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Research Paper

Topical Drug Delivery Systems for Oral Mucosal Ulcers: Role of Analgesic–Antimicrobial Combination Gels in Modern Therapeutics

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Abstract
Oral mucosal ulcers, particularly recurrent aphthous stomatitis (RAS), represent one of the most prevalent inflammatory conditions affecting the oral cavity, impacting 5– 25% of the global population. These painful lesions significantly impair patients' quality of life by interfering with eating, speaking, and daily activities. This comprehensive review examines the current landscape of topical drug delivery systems for oral mucosal ulcers, with particular emphasis on analgesic–antimicrobial combination gels. We explore the pathophysiology underlying oral ulceration, evaluate conventional and emerging drug delivery platforms, and critically analyze the synergistic benefits of combining pain-relieving and antimicrobial agents within advanced mucoadhesive formulations. Recent innovations including nanoparticle- based carriers, stimuli-responsive hydrogels, dissolving microneedles, and polyherbal formulations are discussed in the context of their potential to overcome existing therapeutic limitations. The integration of natural bioactive compounds with novel delivery technologies represents a promising frontier for developing safer, more effective treatments for oral mucosal ulcers.
Keywords: *Oral mucosal ulcers; Recurrent aphthous stomatitis; Mucoadhesive gels; Analgesic; Antimicrobial; Drug delivery systems; Nanoparticles; Microneedles*

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I. Introduction

Oral mucosal ulcers constitute a significant clinical burden worldwide, with recurrent aphthous stomatitis (RAS) representing the most common form of oral mucosal inflammatory disease. These lesions manifest as painful, shallow ulcers on the non- keratinized oral mucosa, including the buccal mucosa, labial mucosa, soft palate, and ventral tongue surface. The prevalence of RAS varies considerably across populations, ranging from 5% to 25% globally, with certain demographic groups experiencing higher rates of occurrence[1].

The etiology of oral mucosal ulcers remains incompletely understood, though research has identified multiple contributing factors including genetic predisposition, immunological dysregulation, nutritional deficiencies, psychological stress, hormonal fluctuations, and local trauma. At the molecular level, RAS is characterized by dysregulated cell-mediated immunity, elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-2, IL-6), and enhanced oxidative stress leading to epithelial cell apoptosis[2].

The management of oral mucosal ulcers presents unique therapeutic challenges distinct from other wound healing scenarios. The oral cavity constitutes a dynamic, hostile environment for drug delivery due to continuous saliva secretion causing drug dilution, constant mechanical forces from tongue movement and mastication, the presence of a complex microbial ecosystem, and the need for patient compliance with frequent applications. These factors collectively contribute to rapid drug clearance, poor mucosal retention, and suboptimal therapeutic outcomes with conventional formulations[3].

Current therapeutic approaches for oral mucosal ulcers primarily aim to alleviate pain, reduce inflammation, prevent secondary infection, and promote healing. While systemic therapies exist for severe or refractory cases, topical treatments remain the first-line approach due to their ability to deliver drugs directly to the affected site while minimizing systemic exposure and associated adverse effects. However, conventional

topical formulations frequently demonstrate inadequate efficacy due to their inability to maintain therapeutic drug concentrations at the ulcer site for sufficient duration[3].

This review provides a comprehensive examination of topical drug delivery systems for oral mucosal ulcers, with specific focus on the therapeutic rationale and technological advances in analgesic–antimicrobial combination gels. We systematically analyze the pathophysiological basis for combination therapy, evaluate various drug delivery platforms from conventional formulations to cutting-edge nanotechnology-based systems, and discuss future directions for research and clinical translation.

Fig 1: Oral Mucosal Ulcer.

II. Pathophysiology of Oral Mucosal Ulcers

2.1 Etiology and Risk Factors

The pathogenesis of oral mucosal ulcers, particularly RAS, involves a complex interplay of genetic, immunological, environmental, and local factors. Despite extensive research, no single causative agent has been definitively identified, suggesting that these lesions result from multifactorial triggers acting upon susceptible individuals[4].

