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Original Article

Synthesis and Evaluation of PVA-Silica Electrospun Nanofibers for Orthopedic Application

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Silica has been used over the years for biomedical applications due to its excellent bioactivity compared to other ceramics used for bone regeneration. Considering other methods in the preparation of silica, the sol-gel method is preferred since it allows the formation of highly pure products with desired properties. Polyvinyl alcohol which has many desirable biomedical applications was incorporated with silica to electro-spun into a nanofibrous sheet which can be used in orthopaedic applications. Higher the porosity of the sample, greater the water absorption capacity. XRD and FTIR spectra were analysed and the results proved the incorporation of silica into electro spun PVA network. SEM analysis and histogram proved the nanofibrous formation since all the samples had a diameter within the range of 150-350 nm. The Biological studies such as haemocompatibility assay proved the samples to be haemocompatible since the samples had the haemolytic ratio below 5. Degradation analysis of the samples proved that PVA-silica electro-spun sheets could be used as scaffolds since they showed excellent degradation rates with respect to time. Cytotoxicity assay provided cell viability >96% for all the concentrations.

Introduction

Biomedical implants for orthopaedic applications become a necessity when a bone is traumatized because of deformation or damage [1]. Natural or synthetic, biomaterials can restore the damages faced by the bone matrix partially or completely according to the material used for implantation. Ceramics, metals, plastics, glass, living cells, and tissues are used for creating biomaterials [2]. The materials used in orthopaedic implants should possess features like corrosion resistance, tissue tolerance, and biocompatibility and they should not cause any adverse reactions in the body [3]. Bio ceramics are defined as ceramic materials that are designed to gain a specific physiological behaviour to use as a material for the construction of prosthetic devices due its various capacities like the ability to interact with living cells without any damage and the capacity to withstand the strain that it could face in everyday activities [4]. The early nineties saw a leap in the use of bioceramics due to the invention of bioactive glass by Hench [5]. It was followed by various modifications to the composition of bioactive glass to increase the biological as well as mechanical properties of the latter [6]. Since bioceramics can induce bioactivity and reduce the rejection of foreign material from the human body due to their ability to develop bone-like apatite on the implant surface, they have been used for direct implant fabrication, coating, and spraying on other metal implants to reduce corrosion and leaching of toxic ions from the metal surface [7]. Among these, silica stands atop due to its easy formation of bone-like apatite and ability to form metal-implant bonds via matrix formation [8]. Uniform porosity, biocompatibility, and large surface area are the main peculiarities of silica but its easily modifiable surface with a large number of silanol groups increases the bioactivity of the latter. Due to these properties, silica possesses greater stability in organic solvents or the presence of temperature fluctuations compared to other traditional drug delivery systems [9]. Silica is prepared by using the sol-gel method which is a bottom-up synthesis [10]. Sol-gel method allows the hydrolysis of silicon atoms in tetraethyl orthosilicate which is used as a most common precursor for the formation of silica, leading to the formation of $Si(OH)_4$. It is followed by the condensation reaction and porous silica nanoparticles are formed when the aqueous media is evaporated [11].

An electrospinning method is a top-down approach and a more versatile, simple, and efficient technique that produces continuous nanofibers. It is smaller than 100-1000 times compared to the

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fibers that are fabricated through other methods like solution and melt spinning [12]. The advantages of using the electrospinning method are simple, facile, and cost-effective. Bioactive compounds can be incorporated easily into the nanofibers and heat is not required during the process. The essential qualities of electrospinning include high specific surface area, lightweight, controllable pore size, high porosity, flexibility in surface functionalities, and excellent mechanical properties. These Properties employ the use of electrospun nanofibers in diverse applications such as tissue engineering, drug delivery, and wound dressing [13]. Polyvinyl alcohol (PVA) is one of the synthetic polymers that has been used extensively in electrospinning for orthopaedic scaffold fabrication due to its biocompatibility, biodegradability, non-toxicity, good fiber forming ability, and high hydrophilic properties. It is usually spun, coagulated, oriented, and cross-linked. It can be conveniently electro-spun in an aqueous medium [14-16].

