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A COMPREHENSIVE REVIEW ON ALOE VERA LEAF GEL HYDROGEL FOR ENHANCED WOUND HEALING: FORMULATION AND EVALUATION APPROACHES

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ABSTRACT:

Aloe vera (L.) Burm. f. is a widely used medicinal plant known for its potent wound healing properties. This review highlights the formulation and evaluation of Aloe vera leaf gel–based hydrogels as advanced topical drug delivery systems. Aloe vera gel contains bioactive compounds such as polysaccharides (acemannan), glycoproteins, vitamins, enzymes, and phenolic constituents that exhibit anti-inflammatory, antimicrobial, antioxidant, and tissue-regenerative activities.

Hydrogels are three-dimensional hydrophilic polymeric networks capable of maintaining a moist wound environment, promoting cell proliferation, and enabling controlled drug release. Incorporation of Aloe vera into hydrogel systems enhances its stability, bioavailability, and therapeutic effectiveness. Various natural and synthetic polymers, including chitosan, alginate, Carbopol, and polyvinyl alcohol, are employed to optimize mechanical strength, swelling behavior, and release kinetics.

This review also outlines formulation approaches, in vitro evaluation parameters, and the mechanisms of wound healing, such as modulation of inflammation, collagen synthesis, antimicrobial action, and angiogenesis. Despite its advantages, challenges including variability in composition and limited clinical evidence remain. Overall, Aloe vera–based hydrogels show significant promise as biocompatible and effective wound healing systems.

KEYWORDS: Aloe vera; Hydrogel; Wound healing; Drug delivery; Acemannan; Biocompatibility; Controlled release; Tissue regeneration.

1. INTRODUCTION

1.1. *ALOE VERA* PLANT:

Aloe vera (L.) Burm. f., a perennial succulent belonging to the family *Asphodelaceae* (or *Liliaceae* in older classifications), has been used for thousands of years as a medicinal and cosmetic plant in traditional systems of medicine worldwide. It is native to the Arabian Peninsula but is now widely cultivated in tropical, subtropical, and arid regions, including India, due to its adaptability and low-maintenance growth. The plant is characterized by thick, fleshy, lance-shaped leaves that store a clear, viscous mucilaginous gel in the inner parenchymatous tissue, which forms the primary source of the therapeutically active material[1][2][3].

Historically, *Aloe vera* has been employed for centuries in Ayurvedic, Chinese, and Greco-Roman systems of medicine for the treatment of burns, cuts, abrasions, and chronic ulcers. Its traditional use in wound management is well supported by modern clinical and preclinical evidence, demonstrating accelerated re-epithelialization, reduced healing time, and lower infection rates in first- and second-degree burns as well as surgical wounds.

Figure 1: *Aloe vera* Plant.

Widely regarded as a "universal panacea" and the "plant of immortality," *Aloe vera* exhibits diverse pharmacological properties, particularly in skin care and wound healing. The gel contains a complex mixture of bioactive constituents, including polysaccharides (mainly acemannan), glycoproteins, vitamins, enzymes, amino acids, and various phytochemicals, which collectively contribute to its anti-inflammatory, antimicrobial, antioxidant, and tissue-regenerative activities. Furthermore, its excellent biocompatibility and biodegradability make *Aloe vera* gel is an attractive natural base for the development of hydrogel wound dressings, capable of promoting moist wound healing while minimizing infection and scarring[2][4][5][6][7][8].

Place in modern wound-healing research: Recent work has focused on *Aloe vera*–based composite or nanocomposite hydrogels that integrate synthetic or natural polymers (e.g., chitosan, alginate, carbopol) to improve swelling, adhesion, and sustained release of bioactives. These systems are being explored not only for acute wound closure but also for chronic and infected wounds, where their anti-inflammatory, antimicrobial, and pro-angiogenic effects synergize to modulate the healing cascade from inflammation through proliferation and remodeling phases[6][7][9][10][11].

1.2. HYDROGEL:

Hydrogels are hydrophilic polymer networks capable of absorbing large amounts of water, making them ideal for biomedical applications like wound dressings. In the context of *Aloe vera* leaf gel hydrogel for enhanced wound healing, they provide a moist environment that promotes tissue regeneration while delivering bioactive compounds from *Aloe vera*. Hydrogels mimic the extracellular matrix due to their high water content (often over 90%) and soft consistency, facilitating cell migration and proliferation during wound repair. They are typically formed via physical or chemical crosslinking of natural or synthetic polymers, such as polysaccharides from *Aloe vera* gel itself, which contains acemannan—a key component aiding anti-inflammatory and antimicrobial effects. Common gelling agents include Carbopol, HPMC, or sodium CMC, which ensure spreadability, pH stability (around 6-7), and controlled release[7][11][12].

1.3. *ALOE VERA* IN HYDROGELS:

Aloe vera leaf gel hydrogel is a promising topical formulation for wound healing due to its biocompatibility, moisturizing properties, and rich in bioactive compounds like polysaccharides, vitamins, enzymes and phenolics that synergistically reduce inflammation, inhibit bacterial growth, and accelerate angiogenesis and wound contraction with promoting tissue regeneration. When formulated into hydrogels, it releases actives via diffusion, swelling, or degradation mechanisms, achieving up to 29% faster healing in studies, with full wound closure in about 15 days[7][11][13][14][15].

1.4. OVERVIEW OF *ALOE VERA:*

Aloe vera is a succulent plant widely recognized for its medicinal properties, particularly in wound healing applications. Its leaf gel serves as a key component in hydrogel formulations due to its biocompatibility and bioactive compounds.

1.4.1. BOTANICAL DESCRIPTION:

Scientific name: *Aloe vera* (L.) Burm.f., also known in older literature as *Aloe barbadensis Miller*.

Family: *Asphodelaceae* (formerly placed under *Liliaceae*).

Common name: *Aloe vera*, "true aloe" or "burn plant"[2].

1.4.2. GROWTH HABIT AND MORPHOLOGY:

Growth form: Short-stemmed or nearly stemless perennial succulent, usually 0.6–1 m tall, spreading by offsets (pups) at the base.

Arrangement of leaves: Leaves are arranged in a terminal rosette, giving the plant a compact, bushy appearance.

1.4.3. LEAF STRUCTURE:

Shape and size: Leaves are thick, fleshy, triangular, and sessile, typically 30–60 cm long and 5–10 cm wide at the base, with a grey-green to green color, sometimes bearing white spots.

Margins: Leaf margins are serrated, bearing small sharp teeth or spines, which help reduce water loss and protect the plant.

Leaf layers: Each leaf is composed of three distinct layers:

- ★ Outer epidermal (protective) layer.
- ★ Middle green parenchymatous layer containing bitter sap.
- ★ Inner transparent, mucilaginous gel layer (the medicinally important part)[2][11].

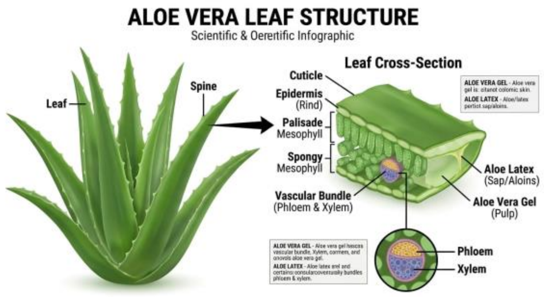

Figure 2: ***Aloe Vera*** **Leaf Structure.**

Figure 3: Internal Anatomy of ***Aloe Vera.***

1.4.4. FLOWERS AND FRUITS:

Inflorescence: Erect, racemose or spiked inflorescence bearing numerous tubular flowers. Flower color and shape: Bright yellow to pale yellow tubular flowers, about 2–3 cm long, arranged in dense spikes.

