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POLYURETHANES AS BIOMATERIALS IN MEDICINE: ADVANCED APPLICATIONS, INFECTION CHALLENGES, AND INNOVATIVE SURFACE MODIFICATION METHODS

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Abstract. Polyurethanes (PUs) are exceptionally versatile polymers widely utilized in medicine due to their outstanding mechanical properties, biocompatibility, and adaptability to various applications. This article explores advanced applications of polyurethane biomaterials in medicine, the challenges posed by infections associated with their use, and innovative surface modification techniques to improve their functionality. PUs are employed in a diverse array of medical devices, including non-implantable applications such as wound dressings, catheters, and infusion sets; short-term implants like bone stabilizers and tracheostomy tubes; and long-term implants such as tissue regeneration scaffolds, artificial blood vessels, and heart valves. Despite their many advantages, their use carries a significant risk of infections, including ventilator-associated pneumonia, infective endocarditis, and urinary tract infections. An important challenge lies in bacterial biofilms, which complicate treatment and enhance bacterial resistance to antibiotics. To address these issues, innovative PU surface modification methods are being developed, including laser texturing, nanoparticle deposition with antibacterial properties, ion implantation, cold metal spraying, the integration of biodegradable and biocompatible components, and plasma modifications. These advanced techniques aim to enhance polyurethane biomaterials' antibacterial properties and biocompatibility, thereby reducing infection risks and improving clinical outcomes. This article underscores the importance of ongoing research to effectively combat biomaterial-associated infections and broaden the medical applications of polyurethanes. The development of advanced surface modification methods holds great promise for improving patient quality of life and the efficacy of medical treatments.

Keywords: biomaterial-associated infections, biomaterials, innovative surface modification methods, medical applications of polyurethanes, polyurethanes

1. Introduction

Polyurethanes (PUs) are widely used in the production of medical devices. Due to their specific properties, some types of PUs can also be classified as biomaterials, depending on their application and compatibility with biological systems. A biomaterial can be described as "any substance or combination of substances, other than drugs, synthetic or natural, that can be used for any period of time and extends or replaces partially or completely any tissue, organ or function of the body" by the U.S. National Institutes of Health (Bergman and Stumpf 2013).

The first research on polyurethanes was carried out by Otto Bayer in 1937. He studied the polyaddition reaction between diisocyanate and polyester diol,

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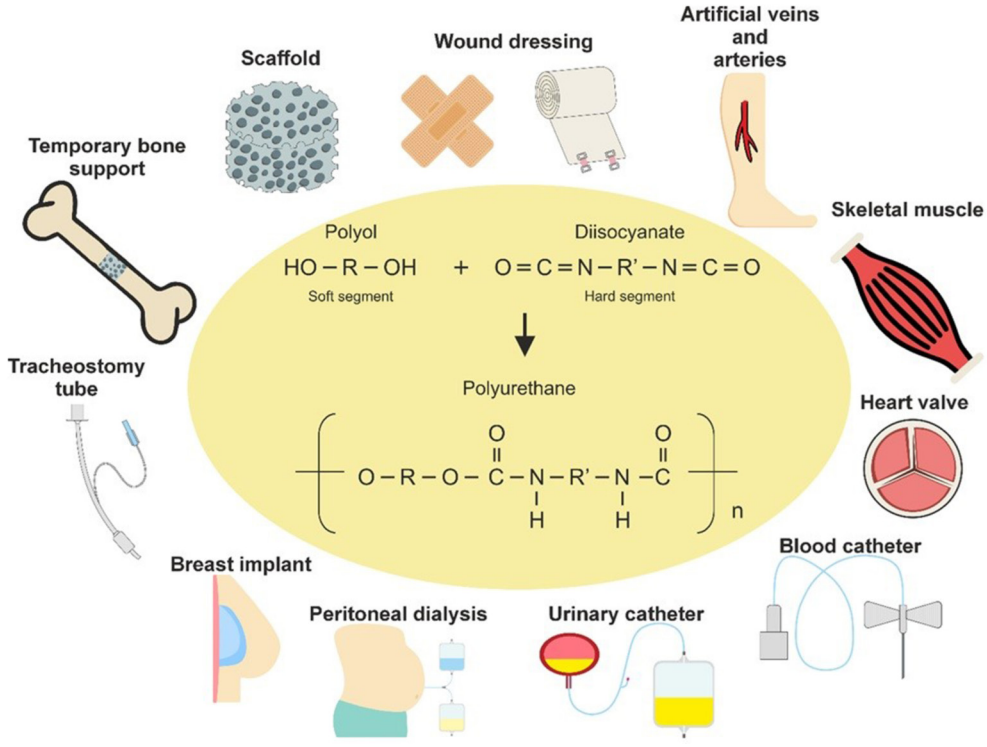

Fig. 1. Diagram of the synthesis of polyurethanes and their application in medical devices.

which enabled their use during the Second World War, mainly as adhesives and foams. Soon after the war, with the development of commercial production of flexible PU foams in the 1950s, PU industrial production began to include elastomers and coatings. During the same period, in response to the commercial success of Nylon 6.6, a condensation polymer developed by Du Pont, German teams led by Bayer investigated new methods of polymerization, which led to the creation of polyurethanes with properties similar to nylon. These new polyurethanes had lower water absorption and better mechanical and electrical stability than nylon. The evolution of PU technology continued, including developing more sustainable bio-based materials and improved production methods in an environmentally friendly direction (Ratner *et al.* 2013; Wendels and Avérous 2021).

Polyurethanes are synthesized through a complex process of urethane linkage. The process starts with a two-step synthesis strategy using three precursors: diisocyanates, diols and chain extenders, which together form the hard and soft segments of the polymer. The key process is the polyaddition reaction, in which the isocyanate NCO group reacts with the labile hydrogen of active compounds such as hydroxyls or amines to form permanent urethane bonds. These bonds a small but essential part of the chain, are formed by the reaction of isocyanates with alcohols (Fig. 1). Macroglycol, the main component, determines most of these bonds, which affect flexibility and fatigue resistance. Because the material is one large molecule, it cannot be dissolved or forced to flow by applying heat and pressure. This feature means that once a thermoset elastomer is formed, it cannot be further processed (Ratner *et al.* 2013). Therefore, PUs have simple architecture. Nowadays, commercially relevant PUs are block copolymers. The polymer molecules have alternating segments consisting of repeating „A" or „B" units. In addition, the materials are designed so that one segment – called the hard segment – is glassy or crystalline at the temperature of use, while the other segment – called the soft segment – is rubbery (Ratner *et al.* 2013).

PUs are a class of polymers that have, today, achieved industrial importance due to their tough and elastomeric properties and good fatigue resistance (Gunatilake *et al.* 2003; Rusu et al. 2020). In addition to their elastomeric properties, PUs have several beneficial interfacial characteristics. Most notably, PUs are abrasion and impact resistant, which makes them suitable for as coatings, and the materials also have good blood contact properties, making them useful in biomaterial applications (Ratner *et al.* 2013).

