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Synthesis, Antimicrobial, Biocompatibility, Toxicity, and Osteogenic Properties of Nanofibrous Gelatin Scaffold Containing Meropenem/Vancomycin-Mesoporous Silica Nanoparticles (Mrp/Van-MSNPs)

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Abstract

Electrospinning scaffolds composed of antibiotics and natural polymers can be helpful in the simultaneous suppression of infectious procedures and inducing tissue healing in the treatment of bone infections. The present study was performed to prepare and determine antimicrobial effects, biocompatibility, and osteogenic effects of gelatin meropenem/vancomycin -mesoporous silica nanoparticles (Mrp/Van-MSNPs) synthesised through an electrospinning method. The scaffolds were examined for physicochemical characteristics, antibacterial activity, biocompatibility, and osteogenic qualities. The scaffolds showed applicable mechanical features, slow drug release patterns, and showed antimicrobial effects for 21 days. Gelatin-Mrp/Van-MSNPs showed higher antimicrobial and bacterial adhesive effects than gelatin and gelatin-Mrp/Van. All prepared scaffolds exhibited in vitro favorable biocompatibility. Gelatin-Mrp/Van-MSNPs significantly induced the MSCs' attachment, viability, and proliferation. It also significantly triggered the alkaline phosphatase (ALP) activity and induced the expression of osteogenic genes in both the early and late stages of differentiation. Therefore, the gelatin scaffolds with Mrp/Van-MSNPs can be considered for treating osteomyelitis. The incorporation of MSNPs and antimicrobial agents into gelatine did not demonstrate a significant association with adverse effects on the properties of gelatine. The MSNPs led to improved antimicrobial, biocompatibility, and increasing cellular proliferation, and induced osteogenesis properties of gelatin.
Keywords:Gelatin, meropenem, mesoporous silica nanoparticles, osteomyelitis, vancomycin.

Introduction

Gelatin is one of the most widely used biomaterials for tissue engineering applications in a variety of forms [1, 2]. Gelatin is a single-helix polymer formed due to collagen denaturation which naturally is present in several tissues of vertebrates such as skin, bone, and ligament [3, 4]. Gelatin recently has attracted considerable attention for usage in biomedicine goals due to its accessibility, natural origin, biocompatibility, biodegradability, low antigenicity, and cost-effectivity relative to other biomaterials [5, 6] .Due to the presence of several superficial active functional motifs, gelatin is easy to modify and crosslink [7]. Impacts of gelatin on the biological properties of composite scaffolds have been described by in vitro and in vivo studies. Gelatin has significantly increased cell adhesion and induced cellular differentiation and proliferation [8]. Due to the inadequate mechanical properties of gelatine, gelatin-based scaffolds require reinforcement through crosslinking and the incorporation of inorganic substances, enhancing their suitability for tissue engineering applications [6, 9, 10]. Mesoporous silica nanoparticles (MSNPs) have been used to improve mechanical activity and increase the antimicrobial effects of naturally origin scaffolds. The favorable surface properties of MSNPs provide an appropriate approach to use in drug loading and controlled release in the treatment of cancer and infections [11-14]. Meropenem and vancomycin are the most effective antimicrobial drugs against Gram-negative and Gram-positive

bacteria, respectively. Vancomycin is a glycopeptide antibiotic primarily effective against infections that result from methicillin-resistant Staphylococcus aureus (MRSA) [15]. Meropenem is a carbapenem and is considered as the last resort option for the treatment of multidrug resistant and ESBLs producing Gram-negative bacteria. Previous studies have demonstrated the efficacy of meropenem and vancomycin in combination with nanoparticles and gelatin scaffolds for treating bone infections. For instance, Zhou et al. [6, 9, 10] developed gelatin-based porous composite scaffolds incorporating vancomycin-loaded mesoporous silica nanoparticles, showing effective antimicrobial activity and sustained drug release for infected bone defects. Similarly, Memar et al. [13, 14, 16] reported that meropenem-loaded MSNPs exhibited significant antimicrobial and antibiofilm effects against carbapenem-resistant Pseudomonas aeruginosa, highlighting their potential in combating resistant bacterial infections. These findings underscore the suitability of combining meropenem, vancomycin, MSNPs, and gelatin scaffolds for osteomyelitis treatment. Electrospinning is a versatile nanotechnology technique that produces nanofibers by applying a high-voltage electric field to a polymer solution, resulting in the formation of fibrous scaffolds with high surface area and porosity. This method is widely used in tissue engineering to fabricate biomimetic scaffolds, such as gelatin-based nanofibers, that mimic the extracellular matrix, promoting cell adhesion and tissue regeneration. In nanotechnology, electrospinning enables the incorporation of nanoparticles, such as MSNPs, into nanofibers, enhancing drug delivery and mechanical properties for applications like bone infection treatment. This study investigates a composite scaffold made of a gelatine matrix combined with vancomycin and meropenem, both with and without MSNPS, focusing on antimicrobial effects, biocompatibility, cell attachment and proliferation, and osteogenic activity.

Materials and Methods

Materials

The materials used in this study included gelatin (Type A, Sigma-Aldrich, USA), mesoporous silica nanoparticles (MSNPs) synthesized using cetyltrimethylammonium bromide (CTAB, Sigma-Aldrich, USA) and tetraethyl orthosilicate (TEOS, Sigma-Aldrich, USA), meropenem (Pfizer, USA), vancomycin (Sigma-Aldrich, USA), 2,2,2-trifluoroethanol (TFE, Sigma-Aldrich, USA) as the solvent, sodium hydroxide (NaOH, Merck, Germany), hydrochloric acid (HCl, Merck, Germany), ethanol (Merck, Germany), and deionized water.

Fabrication of MSNPs

Mesoporous silica nanoparticles (MSNPs) were synthesized via a sol-gel method according to the previously described method [17-19]. A solution of 0.5 g cetyltrimethylammonium bromide (CTAB, a cationic surfactant used as a template to form the mesoporous structure) in 240 mL distilled water was prepared, and 0.14 g sodium hydroxide (NaOH) was added. The mixture was agitated at 80°C for a duration of 120 minutes. Subsequently, 2.5 mL tetraethyl orthosilicate (TEOS, a silica precursor used to form the silica framework) was added dropwise, and stirring continued for an additional 120 minutes. The resulting white precipitate was collected by centrifugation at 10,000 rpm for 10 minutes, washed three times with deionized water and ethanol, and dried. To remove the CTAB surfactant, The precipitate was placed in in a mixture of 160 mL ethanol and 9 mL hydrochloric acid (HCl), and it was agitated at 500 rpm for 24 hours at 80°C. The surfactant-free MSNPs were collected by centrifugation at 10,000 rpm for 10 minutes and lyophilization at -80°C and 0.1 mbar for 48 hours using a freeze-dryer (Labconco, USA).

Scaffolds preparation

A solution was prepared by dissolving 0.8 g gelatin, 0.4 g MSNPs, 0.4 g meropenem, and 0.4 g vancomycin in 200 mL of 2,2,2-trifluoroethanol (TFE), corresponding to a 40:20:20:20 weight ratio. This solution was used to prepare a single scaffold composition via electrospinning. The scaffold preparation was done by electrospinning method using a static collector. The solution was transferred to a 5 mL syringe. The syringe was connected to a Nanospinner (Inovenso Ltd., Turkey), and an appropriate nozzle was connected to the tip of the syringe. The collection plate of the device was covered with aluminum foil, positioned 12 cm from the syringe tip. The apparatus was set on 20 kV voltage and a flow rate of 1 mL/h for solution transfer to the nozzle. At room temperature, the gathered fibres were dried.

Physicochemical characterization

The particle size and zeta potential of MSNPs and nanofibers were measured using dynamic light scattering (DLS) and electrophoretic light scattering, respectively, with a Zetasizer Nano ZS (Malvern Instruments, UK). Samples were dispersed in deionized water at a concentration of 0.1 mg/mL and analyzed at 25°C.

Scanning electron microscopic examination

The morphology of the scaffolds was examined by scanning electron microscopy (SEM, JEOL JSM 5600). The average pore size of the scaffolds was evaluated from geometrical measurements on the scanning electron micrographs [10].

The loading percentage and the yield value

The proportion of vancomycin and meropenem loaded into the nanofibrous scaffolds was determined by dissolving 10 mg of the scaffold in 5 mL dimethyl sulfoxide (DMSO). The solution was analyzed using a UV-Vis spectrophotometer (Shimadzu UV-1800, Japan) at 340 nm for vancomycin and 272 nm for meropenem. The drug concentration was calculated using calibration curves prepared with known concentrations of each drug in DMSO. The loading percentage was calculated using the equation

Loading Percentage (%) = (Mass of Drug in Scaffold / Mass of Scaffold) × 100……Eq.1

The yield value was determined by dividing the weight of the dried nanofibrous scaffold by the total weight of the initial components (gelatin, MSNPs, meropenem, and vancomycin). The yield percentage was calculated as:

Yield Percentage (%) = (Weight of Dried Scaffold / Total Weight of Initial Components) × 100…Eq.2

Drug Release Pattern

Gelatin-Van/Mrp-MSNPs scaffolds (50 mg each) were dipped in a tube containing 4 mL of phosphate-buffered saline (PBS, pH 7.4), which mimics the physiological pH of blood and extracellular fluid in bone tissue, and incubated at 37°C for 21 days. One mL of sample was collected at specific time points (days 1, 3, 5, 7, 10, 14, and 21) from the release suspension, and 1 mL of fresh PBS was added to maintain a constant volume.

Calibration curves for vancomycin and meropenem were established in phosphate-buffered saline (PBS, pH 7.4) using standard solutions ranging from 1 to 100 µg/mL. Absorbance was measured at 340 nm for vancomycin and 272hors nm for meropenem using a UV-Vis spectrophotometer (Shimadzu UV-1800, Japan). The calibration curves exhibited linear relationships ($R^2 > 0.99$), enabling accurate determination of drug concentrations in the release medium.

