

**ALOE VERA MUCILAGE-BASED MUCOADHESIVE BUCCAL FILMS OF
TRIAMCINOLONE ACETONIDE FOR THE LOCALIZED MANAGEMENT OF
RECURRENT APHTHOUS STOMATITIS: CURRENT EVIDENCE, FORMULATION
STRATEGIES, AND FUTURE PERSPECTIVES****Mukesh M.^{1*}, Sudhan D.²**^{1,2}Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur, Tamil Nadu, India.***Corresponding Author: Mukesh M.**

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ABSTRACT

One of the most common ulcerative conditions of the oral cavity is recurrent aphthous stomatitis (RAS), which is characterized by painful, recurrent lesions that greatly impair patients' quality of life. Even though topical corticosteroids, antiseptics, and analgesics are readily available, conventional dosage forms frequently show poor therapeutic effectiveness due to frequent dosing requirements, quick salivary drainage, and insufficient mucosal retention. Mucoadhesive buccal drug delivery devices that can sustain extended contact with the oral mucosa while delivering regulated and localized drug release are becoming more and more popular as a result of these constraints. Mucoadhesive buccal films have become a potential platform among the other dosage forms that have been studied due to its flexibility, patient acceptability, convenience of administration, and capacity to enhance drug bioavailability at the site of action. Because of its strong anti-inflammatory properties, triamcinolone acetonide is still one of the most often prescribed corticosteroids for the treatment of RAS. Because of their superior biocompatibility and multipurpose medicinal qualities, natural polymers have also garnered growing interest in pharmaceutical formulation. Aloe vera mucilage's potential for wound healing, anti-inflammatory action, antioxidant benefits, and ability to promote mucosal tissue regeneration make it especially promising. The present understanding of recurrent aphthous stomatitis, buccal drug transport principles, mucoadhesion mechanisms, pharmaceutical uses of Aloe vera mucilage, and the therapeutic role of triamcinolone acetonide are all critically summarized in this study. Additionally, formulation techniques for mucoadhesive buccal films based on Aloe vera mucilage are covered, along with current research trends, obstacles, and prospects. According to the available data, combining natural bioactive polymers with well-known anti-inflammatory medications may offer a successful localized treatment strategy for recurrent aphthous stomatitis while enhancing patient compliance and reducing systemic exposure. The integration of these systems into standard clinical practice is anticipated to be made easier by ongoing research on formulation optimization, mechanistic comprehension, and clinical validation.

KEYWORDS: Recurrent aphthous stomatitis; Mucoadhesive buccal film; Aloe vera mucilage; Triamcinolone acetonide; Local medication delivery; Natural polymers.**1. INTRODUCTION^[1-5]**

Recurrent aphthous stomatitis (RAS), commonly referred to as recurrent aphthous ulcers or canker sores, is one of the most prevalent chronic inflammatory disorders of the oral mucosa. It is characterized by recurrent, painful, round or oval ulcers covered by a yellowish-white fibrinous pseudomembrane and surrounded by an erythematous halo. The disease affects approximately 5–

25% of the global population, with considerable variation among different geographical regions, age groups, and ethnic populations. Although RAS is not considered life-threatening, the associated pain and discomfort substantially impair mastication, swallowing, speech, oral hygiene practices, and overall quality of life. Frequent recurrence of ulcers also imposes psychological

stress and negatively influences social and occupational activities.

The precise cause of recurrent aphthous stomatitis is still unknown despite decades of research. Genetic predisposition, immunological dysregulation, local trauma, dietary inadequacies, hormonal fluctuations, microbial factors, oxidative stress, and psychological stress all combine intricately to cause the condition, which is thought to be multifactorial. Tumor necrosis factor- α (TNF- α), interleukin-2 (IL-2), and interferon- γ (IFN- γ) are examples of pro-inflammatory cytokines that are produced excessively as a result of T-cell-mediated immune responses, which ultimately destroy the oral epithelium, according to growing evidence. This complex character makes it difficult to achieve long-term treatment control and increases the likelihood of disease recurrence.

The treatment approaches being used currently mostly seek to relieve pain, control inflammation, heal ulcers, and minimize recurrences rather than effecting a definite cure. The topical application of corticosteroids is the main treatment approach that is being used because they are capable of controlling local inflammatory processes without causing any significant side effects systemically. Amongst the different corticosteroids that are available, the triamcinolone acetonide is the most accepted because of its potent anti-inflammatory actions, good safety record, and proven clinical efficacy in the treatment of oral ulcers.

Despite offering symptomatic relief, their clinical efficacy can be hampered by the unique physiological characteristics of the oral cavity. The continuous flow of saliva, the motion of tongue, swallowing, chewing, and the constant renewal of mucous membranes make conventional dosage forms such as mouthwashes, gels, creams, and ointments unavailable at the site of action in a short period of time. Thus, the period of drug contact with the ulcerated area gets considerably shortened, which results in poor absorption, frequent administration, non-uniform patient compliance and treatment outcomes. Such challenges have fueled great interest in more efficient localized drug delivery systems that can ensure drug retention on the target area as well as controlled drug release.

Mucoadhesive buccal films are among a wide range of localized drug delivery systems that gained much attention recently as potential pharmaceutical products for treating diseases of the oral mucosa. The mucoadhesive buccal films are designed to adhere to the buccal mucosa using molecular interaction between the polymers and mucin glycoproteins, thus increasing the period of drug residence and its local concentration. There are many advantages of buccal films compared to other conventional dosage forms. Moreover, the capacity of adhering to the lesion for long durations makes them ideal candidates for continuous therapeutic effects, thus

becoming more relevant to chronic and recurrent oral conditions. Choosing proper polymers is a vital determinant in the effectiveness of mucoadhesive buccal films. Artificial polymers like Hydroxypropyl Methylcellulose (HPMC) and Sodium Carboxymethyl Cellulose (Sodium CMC) are widely used owing to their excellent film-forming ability, mechanical strength, swelling and mucoadhesive nature. But growing focus on natural polymers is encouraging scientists to look at biodegradable natural materials that not only have pharmaceutical significance but also exhibit therapeutic properties of their own.

