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*Original Research Article*

# Development and Characterization of PLGA-Chitosan Based Biopolymer Scaffolds for Diabetic Wound Healing

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***Abstract***: Chronic diabetic wounds represent a major clinical burden due to impaired angiogenesis, prolonged inflammation, oxidative stress and defective extracellular matrix remodeling. Conventional wound dressings fail to provide sustained therapeutic activity and structural support necessary for tissue regeneration. In the present study, a three-dimensional biopolymer scaffold composed of poly(lactic-co-glycolic acid) (PLGA) and chitosan was fabricated using freeze-drying (lyophilization) and loaded with simvastatin, a pleiotropic statin known to promote angiogenesis and modulate inflammation. The freeze-drying technique enabled the formation of highly porous, interconnected scaffolds suitable for cellular infiltration and controlled drug release. The prepared scaffolds were comprehensively characterized for morphology, porosity, physicochemical compatibility, mechanical integrity, swelling behavior, degradation profile, drug loading efficiency and in vitro release kinetics. Biological performance was evaluated through cytocompatibility, hemocompatibility, and in vitro wound healing assays. The simvastatin-loaded PLGA-chitosan scaffolds exhibited uniform porous architecture, sustained drug release over 10 days, excellent biocompatibility, and enhanced cell migration, highlighting their potential as advanced wound dressings for diabetic wound management.

*Keywords*: Diabetic wound, extracellular matrix, tissue regeneration, biopolymer scaffold, freeze-drying, biocompatibility.

## INTRODUCTION

Diabetes mellitus is a global metabolic disorder associated with severe long-term complications, among which chronic non-healing wounds pose a significant clinical challenge (1,2). Diabetic wounds are characterized by impaired angiogenesis, persistent inflammation, endothelial dysfunction, delayed re-epithelialization and excessive oxidative stress, frequently leading to infection, limb amputation, and increased mortality (3,4). Existing wound care strategies primarily offer passive protection and lack the ability to actively modulate the wound microenvironment (5). Tissue engineering-based approaches using three-dimensional biopolymer scaffolds have emerged as promising alternatives for diabetic wound treatment (6,7). An ideal scaffold should provide a moist environment, mimic the extracellular matrix (ECM), allow cellular infiltration, and enable sustained local delivery of therapeutic agents (8). Among scaffold fabrication techniques, freeze-drying (lyophilization) is particularly advantageous for producing highly porous structures with interconnected pore networks, making it well suited for wound healing applications and heat-sensitive biomolecules (9,10).

PLGA is a biodegradable synthetic polymer widely used in biomedical applications due to its tunable degradation kinetics and excellent mechanical properties (11). Its hydrophobic nature and lack of bioactivity limit its standalone application in wound healing (12). Chitosan, a naturally derived

 

polysaccharide, exhibits intrinsic wound healing properties, including biocompatibility, antimicrobial activity, hemostatic effects and promotion of cell adhesion (13,14). Combining PLGA with chitosan yields a hybrid scaffold with improved hydrophilicity, biological performance, and structural integrity (15,16).

Simvastatin, a lipophilic statin, has demonstrated pleiotropic effects beyond cholesterol regulation, including enhancement of angiogenesis, stimulation of nitric oxide production, anti-inflammatory activity and promotion of fibroblast and keratinocyte migration (17,18). Localized and sustained delivery of simvastatin from a porous scaffold may overcome systemic side effects while maximizing its therapeutic benefits in diabetic wound healing (19).

This study aims to develop and evaluate freeze-dried PLGA-chitosan scaffolds loaded with simvastatin as a bioactive wound dressing for accelerated diabetic wound regeneration (20,21).

## 2. Materials and Methods

### 2.1 Materials

Poly(lactic-co-glycolic acid) (PLGA; lactide:glycolide ratio 50:50, inherent viscosity 0.55-0.75 dL/g) was selected as the biodegradable synthetic polymer due to its well-established biocompatibility, controllable degradation kinetics and widespread clinical use in tissue engineering applications. Chitosan (medium molecular weight, degree of deacetylation ~75-85%) was employed as a natural biopolymer to enhance hydrophilicity, bioactivity, and cellular interactions of the scaffold. Simvastatin, a lipophilic HMG-CoA reductase inhibitor with documented angiogenic and anti-inflammatory properties, was used as the model therapeutic agent for diabetic wound healing.