Tensile test

A mechanical tester (Model 5566, Instron Company, USA) was used to evaluate the tensile properties of the nanofibrous scaffolds at room temperature. Firstly, prepared scaffolds were immersed in distilled water for 10 min. Tensile strength was determined with a crosshead speed of 1 mm/min. The mechanical properties of the scaffolds were represented by tensile strength (KPa, kilopascals, a unit of stress), elongation at break (%, percentage of strain at failure), Young's modulus (kPa, kilopascals, a measure of stiffness), and ultimate load (cN, centinewtons, a unit of force) [20].

Susceptibility Tests

Agar diffusion assay

The antimicrobial properties of the prepared nanofibers against *Escherichia coli* and MRSA isolates were studied by agar diffusion assay on the Muller-Hinton Agar (MHA) plates according to the previously described procedure [21]. In brief, the 0.5 McFarland standard suspension (1.5×10^8 CFU/mL) of microorganisms was inoculated on the MHA plates, and after 10 min prepared dicks (6 mm) of scaffolds were put on the agar surface, and plates were incubated at 35ºC for 24 h. After incubation, the zones of inhibition were measured on each plate and concentrations. The test were carried out in triplicates [21].

Time-kill assay

A time-kill assay was used to study the inhibitory effect of the gelatin-Van/Mrp-MSNPs scaffold on the growth rate of *Escherichia coli* and MRSA isolates. Scaffold was added to 1 mL Muller-Hinton broth in wells of plate and a bacterial susception adjusted to 5×10^5 CFU/mL was added to wells and were incubated at 37 °C under shaking at 150 rpm, and the optical density was determined at 600 nm [22].

The antibiofilm effect of scaffolds

Disks of prepared scaffolds (6 mm) were added to microbial suspensions (10^6 CFU/mL) in the wells of a microplate, diluted tenfold in Trypticase soy broth (TSB) supplemented with 1% glucose. For twenty-four hours, the microplates were incubated at 37°C. Following the incubation period, the contents of the wells were extracted, and phosphate-buffered saline (PBS) was used to wash the wells. An MTT test was used to measure the amount of biofilm that developed in the wells. As controls, wells with 0.5 McFarland bacterial solution diluted 1:10 in TSB without scaffolds were used [23].

Swelling property

Swelling testing was performed to determine water absorption in 5 mL of phosphate-buffered saline (PBS, pH 7.4) at 37°C. The dry weight (W_0) of each scaffold (approximately 20 mg) was determined. The scaffold was then immersed in PBS for 24 hours, surface water was removed, and the wet weight (W_x) was measured. This test was performed for 9 samples of each scaffold, and results were presented as mean ± S.D. The swelling of scaffolds was calculated by the following formula [24]:

$$\boldsymbol{Swelling\ Ratio} = (\boldsymbol{W}_x - \boldsymbol{W}_0) / \boldsymbol{W}_0 \ldots\ldots \boldsymbol{Eq.3}$$

Hemolytic effects of prepared scaffolds

According to the previously described method, themolytic properties of the scaffolds were evaluated by measuring hemoglobin release from red blood cells (RBCs). In summary, a 6 mm disc of each scaffold was used to treat 1 mL of diluted RBCs, and the mixture was incubated at 36°C for 6 hours. The samples were centrifuged at 4,000 rpm for 10 minutes, and 120 µL of the supernatant was transferred to a 96-well plate. Absorbance was measured at 540 nm using an ELISA reader

(BioTek, USA). The following equation was used to determine the hemolysis rate:

Hemolysis Rate (%) =

$$[(A_s + A_-)/(A_+ - A_-)] \times 100 \ldots\ldots Eq.4$$

the sample absorbance, the control absorbance, and the positive control absorbance are denoted as A_s, A_-, and A_+, respectively. Additionally, samples were examined using an optical microscope with a magnification of ×100 [25].

Erythrocyte sedimentation rate (ESR) assay

The effects of scaffolds on human red blood cells were determined by measuring the erythrocyte sedimentation rate (ESR) in the presence of scaffolds. Firstly, a 6mm disk of scaffolds was added to a western green tube containing 3.2% sodium citrate containing human blood samples at room temperature for 120 min, and 0.25 mL of PBS (pH 7.4) in a similar tube was considered as the negative control. ESR was determined by measuring the erythrocyte column level by mm/h [14].

Coagulation times

The effects of scaffolds on blood coagulation were studied by detecting prothrombin time (PT) and activated partial thromboplastin time (APTT) of platelet-poor plasma (PPP) in exposure to prepared scaffolds. Extended time of PT or APTT indicates an increased anticoagulant effect of tested materials. The 1 x 1 cm scaffolds were placed in a tube with 300 µL of PPP and left to incubate at 37°C for 45 minutes. Test tube without any scaffolds containing 300 µL of PPP was considered as the negative control. The susceptibility of the test tube was eliminated after incubation, and the clotting time was calculated by means of an automated analyser in accordance with the instructions provided by the manufacturer [26].

Cell proliferation assay

Cell viability and cell attachment assay

Tcell survival of MSCs generated from human bone marrow on the structures was measured using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) assay (Sigma, St Louis, USA). After cell seeding and incubation for 24 h, the culture medium was discarded and 100 µL of fresh medium and each scaffold were added to each well. The same volume of medium was used for negative control (cell culture medium alone) and cytotoxic positive control (1% Triton X-100) (laboratory grade, Sigma Aldrich, St. Louis, MO, USA). After 24 h, 7 days, and 14 days of incubation with scaffolds, 10 µL of MTT (5 mg/mL) was added to each well and incubated for another 3 h at 37 °C. Then the unreacted dye was removed, and DMSO was added to dissolve the intracellular insoluble purple formazan product into a colored solution. The absorbance of this solution was quantified by photospectrometry at 570 nm with a plate reader. The assay is based on the reduction of mitochondria of living cells. This reduction takes place only when mitochondrial reductase enzymes are active [8]. The attachment of hBM-MSCs to nanofibrous scaffolds was determined by using seeding cells (1×10^4/well) on scaffolds for 7 and 14 days. Cells were incubated at 37°C, fixed with 2.5% glutaraldehyde, and dehydrated using a series of graded ethanol concentrations from 50% to 100%. Specimens underwent thermostatic drying overnight, were sputter-coated with gold, and subsequently analysed via SEM at a voltage rise of 15 kV [27, 28].

Live/dead cell staining

The LIVE/DEAD kit, which includes calcein and ethidium homodimer (EthD-1), was utilised to distinguish live cells from damaged cells, indicated by green fluorescence and red fluorescence, respectively, in accordance with the kit instructions. In summary, 100 µL of hBM-MSCs treated with scaffolds were extracted from the well and transferred to separate tubes, to which 150 µL of the LIVE/DEAD® working solution was added. The tubes were incubated at room temperature for 45 minutes, after which a small sample from each tube was collected and placed on a microscope slide for observation under a CFM.

Osteogenic differentiation evaluation in vitro

The in vitro effects of scaffolds on the osteogenic differentiation of MSCs were examined through the assessment of alkaline phosphatase (ALP) activity and the analysis of osteogenesis-related gene expression. The ALP activity was measured by first preparing the scaffolds, then seeding 10^5 cells/well of MSCs onto them in 24-well plates. The cells then underwent incubation at 37ºC for 24 hours to allow them to adhere. Subsequently, the medium was altered to osteogenic medium, consisting of DMEM/F-12 enriched with 50 µg/mL L-ascorbic acid, 10 mM β-glycerol phosphate, and 10-8 M dexamethasone. For another two weeks, the cells were cultured. The Alkaline Phosphatase Assay Kit (Beyotime, China) was used to determine ALP activity at 7 and 14 days, as per the instructions provided by the manufacturer.

The mRNA for collagen-1 (COL I), osteopontin (OPN), alkaline phosphatase (ALP), and osteocalcin (OCN) was detected after the cells were cultivated on scaffolds for 7 and 14 days. First, the TRIzol reagent (Invitrogen, USA) was used to extract the cells' total RNA. The NanoDrop 2000 spectrophotometer (Thermo Scientific, USA) was used to measure the amount of RNA. Complementary DNA (cDNA) was synthesised utilising a Hieff™ First Strand cDNA Synthesis Kit in accordance with the manufacturer's protocol. The expression of the target gene was subsequently analysed using the 7500 Fast Real-time PCR System (Applied Biosystems) with a HieffTM qPCR SYBR Green Master Mix (Low Rox Plus) Kit. The housekeeping gene, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), served as the internal control [9].

Results and Discussion

Physicochemical Features

Determination of the physicochemical properties of nanocomposites is an essential step before their assessment by in vitro and in vivo studies because these properties have been shown to have significant effects on the noncompounds interaction with biological membranes and cellular molecules in both bacterial and host cells. In the present study, the size and zeta potential of used MSNPs were 71.03 nm and -12.3 mV, respectively, measured using a Zetasizer Nano ZS (Malvern Instruments, UK). The morphology of MSNPs and prepared nanofibers are presented in Figure. 1. The prepared nanofibers exhibited a zeta potential of -11.3 mV. Zeta amounts are related to the charge of particles' surface and can be effective to study stability and predict the interaction of a noncompound with cell membranes. Negative amounts of zeta-potential have been demonstrated to have a positive effect on the interaction with cellular molecules and increase *in vitro* and *in vivo* biological activities [29]. Meropenem had a loading amount of 41% and vancomycin of 48%. In terms of yield, meropenem achieved 52% and vancomycin 49%. The loading percentages for meropenem (41%) and vancomycin (48%) were lower than some reported values for other antimicrobial agents in gelatin nanofibers, such as ciprofloxacin (32%-93%) [30]. This may be attributed to the physicochemical properties of meropenem and vancomycin, including their solubility and interaction with the gelatin-MSNP matrix. Meropenem's high water solubility may lead to partial loss during electrospinning, while vancomycin's large molecular size may limit its incorporation efficiency. Additionally, the presence of MSNPs, primarily contributing to sustained release, may reduce the available binding sites for drugs within the gelatin matrix, resulting in moderate loading efficiencies.