Aloe vera, one of the natural biomaterials, has gained much attention due to its versatile pharmacological actions and excellent biocompatibility. The mucilage isolated from the gel layer of Aloe vera leaf is highly loaded with biologically active polysaccharides, such as acemannan and glucomannan, along with other components like vitamins, amino acids, minerals, enzymes, and phenols. This material has shown to be having anti-inflammatory, antioxidant, antimicrobial, immunomodulating, and wound healing actions through many research works. Apart from all these beneficial actions, Aloe vera mucilage has several pharmaceutical features, such as film forming, hydration, and mucoadhesion properties. Hence, it is a promising material for preparing buccal drug delivery systems.

The use of triamcinolone acetonide together with the Aloe vera mucilage in a mucoadhesive buccal film can be regarded as a scientifically logical approach to improve the therapy of recurrent aphthous stomatitis on a local level. The reason is that triamcinolone acetonide helps to suppress inflammation, which causes ulcerations and pain, while Aloe vera may promote faster epithelial healing and decrease oxidative stress. Using such drugs in a mucoadhesive film form may increase efficiency due to their prolonged action and release.

Despite the fact that multiple researches have been performed independently on topical corticosteroids, natural polymers, and mucoadhesive buccal drug delivery system, few comprehensive reviews covering all three aspects of the problem are currently available. Thus, the critical assessment of existing literature is needed to determine the areas of insufficient knowledge, formulation difficulties, and further research needs.

Therefore, the purpose of the review is to critically assess existing knowledge regarding recurrent aphthous stomatitis, mucoadhesive buccal drug delivery system, the application potential of Aloe vera mucilage from a pharmaceutical and therapeutic perspective, and the use of triamcinolone acetonide in targeted treatment. Recent trends in formulations, current limitations, and perspectives are also considered to provide the scientific background for the development of new generation of Aloe vera mucilage based mucoadhesive buccal films for the treatment of recurrent aphthous stomatitis.

2. Recurrent Aphthous Stomatitis (RAS)^[1-8]

2.1 Definition^[1,2]

Recurrent Aphthous Stomatitis (RAS) is a chronic and recurring inflammatory condition that affects non-keratinized mucosa of the mouth. The disease is marked by recurring appearance of small and painful, shallow ulcers covered with yellowish-white fibrinous membrane and having red borders around them. In contrast to ulcers caused by other pathologies and infections, RAS is not associated with any systemic diseases and is not caused by any infectious agent. Despite the fact that the ulcers heal themselves within 7-14 days without any scar formation, they have serious impact on patients' daily routines due to their recurring character.

Recurrent Aphthous Stomatitis is one of the most frequent conditions among oral mucosal diseases. The disease usually develops in early childhood or adolescence; the peak of its frequency is in young adulthood. Most patients suffer from recurrences a few times a year, but the worst cases might have almost continual presence of ulcers. The recurring nature of the disease is the biggest problem in its treatment.

2.2 Epidemiology^[1,3,4]

The prevalence of recurrent aphthous stomatitis has been documented to be between 5% and 25%, with more cases being detected among university students, health care workers, and those who are experiencing stress. The disease has different prevalence in accordance with various factors including ethnicity, geography, socioeconomic status, nutrition, and criteria employed in the epidemiological studies.

It has been documented that females are more predisposed to the disease than males as a result of hormonal differences and immune system differences. There is a high prevalence of positive family history in patients with this disease, which implies a genetic component in the susceptibility to the disease. It has been estimated that 30–40% of patients have at least one relative from the first-degree line with recurrent aphthous ulcers.

RAS may affect individuals of all ages, but it is usually detected in individuals who are in their twenties and thirties. The disease tends to become less recurrent with increasing age; however, persistent or unusual severity of the disease is an indicator of underlying systemic conditions.

2.3 Classification^[1,2,5]

Recurrent aphthous stomatitis is categorized into the following three main types depending on their clinical features:

Minor Aphthous Ulcers

The minor type comprises nearly 80–85% of RAS. Minor aphthous ulcers have a small size – up to 10 mm in diameter, and are shallow and very painful. They tend to occur on the non-keratinized mucosa, namely, the lips

mucosa, buccal mucosa, floor of the mouth, underside of the tongue and soft palate. The ulcerative process heals spontaneously within 7 to 14 days without leaving scars.

Major Aphthous Ulcers

Major ulcers are larger than 10 mm in diameter, deep, last for several weeks, and heal slowly with the possible development of scars. Major aphthae produce significant pain and affect eating and speaking abilities.

Herpetiform Ulcers

Herpetiform aphthous ulcers constitute the rarest clinical type, making up about 5-10% of cases. Contrary to what their name might imply, they have nothing to do with herpes simplex virus infection. Herpetiform ulcers consist of multiple tiny ulcers (1-3 mm) that appear at the same time and sometimes merge into larger, irregular lesions. This type of ulcers is usually associated with severe pain and frequent recurrences.

2.4 Etiology^[2,5-7]

Although the cause of recurrent aphthous stomatitis is not fully known, current knowledge indicates that RAS arises due to various interacting factors rather than a single causative one.

Genetic Predisposition

Inborn susceptibility is a crucial factor in the development of disease. There are data showing higher incidence of RAS among first-degree relatives and HLA alleles association, indicating immunologic regulation disorders.

Immune Disorders

The participation of cell-mediated immunity in RAS development is considered essential. T lymphocytes activation leads to an increase in the production of inflammatory cytokines, such as TNF- α , IL-2, IL-6, IL-8, and IFN- γ , resulting in mucosal tissue damage and ulcers appearance.

Nutritional deficiencies

Deficiencies of vitamin B12, folic acid, iron, and zinc have been found to be linked to recurrent ulceration. It has been found that correction of these deficiencies decreases the frequency of the disease in susceptible patients.

