

OVERVIEW OF MUCOADHESIVE BIOPOLYMERS FOR BUCCAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Mucoadhesive dosage forms may be intended for facilitation of prolonged retention time at the application site hence providing drug release in a controlled rate for enhanced improvement of therapeutic activity and its outcome. The buccal mucosa has been investigated for systemic drug delivery and local drug treatment or therapy that is subjected to first pass metabolism. The applicability of bio-adhesion approach in buccal drug delivery proved great therapeutic potential to overcome the limitation of conventional buccal drug delivery. The delivery via buccal route using mucoadhesive biopolymers such as various natural gums e.g. carrageenans, gum karaya, gum arabic, locust bean gum, khaya gum, gum ghatti, albizia gum, guar gum, starch, cellulose, larch gum and pectin etc. and various thiolated and carboxymethylated polymers has been the subject of interest since the early 20th century. The present article is focused mainly on the oral mucosa, mechanism of drug permeation, and characteristics of the desired polymers, the manuscript then proceeds to cover the theories behind the adhesion of bioadhesive polymers to the mucosal epithelium followed by the factors affecting mucoadhesion. Further the author has also discussed on the new generation of mucoadhesive polymers and their properties, recent mucoadhesive formulations for enhanced buccal drug delivery, various marketed products and patent literature. Various online search engines and scientific journals were employed for the collection of literature and scientific data and information related to the topic using keywords like mucoadhesive polymers, buccal drug delivery, buccal patches, tablets, films, gels, powder from the year 2002 and above.

Keywords: Buccal, Films, Gums, Patches, Therapeutic efficacy, Thiolation

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INTRODUCTION

Mucoadhesion or mucosal adhesion is defined as the state which is responsible for the adhesion between two materials for a definite material of time. With the help of interfacial forces between two materials, the adhesion occurs and the phenomenon known as bioadhesion (biologically adherence between two materials, when one of the material is biological in nature) [1]. The mucoadhesion was first introduced in 1980's for delivering the drug in controlled manner and providing the ease of controlled drug delivery. This concept of mucoadhesion is a new approach for the improvement of drug efficacy for various drug delivery systems. In systemic delivery the formulation is kept for intimate contact with tissue or cells at the site of absorption. In nasal, vaginal and local drug delivery it is carried out by spatial placement within gastrointestinal tract (absorption site is in gastro region) [2]. Over the last two decades mucoadhesion has become an area of interest for the administration of various unstable bioactive via different route of administration (nasal, vaginal, ocular and buccal which are generally difficult to administer by oral route). Mucoadhesive material can also be used as therapeutic agent as it coat and protects the damaged tissues or act as lubrication agents. Mucoadhesion is due to formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymer. Additionally, the residence time of dosage form in the Gastro intestinal mucosa should be prolonged, which allows a constant drug release at a given aim site to maximize the therapeutic effect [3]. There are many factors that depend on mucoadhesion as shown in (fig. 1).

The oral cavity is a preferred site for the transmucosal delivery of drugs. Buccal route offers advantages like avoidance of first pass metabolism and gastrointestinal degradation of drugs, high blood flow which ensures systemic drug bioavailability [4]. Various buccal bioadhesive polymers are available for ascertaining adhesive contact with the buccal mucosa thereby increasing the buccal residence time of the delivery system for optimal drug bioavailability. Some properties of the polymers affecting bioadhesive potential includes, number of hydrogen bonding groups, charge, molecular weight, chain flexibility, and surface energy properties [5]. A range of natural and synthetic polymers are available for developing different bioadhesive drug delivery systems.

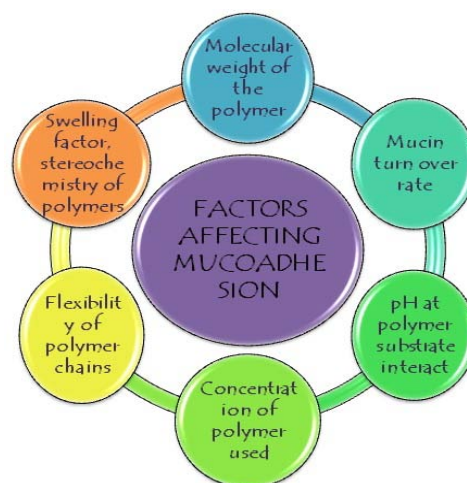


Fig. 1: Different factors affecting the process of mucoadhesion

Approaches/theories of mucoadhesion

Wetting theory

The wetting theory is generally applied in mucoadhesive system (liquid) having low viscosity. The theory postulates about the mucoadhesive polymer ability that easily spreads on biological surface which leads to the extensively spreading ability of active drug delivery systems. This theory describes that the adhesive constituent penetrates in irregularities in surface which hardens and get attached to the surfaces because of drastic changes occurs in surfaces and interfacial energies [2]. The adhesive mechanism of such elastoviscous liquid may be defined by using wettability and spreadability as shown in (fig. 2). The contact angle techniques are based on the principle that lowers the contact angle, these are used to determine the affinity of a liquid to measure contact angle of the liquid on the surface. The theory postulates that the lower the contact angle, the greater will be the affinity of liquid to the solid surface [6].

