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Current Mucoadhesive Drug Delivery System for Recurrent Aphthous Stomatitis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease of the oral mucosa, RAS is characterized by extremely painful, recurring solitary, multiple ulcers in the upper throat and oral cavity, which may lead to difficulty in eating, speaking and swallowing and negatively affects the life standard of the patient's. In patients undergoing fixed orthodontic treatment, the frequency of RAU Increases .The underlying etiology of RAS is noted clear and no curative treatment is available. Current treatment for RAS is often in the form of mouthwashes, creams, or ointments, but these are often ineffective, due to inadequate drug contact times with the lesions and poorly available use of drug. To overcome these problems, it has been proposed to incorporate drugs to mucoadhesive polymers or nanoparticulate systems containing mucoadhesive polymer(s) because of their propensity to interact with the mucosal surface. Mucoadhesions increased the residence time of drug carriers at the site of absorption, improved drug absorption, and controlled drug

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release from the devices used. Smaller size of particles has been supposed to diffuse much higher in the mucus layer and improve the bioavailability of drugs. In the present review, we focus on the mocuadhesive drug delivery system in the treatment of RAS.

Keywords: Recurrent aphthous stomatitis; mucoadhesion; nanoparticles; oral mucosa.

1. INTRODUCTION

The oral mucosa lining has been involved with numerous inflammatory, atrophic, and ulcerative diseases, including lichen planus, erythema multiforme, aphthous stomatitis and Behcet's syndrome. Recurrent aphthous stomatitis (RAS) is one of the most common ulcerative diseases in oral mucosa which about 20 % of the general population have experienced it, especially at young ages. "This condition was first described by Hippocrates in 400 B.C. The word aphthous originated from the Greek word aphtha which mean a mucosal surface ulcer" [1]. It also has known as cold canker sores and recurrent aphthous ulcers (RAU) [2]. The appearance of ulcers are usually multiple, small, oval or roundish with yellow or gray base and erythema in the surrounding tissue. RAS are painful inflammatory lesions that involve the non-keratinized oral mucosa: the gums, cheeks, lips, tongue, and roof or floor of the mouth [2]. Considering the clinical features, three types of RAS have been recognized (Fig. 1). The first one is minor recurrent aphthous stomatitis as the most common form of RAS during childhood. The diameter of erosion is smaller than 1 cm surrounded by an erythematous halo. This form usually heals during two weeks. The second form is major recurrent aphthous stomatitis during puberty with one to ten ulcers larger and deeper than minor aphthous. The lesions are painful and might be affected swallowing and speaking and last up to one month to heal with scar formation. The least common form of RAS is herpetiform recurrent aphthous after puberty. This type, usually accrued in a cluster or crops, consist of 10 – 100 very painful ulcers [3]. "Despite its high prevalence, the ethiopatogenesis of aphthous is not clear, but some potent factors have been predisposed for aphthous ulcers like: genetics, stress, food allergy, smoking, deficiency of certain vitamins and minerals, mechanical injury, hormonal imbalance, immunological disorder, bacterial and viral infections, some drugs (NSAIDs, B blockers) and systemic diseases (e.g., ulcerative colitis, celiac disease, AIDS, Crohn's disease" [3,4]. Hormonal changes do not directly cause periodontitis, but they can be a contributing factor to periodontiti. Changes in hormones (especially estrogen and progesterone) affect the gums by altering blood flow to the gums and the type of tissue response to plaque in the mouth, causing the person to often experience pain or bleeding when brushing and flossing. The effect of hormones on gum health is more common in women than men, because women experience more hormonal changes throughout their lives. Although the risk of gum disease often increases during pregnancy and menopause, many women experience symptoms during puberty and just after menstruation [5]. Studies have shown that deficiencies in B vitamins, including vitamin B12, are one of the most important causes of aphthous [6]. "Vitamin B12 shows a vital role in the formation of hematopoietic stem cells and has been related with oral mucosal diseases, mostly RAS. Also B12 was recommended as a potential treatment given its role in regenerating oral mucosal tissue" [6].

Although there are many clinical observations and researches in the field of RAS, but the real cause of RAS is not completely understood, so there is no specific and defined treatment and therapy is symptomatic to decrease the symptoms, stimulation the healing of ulcers, reduce the number and size ulcers and prevent the recurrence [2] Now, corticosteroids, anti-inflammatories, analgesics, antimicrobial, immunomodulatory agents, lubricating and healing promoting agents are used for treatment and reduction the symptoms of RAS [7]. Semisolid or liquid are the most common dosage forms of traditional system administration with the disadvantage of poor retention time in the oral cavity. Other obstacles in dental therapeutic strategies are systemic effects, rapid clearance of drug at the targeted site, alterations in the type, and microbial flora. Therefore, many attempts have been focused to design controlled and targeted delivery systems to overcome these challenges. Recently, different drug delivery systems including nanoparticles and microparticles, mucoadhesive and responsive systems have been developed to prolong the retention time, localize the drugs to specific regions of the oral cavity to avoid systemic circulation, decrease the dose frequency and

adverse drug interaction. Furthermore, it helps to provide better therapeutic control of the diseased conditions. The main goal of this review is to give an overview of the advanced approach for RAS based on mucoadhesive and nanoparticles systems.

2. METHODS

We conducted a search of the published English-language literature in the Google Scholar ، PubMed ،Magiran ،Science Direct databases, using the search terms Recurrent aphthous stomatitis, Mucoadhesion, Nanoparticles, Oral mucosa. We included all cohort, case–control, and cross-sectional studies that presented original data on any aspect of aphthous stomatitis in patients.