The main objective of this work is to provide a comprehensive overview of polyurethanes and their various applications in medicine and to outline the current challenges of biomaterial infections, especially those involving polyurethane-based devices. In addition, the paper discusses innovative surface modification techniques for polyurethanes to enhance their antimicrobial properties.

2. Characteristics and Applications of Polyurethane-Based Biomaterials

2.1. Segmented Structure of Polyurethanes

PUs stand out as one of the most versatile classes of polymer materials. Their versatility is primarily due to their segmented structure, including hard and soft segments (Rusu *et al.* 2020). The soft segments in polyurethanes are responsible for the material's elastomeric properties. Their chemical structure is based on polyols, such as polyethers and polyesters. The low glass transition temperature of the soft segments allows for flexibility and influences the material's hydrophilicity, which determines the degree of water diffusion into the polymer. As a result, the degradation rate of soft segments is related to hydrophilicity and the presence of labile groups. Polyethers are commonly used to impart flexibility and increase stability to the material. Another class of soft segments includes A-B-A tri-block polyols, which are used in producing resorbable polyurethanes due to their versatile properties (Mirhosseini *et al.* 2019; Zhang *et al.* 2019).

2.2. Mechanical Properties of Hard Segments

The hard segments in polyurethanes provide increased mechanical resistance. They consist of isocyanates and chain extenders. Their high transition temperature and pronounced crystallinity contribute to the material's mechanical strength. The content and chemistry of the hard segments have a direct impact on tensile strength and modulus. The amount of isocyanates and chain extenders determines the physical characteristics of polyurethane, and their type (aromatic or aliphatic) affects reactions with nucleophilic reagents and the material's toxicity. Aromatic isocyanates are highly reactive but can lead to side effects in carcinogenic degradation products, whereas aliphatic isocyanates have a lower toxicity potential (Somdee *et al.* 2019; Rogulska 2023).

2.3. General Characteristics

They are valued for their excellent biocompatibility, exceptional resistance to hydrolytic processes, high abrasion resistance and outstanding mechanical durability, including resistance to bending. Their diversity manifests in adhesives, coatings, sealants or foams, available in a wide range of Shore hardnesses (Shin *et al.* 2018). Thanks to such broad properties, it is possible to use PUs to create short- and long-term biomaterials.

2.4. Classification of Polyurethane Biomaterials

According to the U.S. Food and Drug Administration (FDA) and the European MDCG 2021–24, implants made of biomaterials are devices placed inside the body or on the body's surface (EC 2021; FDA 2023). A distinction can be made between long-term implants, which have a lifespan of 30 days or more in contact with a tissue before biodegradation or removal to promote healing to the tissue remodeling phase. In contrast, short-term implants have less than 30 days of lifespan in contact with living tissues. Finally, non-implantable devices are materials designed to be placed on the body's surface (EC 2021; FDA 2023). The properties mentioned above render polyurethanes ideal materials for various medical device components (Fig. 1).

2.4.1. Non-Implantation Applications of Polyurethanes

Polyurethanes are ideal materials for a wide range of medical devices due to their versatility. In non-implantation applications, they are valued for their excellent mechanical and chemical properties. For instance, polyurethane-based materials are used in wound dressings and membranes (Khodabakhshi *et al.* 2019; Yeoh *et al.* 2020; Li *et al.* 2022). In peritoneal dialysis catheters, polyurethanes provide flexibility and biocompatibility, enhancing patient comfort (Crabtree 2023; Peng *et al.* 2023). Due to their chemical resistance and durability, polyurethanes are also used to manufacture catheters and urine collection bags (Wang and Wang 2012).

2.4.2. Applications in Long-Term Implants

Polyurethanes are also utilized in intravenous line (IV) tubing due to their flexibility and kink resistance, ensuring continuous fluid delivery (Wang and Wang 2012, Tokhadzé *et al.* 2021). However, Tokhadzé *et al.* (2021) found that polyurethane catheters can cause significant drug loss, particularly with diazepam and insulin, which is clinically relevant for long-term infusions (Tokhadzé *et al.* 2021). Polyurethanes are also employed in artificial veins and arteries (Jia *et al.* 2020; Wendels and Avérous 2021; Zhang *et al.* 2021), aligning with blood flow dynamics and reducing thrombosis risk (Kim *et al.* 2016). Additionally, they aid in nerve regeneration, promoting the recovery of peripheral and sciatic nerves (Niu and Galluzzi 2020; Toichi Nasab *et al.* 2022; Zhang *et al.* 2023). In artificial heart valves, polyurethanes provide the necessary flexibility and strength to mimic natural valve function (Santerre *et al.* 2005; Shin *et al.* 2018; Kazerouni *et al.* 2021). Their biostability and low incidence of postoperative complications make them suitable for outer shells in breast implants, enhancing aesthetic results and patient satisfaction (Navas-Gómez and Valero 2020; Catanuto *et al.* 2023).

2.4.3. Applications in Short-Term Implants

Polyurethane tracheostomy tubes increase patient comfort and reduce tissue irritation due to their softness and flexibility (Björling 2009; Guo *et al.* 2020). In long-term implants, the durability and biocompatibility

of polyurethanes are crucial. They are used to create scaffolds supporting the regeneration of various tissues, including cartilage (Wendels and Avérous 2021) and muscle (Ergene *et al.* 2019; Jo *et al.* 2020; Wendels and Avérous 2021). Polyurethanes support healing by acting as bone stabilizers or adhesives in situations that require temporary reinforcement of bone structures (Oliveira *et al.* 2016; Rode *et al.* 2020; Li *et al.* 2023). Li *et al.* (2023) developed an injectable polyurethane adhesive with catechol groups and disulfide bonds that shows strong wet adhesion and biodegradability, making it ideal for complex bone injuries (Li *et al.* 2023).

These examples highlight polyurethanes' versatility and essential role in medical technology, from external devices to long-term implants, significantly contributing to improved patient outcomes and quality of life.

2.5. Trade Names of Polyurethane-Based Biomaterials

Medical-grade PU-based polymers can be found under several trade names, such as Carbothane™, Pellethane® or Tecoflex™ from Lubrizol (USA) and Carbosil® and Bionate® from DSM (Netherlands) (Wendels and Avérous 2021).

3. Instances of infections linked to the utilization of biomaterials

Advances in medical technology have made the use of various PU medical devices an integral part of patient care, significantly improving survival rates and quality of life. However, it should be explicitly stated that parent polyurethanes have no intrinsic antimicrobial activity, which poses additional challenges in preventing infections associated with their use. The colonization of medical devices by microorganisms can lead to severe infections, such as ventilator-associated pneumonia (Pen *et al.* 2020), infective endocarditis (Selton-Suty *et al.* 2012; Cahill *et al.* 2016), or vascular prosthesis infections (Gouveia e Melo *et al.* 2021). Understanding the microbiology of these infections is key to developing effective prevention and treatment strategies.

