Silicone-based biomaterials for biomedical applications: antimicrobial strategies and 3D printing technologies

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Silicone is a synthetic polymer widely used in the biomedical industry as implantable devices since 1940, owing to its excellent mechanical properties and biocompatibility. Silicone biomaterials are renowned for their biocompatibility due to their inert nature and hydrophobic surface. A timeline illustration shows critical development periods of using silicone in varied biomedical applications. In this review, silicone properties are discussed along with several biomedical applications, including medical inserts, speciality contact lenses, drains and shunts, urinary catheters, reconstructive gel fillers, craniofacial prosthesis, nerve conduits, and metatarsophalangeal joint implants. Silicones are prone to microbial infections when exposed and interactions with the host tissue. As in the case of medical inserts, the development of specific antimicrobial strategies is essential. The review highlights silicone implants' interaction with soft and bone tissue and various antimicrobial strategies, including surface coating, physical or chemical modifications, treating with antibiotics or plasma-activated surfaces to develop the resistance to bacterial infection. Finally, 3D printing technology, tissue engineering, regenerative medicine applications, and future trends are also critically presented, indicating the silicone's potential as a biomaterial.

1 Introduction

Silicone or polysiloxane is a synthetic polymer widely used in biomedical applications. It is made up of silicon, oxygen, carbon, and hydrogen. The material is a mixture of semi-inorganic polymeric molecules consisting of an array of polydimethylsiloxane [$(CH_3)_2$-SiO] monomers chains of different length [1]. The physical property of silicone is determined by the average length and the degree of cross-linking between its polymer chains. The highly ionic Si-O bond results in high bond strength, thus giving silicone its high thermal and chemical stability. Fig. 1 shows a synthesis of a common form of silicone (polydimethylsiloxane (PDMS) with chemical structure [2]. Fig. 2 displays some of the key milestones in silicone development as well as its application as a biomaterial.

1.1 Properties of Silicone

Silicone polymers are versatile and can be formulated into various distinct material types, including elastomers, gels, adhesives, and more, depending on the intended application. One of the standout properties of silicone is its low glass-transition temperature at approximately -120°C, enabling the material to retain its flexibility at extreme temperature conditions, for example, in

cold storage. Some other critical physical properties of silicone are high elasticity and high hydrophobicity, with a water contact angle of 101° to 109°. Table 1 summarises a few fundamental properties of PDMS compared to other common soft polymers [1]. One of the advantages of silicones is their ability to maintain their mechanical properties from -40ºC to +185ºC. Silicone elastomers are available in a wide range of hardness, have good UV resistance, excellent thermal and chemical resistance. Also, it possesses good electrical properties, flame resistant, and allows sterilisation using steam, autoclave, or gamma radiation[2]. Silicone is highly permeable to gases, optically transparent, and easy to manufacture [3]. Silicone is very versatile and can be formulated into various forms, depending on its intended applications. Silicone elastomers are widely used in medical device applications. Below are some of the common forms of silicone-based materials [1].

- Silicone elastomer
- Silicone gel
- Silicone adhesive

1.2 Biocompatibility and Biodurability

Silicone is highly biocompatible and bio-durable when interacting with host tissues. The hydrophobicity and low surface tension of silicone results in high hemocompatibility and reduces the potential of encrustation when contacting the various body fluids [4,5]. Silicone is also generally unaffected by host tissue attack and repeated sterilisation due to its widely recognised chemical and thermal stability [5]. These properties favour the use of silicone biomaterial in various biomedical applications. Silicone elastomer is used as tubing for catheters or drains that requires it to be transparent, flexible, inert, lubricant, and biocompatible; insulation for electronic implants (pacemaker leads). Silicone adhesive or elastomer is also used for wound dressing because it is biocompatible, comfortable, and allows air permeability. Silicone gel is used in the treatment of hypertrophic burn scars [6], whilst silicone rubber is widely used in prosthesis [2].

2 Biomedical Applications of Silicone

The silicone applications range from extracorporeal equipment, catheters, drains, shunts, various long-term implants, orthopaedic implants, and aesthetic implants [7]. The following section provides a critical discussion of various biomedical devices applications, highlighting silicone material properties and the antimicrobial strategies for each application. The diverse applications of silicone are given below [4,5].

- Coating, treatment, or assembly of various medical devices
- Inserts and implants to replace various body parts
- Catheters, drains, and shunts used for medical treatment and short-term implant
- Aesthetic implants
- Specialty contact lenses

Table 2 demonstrates diverse examples of silicone implants in various locations in the human body. Silicone can be inserted into almost every part of the human body, highlighting its great versatility and biocompatibility owing to its hydrophobicity and inertness. Some key functional properties of silicone are listed below [5,8].

- Silicone elastomers are relatively firm and flexible.
- Form stability under a wide range of temperature and chemical conditions.

- Hemocompatibility due to its hydrophobicity, thus retaining blood properties.
- Silicone has a high permeability to gases, including oxygen, carbon dioxide and moisture.
- It is inert, non-toxic, and nonbiodegradable.

2.1 Silicone in Biomedical Devices

Silicone surface treatment on glassware and needles helps to preserve blood from clotting for a longer period[2]. Researchers at the Mayo Clinic demonstrated during 1949 that blood has insignificant changes in coagulation time after being left in silicone-coated syringes[5]. Silicone pre-coated needle reduces pain, which was evident in the penetration force diagram (Fig. 3)[8]. Silicone coating significantly reduces the load when the needle penetrates the skin surface, indicating greater ease of penetration, explaining patients' less pain. Since then, silicone is used as a coating for needles, syringes, and blood collection vials. The purpose of precoating is to leverage silicone's favourable surface properties onto these medical devices, such as its ability to preserve blood and lubricating ability, which reduces insertion force. Silicone tubing and membranes are also widely used in kidney dialysis, blood-oxygenator, heart-bypass machines, and heart valves. Silicone tubing is preferred in these applications again due to its stability, hemocompatibility, and high oxygen permeability required when transporting body fluids [2, 4].

2.2 Silicone as Medical Inserts and Implants

It is interesting to note that Frank H. Lahey was the first to report silicone elastomer implant in humans. In April 1946, he reported that 'bouncing clay' was used to repair bile ducts. In 1948, Dr. DeNicola completed the first human male urethra replacement by threading a 9.5cm long silicone tube through catheterisation. Another significant milestone was developing silicone finger joint implants by Dr. Alfred Swanson in 1968, with support from Dow Corning, where silicone was used as a spacer to replace cartilage function and soft tissue at the finger joints. In 1969, silicone was also adopted in the total knee replacement, functioning as a shock absorber between the tibial and femoral components [5].

Implants made of silicone is widely used in various location in the human body. Table 2 illustrates some examples. The primary purpose of these inserts and implants is to repair the damaged body parts such as tracts and soft bones. Fig. 4 illustrates the treatment of arthritis, where a silicone implant is inserted in finger joints to replace the function of cartilage, which is a firm but flexible connective tissue, much like the properties of silicone. The versatility of silicone implants is mainly due to their high elasticity, chemical, and thermal stability. Silicone is also inert to body fluids and nontoxic, which resulted in it being very suitable for long-term implantation without adverse biocompatibility and biodurability complications [6, 7].

2.3 Silicone Speciality Contact Lenses

Silicone hydrogel lenses were first introduced to the market relatively in 1998, in which they were specially designed for continuous wear to facilitate the recovery from ocular tissue injuries. Between October 2000 and April 2002, a clinical trial with 70 patients with various eye conditions conducted in the Department of Ophthalmology of the Medical University of Warsaw. The results showed that silicone hydrogel lenses were effective as therapeutic lenses where 91% of patients over 18 months reported improvement [6]. None of them reported any adverse condition [6]. Yesilirmak et al. reported in 2013 that patients reported no infection after seven years of continuous wear with daily antibiotic drops [9]. Silicone contact lenses can achieve such breakthrough in

continuous wear, mainly due to their high oxygen permeability, which is 5 to 10 times higher than typical disposable hydrogel lenses. It also has a favourable bacterial property which significantly reduces the possibility of bacterial infection [10]. To correct the vision of the wearer, contact lenses are used. When worn, the contact lens interacts with the corneal, conjunctival epithelia, and the ocular surface tear film. Silicone can be used in the fabrication of contact lenses in the form of silicone hydrogel, which was first introduced into the market in 1999 [8, 9].

