AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Comprehensive Overview of Herbal Mucoadhesive Oral Gels For Treatment Of Mouth Ulcers

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ABSTRACT

Mucoadhesive oral gels have gained significant attention in recent years as a localized medication delivery method that works well for treating mouth ulcers, which affect 20–25% of people in general at some point in their lives. By incorporating polymers such as carbopol, HPMC or chitosan, these gels form an intimate bond with the moist oral mucosa, creating a protective film that shields the lesion from mechanical irritation, saliva dilution and secondary infection. These formulations adhere to the oral mucosa, ensuring prolonged contact time and sustained drug release at the site of the lesion, thereby improving therapeutic outcomes and patient compliance. This review article provides a comprehensive overview of herbs used for mouth ulcers such as *Glycyrrhiza glabra* (liquorice), *Ocimum sanctum* (tulsi), *Punica granatum* (pomegranate peel), and *Mentha piperita* (peppermint). Collectively, these herbs deliver a synergistic phytochemical profile, glycyrrhizic acid and ursolic acid provide potent anti-inflammatory and antiviral actions, eugenol and rosmarinic acid offer rapid analgesia and broad-spectrum antimicrobial action while ellagitannins and menthol accelerate epithelial regeneration and impart a cooling, soothing sensation. This article also describes about herbal mucoadhesive gel preparation method and evaluation parameters such as pH, viscosity, spreadability, mucoadhesive strength, and stability, and gives basic knowledge that polyherbal approach offers a safer alternative with fewer side effects and supports the growing preference for natural, plant-based treatments in modern healthcare compared to conventional mouth ulcer treatments.

Keywords: Mucoadhesive oral gel, Mouth ulcer treatment, Herbal formulation, Mucoadhesive strength, wound healing

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Received 15 May 2025, Accepted 17 June 2025

Please cite this article as: Srilakshmi T *et al*., A Comprehensive Overview of Herbal Mucoadhesive Oral Gels For Treatment Of Mouth Ulcers. American Journal of PharmTech Research 2025.

INTRODUCTION

Mouth ulcers are small, painful, and shallow lesions that occur on the mucous membranes within the mouth, often found on the tongue, lips, cheeks, or gums. These are common issues in the oral cavity and can be caused by trauma, infections, aphthous ulceration related to skin conditions, drug-induced ulcers as indicators of systemic disorders, or malignant ulcers. Without therapy, aphthous ulcers, the most common kind of mouth ulcer, typically go themselves in 10 to 14 days.[1]

Categories of Mouth Ulcers: Mouth ulcers can be categorized as minor, major and herpetiform based on their size and quantity.[2]

- **Minor ulcers:** These about 2-8mm in size and heal within 10 days to 2 weeks.
- **Major ulcers:** These are larger and deeper, often characterized by a raised or irregular edge. This type can take several weeks to heal and may result in scarring in the mouth.
- **Herpetiform ulcers:** This variety consists of clusters of numerous smaller sores roughly the size of a pinhead.[3]

Causes of mouth ulcers [4, 5]

The origin of these ulcers remains unclear, yet factors such as

- Stress and anxiety
- Hormonal changes
- Nutritional deficiencies (e.g., iron, folate, vitamin B12)
- Systemic diseases (e.g., Crohn's disease, celiac disease, HIV)
- Local trauma (e.g., cheek bites, burns from hot food or drinks)
- Dental devices (e.g., braces, ill-fitting dentures)
- Irritants in toothpaste or mouth rinses
- Spicy or acidic foods
- Genetic predisposition
- Food sensitivities

Symptoms [6]

The signs of a mouth ulcer can differ based on the underlying cause, but typically include:

- Inflammation of the tissue surrounding the lesions.
- Sensitivity that makes chewing or brushing teeth uncomfortable.
- Foods that are sour, spicy, or salty can irritate the sores.