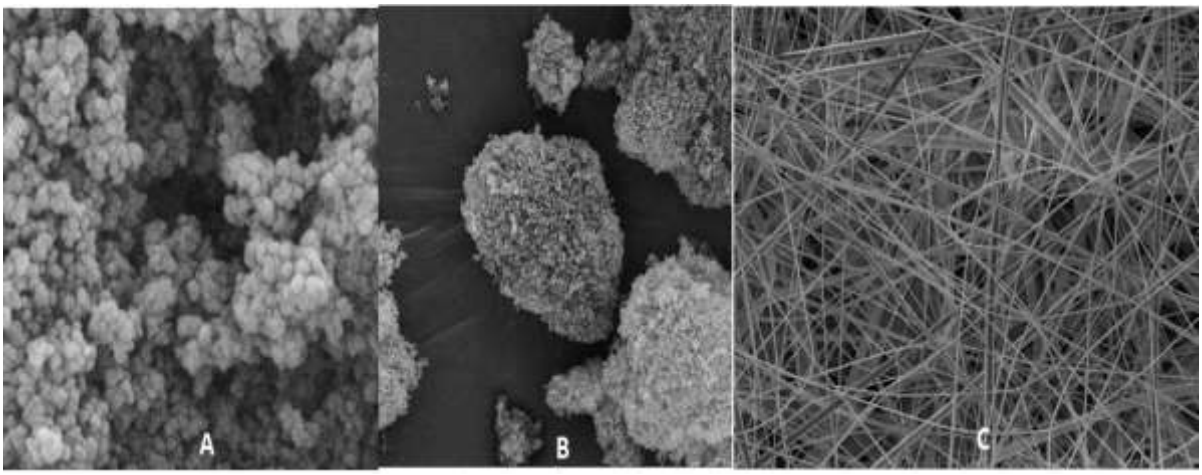


Figure 1. SEM morphology of MSNPs (A and B) and gelatin-Van/Mrp-MSNPs scaffolds (C).

Drug release patterns

The release profile for antibiotics is shown in Figure. 2. The pattern showed that vancomycin was released from the scaffolds in two stages. The first stage was a fast release (72%), with a burst release on the first three days. The second stage was a slower, more steady release that lasted for 21 days. The release profile of meropenem exhibited a pattern akin to that of vancomycin, characterised by a two-step release mechanism. The release profile of a drug from a composite may result from the diffusion of drug molecules, the degradation of the matrix, or a combination of both mechanisms [31]. The sustained release of antimicrobial agents provided by gelatin/ MSNPs can be helpful for the treatment of chronic infections particularly those caused by drug-resistant pathogens such as bone infections or burn-wound infections.

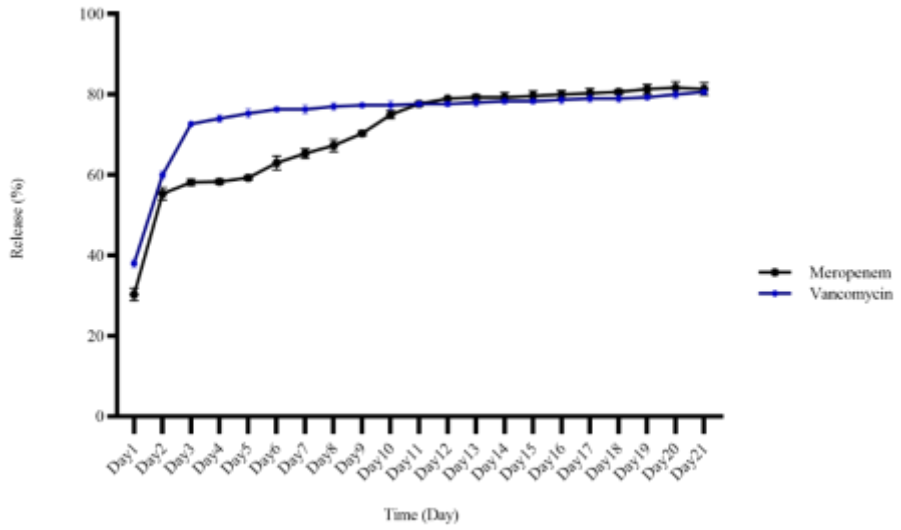


Figure 2. The release pattern of meropenem and vancomycin from gelatin-Van/Mrp-MSNPs nanofibers.

Tensile strength

Tensile strength is referred to as the highest elongation (or stress) that a compound can withstand before breaking when it is stretched. The prepared scaffolds have shown high tensile strength in the waterless condition (Table 1). The tensile strength assay revealed that the gelatin-Van/Mrp-MSNPs scaffolds have higher flexibility than bare gelatin and gelatin-Van/Mrp scaffolds.

The incorporation of MSNPs is linked to an enhancement in the tensile strength of gelatine scaffolds. This could offer a way of quickly adapting the mechanical properties of nanofibers [32].

It was reported that adding the MSNPs electrospinning nanofibers enhanced the mechanical features of the composite scaffolds [33-35].

Table 1. The results related to the tensile strength of the investigated groups.

Scaffolds	Number	Mean (kPa) ± SD	P-value
Gelatin	5	28.7± 0.39	<0.01
Gelatin-Van/Mrp	5	24.4±0.56	
Gelatin-Van/Mrp-MSNPs	5	33.54±0.38	

The tensile strength results are reported in kilopascals (kPa), representing the mean stress at failure for each scaffold group, with standard deviations. The P-value (<0.01) indicates significant differences between groups.

Susceptibility Tests

Agar diffusion assay

Based on the results of the agar diffusion test, the gelatine scaffold lacked detectable antibacterial action. The inhibition zone of Gel-Van/Mrp and Gel-Van/Mrm-MSNPs were 16.3±0.55 mm and 18.73 ±0.83 mm for MRSA, and 18.5±0.55mm and 21.16±1.1 mm for *E. coli* respectively (Figure. 3). The antibacterial effects of Gel-Van/Mrp and Gel-Van/Mrm-MSNPs can indicate appropriate incorporation of meropenem and vancomycin on scaffolds without losing its biological and antimicrobial effects. The potential of gelatin scaffold to preserve the antimicrobial effects of other antibacterial agents after encapsulation has been reported in different studies. Higher antimicrobial effects of Gel-Van/Mrm-MSNPs scaffolds in comparison to Gel-Van/Mrp scaffolds may be because of synergic effects between MSNPs and vancomycin and meropenem that were reported by previous studies [13, 14, 16]. These findings were confirmed by the time-kill assay.

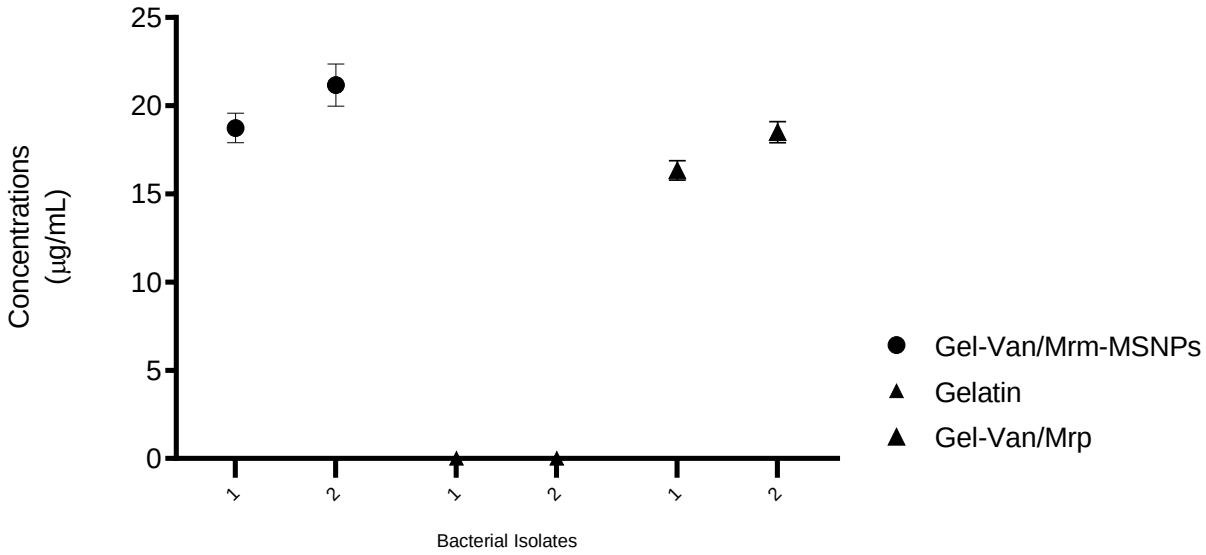
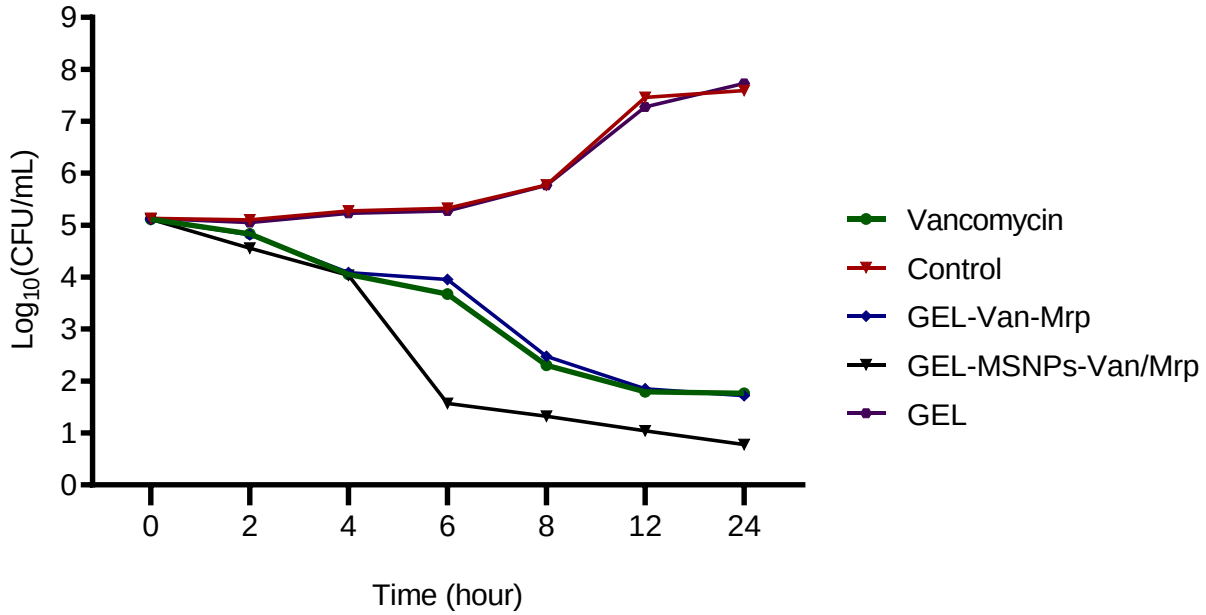


Figure 3. The inhibition zone of bacterial growth around the scaffold's disks.

