

# Review On Mucoadhesive Buccal Drug Delivery For The Treatment Of Aphthous Ulcers

Akash Sharma<sup>1\*</sup>, Aafreen<sup>2</sup>, Nita Yadav<sup>3</sup>

<sup>1,2,3</sup>Shri Ram Murti Smarak College of Engineering & Technology (Pharmacy), Bareilly-243202, Uttar Pradesh, India

\*Corresponding Author:- Akash Sharma

\*Shri Ram Murti Smarak College of Engineering & Technology (Pharmacy), Bareilly-243202, Uttar Pradesh, India.

E-mail address: sharmaakash3669@gmail.com

ORCID ID: 0009-0007-6417-7349

DOI: 10.47750/pnr.2022.13.509.1297

## Abstract

The buccal route of administration has always been the primary method of concentration for both local and systematic drugs because the mucin molecule has the potential to increase the residence time at the site of absorption. The Buccal drug delivery system (BDDS) shows a great impact in the treatment of recurrent aphthous ulcers (RAU). It is a painful and inflammatory disorder. The three stages are minor RAU (lesion < 10 mm), major RAU (lesion > 10 mm), and herpetiform RAU (up to 100 ulcers with lesions diameter 2-3 mm). For its treatment, different types of buccal dosage forms could be used, such as mucoadhesive buccal tablets, gels, films, patches, etc. Buccal formulation is a novel form of drug delivery that influences ulcer healing duration and lesion diameter (mm). For the formulation of containing API, mucoadhesive polymers, backing membranes, penetration membranes, and plasticizers are required. Polymers are essential components for BDDS formulations. The blending of currently approved polymers provided valuable mucoadhesive strength. The mucoadhesive polymers must be dispersed throughout the substrate surface, allowing the dispersion of their chains in the mucus, before proximal contact can occur and superficial contact may be maximized. Therefore, this review discusses the buccal mucoadhesive formulation used for recurrent aphthous ulcers.

**Keywords:-** Buccal drug delivery, Mucoadhesive Polymer, Novel Polymer, Aphthous Ulcers, RAU dosage forms, BDDS Characterization parameters.

## INTRODUCTION:

### Buccal drug delivery system:

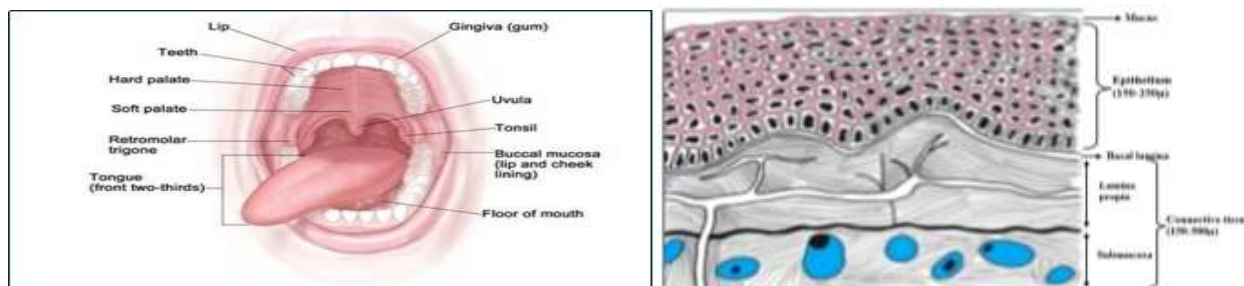
It seems that the oral route is the most efficient way to take medication, according to both the patient and the doctor. Many drugs cannot be administered orally in an efficient way based on our recent understanding of physiological and biochemical variables of ingestion and metabolism. This is because drugs commonly undergo significant pre-systemic clearance, which prevents a connection between membrane permeability, absorption, and bioavailability from forming <sup>1</sup>. Mucosal layers (nasal, vaginal, oral cavity, and rectal) are widely evaluated as prospective locations for drug administration because of their particular advantages for systemic drug delivery, in contrast to the conventional oral route.

These benefits include enhanced absorption and bioavailability due to a putative hepatic bypass effect and the prevention of presystemic clearance in the gastrointestinal tract <sup>2</sup>. Despite research on using the nasal cavity as a route for systemic drug delivery, there are worries that it may impede absorption due to both intrasubject and intersubject variability in mucus production in the nasal mucosa as well as the possibility of irritation and long-term harm to the nasal cavity's ciliary function from prolonged nasal dosage administration. Despite the benefits, rectal, vaginal, and ocular mucosae are not appropriate for systemic medication delivery due to low patient acceptance <sup>3-5</sup>.

Because the buccal route may keep a delivery system in one place for a long time, both local and systemic drug bioavailability find it appealing. The blood supply to the buccal mucosa is robust, and it is also somewhat permeable., thus, absorption occurs quickly and the medication is quickly transported to the systemic circulation without being degraded by digestive enzymes or first-pass hepatic metabolism <sup>6</sup>.

Tablets, patches, and films have all been formulated using mucoadhesive polymers; these polymers either act as a matrix for the medication to be disseminated in, or as a barrier that the drug must diffuse past. The powdered bioadhesive polymers in mucoadhesive ointments and pastes are suspended in a hydrophobic basis. The mucoadhesive ingredients tend to make solutions thick and sticky. Gels, vaginal rods, pessaries, and suppositories are some of the other mucoadhesive formulations that have been considered <sup>7</sup>.

**Oral Mucosa:** The oral mucosa consists of a basement membrane, connective tissue, and epithelium<sup>8</sup>. In the oral mucosa, the topmost layer is made up of mucus-covered stratified squamous epithelium. At most, the epithelium has 40–50 cell layers<sup>9</sup>. Since the oral mucosa acts as a lubricant and is sticky, cells may move more freely in relation to one another. Drug delivery has been used in the gingival area, buccal cavity, lingual region, and palate. As can be seen, the buccal route is the most typical way to provide medication. The buccal mucosa, which is anatomically situated between the cheek and the gum, is the ideal location for drug delivery<sup>10</sup>.



**Fig. 1: A) The Anatomy Of The Oral Mucosa**<sup>11</sup>;

**B) Structure Of Buccal Mucosa**<sup>12</sup>

Showing table no.1 is make up of the oral cavity and the factors that improve its permeability<sup>13-22</sup>.