Local injury

Minor injuries caused by cheek biting, vigorous toothbrushing, orthodontic devices, or sharp teeth may lead to ulceration in genetically susceptible people.

Psychological stress

Emotional stress, anxiety, sleeplessness, and exam stress have been found to be important causes of recurrence in affected individuals.

Hormonal influences

Any changes in the hormone levels especially during menses and pregnancy may affect the disease process in genetically susceptible women.

Microbiological influences

Although no organism has been identified as the causative agent of RAS, bacterial and viral antigens may be responsible for improper immune response in genetically susceptible people.

2.5 Pathophysiology^[2,6,8]

The development of RAS is characterized by an intricate process of inflammation mediated via the immune system. Following exposure to certain predisposing factors, antigen-presenting cells trigger CD4⁺ helper T lymphocytes and CD8⁺ cytotoxic T cells. The activity of these immune cells causes secretion of TNF- α , IFN- γ , IL-2, and IL-6 inflammatory cytokines, causing epithelial cell death, disrupting mucosa integrity, and mobilizing more inflammatory cells.

In addition, oxidative stress increases tissue damage due to overproduction of reactive oxygen species, while failure of antioxidant systems causes delayed healing of mucosa. As a consequence of this damage, ulcers, covered with a fibrinous layer, develop. The process of healing is marked by proliferation of fibroblasts and deposition of collagen fibers, formation of new blood vessels, and epithelial regeneration; however, presence of predisposing factors may cause recurrence.

2.6 Clinical Presentation^[1,5]

Patients suffering from recurrent aphthous stomatitis usually have a prodrome of burning or tingling sensation 24–48 hours before the occurrence of ulcers. Once the ulcers become fully established, they are very painful especially while eating, drinking, talking or performing any oral hygiene procedure. Depending on the severity of the condition, the patient can have problems with nutrition, sleep disturbances, inability to communicate and reduced quality of life.

2.7 Diagnosis^[2,4]

Recurrent aphthous stomatitis diagnosis is made clinically through patient history and lesions' characteristics. Laboratory tests are usually done in cases of severe, atypical or persistent ulcers in order to rule out systemic conditions, hematinic deficiencies, autoimmunity, inflammatory bowel disease, Behcet's disease or immunodeficiency.

2.8 Current Therapeutic Approaches^[3,6,8]

Treatment of recurrent aphthous stomatitis is targeted at reducing symptoms, decreasing inflammation, enhancing healing of ulcers, and avoiding recurrence of the condition. The most preferred treatment for this condition includes topical corticosteroids like triamcinolone acetonide, as they control inflammation without systemic side effects. Other treatment modalities

include topical anesthetics, mouthwashes, anti-inflammatory drugs, immune modifiers, lasers, nutrient supplements, and systemic therapies for severe cases.

Even though there are several treatments for the condition, factors like fast saliva clearance, inability to retain medication in the mouth, need for frequent administration, and non-compliance of patients have been identified as barriers for successful treatments. This has led to development of advanced drug delivery systems especially mucoadhesive films, which can adhere to the oral mucosa and allow continuous release of the drug.

3. Mucoadhesive Buccal Drug Delivery Systems^[9-15]**3.1 INTRODUCTION**

Oral cavity appears to be an ideal site for local and systemic drug delivery systems due to its abundant vasculature, accessibility, and acceptability. Of all the sites available in the oral cavity, buccal mucosa appears to be an excellent choice for administering drugs locally due to its relatively smooth lining, good permeability, and ease of accessibility. During recent years, growing interest has been shown in mucoadhesive buccal delivery systems since they possess many advantages over traditional oral topical products.

Contrary to rinse preparations, gels, and ointments which get washed away from the site of application by saliva and movement in the oral cavity, mucoadhesive systems retain their position on the mucosal lining during extended periods of time. This allows to achieve prolonged drug delivery and better drug absorption, less frequent drug dosing, and improved therapeutic effect. Thus, mucoadhesive buccal films have proved to be one of the best drug delivery systems in treating localized oral diseases, such as recurrent aphthous stomatitis.

3.2 Structure of the Buccal Mucosa

Buccal mucosa comprises the lining of the inner side of the cheeks. This structure is made up of three distinct layers:

a. Stratified Squamous Epithelium

This outer layer acts as a main protective layer against physical damage and bacterial infection. Contrary to hard palate and gingival mucosa, buccal mucosa is not keratinized hence allowing for increased penetration of pharmaceutical preparations.

b. Basement Membrane

Basement membrane is responsible for anchoring the epithelial layer to the subjacent connective tissues as well as regulating molecular transport through the membrane.

c. Lamina Propria and Submucosa

This layer contains collagenous, elastic fibers, fibroblasts, capillaries, lymphatics and nerve endings that help in maintaining tissue integrity and facilitating absorption of drugs.

The overall thickness of the buccal mucosa varies from about 500 to 800 μm .

3.3 Principles of Mucoadhesion

Mucoadhesion is defined as the tendency of an agent to stick to the mucous layer lining the mucous membrane. In terms of drugs, the mucoadhesive agents in a pharmaceutical dosage form interact physically and chemically with mucin glycoproteins to enhance the retention period at the point of application.

A good mucoadhesive dosage form will be characterized by the following qualities:

- Having high adhesion capacity on the mucous membrane.
- Capacity to remain in place for the required time.
- Non-irritant and biocompatible.
- Capable of controlled drug release.
- Easy to apply and remove.
- Easily tolerable by the patient.

This makes the mucoadhesive dosage form very favorable for treating chronic oral disorders.

3.4 Mechanisms of Mucoadhesion

Mucoadhesion involves a series of sequential processes, including wetting, contact, interpenetration of polymer chains, and bond formation.

Stage I: Wetting and Contact

After administration of a dosage form, wetting and subsequent contact with saliva causes hydration of the polymer and its interaction with the mucous membrane.

Stage II: Intercalation of Polymer Chains

Intercalation of hydrated polymer chains takes place in the mucin meshwork, whereas mucin molecules intercalate within the polymer matrix.