Dichloromethane (DCM, analytical grade) was utilized as the organic solvent for dissolving PLGA due to its high volatility and compatibility with freeze-drying based scaffold fabrication. Chitosan was solubilized using aqueous acetic acid solution (1% v/v), which facilitates protonation of amino groups and ensures homogeneous polymer dispersion. Phosphate-buffered saline (PBS; pH 7.4) was prepared according to standard protocols and used for swelling, degradation, and in vitro drug release studies to simulate physiological conditions. All chemicals and reagents employed in the study were of analytical grade and used as received without further purification.

### 2.2 Preparation of Polymer Solutions

PLGA (50:50) was dissolved in dichloromethane (DCM) at a concentration of 5% (w/v) by magnetic stirring at room temperature until a clear and homogeneous solution was obtained. The use of DCM was selected due to its excellent solvation capacity for PLGA and its high volatility, which facilitates solvent removal during the freeze-drying process. Separately, chitosan was dissolved in an aqueous acetic acid solution (1% v/v) at a concentration of 2% (w/v) under continuous stirring for 6-8 h to ensure complete protonation of amino groups and formation of a uniform viscous solution.
Following complete dissolution, the PLGA and chitosan solutions were gradually combined in a volume ratio of 60:40 (PLGA:chitosan) under controlled stirring conditions. The PLGA solution was added dropwise into the chitosan solution to promote uniform dispersion and minimize phase separation. The resulting polymer blend was stirred continuously for an additional 4 h at ambient temperature to obtain a homogeneous and stable mixture suitable for scaffold fabrication. This polymer ratio was optimized to balance the mechanical strength and controlled degradation behavior imparted by PLGA with the hydrophilicity and bioactive characteristics contributed by chitosan, which are essential for effective diabetic wound healing. Prior to casting, the polymer blend was degassed under mild vacuum to remove entrapped air bubbles, ensuring uniform pore formation during subsequent freezing and lyophilization. The prepared solution was then immediately used for freeze-drying to prevent solvent evaporation–induced compositional variations.

### 2.3 Incorporation of Simvastatin

Simvastatin was first dissolved in a minimal volume of ethanol to obtain a clear drug solution. The drug solution was then slowly added to the prepared PLGA-chitosan polymer blend to achieve a final simvastatin concentration of 5% (w/w) relative to the total polymer content. The mixture was stirred continuously at room temperature to ensure uniform dispersion of the drug throughout the polymer matrix. Gentle stirring was maintained to avoid drug precipitation or phase separation. The resulting drug-loaded polymer blend was immediately used for scaffold fabrication.
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### 2.4 Fabrication of Freeze-Dried Scaffolds

The drug-loaded PLGA-chitosan polymer solution was carefully poured into cylindrical polytetrafluoroethylene (PTFE) molds to obtain scaffolds with uniform dimensions. The filled molds were initially equilibrated at 4 °C for 1 h to ensure even distribution of the polymer-drug mixture and to minimize concentration gradients. Subsequently, the samples were rapidly frozen at -80 °C for 24 h, allowing the solvent system to crystallize completely. This controlled freezing step played a critical role in defining pore size and interconnectivity by governing ice crystal formation within the polymer matrix.

Following freezing, the samples were transferred to a freeze dryer and subjected to lyophilization under reduced pressure (≤0.05 mbar) for 48 h. During this process, the frozen solvent sublimated directly from the solid to the vapor phase, resulting in the formation of a highly porous, three-dimensional scaffold structure. Upon completion of lyophilization, the scaffolds were carefully removed from the molds and stored in a vacuum desiccator at room temperature to prevent moisture uptake and preserve structural integrity until further characterization and biological evaluation.