The main challenges faced in the successful fabrication of a scaffold for bone regeneration include the formation of a porous three-dimensional network structure that can induce both cell proliferation and transport of nutrients, controlled biodegradation as new cells are formed along with enough mechanical properties to withstand the fatigue that can be caused due to daily activities and its non-inflammatory response [17]. In this paper, we briefly discuss the scaffold fabrication of nanofibrous PVA-silica sheets for bone tissue engineering.

Materials and Methods

Tetraethyl orthosilicate (SRL India), double distilled water, 1 M HNO_3, etc. were used for the preparation of silica. Polyvinyl alcohol (PVA, mw:60000, Himedia) was used for the electrospinning of the scaffold. Sodium Chloride, Potassium Chloride, Sodium Phosphate Dibasic, and Potassium Phosphate Monobasic (SRL) were used for the preparation of phosphate buffer saline (PBS) solution.

Preparation of silica

Using the sol-gel method mentioned elsewhere [3], 9.5 M silica was prepared using excess water and maintaining the pH to 2 to keep up the isoelectric point of silica. The solution was kept in a magnetic stirrer for an hour to get a homogeneous solution. After keeping it for aging overnight, it was kept in the water bath for 8 hours for gel formation. It was then dried in a hot air oven for 24 hours followed by sintering at 600°C and the powder sample was collected for further procedures.

Electrospinning of PVA-silica composite

For electrospinning, 10% of the PVA solution was prepared in hot de-ionized water. Different weight % of silica (1, 2, 3, 4, and 5 w/v %) was added to it and stirred overnight to get a homogeneous solution. The solution was filled into a 5mL syringe and electrospinning was carried out using 20 KeV power and the flow rate of the solution was set to 1mL/hour. The nanofiber was collected onto the aluminum foil connected to the collector that rotated at 750 rpm and kept at a distance of 15cm away from the needle. The electro-spun samples were peeled off from the foil after drying it and the samples were named PS1, PS2, PS3, PS4, and PS5 according to the w/v% of silica used for electrospinning.

Characterisation of the nanofibrous sheets

The following were the analytical methods used for the structural and morphological characterization of the samples. Fourier transform Infrared (Shimadzu, Japan) analysis of the samples was done at a range of 400-4000 cm^{-1}. X-ray diffraction (Bruker D8 Advance, Germany) analysis was done at a 2θ range of 10°-90° keeping the Cu Kα radiation at 1.5418A°. The morphology of the nanofiber was determined using scanning electron microscopy (JSM-5610 LV) and the average diameter of the electro-spun nanofiber was determined with the aid of ImageJ software using SEM images.

In vitro degradation of the nanofibrous sheet

The *in-vitro* degradation of the sheet samples was studied using the phosphate buffer saline solution at pH 7.4. The pr-weighed sheets were dipped into 5mL of PBS solution and each day the solution was replaced. After 14 and 28 days the samples were taken out, washed with de-ionized water, and dried. After weighing the dried sheets, the percentage of degradation was calculated using the following equation

$$\% \text{ weight loss} = (Wi - Wf)/Wi * 100$$

where Wi represents the initial weight and Wf represents the final weight

Measurement of porosity of the nanofibrous sheet

The measurement of the porosity of the nanofibrous sheets was done using the solvent replacement method. The pre-weighed samples were immersed in ethanol until they attained saturation. Afterward, the samples were taken out, dried, and weighed. The porosity of the samples was calculated using the following formula

$$\% \text{ porosity} = (S2 - S1)/\rho V * 100$$

where $S2$ represents the final weight, $S1$ represents the initial weight, V represents the volume of the sheet sample and ρ is the density of absolute ethanol.

Water absorption study of the nanofibrous sheet

The ability of the nanofibrous sheet to absorb water was measured by soaking the pre-weighed samples in de-ionized water and allowing for saturation. Afterward, the samples were weighed and % of water absorption was calculated using the following formula

$$\% \text{ water absorption} = (S - W)/W * 100$$

where S is the final weight and W is the initial weight of the sheet sample.

Mechanical testing of the nanofibrous sheets

The mechanical properties of the electro-spun sheets were carried out using the universal testing machine (Tinus Olsen H5K5) following the ASTM standards (D695). 50N load cell was applied and samples with 40mm thickness were tested at a strain rate of 3mm/min.

