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Review Article

Cubosomes as Advanced Nanocarriers for Oral Ulcer Treatment: A Review on Their Role in Enhancing Therapeutic Activity

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ABSTRACT

Oral ulcers are painful inflammatory lesions of the oral mucosa that interfere with eating, speaking, swallowing, and overall quality of life. Recurrent aphthous stomatitis, traumatic ulcers, chemically induced ulcers, and inflammatory mucosal lesions are commonly encountered forms. Although topical corticosteroids, antiseptics, local anesthetics, protective gels, and herbal preparations are widely used, their therapeutic action is frequently limited by rapid salivary washout, short mucosal residence time, poor penetration, enzymatic degradation, and the need for frequent application. Recent advances in oral mucosal drug delivery have therefore focused on mucoadhesive and nanocarrier-based systems that can improve drug retention, local bioavailability, and sustained therapeutic action. Cubosomes are lipid-based, self-assembled, bicontinuous cubic phase nanoparticles composed of amphiphilic lipids such as glyceryl monooleate or phytantriol and stabilizers such as Poloxamer 407. Their unique internal architecture contains interpenetrating aqueous channels separated by lipid bilayers, enabling simultaneous incorporation of hydrophilic, lipophilic, and amphiphilic molecules. This makes cubosomes highly suitable for delivering anti-inflammatory, antimicrobial, antioxidant, analgesic, and wound-healing agents to oral ulcer sites. When incorporated into a mucoadhesive gel, cubosomes may improve mucosal adhesion, protect unstable drugs or phytoconstituents, sustain release, enhance local penetration, reduce dosing frequency, and maintain therapeutic concentration at the ulcer surface. Herbal extracts such as *Psidium guajava* leaf extract may particularly benefit from cubosomal delivery because their flavonoid, tannin, and phenolic constituents have reported anti-inflammatory, antioxidant, antimicrobial, and wound-healing potential. Overall, cubosome-loaded mucoadhesive gels represent a promising advanced approach for oral ulcer therapy, although further standardized preclinical and clinical studies are required.

Keywords: Cubosomes, Mucoadhesive Gel, Nanocarrier, Oral Mucosal Drug Delivery, Oral Ulcer, *Psidium guajava*, Recurrent Aphthous Stomatitis, Sustained Release.

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INTRODUCTION

Oral ulcers are localized breaks or erosions in the oral mucosal epithelium, usually associated with pain, inflammation, burning sensation, and difficulty in daily activities such as eating, drinking, speaking, and swallowing. They may occur due to local trauma, immune dysregulation, microbial infection, nutritional deficiency, stress, systemic disease, drug reactions, or chemical irritation. Among them, recurrent aphthous stomatitis is one of the most common ulcerative conditions of the oral mucosa and is characterized by repeated episodes of painful ulcers, usually occurring on non-keratinized mucosal surfaces.[1]

The primary goals of oral ulcer treatment are pain relief, reduction of inflammation, prevention of secondary infection, protection of the ulcerated surface, and acceleration of epithelial healing. Conventional therapy includes topical corticosteroids, antiseptic mouth rinses, local anesthetics, analgesic gels, protective pastes, and herbal formulations. However, despite their availability, these treatments often provide only temporary relief because the oral cavity presents several physiological barriers to effective drug delivery.

Continuous salivary secretion, frequent swallowing, tongue movement, mastication, mucosal turnover, enzymatic activity, and dilution of the applied formulation reduce drug contact time at the lesion site. Recent reviews on oral mucosal drug delivery emphasize that the oral cavity is a challenging site because drug retention, penetration, stability, and local bioavailability are difficult to maintain.[2,3]

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Mucoadhesive drug delivery systems have therefore gained attention for oral inflammatory mucosal diseases because they can prolong drug contact with the mucosa, reduce mechanical irritation, improve patient adherence, and minimize the need for frequent application. A 2025 systematic review on mucoadhesive drug delivery systems for oral chronic inflammatory mucosal diseases reported that these systems may address important limitations of traditional formulations in recurrent aphthous stomatitis and oral lichen planus by improving local residence and sustained release.[4]

Cubosomes are emerging lipid-based nanocarriers that may further strengthen oral ulcer therapy. They are nanosized particles derived from bicontinuous cubic liquid crystalline phases and possess a highly ordered internal structure. Recent comprehensive reviews describe cubosomes as versatile carriers capable of encapsulating hydrophilic, hydrophobic, and amphiphilic molecules while supporting controlled drug release.[5,6] Therefore, cubosomes can be especially useful in oral ulcer treatment, where prolonged local action and protection of therapeutic molecules are essential.