Stage III: Bond Formation

Adhesive bonds are formed through several intermolecular mechanisms: hydrogen bonding, electrostatic interaction, van der Waals forces, hydrophobic interactions, and mechanical interlocking.

The adhesive force and duration of mucoadhesion are affected by the nature of the polymer, namely its molecular weight, flexibility, hydration level, extent of cross-linking, and presence of groups that can interact with mucin.

3.5 Mucoadhesion Theories

A number of mucoadhesion theories have been put forward explaining mechanisms behind this phenomenon.

Electron Theory

According to this theory, there is an electron exchange between the polymer and the mucosal membrane leading

to formation of electrical double layer and hence adhesion.

Adsorption Theory

According to this theory, adhesion is due to secondary chemical interactions such as hydrogen bonds, van der Waals' interactions and hydrophobic interactions between polymer molecules and mucin.

Diffusion Theory

According to this theory, penetration and entanglement of polymer chains within the mucus network leads to formation of adhesive strength.

Wetting Theory

This theory is particularly applicable in liquid and semisolid preparations and is based on the spreading capacity of the adhesive agent.

Fracture Theory

Fracture theory considers mucoadhesive strength in relation to the separating force between polymer and mucosal membrane post adhesion.

From these theories, diffusion and adsorption theories are more relevant to polymeric buccal films.

3.6 Mucoadhesive Polymers

The mucoadhesive polymers influence the mechanical behavior, swelling, drug release mechanism, and adhesive capability of buccal films.

Synthetic polymers

Some of the widely used synthetic polymers are:

- Hydroxypropyl methylcellulose (HPMC)
- Sodium carboxymethyl cellulose (Sodium CMC)
- Carbopol
- Polyvinyl alcohol (PVA)
- Polyvinylpyrrolidone (PVP)

They are known for their good film-forming tendency, reproducibility, and hydration property.

Natural Polymers

Natural polymers have become more popular due to the fact that they are bio-degradable, bio-compatible, and biologically active in nature.

Some of them are

- Mucilage of Aloe vera
- Chitosan
- Sodium alginate
- Guar gum
- Xanthan gum
- Pectin

From the above, mucilage of Aloe vera stands out for its double use as both pharmaceutical excipient and medicine with anti-inflammatory, antioxidant, antimicrobial and wound healing property.

3.7 Advantages of Mucoadhesive Buccal Films

In comparison to the traditional topical delivery systems, there are many benefits that buccal mucoadhesive films have:

- Prolonged retention of the preparation on the target area.
- Controlled and sustained drug delivery.
- Increased local concentration of the drug.
- Less frequent dosing.
- Better compliance.
- Convenience of application without the need for additional instruments.
- Precise dosing.
- Lesser exposure of the systemically absorbed drugs.
- By passing of the first pass effect.
- Better treatment outcomes for conditions affecting oral mucosa.

These features render the use of buccal films especially appropriate in the treatment of recurrent aphthous stomatitis due to the requirement for prolonged contact with the ulceration area.

3.8 Limitations

Although the buccal films have some strengths, there are several drawbacks associated with the buccal films which include:

- Low drug loading capacity.
- Constant secretion of saliva can slowly reduce adhesion.
- Movement of the film due to accidents caused while eating or talking.
- Taste-based problems that may affect patient acceptance.
- Drug administration is difficult in the case of high dosage drugs.
- Variable nature of adhesion depending on physiological differences between patients.

Therefore, proper selection of a suitable polymer and proper formulation variables and patient education are needed for better clinical results.

3.9 Use of Mucoadhesive Buccal Films in Recurrent Aphthous Stomatitis

Since the features of pathogenesis of recurrent aphthous stomatitis makes it the best target for local buccal drug delivery, the drug can be concentrated only at the site of the lesion without entering into the body system.

The use of triamcinolone acetonide and Aloe vera mucilage in the mucoadhesive buccal film can cause sustained anti-inflammatory action while the latter is helpful in wound healing and antioxidant actions.

4. Aloe vera Mucilage: Phytochemistry, Pharmacological Properties, and Pharmaceutical Applications^[16-20]

4.1 Introduction

Natural polymers have received increasing attention in pharmaceutical studies owing to their biocompatibility, biodegradability, lower toxicity, eco-friendliness, and multitherapeutic potentials. Unlike chemical excipients, natural polymers have inherent biological functions that can be used to enhance the efficacy of active drug molecules. Natural polymers such as Aloe vera have been widely studied because of their versatile pharmacological activities and pharmaceutical properties.

Aloe vera (*Aloe barbadensis* Miller) is a plant that belongs to the family of Asphodelaceae and has been employed in herbal medicine for thousands of years. The ancient Egyptian, Greek, Indian, and Chinese civilizations have appreciated the healing potential of Aloe vera in the treatment of wounds, burns, inflammatory conditions, and dermatological diseases. Scientific studies have proven several of the traditionally used claims showing that Aloe vera has anti-inflammatory, antimicrobial, antioxidant, immunomodulatory, and wound healing properties.

The mucilaginous gel that is clear and extracted from the parenchymatous cells inside the Aloe vera leaf comprises water (about 98%-99%), whereas the solids include a number of biologically active components, such as polysaccharides, glycoproteins, vitamins, enzymes, amino acids, minerals, phenolic substances, and organic acids. Out of all of these substances, it is the polysaccharide portion which gives Aloe vera mucilage its medicinal and pharmaceutical properties.

4.2 Phytochemical Composition

The biological effects of Aloe vera are due to the combined effect of more than 200 isolated phytochemicals. They can be divided into several groups.

Polysaccharides

Polysaccharides form the main biologically active component of Aloe vera mucilages. Among the main polysaccharides there are acemannan (acetylated β -(1 $\rightarrow$ 4)-mannan) that demonstrates pronounced immunostimulatory and healing effects and glucomannan, pectic materials, cellulose, arabinogalactans, galactose, and mannoses polymers.

