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Review on Mucoadhesive Drug Delivery System with Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery System for the Effective Delivery of Pharmaceuticals

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Abstract

Since, the last four decades, the concept of mucoadhesion has achieved a much valuable interest in the various fields of pharmaceutics. There are many advantages of mucoadhesive buccal drug delivery system that made this a novel drug delivery system for the local as well as systemic delivery of various drugs. The main advantage of this drug delivery system is that it prolongs the residence time of the dosage form at the site of application. Due to the high blood supply and relatively high permeability of the buccal mucosa, the buccal cavity is the best option for both local as well as systemic delivery of various drugs. The term bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst layer of surface of a biological membrane and the natural or synthetic polymers, which allows the polymer to adhere the surface of that membrane for an extended as well as prolonged period of time. In this review we have discussed the various types of mucoadhesive dosage forms along with a brief knowledge about the various types of mucoadhesive polymers. The buccal mucoadhesive dosage forms can be either of matrix or of reservoir types. The main advantage of this route for drug delivery is that, the delivery by this route by passes the first pass metabolism of various drugs that are prone to the their hepatic first pass metabolism. This review provides the brief knowledge about the oral mucosal drug delivery by discussing briefly the structural features of mucosa, mechanism of bioadhesion, various theories of bioadhesion, general considerations in design of mucoadhesive buccal dosage forms, permeation enhancers, and the various evaluation methods along with the literature survey of the buccal mucoadhesive drug delivery system.

Keywords: Mucoadhesion; Permeation enhancers; Bioadhesive polymer; Bioadhesion

Introduction

Mucoadhesive drug delivery system

Since from the last 40 years, the concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. The use of various mucoadhesive polymers have achieved the significant interest in formulating the sustained release, extended release as well as prolonged release dosage forms. The mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities. The delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora [1]. For the desired mucoadhesive strength of the mucoadhesive dosage forms, there are various mucoadhesive polymers that can be used. These polymers are either natural or synthetic macromolecules which are capable of adhering to the mucosal surfaces. From last three decades, the use of various mucoadhesive polymers has achieved a great interest in the field of pharmaceutical technology. Nowadays, the use of mucoadhesive polymers has been accepted as an important strategy to prolong the residence time and to improve the localized effects of drug delivery systems on various mucus membranes of a biological system [2].

The potential candidates for drug delivery by mucoadhesive dosage form to different sites includes oral, gastrointestinal, nasal, ocular, vaginal, and rectal. A brief comparison was discussed about these sites for drug delivery. Buccal route found to be more suitable for the delivery of pharmaceutical agents using mucoadhesive polymers due to presence of relatively static and smooth surface on which various mucoadhesive dosage forms can be placed. Different dosage forms like films, tablets, gels, ointments and patches can be used for delivery of drug across the buccal mucosa. The drugs may be suitable candidates to be delivered via the oral cavity which are having short biological half-life, poor solubility and permeability, susceptible to enzymatic degradation and for achieving sustain release effect. The other important site is nasal route for mucoadhesive formulations. It has a large surface area of about 150-200 cm^2. The activity of muco-ciliary layer enhanced by presence of any foreign particle matter, therefore the residence time of particles in nasal mucosa varies between 15-30 min. Thus by employing various mucoadhesive formulations the residence time of the drug can be enhanced. Topical delivery of drugs to the eye is most important route for the treatment of various eye related disorders. For achieving the effective delivery of therapeutic agents to the eye, various dosage forms such as eye-drops, ointments, gels and

ocular inserts can be utilized. Due to effective protective mechanism of the eye, the bioavailability of many drugs is very poor. Reflex lachrymation, drainage and blinking of eyes remove drugs from the eye's surface rapidly. This problem can be overcome by employing mucoadhesive polymers like poloxamer, methyl cellulose, PVP, CAP, PAMAM and thiolated PAA. Mucoadhesive dosage form have also employed for delivery of drugs through rectal and vaginal routes. These routes have several advantages like pain avoidance, tissue damage avoidance, first pass metabolism avoidance, and decrease in hepatic side effects which are found very common during parenteral route of administration. The polymers used for delivery of drugs through rectal and vaginal routes are gelatin, mucin, poloxamer and polycarbophil. Various rectal and vaginal formulations include creams, ointments, *in-situ* gels, emulgels, tablets [3].

Advantages of mucoadhesive drug delivery system

- The buccal drug delivery provides a relatively rapid onset of action as compare to the other non-oral routes, hence, has a high patient acceptability.
- Improved patient compliance due to the easy application of dosage forms in comparison to the injections and don't provide any painful sensation
- The mucosal membranes are highly vascularized so that the administration as well as removal of a dosage form is easy.
- The sustained drug delivery can be achieved by using the mucoadhesive polymers of 'SR' grades.
- Due to the high extent of perfusion the rate of drug absorption is faster.
- The side effect that can arise due to oral administration, such as, nausea and vomiting, they can be avoided completely.
- The mucoadhesive drug delivery can be easily used in case of unconscious and less Co-operative patients.
- The drugs, which show poor bioavailability via the oral route, can their bioavailability can be enhanced by formulating their mucoadhesive delivery systems [4-6].

Mechanism of Mucoadhesion

The mucoadhesion can be defined as an interfacial phenomenon in which the two materials, in which one may be artificial such as mucoadhesive polymer and other may be the mucin layer of the mucosal tissue, are held together by means of interfacial forces of attraction. "Mucoadhesive" is defined as an artificial substance that is capable of interacting with mucus membrane and being retained on them or holding them together for extended or prolonged period of time. During the process of adhesion, generally the two stages have been identified are given below. These stages of mucoadhesion are also shown in Figure 1 [7].

