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ORAL MUCOADHESIVE GEL: A NOVEL APPROACH IN DRUG DELIVERY SYSTEM

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ABSTRACT

Mucoadhesive oral gels are emerging as an innovative and effective drug delivery system designed to adhere to the mucosal surface of the oral cavity, enabling prolonged residence time and enhanced bioavailability. These systems are particularly advantageous for the local or systemic delivery of drugs that require sustained release or targeted action. This study focuses on the formulation and evaluation of a mucoadhesive oral gel containing drug, aimed at the treatment of disease/condition, e.g., oral inflammatory pain. The gel incorporates mucoadhesive polymers to ensure strong adhesion and controlled drug release. In vitro and in vivo assessments demonstrate improved therapeutic efficacy, enhanced patient compliance, and reduced dosing frequency. Recent advancements focus on incorporating bio-adhesive polymers, penetration enhancers, and nanocarriers to optimize drug release profiles and mucosal permeability. Using various methods for preparation of oral mucoadhesive gel, a uniform gel base must be prepared using mucoadhesive polymers, into which the drug should be incorporated. The evaluation for physicochemical properties, mucoadhesive strength, drug content, and in-vitro release should be performed. This novel delivery system holds significant potential for the management of various oral and systemic diseases. This review provides a comprehensive overview of the principles, formulation strategies, and evaluation parameters associated with oral mucoadhesive gel systems. It highlights the mechanisms of mucoadhesion, commonly employed polymers, and the physicochemical considerations essential for achieving optimal gel performance. Overall, the findings support the use of mucoadhesive gels as an effective platform for oral drug delivery.

KEYWORDS: Mucoadhesive oral gel, Buccal drug delivery, Oral gel, Mucoadhesive polymers, Controlled drug release, Oral inflammatory pain.

INTRODUCTION

MUCOADHESIVE DRUG DELIVERY SYSTEM[1]

Mucoadhesive drug delivery system are systems which utilize the property of bio-adhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. Bio-adhesion is an interfacial phenomenon in which two materials (at least one of which is biological), are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane.

Mucoadhesive drug delivery systems can be delivered by various routes.

1. Buccal delivery system
2. Oral delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system

ANATOMY & PHYSIOLOGY OF ORAL MUCOSA[2]

Oral mucosal locale is adhesive in nature and goes about as a lubricant, which permits the cells to move comparative with each other with less grating. There are four sites are as follows.

1) Buccal cavity
2) The sublingual area
3) The palate
4) Gingival region

It's utilized for drug organization. The utilized site of the four-locale referenced over that is the buccal cavity. The anatomic site for drug organization between the cheek and gingival is known as the buccal mucosa. The oral cavity is made out of three layers. The primary layer is the delineated squamous Epithelium, under this layer is basement membrane film. The storm cellular layer overlies the lamina propriety and submucosa. The constitution of the epithelium inside the various locales of the oral cavity shows divergence. The epithelium in the slot sense of taste, buccal and sublingual region isn't keratinized, subsequently not containing ceramides and acyl ceramides which are related with giving a boundary work. The mucosa of the buccal & sublingual locale has just modest quantities of ceramide and subsequently more porous. When contrasted with different locales of the oral cavity. A layer of bodily fluid is available on the outer layer of the cells. This assumes a significant part in cell to cell attachment just as muco-adhesion of drug delivery systems. The buccal region has a field of smooth and somewhat stable surface, which is appropriate for arrangement of a retentive framework. For buccal drug delivery, grip to the oral mucosa licenses not just the closeness of contact and the chance of further developed drug retention yet in addition the capacity of accomplish an ideal home time at the site of organization.

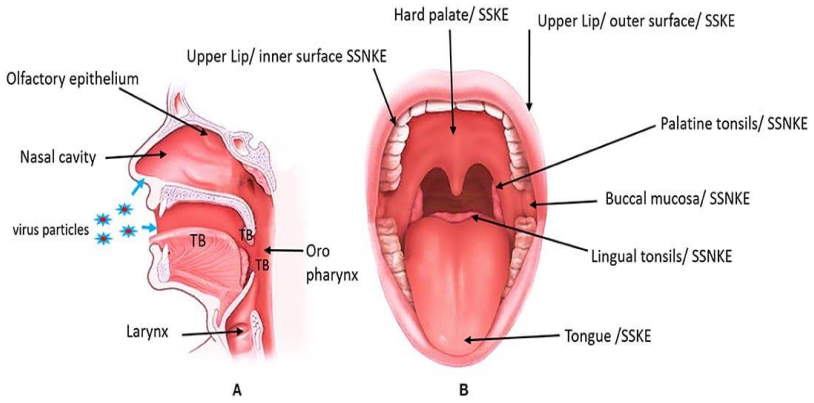

Fig 1: Overview of oral mucosa.[7]