The present review discusses the structure, composition, preparation, characterization, and therapeutic relevance of cubosomes for oral ulcer treatment. It also explains how cubosomes may enhance therapeutic activity when incorporated into mucoadhesive gels, with special attention to herbal extract-loaded cubosomes such as *Psidium guajava* extract-based systems.

Oral Ulcers: Pathophysiology and Therapeutic Challenges

Oral ulceration involves disruption of the epithelial barrier, exposure of underlying connective tissue, inflammatory cell infiltration, and activation of pain pathways. The ulcer base is often covered with a fibrinous pseudomembrane, while the surrounding mucosa appears erythematous due to inflammation. In recurrent aphthous ulcers, immune-mediated mechanisms, genetic predisposition, nutritional deficiency, oxidative stress, and microbial factors may contribute to recurrence and may contribute to recurrence and persistence of lesions.

Inflammation plays a central role in ulcer development and persistence. Tissue injury activates inflammatory mediators, recruits neutrophils and macrophages, and increases local cytokine production. This results in pain, swelling, delayed epithelial repair, and susceptibility to secondary microbial contamination. Pain is a major clinical problem because even small oral ulcers can interfere with food intake and speech due to the rich sensory innervation of the oral mucosa.

The oral environment strongly limits the effectiveness of conventional topical formulations. Saliva dilutes and removes drugs from the ulcer surface, while the movement of the tongue and food causes mechanical clearance. The mucosal surface is moist and dynamic, making it difficult for ordinary gels or ointments to remain in place for a long duration. In addition, some therapeutic molecules have poor solubility, poor permeability, or low stability in oral conditions. Recent work on oral mucosa-targeted delivery platforms highlights that enzymatic degradation, limited penetration, and solubility issues remain major barriers in oral mucosal therapy.[2]

Therefore, an ideal oral ulcer formulation should have good mucoadhesion, controlled release, local retention, non-irritancy, acceptable taste, suitable pH, and the ability to deliver actives into or near the ulcerated tissue. Cubosome-loaded mucoadhesive gels can potentially fulfill many of these requirements.

Conventional Oral Ulcer Therapy and Its Limitations

Conventional oral ulcer treatment is mainly symptomatic and supportive. Topical corticosteroids reduce inflammation, local anesthetics provide temporary pain relief, antiseptics reduce microbial load, and protective gels or pastes cover the ulcer surface. Herbal gels are also commonly explored because plant-derived compounds may provide antioxidant, antimicrobial, anti-inflammatory, and wound-healing benefits.

However, the main problem with conventional formulations is that they do not remain at the ulcer site long enough. Simple topical gels often undergo rapid washout due to saliva and swallowing. Mouth rinses provide even shorter contact time and may require repeated application. Ointments and pastes may be uncomfortable, poorly retained, or unpleasant in taste. Moreover, conventional formulations may show burst release, where the drug is released quickly at the beginning but fails to maintain a therapeutic concentration over time (Figure 1).

Mucoadhesive formulations improve this situation by adhering to mucin and prolonging local contact. Polymers such as Carbopol, chitosan, alginate, pectin, and cellulose derivatives are widely investigated for oral mucoadhesive delivery. Reviews on mucoadhesive carriers state that these polymers can interact with the mucosal surface and increase residence time, thereby improving drug availability at the site of action.[7]

Still, mucoadhesion alone may not fully solve the problem if the active drug has poor solubility, instability, or weak tissue penetration. This is where nanocarriers become useful. Lipid-based nanocarriers can improve drug solubilization, protect sensitive molecules, and provide sustained release. Among lipid-based nanocarriers, cubosomes are particularly attractive because of their unique internal cubic structure.

Cubosomes: Definition, Structure, and Composition

Cubosomes are nanosized dispersions of bicontinuous cubic liquid crystalline phases. They are usually formed by amphiphilic lipids that self-assemble in water into a cubic phase. The internal

structure consists of two continuous but non-intersecting aqueous channels separated by a lipid bilayer. This arrangement creates a large internal surface area and allows the system to carry different types of molecules within the same particle.[5,6]

The most commonly used lipids for cubosome formation include glyceryl monooleate and phytantriol. Glyceryl monooleate is a biodegradable and biocompatible amphiphilic lipid that forms cubic phases in aqueous media. Phytantriol is another lipid frequently used because of its chemical stability and ability to form well-defined cubic structures. Stabilizers such as Poloxamer 407 are usually added to prevent aggregation and maintain nanosized dispersion.[5] The special feature of cubosomes is their capacity to encapsulate hydrophilic, lipophilic, and amphiphilic molecules.[8,9]