Hemocompatibility analysis

The hemocompatibility analysis of the samples was done in the following method mentioned elsewhere [18]. 5 mL of blood was collected from a healthy volunteer following the ICMR protocol and centrifuged at 4000 rpm for 4 minutes. After separating the plasma red blood cells, the pellet was washed in PBS solution and centrifuged again at the same conditions and the procedure was repeated three times. The pellet was then dissolved in 15 mL of PBS solution and stored in cold condition. The samples (1mg each) were immersed into the PBS solution and blood was added to it and incubated for an hour at 37°C. After centrifuging the samples, UV-visible analysis of the samples was done (JASCO (V-670 PC)) at 200-800 nm and the absorbance at 540nm were noted. The haemolytic ratio of the samples was calculated using the

formula,

Haemolytic ratio = $(Abs_{Sam} - Abs_{Neg})/(Abs_{Pos} - Abs_{Neg}) * 100$

Abs_{Sam}, Abs_{Neg}, and Abs_{Pos} are the absorbances of the sample, negative control and postive control respectively.

Cytotoxicity Assay

MTT assay using an L929 cell line was conducted to analyze the cell viability of the sample. PS4 was considered as the optimized sample from the analysis carried out in the previous steps. Various concentrations of the samples were added to the DMEM medium and were transferred to the 96 well plates that were seeded with cells prior to the addition of the samples. Untreated wells were considered as control and further incubation of the sample for 24 hours was followed by the observation of results at 570 nm. The cell viability of the samples is reported in percentage.

Statistical analysis

The studies were carried out in triplicate and the mean ± standard deviation was used in analyzing the results. The significance of the results was analyzed with the aid of GraphPad Prism 8 and the significance was considered at $P \leq 0.05$.

Results and Discussion

The FTIR analysis of the samples is shown in figure 1 which depicts the peaks of both PVA and silica. The peak at 3295 cm^{-1} represents the vibrational stretching frequency of the O-H group present in the sample. Vibrational stretching of $-CH_2$ groups in PVA is observed at 2918 cm^{-1}. The carbonyl stretching band of PVA is observed at 1717 cm^{-1} and $-CH_2$ bending vibrational peaks are at 1418 cm^{-1}. The C-O stretching peak is at 1095 cm^{-1} and the peak observed at 851 cm^{-1} indicates C-C stretching. The peak at 927 cm^{-1} indicates the presence of the Si-OH group which can contribute to the bioactivity of the sample. Si-O-Si asymmetric stretching vibrational bands are observed at 1140 cm^{-1} and bending vibrations at 474 cm^{-1}.

XRD analysis of various samples is depicted in figure 2. The graph shows the presence of amorphous peaks due to the presence of both silica and PVA. The broad peak observed between 18.5° and 25° indicates the merged peak of PVA and silica which is usually observed at 19.5° and 22.3° respectively. Another observation from this graph is that as the concentration of silica increased in the samples, it resulted in a more intense peak indicating the presence of more silica particles in the sample. The peaks all showed an amorphous nature and it was observed that the addition of silica into the PVA network broadened the peaks [19].