**Table 1. Oral Cavity Composition And Permeability Enhancer Mechanisms:**

S. No.	Oral physiology and function	Thickness	Enhancing drug permeability mechanism
1.	<b>Epithelium layer</b> - its layer divided into two types Non-keratinized epithelium It protects the soft palate, the inside of the inner lips, and the tongue. Keratinized epithelium It covers the gingiva, tongue's dorsal surface, and hard palate. <b>Role:</b> Protective layer	500 to 800µm	As an anionic surfactant, sodium lauryl sulphate may be used to expand the protective layer's pores. It is a cation, cetyl pyridinium chloride. Non-ionic compounds like Poloxamer, Brij, Span, and Myrj Tween through lipid transcytosis and the structure of its protein (keratin) domain Chitosan and other cationic polymers (Poly-L-arginine, L-lysine) establish an ionic contact with the negative charge of the mucosal surface, paving the way for increased medication delivery through the mucosa.
2.	<b>Basement Membrane</b> - Between the epithelium and connective layer, it creates a separate layer. offers mechanical support for the epithelial layer by facilitating the adhesion of the epithelium to connective tissue.	1 to 2µm	Drug permeability may be improved by using a surfactant, cyclodextrins, chelators, anionic polymers, or cationic polymers to create a negative charge on the mucosal surface and repel Ca <sup>+</sup> ions.
3.	<b>Connective Tissue</b> - Lamina propria and submucosa layer make up this layer. Collagen fibres, supporting tissues, blood arteries, and smooth muscles make up the lamina propria. <b>Role:</b> Responsible for supplying the mouth cavity with blood. The buccal artery serves as the main blood vessel supplying the cheek lining of the buccal cavity, together with the facial artery and infraorbital artery. It is in charge of improved medicine absorption since it is the main source of blood supply.	150 to 500µm	Bile salts like sodium glycocholate, sodium tauro cholate, and sodium tauro deoxycholate, fatty acids like oleic acid, caprylic acid, and lauric acid, cyclodextrin, chelator (ethylenediaminetetraacetic acid), sodium salicylate, and methyl ethyl ketone, as well as anionic and cationic surfactants, will either make the phospholipid domain more fluid.
4.	<b>Mucus</b> - Secretion that like gel and was persistent and transparent; Composition •Water-95-99% •Water-insoluble glycoprotein (Mucin): 1-5% •enzymes, proteins, electrolytes and nucleic acids. <b>Role:</b> It is a viscoelastic hydrogel that serves as a barrier between the cell and the environment.	<b>Buccal (Nonkeratinized)</b> -500 to 600 µm with 2.40 ml/min/cm <sup>2</sup> <b>Sublingual (Nonkeratinized)</b> -100 to 200µm with 0.97 ml/min/cm <sup>2</sup> <b>Gingival (keratinized)</b> -200 µm with 1.47 ml/min/cm <sup>2</sup>	Drug Permeation enhancement mechanism: by augmenting the BDDS with bile salt and fatty acids, will either improve the fluidity of phospholipid domains.
5.	<b>Saliva</b> -Role: A substance that protects, a place where the enamel of the teeth gets its minerals, drug delivery system for hydration orally.	<b>Palatal (Keratinized)</b> -250 µm with 0.89 ml/min/cm <sup>2</sup> <b>Viscosity</b> - 1.05 cP to 1.29 cP, respectively	

### Buccal Delivery in Recurrent Aphthous Ulcers:

The ancient Greek word "aphthi," meaning "burning," is the source of our modern word "aphtha," which describes a painful or inflamed condition. Hippocrates, who originally used these phrases to describe these conditions, is honoured with the creation of this name<sup>23</sup>. A painful inflammatory disorder of unclear cause, recurrent aphthous ulceration (RAU) manifests as repeated, one or numerous oral mucosal ulcerations<sup>24</sup>. Approximately 5-25% of the population suffers from severe and often recurring inflammation of the intraoral cavity<sup>25</sup>. Repeated episodes of aphthous ulcers need systemic medicine after initial treatment with topical treatments like corticosteroids has failed. Aphthous stomatitis, more commonly known as canker sores, occurs repeatedly<sup>26</sup>. All medical professionals who come into contact with RAS would

benefit from reading this review since it integrates critical features of the illness at the clinical, histological, and molecular levels. Recurrent bouts of single or many painful ulcerations without a connection with systemic illnesses define the clinical presentation of RAS<sup>27,28</sup>. In the absence of a systemic condition, ulceration should be referred to as RAS.<sup>29</sup>

### Description and clinical forms of RAU:

Minor aphthous ulcers, major aphthous ulcers, and herpetiform ulcers are the three primary kinds of recurrent aphthous ulceration, as described by Stanley's classification (1972)<sup>30</sup>.

(1) **Minor RAU (Mi-RAU)** is the most prevalent kind, influencing around 80% of those with RAU<sup>31</sup>. This syndrome is characterised by round or oval superficial ulcers with a thin erythematous halo and a pseudomembrane that is grey-white (fig. 2). The labial mucosa, buccal mucosa, and the floor of the mouth are the most frequent sites of minor RAU, whereas the gingiva, palate, and dorsum of the tongue are far fewer common sites. Most instances of RAU in young people are of the minor kind<sup>32</sup>. There is no scarring each time the lesions clear up in 10-14 days (this might range from once per several years to virtually continually)<sup>31</sup>.

(2) **Major RAU (Ma-RAU)** approximately 10% of individuals with RAU develop recurrent peradenitis mucosa necrotica<sup>33</sup>. The lesions seem like minor RAU, but they're more than 10 mm in diameter, may be solitary or many, and cause excruciating agony. Although the lips, soft palate, and fauces are most often affected by major RAU, any location is fair game. Ma-RAU ulcers may last for weeks, even months, and often heal with scarring. After reaching sexual maturity, most people experience the start of major RAU<sup>34</sup>.

(3) **Herpetiform (Hu-RAU)** This third kind of RAU is the rarest. HSV cannot be distinguished from Hu-RAU lesions or any other forms of RAU, despite the name's indication to the contrary. HSV originated from an alleged resemblance to the intraoral lesions of primary herpes simplex (HSV) infection<sup>35</sup>. Hu-RAU lesions, like other RAU lesions, form immediately as ulcers and are not preceded by vesicular lesions. There are many little, painful ulcers all over the mouth, and they come in crops. Up to one hundred ulcers, each around 2 to 3 mm in diameter, may be present at once; however, these ulcers often fuse together to form larger irregular ulcers. The healing process for a single lesion takes around ten days. A later age of onset and a higher prevalence among females characterise this kind of RAU<sup>34, 36, 37</sup>.

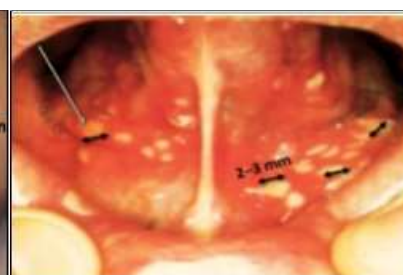
Although most people with RAU will only ever show one form of the illness, it is possible for two forms to coexist or for the disease's clinical presentation to shift over time<sup>38</sup>.



**Fig. 2:** Minor RAU



**Fig. 3:** Major RAU



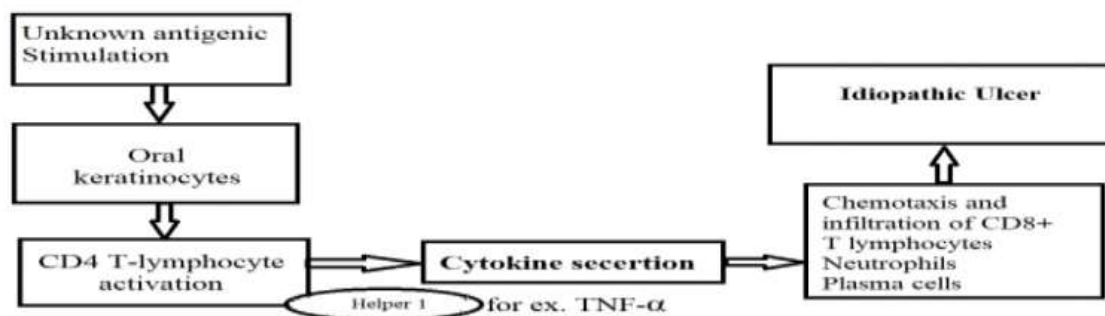
**Fig. 4:** Herpetiform RAU

In Table 2, the clinical characteristics of RAS are described<sup>39, 40</sup>, along with how they vary from ulcerations brought on by intraoral herpes simplex virus infection.

