, 10] and (ii) highly flexible segmented elastanes [7]. In addition to being exceptionally elastic, elastane fibres are also light, soft and delicate, with good dyeing characteristics, and are resistant to wear, sweat and detergents [11]. Polyurethane membrane materials are commonly used as intermediate layers in a variety of high-tech, multi-layer textile polymer composite systems, where they provide air and water impermeability, while demonstrating permeability for humidity [12, 13].

Medicine represents an important area of application for polyurethanes. The first use of polyurethanes for medical implants was proposed by Boretos and Pierce in 1967 [14]. Use later spread to other areas of medicine, including dressings for wound healing [14]. New advanced polyurethane materials for wound dressings are based on good biocompatibility, but should demonstrate an appropriate level of

biological activity (hydrophilicity, absorbency of exudates from a wound, establishment of an appropriate humidity level on a wound, good mechanical properties, gas permeability and antimicrobial activity) that would speed up the wound healing process.
A great deal of attention is also focused on the replacement of raw materials for the synthesis of polyurethanes. Polyols, which are obtained from petroleum fractions, are being replaced by materials derived from naturally renewable resources.

2 Chemical structure of polyurethanes

Polyurethane is a general name for a family of synthetic copolymers containing urethane bonds in a repeated chemical structure [2, 3]. Segmented polyurethanes are represented by three essential components in the following form:

$P\text{-}(D(CD)_n\text{-}P)_n$,

where P is a polyol, D is a diisocyanate and C is a chain extender. Polyol is an oligomeric macromonomer, which includes a flexible chain with hydroxyl (-OH) groups. A chain extender is generally a small molecule with hydroxyl or amine groups. An isocyanate is a component with a low molecular weight that is able to react with either the polyol or chain extender, leading to interesting segmented polyurethane structures [2, 3, 15, 16].
The basic principle of the chemical reaction in polyurethane synthesis is the formation of a urethane bond, i.e. a reaction between an isocyanate and a hydroxyl group [2, 3].

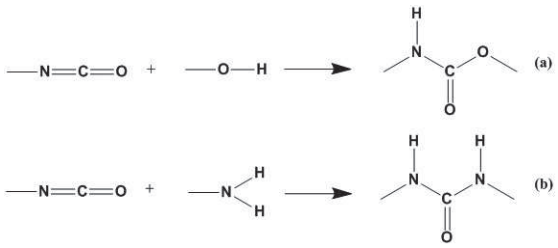

Figure 2: Reaction of a chain extender (diol or diamine) with an isocyanate: (a) if the chain extender is a diol, urethane is formed; (b) if a diamine is used, urea is formed

Linear polyurethanes are formed through the reaction of bifunctional compounds. For branched and cross-linked polyurethanes, multifunctional polyols, isocyanates and even chain extenders are included in the molecule [2, 3].
The reaction between the chain extender (diol or diamine) and the isocyanate is shown in Figure 2. If a diol is used as the chain extender, urethane forms as shown in Figure 2a; if a diamine is used as the chain extender, urea is formed as shown in Figure 2b [2].
The reaction of water with an isocyanate is important in the synthesis of polyurethanes. Isocyanates are highly reactive and react with hydrogen almost immediately [2, 17]. When water is used as a chain extender, the product of the reaction is CO_2 gas, which is used in the production of polyurethane foams [18]. Gas reduces the density of the product; through the appropriate stoichiometric water-to-isocyanate ratio, it is possible to create foams with a density ranging from <16 kg/m^3 (cushioning materials) to 560 kg/m^3 (footwear) [17].

3 Reactants for the production of polyurethanes

The final properties of polyurethane are largely dependent on the chemical and physical nature of the synthesis components [2, 16]. While many combinations of diisocyanates, macro diols and chain extenders are possible for polyurethane synthesis, only a few are used for medical applications [14].

3.1 Polyols

Conventional polyols are usually polyethers (having the repeating structure -R-O-R'-) or polyesters (having the repeating structure -R-COO-R'-) with a molecular weight that typically ranges from a few hundred to a few thousand. At room temperature, they may take a liquid or solid form, depending on their molecular weight. Because of the aliphatic structure and poor intermolecular interactions, in particular with polyols, which are rich with ether bonds, polyol molecules are easily turned and twisted. For this reason, they are a soft material; the polyol sequence in the segmented block copolymer thus relates to soft segments [2, 15]. Until recently, the majority of medical polyurethanes was synthesised from poly (tetra methylene oxide) (PTMO).