Treatment:

Ulcers can be managed or prevented through the use of dietary supplements and adjustments in

lifestyle. If the root cause is unclear or cannot be addressed, treatment focuses on alleviating symptoms[7]. It's also important to realize that most ulcers can heal completely on their own. Some natural treatment options like- Vitamins, Herbs. [8,9]

Mouth ulcers are usual symptoms of the oral cavity that can be aphthous, infectious, traumatic, malignant, or the result of dermatoses. Systemic illness may also be indicated by drug-induced ulceration. The available treatments for this illness focus on symptom management rather than injury prevention and regeneration. Oral rinses offer quick pain relief due to their moisturizing properties but because of brief residence time, oral rinse products are likely to fail because of lack of drug localization. A drug delivery system, like mucoadhesive gels, should be able to reduce salivary flow in order to avoid the restrictions and diluting effects, which effect the frequent drug delivery.[10]

Mucoadhesive drug delivery is the process by which a medication is absorbed through the oral cavity's mucous membranes. In order to provide controlled drug delivery and distribute the medication in a controlled manner, this relatively new drug delivery technology was first used in the 1980s [11]. Drugs in mucoadhesive delivery systems stay in close proximity to the mucous membrane, which serves as the absorption surface. This allows the medication to be released at the site of action, improving bioavailability and causing both local and systemic effects. Mucoadhesive systems have the potential to be used as drug carriers because they increase the duration of adhesion at the absorption site, enabling greater contact with the epithelial barrier.[12]

Many mucoadhesive dosage forms, such as pills, gels, and films, have been created to treat conditions affecting the oral cavity. The most popular type of ulcer treatment is mucoadhesive gel because it can provide a softer and bigger surface area for drug release in the buccal region for a prolonged amount of time because of their compliance and viscosity in terms of comfort and flexibility. [13]

In topical medication gel preparations, mucoadhesive polymers such carbomer 934, sodium carboxymethyl cellulose (Na-CMC), hydroxy propyl methyl cellulose (HPMC), hydroxy propyl ethyl cellulose (HPEC), benzocaine, tragacanth gum, and chitosan have been utilized for oral mucosa[14]. Mucoadhesive polymers can be added to medication formulations to increase the amount of time the drug must come into contact with the oral mucosa [15].

Over 80% of people worldwide still use traditional treatments for a variety of skin conditions. Herbal remedies are increasingly preferred for mouth ulcer treatment due to their proven safety and efficacy compared to synthetic drugs [16]. Natural ingredients like aloevera, liquorice, and tulsi offer powerful anti-inflammatory, antimicrobial, and wound-healing properties that helps to reduce

pain, swelling, and infection effectively[17].

HERBS USED FOR MOUTH ULCERS [18,19,20,21]

Herbal remedies have long been used by herbalists and traditional healers to cure and prevent ulcers. Various herbs, including liquorice, turmeric, betel leaves, guava, aloe vera, and noni fruit, are used to treat mouth ulcers because of its calming, anti-inflammatory, and wound-healing qualities. Flavonoids include anthocyanosides, quercetin, naringin, silymarin, and sophoradin derivatives. Gums, mucilages like gum guar and myrrh, and tannins are some of the primary chemical components that give plants their anti-ulcer properties.