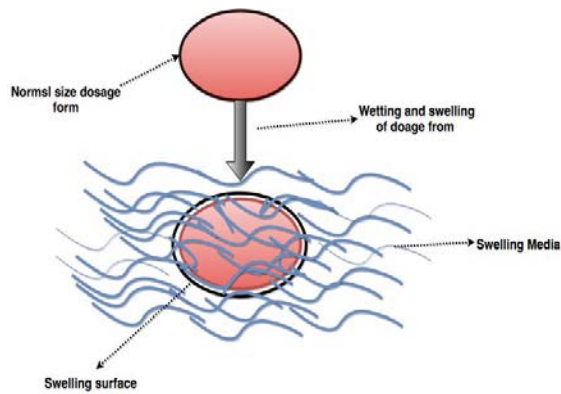


Fig. 2: Shows penetration of dosage form into the surface or tissue of the mucosal layer by wetting or swelling mechanism

Adsorption theory

Adhesion is defined as the result of interactions in various surfaces (primary and secondary) are two types of chemical bonds for adhesive interactions i. e hydrogen bond and Vander waals' forces are deep-rooted between the adhesive polymer and mucus substrate which is depicted in (fig. 3). Primary bonds occurs due to the chemisorptions which results in adhesion due to ionic, covalent and metallic bonding, while the secondary bonds arises mainly due to Vander waals forces, hydrophobic interactions and hydrogen bonding [7].

Electronic theory

This theory tells that the adhesion occurs due to electron transfer between the mucus and the mucoadhesive system which is arises through differences in their electronic structure. The electron transfer between the mucus and the mucoadhesion results in the formation of bi-layer of electronic charges formed at the mucus and mucoadhesive system interface as shown in (fig. 4) [8, 9].

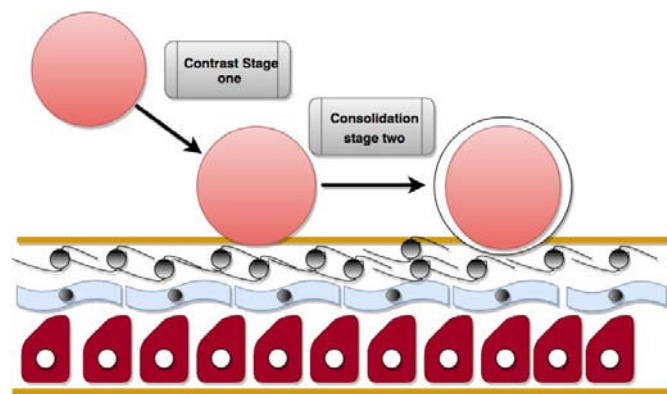


Fig. 3: Indicates the stages concerned with mucoadhesion: first stage shows the interaction of drug delivery system on the surface of mucus membrane; second stage shows several physicochemical interactions, results in prolonged adhesion at the site of action

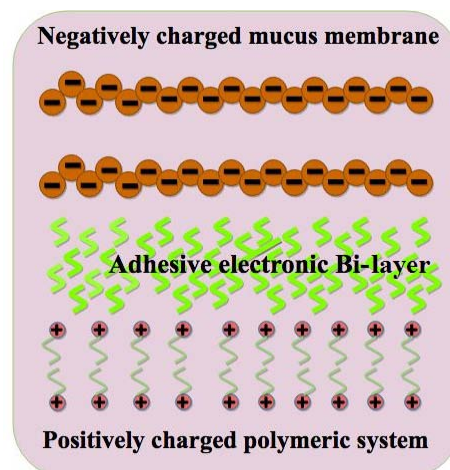


Fig. 4: Adhesion between the mucus membrane (negative charge) and the polymeric system (positive charge), through differences in their electronic structure

Fracture theory

This theory describes the adhesive bonds between systems that are related to the force that are required to impart or separate both surfaces from one another. This includes that the force required for polymer detachment from the mucus to the basic strength of their adhesive bonds. It has been found that when the polymer network strands are longer, or the degree of cross-linking within system is reduced the greater will be the work of fracture. This theory also allows the determination or measurement of fracture strength (σ)

which leads to the separation of two surfaces using young's modulus of elasticity (E), the critical crack length (L) and the fracture energy (ϵ) through following equation [9].

$$\sigma = \sqrt{(E \cdot \epsilon) / l}$$

Diffusion interlocking theory

This theory is a two-way diffusion process which proposes the time dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer and the penetration

rate is being dependent upon the diffusion coefficient of both interacting polymers as indicated in (fig. 5) Moreover, there are many factors and properties that significantly influence this diffusion are cross-linking density, chain mobility or flexibility, molecular weight and expansion capacity of both networks and temperature (as important environmental factor). Although it is recognized that longer polymer chains may diffuse, interpenetrate and ultimately entangle to a greater extent with surface mucus, it should be recognized that a critical chain length of at least 100 kDa is necessary to obtain interpenetration and molecular entanglement. Another significant contributory factor in determining interpenetration is the miscibility of both systems with one another. The time at which maximum adhesion occurs between two substrates during interpenetration has been supported by experimental evidence in recent studies using FTIR and rheological techniques, and may be determined using the depth of interpenetration and the diffusion coefficient [9].

Mechanical theory

The mechanical theory considers adhesion due to filling of irregularities on a rough surface by a mucoadhesive liquid.

Additionally, such irregularity increases the interfacial area available for interaction and can be considered the most important phenomenon of the process as depicted in (fig. 6) [10].

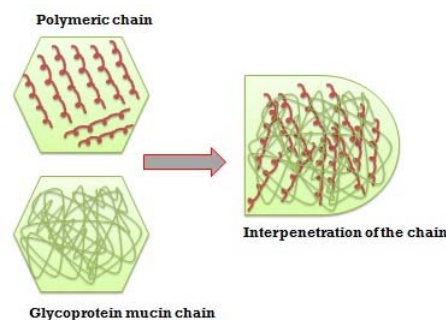


Fig. 5: Diffusion Interlocking of the mucoadhesive polymer with glycoprotein mucin chain