Fruit and seeds: After flowering, the plant produces capsules-like fruits containing many small seeds[2].

1.4.5. ORIGIN AND HABITAT:

Origin: Believed to be native to the Arabian Peninsula, but now widely cultivated in tropical and subtropical regions worldwide.

Ecology: A xerophytic plant adapted to arid and semi-arid conditions; it stores water in leaf mesophyll and tolerates well-drained, sandy soils and full sunlight.

1.5. CHEMICAL CONSTITUENTS:

Aloe vera leaf gel is a water-rich, polysaccharide-dominated matrix containing a complex mixture of bioactive constituents that collectively underpin its wound-healing, anti-inflammatory, and antimicrobial effects. For a review, it is useful to group these constituents by chemical class and briefly link them to their functional roles in wound repair[11][14][16].

Main macro-constituents of *aloe vera* gel:

❖ **Water and polysaccharides:**

Aloe vera gel is about 98–99% water, with the remaining 1–2% dry matter dominated by polysaccharides (mainly acetylated glucomannans and pectic-type heteroglycans), accounting for roughly 55% of the dry gel. These polysaccharides enhance wound-bed hydration, promote fibroblast and keratinocyte proliferation, and support collagen maturation, contributing to re-epithelialization and tensile strength gain[11][16].

❖ **Sugars and saccharides:**

Besides high-molecular-weight polysaccharides, the gel contains free monosaccharides (e.g., glucose, mannose) and oligosaccharides that serve as substrates for cellular energy metabolism and modulate immune and inflammatory responses at the wound site. Some mannose-derived saccharides are reported to exert anti-allergic and immunomodulatory effects relevant to chronic or inflamed wounds[3][11][14].

Vitamins, minerals, and enzymes:

❖ **Vitamins:**

Aloe vera contains several vitamins, including vitamin C, vitamin E, beta-carotene (provitamin A), and B-complex vitamins (folic acid, choline, B12). These vitamins act as antioxidants, scavenge reactive oxygen species at the wound margin, and support epithelial cell differentiation and collagen cross-linking[3][11][14][16].

❖ **Minerals:**

The gel is rich in essential minerals such as calcium, magnesium, zinc, copper, selenium, and potassium, which are cofactors for metalloenzymes involved in collagen synthesis, angiogenesis, and oxidative defense. Zinc, in particular, is critical for DNA synthesis and re-epithelialization, while selenium supports glutathione peroxidase activity[3][11][14].

❖ **Enzymes:**

Aloe vera gel harbors enzymes such as amylase, catalase, peroxidase, bradykinase, and carboxypeptidase. Catalase and peroxidase help detoxify hydrogen peroxide, reducing oxidative stress; bradykinase may modulate bradykinin-mediated pain and inflammation, which is beneficial in thermal and inflammatory wounds[3][14][16].

Phytochemicals with wound-healing relevance:

❖ **Phenolic compounds and flavonoids:**

Aloe vera contains polyphenols, chromones, and flavonoids that contribute to antioxidant, anti-inflammatory, and antimicrobial actions. These compounds stabilize capillary walls, reduce neutrophil-derived free radicals, and limit excessive protease activity in the wound bed[11][14][16].

❖ **Anthraquinones and secondary metabolites:**

The exudate (latex) layer of the leaf is rich in anthraquinones such as aloin and emodin, which have laxative and antimicrobial effects but are generally minimized in purified wound-healing gels because of their irritant potential. In contrast, the inner gel is low in anthraquinones and enriched in gentler constituents such as saponins and sterols that support membrane integrity and microbial control without excessive irritation[3][11][14].

Low-molecular-weight mediators and proteins:

❖ **Glycoproteins and proteins:**

A 5.5 kDa glycoprotein fraction isolated from *Aloe vera* gel has been shown to accelerate keratinocyte migration and enhance epidermal tissue formation in raft and animal models. This class of proteins likely contributes to the moist-wound environment and early re-epithelialization observed in clinical and preclinical settings[16].

❖ **Organic acids and lipids:**

The gel contains small amounts of organic acids (e.g., salicylic acid analogues) and lipids that may exert mild anti-inflammatory and antimicrobial effects while maintaining the skin-barrier-like properties of the hydrogel. Saponins and sterols further enhance the biocompatibility and adhesion of *Aloe vera*-based delivery systems (e.g., hydrogels) to the wound surface[3][11][14].

1.6. PHARMACOLOGICAL ACTIVITIES OF *ALOE VERA*:

1.6.1. WOUND HEALING AND TISSUE REGENERATION:

❖ *Aloe vera* gel accelerates re-epithelialization, collagen deposition, and angiogenesis, thereby shortening wound-closure time in excision, incision, and burn-wound models[15][16].

❖ Polysaccharides such as acemannan and rhamnogalacturonan-type pectins modulate fibroblast proliferation and matrix-protein synthesis, supporting granulation-tissue formation and epithelial regeneration[11][14].

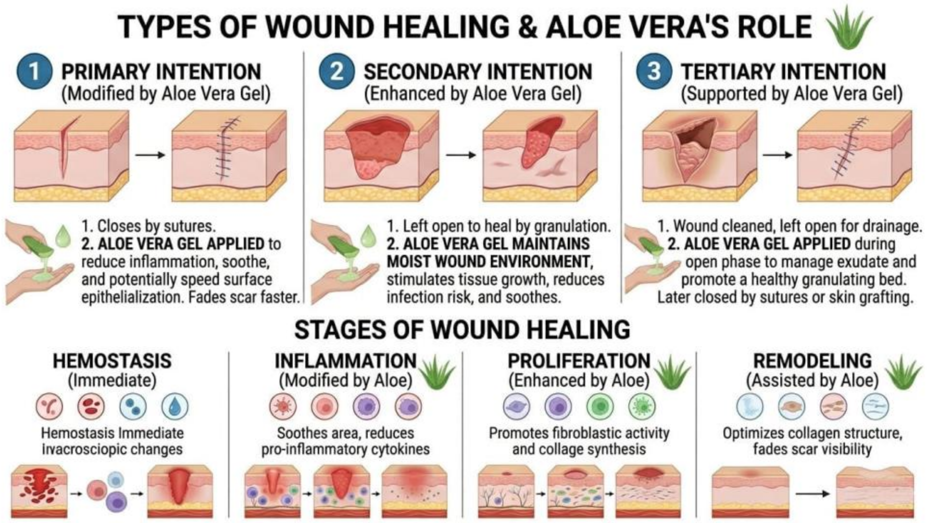

Figure 4: Types of Wound Healing.

1.6.2. ANTI-INFLAMMATORY EFFECTS:

❖ The gel reduces pro-inflammatory mediators (e.g., TNF-α, IL-6, prostaglandins) and inhibits cyclooxygenase and lipoxygenase pathways, easing local edema, pain, and erythema around wounds[3][14].

❖ Topical *Aloe vera* hydrogels in animal studies demonstrate reduced inflammatory cell infiltration and faster progression through the inflammatory phase of wound repair[11][15].