Hydrophilic drugs can be located within aqueous channels, lipophilic molecules can be incorporated into the lipid bilayer, and amphiphilic molecules can localize at the lipid-water interface. A 2022 review in Journal of Materials Chemistry B emphasized that cubosomes are attractive because they can encapsulate different classes of bioactive substances and support controlled release across multiple routes of administration. For oral ulcer treatment, this structural advantage is extremely important for anti-inflammatory action, antimicrobial protection, antioxidant defense, pain reduction, and tissue repair. Cubosomes can potentially deliver single drugs, drug combinations, or complex herbal extracts containing multiple phytoconstituents.

Preparation Methods of Cubosomes

Cubosomes can be prepared using different methods, mainly top-down and bottom-up approaches. In the top-down method, a bulk cubic phase is first formed by mixing lipid, stabilizer, and aqueous phase. This viscous cubic phase is then dispersed into nanoparticles using high-energy techniques such as high-speed homogenization and ultrasonication. This method is commonly used in laboratory-scale formulation development.

In the bottom-up method, cubosomes are formed from molecular precursors or solvent-based systems that self-assemble into nanoparticles upon dilution or hydration. This method may require less energy and can produce smaller particles, but it may involve solvents or more complex processing conditions. Recent reviews describe both top-down and bottom-up methods as important strategies for controlling cubosome size, stability, and drug-loading behavior.[5,6]

For herbal extract-loaded cubosomes, the preparation method should be selected carefully because phytoconstituents such as flavonoids and phenolics may be sensitive to high temperature, oxidation, and prolonged exposure to organic solvents. Therefore, mild processing conditions are preferred. In the case of *Psidium guajava* extract-loaded cubosomes, the extract can be incorporated during lipid hydration or dispersion formation depending on its solubility profile. Since herbal extracts contain both polar and moderately lipophilic compounds, cubosomes are suitable carriers because their structure can accommodate mixed phytoconstituents.

Important formulation variables include lipid concentration, stabilizer concentration, lipid-to-drug ratio, homogenization speed, sonication time, hydration volume, temperature, and pH. These variables influence particle size, polydispersity index, zeta potential, entrapment efficiency, viscosity, release profile, and physical stability.

Characterization of Cubosomes for Oral Ulcer Delivery

Cubosome characterization is essential to confirm that the formulation is suitable for mucosal application. The most important parameters include particle size, polydispersity index, zeta potential, morphology, entrapment efficiency, drug content, *in vivo* release, mucoadhesion, stability, and safety.

Particle size determines the interaction of the formulation with the mucosa. Nanosized particles may improve surface contact, distribution, and penetration into superficial mucosal layers. A lower polydispersity index indicates a more uniform particle population. Zeta potential provides information about surface charge and colloidal stability. Although lipid nanoparticles may be stabilized by steric effects from Poloxamer 407, zeta potential still helps predict aggregation tendency.

Morphological evaluation using transmission electron microscopy, scanning electron microscopy, or cryo-TEM can confirm the shape and surface appearance of cubosomes. Small-angle X-ray scattering is considered one of the strongest methods to confirm internal cubic structure, although it may not always be available in routine academic laboratories. Recent cubosome reviews highlight that characterization of internal nanostructure is important because cubosome performance depends strongly on the cubic phase arrangement.[5,6]

Entrapment efficiency and drug content indicate how much active substance is successfully incorporated into the cubosomal system. *In vivo* release studies help determine whether the formulation provides sustained release. For oral ulcer therapy, sustained release is desirable because it maintains local drug concentration and reduces the need for repeated application.

When cubosomes are incorporated into a mucoadhesive gel, additional gel evaluation parameters become necessary, including pH, viscosity, spreadability, extrudability, homogeneity, mucoadhesive strength, residence time, and release from gel matrix. A suitable oral gel should have near-neutral pH, smooth texture, acceptable viscosity, and non-irritant behavior.

Need for Cubosomes in Oral Ulcer Treatment

The need for cubosomes in oral ulcer treatment arises from the mismatch between the requirements of ulcer healing and the limitations of conventional topical therapy. Oral ulcer healing requires prolonged local contact of active compounds with the lesion. However, conventional formulations are rapidly removed. Cubosomes address this problem through nanoscale encapsulation, sustained release, protection of actives, and improved mucosal interaction.