Table 1: Etiological Factors Associated with Oral Mucosal Ulcers

Category	Specific Factors	Proposed Mechanism
Genetic	Family history, HLA associations	Inherited susceptibility to immune dysregulation
Immunological	T-cell dysfunction, cytokine imbalance	Aberrant inflammatory response
Nutritional	Iron, vitamin B12, folate, zinc deficiency	Impaired epithelial integrity and healing
Psychological	Stress, anxiety, depression	Neuroendocrine-immune axis modulation
Hormonal	Menstrual cycle, pregnancy	Estrogen/progesterone effects on mucosa
Local trauma	Dental procedures, sharp foods, biting	Direct tissue injury
Microbial	Bacterial, viral triggers	Antigenic stimulation, cross-reactivity
Systemic disease	Behçet's disease, IBD, celiac disease	Secondary manifestation of underlying condition

2.2 Inflammatory Cascade and Tissue Damage

The molecular pathophysiology of oral ulceration involves a coordinated cascade of inflammatory events. Initial tissue injury or immune activation triggers the release of pro-inflammatory cytokines from resident immune cells and keratinocytes. TNF-α plays a central role in this process, promoting further immune cell recruitment, vascular permeability, and epithelial apoptosis. Elevated levels of IL-2 and IL-6 amplify the inflammatory response, while increased reactive oxygen species (ROS) contribute to oxidative damage of cellular components[5]. The ulcerative lesion itself represents a breach in the protective epithelial barrier, exposing underlying connective tissue to the oral environment. This exposure creates vulnerability to secondary bacterial colonization, which can perpetuate inflammation and delay healing. The pain associated with oral ulcers results from exposure of sensory nerve endings in the lamina propria to chemical and mechanical stimuli, significantly impacting the patient's

ability to eat, speak, and maintain oral hygiene.

2.3 Healing Process and Therapeutic Targets

Oral mucosal wound healing proceeds through overlapping phases of hemostasis, inflammation, proliferation, and remodeling. Successful therapeutic intervention must address multiple aspects of this process: controlling excessive inflammation, managing pain to maintain patient function and compliance, preventing or treating secondary infection, and promoting epithelial regeneration. This multifaceted healing requirement provides the rationale for combination therapeutic approaches that simultaneously target multiple pathological processes[6].

III.Challenges in Topical Drug Delivery to the Oral Mucosa

3.1 Anatomical and Physiological Barriers

The oral cavity presents a unique set of challenges for effective topical drug delivery that distinguish it from other mucosal surfaces. Understanding these barriers is essential for rational formulation design.

Salivary dilution and clearance: The oral cavity produces approximately 0.5–1.5 liters of saliva daily, creating a continuous washing effect that rapidly dilutes and removes topically applied medications. Salivary flow rates increase during eating and speaking, precisely when ulcer pain is most problematic, further compromising drug retention at the site of action[3].

Mechanical stress: The oral mucosa experiences constant mechanical forces from tongue movement, chewing, swallowing, and speech. These forces can physically dislodge topical formulations, limiting contact time between drug and tissue. Conventional solutions, suspensions, and even some gel formulations are particularly susceptible to mechanical displacement.

Mucosal permeability variations: The oral mucosa exhibits regional differences in permeability based on keratinization status and epithelial thickness. Non-keratinized regions (buccal mucosa, floor of mouth) are more permeable than keratinized areas (hard palate, attached gingiva), but ulcerated tissue presents altered barrier properties that may affect drug penetration unpredictably.

Enzymatic degradation: Saliva contains numerous enzymes including amylases, proteases, and lipases that can degrade certain drug molecules before they reach their target. This enzymatic activity must be considered when formulating peptide-based therapeutics or other labile compounds.

3.2 Patient Compliance Factors

Beyond physiological barriers, patient-related factors significantly impact therapeutic outcomes with topical oral formulations.

Table 2: Challenges and Strategies in Oral Mucosal Drug Delivery

Challenge	Impact on Therapy	Formulation Strategy
Saliva dilution	Reduced drug concentration	Mucoadhesive polymers
Mechanical displacement	Shortened contact time	Bioadhesive films, patches
Taste and texture	Poor patient acceptance	Taste masking agents, optimized viscosity
Application frequency	Reduced compliance	Sustained-release systems
Pain during application	Avoidance of treatment	Rapid-onset anesthetics
Eating and drinking restrictions	Lifestyle disruption	Fast-adhering formulations

The taste and texture of oral formulations profoundly influence patient acceptance and compliance. Bitter or unpleasant-tasting medications may be avoided, particularly by pediatric patients. Similarly, formulations with inappropriate viscosity—either too thin to adhere or too thick to spread comfortably—may discourage consistent use. The need for frequent applications throughout the day further burdens patients and reduces adherence to treatment regimens[1].

IV.Conventional Topical Formulations for Oral Ulcers

4.1 Solutions and Mouthwashes

Medicated mouthwashes and oral rinses represent the simplest topical delivery systems for oral mucosal ulcers. These formulations typically contain antiseptic agents (chlorhexidine, cetylpyridinium chloride), anti-inflammatory compounds, or local anesthetics dissolved or suspended in an aqueous vehicle. While easy to use and capable of reaching all oral surfaces, solutions offer minimal retention time at specific ulcer sites, typically clearing within minutes of application. Their primary utility lies in maintaining overall oral hygiene and reducing microbial load rather than providing sustained local therapy[7].

