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Research Paper

Plasma Influence of Surface Texture of Silicone Rubber for Biomedical Application in Scala Tympani

Mohammad Ajal-Louian[1]; Saeed Golparvaran[2*]; Hamid Mirzadeh[3]; Mohammad Taghi Khorasani[4]

1. New Hearing Technologies Research Center, Baqiyatallah University of Medical Sciences; Tehran, Iran
2. Department of Otorhinolaryngology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Biopolymer, Faculty of Polymer Engineering, Amir Kabir University of Technology, Tehran, Iran
4. Department of Biocompatible Polymers, Iran Polymer and Petrochemical Institute (IPPI), Tehran, Iran

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ABSTRACT

This study aims to fabricate an optimum interface surface for intracochlear catheter applications. The samples were first fabricated of two-component liquid dimethyl siloxane by designing and fabricating a mold, and then the assembly underwent surface treatment using a plasma irradiation device. The water contact angle test results showed an increase in the surface hydrophilicity of this material that water drop contact angle of origin silicone is 105° that after treatment decrease to 60°, which has the property of reducing the effect of cellular cutting in the inner ear when passing through the scala tympani. The surface engagement during passage was also minimized with an increase in surface roughness at the nanoscale. SEM and AFM photomicrographs and nano graphs show that the morphology of catheter surface in nanoscale changed and roughness increased, which is desirable for this purpose. The cell viability test results showed an improved adhesion and cell growth on the modified surface and origin silicone, and 95 % viability of cells confirmed, indicating the optimal biocompatibility of the modified silicone sample. This catheter can be used in cochlear implantation and drug delivery before surgery to enhance therapeutic efficiency.

* **Corresponding Author**:
E-mail Address: golparvaran_saeed@yahoo.com

1. Introduction

Disorders of the inner ear are among the most common and pressing conditions responsible for hearing loss. About 250 million people across the world suffer from hearing loss [1], and the prevalence of profound hearing loss is 1.33 per 1,000 live births [2], by which children need to undergo cochlear implantation. It may be necessary to deliver some medications to the cochlea before, during, and/or after cochlear implantation [3]. In 2008, Swan et al. conducted a comprehensive analysis of various drug delivery systems [4]. They reported three main ways for delivering drugs to the inner ear, namely systemic therapy, intratympanic injection, and intracochlear injection.

In systemic treatment, some restrictions are with drug delivery due to the low blood flow of the cochlea and the existence of the blood labyrinthine barrier (BLB). In this system, prolonged drug administrations can cause systemic side effects [5]. For example, the prolonged administration of corticosteroids in autoimmune inner ear disease can cause some harmful complications [6]. In intratympanic treatment, drug delivery to the inner ear depends on crossing through the round window and, consequently, its structural features as well as the condition of the Eustachian tube (middle ear ventilation tube) [1]. This diminishes the intracellular dose, i.e., the amount of drug that enters the cochlea of the inner ear. Intracochlear injection for drug delivery includes two main systems. The first system utilizes active or passive micropumps installed separately or combined with cochlear implants, though they show poor control and limited half-life. However, the microfluidic system has been recently used to create a stable dose [1].

The second system applies intracochlear catheters for deep drug injection into the cochlea with no damage to its micro-anatomy [7]. The main advantage of these catheters is an injection in the cochlear terminals because, in IT injection, a large portion of the drug residues in the basal cochlear region due to the slow diffusion into the cochlea [7]. These catheters are mainly used in cochlear implants. A well-known treatment for profound hearing loss is cochlear implantation. The cochlear implant has an external part that converts acoustic energy into electrical energy [7] and acts by transmitting signals through spiral ganglion neurons to the central auditory system [8]. Accordingly, the loss of cochlear nerves diminishes the performance of cochlear implants.

Intracochlear catheters applications in cochlear implantation include the following: First, these catheters are used for injecting steroids during implantation, as cochlear implant electrodes cause an acute and chronic immune response in the body, which can be prevented by intracochlear steroids [7]. Second, these catheters are used to inject neurotrophins (stimulants of nerve cell growth). BDNF (Brain-Derived Neurotrophic Factor) and NT-3 (Neurotrophin-3) are expressed in the cochlea and are involved in the survival of cochlear spiral ganglion neurons [8]. Direct injection of BDNF into the cochlea in animals enhances the resistance of cochlear spiral ganglion neurons to ototoxins [9]. The intracochlear injection of this substance could achieve better functional results during cochlear implantation. The intracochlear catheter has been introduced by Med-EL (Innsbruck, Austria) for use in research projects [7], and we enhance the efficiency of cochlear implants as well as healing patients with internal ear problems.

