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Research Article

GOLD, SILVER, COPPER AND SILICONE HYBRID NANOSTRUCTURE CYTOTOXICITY

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ABSTRACT

Porous materials and nanoparticles are now day on the scope of many researches that study different application in all science areas, and the medical field is impacted by this technology. Applications like drug release, sensors, cancer treatments, tissue engineering, implants, etc. On this development the silicone or polydimethylsiloxane (PDMS) play a key role, this polymer is frequently used for medical applications as cardiac pacemakers, mammary prostheses, implants, heart valves, etc.
Porous silicone materials with immobilize nanoparticles can resolve some limitations from the non-porous silicone. At leaching method with sieve sugar was used to prepare a porous silicone with a controlled pore size distribution and mean pore size of 160 micro meters. Later this material was used to immobilized gold, silver and copper nanoparticles, cytotoxic study with MTT assay was running through ISO/EN 10993-5 and ISO/EN 10993-12, and the study non evidence statistical cytotoxicity differences between pure porous silicone matrix and porous silicone matrix with silver, gold nanoparticles or their combination, but copper nanoparticles immobilized over the silicon porous matrix evidence statistical difference on cytotoxic effect over the same cells (L929 fibroblast).

INTRODUCTION

Tissue engineering and human implants technology are a medical field that change every year, the nanomedicine combines different engineering techniques and science, like medicine, material engineering, biology, physics, chemist and others expertise to continue with the develop of new materials that could be addressed all requirement from our body.

This medical field associated with repairing or replacing parts or the whole damaged tissues such as bones, cartilages, blood vessels, and bladder utilizes living cells that are implanted or seeded in a scaffold to act as substrates for holding cells that will create a new tissue. To achieve tissue reconstruction as hard tissues and scaffolds, the materials must fulfill some specific requirements such as high porosity, adequate pore size, biodegradability, and biocompatibility. Therefore, scaffolds or implant materials characteristics are important for the success of the implantation process and extremely depend on the tissue to be regenerated or body place to be used for the implant. (Zandi, Mirzadeh, Mayer, Urch, Eslaminejad, Bagheri and Mivehchi, 2009).

Biocompatible implants and scaffolds allow the human body to restore the biological and mechanical functions; therefore manage to increase the quality of life. Depending on the biomedical application, the material has to withstand mechanical loads, while conducting a long term interaction with the surrounding biological tissue is promoted. Bulk material properties of the implants and scaffolds are primarily responsible for the load bearing capacities, where the interaction with the surrounding tissue is governed by the material surface (Doak, Gupta, Manivannan, Ghosh and Kahol, 2010; Feng, Gu, Yang, Hu, Lu and Huang, 2009).

The properties of porous materials, micro, meso and macroporous surfaces, based on the application and the requirement for porous size, roughness, interconnected channels, functionalized surface, to be able to induce tissue regeneration could be addressed today, and these material porous design have been combined with different properties and abilities to host (adsorption or absorption) and release specific biomolecules that promoted cell growing inside and over the porous surface (Solano-Umaña and Vega-Baudrit, 2015). Immense research during the last decade has been devoted to adjust the morphology (the size and shape) of solids at various length scales from the nanometer to the micrometer scale (Kuschel, and Polarz, 2008; Qin, Ren, Zhu, Zhang, Shang, and Wei, 2011). The porous materials research has been done with a variety of pore sizes, shapes and densities, but

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crucial feature is the increase in the material surface, which helps improve absorbent and adsorbent properties (Mitra, Vazquez- Vazquez, Lopez-Quintela, Bidyut, and Bhaumik, 2010; Park, Jung, Myung, Kim, Moon, Shin, and Seo, 2008).

The supporting materials with a porous structure control have been proposed to attain both biological and mechanical requirements, on this subject the pore-forming agents place an important role, when pore-forming agent is a crystal that could be removed with a solvent and release the porous matrix, the size of the pore is directly related with the pore-forming crystal size, also pore density and pore connections are related to the pore-forming crystal quantity, with this technology it is possible to obtain silicone (PDMS) porous matrix with the required porous size, connections and porous density (Solano-Umaña and Vega-Baudrit, 2015).

The porous silicone (PDMS) could be form a nanocomposite with metal nanoparticles. Advances in the field of nanotechnology have provided new forms of gold and silver available for use in biosensors or implantable devices, implants or scaffolds (Kleps, Danila, Angelescu, Miu, Simion, Ignat, Bragaru, Dumitru and Teodosiu, 2007). The surface modifications for polymers or applying coatings using metal nanoparticles increase the biocompatibility properties, nanofilms favor interactions of living cells with the biomaterial, especially for its beneficial effect on cell adhesion and proliferation. Along with the control of porosity in these materials, the application of metal helps allow vascularization and the growth of cells inside. The key biological processes integration, protein adsorption and cell proliferation, is the use of chemical methods to modify the surface properties (Solano-Umaña and Vega-Baudrit, 2015). Within the biocompatible metals that are used to increase biocompatibility properties of the various polymers are found Ag, Au, Ti, Ni, etc. A metal is considered biocompatible when it is:

- Accepted by the body without rejection reaction.
- Not toxic
- Inert or stable.