4.2 Conventional Gels and Ointments

Gel formulations offer improved retention compared to solutions due to their higher viscosity and ability to coat mucosal surfaces. Conventional gels for oral ulcers typically incorporate corticosteroids (triamcinolone acetonide), local anesthetics (lidocaine, benzocaine), or protective agents in hydrophilic or hydrophobic bases. However, these formulations still suffer from relatively rapid clearance, often requiring application four to six times daily for adequate symptom contro[8].

Ointments provide superior barrier protection and longer retention due to their lipophilic nature but may feel uncomfortable in the moist oral environment and can interfere with taste sensation. Their greasy texture and tendency to spread beyond the intended application site limit patient acceptance[9].

4.3 Protective Pastes and Barriers

Dental protective pastes, exemplified by products containing carboxymethylcellulose in an adhesive base (such as Orabase), function primarily as physical barriers rather than drug delivery systems. These formulations adhere to the ulcer surface, protecting exposed nerve endings from mechanical and chemical irritation. While effective for symptomatic relief, they do not address underlying inflammation or infection risk and may incorporate drugs for enhanced therapeutic effect[10].

V.Mucoadhesive Drug Delivery Systems

5.1 Principles of Mucoadhesion

Mucoadhesion refers to the attachment of natural or synthetic materials to mucosal surfaces through interfacial forces. This phenomenon is mediated by polymer chain interpenetration into the mucus layer and subsequent formation of physical or chemical bonds with mucin glycoproteins. Effective mucoadhesion prolongs drug residence time at the application site, enhances drug penetration, and reduces the frequency of required applications[11].

The mucoadhesive process involves three stages: contact and spreading of the formulation on the mucosal surface, interpenetration of polymer chains with the mucus layer, and formation of entanglements and secondary bonds (hydrogen bonds, electrostatic interactions, van der Waals forces) that secure attachment. Optimal mucoadhesion requires appropriate polymer selection, adequate hydration for chain mobility, and compatibility with the physiological environment[12].

5.2 Mucoadhesive Polymers

Table 3: Commonly Used Mucoadhesive Polymers in Oral Drug Delivery

Polymer	Type	Key Properties	Applications
Carbopol (Carbomer)	Synthetic, anionic	High bioadhesion, pH-dependent gelation	Gels, films
Hydroxypropyl methylcellulose (HPMC)	Semi-synthetic, nonionic	Film-forming, controlled release	Films, tablets
Chitosan	Natural, cationic	Antimicrobial, wound healing promotion	Gels, nanoparticles
Sodium carboxymethylcellulose (NaCMC)	Semi-synthetic, anionic	High viscosity, biocompatible	Pastes, gels
Polyvinyl alcohol (PVA)	Synthetic, nonionic	Film-forming, mechanical strength	Films, patches
Sodium alginate	Natural, anionic	Gel forming with calcium ions	Hydrogels, beads
Hyaluronic acid	Natural, anionic	Wound healing, hydration	Gels, films
Gelatin	Natural, amphoteric	Biodegradable, cell adhesion	Films, microneedles

The selection of mucoadhesive polymer depends on multiple factors including the desired adhesion strength, drug compatibility, release kinetics, and patient acceptability. Many formulations employ combinations of polymers to optimize performance characteristics. For instance, combining a highly adhesive but brittle polymer with a flexible film-former can yield formulations with both strong attachment and mechanical durability[13].

5.3 Mucoadhesive Gel Formulations

Mucoadhesive gels represent a significant advancement over conventional gel formulations for oral ulcer treatment. By incorporating mucoadhesive polymers into the gel matrix, these systems achieve substantially longer residence times on the oral mucosa, allowing for sustained drug release and reduced application

frequency[14].
The design of mucoadhesive gels requires balancing multiple parameters: adhesive strength must be sufficient to resist displacement by saliva and mechanical forces but not so strong as to cause mucosal damage upon removal. Gel viscosity influences both spreadability during application and retention post-application. Drug release kinetics depend on polymer network density, drug-polymer interactions, and environmental factors such as salivary dilution[15].