Table 1: List of herbs used for mouth ulcers

S.no	Taxonomy	Chemical constituents	Part used	Activities
1	Guava Botanical name: Psidium guajava Family: Myrtaceae	Contains tannins and flavonoids, including quercetin and its glycoside derivatives.	Leaves, roots, fruits.	Characteristics that are antimalarial, anthelmintic, antiulcer, antispasmodic, and analgesic.
2	Tulsi Botanical name: Ocimum sanctum Family: Lamiaceae	Eugenol, Cirsilineol, Circimartin, Isothymusin, Apigenin.	Leaves	Antimicrobial, Anti-inflammatory.
3	Aloe vera Botanical name: Aloe barbadensis Family: Liliaceae	Barbaloin, Aloin A & B	Leaves, flowers, stems, roots, fruits, seed.	It demonstrates antiseptic, anti-inflammatory, antiviral, antifungal, antioxidant, immunomodulatory, and pain-relieving properties.
4	Liquorice, Botanical name: Glycyrrhiaglabra L., Family:Leguminoseae	Compounds such as triterpene glycosides (e.g., glycyrrhizin), along with liquirtin, isoliquiritin, rhamnoliquirilin, saponins, and flavonoids are present	Roots and stolen	It exhibits hormonal activity, helps alleviate cough, and possesses anti-inflammatory and expectorant properties.
5	Turmeric Botanical name: Curcuma longa Family: Zingiberaceae	Diarylheptanoids, curcumin, bisdemethoxycurcumin, and diethoxycurcumin.	Rhizomes and stem	Anti-arthritic and anti-inflammatory properties anti-ulcer properties
6	Capsicum Botanical name: Capsicum annuum L. Family: Solanaceae	Capsaicin, paprika oleoresin, and dihydrocapsaicin	Fruit	Gas in the stomach, cramps, stomach pain, diarrheal, and mouth ulcers are examples of gastrointestinal problems.
7	Noni Fruit Botanical name: Morindacitrifolia Linn. Family: Rubiaceae	Anthraquinones, flavonoids and phenolics	Fruit	An irregular menstrual cycle, acne or boils, constipation, diarrhoea, diabetes, arthritis, fever, high blood pressure, stomach ulcers, and other ulcers.
8	Pomegranate Botanical name: Punica m L. Family: Punicacea	Polyphenols, gallic acid, ellagic acid.	Flowers	Antioxidative, antibacterial, anti-inflammatory, analgesic, wound-healing properties, peptic ulcers, oral and anal ulcers, and intranasal ulcers.
9	Papaya Botanical name: Carica papaya	Enzymes like papain and chymopapain. Carotenoids(lutein, beta-carotene, lycopene)	Leaves and fruit	Papain, derived from it, is commonly used as a meat tenderizer and also aids

	Linn Family: Caricaceae			in protein digestion
10	Betel leaves Botanical name: Piper betle L. Family: Piperaceae	Alkaloids, carbohydrates, amino acids, tannins and steroids	Leaves	Anti-ulcer, Anti-bacterial, Antifungal, Antioxidant, Anti-inflammatory activities.

MUCOADHESIVE GELS:

A mucoadhesive oral gel is a gel formulation designed specifically to adhere to the mucosal surfaces inside the mouth, such as the inner cheeks, gums, tongue, and the roof of the mouth.[22] The primary goal of mucoadhesive oral gels is to provide localized relief and therapeutic effects for conditions like mouth ulcers, gum disease, and other oral mucosal irritations. These gels have unique properties that enable them to stay in oral mucosa longer than regular gels or liquids, enhancing their effectiveness.[23]

Advantages of mucoadhesive gels [24, 25]

- Prolonged release
- Improved bioavailability
- Targeted delivery
- Patient compliance
- Flexibility
- Reduced dosing frequency

Disadvantages [26,27]

- Limited shelf-life
- Sensitivity to pH and temperature
- Potential for irritation
- Difficulty in manufacturing
- Regulatory challenges

Mucus Membrane (Mucosa)

The mucous membrane is a protective lining that covers the internal surfaces of various body cavities exposed to the external environment, including the oral cavity, gastrointestinal tract, nasal passages, and genitourinary tract. A layer of epithelial cells, either simple columnar epithelium or stratified squamous epithelium, is present in mucous membranes.[28]. A key feature of the mucosa is the presence of mucus. The mucus is a viscous secretion discharged by goblet cell or by uncommon exocrine organs with the mucus cells. Functions of mucus mainly include lubrication and protection, also including cell-cell adhesion and bioadhesion.[29]

Mechanism of Mucoadhesion[30,31,32]

The term "mucoadhesion" describes the interfacial force of attraction that holds a mucoadhesive substance to the mucosal surface. This process includes two stages:

➢ **Contact Stage**

When the mucoadhesive polymer comes into touch with the mucous membrane, it wets and swells. The mucus in the mucosal membrane is responsible for this wetting.

➢ **Consolidation Stage-**

Formation of secondary interactions such as hydrogen bonding, van der Waals forces, electrostatic interactions, and physical entanglement between the polymer and mucin glycoproteins. It results in firm adhesion, which allows the formulation to remain in place and release active agents locally or systemically.

After both stages, the mucoadhesion process is finished.