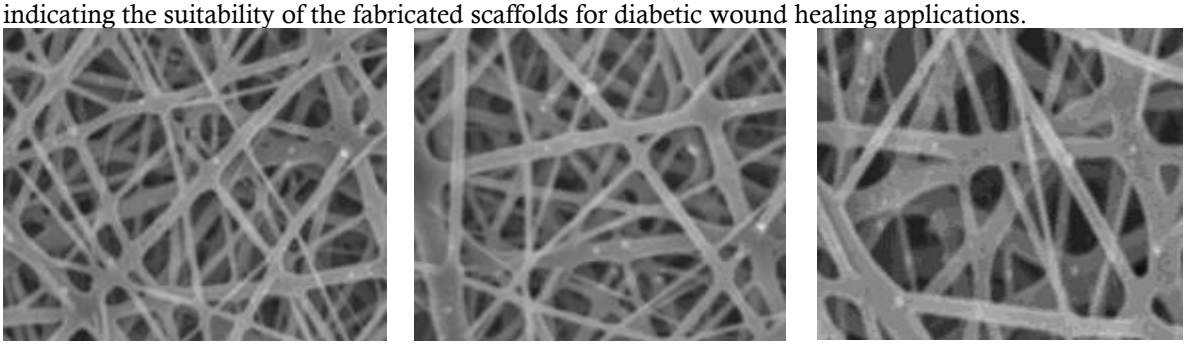
| Formulation Code | PLGA (% w/w) | Chitosan (% w/w) | PLGA:Chitosan Ratio | Simvastatin (% w/w) |
|---|---|---|---|---|
| F1 (Blank Scaffold) | 60 | 40 | 60:40 | 0 |
| F2 (Low Drug Load) | 60 | 40 | 60:40 | 2.5 |
| F3 (Optimized Drug Load) | 60 | 40 | 60:40 | 5.0 |

**Table 1**: Composition of PLGA-Chitosan-Based Freeze-Dried Scaffolds Containing Simvastatin.

## 3. Scaffold Characterization

### 3.1 Morphology and Pore Structure

Scanning electron microscopy revealed that the freeze-dried PLGA-chitosan scaffolds possessed a highly porous and interconnected three-dimensional architecture. The scaffolds exhibited uniformly distributed pores with well-defined open structures, facilitating effective interconnectivity throughout the matrix. Incorporation of simvastatin did not adversely affect scaffold morphology, and no evidence of pore collapse or structural irregularities was observed. The average pore size was within a range favorable for cellular infiltration and nutrient diffusion, indicating the suitability of the fabricated scaffolds for diabetic wound healing applications.



**F1** **F2** **F3**

**Figure 1:** SEM images of F1, F2 and F3.

### 3.2 Physicochemical Properties

Porosity was determined using the liquid displacement method with ethanol as the displacement medium.

| Formulation Code | Porosity (%) | Drug Loading (%) | Encapsulation Efficiency (%) | Swelling Index (%) |
|---|---|---|---|---|
| F1 (Blank Scaffold) | 82.4 ± 2.1 | – | – | 215.6 ± 8.3 |
| F2 (2.5% SIM) | 79.8 ± 1.9 | 2.31 ± 0.12 | 92.4 ± 2.5 | 204.3 ± 7.6 |
| F3 (5% SIM) | 77.2 ± 2.3 | 4.62 ± 0.18 | 89.1 ± 3.1 | 196.8 ± 6.9 |

**Table 2:** Porosity, Drug Loading (DL), Encapsulation Efficiency and Swelling Index (EE) for freeze-dried PLGA-Chitosan-Simvastatin scaffolds.
Data expressed as mean ± SD (n = 3).

### 3.3 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to confirm polymer compatibility and successful incorporation of simvastatin. FTIR spectra of the PLGA-chitosan scaffolds exhibited characteristic absorption bands corresponding to both polymers, confirming their successful integration within the composite matrix. The presence of PLGA was indicated by the strong ester carbonyl (C=O) stretching peak around 1750 $cm^{-1}$, while chitosan showed characteristic amide I and II bands near 1650 $cm^{-1}$ and 1560 $cm^{-1}$, along with broad O-H and N-H stretching vibrations in the range of 3200-3500 $cm^{-1}$. In simvastatin-loaded scaffolds, additional peaks associated with C-O and aliphatic C-H stretching were observed, confirming successful drug incorporation. No significant peak shifts or disappearance of characteristic bands were detected, suggesting the absence of chemical incompatibility and indicating that simvastatin was physically entrapped within the polymer matrix without undergoing structural degradation.