VI.Analgesic Agents in Oral Ulcer Therapy

6.1 Rationale for Pain Management

Pain represents the most immediate and debilitating symptom of oral mucosal ulcers, often serving as the primary driver for patients seeking treatment. The intensity of ulcer pain can be disproportionate to lesion size, as the oral mucosa is richly innervated and ulceration exposes nerve endings to constant stimulation from saliva, food, and mechanical contact. Effective pain control is therefore essential not only for patient comfort but also for maintaining adequate nutrition, hydration, and oral hygiene during the healing period[16].

6.2 Local Anesthetics

Local anesthetics remain the mainstay for rapid pain relief in oral ulcer management. These agents block voltage-gated sodium channels in sensory neurons, preventing action potential propagation and thereby interrupting pain signal transmission[17].

Table 4: Local Anesthetics Used in Oral Ulcer Formulations

Agent	Onset	Duration	Concentration Range	Considerations
Lidocaine	2-5 min	30-60 min	2-5%	Most widely used, good safety profile
Benzocaine	1-2 min	15-30 min	5-20%	Rapid onset, risk of methemoglobinemia
Tetracaine	3-8 min	60-120 min	0.5-2%	Longer duration, higher potency
Prilocaine	2-4 min	30-60 min	2-4%	Lower systemic toxicity
Dyclonine	2-10 min	30-60 min	0.5-1%	Alternative for amide sensitivity

Lidocaine is the most frequently incorporated local anesthetic in oral mucosal formulations due to its favorable balance of efficacy, onset time, duration, and safety. However, the relatively short duration of action (typically 30-60 minutes) necessitates frequent reapplication for continuous pain control, highlighting the value of sustained-release formulations[18].

6.3 Anti-inflammatory Analgesics

Beyond direct anesthesia, anti-inflammatory agents provide analgesia by reducing the inflammatory mediators that sensitize nociceptors and propagate pain signaling. Corticosteroids such as triamcinolone acetonide, dexamethasone, and betamethasone are widely used for their potent anti-inflammatory effects, suppressing cytokine production, reducing edema, and limiting immune cell infiltration at the ulcer site[19].

Non-steroidal anti-inflammatory drugs (NSAIDs) offer an alternative mechanism, inhibiting cyclooxygenase enzymes and thereby reducing prostaglandin synthesis. Topical formulations of benzydamine, a locally acting NSAID with additional local anesthetic properties, have demonstrated efficacy in oral ulcer management[20].

6.4 Natural Analgesic Compounds

Growing interest in natural products has identified several plant-derived compounds with analgesic properties suitable for oral ulcer formulations. These agents often provide analgesia through multiple mechanisms, potentially offering advantages over single-target synthetic drugs[21].
Eugenol, derived from clove oil, possesses both analgesic and antiseptic properties and has a long history of use in dental applications. Curcumin demonstrates anti- inflammatory activity through multiple pathways including NF-κB inhibition. Capsaicin, while initially causing a burning sensation, can desensitize TRPV1 receptors to provide prolonged analgesia. These natural compounds are increasingly being incorporated into modern oral ulcer formulations, often in combination with conventional agents[22].

VII.Antimicrobial Agents in Oral Ulcer Therapy

7.1 Rationale for Antimicrobial Therapy

While oral mucosal ulcers are not primarily infectious in etiology, the breach in mucosal integrity creates vulnerability to secondary bacterial colonization. The oral cavity harbors a complex microbiome comprising

hundreds of bacterial species, along with fungi and viruses, any of which may opportunistically colonize ulcerated tissue. Secondary infection can perpetuate inflammation, delay healing, and in immunocompromised patients, potentially lead to more serious complications[23].

Additionally, some evidence suggests that specific microbial antigens may play a role in triggering or perpetuating the inflammatory response in RAS through molecular mimicry or superantigen mechanisms. Antimicrobial therapy may therefore provide benefits beyond simple infection prevention[24].

7.2 Antiseptic Agents

Table 5: Antimicrobial Agents Used in Oral Ulcer Formulations

Agent	Class	Spectrum	Mechanism	Advantages/Limitations
Chlorhexidine	Bisbiguanide	Broad spectrum	Membrane disruption	Excellent efficacy; staining, taste alteration
Cetylpyridiniu m chloride	Quaternary ammonium	Gram-positive > Gram-negative	Membrane disruption	Good tolerability; limited spectrum
Triclosan	Phenol derivative	Broad spectrum	Multiple targets	Concerns about resistance
Povidone- iodine	Halogen	Broad spectrum	Oxidation	Rapid action; taste, staining
Metronidazole	Nitroimidazo le	Anaerobes, protozoa	DNA damage	Specific spectrum
Tetracycline	Antibiotic	Broad spectrum	Protein synthesis inhibition	Anti-collagenase activity; resistance concerns

Chlorhexidine gluconate remains the gold standard antiseptic for oral applications due to its broad-spectrum activity, substantivity (ability to bind to oral surfaces and provide prolonged effect), and extensive clinical evidence supporting its efficacy. However, its association with tooth staining, taste disturbance, and occasional hypersensitivity reactions has motivated the search for alternative antimicrobial agents[25].