COMPONENTS AND STRUCTURAL FEATURES OF ORAL CAVITY[2]

The oral mucosa is for the most part emitted by different organs of oral cavity that are sublingual organ, parotid organ and other salivary organs. The mucus is a clear gel discharged by goblet cell or by uncommon exocrine organs with the mucus cells.

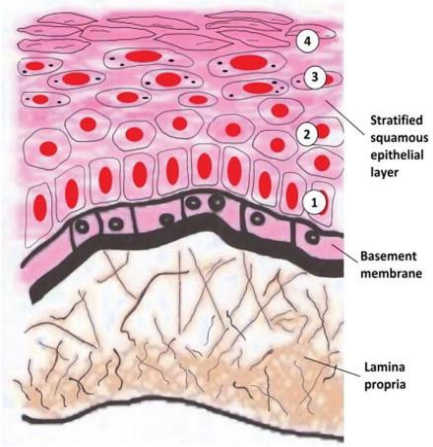

Fig 2: Composition of mucus.[7]

Table No. 1: Component Of Mucus Layer.

COMPONENTS	PERCENTAGE
Water	95
Glycoproteins and lipids	0.5-5
Minerals and salts	1
Free proteins	0.5-1

ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY SYSTEM[3]

1) Hepatic first-pass metabolism is overcome.
2) This technique can be used to administer medications that are unstable in an acidic environment and are broken down in an alkaline or enzymatic environment in the intestines.
3) It can be administered to patients who are currently unconscious.
4) Quick onset of action.
5) Improved patient compliance.
6) Dosage form ease of administration.
7) Operates using a passive drug absorption system that does not need to be triggered.

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM[4]

1) The buccal membrane exhibits low permeability, especially in comparison to the sublingual membrane.
2) The involuntary removal of the dosage form may result from swallowing saliva, which may also cause the loss of dissolved or suspended drug.
3) Saliva secretion (0.5-2 l/day) is continual and causes the medication to be diluted later.

MECHANISM OF MUCOADHESION[1]

Mucoadhesion is the process by which a material (usually a polymer) adheres to the mucosal membrane, helping to prolong drug retention at the site of action. The mechanism occurs in two main stages.

1. Contact Stage (Initiation Stage): The mucoadhesive polymer comes into contact with the mucosal surface. Wetting and swelling occur due to the hydration of the polymer, allowing it to spread over the mucosal layer. Electrostatic attraction or physical entanglement may help in the initial adhesion.

2. Consolidation Stage (Strengthening of Adhesion)

After initial contact, polymer chains interpenetrate with mucin glycoproteins. Various intermolecular interactions strengthen adhesion, including.

- Hydrogen bonding (between polymer functional groups and mucus)
- Electrostatic interactions (between charged groups)
- Van der Waals forces
- Hydrophobic interactions.

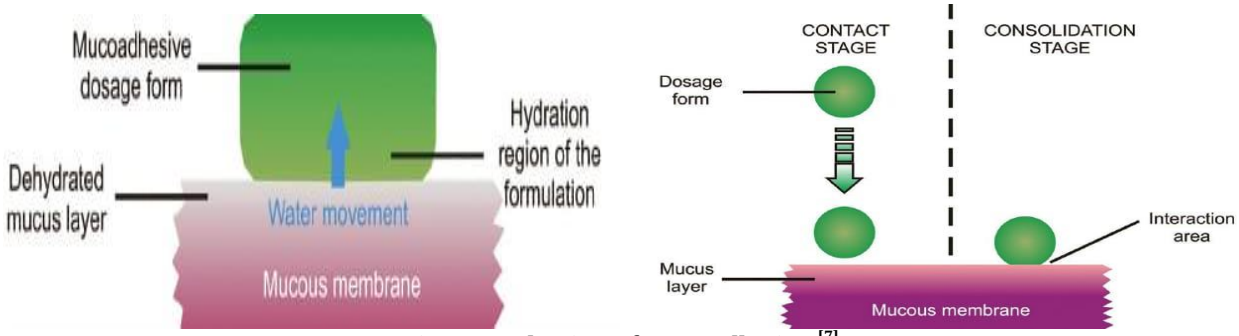

Fig. 3. Mechanism of Mucoadhesion.[7]