Silicone has excellent oxygen solubility and low chemical reactivity, allowing it to retain hydrogels positive attribute when incorporated with the soft lens. However, silicone is hydrophobic by nature and can cause discomfort to the user through the destabilisation of the tear film [12]. A hydrophobic lens can also lead to the accumulation of deposits on the lens; thus, modification is required for silicone hydrogel to be compatible with the ocular surface. Typical modification includes surface treatment or the application of a soluble polymer in the material to produce an interface between the tear film and the lens [11,12].

The incorporation of siloxane with soft contact lens material increases the contact lens oxygen permeability compared to a conventional contact lens, as summarised in Table 3. The increase in oxygen permeability allows silicone hydrogel contact lenses to be worn for a more extended period than conventional contact lenses [13,14]. Besides extending the wear capabilities, the use of silicone hydrogel contact lenses leads to fewer complications when compared to conventional contact lens such as eliminating lens-induced hypoxia in the most wearer and reducing the stress-induced corneal homeostasis compared to conventional contact lenses [12,14]. Despite its advantage, users of silicone hydrogel contact lenses are still susceptible to irreversible effects on corneal homeostasis from prolonged use of contact lenses. Also, the high elastic modulus of silicone hydrogel lens can lead to a more significant mechanical abrasion impact on the corneal surface than the conventional lens, which can be minimised by optimising the lens design [12].

2.4 Drains and Shunts

A shunt is a flexible tube used to drain the brain's excess fluid, usually in the brain's lateral ventricles. Hydrocephalus is a condition that causes the head to swell due to the build-up of cerebrospinal fluid in the brain. The shunt is a medical device that consists of three components – inflow or proximal catheter that drains the cerebrospinal fluid from the lateral ventricles; a valve mechanism that regulates the pressure by controlling the fluid flow in the tubing; and the third part is the outflow or distal catheter that drains the cerebrospinal fluid to the abdominal cavity or suitable drainage site [15]. Casey Holter, a months-old baby, suffered from this condition. A shunt catheter was implanted made of polyethylene, which did not have a valve to prevent backflow. This was later rectified using a silicone elastomer supplied by Dow Corning. The first successful implant of Holter Shunt was completed in March 1956 and is still in use saving many children from this health condition which, if not treated in time, will cause brain damage (Fig. 5) [16]. A surgical drain is a thin and flexible tube but is mainly used to drain fluids such as pus and blood out from the body. On the other hand, a shunt is a passage that facilitates movement from one part of the body to another and is usually a more complicated system that requires valves to control the direction of fluid movement. [5,17].

2.5 Urinary catheter

A catheter is a thin and flexible tube that is used commonly in medical treatment for various purposes. Urinary catheters can be used for urine drainage from the bladder for patients with a

physical obstruction that obstructs urine flow, faulty bladder muscles or nerves, incontinence, and unconscious patients. They can also be used to measure urine from patients who are incapacitated or young children that are not toilet trained and obtained a clean urine sample that is uncontaminated [18]. It is inserted into a body cavity, duct or vessel to allow draining or administration of fluids [18]. Some common examples are urinary catheter and peritoneal Catheter [7,19].

A catheter can be made from various materials or combinations such as silicone, latex rubber, or polyvinyl chloride (PVC). The choice of material can depend on various factors such as the specific application and the intended duration in situ. As shown in Table 4, silicone is inert and can be used without any lubrication yet achieve the longest time in situ [19]. Also, the hydrophobicity of silicone surface limits encrustation, which again explains its suitability for long-term usage. Silicone adhesive also adheres well to the skin and does not cause irritation, and possesses good permeability to gasses and moisture [5]. Silicone's biocompatibility, modest resistance to abrasion, low surface tension, good thermal and chemical stability make it the ideal choice[20]. Numerous urinary catheter variations are available in the market; however, specific attention is offered to condom and foley catheters in this review (Fig. 6).

Condom catheters are typically used by a male patient who suffers from urinary incontinence. It comprises a sheath, known as the condom, which houses the penis and a tube that connects the tip of the sheath to a collection bag where the urine will be collected. While a condom catheter can be an attractive choice as it is being worn externally, the condom is susceptible to detachment leading to urine leakage. Also, it was reported that 15% of condom catheter users suffered from either necrosis, ulceration, inflammation, gangrene, or constriction of the skin of the penis, and 40% of users developed a urinary tract infection [21].

The foley catheters comprise two channels, the drainage channel and the inflation channel. The drainage channel is used to drain the urine, while the inflation channel inflates the balloon at the end of the catheter with sterile water. The inflated balloon allows the catheter to be retained within the bladder. Foley catheter can be connected to the bladder by either transurethral or suprapubic catheterisation [21]. Transurethral catheterisation refers to the insertion of a foley catheter through the natural ureteral passage. In contrast, suprapubic catheterisation refers to creating a track from the bladder to the lower abdominal wall.

Antimicrobial strategies for urinary catheters are achieved through the use of coatings with antifouling or biocidal properties. The use of antifouling coasting hinders the formation of biofilm by preventing bacteria attachment on the surface. There are three mechanisms of antifouling coating to prevent bacteria attachment on the surface of the urinary catheter. They are electrostatic repulsion, steric repulsion, and low surface energy. Biocidal coatings decrease the deposition in the urinary catheters by killing the microbes. Silver and antibiotics have been identified as active ingredients among the clinically tested biocidal coatings [20]. The mechanism of biocidal action can be broadly categorised into five categories, as summarised in Table 5.

2.6 Silicone as Reconstructive Gel Fillers in Plastic Surgery

The breast reconstruction procedure has been around for more than a century since the first lipoma transplant was conducted in 1895 [22]. Since then, various materials have been used as breast fillers, including glass balls and uniquely formulated poly (vinyl alcohol). Silicone was first introduced

in 1961, where a silicone gel-filled breast implant was developed by Doctors Cronin and Gerow, with materials supplied by Dow Corning. Subsequently, the first pair of silicone gel-filled breast was implanted in 1962. Silicone breast filler was popular for decades, but controversies related to breast cancer, tissue disease, and quality complications lead to rupture, infection, or capsular contracture resulting in FDA restrictions in 1992. In 2006, FDA restrictions were lifted with improved manufacturing practices and the lack of credible causal relationship between breast implants and diseases related to connective tissues [5].

Silicone gel has been used to recover soft tissue mass in the breast, scrotum, chin, nose, cheek, calf, and buttocks via reconstructive plastic surgery. These implants sometimes consist of an outer shell made of silicone-containing filler made of either silicone gel or saline [5]. The fundamental properties of silicone that made it such a popular choice as soft tissue replacement are its ideal texture and stability. Besides, the implant must be nonbiodegradable, non-toxic, porous, and must not spread in order for it to be successfully accepted by the host [23].

One of the most well-known biomedical applications of silicone implants is their use in mammary prosthesis, most known as breast implants. The primary function of breast implants is to enhance the dimensions of the person's breast. There are typically administered to restore the breast's shape for patients who have to undergo mastectomy or correct deformities from congenital disabilities. Besides its use in reconstructive plastic surgery, individuals have also used breast implants for aesthetic purposes.

The primary construct of a silicone breast implant comprises a shell made from Silastic silicone rubber that is filled with soft silicone gel [14]. Silicone's biocompatibility, thermal stability, low surface tension, and low chemical reactivity make it suitable for use as a shell for implant [1]. First-generation silicone breast implants were introduced in 1962 by Cronin and Gerow; since then, significant improvement has been made on the implants' shell and filler material. For example, the shell has been made thicker with three silicone elastomers layers to reduce the gel bleed occurrence. The silicone used in the breast implant filler has also been modified to increase its durability and reliability [1].

