Transdermal Patches for Diabetic Wound Healing Using Moringa Oleifera

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Abstract—**Diabetic wounds are among the most serious and common complications associated with diabetes mellitus. These wounds are characterized by delayed and impaired healing due to prolonged inflammation, excessive oxidative stress, reduced collagen synthesis, compromised angiogenesis and a higher susceptibility to microbial infections. Such pathological conditions often lead to chronic, non-healing ulcers, significantly affecting patient quality of life and increasing the risk of infection, hospitalization, and limb amputation.**

In recent years, herbal therapies have gained considerable attention in wound management owing to their safety, biocompatibility, and multifunctional therapeutic effects. Among various medicinal plants, Moringa oleifera has been extensively studied for its rich phytochemical composition. The plant is a valuable source of flavonoids, polyphenols, vitamins, and essential amino acids, which collectively contribute to its strong antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties. These bioactive constituents play a crucial role in reducing oxidative damage, controlling inflammation, preventing infection, and promoting tissue regeneration.

The present study was designed to develop and evaluate transdermal patches containing Moringa oleifera extract as a novel approach for diabetic wound healing. Transdermal patches were formulated using suitable polymeric materials by the solvent casting method to ensure uniformity, flexibility, and controlled drug delivery. The prepared patches were systematically evaluated for physicochemical characteristics, drug content uniformity, in vitro drug release behavior, and wound healing potential.

The optimized transdermal patch exhibited satisfactory mechanical strength, uniform distribution of the herbal extract, and a sustained drug release profile, which is essential for maintaining continuous therapeutic levels at the wound site. Enhanced wound healing activity observed with the optimized formulation can be attributed to prolonged drug residence time, improved skin permeation, and the synergistic biological effects of Moringa oleifera phytoconstituents.

In conclusion, transdermal patches loaded with Moringa oleifera extract offer a promising, non-invasive, and patient-friendly strategy for the effective management of diabetic wounds. This delivery system not only improves therapeutic efficacy but also has the potential to enhance patient compliance and overall wound healing outcomes.

I. INTRODUCTION

Diabetes mellitus is a complex and chronic metabolic disorder characterized by sustained hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Persistent hyperglycemia leads to a cascade of metabolic disturbances that significantly impair normal physiological processes, including wound healing. Diabetic wounds are among the most severe and costly complications of diabetes mellitus and represent a major global healthcare burden (Falanga, 2005). The impaired healing of diabetic wounds is multifactorial and involves prolonged inflammation, reduced fibroblast proliferation, impaired collagen deposition, defective angiogenesis, increased oxidative stress, and heightened susceptibility to microbial infections (Brem and Tomic-Canic, 2007).

Physiologically, wound healing is a dynamic and highly regulated process comprising four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. In diabetic conditions, this finely balanced process is severely disrupted at each stage. Excessive and prolonged inflammation leads to elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukins, which delay progression to the proliferative phase. Concurrently, oxidative stress resulting from overproduction of reactive oxygen species (ROS) damages cellular structures, inhibits fibroblast migration, and impairs keratinocyte function, ultimately delaying re-epithelialization (Guo and

DiPietro, 2010). Furthermore, reduced angiogenesis limits oxygen and nutrient supply to the wound site, while impaired collagen synthesis weakens newly formed tissue, leading to chronic non-healing ulcers.

Diabetic foot ulcers represent one of the most serious manifestations of impaired wound healing in diabetic patients. These ulcers are frequently complicated by neuropathy, ischemia, and infection, often resulting in prolonged hospitalization and lower limb amputation. Despite advances in wound care, the recurrence rate of diabetic ulcers remains high, highlighting the urgent need for novel and effective therapeutic strategies (Armstrong et al., 2017).

In recent years, increasing attention has been directed toward herbal and plant-based therapies for wound healing due to their safety, biocompatibility, affordability, and ability to target multiple pathological pathways simultaneously. Herbal medicines are rich in bioactive phytoconstituents such as flavonoids, polyphenols, alkaloids, vitamins, and trace elements, which exhibit antioxidant, anti-inflammatory, antimicrobial, and angiogenic activities. These properties make herbal formulations particularly suitable for managing complex chronic wounds such as diabetic ulcers, where multifactorial pathophysiology demands a multitargeted therapeutic approach (Süntar et al., 2014).

Among various medicinal plants, Moringa oleifera has gained considerable scientific interest due to its remarkable pharmacological profile. Moringa oleifera, commonly referred to as the drumstick tree, has been widely used in traditional systems of medicine for the treatment of wounds, inflammation, infections, and skin disorders. The leaves of Moringa oleifera are a rich reservoir of flavonoids, polyphenols, vitamins, essential amino acids, and minerals. Notably, bioactive compounds such as quercetin, kaempferol, chlorogenic acid, and vitamin C have been shown to play a crucial role in wound healing by enhancing collagen synthesis, stimulating angiogenesis, accelerating epithelialization, and scavenging free radicals (Anwar et al., 2007; Saini et al., 2016).

Several experimental studies have demonstrated the wound healing potential of Moringa oleifera through modulation of oxidative stress and inflammatory pathways. The antioxidant activity of its flavonoids reduces ROS-mediated tissue damage, while its anti-inflammatory constituents help normalize cytokine levels, thereby facilitating the transition from inflammation to proliferation. Additionally, the antimicrobial activity of Moringa oleifera helps prevent wound infection, a major impediment to healing in diabetic patients (Leone et al., 2015). Despite these promising biological properties, the therapeutic application of Moringa oleifera in wound management remains limited due to formulation challenges.

