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Research Article

Section: Zoology

Design, Optimization & Evaluation of Lovastatin-Loaded Polymeric Micelles for Enhanced Healing of Diabetic Wounds

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HIGHLIGHTS

- Enhanced lovastatin delivery
- Sustained drug release achieved
- Accelerated diabetic wound healing
- Improved collagen formation
- Promising polymeric micellar gel

Key Words:
Diabetic wound
Polymeric micelles
Lovastatin
Nano gel
Angiogenesis
Drug delivery
Statin repurposing

ABSTRACT

Introduction: Diabetic wounds are a major clinical challenge because of persistent inflammation, impaired angiogenesis, oxidative stress, and delayed extracellular matrix remodeling, all of which contribute to prolonged healing and increased risk of infection and amputation. Lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, possesses pleiotropic properties such as anti-inflammatory activity, antioxidant effects, and upregulation of vascular endothelial growth factor (VEGF), making it a promising candidate for wound healing. However, its poor aqueous solubility and limited skin permeation restrict its topical therapeutic efficacy. **Aims & Objectives:** This study aimed to develop and evaluate a lovastatin-loaded PEG–PCL polymeric micellar gel to enhance topical drug delivery and accelerate diabetic wound healing. **Materials & Methods:** Lovastatin-loaded PEG–PCL polymeric micelles were prepared using the solvent evaporation method and incorporated into a carbopol gel. The formulation was characterized for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, in vitro drug release, and stability. Therapeutic efficacy was evaluated in streptozotocin-induced diabetic Wistar rats through wound contraction studies, epithelialization time, histopathological examination, and collagen deposition analysis. **Results:** The optimized micellar formulation exhibited a particle size of 92.4 ± 6.3 nm, PDI < 0.2, and an entrapment efficiency of 88.6 ± 2.1%, with sustained drug release of approximately 85% over 24 h. In vivo studies demonstrated significantly enhanced wound contraction (95% by day 14), shorter epithelialization time, greater collagen deposition, and improved tissue regeneration compared with the conventional lovastatin gel ($p < 0.001$). Histopathological analysis confirmed increased angiogenesis, organized granulation tissue, and accelerated wound remodeling. **Conclusion:** Lovastatin-loaded PEG–PCL polymeric micellar gel is a promising topical nanocarrier for improving diabetic wound healing by enhancing drug solubility, sustained release, angiogenesis, and tissue regeneration.

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INTRODUCTION

The prevalence of diabetes mellitus is increasing rapidly across the globe, impacting hundreds of millions of individuals and causing significant financial strain [1–3].[M]. Diabetic foot ulcers (DFUs) are a significant debilitating condition that affect around 15-20% of diabetic individuals throughout their lifespan and are frequently linked to lower-limb amputations. A combination of chronic inflammation, hyperglycemia, oxidative stress, micro-vascular dysfunction (hypertension), neuropathy and vulnerability to infection are responsible for the slow healing of diabetic wounds. These pathological conditions cause prolonged inflammation, reduced angiogenesis, impaired fibroblast proliferation, defective collagen synthesis, and delayed remodeling of the extracellular matrix during wound healing. The clinical necessity for efficient therapeutic approaches that address various aspects of wound healing is still unfulfilled. Recent drug repurposing discoveries have highlighted the potential of statins to enhance tissue repair, in addition to their conventional lipid-lowering effects.

Various pleiotropic pharmacological effects, including anti-inflammatory, antioxidant, immune-modulatory, and pro-angiogenic, are demonstrated by Lovastatin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [10-14]. The experimental findings indicate that lovastatin enhances endothelial function by upregulating vascular endogenous growth factor (VEGF) expression, improving nitric oxide bioavailability, inhibiting inflammatory protein production, and stimulating collagen synthesis, ultimately leading to faster wound healing [11–15]. Lovestatin's biological properties make it a valuable therapeutic agent for diabetic wound management. Despite being a topical formul-ation with poor soluble pH, limited skin penetration, and inadequate local bioavailability, its clinical use is restricted [16]. The use of nanotechnology-based drug delivery systems has been proven to enhance the delivery of drugs that can be dissolved in water [17]. The **Figure 1** illustrates the sustained delivery of lovastatin from PEG–PCL micelles within a Carbopol hydrogel matrix to the diabetic wound bed, promoting anti-inflammatory effects, macrophage polarization, VEGF-mediated angiogene-sis, collagen synthesis, extracellular matrix remodeling, and fibroblast proliferation, ultimately accelerating wound healing and tissue regeneration

Polymeric micelles, especially amphiphilic block copolymers like PEG-PCL, have a hydrophobic core that can effectively encapsulate lipophilic drugs and envelop an hygrophilous shell that improves soluble stability and biocompatibility. Due to their nano-scale nature, they can facilitate close interaction with damaged tissue, enhance drug solubilization and prevent degradation of encapsulated drugs, or enable sustained and localized drug release [17-20]. Furthermore, the biocompatibility of PEG–PCL micelles, their long duration of life at the wound site and ability to biodegrade over time make them a valuable carrier for topical wound healing applications [19–22]. The addition of polymeric micelles to a carbopol-based hydrogel enhances their suitability for topical administration by providing an appropriate viscosity, ease of application, prolonged retention at the wound surface, and promoting tissue regeneration in breathable microenvironments [23-25].