Experimental Procedures

Materials

In this study, the used materials were Poly-dimethylsiloxane (PDMS) product of Nusil Silicon technology (MED-4860), N-heptane puriss. p.a., Reag. ≥99% pure product of Sigma-Aldrich, Hydrochloric acid 37% ACS reagent product of Exaxol Chemical Corporation, Commercial fine sugar (SCS, brand), $AgNO_3$ (99.99%, Sigma-Aldrich), $HAuCl_4 \cdot 3H_2O$ (99.99%, Sigma-Aldrich), L-Ascorbic acid (99%, Sigma-Aldrich), Disodium ethylenediaminetetra-acetate (EDTA-2Na) ACS reagent (99.4 %, powder, Sigma-Aldrich), Dextrose monohydrate (USP grade, Sigma-Aldrich), Sodium hydroxide (ACS reagent, ≥97.0%, pellets, Sigma-Aldrich), Ammonium hydroxide solution (ACS reagent, 28.0-30.0%, Sigma-Aldrich), anhydrous Sodium Sulfite (≥98%, Sigma-Aldrich), and Copper(II) sulfate anhydrous, powder, ≥99.99% (Sigma-Aldrich), all chemicals were procured and used as received.

Methods

Porous Silicone matrix

Porous Silicone matrix was prepared by process called Molding and injection. The sugar crystals with a control crystal size from 100 to 300 micro meters were mixed with 5% water by weight, and later a mold was filled up with this mixture, one small channel was opened in the middle of the sugar mold, then the silicon was mixed with heptane in a proportion 80/20 and the mix was injected into the internal channel from the sugar mold, the silicone was cured at 100 C, the mold was placed in di-ionize water at 50 C, then stirring to remove the sugar and release the silicone matrix, finally the matrix was dried in an oven at 50 C.

Silver nanoparticles immobilization on porous silicone matrix

Prepare at 0.0131 mol/L $AgNO_3$ solution in DI-water and add an ammonia to form an ammoniacal silver complex $(Ag(NH_3)_2]OH)$, later a EDTA-2Na solution was added, molar ratio 1:1 respect $AgNO_3$, adjust the pH at 9.0 with ammonia, add the porous silicone matrix, then add a dextrose monohydrate solution and finally reaches temperature required (50 C). The molar ratio from silver nitrate to dextrose monohydrate was 1:5. Remove the porous silicone matrix after one hour to reach the required temperature.

Gold nanoparticles immobilization on porous silicone matrix

Prepare at 0.0013 mol/L $HAuCl_4 \cdot 3H_2O$ solution in DI-water, and add to a Sodium Sulfite (Na_2SO_3) solution, molar ratio from $HAuCl_4 \cdot 3H_2O$ to Na_2SO_3 1:10. Dissolve an EDTA in DI-water and add to the mixed solution, molar ratio from $HAuCl_4 \cdot 3H_2O$ to EDTA was 1:1, adjust the pH at 8.5 with NaOH 10% solution, add the porous silicon matrix, then add the L-Ascorbic acid solution and finally reaches temperature required (50 C). Molar ratio from $HAuCl_4 \cdot 3H_2O$ to L-Ascorbic acid was 1:10. Remove the silicone porous matrix after one hour to reach the required temperature.

Copper nanoparticles immobilization on porous silicone matrix

Prepare at 0.0080 mol/L $CuSO_4$:$5H_2O$ solution in DI-water, and add to a Sodium Sulfite (Na_2SO_3) solution, molar ratio from $CuSO_4$:$5H_2O$ to Na_2SO_3 1: 4. Dissolve an EDTA in DI-water and add to the mixed solution, molar ratio from $CuSO_4$:$5H_2O$ to EDTA was 1:1, adjust the pH at 8.5 with NaOH 10% solution, add the porous silicon matrix, then add the L-Ascorbic acid solution, and finally reaches temperature required (50 C). Molar ratio from $CuSO_4$:$5H_2O$ to L-Ascorbic acid was 1:1. Remove the silicone porous matrix after one hour to reach the required temperature. Copper nanoparticles could be synthesized through the chemical reduction of copper sulfate, and the ascorbic acid acts as reducer agent but also prevent the nascent Cu nanoparticles from oxidation during the synthesis process and storage (Dang, Le, Fribourg-Blanca and Dang, 2011)

Silver and gold nanoparticles immobilization on porous silicone matrix

Repeat the section 2.2.3, later collect the silicon porous matrix with silver nanoparticles and place in a dextrose monohydrate solution 0.15 mol/L, mix for 30 minutes and add the gold colloid solution. Prepare the gold colloid base on section 2.2.3,then add to the monohydrate solution that has the porous matrices, the volume ration between both solutions must be 1:1.