Silicones are synthetic polymers made of repeated oxygen-silicon backbones. Polymer chains are formed by silicon-oxygen bonds and the formation of bonds between silicon atoms and organic groups such as methyl. Siloxanes constitute a backbone of alternating silicon-oxygen [-Si-O-] units, with polydimethylsiloxane n[-SiO$(CH_3)_2$] as the most common silicone [10-12]. Polysiloxanes are polymers made of organic and inorganic compounds. The general formula of these materials is n[-R2SiO], in which organic groups such as methyl, ethyl, and phenyl are included as side groups. The backbone of these materials consists of -Si-O-Si-O- chains [7]. Compounds with different properties can be achieved by altering the length of the -Si-O-Si-O- chain, side groups, and lattice factors. Thus, such a structure can be a liquid, gel, rubber, or rigid plastic [7]. In recent years, numerous studies have been done on efficient elastomers based on mineral polymers to tackle the shortcomings in the field of organic elastomers and uncover new opportunities. Silicone rubbers are used to make implants.

The term surface is a key concept in biological science and medicine. Because many biological reactions take place at cell-surface interfaces. We assume that polydimethyl-siloxane molecules take a helical structure, the inner part of the helix consists of siloxane units (Si-O-Si), and the outer part includes methyl groups. Thus, they give the molecules a large molar volume and hydrophobic nature. (The surface contact angle of the water drop is 105 degrees). As reported, the oxygen bond angle in the siloxane group is large (14-16 degrees). Thus the siloxane chain is highly mobile [13-14]. CH_3 groups form a hydrophobic surface for polymers. It is generally accepted that CH_3 is hydrophobic, improves protein absorption, and normally causes an adverse reaction to the cell. The surface of the

material affects cell adhesion and cellular behavior and, ultimately the tissue restoration. Surface engineering includes surface dynamics, roughness, hydrophobicity, hydrophilicity, surface load, morphology, topography, surface energy, etc. Cellular behaviors generally depend on physical, biochemical, and chemical stimuli. It can be said that cells are intelligent and are affected by their environment [15-16]. Silicone rubbers have been widely used in medical applications over the past three decades due to physiological neutrality, good blood compatibility, low toxicity, good thermal stability, low modulus, and anti-adhesion properties, all of which have made silicone rubber acceptance in medicine so far [17]. Plasma-induced surface modification is among the most appealing trends in medicine and engineering. In the past, the medical application of plasma was more focusing on surface sterilization as well as modification to control the biocompatibility of materials. In recent years, plasma-induced surface modification has been widely used to fix new and complicated obstacles with tissue engineering and sterilization of reusable and heat-sensitive medical equipment. In this technique, the surface is modified without using chemical solvents and the production of waste, which provides the driving force for its use in biomedical applications.

Four main categories of plasma reactions can be identified considering the interaction between the activated species and the surface of the material, including 1) functionalization, 2) coating and deposition, 3) cutting and etching, and 4) polymerization and implementation [18]. In this study, we succeeded in designing and fabricating a new catheter. Due to the fact that the intracochlear catheter, which was manufactured by Med-EL (Innsbruck, Austria), was not available for us. Fabrication of this catheter provides a valuable opportunity for the growth of research and treatment capability (increase the efficiency of cochlear implants and also helping patients with inner ear diseases), which was not possible before.

2. Experimental section

The catheter was first fabricated of polydimethylsiloxane as the raw material and then underwent plasma surface modification. Then the surface mechanical properties of the catheter were investigated. Ultimately, in vitro tests were performed using the relevant model.

2.1. Materials

Silicones were purchased from Waker Company (Silicone: R 401/30 OH and R401/70). 3-(4,5-Dimethylthiazol-2- yl)-2,5-diphenyltetrazolium bromide (MTT) for measuring cell viability from Sigma.