Conventional topical formulations such as creams, ointments, and gels often suffer from inadequate skin penetration, poor retention at the wound site, instability of active phytoconstituents, and the need for frequent application. These limitations are particularly problematic in chronic conditions like diabetic wounds, which require prolonged and consistent therapeutic intervention. Rapid removal of topical formulations due to exudate, washing, or movement further compromises their effectiveness and patient compliance.

Transdermal drug delivery systems, especially transdermal patches, have emerged as a promising alternative to conventional topical dosage forms for wound management. Transdermal patches offer controlled and sustained drug release, improved skin permeation, prolonged residence time at the application site, and maintenance of a moist wound environment conducive to healing. Moreover, such systems minimize dosing frequency, enhance patient compliance, and protect sensitive phytoconstituents from environmental degradation (Prausnitz and Langer, 2008).

The integration of herbal therapeutics with transdermal drug delivery technology represents an innovative strategy for enhancing the clinical effectiveness of plant-based wound healing agents. By incorporating Moringa oleifera extract into transdermal patches, it is possible to achieve sustained delivery of bioactive constituents, improved bioavailability, enhanced wound site retention, and superior therapeutic outcomes.

Therefore, the present research focuses on the development and evaluation of transdermal patches loaded with Moringa oleifera extract for diabetic wound healing. By combining the potent wound healing properties of Moringa oleifera with the advantages of transdermal drug delivery, this study aims to address the limitations of conventional formulations and contribute to the development of an

effective, safe, and patient-friendly therapeutic system for the management of diabetic wounds.

II. PLANT PROFILE AND PHYTOCONSTITUENTS

1.1 Botanical Name
Moringa oleifera

1.2 Synonyms
- Drumstick tree
- Horseradish tree
- Miracle tree

1.3 Family
Moringaceae

1.4 Common Names
- English: Drumstick tree
- Hindi: Sahjan
- Marathi: Shevga
- Tamil: Murungai

1.5 Geographical Distribution
Moringa oleifera is native to the Indian subcontinent and is widely cultivated in tropical and subtropical regions of Asia, Africa, South America, and the Middle East. The plant grows well in arid and semi-arid climates and is commonly found in India, where it has extensive medicinal and nutritional use.

1.6 Morphological Description
- Leaves: Pinnate, tripinnate, light green, rich in bioactive phytoconstituents. Leaves are the most commonly used part for medicinal purposes.
- Flowers: Creamy white, fragrant, rich in flavonoids and antioxidants.
- Fruits (Pods): Long, cylindrical pods commonly used as vegetables.
- Bark and Roots: Contain alkaloids and bioactive compounds but are less commonly used due to safety concerns.

1.7 Parts Used
- Leaves (major medicinal part)
- Flowers
- Seeds (limited topical use)

👉 Leaves are primarily selected for wound healing studies due to high flavonoid and polyphenol content.

1.8 Phytochemical Constituents of Moringa oleifera
Moringa oleifera leaves are a rich source of diverse phytochemicals, including:
- Flavonoids
- Polyphenols
- Phenolic acids
- Vitamins (A, C, E)
- Essential amino acids
- Minerals (Ca, Fe, Zn)
- Alkaloids (trace amounts)

1.9 Pharmacological Activities
- Antioxidant
- Anti-inflammatory
- Antimicrobial
- Wound healing
- Antidiabetic
- Immunomodulatory

2. Phytoconstituents for Wound Healing

The wound healing potential of Moringa oleifera is primarily attributed to specific phytoconstituents that actively participate in tissue repair, inflammation control, and oxidative stress reduction. These constituents are considered responsible phytosomes when complexed with phospholipids or delivered via advanced systems.

2.1 Flavonoids (Major Responsible Phytosomes)

- Quercetin
- Kaempferol

Role in wound healing:

- Potent antioxidant activity
- Scavenging of reactive oxygen species (ROS)
- Reduction of oxidative tissue damage
- Promotion of fibroblast proliferation
- Enhancement of collagen synthesis

Flavonoids possess multiple hydroxyl groups that readily form hydrogen bonds with phospholipids, making them ideal candidates for phytosome formation. Their improved lipid compatibility enhances skin permeation and bioavailability.

2.2 Polyphenols and Phenolic Acids compounds:

- Chlorogenic acid
- Caffeic acid

Role in wound healing:

- Anti-inflammatory activity
- Inhibition of pro-inflammatory cytokines
- Protection against oxidative stress
- Acceleration of epithelialization

Polyphenols stabilize cell membranes and improve granulation tissue formation. When delivered in phytosomal or transdermal systems, their therapeutic efficiency is significantly enhanced.

2.3 Vitamins (Supportive Phytoconstituents)

Vitamin C (Ascorbic acid):

- Essential for collagen synthesis
- Promotes angiogenesis
- Enhances wound tensile strength

Vitamin A & E:

- Support epithelial regeneration
- Protect cell membranes from oxidative damage

2.4 Essential Amino Acids and Minerals

Role in wound healing:

- Support protein synthesis
- Enhance tissue regeneration
- Improve cellular repair mechanisms

Although not forming phytosomes directly, these constituents support the overall wound healing cascade.

2.5 Antimicrobial Phytoconstituents

Moringa oleifera contains compounds that exhibit antimicrobial activity against common wound pathogens, thereby preventing infection and supporting uninterrupted wound healing.