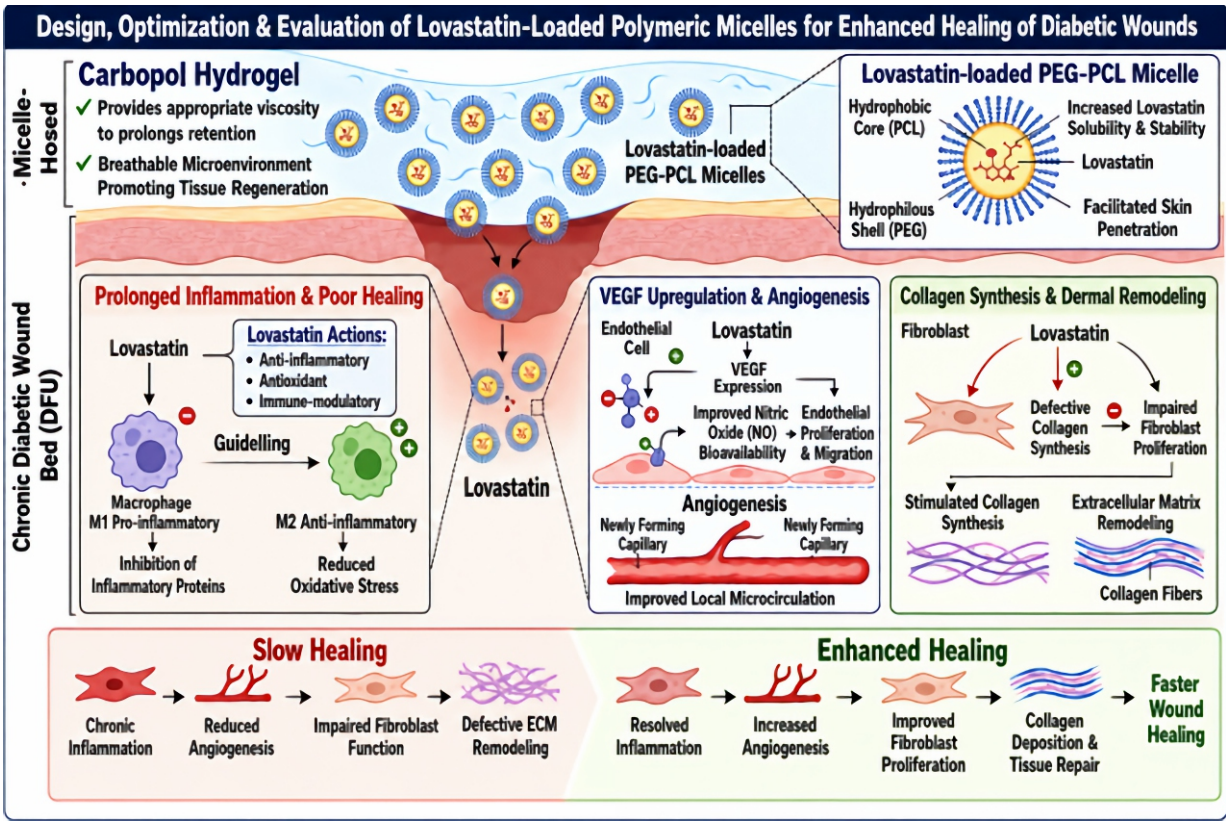

Figure 1: Mechanism of enhanced diabetic wound healing by lovastatin-loaded PEG–PCL polymeric micelles incorporated into Carbopol hydrogel.

Materials & Methods

Lovastatin (API grade), PEG–PCL copolymer, Carbopol 934, streptozotocin, and analytical-grade reagents were used.

Preparation of Polymeric Micelles

Micelles were prepared using solvent evaporation technique:

1. Drug and polymer dissolved in acetone.
2. Organic phase added to aqueous phase under stirring.
3. Solvent evaporated under reduced pressure.
4. Suspension filtered and stored at 4°C.

Characterization

- Particle size and PDI: Dynamic light scattering
- Zeta potential: Electrophoretic mobility
- Entrapment efficiency: Ultracentrifugation
- Drug loading percentage
- In vitro release: Dialysis membrane method
- Stability studies: 3 months (4°C and 25°C)

Preparation of Micellar Gel

Optimized micelles incorporated into 1% Carbopol gel neutralized with triethanolamine. Evaluated for pH, viscosity, spreadability, and drug content.

In Vivo Wound Healing Study

Diabetes induced in Wistar rats using streptozotocin (45 mg/kg, i.p.). Excision wound model created. Animals divided into control, plain gel, and micellar gel groups (n=6).

Parameters:

- Percentage wound contraction
- Epithelialization period
- Hydroxyproline estimation
- Histopathology (H&E, CD31 staining)

Statistical Analysis

Data expressed as mean ± SD. One-way ANOVA followed by Tukey's post hoc test. $p < 0.05$ considered statistically significant.

RESULTS

Lovastatin-loaded PEG–PCL polymeric micelles were successfully prepared using the solvent evaporation method and subsequently incorporated into a Carbopol 934 gel. The optimized formulation exhibited a mean particle size of 92.4 ± 6.3 nm with a polydispersity index (PDI) below 0.2, indicating a uniform nanosized particle distribution. The formulation showed a high entrapment efficiency of 88.6 ± 2.1%, demonstrating efficient encapsulation of the hydrophobic drug within the PEG–PCL micellar core. The micellar system also provided sustained in vitro drug release of approximately 85% over 24 h, suggesting controlled release behavior suitable for prolonged topical therapy. Stability studies conducted for 3 months at 4°C and 25°C indicated no significant changes in physicochemical characteristics, confirming formulation stability.