Cubosomes can retain therapeutic compounds inside their internal nanostructure and release them slowly. This sustained release is beneficial because oral ulcer healing is a continuous biological process involving inflammation control, epithelial migration, collagen deposition, and tissue remodeling. If the drug is rapidly removed, healing may be delayed. If the drug remains available for a longer time, the therapeutic response may improve.

Another important need is protection of unstable compounds. Many anti-inflammatory agents and herbal phytoconstituents are sensitive to oxidation, light, and enzymatic degradation. Cubosomes can protect these compounds by incorporating them into lipidic domains or aqueous channels. This is particularly relevant for plant extracts rich in flavonoids, tannins, and phenolic acids.

Recent reviews on topical cubosome applications show that cubosomes are increasingly investigated for inflammatory, infectious, and barrier-related conditions because they can improve drug localization and sustained activity.[9] Although direct clinical evidence for cubosomes in oral ulcers is still limited, their properties strongly match the formulation needs of oral ulcer therapy.

Mechanism by Which Cubosomes Enhance Therapeutic Activity

Cubosomes may enhance oral ulcer therapy through several interconnected mechanisms. First, they improve local retention. When cubosomes are dispersed into a mucoadhesive gel, the gel adheres to the oral mucosa and resists immediate washout. This increases the contact time between the formulation and ulcer surface. Prolonged contact allows more drug to be delivered locally.

Second, they sustain drug release. The bicontinuous cubic structure acts as a diffusion-controlled matrix. The drug must move through aqueous channels, lipid bilayers, or the gel network before reaching the ulcer surface. This slows release and maintains therapeutic concentration for longer periods.

Third, they improve solubilization. Poorly soluble drugs and phytoconstituents can be incorporated into the lipid bilayer, improving their dispersion and availability. This is important for flavonoids and other plant-derived compounds that often show poor water solubility.

Fourth, they protect active molecules from degradation. Encapsulation inside the cubosomal matrix may reduce exposure to saliva, enzymes, oxygen, and external pH fluctuations. Fifth, they improve mucosal interaction. Lipid-based nanoparticles can interact with biological membranes and may enhance local penetration. The nanoscale size increases surface area and contact with the ulcerated mucosa.

Sixth, they support multifunctional therapy. Oral ulcer treatment ideally requires anti-inflammatory, antimicrobial, antioxidant, analgesic, and wound-healing actions. Cubosomes can carry complex extracts or combinations of actives, making them useful for multi-target treatment (Figure 2).

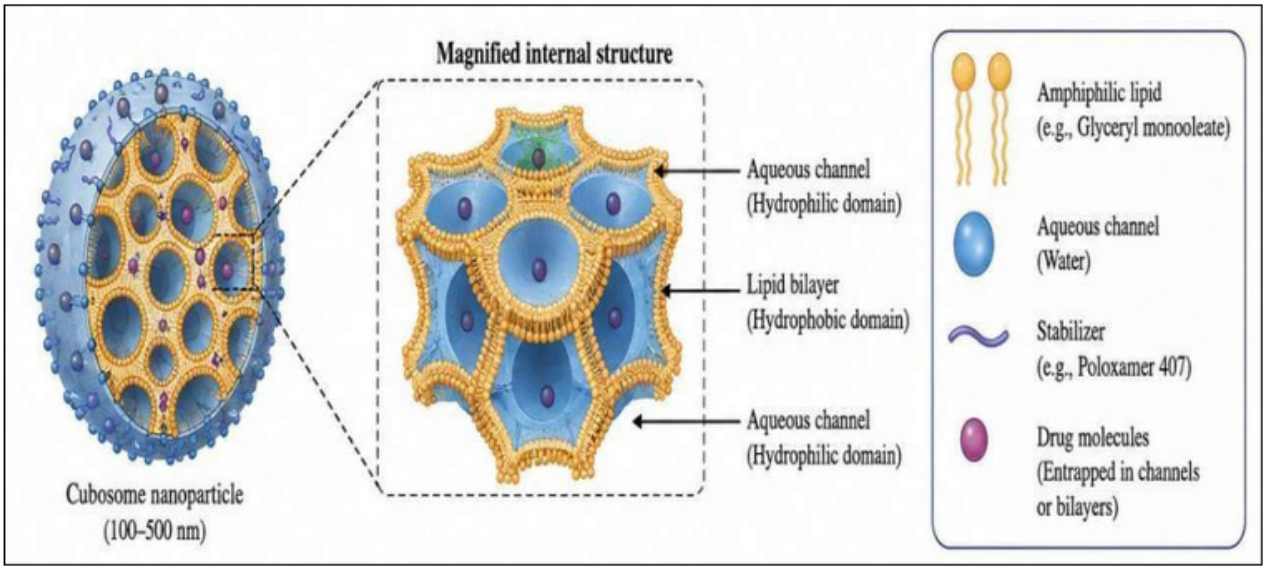

Figure 1: Structure of Cubosome.