New polyols are being developed for biomedical and industrial applications, such as polyalkyl polyols, polydimethylsiloxane polyols or polycarbonate polyols [2, 14, 15].

3.2 Isocyanates

The most important isocyanate used in the production of polyurethanes is diisocyanate, comprising of two isocyanate groups (R-NCO) per molecule. The use of multifunctional isocyanates leads to the formation of a network or cross-linking. Because of strong intermolecular interactions, the segments formed by isocyanates and chain extenders are stiffer than polyols, are typically vitreous at room temperature and for that are called hard segments [2, 15].

Diisocyanates may be aromatic or aliphatic. Some commercially important diisocyanates are shown in Figure 3. They are Hexamethylene diisocyanate and derivatives thereof, Naphthalene 1,5-diisocyanate, Triphenylmethane-4,4'4"-triisocyanate and Trimethyl-heksa-methylene diisocyanate (TMDI) [3]. Diphenylmethane-4,4'-didsocyanate (MDI) is often used for the synthesis of medical polyurethanes due to its easy handling, symmetric structure and high reactivity [17]. Hydrogenated MDI and trans-cyclohexane-1,4-diisocyanate are used less frequently for medical purposes [17]. Another equally or even more industrially important diisocyanate is toluene methyl diisocyanate (TDI), which is also aromatic by nature [2, 18].

It should be noted that isocyanates are toxic, particularly to the respiratory system. They are highly reactive compounds. Their carbon atom is a strong electron acceptor, while their nitrogen atom is a strong electron donor and their oxygen atom is a bad electron donor [3].

Despite the popularity of the use of aromatic isocyanates for medical polyurethane synthesis, it is a well-known fact that the in vivo degradation of aromatic diisocyanates leads to the formation of carcinogenic aromatic amines. For this reason, recent studies addressing the synthesis of medical polyurethanes avoid aromatic isocyanates and replace them with aliphatic [19, 20].