2.2. Manufacturing process

Since this catheter enters the scala tympani through the round window, the diameter and length of the duct are critical for the design of the catheter. The average cochlear length (A) from the round window to the apex of the cochlea (Helicotrema) was 33.01 mm [19]. The thickness of the cochlear implant electrode, which here determines the outer diameter of the catheter, was between 0.4 to 0.6 mm [20]. The catheter was about 12 cm in length, containing a proximal part with a length of 2 cm and a distal part with a length of 10 cm. The length of the distal part to enter the end of the cochlea was about 7 cm, considering the total length of the cochlea (about 3 cm) and the distance from the round window to the site of mastoidectomy (about 7 cm). The proximal conical part had an inner diameter of 3 mm and an outer diameter of 5 mm to be fixed to the insulin syringe for injecting the drug into the cochlea. The distal part had an outer diameter of about 600 μm and an inner diameter of 300 μm. Thus, a tube with a wall thickness of 150 μm was designed (Figure 1).

For molding, RTV silicone rubber (ELASTOSIL® R 401/30 and 401/70 OH Wacker) that is polymerized at room temperature was used, and the mold was designed and manufactured with predefined dimensions. Components A and B in a double-component liquid silicone (including) was mixed in a certain ratio and injected into the designed mold. The silicone was removed from the mold and sterilized after 4 hours and ensuring the formation of silicone polymer and end of the curing step. The silicone sheet made by this method was used to evaluate the tests. Then, the viscosity of the material to pass through the catheter was examined. A total of 10 ml of blood was taken from a person, and the blood sample was put in a centrifuge at 3000 rpm for 9 minutes, and PRP (Platelet-rich Plasma) was extracted from it. This substance can contain BDNF, which may remarkably affect the success of the cochlear implantation and possibly stimulate the auditory afferent neurons to help enhance the effect of the implanted electrode. To prevent PRP deformation, the syringe was kept in ice serum and transferred to the polymer center. Hardness (indicating catheter flexibility) was then evaluated against insertion force (indicating the amount of force required for the catheter to enter the round windows). A sample of the artificial cochlea made at Polymer Research Institute at the Amir Kabir University of Technology was used. This sample was made considering the real dimensions of the ear cochlea (Figure 2).

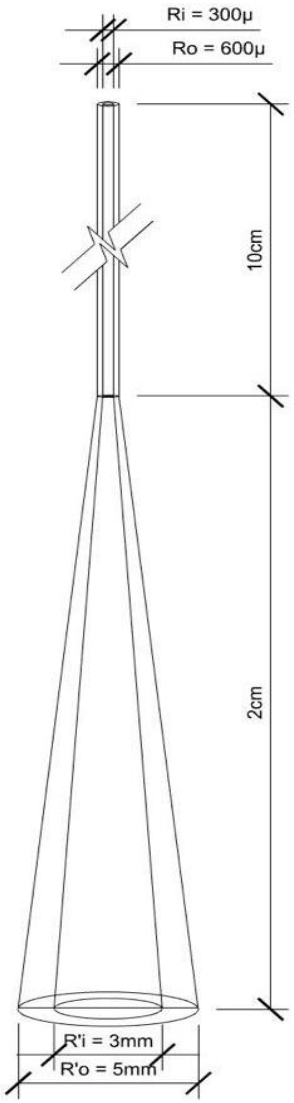


Fig. 1. Designed catheter of silicone

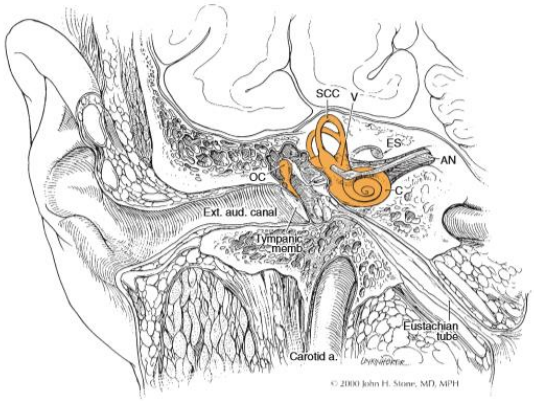


Fig. 2. Anatomy of the external, middle, and inner portions of the ear. AN, auditory nerve; C, cochlea; ES, endolymphatic sac; OC, ossicular chain; SCC, semicircular canals; V, vestibule. [21].