The optimized micelles were successfully incorporated into a 1% Carbopol gel, which exhibited acceptable physicochemical properties, including suitable pH, viscosity, spreadability, and uniform drug content for topical application.

In vivo wound healing studies using streptozotocin-induced diabetic Wistar rats demonstrated that the lovastatin-loaded micellar gel significantly enhanced wound healing compared with the plain gel and untreated control groups. The optimized formulation achieved approximately 95% wound contraction by day 14 ($p < 0.001$) and significantly reduced the epithelialization period. Hydroxyproline estimation indicated increased collagen deposition, reflecting enhanced extracellular matrix formation and tissue remodeling.

Histopathological examination further confirmed the superior healing efficacy of the micellar gel, revealing well-organized granulation tissue, complete re-epithelialization, increased angiogenesis (CD31-positive staining), and dense collagen fiber deposition compared with the control and conventional gel groups. These findings demonstrate that PEG–PCL polymeric micelles effectively enhanced the topical delivery of lovastatin, resulting in accelerated diabetic wound healing through sustained drug release, improved tissue regeneration, and enhanced angiogenic response.

Figures 2–8 and **Table 1** summarize the physicochemical characterization, drug release behavior, and therapeutic efficacy of lovastatin-loaded PEG–PCL polymeric micelles for diabetic wound healing. Particle size and morphology analysis **(Figure 2)** confirmed the formation of nano-sized micelles,

Optimized micelles exhibited:

- Mean size: 92.4 ± 6.3 nm
- PDI < 0.2
- Zeta potential: −20 mV
- Entrapment efficiency: 88.6 ± 2.1%

while **Figure 3** illustrates how their nanoscale dimensions enhance dermal permeation and retention at the wound site. In vitro drug release studies **(Figures 4–6)** demonstrated the influence of formulation composition on release behavior, with formulation B3 exhibiting the highest cumulative drug release and the optimized formulation showing an initial burst release (~20% within 2 h) followed by sustained release (~85% at 24 h), indicative of diffusion-controlled kinetics. **Figure 5** presents schematic illustrations of the dialysis bag, reverse dialysis bag, and dialysis cell methods used for drug release evaluation. The in vivo wound healing study in streptozotocin-induced diabetic Wistar rats **(Figure 7)** revealed significantly improved wound contraction, shorter epithelialization period, and increased collagen content in the micellar gel-treated group compared with control and conventional gel groups ($p < 0.05$, $p < 0.01$, $p < 0.001$). Histopathological findings **(Figure 8)** further confirmed enhanced re-epithelialization, granulation tissue formation, collagen deposition, and extracellular matrix remodeling. Consistently, **Table 1** demonstrates that treatment with lovastatin loaded PEG–PCL polymeric micellar gel significantly promoted angiogenesis, collagen remodeling, and overall diabetic wound healing.