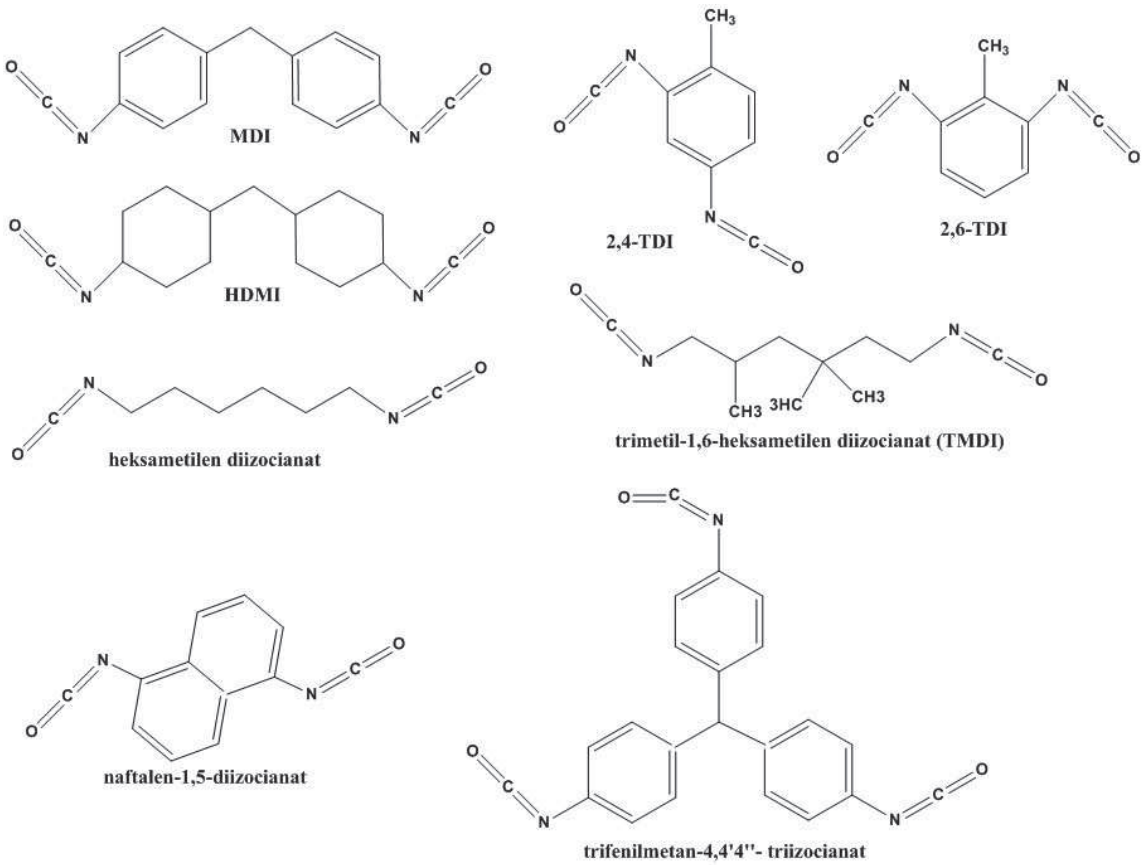

Figure 3: Some of the most important isocyanates

3.3 Chain extenders

The product generated as a direct result of the reaction between a polyol and diisocyanate is a soft rubber with poor mechanical strength. These properties may be improved through the addition of a chain extender, which is most frequently a molecule with a low molecular mass (<400), such as 1,4-butandiol, etc. The roles of the chain extender include the guidance of growth, the organisation of the chain and the dissemination of sequences in the copolymer, consisting of a reciprocating chain extender and diisocyanate. These extended segments act as physical cross-linkers, which increases mechanical strength. If the chain extender is a diol, thermally processable polyurethanes are obtained. If the chain extender is a diamine, polyurethane-urea is obtained [2, 14, 15]. In this process, the polyurethane material is obtained by casting the dissolved polyurethane into a mould and evaporating the solvent.

3.4 Additives for the production of polyurethanes

In the production of polyurethanes, a broad range of additives such as plasticisers (to modify the physical properties of polyurethane products), catalysts (for the control of the reaction between isocyanates and polyols), foaming agents (for the production of polyurethane foams), surfactants (to aid in mixing incompatible components in the reaction mixture), pigments (for adjusting the density of the foam, and UV protection), fillers and flame retardants are also added [3].

3.5 Polyurethanes from renewable resources

Polymerisation reactants to replace reactants derived from raw fossil materials are a relatively new field of research [21]. They mainly comprise natural renewable materials obtained from soybean oil, sunflower oil and canola oil. Non-food sources of polyols, such as algae, vernonia oil, mustard seed oil from Physaria tenella, castor oil [22] and liquefied wood, [23] are also being introduced. Recent studies address the preparation of polyurethanes from glucomannans [24], chitin and chitosan [25], lignin [26], heparin [27], starch [28], collagen [29] and alginate [30], where all of these materials have potential medical applications, including the treatment of wounds.

If, however, the replacement results in deterioration or changed polymer properties, replacement is more problematic and compromises are necessary [21]. Limitations in the effectiveness of obtaining derivatives from vegetable oils have been observed with respect to both foams and elastomers [31]. Some problems can be attributed to limitations related to the chemical structure of the molecular chains in vegetable oils. In order to meet the customer's requirements, the dilution of vegetable oil derivatives with non-vegetable oils is necessary [32].

The first attempts to use vegetable oils in the synthesis of polyesters and polyurethanes were based on the use of ricinoleic acid, which is present in castor seeds, where the low proportion of ricinoleic acid in the seeds, geographical availability and inertia of ricinoleic secondary alcohols represent limitations [33]. The epoxidation of unsaturated vegetable oils from seeds, which was followed by alcoholisation was also investigated, but not very successfully [34]. Recent research has focused on the study of the structural limitations of triglycerides in the seed oil, where the fatty acids are separated to glycerol and fatty acid methyl esters [35].

Recent studies of the structural properties of polyurethanes from seed oils have been intensive, and revealed both the associated potentials and limitations. Ryan et al. have studied the hydroformylation and reduction of fatty acid methyl esters with polyether triols used for further reaction with toluene diisocyanate. The cross-linking density, network design and mechanical properties were analysed [36]. Macosko et al. studied the substitution of soft segments with soy oil (through epoxidation and alcoholisation) in flexible foams. It has been noted that foam properties are highly dependent on polyols based on seed oils [37]. In general, the properties of these materials are inferior when compared to conventional petro-chemical materials, unless they are used as highly diluted additives to products based on petro-chemicals [35].

