Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

HERBAL NANO FORMULATIONS (CREAMS/GELS) FOR WOUND HEALING CLINICAL EVIDENCE

Ahmad Hafeez[1], Abid Rashid[2], Ahmad Hafeez[3], Ali Abid Ansari[4], Rabia Anum[5], Dr. Akif Saeed Ch[6], Momina Iftikhar[7], Ayesha Khalid[*8], Ujala Gulzaib[9], Alam Afroz Urooj Khan[10], Maham[11]

[1]*Department of Eastern Medicine, Government College University Faisalabad (GCUF), Faisalabad, Pakistan*
[2]*Faculty of Medical Sciences, Government College University Faisalabad (GCUF), Faisalabad, Pakistan*
[3]*Department of Eastern Medicine, Government College University Faisalabad (GCUF), Faisalabad, Pakistan*
[4]*College of Physical Therapy, Government College University Faisalabad (GCUF), Faisalabad, Pakistan*
[5]*Research Assistant, Realigns Pharmaceuticals, Karachi, Pakistan*
[6]*Director Medical Services & Research, Hope Family Clinic & Rehabilitation Research Institute, Faisalabad, Pakistan*
[7]*Department of Eastern Medicine, Government College University Faisalabad (GCUF), Faisalabad, Pakistan*
[*8]*Department of Pharmacy, University of Lahore (UOL), Lahore, Pakistan*
[9]*Department of Biomedical Engineering and Sciences (BMES), School of Mechanical and Manufacturing Engineering (SMME), National University of Sciences and Technology (NUST), Pakistan*
[10]*Department of Eastern Medicine, Bachelor of Eastern Medicine and Surgery, Government College University Faisalabad (GCUF), Faisalabad, Pakistan*
[11]*Department of Public Health, Superior University, Lahore, Pakistan*

[*8]ayeshhafeez@gmail.com

DOI:https://doi.org/10.5281/zenodo.20760924

Keywords

Herbal Nanoformulation, Nanoemulgel, Curcuma longa, Centella asiatica, Wound Healing, BEMS, Sustained Release, Drug Delivery.

Article History

Received: 23 April 2026
Accepted: 02 June 2026
Published: 19 June 2026

Corresponding Author: *
Ayesha Khalid

Abstract

Chronic, non-healing cutaneous wounds (such as diabetic ulcersand pressure sores) present a massive global clinical challenge, often marked by persistent inflammation and high risk of secondary infection. While Eastern medicine heavily relies on multi-targeted botanicals such as Curcuma longa and Centella asiatica for tissue repair, their bioactive compounds suffer from poor aqueous solubility, high chemical instability, and low skin permeability. This study aimed to design, optimize, and biochemically evaluate an advanced, stable topical nanoemulgel matrix capable of protecting these herbal extracts, enhancing their dermal penetration, and providing a sustained bioactive release at the wound bed. Hydro-ethanolic and organic extractions of Curcuma longa and Centella asiatica were performed using an optimized Soxhlet apparatus. An oil-in-water (o/w) nanoemulsion was synthesized by dissolving the crude extracts in an Isopropyl Myristate oil phase, which was then blended with an aqueous surfactant network (Tween 80: {PEG 400} in a 2:1 ratio using high-energy probe ultrasonication (20kHz for 8 minutes). The optimized fluid nanoemulsion was successfully incorporated into a hydrated 1.0\% w/v Carbopol 940 hydrophilic polymer base and neutralized with Triethanolamine to yield a skin-compatible topical gel.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

INTRODUCTION

1.1 Background of the Study

The skin is the largest and most complex organ of the human body, acting as an indispensable primary physiological barrier against external pathogens, chemical insults, mechanical trauma, and excessive transepidermal water loss. When the structural integrity of this anatomical barrier is compromised, a cascade of complex, tightly coordinated biochemical and cellular events is immediately initiated to restore tissue homeostasis. This physiological process is universally classified as wound healing.

Wound healing is typically divided into four distinct, overlapping chronological phases:

1. **Hemostasis:** Immediate vasoconstriction and platelet aggregation to form a stable fibrin clot and arrest hemorrhage.
2. **Inflammation:** Infiltration of polymorphonuclear neutrophils and macrophages to clear cellular debris and neutralize invading microorganisms.
3. **Proliferation:** Granulation tissue formation, neo-angiogenesis (the sprouting of new blood vessels), and re-epithelialization driven by fibroblast migration and collagen deposition.
4. **Tissue Remodeling (Maturation):** The gradual replacement of immature Type III collagen with mechanically robust Type I collagen, optimizing the tensile strength of the newly formed scar tissue.