After implantation, the host tissue's immune response would be triggered as it identifies the silicone implant as a foreign object. The initiated immune response results in a collagen fibre capsule to be formed around the surface silicone implant. While the formation of the capsule is a normal tissue response and is relatively harmless, it becomes problematic when the capsule around the silicone implant contracts. The contraction will cause the breast to deform and harden, resulting in a complication known as capsular contracture [24].

Capsular contraction formation can be exacerbated by infection, haematoma, silicone implant leakage, and trauma. Several studies have associated capsular contraction formation with the biofilm formed by *Staphylococcus epidermidis* on the implant's surface. Prevention of initial formation of biofilm is achieved by administering systemic antibiotics or antiseptic washing of the breast cavity to a varying degree of success. In-vitro experiment exploring the application of the antimicrobial coating on breast implants, chloramphenicol, fusidic acid, and oxytetracycline was shown to prevent biofilm formation for a minimum of 7 days [25].

2.7 Craniofacial prosthesis

Silicone is used extensively in the fabrication of craniofacial prostheses such as ear, nose, or eye/eyelids prosthesis. Modern silicone is a suitable material for the fabrication of craniofacial prosthesis as they are flexible and adapts readily to body temperature [26]. These silicones can be manipulated to be transparent by restricting the material's thickness, which increases the material's ability to blend into the face seamlessly when applied. In addition, modern silicone can be infused with pigments and hairs to improve the overall aesthetic of the prosthetic [26].

A craniofacial prosthesis is artificially fabricated to replace part of the face that has been lost by trauma, disease, or congenital disabilities [27]. It can be both physically and psychologically traumatising for a patient living with facial defects leading to psychosocial dysfunction of the patients [26,28]. The use of well-made craniofacial prosthesis can improve the patient's self-confidence and self-esteem, thereby enhancing their quality of life [26,28].

Fig. 7 shows an auricular prosthesis and a completed orbital prosthesis, respectively. An auricular prosthesis needs to be replaced every 2-3 years because of a change in colour and structure [26]. An orbital prosthesis consists of an ocular prosthesis insert, artificial eyelashes, and fixed eyelids [28]. To reduce the chance of infection of tissues in contact with the silicone prosthesis, regular cleaning of the silicone prosthesis using chemical disinfectant is required. Common antimicrobial strategies employed involve removing biofilm through toothbrushing or washing by hand with a mild soap solution [29].

With the advancement of additive manufacturing, direct 3D printing of silicone prosthetics is possible. CAD/CAM technology precisely develops prosthesis with soft tissues with 3D printing and rapid prototyping [30,31]. Fig. 8 illustrates direct 3D printed silicone nose prosthetic and silicone ear prosthesis, respectively. It is evident from both figures that the technology is far from ideal and requires post-processing, such as surface finishing, to improve the silicone prosthetic aesthetic.

2.8 Peripheral nerve conduit

Silicone tube segments can be used as a nerve conduit to assist in nerve regeneration for patients with peripheral nerve gaps [32,33]. This treatment is known as tubulisation. It involves enclosing both ends of the severed nerve in a tube [32]. In addition to bridging the nerve gap, the usage of the silicone tube segment helps to shield the nerve from surrounding tissues preventing scar formation and helps to guide the regenerating axons to the distal nerve stump [32,34] Fig. 9A illustrates the transplantation of the silicone tubing to the severed sciatic nerve of a rat and Fig. 9B shows the regenerated nerve eight weeks after the implant surgery.

Silicone tubes are soaked in either heparin saline or standard saline solution before used [32]. Also, to prevent the formation of blood products and clots in the enclosed area, the conduit's lumen is filled with sterile saline water [32]. Silicone is a suitable material for synthetic nerve conduits as it is biocompatible and does not break down readily. Its resistance to degradation ensures sufficient time for axons to regenerate, thereby allowing the nerve to regenerate and mature [32]. However, the material also has its drawbacks. Firstly, silicone is nonabsorbable and not biodegradable. It will remain in the body after the nerve has regenerated and will result in the formation of a permanent fibrotic encapsulation around the implant leading to the compression of the newly generated nerve [32]. The compression of axons in the silicone implant can lead to the late loss of functional recovery [32]. Also, the use of silicone tubing can cause discomfort, as discussed in a study investigating the

repair of the forearm median and ulnar nerve using silicone tubing [33]. In a study, seven out of 26 participants wanted removal of silicone tube due to the irritation caused by the implant and the loss of nerve function [25, 26].

2.9 First metatarsophalangeal joint implant

This section will discuss the use of silicone implants as a replacement for the first metatarsophalangeal joint. The usage of the first metatarsophalangeal joint implant is an alternative treatment for patients with end-stage arthritis [35]. The primary goal of the joint implant is to restore motion and relieve pain to the patient [36].

The use of the silicone implant to replace the first metacarpophalangeal joints was introduced in 1967 [36]. Before the use of silicone, the uncemented metal metatarsophalangeal joint implant was used in the 1950s [35]. These early implants lead to significant complications such as implant loosening, implant instability, and bone resorption [36]. Silicone became a favourable choice for the implant as it is biocompatible, has good thermal and chemical stability.

In the original iteration of the silicone implant, a single-stem silicone rubber implant was used following a resection arthroplasty to replace the base of the proximal phalanx [36]. Subsequently, a constrained double-stemmed silicone elastomer implant with a flexible hinge was introduced. These flexible hinges of the implant were used to replace both the base of the proximal phalanx as well as the head of the first metatarsal. These implants have a high failure rate that is attributed to the wear and tear caused by high shear force and the interaction of the implant with sharp edges of bones [36]. Metal grommets were added to reduce the double-stemmed implant's failure rate by creating an interface between the hinge of the implant, and the bones [35,36]

The silicone implants act as a dynamic spacer, and it restores the joint user motion while retaining its alignment and joint space [36]. However, these implants are susceptible to degradation from ageing, leading to failure. When the silicone implant fails, it will shorten the first ray, leading to a cock-up deformity of the hallux [35]. The patient will then have to decide to either remove or replace the silicone implant or arthrodesis treatment [35]. Besides, the particulate debris from silicone implants can cause lymphadenopathy, reactive synovitis, osteolysis, and granulomatous reactions [36]. Antimicrobial strategies applied to orthopaedic implant includes the application of antiseptic, antibiotic, antiseptic, photoactive-based, and nano-silver coatings [37].

3 Antimicrobial Strategies of Silicone Biomaterial

Antimicrobial strategies use on contact lenses can be broadly categorised as active and passive chemical strategies. Active chemical strategies use microbicidal chemicals to eliminate microorganisms by meddling with key microbial cell processes, while passive chemical strategies prevent microorganism adhesion. Examples of active strategies include producing concentrated superoxide toxic to microbial cells or causing cell lysis by physically disrupting the microbial cell membrane. Some of the antimicrobial agents categorised under active chemical strategies include silver, free-radical producing agents, antimicrobial peptides, quorum-sensing blockers (furanone), non-steroidal anti-inflammatory drugs [38]— Fig. 10 schematic displaying different explored antimicrobial agents to design antimicrobial contact lenses.

Passive chemical strategies modify the surface properties to prevent microorganism adhesion and the formation of biofilm. One such example would be the covalent attachment of 2-methacryloyloxyethyl phosphorylcholine to the silicone lens. This treatment increases the hydrophilicity of silicone lenses, reducing macrophage's surface adhesion, lens epithelial cell, and platelet. Alginic acid, poly(ethylene glycol) of varying chain lengths, and superhydrophilic zwitterionic interfaces are other coatings studied that hinder microorganism adhesion [17]. While being extremely biocompatible, silicones are highly hydrophobic and a significant attraction for bacterial, proteins, and biomolecules adherence, potentially leading to severe infection that might cause death [7].