Contact stage: During this stage, when the mucoadhesive material comes in contact with mucus membrane, an intimate wetting occurs between the mucoadhesive and mucous membrane. This wetting of the mucoadhesive is done by the mucus present in the mucosal membrane.

Consolidation stage: By means of different physicochemical forces of attraction the mucoadhesive material gets joined to the mucus membrane and resulting in a long lasting mucoadhesion. This is called as the consolidation stage. After these two stages the process of mucoadhesion completes.

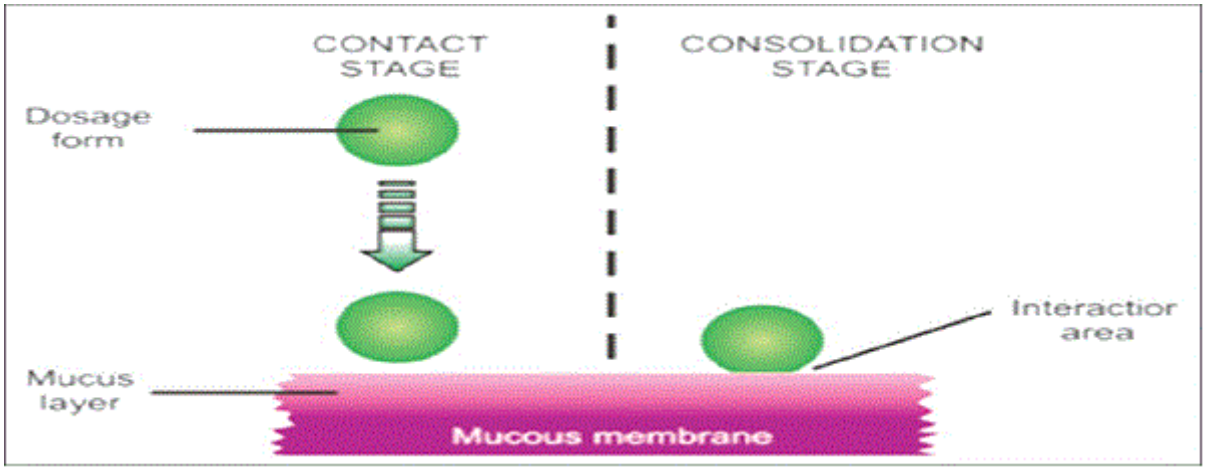

Figure 1: Mechanism of mucoadhesion: The mucoadhesion takes place in two stages. (A) Contact stage: Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon). (B) Interactive stage: Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration).

Theories of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

Chemical bond

It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc.

Mechanical bond

This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system.

On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated [8].

Electronic theory

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the interface of the two surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion [8].

Adsorption theory

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond [8].

Wetting theory

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion [9].

Diffusion interlocking theory

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. The other factors that may influence the inter movement of polymeric chain are molecular weight, cross linking density, chain flexibility, and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion [9].

Fracture theory

The fracture theory is mainly based on the fact that, the force required to detach the polymeric chain from the mucin layer is the strength of their adhesive forces. This strength may be also called as fracture strength. The fracture strength can be determined by using the formula given below

$$G=(E.\ e/L)^{1/2}$$

G-Fracture strength,

E-Young's modules of electricity,

e-Fracture energy,

L-Critical crack length.

Factors Affecting Mucoadhesion

Polymer related factors

Molecular weight: The mucoadhesion strength of a mucoadhesive polymer mainly depends upon its molecular weight and polymeric linearity. Generally, for the linear polymers (e.g., Polyethylene glycol), the bioadhesive property is directly proportional to the molecular weight i.e., PEG-200000 having greater mucoadhesive strength than that of PEG-20000. But in case of nonlinear polymer, the mucoadhesive strength of polymer may or may not be dependent of its molecular weight. This is mainly because the helical or coiled structures of such polymer may shield some of the adhesive group, which are mainly responsible for the adhesive property.

Concentration of polymer: The concentration of a mucoadhesive polymer is a significant factor of determining its mucoadhesive strength. There is an optimum concentration for a mucoadhesive polymer where it produces the maximum mucoadhesion. For some highly concentrated polymeric systems, beyond the optimum level of polymer, the mucoadhesive strength of polymer starts to fall down significantly because the concentration of polymer molecules starts rising over the molecular concentration of the liquid medium so that there is no further chain formation between liquid medium and polymer. As a result of this, the polymer particles remain separated from liquid medium, due to this the mucoadhesive strength of that polymer starts fallen down. On the other hand, when the concentration of the polymer is too low as compare to the concentration of liquid medium, the number of polymer chains per unit volume of liquid medium is less, the mucoadhesive strength of polymer at that concentration is also very less.

Flexibility of polymer chains: Greater the flexibility of the mucoadhesive chain causes the greater diffusion into the mucus network of buccal cavity. This results in increased mucoadhesion. The flexibility of polymer chain decreases with increase in the concentration of polymer. For an effective bioadhesion, the polymer chain should effectively diffuse into the mucus layer. The flexibility of polymer chain depends on the viscosity and diffusion coefficient of that chain.

Spatial confirmation: The mucoadhesive strength of a polymer is also dependent on the conformation or spatial arrangement of polymers i.e., helical or linear. The polymers showing linear conformation having the greater mucoadhesive strength as compare to the polymers showing helical conformation. Because, the helical conformation of polymer may shield various active groups, that are primarily responsible for mucoadhesion, thus reducing the mucoadhesive strength of the polymer.

Swelling or hydration: The proper hydration of mucoadhesive polymer is essential for the desired mucoadhesive strength. With

increase in hydration the pore size of polymer increases which results induced mobility and enhanced interpenetration.