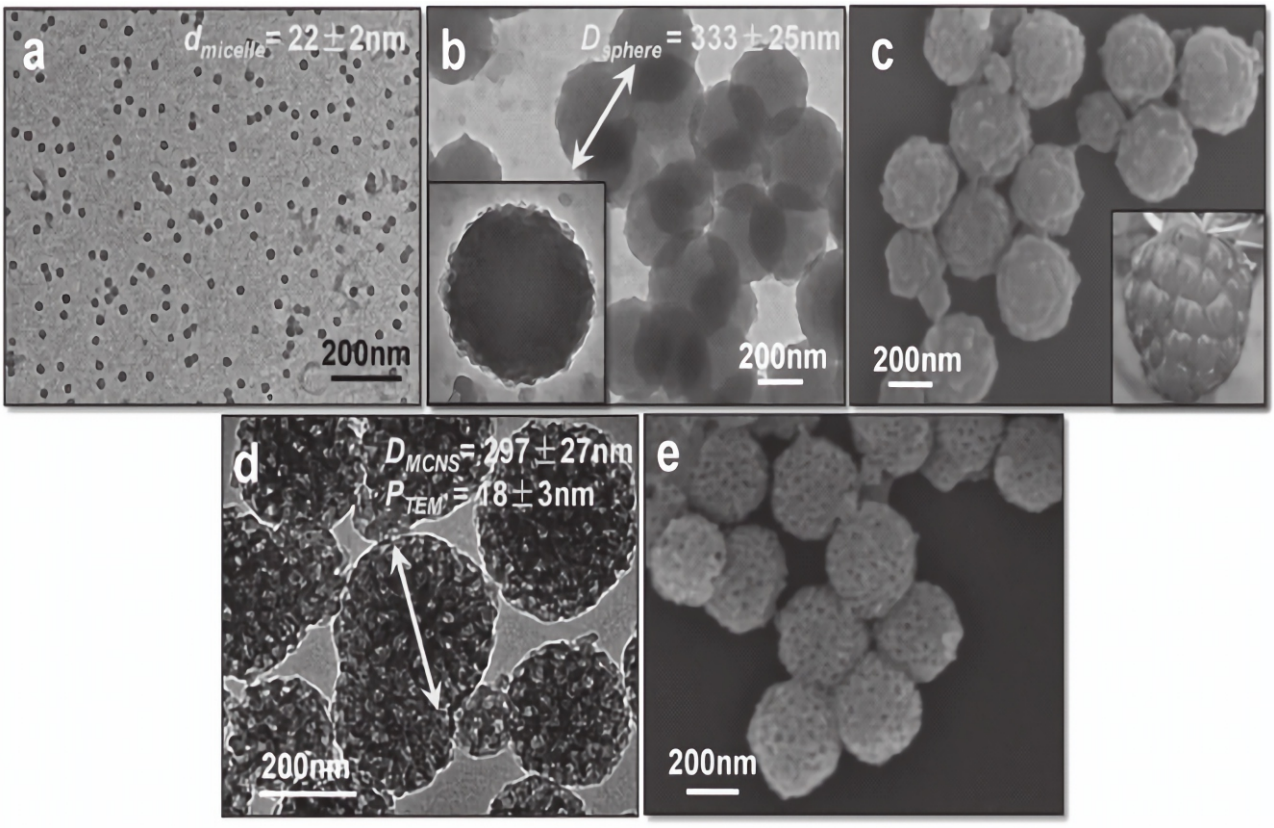

Figure 2: Particle Size and Morphology

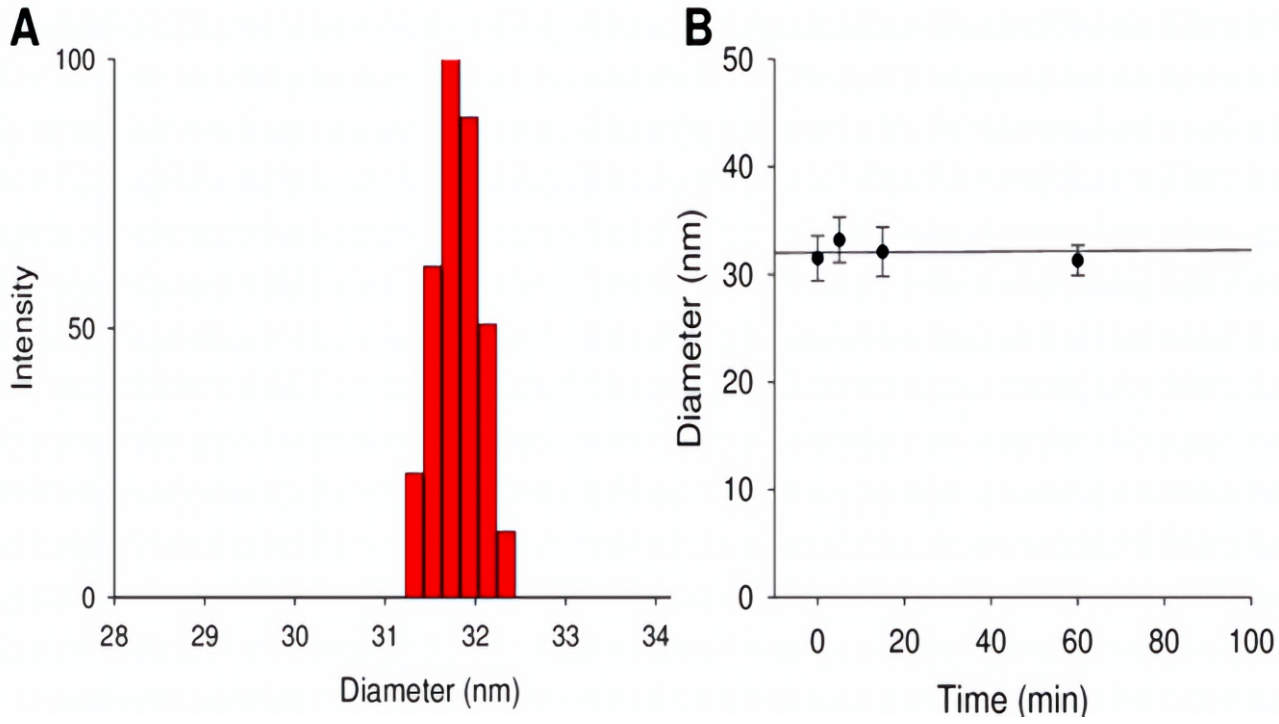

Figure 3: Nano-scale size enhances dermal permeation and wound-site retention.