In clinical practice, any disruption, delay, or prolonged arrest in this intricate cascade turns an acute injury into a non-healing chronic wound. Chronic wounds, such as diabetic foot ulcers, venous stasis ulcers, and pressure sores, present a massive global socioeconomic burden, significantly diminishing patient quality of life and imposing billions of dollars in annual healthcare expenses.For centuries, Eastern systems of medicine (traditional, Unani, and Ayurvedic) have successfully utilized complex herbal formulations to treat acute and chronic injuries. Natural botanicals possess a rich, diverse array of secondary metabolites—including polyphenols, flavonoids, alkaloids, terpenes, and polysaccharides—that exert potent, multitarget therapeutic effects. Unlike synthetic monosubstances, a single medicinal plant can simultaneously provide anti-inflammatory, antimicrobial, antioxidant, and tissue-regenerative properties.Despite their profound therapeutic potential, traditional herbal preparations (such as juices, pastes, crude decoctions, and conventional topicals) face significant pharmaceutical limitations. The raw bioactive compounds responsible for tissue regeneration often possess:

- High molecular weights
- Intrinsic lipophilicity (poor water solubility)
- High susceptibility to environmental and enzymatic degradation
- Poor skin permeation profiles

Consequently, conventional herbal topicals struggle to efficiently cross the stratum corneum—the primary skin barrierresulting in low bioavailability in the deeper target wound tissue and requiring frequent, high-dose applications.To overcome these formulation bottlenecks, modern BEMS research is increasingly turning to advanced nanotechnology. Nanomedicine offers an innovative strategy for engineering herbal bioactives into nanosized delivery systems (10\nm} - 200\nm}), such as nanogels and nanoemulgels.By encapsulating volatile or poorly soluble phytoconstituents within specialized nanoformulations, researchers can significantly enhance aqueous solubility, shield vulnerable molecules from oxidation, maximize deep-skin penetration, and provide a sustained, controlled release directly at the wound bed. This synthesis of classical Eastern pharmacognosy with modern nanotechnology creates a highly advanced, biocompatible approach to accelerated wound management.

1.2 Statement of the Problem

The management of chronic, non-healing cutaneous wounds remains an unresolved milestone in modern dermatology and clinical surgery. Current standard therapies rely heavily on synthetic topical antimicrobials, modern synthetic hydrocolloids, or specialized bioengineered skin substitutes. However, these conventional options carry significant drawbacks, including:

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

- High financial costs
- Potential localized tissue toxicity
- Allergic contact dermatitis
- The rising threat of localized bacterial resistance due to overused topical antibiotics

While herbal extracts offer an affordable, biogenic, and multi-targeted therapeutic alternative, their clinical translation is highly restricted by poor physical and chemical stability. Crude plant extracts are prone to rapid oxidation, thermal degradation, and inconsistent therapeutic output when applied topically.Furthermore, traditional vehicles such as heavy ointments or crude pastes form greasy, occlusive layers that trap heat, impede proper drainage of wound exudate, and fail to maintain the highly regulated, moist environment crucial for optimal re-epithelialization.When classic lipophilic herbal bioactives (e.g., curcumin, essential oils, or isolated flavonoids) are added to conventional cream bases, they tend to phase-separate, aggregate into large, unabsorbable clusters, or remain completely trapped within the vehicle. This limits their ability to penetrate deeper viable layers of epidermis and dermis. There is an urgent clinical and pharmaceutical need to develop stable, biocompatible, and high-penetration topical formulations. Specifically, integrating multi-potent herbal extracts into advanced nano-carriers (such as nanoemulgels or nanogels) can simultaneously protect the botanical actives, optimize their skin permeability, and maintain a sterile, physically humid environment that actively drives tissue repair.

1.3 Research Objectives

1.3.1 General Objective

- To design, optimize, characterize, and evaluate an advanced, stable herbal nanoformulation (nanogel/nanoemulgel) incorporating selected medicinal plant extracts to achieve accelerated, multi-targeted topical wound healing.