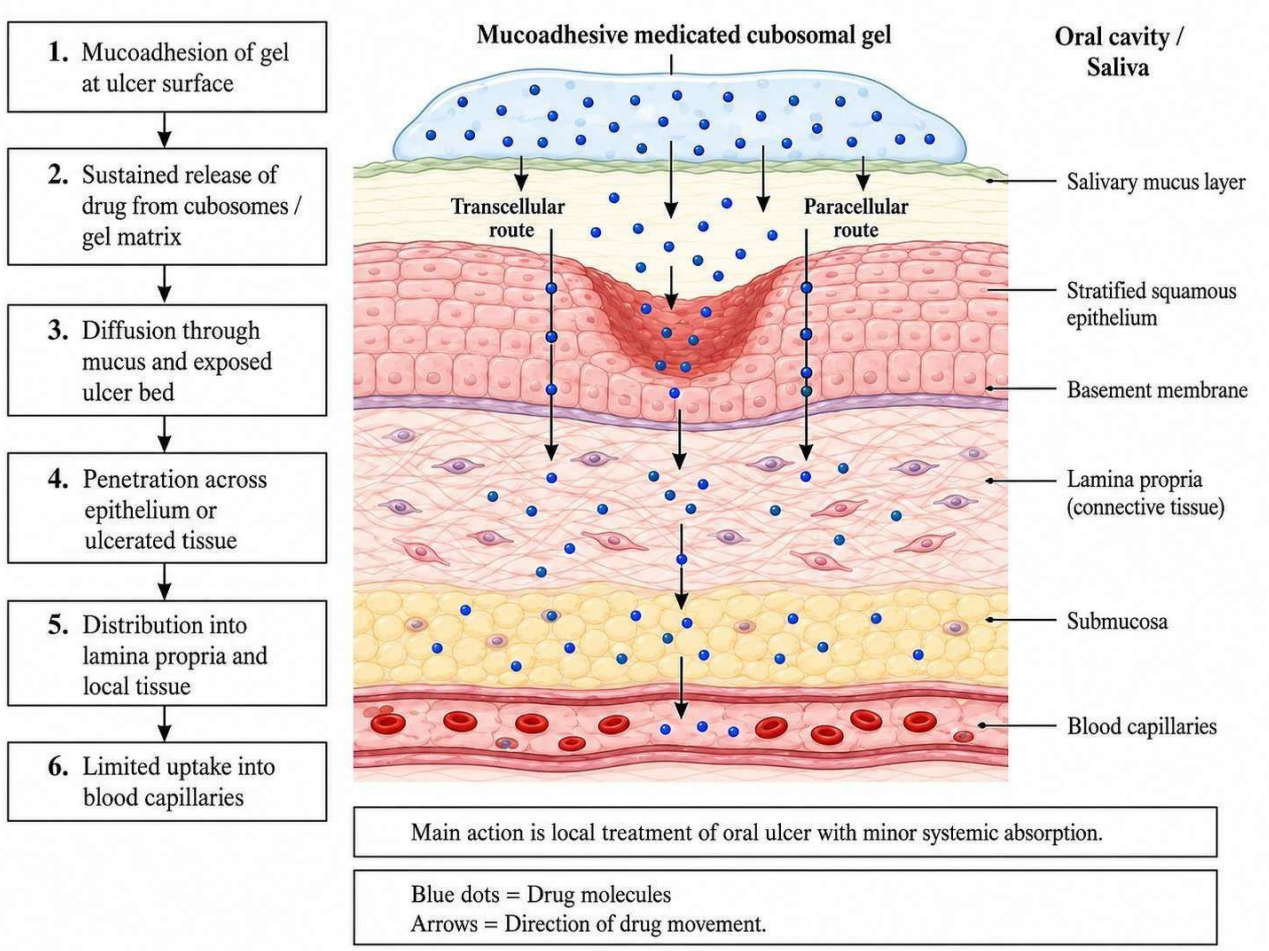

Figure 2: Mechanism of drug delivery from cubosome-loaded mucoadhesive gel in oral ulcer treatment.