Hydrogen bonding capacity: Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc.,). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate and poly (methacrylic acid) as well as all their co-polymers are having good hydrogen bonding capacity.

Cross linking density: The cross linking density of the polymer determines its higher molecular weight. The cross linking density indicates the number of average molecular weight of the cross linked polymer, which determines the average pore size. When the cross linking density of polymer is higher, it reduces the pore size of polymer chain which results in reduced diffusion of water into the polymer network. The reduced diffusion results in the decreased penetration of polymer into the mucin and finally decreases the mucoadhesive strength.

Charge: The bioadhesive property of ionic polymer is always higher than that of non-ionic polymer. In neutral or slightly alkaline medium, the cationic polymer shows superior mucoadhesive property. It has been proven that, cationic high molecular weight polymer such as chitosan possess good bioadhesive property [10,11].

Environment related factors

pH of polymer-substrate interface: The pH of polymer-mucin interface should be same as it is possible, because, the difference in pH amongst the two systems may results in the transfer of charge due to the higher pH gradient. This may affect the mucoadhesion.

Applied strength: While placing a buccal mucoadhesive drug delivery system, sufficient strength should be applied in order to provide a good bioadhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient long time make the polymer become bioadhesive with mucus.

Initial contact time: Greater the initial contact time between the mucoadhesive polymer and the mucus layer results in the increased swelling as well as interpenetration of the mucoadhesive polymer chain. Hence, increases the mucoadhesion strength of the polymer chain.

Moistening: Moistening is required to allow the mucoadhesive polymer to spread over the surface. It creates a network of polymer chains of sufficient pore size. Through these pores, the interpenetration of polymer and mucin molecules takes place that results in increasing the mobility of polymer chains for the proper diffusion of mucoadhesive polymer in mucin layer [12,13].

Physiological factors

Mucin turnover: High mucin turnover is not beneficial for the mucoadhesive property because of following reasons: The high mucin turn over limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though it has a good bioadhesive property. High mucin turn over may produce soluble mucin molecule, thus molecule interact with the polymer before they interact with mucin layer. Hence there will not be sufficient mucoadhesion.

Disease state: In some disease states, the secretion of mucus from the mucus membrane gets decreased (e.g., in Dry Mouth Syndrome and in old age). So that there is not sufficient amount of mucus present at the site of attachment of mucoadhesive dosage form. This may leads to improper moistening and swelling of polymer. Due to which there is decreased mucoadhesive strength of mucoadhesive dosage form.

Rate of renewal of mucosal cells: Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

Concomitant diseases: Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation.

Tissue movement: Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms [14].

Buccal Mucoadhesive Drug Delivery System

- The mucoadhesive drug delivery system in the mucus membrane of oral cavity can be categorized into three delivery systems:
- Sublingual delivery
- Buccal delivery
- Local delivery
- These oral sites provide the high blood supply for the greater absorption of drug with sufficient permeability. From these three sites of oral mucoadhesive drug delivery system, the buccal delivery is the most convenient site. There are many advantages of buccal mucoadhesive drug delivery system over other drug delivery systems are given as follow:
- The buccal mucoadhesive drug delivery system can be used for both local as well as systemic delivery of many drugs.
- Buccal mucoadhesive dosage forms are easy to applicate as compare to other adhesive dosage forms.
- Increased patient compliance over the injectables.
- It is the most preferred delivery system for the local treatment of drugs. So that there are wide range of mucoadhesive formulations has been [15].

Limitations

- The drugs having bitter taste cannot be formulated.
- The drugs which irritate oral mucosa, cause allergic reactions and discoloration of teeth cannotbe formulated.
- If formulation contains antimicrobial agents, affects the natural microbes in the buccal cavity.
- The patient feels discomfort in eating, drinking and speaking.
- Only the drugs which are absorbed by means of passive diffusion can be administered by buccal route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Sometimes, the degradation of moisture sensitive drugs may take place by saliva [16].

Disadvantages of Buccal Drug Delivery System

- Low permeability of the buccal membrane, specifically when compared to the sublingual membrane.
- Smaller surface area. The total surface area of membranes of the oral cavity available for drug absorption is 170 cm^2 of which ~50 cm represents non-keratinized tissues, including the buccal membrane.
- The continuous secretion of saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form [17].
- These are some of the problems that are associated with current buccal drug delivery system

Overview of oral mucosa

The oral mucosa acts as the one of most important route for the delivery of drugs. It provides the delivery of drugs by both systemic as well as local pathways. The oral cavity contains a large surface area of mucus membranes for the complete absorption of various drugs. The total surface area of oral cavity i.e., lined by mucus membranes is near about 100 cm^2. Following are the several parts of the oral cavity:

- The floor of mouth (sublingual)
- The buccal mucosa (cheeks)
- The gums (gingiva)
- The palatal mucosa and
- The lining of lips.

The oral mucosal cavity consists of the multi-layered epithelial tissues that are further covered by mucus. There is a basal membrane present inner to the epithelial tissues. Inside the basement membrane there is a layer of connective tissues called as lamina propria. The lamina propria functions as providing the mechanical support. After this, the sub-mucosal part starts. Is contians the various blood vessels as well as nerves from central nervous system. The sub-mucosal part provides the highest vascularity for the complete absorption of the drugs. The human oral mucosa contains both keratinized epithelium (found in the gingiva and part of the hard palate) and the non-keratinized epithelium (founds in the surface of the distensible lining mucosa of the soft palate, floor of mouth, lips and cheek). The oral mucosa mainly composed of three layers as shown in Figure 2 [19].