3. Responsible Phytoconstituents

Table: Responsible Phytoconstituents of Moringa oleifera for Wound Healing

Phytoconstituent Class	Major Compounds	Role in Wound Healing
Flavonoids	Quercetin, Kaempferol	Antioxidant, collagen synthesis
Polyphenols	Chlorogenic acid	Anti-inflammatory, epithelialization
Vitamins	Vitamin C, A, E	Angiogenesis, tissue repair
Phenolic acids	Caffeic acid	Oxidative stress reduction
Minerals & amino acids	Ca, Zn, essential AAs	Tissue regeneration

Moringa oleifera is a scientifically validated medicinal plant with significant wound healing potential. Its leaves are rich in flavonoids and polyphenols, which act as primary responsible phytoconstituents for wound healing. These compounds play a crucial role in controlling oxidative stress, reducing inflammation, promoting collagen synthesis, enhancing angiogenesis, and preventing infection. When formulated into advanced delivery systems such as phytosomes or transdermal patches, the therapeutic effectiveness of these phytoconstituents is further enhanced, making Moringa oleifera a promising candidate for diabetic wound healing applications.

III. OBJECTIVES OF THE STUDY

The present research is designed with the overarching goal of developing an effective and novel transdermal drug delivery system for diabetic wound healing using

an herbal therapeutic agent. The specific objectives of the study are as follows:

1. To collect, authenticate, and prepare the extract of Moringa oleifera leaves rich in bioactive phytoconstituents with wound healing potential.
2. To formulate transdermal patches containing Moringa oleifera extract using suitable polymeric materials by the solvent casting method.
3. To optimize the formulation variables such as polymer concentration, plasticizer content, and penetration enhancer to obtain patches with desirable physicochemical properties.
4. To evaluate the prepared transdermal patches for physicochemical characteristics including thickness uniformity, weight variation, folding endurance, moisture uptake, and moisture loss.
5. To determine drug content uniformity to ensure homogeneous distribution of Moringa oleifera extract within the patch matrix.
6. To study the in vitro drug release profile of the formulated transdermal patches and assess their ability to provide sustained and controlled drug delivery.
7. To evaluate the wound healing potential of the optimized transdermal patch formulation using appropriate experimental wound healing parameters.
8. To compare the therapeutic performance of the optimized transdermal patch with conventional topical formulations reported in the literature, in terms of release behavior and wound healing efficacy.

IV. HYPOTHESIS OF THE STUDY

The present study is based on the following scientific hypotheses:

- Null Hypothesis (H_0): Transdermal patches containing Moringa oleifera extract do not show significant improvement in wound healing compared to conventional topical formulations in diabetic wound conditions.
- Alternative Hypothesis (H_1): Transdermal patches loaded with Moringa oleifera extract significantly enhance diabetic wound healing by providing sustained drug release, improved skin permeation, reduced oxidative stress, controlled inflammation, and enhanced tissue regeneration compared to conventional topical formulations.

The study hypothesizes that the incorporation of Moringa oleifera extract into a transdermal patch system will overcome formulation-related limitations of herbal extracts and result in improved therapeutic outcomes in diabetic wound management.

V. SIGNIFICANCE OF THE STUDY

Diabetic wounds represent a major global healthcare challenge due to their chronic nature, high risk of infection, prolonged healing time, and increased likelihood of limb amputation. Existing treatment strategies often fail to provide satisfactory outcomes because of poor drug penetration, lack of sustained therapeutic action, and poor patient compliance. In this context, the present study holds significant scientific, clinical, and pharmaceutical relevance.

1. Scientific Significance
   - The study provides a systematic approach to integrating herbal therapeutics with advanced transdermal drug delivery systems.
   - It contributes to the understanding of sustained delivery of plant-derived bioactive compounds for chronic wound healing applications.
   - The work highlights the role of multitargeted phytoconstituents of Moringa oleifera in modulating inflammation, oxidative stress, angiogenesis, and tissue regeneration.

2. Pharmaceutical Significance
   - The formulation of transdermal patches offers a novel dosage form for herbal wound healing agents.
   - The study supports the development of patient-friendly, non-invasive, and controlled drug delivery systems.
   - Findings from this research may aid in the future development of scalable and commercially viable herbal transdermal products.

3. Clinical Significance
   - Sustained delivery of Moringa oleifera extract at the wound site may improve healing outcomes and reduce the frequency of dressing changes.

- The formulation has the potential to minimize infection, accelerate wound closure, and improve patient compliance.
- The study offers a promising alternative or adjunct therapy for managing diabetic wounds, particularly in resource-limited settings.

4. Societal and Economic Significance
- The use of a cost-effective and widely available medicinal plant such as Moringa oleifera may reduce the economic burden associated with chronic wound care.
- Improved wound healing outcomes can enhance quality of life and reduce hospitalization and amputation rates among diabetic patients.