The resistance of the inside fluid and the round window was quite similar to the real sample [21]. Several catheter prototypes with different resistances were made and tested, and ultimately, a plasma-modified specimen that could pass easily without cochlea damage and with the possibility of PRP injection was selected. The end of the catheter was calibrated at 10 mm intervals so that its entry depth could be controlled. As a prerequisite, samples ultimately underwent gamma-ray sterilization. Two

measures were taken to ensure that the catheter carefully enters the inner ear and does not rotate. First, in some parts of the catheter, the thickness of the tube was increased to enhance the modulus of the desired piece because, at elevated modulus, the bending of the catheter when entering the ear is minimized. Second, the inner part of the tube was selected from high modulus silicone. To prevent damage to the cells of the cochlea wall, the outer part of the tube was made of soft silicone.

2.3. Characterization Technique

2.3.1 Atomic Force Microscopy (AFM) analysis

Atomic force microscopy (AFM) analysis was used to examine the roughness of silicone surfaces. Topographic analysis of the modified surface was performed by scanning probe microscopy (SPM) in contact mode as the basis for an atomic force microscope (AFM) [22]. In this project, the AFM microscope (model DS 95-50-E; Semilab DME; Germany) was used to study the topography and surface roughness and compare it with a pure sample. The roughness parameters of each sample were calculated in DME-SPM [23].

2.3.2 Scanning Electron Microscope (SEM)

SEM was used to evaluate the surface morphology of the samples before and after the reaction. After drying in a vacuum oven, small sections of the samples were examined using a VEGA SEM made by TESCAN-LMU and a FESEM MIRA3 device made in the Czech Republic at a voltage of 15 kV.

2.3.3 Water drop contact angle test

To investigate variations in the hydrophilicity of the modified sample surface and compare it with pure and plasma-induced modified samples, the samples were examined using the KRUSS G10 device (Germany) by the droplet attached to a surface [24-25]. In this technique, a drop of water is gently put on the surface of the samples with a syringe and are imaged. The volume of water droplets was 10-15 microliters, and the test was performed under environmental conditions. Measurements were made at 5 points in each sample and were examined using ImageJ, and their mean and standard deviation were reported.

2.4. MTT test

MTT test is a colorimetric assay based on the reduction and breakage of yellow tetrazolium crystals [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. This assay is simpler than other cell proliferation techniques and can be performed with the facilities available in most laboratories. All experimental steps were done on 24-well culture plates and the results were read by BIOTEC ELISA REDMODEL. The test was repeated three times for each sample. Following the cell culture, this test was performed within two 24 and 48-hour periods. After incubation, the upper culture medium was removed and 1 ml of culture medium containing 100 µl of MTT solution was added to each well and put in an incubator containing CO2 at 37 °C for 4 hours. During incubation, MTT was regenerated by the succinate dehydrogenase system, one of the enzymes of the mitochondrial respiratory cycle. This ring is regenerated and broken to form blue formazan crystals that are easily detectable under a microscope. The volume of dye produced is directly related to the number of metabolically active cells. Formazan crystals are insoluble in water and need to be solved in a solvent such as DMSO before colorimetric assays. Ultimately, the optical absorption of the solution was read at 490 and 630 nm using the Alizar Reader.

2.5. Oxygen plasma-induced silicone surface activation

O2 (>99%) was used in the process of surface modification using oxygen plasma. Ionized oxygen gas was used, and an energy transfer mechanism was done on the surface of samples, which led to chemical bonding and double bonding. The German Diener Electronics radiofrequency device (W30) was used and plasma-induced modification was achieved applying KA150 current for 60 seconds. Samples were prepared and then put in the chamber of the plasma device. The device was equipped with a low-frequency generator with a voltage of 400 v and a current of 250 mA to produce plasma. O2 gas (>99%) was used. The pressure inside the plasma chamber was kept constant at 0.5 mbar. The power of the electrode for a plasma modification in 120 seconds was W100. The plasma pressure was adjusted to obtain the aforementioned plasma. Samples were exposed to ambient air for one hour before the reaction. The contact angle test was done on samples for initial evaluation of changes due to plasma application.