The stimulating effect of acemannan on the activation of macrophages, fibroblasts' growth, collagen production, angiogenesis, and epithelial regeneration makes it especially useful in the treatment of oral ulcers.

Vitamins and Antioxidants

Aloe vera is a source of vitamins A, C, and E, B vitamins and folic acid. Being antioxidants, they eliminate the harmful products of inflammation reaction – reactive

oxygen species. Lowering the level of oxidation is helpful for tissue regeneration and prevention of damage to the oral mucosa.

Enzymes

There are many biologically active enzymes such as amylase, lipase, catalase, cellulase, alkaline phosphatase, and superoxide dismutase that are found in Aloe vera gel.

Amino Acids and Mineral Compounds

The aloe vera plant is composed of essential and non-essential amino acids along with minerals including calcium, magnesium, zinc, selenium, potassium, sodium, iron, copper, and manganese. These nutrients assist in facilitating cellular metabolism, enzyme function, collagen production, and epithelization.

Phenolic Compounds

These include anthraquinones, chromones, flavonoids, and phenolic acids, which have antibacterial and antioxidative properties. The anthraquinone rich latex present in the leaf rind must be excluded from mucilage preparation due to its potential to irritate.

4.3 Pharmacological Activities

Anti-inflammatory Activity

The anti-inflammatory effect of Aloe vera is among the most significant biological properties of the plant for treating recurrent aphthous stomatitis. Bioactive polysaccharides block cyclooxygenase pathways and decrease the production of various inflammatory mediators, such as prostaglandins, TNF- α , IL-1 β , and IL-6. Such a modulation leads to the inhibition of inflammatory cell infiltration, edema, erythema, and pain in the ulcers.

Wound-Healing Activity

There are several ways by which Aloe vera speeds up wound healing. Firstly, acemannan stimulates the growth of fibroblasts and collagen accumulation, which leads to the improvement of connective tissue synthesis. Moreover, Aloe vera promotes angiogenesis and epithelial cell migration, thus ensuring the fast closing of ulcerated wounds. Additionally, the increase in the synthesis of extracellular matrix proteins helps to strengthen newly generated tissues.

Antioxidant Activity

Tissue injury in inflammatory conditions often results from oxidative stress. However, Aloe vera has several antioxidant compounds that scavenge free radicals and protect oral tissues from oxidative damage. The increase in endogenous antioxidant enzyme activity contributes to accelerated tissue repair as well.

Antimicrobial Activity

There are many research works demonstrating inhibitory activity of Aloe vera against a variety of bacteria, fungi, and some viruses. Though recurrent aphthous stomatitis

is not primarily an infectious disease, secondarily occurring microbial infection can slow down ulcer healing. Consequently, antimicrobial activity of Aloe vera can indirectly facilitate the process.

Immunomodulatory Activity

Acemannan regulates both innate and adaptive immunity functioning by affecting macrophages activity, cytokines production and lymphocytes. Unlike causing universal immunosuppression, Aloe vera restores balance in immune system, which helps to reduce recurrence of oral ulcers.

4.4 Pharmaceutical Properties of Aloe vera Mucilage

Apart from therapeutic properties, there are many pharmaceutical properties of Aloe vera mucilage that make it very good natural excipient.

Film Forming Property

Mucilage rich in polysaccharides forms easily flexible polymeric films able to accommodate pharmaceutical components. Films formed show sufficient mechanical strength and elasticity in combination with some synthetic polymers.

Mucoadhesive Property

Polysaccharides rich in hydroxyl groups form hydrogen bond with mucin glycoproteins existing in buccal mucosa thus prolonging time of localization of drug in this area.

Biocompatibility

Aloe vera mucilage shows high biocompatibility and low toxicity.

Biodegradability

Being a naturally produced polysaccharide, Aloe vera is totally biodegradable without formation of any toxic metabolites thus increasing environmental sustainability as opposed to certain synthetic polymers.

4.5 Aloe Vera Mucilage in Mucoadhesive Buccal Films

Pharmaceutical activity alongside biological functionality makes Aloe vera mucilage stand out against many standard excipients. Being included into buccal films, Aloe vera fulfills several functions at once:

- Natural film-forming polymer.
- Mucoadhesive substance.
- Wound healing promoter.
- Anti-inflammatory agent.
- Antioxidant.
- Moisturizer.
- Physiologically acceptable natural biomaterial.

The use of Aloe vera mucilage along with HPMC E15 or Sodium CMC can increase flexibility and hydration capacity of film along with its mucoadhesiveness and offer inherent pharmacological properties which could

positively influence effectiveness of the drug being incorporated into it.

Such functionality becomes especially useful for treating recurrent aphthous stomatitis because, apart from delivering triamcinolone acetonide onto the ulcer, the formulation actively takes part in wound healing process. Biodegradability Being a naturally produced polysaccharide, Aloe vera is totally biodegradable without formation of any toxic metabolites thus increasing environmental sustainability as opposed to certain synthetic polymers.

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4.6 Research Gaps and Future Opportunities

Despite the detailed study on the potential of Aloe vera in wound healing and oral disease management, there are certain deficiencies that need to be fulfilled in order to develop an effective mucoadhesive drug delivery system using **Aloe vera**

- Few comparisons of the performance of Aloe vera mucilage compared to other synthetic mucoadhesive polymers.
- Few studies on the optimal concentration of Aloe vera in buccal film formulations.
- Little information on the molecular interactions between the polysaccharides of Aloe vera and oral mucin.
- The absence of randomized clinical studies on the effectiveness of Aloe vera based buccal films on recurrent aphthous stomatitis.

5. Triamcinolone Acetonide: Pharmacology and Clinical Applications in Recurrent Aphthous Stomatitis^[3,6,21-23]

5.1 Introduction

Triamcinolone acetonide is a man-made glucocorticoid possessing fluorine and is commonly employed in the treatment of various inflammatory and immune conditions. Since being introduced in the medical practice, it has been used as one of the most prescribed topical steroids in cases of inflammatory conditions of the mucosa due to its strong anti-inflammatory properties and good safety profile allowing the patients to obtain prompt relief of symptoms. For the treatment of RAS, triamcinolone acetonide is still considered to be the gold standard of the first-line therapy because of its efficacy in decreasing pain, inhibiting inflammation, and accelerating healing of the ulcers without causing serious systemic side-effects.