One author performed the systematic search, screened all titles and abstracts, obtained all potentially eligible papers in full text, and checked their eligibility. This author also screened the reference lists of all eligible studies. All titles identified via references were obtained in full text and checked for eligibility. Two author extracted the data from all eligible studies, entered them into a Microsoft Excel database, and synthesized the results in a narrative review in consultation with the other authors.

3. ORAL MUCOUS MEMBRANE

“The mucous membranes of the oral cavity consist of the floor of the mouth (sublingual), the gums (gingiva), the buccal mucosa (cheeks), the palatal mucosa, tongue and the lining of the lips” [8]. Types of mucosa are differentiated into lining mucosa, masticatory mucosa, and specialized mucosa based on their function: [9].

“Structurally, the oral mucosa consists of two distinct layers: the superficial stratified squamous epithelium and the underlying connective tissue, called the lamina propria” [9]. The epithelium functions as a mechanical barrier and protect the underlining tissue, whereas the lamina propria serve as a mechanical support. “There is a submucosa region under the lamina propria containing the major blood vessels and nerves that supply the mucosa” [10]. “The lining mucosa is located on floor of the mouth, soft palate, buccal regions, undersurface of the tongue, and lips and cheek which have normally non-keratinized epithelium. These regions are flexible to authorize for speech or accommodation of a food bolus” [9,11]. The gingivae and part of the hard palate are the regions of the masticatory mucosa, firmly attached to the underlying connective tissue and bone to tolerate mechanical stress during mastication. These parts have keratinized epithelium [8,12]. “Specialized zone is found in the borders of the lips and the dorsal surface of the tongue, shows selective keratinization, and includes lingual papillae and taste buds as specialized structures” [10,13]. There are regional differences in tissue thickness and cell turnover time apart from keratinization. The buccal mucosa epithelium has the turnover time of 14 days, whereas it is 24 days for hard palate and 28 days for skin in average [11]. “The oral epithelium is about 40 to 50 cell layers and its thickness is variable. The buccal mucosa has the thickest epithelium ranging from 500-600 μm thick and the thinnest one is the floor of the mucosa with about 100-200 μm” [14].

4. PERMEABILITY

“Nowadays, more attention has been focused on the drug delivery through the oral mucosa due to the suitable permeability of the oral mucosa. Lipid composition of intercellular material, derived from the membrane coating granules (MCGs), plays an important role in the permeability of the substances” [15]. “The lipid components in keratinized and non- keratinized of epithelium are different. Lipid components including glucosylceramides, sphingomyelin and ceramides and other nonpolar lipids are found in keratinized epithelium in a lamellar phase. Whereas, non-keratinized epithelium which comprise cholesterol esters, cholesterol and glycosphingolipids in a nonlamellar lipid phase” [10,16]. “It was estimated that the permeability of the oral mucosa is 4-4000 times greater than that of the skin. Generally, the permeability of the oral mucosa increases in the order of palate greater than buccal and buccal greater than sublingual” [13].

5. MUCOADHESION AGENTS

“The concept of mucoadhision has gained more attention since the early 1980s. Bioadhesion is defined as the ability of a dosage form to come into close contact with a biological surface by interfacial forces, which may consist of valence forces, interlocking action, or both. When the biological surface is the mucosal surface or mucous coat, this process is termed mucoadhesion” [17]. There are various absorptive mucosa including nasal, ocular, rectal, vaginal, pulmonary, and oral membranes. “The

mucosa of the oral cavity is viewed as a convenient and easily accessible site for the delivery of therapeutic agents. Mucoadhesive drug delivery systems possess several advantages including passing hepatic first-pass metabolism by preventing enzymatic degradation of drugs in the gastrointestinal tract, good patient compliance, abundant blood supply, improving barrier permeability due to having a larger surface area compared to nasal and ocular roots, prolong the residence time of the dosage form at the site of application or absorption and increase the drugs bioavailability" [17,18]. "Contact between the mucoadhesive polymer and mucous membrane happens due to wetting, spreading, and swelling of the formulation. In the consolidation stage, the mocuadhesive molecules are broken by moisture and interpenetration, attractive interaction between mucoadhesive materials and the surface of the mucosal layer occurs by hydrogen bonding, covalent bonding, ionic bonds and Van der Waals' interactions" [17,19]. "Mucins, the main family of proteins in the mucosa, are negatively charged and can interact electrostatically with positively-charged systems" [20]. "Cysteins amino acids are presented in some regions of mucines, therefore disulfide bonds (S-S) can form between these free thiol groups or intra-protein disulfide bonds with thiol groups on some polymers" [21]. "Mocuadhesive dosage forms should be small and flexible to be acceptable for patients, non - irritating, having high drug loading capacity, good mucoadhesive properties, tastelessness, easy to use and controlled drug release" [22].

Several polymers have been used for the mucoadhesive systems including:

"Hydrophilic polymers which contain carboxylic groups and possess excellent mucoadhesive properties. These are PVP (Poly vinyl pyrrolidine), MC (Methyl cellulose), SCMC (Sodium carboxyl methyl cellulose), HPC (Hydroxyl propyl cellulose) and HPMC (Hydroxylpropylmethylcellulose" [17].