3. Results and discussion

3.1. Water drop contact angle test

The contact angle test images taken of the samples are shown in Figure 3. The contact angle of a water drop with the surface was measured using ImageJ, as an average of five measurements at different points on the sample surface. The contact angle of water with a sample is a measure of surface wettability. Silicone is a rather hydrophobic material and, as shown in Figure 3, the water droplet is at an angle of

about 105 degrees. However, after irradiation of the surface with plasma, due to the formation of hydrophilic groups or other polar groups due to oxidation (e.g., hydroxyl, carbonyl, carboxyl, and other oxygenated functional groups), the angle of contact of water is reduced to about 60 degrees (Figure 3).

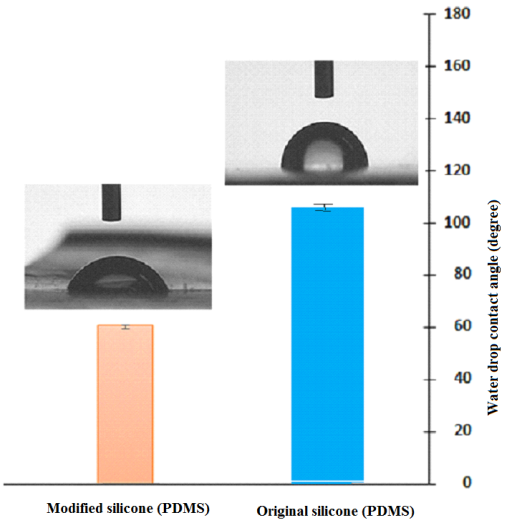


Fig. 3. Water drop contact angle onto original and modified silicone.

As a result of modification with oxygen plasma, the contact angle of the water droplet with the silicon surface is reduced. Oxygen plasma modification is highly efficient in altering the wettability of polymer surfaces so that even after the polymer has been exposed to plasma for a short time, the contact angle with the sample water decreases and the wettability of different surfaces varies only during the modification of the surface with plasma [26].

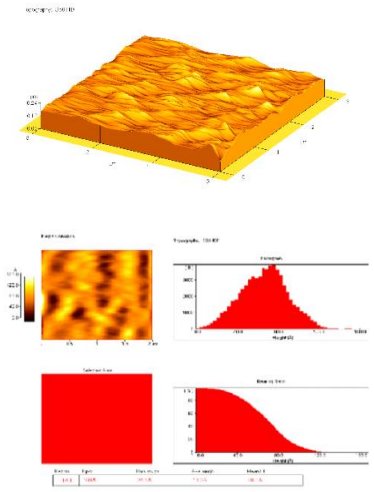
Wettability is presumably among the most important surface parameters determining the biocompatibility of materials. Thus, we investigated the wettability properties of silicone catheters before surface modification and alterations in their surface contact angle with water after plasma correction [27]. Elevated hydrophilicity of the catheter surface causes a layer of water to settle on the catheter surface so that when it crosses through the canal, the middle ear cells have less adhesion on this surface and the catheter passes easily. As will discuss in the section on in-vitro results, this sample passes more easily than the unmodified sample.

3.2. Investigation of surface roughness using atomic force microscope

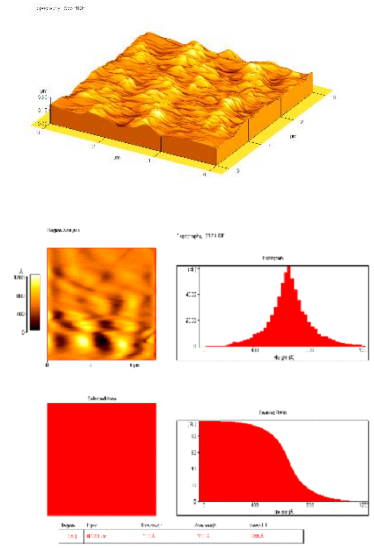
The atomic force microscope test results are shown in Figure4, in which, from top to bottom, unmodified silicone samples and modified silicone are demonstrated. The 3-D images of the surface are shown on the right, and the histogram is shown on the left. For quantitative analysis and better comparison, the roughness parameters of each sample were calculated in DME-SPM and reported in the table. As shown in Figure 4, the average height values of grooves and peaks have decreased in the unmodified silicone sample. Since the surface is not modified with plasma, the mean peaks are reduced, and a different distribution of similar peaks and grooves is visible on the surface (mean roughness = 37.5Å). The Rp-v (average length between the highest peak and the lowest groove in each sample) indicates that the surface has no pointed peak while shallow grooves have been formed on the surface. After irradiation, the square root, the average peaks, mean roughness, and Rp-v of the modified sample increased compared to the un-irradiated sample (mean roughness = 160Å). The roughness values show that the plasma application has resulted in a more uniform surface. Another reason for reducing the contact angle of the samples after plasma application also increased the surface roughness of the samples (Figure 5). Roughness (r) is one of the parameters that represent the relationship between roughness and wettability. According to Wenzel's equation [28], the apparent contact angle on a rough surface is proportional to the actual contact angle and the surface roughness coefficient (equation 1). Thus, for hydrophilic surfaces, the measured (apparent) contact angle decreases with increasing surface roughness. According to the calculated values of r, it is observed that the value of the irradiated silicone sample coefficient is higher than that of the pure sample.