1.6.3. ANTIMICROBIAL AND ANTISEPTIC ACTIVITY:

❖ *Aloe vera* exerts mild antibacterial, antifungal, and antiviral effects attributed to compounds such as anthraquinones (aloin, aloe-emodin), lectins, and saponins, which interfere with microbial membranes and biofilm formation[3][14].

❖ In burn and chronic-wound models, *Aloe vera*–based hydrogels reduce bacterial load and help maintain a relatively clean wound bed, minimizing secondary infection-related delays in healing[11].

1.6.4. ANTIOXIDANT AND CYTOPROTECTIVE ACTIONS:

❖ The gel is rich in flavonoids, polyphenols, vitamins (C, E), and enzymes (e.g., superoxide dismutase) that scavenge reactive oxygen species and protect keratinocytes and fibroblasts from oxidative stress[3][14].

❖ This antioxidant activity supports cell survival at the wound margin, reduces oxidative-damage-induced necrosis, and may help mitigate hypertrophic scarring[16].

1.6.5. IMMUNOMODULATORY AND PRO-ANGIOGENIC EFFECTS:

❖ Aloe polysaccharides act as immunostimulants by enhancing macrophage phagocytosis, cytokine production, and antigen-presentation, thereby fine-tuning the wound-healing immune response[3][14].

❖ *Aloe vera* hydrogels have been shown to stimulate vascular-endothelial growth factor (VEGF)-mediated angiogenesis, improving micro-circulation and oxygen/nutrient supply to the healing tissue[11][15].

1.7. HYDROGELS IN DRUG DELIVERY

Hydrogels are three-dimensional (3D) cross-linked polymer networks capable of absorbing large amounts of water or biological fluids while maintaining their structural integrity. In drug delivery, they act as reservoirs or matrices that entrap active pharmaceutical ingredients (APIs) and release them by diffusion, swelling, or polymer degradation at the target site. For wound healing, hydrogels are usually applied as topical dressings or in situ-forming gels that conform to the wound bed[11][18][22].

1.8. TYPES OF HYDROGELS:

❖ **Natural polymer-based hydrogels:**

Derived from polysaccharides (e.g., alginate, chitosan, hyaluronic acid) or proteins (e.g., collagen, gelatin). These are biocompatible, often biodegradable, and mimic aspects of the extracellular matrix (ECM)[18][19].

❖ **Synthetic polymer-based hydrogels:**

Based on polymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), or polyacrylic acid (e.g., Carbopol). These allow better control of mechanical and release properties[18][22].

❖ **Composite / hybrid hydrogels:**

Combinations of natural and synthetic polymers, sometimes with inorganic additives (e.g., nanoclays, nanocellulose) to improve strength, swelling, or antimicrobial activity[18][19].

❖ **Stimuli-responsive (smart) hydrogels:**

Respond to changes in pH, temperature, enzymes, or reactive oxygen species (ROS) at the wound site to modulate drug release[20][21].

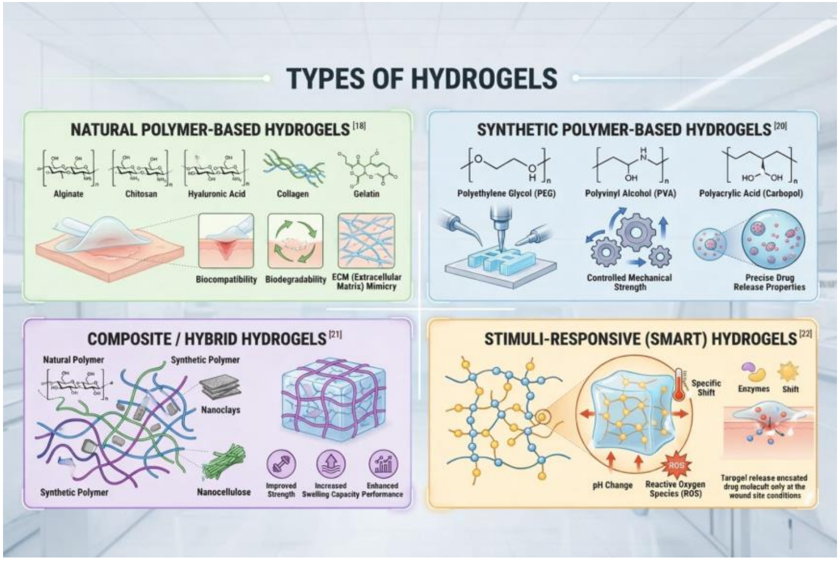

Figure 5: Types of Hydrogels.

1.9. ADVANTAGES OF HYDROGELS IN WOUND HEALING:

❖ Hydrogels are increasingly preferred over conventional dressings because they:

- Maintain a moist wound environment, which favors re-epithelialization and reduces scab formation.
- Provide a physical barrier against microbes while allowing gas exchange, reducing the risk of infection.
- Offer cushioning and lubrication, which helps alleviate pain and minimizes mechanical trauma during dressing changes.
- Can be loaded with drugs, growth factors, or cells and release them in a controlled or stimuli-responsive manner, matching the dynamic phases of wound healing.
- These properties make hydrogels suitable for chronic wounds (diabetic ulcers, burns, pressure sores) as well as acute injuries[18][20][21].

1.10. ROLE OF *ALOE VERA* IN HYDROGELS:

Aloe vera leaf gel contains a complex mixture of polysaccharides (e.g., acemannan-type rhamnogalacturonan, pectin-like moieties), glycoproteins, enzymes, and other bioactive compounds that exert anti-inflammatory, antioxidant, antimicrobial, and tissue-regenerative effects. However, the raw gel is often unstable, highly viscous, and difficult to standardize for topical use[11][22][23].

Hydrogels address these limitations by:

❖ Protecting *Aloe vera* bioactive from degradation (e.g., oxidation, enzymatic breakdown) and extending their local residence time.

❖ Providing a controlled, sustained release of *Aloe vera* components (via diffusion, swelling, and polymer relaxation), which can modulate inflammation, angiogenesis, and collagen deposition over days rather than hours[11][22].

❖ Enabling combination therapy, where *Aloe vera* is blended with antimicrobials (e.g., povidone-iodine, silver, honey) or other wound-healing agents within the same hydrogel matrix[19][22][23].

❖ Studies on *Aloe vera*-hydrogel formulations (e.g., Carbopol-based or alginate–chitosan gels) report faster wound contraction, reduced healing time, and improved histological remodeling compared with control[15][22][23].

2. MATERIALS AND METHODS

2.1. MATERIALS USED:

For an *Aloe vera* hydrogel intended for wound healing, typical materials include:

***Aloe vera* leaf gel:**

➢ Inner leaf parenchyma (gel) extracted from mature, undamaged leaves after removal of the outer rind and yellow latex (which may be irritant [11][24].

➢ Often processed as fresh gel, aqueous extract, or lyophilized powder, then re-dissolved in water[11][24].