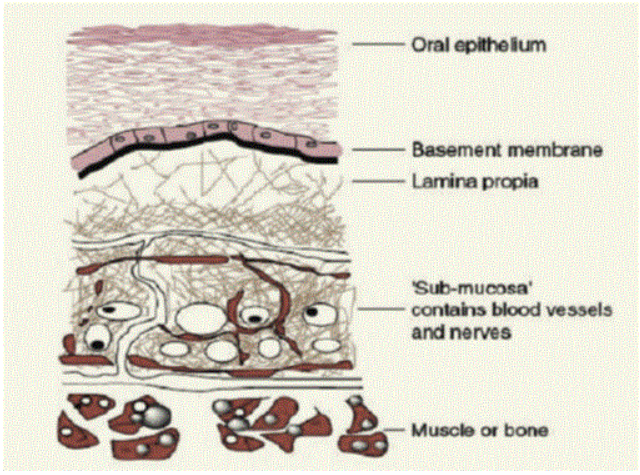

Figure 2: Anatomical structure of buccal route.

Mucus composition

The oral mucus is generally secreted by various glands of oral cavity that are sublingual gland, parotid gland, and other salivary glands. The mucus is a translucent gel secreted by goblet cell or by special exocrine glands with the mucus cells [18]. The components are given in Table 1 [18].

Components	Percentage
Water	95%
Glycoproteins and lipids	0.5-5%
Mineral salts	1%
Free proteins	0.5-1%

Table 1: Composition of mucus.

Mucus glycoproteins are the high molecular proteins that contain attached oligo-polysaccharide units. The mucus contains following oligosaccharide units [19].

- L-fructose
- D-galactose
- N-acetyl-D-glucosamine
- N-acetyl-D-galactosamine
- Sialic acid

Functions of mucus

- Cell-cell adhesion
- Lubrication
- Bioadhesion
- Protective
- Barrier

Buccal Mucoadhesive Dosage Forms

An ideal drug delivery system should possess the two main properties that are given below:

a) Spatial placement (for targeting drug to specific organs/tissues)

b) Temporal delivery (for controlling the rate of drug delivery)

Today, it is very difficult to formulate an ideal drug delivery. This led to development of sustained/controlled release delivery systems. Still, sustained or controlled delivery system lacks in preventing drug loss by either hepatic first pass metabolism or pre-systemic elimination like gastric, intestinal, or colonic degradation. So, several approaches have been tried to form a suitable dosage form for the above said conditions. Oral mucosal drug delivery, one of the physiological approaches, was reported to be a method to formulate these drugs into suitable dosage form with good therapeutics effects. Oral mucosal drug delivery of different drugs can be achieved by bioadhesive polymer systems [20].

General considerations in designing dosage forms

Physiological aspects: Due to the constant flow of saliva and regular movement of tissues present in the oral cavity the local delivery of the drugs in oral cavity is the most challenging aspect. Due to this, the residence time of the drugs for this route is very short. The buccal mucoadhesive formulations are being used to overcome this problem. The bioadhesive polymers are been use for improving the residence time in the buccal mucosa, and hence increase the absorption of drugs delivered by this route. Due to the local absorption of drugs, side effects are also being reduced as compared to in case of systemic delivery [21,22]. Generally, a buccal delivery device should have the size of about 1-3 cm^2 and the daily drug dose should be not more than 25 mg. An ellipsoid or circular shapes are being the most acceptable shapes for buccal delivery device.

Pathological aspects: The barrier property of buccal mucosa is mainly due to the presence of epithelial tissue. The thickness of epithelial tissue can be affected by many diseases that may change the barrier property of epithelial tissue. Some diseases or treatments may cause the alteration in rate of mucus secretion. These changes at the mucosal surface due to various pathological conditions may affect the residence time buccal delivery device [23-25].

Pharmacological aspects: The design and formulation of a buccal delivery dosage form depends upon the nature of delivery (local or systemic), drug targeting site and mucosal site to be treated. The buccal delivery is generally preferred for systemic delivery as compared to the local delivery of drugs [26].

Pharmaceutical aspects: The buccal drug delivery system is generally used for desired absorption of poorly water soluble drugs. For this purpose, firstly, the water solubility of the drug is enhanced by using specific solubility enhancement method e.g., by forming complex with cyclodextrin. Hence by improving solubility, the absorption of drug also get increased in buccal mucosa [27]. There are many other factors that affect the release and penetration of drug, must be optimized during formulation design. In addition to this required physicochemical characteristics required for desired release of and absorption of drug, organoleptic properties of the drug as well as buccal dosage form should also be considered during its formulation design. Some excipients such as plasticizers and penetration enhancers can be used in the formulations to enhance their effectiveness and acceptability. As the buccal mucosa is less permeable, so in order to enhance the permeability, various penetration enhancers can be used. Some commonly used penetration enhancers are bile salts, fatty acids, and sodium lauryl sulphate. Some enzyme inhibitors may be used to inhibiting the degradation of drug by various enzymes present in the saliva due to which the bioavailability of drug can be improved. There are some polymers such as carbopol, polycarbophil that can inhibit certain proteolytic enzymes (trypsin, carbo-peptidases etc.,) [28]. pH of delivery device is another pharmaceutical factor that should be considered during formulation of buccal delivery devices containing ionisable drugs. The pH of buccal device should be near to neutral as the pH of saliva is from 6.6 to 7.4. The large differences in pH may cause irritation on the mucosal site. On the basis of their geometry, the buccal mucoadhesive dosage forms can be categorized into three types as given below.

Type I: In this there is a single layer containing dosage form which provides multidirectional drug release. The main disadvantage of this type is that the drug loss is high by swallowing.

Type II: It contains the drug loaded bioadhesive layer covered by impermeable backing membrane. The backing membrane covers only the opposite side from the site of attachment hence preventing the drug loss from the upper surface of device.