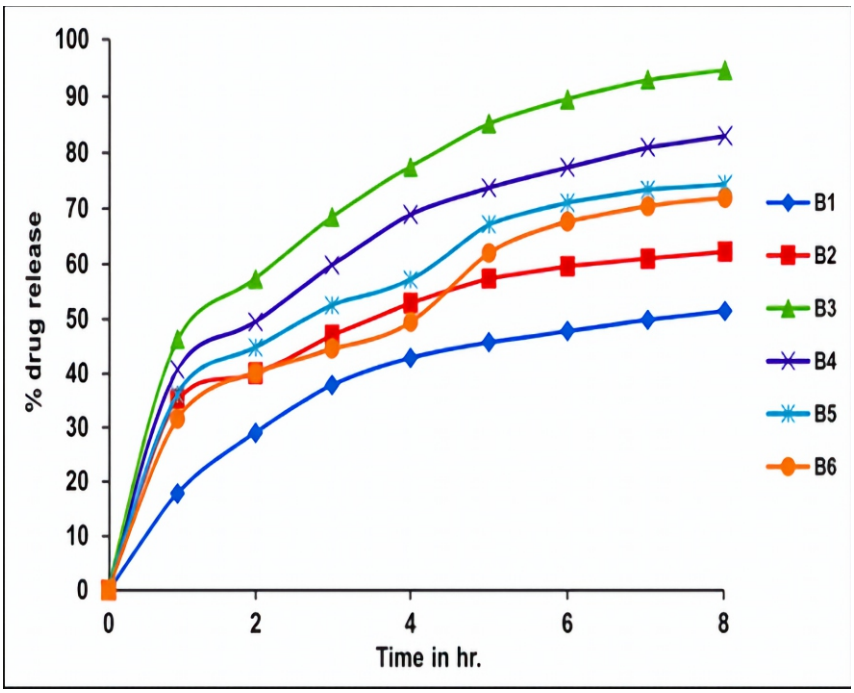

Figure 4. In vitro drug release profile of lovastatin-loaded PEG–PCL polymeric micelle formulations (B1–B6) over an 8-hour period. Formulation B3 exhibited the highest cumulative drug release, followed by B4, while B1 showed the lowest release, demonstrating the influence of formulation composition on sustained drug release behavior.

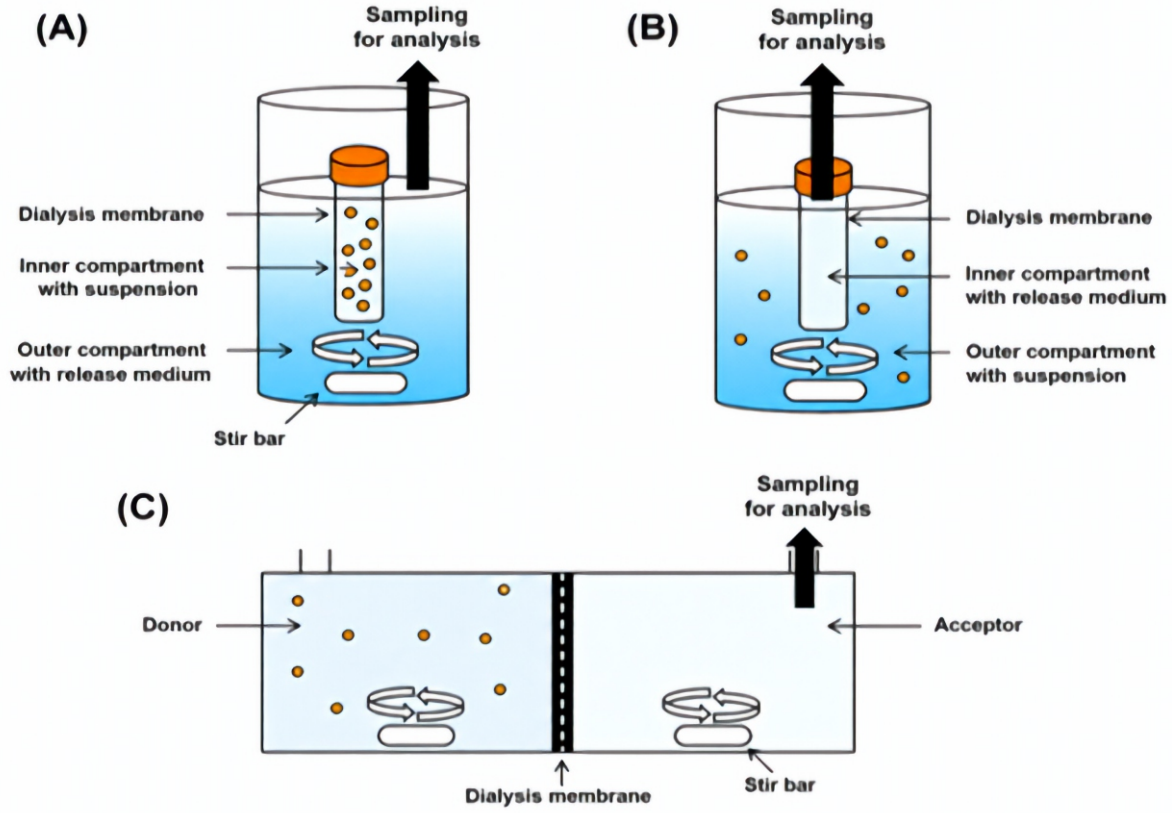

Figure 5: Schematic representation of dialysis methods used for in vitro drug release studies: (A) dialysis bag method, (B) reverse dialysis bag method, and (C) dialysis cell method. The illustrations show the arrangement of donor and receptor compartments, dialysis membrane, release medium, stirring conditions, and sampling points for drug release analysis.