Despite the high efficacy of traditional dosage forms such as oral pastes, gels, ointments, and mouthwashes, their therapeutic efficiency can be compromised by the presence of the active process in the oral cavity. The salivary secretion, chewing, tongue movement, and swallowing decrease the contact time of the drug with the ulcer surface and thus reduce its availability. These factors have motivated the development of innovative approaches to the drug delivery.

5.2 Chemical and Physicochemical Properties

Triamcinolone acetonide is a very potent artificial corticosteroid prepared from prednisolone. Triamcinolone acetonide exists in the form of a white to virtually white crystalline powder which is virtually insoluble in water but soluble in organic solvents like ethanol. However, the insolubility of the compound in aqueous medium poses some formulation problems, especially in the preparation of aqueous formulations, but at the same time offers an advantage in designing sustained release formulations.

The physical and chemical stability of triamcinolone acetonide coupled with potent anti-inflammatory properties make it a good candidate for inclusion in polymer-based drug delivery systems like mucoadhesive buccal films.

5.3 Mechanism of Action

The mechanisms of action of triamcinolone acetonide are brought about by activation of glucocorticoid receptors within the cells. The drug enters the cells, binds with cytoplasmic glucocorticoid receptors, and enters the nucleus, thus influencing the expression of many genes that contribute to inflammation.

Triamcinolone acetonide reduces the production of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-2 (IL-2), interleukin-6 (IL-6), and interferon gamma (IFN- γ). In addition, it reduces the activity of phospholipase A₂,

which causes the reduction of the production of the prostaglandins and leukotrienes, which play a significant role in causing pain, swelling, and inflammation.

Furthermore, triamcinolone acetonide reduces the migration of leukocytes, makes the lysosomal membranes stable, lowers the permeability of capillaries, and suppresses the activation of immune cells. These activities relieve the pain, reduce tissue destruction, and promote healing of oral ulcers.

5.4 Clinical Applications in Recurrent Aphthous Stomatitis

Topical application of triamcinolone acetonide is preferred as the primary therapy for patients suffering from recurrent aphthous stomatitis of mild to moderate severity. Several clinical studies have shown that the use of the medication at the beginning stages of an outbreak results in decreased ulcer sizes, reduced pain levels, and faster healing periods.

Commercial medications are typically provided in the form of mouth pastes and dental medicines. This kind of medications is usually applied directly onto the ulcer two to four times a day. Even though the medication proves to be effective in many cases, its efficiency is significantly reliant upon patient's adherence to the regimen.

It is especially advantageous to apply triamcinolone acetonide during the prodromal stage of the disease before full development of ulcers.

5.5 Advantages of Topical Administration

The topical use of triamcinolone acetonide has a number of distinct benefits over the use of systemic steroids.

- The drug is applied directly to the ulcer site.
- A quick anti-inflammatory action at the site is achieved.
- The dose is not absorbed into the body.
- The occurrence of corticosteroids-related side effects is reduced.
- The patient's safety in case of multiple applications is improved.
- The treatment can be administered independently without the presence of special medical personnel.

5.6 Limitations of Conventional Topical Formulations

Although there have been demonstrated clinical efficiencies of these formulations of triamcinolone acetonide, there are certain drawbacks associated with them.

The constant secretion of saliva and movement in the mouth quickly wash out the formulation from the surface of the lesion. This results in reduced time during which the drug stays at the target site. As such, a lesser amount of the drug can be present at the ulcer site to produce its therapeutic effect. This would necessitate frequent

applications that could decrease the level of adherence by the patients.

Furthermore, the topical application of semisolid formulation might result in its dispersion in the mouth, leading to an uneven distribution of the drug in the mouth.

5.7 Rationale for Incorporation into Mucoadhesive Buccal Films

Mucoadhesive buccal films are one of the most efficient approaches to address the problems linked with traditional dosage forms. Integration of triamcinolone acetonide in a polymeric film ensures sustained drug release along with prolonged adhesion to the surface of the ulcer.

Integration of Aloe vera mucilage, HPMC E15, and Sodium CMC results in the development of the matrix with numerous beneficial properties that enhance film strength, flexibility, hydration, and mucoadhesivity. In addition, Aloe vera provides the formulation with wound healing, antioxidant, and anti-inflammatory properties.

The integration of such a formulation can offer a number of advantages:

- Prolonged presence of the drug on the ulcer.
- Sustained local drug delivery.
- Better coverage of the ulcer.
- Enhanced patient comfort.
- Reduced administration frequency.
- Improved healing of oral ulcers.
- Reduced systemic exposure to the drug.
- Increased patient compliance.

Therefore, Aloe vera mucilage mucoadhesive buccal films may be considered an advanced approach to the treatment of recurrent aphthous stomatitis.

5.8 Future Perspective

Whereas triamcinolone acetonide continues to be regarded as the best treatment modality for recurrent aphthous stomatitis using topical administration, efforts should be made in the future to enhance the delivery of this medication rather than trying to modify it. In other words, there is great promise for the use of the incorporation of bioactive natural polymers, advanced film formulations, and release mechanisms, which could help maximize its effectiveness while reducing side effects. More preclinical and clinical studies need to be conducted in order to determine the safety and efficacy of this product.

This is how the pharmacology part of your review ends. The rest of the sections to come include formulation approach, recent work, knowledge gap, future perspectives, and conclusion.