Cytotoxic t with MTT assay

The cytotoxic from porous matrix silicone nanocomposite samples with silver, gold, silver/gold, and copper were assessed on L929 fibroblast cell line according to ISO/EN 10993-5. Extracts of all silicone porous matrix nanocomposite samples with silver, gold, silver/gold, and copper were prepared based on ISO/EN 10993-12. After achieving this, a cell suspension seeded in 96-well plates at a density of 1 × 104 cells/ ml [1]were prepared and treated with four different extraction level concentrations (12.5%, 25%, 50% and 100%) of the different silicone porous matrix nanocomposites samples. After 24 h incubation, MTT reagent was added to each well and 2 h later, the number of living cells was evaluated at 570 nm.

The relative cell viability (%) was calculated for each extracts according to:

Viab. % = (100 X OD_{570e})/(OD_{570b})

OD represents the optic density.

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay was the first homogeneous cell viability assay, MTT substrate is prepared in a physiologically balanced solution, added to cells in culture, usually at a final concentration of 0.2 - 0.5mg/ml, and incubated. Viable cells with active metabolism convert MTT into a purple colored formazan product with an absorbance maximum near 570 nm, when cells die, they lose the ability to convert MTT into formazan (Riss, T. and Moravec, R., 2004)

Characterization method

Optical inspection

A visual inspection was performed on a SmartScope Flash 200, model CNC200, serial SVW2003849. SmartScope Flash is automatic dimensional equipment, with a measurement system, and optical metrology that used a large capacity video system for the dimensional manufacturing parts verification and control.

Fluorescence X-Ray Spectrophotometer

A thickness measurement from a Silver and Gold deposition over the porous silicone matrix was performed on X-ray fluorescence (XRF) spectrometer.

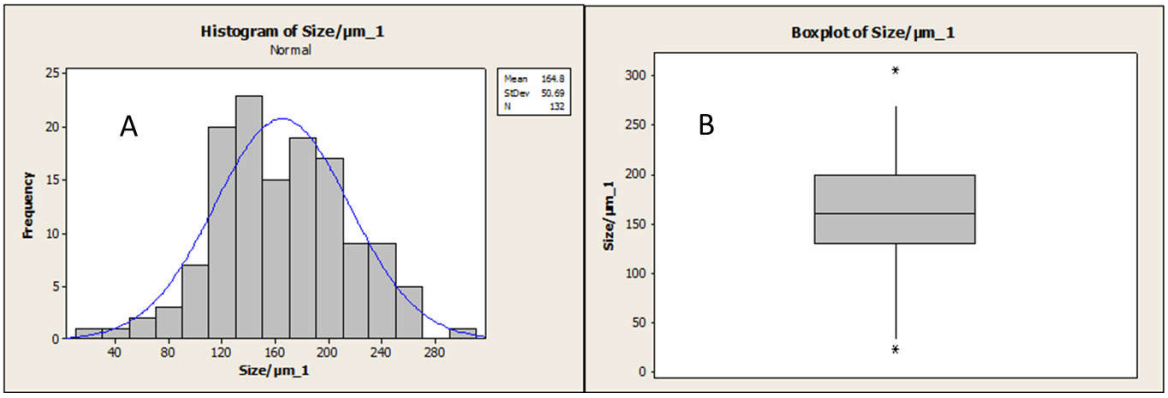

Figure 1 Pore size from the porous matrix silicone, A: histogram, B: box plot.

The Fischerscope XRF model XDLM-C4 equipment is used for routine of different materials, also XRF is a non-destructive method and this analytical technique can determine the elemental composition of materials. This analytical equipment determines the chemistry of a sample by measuring the fluorescent emitted from the material surface when it is excited by a primary x-ray source. Each metal from the sample produces a characteristic fluorescent x-rays pattern or fingerprint unique for that specific metal, the equipment is capable to give qualitative and quantitative analysis from the sample.

Scanning electron microscopy (SEM)

SEM images were obtained, using a JEOL JSM-6390LV Scanning Electron Microscope, particle size measurements could be confirmed, and in combination with the energy dispersive X-ray analysis (EDX) and elemental qualitative analysis was performed.

RESULTS AND DISCUSSION

The optical inspection and measurement from the porous silicone matrix prepared, evidence the pore size with a mean value of 160 micro meters and the Figure 1 show a distribution between 100 and 300 micro meters with a little pores below 100 micro meters. The mean pore size affects the cell behavior within the scaffold or implant. As pore size increases permeability increases due to a reduction in specific surface area. Moreover, too small pores limits cell migration, resulting in the formation of a cellular capsule around the edges of the scaffold. This condition reduces the distribution of nutrients and removal of waste products that results in necrotic sections. On contrary too large pores lacks specific surface area that limits the beneficial effect of initial cell attachment. Hence, optimal pore size and specific surface area are important factor for migration and for cell attachment (Nayak, and Kundu, 2014). Composite scaffolds with preserved morphology and micro-structure at micrometer scale are promising for tissue engineering; the pore size distribution from 164 ± 52 µm could better support the cells attachment on the porous material for medical applications (Qian, Xu, Yong, Jin, and Zhang, 2014).