The available literature data is general and does not apply exclusively to polyurethane medical devices. This is because hospitals and clinical teams often do not consider the diversity of biomaterials used in medical devices, which significantly hinders detailed analyses of their impact on infection risk.

3.1. Infections involving biomaterials in the respiratory system

The insertion of respiratory biomaterials, such as tracheostomy tubes, is often essential in treating patients requiring long-term respiratory support. The tracheostomy procedure is an alternative to prolonged endotracheal intubation, offering better control of the patient's airway and reducing the risk of nosocomial infections. Nevertheless, using such devices may be associated with complications, such as granuloma formation, which can lead to bleeding, airway obstruction or scab formation. In addition, tracheostomy tubes may provide a site for colonization by microorganisms, promoting infection development (Cheung and Napolitano 2014).

These include different bacterial species such as *Klebsiella pneumoniae*, *Pseudomonas. aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii* (Restrepo *et al.* 2013; Huang *et al.* 2018; Ścibik *et al.* 2020; Thirumurthi *et al.* 2021; Raveendra *et al.* 2022) and *Streptococcus pneumoniae* (Thirumurthi *et al.* 2021). Bacterial colonization on tracheostomy tubes can further lead to ventilator-associated pneumonia (VAP) (Restrepo *et al.* 2013; Ferro *et al.* 2021), which can be caused by a single pathogen or have a polymicrobial origin (Ścibik *et al.* 2020).

A study conducted in twenty-seven intensive care units across nine European countries reported a VAP rate of 18.3 cases per 1,000 days of mechanical ventilation. The predominant pathogens were *S. aureus*, *P. aeruginosa*, and *Acinetobacter* spp. (Koulenti *et al.* 2016). Additionally, it was shown that patients with SARS-CoV-2 infection had a higher risk of developing VAP (50.5%) compared to patients without viral infections (25.3%) (Rouzé *et al.* 2021). On the other hand, a meta-analysis that included 8,282 cases from twenty provinces in China revealed that the cumulative incidence of VAP in mainland China was 23.8% between 2006 and 2014 (Ding *et al.* 2017).

In addition to colonizing the tracheostomy tube, the natural microbiome colonizing patients is also essential. It is estimated that approximately 20% of healthy individuals are chronically colonized by *S. aureus* (Pickens and Wunderink 2022). Studies indicate that between 15.2% and 22.1% of VAP cases are caused by MRSA strains (Feeney *et al.* 2018; Pasha *et al.* 2020). Furthermore, a systematic review and meta-analysis suggest that MRSA colonization status may be helpful as an indicator of the risk of developing a VAP infection, which may support decision-making about the use of empiric therapy (Butler-Laporte *et al.* 2018).

In addition, patients colonized by MRSA tend to have more prolonged mechanical ventilation and poorer clinical outcomes, highlighting the need for strict infection control and targeted therapies (Feeney *et al.* 2018)

As a result, it can lead to patient death. Scientific sources report that VAP mortality rates range from 20–30% (Restrepo *et al.* 2013), with some studies indicating that the mortality rate can be as high as 49.2% (Tamaya *et al.* 2012). In patients who have undergone heart surgery, VAP was identified as the most significant independent risk factor for in-hospital mortality.

The mortality rate in patients with VAP was 49.2%, compared to 2% among those without VAP (Tamaya *et al.* 2012).

3.2. Cardiovascular infections with the use of biomaterials

The use of medical devices, including pacemakers, defibrillators, stents, and heart valves, has increased dramatically over the past fifty years. Today, more than 1.7 million cardiovascular devices and over one million other medical devices are implanted worldwide annually (Scialla *et al.* 2021).

Infective endocarditis (IE) associated with implantable devices, such as artificial valves, is referred to as prosthetic valve endocarditis (PVE). PVE is a severe complication of heart valve replacement surgery, with a reported mortality rate ranging from 20% to 80% (Angelina *et al.* 2016). The pathophysiology of PVE varies depending on the time elapsed since the operation, allowing for a distinction between two types of PVE: early and late. Early PVE is diagnosed within the first year after the implantation of an artificial valve, while late PVE is diagnosed after this period (Ramos-Martínez *et al.* 2023).

In early PVE, the lack of endothelialization of the suture ring and adjacent tissue plays a key role. When combined with the presence of adhesion proteins such as fibrinogen and fibronectin, it facilitates the development of infection. Additionally, early PVE often results from accidental contamination during surgery or hematogenous spread occurring postoperatively within the first hours to months. In contrast, during late PVE, the heart valve structures are fully covered by endothelium, and the pathogenesis of the disease more closely resembles that of native valve endocarditis (NVE) (Galar *et al.* 2019). A large cohort study involving 1,354 cases of PVE demonstrated that early PVE is more commonly associated with nosocomial pathogens, whereas late PVE is characterized by greater microbiological diversity. The hospital mortality rate for PVE was reported to be 32.6% (Ramos-Martínez *et al.* 2023; Ivanovic *et al.* 2019). In contrast, other studies suggest that the most common microorganisms responsible for early PVE (within two months of implantation) are *S. aureus* (36%), coagulase-negative staphylococci (17%), and fungi. For PVE occurring later, the incidence of *S. aureus* and coagulase-negative staphylococci decreases to 18–20%, with a corresponding increase in infections caused by enterococci and streptococci (10–13%) (Ivanovic et al. 2019). Patients with *S. aureus*-induced PVE represent a unique subgroup characterized by an increased risk of complications and a higher mortality rate (Tan *et al.* 2015). The causative factors in late PVE are similar to those in native valve endocarditis. It is usually caused by bacteria, such as α-haemolytic streptococci and CoNS (Coagulase Negative Staphylococci), which colonize various human body surfaces (Ivanovic et al. 2019; Berisha *et al.* 2022). Patients with *S. aureus*-induced PVE represent a distinct subgroup characterized by an increased risk of complications and a higher mortality rate (Rivoisy *et al.* 2018).

Other examples of biomaterial-related infections include infections of synthetic blood vessels, which typically result from direct contamination during surgery (Hasse *et al.* 2013). These infections affect approximately 1–6% of patients, with a higher risk (around 6%) for prostheses placed in the groin region (Wilson *et al.* 2016). Treatment usually involves antibiotic therapy and surgical prosthesis removal, a particularly challenging process due to the biofilm's presence and the infection's depth (Leroy *et al.* 2012). Gram-positive bacteria, such as *S. aureus* and coagulase-negative staphylococci, and less commonly Gram-negative bacteria like *Escherichia coli*, are most frequently responsible for these infections. The biofilms produced by these bacteria significantly complicate the elimination of infections (Gharamti and Kanafan 2018). However, a recent retrospective study revealed that vascular prosthesis infections have evolved, with a notable increase in infections caused by Gram-negative bacteria exhibiting high antibiotic resistance, particularly in early infections (Gouveia e Melo *et al.* 2021).