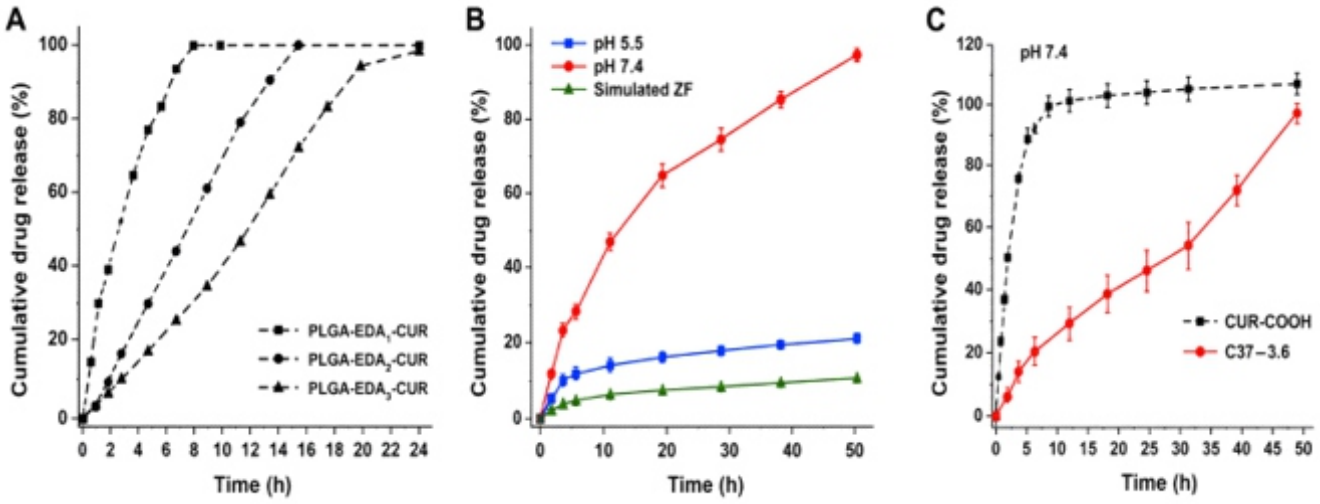

Figure 6. In vitro cumulative drug release profile of the optimized lovastatin-loaded PEG–PCL polymeric micellar formulation, showing an initial burst release (~20% within 2 h) followed by sustained drug release (~85% at 24 h), indicating diffusion-controlled release kinetics.

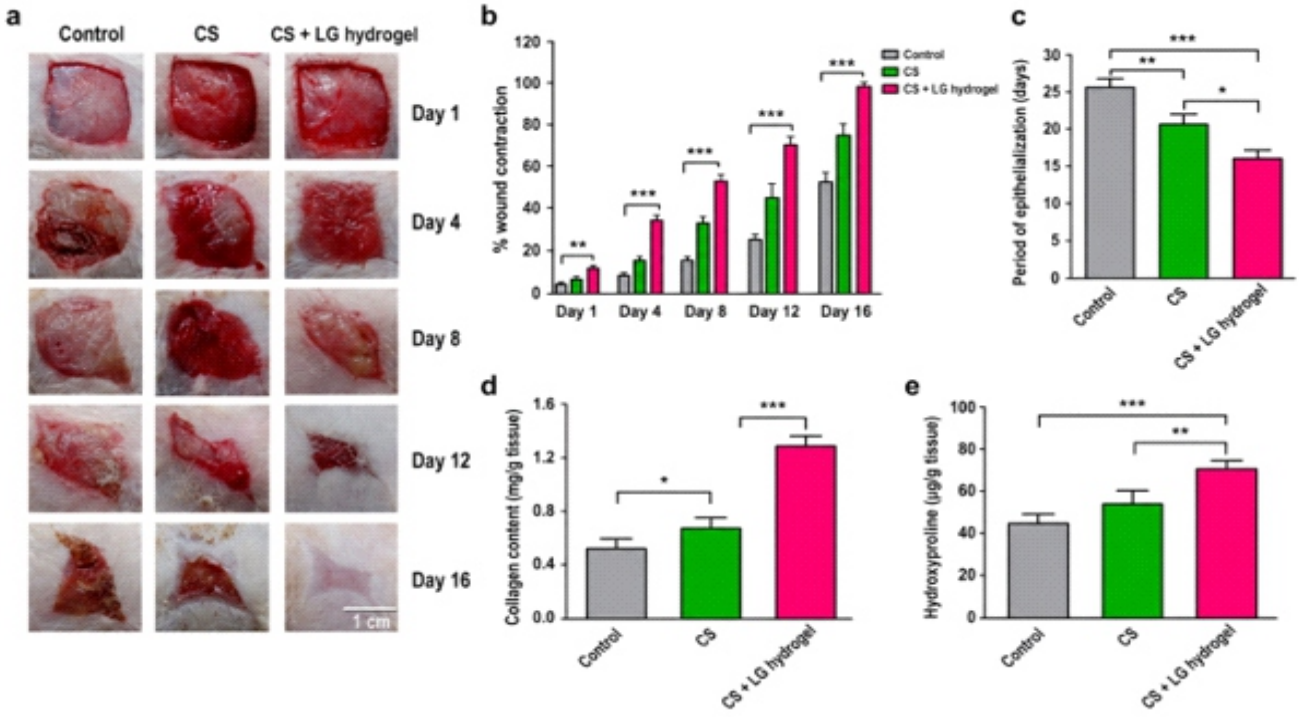

Figure 7. In vivo wound healing evaluation of lovastatin-loaded PEG–PCL polymeric micellar gel in streptozotocin-induced diabetic Wistar rats. (A) Representative photographs of wound closure at different time points. (B) Percentage wound contraction. (C) Epithelialization period. (D) Collagen content (hydroxyproline estimation). (E) Hydroxyproline content. The micellar gel group demonstrated significantly accelerated wound healing compared with the control and conventional gel groups ($p < 0.05$, $p < 0.01$, $p < 0.001$).*

Table 1. Effect of lovastatin-loaded PEG–PCL polymeric micellar gel on diabetic wound healing parameters.

