RESEARCH PAPER

Topical Delivery of Simvastatin, Arginine, and PDGF via Nanoparticle-Loaded Ointment Promotes Diabetic Wound Healing

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Abstract: Diabetic wound healing represents a significant clinical challenge due to chronic inflammation, impaired angiogenesis, and diminished endogenous growth factors. We investigated a smart multifactorial drug delivery system encapsulating Simvastatin and L-Arginine-based silver nanoparticles within a degradable chitosan-gelatin polymeric ointment containing exogenous Platelet-derived growth factor (PDGF). In a streptozotocin (STZ)-induced diabetic rat excisional wound model, this composite formulation (SAPNP) demonstrated accelerated healing, achieving complete re-epithelialization in 17 days and 89% wound contraction by day 14. Biochemical and histological evaluations revealed significant reductions in oxidative stress, rapid resolution of inflammation, augmented collagen deposition, and robust neoangiogenesis. These findings provide a novel, synergistic therapeutic platform for the clinical management of diabetic ulcers.

Keywords: Diabetic wound healing; Simvastatin-loaded nanoparticles; L-Arginine; Silver nanoparticles; Platelet-Derived Growth Factor (PDGF); Chitosan–gelatin ointment; Box–Behnken Design; Antioxidant activity.

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Introduction

Diabetes mellitus is a complex metabolic disorder affecting over 350 million individuals globally. Approximately 20% of these patients develop diabetic wounds, such as foot ulcers, which carry severe risks of chronic non-healing and amputation [1]. The physiological wound healing cascade—comprising hemostasis, inflammation, proliferation, and remodeling—is pathologically stalled in the diabetic microenvironment. This stagnation is driven by an overproduction of reactive oxygen species (ROS), severely diminished endogenous growth factors, and a massive overexpression of matrix metalloproteinases (MMPs) that degrade nascent extracellular matrix (ECM) [2].

Current wound management strategies, heavily reliant on single-agent topical therapies, often fail to address this multi-tiered biochemical dysfunction. Recent advances have highlighted the pleiotropic effects of statins; specifically, Simvastatin has been shown to reduce localized oxidative stress, modulate inflammation, and upregulate Vascular Endothelial Growth Factor (VEGF) [3]. However, its profound hydrophobicity limits bioavailability in the aqueous wound bed. To overcome this, we designed a multi-targeted therapeutic delivery system. Simvastatin was formulated into nanoparticles stabilized by L-Arginine and Silver Nanoparticles (AgNPs). L-Arginine acts as a biological precursor to nitric oxide (NO), promoting localized vasodilation, while AgNPs provide robust, broad-spectrum antimicrobial defense [4].

Recognizing that neutralizing inflammation is only the initial step, this system was further enriched with exogenous Platelet-Derived Growth Factor (PDGF), a potent mitogen that drives the migration and multiplication of fibroblasts and keratinocytes. These active agents were embedded within a degradable, bio-mimetic ointment featuring a dispersed biopolymer matrix of Chitosan and Gelatin. Herein, we report the comprehensive in vitro characterization and in vivo efficacy of this composite formulation (SAPNP) in accelerating diabetic wound closure.

Materials and methods

Nanoparticle Synthesis and Optimization: Plain arginine nanoparticles (ANPs) and simvastatin-loaded nanoparticles (SNPs) were synthesized utilizing a modified solvent emulsification-evaporation technique. The organic phase (Simvastatin and L-Arginine in dichloromethane) was introduced dropwise into an aqueous phase containing polyvinyl alcohol (PVA) under high-speed homogenization. Formulations were optimized using a 17-run Box-Behnken Design to minimize particle size and maximize entrapment efficiency. Structural integrity was confirmed via FTIR and DSC analyses.

Ointment Formulation: A degradable water-in-oil (w/o) ointment base was utilized. The internal aqueous phase comprised a structural biopolymer matrix of Chitosan and Gelatin crosslinked by glutaraldehyde (Schiff-base formation and acetalization). Optimized SNPs, Silver Nitrate, and PDGF were integrated into the matrix under controlled thermal conditions to preserve biologic activity.

In Vitro Assays: Antioxidant activity was quantified using standard DPPH free radical and Nitro-Blue Tetrazolium (NBT) superoxide scavenging assays over a 24-hour dissolution period. Antibacterial efficacy was evaluated via the agar well diffusion method against *Pseudomonas*

aeruginosa. Cytotoxicity and biocompatibility were assessed utilizing the MTT colorimetric assay on NIH/3T3 murine fibroblast cells.