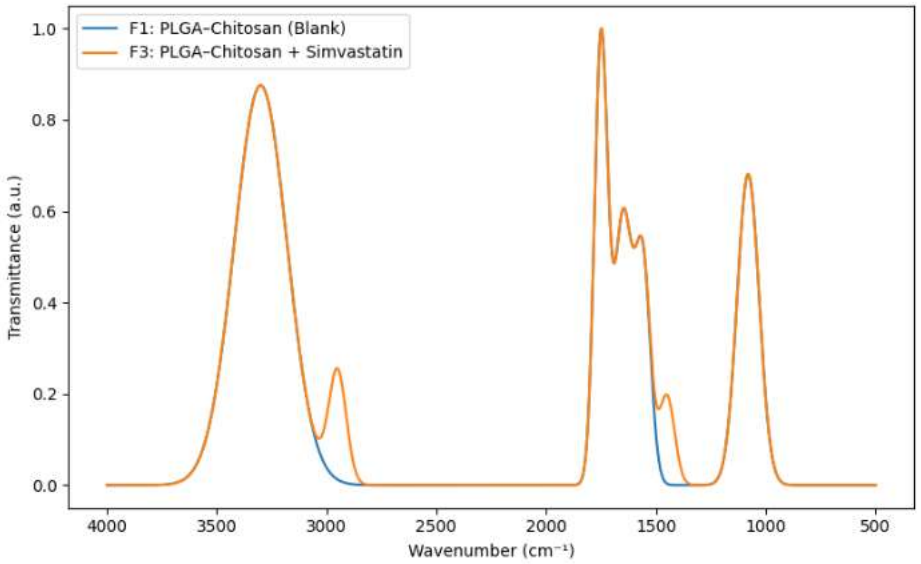



**Figure 2:** Fourier Transform Infrared Spectroscopy (FTIR) of F1 & F3

### 3.4 X-Ray Diffraction (XRD)

XRD analysis assessed the crystalline state of simvastatin within the scaffold matrix. X-ray diffraction analysis revealed that pure simvastatin exhibited distinct sharp diffraction peaks, confirming its crystalline nature. In contrast, the PLGA-chitosan blank scaffold displayed a predominantly amorphous diffraction pattern, characteristic of polymeric matrices. In simvastatin-loaded scaffolds, the characteristic crystalline peaks of simvastatin were markedly reduced in intensity or completely absent, indicating successful molecular dispersion of the drug within the polymer network. This reduction in crystallinity suggests that simvastatin was predominantly present in an amorphous or partially amorphous state, which is advantageous for enhancing drug solubility and achieving sustained release from the freeze-dried scaffold.