Hydrogel polymers which have the ability to hold water in their porous structure, swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge to:

Anionic polymers - carbopol, polyacrylates, alginate

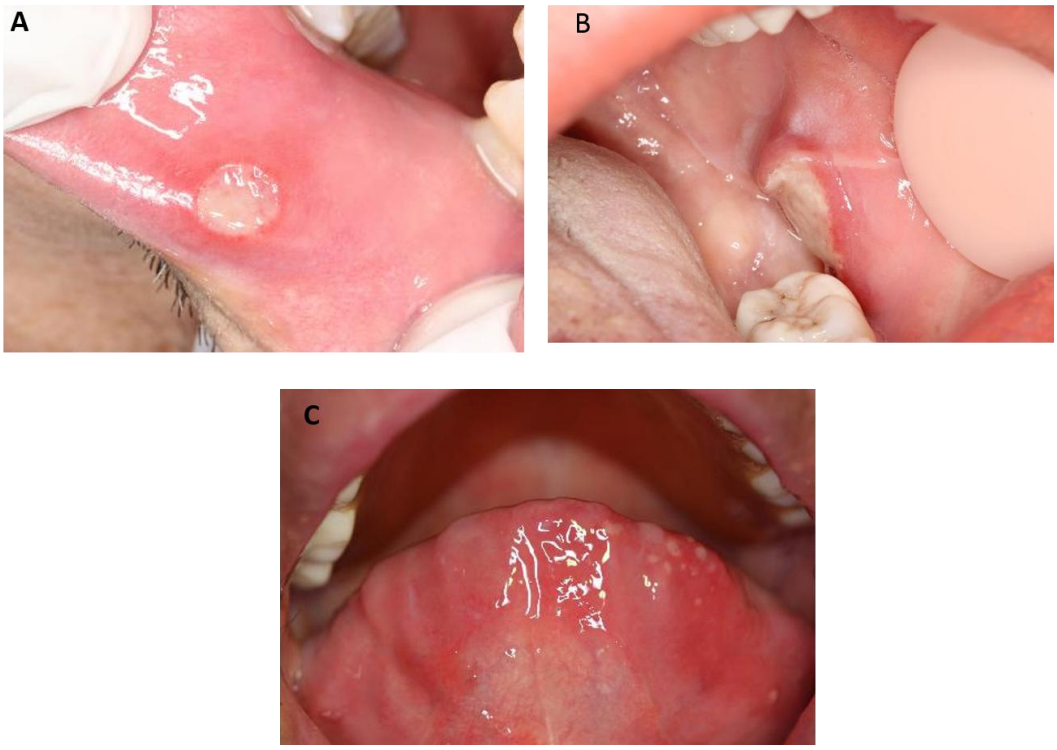

Fig. 1. RAS is categorized into three types including minor aphtae (A), major aphtae (B), and herpetiform (C) [110]

Cationic polymers – chitosan

Neural/ non-ionic polymers - eudragit analogues [23]. And Novel polymers such as pectin, lectins, thiolated polymers [17].

6. ORAL MUCOSAL ROUTE OF DRUG TRANSPORT

There are two permeation pathways for passive transport of drugs across the oral mucosa. They are paracellular or intercellular and trancellular or intracellular routes. Although compounds can use these ways simultaneously, but depending on their physiological properties, one route is usually preferred over the other. “The hydrophilic nature of intercellular space and cytoplasm create a major barrier to the permeation of lipophilic compounds due to their low solubility in these spaces” [8].

Targeted drug delivery in the oral cavity is highly favorable for local treatment of a variety of oral diseases such as malignant lesions, oral mucositis, RAS, periodontitis, and certain oral infections.

Drug delivery within the oral mucosa is classified into three categories [24,25]. (Fig. 1):

1- Sublingual delivery: it is a drug administration route via the mucosal membranes lining the floor of the mouth to reach the systemic circulation. Sublingual absorption is 3 to 10 times greater than oral use with a rapid action for treating acute disorders.
2- Buccal delivery: it is drug administration through the buccal mucosa lining the cheeks to systemic and/ or local delivery. This route is preferred for sustained drug delivery to treat chronic diseases.
3- Local delivery: is drug administration for local treatment of oral diseases such as bacterial and fungal infections, periodontal disease, and oral ulcers via gingival and hard palatal mucosa.

Mucoadhesive systems for oral local drug delivery have been developed, including adhesive tablets, adhesive films or pellicles, adhesive patches, adhesive semisolid systems (gels, ointments), adhesive liquid systems (sprays, mouthwash), liposomes, micro/ nanoparticles, nanosuspensions, microemulsions and colloidal dispersions. In this part, we review the advanced treatment based on mucoadhesive and nanoparticle drug delivery system for RAS [26].

7. ORAL MUCOADHESIVE DRUG DELIVERY SYSTEM FOR RECURRENT APHTHOUS STOMATITIS

Different therapeutic agents formulated in various mucoadhesive drug delivery systems have been developed for recurrent aphthous stomatitis. In Table 1, some of these delivery systems have been summarized.

8. CORTICOSTEROIDS

“Corticosteroids are accepted as a main strategy for treating RAS and other inflammatory conditions of the mouth. Corticosteroids have been used in the form of mouthwashes, creams, or ointments, but drug contact with the lesion is inadequate and the treatment process is often became ineffective” [27]. “Triamcinolone acetonide is a medium to high potency corticosteroid that is effective in the treatment of asthma and allergic rhinitis. It is used as a dental past for decreasing the signs and symptoms of many oral inflammatory conditions, including RAS” [28]. “For providing the formulation with longer contact time, an oral paste formulation was provided by compositions of polymers including gelatin, pectin and carboxy methyl cellulose with different ratios, and a base comprised of mineral oil containing polyethylene (Plastibase®).The optimized oral paste formulation of triamcinolone acetonide containing 60% plastibase, 3.3% pectin, 6.6% gelatin and 30% carboxy methylcellulose showed similar properties in durability of adhesion, spread ability and rheology compared with reference formulation (Adcortyl®)” [29]. Triamcinolon acetonide mucoadhesive film was prepared in another study. First layer of the film composed of bioadhesive polymers such as chitosan, HPMC K4M, K15M, eudragit RL100, and the second layer contained ethyl cellulose. Evaluation of the pharmaceutical and physicochemical properties of the film revealed that formulations containing chitosan had high flexibility and maximum adhesion to the mucosa, but most of them were shrinking, whereas Eudragit had less adhesion to the mucosa compared to chitosan and HPMC. The rate of drug release was not the same in different formulations. The suitable release was observed in eudragit and ethyl cellulose containing formulations as well as good adhesion property [30]. In another study, betamethasone-17-