6. Formulation Strategies for Aloe vera Mucilage-Based Mucoadhesive Buccal Films^[9-23]

6.1 Rationale for Developing Mucoadhesive Buccal Films

Treatment of recurrent aphthous stomatitis necessitates sustained and targeted administration of drugs to optimize their efficacy with minimal systemic absorption. The use of conventional drug delivery systems, such as mouthwash, gel, and ointment, is often hindered due to constant saliva secretion, tongue movements, swallowing, and mastication. In this case, the drug stays in contact with the ulcers for a short time period, thus, limiting its efficiency.

Mucoadhesive buccal films represent an innovative drug delivery system that can address these challenges. The capacity of mucoadhesion helps to retain drug in contact with target site for a longer period and ensures sustained release of medication. In addition, buccal films are flexible, non-invasive, and thin drug delivery system that is well-tolerated by the patients.

6.2 Selection of Polymers

The success of mucoadhesive buccal film is greatly influenced by the choice of polymers. The perfect polymer would have great film-forming characteristics, high mechanical strength, flexibility, hydration capability, and mucoadhesiveness together with being biocompatible and non-irritant to the mouth tissues.

Man-made polymers such as **Hydroxypropyl Methylcellulose (HPMC E15)** and **Sodium Carboxymethyl Cellulose (Sodium CMC)** have been widely employed due to their consistent quality and good film-forming capability and controlled swelling capacity. Nonetheless, increased attention towards natural polymers has led to the use of bioactive materials such as Aloe vera mucilage that acts as a polymer while providing healing properties, anti-inflammatory activity and antioxidant protection.

Use of man-made and natural polymers gives a good balance in that there is enhancement in the physical properties and biological activity of the film.

6.3 Plasticizers and Their Role

The use of plasticizers in buccal films enhances flexibility and reduces brittleness of the product in order to provide increased comfort to the patients. Plasticizers achieve this through the reduction of intermolecular forces between polymer molecules thus increasing the polymer chains mobility.

Of the various plasticizers available, **glycerin** and **propylene glycol** have found much application in the manufacture of buccal films due to their safety and compatibility with hydrophilic polymers. Optimization of the concentration of plasticizers is necessary since low concentrations lead to brittle films and high concentrations make films sticky.

6.4 Drug Incorporation Strategies

Triamcinolone acetonide is poorly soluble in water but is highly soluble in ethanol. As a result, it is dissolved in a relatively small amount of ethanol prior to mixing in the polymeric solution. This ensures homogenous distribution of the drug within the film and prevents possible drug precipitation.

Homogeneous drug distribution in the polymeric matrix is extremely important in order to ensure drug dose uniformity.

6.5 Solvent Casting Technique

Solvent Casting Method

From all the manufacturing methods available, solvent casting method is the most commonly used laboratory scale method for the preparation of mucoadhesive buccal films. In the solvent casting method, the polymers are dissolved or dispersed in a suitable solvent, and the drug and excipients are then added to the solution and cast on a plane surface to evaporate the solvent slowly and form a film.

Advantages of solvent casting method include:

- Excellent content uniformity.
- Cost effective production.
- Low equipment requirement.
- Uniform film thickness.
- Best mechanical strength.
- Suitable for heat sensitive drugs and natural polymers.

Solvent casting method is ideal for the preparation of Aloe vera mucilage based buccal films.

6.6 Critical Quality Attributes

A variety of physico-mechanical properties contribute to the quality and efficacy of mucoadhesive buccal films. These are:

- Film thickness and weight.
- Folding resistance.
- Surface pH value.
- Content homogeneity.
- Humidity uptake and humidity loss.
- Swellability.
- Mucoadhesion.
- In vitro retention time.
- Drug release profile.
- Accelerated stability.

The assessment of these parameters is necessary for determining the optimal formulation which provides both prolonged activity and comfort for the patients.

6.7 Current Research Trends

Latest trends in buccal drug delivery have been towards designing multifunctional drug dosage forms which would exhibit pharmaceutical properties along with therapeutic activity. Biodegradable and environmentally

sustainable natural polymers have gained popularity due to their inherent biological activity.

Some of the current trends in research are:

- Hybrid polymeric films made up of natural and synthetic polymers.
- Bioactive films made from plant derived polysaccharides.
- Buccal drug delivery through nanotechnology.
- Polymeric systems responding to stimuli.
- 3D-printed buccal films.
- Personalized drug delivery systems for mouth.

Among the above mentioned techniques, buccal films made from mucilage of Aloe vera constitute a novel approach to this problem.

6.8 Knowledge Gaps

Notwithstanding all the achievements made, there are still some difficulties that must be overcome for the successful utilization of Aloe vera mucilage films in clinics.

They include the following:

- The absence of any standard procedure for the extraction and purification of Aloe vera mucilage.
- The variability between batches of natural polymer composition.
- The scarcity of comparative studies compared to the commercial counterparts.
- The lack of sufficient information on the stability of the product.
- The absence of any studies regarding pharmacokinetics and pharmacodynamics.
- The lack of randomized clinical trials for its efficacy for the treatment of recurrent aphthous stomatitis.

6.9 Future Formulation Perspective

In terms of future research, the area of study that should be considered is the integration of pharmaceutical technology with biomaterials found in nature to produce more efficient localized drug delivery systems. Polymer combinations optimization, application of advanced characterization techniques, and conducting preclinical and clinical trials will be important for commercial success.

The combination of Aloe vera mucilage, HPMC E15, Sodium CMC, and Triamcinolone acetonide constitutes a scientifically sensible formulation technique that can enhance localized treatment results by utilizing the advantages of drug release and wound healing characteristics of a natural polymer.

7. Current Evidence, Research Gaps, and Future Perspectives^[1-25]

7.1 Current Evidence

In recent years, an increasing amount of research on pharmaceutical preparations has been dedicated to the creation of localized drug delivery systems intended for

the treatment of diseases of the oral mucosa. Mucoadhesive buccal films have been of particular interest to researchers due to their capability to provide long retention, controlled release, good patient compliance, and low systemic exposure. Various synthetic polymers, including HPMC, sodium carboxymethyl cellulose, Carbopol, and polyvinyl alcohol, have been tested for their ability to form satisfactory films with appropriate drug release profile. However, most of these polymers possess no intrinsic biological activity and provide no benefit except pharmacological action of the loaded drug.