Silicone is a material being used in medical science for a variety of prosthetic applications, because of its excellent biocompatibility and cost-effectiveness.

But the inability to permit fibrovascular ingrowth into implants was the major limitations of silicone implantation, today this limitation can be avoid with the used of porous silicone

implants, the porous silicone could replace, the commercially available and expensive porous implants from other materials (Son, Kim, and Yang, 2012).

The pore size distribution obtain on the porous matrix is directly correlated to the sugar size crystals used as pore-forming agent, this method to control the pore size distribution on scaffold or implants for a silicone material represent an easy and cheaper process that can achieve an important requirement for the medical application. Materials and fabrication technologies are critically important for tissue engineering in designing scaffolds or implants and the control of certain properties such porosity and pore size distribution are the key factor (Zadegan, Hosainalipour, Rezaie, Ghassai, and Shokrgozar, 2011; Wu, Zhu, and Tao, 2013). Cells invasion and growth on scaffold or implants is controlled by the size and structure of the matrix pore (µm) (Zhijiang, Chengwei, and Guang, 2012; Machado, and Santos, 2009).

The pore distribution between 100 and 300 was confirmwith the SEM imagine that also show the connectivity between pores, as show the Figure 2. Scaffolds and implants with a pore size distribution control around 200 µm have shown great promised for cells growing and nutrient movement, on porous materials that can beprepared through leaching method. Sieved sodium chloride salt (99% purity), with controlled crystal size can mix with polymers, prepare a slurry, cure the polymer and then remove the salt with water to obtain a porous material with a pore size distribution controlled (Tran, Thevenof, Zhang, Gywali, Tang, and Yang, 2010; Yoshimuraa, Nakanoa, Okamotoa, and Miyakeb, 2012).

The pore structures typically consist of irregularly shaped voids and connecting channels that can be difficult to define due to merging of adjacent cavities in the void walls, pore size and interconnectivity plays key requirements in cells interaction with scaffolds or implants (Chang, and Wang, 2011).

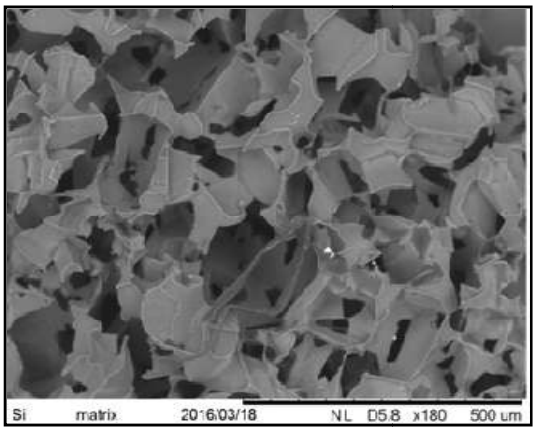

Figure 2 SEM imagine from porous matrix silicone.

After porous silicone matrix production the samples were added to the prepared metal colloid solutions, silver, gold and copper base on the process instructions and few minutes later the porous silicone matrix surface started to catch and immobilized the metal nanoparticles. The silicon changed from the white color to little brown, ruby (purple to pale rose), red and orange color depends of the colloid solution, see Figure 3.

All porous silicone matrix samples with silver, silver/gold, gold, and copper particles present a bright and nice color that indicated a nano level size. The optical attributes of metal nanoparticles, as reflected in their bright intense colors, are due to their interaction with light. In the presence of the oscillating electromagnetic field of light, the free electrons starts to excite, and this motion is resonant at a particular light frequency, this effect is called plasmon resonance (Tauran, Brioude, Coleman, Rhimi and Kim, 2013; Moores and Goettmann, 2006; Zhang, Xie, Yu, and Lee, 2010; Larguinhoa, and Baptista, 2012).

All samples were inspected with XRF (X-ray fluorescence spectroscopy), and EDX (energy dispersive X-ray spectroscopy), the Figure 4 shows the current X-ray fluorescence spectrum from the silicone (PDMS) and the dispersive X-ray spectrum shows the element composition from PDMS (silicon, carbon and oxygen), after the treatment with the silver colloid the silicone porous matrix turn brown and the XRF show a strong peak the indicated the presence of silver, also the EDX spectrum confirm this data, see Figure 3 and 5. The same situation was observe after the treatment of silicone porous matrix with silver and gold colloids one after the other (Figure 3 and 6), gold colloid (Figure 3 and 7), and copper colloid (Figure 3 and 8). The silicone porous matrix shows different bright colors depend from the metal nanoparticle and the peaks from the different metal presence over the silicone surface were evidence on the XRF and EDX spectrums.