Another group of biomaterials, some made from polyurethanes, includes implantable cardiac electronic devices (ICEDs). This group comprises implantable cardiac defibrillators (ICDs), cardiac resynchronization therapy devices (CRTDs), and permanent pacemakers (PPMs) (Armaganijan and Healey 2011). In 2010, approximately 40,000 ICEDs were implanted in the UK (Sandoe *et al.* 2014).

Studies indicate that the infection rate associated with ICEDs is relatively low, ranging from 0.5% to 2.2%. However, the mortality rate of these infections is as high as 35% (Sandoe *et al.* 2014; Sławiński *et al.* 2019). In Poland, the infection rate is reported to be 1.2% (Sławiński *et al.* 2019). More than eighteen scientific reports, including at least 100 patients each, were analyzed in recent guidelines on diagnosing, preventing, and treating infections associated with implantable cardiac electronic devices (ICEDs). The etiological agents were found to be highly recurrent. Gram-positive bacteria were the predominant group, isolated in 67.5% to 92.5% of cases, with CoNS and *S. aureus* being the most common pathogens. Gram-negative bacilli accounted for 6% to 10.6% of all isolates. Polymicrobial infections were reported in seven studies, ranging from 2% to 24.5%. Fungal infections, in contrast, were rare, with a prevalence of less than 2% (Sandoe *et al.* 2014).

Central venous catheters (CVCs) are essential in managing critically ill patients, particularly those in intensive care units (ICUs). They facilitate intravenous

access, enabling the administration of drugs and fluids, as well as the collection of blood for laboratory analysis (Gomes Resende de Souza da Silva *et al.* 2021). However, their use requires proper preparation and precise insertion techniques to minimize the risk of procedural complications. Central line-associated bloodstream infections (CLABSIs) are among the most common infections in ICUs. In developing countries, incidence rates range from 1.7 to 44.6 cases per 1,000 catheter days (Fontela *et al.* 2012). These infections are caused by various species, with CoNS (e.g., *Staphylococcus epidermidis*) being predominant, particularly in patients using long-term central catheters (Özalp Gerçeker *et al.* 2019; Akaishi *et al.* 2023). Other common pathogens include *S. aureus* (Sellamuthu *et al.* 2023), *Enterococcus faecium* and *Enterococcus faecalis* (Belloni *et al.* 2022). Gram-negative bacteria, such as *Klebsiella* spp. and *Pseudomonas* spp., are responsible for many infections, particularly in pediatric and oncology wards (Tomar *et al.* 2015). This group also includes Gram-negative bacteria, such as *Klebsiella* spp. and *Pseudomonas* spp., responsible for many infections, particularly in pediatric and oncology wards (Tomar *et al.* 2015). Furthermore, the emerging phenomenon of antimicrobial resistance among clinically significant Gram-positive and Gram-negative bacteria, particularly those in the ESKAPE group (*E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa,* and *Enterobacter* spp.), poses a significant challenge for the prevention and treatment of infections (De Oliveira et al. 2020).

3.3. Urinary Tract Infections Associated with Biomaterial Usage

Another infection associated with biomaterials is catheter-associated urinary tract infection (CAUTI). CAUTI occurs when bacteria enter the urinary tract due to using a urinary catheter, a tube inserted into the bladder through the urethra to drain urine when a patient cannot urinate independently.

Catheter-associated urinary tract infections are significant due to their high prevalence, as they are one of the most common healthcare-acquired infections, accounting for up to 40% of hospital-acquired infections (Rubi *et al.* 2022). Moreover, 15–25% of hospitalized patients use urinary catheters, and approximately 75% of UTIs developing in hospitals are associated with catheter use (CDC 2024). Some studies indicate that the costs per patient with CAUTI range from $876 when a patient requires hospitalization, additional diagnostic tests, and medications to as much as $10,197 when a patient is hospitalized in the ICU (Hollenbreak and Schilling 2018). Other data suggest that reducing the incidence of CAUTIs can lower healthcare costs by $4,501 for every 1,000 catheterized patient days (Sutherland *et al.* 2015).

The most commonly identified microorganisms in the biofilms of long-term catheterized patients include *Proteus mirabilis* (Melo *et al.* 2016; Yuan *et al.* 2021; Herout *et al.* 2023), *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *Proteus stuartii*, *Morganella morganii*, and *E. faecalis* (Lassek *et al.* 2015; Puspitasari *et al.* 2021). Less frequently, *S. aureus* has been found to be responsible for 0.5% to 2% of all CAUTIs (Walkera *et al.* 2017).

4. Biofilm formation on polyurethanes

Bacterial biofilm represents a significant challenge in each of the infections mentioned above. A biofilm is a structured community of microorganisms growing within a self-produced matrix of polymeric materials (Das *et al.* 2019). It is estimated that 40% to 80% of all bacterial and archaeal cells exist within biofilm structures (Flemming and Wuertz 2019). An example of such biofilm formation on polyurethane surfaces, derived from the author's research, is shown in Fig. 2.

The formation of a biofilm occurs in four stages: initial attachment, biofilm accumulation, maturation, and dispersion (Fig. 3).

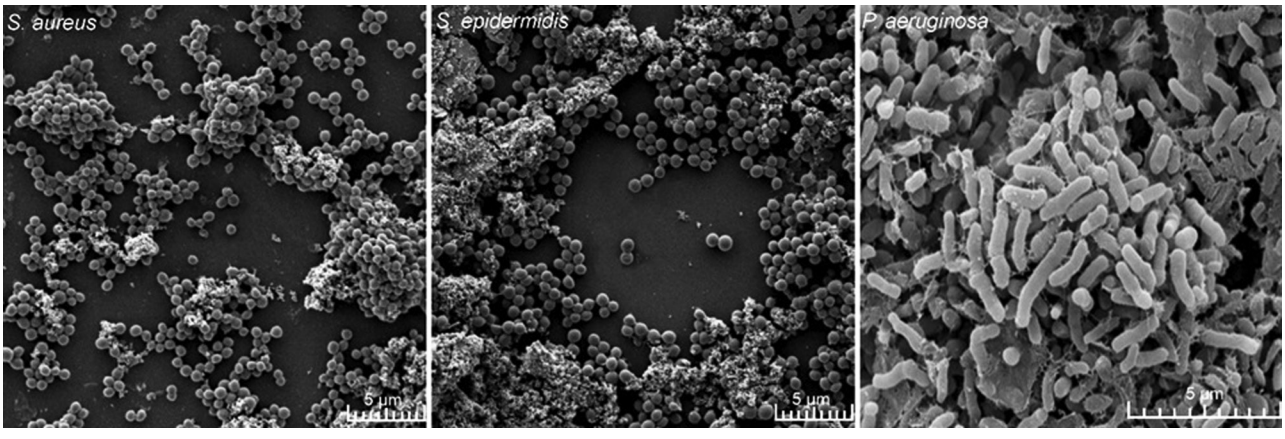

Fig. 2. Biofilm formation by *S. aureus*, *S. epidermidis* and *P. aeruginosa* on polyurethane surfaces. Images were obtained by this paper authors using a conventional scanning electron microscope (SEM) protocol at 10,000× magnification.