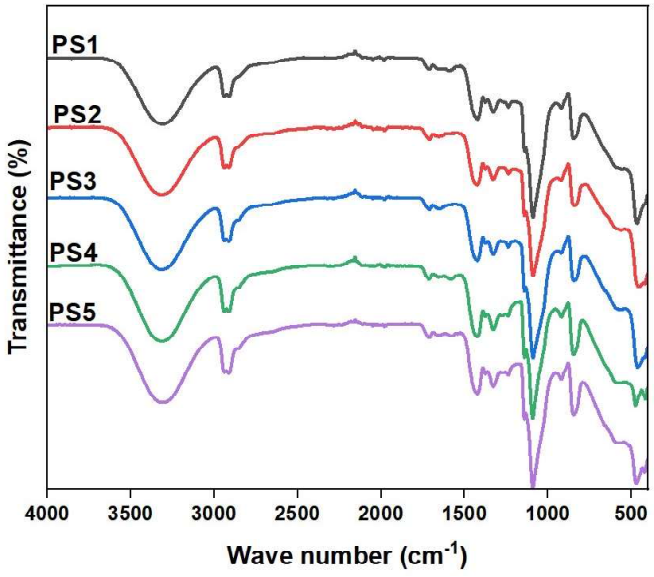

Figure 1: FTIR analysis of various PVA-silica samples

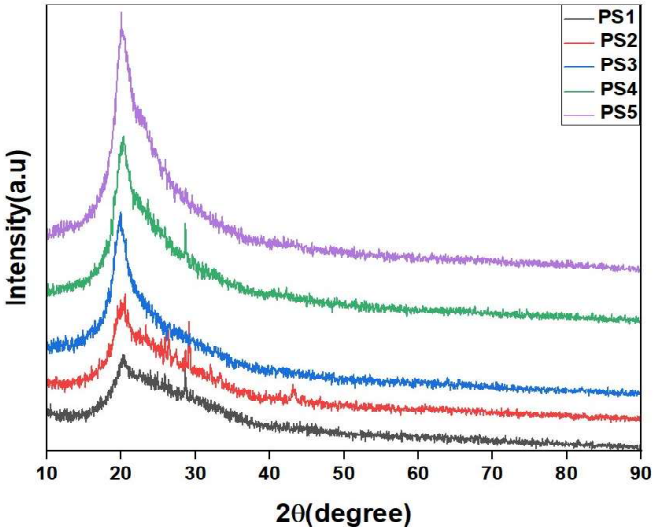

Figure 2: X-ray diffraction spectra of PVA- silica scaffolds

The degradation of the electro-spun samples was analyzed to confirm its suitability as a biodegradable scaffold. The samples immersed in the PBS solution at a pH of 7.4 were taken out on the 14th and 28th days to analyze their ability for degradation. The samples showed excellent degradation properties and it was also noted that the rate of degradation increased as the concentration of silica increased in the sample. The rate of degradation was analyzed in a bar graph as in figure 3 and it is observed to be 36.41, 37.74, 42.97, 49.41, and 61.7% at 14 days and 39.84, 43.74, 48.32, 58.73, and 69.5 % at 28 days for PS1, PS2, PS3, PS4, and PS5. This might be due to the ability of silica nanoparticles to leach out which also can enhance the bioactivity of the sample. The biodegradation of silica greatly depends on its surface area and its ability to interact with the aqueous media [20]. Moreover, PVA nanofiber itself has a greater degradation rate due to its hydrophilicity. Biodegradation of polymers can occur by chemical, physical, or biological interactions. The degradation may occur due to the presence of ionic species in the testing medium, depolymerization, and cleavage of carbonyl groups. When a scaffold is implanted into the human body, the absorption of water molecules from the surroundings leads first to swelling, and degradation from exterior to interior takes place leading to the weight loss of the implant [21]. They also can undergo some physiochemical change due to the interactions with the body fluids that surround the implant. This leads to the diffusion of the particles to the solution and hydrophilicity of the polymer leading drive for this degradation phenomenon [22]. Another observation was that the rate of degradation for silica-incorporated samples was less than that of pure PVA which is highly hydrophilic due to the bonding between the terminal -OH group of PVA and the silanol group in silica [23].

SEM analysis is done for the electro-spun samples to analyze the nanofibrous pattern of the electro-spun sheet and the images are