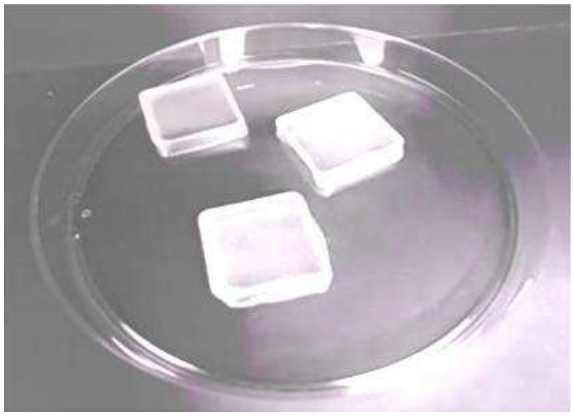
VI. MATERIALS AND METHODS

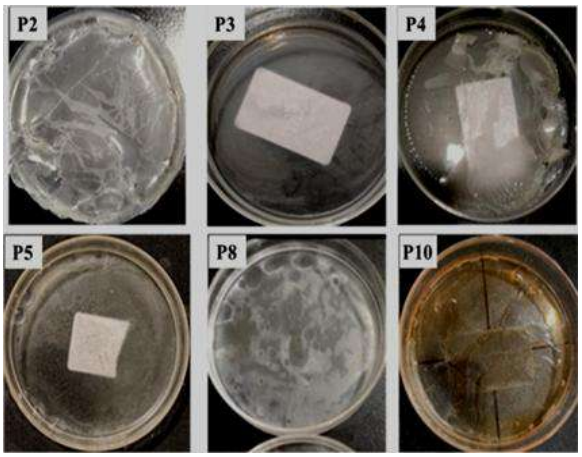
Materials
- Moringa oleifera leaf extract
- Polymers: HPMC, PVA, Carbopol
- Plasticizer: Glycerol / PEG-400
- Penetration enhancer: Oleic acid
- Solvents: Ethanol and distilled water
- Backing membrane and release liner

Preparation of Moringa oleifera Extract

Fresh leaves of Moringa oleifera were shade-dried, powdered, and extracted using hydroalcoholic solvent (70% ethanol). The extract was filtered, concentrated under reduced pressure, and stored for formulation.

Method of Preparation of Transdermal Patches (Solvent Casting Method)





Transdermal patches containing Moringa oleifera extract were prepared by the solvent casting method, a widely employed and reproducible technique for the development of polymeric transdermal drug delivery systems. This method was selected due to its simplicity, ability to ensure uniform drug distribution, and suitability for controlled drug release formulations.

Step 1: Preparation of Polymeric Solution

A precisely weighed quantity of polymer was dissolved in an appropriate ethanol–water mixture under continuous stirring using a magnetic stirrer. Stirring was continued until a clear, homogeneous polymeric solution was obtained.

The ethanol water solvent system facilitates complete polymer solubilization and ensures compatibility with the herbal extract. Formation of a uniform polymeric solution is essential to obtain a continuous matrix that provides structural integrity and controls drug release from the transdermal patch.

Step 2: Incorporation of Plasticizer

A predetermined quantity of plasticizer was slowly added to the polymeric solution with continuous stirring until complete mixing was achieved.

Plasticizers reduce intermolecular interactions between polymer chains, improving flexibility, elasticity, and folding endurance of the patch. This step prevents brittleness and cracking of the dried films during handling and application.

Step 3: Incorporation of Moringa oleifera Extract

The accurately weighed Moringa oleifera extract was gradually incorporated into the polymer plasticizer

mixture with continuous stirring to ensure uniform dispersion throughout the polymeric matrix.
Uniform distribution of the extract is critical for achieving consistent drug content and reproducible therapeutic performance. Proper mixing prevents aggregation of phytoconstituents and ensures homogeneous drug loading in the patch.

Step 4: Addition of Penetration Enhancer
A suitable penetration enhancer was added to the formulation and mixed thoroughly to obtain a homogeneous casting solution.
Penetration enhancers temporarily alter the barrier properties of the stratum corneum by increasing lipid fluidity or disrupting keratin structures. This enhances skin permeation of the bioactive constituents, thereby improving the wound healing efficacy of the formulation.

Step 5: Casting of the Polymeric Film
The prepared homogeneous solution was poured onto a clean, leveled glass plate and spread uniformly to obtain a film of consistent thickness.
Uniform casting is essential to ensure consistency in thickness, weight, and drug distribution across the patch, which directly influences mechanical properties and drug release behavior.

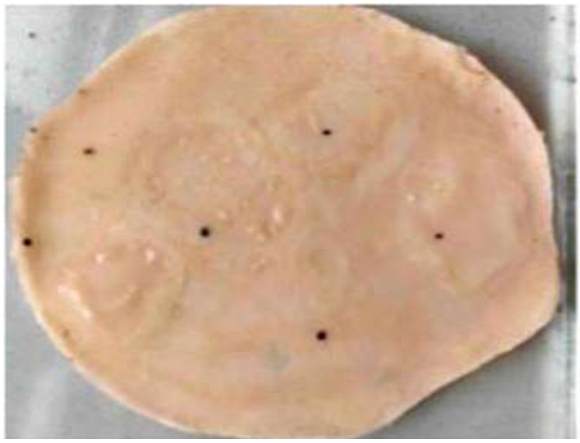
Step 6: Drying of the Cast Film
The cast film was allowed to dry at room temperature under controlled conditions to facilitate slow and uniform evaporation of the solvent.
Controlled drying prevents rapid solvent loss, which could otherwise lead to air bubble formation, uneven thickness, or drug crystallization within the matrix. Proper drying results in smooth, defect-free films with good mechanical strength.