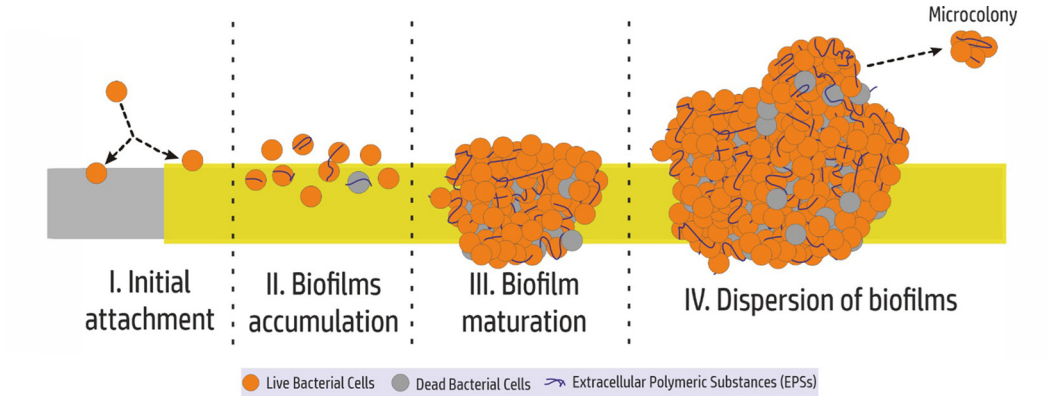

Fig. 3. Stages of bacterial biofilm formation on polyurethane medical devices: stage I – Initial attachment, stage II – Biofilm accumulation, stage III Biofilm maturation, stage IV – Dispersion of biofilms.

The first and most critical stage of biofilm formation by bacteria is the reversible adhesion of planktonic bacteria. This process occurs due to the ability of bacteria and surfaces to form covalent or ionic bonds. Additionally, weaker forces, such as polar bonds, hydrogen bonds, or Lifshitz-van der Waals interactions, can enhance or lead to strong interactions when many contact points are involved (Carniello *et al.* 2018; Joshi *et al.* 2020). Bacteria can also be modeled as smooth, inert colloidal microparticles. Many researchers utilize the Derjaguin-Landau-Verwey-Overbeek (DLVO) model to describe this process (Carniello *et al.* 2018). However, this model is a generalization due to the high variability in bacterial surface properties, which depend on species, strain, population heterogeneity, and even the cell cycle phase. Bacterial cell protrusions, such as nanofibers, pili, or fimbriae, act as adhesins, further facilitating attachment (Arciola *et al.* 2018; Vissers *et al.* 2018). The roughness of bacterial surfaces, caused by protrusions of varying lengths and widths, complicates the classical approach to adhesion, as the concept of distance between surfaces becomes ambiguous in these cases (Carniello *et al.* 2018).

In the second stage, bacterial adhesion transitions from a reversible to a more permanent state through physicochemical mechanisms that do not yet involve changes in gene expression. This process occurs on a timescale of minutes and depends on surface characteristics (e.g., hydrophobicity, charge) and environmental conditions (Carniello *et al.* 2018). The contact time between bacteria and the surface influences the binding strength amplification. This process is described by models incorporating changes in adhesion forces, browning motion, and temporal desorption (Fang *et al.* 2014; Carniello *et al.* 2018).

Mechanisms of bond strengthening and the transition to irreversible adhesion include:

Removal of interfacial water: This allows closer contact between bacteria and the surface, enabling the formation of acid-base interactions (Olsson *et al.* 2010).

Nanoscopic deformation of the cell wall: Deformation under adhesion forces increases the interactions between the bacterium and the surface, thereby strengthening adhesion (Chen *et al.* 2014).

Multi-molecule binding: Over time, additional adhesion structures (e.g., pili) become involved in binding to the surface, reducing the likelihood of simultaneous detachment (Sjollema *et al.* 2017).

Subsequently, extracellular polymeric substances (EPS) production begins, marking the transition to a strictly biological process. Studies indicate that pili-mediated adhesions in *P. aeruginosa* stimulate gene expression changes, initiating EPS production within 1–2 hours after contact with the surface (Crouzet *et al.* 2017). In *S. aureus*, EPS production reinforces binding in response to environmental conditions that weaken adhesion forces. Notably, in 3–24 hours of biofilms, the production of eDNA and poly-N-acetylglucosamine (PNAG) and the expression of their associated genes decreased as adhesion forces strengthened (Harapanahalli *et al.* 2015).

The third stage is biofilm maturation, during which bacteria proliferate to form a heterogeneous three-dimensional structure. Within this structure, zones of variable cell growth and gene expression emerge. At this stage, a high density of bacterial cells is established, enabling communication through quorum sensing. This process facilitates biofilm growth and supports a coordinated response to environmental changes, such as fluctuations in nutrient availability and stress conditions (Mukherjee *et al.* 2017).

The final stage of biofilm development is dispersion, during which individual bacterial cells or microcolonies are released, potentially producing new biofilms (Arciola *et al.* 2018). A combination of biological mechanisms and environmental factors regulates biofilm dispersion. Key processes include the activity of enzymes that degrade the extracellular polymeric matrix (EPS) and quorum sensing systems that synchronize the release of bacteria from the biofilm (Le *et al.* 2019).

Additionally, changes in nutrient and oxygen availability can trigger dispersal, enabling bacteria to adapt to fluctuating environmental conditions (Wang *et al.* 2020). This process is further associated with activating motility-related genes, facilitating the colonization of new surfaces following release from the biofilm (Rumbaugh and Sauer 2020).

Biofilms on biomaterials present a serious challenge in medicine and engineering, causing infection-related complications, device durability, and treatment efficacy. Antibiotic resistance, recognized as one of the most significant global health threats, is increasingly associated with biofilms, which exhibit adaptive resistance depending on their growth stage. As a community of microorganisms embedded in an EPS, biofilms enable bacteria to survive environmental stresses, enhancing their resistance to antibiotics and host defense mechanisms (Dostert *et al.* 2021). Biofilms are multiresistant to antibiotics and play a critical role in chronic infections, accounting for over 65% of all human infections (Dostert *et al.* 2021). The National Institutes of Health (NIH) also estimates that approximately 80% of surgical site infections in the U.S. are linked to biofilm formation (Hrynyshyn *et al.* 2022). No specific countermeasures targeting biofilms have been developed (Dostert *et al.* 2021). Furthermore, the lack of reliable and standardized clinical methods for detecting biofilms makes diagnosis and treatment challenging (Xu *et al.* 2020).

When biofilms develop on medical devices made of various biomaterials, long-term therapy is often required, and in many cases, implant removal becomes necessary (Li *et al.* 2023).

The economic burden of treating biofilm-related infections is substantial. For example, treating *P. aeruginosa* biofilm infections in hospital settings costs between $20,000 and $80,000 per patient (Gupta and Ayan 2017). Additionally, biofilm-associated infections on medical devices, such as joint prostheses and implants, cost $1 billion annually in the U.S. (Rogers and Hudson 2013).