**Table 2.** Aphthous Ulcers That Recur, And Their Classification (RAU)

Variable	Minor RAU	Major RAU	Herpetiform ulcers
Prevalence (%)	80%	10%	10%
Sex distribution	F=M	F=M	F>M
Typical age of onset (Years)	10-19	10-19	20-29
Size of lesions (mm)	<10	≥10	1-2
No. of lesions	1-5	1-10	10-100
Location of lesions	Anterior	Anterior > posterior	Anterior and posterior
Time to healing (Days)	10-14	10-30	7-30
Scarring	Uncommon	Common	Common

**Pathogenesis:** When it comes to RAS, both its cause and its development are mysteries. The onset of this condition is influenced by a favourable family history, food hypersensitivity, stopping smoking, psychological stress, and immunological disturbance<sup>41, 42</sup>. However, statistical risk analysis is generally lacking for such data. It's possible that RAS development is aided by immune dysregulation connected to many stressors. Recent large-scale bioinformatics analysis has verified the functions played by the immune system and inflammatory processes<sup>43, 44</sup>. Inflammatory processes leading up to ulcerations are known to be more likely to manifest in the presence of a Th1-type hyperimmune response (fig. 5)<sup>45, 46</sup>.



**Fig. 5:** Involvement Of Cell-Mediated Immunity In The Development Of Recurrent Aphthous Stomatitis.

Edema and lymphocytic infiltration of the oral epithelium originate from inflammatory stimulation. Papules form due to vacuolization of keratinocytes and regional vasculitis. Ulceration of the papule, infiltration by neutrophils, lymphocytes, and plasma cells, and subsequent epithelial restoration are the stages that follow. Reworked from the original work by Cui et al <sup>47</sup>.

In addition, a person's vulnerability to RAS may be determined by their genes; Specifically, DNA polymorphisms in the NOD-like receptor 3, toll-like receptor 4, interleukin (IL)-6, E-selectin, IL-1, and TNF 48-52 genes. Despite the vast number of factors that have been explored, the fundamental mechanism responsible for ulcer outbreaks has not yet been found. Therefore, from a clinical standpoint, new lesions are now unavoidable.

**Disease Phases:** The progression of a disease consists of the following steps: There are four stages of peptic ulcer disease: premonition (24 hours), which has symptoms but no obvious illness signs; pre-ulcerative (between 18 hours and 3 days), characterised by erythema and mild oedema; ulcerative (1-16 days), characterised by active ulceration; healing (4-35 days, usually <21 days), characterised by a decrease in symptoms and progressive healing; and remission, in which there are no signs of ulcers.<sup>53</sup> There is more room for objective assessment during the ulcerative and remission periods of dental exams. The emergence of fresh ulcers is definitive evidence of a disease's return. A patient's quality of life and the impact of the condition may be evaluated based on elements including the quantity, size, and location of lesions as well as their degree of pain, how long they go without an ulcer, and how long they have ulcers <sup>54-56</sup>.

**Diagnosis Therapy:** Both topical and systemic treatments, as shown in table no. 3, may use medicinal agents as options to shorten the length of the infection and lessen the severity of oral aphthous ulcers <sup>57</sup>.

**Table 3.** Recurrent Aphthous Stomatitis: Topical And Systemic Agents

Agent	Comment
<b>Topical agent</b>	
Amlexanox	only medication for RAS that has been authorised by the FDA
Antibiotics	Patients suffering from multiple ulcers have the alternative of using this as a rinse
Chlorhexidine gluconate	Unpredictability characterises effectiveness
Corticosteroids	The effectiveness of superpotent strength formulations is superior to that of potent or midpotent drugs
OTC preparation	Minor ulcers may have a reduction in discomfort and have a shorter duration if treatment is received.
<b>Systemic agent</b>	
Colchicine	Suppressive treatment that is restricted due to gastrointestinal toxicity
Dapsone	Treatment that suppresses or inhibits growth needs to be examined thoroughly in the laboratory
Pentoxifylline	Treatment with the least amount of potential toxicity it is necessary to conduct controlled effectiveness trials
Prednisone	Acute treatment for individuals who have ulcerations that have not responded to topical therapy or those that are located in the oropharynx
Thalidomide	The most effective treatment for suppressing symptoms. For the purpose of rigorous monitoring of side effects, pharmacies and medical professionals are required to adhere to the System for Thalidomide Education and Prescribing Safety Program

### **Bioadhesion or Mucoadhesion:**

Longer and Robinson define bio-adhesion (occasionally called mucoadhesion) as the binding of a synthetic or natural macromolecule on mucus and/or its surface. Polymer adhesion to biological (bio-adhesive) and mucosal (mucoadhesive) surfaces is still a widely held idea. A bio-adhesive is a substance that bonds with living tissue and maintains its grip over time via cooperative efforts <sup>58</sup>.

**Bucco-adhesive polymers used in the oral cavity:** Bioadhesive systems' main benefits include localising medications to a specific location and lengthening the amount of time a drug-containing device spends in the mouth. Several hypotheses, including those of electronics, wetting, diffusion, fracture, and adsorption, have been proposed to account for the phenomenon of bioadhesion <sup>59</sup>. High molecular weight, flexible chains, surface energy that promotes diffusion into the mucus layer, and strong hydrogen bonding groups are all characteristics of bioadhesive polymers <sup>60</sup>. Polymers used as adhesives might be either natural or synthetic, water-soluble or insoluble, charged or uncharged. In table 4 we see some examples of the most up-to-date bioadhesive buccal polymers. All of the polymers included in table 4 are

examples of first-generation bioadhesives, despite the fact that they are not unique to any particular biological substrate. Fast mucus layer turnover is a major factor in determining the length of bioadhesion<sup>61-63</sup>. In table 5 are examples of Second-generation bioadhesive polymers, explain the improved mucoadhesion the polymers lectins, bacterial adhesions and thiolated<sup>64-67</sup>.

**Table 4.** Polymers That Adhere To Mucus Membranes Used In Buccal Delivery Systems:

Principles	Type	Examples
Source Dependent Polymers	Semi-natural/natural	gelatin, chitosan, and agar several gums (guar, xanthan, pectin, and sodium alginate)
	Synthetic	CMC, Thiolated CMC, sodium CMC, HPMC, HPC, and methyl hydroxyethyl cellulose are all derivatives of cellulose. Polymers with an acrylic acid base for instance, polyoxyethylene, polyacrylates, poly (methyl vinyl ether-co-hexyl acrylates), polyvinyl pyrrolidone, polyvinyl acetate, and thiolated polymers.
Aqueous solubility	Water-soluble	HPMC, flax seed, Sodium CMC, Sodium alginate, HPC, HEC
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), PC, EC
Charge	Anionic	Sodium alginate, Sodium CMC, Chitosan, Xanthan gum, CMC, Pectin, PAA
	Cationic	Chitosan trimethylated, Amino dextran, Dimethyl aminoethyl- dextran
	Non-ionic	Hydroxyethyl starch, HPC, poly (ethylene oxide), PVP, PVA
Potential bioadhesive forces	Covalent	Hydroxyethyl starch, HPC, PVA, PVP
	Hydrogen bond	Acrylates, poly (methacrylic acid), PVA
	Electrostatic interaction	Chitosan

**Table 5.** Second-Generation Mucoadhesive Polymers

Novel polymers	Properties
<b>Lectins</b>	Human buccal cells bound to lectins within 20 seconds, and this binding was not disrupted by rinsing with saliva.
<b>Bacterial adhesion</b>	specific appendages or components of the cell's surface, called fimbriae, are responsible for the adherence of bacteria to their targets, whether such targets are inanimate surfaces or other cells. Extracellular protein polymers known as bacterial polysaccharide threads play a crucial role in a broad range of disorders. The epithelium lining the lymphoid follicles in the ileal Peyer's patch of rabbits has been shown to be a particular adhesion site for Escherichia coli ( <i>E.coli</i> ).
<b>Thiolated</b>	Thiol groups increase the formation of covalent connections with the subdomains of the mucus gel layer that are rich in cysteine, which leads to an increased residence duration and better bioavailability.