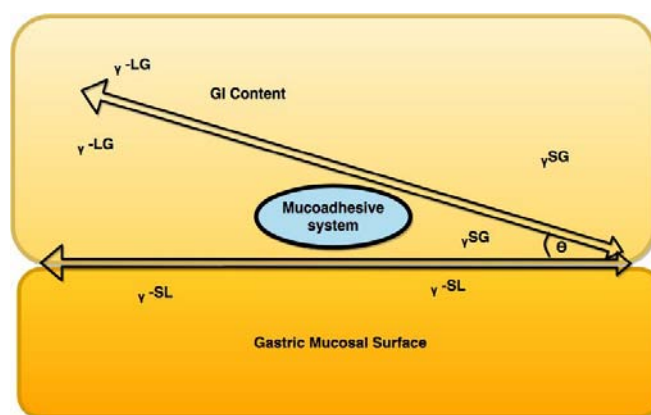


Fig. 6: Formation of contact angle between the gastric mucosal surface and the interface

Muco-adhesive polymers

Muco-adhesive polymers are mainly water soluble in nature however some can be water insoluble too. These polymers have swellable networks. Networks are joined with the help of some cross linking agents. These cross linking agents have various important properties which are required for muco-adhesion like easy wetting, better mutual adsorption and better penetration and interpenetration ability within the polymer and the oral mucus. These muco-adhesive polymers which have ability to bind with the mucus present on the epithelial cells surfaces can further be divided into three classes [11-13].

1. Polymers which have ability to become sticky when these are placed in water. These polymers also have their own muco-adhesion power to achieve better stickiness. Examples are collagen, gelatin, starch, alginate, and agarose [14].
2. Polymers which have ability to adhere with the epithelia surface by virtue of their electrostatic nature (Hydrogen bonding can play significant role in these polymers in order to achieve better adhesion). Examples are carboxy methyl cellulose, carbopol, sodium alginate, hydroxyl propyl methyl cellulose [15].
3. Polymers that have ability to bind with the specific receptors and hence can be helpful in order to achieve better drug targeting through their site specific recognition power [16].

Some important characteristics of ideal muco-adhesive polymers

The mucoadhesive polymer as well as its degradation products must be non-toxic in nature. Other than the non-toxicity these

degradation products and the polymer should be non-absorbable from the site of administration. The mucoadhesive polymer as well as its degradation products must be non-irritant to mucous surface where it is applied. The mucoadhesive polymer as well as its degradation products should have ability to form strong non covalent bonds with mucin epithelial cells [17]. This will avoid the polymeric buccal formulation to shift from the site of administration because of the buccal movements which are produced by talking, drinking and eating etc. The mucoadhesive polymer should have ability to adhere quickly to most of the tissues where it is applied. It should also have site specificity [18]. The mucoadhesive polymers should have ability to allow the incorporation of the daily requirement of the drug. These polymers should not produce any hindrance in the way of drug release. These polymers should not decompose during their storage period. These should have required shelf life which can help to make the preparation same as before without any degradation for long period of time. These muso-adhesive polymers should be low of cost and should be easily accessible and easy to produce and manufacture [19].

Classification of muco-adhesive polymers

These muco-adhesive polymers can be divided into two broad categories:

Natural Polymers: Derived from natural origin for example: collagen, albumin, alginates, gelatin, cyclodextrins, chitosan, dextran, starch, agarose, cellulose, hyaluronic acid extra.

Synthetic polymers: These are further divided into two categories:

A) **Bio-degradable polymers:** Polylactic acid, Polyhydroxyl butyrate, Polyglycolic acid, Polycaprolactone, Poly-Doxanones, Polyadipic acid,

Polysebacic acid, Polyterphthalic acid, Poly iminocarbonates, Poly amino acids, Polyphosphates, Polyphosphazenes, Polyphosphonates, Poly urethanes, Polyacetals, Poly-ortho esters etc [20].

B) Non biodegradable polymers: Carboxymethylcellulose, Ethyl cellulose, Polydimethyl siloxanes, Cellulose acetate HPMC, Colloidal silica, Polymethacrylates, Poloxamines etc.

Polymers used in buccal drug delivery based upon their category are depicted in (table 1) [21].

Natural polymers

Collagen

Collagen is one of the natural protein polymers which is widely used for muco-adhesion. Collagen polymer has a triple helical structure. With time the collagen polymer is further modified and various types of these polymers have been isolated. There are about nineteen different types of collagen monomers which have been isolated, characterized, and tested for both pharmaceutical and medical interests [22]. Collagen has various attractive properties like good biocompatibility, degradability, low antigenicity which makes the collagen polymer to be used widely in various pharmaceutical, tissue and medical applications in drug delivery systems [23].

Abruzzo *et al.*, 2012, successfully discovered buccal delivery of active drug propranolol hydrochloride by using chitosan and gelatin dual polymeric films. The FT-IR and TGA studies showed that there are appropriate and acceptable interactions between the gelatin and chitosan polymers. The investigator used the high concentration of chitosan in the chitosan/gelatin films because by using the high amount of chitosan there is lowest percentage of water uptake ability which is found to be about 235.1±5.3 % [24]. The high amount of chitosan in the dual polymeric films also helped in high residence time of the prepared formulation in the buccal cavity when tested *in vivo*. The residence time was found to be about 240±13 min. The use of mannitol in prepared formulation showed better permeation of the drug when tested through porcine buccal mucosa. Near about 80% drug permeation was found when tested on porcine buccal mucosa when applied for around 5 h. Another interesting point of using the chitosan/gelatin conjugated dual polymeric films was their better compatibility with the microflora environment of buccal mucosa [25].

Gelatin

Gelatin is an example of natural polymers commonly found in nature. Gelatin is a water soluble polymer which is basically produced through the process known as denaturation. Denaturation of collagen polymer resulted in the formulation of gelatin [25]. This polymer is also widely used in pharmaceutical, tissue and medical

applications. Gelatin polymer has outstanding physical and chemical properties. It is biocompatible, biodegradable and of low antigenicity. Gelatin is also a supporting material which can be used for cell culture, gene delivery and tissue engineering. The formulations, in which gelatin is used, have the ability to incorporate as well as release the bioactive agents like active drugs, proteins and peptides, dual growth factors etc. [26].