Parameter	Control	Plain Gel	Micellar Gel	p-value
Wound contraction (Day 14)	72 ± 4.2	85 ± 3.1	**95 ± 2.4**	<0.001
Epithelialization (Days)	18 ± 1.2	15 ± 1.0	**12 ± 0.8**	<0.01
Hydroxyproline (µg/mg)	38 ± 2.5	52 ± 3.4	**68 ± 4.1**	<0.001

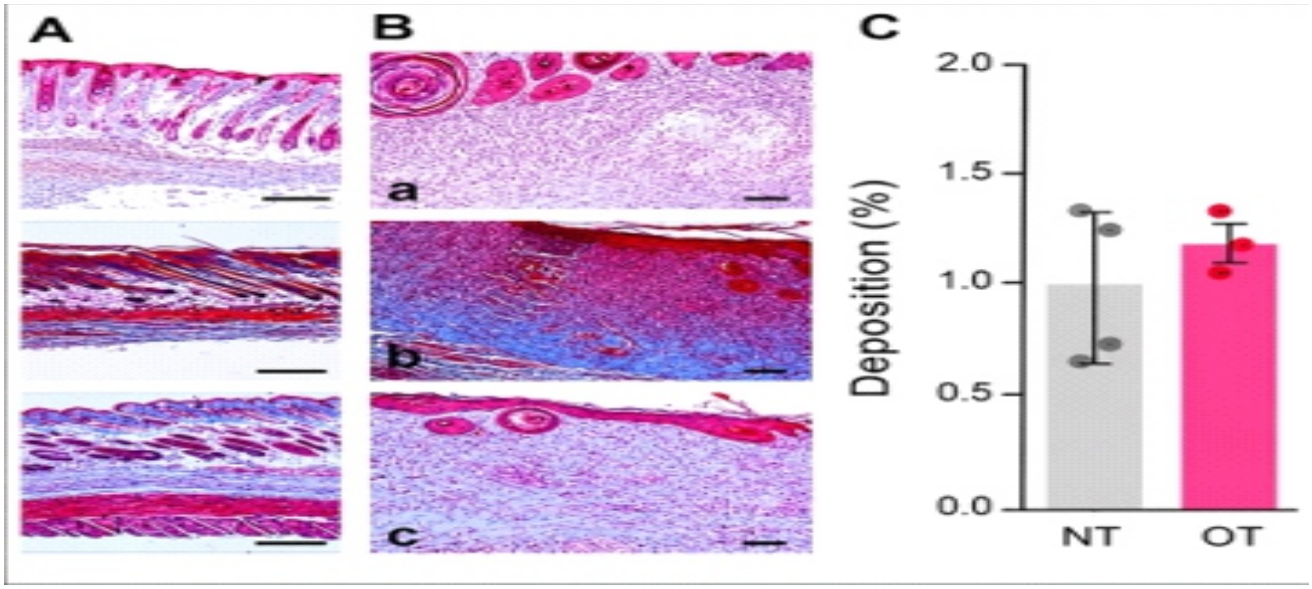

Figure 8. Histopathological evaluation of wound healing following treatment with lovastatin-loaded PEG–PCL polymeric micellar gel. (A) Hematoxylin and eosin (H&E)-stained skin sections showing re-epithelialization and granulation tissue formation. (B) Masson's trichrome-stained sections demonstrating collagen fiber deposition and tissue remodeling. (C) Quantitative analysis of collagen deposition, indicating enhanced extracellular matrix formation in the micellar gel-treated group compared with the control group.

DISCUSSION

In the current study, a topical gel based on PEG–PCL polymeric micelle was developed for local delivery of lovastatin and showed that it can speed up diabetic wound healing. This was confirmed. The optimal formula demonstrated desirable physicochemical traits, such as a nano-scale particle size of 92.4 6.3 nm, narrow size distribution (PDI 0.2), high drug entrapment efficiency (88.6 y/ 2.1%), and extended drug release period of 24 h. Streptozotocin-induced diabetic rats showed significant improvements in wound healing, including faster wound contraction, quicker epithelialization time, and stronger collagen deposition. Collectively, these findings show that the use of PEG–PCL polymeric micelles effectively addressed limitations in lovastatin topical administration and improved its therapeutic efficacy in diabetic wound healing. The performance of topical nano-carrier systems is heavily influenced by particle size, which is one of its key parameters [26-27]. Approximately 92 nm of micelle diameter, which is the average for dermal drug delivery, has been obtained in this study within the optimal nano-scale range [27-28]. These nano-carriers are particularly effective because of their large surface-area-to-volume ratio, which allows them to make intimate contact with the outside world while allowing for penetration into damaged tissue and retain within an extracellular matrix. The narrow polydispersity index indicates a uniform particle population, consistent formulation characteristics and predictable drug release behavior. [30]. Optimal dosages for therapeutic purposes are dependent on monodispersity, which decreases particle accumulation during storage and enhances formulation stability. The PEG-PCL micelles exhibit high encapsulation efficiency, suggesting that this amphiphilic copolymer is well-suited for the inclusion of hydrophobic drugs like lovastatin [31,32].