valerate (BWV) was incorporated in to mucoadhesive membrane as a drug delivery system for treatment of RAS [31]. In this system, chitosan was used as a cationic natural polysaccharide with excellent mucoadhesive properties [32]. Chitosan is a nontoxic biocompatible polymer that has been widely used in the formulation of transdermal drug delivery system [33] with the ability to interact with human cells [34]. It has low mechanical stability that could be improved by simple blending with other non-ionic water-soluble polymers [35-37]. "Blend of chitosan with poly vinyl pyrrolidone (PVP), a nontoxic and biocompatible synthetic copolymer, improved the mechanical/physical and thermal properties of chitosan. Furthermore, PVP caused changes in swelling ratio which improved the BMV release rate up to 80% in less than 1 h. Moreover higher mucoadhesion property was observed in the membranes containing PVP polymers" [31].

9. NATURAL COMPOUNDS

Natural compounds have been found to be effective in RAS. They have different properties such as antibacterial, antioxidant, anti-inflammatory, and immunomodulatory activities [38]. "Pomegranate flowers of (*Punica granatum* L.) from the punicacea family, which have been used for treating oral ulcers, strengthen the gum in Iranian folk and traditional medicine" [39]. "As mentioned above, free radicals play an important role in the etiology of RAS, therefore, using antioxidant agents might be effective in aphthous healing. The pomegranate flower have high antioxidant content [40], antibacterial effect [41], anti-inflammatory [42], and analgesic effects [43] that seems to have a positive effect on the treatment of aphthous symptoms". A mucoadhesive formulation containing of carbomer 934, sodium carboxymethylcellulose (SCMC), and hydroxypropyl methylcellulose K4M

Table 1. Different therapeutic agents formulated in various mucoadhesive drug delivery systems

Therapeutic agents	Mucoadhesive drug delivery agents	Dosage forms	Ref
Triamcinolon acetonide	Plastibase, Pectin, Gelatin, Carboxy methylcellulose	Paste	[29]
Triamcinolon acetonide	chitosan, Hydroxypropyl methylcellulose K4M, K15M, eudragit RL100 , contained ethyl cellulose	Film	[30]
betamethasone-17-valerate (BWV)	Chitosan-PVP	Membran	[31]
Punica granatum L.)	Carbomer 934, Sodium carboxymethylcellulose and hydroxypropyl methylcellulose K4M	Gel	[44]
Myrtus communis	Polyvinyl pyrrolidone , Gelatin, Methylcellulose and Pectin	Patch	[48]
Zingiber officinale Roscoe			[50]
Citrus oils	Polyacrylic acid, Hydroxylpropyl cellulose	Patch	[53]
Ziziphus jujube	Carbopol 934, PVP K30 , gelatin	Disc	[56]
Aloe Vera and myrrh		Gel	[60]
Ambroxol	Alginate	Buccal	[64]
Zinc		Tablet	[73]
Hyaluronic acid GUM® AftaClear® GUM® AftaClear®		Gel Rinse	[80]
Hyaluronic acid	Hydroxy ethyl cellulose medium viscosity, Polyvinyl alcohol	Buccal film	[81]
Chitosan	Chitosan	Film	[89]
Choline salicylate	Carmellose sodium, Glycerol, Polyethylene oxide	Buccal film	[92]
Acacia nilotica and Glycyrrhiza species or amlexanox + laser			[95]
Dermovitamina aftaclin + laser		Gel	[96]

were used as gelling polymers and the condensed extract of Pomegranate flowers dispersed in polyethyleneglycol (PEG) 400 was added to this gel. Formulation which contained higher carbomer 934 and SCMC polymers showed higher viscosity and mucoadhesion values that would be remaining on the mucous surface long enough to release its active ingredient [44]. "The effect of this mucoadhesice gel was evaluated in a double-blind clinical trial in 60 patients with oral RAS and the age range of 18 to 50 years old" [45]. "The patients were randomly treated with *Punica granatum* mucoadhesive gel*,* Trident oral paste, and placebo. The survival analysis revealed that the duration of wound healing in *Punica granatum*group was significantly lower than the other two groups, but no difference in pain relief time was observed between *Punica granatum* group and patients received Triadent oral paste" [45].