**Mechanism of Mucoadhesion:** Some macromolecules' attachment process on the surface of mucous tissue is poorly known at present. The mucoadhesive must be dispersed throughout the substrate surface, allowing the dispersion of their chains in the mucus, before proximal contact can occur and superficial contact may be maximised. The attraction forces must outweigh the repulsion forces for a mucoadhesive to be effective. Different phases may be supported by different dose types and administration methods. Additionally, mucoadhesion often involves a two-stage process<sup>68</sup>.

The mucoadhesion process is often separated into two steps:

**Contact stage-**In this step, the mucoadhesive substance makes contact with the mucous membrane, and the two form a close contact.

**Consolidation stage-**Consolidation refers to the period when mucoadhesive substance has attached to the mucous membrane by a number of physical and chemical factors, resulting in a prolonged and deep intimate adherence<sup>69</sup>.

## THEORIES OF MUCOADHESION:

The following are some of the hypotheses about mucoadhesion:

- Electronic theory-** As mucoadhesive and biological components contain opposing electrical charges, electrons transfer at the interface, forming a double electronic layer. Attractions determine mucoadhesive strength.
- Adsorption theory-** Primary and secondary chemical linkages are formed upon first contact of mucus and mucoadhesive polymer (Covalent and Non-covalent).
- Wetting theory-** The illustrates the potential spread of a bioadhesive polymer across a live surface. In this case, we are interested in how the two surfaces contact each other. Strong adherence to epithelial surfaces is a hallmark of wetttable polymers.

d. **Diffusion theory-** Mucin and polymer chains must penetrate the skin to form a semi-permanent adhesive bond because diffusion cannot occur unless the components are very soluble in one another.

e. **Fracture theory-** It is established how much force is needed to break the polymer and let the mucus out. The mechanical strength of mucoadhesion has been measured, which supports this notion.

f. **Mechanical theory-** According to this explanation, adhesion takes place when a mucoadhesive liquid flows into and fills the surface's imperfections <sup>70</sup>.

#### Designing buccal drug delivery formulations:

Ideally, a buccal adhesive medication delivery system would be between 1-3 cm<sup>2</sup> in size and dispense no more than 25 mg once day. Maximum time for buccal administration is 4-6 hours <sup>71</sup>.

a. **Matrix type:** The configurable of the patch is a matrix, and it contains medicine as well as adhesive and other combined components.

b. **Reservoir type:** The buccal patch structure includes a drug chamber and several adhesive components in a reservoir system. In order to prevent drug degradation, distortion, and breakdown in the mouth, and to monitor medication distribution, an impermeable backup is provided <sup>72</sup>.

#### NOVEL BUCCAL DOSAGE FORM:

There are three distinct types of buccal mucoadhesive dose forms based on their shape:

**Type 1** is an interface with several directions that only requires one layer. the release of drugs Problems with this dosing type include considerable drug loss due to Swallow.

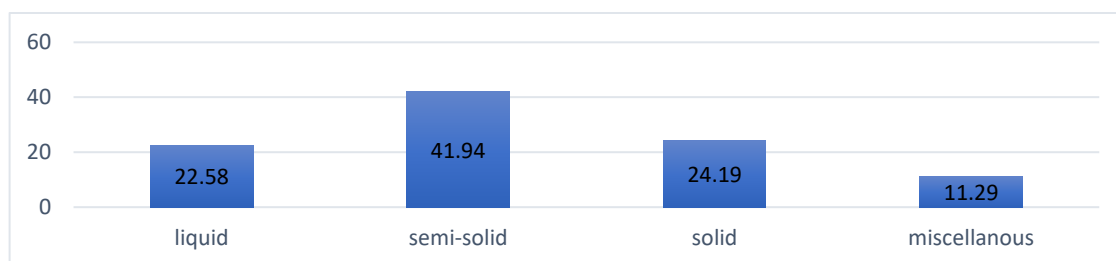
**Type 2** devices, to create a double-layered device, An impermeable backing layer is applied on top of the drug-loaded bioadhesive layer. This inhibits medication leakage via the dosage form's top.

**Type 3** minimises drug loss by only dispensing medication from the side closest to the buccal mucosa. Cover all dosage form surfaces except the one that contacts buccal mucosa. For longer bioadhesion and controlled medication release, the device should be designed to maximise the bioadhesive polymer's swelling rate <sup>73</sup>.

In its most basic forms, buccal adhesive dosage types may be categorised into four groups:

For both local and systemic effects, scientists have developed a wide range of buccal drug delivery devices. The BDDS included in the articles were separated into their respective preparation forms, which were categorised as either liquid, semisolids, solids, and miscellaneous.

**LIQUID:** This research identified 14 (22.58%) of the BDDS for RAS to be in liquid form (Figure 6). Liquid drugs for RAS include mouthwashes, oral liquids, lotions, and inhalers.



**Fig. 6:** The Variety Of BDDS Preparation Forms Used For Recurrent Aphthous Stomatitis (RAS).

**Mouthwash/Mouthrinse:** Mouthwash, often known as gargles or mouth rinsing solutions, are medicinal solutions that are not sterile. Alcohol is the active ingredient in several types of mouthwash, which are aqueous solutions. anything from 18% to 26% Since mouthrinses and mouthwashes may reach even the farthest reaches of the oral cavity, they are used to deliver topical oral drugs <sup>74</sup>.

**Oral Liquid:** To give the herbs in topical treatment for RAS, oral solutions have been employed. The processes were comparable to mouthwash or mouth rinse. In contrast to mouthwashes, oral liquids are ingested to have a systemic anti-inflammatory impact. This makes oral liquids distinct from mouthwashes <sup>75, 76</sup>.

**Lotion:** Certain polymers may be used as a suspending agent in lotions. The polymer might adhere to the oral mucosa and prolong how long the drug is kept in the mouth. As lotion is simpler to use than pastes or gels, which have trouble sticking to the mucosa, In RAS formulations, it has served as the BDDS for mometasone furoate <sup>77, 78</sup>.

**Inhaler:** The interaction between mucin and a water-soluble polymer provides the basis for the creation of mouth inhalers for aphthous ulcers. Mucin, which coats all surface of the oral mucosa, presents a risk for medicine delivery and retention in the oral cavity. Corticosteroid has been administered into the oral mucosa using an inhaler formulation. Patients were instructed to administer the dosage by placing an inhaler over the lesion. For a sustained drug delivery method, polymers including cyclodextrin, chitosan, gum, amylose, and cyclodextrin have been studied. The conventional method of treatment, such as mouthwash, might sometimes result in nausea and vomiting, thus this formulation was selected to administer irsogladine maleate for oral ulcers. Inhalers were thus a preferable option to administer the medication without coming into touch with the ulcer <sup>79, 80</sup>.