Albumin

In order to prepare muco-adhesive gels by using albumin, it is first modified by conjugating with the PEG. These modified albumin containing hydrogels were later used in tissue engineering scaffold materials. Albumin and its derivatives are widely used for drug delivery by various pharmaceutical researchers. These are also used in tissue engineering applications. These polymers have adequate biocompatibility, low toxicity, biodegradability, non-immunogenicity, relatively low cost, water solubility, gelling ability, high viscosity and stabilizing properties [27].

Dextran

Dextran is also one of the most widely used natural polymer for mucoadhesive gel formulation. This dextran polymer is a type of natural linear polymer in which 1-6 glucopyranoside linked polymer. Dextran is basically synthesized from certain types of lactic acid bacteria mainly *Leuconostoc mesenteroides*, *Streptococcus* mutants. These pharmaceutical polymers have ability to get better water solubility, better biocompatibility, and appropriate biodegradability [28, 29].

Chitosan

Chitosan and its derivatives are widely used for drug delivery by various pharmaceutical researchers [30]. These are also used in tissue engineering applications. These polymers have adequate biocompatibility, low toxicity, biodegradability, non-immunogenicity, relatively low cost, water solubility, gelling ability, high viscosity and stabilizing properties [31]. Peluso *et al.*, 2012, have successfully discovered the gels for local application in the buccal inflammation which is found to be a promising gel to reduce toxicity at the site of administration [32]. In the study, the investigators do the *in vitro* study and performed the characterization of chitosan based polymeric gels to test the action of formulation in buccal mucosal epithelial cells. The rheological properties of the prepared gels were tested by using cone-plate rheometer [33]. The *in vitro* showed better drug release and high permeability on pig cheek mucosa. The mucoadhesion ability was tested by using universal test machine [34]. All the results showed the prepared gels containing chitosan a better candidate to treat the oral disorders [35]. Factors affecting mucoadhesion of natural and synthetic polymers are depicted in [table 2].

Table 1: Examples of polymers used in buccal drug delivery (BDD)

Criteria	Category	Examples	References
Source	Semi-natural/natural	Agarose, chitosan, gelatine	
	Synthetic	Hyaluronic acid Various gums (xanthan, guar, gellan, pectin and sodium alginate) Cellulose derivatives (CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC) Poly(acrylic acid)-based polymers (CP, PC, PAA, copolymer of acrylic acid and PEG) Others PVA, PVP, thiolated polymers	[36] [37]
Aqueous solubility	Water solubility	CP, HEC, HPC, HPMC PAA, sodium CMC, sodium alginate	[38]
	Water-insoluble	Chitosan, EC, PC	[39]
Charge	Cationic	Aminodextran, dimethylaminorthyl (DEAE)-dextran trimethylated chitosan	[40]
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum	[41] [42]
	Non-ionic	Hydroxyethyl starch, HPC, PVA, PVP, scleroglucan	
Bioadhesive force	Covalent	Cyanoacrylate	[43]
	Hydrogen bond	Acrylates [hydroxylated methylate, poly(methacrylic acid)], CP, PC, PVA	[44]
	Electrostatic interaction	Chitosan	[45]

Table 2: Various factors affecting the mucoadhesion of natural and synthetic polymers

S. No.	Factors affecting	Details	References
1	Flexibility of polymeric chains	It is one of the important factors which affect the polymeric mucoadhesion. The mucoadhesion strength depends upon the polymer flexibility. The appropriate flexibility of the polymer within the standard limits shows increase in degree of diffusion through the mucus layer which further results in better and strong mucoadhesion. It is seen than most of the water soluble (hydrophilic) polymers show lower flexibility and hence have less depth of penetration resulting in low strength of mucoadhesion.	[46]
2	The ability of the polymer to show hydrogen bonding	If the polymer showed strongest bonding that is covalent bonding then because of very high bioadhesion, the formulation become toxic to the body. The polymers which have ability to show hydrogen bonding are accepted here because they show bioadhesion too with the acceptable strength. Higher the capacity of producing the hydrogen bonding, higher will be the increase in total adhesion.	[47]
3	Polymer concentration	The optimization of polymer concentration can help in producing the mucoadhesion with required strengths like high, medium or low. High the Polymer strength high will be the polymeric mucoadhesion. However, its low concentration will represent in low mucoadhesion strength. High polymeric strength represents high amount of polymeric networks for the interaction with the mucous which produces better mucoadhesion.	[48]
4	Molecular weight of the polymer	It has been seen that different polymers show good adhesion property with mucin epithelial cells layer only at most favorable molecular weight amount of the polymer. Usually, it has been seen that the optimum molecular weight of the polymer ranges from 1×10^4 to 4×10^6 Daltons. Usually high molecular weight of the polymeric structure resulted in the increase in the entanglement between the mucin layer network and the polymeric structure. However, Low molecular weight of the polymeric structure resulted in the increase in the flexibility of the polymeric chain which further increases the penetration process which further resulted in increase in degree of diffusion through the mucus layer which further results in better and strong mucoadhesion.	[49]
5	Degree of hydration	Wettability is important since the polymeric formulation need to be in contact with the mucin layer at the very first stage. Only after that penetration and mucoadhesion will take place. High wettability becomes important at the initial stage of contact of the polymeric surface with the mucous layer. However it is important to note that the degree of hydration should be in the required range. Because lesser wettability will result in lesser degree of contact and hence lesser mucoadhesion between the polymeric surface with the mucous layer. However high wettability will result in the slippery contact between polymeric surface with the mucous layer which resulted in the lesser mucoadhesion.	[50]
6	Cross-linking density	Increase in the cross-linking density of the polymer would result in the decrease of the adhesion between the polymeric surface and the mucous layer. This is because of the decrease in the polymer network mobility.	[51]
7	Molecular charge on the polymer	Cationic charge on the surface of the polymer enhances the interaction between its surface and mucin. This is because of the high electrostatic attractions as the mucin carries negative charge on its surface. On contrary, the use of anionic polymer reduces the chances of mucoadhesion because of reduced electrostatic attractions between polymeric surface and mucin layer.	[52]
8	Ionic Strength	Ionic strength whether it is cationic or anionic strength can affect the internetwork between the structure of polymer and mucin layer of the epidermal cells. This is mainly because of the change in the polymeric structures. The conformation of polymeric structures changes with the change in the ionic strength (or shift in the environmental conditions from anionic to cationic or from cationic to anionic).	[53]
9	Moisture level at the site of administration	The moisture level of the mucin layer also affect the degree of mucoadhesion. This moisture level varies with the type of body part where mucin layer is present. In the buccal cavity usually moisture level is high so will not cause any problem regarding mucoadhesion. However, during the buccal disorders like dryness of mouth and some other related disorders, this moisture level can change which may impact the degree of mucoadhesion. The degree of swelling of polymer also depends upon the moisture level present at the site of administration.	[54]
10	Applied pressure or force	The depth of the mucoadhesion penetration is affected by the amount of total force or pressure which is applied on the delivery systems. By using the appropriate strength and suitable contact time, an adequate mucoadhesion can be achieved.	[55]