Given these challenges, there is an urgent need to develop alternatives to traditional antibiotics that can directly inhibit or eliminate biofilms.

5. Surface Modification Techniques for Polyurethanes to Enhance Antimicrobial Properties

Modern materials engineering and biomedicine increasingly utilize advanced surface modification techniques to meet the demands placed on contemporary biomaterials. It is essential to tailor the mechanical properties and optimize polymeric materials' chemical and topographical characteristics to enhance their functionality in various medical and technological applications. Developing innovative modification methods opens up new opportunities in designing materials with highly specific properties. This progress can drive advancements in tissue engineering, implant manufacturing, and drug delivery technologies (Fig. 3).

5.1. Laser Surface Texturing

One technique for processing polyurethanes is laser surface texturing (LST). This method modifies the surfaces of polymer biomaterials using a laser beam. LST offers numerous advantages, such as altering surface roughness and chemistry in a single step without using toxic substances. Laser surface texturing can also alter polymer surfaces on the macro-, micro, and nanoscale with high spatial and temporal resolution (Lippert 2004) (Fig. 4a).

Laser processing technology enables the creation of submicrometer structures on polyurethane surfaces, first documented for components around 250 nm in size. Studies have shown that periodic line-like patterns with spatial periods of up to 500 nm can be achieved using this technique. The depth of these structures ranges from 0.88 to 1.25 μm for periods larger than 2.0 μm. It reaches up to 270 nm for periods between 500 nm and 1.0 μm, demonstrating precise control over the parameters of the textures obtained (Estevam-Alves *et al.* 2016).

In comparison, the average size of most bacteria falls within the 1–2 μm range. As a result, surfaces with submicron topographies have been found to exhibit antimicrobial properties (Siddiquie *et al.* 2020). These properties are particularly relevant in the context of biomaterial-associated infections (BAI), where bacterial adhesion to the biomaterial surface is a critical first step in biofilm formation (Arciola *et al.* 2018). Submicron surface structures reduce bacterial adhesion by inducing stress on bacterial cell walls when the spacing between protrusions is less than 1.5 μm and by trapping air to decrease the apparent solid surface area available for bacterial attachment. While this does not equate to bacteriostatic or bactericidal activity, limiting bacterial adhesion is an important indicator of antimicrobial efficacy in preventing biofilm formation and subsequent infections (Siddiquie *et al.* 2020).

5.2. Nanoparticle Grafting

Nanoparticle grafting involves attaching nanoparticles to the surface of a polymer, often through covalent bonds, to enhance surface properties. This process allows for the modification of both the physical and chemical properties of the polymer and the nanoparticles, thereby expanding their application potential across various technological fields. Grafting nanoparticles onto polymers is typically achieved using chemical methods such as 'grafting to' and 'grafting from.'

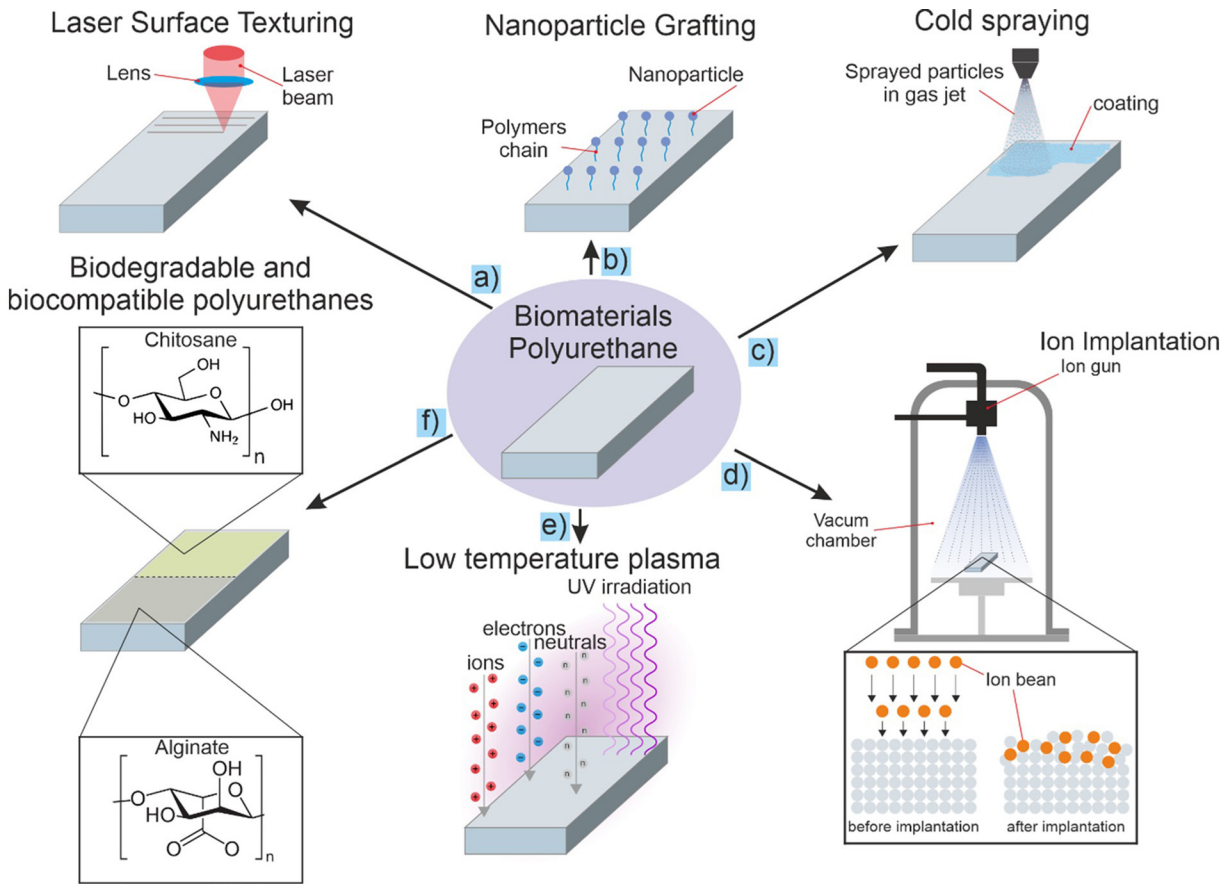

Fig. 4. Methods applied for the surface treatment of polyurethane polymers: a) Laser Surface Texturing, b) Nanoparticle Grafting, c) Cold spraying metallization, d) Ion Implantation, e) Low-temperature plasma, f) Biodegradable and biocompatible polyurethanes.

This technique is gaining popularity due to its ability to improve nanoparticles' dispersion, chemical reactivity, and stability within polymer matrices, making them more effective in advanced material applications (Kango *et al.* 2013) (Fig. 4b).

Various chemical techniques, including silane coupling agents, atom transfer radical polymerization (ATRP), and reversible addition-fragmentation chain transfer (RAFT) polymerization, are employed to graft polymers onto nanoparticles. These techniques allow fine-tuning of the surface properties of nanoparticles and their compatibility with polymer matrices, making them more versatile and practical in a wide range of applications (Kango *et al.* 2013).