**SEMI SOLIDS:** About RAS preparation in semi-solid form, there are 26 (41.94%) publications (Figure 6). These dosage forms include cream, paste, patch, gel, and ointment. Due to the effect of "saliva wash out," polymers have a longer residence duration in the oral mucosa than liquids do, hence the semisolid form was chosen.

**Cream:** The film-forming cream AphtoFix<sup>®</sup> offers protective qualities akin to the adhesive qualities previously mentioned that speed up the healing of mouth ulcers. This treatment is an innovative, scientifically-developed oral ulcer cream formulation by Sakly et al<sup>81</sup>. The medicine may form a protective barrier and be present as a layer over the ulcer site for a long period thanks to the cream application<sup>81</sup>.

**Paste:** A BDDS for a Diosmectite and fundamental Fibroblast Growth Factor were used to create the paste (bFGF). The release of bGF at the mucosa was controlled by the use of diosmectite as a carrier. Diosmetit creates a protective barrier over the ulcer when the paste is administered, shielding it from the physiochemical impacts. Diosmetit may also take in poisons and other RAS components like bacteria<sup>82</sup>. This preparation will control medication release and extend drug retention at the oral mucosa in conjunction with HPMC<sup>83</sup>.

**Patch:** A patch needs a bioadhesive surface, a reservoir layer that stores the medication in order for it to adhere to the mucosa, as well as an impermeable backing layer. They offer advantages over topical lotions and ointments in terms of correctly administering the medication at the site<sup>84</sup>. Licorice containing bioadhesive patches have been investigated for the treatment of RAS. When tragacanth gum was employed as a basis, the ulcer's size was significantly reduced. The mechanical protection provided by licorice bioadhesive patches and their anti-inflammatory qualities help to treat ulcers. When the dry patches are placed on the mucosal surface of RAS ulcers, saliva contacts them, causing them to enlarge and generate a bioadhesive hydrogel layer that adheres to the ulcer<sup>85-88</sup>.

**Gel:** Drugs may be continuously released while being delivered via the buccal mucosa using a variety of sticky gels. One of the gel-forming bioadhesive polymers used to adhere to mucosal surfaces for extended periods of time and enable regulated drug release at the site of absorption is crosslinked polyacrylic acid. It has been shown that gel-forming bioadhesive polymers are superior to conventional techniques for mucosal adherence. According to reports, a unique hydrogel-based intelligent response system for controlled medication release has been developed. It exhibits bioadhesive properties<sup>89</sup>.

**Ointment:** As clobetasol propionate has a high corticosteroid efficacy in topical applications, it was employed in the research of ointments. This benefit led to the administration of clobetasol propionate in the form of an ointment formulation<sup>90</sup>. The medication and an adhesive paste were combined to create the BDDS (Orabase). Orabase paste is used as a base for 0.05% clobetasol propionate ointment to treat oral illnesses including RAS. The orabase was applied to the oral surface as a mucoadhesive agent. The adhesive paste is added to the ointment in order to increase adhesiveness and lengthen retention time at the oral ulcer in order to strengthen the protective activity at the oral mucosa<sup>91</sup>.

**SOILDS:** Just 16 (12.90%) solid forms were employed in the development of the RAS in this research. For the treatment of RAS, solid formulations such as powder, granules, and tablets are often utilised as BDDS.

**Powder:** Rats' oral mucosa is sprayed with powdered HPC and beclomethasone, and the residence duration is much longer than with an oral solution. During around 4 hours, a 2.5% beclomethasone concentration is maintained on the buccal mucosa<sup>92</sup>.

**Granules:** Wet granulation technique was used to create Koukinig granules for this preparation. To guarantee the consistent quality of the finished goods, the granules' preparation was carefully monitored. These granules have been shown to be useful in treating RAS ulcers and are worthy of use in clinical settings. The herbal extract was delivered to the ulcer site using granules as a delivery system. The purpose of this method was to get drugs with continuous release<sup>93</sup>.

**Tablet:** Tablets have been the most studied form of buccal drug dosing. There have been many attempts in recent years to develop bioadhesive buccal tablets for systemic or local medication delivery using the direct compression method. Depending on their design, they may target the buccal mucosa for a unidirectional release of the drug into the saliva or many directions<sup>94</sup>. The clinical investigation demonstrated that the size of the lesions and the degree of erythema were successfully decreased with this novel tablet technique, as well as in lowering the ulcer's exudation level and reducing discomfort. Resveratrol was also used in another trial to prevent inflammatory lesions in the mouth. The penetration investigation confirms the drug's ability to diffuse into the buccal mucosa and forecasts in vivo human behaviour. To maintain the medicine on the mouth's surface and stop it from entering the bloodstream, the drug delivery technique was developed.<sup>95</sup>

Several BDDS for mouth preparations have been created throughout time. Table 6 lists sixty-two studies that investigated at various drug delivery approaches used to treat RAS. In the studies, four different preparation forms were used for the BDDS: liquids, semisolids, solids, as well as other<sup>96</sup>.

**Table 6.** Different kinds of RAS Buccal Drug Delivery System:

Dosage form	Route of administration	Drug formulation example of drug
Liquid (mouthwash/oral liquid/ inhaler/ lotion)	Topical	Alcohol-aqueous mouthwash with chlorhexidine gluconate
	Topical	Listerine is an antiseptic/LA mouthwash that has 9.6% alcohol in it.
	Topical and systemic	Pudilan xiaoyan contains a variety of plants that are dispersed in aqueous solution.
	Topical	Mometasone furonate lotion dispersed in an aqueous solution
	Topical	Triamcinolone acetonide inhalers
	Topical	Hyaluronic gel

Semi-solid (gel/ paste/ patch/ ointment/ Cream)	Topical	Using a mixture of Carbopol and HPMC K100M, cyclosporine SLNs gel was created.
	Topical	Licorice paste
	Topical	Pudilan Keyaning Toothpaste
	Topical	In film-former cream, cellulose gum is combined with a calcium/sodium-methyl vinyl ether and maleic anhydride copolymer.
Solid (granule/adhesive tablet/Powder/lozenges/troches)	Topical	Dexamethasone, Debacterol, and Clobetasol propionate topical ointment
	Topical	Amlexanox adhesive oral tablet
	Topical	Nicotine lozenges
Miscellaneous	Topical	Penicillin G potassium troches
	Topical	
Adhesive alginate	Topical	Sodium alginate adhesive
Film	Topical	Triamcinolone acetonide mucoadhesive film
patch	Topical	Mucoadhesive buccal film of benzydamine hydrochloride
	Topical	Bioadhesive patch licorice
Dentifrice	Topical	Glucose oxidase and amyloglucosidase
Oradisc	Topical	Collagen
Membrane	Topical	Betamethasone-17-valerate 4% membrane
Pellicle	Topical	Amlexanox 2 mg

### Characterization of the many parameters of the buccal drug delivery system:

In table, the buccal drug delivery is determination of the value, nature, character, or quality of something or someone showing parameter<sup>97</sup>.