Time-kill assay

According to the Figure. 4, the gelatin scaffold had no antimicrobial properties against both *E. coli* and MRSA isolates. CFU counting during overnight incubation in a well treating with gelatin scaffolds showed a parallel pattern with well without antibacterial compounds with increasing patterns (increased 3 times the initial Log10 CFU/mL). Gel-Van/Mrp and vancomycin have shown a similar pattern in decreasing CFU counting in MRSA. Gel-Van/Mrp and meropenem have also shown a similar pattern in decreasing CFU counting of *E. coli*. Gel-Van/Mrm-MSNPs dramatically reduced the CFU counting between 4-5 hours after incubation. Gel-Van/Mrp and Gel-Van/Mrm-MSNPs exhibited a 3-fold and 4-fold decrease in the Log10 CFU/mL after 24 hours, respectively against both *E. coli* and MRSA isolates.



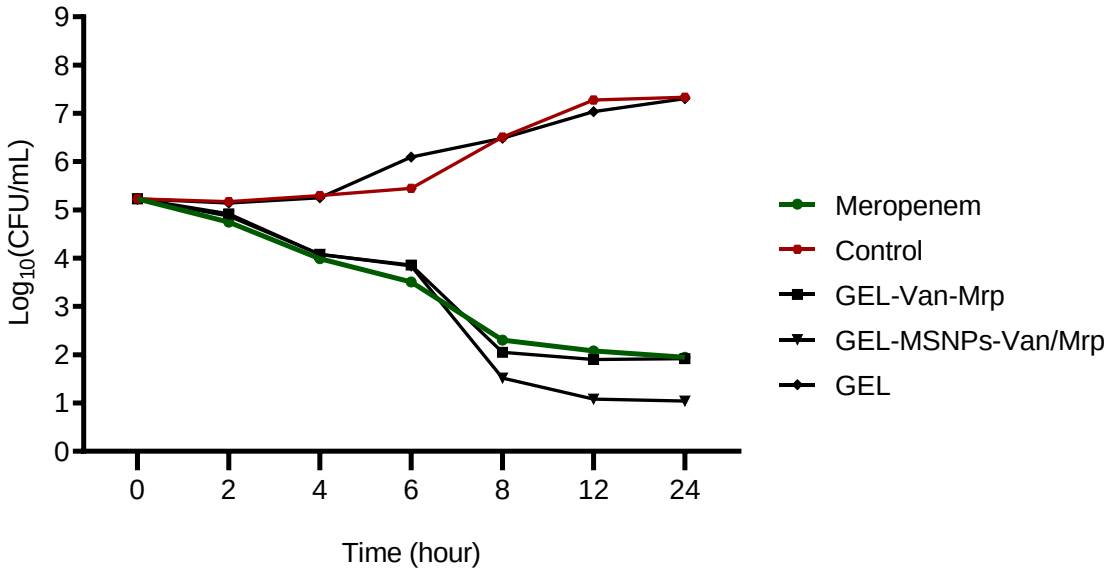


Figure 4. Colony forming unit (CFU) count in the presence of the scaffolds during 24 h.

The effect of scaffolds on the adhesion of bacteria

Communities of bacteria adhered to a surface and gathered in an extracellular polymeric matrix are known as biofilms. Biofilm formation is a critical microbial factor in the development of chronic infections, such as osteomyelitis, wound infections, and infections associated with foreign bodies. Biofilm protects bacteria from the host immune mechanisms and resistance to antimicrobial agents [23]. Therefore, in most cases for the treatment of biofilm-related infections the tissue involved should be removed. Microbial adhesion is a critical primary stage in the biofilm establishment of bacteria on biotic and abiotic surfaces. The potential of antibacterial drugs to suppress microbial adhesion to host tissues or prosthetic bodies can be useful to prevent biofilm-forming pathogens colonization. The anti-adhesion activities of the MSNPs alone or in combination with vancomycin and meropenem have been reported on some bacteria *in vitro* conditions. In the current study, gelatin scaffold has not exhibited a detectable inhibitory effect on the attachment of *E. coli* and MRSA isolates (Figure. 5). Gel-Van/Mrm-MSNPs showed greater inhibitory effects on bacterial adhesion in both MRSA and E. coli isolates compared to controls. These findings demonstrate that the addition of MSNPs has enhanced the scaffolds' ability to suppress in vitro microbial adherence. Additionally, MSNPs and vancomycin and meropenem in gelatine were found to have an additively inhibiting effect on bacterial adherence.

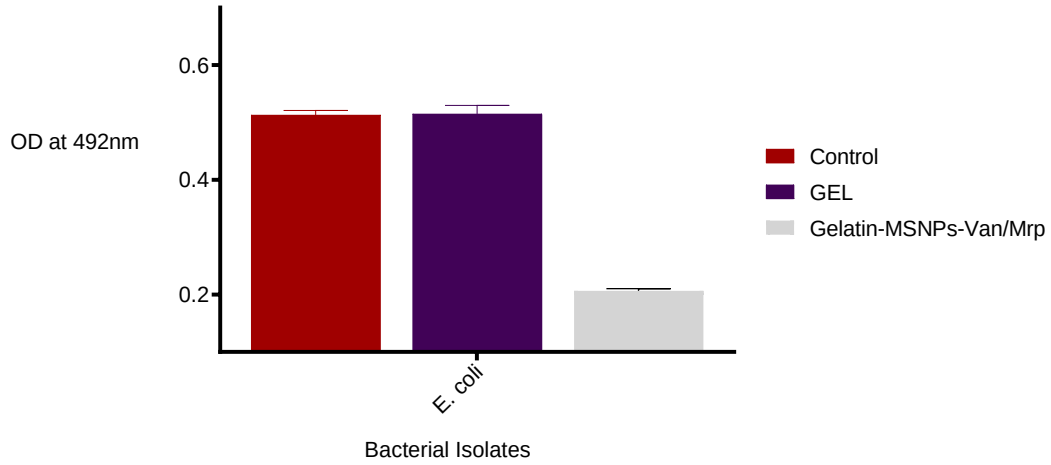
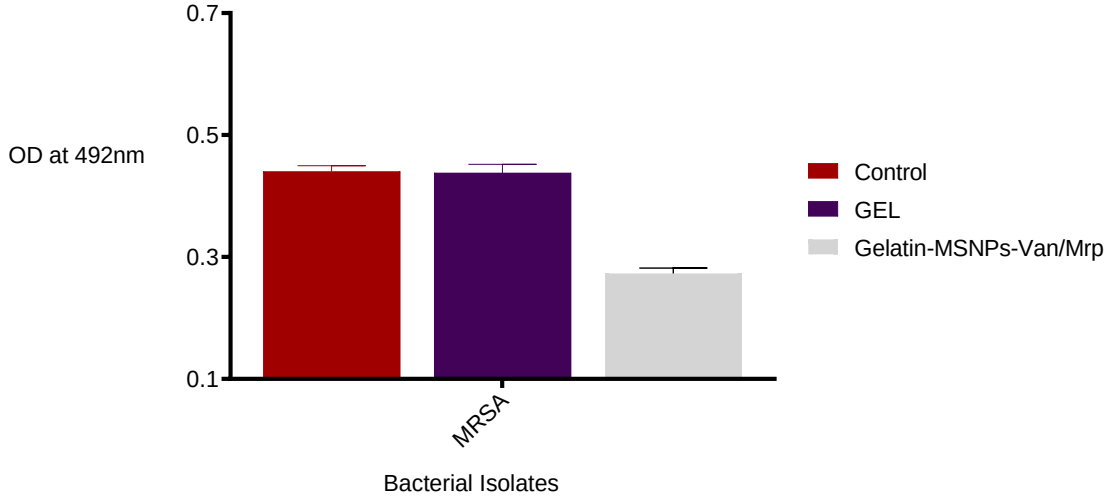


Figure 5. Effects of Gel-Van/Mrm-MSNPs and gelatin scaffolds on the attachment of bacteria to plastic surfaces. Bacteria in the absence of scaffolds were considered as control.



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Antimicrobial effects of released vancomycin and meropenem from scaffolds

The treatment of some chronic infections such as wounds and bone tissue infections may need more than 14 days of antimicrobial therapy. Therefore, the design of drug delivery systems in tissue engineering with the ability of long-term release of antibiotics will be very useful in the treatment of these infections. The compounds released from Gel-Van/Mrp showed antimicrobial effects for 9 and 11 days against *E. coli* and *MRSA* isolates, respectively (Figure. 6). The inhibitory effects of Gel-Van/Mrm-MSNPs were sustained for 21 days against *E. coli* and MRSA isolates. The inhibition zones around the Gel-Van/Mrm-MSNPs were higher than Gel-Van/Mrp. These findings indicated that adding MSNPs to the gelatin scaffold not only increases the antimicrobial effects of meropenem and vancomycin but also increases the duration of their release from the scaffold. The antimicrobial effects of MSNPs alone (without gelatin) were not evaluated in this study, as the focus was on the composite gelatin-MSNP scaffolds. Previous studies, such as Memar et al. [13, 14, 16], have reported that MSNPs alone exhibit moderate antimicrobial activity, which is significantly enhanced when combined with antibiotics like vancomycin and meropenem, as observed in our results.