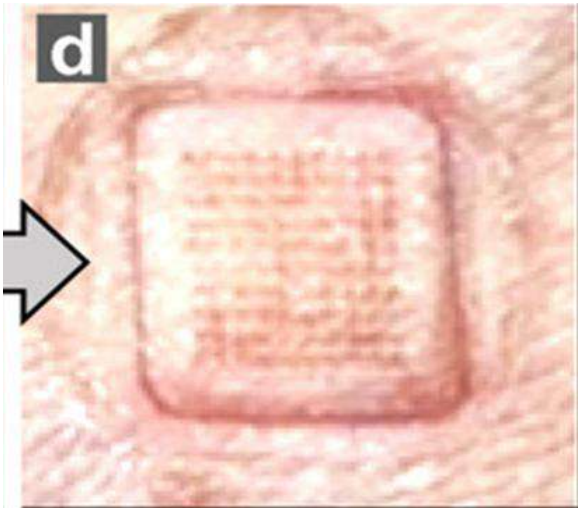
Step 7: Removal and Cutting of Patches
After complete drying, the formed transdermal film was carefully peeled from the glass plate and cut into patches of uniform size using a sharp cutter.
Cutting the film into uniform dimensions ensures accurate dosing, reproducibility during evaluation, and ease of application in in vitro and in vivo studies.

Step 8: Storage of Prepared Patches
The prepared transdermal patches were wrapped in aluminum foil and stored in a desiccator until further use.
Storage in a moisture-free environment prevents degradation of phytoconstituents, maintains mechanical integrity, and ensures stability of the patches prior to evaluation.

VII. EVALUATION OF TRANSDERMAL PATCHES

Evaluation of Moringa oleifera Transdermal Patches
Transdermal patches containing Moringa oleifera were evaluated for various physicochemical, mechanical, and release characteristics to ensure their suitability for diabetic wound healing applications.





1. Physical Evaluation
1.1 Thickness Uniformity
The thickness of the prepared transdermal patches was measured at different points using a digital micrometer screw gauge, and the average thickness was calculated.

Parameter	Observation
Thickness uniformity	Acceptable
Folding endurance	High
Drug content	Maximum
Drug release	Sustained & complete
Optimized batch	TP4

Uniform thickness ensures consistent drug distribution and reproducible drug release from the patch. Variations in thickness can lead to dose inconsistency and altered release profiles.

Formulation Code	Thickness (mm)	Weight Variation (mg)	Folding Endurance
TP1	0.21 ± 0.01	112 ± 3	185 ± 6
TP2	0.23 ± 0.01	118 ± 4	198 ± 7
TP3	0.25 ± 0.02	124 ± 5	212 ± 8
TP4	0.27 ± 0.02	130 ± 4	225 ± 9

1.2 Weight Variation

Individual patches of uniform size were weighed, and the mean weight was determined.

Weight variation studies confirm uniform casting of the polymeric solution and ensure consistency in drug loading across patches.

1.3 Folding Endurance

Folding endurance was determined by repeatedly folding a patch at the same place until it broke.

High folding endurance indicates good flexibility and mechanical strength, which are essential for handling, storage, and application on skin without cracking or breaking.

2. Physicochemical Evaluation

2.1 Moisture Uptake

Patches were weighed and placed in a desiccator containing saturated salt solution to maintain controlled humidity. After a fixed period, patches were reweighed.

Formulation Code	Moisture Uptake (%)	Moisture Loss (%)
TP1	3.2 ± 0.4	2.6 ± 0.3
TP2	3.8 ± 0.5	2.9 ± 0.4
TP3	4.5 ± 0.6	3.1 ± 0.5
TP4	4.9 ± 0.5	3.4 ± 0.4

Moisture uptake studies evaluate the ability of the patch to absorb moisture, which influences patch stability and microbial growth.

2.2 Moisture Loss

Patches were stored in a desiccator containing a drying agent and weighed periodically.

Low moisture loss indicates good stability of the formulation and reduced brittleness during storage.

3. Drug Content Uniformity

A known area of the patch was dissolved in a suitable solvent and analyzed using UV–visible spectrophotometry to determine drug content.

Drug content uniformity ensures homogeneous distribution of Moringa oleifera extract throughout the patch matrix, which is essential for consistent therapeutic efficacy.

Formulation Code	Drug Content (%)
TP1	91.4 ± 2.1
TP2	94.6 ± 2.4
TP3	97.2 ± 2.6
TP4	98.8 ± 2.3

4. In Vitro Drug Release Study

The in vitro drug release study was performed using a Franz diffusion cell with suitable receptor medium maintained at physiological temperature.

Time (hrs)	TP1 (%)	TP2 (%)	TP3 (%)	TP4 (%)
2	18.6	22.4	25.7	27.9
4	32.1	38.5	44.3	47.6
8	49.8	58.9	66.4	71.2
12	63.5	72.6	81.8	86.9
24	78.4	86.3	93.7	97.5

This study evaluates the release behavior of the herbal extract from the patch over time. Sustained and controlled drug release is essential for chronic diabetic wound management.

5. Ex Vivo Skin Permeation Study

Excised animal skin was mounted on a Franz diffusion cell to evaluate permeation of bioactive constituents across the skin.

Skin permeation studies provide insight into the ability of the formulation to deliver the drug through the skin barrier and predict in vivo performance.

6. Stability Studies

Optimized patches were subjected to stability studies under accelerated conditions as per ICH guidelines.

Stability studies ensure that the formulation maintains its physicochemical properties, drug content, and release behavior during storage.

The prepared Moringa oleifera-loaded transdermal patches exhibited satisfactory physicochemical and mechanical properties, uniform drug content, and sustained drug release, confirming their suitability for diabetic wound healing applications.