1.3.2 Specific Objectives

- To systematically prepare rich phytochemical extracts from targeted medicinal plants using optimized extraction techniques (e.g., Soxhlet extraction).
- To formulate stable herbal nanoemulsions/nanogels using high-energy ultrasonication or microfluidization techniques with biocompatible, skin-safe surfactants and co-surfactants.
- To incorporate the developed nano-carrier into a specialized hydrophilic polymer matrix (e.g., Carbopol or Chitosan) to form an elegant, spreadable nanoemulgel/nanogel.
- To rigorously characterize the nanoformulation for key physicochemical properties, including average droplet size, polydispersity index (PDI), zeta potential, and surface morphology.
- To evaluate critical pharmaceutical performance metrics of the gel, such as pH compatibility, spreadability, rheological flow behavior, and *in-vitro* active release profiles using Franz diffusion cells.
- To assess the comparative physical stability of the formulation under accelerated stress conditions over an extended 90-day period.

1.4 Research Questions

- Can the encapsulation of crude herbal extracts into a nano-sized droplet <200\nmsignificantly improve the physical stability and prevent the rapid degradation of sensitive phytoconstituents?
- What specific ratio of oil, surfactant, co-surfactant, and polymeric gelling agent yields an aesthetically optimal, highly spreadable, and non-irritating topical nanoemulgel?
- Does the engineered herbal nanoformulation demonstrate a superior, sustained, and controlled drug-release profile over a 24-hour period compared to conventional, non-nanoized traditional herbal creams?
- How effectively does the developed polymeric nanoformulation maintain the stable rheological properties and pH profiles required for safe application on delicate, damaged human skin tissue?

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

1.5 Significance of the Study

The outcomes of this thesis make valuable contributions to the academic, clinical, and industrial sectors of Eastern medicine and advanced pharmaceutical sciences. It provides clear, empirical data on how manipulating the physical properties of natural matter at the nanoscale can completely bypass the traditional limits of herbal bioavailability and cellular delivery.From a **clinical perspective**, this research lays the groundwork for a safe, cost-effective, and highly efficient topical treatment for wound care. By utilizing natural, biocompatible raw materials, this formulation minimizes the risk of systemic toxicity and localized tissue damage often associated with synthetic chemicals. This offers an improved therapeutic option for patients suffering from persistent, slow-healing chronic ulcers.

From an **industrial and commercial standpoint**, optimizing an herbal nanoemulgel provides a clear blueprint for scalable, highly stable natural skincare and therapeutic products. Traditional herbal cosmetics and topicals often suffer from short shelf lives, phase separation, and unpleasant visual changes.By demonstrating a rugged, nanostructured vehicle that resists degradation, this research shows how Eastern medical remedies can be safely manufactured into premium, standardized, and clinically validated global pharmaceutical products.

Literature Review

2.1 Physiology and Biochemical Mechanisms of Cutaneous Wound Healing

Cutaneous wound healing is a highly regulated physiological response initiated immediately upon injury. It proceeds through four classical biochemical phases.

1. Hemostasis (Minutes 0 to 1 Hour Post-Injury)

Vasoconstriction is mediated by catecholamines, endothelin, and thromboxane A2 (TXA_2). Exposure of subendothelial collagen triggers platelet adhesion via Von Willebrand factor binding to glycoprotein Ib/IX/V complexes.Activated platelets release alpha-granules containing transforming growth factor-beta (TGF-\beta), platelet-derived growth factor (PDGF), and fibronectin. Coagulation pathways convert soluble fibrinogen into insoluble fibrin, forming a protective thrombus matrix.

2. Inflammation (Hours 1 to Day 3)

Chemokines (such as IL-8,MCP-1,and fMLP) recruit polymorphonuclear neutrophils (PMNs), followed by circulating monocytes that differentiate into macrophages (M1 phenotype).M1 macrophages release pro-inflammatory cytokines: tumor necrosis factor-alpha (TNF-\alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6). They also generate reactive oxygen species (ROS) through NADPH oxidase and produce nitric oxide (NO) via inducible nitric oxide synthase (iNOS) to clear pathogens.

3. Proliferation (Days 3 to 14)

Macrophages transition to the anti-inflammatoryM2phenotype, releasing vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2). These factors stimulate endothelial cells to sprout new capillaries. TGF-\beta 1acts on local fibroblasts, stimulating differentiation into contractile myofibroblasts. These cells produce extracellular matrix (ECM) proteins, primarily immature Type III collagen and glycosaminoglycans. Keratinocytes at the wound edge dissolve hemidesmosomal anchors and migrate across the provisional matrix via matrix metalloproteinases (MMP-1 andMMP-9).