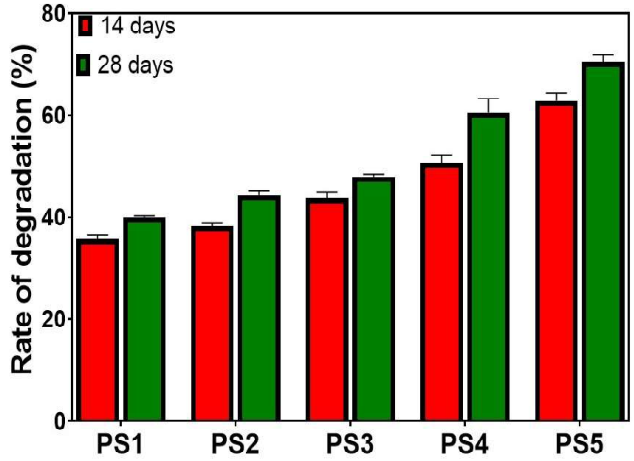

Figure 3: Rate of degradation

shown in figure 4. All the sheets provide a random alignment of the fiber with a diameter range from 150 to 350 nm. Our findings indicate that there is a direct relationship between the diameter of the nanofiber and the concentration of silica in the electrospun scaffold. According to histogram analysis, when 1w/v% of silica was added, the diameter of the fiber was observed to be 185.05 ± 5, and for 2%, it was 210.58 ± 16, for 3%, it was 230.56 ± 16, for 4%, it is 252.23 ±10, and for 5%, it is observed to be 324.69 ± 21. As the concentration of silica increased a more flattened morphology of the fiber also was observed which is possibly due to the increase in molecular weight of the silica/PVA network. This increase in molecular weight can increase the viscosity of the solution, thus increasing the electrostatic force and thus increase in fiber diameter though not much.

Porosity is an important factor when considering a scaffold since higher porosity of the sample can induce greater cell viability and proliferation due to its ability to transfer nutrients and exchange oxygen when acting as a scaffold in the human body [24]. It has been said that the high porosity of a scaffold can facilitate a better cell-polymer interaction due to more surface area and more space for extracellular matrix regeneration [25]. The porosity of various electro-spun sheets was analyzed via the liquid displacement method is depicted in figure 5. As seen in the figure the porosity of the samples increases as the concentration of silica increases. This might be because of the change in arrangement of the fibres as explained in the SEM analysis in figure 4.

To evaluate the tissue engineering properties of the scaffold, its ability to retain the water molecule is considered. The percentage of water absorption is directly related to the pores present in the scaffold due to the random alignment of the fibers formed when the electrospinning was done. Capillary force can act as the driving force to keep the water absorbed in the sample. Moreover, PVA is also an excellent hydrophilic polymer that can absorb water in a large quantity [26]. The presence of silica on the surface of the electro-spun sheet can increase the surface roughness and in turn, increase the viability of cells and their proliferation. Since PVA has many hydroxyl groups present in itself, water absorption can take place more easily. The porosity and interconnectivity of the scaffold also aid in the water absorption capacity [27]. As shown in figure 6, 242.02% of water absorption was observed by PS5 whereas 133.33% was observed by PS1. For more space for the growth of new cells and the passage of nutrients, higher porosity is preferred and it is an important criterion for tissue regeneration [28].

The swelling percentage can also represent the substantiality of the electrospun scaffold. The mechanism of the swelling property of the scaffold directly depends on the osmotic pressure that is in action due to the porous structure of the scaffold [29]. Since there is a difference in osmotic pressure between the solution and the nanofibrous scaffold, the pressure difference is brought to law by the uptake of water into the scaffold which leads to a reduction in osmotic pressure. This action can continue until the equilibrium state is reached [30].

Haemolytic Assay

Haemolytic assay is a crucial study for the determination of the haemocompatibility of the sample. According to ICMR guidelines haemolytic ratio of the sample should not exceed a value of 5% to