Cubosomal Mucoadhesive Gel: A Suitable Dosage Form for Oral Ulcers

Cubosomes as a dispersion may still be removed from the oral cavity if applied alone due to continuous salivary flow, tongue movement, and mechanical disturbances. Therefore, incorporation into a mucoadhesive gel is a more suitable strategy for oral ulcer treatment. A cubosomal mucoadhesive gel combines the advantages of two systems: the nanocarrier provides protection to the encapsulated phytoconstituents, enhances their stability, and ensures sustained and controlled drug release, while the mucoadhesive gel offers prolonged residence time at the site of application by forming strong interactions with the mucin layer of the oral epithelium. Additionally, the gel acts as a protective barrier over the ulcer surface, reducing irritation, preventing secondary infections, and promoting faster healing. This dual-function system also improves patient compliance due to ease of application, non-invasiveness, and reduced dosing frequency. Overall, such a formulation enhances bioavailability at the target site and maximizes therapeutic efficacy in the management of oral ulcers.

Mucoadhesive polymers such as Carbopol, chitosan, sodium alginate, hydroxypropyl methylcellulose, and pectin can be used to prepare oral gels. Carbopol is frequently used because of its strong mucoadhesive property and ability to form clear gels at suitable pH. Chitosan provides additional mucoadhesion and may also contribute antimicrobial activity. Alginate and cellulose derivatives can improve gel consistency and patient acceptability.

The ideal cubosomal gel for oral ulcers should have the following properties: pH compatible with oral mucosa, smooth texture, good spreadability, suitable viscosity, uniform drug content, adequate mucoadhesive strength, sustained release, non-irritant behavior, and physical stability. Recent studies on hydrogels for mucosal drug delivery also support the importance of hydrogel-based systems for local delivery to oral cavity conditions.[10]

A cubosomal gel may also act as a protective barrier over the ulcer surface. This barrier can reduce mechanical irritation from food and tongue movement, while simultaneously releasing therapeutic agents. Such a dual action is highly desirable in painful oral ulcers.

Role of Herbal Extract-Loaded Cubosomes in Oral Ulcer Therapy

Herbal medicines have long been used for oral ulcer management because many plant extracts possess anti-inflammatory,

antimicrobial, antioxidant, analgesic, and wound-healing properties. However, crude herbal extracts face several formulation challenges, including poor stability, low solubility, variable absorption, unpleasant taste, and rapid clearance from the oral cavity.

Nanocarrier-based herbal delivery can improve the performance of plant extracts by protecting phytoconstituents, improving dispersion, sustaining release, and enhancing local bioavailability. Cubosomes are especially suitable for herbal extracts because plant extracts often contain compounds of different polarities. Hydrophilic phenolics may occupy aqueous regions, lipophilic components may partition into lipid bilayers, and amphiphilic constituents may locate at interfaces.

Psidium guajava leaves are rich in flavonoids, tannins, phenolic acids, triterpenoids, and other phytoconstituents. These constituents are associated with antimicrobial, antioxidant, anti-inflammatory, and wound-healing activities. A clinical study on *Psidium guajava*-based herbal gel for mouth ulcers reported its potential usefulness in ulcer management, supporting the relevance of guava-based topical therapy.[11] Reviews and experimental studies also describe the pharmacological potential of *Psidium guajava* leaves due to their phytochemical composition.[12,13]

Loading *Psidium guajava* extract into cubosomes can theoretically enhance its activity in several ways. The cubosomal system can protect phenolic and flavonoid compounds from degradation, improve their distribution in the gel, sustain their release, and increase local contact with the ulcerated mucosa. When incorporated into a mucoadhesive gel, the formulation may provide prolonged retention and better therapeutic performance than a simple guava extract gel.

Therefore, *Psidium guajava* extract-loaded cubosomal mucoadhesive gel is a scientifically justified formulation concept for oral ulcer treatment.

Comparison Between Conventional Gel and Cubosomal Gel

A conventional oral ulcer gel mainly acts by direct contact of the drug with the ulcer surface. However, it may release the drug rapidly and then be removed by saliva. This leads to short duration of action and repeated dosing. In contrast, a cubosomal gel provides both mucoadhesive retention and nanocarrier-controlled release.