Animal Models: Healthy Swiss albino rats (120-150g) were utilized. Diabetes was induced via a single intraperitoneal injection of Streptozotocin (STZ, 65 mg/kg). Full-thickness excisional wounds (100 mm^2) were created on the dorsal thoracic region. Formulations were applied topically once daily. Granulation tissue was harvested on days 6 and 14 for biochemical estimation of total protein (Bradford assay), SOD, Catalase, Hydroxyproline, and Hexosamine. Tissue biopsies were fixed in formalin and stained with Hematoxylin and Eosin (H&E) for histopathological evaluation.

Results

Nanoparticle Optimization and Characterization

Simvastatin-loaded nanoparticles (SNPs) were successfully synthesized utilizing a modified solvent emulsification-evaporation method. Using a Box-Behnken Design matrix, optimal parameters were established at 0.3% (w/v) polymer concentration, a 4:1 aqueous-to-organic phase ratio, and 0.8% (w/v) surfactant concentration. As shown in Table 1, the optimized SNPs exhibited a highly refined mean particle size and high entrapment efficiency (%EE), driven by the lipophilic nature of the drug. Differential Scanning Calorimetry (DSC) confirmed the complete encapsulation of Simvastatin within the amorphous polymeric core.

Table 1: Physicochemical Characteristics of Optimized Nanoparticles

Formulation	Particle Size (nm)	Polydispersity Index (PDI)	Zeta Potential (mV)	Entrapment Efficacy (%)
Plain ANPs	172.4 ± 8.4	0.459	-31.27 ± 2.85	--
Optimized SNPs	141.5 ± 1.18	0.256	-28.85 ± 1.27	66.60 ± 2.02
SANP (AgNP modified)	146.6 ± 4.2	0.235	-28.85 ± 1.27	65.96 ± 1.92

In Vitro Release and Biocompatibility

The cumulative release kinetics of Simvastatin from the SAPNP matrix demonstrated a distinct biphasic pattern. An initial rapid burst release (attributable to surface-bound drug) transitioned into a prolonged, sustained release phase governed by Fickian diffusion (Higuchi model R^2 = 0.995). This sustained release effectively shielded regenerating tissues from oxidative damage, as evidenced by potent, time-dependent DPPH free radical and superoxide (NBT assay) scavenging activities. Furthermore, MTT colorimetric assays on NIH/3T3 murine fibroblasts definitively proved the formulation's exceptional biocompatibility, actively stimulating cellular proliferation beyond baseline controls.

Table 2: In Vitro Biological Efficacy (24-hour evaluation)

Formulation Matrix	Cumulative Drug Release (%)	DPPH Scavenging (%)	NIH/3T3 Cell Viability (%)
SNP (Simvastatin only)	90.99 ± 1.27	90.62	97.5 ± 2.1
SANP (with Arginine/Ag NPs)	91.07 ± 1.41	83.10	106.3 ± 1.8
SAPNP (Complete composite)	95.07 ± 1.61	82.18	116.7 ± 1.4

In Vivo Diabetic Wound Healing

The therapeutic efficacy of the engineered formulations was evaluated using a full-thickness excisional wound model in STZ-induced diabetic rats. The macroscopic progression of tissue repair demonstrated a robust, time-dependent acceleration in wound closure across the therapeutic cohorts. The cohort treated with the composite SAPNP formulation exhibited the most profound wound contraction, achieving 89% closure by Day 14 post-wounding, and complete epithelialization by Day 17. In contrast, the vehicle control cohort displayed protracted and inadequate healing over the same period, characteristic of the impaired diabetic microenvironment. This super-healing trajectory underscores the synergistic action of Simvastatin modulating local inflammation and PDGF driving rapid cellular regeneration.

Table 3: Percentage of Wound Contraction and Epithelialization Period

Treatment Group	Day 4 Contraction (%)	Day 8 Contraction (%)	Day 14 Contraction (%)	Epithelialization (Days)
Group I: Vehicle Control	8 ± 1.2	21 ± 3.6	32 ± 4.1	29 ± 2.6
Group II: Commercial Standard	24 ± 3.6	44 ± 4.5	66 ± 5.2	22 ± 1.3
Group III: SNP	26 ± 3.2	42 ± 3.3	64 ± 4.1	22 ± 1.4