7.3 Natural Antimicrobial Compounds

Natural products offer a rich source of antimicrobial compounds, many with favorable safety profiles and multiple mechanisms of action that may reduce the risk of resistance development[26].

Honey, particularly Manuka honey, demonstrates significant antimicrobial activity through multiple mechanisms including high osmolarity, low pH, hydrogen peroxide generation, and the presence of methylglyoxal. Propolis, a resinous substance produced by bees, contains flavonoids and phenolic compounds with antimicrobial and anti-inflammatory properties[27].

Plant-derived essential oils including tea tree oil (containing terpinen-4-ol), thyme oil (thymol), and oregano oil (carvacrol) exhibit broad-spectrum antimicrobial activity. These compounds typically act by disrupting microbial cell membranes, though additional mechanisms have been identified for specific oils[28].

Chitosan, derived from crustacean shells, possesses inherent antimicrobial activity against bacteria, fungi, and some viruses. Its cationic nature allows interaction with negatively charged microbial cell surfaces, leading to membrane disruption and cell death. This dual functionality as both a mucoadhesive polymer and antimicrobial agent makes chitosan particularly attractive for oral ulcer formulations[29].

VIII.Synergistic Benefits of Analgesic–Antimicrobial Combinations

8.1 Therapeutic Rationale

The combination of analgesic and antimicrobial agents in a single formulation addresses multiple pathophysiological aspects of oral mucosal ulcers simultaneously. This multimodal approach offers several advantages over monotherapy:

1. **Comprehensive symptom management:** Pain relief enables patients to maintain normal eating, drinking, and oral hygiene, which in turn supports the healing process.
2. **Infection prevention:** Antimicrobial activity prevents or treats secondary colonization that could perpetuate inflammation and delay healing.
3. **Reduced application burden:** A single formulation addressing multiple therapeutic needs simplifies the treatment regimen and may improve patient compliance.
4. **Potential synergistic interactions:** Some drug combinations demonstrate effects greater than the sum of individual contributions[30].

8.2 Formulation Considerations

Developing effective combination formulations requires attention to potential drug- drug interactions, compatibility with excipients, and optimization of release kinetics for each active component[31].

Table 6: Common Analgesic–Antimicrobial Combinations in Commercial and Experimental Formulations

Analgesic Component	Antimicrobial Component	Formulation Type	Key Features
Lidocaine	Chlorhexidine	Gel	Rapid pain relief, broad-spectrum activity
Benzocaine	Cetylpyridinium chloride	Gel, lozenge	OTC availability, good tolerability
Choline salicylate	Cetalkonium chloride	Gel	Anti-inflammatory + antiseptic
Triamcinolone	Neomycin/Gramicidin	Paste	Prescription, anti- inflammatory + antibiotic
Lidocaine	Metronidazole	Gel	Anaerobic coverage
Curcumin	Chitosan	Mucoadhesive gel	Natural combination, wound healing
Eugenol	Tea tree oil	Gel	Plant-derived, multiple mechanisms

The release profiles of combination products must be carefully designed to provide appropriate onset and duration for each component. For instance, rapid release of a local anesthetic provides immediate pain relief, while sustained release of an antimicrobial agent maintains protective concentrations over extended periods[32].

8.3 Evidence for Combination Efficacy

Clinical and preclinical studies have demonstrated the benefits of combination approaches. Formulations containing both local anesthetics and antimicrobials show improved patient-reported outcomes compared to single-agent products. The combination of anti-inflammatory and antimicrobial agents addresses both excessive inflammation and infection risk, potentially accelerating the transition from the inflammatory to the proliferative phase of wound healing[33].