Parameter	Conventional Oral Ulcer Gel	Cubosome-Loaded Mucoadhesive Gel
Residence time	Short due to salivary washout	Prolonged due to mucoadhesion
Drug release	Often rapid or burst release	Sustained and controlled release
Drug protection	Limited	Improved protection inside nanostructure
Local bioavailability	Reduced by dilution and clearance	Improved by retention and nanoscale delivery
Dosing frequency	Frequent application required	May reduce application frequency
Herbal extract stability	May be low	May improve stability of phytoconstituents
Patient compliance	Moderate	Potentially improved
Healing support	Short-term effect	Prolonged anti-inflammatory and healing action

This comparison shows why cubosomal gels are more advanced than ordinary topical gels for oral ulcer treatment.

Safety, Biocompatibility, and Patient Acceptability

For oral ulcer therapy, safety is extremely important because the formulation is applied directly to damaged mucosa. Excipients should be non-irritant, biocompatible, and acceptable for oral use. Glyceryl monooleate and Poloxamer 407 are commonly used in lipid-based systems and are generally considered suitable excipients when used appropriately. However, the final formulation must still be tested for cytotoxicity, irritation, pH compatibility, and mucosal tolerance.

The pH of the formulation should be close to oral mucosal pH to avoid irritation. The gel should be smooth, non-gritty, and easy to apply. Taste and mouthfeel are also important because unpleasant formulations reduce patient compliance. For herbal formulations, bitterness or astringency may need to be masked.

Preclinical safety evaluation may include cytotoxicity studies using oral epithelial cells, hemolysis testing if relevant, mucosal irritation studies, and histopathological evaluation.

For animal models of oral ulcers, safety and efficacy should be assessed through ulcer score, ulcer area reduction, epithelial regeneration, inflammatory cell infiltration, and collagen deposition (Figure 3).

Current Research Gaps

Although cubosomes have strong theoretical and experimental potential as drug delivery systems, direct research on cubosome-based formulations specifically for oral ulcers is still limited. Most cubosome studies focus on topical skin delivery, ocular delivery, cancer therapy, oral systemic delivery, and transdermal delivery.[5,9] Therefore, more research is needed