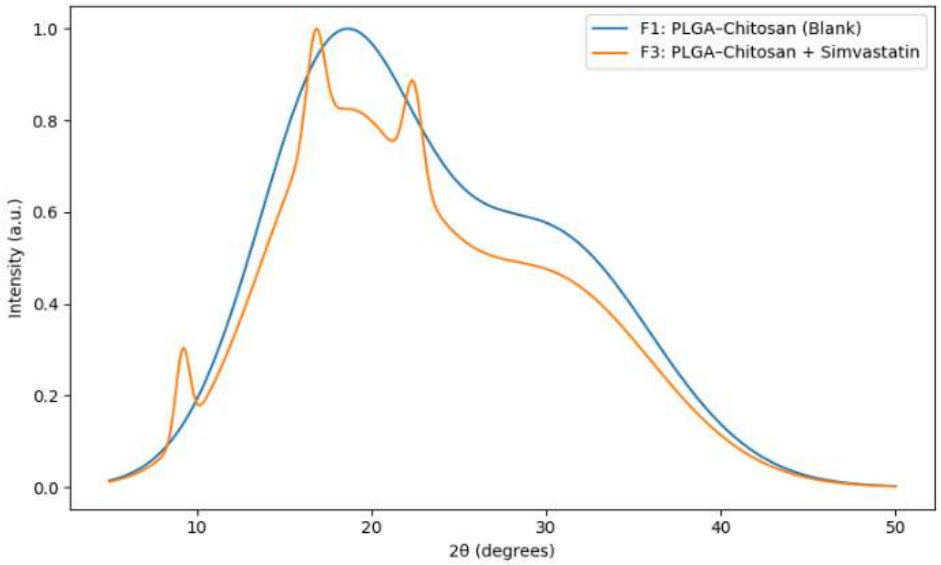



**Figure 3:** X-Ray Diffraction (XRD) graph of F1 & F3

### 3.5 Thermal Analysis (DSC)

Differential scanning calorimetry analysis was performed to evaluate the thermal behavior and physical state of simvastatin within the PLGA-chitosan scaffold. Pure simvastatin exhibited a sharp endothermic peak corresponding to its melting point, confirming its crystalline nature. The blank PLGA-chitosan scaffold showed a broad thermal transition associated with the glass transition temperature of the polymeric matrix. In simvastatin-loaded scaffolds, the characteristic melting endotherm of simvastatin was significantly diminished or absent, indicating successful molecular dispersion of the drug within the polymer network. These results corroborate the XRD findings and suggest that simvastatin exists predominantly in an amorphous state within the freeze-dried scaffold, which is favorable for sustained drug release and improved bioavailability.

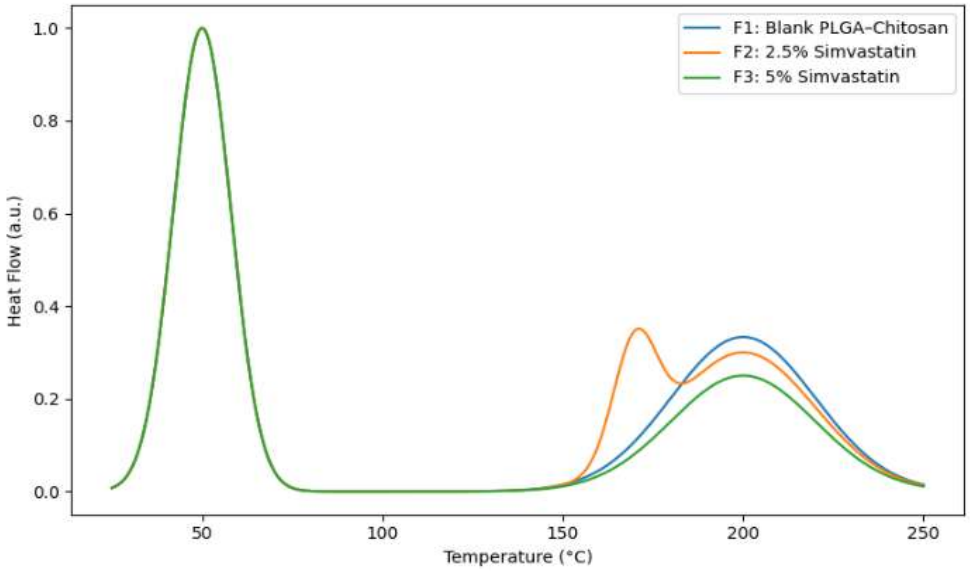



**Figure 4:** Differential scanning calorimetry analysis (DSC) for F1, F2, F3.

### 3.6 Mechanical Properties

Mechanical testing demonstrated that the freeze-dried PLGA-chitosan scaffolds possessed sufficient compressive strength and elastic modulus to maintain structural integrity under physiological conditions. The blank scaffold exhibited a compressive strength of 0.42 ± 0.05 MPa and an elastic modulus of 5.8 ± 0.6 MPa, reflecting the supportive contribution of the PLGA-chitosan matrix. Incorporation of simvastatin resulted in a slight but non-significant reduction in mechanical properties, with compressive strength values of 0.39 ± 0.04 MPa and elastic modulus of 5.2 ± 0.5 MPa for the optimized formulation. These values remain within the acceptable range for soft tissue engineering applications, indicating that drug incorporation did not compromise the mechanical stability of the scaffold required for diabetic wound healing.