However, polyols based on seed oils are a promising material in the production of polyurethane elastomers, primarily because of their hydrophobicity. It is known that the modulus and tensile strength of polyurethane elastomers depend on the ability of microstructural separation of hard and soft segments into domains. The rate of such microphase separation depends, *inter alia*, on the thermodynamic incompatibility described by the Flory-Huggins parameter χ between the hard and soft segments. An increase in the hydrophobicity of soft

segments usually leads to greater χ, better phase separation, and therefore high modulus and strength (at a given solid content and the molecular mass of the soft segments). All of these characteristics also depend on the kinetics of the reaction, polydispersity and the method of polyol preparation [35].

Sonnenschein et al. found that reactants from seed oil are more useful when triglycerides are separated into fatty acid methyl esters, saturated components are removed and olefin components are properly functionalised [38]. With the seed oil obtained from genetically modified plants, it is possible to achieve a high proportion of oleic fatty acid and a small proportion of saturated components. For this reason, the aforementioned method seems both economically and practically reasonable [38]. Monomers were obtained through the hydroformylation of oleic methyl esters into corresponding aldehydes, which were hydrogenated to primary alcohols. Those monomers exhibit a very high utility value and versatility, which makes them an excellent replacement for certain applications [39].

4 Structure of polyurethanes

4.1 Segmented polymers

The science of polymers describes the intermolecular arrangement as a geometric relationship between adjacent polymer molecules and their arrangement in a polymeric material. There are three different states of intermolecular arrangements: crystalline, amorphous and segmented. Completely randomly arranged polymer molecules are amorphous, as opposed to crystalline segments built of properly spatially arranged polymer molecules or parts thereof in crystal lattices. Polyurethane elastomers have a two-phase segmented structure, where soft segments separate the hard rigid segments. Hard segments enhance the soft segmentation matrix [40, 41].

An example is a segmented polyurethane elastomer synthesised from polyether [poly (oxytetramethylene)], polyester, MDI and ethylene diamine. In a non-tensile state, spatially separated hard and soft segments are distinguishable. Hard segments are connected into discrete domains by van der Waals interactions and hydrogen bonds. The crystallisation of soft segments is achieved by extending the polymer. This concept is shown in Figure 4a, where the partial crystallisation of soft segments is achieved by elongating the polymer by up to 200%. Crystallisation is increased, as shown in Figure 4b, by further elongating the polymer by 500%.

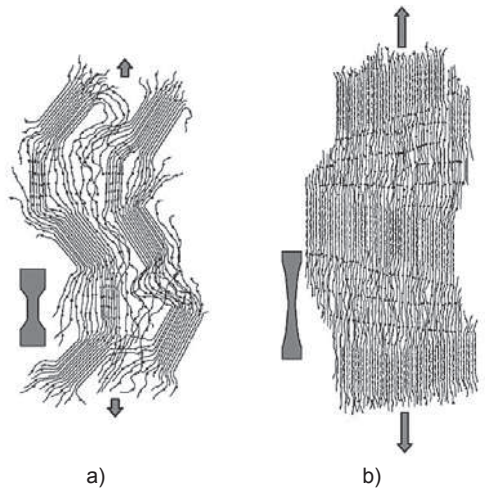

Figure 4: Segmented polyurethane elastomer: (a) polyester soft segment at 200% elongation, and (b) at 500% elongation

Hydrogen bonds are also formed in the soft segments between the polymer chains during tensile crystallisation. Hydrogen bonding between two adjacent polymer chains significantly improves the physical properties of polyurethane elastomers. This leads to a three-dimensional "quasi cross-linked" molecular structure [41].

Attractive forces between the polymer chains of hard segments are much greater than those present in soft segments, which is the result of the high concentration of polar groups and the possibility of the formation of hydrogen bonds. Hard segments significantly influence mechanical properties, particularly the modulus of elasticity, hardness and tensile strength. The behaviour of elastomers at elevated temperatures varies depending on the structure of hard segments and their ability to stay linked at elevated temperatures. The properties of rigid segments are contributed by diisocyanates and chain extenders [4, 40, 41].

Quasi cross-linking is reversible, depending on the temperature, polymer composition and solvation (dissolution), and it offers many interesting possibilities for the processing of thermoplastic polyurethanes (e.g. extrusion or moulding, coatings, etc.) [4, 41].