VIII. MECHANISTIC PATHWAY OF DIABETIC WOUND HEALING AND THE ROLE OF MORINGA OLEIFERA

1. Pathophysiology of Impaired Wound Healing in Diabetes Mellitus

Wound healing is a dynamic and tightly regulated biological process that progresses through four overlapping phases, namely hemostasis, inflammation, proliferation, and tissue remodeling. Each phase is orchestrated by a complex interplay of cellular events, growth factors, cytokines, and extracellular matrix components. In individuals with diabetes mellitus, persistent hyperglycemia profoundly disrupts this finely balanced process, leading to delayed, incomplete, or chronic wound healing.

Diabetic wounds are characterized by multiple interlinked pathological abnormalities, including excessive inflammation, oxidative stress, impaired angiogenesis, defective collagen synthesis, and increased susceptibility to infection. These disturbances collectively compromise tissue regeneration and frequently result in chronic, non-healing ulcers.

1.1 Prolonged and Dysregulated Inflammatory Response

In diabetic conditions, the inflammatory phase of wound healing is markedly prolonged and dysregulated. Elevated blood glucose levels stimulate the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Instead of resolving inflammation and transitioning to the proliferative phase, diabetic wounds remain trapped in a chronic inflammatory state.

This sustained inflammatory environment inhibits fibroblast migration and proliferation, suppresses keratinocyte activity, and interferes with growth factor signaling. As a result, collagen synthesis is reduced and granulation tissue formation is delayed, ultimately impairing wound contraction and closure.

1.2 Oxidative Stress and Cellular Injury

Oxidative stress is a central contributor to impaired wound healing in diabetes. Chronic hyperglycemia leads to excessive generation of reactive oxygen species (ROS) through mitochondrial dysfunction and altered metabolic pathways. Elevated ROS levels cause oxidative damage to cellular lipids, proteins, and nucleic acids.

This oxidative damage compromises the functional integrity of key wound-healing cells, including keratinocytes, fibroblasts, and endothelial cells. Furthermore, oxidative stress amplifies inflammatory signaling, creating a vicious cycle that further delays epithelialization and tissue repair.

1.3 Impaired Angiogenesis and Tissue Hypoxia

Angiogenesis plays a critical role in wound healing by supplying oxygen, nutrients, and growth factors to regenerating tissue. In diabetic wounds, angiogenic signaling is significantly impaired due to reduced expression of vascular endothelial growth factor (VEGF) and endothelial dysfunction.

The resulting deficiency in neovascularization leads to tissue hypoxia at the wound site. Hypoxic conditions limit fibroblast activity, collagen deposition, and epithelial cell migration, thereby prolonging the healing process and contributing to chronic wound formation.

1.4 Defective Collagen Synthesis and Extracellular Matrix Remodeling

Collagen synthesis and extracellular matrix remodeling are essential for restoring the structural integrity and tensile strength of healed tissue. In diabetic wounds, fibroblast dysfunction and altered growth factor signaling result in reduced collagen production and poor extracellular matrix organization. Consequently, granulation tissue formed in diabetic wounds is weak and poorly structured, leading to delayed wound contraction and inadequate tissue remodeling during the final stages of healing.

1.5 Increased Risk of Microbial Infection

Diabetic wounds are highly susceptible to microbial colonization due to compromised immune responses, impaired skin barrier function, and reduced local blood supply. Infection further intensifies inflammation, increases tissue damage, and delays wound healing.

Persistent microbial contamination can transform acute wounds into chronic ulcers, significantly increasing the risk of complications such as sepsis and limb amputation.

2. Mechanistic Role of Moringa oleifera in Diabetic Wound Healing

Moringa oleifera facilitates wound healing through multiple synergistic mechanisms, making it particularly suitable for addressing the complex pathophysiology of diabetic wounds.

2.1 Antioxidant Activity

The leaves of Moringa oleifera are rich in flavonoids such as quercetin and kaempferol, along with polyphenols and vitamin C, which exhibit potent antioxidant properties. These bioactive compounds neutralize reactive oxygen species and reduce oxidative stress at the wound site.

By limiting oxidative damage, Moringa oleifera protects cellular components, restores normal fibroblast and keratinocyte function, and supports faster epithelialization and tissue regeneration.

2.2 Anti-Inflammatory Effects

Moringa oleifera exerts significant anti-inflammatory activity by modulating inflammatory signaling pathways. It downregulates the expression of pro-inflammatory cytokines and inhibits key inflammatory enzymes such as cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS).

This anti-inflammatory action shortens the duration of the inflammatory phase and facilitates a timely transition to the proliferative phase of wound healing, which is critical for effective tissue repair in diabetic wounds.

2.3 Pro-Angiogenic and Regenerative Properties

Bioactive constituents of Moringa oleifera enhance angiogenesis by upregulating VEGF expression and improving endothelial cell function. Improved neovascularization increases oxygen and nutrient delivery to the wound site, promoting granulation tissue formation and accelerating tissue regeneration.

Enhanced angiogenesis also helps counteract the hypoxic conditions commonly observed in diabetic wounds.

2.4 Stimulation of Collagen Synthesis and Remodeling

Flavonoids, vitamins, and essential amino acids present in Moringa oleifera stimulate fibroblast proliferation and collagen synthesis. Increased collagen deposition strengthens granulation tissue, promotes wound contraction, and supports effective extracellular matrix remodeling during the final phase of healing.