Buccal drug delivery system

In 1847, it was first ever discovered that the drug absorption can also be possible when it is given through buccal cavity. The systemic absorption of the drug when it is given through buccal cavity is first ever tested on 1935. The results showed better results with better patient compliance as compared to other routes like nasal, ocular, vaginal extra routes. The buccal cavity is easily reachable (accessible) and heal itself rapidly after any damage of local stress. The buccal lining is also one of the robust lining of human body and can be used for systemic drug delivery [56]. As compared to other oral linings like sublingual route (floor of the mouth) [57], gingival route (gums) [58], linings around the lips, palatal mucosal route etc. [59], The buccal lining have different permeability to selective drugs, different anatomy, and desired length in order to keep the hold on the drug delivery dosage form like patches, tablets, semi-solid

dosage form [60]. This buccal lining can be used not only for local drug delivery but can also be used for systemic drug delivery with better bioavailability. The local therapy by using buccal route mainly included the treatment of diseases like oral candidiasis, xerostomia, neuropathic pain, oral cancer, mucositis, dental caries, oral lesions, gingivitis, severe dryness of mouth due to lack production of saliva or lack in release of saliva etc [61-63]. The systemic therapy by using buccal route mainly includes the treatment of disorders in which prolonged and sustained release of drug is required. The buccal route is mainly used due its better trans-mucosal permeability which allows huge types of drugs to penetrate through it and reaches the systemic circulation [64]. However when compared with the sublingual route, buccal route becomes less permeable and does not allow the rapid action of the drug. In other words, the onset of action is slow when we select buccal route for drug delivery. However, this disadvantage of buccal route becomes advantageous if

we want to get prolonged and sustained release of the drug [65]. Hence, for the scientists, working on diseases where long release of drug is required with better bioavailability, then they prefer buccal route. This is because, the buccal route has a smooth, immobile and large surface which makes it better route for retentive drug delivery systems so that prolonged and sustained release of drug can be achieved [66].

Advantages and disadvantages of buccal drug delivery

Advantages

- The buccal lining is highly vascularised and better accessible for any dosage form to get better administered in the impacted area and can be easily removed from the impacted area.
- Better patient compliance.
- Buccal mucosa does not have the same harsh environmental factor like pH, enzymatic degradation, temperature sensitivity etc. as that of oral mucosa and hence can be used for harsh environment sensitive drugs.
- As compared to other mucosal routes, in the buccal route there is very low enzyme activity. Hence, there is less enzymatic degradation of drug
- Buccal delivery protects the active drug from acid hydrolysis which is possible in gastrointestinal tract and hence is helpful in avoiding the first pass metabolism of drug.

Disadvantages

- When compared with the sublingual route, buccal route becomes less permeable and does not allow the rapid action of the drug.
- There is continuous salivary secretion in the mouth, near about 0.5–2 liters per day. Such continuous salivary secretions lead to the dilution of the drug reducing the drug effectiveness.

Various dosage form available for buccal delivery

Till date various dosage forms like semisolid dosage forms (ointments, gels, pastes), tables, capsules etc. have been discovered which can be used in the buccal route for the drug release. Some of these dosage forms have been explained below:

Semi-solid dosage forms (gels, pastes, ointments)

Various semi-solid dosage forms like gels, ointments, pastes etc have been used in the oral buccal cavity. The sticky nature of these gels, ointments and pastes, resulted in better contact with the mucosal layer and the hydrophobic nature of the polymer used within these dosage forms do not allow the formulation to get diluted by salivary release [67].

Bioadhesive gels (Bioadhesive ointments) are frequently used for local wound therapy of the oral cavity. Bioadhesive pastes are also used for oral cavity. Now a day, most popularly used bioadhesive paste is marketed as Orabase. Orabase is a type of first generation bioadhesive paste and is widely used to treat mouth ulcers for a long time period. The paste acts as a barrier between the ulcers and saliva and do not allow the drug to get diluted and hence allow better and more penetration of drug to treat ulcers. The paste basically consists of finely ground pectin, fine gelatin and sodium CMC is dispersed in the combination of mineral oil and polyethylene gel base. This combination of mineral oil and polyethylene gel help to maintain the paste at its application site for about 15-150 min [68]. Usually the neutral poly-methacrylic acid and methyl ester were also used in the Orabase in order to avoid the irritation which is caused by the conventional ointments. The Bioadhesive ointments are usually more viscous than the bioadhesive gels and pastes and the high viscosity ointments usually contain carbopol (CP), which is mainly responsible for the high viscosity [69]. About 12.5% concentration of carbopol mainly responsible for sustained release of the drug from the ointment and showed increase in the absorption of the drug for about 5 h as compared to pastes/gels [70]. The release of Prednisolone drug in the high viscosity carbopol

containing ointment in combination with the white petrolatum base has been tested by some researchers and the results showed better results as compared to that of pastes and gels containing same amount of active drug (Prednisolone) [71].