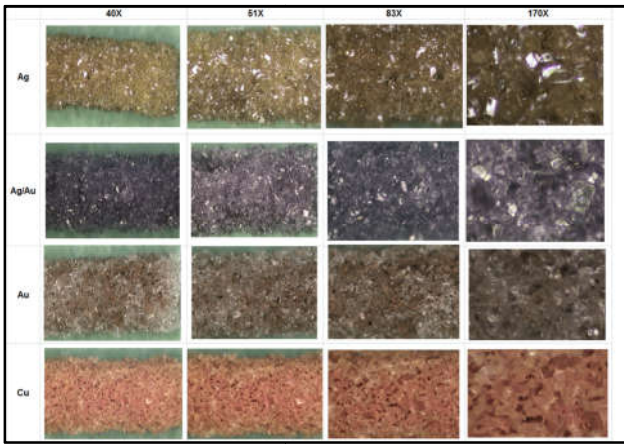

Figure 3 Optical micrographs of porous silicone matrix nanocomposite with silver, silver and gold together, gold and copper at different magnifications.

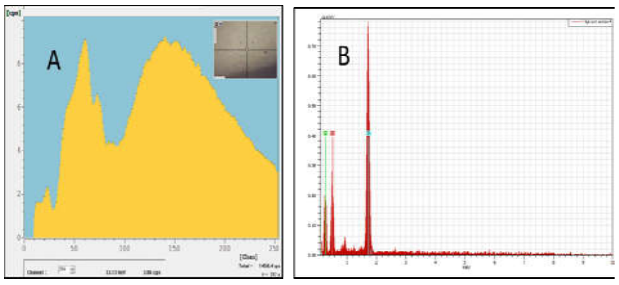

Figure 4 X-Ray porous silicone matrix spectroscopy spectrums, A:XRF, B:EDX.

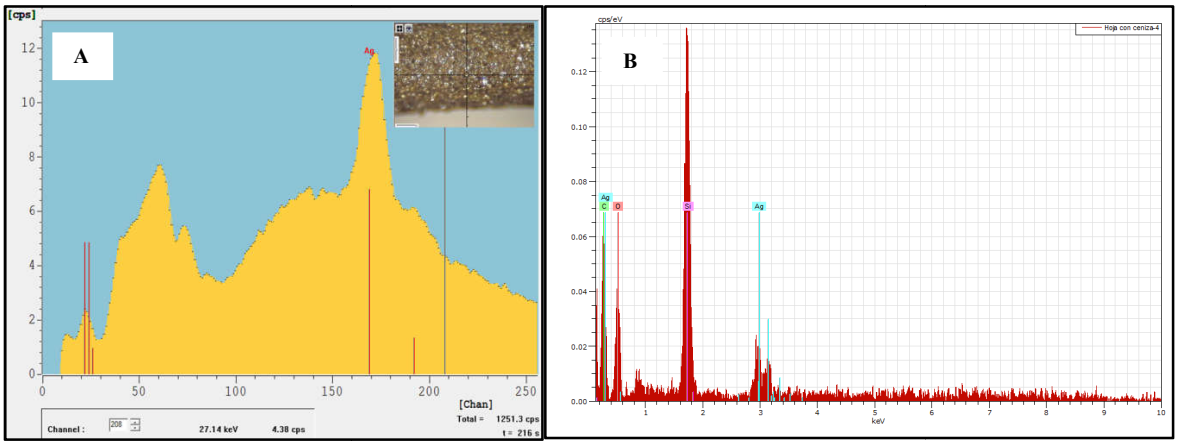

Figure 5 X-Ray porous silicone matrix/Ag nanocomposite spectroscopy spectrums, A: XRF, B: EDX.

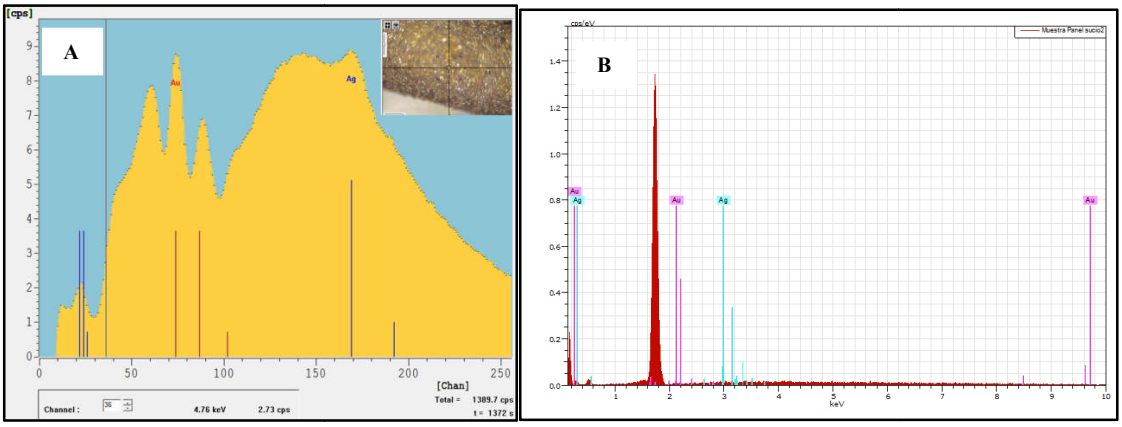

Figure 6 X-Ray porous silicone matrix/Ag/Au nanocomposite spectroscopy spectrums, A: XRF, B: EDX.