THEORIES EXPLAINING MUCOADHESION[5]

1. Electronic Theory – Oppositely charged surfaces (polymer and mucus) create electrostatic attraction.
2. Wetting Theory – Good wetting and surface tension allow the polymer to spread and adhere effectively.
3. Diffusion Theory – Polymer chains diffuse and intertwine with mucin chains, enhancing adhesion.
4. Adsorption Theory – Adhesion is strengthened by hydrogen bonds and van der Waals forces.
5. Fracture Theory – Defines muco-adhesion by measuring the force needed to break the bond.

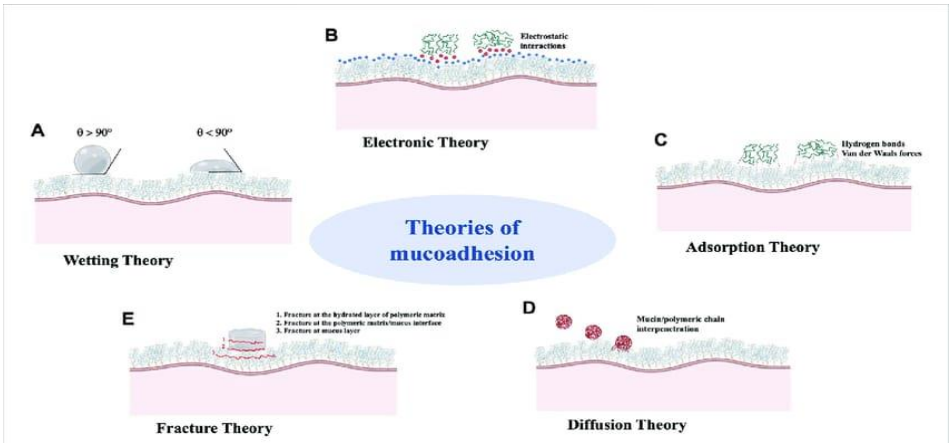

Fig. 4: Theories of Mucoadhesion.[7]

VARIOUS METHODS OF PREPARATION OF GEL[8&9]

Method	Process Steps
Direct Dispersion Method	1. Polymer is dispersed in water with stirring. 2. API is dissolved separately and added. 3. pH is adjusted for gel formation. 4. Final gel is stored properly.
pH-Triggered Gelation	1. Polymer swells in water. 2. API is dissolved and mixed in. 3. pH is adjusted using neutralizers. 4. Gel forms due to pH change.
Cold Process Method	1. Polymer is dissolved in cold water. 2. Solution is refrigerated for proper hydration. 3. API is added and mixed. 4. Gel forms at low temperature.
Solvent Evaporation Method	1. Polymer & API are dissolved in a volatile solvent. 2. Solution is stirred for uniform dispersion. 3. Solvent evaporates under controlled conditions. 4. Gel forms as solvent disappears.
Ionic Gelation Method	1. Polymer is dissolved in water. 2. API is added separately. 3. Cross-linking agent (e.g., CaCl2) is added. 4. Ionic interactions cause gel formation.
Heat-Induced Gelation	1. Polymer is dissolved in hot water. 2. API is added & mixed. 3. Cooling results in gel formation. 4. Stored at controlled temperature.

POSSIBLE METHOD OF PREPARATION OF ORAL MUCOADHESIVE GEL

1. Direct Dispersion Method[6]

Accurately weigh required amount of mucoadhesive polymer

↓

Gradually disperse polymer into warm distilled water (with continuous stirring at 400–600 rpm)

↓

Continue stirring for ~1 hour until clear, uniform solution

↓

Ensure no lumps form during dispersion

↓

Accurately weigh active ingredient (drug substitute)

↓

Incorporate it into the polymeric solution with continuous stirring for 3–4 hours

↓

Add gelling agent + additional distilled water slowly under gentle stirring (~100 rpm)

↓
Adjust final weight of formulation with distilled water
↓
Take precautions to minimize air bubble entrapment
↓
Allow gel to stand undisturbed to remove trapped air bubbles
↓
Adjust pH to ~6.75 ± 0.05 using suitable pH adjuster
↓
Keep gel aside for 24 hours for complete hydration and stabilization