It is currently being recognized that natural polymers are more and more frequently used in modern drug delivery systems. Of all natural polymers, the use of Aloe vera mucilage has gained popularity recently due to its pharmaceutical qualities and biological activity. Several experimental works have proved that Aloe vera stimulates proliferation of fibroblasts, collagen formation, angiogenesis, epithelization, and exhibits anti-inflammatory, antioxidative, and antimicrobial properties. It means that Aloe vera mucilage can be used as both film-forming agent and bioactive component.

The choice of the triamcinolone acetonide as the topical corticosteroid for treating the recurrent aphthous stomatitis is justified by its high efficiency in providing anti-inflammatory effects, reducing pain, and reducing healing period. However, the existing oral pastes and gels have a problem with retaining the medication on the oral mucosa, and their use requires regular application. Thus, the development of the triamcinolone acetonide containing mucoadhesive buccal film seems to be a rational approach in improving local availability of the drug.

There are enough studies devoted to the investigation of the topical corticosteroids, natural polymers, and mucoadhesive buccal films separately, but there are few studies on combining the triamcinolone acetonide with the Aloe vera mucilage in one preparation.

7.2 Critical Analysis of the Literature

From the available scientific literature, it is evident that mucoadhesive buccal films are quite effective in achieving localized oral drug delivery. Prolonged retention time, favorable mechanical properties, and improved acceptability as compared to conventional topical drug delivery systems are common characteristics of the systems under study. However, there is a lot of variability in terms of the choice of the polymer, formulation, use of plasticizer, and assessment criteria. This makes it difficult to compare studies.

One of the most evident gaps that have been highlighted in almost all the articles reviewed here is the lack of standardized extraction procedures of natural polymers. The variability in Aloe vera cultivation process, extraction procedure, and even storage process affects

the composition, viscosity, and biological activity of the polysaccharides, which ultimately affect the performance of the system. Standardizing the extraction procedure will make comparison easy in the future.

Another evident gap in the review of the literature is the lack of adequate clinical trials. Although most of the reports present impressive findings from laboratory and pre-clinical experiments, only a few randomized clinical trials have assessed the effectiveness, safety, and patient acceptability of the formulations in the management of recurrent aphthous stomatitis.

7.3 Research Gaps

While considerable advancements have been made in the area of buccal drug delivery systems, many scientific uncertainties still exist in this field:

- The standard protocol for isolation and analysis of mucilage from Aloe vera is yet to be developed.
- The best concentration of Aloe vera mucilage for the balance of film features and biological activity has not been revealed.
- There are no comparative analyses between Aloe vera films and commercial preparations containing triamcinolone.
- The long-term stability of Aloe vera films under various storage conditions has not been studied well enough.
- No sufficient pharmacokinetic and pharmacodynamic information exists on buccal films based on Aloe vera.
- The need arises for randomized clinical trials of such systems.

7.4 Future Perspectives

The future studies must pay attention to the creation of multifunctional mucoadhesive films for the application in buccal cavity utilizing advanced pharmacy technologies along with bioactive natural polymers. Inclusion of Aloe vera mucilage in combination with already used mucoadhesive polymers such as HPMC E15 and sodium carboxymethyl cellulose is expected to provide the possibility to receive the optimal films with additional beneficial properties.

Advanced technologies, such as nanotechnology of drug delivery, three-dimensional printing, and personalized medicine can also be used for enhancing the properties of buccal films. Using nanosystems or bioactive nanoparticles in films can help to improve the dissolution of drugs, controlled release, and penetration into ulcerative tissues.

Moreover, future studies should pay special attention to the detailed characterization of natural polymers, elucidation of mechanisms of interaction of polymers with mucin as well as the multicenter clinical studies devoted to the assessment of efficacy, safety, and cost-effectiveness of studied materials.

8. CONCLUSION^[1-25]

Recurrent aphthous stomatitis is still among the most prevalent oral inflammatory conditions characterized by intense pain and discomfort and impairing patients' quality of life. Even though different treatment methods exist, conventional topical dosage forms prove to be rather ineffective due to fast clearance from saliva, poor local retention properties, and the necessity for repeated dosing. Therefore, the development of novel advanced localized drug delivery systems seems to be crucial.

Buccal films represent a promising delivery system for treatment of oral mucosal conditions owing to their prolonged residence time, controlled drug delivery, improved local availability, and patient compliance. The use of triamcinolone acetonide in such systems provides targeted therapy in addition to avoiding any systemic side effects. Thus, these preparations can be used for treating recurrent aphthous stomatitis.

Among numerous polymers used for buccal films development, the mucilage of Aloe vera is an exceptional multifunctional natural biomaterial. In addition to high film forming and mucoadhesion capabilities, Aloe vera mucilage has many intrinsic anti-inflammatory, antioxidant, antimicrobial, immunomodulating and wound healing properties that might add to the therapeutic action of triamcinolone acetonide. These therapeutic and pharmaceutical properties make a good scientific justification for the development of mucoadhesive buccal films based on Aloe vera mucilage as a novel drug delivery system.

Currently, there is much encouraging information about the development of mucoadhesive buccal formulations, but certain problems still remain. Standardization of mucilage of Aloe vera extraction, selection of suitable polymer combinations, stability studies and clinical trials are necessary before application of such preparations in clinical practice. Moreover, well-designed randomized clinical trials comparing Aloe vera based buccal films with commercially available formulations of topical corticosteroids are needed.

In summary, the use of natural bioactive polymers along with current drug delivery technology provides a potential avenue for future research. Buccal films made up of Aloe vera mucilage with a mucoadhesive property and triamcinolone acetonide can provide a solution to overcome most shortcomings that are seen in conventional treatment methods. The use of a multidisciplinary approach in future research from the field of pharmaceutical science, clinical research, and biomaterials would help in the development of safer and effective therapeutic systems for managing recurrent aphthous stomatitis.

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