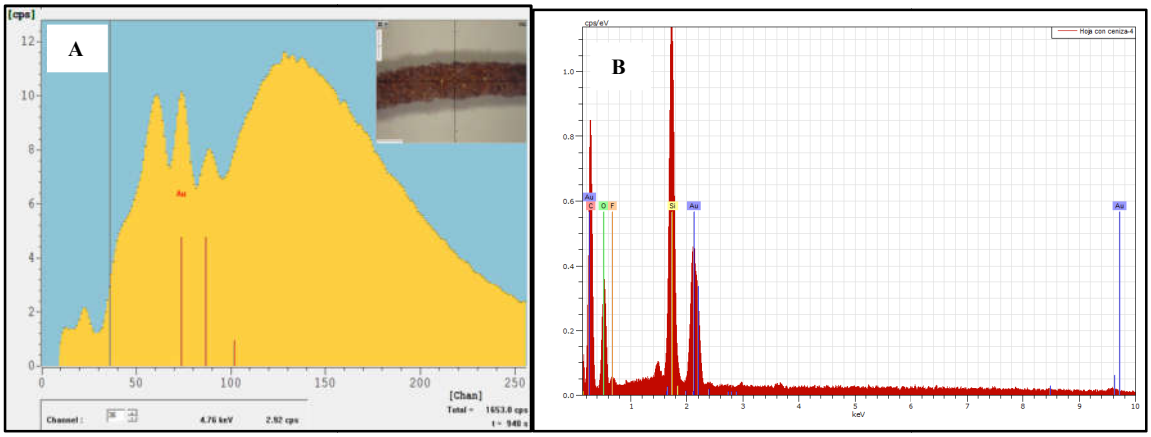

Figure 7 X-Ray porous silicone matrix/Au nanocomposite spectroscopy spectrums, A: XRF, B: EDX.

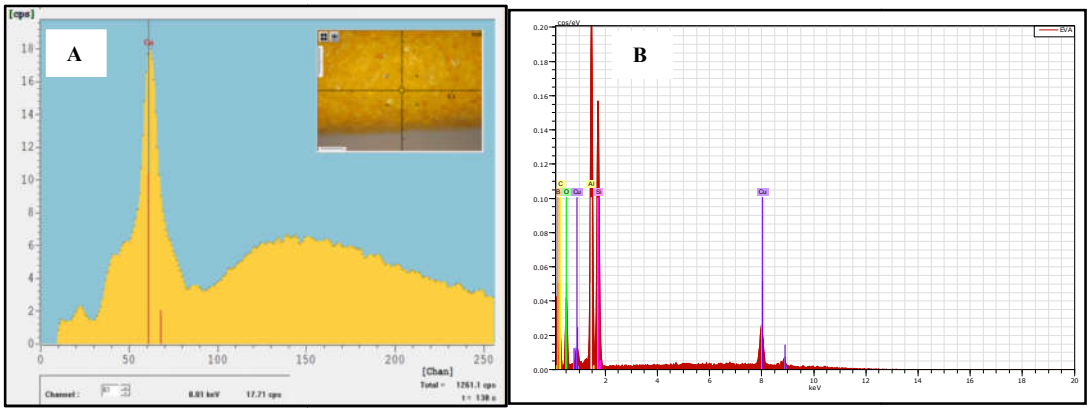

Figure 8 X-Ray porous silicone matrix/Cu nanocomposite spectroscopy spectrums, A: XRF, B: EDX.

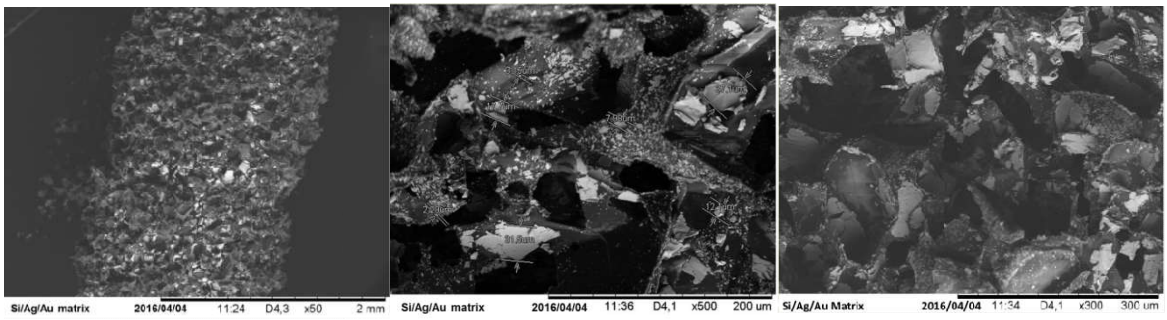

Figure 9 SEM image of silver and gold nanoparticles immobilized over a porous silicone matrix at different magnifications.