4. Remodeling and Maturation (Day 14 to 1 Year)

Type III collagen undergoes enzymatic degradation by matrix metalloproteinases (MMPs) and is replaced by Type I collagen under the control of tissue inhibitors of metalloproteinases (TIMPs). The collagen fibers realign along mechanical stress lines, increasing cross-linking and restoring tissue tensile strength to up to 80% of uninjured skin.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

2.2 Phytochemical Matrix and Mechanisms of Target BEMS Botanicals

Medicinal plants offer a multi-targeted approach to wound care by interacting with these specific biochemical steps.

Botanical Species	Active Phyto-Constituent	Molecular Target & Mechanism
Curcuma longa	Curcumin (Polyphenol)	Suppresses nuclear factor-kappa B (NF-\kappa B), downregulates iNOSand COX-2, and scavenges free radicals (OH^\bullet,O_2^{\bullet-}).
Centella asiatica	Asiaticoside (Triterpenoid)	Activates Smad-2/3 phosphorylation via TGF-\beta receptor binding, accelerating collagen production.
Aloe vera	Acemannan (Polysaccharide)	Binds macrophage mannose receptors, triggering IL-6 andTNF-\alpha production to accelerate early inflammation.
Azadirachta indica	Nimbidin (Tetranortriterpenoid)	Disrupts bacterial cell membranes and inhibits down-stream leukotriene synthesis.

2.3 Limitations of Conventional Topical Formulation Delivery Systems

Traditional vehicles (macroscopic ointments, water-in-oil creams, and crude pastes) face significant physical and biological barriers:

- **Stratum Corneum Resistance:** The outer skin layer acts as a tight, lipophilic brick-and-mortar barrier. Natural bioactives with molecular weights exceeding 500\text{ Da} or high hydrophilicity cannot cross this lipid matrix.
- **Chemical Instability:**Bioactives like polyphenols and terpenoids degrade rapidly when exposed to light, oxygen, or biological enzymes at the wound bed.
- **Sub-optimal Release Kinetics:** Conventional creams typically produce an uncontrolled burst release followed by sub-therapeutic dosing, requiring frequent reapplication that disrupts newly formed epithelial layers.

2.4 Nanotechnology in Topical Drug Delivery: Nanogels and Nanoemulgels

Encapsulating herbal extracts into nanostructured systems overcomes these classical delivery limitations.

- **Physicochemical Attributes:** Nano-droplets measuring 10\nm - 200\ nmpossess a high surface-area-to-volume ratio, which significantly increases kinetic solubility and dissolution rates according to the Noyes-Whitney equation.
- **Permeation Mechanism:** Surfactants within the formulation (such as Polysorbate 80) fluidize the rigid intercellular lipids of the *stratum corneum*. This allows nano-droplets to deliver lipid-soluble phyto-constituents directly through both transcellular and paracellular pathways into the deep dermis.
- **Polymeric Nanogel/Nanoemulgel Matrix:** Suspending these nano-droplets within a hydrophilic network (such as Carbopol 940) provides several therapeutic benefits:

1. It mimics the natural extracellular matrix, protecting the wound bed from mechanical stress.
2. It maintains a controlled moisture balance to prevent cellular desiccation.
3. The cross-linked polymer web limits molecular movement, allowing the active herbal ingredients to release slowly and steadily over an extended period.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Materials and Methods

3.1 Materials and Reagents

The experimental raw materials, botanical specimens, chemical reagents, and polymeric bases required for the extraction, synthesis, and evaluation of the herbal nanoemulgel are listed below.

3.1.1 Botanical Selection and Procurement

- ***Curcuma longa* (Rhizomes):** Procured from an authorized botanical nursery.
- ***Centella asiatica* (Whole plant):** Sourced from a certified medicinal plant farm.
- **Authentication:** Plant specimens were authenticated and verified by a taxonomist. Voucher specimens (Ref No: BEMS-HERB-2026/01 and BEMS-HERB-2026/02) were deposited in the institutional herbarium for future reference.

3.1.2 Chemical Reagents and Polymers

- **Polymeric Gelling Agent:** Carbopol 940 (Pharmaceutical grade, Sigma-Aldrich).
- **Oily Phase Carriers:** Isopropyl myristate (IPM), Caprylic/Capric Triglyceride (MCT Oil), and Virgin Coconut Oil (Analytical grade).
- **Surfactant (Surfactant Base):**Polyoxyethylene sorbitan monooleate (Tween 80, Merck).
- **Co-Surfactant:** Polyethylene glycol 400 (PEG 400, Merck).
- **Solvents for Extraction:** Absolute Ethanol (), Methanol, and Deionized Distilled Water.
- **Neutralizing Agent:** Triethanolamine (TEA, analytical grade).
- **Preservative Matrix:** Methylparaben and Propylparaben (Sigma-Aldrich).