2. Heating & Cooling Method (Thermoreversible Gels)[24]

Heat water to required temperature (50–90°C)
↓
Add polymer and continue heating until fully dissolved
↓
Add drug (if heat-stable)
↓
Cool the solution gradually
↓
Gel forms upon cooling

3. Ionic Gelation / Ion-Induced Gelation[25]

Prepare aqueous polymer solution (alginate, gellan, pectin)
↓
Add ionic cross-linker (e.g., $CaCl_2$)
↓
Ions interact with polymer chains
↓
Three-dimensional gel network forms

4. Solvent Evaporation Method (Hydroalcoholic Gels)[26]

Dissolve polymer in organic solvent (e.g., ethanol)
↓
Add drug + additives
↓
Mix to uniformity
↓
Allow solvent to evaporate partially
↓
Gel consistency achieved

5. pH-Induced Gelation Method[27]

Prepare polymer solution (e.g., Carbopol)
↓
Add drug + excipients
↓
Adjust pH using neutralizer
↓
Polymer cross-links → Gel forms

POSSIBLE DRUGS USED FOR ORAL MUCOADHESIVE GEL

1. **Miconazole nitrate**: A Broad-spectrum antifungal agent, used in mucoadhesive oral gel for oral candidiasis. Also extensively applied for dermal, buccal, vaginal candidiasis. Commonly used in concentration of 2% for four times daily.[10]
2. **Itraconazole:** Example of triazole antifungal drug used in mucoadhesive gel for oral candidiasis to overcome limitations like drug retention, prolonged contact with affected surfaces, controlled drug release when administered orally.[11]
3. **Fluticasone propionate**: A Potent corticosteroid used in mucoadhesive proniosome gel for oral ulcerative lesions. Its potency, optimised topical activity, lower oral systemic bioavailability is lower in comparison to other corticosteroids making it excellent choice for oral lesions.[12]

4. **Silymarin**: A flavonolignan derived from milk thistle, used as an anti-inflammatory/antioxidant agent in an oral mucoadhesive gel for inflammatory oral mucosal diseases. Also used for chronic liver disorders, cirrhosis, etc. It has good safety profile without toxicity even after prolonged administration.[13]
5. **Chlorhexidine (CHX)**: Example of antiseptic drug in buccal mucoadhesive aqueous gels. It is an adjunctive supplement in oral candidiasis, since it reduces the adhesion of Candida albicans to oral mucosal cells. However, its prolonged use, e.g. in mouthwash, has a disagreeable taste and can lead to the formation of brown spots on the surface of the teeth, leading decreased patient compliance.[14]
6. **Ketorolac Tromethamine**: Ketorolac tromethamine (KRT) is a member of the pyrrolo-pyrrole group of NSAIDs that exhibits analgesic, anti-inflammatory and antipyretic activity. It inhibits the cyclooxygenase enzyme system and hence prostaglandin synthesis. It has more pronounced analgesic activity than most NSAIDs.[15]

POSSIBLE EXCIPIENTS USED FOR ORAL MUCOADHESIVE GEL[16]

There are various excipients used in oral mucoadhesive gel.

1. Mucoadhesive polymer: Provides adhesion, viscosity, structure to gel.

- Carbopol / Carbomer (934, 940, 974)
- HPMC (Hydroxypropyl methylcellulose)
- CMC / NaCMC (Carboxymethyl cellulose)
- Chitosan
- Sodium alginate
- Pectin
- Gellan gum
- Xanthan gum
- Poloxamer 407/188 (if thermo-gelling)

2. Neutralizing / pH Adjusting Agent — Required for Carbopol systems. Used to convert the polymer dispersion into a gel and adjust pH to ~6–7.

- Triethanolamine (TEA)
- Sodium hydroxide (NaOH)
- Potassium hydroxide (KOH)

3. Solvent / Vehicle — Required Purified water / Distilled water.
Some APIs may require:

- Ethanol (small amount)
- Propylene glycol / PEG 400 (cosolvent + penetration enhancer)

4. Humectant / Plasticizer — Optional, improves texture. Helps prevent drying and improves spreadabilty.

- Glycerine
- Propylene glycol
- Sorbitol

5. Preservative — Required since it is a water-based formulation. To avoid microbial contamination (oral mucosal products must have low bioburden).