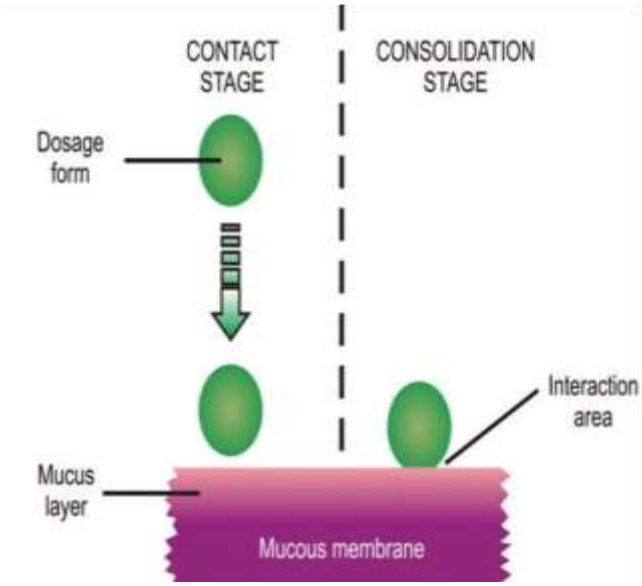

Figure 1: Mechanism of Mucoadhesion

THEORIES OF MUCOADHESION

Several theories have been proposed to explain mucoadhesion, each focusing on different molecular interactions:

Wetting Theory

Describes mucoadhesion as the ability of a liquid or semi-solid adhesive to spread and make intimate contact with the mucosal surface. By measuring the contact angle of the liquid on a surface using methods like contact angle geometry, one can determine the affinity of a liquid for a surface. The basic rule is that, the affinity of a liquid for a solid increases with decreasing contact angle.[33]

Electronic Theory

Proposes that electron transfer occurs when mucoadhesive polymers and mucosal surfaces have different electrical charges, leading to the formation of an electrical double layer and attractive forces.[34]

Adsorption Theory

Suggests that adhesion is due to secondary chemical bonds (e.g., hydrogen bonds, van der Waals forces) between the adhesive and mucosal surface.[35]

Diffusion Theory

Involves the interpenetration of polymer chains and mucin glycoproteins to a sufficient depth, creating a semi-permanent bond through entanglement.[36]

Fracture Theory

Focuses on the force required to separate two surfaces after adhesion. It is useful for quantifying mucoadhesive strength.[37]

Mechanical Theory

Suggests that adhesion is enhanced by interlocking of the adhesive material into the rough surface of the mucosa, increasing physical retention.[38]

Factors effecting Mucoadhesion[39,40,41]

- **Polymer Molecular Weight**: Better chain entanglement results from a higher weight, which improves adhesion.
- **Polymer concentration:** Adhesion is improved by optimal polymer concentration; adhesion is decreased by excessively high or low concentrations.
- **Cross-Linking Degree:** Better adhesion and swelling are made possible by low cross-linking.
- **Chain Flexibility:** More effective interpenetration of mucin is achieved by flexible chains.
- **Water Level:** Adhesion is weakened by excessive water, yet it is necessary for swelling.
- **pH:** Environmental pH has an impact on polymer ionization and bonding strength.
- **Functional Groups:** Groups that encourage hydrogen bonding include -COOH and -OH.
- **Contact Time & Pressure:** Adhesion is improved by longer, stronger contact.
- **Fluid Flow & Mucin Turnover:** Saliva or high turnover can lessen retention.
- **Mucosal Surface Properties:** Adhesion is influenced by surface thickness and texture.
- **Temperature:** At body temperature, temperature has an impact on polymer swelling and interaction.
- **Excipients:** Some excipients have the ability to either promote or inhibit mucoadhesion.
- **Types of mucoadhesive gels** [42,43]
- **Hydrocolloid Gels:** These gels are formed by using water-absorbing colloidal substances like gelatin or pectin. They maintain moisture forms a protective barrier, and promotes wound healing.

- **Polymer-Based Gels:** Polymer-based gels are a type of gel that utilizes polymers as the primary component offers strong mucoadhesion.
- **Local Anesthetic Gels:** Local anesthetic gels are topical formulations that contain anesthetic agents to numb the skin or mucous membranes, providing temporary pain relief.
- **Antimicrobial Gels:** These gels are formulated with agents like chlorhexidine or herbal antimicrobials to reduce infection and helps to control bacterial load and promote faster healing of ulcers.
- **Herbal-Based Gels:** Herbal-based products are prepared by using herbs. Herbs are often used for their medicinal, therapeutic, or preventative properties and helps in treating oral lesions due to its natural bioactivity and safety.