The morphological and structural arrangement of segmented polyurethane polymers is determined by the following:

- Hard and soft segments are incompatible with each other, while elastomers exhibit a two-phase morphology, despite the high degree of mixing of both segments.
- Soft segments containing glycols form an amorphous matrix in which hard segments are dispersed.
- Hard domains containing chain extenders act as multifunctional cross-linkers, which influence the behaviour of elastomers. Hydrogen bonds can form between hard and soft segments, although it is uncertain to what extent they affect physical properties.
- Hydrogen bonds between the molecules of hard segments create a three-dimensional molecular structure in certain areas.

Morphology is unstable with respect to temperature, and is dependent on the chemical composition and thermal history of the polymer [4, 41].

5 Polyurethanes for medical use

The use of polyurethane covers many medical fields, such as [2, 6, 42]:

– cardiovascular devices (catheters, vascular prostheses, pacemakers, etc.),
– materials for reconstructive surgery (wound dressings, breast implants, maxillofacial prosthetics, other implants, etc.),
– obstetrics and gynaecology (condoms, contraceptive sponges, etc.), and
– textile materials (hospital sheets, surgical drapes, etc.).

Natural or synthetic materials used in contact with biological systems for the treatment, growth or replacement of tissues, organs or body functions must meet the basic requirements of biocompatibility (i.e. minimal biological response), because the human organism or a biological environment with a high concentration of chloride ions and proteins is a relatively aggressive environment. Biocompatibility means the interactions between a material and body tissue. Both the response of tissue or an organism (host) to a material and the response of a material to tissue or blood are possible [42, 43].

From the full range of polyurethanes, segmented copolymers with good mechanical properties and relatively good biostability are used for medical purposes. Besides polyurethane, silicone rubber is used in biomedical applications. But although it demonstrates excellent biocompatibility, it also demonstrates lower tensile strength and is much more subject to wear, which could represent a limitation in medicinal use [14].

Since 1967, when Boretos and Pierce, and later in 1971, when Lyman et al. discovered that polyurethane-urea polymers are haemocompatible, these elastomeric materials have been intensively introduced in biomedical applications, such as artificial hearts, intra-aortic balloon catheters, heart valves and haemodialysis membranes. Shortly thereafter it was found that polyurethane haemocompatibility depends on the proportion of hard and soft segments, where higher thrombogenicity is demonstrated by polyurethanes with a higher content of solid segments [2].

5.1 Current situation and future perspective in the development of biomedical polyurethanes

In recent years, significant effort has been placed on the development of resorbable polyurethanes for use in a variety of biomedical applications, including tissue engineering scaffolds, controlled release applications, wound dressings, abdominal wall reconstruction and many others. The design of biodegradable polyurethane devices depends on the balance between mechanical property requirements and the desired degradation rate. Current research focuses on both of these key topics: decoupling mechanical properties from the degradation rate and expanding the available properties [44].

5.2 Surface characterisation techniques in the development of biomedical polyurethanes

Surface characterisation also represents a special area in the development of biomedical polyurethanes. In typical applications, including artificial hearts, catheters, feeding tubes, surgical drains, dialysis devices, wound dressings and more, polyurethane surfaces must interact with various bodily fluids, tissues or organs. The surface properties of polyurethane biomaterials are thus key factors in determining the performance of finished products. For this reason, a tremendous amount of research has

focused on the surface modification of polyurethane biomaterials to improve their lubricity, hydrophilicity/hydrophobicity, haemocompatibility, antithrombogenicity and antimicrobial activity. It is equally important that proper surface characterisation techniques are applied during such research [45].

The use of medical devices, such as catheters, angioplasty balloons and cardiovascular stents, usually involves the insertion of those devices into the urinary tract or veins. During insertion, the high surface lubricity of devices helps to facilitate the insertion process and reduce insertion-associated tissue damage, which benefits both the patients and the surgeon. Early approaches to decreasing insertion friction involve using lubricants such as olive oil and silicon oil, or low friction materials, such as polyethylene. However, 90% of total friction is believed to derive from interatomic adhesion between two surfaces. A reduction in interatomic adhesion thus results in a reduction in friction force. When water, as the most abundant fluid in the body, easily wets the polymer surface and creates a thin layer between two surfaces to eliminate solid/solid contact, friction force is significantly reduced. A general approach to friction reduction is thus an increase in the surface hydrophilicity of polyurethanes through coating or surface chemical modification [45].