**Table 7.** BDDS Characterization Parameters:

S. no.	Characterization Parameter	Method Used	Instrument	Used For Dosage Form
1.	Surface ph	Visual colour change	pH meter	Mucoadhesive tablet, Patch, tablet Films
2.	Swelling index	Swelling of Tablet and patch in pH 6.4 phosphate buffer	Agar gel plates	Tablet films, wafers, Patches, films
3.	Morphology	Microscopy	Scanning Electron Microscopy (SEM)	Tablets, Patches, film
4.	Drug compatibility	Spectral analysis, Thermal analysis	DSC, XRD, FTIR	Films Tablets, Wafers, patches
5.	Folding endurance	constant folding at the same point	Manually folded	Patches, Films
6.	Thickness	Standard deviation	Electronic digital micrometer, vernier calipers, screw gauze	Films tablets, wafers, patches
7.	Water absorption capacity test	Agar plate technique	desiccator	Patches or film
8.	Mucoadhesive strength	Tensile strength	Texture analyzer	Films tablet, patches
9.	<i>In-vitro</i> drug release	Beaker method; Rotating peddle method; Dissolution method	Kesary chein cell; Franz diffusion cell	Tablets, Microspheres, patches or films
10.	Residence time	Disintegration	Modified disintegrator	Patches, film
11.	Mechanical properties	Wilhelmy plate technique	Modified tensile strength tester or micro process	Patches, film, buccal hydrogel
12.	Hardness	Crushing force	Monsanto hardness tester	Tablets, wafers
13.	Friability	weighing	Roche friabilator	tablets
14.	Drug content	Titration	UV spectrophotometer, RP-HPLC	Tablets, patches or films
15.	Flatness	Constriction	Vernier Calipers	Patches, films
17.	Contact angle	Optical tensiometer	Optical tensiometer	Films
18.	Bio-adhesion	Colloidal gold staining method, Florescence probe method	Dissolution cells	Patches, Films
19.	Water vapour transmission rate	Dressing method	Ovens	Patches, Films
20.	Drug entrapment	Assay	UV spectrophotometer	Films, Patches, Microspheres
21.	Transparency	Transmittance	UV spectrophotometer	Films
22.	<i>Ex- vivo</i> residence time (rt)	Disintegration test	Modified disintegration test apparatus	Patches, Films Tables
23.	Percentage moisture loss	Gravimetry method	Desiccator	Patches, Films

### CONCLUSION:

For the treatment of RAS, several formulations combining both active ingredients and excipients have been produced. Based on their adhesiveness and other properties, the excipients used in RAS preparations perform a variety of functions in either transporting the medicine to the target region or producing a therapeutic effect help protect the oral mucosa. The five different kinds of semi-solid forms of BDDS, which comprise BDDS, are the most suitable for RAS processing. A side than liquid, solid forms have four different kinds of BDDS. There are four different sorts of forms. New BDDS have

been created in liquid, semi-solid, and solid forms, includes Dentifrice, OraDisc, pellicles, gelsomes, sticky alginates, membranes, and bioresorbable plates. The majority of BDDS are topical treatments that use several mucoadhesive polymers to extend medication residence times and reduce RAS ulcer discomfort. These arrangements are meant to improve medication activity and delivery when used to treat RAS ulcers.

## ACKNOWLEDGMENT:

I would like to express my heartfelt gratitude to the Shri Ram Murti Smarak College of Engineering and Technology (Pharmacy) Bareilly, Uttar Pradesh, for your steadfast aid in providing all the resources I need for my review work.

## CONFLICTS OF INTEREST:

There is no conflict of interest to declare.

## REFERENCES:

1. Harris D, Robinson JR. Drug Delivery via the Mucous Membranes of the Oral Cavity. *Journal of Pharmaceutical Sciences*. 1992;81(1):1–10.
2. Md. Habban A, Jeetendra G, Md. Mohiuddin, Md. Shah Faisal Comprehensive Review on Buccal Drug Delivery System, *International Journal of Pharmaceutical Research & Development* [electronic article]. 2011; Vol 3(11): January-2012 (59 - 77).
3. Mamatha Y, Selvi A, Prasanth VV. Buccal Drug Delivery: A Technical Approach. *Journal of Drug Delivery and Therapeutics*. 2012;2(2).
4. Chinna Reddy, P., Chaitanya, K. S., & Madhusudan Rao, Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. *Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences*. 2011;19(6), 385–403.
5. Mujoriya, R.Z., Dhamande, K., Wankhede, U.R., & Angure, S. A Review on study of Buccal Drug Delivery System. *Innovative Systems Design and Engineering*. 2011;2, 24-35.
6. Patel, J.G., Solanki, S.S., Patel, K.B., Patel, M.P., & Patel, J.K. (2012). Buccal Drug Delivery System: A Review. *Research Journal of Pharmacy and Technology*. 2012; 5, 883-888.
7. Woodley J. Bioadhesion. *Clinical Pharmacokinetics* .2001;40(2):77–84.
8. Khalil S.S, Wankhade V.P. Mucoadhesive buccal drug delivery system. *European Journal of Biomedical and Pharmaceutical Sciences*, 2020; 7(5):279-288.
9. Prasanth V.V, Mudiyaala S, Mathew S.T, Mathapan R. Buccal tablets- as mucoadhesive drug delivery- An overview. *Journal of Pharmacy Research*, 2011;4(3):706-709.
10. Şenel S, İkinci G, Kaş S, et al. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. *International Journal of Pharmaceutics*. 2000;193(2):197–203.
11. Madhavi B R. Buccal Film Drug Delivery System-An Innovative and Emerging Technology. *Journal of Molecular Pharmaceutics & Organic Process Research*. 2013;1(3).
12. Pather SI, Rathbone MJ, Şenel S. Current status and the future of buccal drug delivery systems. *Expert Opinion on Drug Delivery*. 2008;5(5):531–542.
13. Hearnden V, Sankar V, Hull K. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Advanced Drug Delivery Reviews*. 2012;64(1):16–28.
14. Hoogstraate JAJ, Wertz PW, Wertz PW. Drug delivery via the buccal mucosa. *Pharmaceutical Science & Technology Today*. 1998;1(7):309–316.
15. Mathias NR, Hussain MA. Non-invasive Systemic Drug Delivery: Developability Considerations for Alternate Routes of Administration. *Journal of Pharmaceutical Sciences*. 2010;99(1):1–20.
16. Shojaei A. H. Buccal mucosa as a route for systemic drug delivery: a review. *Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques*, 1998;1(1), 15–30.
17. Sá, Laisa L.F. de, Naiane Carvalho Nogueira, Edson C. da Silva Filho, Ana Figueiras, Francisco J Veiga, Lívio César Cunha Nunes and José Lamartine Soares-Sobrinho. Design of buccal mucoadhesive tablets: understanding and development. *Journal of Applied Pharmaceutical Science*. 2018; 8:150-63.
18. R V, Nallaguntla L. Review Article on Pulsatile Drug Delivery System. *Asian Journal of Pharmaceutical and Clinical Research*. 2021; 14:48–59.
19. Carvalho FC, Bruschi ML, Evangelista RC. Mucoadhesive drug delivery systems. *Brazilian Journal of Pharmaceutical Sciences*. 2010;46(1):1–17.
20. Satishbabu B, Srinivasan B. Preparation and evaluation of buccoadhesive films of atenolol. *Indian Journal of Pharmaceutical Sciences*. 2008;70(2):175-9.
21. Palem CR, Gannu R, Yamsani SK, et al. Development of bioadhesive buccal tablets for felodipine and pioglitazone in combined dosage form: In vitro, ex vivo, and in vivo characterization. *Drug Delivery*. 2011;18(5):344–352.
22. Chinna Reddy, P., Chaitanya, K. S., & Madhusudan Rao, Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. *Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences*.2011;19(6), 385–403.
23. Compilato D, Carroccio A, Calvino F, et al. Haematological deficiencies in patients with recurrent aphthosis. *Journal of the European Academy of Dermatology and Venereology*. 2009;24(6):667–673.
24. Graykowski EA. Recurrent aphthous stomatitis. Clinical, therapeutic, histopathologic, and hypersensitivity aspects. *JAMA: The Journal of the American Medical Association*. 1966;196(7):637–644.
25. Chavan M, Jain H, Diwan N, et al. Recurrent aphthous stomatitis: a review. *Journal of Oral Pathology & Medicine*. 2012;41(8):577–583.
26. N.R. Edgar, D. Saleh, R.A. Miller. Recurrent Aphthous Stomatitis: A Review. *The Journal of Clinical and Aesthetic Dermatology*. 2017;10: 26–36.
27. Preeti L, Magesh K, Rajkumar K. Recurrent aphthous stomatitis. *Journal of Oral and Maxillofacial Pathology*. 2011;15(3):252.
28. Jin L, Lamster I, Greenspan J. Global burden of oral diseases: emerging concepts, management and interplay with systemic health. *Oral Diseases*. 2016;22(7):609–619.
29. Rivera C. Essentials of recurrent aphthous stomatitis. *Biomedical reports*. 2019 11(2), 47–50.
30. Stanley HR. Aphthous lesions. *Oral Surgery, Oral Medicine, Oral Pathology*. 1972;33(3):407–416.
31. Porter SR, Scully C, Pedersen A. Recurrent Aphthous Stomatitis. *Critical Reviews in Oral Biology & Medicine*. 1998;9(3):306–321.
32. Field Ea, Brookes V, Tyldesley Wr. Recurrent aphthous ulceration in children-a review. *International Journal of Paediatric Dentistry*. 2009;2(1):1–10.
33. Rennie JS, Reade PC, Hay KD. Recurrent aphthous stomatitis. *British Dental Journal*. 1985;159(11):361–367.
34. Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. *Journal of Oral Pathology and Medicine*. 1989;18(1):21–27.
35. MacPhail LA, Greenspan D, Feigal DW. Recurrent aphthous ulcers in association with HIV infection. *Oral Surgery, Oral Medicine, Oral Pathology*. 1991;71(6):678–683.
36. Lehner T. Oral ulceration and Behcet's syndrome. *Gut*. 1977;18(6):491–511.
37. Porter Sr, Scully C. Aphthous stomatitis-an overview of aetiopathogenesis and management. *Clinical and Experimental Dermatology*. 1991;16(4):235–243.
38. VanHale, H M. Immunofluorescence microscopic studies of recurrent aphthous stomatitis. *Archives of dermatology*. 1981;(117)12: 779-81