In most catheter applications, antimicrobial strategies are critical as the catheter exposes the implant location to the atmosphere and invites bacterial adhesion. Ironically, the second most common cause of death to peritoneal dialysis (PD) patients is through the PD catheter, where omental wrapping and infection occurs either through biofouling from protein adsorption and cell adhesion or bacterial attachment [39].

Silicone breast implant augmentations were noted to promote inflammatory responses. Visible deformation was noticed around the prosthetic, and over a long term, calcification was observed (fibrous envelope around the implant), leading to pain and skin deformation resulting in removal or replacement of implants. It is worth noting that bacterial contamination from *Staphylococcus epidermidis* at the implant's surface results in excessive fibrotic reaction [3]. Various antimicrobial strategies are reported to ensure the implant is antimicrobial such as bacteria repelling, bacteria-killing, adsorption of proteins or protein conformation, immobilisation of biomolecules – enzymes, peptides, drugs, bioactive polymers, and introduction of inorganic components (SiO_2, TiO_2, ZnO metal) and nanoparticles [3,40,41].

Bacterial contamination of breast implants due to infection and capsular contractures is significant [42]. The post-operative capsule around the implant is a thin and protective barrier between the foreign material and body that can become pathogenic form called capsular contractures [3,42]. Surface coatings of implants are pretty standard by immersing the implant with an antiseptic solution (betadine or hydrogen peroxide) before surgery; however, most complex coatings using nanoparticles or antibiotics were recently developed to resist bacterial growth using the bactericidal mechanism. Studies have shown that plasma-activated silicone surfaces offer better coating with antibiotics that inhibited both gram-positive and gram-negative growth [43]. Researchers added that plasma activation of silicone implant changes its surface properties from water-repelling to water-absorbing, allowing antibacterial agents to get adsorbed on the implant's surface. Plasma activated silicone discs were treated with 10% povidone, iodine, Cefazolin, or Gentamicin and were exposed to *Staphylococcus aureus* or *Pseudomonas aeruginosa.* They added that plasma-activated silicone discs with antibiotics inhibited bacterial growth compared to non-plasma activated discs [43].

Surface modification techniques have been commonly employed to improve the antibacterial properties of catheters. Anjum et al. presented four major biomodification strategies for urinary catheters: functionalisation, coating, drug impregnation, and blending. The first two results in bacteriostatic surfaces, whereas the latter two results in bactericidal surfaces (Fig. 11) [44]. Functionalisation can be achieved through gamma, UV or plasma activation, where free radicals are grafted to the functionalised catheter surface, thus adding polymer brushes and bioactive agents, preventing adhesion of bacteria. Silicone catheter surface can also be coated with

combinations of antimicrobial agents and antibiotics. The drug impregnation process submerges the catheter in antimicrobials, such as chlorhexidine and triclosan, allowing the solvent to swell the catheter overtime before drying it and leaving the silicone catheter with a bactericidal surface. For blending, a bioactive agent is directly added to the formulation of the catheter material. However, it was not discussed if this method is used on silicone catheter [44].

Li et al. noted that hydrophilisation of silicone PD catheter surface is usually temporary, as PDMS can recover the hydrophobic surface within hours by rearranging its polymeric chains. They have also presented a more effective technique through the attachment of hydrophilic functional polymers via covalent bonding, such as PEG polyethylene glycol, which delayed hydrophobic recovery of silicone surface longer than 30 days [5, 37]. It is important to note that bacterial infection of the catheter is still a significant issue in the healthcare industry, and a combination of antibacterial strategies should be employed to maximise the effectiveness of preventing bacterial adhesion. There has also been increasing interest in applying nanomaterials in the delivery of antimicrobial agents, with the promising potential of penetrating the biofilm that has so far been providing a very effective microbial resistance towards conventional antibiotics [44].

4. Interaction of Silicone Biomaterial with Host Tissue

4.1 Soft Tissue

Human soft tissue acts as the host for the silicone soft tissue filler in aesthetic implant and reconstruction. The host's short and long-term response has been researched extensively in cases involving facial scars correction and breast implant [23,45,46]. As with any implants, silicone gel triggers the foreign body reaction, a defence mechanism of the immune system. When the foreign body is introduced, the immune system will trigger wound healing cells such as macrophages, causing inflammation or isolation through fibrosis, and eventually, a fibrous capsule will form and surround the implant [8].

In a microscopic examination conducted by Zappi et al., 35 skin biopsies samples were observed in which liquid injectable silicone [LIS] was administered in 25 patients for face scar correction between 1 and 23 years. No significant adverse effect was observed around the silicone droplets that demonstrated inertness and high permanence of silicone [45]. Authors reported that if LIS is used appropriately, it could be a valuable filler for tissue augmentation, especially for treating depressed scars and defects[31]. Christensen reported the clinical observations of gel-host tissue interaction, showing the foreign body reaction and fibrous network around the gel formed by macrophages, preventing further migration and fixing its location within the surrounding host tissue [46]. The literature has sufficiently proven the biocompatibility and permanence of silicone soft tissue filler in the host. However, silicone implants are not without complications. As excessive fibrous connective tissues accumulate around the implant, a strong enough contractile force from the collagen and myofibroblasts may rupture the silicone implant [47]. Hence, the manufacturing quality of silicone implants needs to be well regulated.

4.2 Bone Tissue

In the treatment of arthritis, silicone is inserted as a spacer and hinge to replace cartilage and soft tissues between bones. Since the initial development in 1966, silicone implant arthroplasty has gone through multiple revisions due to failures relating to wear and fracture of the silicone implant [48]. These failures were initially attributed to tears due to bone spikes, which eventually propagated,

leading to structural failure. Later, it was also discovered that ulnar deviation reduces the number of cycles before failure, as proven by Drayton et al. [49]. When comparing the mechanical properties, bones are a few magnitudes harder than silicones; hence, repeated cycles would eventually result in wearing the silicone implant.

4.3 Ocular Tissue

The corneal epithelium is the outermost surface of the cornea, which acts as a host to contact lenses. It is constantly renewing to defend against invading pathogens, as well as to provide the refractive surface which is required for vision. The presence of a contact lens triggers an immune reaction known as epithelial homeostasis, which is an inflammatory reaction of the cornea, found to be associated with dryness and lack of oxygen due to extended wear. Silicone hydrogel lenses have been shown to have significantly reduced the response on short-term proliferation, mainly due to its high permeability [50].

5. 3D Printing for Silicone-based Applications

3D printing is an additive manufacturing process that produces a 3D object directly from a CAD model by depositing materials layer by layer[51]. Established material deposition methods are either droplet-based, extrusion-based or laser-based. Complex silicone-based materials such as PDMS have been a challenge for 3D printing due to their low elastic modules and support requirement[52]. Hence, there has not been prominent usage of 3D printing in the biomedical industry using silicone biomaterials.

Recent advances have seen the emergence of silicone-based printing technologies, which promises the future development of silicone-based bioprinting. 3D printing of PDMS polymer for complex structures is a challenge due to its low elastic modulus. Hinton et al. reported an innovative technique of using hydrophilic Carbopol gel to support the printing of hydrophobic PDMS prepolymer resins, using freeform reversible embedding (FRE)[52]. Carbopol supports and acts as Bingham plastic, and when the 3D printer syringe moves through the gel and serves as a solid for PDMS. After curing for 72 h while maintaining the dimensional stability, the gel is removed using a phosphate saline solution. The authors reported the use of Sylgard 184 PDMS to print helical and cylindrical tubes, highlighting the potential of the FRE printing technique for research applications. This FRE technology has been adopted by Abdollahi et al. in the printing PDMS elastomer cuffs for the wearable pulse oximeter that can be modelled specific to the patient's finger (Fig. 12) [53].