Surface characterisation methods for such materials include coefficient of friction measurements, typically applying the ASTM D1894-14 standard method [46], contact angle measurements [47, 48], X-ray photoelectron spectroscopy [47], secondary ion mass spectrometry [49], scanning electron microscopy [48] and atomic force spectroscopy [47]. When a medical device is in contact with a bodily fluid such as blood, the first thing that occurs on the surface is protein adsorption, which can be determined with the use of quartz crystal microbalance [50] and iodination radiolabelling [51]. Polyurethane medical devices frequently require good haemocompatibility. There are several in vitro and ex vivo tests available to evaluate haemocompatibility. In vitro platelet adhesion can be measured through radioactive isotope labelling, lactate dehydrogenase assay and acid phosphate assay [45]. An in vitro blood loop standard method or an ex vivo shunt blood loop test are also used to determine haemocompatibility [45]. The antimicrobial efficiency of polyurethanes, which are surface modified/coated with antimicrobial active agents/groups, can be tested by measuring the inhibition zone or through a contact kill test [52, 53].

5.3 Innovative medical applications of biodegradable polyurethanes

The study of polyurethane degradation mechanisms has stimulated the development of innovative degradable polyurethane materials, particularly in the areas of wound dressings, tissue engineering applications, vascular applications, nanoparticles, nanocapsules and nanofibres. The most recent studies also address controlled drug [54–58], cell [59] and gene [60] delivery, antimicrobial polyurethanes [61], polyurethanes for bone tissue engineering [62], nerve and muscle regeneration [63] and dermal scaffolds [64]. New-found formulations have resulted in different medical applications and the latter are far from exhausted. Below we present some fields that are currently the most intensively engaged in the development of new polyurethane materials.

Polyurethane wound dressings and plasters

Polyurethanes are widely used as wound dressings because they are soft, flexible for uneven surfaces, do not stick to wounds, do not leave residues and have good barrier properties (impermeable to bacteria but permeable to oxygen) [65]. Common polyurethane wound dressings are semi-permeable adhesive films, perforated films, hydrocolloids and foams [2]. Depending on the shape (film, membrane, foam, etc.), chemical composition and functionalisation, they are suitable for wounds with different amounts of exudate [2, 65]. Thin and transparent polyurethane films are particularly suitable for the protection of surfaces and for post-operative wounds with no or weak exudate secretion. They do not permeate bacteria and water, but permeate gases, thus allowing wounds to breathe. Polyurethane foams are suitable for wounds with more exudate, as they are highly absorbent and able to retain exudate [65]. Polyurethane coatings may be the only component forming a wound dressing, but are more frequently used in multi-component dressings, such as hydrocolloid wound dressings. There are currently several commercial products on the market. Polyurethane wound dressings contain various active substances, such as pharmacologically active substances, antibacterial (chlorhexidine (Opsite® CH) and iodine (Tegaderm® Plus)), local anaesthetics, agents with

bacteriostatic effects and antifungal agents. Dressings for the treatment of leg ulcers are treated with glycerine, zinc or collagen. Other dressings, primarily hydrocolloid coatings, contain absorbents and gel-forming agents. Granuflex® and Borderex Granuflex® contain a dispersion of gelatine, pectin and carboxymethyl cellulose with other polymers [2].

Despite numerous publications regarding research on polyurethanes in the past 10 years, there are only a few scientific papers on the biocompatibility testing of medical polyurethane wound dressings. The main topic of research is the development of new polyurethane materials that would, in addition to biocompatibility, also contribute to faster wound healing. The requirements for these materials are good mechanical properties, the ability to maintain the appropriate humidity level of a wound and antimicrobial protection [66].

Yari et al. synthesised a new polyurethane membrane designed for wound care, which has the ability to absorb wound exudates and demonstrates antimicrobial properties. The membrane was synthesised by means of an amine reaction from an epoxy-polyurethane pre-polymer, and an antibacterial epoxy-quaternary ammonium component (glicidyl triethylammonium chloride). In order to increase the absorbency, poly (ethylene glycol) polyol was added. Suitable bio-compatibility was demonstrated by using an MTT test (with the use of 1-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide), and the direct contact method with two cell lines: fibroblasts and epidermal keratinocytes [67].

Recent studies in the preparation of biocompatible polyurethanes focus on the replacement of raw materials derived from petroleum fractions with polyols of natural origin, in particular from natural oils (plant and animal) [10], which is useful in the field of wound dressings [68]. Ozkaynak et al. prepared a polyester polyurethane membrane from linseed oil, from which a polyol for the further synthesis of polyurethane was prepared. The results of the characterisation showed good mechanical properties, good gas permeability and good acid resistance. It has therefore been suggested that the material is suitable as a medical wound dressing [68, 69].