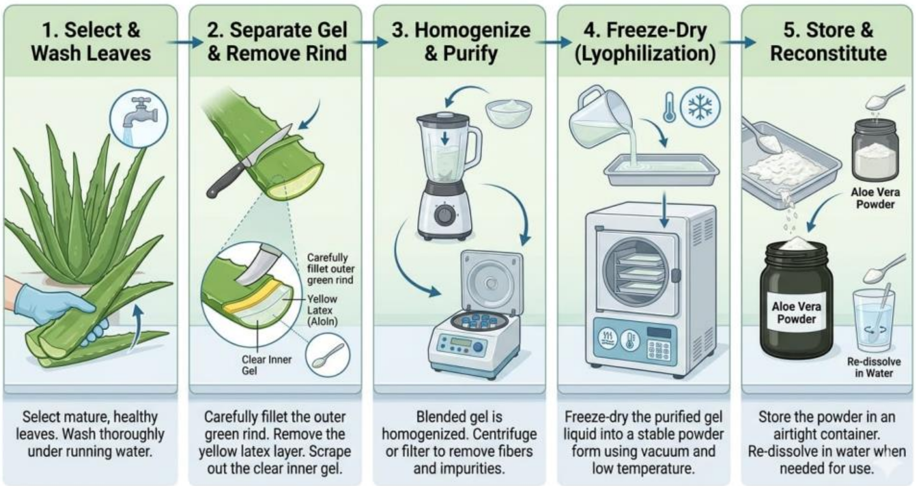

Figure 6: Extraction of *Aloe vera* leaf gel.

Hydrogel-forming polymers / matrix materials:

Natural polymers: Polysaccharides such as xanthan gum, alginate, chitosan, sterculia gum, and sometimes acacia or HPMC[11][24][25][26]

Synthetic polymers: Carbopol 934/940 (polyacrylic acid-based), polyvinyl alcohol (PVA), or polyacrylamide-type networks[11][24][27][28].

Optional additives and excipients: Plasticizers / humectants: glycerin or propylene glycol to improve elasticity and prevent cracking[28].

Preservatives: potassium sorbate, sodium benzoate.

Buffers / pH adjusters: triethanolamine, tartaric acid, or NaOH/HCl to adjust pH to ~5–7 suitable for skin[28].

Cross-linkers: Ca^{2+} salts for alginate; glutaraldehyde or genipin for chitosan; physical cross-linking via freeze-thaw or heating-cooling cycles for PVA[26][29].

Polymers and formulation considerations:

When designing an *Aloe vera* hydrogel for wound healing, several key polymer-related and formulation factors must be considered.

Choice of polymer and matrix type:

Natural vs synthetic polymers:

➢ Natural polymers (alginate, chitosan, sterculia gum, xanthan, HPMC) offer better biocompatibility, biodegradability, and often intrinsic antimicrobial or mucoadhesive properties, but may have higher batch variability[11][24][26][29].

- Synthetic (Carbopol, PVA) give more reproducible rheology and mechanical strength; PVA-based networks are common for hydrogel films, whereas Carbopol is preferred for topical gels[27][28][30].

Hydrophilicity and swelling:

- The polymer should allow sufficient swelling in wound exudate to maintain a moist environment, which is critical for re-epithelialization[11][24].
- Swelling ratio is tuned by polymer concentration, cross-link density, and *Aloe vera* content (high *Aloe vera* can increase swelling but may reduce mechanical strength)[11][24][25].

Mechanical and rheological properties:

- The gel must be strong enough to cover the wound, yet soft and conformable; too rigid gels can crack and cause patient discomfort[11][24].
- For topical gels, Carbopol-based systems are often optimized for spreadability and peel-adhesion; for films, sterculia gum- or PVA-based networks are tuned for tensile strength and elasticity[26][27][28][30].
- *Aloe vera* loading level: Studies report *Aloe vera* content ranging from ~5–20% w/v in solution (or ~38–71 wt% in dry gel) in composite hydrogels.
- Very high *Aloe vera* may dilute the polymer network and reduce cohesion; an intermediate content (e.g., ~10% w/v) often gives balanced strength, elasticity, and absorption capacity[11][25].

Biocompatibility and antimicrobial activity: Polymers and cross-linkers should be non-cytotoxic and non-sensitizing; chitosan and *Aloe vera* themselves contribute to antimicrobial and anti-inflammatory effects[11][24][26].

2.2. METHODS OF PREPARATION:

Here are representative, generic procedures you can paraphrase into your review (with example ranges rather than exact numbers, unless you are citing a specific study).

2.2.1. EXTRACTION AND PREPARATION OF *ALOE VERA* GEL:

- ✓ Select mature, disease-free leaves and wash thoroughly.
- ✓ Remove the outer rind and yellow latex layer, then scrape or homogenize the inner gel[11][24].

✓ Centrifuge or filter to remove fibers; optionally freeze-dry the gel and store as powder to be re-dissolved in water[11][24].

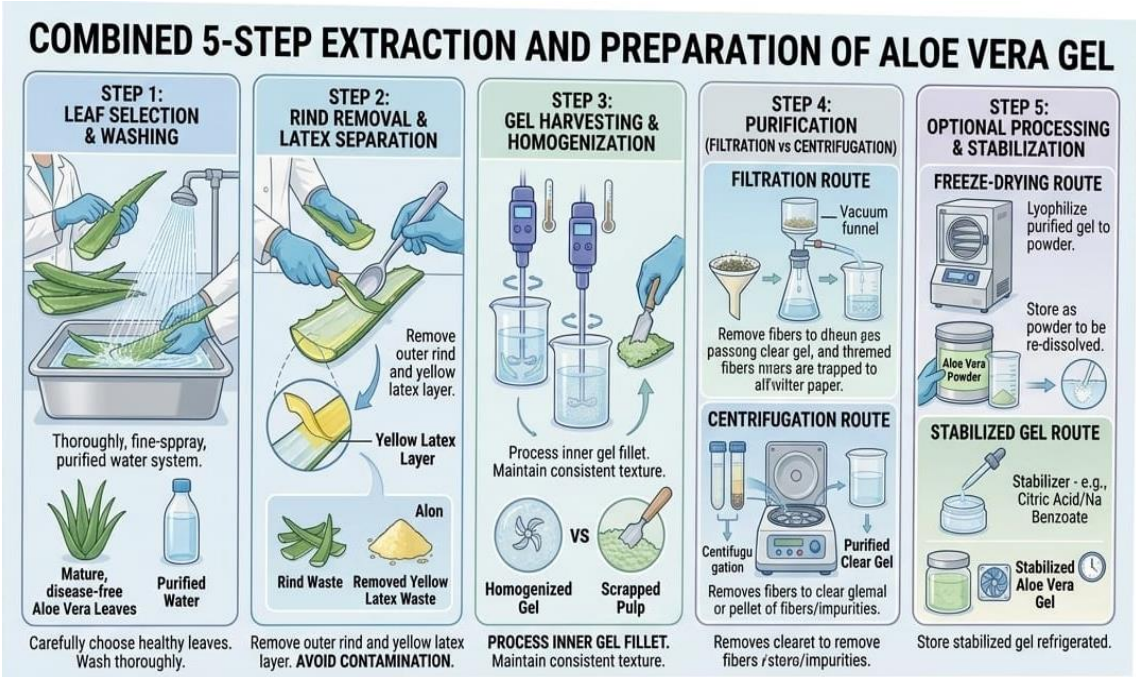

Figure 7: Extraction and Preparation of *Aloe Vera* Gel.

2.2.2. PREPARATION OF POLYMER SOLUTION (COLD-DISPERSIBLE VS HEAT-ACTIVATED):

For Carbopol / PAA-type gels:

Disperse Carbopol 934/940 slowly in water under gentle stirring to avoid lumping; allow to hydrate overnight[28].

For xanthan gum / HPMC / sterculia gum:

Add the polymer to cold water and stir until fully hydrated; some work heats the solution briefly to aid dispersion and then cools before adding *Aloe vera*[25][26].