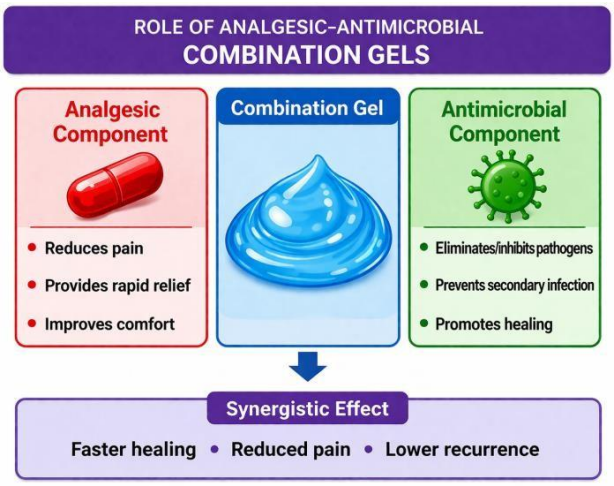

Fig 2: Role of Analgesic-Antimicrobial Combination Gels

IX.Advanced Drug Delivery Technologies

9.1 Nanoparticle-Based Systems

Nanotechnology has opened new possibilities for oral mucosal drug delivery, offering enhanced drug protection, controlled release, improved mucosal penetration, and the ability to target specific cellzz populations or tissues[34].

Polymeric nanoparticles: Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone can be formulated into nanoparticles that encapsulate drugs, protect them from degradation, and provide sustained release. Chitosan nanoparticles are particularly attractive due to their mucoadhesive properties and inherent antimicrobial activity[35].

Lipid-based nanocarriers: Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) offer excellent biocompatibility and the ability to encapsulate both hydrophilic and lipophilic drugs. These

systems can enhance drug penetration through the mucosal barrier and provide sustained release[36].

Metal-organic frameworks: Zeolitic imidazolate framework-8 (ZIF-8) and similar structures have emerged as promising drug carriers with high loading capacity, controlled release properties, and inherent antimicrobial activity due to zinc ion release[37].

9.2 Stimuli-Responsive (Smart) Hydrogels

Stimuli-responsive or "intelligent" hydrogels undergo physical or chemical changes in response to environmental triggers, enabling on-demand or site-specific drug release[38].

Thermoresponsive hydrogels: Polymers such as poloxamers (Pluronics) exhibit reverse thermal gelation, existing as liquids at room temperature but forming gels at body temperature. This property allows easy application as a liquid that transforms into a retentive gel upon contact with the oral mucosa[39].

pH-responsive systems: The pH of oral ulcer sites may differ from healthy mucosa due to inflammatory exudates and bacterial metabolism. pH-sensitive polymers can be designed to release drugs preferentially in the altered pH environment of the ulcer[40].

Enzyme-responsive systems: Matrix metalloproteinases (MMPs) and other enzymes are upregulated in inflamed and wounded tissues. Hydrogels incorporating enzyme- cleavable crosslinks can achieve targeted drug release specifically at sites of active inflammation or tissue remodeling[41].

Table 7: Stimuli-Responsive Hydrogel Systems for Oral Drug Delivery

Stimulus	Responsive Material	Mechanism	Application
Temperature	Poloxamer 407, PNIPAM	Sol-gel transition at 32-37°C	In situ gelling formulations
pH	Eudragit, chitosan	Ionization changes	Ulcer-targeted release
Enzymes	MMP-cleavable peptides	Enzymatic degradation	Inflammation- responsive
Ionic strength	Alginate, gellan gum	Ion-mediated crosslinking	Saliva-activated gelation

9.3 Microneedle Systems

Microneedle (MN) technology represents an innovative approach to overcoming the mucosal barrier and delivering drugs directly into the epithelium or submucosa. These devices consist of arrays of microscale needles (typically 100-1000 μm in length) that painlessly penetrate the superficial mucosa to enhance drug delivery[42].

Dissolving microneedles: Fabricated from water-soluble or biodegradable polymers, these needles dissolve upon insertion, releasing encapsulated drugs directly into the tissue. A particularly elegant design involves core-shell microneedles with different materials in the core and shell, enabling programmed sequential release of multiple drugs[43].

A recent study developed a multifunctional dissolving microneedle patch for oral ulcer treatment containing a gelatin methacryloyl (GelMA) shell loaded with basic fibroblast growth factor (bFGF), a hyaluronic acid core containing dexamethasone, and a backing layer with ZIF-8 for antimicrobial effects. This sophisticated design achieved anti-inflammatory, antimicrobial, and pro-healing effects through staged release of its components[44].

Coated microneedles: Drug is coated onto solid microneedle surfaces and deposited in the tissue upon insertion. This approach is suitable for potent drugs requiring small doses[45].

Hollow microneedles: These function as miniature hypodermic needles, allowing infusion of liquid drug formulations through the needle lumen[46].

9.4 Mucoadhesive Films and Patches

Mucoadhesive films and patches offer advantages over semi-solid formulations including precise dosing, unidirectional drug release toward the mucosa, and extended residence time without the messiness associated with gels[47].

Single-layer films: Simple matrix systems where the drug is dispersed throughout a mucoadhesive polymer film[48].