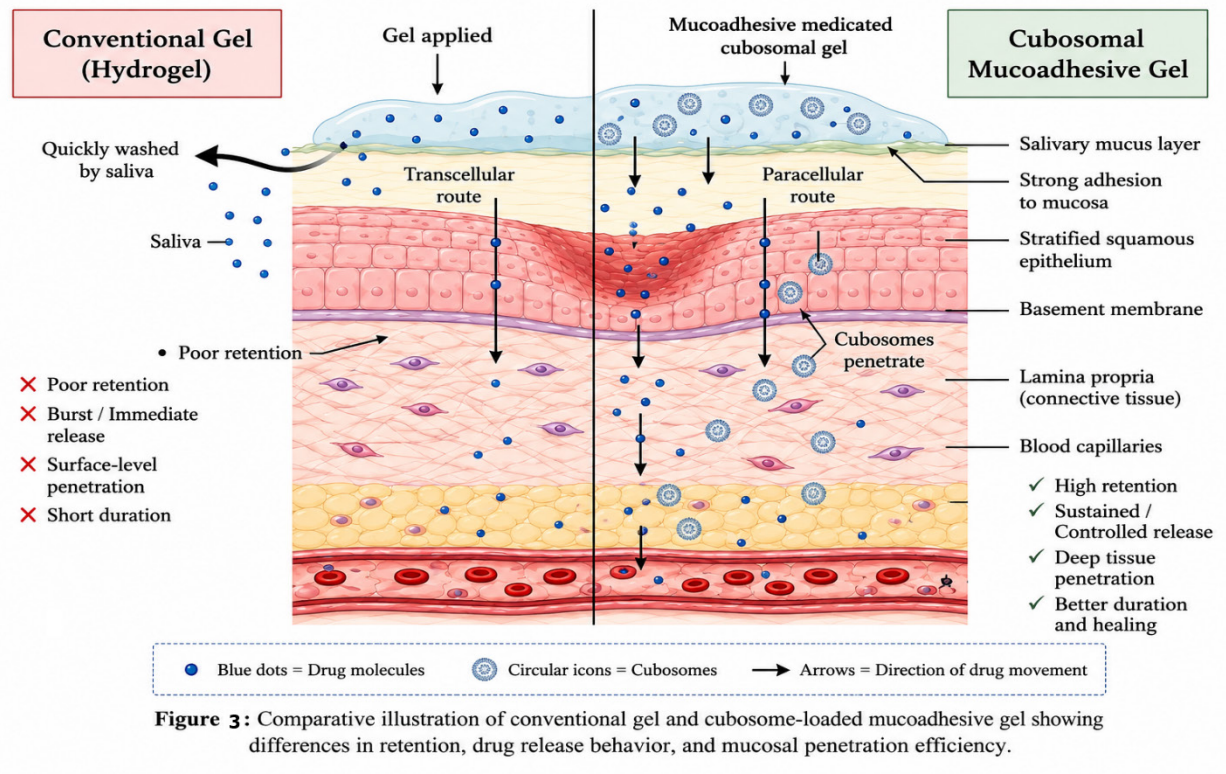

Figure 3: Comparative illustration of conventional gel and cubosome-loaded mucoadhesive gel showing differences in retention, drug release behavior, and mucosal penetration efficiency.

Figure 3: Comparative Illustration of Conventional Hydrogel and Cubosome-Loaded Mucoadhesive Gel for Oral Mucosal Drug Delivery.

to establish cubosomes as a standard platform for oral ulcer treatment.

Important research gaps include lack of standardized oral ulcer cubosome formulations, limited *ex vivo* oral mucosal permeation data, limited *in vivo* oral ulcer healing studies, absence of clinical trials, and insufficient long-term stability data. There is also a need to compare cubosomal gels directly with conventional gels, marketed oral ulcer products, and other nanocarriers such as liposomes, nanoemulsions, and polymeric nanoparticles.

Another important gap is herbal standardization. If plant extracts such as *Psidium guajava* are used, the extract should be standardized using phytochemical markers such as total flavonoid content, total phenolic content, or marker compounds like quercetin, rutin, or gallic acid. Without standardization, reproducibility becomes difficult.

FUTURE PERSPECTIVES

Future research should focus on developing cubosomal mucoadhesive gels with optimized particle size, polydispersity index, zeta potential, entrapment efficiency, release profile, mucoadhesive strength, and stability. Advanced characterization techniques such as small-angle X-ray scattering, cryo-TEM, and rheological analysis can provide better understanding of internal structure and gel behavior.

In vivo studies should include drug release, antioxidant activity, antimicrobial activity, anti-inflammatory assays, cytotoxicity testing, and cell migration assays. *Ex vivo* studies using animal or human oral mucosa can help evaluate mucosal penetration and retention. Recent reviews on *in vivo* and *ex vivo* oral mucosa models emphasize their importance as predictive platforms for oral drug delivery evaluation.[14]

In vivo oral ulcer models should assess ulcer size, ulcer score, healing percentage, histopathological changes, inflammatory infiltration, epithelial regeneration, and collagen deposition. Finally, clinical studies are required to evaluate pain relief, healing time, recurrence, patient acceptability, safety, and comparison with standard treatment.[15,16]

In the future, cubosomal gels may also be combined with smart polymers, stimuli-responsive systems, antimicrobial peptides, growth factors, exosomes, or natural wound-healing agents. These innovations may lead to more effective and personalized oral ulcer therapy.

CONCLUSION

Cubosomes are promising lipid-based nanocarriers for oral ulcer treatment because they combine high drug-loading capacity, protection of active molecules, sustained release, and improved local delivery. Oral ulcer therapy requires prolonged contact of anti-inflammatory, antimicrobial, antioxidant, analgesic, and wound-healing agents with the ulcerated mucosa. Conventional gels and mouth rinses are limited by rapid salivary washout, short residence time, poor penetration, and frequent dosing.

Cubosomes can overcome many of these limitations, especially when incorporated into mucoadhesive gels.

The unique bicontinuous cubic structure of cubosomes allows them to entrap hydrophilic, lipophilic, and amphiphilic compounds, making them especially suitable for complex herbal extracts. *Psidium guajava leaf extract* is a relevant herbal candidate because of its flavonoid, tannin, and phenolic content, which may contribute to anti-inflammatory, antimicrobial, antioxidant, and wound-healing effects. A *Psidium guajava* extract-loaded cubosomal mucoadhesive gel may therefore provide improved retention, sustained release, protection of phytoconstituents, and enhanced ulcer healing activity.

Although the concept is scientifically strong, further standardized studies are required to confirm its effectiveness. Future research should include detailed formulation optimization, *ex vivo* mucosal studies, *in vivo* oral ulcer healing models, stability testing, safety evaluation, and clinical trials. Overall, cubosome-based mucoadhesive gels represent an innovative and promising approach for improving oral ulcer management.

ABBREVIATIONS

RAS: Recurrent Aphthous Stomatitis; **PDI:** Polydispersity Index; **TEM:** Transmission Electron Microscopy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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