Figures 9 and 10 show the metal nanoparticles immobilization over the porous silicone surface, the silver and gold nanoparticles immobilization shows some particles agglomeration but trough the SEM inspection all pores from the matrix are free of obstructions, also the matrix was cut and the cross section inspection evidence a free channels and voids on the porous matrix, the gold and silver particles agglomeration form at film or coating, Figure 10 presents more uniform distribution from the copper nanoparticles respect to silver and gold.

Statistical analysis was performed by SPSS 15.0. Data were expressed in terms of mean ± SD at a significance level of $p < 0.05$. The data were not normally distributed in all cases. Therefore, the non-parametric Mann–Whitney U was used on the test to compare cell viability rates of the sample extracts and their different concentrations.

As shown in Figure 11, the highest concentration of the different silicone porous nanocomposite have low cell viability, and this situation is worst for the copper/silicone porous nanocomposite.

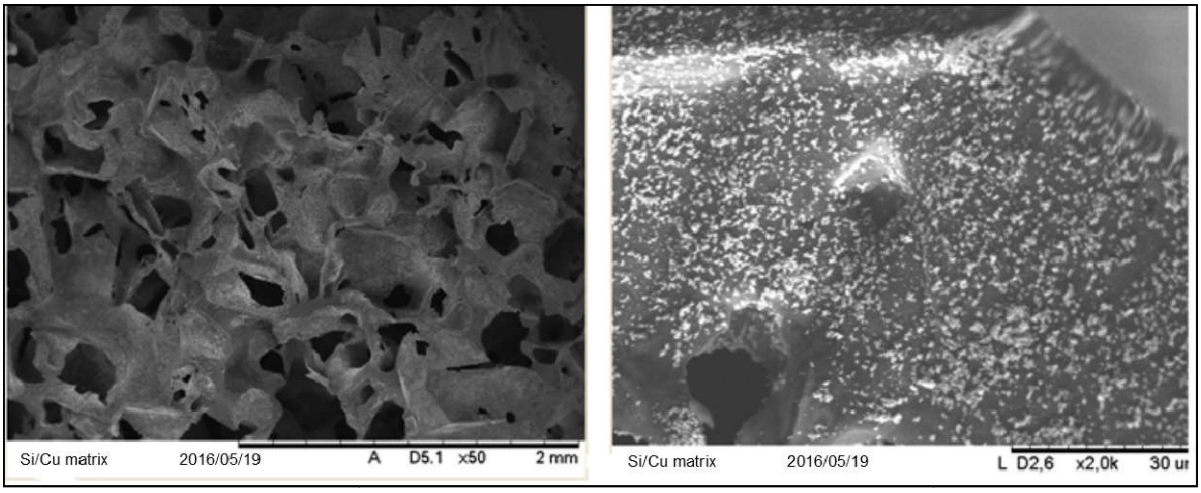

Figure 10 SEM image of copper nanoparticles deposition over a porous silicone matrixat different magnifications.

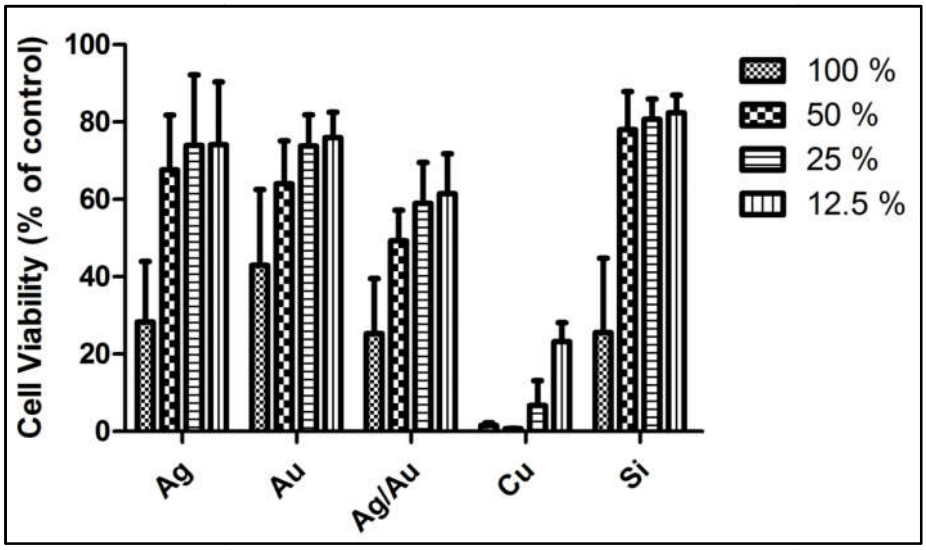

Figure 11 Cell viability of L929 mouse fibroblast cells on different porous matrix: silicone (PDMS), silicone/Ag nanoparticles, silicone/Au nanoparticles, silicone/Ag/Au nanoparticles, and silicone/Cu nanoparticles.