"Myrtus communis is a perennial shrub widely has been used in Persian traditional medicine due to its antibacterial, anti-inflammatory, anti-hyperglycemic and analgesic effects" [46]. "These properties suggest the potential efficacy of myrtle in RAS treatment" [47]. "High solubility of myrtle in media resembling saliva carry on reduction retention time and contact of myrtle with aphthous ulcer in aqueous form. Applying a mucoadhesive systems can increase the drug exposure time and, hence, treatment efficiency. For example, oral mucoadhesive patches of myrtle were formulated from polymers such as Polyvinyl pyrrolidone (PVP), Gelatin, Methylcellulose (MC) and Pectin and evaluated by Box Behnken Design" [48]. A total of 29 myrtle extracts with different polymer combinations were prepared. According to the results of different parameters(tensile strength, folding endurance, swelling index, thickness, mucoadhesive strength, and the pattern of myrtle release), the optimal formulation was selected by of 35.04 mg of gelatin, 7.22 mg of pectin, 7.20 mg of polyvinyl pyrrolidone, 50.52 mg of methyl cellulose and 20 mg of Myrtle extract. This myrtle patch showed degradation time more than 24 h, a release rate of 27.5 (min^{-1}), and swelling ratio of about 300% [48].

Ginger is one of the most important medicinal herbs that comprises the dried rhizome of *Zingiber officinale* Roscoe. Several studies have been establishing on the health benefits of ginger in oral care.

"It possess antifungal, antimicrobial, anti-nausea, oral anticancer, antiplaque, and anti-carries properties. Additionally, it is known to promote dentine remineralization and help to harden the teeth. Due to these properties, ginger is useful for the treatment of various oral disorders like RAS" [49]. Haghpanah et al., developed ginger-containing mucoadhesive system and its efficacy was evaluated in management of aphthous stomatitis [50]. It was a randomized double-blind placebo trial performed on 15 patients with an average age of 22.86±2.25 years. The placebo contained tragacanth gum and the mucoadhesive system consisted of an alcoholic extract of ginger. Volunteers were asked to apply the preparation daily for 20 min after every meal and before going to bed for a period of 7 days. The diameter of the inflammatory zone and ulcers, pain, and healing process were evaluated on the first, third, fifth, and seventh days of study. The outcomes of study revealed a significant decrease in pain severity on the fifth day. Its effect on the ulcer diameter, inflammatory zone, and duration of treatment was not significant [50].

Citrus oils are another natural compound with antioxidant, anti-inflammatory, anticancer, and antimicrobial properties [51]. In a research, citrus oil and magnesium salts were incorporated into a bioadhesive patch which had been prepared by mixing powders of cross-linked polyacrylic acid and hydroxylpropyl cellulose. Magnesium is one of the active ingredients of the patch and has anti nociceptive effects [52]. Application of the mucoadhesive patch reduced the duration of pain and about 78.4% of patients claimed a significant improvement in oral functions [53]. *Ziziphus jujubeis,* traditional medicine, has been used in Iran as an antitussive, laxative, and blood pressure reducer [54]. The powder of stem bark and leaves of jujube were used to cure wounds and oral wounds as aphthous stomatitis [55]. Carbopol 934, PVP K30, and gelatin polymer were used for preparation mucoadhesive disc containing 10% of stem bark extract of *Ziziphus jujube*for for buccal administration. According to the results, the disc has good adhesion to the mucusa for 2 hr. The average of drug release was 47% in one hour which seems to be high enough for treatment of lesion [56]. *Aloe vera* is a beneficial plant full of vitamins and minerals with wide applications in health, medicinal, and skin care. It has various biological effects such as antifungal, anti-cancer, anti-inflammatory and immunomudolatory, healing properties, moisturizing and anti- aging and antiseptic [57] Due to biological properties, *Aloe vera* has been

used in dentistry to treat lichen plants, recurrent aphthous stomatitis, periodontitis, oral submucous fibrosis, radiation-induced mucositis and ect [58]. Myrrh is a dried resin secreted by Commiphora species plants with anti-inflammatory effect and wound healing properties, local anaesthetic activity, and antibacterial activity [59]. Clinical efficacy of *Aloe vera* and myrrh based mucoadhesive gels was assessed by RAS in a randomized, double-blind, vehicle-controlled study. In RCT, 90 subjects with RAS was conducted and instructed to use either one of these two mocoadhesive gels or placebo four times a day for 5 days. Applying *Aloe vera* and myrrh reduced the ulcer size and pain intensity in both groups compared to placebo without showing side effects. The authors reported complete ulcer healing, subsidence of erythema, and exudation in 76.6% , 86.7%, and 80% of patients using *Aloe vera* mucoadhesive gels. Results of this study demonstrated that *Aloe vera* was superior in reducing the ulcer size, erythema, and exudation; whereas myrrh resulted in more pain reduction due to its anaesthtic activity [60].

10. CURCUMIN

A mucoadhesive film containing chitosan-coated PCL nanoparticles loaded curcumin was developed for buccal delivery [61]. These nanoparticles were prepared using the nanoprecipitation method. Mucoadhesive matrices were also prepared by casting/solvent evaporation technique using chitosan and glycerol as a plasticizer agent. Investigation of the physicochemical characteristics of curcumin-loaded nanoparticles displayed a monodisperse distribution of particles (PdI <0.3), with hydro dynamic diameter (2Rh) ranging between 218 and 256 nm. Addition of chitosan to the nanoparticle increased the mean size particle and provided positive surface charged which is attributed to the amino groups positively charged of chitosan molecules on the nanoparticle surface [62] and the curcumin encapsulation efficacy obtained about 98%.Atomic force microscopy images demonstrated the mean partice size between 200 and 700 nm dispersed in a uniform surface of chitosan and the presence of nanoparticle inside the films was shown by FEG-SEM images. Swelling studies proved the suitable rate of hydration displayed a maximum swelling of 70%–80% in the saliva medium film containing curcumin nanoparticles showed prolonged controlled delivery of curcumin compared to films containing free curcumin. Overall, This developed nano-structured film composed of amucoadhesive matrix of chitosan containing curcumin-loaded chitosan-coated nanoparticles may be useful for the treatment of oral disorders such as aphthous stomatitis [61].