Lovastatin molecules were well-bound by the hydrophobic poly (-caprolactone) core and the nanostructure was stabilized in water by an effective hydrophilic polyethylene glycol shell. Improved drug encapsulation reduces the risk of premature drug leakage by increasing the apparent solubility of compounds that are poorly water-soluble, which is particularly advantageous. Therefore, a greater amount of the administered medication is still accessible for sustained healing at the site. Controlled diffusion of lovastatin from the polymeric matrix was demonstrated by an in vitro release profile that showed sustained release (roughly 85%) of the drug over 24 h. Sustained drug release is a highly preferred strategy for chronic wound management because it preserve the persistence of therapeutic drugs over long periods while reducing the need for frequent dressing changes. Lovatistatin exposure for an extended period may result in sustained modulation of inflammatory pathways and angiogenic signaling during wound healing [31,32]. Also, it is probable that adding the micellar formulation to a carbopol gel prolonged its stay on the wound surface, increasing drug accessibility and decreasing loss by exudate or mechanical removal. The use of lovastatin-loaded polymeric micellar gel on diabetic rats has led to an important finding, as it increased wound contraction in the study. This is noteworthy. On day 14, wound closure was at approximately 95% with the improved formulation, which was significantly higher than that observed with conventional lovastatin gel. Diabetic wounds experience delayed contraction due to impaired fibroblast migration, reduced angiogenesis during wound healing, persistent inflammation, and defective extracellular matrix remodeling [18]. Following treatment with the micellar gel, wound closure that was faster and more rapid suggests that nano-encapsulation significantly increased the local bioavailability of lovastatin as

well as its biological activity. Better drug penetration and sustained release likely maintained effective tissue concentrations that could continuously promote healing processes [27,18].

Multiple biological mechanisms may account for the superior therapeutic efficacy of the micellar formulation. Apart from lowering cholesterol levels, lovastatin has several pleiotropic effects that have direct consequences on wound healing. E.g. Statistical studies indicate that statins can enhance endothelial nitric oxide synthase activity, stimulate NI3+ oxidative stress production, inhibit pro-inflammatory cytokines such as tumor necrosis factor- and interleukin-6, and promote vascular endoscopic angiogenesis (VEGF)-mediated activation. These actions, when taken together, enhance microvascular perfusion, attract reparative cells, and restore tissue oxygenation in individuals with diabetes [11]. PEG-PCL micelles can be utilized to maintain sustained local delivery, which can enhance the beneficial effects of drugs by preventing drug distribution. Further histo-pathological analysis confirmed the enhanced regenerative response produced by this optimized formulation. Animals were treated with lovastatin-loaded micellar gel, which resulted in enhanced angiogenesis, organized granulation tissue, and higher levels of collagen deposition and complete re-epithelialization. The evidence points to the advancement during the proliferation and regrowth phases of wound healing, while diabetic wounds tend to be delayed in the inflammation phase [6]. The significance of increased neovascularization cannot be overstated, as diabetic wounds experience impaired vascularisation and reduced oxygen delivery, both of which hinder the process of tissue regeneration. Better organizational qualities in the collagen also indicate increased activity of the fibroblasts and extracellular matrix remodeling, leading to greater wound strength and structural integrity [6].

PEG-PCL polymeric micelles exhibit distinct characteristics that enhance their healing response. The biodegradable PCL core serves as an efficient reservoir for sustained drug delivery, while PEG provides steric stabilization, increased hydration, and improved biocompatibility [18-19]. They have an amphiphilic structure that allows them to spontaneously self-assemble into stable nanosized carriers, which can solubilize highly lipophilic molecules. A carbopol hydrogel is incorporated into the micellar system, which incorporates nanotechnology's advantages and hydrogeological and moisturizing properties.

Note: LOVATATINI activity is complemented by the fact that maintaining a moist wound environment promotes cell migration, reduces dehydration, facilitates autolytic debridement, and supports angiogenesis. Recent studies have revealed that statins can enhance cutaneous wound healing, and their use has been linked to improved dermal delivery through polymeric nanocarriers. Previous studies have indicated that topical statin formulations can boost angiogenesis, enhance collagen synthesis and decrease inflammatory cell infiltration [32]. These findings are consistent with previous research. Also, the use of polymeric micelles derived from PEG has been consistently demonstrated to result in better solubility of hydrophobic drugs [27,18,19], as well as better skin retention and longer drug release. This study builds on earlier research by combining the findings of these observations with both methods of delivery, showing that nanocarrier-mediated delivery can dramatically improve the therapeutic efficacy of diabetic lovastatin.

CONCLUSION

The developed lovastatin-loaded PEG–PCL polymeric micellar gel significantly enhanced the solubility, sustained release, and topical bioavailability of lovastatin. The optimized formulation accelerated diabetic wound healing by promoting faster wound contraction, improved angiogenesis, enhanced collagen deposition, & reduced epithelialization time compared with the conventional formulation. Histopathological findings confirmed superior tissue regeneration and organized granulation tissue formation. Overall, the PEG–PCL micellar gel represents a promising nanocarrier-based topical delivery system with strong potential for the effective management of chronic diabetic wounds.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-.care, diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patientworld relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

HMG-CoA: 3-Hydroxy-3-methylglutaryl Coenzyme A
VEGF: Vascular Endothelial Growth Factor
PEG: Poly(Ethylene Glycol)
PCL: Poly(ε-Caprolactone)
PDI: Polydispersity Index
STZ: Streptozotocin
EE: Entrapment Efficiency
DL: Drug Loading
ECM: Extracellular Matrix
TA: Triamcinolone Acetonide
HMGCR: 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

FUNDING

None

ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research diretions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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