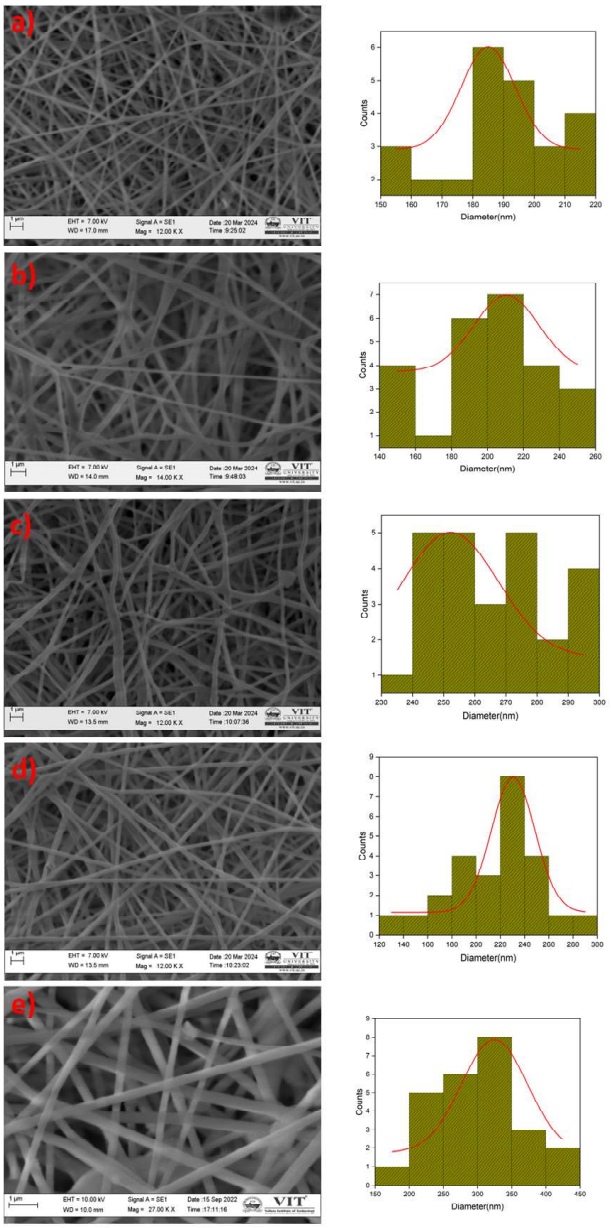

Figure 4: SEM analysis of PVA-silica samples with histogram

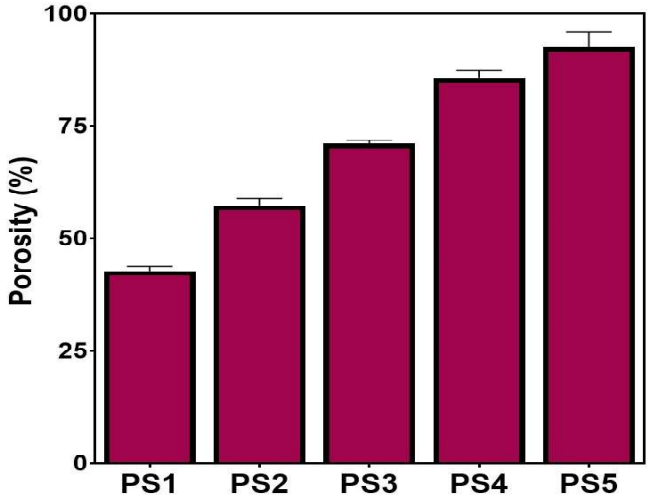

Figure 5: Porosity analysis of PVA- silica scaffolds

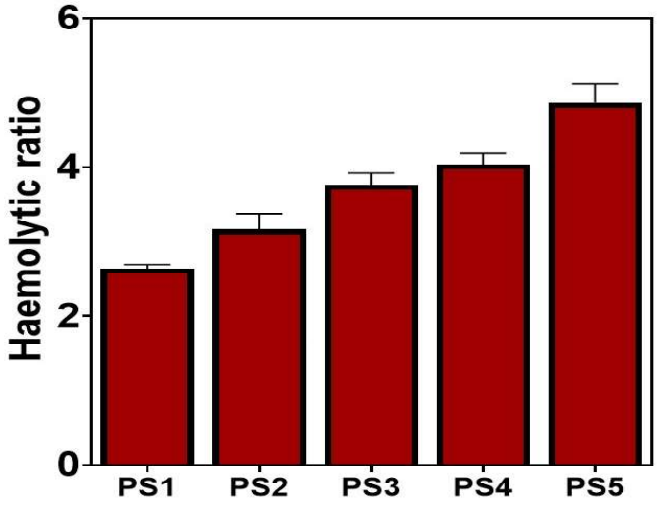

Figure 7: Haemolytic Assay of various PVA-silica samples

consider that sample as haemocompatible. More than 5% of haemolytic ratio shows that the sample is highly haemolytic which can destroy red blood cells at the site of implantation [31]. The haemolytic ratio of all the electro-spun samples was analyzed and is shown in figure 7 and it was observed that the haemolytic ratio of all the samples was less than 5. The presence of more silica nanoparticles showed a higher value of haemolysis of 4.8. It was reported by Slowing et al that as the number of silanol groups increases, it can increase the haemolysis to an extent since SiO^- ions formed due to the interaction with water molecules can bring about the electrostatic reaction between tetra-alkyl ammonium groups present in RBC [32]. But another study done by Shi et al argued that as the surface area and porosity of the sample increase it can induce more haemolysis due to its increased exposure to blood [33].