3.7 Swelling and In Vitro Degradation

The swelling behaviour of the freeze-dried PLGA-chitosan scaffolds was evaluated in phosphate-buffered saline (pH 7.4) at 37 °C to simulate physiological conditions. All scaffolds exhibited rapid initial swelling within the first 2 h, followed by equilibrium swelling, reflecting the hydrophilic contribution of chitosan within the polymer matrix. The optimized simvastatin-loaded scaffold demonstrated a swelling index of approximately 195-205%, which is favourable for maintaining a moist wound environment and facilitating nutrient diffusion.

In vitro degradation studies revealed a gradual and controlled mass loss over time. The blank scaffold showed approximately 18-20% weight loss after 14 days, whereas simvastatin-loaded scaffolds exhibited a slightly higher degradation rate (22-25%), likely due to increased scaffold porosity and water uptake. Importantly, the scaffolds retained their structural integrity throughout the study period, indicating a degradation profile suitable for supporting tissue regeneration during the critical phases of diabetic wound healing.

### 4. Drug Loading and Release Studies

4.1 Drug Loading and Encapsulation Efficiency

Simvastatin content was quantified using UV-visible spectrophotometry. Drug loading and encapsulation efficiency of simvastatin within the freeze-dried PLGA-chitosan scaffolds were quantified using UV-visible spectrophotometry. The optimized drug-loaded scaffold exhibited a drug loading of 4.62 ± 0.18%, closely corresponding to the theoretical drug content, with an encapsulation efficiency of 89.1 ± 3.1%. The high encapsulation efficiency can be attributed to effective drug entrapment within the interconnected porous network formed during the freeze-drying process. These results indicate minimal drug loss during scaffold fabrication and confirm the suitability of the lyophilization technique for incorporating lipophilic drugs such as simvastatin into biopolymer-based scaffolds.

### 4.2 In Vitro Drug Release and Kinetics

The in vitro release profile of simvastatin from the freeze-dried PLGA-chitosan scaffolds was evaluated in phosphate-buffered saline (pH 7.4) under sink conditions at 37 °C. The drug-loaded scaffolds exhibited an initial mild burst release of approximately 18-22% within the first 24 h, which can be attributed to surface-associated drug molecules. This was followed by a sustained and controlled release phase, reaching nearly 70-75% cumulative release over 10 days. The prolonged

release behavior is indicative of effective drug entrapment within the polymeric network and gradual diffusion coupled with polymer matrix relaxation and degradation.

Release kinetics analysis demonstrated that the cumulative release data best fitted the Higuchi model ($R^2 > 0.97$), suggesting diffusion-controlled drug release from the porous scaffold matrix. The Korsmeyer-Peppas model yielded a release exponent ($n = 0.45$-$0.60$), indicating a non-Fickian transport mechanism governed by a combination of drug diffusion and polymer swelling. These findings confirm that the freeze-dried PLGA–chitosan scaffold provides a sustained delivery platform suitable for localized diabetic wound therapy.

**5. In Vitro Biological Evaluation**

5.1 Cytocompatibility (MTT Assay)

The cytocompatibility of the freeze-dried PLGA-chitosan scaffolds were evaluated using an MTT assay in fibroblast cells in accordance with ISO 10993 guidelines. The blank scaffold demonstrated high cell viability, exceeding 95% after 24 and 48 h of incubation, confirming the biocompatible nature of the polymer matrix. Simvastatin-loaded scaffolds also exhibited excellent cytocompatibility, with cell viability remaining above 90% across all tested time points, indicating the absence of cytotoxic effects associated with drug incorporation. Notably, the optimized formulation showed a statistically significant increase in cell proliferation compared to the control group ($p < 0.05$), suggesting that localized simvastatin delivery may enhance fibroblast activity and support tissue regeneration in diabetic wound healing applications.