Other than pastes, gels, ointments, the use of hydrogels has also been discovered in order to treat buccal cavity related disorders. In 1961, the first hydrogels are prepared by using poly (2-hydroxy ethyl methacrylate) by Wichterle and Lim. Hydrogels are basically hydrophilic polymer networks which are oriented in a three dimensional orientation. These hydrogels are capable to swell in water and also equally capable to spread in biological fluids like saliva. These hydrogels are able to absorb water just because of the presence of various types of hydrophilic group's like-OH,-COOH,-CONH₂,-CONH,-SO₃H etc [72]. The drug release from the hydrogels can be controlled and release mechanisms of the drug from the hydrogels can be modified by adjusting the factors like water content, polymer composition, crystallinity, and crosslinking density [73]. The delivery of lidocaine hydrochloride drug is tested by using the hydrogel prepared from the chitosan glutamate polymer. Chitosan glutamate polymer is basically a soluble salt form of the chitosan polymer. The buccal delivery of the drug lidocaine hydrochloride as an anaesthetic drug is found to show effective and better relief buccal cavity disorders like aphthosis and some other painful buccal cavity diseases [74].

Tablets

Although semi-solid dosage forms are easy to administer and comfortable, however the active ingredient stability in the semi-solid dosage forms is comparatively less as compared to the tablets. The tablets as well as patches offer better drug stability, long period of therapeutic drug concentration level at site of action and improved residence time [75]. These days some engineered tablets and patches have multi-layer systems and matrix devices. These engineered tablets contain adhesive layer and some other drug layers from which drug is released continually for long period of time [76, 77]. One more layer considered as drug impermeable layer is also included in these engineered and matrix tablets, to enhance the drug release unidirectional. This unidirectional release mechanism of the drug is important because this avoid the clearance of the drug through saliva released by the salivary glands. The most appropriate site of administration for the tablets, which avoids the chances of drug clearance from the buccal cavity, is by administrating the tablets or any other dosage form under the upper lip of the buccal cavity [78]. The marketed Buccastem®, is an adhesive tablet used for anti-emetic action. This buccastem contains the active ingredient as prochlorperazine maleate which is placed under the upper lip and shows better release of drug for prolonged period of time. Other than these benefits of using the oral buccal tablets, some other mechanisms like oscillatory action produced by talking and mastication action produced during chewing of any eatable item, can produce patient compliance making the use of tablets uncomfortable [79, 80].

Till date a large number of muco-adhesive tablets have been investigated which are considered to have better muco-adhesive strength as they are used in combination with different polymers: Some of these muco-adhesive tablets have been mentioned below (table 3).

Powder dosage forms

Basically, a physical mixture of the drug with the bio-adhesive polymer can act as the powder dosage form which can be sprayed to the buccal mucosa in order to treat buccal disorders. Yamamoto *et al.*, have successfully prepared a bio-adhesive buccal powder containing hydroxypropyl cellulose and active drug as beclomethasone dipropionate. The prepared bio-adhesive powder is then sprayed on the buccal cavity of the rats and the results were evaluated. The results showed that there is a significant increase in the residence time when we spray the powdered dosage form on the buccal cavity as compared to the related oral solution containing same drug and polymer in same concentration. The results showed that there was about 2.5% retention power of the active ingredient beclomethasone on the buccal mucosa after spraying for about 4 h [104].

Table 3: Various combinations of API and polymers used in mucoadhesion of solid and semi-solid dosage form

S. No.	Active ingredient used	Polymer used	Reference
1	Nifedipine	Sodium alginate, Poly Vinyl Pyrrolidone, and Poly Ethylene Glycol	[81]
2	Nimesulide	Carbomer	[82]
3	Ondansetron	Sodium carboxy methylcellulose, Hydroxy propylmethylcellulose	[83]
4	Metoclopramide	Sodium carboxy methylcellulose, Hydroxy propylmethylcellulose	[84]
5	Benzylamine	Gelatin, Sodium carboxy methylcellulose, Hydroxy propylmethylcellulose	[85]
6	Lignocaine HCl	Sodium carboxy methylcellulose, Poly Vinylpyrrolidone	[86]
7	Ergotamine tartrate	Carboxyvinyl polymer and Hydroxy Propyl Cellulose	[87]
8	Cyanocobalamin	Polyoxyethylene	[88]
9	Chlorpheniramine maleate	Polyoxyethylene	[89]
10	Baclofen	Sodium carboxymethyl cellulose, sodium alginate, and Methocel	[90]
11	Ketoprofen	Sodium alginate and shitosan	[91]
12	Lactoferrin	Sodium alginate	[92]
13	Omeprazole	Sodium alginate, Hydroxy propyl methyl cellulose	[93]
14	Salmon calcitonin	Hakea gum obtained from Hakea gibbosa	[94]
15	Propranolol HCl	Sodium carboxymethyl cellulose	[95]
16	Pravastatin sodium	Carageenan	[96]
17	Piroxicam	Hydroxy propyl methyl cellulose	[97]
18	Morphine sulfate	Hydroxy propyl methyl cellulose	[98]
19	Metoprololtartarate	Sodium carboxy methylcellulose, Hydroxy propylmethylcellulose	[99]
20	Testosterone	Drum dried waxy maize	[100]
21	Itraconazole	Carbopol 934P, HPMC, Eudragit E 100	[101]
22	Furosemide	Soluphore, PEG 400, Polyvinyl alcohol, Cremophore, Eudragit, HPMC	[102]
23	Ranitidine	HPMC, Carbopol 934P, Sodium Bicarbonate	[103]