For chitosan / alginate:

Dissolve chitosan in dilute acetic acid (e.g., 1–2% v/v) and neutralize after casting; dissolve alginate in water at the desired concentration[11][24][29].

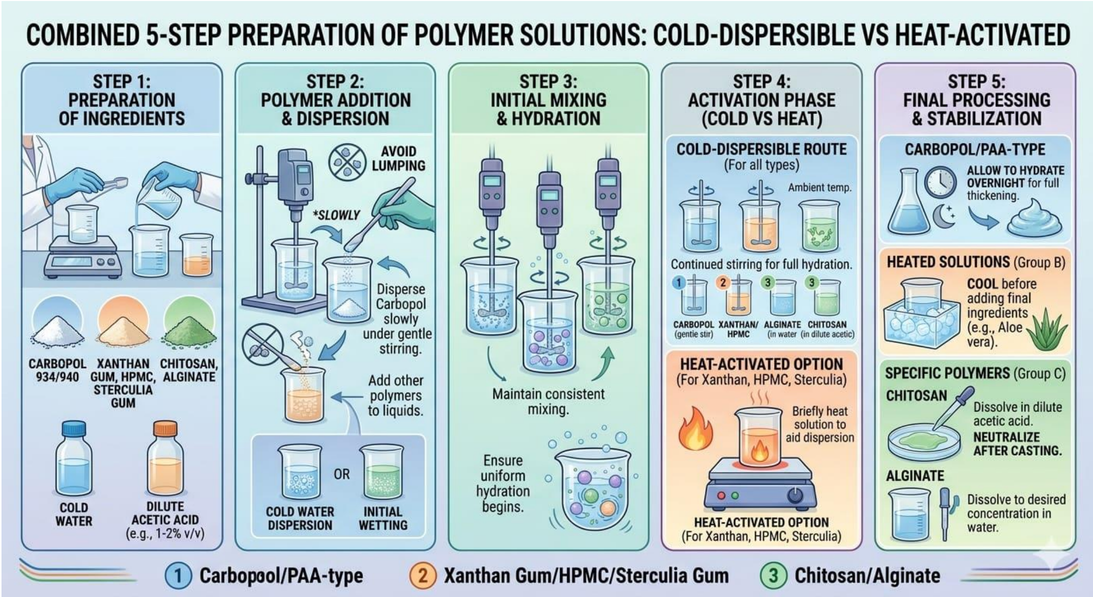

Figure 8: Preparation of Polymer Solution (Cold-Dispersible Vs Heat-Activated)

2.2.3. BLENDING *ALOE VERA* INTO THE POLYMER MATRIX:

- ✓ Adjust water temperature to ~40–50 °C (or room temperature for heat-sensitive *Aloe vera*) and slowly add the *Aloe vera* gel or re-constituted extract to the polymer solution under continuous stirring[11][25][28].
- ✓ Stir until a homogeneous, translucent or semi-transparent gel is obtained; this may take several hours depending on polymer type and concentration[25][28].

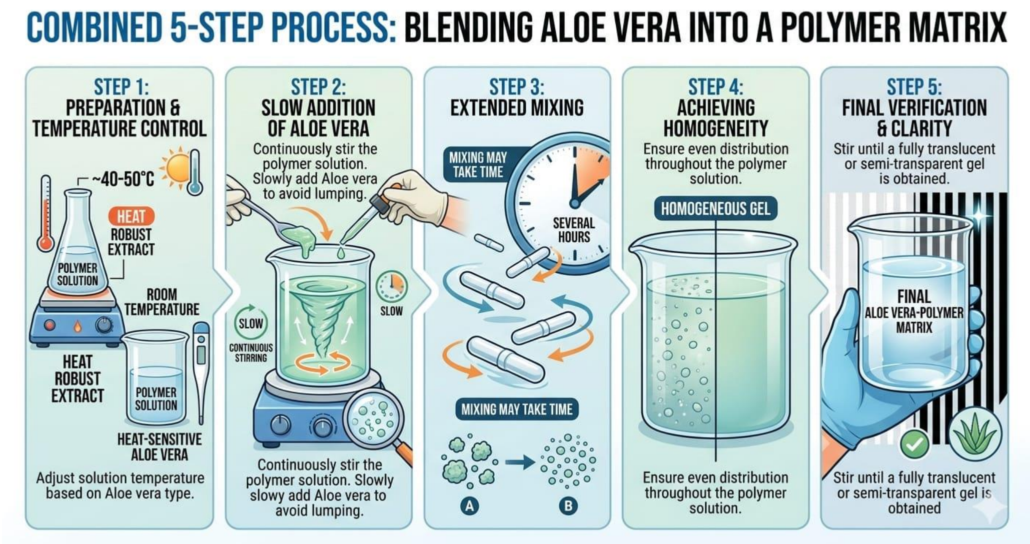

Figure 9: Blending *Aloe Vera* into the Polymer Matrix.

2.2.4. OPTIONAL CROSS-LINKING OR FILM FORMATION:

For alginate-based hydrogels: Pour the alginate-*Aloe vera* solution onto a plate and expose to a $CaCl_2$ solution (via immersion or spraying) to form a physically cross-linked hydrogel film[27][29].

For chitosan-based gels / films: Cast the chitosan-*Aloe vera* solution and allow it to dry at mild temperature; cross-linking may be added using genipin or via ionic interactions[24][26].

For PVA-based films: Dissolve PVA in hot water, add *Aloe vera*, stir, cast into molds or on plates, and use repeated freeze-thaw cycles or chemical cross-linking to form a robust hydrogel film[24][27].

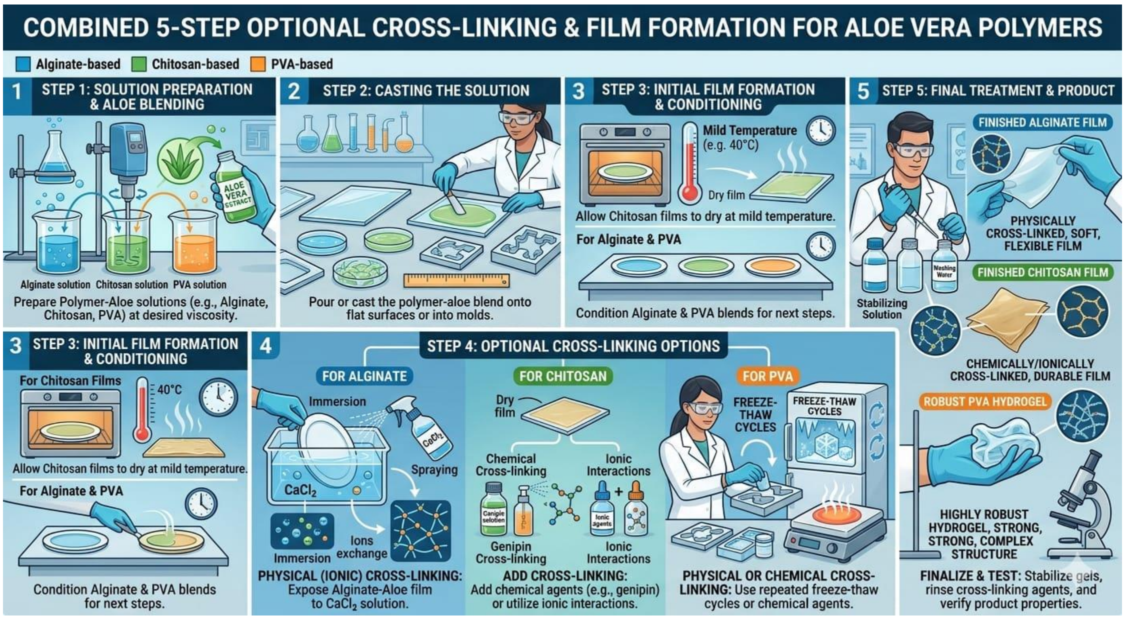

Figure 10: Optional Cross-Linking or Film Formation.