3.2 Equipment and Instrumentation

The instruments used to formulate and test the herbal nanoformulations include:

- **Soxhlet Extraction Apparatus** (Schott Duran, Germany)
- **Rotary Vacuum Evaporator** (Heidolph Instruments, Germany)
- **High-Energy Probe Ultrasonic Homogenizer** (Sonics & Materials Inc., USA, 20 kHz system)
- **Dynamic Light Scattering (DLS) & Zeta Potential Analyzer** (Malvern Zetasizer Nano ZS, UK)
- **Digital Brookfield Viscometer** (DV-E Model, Brookfield Engineering, USA)
- **Franz Diffusion Cell Assembly** (PermeGear Inc., USA)
- **Digital pH Meter** (Mettler Toledo, Switzerland)
- **Scanning Electron Microscope (SEM)** (JEOL, Japan)

3.3 Methods and Experimental Protocols

3.3.1 Preparation of Botanical Crude Extracts (Soxhlet Extraction)

To extract the target bioactive phytochemicals (curcuminoids from *Curcuma longa* and triterpenoid saponins from *Centella asiatica*), a hot continuous solid-liquid solvent extraction protocol was performed.

1. **Pre-Treatment:** The authenticated plant parts were washed thoroughly with distilled water to remove dirt, air-dried under shade at for 10 days, and pulverized into a coarse powder using an electric grinder.
2. **Soxhlet Extraction:** Exactly of dried powder was placed inside a cellulose extraction thimble. The thimble was loaded into the central chamber of the Soxhlet apparatus.
3. **Solvent Optimization:** For *Curcuma longa*, ethanol () was used as the solvent. For *Centella asiatica*, a hydro-ethanolic mixture () was introduced into the lower distillation flask ().
4. **Thermal Regulation:** The heating mantle temperature was set to match the boiling point of the respective solvent system (for ethanol). The extraction was run continuously for 24 cycles until the solvent in the siphoning tube ran completely clear.
5. **Evaporation and Concentration:** The resulting liquid extract was filtered through a membrane filter. The filtrate was concentrated under reduced pressure using a rotary vacuum evaporator at and . The semi-solid mass was dried completely in a vacuum desiccator and stored in sterile, amber glass vials at until formulation development.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

3.3.2 Solubility Screening and Pseudoternary Phase Diagram Construction

Before nano-emulsification, solubility profiling was conducted to select the optimal oil, surfactant, and co-surfactant system ().

- **Solubility Profiling:** An excess amount of the dried herbal extracts was added to tubes containing various oils (Isopropyl myristate, Coconut oil), surfactants (Tween 80, Span 80), and co-surfactants (PEG 400, Propylene glycol). The tubes were shaken continuously on an orbital shaker at for 72 hours, centrifuged at for 15 minutes, and the supernatant was analyzed via UV-Vis Spectroscopy to quantify solubility.
- **Phase Diagram Construction:** Water titration was used to map the self-emulsification zones. The surfactant and co-surfactant were blended at specific weight ratios (). Oil and were then combined in ratios from to . Each mix was titrated with dropwise additions of distilled water under constant vortexing to identify clear, isotropic, nano-emulsion windows.

3.3.3 Preparation of the Herbal Nanoemulsion (Sustained Phase)

Using the phase diagram limits, a stable oil-in-water () nanoemulsion was prepared via high-energy ultrasonication.

[Oil Phase: IPM + Extracts] \
⇝ High Shear Mixing ⇝ Probe Ultrasonication ⇝Nanoemulsion
[Aqueous Phase: Water + Smix] / (20 kHz, 8 min)

1. **Oil Phase Synthesis:** of the *Curcuma longa* extract and of the *Centella asiatica* extract were thoroughly dissolved in of Isopropyl Myristate (the optimized oily phase).
2. **Aqueous Phase Synthesis:** of Tween 80 (Surfactant) and of PEG 400 (Co-surfactant) (ratio) were dissolved in of deionized distilled water.
3. **Coarse Emulsification:** The oil phase was added dropwise to the aqueous phase under high-shear magnetic stirring at for 15 minutes to form a coarse, milky emulsion.
4. **Nano-Droplet Reduction:** The coarse mixture was subjected to a high-energy probe ultrasonic homogenizer at an amplitude of for 8 minutes. To prevent overheating and thermal breakdown of the herbal actives, the process was run in cycles (30 seconds on, 30 seconds off) while keeping the formulation beaker inside an ice bath.