39. Lehner T. Autoimmunity in oral diseases, with special reference to recurrent oral ulceration. *Proceedings of the Royal Society of Medicine*, 1968; 61(5): 515–524.
40. Rennie JS, Reade PC, Hay KD. Recurrent aphthous stomatitis. *British Dental Journal*. 1985;159(11):361–367.
41. Akintoye SO, Greenberg MS. Recurrent Aphthous Stomatitis. *Dental Clinics of North America*. 2014;58(2):281–297.
42. de Barros Gallo C, Mimura MAM, Sugaya NN. Psychological Stress and Recurrent Aphthous Stomatitis. *Clinics*. 2009;64(7):645–648.
43. Rivera C. Immune system and zinc are associated with recurrent aphthous stomatitis. An assessment using a network-based approach. *Journal of Oral Research*. 2017;6(9):245–251.
44. Wu J, Chen Z-P, Shang A-Q, et al. Systemic bioinformatics analysis of recurrent aphthous stomatitis gene expression profiles. *Oncotarget*. 2017;8(67):111064–111072.
45. Mimura MAM, Borra RC, Hirata CHW and de Oliveira Penido N: Immune response of patients with recurrent aphthous stomatitis challenged with a symbiotic. *Journal of Oral Pathology & Medicine*. 2017; 46: 821–828.
46. Ślebioda Z, Krawiecka E, Szponar E, et al. Evaluation of serum zinc levels in patients with recurrent aphthous stomatitis (RAS). *BMC Oral Health*. 2017;17(1).
47. Cui RZ, Bruce AJ, Rogers RS. Recurrent aphthous stomatitis. *Clinics in Dermatology*. 2016;34(4):475–481.
48. Slezakova S, Borilova Linhartova P, Masopustova L, et al. Association of the NOD-like receptor 3 (NLRP3) gene variability with recurrent aphthous stomatitis in the Czech population. *Journal of Oral Pathology & Medicine*. 2018;47(4):434–439.
49. Karasneh J, Bani-Hani M, Alkhateeb A, et al. TLR2, TLR4 and CD86 gene polymorphisms in recurrent aphthous stomatitis. *Journal of Oral Pathology & Medicine*. 2014;44(10):857–863.
50. Karakus N, Yigit S, Rustemoglu A, et al. Effects of interleukin (IL)-6 gene polymorphisms on recurrent aphthous stomatitis. *Archives of Dermatological Research*. 2013;306(2):173–180.
51. Alkhateeb A, Karasneh J, Abbadi H, et al. Association of cell adhesion molecule gene polymorphisms with recurrent aphthous stomatitis. *Journal of Oral Pathology & Medicine*. 2013;42(10):741–746.
52. Guimarães ALS, Correia-Silva J de F, Diniz MG, et al. Investigation of functional gene polymorphisms: IL-1B, IL-6 and TNFA in benign migratory glossitis in Brazilian individuals. *Journal of Oral Pathology & Medicine*. 2007;36(9):533–537.
53. Boras VV, Savage N. Recurrent aphthous ulcerative disease: presentation and management. *Australian Dental Journal*. 2007;52(1):10–15.
54. Tappuni AR, Kovacevic T, Shirlaw PJ. Clinical assessment of disease severity in recurrent aphthous stomatitis. *Journal of Oral Pathology & Medicine*. 2013;42(8):635–641.
55. Rajan B, Ahmed J, Shenoy N. Assessment of Quality of Life in Patients with Chronic Oral Mucosal Diseases: A Questionnaire-Based Study. *The Permanente Journal*. 2014;18(1).
56. Brocklehurst P, Tickle M, Glenny A-M, et al. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). *Cochrane Database of Systematic Reviews*. 2012
57. Eisen, D., & Lynch, D. P. Selecting topical and systemic agents for recurrent aphthous stomatitis. *Cutis*. 2001; 68(3), 201–206.
58. Shinkar DM, Dhake AS, Setty CM. Drug Delivery from the Oral Cavity: A Focus on Mucoadhesive Buccal Drug Delivery Systems. *PDA Journal of Pharmaceutical Science and Technology*. 2012;66(5):466–500.
59. Ahuja A, Khar RK, Ali J. Mucoadhesive Drug Delivery Systems. *Drug Development and Industrial Pharmacy*. 1997;23(5):489–515.
60. Gu, J, J. R. Robinson and Sau-Hung Spence Leung. Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships. *Critical reviews in therapeutic drug carrier systems*. 1988;51: 21–67.
61. Khanvilkar K. Drug transfer through mucus. *Advanced Drug Delivery Reviews*. 2001;48(2–3):173–193.
62. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. *European Journal of Pharmaceutics and Biopharmaceutics*. 2011;77(2):187–199.
63. Singh J and Deep P: A Review Article on Mucoadhesive Buccal Drug Delivery System. *International Journal Pharmacy Science Research*. 2013; 4(3); 916–927.
64. Clark MA, Hirst BH, Jepson MA. Lectin-mediated mucosal delivery of drugs and microparticles. *Advanced Drug Delivery Reviews*. 2000;43(2–3):207–223.
65. Savage DC. Microbial Ecology Of The Gastrointestinal Tract. *Annual Review of Microbiology*. 1977;31(1):107–133.
66. Inman LR, Cantey JR. Specific adherence of *Escherichia coli* (strain RDEC-1) to membranous (M) cells of the Peyer's patch in *Escherichia coli* diarrhea in the rabbit. *Journal of Clinical Investigation*. 1983;71(1):1–8.
67. Albrecht K, Greindl M, Kremser C. Comparative in vivo mucoadhesion studies of thiomers formulations using magnetic resonance imaging and fluorescence detection. *Journal of Controlled Release*. 2006;115(1):78–84.
68. Kaul M, Verma S, Rawat A, et al. An Overview on Buccal Drug Delivery System | *International Journal of Pharmaceutical Sciences and Research*. 2011; 2(6): 1303–1321.
69. Akshay V. Patil, Prof. G. D. Mehete and Akshay M. Akotkar, et al. A review on mucoadhesive buccal drug delivery system. *World Journal of Pharmacy and Pharmaceutical Sciences*, 2020; 9(5):237–260.
70. Chaudhari V.A, Sarode S.M, Sathe B.S, Vadnere G.P. Mucoadhesive buccal drug delivery system: a review. *International Journal of Pharmaceutical Sciences*, 2014; 5(2):142–162.
71. James C, Boylan. Drug delivery buccal route. In: James Swarbrick, editor. *Encyclopedia of Pharmaceutical Technology: Supplement 3*, Marcel Dekker INC 2001; Vol 20:P. 800–11
72. Budhrani AB, Shadija AK. Mucoadhesive Buccal Drug Delivery System: A Review. *American Journal of PharmTech Research*. 2020;10(2):274–285.
73. Hao J, Heng PWS. Buccal Delivery Systems. *Drug Development and Industrial Pharmacy*. 2003;29(8):821–832.
74. Parashar A. Mouthwashes and their use in different oral conditions. *Scholars Journal of Dental Sciences*. 2015;2(2B):186–191.
75. Vranić E, Lačević A, Mehmedagić A, et al. Formulation ingredients for toothpastes and mouthwashes. *Bosnian Journal of Basic Medical Sciences*. 2004;4(4):51–58.
76. Jin Y, Lin X, Song L, et al. The effect of pudilan anti-inflammatory oral liquid on the treatment of mild recurrent aphthous ulcers. *Evid-Based Complement Altern Med*. 2017;2017:1–6.
77. Deng W, Xu Y, Kong Q, et al. Therapeutic efficacy of Pudilan Xiaoyan Oral Liquid (PDL) for COVID-19 in vitro and in vivo. *Signal Transduct Target Ther*. 2020; 5:1–3.
78. Teixeira F, Mosqueda-Taylor A, Montano S, Dominguez-Soto L. Treatment of recurrent oral ulcers with mometasone furoate lotion. *Postgr Med J*. 1999;75(887):574.
79. Jones D. *Pharmaceutics-Dosage Form and Design*. Pharmaceutical press; 2008.
80. Kawano Y, Imamura A, Nakamura T, Akaishi M, Satoh M, Hanawa T. Development and characterization of oral spray for stomatitis containing irsogladine maleate. *Chem Pharm Bull*. 2016;64(12):1659–1665.
81. Liguori V, Guillemain C, Pesce GF, Mirimanoff RO, Bernier J. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. *Radiother Oncol*. 1997;42(2):155–161.
82. Sakly A, De Wever B, Jutla B, Satia M, Bogaert JP. The safety and efficacy of AphtoFix® mouth ulcer cream in the management of recurrent aphthous stomatitis. *BMC Oral Health*. 2016;16(1):1–7.
83. Jiang XW, Zhang Y, Zhang H, Lu K, Yang SK, Sun GL. Doubleblind, randomized, controlled clinical trial of the effects of diosmectite and basic fibroblast growth factor paste on the treatment of minor recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116(5):570–575.
84. Ghosal K, Chakrabarty S, Nanda A. Hydroxypropyl methylcellulose in drug delivery. *Der Pharmacia Sinica*. 2011;2(2):152–168.