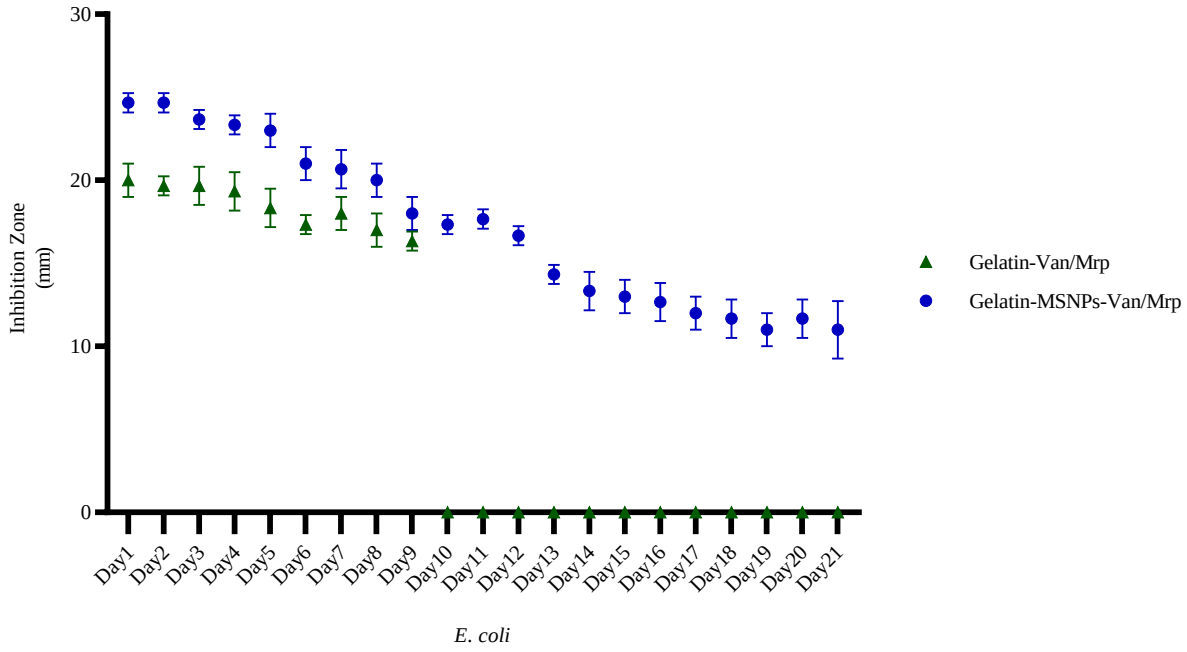
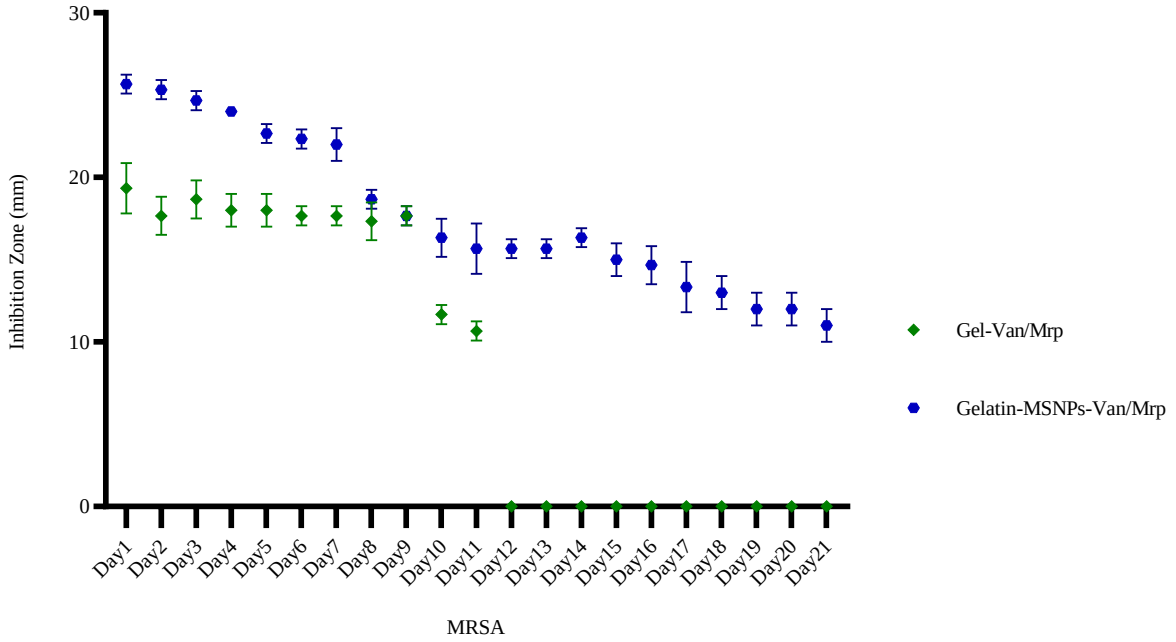


Figure 6. The inhibitory effects of compounds released from Gel-Van/Mrm-MSNPs during 21 days.



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The hemolysis assays

Prior to in vivo testing, the hemocompatibility of scaffolds made for tissue engineering applications should be ascertained. The amount of haemoglobin released from red blood cells into the extracellular environment can be measured by a compound's hemolytic property [(26)]. The results of hemolysis assays after treating human RBCs with scaffolds for 4h indicated that hemolysis rates of gelatin, Gel-Van/Mrp and Gel-Van/Mrm-MSNPs as 1.93±0.05, 2.16±0.22 and 4.11±0.131, respectively (Figure. 7). The hemolysis rate of gelatin scaffold was lower than 2% are considered as non-hemolytic [(36)].

Gelatin is a nonhemolytic compound and is used as an expander of plasma volume. It does not interfere with RBC and leucocytes. Some studies have reported partial hemolytic effects of MSNPs, which mostly depend on the concentrations and the physicochemical properties of the nanoparticles. A considerable hemolytic effect (14.2%) of MSNPs has been reported at the concentration of 50 mg/mL [(37)]. The effect of MSNPs on RBCs may be due to ROS and silanol groups on their surface. MSNPs also show a high affinity to tetra-alkyl ammonium residue on the RBCs surface and electrostatically interact with membranous peptides.

According to our results, the incorporation of MSNPs increased the hemolytic effects of Gel-Van/Mrm-MSNPs. The potential of compounds to induce RBCs aggregation can be determined by ESR testing in the absence and presence of the material. In the current study, ESR was not affected by exposure to scaffolds and was at the normal values in comparison to control. These results indicate the interaction of prepared scaffolds with the RBCs is insignificant. When seen under a light microscope, the morphology of red blood cells did not significantly alter from the control.

PT results of gelatin, Gel-Van/Mrp, and Gel-Van/Mrm-MSNPs were 13.9±0.2, 13.2± 0.7, and 13.6±0.7, respectively. PTT results of the gelatin, Gel-Van/Mrp, and Gel-Van/Mrm-MSNPs were 40.02±1.53, 40.45±1.61, and 40.97±1.08, respectively. Therefore, in exposure to prepared scaffolds, the results of PT and PTT were within the normal values, exhibiting that the scaffolds did not have a significant effect on the coagulation factors. These results also described gelatin, Gel-Van/Mrp, and Gel-Van/Mrm-MSNPs cannot induce blood coagulation via either intrinsic or extrinsic pathways [(38)].

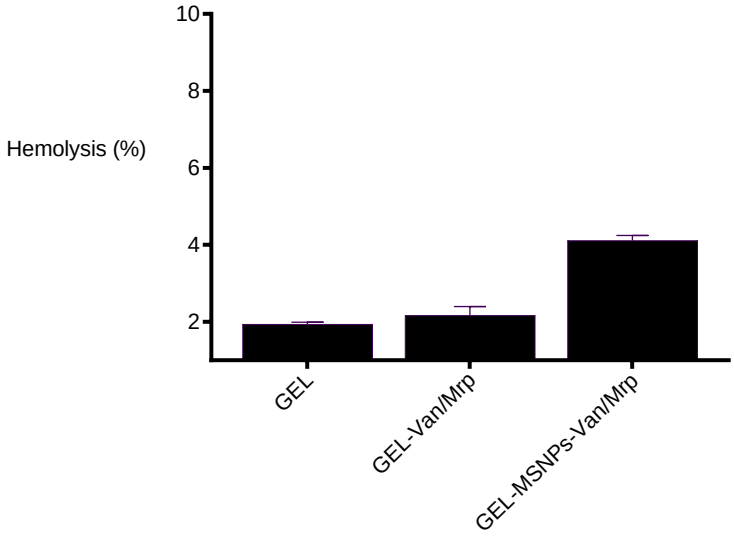

Figure 7. Hemolysis rate in the presence of prepared scaffolds

Swelling

The ability to absorb water or swelling is an essential property of the scaffolds that should be studied before usage for tissue engineering. Scaffold swelling has a considerable effect on the body's fluid absorption and transfer of nutrients and metabolites to host cells. It is significantly affected by the physicochemical properties of scaffolds such as size pore and volume and contained compounds in the scaffold's compsition. The swelling value of the Gel-Van/Mrp and Gel-Van/Mrm-MSNPs were 61.53% and 64.07, respectively. The high values of swelling indicate the higher ratio of composite surface area/volume and provide a favorable environment for cell infusion, adherence, growth, and proliferation on the surfaces.

Cell proliferation

MTT assay

Since they can greatly accelerate the rate at which damaged tissues regenerate, the ability of composites and scaffold candidates to effectively adhere to cells and promote proliferation is a crucial aspect of their research in tissue engineering.