2.2.5. pH ADJUSTMENT, PRESERVATIVES AND FINISHING:

- ✓ Adjust pH to the skin-compatible range (typically ~5.5–7.0) using dilute NaOH, triethanolamine, or weak acids (e.g., tartaric acid)[28].
- ✓ Add preservatives (e.g., potassium sorbate, sodium benzoate) and glycerin/propylene glycol, then continue stirring until uniform.
- ✓ Finally, degas the mixture if necessary and pack into sterile jars or tubes; films may be cut into sterile sheets and stored with desiccants[11][24].

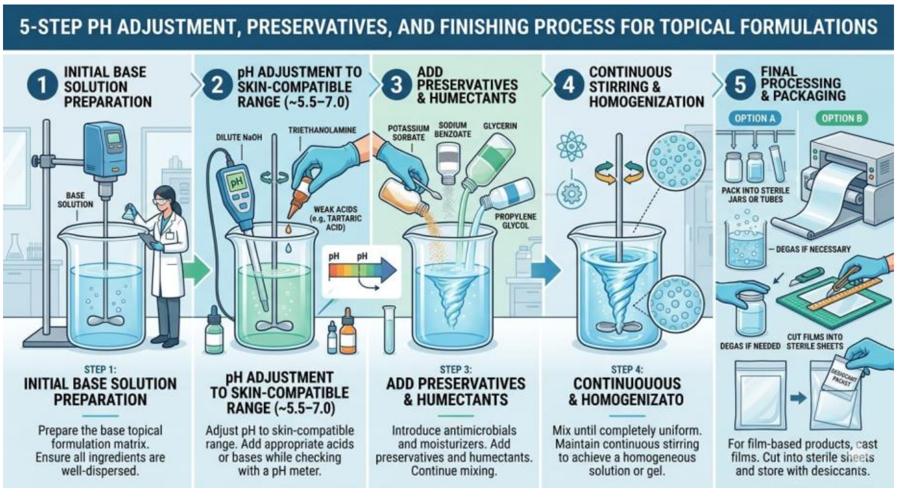

Figure 11: pH Adjustment, Preservatives and Finishing.

3. RESULTS AND DISCUSSION

3.1. EVALUATION PARAMETERS (*IN-VITRO* STUDIES):

Aloe vera leaf gel hydrogel is a promising topical formulation for wound healing due to its natural polysaccharides, antioxidants, and anti-inflammatory compounds that promote tissue regeneration and antimicrobial activity. *In vitro* evaluation ensures its physicochemical suitability, while stability studies confirm shelf-life reliability for practical use.

3.1.1. PHYSICAL EVALUATION:

Physical checks assess appearance, homogeneity, color, odor, and grittiness through visual inspection and texture analysis. These confirm the hydrogel's uniformity, clarity, and absence of particles, which are critical for patient compliance and even application on wounds. pH measurement (typically 5.5-6.5 for skin compatibility) and viscosity testing via rheometer evaluate spread on skin without irritation[34][35].

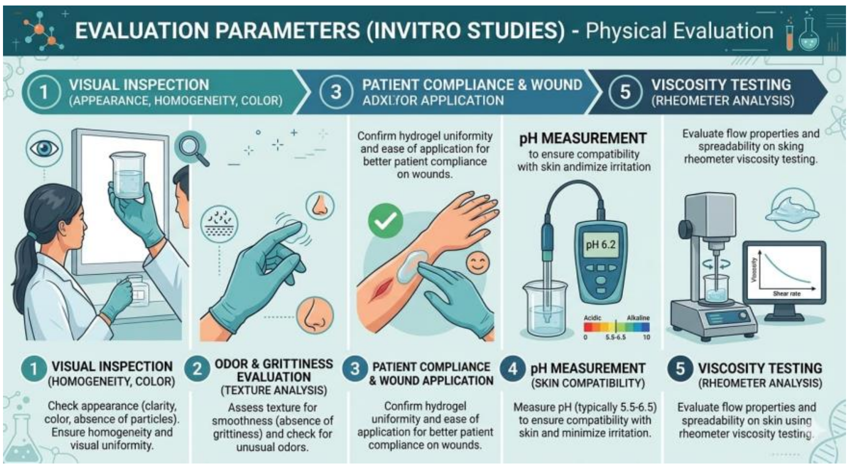

Figure 12: Physical Evaluation.

3.1.2. SPREADABILITY:

Spreadability measures the ease of application, determined by placing 0.5 g gel between glass plates under a 1 kg load and calculating area spread over time ($S = M \times L / 100$, where M is weight and L is length). Good spreadability (e.g., 10-20 cm²) ensures uniform coverage and enhances bioavailability. Poor values indicate high viscosity hindering efficacy[23].

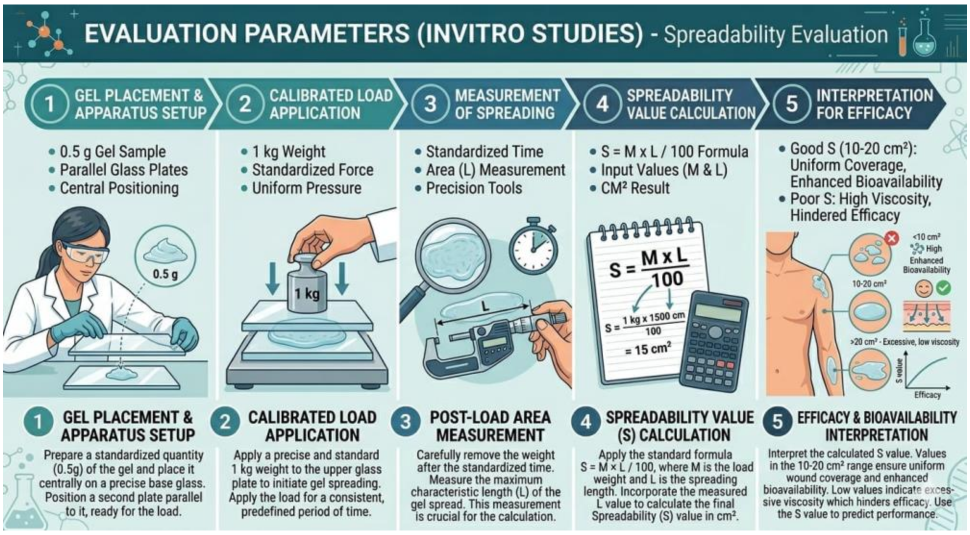

Figure 13: Spreadability.

3.1.3. DRUG CONTENT:

Drug content uniformity is quantified by extracting *Aloe vera* actives (e.g., via methanol) and analyzing via UV spectroscopy at 270-300 nm, aiming for 95-105% loading. This verifies extraction efficiency and even distribution, preventing dose variability in healing applications. HPLC may refine polysaccharide or anthraquinone quantification[35].