11. AMBROXOL

Ambroxol is a bromhexin metabolite, widely used as a mucolyticor expectorant agent in respiratory diseases associated with increased mucus production like acute or chronic bronchitis. Ambroxal has local anesthetic and anti-inflammatory effects which might be a benefit for the management of chronic neuropathic and inflammatory pain [63]. A sulfhydryl anchored alginate dosage form consisting of ambroxol was developed for buccal application in the management of aphthous stomatitis. Sulfhydryl moiety of amino acid cysteine (SH) were anchored to the carboxylic group of anionic alginate polymer. The sulfunyl anchored alginate (Al-SH) was safe and its stability was 3.52 fold greater than alginate (Al). The mucoadhesive potential of AL-SH was improved (11.56 fold) on mucosa compared to AL. It is because of the strong interaction of anionic sulfhydryl linked polymer with cysteine group in the mucosa compared to the weak interactions of native alginate. AL-SH released the drug in a sustained release manner compared to AL [64].

12. ZINC SULPHATE

Zinc is one of the critical, biologically active trace elements in humans. It acts as co-enzyme and plays important roles in the metabolism of lipids, proteins, and carbohydrates, growth and reproduction of cells, and regulation of RNA and DNA biosynthesis [65]. It has been shown that zinc effects on the normal function of the immune system. Zinc can stimulate the production of IL-6, IL-1, and Tumour necrosis factor α (TNFα) in peripheral blood mononuclear cells and separated monocytes [66]. The secretion of interleukin 2 (IL-2) and the number of T1- helper cytokines (Th1) are reduced in deficiency of zinc supplement. Several studies suggest that Th1-type immunologic response plays a crucial role in the etiopathogenesis of RAS [67,68]. Deficiency of antioxidants is one of the main causes of RAS and zinc is a potent antioxidant agent for balancing cellular oxidation and reduction reactions [69]. Therefore, considering the potential role of zinc, it has been suggested that zinc may cause the RAS in the deficient

cases. The efficacy of oral zinc in the treatment of RAS has been reported in several studies [70-72]. The effect of mucoadhesive formulation of zinc sulfate on RAS was evaluated in a randomized double-blind, placebo-controlled clinical trial [73]. Forty-six patients with RAS were conducted in the intervention and randomly received a zinc sulfate mucoadhesive tablet or placebo for 7 days. It was indicated that the reduction in both ulcer size and pain intensity in the treated group with zinc sulphate mucoadhesive tablets was significantly more than that of the control group during the days of the study [73].

13. HYALURONIC ACID

Hyaluronic acid (HA), is a biocompatible, biodegradable, mocuadhesive linear polymer formed by polymerization of glucuronic acid N acetyl glucosamine disaccharide [74]. It is a primary component of the extracellular matrix of tissues with tissue healing properties. The healing potential of HA is related to activate and moderate of the inflammatory response, promote of cell proliferation, migrate, angiogenesis, and promotion of re-epithelization via proliferation of basal keratinocytes and formation of a physical barrier protecting the wound [75]. There is an utmost abundant of High-molecular-weight HA in the extracellular matrix of soft periodontal tissues, which is a benefit to support gingival health [76].

HA (0.2%) has been used topically for the treatment of recurrent aphthous ulcers in clinical trials [77-79]. The major drawback of topically applied HA is the fast wash of preparations.

Two topical products containing hyaluronic acid mucoadhesive components are recently available in the market named: GUM® AftaClear® gel (Etoy, Switzerland) is a gel formulation that can be applied directly to the ulcer and GUM® AftaClear® rinse (Etoy, Switzerland) is a mouth rinse formulation forming a thin layer in situ after rinsing. They're-efficacy in the treatment of RAS was evaluated in a single-center retrospective study. Both formulation was very effective in treating of minor and herpetiform of RAS. The diameter of the lesion was significantly reduced in both groups during the treatment time and 60% and 56% of cases showed complete lesion closure in the rinse and gel groups, respectively. However, a significant higher percentage of lesions in the gel group (72%) showed an improvement in lesion size compared to the rinse group (40%) already after 3 days. The pain severity also reduced significantly in both groups [80]. A controlled release mucoadhesive buccal film containing HA was developed by applying the freeze and thaw crosslinking technique [81].

Hydroxy ethyl cellulose medium viscosity (HEC) and Polyvinyl alcohol (PVA) polymers were used for the preparation of mucoadhesive buccal films. Polyethylene glycol 400 30 %w/w and Glycerol 5% v/v were added to PVA and HEC solution formulations as plasticizer, respectively.

The optimal formulation consisted of 10 mg/ film HA, 150 mg/ film HEC, and 5% v/v glycerol and has suitable physical properties, high tensile strength, good mucoadhesion properties and release 50% of HA. The HA- loaded buccal film was assessed among 12 patients with aphthous ulcer.

In a clinical study and its efficacy compared with the marketed products of HA(Gengigel®).HA-loaded buccal film was found to be efficient in reducing ulcer size at days 3 and 5 and more reduction in pain due to longer contact with the ulceration area compared to Gengigel® [81].