Mechanical testing

The mechanical property of a scaffold plays a crucial role in the selection of a scaffold for tissue regeneration it was observed that as the concentration of silica increased in the solution, the mechanical properties of the scaffold increased significantly (figure 8). The tensile strength was observed to be 0.80, 0.98, 1.12, 1.48 and 2.46 MPa for PS1, PS2, PS3, PS4, and PS5 samples respectively. The increase in mechanical properties may be due to an increase in the interaction between the polymer and silica as the concentration increased.

Cytotoxicity Assay

The cytotoxicity assay of PS4 proved the sample to be non-cytotoxic since the study of the sample under various concentrations had cell viability > 96% which proves its non-toxicity and allows it to be used in orthopaedic applications. The microscopic images of the study are provided in figure 9a and the cell viability graph in figure 9b. This also suggests the sample could be optimal for cell proliferation and differentiation if treated longer with cells.

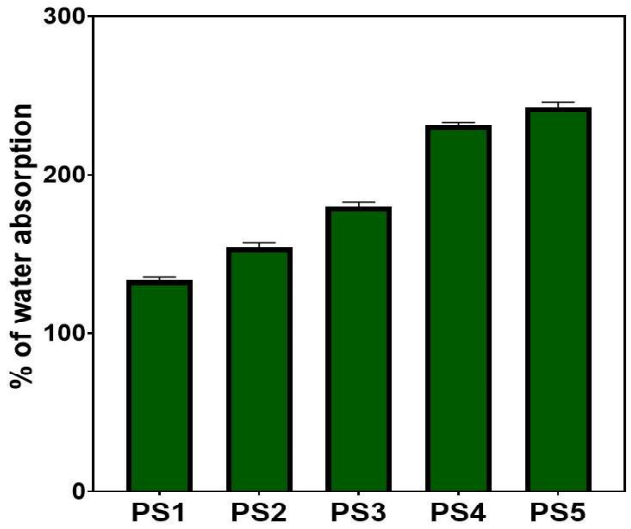

Figure 6: Analysis of %of water absorption of various PVA-silica scaffolds

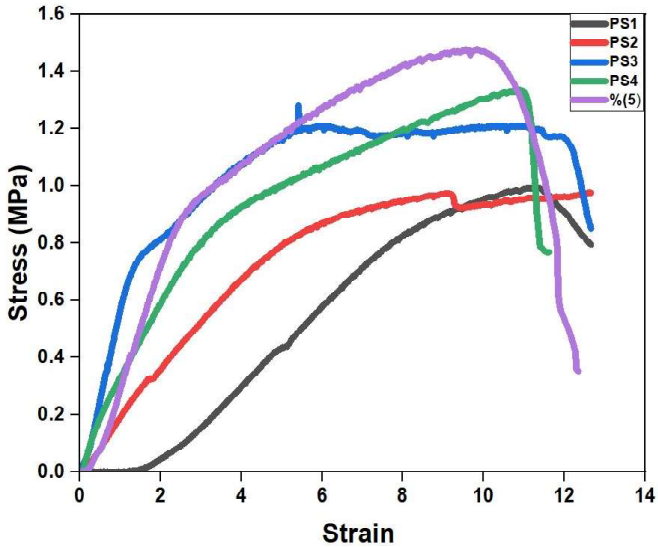