Polymeric films

Polymeric films are mainly used as coating formulation for various pharmaceutical tablet dosage forms, and the use these films was not attempted for buccal release. Later on 1990, the buccal film were considered to be more preferable over other adhesive dosage forms like tablets, capsules etc. as these polymeric buccal films have better flexibility and comfort related properties [105]. In addition to these properties, buccal polymeric films can show comparatively better residence time on the mucosa as compared to other dosage forms which can be easily diluted and easily washed away and can be removed from the buccal cavity by saliva. Other than these, these buccal polymeric films have the ability to protect the wound surface from various other bacterial infectious diseases and they are also helpful in reduction of pain [106].

Better flexibility, elasticity and softness are the ideal properties of polymeric buccal film. An ideal polymeric buccal film should also have be adequately strong so that it can withstand the stress conditions produced by mouth activity and should not get broken into pieces in mouth. In addition to these properties, an ideal polymeric buccal film must also have good bio-adhesive strength such that it should retain in the required area without breakage for the desired period of time [107]. Swelling of the polymeric films is a very common problem which cannot be neglected and cannot be completely removed. However, it can be reduced to some extent. An ideal polymeric buccal film if swell, then the swelling should be in the required range, such that it should not alter the physical and mechanical properties of the film [108]. The elasticity, softness, flexibility, bio-adhesive strength and other related properties should not get changed with the swelling of the film. Hence, we can say that the bio-adhesive, mechanical and swelling properties are the most critical properties in order to judge the efficiency of polymeric buccal film and hence these properties should be evaluated properly with standard tests and procedures [109]. These days polymeric buccal films have been prepared by using polymers like sodium CMC, PEG 400, CP

934P, HPMC, PEG 400 etc. It has been seen that HPMC (hydroxypropyl methylcellulose) related polymeric buccal films were tougher and have more elasticity with more bio-adhesive property as compared to the polymeric buccal films prepared from sodium CMC films [110]. *In vivo* studies have also showed that the polymeric buccal films containing HPMC showed tolerable swelling as compared to the polymeric buccal films containing sodium CMC [111].

Polymeric patches

On the other hand, polymeric buccal bio-adhesive patches are laminated thin films which can be single or multi layered depending on the need. These patches are available in various shapes. These patches can be round or can be oval in shape. These polymeric buccal patches have drug reservoir layer which is further connected with impermeable layer known as backing layer. This backing layer is very helpful in providing the unidirectional flow of the drug, contained in the polymeric layer, across buccal mucosa. These patches can be 1-3 cm of range in their sizes. This small size of the polymeric buccal patch makes them more convenient and more comfortable for the user and hence increases the patient compliance. An ideal buccal polymeric patch should be flexible and ellipsoid in the shape so that it can fit easily onto the centre of buccal mucosa [112].

The drug Acyclovir was delivered in the buccal cavity by using the polymeric buccal adhesive patches. The patch contained the polymer PEG, with copolymer acrylic acid, monomethyl ether monomethacrylate, an impermeable layer which is helpful in preventing the excessive dilution and washout through saliva. The *in vivo* studies showed that the patch once administered on the site remain there and releases the active drug Acyclovir for a period of about 22 h [113]. These evaluation tests showed it a good candidate for buccal delivery of the drug.

Some literatures were studied in which the authors mentioned the formulation which contains API and some polymers (table 4).

Table 4: Various combinations of API and polymers used in the formulation of mucoadhesive patches for buccal drug delivery

S. No.	Active ingredient used	Polymer used	Reference
1	Isosorbide dinitrate	HPMC phthalate	[114]
2	Lidocaine	Hydroxy propyl Cellulose	[115]
3	Nifedipine	Sodium alginate, Poly Ethylene Glycol	[116]
4	Protirelin	Poly Vinyl Pyrrolidone	[117]
5	Tetracaine	Hydroxy Propyl Cellulose	[118]
6	Ofloxacin	Hydroxy Propyl Cellulose	[119]
7	Tetracycline	Atelocollagen	[120]
8	Triamcinolone acetonide	Poloxamer, Hydroxy propyl methylcellulose	[121]
9	Insulin	Gelatin	[122]
10	Glibenclamide	Chitosan	[123]

Table 5: Commercial formulation intended for buccal delivery

Product	Manufacturer
Testosterone Buccal Tablet (Straint)	Columbia Laboratories Inc.
Desmopressin Buccal Tablet	
Androdiol Buccal tablets (Cyclo-Diol SR)	Ergo Pharm
Norandrodiol Buccal Tablets (Cyclo-Nordiols SR)	
Insulin Buccal Spray	Generex Biotechnology Corporation
ORALGEN (US)	
ORALIN (Canada)	Cytokine Pharma Sciences Inc.
Pilocarpine Buccal Tablet (PIOLOBUC)	
Glyceryl Trinitrate (Suscard Buccal Tablet)	Pharmax Limited
Prochlorperazine Buccal Tablets (Buccastem)	Britannia Pharmaceutical Ltd.
Oral Transmucosal Fentanyl Citrate Solid Dosage Form (ACTIQ)	Cephalon Inc.
Vitamins Trans Buccal Spray	Regency Medical research
Lorazepam Buccal Tablets	Wyeth Pharmaceuticals
Oxazepam Buccal Tablets	
Nicotine Mucoadhesive Tablets	Leo Pharmaceuticals
Nicotine Chewing Gum	
Prochlorperazine Bioadhesive Buccal controlled release Tablet(Buccastem)	Reckitt Benckiser
Buprenorphine HCl Tablets (Subutex)	
Buprenorphine HCl, Naloxone HCl (Suboxone)	Ciba-Geigy
Methyltestosterone Buccal Tablets (Metandren)	