Bilayer and multilayer films: Consist of a mucoadhesive drug-loaded layer facing the tissue and a backing layer that prevents drug loss to the oral cavity and provides mechanical support[49].

Electrospun nanofiber mats: Electrospinning produces ultrafine fibers with high surface area, enabling rapid dissolution, high drug loading, and the ability to create complex multilayer structures[50].

Recent innovations include films incorporating growth factors for enhanced healing, antimicrobial agents for infection prevention, and combinations of immediate-release and sustained-release layers for optimized drug delivery profiles[51].

X.Polyherbal Gel Formulations

10.1 Rationale for Herbal Approaches

Interest in herbal and natural product-based formulations for oral ulcer management has grown substantially, driven by several factors: concerns about adverse effects of synthetic drugs (particularly corticosteroids), the emergence of antimicrobial resistance, the multitarget mechanisms of many natural compounds, and patient preference for "natural" treatments[52].

Polyherbal formulations combine multiple plant extracts or purified compounds to achieve synergistic therapeutic effects. This approach aligns with traditional medical systems such as Ayurveda and Traditional Chinese Medicine, which have long used multi-component herbal preparations for oral diseases[53].

10.2 Network Pharmacology Approaches

Modern analytical approaches including network pharmacology and systems biology are providing mechanistic insights into how polyherbal formulations exert their therapeutic effects. By mapping the interactions between multiple active compounds and their biological targets, researchers can identify synergistic combinations and optimize formulation composition[54].

These approaches have revealed that effective polyherbal formulations often modulate multiple pathways simultaneously—inflammatory signaling, oxidative stress, microbial virulence factors, and tissue regeneration—providing a pharmacological basis for the observed clinical benefits of traditional multi-herb preparations[55].

XI.Evaluation Parameters for Oral Ulcer Formulations

11.1 Physicochemical Characterization

Table 8: Evaluation Parameters for Mucoadhesive Gel Formulations

Parameter	Method	Significance
pH	pH meter	Mucosal compatibility (target: 5.5- 7.0)
Viscosity	Rheometer/viscometer	Application properties, retention
Spreadability	Parallel plate method	Ease of application
Drug content	HPLC, UV spectroscopy	Dose accuracy
Homogeneity	Visual inspection, microscopy	Quality control
Gel strength	Texture analyzer	Mechanical properties
Syringeability	Force measurement	Packaging compatibility

11.2 Mucoadhesive Strength Assessment

Mucoadhesive strength is typically evaluated using texture analyzers or modified balance methods that measure the force required to detach a formulation from mucosal tissue (often porcine or bovine buccal mucosa as a model). Results are expressed as peak detachment force, work of adhesion, or adhesion time[55].

In vitro residence time studies using inclined plate or rotating cylinder methods complement force measurements by assessing how long formulations remain attached under conditions simulating the oral environment[57].

11.3 Drug Release Studies

In vitro drug release testing employs Franz diffusion cells or similar apparatus with appropriate receptor media and membrane barriers. Release kinetics are analyzed using mathematical models (zero-order, first-order, Higuchi, Korsmeyer-Peppas) to understand the release mechanism and predict in vivo performance[58].

For combination products, simultaneous quantification of multiple active components is essential to characterize the release profile of each drug and ensure appropriate timing of therapeutic effects[59].

11.4 Antimicrobial Efficacy Testing

Antimicrobial activity is assessed through agar diffusion methods, minimum inhibitory concentration (MIC) determination, and time-kill kinetics against relevant oral pathogens. Common test organisms include Streptococcus mutans, Candida albicans, Porphyromonas gingivalis, and other species implicated in oral infections[60].

11.5 Biocompatibility and Safety Assessment

Cytotoxicity testing: Cell viability assays (MTT, alamarBlue) using oral keratinocytes or fibroblasts evaluate formulation toxicity[61].

Mucosal irritation: The hen's egg test-chorioallantoic membrane (HET-CAM) or slug mucosal irritation test

provides alternatives to animal testing for initial irritation screening[62].

Wound healing assays: Scratch assays and cell migration studies assess the effects of formulations on epithelial regeneration[63].

11.6 In Vivo Evaluation

Animal models for oral ulcer research include chemically induced ulcers (acetic acid, phenol), thermally induced lesions, and radiation-induced mucositis in rats, hamsters, or rabbits. Evaluation endpoints include ulcer size reduction, histopathological healing assessment, and biomarker analysis[64].

Clinical trials assess efficacy through validated outcome measures including visual analog scales for pain, ulcer size measurements, healing time, and quality of life instruments specific to oral conditions[65].