One example of nanoparticle grafting is the creation of polyurethane nanofibers with incorporated ZnAg composite nanoparticles for use in antibacterial wound dressings. The grafting process involved synthesizing ZnAg composite nanoparticles (silver and zinc oxide) and incorporating them into polyurethane nanofibers (PUZnAg) through electrospinning. The resulting PUZnAg nanofibers demonstrated excellent antibacterial properties. Specifically, the $PUZnAg_2$ sample, containing 8% ZnAg by weight, exhibited 100% antibacterial efficacy against *E. coli*, *S. aureus*, and *Bacillus subtilis*, completely inhibiting bacterial growth. Furthermore, the nanofibers effectively prevented bacterial growth in the medium for up to 72 hours (Jatoi *et al.* 2020).

A similar technique was used for the single-phase synthesis of silver (Ag) nanoparticles embedded in polyurethane (PU) nanofibers. These PU/Ag nanofibers showed antibacterial efficacy against *E. coli* and *S. aureus*, forming inhibition zones of 11.4 mm and 10.8 mm in diameter, respectively. Additionally, the PU/Ag nanofibers were shown to be biocompatible, promoting fibroblast proliferation making them promising materials for medical applications, such as wound dressings (Pant *et al.* 2019).

Another potential application of polyurethanes is in flexible nanocomposite foams based on biocompatible thermoplastic polyurethane (TPU) and ZnO nanoparticles, which have potential uses as wound dressings. The TPU/ZnO foams were produced using the thermally induced phase separation (TIPS) method. This resulted in a highly porous structure with pore sizes ranging from 10 to 60 µm, allowing water vapor transport up to 8.9 mg/cm^2-h. The TPU/ZnO foams exhibited strong antibacterial activity against Gram-positive bacteria, such as *E. faecalis* and *S. aureus*, and Gram-negative bacteria, such as *E. coli* and *P. aeruginosa*. The highest

reduction in bacterial numbers, by up to 10^3 Colony Forming Units (CFU), was observed in foams containing 10% ZnO (Bužarovskaa *et al.* 2019).

5.3. Ion Implantation

Ion implantation is a process in which ions of a specific element are accelerated and introduced into the surface of a polymer, leading to the formation of metallic nanoparticles within the polymer matrix. This technique allows for the modification of both the chemical and physical properties of the surface without altering the bulk material's properties. Ion implantation enables the creation of advanced metal-polymer nanocomposites with enhanced mechanical properties, such as increased strength, wear resistance, and improved electrical conductivity. This method is widely applied in medical implants, biomaterials, and electronics (Popok *et al*. 2014). Ion implantation also provides precise control over the depth and distribution of nanoparticles within the polymer, influencing properties such as surface conductivity and roughness. This level of control is crucial for applications like surface plasmon resonance, which plays a key role in photonics and sensor technology (Salvadori *et al*. 2014) (Fig. 4d). PUs are being modified to enhance their antimicrobial properties, which are essential for reducing the risk of infections associated with medical implants.

Recent studies have demonstrated significant microbiological effects of modifying polyurethane (PU) surfaces using nitrogen ion implantation (N_2^+). This treatment substantially reduced the viability of *S. epidermidis* colonies, decreasing their survival by 3 to 5 times compared to unmodified PU. Additionally, a significant reduction in the total number of bacteria adhering to the surface was observed. These effects remained stable over time, with antibacterial properties persisting for up to 11 months post-treatment. The reduction in bacterial adhesion and viability was closely associated with structural changes in the surface, including increased roughness, the development of an undulating morphology, and enhanced surface hydrophilicity (Morozov *et al*. 2019).

The plasma ion implantation (PIII) method also shows great promise in improving the antimicrobial properties of polymeric biomaterials, such as polyurethane (PU) and polyethylene terephthalate (PET). This technique significantly reduces bacterial adhesion on modified materials, crucial for preventing infections related to medical implants. For instance, PIII-modified PET surfaces treated with acetylene (C_2H_2) exhibited a marked decrease in the adhesion of bacteria, including *S. aureus*, *S. epidermidis*, *E. coli*, and *P. aeruginosa*. Structural changes induced by the modification, such as increased roughness and enhanced hydrophilicity, were key factors contributing to the reduction in bacterial growth. These findings highlight the potential of the PIII method as an effective tool for creating antimicrobial biomaterials that reduce infection risks and enhance the safety of medical implants (Huang *et al*. 2004).

5.4. Cold spraying

Cold spraying, also known as cold dynamic gas spray (CGDS) technology, is an advanced method of applying coatings and depositing powder materials to various surfaces. The process involves accelerating powder particles to supersonic speeds (300–1200 m/s) using a gas jet (e.g., nitrogen, helium or air) passed through a special nozzle. After hitting the substrate, the particles experience intense plastic deformation phenomena, which enables effective adhesion without melting the material (Dai *et al*. 2024).

Cold spraying is emerging as a promising technique for biomedical applications, particularly for improving the properties of PUs. The process involves the deposition of various materials, including metals, ceramics, and composites, onto the surface of polymers without the risk of thermal degradation, which is essential for medical materials. One of the key application areas for this technique is to improve biomaterials' biocompatibility and antimicrobial properties, which is particularly important in medical devices such as prostheses and internal fixation systems. With cold spraying coatings, these biomaterials can achieve improved cell adhesion, reduced cytotoxicity, and improved mechanical properties, making them ideal for implant applications (Vilardell *et al*. 2015; Dosta *et al*. 2018) (Fig. 4c).

Another example of using cold spray metallization techniques is the production of copper coatings on carbon steel. Silva *et al.* (2019) demonstrated that these coatings, characterized by a dense microstructure and low porosity, exhibit strong antibacterial properties against *S. aureus*, achieving complete bacterial mortality (100%) within 10 minutes of direct contact under controlled experimental conditions. The antibacterial mechanism involves the release of copper ions, which damage bacterial cell membranes and disrupt protein structures. The high copper content on the surface is essential for antibacterial efficacy. Notably, the coating produced by this method is nearly oxide-free, ensuring direct contact between the copper and bacteria, which enhances its antimicrobial performance. These findings suggest that copper cold spraying coatings could be effective antibacterial surfaces, with potential applications in hospital equipment and touch surfaces in public spaces (Silva *et al.* 2019).