Later, Gultekin et al. prepared several polyurethane films intended for medical coatings through the esterification of linoleic acid (from linseed oil) and glycerol. Toluene 2,4-diisocyanate was used for the isocyanate component. Polyurethane films were prepared with and without a catalyst (calcium octoate) and with and without cross-linking, in an effort to determine the effect of these parameters on biocompatibility. The commercial medical polyurethane coating Opsite® (Smith & Nephew) was used as a reference material. A calorimetric test with MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) and a direct contact test were used for the in vitro determination of cytotoxicity. Mouse NIH 3T3 fibroblasts were used. Cell growth was most extensive on the commercial wound dressing, although the polyurethane sample prepared without a catalyst that was not cross-linked also showed a very similar result. The worst fibroblast growth was demonstrated on a polyurethane surface prepared with the catalyst and cross-linked [70].

Yücedag et al. more accurately characterised polyurethane prepared from linseed oil in terms of biocompatibility. An in vitro degradation test in a phosphate buffer at a temperature of 37 °C using a gravimetric method, Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM) were performed. A higher degradation rate was observed when diisocyanate HDMI was used, relative to the samples with MDI and HDMI. An MTT test and a direct contact test using mouse NIH 3T3 fibroblasts were also performed, with the materials showing no cytotoxic effect [66].

Polycarbonate polyurethanes are replacing polyether polyurethanes synthesised from polyols derived from petroleum fractions. On average, polyether-polyurethanes have better mechanical properties than polycarbonate polyurethanes, which are more biostable due to the absence of sensitive ester and ether links in soft segments [71–73]. Although potential as medical wound dressings has been demonstrated [74], there are not currently many studies on this topic.

Polyurethane scaffolds for tissue engineering

Tissue engineering combines three-dimensional (3D) biodegradable scaffolds and cells to grow 3D in vitro tissues for drug screening and in vivo regeneration [75]. One of the requirements imposed on scaffolds is a suitable, porous structure with uniformly distributed interconnected pores. Materials should possess a high degree of porosity (in excess of 90%) and proper pore dimensions (from ten to hundreds of μm), depending on the application. According to literature, scaffolds for liver regeneration should have a pore diameter of 20 μm to allow the

growth of hepatocytes, while the proper pore diameter for skin should be within the range of 20 to 150 μm. The best pore size for bone is between 200 and 400 μm. Moreover, pores must be interconnected to allow cell and tissue ingrowth [76]. A wide variety of techniques has been developed to create either fibrous or porous scaffolds from polyurethane. Generally, those techniques can be divided into two groups: conventional and advanced. Conventional techniques include solvent casting/particle leaching (SCPL) [77], thermally-induced phase separation [78], gas foaming and melt moulding, while advanced techniques include, *inter alia*, electro-spinning and 3D printing [76].

Three-dimensional bio-printing is being applied to regenerative medicine to address the need for tissues and organs suitable for transplantation. Compared to non-biological printing, 3D bio-printing involves additional complexities, such as the choice of materials, cell types, growth and differentiation factors, and technical challenges related to the sensitivities of living cells and the construction of tissues [79]. Initially, polyurethanes in medical applications were used as artificial skin, vascular grafts, neural connections, bone grafts and materials for the repair of articular cartilage [76]. Recent literature describes many polyurethane systems that are suitable for 3D printed scaffolds.

Recently, Hung et al. developed water-based polyurethane 3D printed scaffolds with a controlled release function for customised cartilage tissue engineering [75]. The prepared printing ink contained a water dispersion of synthetic biodegradable polyurethane elastic nanoparticles, hyaluronan, and bioactive TGFβ3 ingredients or a small molecule Y27632 drug in place of TGFβ3. Compliant scaffolds were printed from the ink at low temperatures. They show that the prepared scaffolds promote the self-aggregation of mesenchymal stem cells (MSCs) and, through the timely release of bioactive ingredients, induce the chondrogenic differentiation of MSCs and produce a matrix for cartilage repair [75].

Hernandez-Córdora et al. synthetisised an innovative polycaprolactone based polyurethane-urea copolymer that demonstrated improved mechanical properties compared to its previously published counterparts. This study shows that indirect 3D printing could provide the means to fabricate this innovative biodegradable polymer into a scaffold suitable for cardiac tissue engineering [80].