Reports indicate that the inclusion of gelatine in composites designed for bone tissue engineering can promote the attachment and proliferation of in vitro MC3T3-E1 and bone marrow stromal cells (BMSCs) [39, 40]. Bone tissue scaffolds are the primary focus of extensive research on gelatin-based biomaterials, which are used to create scaffolds that exhibit favourable effects on cell proliferation [40, 41].

MSNs have the potential to increase bone cells proliferation and also provide the concurrent loading of biomolecules and drugs. MSNs are reported as appropriate scaffolds for bone tissue engineering due to biocompatibility and potential to promote both cell growth and osteogenic effects on progenitor cells. MSNs physiochemical features have desirable effects on the cell spreading procedure and help the cell-cell communication procedure through bone tissue engineering. The effects of prepared scaffolds on hBM-MSCs proliferation after 7 and 14 days are presented in Figure. 8. After 24h treatment, Gelatin, Gelatin-Mrp/Van scaffolds increased the hBM-MSCs proliferation, but Gelatin-Mrp/Van-MSNPs decreased cell viability than untreated control. All prepared scaffolds demonstrated an increase in cell viability compared to the control after both 7 days and 14 days. Cell in exposure to Gelatin-Mrp/Van-MSNPs scaffold showed higher proliferation (115.64±4.6% at 7 days and 130.76±3.22% at 14 days) followed by gelatin (108.05±3.33% at 7 days and 123.71±1.07% at 24 days) and gelatin-Mrp/Van scaffold (107.81%±105% at 7 days and 119.22± 1.5% at 14 days).

Cell proliferation significantly increased over time after treatment by all scaffolds (Figure. 8). It was reported that gelatin induced the cell to fast grow than collagen, fibronectin, and laminin [42].The 3T3-L1 adipocytes proliferation and C2C12 cell line attachment have also been induced in the presence of gelatin [43]. In vitro study results indicate that vancomycin inhibits osteoblast proliferation at concentrations of 10 mg/mL or higher, while no significant effect is observed at 1 mg/mL or lower concentrations [44].

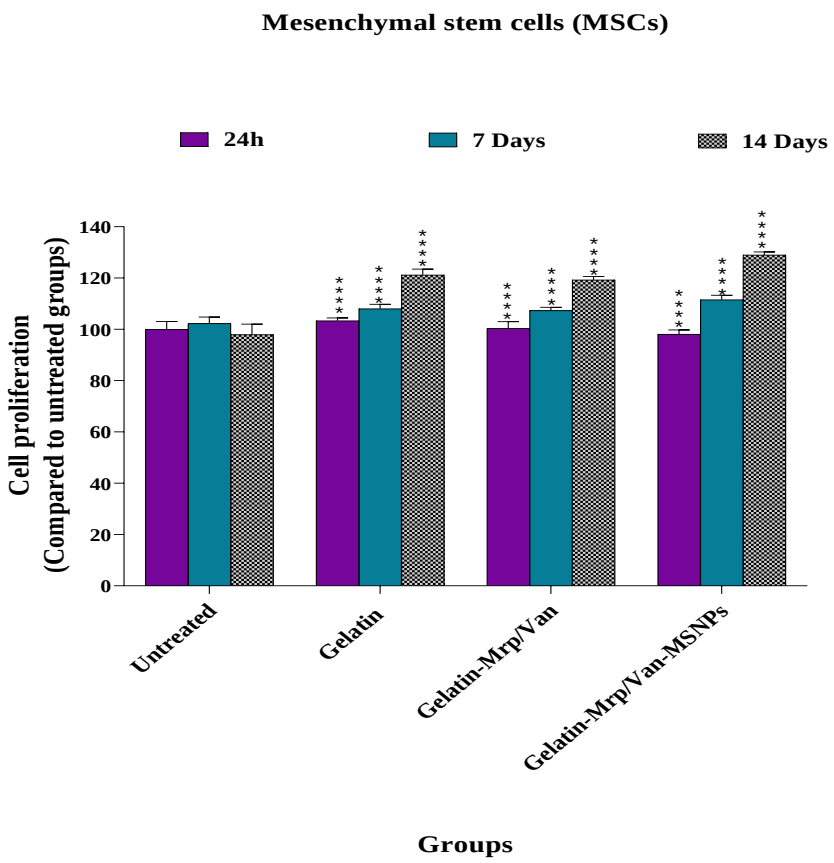

Figure 8. hBM-MSCs cell proliferation in exposure to scaffolds after 24h, 7 days, and 24 days.

Cell attachment assay

Gelatin electrospun nanofibers have been extensively used in bone tissue engineering as scaffolds for inducing cell growth and proliferation and regulating cellular behavior. The large ratio of surface to volume of nanofibers and their porous structure provides a favorable matrix for cell attachment, growth, and proliferation, which are considered the desired features in tissue engineering [45].

After seven and fourteen days of treatment, a SEM test of the MSCs-nanofibers was conducted to investigate the cell adhesion of MSCs to the scaffolds that were constructed for this investigation. Figure. 9 shows the SEM data showing that the scaffolds were well-adherent and that the MSCs proliferated on them. SEM images taken on day 14 showed that the gelatine scaffolds with MSNPs had a higher cell density. These results may indicate the additive effects of gelatin nanofibers and MSNPs in providing a suitable environment for cell attachment and inducing cell proliferation. The SEM assay also confirmed cell proliferation results, in which MSCs proliferation on gelatin-Mrp/Van-MSNPs scaffolds was more enhanced at day 14 than on day 7. The potential of MSNPs in inducing *in vitro* proliferation and promoting cell cycle progression has been described in A375 cells. It has been reported that MSNPs can affect molecular events of A375 cells following cellular uptake which may be owing to the reducing reactive oxygen species (ROS). MSNPs have also promoted cell proliferation in a redox-sensitive signal mechanism due to inducing overexpression of anti-apoptotic agents Bcl-2 and decreasing the NF-κB effects [45].

Our findings align with the results of other studies, which also indicated that gelatin-containing scaffolds offer a favourable surface for cell proliferation [28]. Researchers Ghavimi et al. found that adding curcumin to gelatine scaffolds caused DPSCs (dental pulp stem cells) to proliferate more rapidly [46]. Similarly, Mamidi et al. also found that human fibroblast cells proliferated and cell attachment enhanced following three days of treatment on curcumin-embedded gelatin/polylactic acid scaffolds [47].

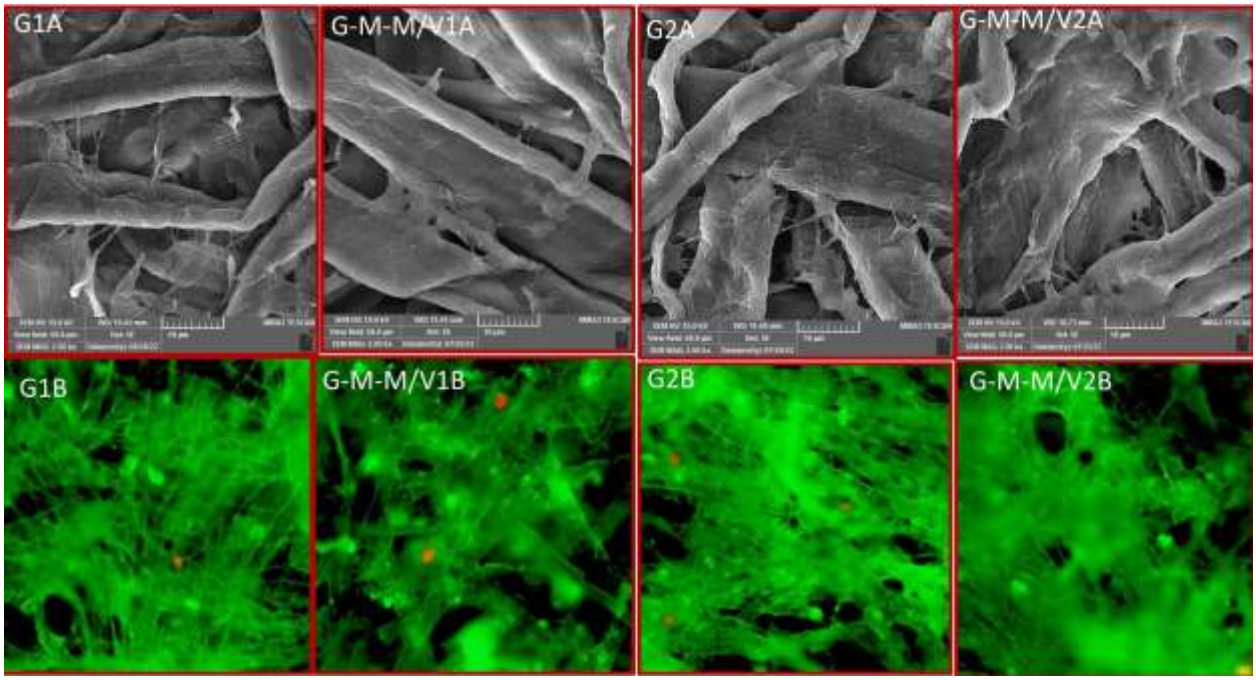

Figure 9. The SEM morphology of cell attachment and cell proliferation on the scaffolds after 7 days (G1A and G-M-M/V1A) and 14 days (G2A and G-M-M/V2A). The cells viability was cultured on the scaffolds after 7 days (G1B and G-M-M/V1B) and 14 days (G2B and G-M-M/V2B). (G: gelatin and G-M-M/V: Gel-Van/Mrm-MSNPs).

Live-dead assay

The viability and proliferation of MCSs on the prepared scaffolds were assessed using a Live-dead assay (Figure. 9). Live cells exhibit green fluorescence, whereas red fluorescence signifies dead cells. Live-dead assay confirmed the prepared scaffolds did not show toxic effects and significantly increased the MSCs density. The high density of live MCSs population was observed consistently distributed throughout the scaffold's surfaces.