Figure 8: Mechanical strength analysis of PVA-silica samples

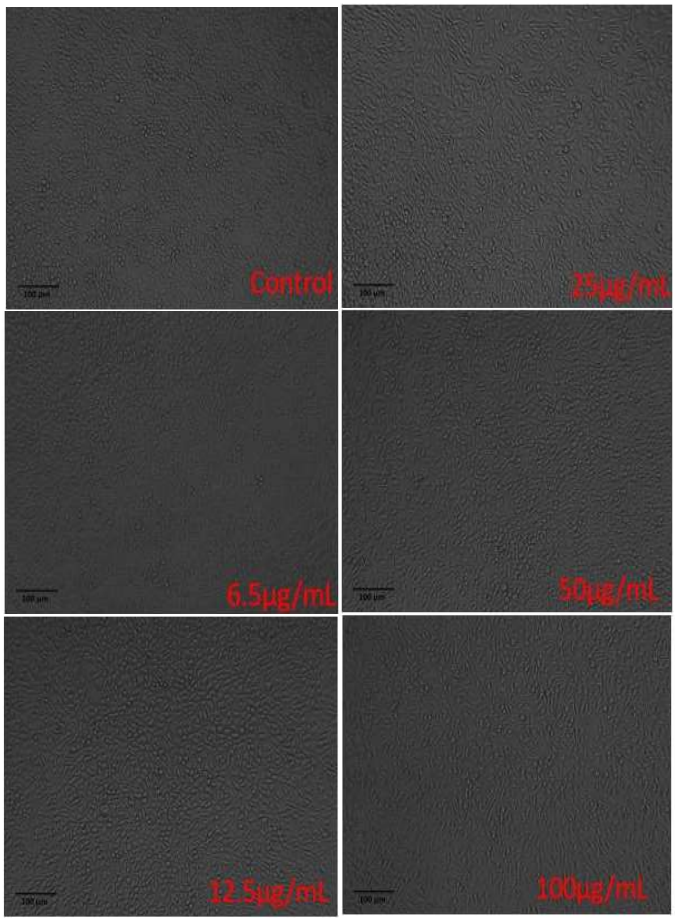

Figure 9a: Microscopic image of the cytotoxicity assay of PS4 at various

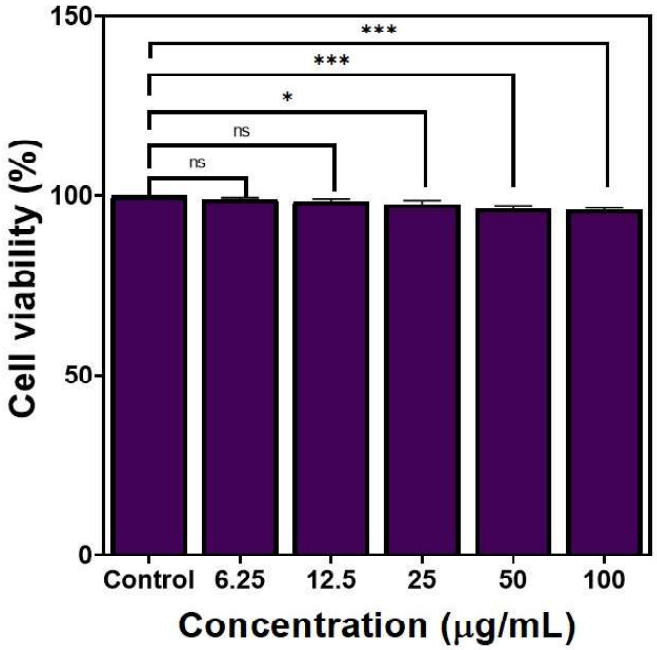

Figure 9b: Analysis of cell viability of PS4 at various concentrations

Conclusion

Electrospinning of PVA sheets incorporating various w/v % of silica was fabricated successfully at 20KeV with a collector rotation speed of 750 rpm. The XRD and FTIR analysis showed a proper blending of PVA and silica and no beads were found in SEM images showing that the fabrication provided a well-aligned nanofibrous sheet. As the concentration of silica increased a more flattened arrangement of fibers was also observed. Water absorption analysis and porosity measurements showed that as the concentration of silica increased, these properties also increased. The presence of silica could give a higher mechanical strength to PVA sheets and haemolytic assay proved the samples to be non-haemolytic. The cell viability analysis proved the non-toxicity of the scaffold. From these studies, it is deduced that the electro-spun PVA- silica sheets are good candidates to be used as orthopaedic scaffolds.

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