On copper composite all test performed with the different extraction concentrations (12.5%, 25%, 50% and 100%) have low cell viability. The cell viability from copper/silicone porous nanocomposite was observed at the different extracts levels and the mean cell viability were statistically different from control (porous silicone matrix, blank), silver/silicone porous nanocomposite matrix, gold/silicone porous nanocomposite matrix and gold/silver/silicone porous nanocomposite matrix mean, p values were ≤ 0.05, and the cell viability rate exceed the 70% from the blank cell viability value.

Silver and gold nanoparticles have antibacterial and antifungal activity and this property produce incremental research activities, on the application for this property for human help and medical applications, but these are expensive metals, copper shares properties similar to silver and gold, it is in the same Elements Periodic Table group. In Periodic Table of Elements, the chemical elements are organized according to chemical and physical properties. Copper, silver and gold form a vertical triad, called group 11, within the transition metals. They are also found together at the bottom of the reactivity series, which means that these metals are not easily oxidized, and this property is related to biocompatibility, if the metal have a good oxidation resistance it could be go for a medical applications because it is a requirement from a biocompatible material. The attack by components such as oxygen or acids on these metals is slow; but this resistance decreases from gold to silver and copper. Copper nanoparticles have antimicrobial activity against a number of species of bacterial and fungi, but for its oxidation resistance, the application on humans or animals is more restricted compared with silver and gold, because an excess of copper nanoparticles in the human or animal body leads to produce damaging radicals such as the hydroxyl radical, that could damage or killing body cells (Usman, Zowalaty, Zainuddin, Salama, and Ibrahim, 2013).

On this application, where the copper nanoparticles were immobilized over the porous silicone matrix, all extraction concentrations (12.5%, 25%, 50% and 100%) show a toxicity effect, but other researches evidence a good copper biocompatibility and non-toxicity effect, if the copper nanoparticles are stabilized inside the polymer not over the surface. Copper nanoparticles stabilized inside latex polymer have non-toxicity effect and are biocompatible (Harne, Sharma, Dhaygude, Joglekar, Kodam, and Hudlikar, 2012).

The mean cell viability values from silver/silicone porous nanocomposite matrix, gold/silicone porous nanocomposite matrix and gold/silver/silicone porous nanocomposite matrix were not statistically different from control sample (porous silicone matrix, blank), p values were > 0.05 per each extraction level (12.5%, 25%, 50% and 100%), and the cell viability rate did not exceed the 70% from the blank cell viability value per each extraction level (12.5%, 25%, 50% and 100%).

When extract concentrations increases, the surviving L929 cells decrease of which were exposed to silver/silicone porous nanocomposite matrix, gold/silicone porous nanocomposite matrix and gold/silver/silicone porous nanocomposite matrix extracts. However, cell viability rate did not exceed 70% margin for safety respect to control sample (porous silicone matrix, blank). Some studies indicated cytotoxic effects of acetic acid used in preparation of scaffolds (Algul, Sipahi, Aydin, Kelleci, Ozdatli, and Yener, 2009). In this study, acetic acid were not used directly but some residues on the silicone or residues from the used chemicals could explain cell viability values at the high extraction concentrations (100%).

The Figure 11 results showed that 50% of all extracts were higher than the 100%, and these results are according to ISO standards (50% extract of the sample should have at least the same or highest viability than the 100% extract), these results confirm that non cytotoxic effect were induce from the silver or gold immobilization over the porous silicone matrix.

CONCLUSION

The leaching method with the used of pore-forming agents can play an important role for the scaffolds and implants production from silicone polymer, when pore-forming agent is a crystal, it could be sieve to control the crystal size distribution, thatis directly proportional to polymer pores size obtained, on this study the select pore-forming agent was sugar but others research report a good results with different water soluble salts like sodium chloride.

The porous matrix properties can be improve through the addition of functional groups or metal nanoparticles, porous silicon matrix can add to a gold, silver and copper colloids an immobilized these particles over the silicone surface and also this immobilization can be controlled to not affect the pore size distribution. Gold, silver and copper have a appreciate properties for a medical applications, gold have a great biocompatibility properties, it can use on implants, scaffolds, cancer treatment, medical sensors, drug release, diagnostic, etc., silver is identified by antimicrobial, anti-inflammatory properties, it can use on cancer treatment, implants, scaffolds, diagnostic, etc., and copper that can use as antimicrobial and contraceptive agent. Based on these application cytotoxicity studies for the different nanocomposites and application are very important.

Gold and silver nanoparticles immobilized over the silicone porous matrix non evidence cytotoxic effect on L929 fibroblast compare with the pure silicone porous matrix (Poly-dimethylsiloxane (PDMS) product of Nusil Silicon technology, MED-4860), that is a FDA approve product for medical use, but copper nanoparticles immobilized over the silicone porous surface evidence statistical cytotoxicity difference compare with the pure silicone porous matrix.The obtained results could be useful for a different medical applications, for example copper nanoparticles on contraceptive agents.

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