Electrospinning is also a popular technique for the production of scaffolds for different areas of tissue engineering. Carlberg et al. found that electrospun polyurethane porous scaffolds, which mimic the natural three-dimensional environment of the in vivo extracellular matrix and provide physical support, are promising candidates for central nervous system tissue engineering [81]. Jing et al. found that electrospun thermoplastic polyurethane/graphene oxide tubular scaffolds have the potential to be used in vascular tissue engineering [82].

Polyurethane nanoparticles and nanocapsules

In recent years, polymeric nanoparticles and nanocapsules have gained in popularity as promising vehicles for delivering drugs and others agents. In addition, the development of biocompatible polyurethanes has drawn much attention due to their excellent physical properties, biocompatibility and biodegradability, while the potential value has been discussed for a variety of pharmaceutical, medical, and cosmetic applications, such as a medium for controlled release [83]. Significant advances have been made in the design, formation and characterisation of polyurethane nanoparticles. Different approaches have been employed to synthesise polyurethane nanoparticles as carriers of imaging agents, as drugs or as copolymers to form different versatile matrices [84]. Polyurethane particles have been synthesised using several techniques, such as suspension-polycondensation, interfacial polycondensation combined with spontaneous emulsification, suspension-polyaddition, dispersion in organic solvent, and supercritical carbon dioxide and miniemulsion technique [85].

The chemical reactivity and properties of these polymers make them suitable for binding peptides, nucleic acids, antibodies and other biomolecules to obtain functionalised nanoparticles for an array of medical applications. Further work is still required to develop new methods to obtain nanoparticle matrices with tuned porosity and degradability for sustained controlled drug release. The goal in the future is to obtain smart multifunctional nanoparticles and nanocapsules to target specific cells for the release of drugs or imaging agents controlled and triggered by external signals or the local environment [84]. For example, Cusco et al. recently developed a new drug delivery system for cancer chemotherapy based on polyurea/polyurethane nanocapsules that might protect the drug from premature activation

and specifically release it inside cancer cells [86]. Rosenbauer et al. prepared stimuli-responsive polyurethane nanocapsules consisting of an aqueous core and a polymeric shell, where an encapsulated fluorescent dye is released via pH, UV-light or temperature stimulation [87]. Other release mechanisms of polyurethane nanocapsules, such as laser light, ultrasound, magnetic force or enzymatic degradation, still represent a challenge for future research.

Polyurethanes that represent an important class of biomaterials could be even more advantageous if they exhibited X-ray contrast properties in applications, such as heart valves, catheters and vascular stents [88]. Radiopaque polyurethanes are commercially available, but usually contain additives, such as barium sulphate, tungsten or bismuth salts. Kiran et al. covalently bound iodine to bisphenol-A to obtain 4,4'-isopropylidinedi-(2,6-diiodophenol) (IBPA), which was used as a chain extender for the preparation of a non-cytotoxic radiopaque polyurethane [89]. To the best of our knowledge, the preparation of such non-cytotoxic material in nanoparticle or nanocapsule form has not been reported to date.

6 Conclusion

Polyurethanes are one of the most versatile polymeric materials. The chemical nature of polyurethanes enables them to be transformed into different shapes and used in consumer products, where they contribute to comfort, strength, and heat and sound insulation. They are found almost everywhere: in medicine, the automotive and marine industries, construction, textiles, household appliances, etc.

In medicine, polyurethanes are used in the fields of gynaecology, reconstructive surgery materials and cardiovascular devices. Their advantage over other materials lies in their good mechanical properties and biostability. The development of biomedical polyurethanes is still aimed at producing new materials, particularly in the fields of wound dressings, tissue engineering and controlled drug release. New formulations include not only different reactant combinations and the replacement of reactants derived from petroleum fractions with naturally renewable reactants, but also the preparation of composite materials, and their surface functionalisation and transformation into other forms, such as nanofibers, nanoparticles, nanocapsules or fine dispersions, which facilitates new possibilities for their use. There are practically unlimited possibilities in terms of variations in the choice of raw materials for the manufacture of polyurethanes, as well as an unlimited choice of substances (drugs, molecules, cells, etc.) for their functionalisation. Moreover, numerous methods for the creation of materials in various forms facilitate the future development of new, safer and more efficient polyurethane materials that will find their place in the field of new biomedical applications.

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