Type III: In this type, all sides of drug loaded mucoadhesive layer are covered by impermeable except the side that attaches the target area. It is a unidirectional drug flow preventing all kinds of unwanted drug loss. The Figure 3 shows various types of buccal dosage forms [29].

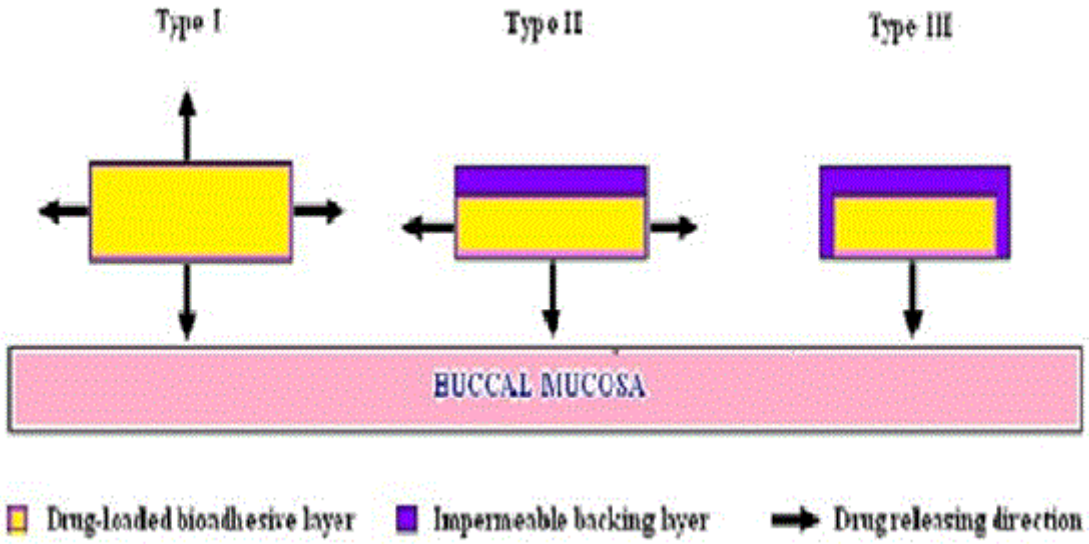

Figure 3: Types of buccal mucoadhesive dosage form.

Basic Components of Buccal Drug Delivery System

Drug substance

The suitable active pharmaceutical ingredient or drug substance should be selected on the basis of its pharmacokinetic properties. The drug should be of following characteristics:

- The one time dose of drug should be small (dose ≤ 25 mg).
- The drug should be having short biological half life ranging from 2 to 8 hrs.
- The drugs showing first pass metabolism can be used for buccal drug delivery for avoiding the first pass metabolism [30].

Bioadhesive polymer

The use of bio adhesive polymer determines the various parameters such as mucoadhesive strength, thickness, *in-vitro* release and the residence time of the drug delivery device. Generally the polymers with high molecular weight are preferred because; they show effective release rate controlling properties. An ideal polymer should have following characteristics for achieving the optimized results [31]:

- It should be inert.
- It should be compatible with the environment and drug.
- It should be adhere quickly with the mucus membrane and adherence should be long lasting for required time.

The classification of Bioadhesive Polymers is given in Table 2 [32].

Criteria	Categories	Examples
Source	Semi natural	Agarose, chitosan, elatine, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Cellulose derivatives [CMC, thiolated CMC, Sodium CMC, HEC, HPC, HPMC, MC, MHEC]	Thiloated CMC, HEC, HPC, Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), PVA
Aqueous Solubility	Water-soluble	CP, HEC, HPC (water below 38.8°C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum

	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan

Table 2: Bioadhesive polymers in buccal drug delivery.

Backing membrane

Backing membrane used for the formulations should be impermeable to drug as well as mucus in order to prevent the unnecessary drug loss from all sides of the device. The materials used for preparing backing membrane should be inert, insoluble or should have low water solubility. The commonly used materials in backing membrane include ethyl cellulose, carbopol, sodium alginate, HPMC, polycarbophil etc., [33].

Plasticizers

The plasticizers are used in order to improve the folding endurance of the delivery device. They provide enough flexibility to the dosage form for improving its patient acceptability and patient compliance. Few examples of commonly used plasticizers are PEG-400, PEG-600, dibutyl phthalate, propylene glycol etc.,

Permeation enhancers

These are the chemicals or liquids used to improve the permeation of drug from device into the mucus membrane. The permeation enhancers work by following mechanisms.

Mechanisms of action of permeation

- By reducing the viscosity of mucus.
- By increasing the fluidity of lipid bilayer membrane.
- By countering the enzymatic barrier.
- By increasing the thermodynamic activity of drugs [34].

Classification of Buccal Adhesive Dosage Forms

Solid dosage form

Buccal tablet: The bioadhesive tablets are most preferable mucoadhesive device in order to improve bioavailability of drugs. Mucoadhesive tablet can be prepared by methods such as wet granulation and direct compression. In case of buccal drug delivery, the tablets are placed in buccal pouch below the muscles of teeth. Mechanism of drug release is erosion.

Advantages: The buccal tablet can developed for verity of drug including insoluble to soluble, low dose to high dose, hydrophilic to lipophilic. As compared to conventional tablet, buccal tablet are flat, small and retained at site until release and/or dissolution is complete.

Disadvantages: They provide little bit of discomfort to the buccal cavity because of their solid nature [34].

Bioadhesive microsphere: Microsphere is an important part in case of novel drug delivery system. This mucoadhesive microsphere is mainly used for purpose of targeting to specific body cavity.

Advantages: They provide high absorption and enhanced bioavailability of drug due to their surface-to-volume ratio that provide highest contact of microspheres with mucus membrane.