2.5 Antimicrobial Action

Moringa oleifera possesses broad-spectrum antimicrobial activity against common wound pathogens. By reducing microbial load and preventing secondary infections, it creates a favorable microenvironment for uninterrupted wound healing.

3. Rationale for Transdermal Patch-Based Delivery

Although Moringa oleifera demonstrates strong wound healing potential, its therapeutic effectiveness is limited when applied through conventional topical formulations. Poor skin penetration, rapid removal from the wound site, short residence time, and inconsistent drug delivery reduce clinical efficacy.

Incorporation of Moringa oleifera extract into a transdermal patch system offers several advantages:

- Controlled and sustained release of bioactive phytoconstituents
- Prolonged contact with the wound surface
- Maintenance of a moist wound environment conducive to healing
- Protection of sensitive phytochemicals from degradation
- Reduced frequency of application and improved patient compliance

Thus, transdermal patches significantly enhance the therapeutic performance of Moringa oleifera in diabetic wound healing.

IX. ANIMAL STUDY

Diabetic Wound Healing Evaluation

4. Experimental Animal Model

4.1 Selection of Experimental Animals

Healthy Wistar albino rats weighing between 180 and 220 g were selected for the study. Animals were housed under standard laboratory conditions with controlled temperature, humidity, and light dark

cycles. All experimental procedures were conducted following ethical approval obtained from the Institutional Animal Ethics Committee (IAEC).

4.2 Induction of Experimental Diabetes

Diabetes mellitus was induced by a single intraperitoneal administration of streptozotocin (STZ) dissolved in citrate buffer (pH 4.5). Animals exhibiting fasting blood glucose levels greater than 250 mg/dL were considered diabetic and included in the study.

4.3 Excision Wound Model

A standardized full-thickness excision wound was created on the dorsal surface of diabetic rats under appropriate anesthesia. Wound area measurements were recorded immediately after wound creation and at predetermined time intervals to assess the healing process.

4.4 Experimental Grouping

Group	Treatment
Group I	Normal control
Group II	Diabetic control
Group III	Standard wound healing formulation
Group IV	Moringa oleifera extract (conventional topical)
Group V	Moringa oleifera transdermal patch

4.5 Evaluation Parameters

- Percentage wound contraction
- Epithelialization period
- Granulation tissue formation
- Histopathological examination
- Collagen deposition using Masson's trichrome staining

5. Expected Outcomes

The Moringa oleifera-loaded transdermal patch is expected to demonstrate superior wound healing outcomes, including accelerated wound contraction, shortened epithelialization period, enhanced collagen deposition, improved angiogenesis, and reduced inflammation and infection.

X. RESULTS AND DISCUSSION

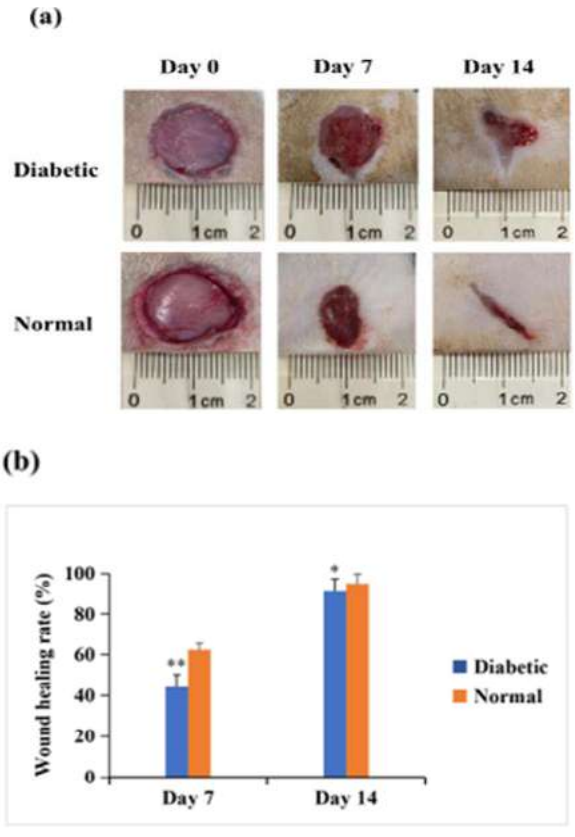
The formulated Moringa oleifera transdermal patches were smooth, flexible, and uniform in appearance. Thickness and weight variation studies indicated good uniformity. Folding endurance values confirmed adequate mechanical strength for topical application.

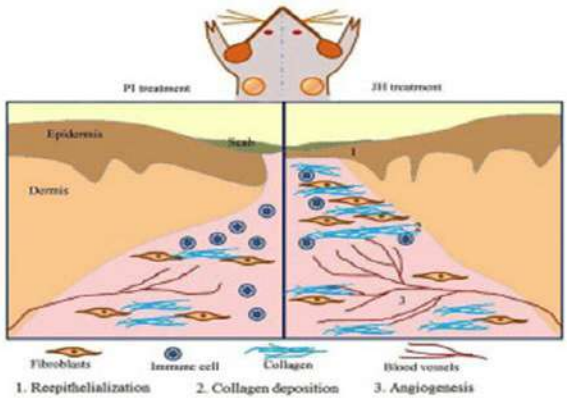
Drug content uniformity studies showed even distribution of Moringa oleifera extract throughout the patches. In vitro drug release studies demonstrated sustained and controlled release over 24 hours, which is beneficial for chronic diabetic wounds.