$$\cos\theta_w = r\cos\theta_y \quad (1)$$

where θ_w is wenzel angle, and θ_y is Young angle and r is roughness factor.



(a)



(b)

Fig. 4. AFM images of samples, a) unmodified silicone, b) modified silicone

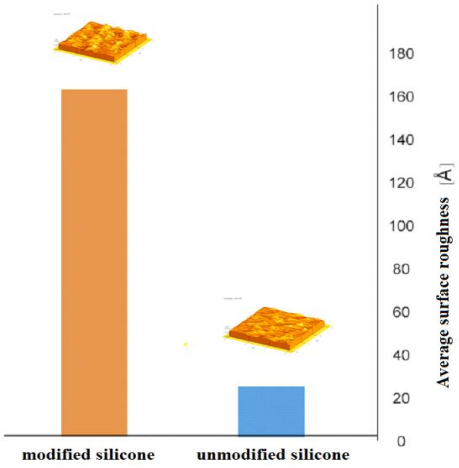


Fig. 5. Average surface roughness of samples.

3.3. SEM examination of the surface morphology of the samples

SEM images of pure and plasma-modified samples are shown in Figure 6. As can be seen from the figure, there is no fracture on the surface of the unmodified silicone, and the surface is resistant to plasma modification. After modification with plasma, it has been shown that molecular chains are attached to the surface, while some noises on the SEM image. Thus, in the micro-scale, the surface remains intact, although in the nanoscale, the erosion of surface polymer chains occurs, the surface becomes porous, and the surface roughness increases [29]. As shown in the SEM images, silicone has a smooth surface while its smoothness is reduced after modification by plasma [30].

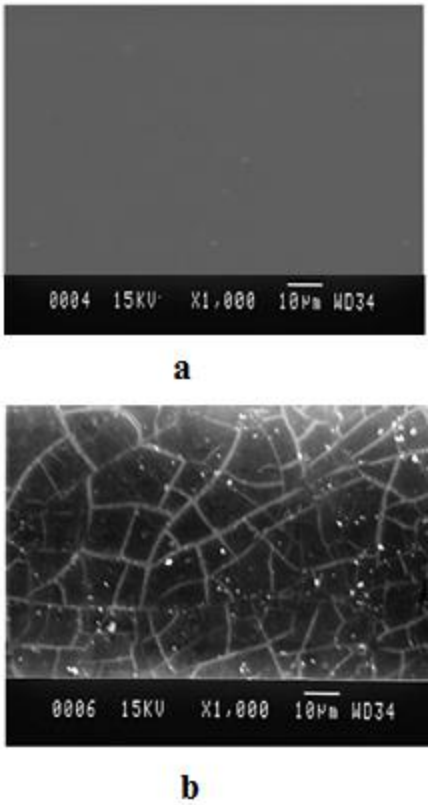
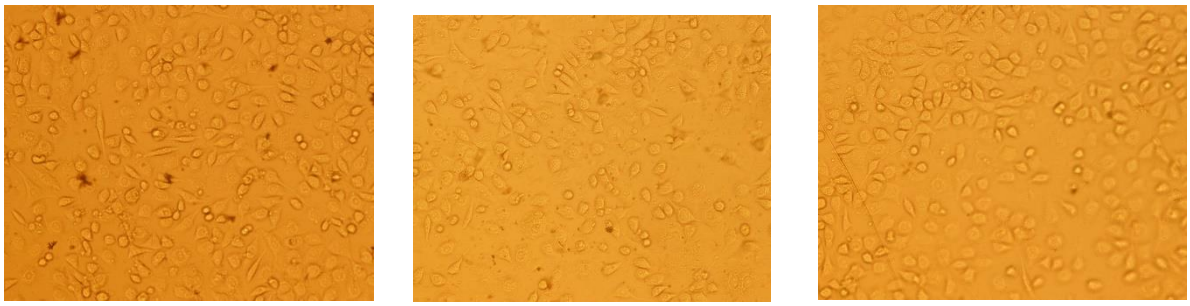