Bioadhesive wafers: It is a newer dosage form for bioadhesive buccal delivery. It is used at the periodontal region for the treatment of infections related with periodontitis [35].

Bioadhesive lozenges: Bioadhesive lozenges are generally used for delivery of drugs that are antimicrobials, corticosteroids, local anesthetics, antibiotics and anti-fungals and are used topically in the buccal cavity.

Advantages: Better patient compliance and easy to swallow.

Disadvantages: The lozenge produce a high release rate of drug at initial stage and rapidly reaches the sub-therapeutic level [35].

Semisolid dosage form

Bioadhesive patch/film: Patches or film are preferred over tablet because of their comfort and flexibility. They are formulated such that it can provide contact between bioadhesive formulation and mucosa. Thickness of patch is a constraint which cannot provide control release of drug for longer period of time. In case of drug containing reservoir layer type; drug is released in controlled manner. Patches and film are mostly preferred for local action to treat oral diseases. There are many methods used for formulation of patch or films such as solvent casting method, hot melt extrusion technique, direct milling, semisolid casting, solid dispersion extrusion etc. Among that solvent casting is most popular method and widely used [36].

Buccal gel and ointment: As the advantage of dispersion gel and ointment has come in focus. They do not have accurate dosing as unit dosage form like tablet, patches or films, hence they are mostly preferred for local action where dose accuracy is less or not concern.

Advantages: local application of steroidal gel for treatment of mucosal ulceration in order to decrease the side effects of steroids.

Disadvantages: It has less patient acceptability than other mucoadhesive formulation [37].

Medicated chewing gum: Medicated chewing gum contains drug which after chewed, offer high amount of drug to prove local action in mouth. It can also shows absorption through systemic circulation. The medicated chewing gum for nicotine replacement therapy is available. Likewise caffeine chewing gums are also available [38].

Liquid dosage form: These are available in form of solution or suspension of drug in suitable vehicle. There are many liquid dosage forms that are available in market such as mouthwashes, mouth freshener, and are generally used for local delivery of drugs. Wide varieties of polymers are use from that chitosan has greatest binding capacity than other. Viscous liquid formulations are preferred to coat buccal cavity either as vehicle or as protectant [39].

Evaluation of Buccal Mucoadhesive Dosage Forms

Experimental methodologies for buccal absorption/ permeability study

In-vitro **and** *ex-vivo* **methods of evaluation:** The *in-vitro* studies are used to determine the release, solubility and dissolution of dosage forms. The *ex-vivo* studies conducted on the animal tissues and membranes by preparing animal models. The tissues are taken from the freshly died animals and are been used within 2 hrs after their separation. The membranes are then placed and stored in ice-cold (4°C) Kreb's buffer upto the time before they are mounted between diffusion cell for the *ex-vivo* permeation experiments [40].

In-vivo **methods:** It is also called as buccal absorption test. For kinetic drug absorption measurement this method can be used. The procedure involves the swirling of a 25 ml sample of the test solution for up to 15 min by human volunteers in their buccal cavity. After 15 min the solution expelled out. In order to calculate the amount of drug absorbed, the amount of drug present in expelled volume can be calculated. The main disadvantages including salivary dilution of drug and accidental swallowing of sample solution may arise.

Experimental animal species: Choice of animal for the experimental study is very important factor. To perform *in-vivo* study researchers can prefer the animals depending on test to be perform. Most of animals having the keratinized buccal mucosa, but the rabbit and pig are the only animals which having non-keratinized mucosa as like humans. To study permeation of drug monkey, dog, pig animals are mostly used.

In-vitro **release study:** For simulating *in-vivo* conditions, researchers have developed different apparatus like:

- Beaker method
- Dissolution apparatus
- Interface diffusion system
- Modified Keshary Chien cell

Methods to Study Mucoadhesive Strength

Polymer characterization can be done by evaluating their mucoadhesive strength both *in-vivo* and *in-vitro* technique.

In-vitro evaluation techniques

Measurement of tensile strength: In this method, the force required for breaking the bioadhesive bond between mucus membrane and bioadhesive polymer is calculated. The following formula can be used for determining the tensile strength of buccal mucoadhesive device.

Force of adhesion (N) =Mucoadhesive strength × 9.81/1000

Bond strength (N/m^2) = Force of adhesion (N)/Surface area of tablet (m^2)

For the measurement of tensile strength, various instruments are used that are as follows [39].

Modified physical balance or tensile tester

Wilhelmy Plate Technique

Measurement of shear strength: In this technique the mucoadhesive strength is determined means of measurement of shear stress applied to the adhesive device. In this technique, firstly select two smooth polished glass box, sand fix one box on a glass plate with adhesive, on a leveled table. To the upper block, tied a thread and then pass down the block through a pulley. The length of the thread from the pulley should be 12 cm. At the bottom side of the thread, attach a 17 g pan along with weights. And hence the shear strength was determined using an appropriate method by correlating the weight required to break the adhesion [40].

Other *in-vitro* methods

Rheological study: The rheological information of polymer–mucus mixtures can offer an acceptable *in-vitro* model which can correlate with *in-vivo* performance of a mucoadhesive polymer. It is best method for determination of mucoadhesive potential of polymer by comparing binary mucus/polymer blends to the equally concentrated monocomponent mucus/polymer system. The rheological behaviour of two macromolecular species can by changed by techniques such as chain interlocking, and chemical interaction that occur between the bioadhesive polymer and mucin chains.

Colloidal gold staining method: This is a new *in-vitro* method which was described for comparison of mucoadhesive property of various hydrogels. In this technique, there is a use of red colloidal gold particles which are stabilized by the partially or fully adsorbed mucingold. Because of interaction mucoadhesive develops red colour on its surface. The mucoadhesive properties of the mucoadhesive device can be compared by measuring the intensity of red colour.