It was also interesting to note that a 3D printed PLA (polylactic acid), silicone elastomer-based prosthesis fitted with a leather glove, nylon, and elastic wire was reported. The authors added that patients fitted with 3D printed prosthesis had better hand performance than without aid. The patient performed complex tasks such as opening a plastic bag [54]. Unkovskiy et al. (2020) reported direct silicone printing of facial prostheses with multi-material silicone with four nozzles [55]. The auricular prosthesis made of silicone with various grades of flexibility and shore hardness will enable patient's perception of rehabilitation and fitted well with their anatomy.

Some of the problems of 3D printing silicone inks with high viscosity are difficulty mixing and changing inks to produce devices and limited to one-part (modulus) or two parts (high viscosity) objects of a single modulus. Recently researchers Zheng et al. (2018) reported the use of rapidly curing low viscosity silicone inks with a single nozzle to produce soft elastomeric materials[56].

Elastomers of different modulus in different ratios are mixed, and extrusion is delivered by low-pressure devices that are controlled for ink switching and producing multiple objects without causing any dripping during 3D printing. Rapid curing using a UV exposure system (cure <2 seconds and complete cure <20 seconds) avoids the use of support material and offers excellent adhesion between printed layers. Such developments will enable producing complex 3D-printed prosthetic structures with different colours or modulus with rapid prototypes, which enables visualising and identifying the desired fit with the human anatomy.

Along with further advancements in 3D printing techniques, we can expect to see more useful silicone-based bioprinting applications. Coupled with silicone biomaterials' versatility, this should be an exciting development in the field of biomedical. In finger joint implants, 3D printing allows the silicone spacer's complex design to distribute better load catered to each patient's unique condition. Nevertheless, silicone-based bioprinting is still in the early stage, and this application must achieve high standards of quality before it can serve as an implant in the human body.

6 Tissue Engineering and Regenerative Medicine Applications

Silicone biomaterial has been adopted in regenerative medicine applications. In 2009, Di Girolamo et al. reported the successful use of silicone hydrogel contact lenses to culture. They transferred limbal stem cells to reconstitute the ocular surface of patients with limbal-SC deficiency (LSCD), which is a promising new technique for ocular surface rehabilitation [57].

Regenerative medicine application towards medical implants is still very much in the conceptual stage. However, it is an area that should be invested in the future development of implants. As silicone implants today are mostly inserted and isolated in the body, tissue-engineered implant potentially has the capability of being totally and permanently integrated as a part of the body.

7 Outlook of silicone as a biomaterial

The future of silicone biomaterial application will probably lie in its use as a filament material to create prostheses and joint implants. Recent research has shown the possibility of direct 3D printing of silicone facial prosthesis as discussed in section 2.5 and multi-material printing of silicone prosthesis with different flexibility grades [55]. Despite the progress, these 3D-printed prostheses are far from perfect and require post-processing procedures to achieve a natural aesthetic. Future work in the area could be refining the print resolution to achieve better print texture and the incorporation of complex colouring schemes to produce higher quality prints.

For the silicone implant, a recent breakthrough in direct 3D printing of medical-grade silicone meniscus implant opens the door for printing personalise silicone implants [58]. Despite the progress, the printing technology will likely be restricted to printing purely silicone parts or implants instead of multi-material print such as the double-stem silicone first metatarsophalangeal joint implant with a metal grommet. Incorporating a different material introduces a second set of settings that will likely differ from the ideal setting required for successful direct printing of silicone whose quality is susceptible to variables such as the nozzle diameter, platform temperature, nozzle temperature, and material flow rate [58].

It is worth noting that silicone's future as a biomaterial depends on its ability to demonstrate antimicrobial properties, particularly for applications including mammary prosthesis, contact

lenses, and urinary catheters. The application of silicone for peripheral nerve regeneration will likely be phase out in favour of a 3D bio conduit in the future. Bio conduit offers a safer alternative to silicone conduit as it is composed of pure biological tissues. Thus patients who undergo bio conduit transplantation will likely have a lower chance of infections, allergies, and foreign-body reaction than patients with silicone conduit transplantation [34]. Furthermore, bio conduit yields significantly better results compared to silicone conduit in terms of the wet muscle weight, morphology, electrophysiology, and kinematics of the regenerated nerve [34].

8 Conclusions

From work presented here, it can be concluded that silicone has found application in the biomedical industry due to its chemical stability, excellent mechanical properties, biocompatibility, and bio durable when interacting with host tissues. Silicone polymers are versatile and can be formulated into various distinct material types, including elastomers, gels, adhesives, fillers, and more, depending on the desired application. Silicone elastomers are used in medical devices, whilst silicone gel for treating hypertrophic burn scars. Besides being thermally stable, it allows for sterilisation using steam or gamma radiation, making them suitable for therapeutic applications.

In this review, eight different applications [medical inserts, speciality contact lens, drains and shunts, urinary catheter, reconstructive gel fillers, craniofacial prosthesis, nerve conduit, and metatarsophalangeal joint implants] were critically discussed to highlight the expansiveness of the healthcare applications. These applications that use silicone polymers are highlighted, indicating the field's development and the specific changes required to suit the intended application and challenges incurred when using silicone in different forms. The timeline also reiterates that silicone's application as biomaterial commenced way back in the 1950s as implants or coating syringes that significantly reduced pain due to less insertion force and early 1960s for breast implants that created enormous attention in reconstructive plastic surgery. Silicone tubing used as biomedical devices also highlights silicone's stability, hemocompatibility, and high oxygen permeability when serving to transport body fluids.

One of the significant developments in using silicone hydrogels as a contact lens is where continuous wear was reported with no infection replacing the disposal hydrogel lenses. These were possible due to their high oxygen permeability and low chemical reactivity. It is also worth noting the silicone gel fillers and their reconstructive plastic surgery application, mainly in breast implants. Capsule formation around the silicone implant and later its contraction was resulting in infection, leakage, and trauma. There were concerns due to the implant being susceptible to bacterial infection - various aspects of enabling silicone polymer resistance to microbial infection with antibiotics were critically presented. These include surface coating, modification or impregnating with antibiotics, adsorption of proteins or protein conformation, immobilisation of biomolecules – enzymes, peptides, drugs, bioactive polymers, and introduction of inorganic components (SiO_2, TiO_2, metal) and nanoparticles.

One of the silicone's fundamental properties as the first choice for soft tissue replacement is its texture and stability. Recent developments enabled manipulating silicone properties, being flexible in various thicknesses, and blended with the human anatomy for use as craniofacial prosthesis - ear, nose, and eye/eyelids. Additive manufacturing enabled 3D printing of silicone inks of low viscosity with varying modulus to produce complex structures and allow rapid prototyping. Future

work would aim to refine the print resolution to achieve better texture and incorporate complex colouring schemes to produce higher quality prints. Also, direct 3D printing of medical-grade silicone meniscus implants opens the opportunity for printing personalised silicone implants.

It is worth noting that silicone's future as a biomaterial depends on its ability to demonstrate antimicrobial properties, particularly for applications including mammary prosthesis, contact lenses, and urinary catheters. These could be surface coatings with nanoparticles or treated with antibiotics or plasma-activated silicone implants treated with antibiotics to resist bacterial growth. Surface modification techniques using functionalisation are achieved by gamma and UV treatment where free radicals are grafted to the surface, thus adding polymer brushes and bioactive agents to prevent bacterial growth. It is also noteworthy to highlight silicone biomaterial interactions with host tissue (soft tissue, bone tissue, and ocular tissue) and their unique ability to be inert, chemically stable, and high permanence. Silicone-based biomaterials' future remains bright if the device manufacturers maintain their responsibility to appropriately screen and source their raw materials. Besides, with the emergence of silicone-based 3D bioprinting and tissue engineering technologies, silicone has a large part to play in the medical industry's future. Besides, it remains a challenge to ensure the implants are safe, biocompatible; the material is high quality and well-regulated to avoid adverse reactions. In this review, the critical properties of silicone are highlighted for biomedical uses showing its versatility and how it can be used in varied formats to suit different applications. It is essential to note that the application's specific requirements should be thoroughly studied before selecting and designing an optimal silicone to meet their needs.