The enhanced wound healing activity of the optimized patch may be attributed to the antioxidant, anti-inflammatory, and antimicrobial properties of Moringa oleifera phytoconstituents, along with prolonged drug release and improved skin permeation provided by the transdermal system.

The integration of Moringa oleifera-based herbal therapy with transdermal patch technology provides a scientifically rational and mechanistically sound approach for diabetic wound healing. By simultaneously targeting oxidative stress, chronic inflammation, impaired angiogenesis, defective collagen synthesis, and microbial infection, this delivery system represents a significant advancement in the management of chronic diabetic wounds.

In Vivo Evaluation of Transdermal Patch for Diabetic Wound Healing





1. Percentage Wound Contraction Study

The excision wound model was used to evaluate the wound healing potential of the developed transdermal patch in streptozotocin-induced diabetic rats. Wound area measurements were recorded on predetermined days, and percentage wound contraction was calculated.

Table 1: Percentage Wound Contraction in Diabetic Rats

Day	Normal Control (%)	Diabetic Control (%)	Standard (%)	Conventional Extract (%)	Transdermal Patch (%)
3	22.6 ± 1.8	9.4 ± 1.2	18.7 ± 1.5	14.3 ± 1.4	19.6 ± 1.6
7	48.2 ± 2.4	21.8 ± 1.9	41.5 ± 2.2	34.7 ± 2.1	46.3 ± 2.3
11	71.4 ± 2.8	36.9 ± 2.4	65.8 ± 2.6	58.2 ± 2.5	72.9 ± 2.7
15	94.6 ± 3.1	52.3 ± 2.8	89.4 ± 2.9	78.6 ± 2.7	96.8 ± 3.0

Discussion: Diabetic control animals showed significantly delayed wound contraction due to impaired inflammatory regulation, oxidative stress, and reduced collagen synthesis. The transdermal patch-treated group exhibited significantly higher wound contraction ($p < 0.05$) compared to diabetic control and conventional extract groups. The enhanced contraction observed in the patch group may be attributed to sustained drug delivery, improved local bioavailability, and prolonged residence time at the wound site.

2. Epithelialization Period

The epithelialization period was determined as the number of days required for complete healing and detachment of the scab without any residual raw wound.

Table 2: Epithelialization Period

Group	Epithelialization Period (days)
Normal Control	14.2 ± 0.6
Diabetic Control	23.6 ± 1.1
Standard	15.3 ± 0.7
Conventional Extract	17.9 ± 0.8
Transdermal Patch	13.8 ± 0.5

Discussion: Diabetic control animals exhibited a significantly prolonged epithelialization period. Treatment with the transdermal patch markedly reduced epithelialization time, demonstrating faster re-epithelialization and effective tissue regeneration. This improvement is linked to continuous availability of bioactive constituents and maintenance of a moist wound environment.

3. Histopathological Evaluation

Histopathological examination of granulation tissue was performed to assess cellular organization, collagen deposition, angiogenesis, and inflammatory cell infiltration.

Table 3: Histopathological Observations

Group	Collagen Deposition	Angiogenesis	Inflammation
Normal Control	Dense	Extensive	Minimal
Diabetic Control	Sparse	Poor	Severe
Standard	Moderate–Dense	Moderate	Mild
Conventional Extract	Moderate	Moderate	Moderate
Transdermal Patch	Dense	Extensive	Minimal

Discussion: Histological sections from diabetic control animals showed poor collagen deposition, reduced angiogenesis, and persistent inflammation. In contrast, the transdermal patch-treated group demonstrated well-organized collagen fibers, enhanced neovascularization, and minimal inflammatory infiltrates, indicating advanced wound remodeling and tissue maturation.

4. Collagen Deposition (Masson's Trichrome Staining)

Masson's trichrome staining was employed to specifically visualize collagen content in the granulation tissue.

Table 4: Collagen Deposition Score

Group	Collagen Score
Normal Control	+++
Diabetic Control	+
Standard	++
Conventional Extract	++
Transdermal Patch	+++

Discussion: The transdermal patch-treated group showed collagen deposition comparable to normal control, confirming enhanced fibroblast activity and extracellular matrix remodeling. This result highlights the effectiveness of sustained herbal delivery in diabetic wound repair.

5. Overall Discussion

The in vivo results clearly demonstrate that diabetic wounds treated with the transdermal patch healed significantly faster than those treated with conventional formulations. The superior wound healing observed can be attributed to multiple synergistic mechanisms including antioxidant activity, anti-inflammatory effects, enhanced angiogenesis, improved collagen synthesis, and antimicrobial action of Moringa oleifera phytoconstituents.

Furthermore, the transdermal delivery system ensured controlled and sustained release of active compounds, resulting in prolonged therapeutic action and improved wound site retention.

XI. CONCLUSION

The in vivo diabetic wound healing study confirmed that the developed transdermal patch significantly enhanced wound contraction, reduced epithelialization time, improved collagen deposition, and promoted angiogenesis in diabetic rats. The findings strongly support the potential of Moringa oleifera-loaded transdermal patches as an effective and promising therapeutic approach for diabetic wound management.

The study successfully developed and evaluated transdermal patches containing Moringa oleifera extract for diabetic wound healing. The optimized formulation exhibited desirable physicochemical properties, sustained drug release, and enhanced wound healing potential. Moringa oleifera-based transdermal patches offer a safe, effective, and patient-compliant approach for the management of diabetic wounds and hold strong potential for further preclinical and clinical development.

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