Common method used for preparation of Herbal Mucoadhesive gel [44]

Extraction of Herbal constituents

(By using maceration, percolation, or Soxhlet methods)

⇩

Preparation of Gel Base

(Suitable gelling agents such as Carbopol 934, HPMC, or Sodium alginate dispersed in purified water with continuous stirring)

⇩

Neutralization and pH Adjustment (eg: triethanolamine)

⇩

Incorporation of Herbal Extract

(The gel base is gently mixed with herbal extract)

⇩

Addition of Excipients

(Preservatives [e.g., methylparaben], humectants [e.g., glycerin], flavoring agents added)

⇩

Blended well to create a gel and then packed

(Final gel is thoroughly mixed and packed in suitable containers for storage and evaluation)

EVALUATION OF HERBAL MUCOADHESIVE GEL

1. **Physical evaluation:** Herbal mucoadhesive gel is evaluated for color, odour, and consistency.
2. **Homogenecity:** The gel tested for homogenecity by visual inspection and examined for appearance of any aggregates.[45]

3. **Spreadability:** Under a specific weight, spreadability is the measure of time in seconds it takes for two slides to separate from gel that's deposited between them. More spreadability results from a shorter time needed to separate two slides.

The formula for calculating spreadability is S = M × L/ T, where M is the weight attached to the advanced slide.

L is the glass slide length.

T is the measure of time required to separate the slides.[46]

Viscosity:

Using spindle number 96 at 10 rpm, the Brookfields viscometer analyzes the viscosity of gel.

pH measurement:

A digital pH meter is used to measure the gel's pH.[47]

Extrudability:

The collapsible tubes are filled with gel. The weight in grams needed to extrude a 0.5 cm gel ribbon in 10 seconds was used to calculate the extrudability. The gel extrude percentage is computed.

Stability:

A 90-day visual assessment is used to conduct the stability research. The gel is kept at room temperature after being filled into collapsible tubes. The observation is shown in the tables both with and without lids, at room temperature. Studies on pH, spreadability, and extrudability show slight variations over time.[48]

Mucoadhesive Studies:

After applying the polymers to the glass plates, they are submerged in a mucous result that is regulated in temperature. Constant experimental circumstances are used to calculate the force demanded to remove the plate from the result. The amount of time demanded until the adhesive gel fully disappears and tenacious contact with the mucosa is measured is known as the duration of mucosal adhesion.[49]

In-vitro release study:

Using a Franz diffusion cell and a cellophane membrane, the produced gels were subjected to diffusion investigations. The sample is placed on a cellophane membrane, and 250 milliliters of 6.8 phosphate buffer are used as the dissolution medium for the diffusion study, which is conducted at 37±100 degrees Celsius. At 1, 2, and 3 hours, 5 ml of each sample was taken out and replaced with an equivalent volume of brand-new dissolving medium. Phosphate buffer is used as a blank in order to evaluate the sample for drug content.[50]

Antimicrobial activity:

Various culture media, such as the nutrient agar method and dextrose agar media, are used to test the antibacterial activity of gel. An aliquot (0.1 ml) of the bacterial suspension (Candida Albicans, Ecoli) is added to the plate and evenly distributed across the medium's surface. After 15 minutes, 0.5g of gel is added to wells that are 6 mm in diameter and created in the solid medium using a sterile cork borer. The plates are incubated at 37 °C for 24 hours. The antibacterial exertion is measured in millimeters (mm) using the zone of inhibition (ZOI) fringe.[51]

CONCLUSION

Herbal mucoadhesive oral gels represents a novel and effective approach for the management of mouth ulcers and alternative to synthetic medications, combining the therapeutic potential of medicinal plants with targeted drug delivery systems. Their ability to remain in contact with the mucosal tissue ensures sustained release and localized action, enhancing healing and reducing discomfort. With growing demand for safer, nature-based therapies in oral healthcare compared to conventional treatments, herbal gels are biocompatible, have minimal side effects, and offer a cost-effective and patient-friendly option. Further investigation and clinical trials are necessary to fully explore the potential of herbal mucoadhesive gels in oral healthcare and to confirm their efficacy, safety, and commercial feasibility on a broader scale.

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