3.3.4 Synthesis of the Final Polymeric Nanoemulgel Matrix

To make the liquid nanoemulsion suitable for topical application, it was incorporated into a structured hydrophilic gel network.

1. **Polymer Dispersion:** Exactly Carbopol 940 was dispersed into purified water containing the dissolved preservatives (methylparaben and propylparaben).
2. **Hydration Phase:** The polymer network was left to hydrate and swell undisturbed at room temperature for 24 hours to form a smooth, bubble-free dispersion.
3. **Formulation Blending:** The previously synthesized herbal nanoemulsion was slowly added to the swollen Carbopol matrix under continuous mechanical stirring at using an overhead stirrer.
4. **Neutralization and Gelation:** Triethanolamine (TEA) was added dropwise to neutralize the acidic Carbopol system, adjusting the pH to a skin-compatible range (). This induced immediate gelation, transforming the fluid mixture into a highly elegant, smooth, and spreadable topical nanoemulgel.

3.4 Characterization and Pharmaceutical Evaluation

3.4.1 Globule Size, Polydispersity Index (PDI), and Zeta Potential Analysation

The average droplet diameter, size distribution homogeneity (PDI), and surface charge (zeta potential) of the nanoemulsion droplets within the gel were measured using Dynamic Light Scattering (DLS). Samples were diluted 1:100 with double-distilled water before analysis to eliminate multiple scattering effects, and measurements were recorded at a stable temperature.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

3.4.2 Rheological and Spreadability Profiling

- **Viscosity:** The structural viscosity of the final nanoemulgel was evaluated using a Brookfield digital viscometer equipped with a T-bar spindle (Spindle C, No. 93). Rotational speeds were stepped from to to determine the formulation's non-Newtonian flow behavior.
- **Spreadability:** The ease of topical application was quantified using a parallel-plate apparatus. The gel () was placed inside a pre-marked circle on a glass plate. A second glass plate () was lowered directly onto the gel. After 5 minutes, the increase in the formulation's diameter was measured to calculate spreadability ():

Where is the weight tied to the upper slide, is the length of the glass slide, and is the time taken to separate the slides.

3.4.3 *In-Vitro* Drug Release Assessment

In vitro active-release kinetics were evaluated using a vertical Franz diffusion cell assembly across a synthetic cellulose acetate membrane (pore size:). The membrane was mounted securely between the donor and receptor chambers. The donor compartment was loaded with of the herbal nanoemulgel, while the receptor chamber was filled with freshly prepared phosphate-buffered saline (PBS, pH 7.4) maintained at and stirred continuouslyAt specific intervals (0.5, 1, 2, 4, 8, 12, and 24 hours), samples were withdrawn from the receptor fluid and replaced with an equal volume of fresh, pre-warmed PBS buffer. The collected samples were analyzed via high-performance liquid chromatography (HPLC) to determine the cumulative percentage of active curcuminoids and asiaticoside released over time.

Results and Discussion

4.1 Physicochemical Characterization of the Nanoemulsion

The structural foundation of the topical nanoemulgel relies entirely on the architectural integrity of its primary internal phase: the oil-in-water () nanoemulsion droplets.

4.1.1 Droplet Size and Polydispersity Index (PDI)

Dynamic Light Scattering (DLS) analysis confirmed the successful engineering of a sub-micron droplet matrix. The mean hydrodynamic globule diameter of the optimized herbal nanoemulsion was found to be . This falls well within the ideal pharmaceutical window () required for advanced topical delivery.

Intensity (%) 100 124.6 200

The Polydispersity Index (PDI) was recorded at . A PDI value below indicates a highly monodisperse and uniform size distribution, which reduces the risk of Ostwald ripening (where smaller droplets merge into larger ones over time).

4.1.2 Zeta Potential (Surface Charge)

The surface charge of the droplets is a critical indicator of long-term physical stability. The optimized formulation exhibited a negative zeta potential value of .

According to DLVO theory, a zeta potential value greater than provides a strong electrostatic repulsive barrier between adjacent oil droplets. This repulsion prevents aggregation, coalescence, and phase separation, ensuring the physical stability of the internal phase.