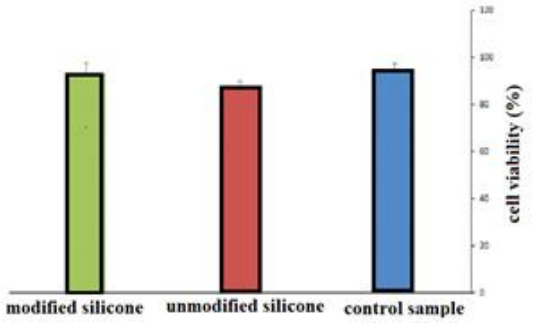
Fig. 6. SEM photomicrographas of; a) unmodified silicone surface; b) modified silicone surface.

3.4. Investigation of cell biocompatibility of samples

Cell culture and MTT tests were performed to evaluate the cytotoxicity and biocompatibility of the samples. Cellular behavior on biomaterials is an important factor in determining biocompatibility. The first physiological process that occurs in the early stages of contact is surface adsorption, which is usually associated with cellular interactions. The overall process of cell adhesion and diffusion after exposure to biomaterials includes cell adhesion, cystoplasty network growth, cell mass smoothing, and cell proliferation, all of which proceed sequentially [31]. Many experimental results have been reported about the interaction between the polymer and the cell, indicating that these interactions depend largely on the physical and chemical properties of the sample surface, such as chemical composition, surface charge, wettability, microstructure, and hardness. In cytotoxicity and cell culture tests, the growth and proliferation of L929 fibroblasts on the samples were evaluated as compared to the negative control (polystyrene container). Figure 7 shows the results of the MTT test. The right and left columns respectively refer to 24 hours and 48 hours after cell culture. The optical microscope images of the surface of the pure sample and the modified sample are further shown in Figure 7.



(a)



(b)

Fig. 7. a) optical photomicrographs of cell attachment onto samples; b) MTT test results of the samples.

As shown in the diagram, the samples exerted no toxicity to the cells, and even the cell viability on the surface of the modified film was increased. The surface of the modified sample is highly hydrophilic, and this has somewhat improved the tendency of the cells to adhere to this surface. Such studies are necessary to find information about the compatibility of these materials for medical engineering applications [32]. The MTT cell results for each sample in Figure 7 show respectively 90% and 95% of the cell viability of the unmodified and modified samples.

4. Conclusion

The catheter was made of modified silicone. The MTT test results show the good biocompatibility of this silicone. Furthermore, water droplet contact angle tests show better wetting of the modified sample, and the AFM test confirms that the surface roughness of the modified silicone is significantly improved. These two factors play a critical role in advancing the catheter into the scala tympani. A leading point about the catheter is a balance between roughness and insertion force, which was done by testing on a sample of the artificial cochlea. When roughness is low on the nanoscale, the catheter fails to rotate inside the cochlea. Likewise, the catheter has a minimum contact surface area to tolerate the insertion force required to enter the round window when roughness is high. Research in this field is in its early stages, indicating that the fabricated electrode has no damage to inner cochlear tissues, such as scala tympani, modiolus, and scala media. Our research enabled conducting studies on the construction of this catheter for cochlear implants and alleviating inner ear disorders, which could not have been done in Iran previously. Medical and industrial equipment is costly to be designed and manufactured and requires great accuracy. Thus, any self-sufficiency in the manufacture and fabrication of this equipment can be regarded as an achievement.

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