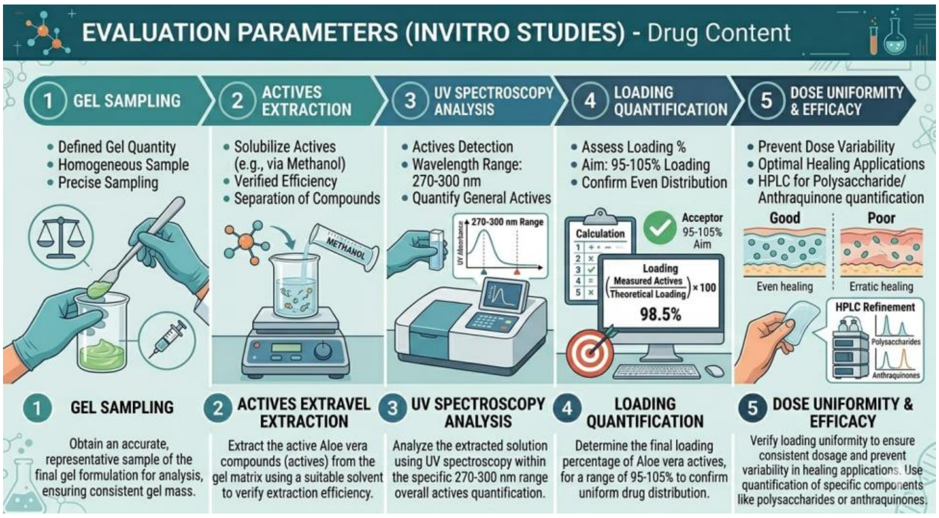

Figure 14: Drug Content.

3.1.4. *IN VITRO* DRUG RELEASE:

Release profiles use Franz diffusion cells with dialysis membrane, sampling receptor medium (PBS pH 7.4) at intervals up to 24-72 hours, analyzed spectrophotometrically. Profiles fit zero-order, Higuchi, or Korsmeyer-Peppas models, showing sustained release (e.g., 80% over 12 hours) ideal for prolonged wound moistening. Swelling index (% = [(Wt - W0)/W0] × 100) correlates with hydration capacity[15].

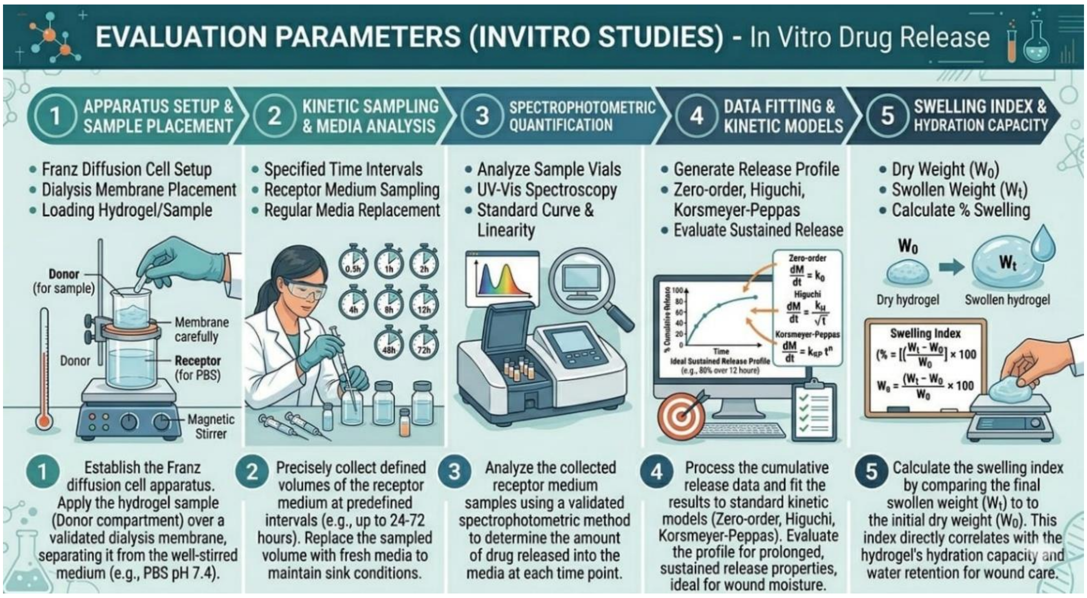

Figure 15: *In Vitro* Drug Release.

3.1.5. STABILITY STUDIES:

Accelerated stability (40°C/75% RH, 6 months) monitors pH, viscosity, drug content, and microbial load per ICH guidelines, alongside real-time (25°C/60% RH). Aloe hydrogels retain >90% active with minimal degradation, confirming robustness. Photostability and freeze-thaw cycles assess structural integrity[35].

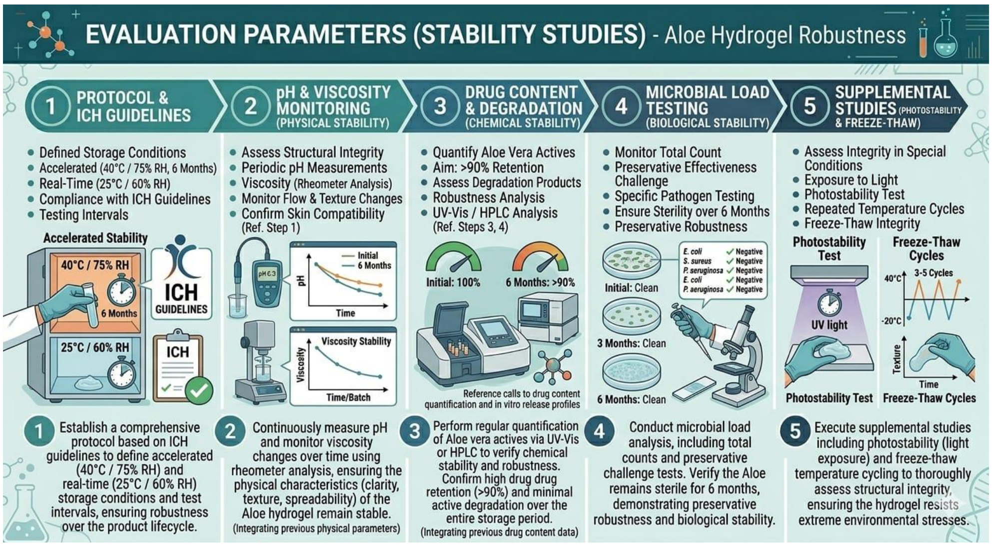

Figure 16: Stability Studies.

3.2. MECHANISM OF WOUND HEALING BY *ALOE VERA*

Aloe vera leaf gel hydrogel is a promising natural formulation for wound healing, leveraging the plant's bioactive compounds for enhanced topical application. It's *in vitro* evaluation typically confirms biocompatibility, controlled release, and bio adhesive properties suitable for pharmaceutical review articles.

Hydrogel Formulation:

Aloe vera gel is extracted from fresh leaves, filtered, and incorporated into a hydrogel matrix using gelling agents like Carbopol 934, xanthan gum, or collagen blends at concentrations of 5-10% *Aloe vera* for optimal viscosity and spreadability. Propylene glycol or triethanolamine may stabilize pH (around 6-7), while salicylic acid or allantoin enhances biocompatibility; formulations are optimized via response surface methodology for homogeneity and superabsorbent capacity up to 2850%. This all-green synthesis ensures renewability and avoids synthetic crosslinkers[15][23][31][33].