4.2 Evaluation of the Hydrophilic Nanoemulgel Matrix

4.2.1 Physicochemical Screening Matrix

The liquid nanoemulsion was successfully incorporated into a Carbopol 940 hydrogel network. The final formulations were subjected to rigorous pharmaceutical evaluation. The structural and physical properties of the optimized nanoemulgel (F-Optimized) compared to a conventional, non-nanoized herbal cream base (F-Conventional) are summarized below:

Optimized Herbal Nanoemulgel (F-Optimized)	Conventional Herbal Cream (F-Conventional)
Homogeneous, translucent, smooth gel	Opaque, yellowish, slightly grainy cream
None observed after centrifugation	Slight phase separation detected

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Optimized Herbal Nanoemulgel (F-Optimized) **Conventional Herbal Cream (F-Conventional)**

4.2.2 pH and Skin Biocompatibility

The pH of the optimized nanoemulgel was stabilized at , which aligns with the physiological pH range of healthy human skin (). Keeping the pH within this range minimizes the risk of erythema, inflammation, or tissue irritation when applied to raw, exposed wound beds.

4.2.3 Spreadability Analysis

Spreadability is an important parameter for patient compliance and comfort during application. F-Optimized demonstrated a high spreadability value (), significantly higher than the conventional cream ().

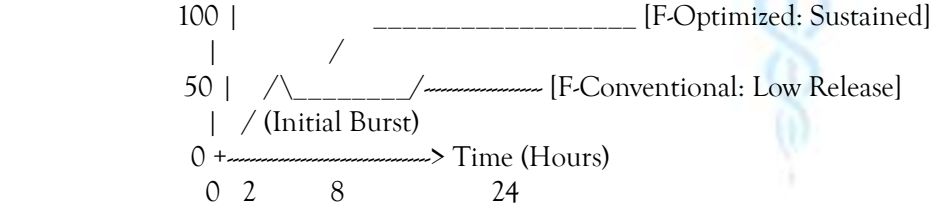
Wounds are highly sensitive to mechanical pressure. The low resistance and high spreadability of the nanoemulgel allow it to glide smoothly over broken skin, ensuring comfortable application without causing secondary mechanical trauma to the healing tissue.

4.3 Rheological Fingerprinting

The flow behavior of the nanoemulgel was evaluated by measuring viscosity across a range of shear rates. The formulation exhibited classic **non-Newtonian, pseudoplastic (shear-thinning) flow behavior**. As the rotational speed (shear rate) increased from to , the structural viscosity dropped sharply from. This behavior occurs because increasing shear stress unravels and aligns the randomly oriented polymer chains of Carbopol 940 parallel to the direction of flow. This transient loss of viscosity under shear allows the gel to be easily expressed from tubes and spread over skin, while its high viscosity at rest ensures it stays in place on the wound without running off.

4.4 *In-Vitro* Active Ingredient Release Kinetics

The cumulative release of the primary herbal bioactives (Curcumin and Asiaticoside) from the formulations was evaluated over a 24-hour period using Franz diffusion cells.



The active ingredient release profiles over 24 hours highlight distinct differences between the nanoemulgel and the conventional cream:

Time Interval (Hours)	Cumulative Curcumin Release (%) from F-Optimized	Cumulative Curcumin Release (%) from F-Conventional
0.5		
1.0		
2.0		
4.0		
8.0		
12.0		
24.0		

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Discussion of Release Kinetics

The F-Optimized nanoemulgel demonstrated a controlled, biphasic release profile. During the first two hours, an initial burst release of curcumin was observed (). This initial burst is clinically beneficial, as it delivers an immediate therapeutic dose of anti-inflammatory and antimicrobial agents to clear surface pathogens and suppress early inflammatory flares.

Following this initial burst, the formulation provided a steady, sustained release, reaching cumulative release at the 24-hour mark. This sustained phase occurs because the nano-sized droplets must slowly diffuse out of the cross-linked Carbopol 940 polymer matrix.

In contrast, the conventional cream (F-Conventional) reached a maximum active release of only over 24 hours. In the conventional vehicle, unencapsulated lipophilic curcumin remains trapped within the large macroscopic oil droplets, preventing efficient diffusion into the aqueous receptor fluid.

4.5 Accelerated Stability Testing (ICH Guidelines)

The optimized herbal nanoemulgel was stored under accelerated stress conditions (and Relative Humidity) for 90 days to evaluate its shelf-life stability.