14. CHITOSAN

Chitosan is a natural polysaccharide composed of N-acetyl-d-glucosamine and d-glucosamine linked by 1-4-β-glycosidic bonds It can be prepared from the deacetylation of chitin. Chitin is naturally found in the crustacean exoskeleton [82]. Chitosan is a renewable, biocompatible, andbiodegradable polymer without being tetratogenic, cytotoxic or genotoxic [83]. It has been widely used in biological application due to antibacterial activity [84], analgesic [85] ,anti-inflammtory, wound healing [86] and immunomudolatory effects [87]. In addition, chitosan exhibits mucoadhesive properties and has been widely used in the design of mucoadhesive dosage forms [83]. The mucoadhesive properties of chitosan are based on the interaction between the positively charge of chitosan and the negatively charge of sialic acid and sulfonic acid substructures of mucin which provide a prolonged contact time between the drug and the absorptive surface, and thereby promoting the absorption [88]. Chitosan has considerable permeation enhancing activity. Interaction of positive groups of chitosan with the cell membrane resulted in a structural reorganization of the tight junction which helps

the protein /peptide drug to overpass the mucosal cells [88]. Yanxiong Shao et al., prepared an oral mucoadhesive film containing chitosan to evaluate the effect of chitosan on the healing of RAS in a randomized, parallel-controlled, double-blind clinical trial. As the results showed, the chitosan-containing film promoted the healing and relieved the pain of RAS. Chitosan was able to decrease the ulcer size significantly greater in the treatment group than in the control group. However, no significant difference was reported between the two groups in terms of pain score and ulcer size [89].

15. CHOLIN SALICYLAS

Choline salicylate is an anti-inflammatory pain reliever agent, used as an analgesic, antipyretic and antirheumatic [90]. A flexible buccal film was prepared by using mucoadhesive polymers including 2% of carmellose sodium as the basic mucoadhesive and film forming polymer; 2% of glycerol as plasticizer and 0.5% of polyethylene oxide as the second mucoadhesive polymer and mucoadhesive layer was coated with ethyl cellulose to prolong the time of residence at the site of application [91]. The efficacy of this mucoadhesive buccal film containing cholin salicylas compared with conventional form of its oral gel on aphthous ulcers. In the study, patients suffering from aphthous lesions were treated with oral gel or mucoadhesive buccal film three times per day after meal. The application of buccal films resulted in lessening the pain from the third day in the experimental group. In the control group, pain improvement was apparent on day 5. The size of the lesion was significantly reduced on day 5 in both groups, but the healing process was better in the experimental group. The result indicated that the resistance time of the buccal film was longer than that of the gel in control group [92].

16. COMBINATION OF MUCOADHESIVE SYSTEM AND LASER THERAPY

Laser therapy in the management of patients with RAS is the subject of several studies [93]. The use of laser is effective in the stimulation of wound healing and analgesic effects. For example, Prasad and Pai reported the immediate pain relief of RAS by CO2 laser [94]. Several clinical studies approve the effect of laser therapy in reducing pain and ulcer size in patients with RAS.

In a randomized clinical trial employing 60 patients with miRAS, the effect of laser diode was evaluated with biadhesive preparation of Acacia nilotica and Glycyrrhiza species or adhesive oral tablets of 2 mg amlexanox diode laser was significantly superior in reduction pain and ulcer size than all other groups [95]. In the other clinical trials performed by Genovesi et al., the clinical efficacy of a mucoadhesive gel (Dermovitamina aftaclin) alone or in combination with laser therapy in reducing the symptoms of RAS was evaluated. Both test groups indicated better results in reducing ulcer size, pain relief, lesion healing time than the control group without any significant adjunctive benefit from the use of laser [96] (Table 1).

As described above, the mucoadhesive systems prolongs the resident time of drug at the site of absorption, improve control drug release and drug absorption. In the past decade, nanotechnology has received much attention in the field of dentistry. Nanotechnology helps to alter the physicochemical characteristics of drugs like shape, surface charged, and solubility to adjust accordingly to their target [97]. Increase the surface area, solubility, bioavalibility, rate of dissolution, decrease, fed/fast variability, and patient-to-patient variability are the main advantages of nanosizing [98]. “Combination advantages of mucoadhesion and nanoparticle, improve bioavailability, extend release of the drug, and maintain the local effect in the targeted area. Particulates have the advantage of being relatively small and are more likely to be accepted by the patients” [99]. Mucoadhesive and nanoparticles could improve the ability of interaction with the biological substrate in comparison with conventional mucoadhesive formulations and have emerged as a potential strategy for drug delivery via the mucosa.

17. CORTICOSTEROID

“Clobetasol-17-propionate (high potency corticosteroid) -loaded patches were evaluated in a preclinical study for the treatment of oral conditions such as OLP (oral lichen planus) and RAS.

A novel electrospun dual-layer mocoadhesive system was fabricated [100] and loaded with clobetasol-17-propionate” [101]. “This mucoadhesive structure comprise of an outer hydrophobic polycaprolactone (PLC) backing layer and an inner mucoadhesive layer containing polyvinylpyrrolidone (PVP) and Eudragit® RS100 (as fibre-forming polymers) created by electrospining method” [100]. “The device was optimized by adding polyethylene

oxide (PEO) to the inner layer to enhance the mucoadhesive properties of the system. Electrospining method produced a nanofiber structures with high porosity and surface that increase drug bioavalibility and improved the interaction with the epithelium of the oral mucosa" [100]. "In vitro release of patch-loaded clobetasol-17-propionate demonstrated that about 80% of the drug released within 6 h. The sustained release manner of clobetasol-17-propionate incorporated into the patches was established in tissue-engineered mucosa and ex vivo porcine mucosa as well as in an in vivo animal model" [101]. A mucoadhesive triamcinolon gel was prepared and in a three-blinded trial, 60 patients who had minor recurrent oral ulcers were prescribed bioadhesive nano-triamcinolone or conventional form of traimcinolon as control. At the end of follow-up period, the size of the lesion was significantly reduced on the 2 Nd and 4 th days in nano-triamcinolon group in comparison with control group [102].