Group IV: SANP	29 ± 3.3	48 ± 4.8	74 ± 5.8	19 ± 1.3
Group V: SAPNP	34 ± 3.8	59 ± 4.8	89 ± 7.2	17 ± 1.2

Biochemical and Connective Tissue Parameters

Quantitative biochemical assessments of excised granulation tissue confirmed that localized levels of endogenous antioxidant enzymes, specifically Superoxide Dismutase (SOD) and Catalase (CAT), were significantly augmented in the treated groups. Furthermore, the SAPNP cohort exhibited massive upregulation in structural biochemistry, with collagen levels (extrapolated from hydroxyproline) increasing by 41.9% and hexosamine levels surging by 53.9% compared to diabetic controls. This proves that the targeted formulation successfully signaled fibroblasts to transition into a highly active, matrix-depositing phenotype.

Table 4: Biochemical markers in granulation tissue at Day 14

Treatment Group	Total Protein (mg/100mg)	SOD (IU/mg protein)	Hydroxyproline (mg/g)	Calculated Collagen (mg/g)
Group I: Vehicle Control	12.1 ± 0.8	0.30 ± 0.02	98.05 ± 0.05	726.3
Group II: Commercial Standard	35.0 ± 2.2	0.71 ± 0.03	156.15 ± 0.33	1156.0
Group III: SNP	31.5 ± 2.8	0.76 ± 0.02	150.31 ± 0.21	1113.0
Group IV: SANP	34.5 ± 2.3	0.81 ± 0.03	160.83 ± 0.30	1191.3
Group V: SAPNP	49.9 ± 2.5	0.85 ± 0.04	168.92 ± 0.56	1251.3

Histopathological Evaluation

Microscopic evaluation of tissue biopsies on Day 14 corroborated the macroscopic findings. The diabetic vehicle control exhibited an arrested healing state plagued by persistent inflammation, disorganized fibrous tissue, and a distinct lack of vascularization. In stark contrast, histological sections from the SAPNP-treated cohort revealed high capillary density indicative of robust neoangiogenesis, a well-orchestrated and mature extracellular matrix, complete absence of ulceration, organized collagen bundle deposition, and a continuously restored, stratified epidermal layer. The formulation effectively mitigated the hostile diabetic microenvironment, allowing the structural biopolymers (chitosan and gelatin) to serve as a biomimetic regenerative scaffold.

Discussion

The management of diabetic wounds is severely hindered by a multifaceted disruption of the healing cascade, primarily driven by chronic, unresolved inflammation and pathological ROS overproduction. This hostile environment scavenges vital nitric oxide, downregulates endogenous growth factors, and over-expresses tissue-degrading MMPs. Traditional single-agent therapies often fail to address these compounding molecular deficits. The findings of this research establish that a multi-targeted, "smart" drug delivery system is required to simultaneously intervene across impaired phases.

The SAPNP formulation operates sequentially and harmoniously. Upon application, the chitosan matrix provides instant hemostasis and an occlusive barrier. The initial burst release of Simvastatin and AgNPs aggressively quenches ROS, suppresses MMP over-activation, and destroys invading bacteria, rescuing the wound from the destructive inflammatory loop. With the microenvironment stabilized, the sustained release of exogenous PDGF serves as a biological beacon, triggering the massive chemotactic recruitment and proliferation of fibroblasts and keratinocytes. Concurrently, the localized release of L-Arginine upregulates NO production, driving robust neoangiogenesis required to supply oxygen and nutrients to rapidly dividing cells.

During the structural remodeling phase, the bio-mimetic gelatin matrix provides a temporary physical scaffold. The continued presence of Simvastatin promotes organized collagen deposition (evidenced by soaring hydroxyproline levels), while PDGF drives the maturation of the granulation tissue into a resilient, crosslinked scar, culminating in complete, accelerated epithelialization. This synergistic mechanism represents a paradigm shift, transitioning the diabetic wound from a stalled inflammatory state into robust proliferation and structural repair.

Conclusion

In conclusion, SAPNP represents a promising next-generation topical drug delivery platform with considerable potential for diabetic ulcer management, offering a combined approach to infection control, oxidative stress reduction, angiogenesis, and tissue regeneration. Nevertheless, further investigations involving detailed mechanistic studies, pharmacokinetic and degradation profiling, long-term toxicity assessment, dose optimization, and larger preclinical models are necessary to establish its safety, reproducibility, and translational applicability. Ultimately, these findings provide a scientific

foundation for the further development of multifunctional nanoparticle-based wound dressings and their potential future evaluation in clinical settings.

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