5.5. Polyurethane-biopolymer composites for antimicrobial and biofilm-preventive applications

The integration of natural biopolymers into polyurethane (PU) matrices is a promising approach to enhance their antimicrobial properties and prevent

biofilm formation. Modifying PUs with components like chitosan and alginate during synthesis makes it possible to create materials with improved biocompatibility, biodegradability, and antimicrobial properties (Uscátegui *et al*. 2019) (Fig. 4f). Composites are materials composed of two or more components with different physical, chemical or mechanical properties that remain separate but work together to produce unique properties (Biermann 2019)

Chitosan is a natural polysaccharide derived from crustaceans, making it a dedicated and renewable resource. Studies have shown that it is biocompatible, biodegradable, bioadhesive, non-toxic, and possesses antimicrobial properties (Confederat *et al*. 2021). Due to these attributes, chitosan is widely used in applications such as wound dressings, surgical sutures, and scaffolds in tissue engineering, among others (Wu *et al*. 2018). Similarly, alginate, a polysaccharide derived from brown algae, is valued for its biocompatibility and capacity to support tissue regeneration. Alginate-modified PUs form hydrogels that can trap bacteria, limiting their mobility and reducing biofilm growth. These composites have demonstrated antimicrobial activity by acting as physical barriers and delivering antimicrobial agents directly to the infection site (Zafar *et al*. 2022).

Building on this foundation, the research team led by Villani *et al*. developed a polyurethane composite incorporating chitosan (Chit) as a functional filler within a thermoplastic polyurethane (TPU) matrix. With its well-documented antimicrobial properties, chitosan was integrated into the TPU matrix to enhance biological performance. The resulting TPU-Chit composite exhibited significant antimicrobial activity, particularly against *S. aureus*. This antimicrobial effect was primarily attributed to the anti-adhesion properties of chitosan, which reduced bacterial attachment to the composite surface and inhibited biofilm formation. The effectiveness of the composite was selective, with *S. aureus* growth reduced by 20% to over 50%, depending on bacterial concentration, while no significant effect was observed against *E. coli*. Additionally, scanning electron microscopy (SEM) confirmed structural damage to *S. aureus* bacteria adhering to the composite surface, including cell wall deformation, indicating a reduced capacity for growth and adhesion (Villani *et al*. 2020).

The research conducted by Khan *et al*. focused on the development of polyurethane (PUR) membranes modified with sodium alginate (SAg) to enhance their antimicrobial properties. By incorporating sodium alginate as a filler, the team explored its impact on the structural and functional characteristics of the membranes. Antimicrobial testing of the PUR-alginate membranes was performed using Gram-negative (*E. coli*) and Gram-positive (*Bacillus cereus*) bacteria. The study revealed that the membranes effectively inhibited bacterial growth, with *B. cereus* demonstrating a higher sensitivity to the alginate content. Membranes with increased alginate concentrations produced larger bacterial growth inhibition zones, indicating a clear link between alginate levels and antimicrobial efficacy. In the case of *E. coli*, a gradual reduction in bacterial proliferation was observed, likely due to the enhanced hydrophilicity of the alginate-modified membranes. Khan *et al.* proposed that the antimicrobial mechanism arises from the interaction of alginate's carboxyl groups (-COOH) with bacterial cells. The dissociation of protons from these groups lowers the local pH, compromising bacterial cell walls. Additionally, carboxylate ions can bind to positively charged components of bacterial cells, disrupting essential cellular processes. Overall, incorporating alginate into polyurethane membranes improved their hydrophilicity and significantly enhanced their antimicrobial performance, particularly against *B. cereus* (Khan *et al*. 2021).

In summary, incorporating natural biopolymers like chitosan and alginate into polyurethane matrices enhances their antimicrobial efficacy by disrupting bacterial adhesion and biofilm formation. These modifications address critical challenges in biomaterials engineering, particularly for medical devices prone to infection.

5.6. Plasma modification

Plasma, often referred to as the fourth state of matter, is a powerful tool for surface modification of polymers, including polyurethanes. Plasma treatment involves the exposure of polyurethane surfaces to a gaseous environment containing ions, radicals, and photons (visible and near-UV), leading to physical and chemical surface modifications (Friedrich *et al*. 2012; Thakur and Vasudevan 2021). The concept of polymer functionalization is based on exposing the modified surface to plasma, which results in the attachment of atoms or fragments of dissociated plasma gas as functional groups through H-substitution in the polymer chain. Since many different fragments and atoms are present in plasma, a wide range of functional groups can be produced (Friedrich *et al*. 2012; Thakur and Vasudevan 2021) (Fig. 4e).

The interaction of plasma with polymer materials can be divided into three stages:

Surface cleaning: In this stage, organic impurities are mainly removed.

Chemical modification: In this stage, C-C and C=C bonds are broken, and fragments of dissociated plasma gas are incorporated as functional groups through H-substitution in the polymer chain.

Surface etching and nanotopography creation: For longer exposure times, plasma etches the surface and creates nanotopography.

However, a significant challenge lies in introducing plasma energy into polyurethanes. While this energy is necessary to sustain the plasma state, it also poses a risk of degrading the polymer material. Excessive energy delivery can break C-H and C-C chemical bonds, which are crucial for the structural stability of polymers (Friedrich *et al*. 2012; Thakur and Vasudevan 2021).

In biomaterials engineering, there are various surface treatment methods in which plasma plays a key role. Low-temperature plasma is one of the most effective techniques for surface modification of biomaterials, such as polyurethanes. Due to its unique properties and wide range of applications, this method allows selective surface modification in inert (e.g., argon) or reactive (e.g., oxygen) atmospheres, providing precise control over the chemical changes introduced. For polyurethanes, the modification must be tailored to the specific material, considering chemical composition, crystallinity, and thickness factors. It is essential to optimize parameters like the type of feed gas (oxidizing, reducing, inert), gas partial pressure, plasma generator power, and exposure time. Thanks to its flexibility, low-temperature plasma is particularly effective in enhancing the surface properties of polyurethanes without altering their bulk characteristics (Alves *et al.* 2011; Cvrček *et al*. 2019; Drożdż *et al*. 2024).

6. Summary

Polyurethanes (PUs) have emerged as highly versatile materials in modern medicine, offering unparalleled opportunities for innovation in medical devices ranging from wound dressings to artificial heart valves. Their exceptional mechanical properties, adaptability, and biocompatibility make them indispensable in diverse medical applications. However, parent PUs lack intrinsic antimicrobial properties, posing significant challenges in preventing biofilm formation and associated infections.

Innovative surface modification techniques, such as laser texturing, nanoparticle deposition, ion implantation, and plasma treatments, show great promise in addressing these challenges. These methods enhance the antimicrobial properties of PUs and improve their biocompatibility, paving the way for safer and more effective medical devices. Furthermore, integrating natural polymers and biodegradable components into PU matrices offers an additional avenue for enhancing their functionality while aligning with sustainability goals.

Looking forward, further research should focus on translating these laboratory advancements into clinical settings, optimizing the long-term performance of PU-based biomaterials, and exploring their applications in regenerative medicine and personalized therapies. Overcoming these challenges will require multidisciplinary collaboration, combining materials science, microbiology, and clinical expertise to unlock the full potential of polyurethanes in healthcare.

By advancing the design and functionality of polyurethane biomaterials, the scientific community can contribute to groundbreaking innovations that will enhance patient outcomes and inspire new directions in biomaterials science. This review underscores the need for continued focus on addressing infection risks while maximizing the unique advantages of polyurethanes in modern medicine.

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