In Vitro Evaluation Methods:

Standard tests include rheological analysis for shear-thinning behavior, swelling index (>200% for moist healing), and drug release kinetics via Franz diffusion cells, showing sustained *Aloe vera* release over 24-48 hours. Scratch assays on fibroblast cell lines (e.g., NIH-3T3) demonstrate >80% wound closure in 24 hours, with MTT assays confirming >90% cell viability; antimicrobial zones against S. aureus exceed 15 mm. Bio adhesion and antioxidant activity (DPPH assay) further validate efficacy[7][13][15][33][34].

Wound Healing Mechanisms:

Aloe vera promotes all phases of healing through synergistic phytocompounds like polysaccharides, mannose-6-phosphate, lectins, and anthraquinones[32].

Anti-Inflammatory Action:

It inhibits pro-inflammatory cytokines (TNF-α, IL-6) and COX-2 via aloin and salicylic acid derivatives, reducing edema by 40-50% in models; this modulates macrophage activity for faster resolution[33][34].

Collagen Synthesis:

Mannose-6-phosphate boosts fibroblast proliferation and collagen types I/III deposition, increasing tensile strength by 20-30%; lectins enhance organization, as seen in upregulated hydroxyproline levels[23][32].

Antimicrobial Effect:

Polysaccharides and anthraquinones disrupt bacterial membranes (S. aureus, P. aeruginosa), achieving >99% inhibition; this prevents biofilm formation in moist environment[33][34].

Moist Wound Environment:

High water content (>98%) and humectant polysaccharides maintain hydration, promoting re-epithelialization and reducing scab formation for 20-30% faster closure[7].

Table 1: Formulation Components.

FORMULATION	KEY COMPONENTS	PREPARATION METHOD	*IN VITRO* EVALUATION
Propanediol-TEA Aloe gel	*Aloe vera* gel (98-99% water), propanediol (humectant), triethanolamine (pH stabilizer), carbomer	Extraction from leaves, homogenization, stabilization; dried to xerogel for analysis	Swelling 12,693%; contact angle 43°; microstructure promotes adhesion; rapid penetration without drying tissue[15]
AV5 vs AV10 (biocompatible)[9]	*Aloe vera* at 5% or 10% (w/v), natural polymers	Cross-linking; dry/wet application	Scratch assay: AV5 67.75% closure at 50 mg/mL, AV10 optimal at 10 mg/mL (63.24%); good antibacterial, cytocompatibility[9]
Chitosan/Aloe hydrogel[36]	Chitosan, *Aloe vera* gel	Blending, viscosity adjustment	Viscosity, antibacterial activity; promoted re-epithelialization in full-thickness models[36]

Carbopol Aloe gel[23]	*Aloe vera,* Carbopol 934 (viscosity enhancer)	Concentration optimization for spreadability	Excision model prep; good consistency for release kinetics[23]

3.3. ADVANTAGES AND LIMITATIONS

Advantages / benefits of *Aloe vera* hydrogel:

- ✓ Excellent biocompatibility and low systemic toxicity, making it suitable for topical application on open wounds and sensitive skin[9][11].
- ✓ High water-holding capacity and moisture-retentive nature, which maintain a moist wound environment and support epithelial migration and granulation.
- ✓ Natural hydrogel matrix facilitates sustained release of *Aloe vera* bioactives (e.g., acemannan, polysaccharides, phenolics) at the wound site[11][13].
- ✓ Demonstrated anti-inflammatory activity via inhibition of cyclooxygenase and prostaglandin E_2 pathways, helping to reduce wound-site inflammation.
- ✓ Mild antimicrobial and antioxidant effects, which can help control microbial load and oxidative stress in the wound bed[9].
- ✓ Promotes key phases of wound healing: angiogenesis, fibroblast proliferation, collagen deposition, and wound contraction, often reducing total healing time in preclinical models[11][15].
- ✓ Non-sticky or moderately adhesive surface in many formulations allows easy application and removal without causing significant trauma to regenerated tissue[9][11].
- ✓ Can be readily combined with polymers (e.g., Carbopol, natural gums) to tailor rheology, swelling, and mechanical properties for different wound types[11][23].

Limitations / drawbacks and challenges:

- ✓ Variability in chemical composition of *Aloe vera* gel (batch-to-batch, plant age, extraction method), leading to inconsistent therapeutic activity and stability[11][13].
- ✓ Limited mechanical strength and poor resistance to shear in some simple *Aloe vera*-only hydrogels, requiring synthetic or semi-synthetic polymers for robust wound-dressing performance[9][11].
- ✓ Potential for rapid muco-adhesion or sticking to wound surfaces if not properly optimized, which may cause pain or minor trauma on dressing change[11].
- ✓ Risk of microbial contamination during processing or storage because the aqueous, nutrient-rich gel is prone to spoilage unless adequately preserved or sterilized[11].

- ✓ Possible irritant or allergic reactions (rare but reported), especially with repeated use or in hypersensitive individuals, necessitating safety testing.
- ✓ Instability of certain phytoconstituents (e.g., enzymes, polysaccharides) over time or under light/temperature stress, compromising long-term efficacy[11][13].
- ✓ Regulatory and quality-control hurdles for natural products, including standardization of active markers, extract potency, and equivalence between fresh and processed *Aloe vera*[11].
- ✓ Limited evidence from large-scale human clinical trials; many supportive data are from *in vitro* or animal studies, so translation to routine clinical practice remains cautious[11][15].

3.4. FUTURE PROSPECTS

3.4.1. SCOPE OF RESEARCH:

✓ Investigate hybrid hydrogels combining *Aloe vera* with synthetic polymers (e.g., PVA, chitosan) for tunable mechanical strength and sustained release[7][37].

✓ Explore standardization of *Aloe vera* gel extraction to minimize batch variability in bioactive content and gelation properties[38].

✓ Conduct long-term stability studies under ICH guidelines, focusing on polysaccharide degradation and antimicrobial preservation[11].

3.4.2. ADVANCED DELIVERY SYSTEMS:

- ✓ Develop stimuli-responsive hydrogels (pH-sensitive or thermosensitive) for on-demand drug release in infected wounds[37].
- ✓ Incorporate nanoparticles or nanogels loaded with *Aloe vera* extracts to enhance skin penetration and bioavailability[38].
- ✓ Design 3D-printed or electrospun *Aloe vera* hydrogel scaffolds for tissue-engineered skin substitutes[7].

3.4.3. CLINICAL APPLICATIONS:

- ✓ Target chronic wounds like diabetic ulcers, leveraging anti-inflammatory and angiogenic effects observed *in vitro*[11][15].
- ✓ Formulated as sprayable or injectable hydrogels for burn dressings, reducing pain and scarring in clinical settings[9].

✓ Advance to Phase II/III trials for FDA approval as adjunct therapy in postoperative wound care[11].

4. CONCLUSION

Aloe vera–based hydrogels offer a promising and effective approach for wound healing by combining the natural therapeutic properties of Aloe vera with the advantages of hydrogel drug delivery systems. The bioactive constituents, including polysaccharides, vitamins, and antioxidants, contribute to anti-inflammatory, antimicrobial, antioxidant, and tissue-regenerative effects, while hydrogels provide a moist environment and controlled release that enhances the healing process. Despite challenges such as variability in composition and limited clinical data, these formulations demonstrate significant potential as safe, biocompatible, and economical alternatives to conventional wound dressings, with future research expected to further improve their clinical applicability in modern wound care.

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