Osteogenic properties

ALP activity

ALP activity is an *in vitro* indicator to determine the osteogenesis properties of different materials. ALP plays an important role in the calcification for bone formation and its activity is commonly used to identify osteoblast cells, which are the cells that initiate the mineralisation of bone matrix. In this study, after 7 days of treatment, MSCs treated with gelatin-Van/Mrp-MSNPs had a greater ALP activity (34.2 IU/mg protein), as measured by both gelatine (32.2 IU/mg protein) and gelatin-Van-Mrp (31.7 IU/mg protein). A quantitative comparison of ALP assay results obtained on days 7 and 14 revealed enhanced amounts during both time points. The results of a study carried out by H. Kanniyappan et al., revealed ALP activity of MG-63 cells enhanced by more than 1.5-fold following 7 days in the presence of 1 mg/mL of MSNPs than untreated control which may be because of the release of silica ions from MSNPs, induced the calcification for bone formation. In the presence of 2.5 mg/ml MSNPs, a slight decrease has been reported in MG-63 cell's ALP activity. This decrease may be due to the very high concentration of MSNPs, which could be detrimental to the cells as reported from in vitro cytotoxicity results [48].

qRT-PCR of osteogenic genes

The detectable genes indicator osteogenic differentiation includes COL I and ALP as markers for the early differentiation stage and OCN and OPN as later stages. The results of qRT-PCR indicated that the presence of gelatine, gelatin-Van/Mrp, and gelatin-Van/Mrp-MSNPs scaffolds promoted the transcription of early and late gene markers associated with osteogenic differentiation in MSCs following 7- and 14-day treatments. The expression of COL I and ALP as markers for the early differentiation stage increased after 7 days of treating MSCs with scaffolds, but this enhancement was not significant (Figure. 12). After 14 days incubation, gelatin-Van/Mrp-MSNPs scaffolds have significantly induced the expression of COL I and ALP (Figure. 10). The OCN and OPN expression as markers for late differentiation stage was not significantly increased after 7 days of treating MSCs with scaffolds, but a slight increase was observed compared to the control (Figure. 11). After 14 days incubation, gelatin and gelatin-Van/Mrp-MSNPs scaffolds significantly increased the expression of OCN and OPN (Figure. 12). Based on the comparison of the qRT-PCR results on day 7 and 14, only the scaffold of gelatin-Mrp/Van-MSNPs significantly increased the expression of genes markers for late differentiation stage during the time (Figure. 12). These results show that scaffolds made

of gelatin have not a favorable effect on the osteogenic procedure. The gelatin's ability to promote the transcription of osteogenic-related genes has been reported in different stages of bone tissue differentiation [49]. Moreover, the results revealed incorporation of antibiotics and MSPNs not only had not a significant inhibitory impact on the osteogenic properties of gelatin, but MSNPs significantly increased the osteogenic effects of gelatin.

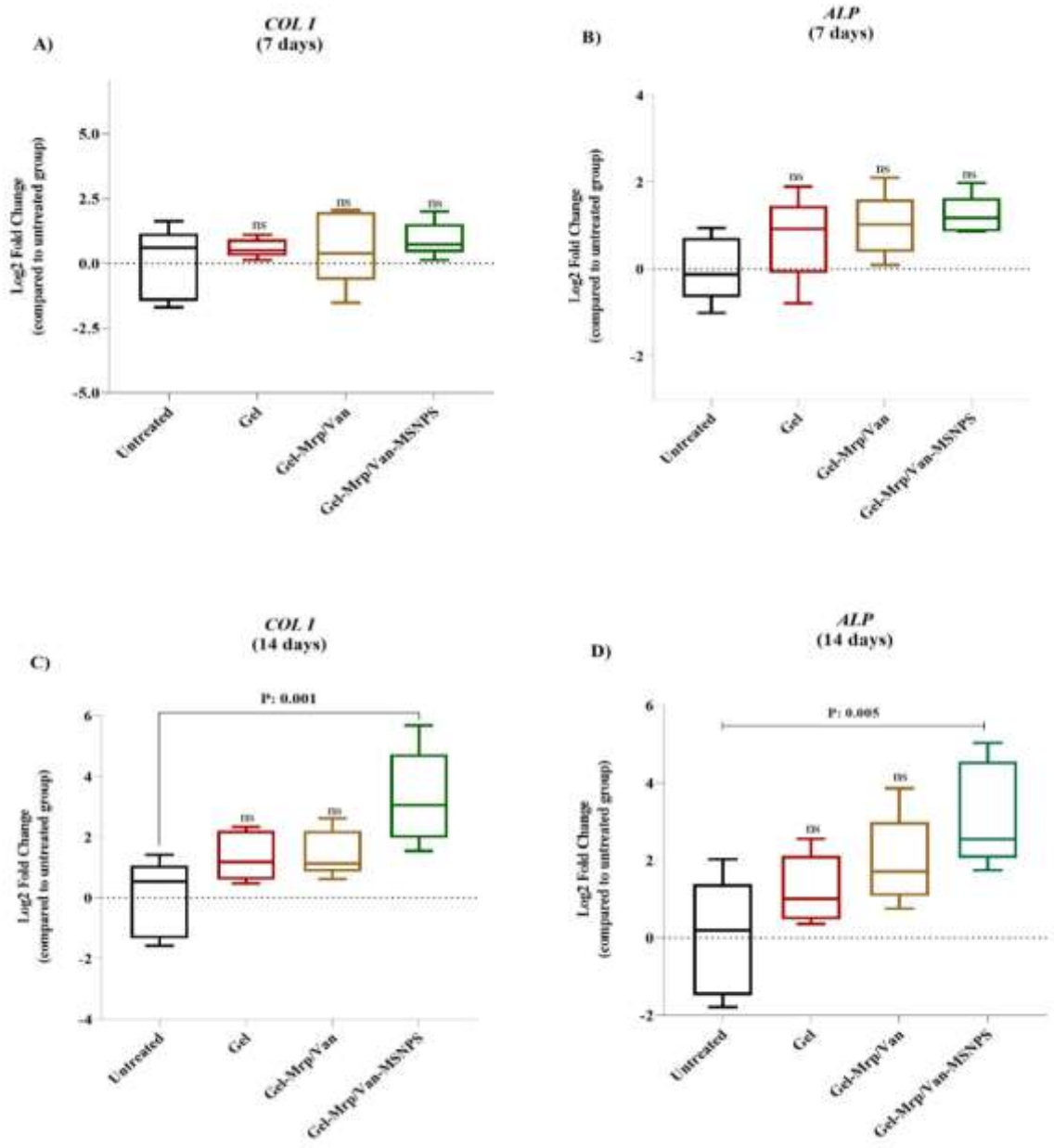

Figure 10. Comparison of the expression level of early genes (COL1 and ALP) regulation of osteogenesis between the studied groups in 7 and 14 days. After treatment with gelatin, gelatin-Mrp/Van, and gelatin-Mrp/Van-MSNPS for 7 days, no statistically significant differences appeared in the mean fold change of COL I and APL in comparison to the untreated group (A-B). However, the expression level of COL I and APL in the gelatin-Mrp/Van-MSNPS group after treatment for 14 days was significantly higher than that of the untreated group (C-D).