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Figure Captions

Fig. 1 Schematic synthesis of silicone, R_1=R_2=CH_3-Polydimethylsiloxane (PDMS), R_1=CH_3, R_2=Phenyl-Polydimethylsiloxane, R_1=R_2= Phenyl- Polydimethylsiloxane, R_1=CH_3, R_2= Fluoro, polyether, other functional groups

Fig. 2 Key milestones in the development of silicone chemistry

Fig. 3 A) Penetration force of silicone coated and noncoated hypodermic needles, as measured by B) Melab equipment

Fig. 4 - X-ray view of a right hand with arthritis before (left) and after (right) restorative implant surgery

Fig. 5 - Holter shunt use for treatment of hydrocephalus

Fig. 6 A) Condom catheters B) Foley catheters

Fig. 7 A) Image of a patient with auricular deformity B) Image of a patient with an auricular prosthesis. The Image of a completed orbital prosthesis with coloration applied. A) Front view B) Sagittal view C) Posterior view

Fig. 8 Image of direct 3D printed silicone ear prosthesis. A) Print without post-processing B) Print ground with polishing paper C) Polish print with silicone material seal in areas unreachable by polishing tools D) Coloured polished print. The Image of direct 3D printed silicone nose prosthesis. E) Print without post-processing F) Print that has been coloured and sealed with silicone coating G) Print that has been coloured, sealed with a silicone coating, and polished with a fine milling cutter

Fig. 9 A) Image of the transplantation of a silicone tube to the sciatic nerve defect model of a rat. B) Image of the regenerated nerve 8 weeks after surgery

Fig. 10 - Schematic representation of bacterial activity on bacteriostatic and bactericidal surfaces

Fig. 11 Schematic revealing different chemical strategies to design antimicrobial contact lenses

Fig. 12 - Printed PDMS elastomer cuffs tailored to a specific patient and integrated into a wearable pulse oximeter

Table Captions

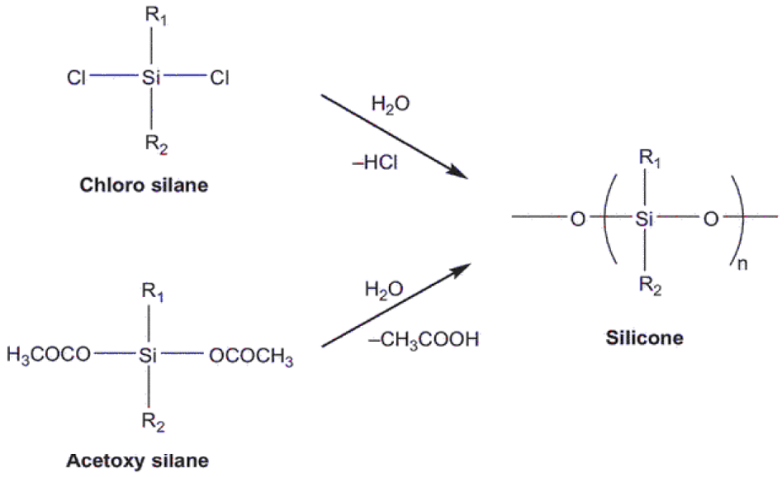
Table 1 - Properties of silicone and other common soft polymers

Table 2 - Examples of silicone implant in human body

Table 3 Characteristics of conventional hydrogel and silicone hydrogel contact lens.

Table 4 - Catheter materials and comparison

Table 5 Summary of 5 of the most common biocidal mechanism in the biocidal coating.



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A BRIEF HISTORY OF

DEVELOPMENT OF SILICONE

KEY MILESTONES IN THE DEVELOPMENT OF SILICONE CHEMISTRY

1824

Discovery of silicone, extracted from the reduction of postassium fluoro silicate with potassium; $4K + K_2SiF_6 \rightarrow Si + 6KF$

Formation of tetrachlorosilane by reacting with silicone with chlorine; $Si + 2Cl_2 \rightarrow SiCl_4$

1863

Successful synthesis of first silicone organic compound –tetraethylsilane

$2Zn(C_2H_5)_2 + SiCl_4 \rightarrow Si(C_2H_5)4 + 2ZnCl_2$

1871

Observation of diethyldiethoxysilane $(C_2H_5)\,2Si(OC_2H_5)_2$ in diluted acid

1901- 1930

Frederic Kipling develops various silane preparation methods and helping to establish the study of organosilicone chemistry

1940

James Franklin Hyde of Dow Corning demonstrated the high electrical resistance and thermal stability of silicone resins. Eugene George Rochow of General electric discovery of silicone preparation directly from methylchloride and silicone observation of diethyldiethoxysilane

1946

First published record of silicone elastomer implant in humans for bile duct repair

1948

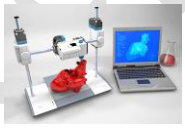
First successful replacement of human male urethra with artificial urethra made from silicone

1949

Prevalent use of silicone precoating in blood collection vials, syringes, and needles after researchers at Mayo clinic demonstrated that there is no significant effect on blood left in the silicone-coated syringe

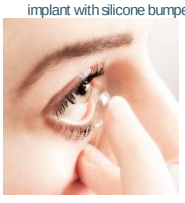
1962

Implantation of the first pair of silicone gel breast implants in a woman



1969

Introduction of posterior offset hinged total knee implant with silicone bumper incorporated for shock absorption

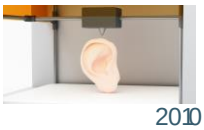


1979

The Anglechik antireflux prosthesis use of gastro-esophageal reflux management became first device with silicone gel that is approved by FDA

1999

Launch of silicone hydrogel contact lenses



2008

Silicone biodurability after long term implantation was examined by highly sensitive NMR spectroscopy technique

2010 onwards

3D printing and antimicrobial strategies using various surface modifications

Development of silicone

Application of silicone as biomaterial

Images source: canva.com

1

Fig. 2 Key milestones in the development of silicone chemistry [59,60]

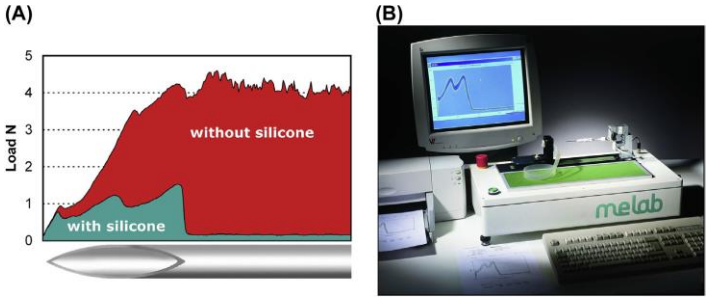


Fig. 3 (A) Penetration force of silicone coated and noncoated hypodermic needles, as measured by (B) Melab equipment using DIN 13097

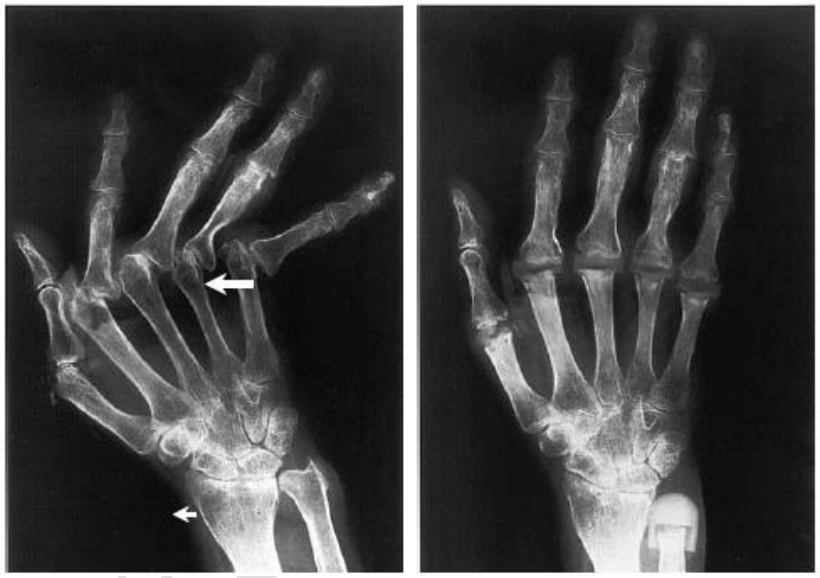


Fig. 4 X-ray view of a right hand with arthritis before (left) and after (right) restorative implant surgery [5]