18. IMMUNOMODULATORY AGENTS

As RAS is known to be an immunologically-mediated disease, immuno-modulatory agents may be helpful in treating process [103]. "Cyclosporine A (CsA) is a potent immunosuppressant agent widely used in preventing organ transplant rejection and in the treatment of various systemic and local immune diseases. The topical dosage form of CsA for buccal delivery has limited due to its low water solubility" [104]. "To increase the bioavailability of CsA, topical bio-adhesive gel of cyclosporine A loaded solid lipid nanoparticles (SLN/CsA-loaded) was developed for the treatment of recurrent aphthous stomatitis" [105]. CsA loaded SLN was developed by high shear homogeniza-tion using Compritol 888 ATO (C888) and CsA as lipid phase and poloxamer 188 (P188) and Tween 80 (Tw 80) as the aqueous phase. The CsA-loaded SLN dispersed in a bioadhesive gel consisted of Carbopol 974 P NF and HPMC K polymers. The entrapment efficacy of CsA was as high as 94.81%. Ex vivo drug-release studies showed that 71.69% ± 1.05% of CsA was extracted from the mucosa after 24 hr , which confirmed that the SLNs were localized in this tissue. The optimal formulation with approprite mechanical properties and the highest mucoadhesion was selected for in-vivo study in rabbits. In vivo distribution studies were conducted with IRDye in rabbits showing that about 65% of the formulation remaining on the buccal mucosa 6 hours after application, wound healing speed was determined by measuring the ulcer area on days three, six, nine and 12, in addition to histological observations. The results revealed that on days three, six, and nine, the ulcer sizes in the group treated with gel and the group treated with the NLS/CsA-loaded gel were smaller than those of the control group. "The smallest size of ulcer was observed on day 12 in the group treated with NLS/CsA-loaded gel. On day 12, complete epithelization was observed in both treated groups, The NLS/CsA-loaded bioadhesive gel formulation significantly increased the rate of mucosal repair" [105].

19. REBAMIPIDE

Rebamipide is an amino acid derivative of quinolinone. It is a mucosal protective agent used for the healing of gastric ulcers. It mechanism is enhancing mucosal defense, preventing inflammatory cell infiltration, inhibition of the production of inflammatory cytokines such as IL-1, IL-8, and TNF-α, scavenging free radicals and temporarily activating genes encoding cyclooxygenase [106]. Formulation of rebamipide in nanosuspension using various hydroxypropyl cellulose (HPC-L, HPC-SL, and HPC-SSL) polymers and sodium lauryl sulfate (SLS) consequences to obtain particle size between 126.6 and 286.8 nm and stable nanoparticles. Evaluation of the adhesion properties of nanoparticles to the mucous membrane in the oral cavity using quartz crystal microbalance with dissipation monitoring (QCM-D) technology indicated the suitable interaction of HPC-SSL molecules with mucin led to increasing the retention time of rebamipide nanosuspension at the site of inflammation. Overall, rebamipide nanoparticles dispersed in HPC-SSL solution seems to be feasible to apply the mouthwash to prevent the stomatitis [107].

20. PROPOLIS

Propolis, a natural resinous mixture produced by honeybees, is collected from parts of plants, buds, and exudates. Polyphenols, aromatic acids, and diterpenic acids are the main essential compounds responsible for the biological activities of propolis including antiviral, antibacterial, antioxidant, antitumoral, anti-inflammatory, immunomodulatory and wound healing activities [26]. Propolis extract was formulated in a noisome mucoadhesive film to deliver propolis in a controlled manner with good mocoadhesion properties and enhanced bioavailability [108]. Niosome adhesive films is for buccal delivery of Propolis extract (PPE)

entrapped in niosomes, suspension was prepared by the reversed phase evaporation method by a mixture of Span 60 and cholesterol. A combination of EudragitmL-100 (EU-L100) (polymer for unique precise drug targeting in the gastrointestinal tract), hydroxypropyl methylcellulose (HPMC), and polyvinyl alcohol (PVA) were used to prepare mucoadhesive film. The principal parameters of noisome were acceptable with good entrapment efficacy of 91%. The in vitro release was higher in noisome dispersion compared to the film after 8 hr. Clinical results obtained from 24 subjects suffering from RAS indicated the superiority of propolis-based niosome oromuco-adhesive films in the reduction of ulcer size in contrast to the control group (film without propolis). The time to complete healing was shorter in the treatment group than the control group. Additionally, the patients experienced prolonged duration of pain relief and a high level of patient satisfaction in treatment group [108]. In addition in some countries such as Venezuela used chamomile in cold tea or warm water with salt as thermal and anti-inflammatory therapy becuse of natural agent and something less expensive for patients [109].

21. CONCLUSION AND FUTURE PERSPECTIVE

Topical treatment in the oral cavity is limited by poor bioavailability and insufficient contact between drugs and lesions. Different therapeutic agents formulated in various mucoadhesive drug delivery systems have been developed for recurrent aphthous stomatitis. These systems provide an opportunity to improve drug bioavailability through prolonging the contact time between the drug and at the site of absorption. They also provide cost-effective, patient compliance via reduction in dosage frequency and drug-induced side effects, easy administration, and withdrawal. Combination of nanotechnology and mucoadhesive principles led to develop a formulation for poorly soluble drugs. In addition, this systems are useful carriers for improving oral mucosal delivery due to their prolonged retention time in the oral cavity and excellent penetration into the mucus layer in comparison with conventional mucoadhesive formulations.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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