- Methyl paraben
- Propyl paraben
- Sodium benzoate
- Potassium sorbate
- Benzyl alcohol

EVALUATION OF ORAL MUCOADHESIVE GEL[17]

1) Spreadability: Determined by placing a fixed amount of gel between two glass slides and measuring the diameter after applying a specific weight. This test indicates the spreadability of gel by small amount of shear and its behaviour when dispensed out of tube.

2) pH: pH of all the formulated batches was evaluated by digital pH meter to ensure its compatibility with oral mucosa.

3) In vitro diffusion study: In vitro drug diffusion studies of the Mucoadhesive oral were carried out in modified diffusion cell using dialysis membrane (dry, unwashed, flat width:28.46mm, inflated diameter:17.5mm, length:1mm). The membrane was soaked in phosphate buffer of pH 6.8 for 9-12 hours. The gel was spread evenly on the membrane and clamped at end of hollow dialysis cell. 20 ml Phosphate buffer was placed in receptor compartment. The donor compartment was kept in contact with receptor compartment. The assembly was placed on magnetic stirrer and stirred continuously using magnetic bead and temperature was maintained at 37°C. 1 ml sample was withdrawn at suitable time intervals and replacing with equal amount of fresh dissolution media. The samples were analysed by UV spectroscopy at 322 nm and percentage drug release was calculated.

4) Viscosity determination: The viscosity of oral Mucoadhesive gel was determined by Brookfield viscometer. 100 ml gel was rotated at 10 to 30 rpm using spindle no. 64.

5) Drug content uniformity: This study is to evaluate uniform distribution of drug throughout gel formulation. For studies, the oral mucoadhesive gel was weighed 100 mg and dissolved in 100 ml of phosphate buffer with pH 6.8. This solution was continuously stirred for 24 hours and then sonicated. The drug content uniformity was estimated by UV spectroscopy.

FACTORS INFLUENCING MUCOADHESIVE GEL ABSORPTION

1. Mucoadhesive Polymer Properties[18]: Determines gel residence time and drug release.

- Polymer type (e.g., Carbopol, HPMC, CMC)
- Molecular weight
- Degree of cross-linking
- Charge (anionic/cationic)
- Hydration and swelling ability

2. Mucoadhesion Strength[16]: Higher adhesion → longer retention → better absorption.

- Contact time with mucosa
- Polymer–mucin interaction (hydrogen bonding, electrostatic forces)

3. Drug Physicochemical Properties[8]: Determines permeability across oral mucosa.

- Molecular weight (small MW absorbs better)
- Solubility and dissolution rate
- Lipophilicity (log P)
- Ionization (pKa)

4. Drug Concentration and Dose[19]**:** Higher concentration → better gradient → faster absorption. But too high concentration may lead to saturation or irritation.

5. Gel Viscosity & Rheology[20]**:** Must be optimized for release + adhesion.

- Higher viscosity → slower drug diffusion
- Lower viscosity → poor retention

6. pH of Gel and Saliva[21]**:** pH affects drug ionization and polymer swelling. Salivary pH (6.2–7.4) may alter drug stability and release.

7. Mucosal Permeability[22]**:** Varies in:

- Buccal mucosa
- Sublingual mucosa
- Gingival mucosa

Sublingual mucosa is most permeable → fastest absorption.

8. Salivary Flow[23]

- High saliva → dilution + drug washout
- Low saliva → improved retention

9. Patient-Related Factors[22]

- Mucosal health (ulcers, keratinization)
- Movement (speech, eating)
- Hydration level

CONCLUSION

Oral mucoadhesive gels are semi-solid drug delivery systems designed to adhere to the mucosal surfaces in the oral cavity. These gels enhance the residence time of drugs at the site of action or absorption, leading to improved therapeutic efficacy and bioavailability. They are particularly useful for local treatment of oral conditions such as ulcers, infections, and inflammation. The key components include bio-adhesive polymers (e.g., carbopol, HPMC, gellan gum), active pharmaceutical ingredients, and suitable bases that provide the desired viscosity and spreadability. The gels are easy to apply, non-invasive, and improve patient compliance due to their localized and sustained drug release. Oral mucoadhesive gels represent a promising platform for targeted and sustained drug delivery in the oral cavity. Their ability to adhere to mucosal tissues and release drugs over an extended period makes them highly effective for treating various oral and systemic conditions.

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