Fluorescent probe method: In this method lipid bilayer of cultured human conjunctiva cells is labelled with pyrine which is used as a fluorescent probe. If the polymer can adhere to this cell, it can caused change in fluorescence due to chance in surface compression when compared with control cell. This change in degree of fluorescence is directly proportional to amount of polymer binding. To determine density on adhesion, polymer charge, and charge sign another probe can also be used. It states that determination of bioadhesive bond is based on molecular interaction of polymer with mucus [40].

In-vivo methods of evaluation

Gamma scintigraphy techniques: It is a non destructive method for the evaluation of pharmaceutical dosage forms. This technique is used to get the different information of the different areas of GI tract, the site of drug absorption, the time and site of disintegration of dosage forms. This instrument also used to check the effect of disease and food size on the biopharmaceutical characteristics of the dosage forms. Generally this method is used to study the distribution and the retention time of mucoadhesive tablets.

GIT transit using the radio-opaque technique: In this technique radio opaque markers are used to determine effect of polymer in GI transit time. Non invasive method such as faeces examination and x-ray evaluation can provide sufficient data to study GI residence time. Cr 51, Tc99 m, In113 m or I123 these are some examples of marker which are used for mucoadhesive drug delivery.

Moisture absorption studies for buccal patches: The determination of moisture absorption by the buccal films or patches is necessary for evaluation of the drug absorption and drug release parameters. Moisture absorption studies can be performed in 5% w/v agar in distilled water. Heat the solution and then transferred to petri plates and allowed to solidify. Then select the six buccal patches from each

batch weigh properly. After solidification of agar positioned them on the surface of agar plate and incubate at 37°C in incubator. Weigh all the patches again, and calculate the percentage of the absorbed moisture by using the following formula-

% Moisture absorbed=Initial weight–Final weight/Initial weight×100

Thickness: Select randomly five different patches and with the help of screw gauge measure the thickness.

Folding endurance: Select a patch and fold it repeatedly at the same point until it ruptures. The total number of folding required for cracking or breaking a patch is called as its folding endurance. The folding endurance of the buccal patch should be greater than 150 times.

Swelling study for tablet: Weigh the mucoadhesive dosage form accurately and place in a beaker containing 200 ml of buffer media. Remove the dosage form after each interval and weigh it again. Follow this process up to 8 hours. The following formula can be used for calculating the swelling index:

Swelling Index (S.I.)=(Wt-Wo)/Wo

Where,

S.I.=Swelling index

Wt=Weight of the dosage form at time t

Wo=Initial weight of dry dosage form.

Surface pH study: The surface pH of the buccal dosage form is calculated in order to examine the possibility of any side effects that may be arise *in-vivo* because of acidic or basic pH. In this method a glass electrode is used for determining pH. Allow the dosage form to swell by keeping it in contact with distilled water at room temperature for 2 hrs. Then measure the pH by taking the electrode in contact with the surface of the dosage form [40].

Residence time: For determining the residence time of the buccal dosage forms the modified disintegration apparatus. 800 ml isotonic buffer pH 6.75 solution can be used as disintegration medium 3 cm long rabbit mucosa was attached to glass slide and it was vertically attached to side arm. One surface of mucoadhesive tablet was hydrated with 15 ml of isotonic phosphate buffer solution then it was taken in mucosal contact. The movement of glass slide was allowed to up and down for complete immersion. Then time for detachment of tablet from mucosal surface can be noted [41].

Previous Work Done on Buccal Mucoadhesive Drug Delivery System

In 2007, Ramana et al. designed and evaluated the buccal mucoadhesive drug delivery systems of Metoprolol Tartrate using the mucoadhesive polymers i.e., Carbopol-934, hydroxy methyl propyl cellulose, hydroxyl ethyl cellulose and sodium carboxy methyl cellulose. The best mucoadhesive performance and *in-vitro* drug release profile were exhibited by tablets containing hydroxyethyl cellulose and Carbopol-934 in 1:2 [42]

In 2008, Kolli et al. developed the buccal mucoadhesive patch of Prochlorperazine using various concentrations of HPMC E15 and Polyester backing membrane. They concluded that the formulation containing 2500 mg of HPMC E15 and 375 µl of Propylene glycol was the optimized formulation after evaluating it *in-vitro* as well as *ex-vivo* studies [43].

In 2010, Chaudhary et al. developed the mucoadhesive buccal patches of Methotrexate. They used the backing membrane prepared by ethyl cellulose (5%) in mixture of acetone and isopropyl alcohol (60:40). Glycerol (5%) was added as plasticizer. The mucoadhesive polymers used were Sodium Alginate, carbopol-934, sodium carboxy methyl cellulose and polyvinyl pyrrolidine. The cumulative drug release of the formulation containing sodium alginate with a secondary polymer was found in order of Sodium alginate >carbopol-934 >Sodium Carboxy methyl cellulose >polyvinyl pyrroliidine at the end of 8 hours. The formulation containing Sodium Alginate (800 mg), Carbopol-934 (200 mg), glycerol (10%) and water (30 ml) waste optimized formulation [44].

In 2010, another study was also conducted by Velmurugan et al. They formulated the buccal tablets of Piroxicam using HPMC K4M and Carbopol-934 in different ratios. In this study H3 formulation comprising of piroxicam and HPMC K4M (1:3) show edoptimum drug release and satisfactory bioadhesive properties [45].

In 2011, Naga Raju et al. formulated the buccal tablets of Metoprolol Tartrate using different Mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination. The prepared tablets were evaluated for bioadhesive strength and *in-vitro* drug release. *In-vitro* bioadhesive strength and *in-vitro* release studies showed that formulation containing 1:1.25 ratio of drug and polymer (Carbopol-934 and HPMC K4M) combination showed optimum bioadhesive and exhibited optimum drug release (77.33 ± 0.23) [46].