Table 6: Mucoadhesion polymers and their bioadhesion strength

S. No.	bioadhesion strength high	Bioadhesion strength medium	Bioadhesion strength low
1	Carboxymethylcellulose	Gelatin	Polyethylene glycol
2	Tragacanth	Guar Gum	Psyllium amberlite
3	Sodium alginate	Gum Karaya	Thermally modified starch
4	Carbopol 934	Chitosan	Hydroxypropylcellulose
5	Poly(acrylic acid/divinyl benzene)	Acacia	Polyvinyl pyrrolidone

Table 7: Patented mucoadhesive formulations

Patent number	Inventor	Original assignee	Title
US9320721B2	Ulrike Vollmer	TESA LABTEC GmbH	Mucoadhesive patch with opposite ratios of nonionic and anionic hydrocolloids in adhesive and backing layer
US20020142042A1	Russell Mumper, Michael Jay	University of Kentucky Research Foundation	pH-sensitive mucoadhesive film-forming gels and wax-film composites suitable for topical and mucosal delivery of molecules
EP2509586A1	Pierre Attali, Dominique Costantini, Caroline Lemarchand	BioAlliance Pharma SA	Mucoadhesive buccal tablets for the treatment of orofacial herpes
EP1231900A1	David Francis Bain, Dale Munday, Calum Park, Omar Shakoob	The Robert Gordon University, Univ Robert Gordon	Bilayered buccal tablets comprising nicotine
EP3173067A1	Ayca Yildiz Pekoz, Yildiz ozsoy Erginer, Derya Arslan	Yildiz Pekoz Ayca	Mucoadhesive buccal in situ gel formulation
US8529939B2	David B. Masters, Eric P. Berg	Gel-Del Technologies Inc	Mucoadhesive drug delivery devices and methods of making and using thereof
EP1107733A1	Douglas Joseph Dobrozsi	Procter and Gamble Co	Oral liquid mucoadhesive compositions
WO2006105615A1	Ernest Alan Hewitt, Richard James Stenlake	Ozpharma Pty Ltd	Buccal delivery system
US8475832B2	Garry L. Myers, Samuel D. Hilbert, Bill J. Boone, B. Arlie Bogue, Pradeep Sanghvi, Madhusudan Hariharan	RB Pharmaceuticals Ltd	Sublingual and buccal film compositions
US20060198873A1	Shing Chan, Li-Lan Chen, Dushendra Chetty, John Liu	SmithKline Beecham Corp	Orally dissolving films
WO2008077130A2	Hassan Nached, Keith Freehauf, Peter Hanson	Merial Limited	Homogeneous paste and gel formulations
US3257276A	Robert H Broh-Kahn, Ernest J Sasmor	Laboratories for pharmaceutical Development Inc	Oral analgesic preparation
US5955098A	Harry A. Dugger, III	Flemington Pharmaceutical Corp	Buccal non polar spray or capsule
US6110486A	Harry A. Dugger, III	Flemington Pharmaceutical Corp	Buccal polar spray or capsule
US20090263476A1	Christopher N. Jobdevairakkam, Vikram Katragadda	Navinta LLC	Composition of Rapid Disintegrating Direct Compression Buccal Tablet
US20060002989A1	Salah Ahmed Lianli Li Venkatesh Naini	Teva Women s Health Inc	Formulations of sumatriptan for absorption across biological membranes, and methods of making and using the same
CA1299105C	John A. Mccarty	Key Pharmaceuticals Inc	Buccal formulation

Factors affecting polymeric bioadhesion

1. Hydrophilicity of the drug.
2. Formulation type (Tablets, gels, semi-solid dosage forms, patches, films etc).
3. Molecular weight of the polymer used.
4. Hydrogen bonding and glass transition temperature of polymer used.
5. pH of saliva.
6. Buccal cavity movement by talking, drinking and eating etc.
7. Acid dissociation constant of the drug.
8. Concentration of the polymer used.
9. Swelling index of the polymer.
10. Contact time of prepared formulation on the applied surface.

Gels

Gels are the classical formulations which are used for topical administration of various drugs. These gels offer various beneficial properties as compared to other dosage forms for example: gels are easy to get applied on the surface, they show better spreadibility and better bio-compatibility. These gels also show better physico-chemical properties which make these gels more appropriate dosage formulations as compared to others. For example, Hydrogels [124]. These hydrogels are modified form of gels with better hydrophilicity which make them easy to penetrate and better spreadibility. Hydrogels are three dimensional polymers with better cross linking which are basically synthesized from same or different monomers with hydrophilic nature [125]. These polymers have the ability to shrink or swell depending upon the environmental conditions where they have applied. Hydrogels have ability to get modified as per the needs of the drug's physical and chemical properties which itself increases the stability and release of the drug incorporated. The gels have three dimensional cross linking structures and hence there are a number of gaps in between these linking where the drug can be easily placed. All these properties make the gels a better candidate for tissue engineering, regenerative medicine, diagnostic biomedical sensors, and controlled drug delivery [126]. List of patented mucoadhesive formulation is depicted in (table 7).

CONCLUSION

This outline is about the mucoadhesive dosage forms which may be constructive tool for the capable of designing novel mucoadhesive drug delivery system as it offers prolonged contact at the site of administration. The formulation of mucoadhesive drug delivery system depends on the selection of appropriate polymer with immense mucosal adhesive properties and biocompatibility. There is no uncertainty that the oral route is the most favorable route of drug delivery. Mucoadhesive drug delivery has diverse applications including development of novel mucoadhesive, design of the novel devices, mechanisms and permeation enhancement.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The authors confirm that this article content has no conflict of interest.

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