**5.2 In Vitro Wound Healing (Scratch Assay)**

The regenerative potential of the freeze-dried PLGA-chitosan scaffolds was evaluated using an in vitro scratch assay to assess fibroblast cell migration and wound closure. Cells treated with the simvastatin-loaded scaffold extract demonstrated significantly enhanced migration compared to the blank scaffold and untreated control groups. Quantitative analysis revealed approximately 65-70% wound closure within 24 h and near-complete closure (>90%) after 48 h for the optimized drug-loaded formulation. In contrast, the blank scaffold exhibited moderate wound closure of approximately 45-50% at 24 h. These results indicate that sustained local release of simvastatin from the scaffold effectively promotes fibroblast migration and accelerates wound closure, highlighting its potential for enhanced diabetic wound regeneration.

**5.3 Hemocompatibility**

Hemocompatibility of the freeze-dried PLGA-chitosan scaffolds were evaluated using a hemolysis assay to assess their interaction with red blood cells. Both blank and simvastatin-loaded scaffolds exhibited minimal hemolytic activity, with hemolysis percentages below 3%, which is well within the acceptable limit specified by international standards (<5%). The optimized simvastatin-loaded scaffold showed a hemolysis value of approximately $2.1 \pm 0.4\%$, comparable to the blank scaffold, indicating that drug incorporation did not adversely affect blood compatibility. These findings confirm the suitability of the developed scaffolds for direct contact with wound exudate and blood in diabetic wound healing applications.

## RESULTS AND DISCUSSION

The freeze-dried PLGA-chitosan scaffolds displayed a highly porous and interconnected three-dimensional architecture, which is essential for effective cellular infiltration, oxygen transport and nutrient diffusion (22,23). The incorporation of chitosan markedly enhanced scaffold hydrophilicity and equilibrium swelling behavior, thereby supporting a moist microenvironment favorable for wound repair (24,25). Simvastatin was homogeneously distributed within the polymer matrix and exhibited a controlled and sustained release profile over a 10-day period, minimizing burst release and maintaining prolonged local drug availability (26). In vitro biological evaluations demonstrated excellent cytocompatibility in accordance with ISO 10993 standards, negligible hemolytic activity and significantly enhanced fibroblast migration and wound closure (27). Collectively, these findings indicate that the developed freeze-dried PLGA-chitosan scaffold provides a structurally and biologically optimized platform with strong potential to accelerate diabetic wound healing (28,29).

## CONCLUSION

Freeze-dried PLGA-chitosan scaffolds loaded with simvastatin demonstrated a well-defined porous architecture, favorable physicochemical properties and sustained drug release behavior suitable for diabetic wound applications. The synergistic integration of biodegradable polymers and localized statin delivery effectively enhanced scaffold hydrophilicity, swelling capacity, and biological performance. In vitro evaluations confirmed excellent cytocompatibility, minimal hemolytic activity, and significantly improved fibroblast migration. The sustained release of simvastatin contributed to prolonged bioactivity, supporting key cellular processes involved in wound repair. Importantly, the scaffold maintained structural integrity while undergoing controlled degradation under physiological conditions. These findings highlight the potential of freeze-dried PLGA-chitosan scaffolds as an advanced wound dressing system. Overall, this platform represents a promising

tissue-engineered approach for accelerating diabetic wound healing and warrants further in vivo investigation.

**8. Future Perspectives**

Future research should focus on comprehensive in vivo evaluation of the developed scaffolds using clinically relevant diabetic wound models. Detailed analysis of angiogenic, inflammatory and extracellular matrix remodeling markers will provide deeper insight into the underlying healing mechanisms. Optimization of scaffold composition and drug loading may further enhance therapeutic outcomes. Long-term biocompatibility and degradation studies are required to assess safety and performance. Additionally, scalability and sterilization strategies should be explored to facilitate clinical translation.

**9. Conflict of Interest**

The authors declare no competing interests.

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