In 2011, the further study was conducted by Deshmukh et al. They formulated Propranolol hydrochloride buccal mucoadhesive gel using Natural Mucoadhesive agent obtained from the Fruits of Ficuscarica L. The formulation F1, F3, F4 and F5 showed Fickian diffusion, formulation F2 showed Anomalous (non-Fickian) diffusion [47].

In 2012, Mishra et al. formulated the buccal patches of Simvastatin. The buccal patchs were prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC. The formulation containing eudragit-RS100 and PVP(1:1) showed the maximum and faster release [48].

In 2013, Sandhya et al. formulated buccal films of Ketorolac Tromethamine. These films were prepared by polymers like HPMC K 100M, HPMC E15, HPMC E50, Eudragit RLPO and developed by solvent casting method. Formulation F5 (HPMC E15-Polysorbate - Eudragit RLPO) exhibited best mucoadhesive performance and matrix controlled release. Swelling behaviour and duration of mucoadhesion are critical factors in the selection of satisfactory formulation [49].

In 2013, the further study was conducted on Formulation and *in-vitro* evaluation of Losartan Potassium mucoadhesive buccal tablets by Velmurugan et al. They used mucoadhesive polymers such as Carbopol -940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in alone and in combination as release retarding agent to prolong the drug release and to avoid first pass metabolism. *Ex-vivo* mucoadhesive strength, *ex vivo* residence time and *in-vitro* release studies showed that formulation F10 (sodium alginate and HPMC K100M) containing 1:1.25 ratio of drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release (91.33 % after 12 hrs) [50].

In 2014, Ganaie et al. formulated the mucoadhesive buccal film of Methyldopa using Hydroxy propyl methyl cellulose K-47 (HPMC

K-47), poly vinyl pyrrolidine K-30 (PVP K-30), sodium CMC and ethyl cellulose. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation F5 (HPMC K-47 and PVP K-30). The correlation coefficient value (r) indicates the kinetic of drug release was zero order [51].

In 2015, Madhuri et al. designed the solid dosage form for buccal drug delivery of Diltiazem Hydrochloride using various polymers i.e., Carbopol971P (CP) and secondary polymers such as Hydroxy propyl methyl cellulose (HPMCK4M) and Psyllium husk in Six formulations. They concluded that the formulation B3 containing Carbopol971P and HPMC K4M in the ratio of 1:5 showed good mucoadhesive strength (51.34 gm) and maximum drug release of 94.72% in 8 hrs. Swelling of tablets increased with increase in concentration of HPMC K4M [52].

In 2016, Nagarani et al. formulated the Esomeprazole mucoadhesive buccal tablets using mucoadhesive polymers like hydroxy propyl methyl cellulose K 100 M, Carbopol 934, HPMC K 15 M. Drug: polymer ratio for F5 is 1:1, this F5 (guar gum and carbopol -971P) formulation was considered as an optimized formulation among all these formulations because it released maximum amount of drug in desired period of 6 hrs and showed good swelling index properties [53].

In 2016, the further study was conducted by Marimutho et al. On formulation and evaluation of Zidovudine mucoadhesive buccal patches using polymers i.e., HPMC E15, Sodium Alginate and gelatine. They concluded that the release of Zidovudine from the formulated patches followed zero order kinetics so that the drug release mechanism was controlled release [54].

Future Perspectives

A buccal adhesive system offers countless advantages in terms of economy, accessibility, administration, withdrawal and patient compliance. Research scientists are now looking out the traditional polymers for novel drug transport systems. From the recent years, pharmaceutical experts are finding various methods to develop buccal adhesive dosage forms and to improve the bioavailability of less orally bioavailable drugs. It is found that the second generation muco adhesive polymer having great potential. Micro particulate or nanoparticulate systems of less bioavailable drugs are being designing in the bio adhesive systems are showing much more satisfactory results as compared to conventional buccal drug delivery systems in Table 3.

Commercially Available Oral Mucoadhesive Drug Delivery Systems				
Drug	**Dosage form**	**Type of release**	**Product name**	**Manufacturer**
Chlorhexidine digluconate	Oromucosal gel	Controlled	Corsodyl gel	GalaxoSmithKline
Hydrocortisone sodium succinate	Oromucosal pallets	Controlled	Corlan pellets	Celltech
Buprenorphine HCl and Naloxone	Tablet	Quick	Sulbutex	Reckitt Benckiser
Proclorperazine	Tablet	Controlled	Buccastem	Reckitt Benckiser
Testosterone	Tablet	Controlled	Straint SR	Columbia Pharmaceuticals
Zolpidem	Spray	Quick	Zolpimist	NovaDel

Table 3: Some commercially available oral mucoadhesive drug delivery system.

Conclusion

Today, drug delivery systems designed with the aim to improve patient compliance and convenience is more important than ever. Therefore huge work is going on to develop novel dosage forms to satisfy increased patient demands of more convenient dosage forms. Oral mucosal delivery offers a convenient way of dosing medication, not only to special populations with swallowing difficulties, but also to the general population. Mucoadhesive dosage forms provide prolonged contact time at the site of attachment, having high patient compliance and are economic as compare to other dosage forms. The use of mucoadhesive polymers has made this delivery system of controlled release application. There are significant advancements have been achieved in the field of mucoadhesives, but there are still many challenges are not been sought out in this field. However, a lot of research has been done of this drug delivery system. But, these novel mucoadhesive formulations require much more research work to understand how to deliver drug clinically for the treatment of both systemic and topical diseases.

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