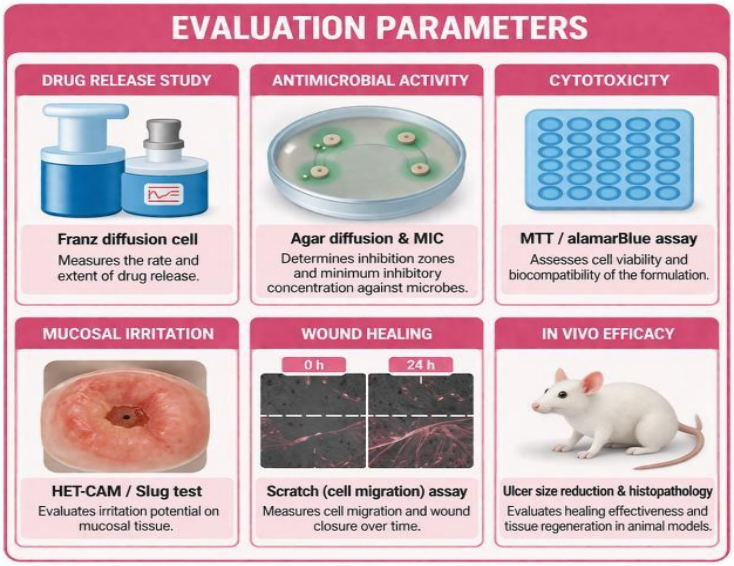

Fig 3: Evaluation Parameters

14. Conclusion

Oral mucosal ulcers remain a significant clinical challenge affecting millions of patients worldwide. The unique physiological environment of the oral cavity—with its continuous salivary flow, mechanical stresses, and complex microbiome—demands sophisticated drug delivery approaches beyond conventional formulations.

Analgesic–antimicrobial combination gels address the multifactorial nature of oral ulcer pathophysiology by simultaneously providing pain relief and preventing secondary infection. The integration of these therapeutic agents within mucoadhesive matrices extends drug residence time and enhances efficacy compared to non-adhesive formulations.

Emerging technologies including nanoparticle-based carriers, stimuli-responsive hydrogels, dissolving microneedles, and advanced mucoadhesive systems offer promising solutions to longstanding delivery challenges. These platforms enable sustained drug release, improved mucosal penetration, and reduced application frequency, potentially transforming patient outcomes and compliance.

The growing evidence supporting natural and polyherbal formulations provides alternatives to synthetic drugs with potentially superior safety profiles and multitarget mechanisms. Network pharmacology approaches are elucidating the scientific basis for traditional multicomponent therapies and guiding rational formulation optimization.

Future research should focus on clinical translation of promising technologies, development of personalized treatment approaches, and integration of natural compounds with advanced delivery systems. Addressing the current gaps between laboratory innovation and clinical availability will be essential for improving the lives of patients suffering from oral mucosal ulcers.

Future Perspectives

The field of topical drug delivery for oral mucosal ulcers is evolving rapidly, with analgesic– antimicrobial combination gels emerging as a promising therapeutic strategy. Future developments are expected to focus on improving therapeutic efficacy, patient compliance, and targeted delivery through advanced technologies and interdisciplinary approaches.

One of the key future directions involves the integration of nanotechnology-based delivery systems such as nanoparticles, nanoemulsions, and nanofibers. These systems can enhance drug solubility, stability, and penetration across the oral mucosa, enabling controlled and sustained release of both analgesic and antimicrobial agents. This approach may significantly reduce dosing frequency and improve patient adherence, particularly in chronic or recurrent ulcerative conditions.

Another promising area is the development of stimuli-responsive (smart) mucoadhesive gels**,** which can release drugs in response to environmental triggers such as pH, temperature, or enzymatic activity in the oral cavity. Such systems could ensure on-demand drug release**,** delivering higher concentrations of drugs specifically at inflamed or infected sites while minimizing systemic exposure and adverse effects.

Advancements in biopolymer-based mucoadhesive systems (e.g., chitosan, hyaluronic acid, and alginate) are also expected to play a crucial role. These polymers not only improve adhesion and residence time but may also possess intrinsic wound healing and anti-inflammatory properties**,** thereby providing a synergistic therapeutic effect alongside the incorporated drugs.

The incorporation of novel antimicrobial agents, including antimicrobial peptides, probiotics, and plant-derived phytoconstituents, offers an alternative to conventional antibiotics and may help address the growing issue of antimicrobial resistance. Combining these agents with fast- acting analgesics could lead to more effective and safer treatment options.

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