85. Chinna Reddy P, Madhusudan Rao Y. Buccal Drug Delivery Systems. In: Madhusudan Rao Y, Jithan A.V. ed. *Advances in drug delivery* vol.1 2010; 139-210.
86. Moghadamnia AA, Motallebnejad M, Khanian M. The efficacy of the bioadhesive patches containing licorice extract in the management of recurrent aphthous stomatitis. *Phyther Res.* 2009;23 (2):246–250.
87. Kutcher MJ, Ludlow JB, Samuelson AD, Campbell T, Pusek SN. Evaluation of a bioadhesive device for the management of aphthous ulcers. *J Am Dent Assoc.* 2001;132(3):368–376.
88. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc.* 2003;134(2):200–207.
89. Fujisawa Y, Sakamoto M, Matsushita M, Fujita T, Nishioka K. Glycyrrhizin inhibits the lytic pathway of complement - possible mechanism of its anti-inflammatory effect on liver cells in viral hepatitis. *Microbiol Immunol.* 2000;44(9):799–804.
90. He H, Cao X, Lee LJ. Design of a novel hydrogel-based intelligent system for controlled drug release. *Journal of Controlled Release.* 2004;95(3):391–402.
91. Lozada-Nur F, Huang MZ. Open preliminary clinical trial of clobetasol propionate ointment in adhesive paste for treatment of chronic oral vesiculoerosive diseases. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 1991;71(3):283–287.
92. Rao, N. G. Raghavendra, Bezawada Shravani and Mettu Srikanth Reddy. Overview on Buccal Drug Delivery Systems. *Journal of pharmaceutical science and research.* 2013;5(4):80-88
93. Gao MS, Liu S, Wang AW. Preparation and clinical observation of Koukuining granules in 50 patients with recurrent aphthous ulcer. *Shanghai journal of Stomatology.* 2016; 25:579–582.
94. James C, Boylan. Drug delivery buccal route. In: James Swarbrick, editor. *Encyclopedia of Pharmaceutical Technology: Supplement 3*, Marcel Dekker INC 2001; Vol 20:P. 800-11
95. Martins ICF, Raposo NRB, Mockdeci HR. Delivering resveratrol on the buccal mucosa using mucoadhesive tablets: a potential treatment strategy for inflammatory oral lesions. *Current Drug Delivery.* 2018; 15:254–259.
96. Suharyani I, Fouad Abdelwahab Mohammed A, Muchtaridi M, Wathoni N, Abdassah M. Evolution of Drug Delivery Systems for Recurrent Aphthous Stomatitis. *Drug Design, Development and Therapy.* 2021; 15:4071-4089.
97. V., Leela & Marakanam Srinivasan, Umashankar & Muthumanickam, Alagusundaram. (2021). An Assessment on Buccal Mucoadhesive Drug Delivery System. *International Journal of Applied Pharmaceutics.* 2021;66-74.