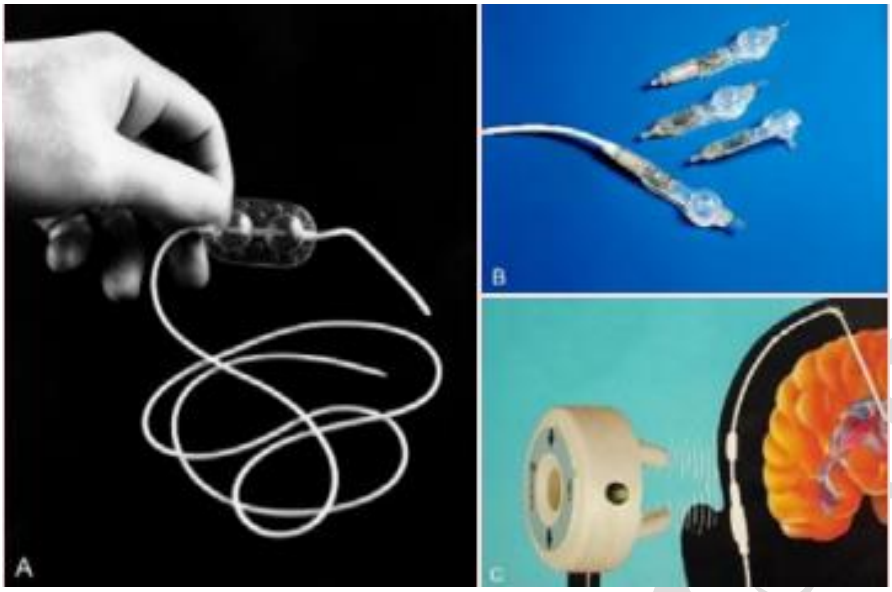
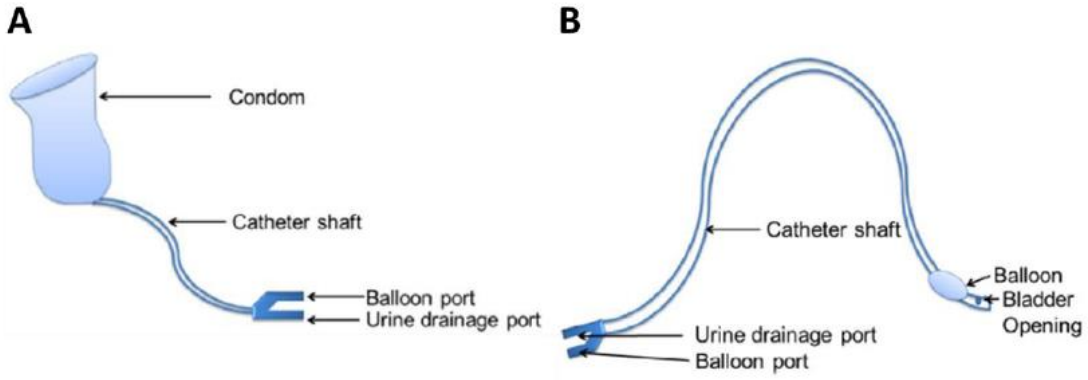


Fig. 5 Holter shunt used for treatment of hydrocephalus [5]



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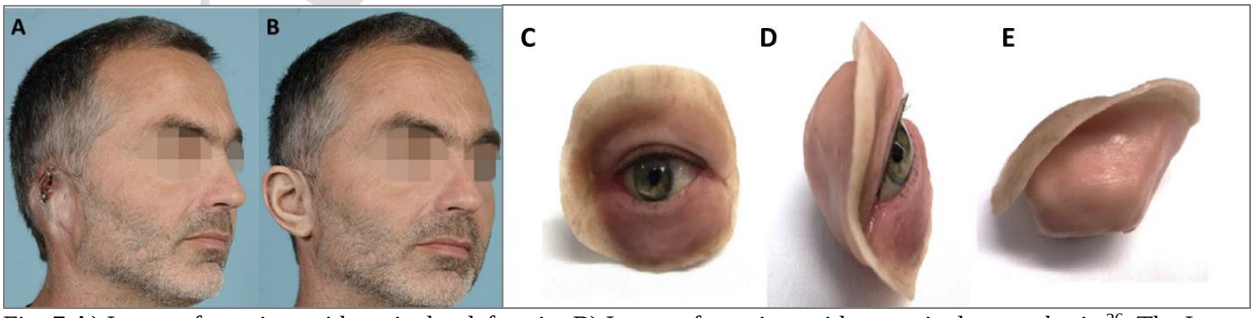

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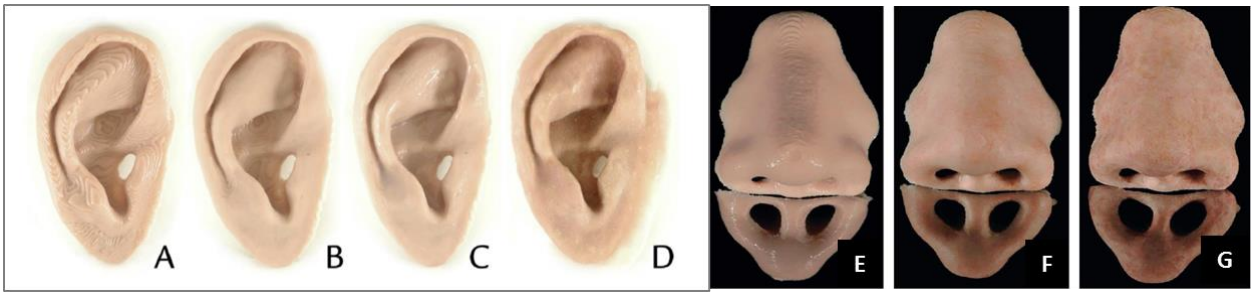

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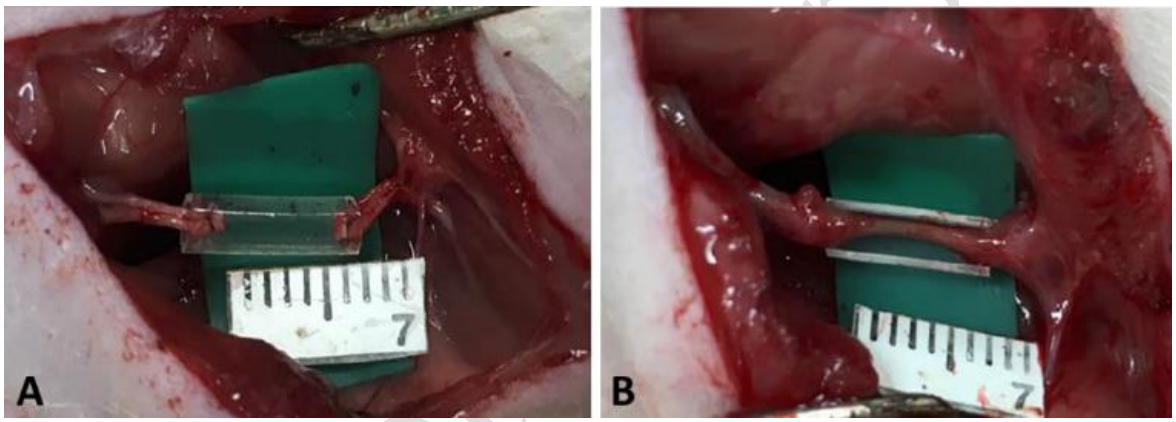

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Fig. 10 Schematic revealing different chemical strategies to design antimicrobial contact lenses.