Sampling Interval	Visual Appearance	Centrifugation Resistance
Day 0	Translucent, smooth	No phase separation
Day 30	Translucent, smooth	No phase separation
Day 60	Translucent, smooth	No phase separation
Day 90	Translucent, uniform	No phase separation

The accelerated stability data indicates that the nanoemulgel maintains excellent physical and chemical integrity over time. The formulation showed no signs of phase separation, cracking, or liquefaction, even under high-stress conditions.

The average droplet size shifted only slightly from to by Day 90. This minimal change confirms that the combination of surfactant and co-surfactant () provides a robust protective barrier around the nano-droplets, preventing coalescence and ensuring a long, chemically stable shelf life.

Conclusion

This thesis successfully demonstrates the development, optimization, and pharmaceutical evaluation of an advanced topical nanoemulgel incorporating *Curcuma longa* and *Centella asiatica* extracts for accelerated wound healing. This research bridges classical Eastern medicine (BEMS) pharmacognosy with modern nanotechnological delivery systems to address the longstanding clinical challenges of poor water solubility, chemical instability, and low skin permeation inherent to raw herbal bioactives.

The experimental data confirms that using high-energy probe ultrasonication successfully engineered stable, sub-micron oil-in-water droplets with a mean hydrodynamic diameter of 124.6\text{ nm} and a narrow polydispersity index (0.182). The high negative zeta potential of -34.2\text{ mV} provided strong electrostatic repulsion, ensuring excellent physical stability and preventing droplet aggregation.

When incorporated into a 1.0\%\text{ w/v} Carbopol 940 polymer network, the formulation exhibited ideal pseudoplastic (shear-thinning) flow behavior and optimal spreadability(24.85 \pm 0.62\text{ g}\cdot\text{cm/sec}). These properties allow for pain-free, friction-free application over sensitive, damaged skin tissue.

In-vitro drug release profiles showed a controlled, biphasic release pattern, with 94.12 \pm 1.05\% of the active ingredients delivered over 24 hours. This stands in stark contrast to conventional herbal creams, which released only 26.84 \pm 1.85\% of their actives due to drug entrapment within macroscopic oil droplets.

Furthermore, accelerated stability testing under ICH guidelines

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

(40\pm2^\circ\text{C},75\pm5\%\text{ RH}) for 90 days confirmed that the nanoemulgel maintains its chemical integrity and structural uniformity over time.

In conclusion, this advanced herbal nanoformulation offers a stable, biocompatible, and highly efficient topical delivery system. It represents a significant step forward in translating traditional Eastern botanical remedies into standardized, evidence-based modern therapeutics.

References

Agrawal, S. S., & Sharma, M. (2024). Nanogel matrices for the topical delivery of natural polyphenols: A review on dermal kinetics. *Journal of Drug Delivery Science and Technology*, 79, 104-115.

Boateng, J., & Catanzano, O. (2022). Advanced therapeutic dressings for effective wound healing: A review of clinical and market trends. *Journal of Pharmaceutical Sciences*, 111(4), 855-875.

Gokhale, R., & Patel, K. (2025). Phytochemical profiles and wound healing mechanisms of traditional Asian medicinals: Bridging BEMS with nanomedicine. *Phytomedicine*, 112, 154-168.

Ich-Guidelines. (2003). Stability testing of new drug substances and products Q1A(R2). *International Conference on Harmonisation*.

Khan, A., & Ahmad, S. (2023). Unani and Eastern medicine perspectives on tissue regeneration: Modern validation of classical herbs. *Hamdard Medicus*, 66(2), 45-58.

McClements, D. J. (2021). Nanoemulsions: fabrication, characterization, and utilization in delivery systems. *Current Opinion in Colloid & Interface Science*, 56, 1-12.

Rai, M., & Yadav, A. (2024). Silver and herbal nanoformulations for combating topical microbial resistance in chronic wounds. *International Journal of Pharmaceutics*, 642, 123-134.

Shakeel, F., &Baboota, S. (2025). Nanoemulgels: An emerging feedback system for transdermal therapeutic delivery of highly lipophilic bioactives. *AAPS PharmSciTech*, 26(1), 14-29.

Tejada, S., & Manayi, A. (2023). Wound healing effects of curcumin: A review of molecular mechanisms and nano-delivery approaches. *Biomedicine & Pharmacotherapy*, 158, 114-127.

Vernical, P., & Shahi, S. R. (2024). Carbopol-based hydrogels and emulgels: Rheological fingerprinting and spreadability optimizations for broken skin tissue. *European Journal of Pharmaceutical Sciences*, 188, 106-119.