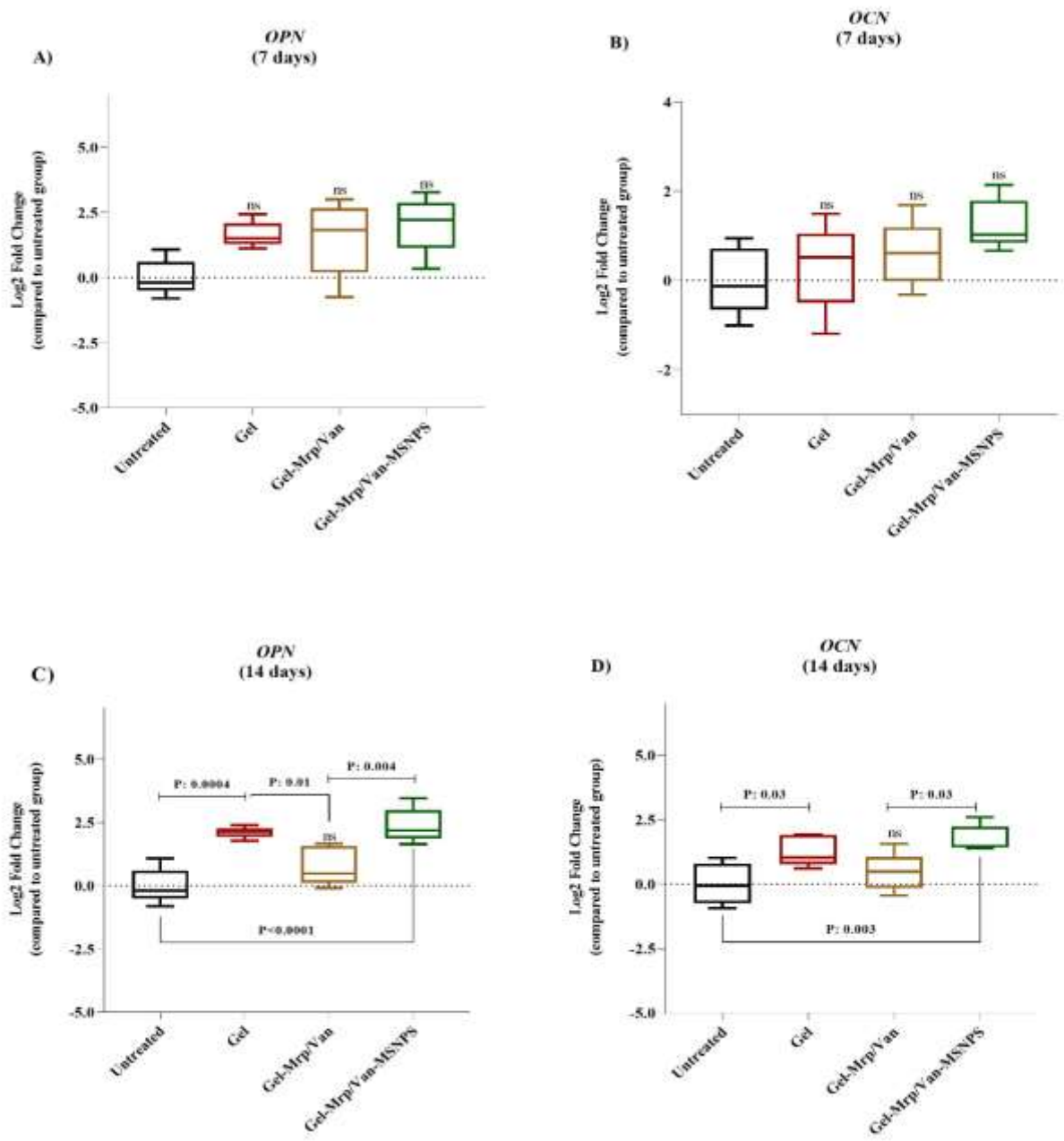

Figure 11. Comparison of the expression level of the late genes (OPN and OCN) involved in osteogenesis regulation between the untreated group with gelatin, gelatin-Mrp/Van, and gelatin-Mrp/Van-MSNPS treated groups after 7 and 14 days. There were no significant differences in the expression level of OPN (A) and OCN (B) between the treated groups and the untreated group. Besides, in the gelatin and the gelatin-Mrp/Van-MSNPS treatment groups, after 14 days, significantly upregulated the level of OPN (C) and OCN (D). Moreover, expression levels of OPN and OCN After treatment with the gelatin and the gelatin-Mrp/Van-MSNPS significantly increased in comparison to the gelatin-Mrp/Van group.

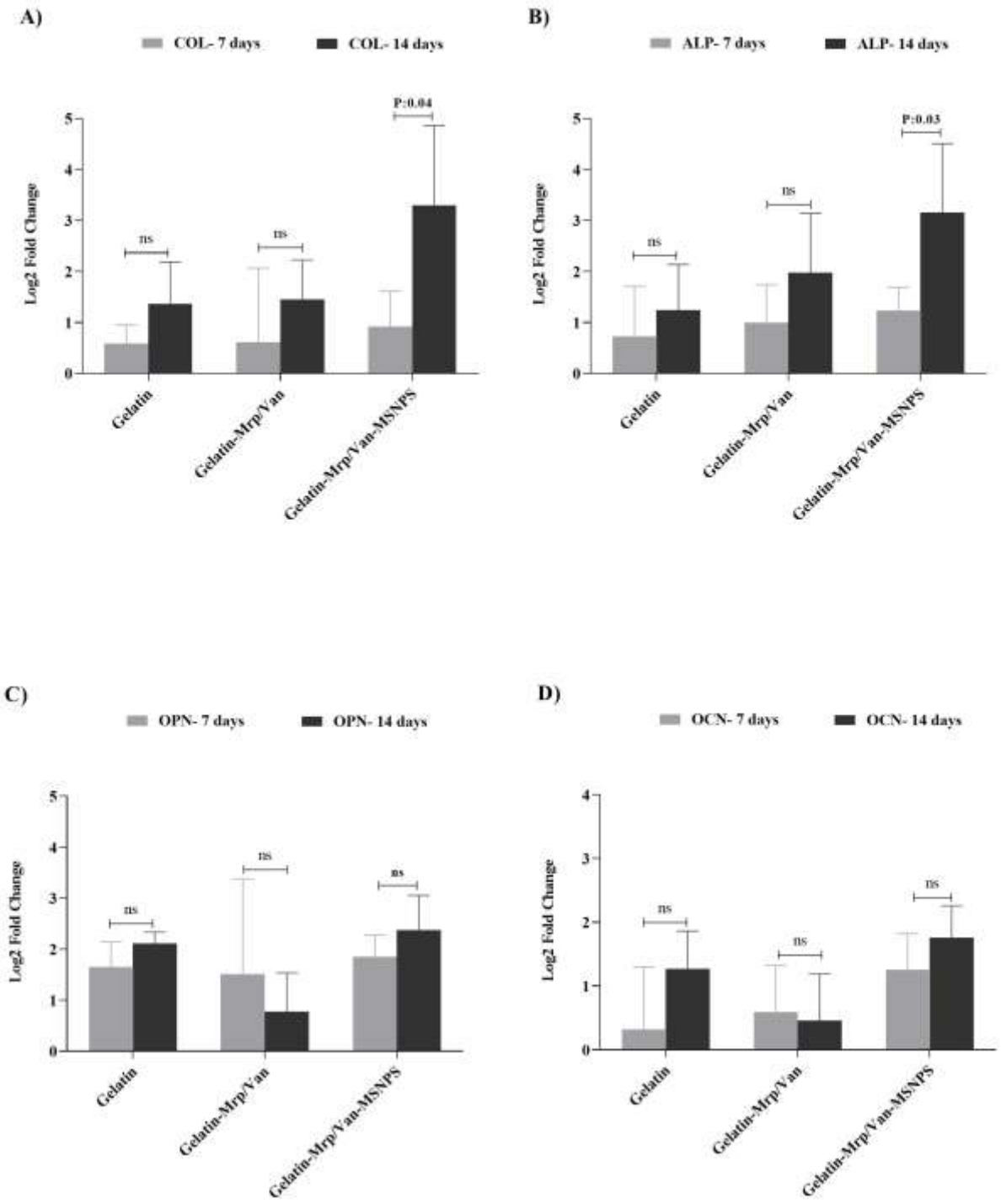

Figure 12. Comparison of the levels of COL1, ALP, OPN, and OCN between 7 and 14 days after treatment with gelatin, gelatin-Mrp/Van, and gelatin-Mrp/Van-MSNPS. There was a significant upregulated in the expression level of COL I and ALP between 7 and 14 days after treatment with gelatin-Mrp/Van-MSNPS.

Conclusion

According to the findings, gelatin-Mrp/Van-MSNPs indicate considerable antimicrobial effects and biocompatibility. Continuous release of antimicrobial agents from scaffolds provided long inhibitory effects on bacteria. The presence of MANPs and antimicrobial agents was not significantly associated with decreasing biocompatibility and induced the in vitro proliferation and adhesion of MCSs. The incorporation of antimicrobial drugs and MSPNs not only had not a significant inhibitory impact on the

osteogenic properties of gelatin, but MSNPs significantly increased the osteogenic effects of gelatin.

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Conflicts of Interest

The authors reported no potential conflict of interest.

Funding

Declared none.

Ethics Statements

The authors declared the Iraqi Center for Cancer Research/Mustansiriyah University's animal ethical council (approval no. ICCMGR2024 -037).

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: YQ Almajidi; data collection: R. Raad; analysis and interpretation of results: AA. Issa; draft manuscript preparation: YQ Almajidi. All authors reviewed the results and approved the final version of the manuscript.

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التخليق ، ومضادات الميكروبات ، والتوافق الحيوي ، والسمية ، والخصائص العظمية لسقالة الجيلاتين النانوية الليفية التي تحتوي على الميروبينيم / فانكومايسين ـ جزيئات السيليكا النانوية المسامية (Mrp / Van-MSNPs)

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[٢] قسم الصيدلانيات، كلية الصيدلة، جامعة الاسراء، بغداد، العراق.

الخلاصة

يمكن أن تكون سقالات الغزل الكهربائي المكونة من المضادات الحيوية والبوليمرات الطبيعية مفيدة في إجراء قمع الاجراء المعدي المتزامن وتحفيز التئام الأنسجة في علاج التهابات العظام. أجريت الدراسة الحالية لتحضير وتحديد التأثيرات المضادة للميكروبات والتوافق الحيوي والتأثيرات العظمية للجيلاتين ميروبينيم / فانكومايسين - جسيمات السيليكا النانوية المسامية (المحضرة باستخدام إجراء الغزل الكهربائي. تم فحص السقالات من حيث الخصائص الفيزيائية والكيميائية ومضادات الميكروبات والتوافق الحيوي والخصائص العظمية. أظهرت السقالات خصائص ميكانيكية قابلة للتطبيق ، ونمطًا بطيئًا لإطلاق الدواء، وأظهرت تأثيرات مضادة للميكروبات لمدة ٢١ يوما. أظهر الجيلاتين- ميروبينيم / فانكومايسين - جسيمات السيليكا النانوية المسامية تأثيرات لاصقة مضادة للميكروبات والبكتيريا أعلى من الجيلاتين والجيلاتين- ميروبينيم / فانكومايسين. أظهرت جميع السقالات المحضرة توافقًا حيويًا ملائمًا في المختبر. تم تحفيز الجيلاتين- ميروبينيم / فانكومايسين - جسيمات السيليكا النانوية بشكل ملحوظ على ارتباط الخلايا الجذعية الوسيطة المشتقة من نخاع العظم البشري وقابليتها للبقاء والانتشار. كما أنه أدى بشكل كبير إلى نشاط الفوسفاتيز القلوي وأدى إلى التعبير عن الجينات العظمية في كل من المراحل المبكرة والمتأخرة من التمايز. لذلك ، يمكن اعتبار سقالات الجيلاتين مع ميروبينيم / فانكومايسين - جسيمات السيليكا النانوية المسامية لعلاج التهاب العظم والنقي. لم تكن إضافة جسيمات السيليكا النانوية المسامية والأدوية المضادة للميكروبات في الجيلاتين مرتبطة بشكل كبير بالتأثيرات السلبية على خصائص الجيلاتين. أدت جسيمات السيليكا النانوية المسامية إلى تحسين مضادات الميكروبات والتوافق الحيوي وزيادة التكاثر الخلوي وخصائص تكوين العظم المستحثة للجيلاتين.
الكلمات المفتاحية: الجيلاتين ، ميروبينيم ، جزيئات السيليكا النانوية المسامية ، التهاب العظم والنقي ، الفانكومايسين.