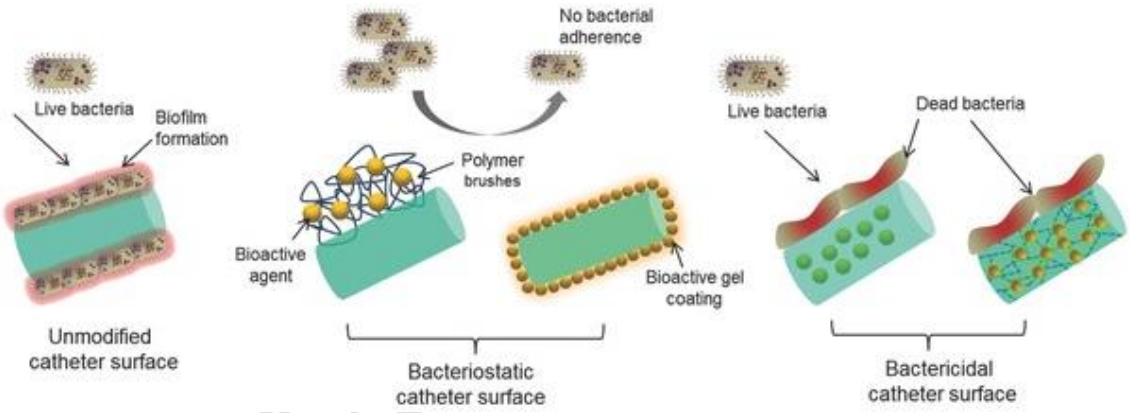

Fig. 11 Schematic representation of bacterial activity on bacteriostatic and bactericidal surfaces [44]

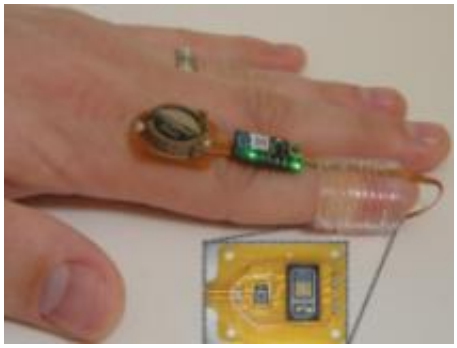

Fig. 12 Printed PDMS elastomer cuffs tailored to specific patient and integrated into a wearable pulse oximeter [53]

Tables

Table 3 Properties of silicone and other common soft polymers [2,8]

Polymer	Tensile strength (Mpa)	Elongation (%)	Tg (°C)	Tm (°C)	Water absorption (%)	Water contact angle (°C)	Biomedical applications
Polydimethylsiloxane (PDMS) or silicone	2-10	100-600	120-123	-	0.02	101-109	Oxygenator membrane, tubing, Shunts, prostheses, heart peacemaker leads, heart valve structures, burn dressing
Silicone Elastomers	8-10	300-800	-130	-	<0.03	-	Wound dressing
Low density polyethylene (LDPE)	4-16	90-800	-20	95-115	<0.01	93-95	Tubing, shunts, catheters
High density polyethylene (LDPE)	21-38	20-1000	-125	135-138	<0.01	91	Plastic surgery implants, catheters
Polypropylene (PP)	30-38	200-700	-12	125-167	<0.01	104	Heart valve structure, oxygenator and plasmapheresis membranes, finger joint prosthesis

Table 4 Examples of silicone implant in human body [5,8,62]

Location	Body parts	Applications
Head and neck	Brain	Hydrocephalus shunts
	Skull	Burr hole covers
	Eye	Scleral bands and buckles
		Vitreous fluid replacement
		Intraocular lenses
		Contact lenses
	Ear	Elastomer tubes for ontological ventilation
		Cochlear implants (encase in silicone)
	Throat	Voicebox prothesis, post- laryngectomy
Torso	Cardiac	Peacemaker encapsulated and leads insulated with silicone
		Mechanical heart valves
	Gastric	Gastric band implant (Lap-Band, Realise)
Urinary system	Urinary tract	Silicone urological catheters
		Urethral stents
		Artificial urethra
Skeletal joints	Hip	Silicone drainage systems
	Knee	Shock-absorbing silicone bumper for knee replacement
	Foot	Foot and toe joint implants
Other	Breast	Breast implant for post-mastectomy reconstruction or aesthetic augmentation
	Scrotum	Testicular implants for congenital defects or post-orchiectomy surgery
	Cell therapies	Bio-scaffolds: 3D porous, cellular therapies used to treat Type I diabetes, formed by solvent casting and particulate leaching or free form rapid prototyping; PDMS is surface treated to enhance hydrophilicity and cell attachment

Table 3 Characteristics of conventional hydrogel and silicone hydrogel contact lens [12,63].

Material	Silicone Hydrogel	Conventional Hydrogel
Monomers	DMA, siloxane macromer, TRIS	MA, HEMA
Initial modulus (MPa)	1.4	0.35
Oxygen permeability	175×10^{-11}	28×10^{-11}
Oxygen transmissibility	175×10^{-9}	31×10^{-9}
Water content	24%	58%
Limitations	Requires hydrophilic monomer, can be abrasive	Protein deposition issues, low oxygen permeability, low water contents,
Advantages	Durable, comfortable	Flexible, inexpensive

Table 4 Catheter materials and comparison [19,64–66]

Type of catheter	Maximum time *in-situ*	Special features
Polytetrafluoroethylene (PTFE) (Teflon) coated latex	28 days	
Hydrogel-coated latex	12 days	Hydrogel; smooth, compatible with body tissue
Hydrogel-coated silicone	12 days	
Silicone-elastomer coated latex	28 days	Silicone; inert but more rigid
Silver alloy-hydrogel with latex core	28 days	Antibacterial properties
Silicone, hydrogel-coated; phosphate silver ions in coating	12 weeks antimicrobial properties	Antibacterial properties
100% silicone	≤30 days 12 weeks	Thin-walled, large lumen. More rigid than silicone-coated catheters. The surface is less smooth, offers excellent balloon 'cuffing' (unevenness) on deflation of the balloon
HydroSil gripper - hydrophilic silicone - male HydroSil Rose for female		Intermittent catheters for self-catheterisation – for those suffering from urinary retention

Table 5 Summary of the most common biocidal mechanism in the biocidal coating [20].

Mechanism of action	Description of action	Examples of agents
Inhibition of cell wall synthesis	The presence of biocide hinders dephosphorylation and peptidoglycan of phospholipid carrier in peptidoglycans formation	Penicillin, chlorhexidine, and vancomycin
Inhibition of protein synthesis	Biocides attachment to the ribosomal subunits in bacteria	Nitric oxide, silver ions, and minocycline
Inhibition of nucleic acid synthesis	Biocides hinder mRNA DNA gyrase, nucleic acid, and topoisomerases synthesis.	Quinolones, sparfloxacin, rifampin, and nitric oxide
Effects on cell membrane sterols	Biocides alter the cell membrane sterols. This mechanism can cause cytotoxicity and is typically used as the final barrier against bacteria.	Antimicrobial peptides, triclosan, silver ions, and antifungal agents (amphotericin)
Inhibition of unique metabolic steps	Biocides hinder the synthesis of cofactors for nucleic and mycolic acid synthesis. Biocides agent can either remain on the surface and eliminate microbes on contact or be released to eliminate the bacteria.	Nitrofuran, triclosan, sulphonamide, and bacteriophages