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Mucoadhesive Buccal Drug Delivery System: A Review

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ABSTRACT

Current innovation in pharmaceuticals determine the merits of mucoadhesive drug delivery system is particularly relevant than oral control release, for getting local systematic drugs distribution in GIT for a prolong period of time at a predetermined rate. The demerits relative with the oral drug delivery system is the extensive presystemic metabolism, degrade in acidic medium as a result insufficient absorption of the drugs. However parental drug delivery system may beat the downside related with oral drug delivery system but parental drug delivery system has significant expense, least patient compliance and supervision is required. By the buccal drug delivery system the medication are directly pass via into systemic circulation, easy administration without pain, brief enzymatic activity, less hepatic metabolism and excessive bioavailability. This review article is an outline of buccal dosage form, mechanism of mucoadhesion, in-vitro and in-vivo mucoadhesion testing technique.

Keywords: Buccal drug delivery system, Mucoadhesive drug delivery system, Mucoadhesion, mucoadhesive polymers, Permeation enhancers, Bioadhesive polymers.

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INTRODUCTION

Amongst the numerous routes of drug delivery system, oral drug delivery system is possibly the maximum preferred to the patient. However, it has following demerits together with hepatic first pass metabolism and enzymatic degradation within the gastro intestinal tract, that restrict oral administration of certain classes of drugs mainly peptides and proteins. Consequently, different absorptive mucosa is taken into consideration as potential sites for drug administration [1]. Transmucosal routes of drug delivery system like the mucosal linings of the rectal, vaginal, ocular, nasal, and oral cavity offer distinct merits over peroral administration for systemic drug delivery system. These merits consist of possible bypass of first pass effect, avoidance of pre systemic elimination in the gastrointestinal tract, and, contingent upon the specific medication, a superior enzymatic flora for drug absorption [2]. The different transmucosal routes, buccal mucosa has first-rate accessibility, an expanse of smooth muscle and generally stationary mucosa, hence appropriate for administration of retentive dosage forms. Buccal adhesive drug delivery structures as promising alternative for persisted research [3]. The buccal mucosa lines the inner cheek and buccal dosage form are put in the mouth between the upper gums and cheek to treat systemic and local conditions. The buccal route gives one of the potential routes for generally large, unstable proteins and hydrophilic, oligonucleotides and polysaccharides, as properly as conventional small drug molecules. The oral cavity has been utilized as a site for systemic and local drug delivery [4].

Drug delivery through the membranes of the oral cavity may be sub classified as follows [5]:

- Sublingual drug delivery system delivered the drug through mucosal membrane lining the floor of mouth into blood circulation.
- Buccal drug delivery system delivered the drug through mucosal membrane into blood circulation by putting a drug in between cheeks and gums.
- Local drug delivery system delivered the drug into the oral cavity.

Mechanism of Bioadhesion:

Bioadhesion is an interfacial phenomenon in which, two materials, at least one among which is biological, are held collectively via interfacial forces. The attachment can be between an artificial material and biological substrate, like the adhesion between polymer-copolymer and a biological membrane. Whereas mucoadhesion is a process in which polymer is attached to the mucin layer of mucosal tissue.

The mechanism of mucoadhesion is broadly classified in two stages:

Contact stage:

An intimate contact (wetting) takes place among the mucoadhesive and mucus membrane both from a decent wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.

Consolidation stage:

Various physicochemical interactions such as hydrogen bonding, hydrophobic interactions and dispersion forces, takes place to consolidate and give a boost to the adhesive joint, leading to prolonged adhesion [6].

Structure and Design of Buccal Dosage Form:

Buccal Dosage form may be of [7]:

a. Matrix type: The design of buccal patch is a matrix configuration incorporates drug, adhesive, and components mixed together.

b. Reservoir type: In a reservoir system the design of buccal patch include a cavity for a drug and components separate from the adhesive. To prevent the loss of drug, to reduce deformation of patch and disintegration while in the mouth; and to control the direction of drug delivery an impermeable backing is applied.

IDEAL CHARACTERISTICS OF BUCCAL ADHASIVE DRUG DELIVERY SYSTEM [8]:

- Should facilitate the rate of drug absorption
- Should not cause any inconvenience or irritation to the patient
- Should stick to the site of attachment for a few hours
- Should discharge the medication in a controlled manner and
- Should allow the release of medication in an unidirectional way toward the mucosa

Classification of Buccal Bioadhesive Dosage Forms: [9, 10]

Buccal Bioadhesive Tablets:

Buccal bioadhesive tablets are dry dosage forms that are to be moistened after placing in touch with buccal mucosa. Double and multilayered tablets are already prepared using bioadhesive polymers and additives. These tablets are solid dosage forms that are formulated through the direct compression of powder and can be set into contact with the oral mucosa and permitted to dissolve or adhere depending on the sort of additives integrated into the dosage form. This dosage form can deliver drug multi-directionally to the mucosal surface or into the oral cavity.

Buccal Bioadhesive Semisolid Dosage Forms:

This dosage forms contain natural or synthetic polymers in powdered form which is dispersed in a polyethylene or in aqueous solution.

For example: Arabase.

Buccal Bioadhesive Patches and Films:

This films or patches include multilayered thin film or two poly laminates that are oval or round in shape, containing of basically of bioadhesive polymeric layer and impermeable backing layer to allow unidirectional flow of drug across buccal mucosa. These films are prepared by incorporating the medicament in alcohol solution of bioadhesive polymers.

Buccal Bioadhesive Powder Dosage Forms:

This dosage forms are a mixture of the drug and bioadhesive polymers and are sprayed onto the buccal mucosa the reduction in diastolic blood pressure after the administration of buccal film and buccal tablet of Nifedipine.

Advantages of buccal drug delivery system [11]:

- Drug is effortlessly administered and extinction of therapy in emergency may be facilitated.
- Drug release for prolonged duration of time.
- In unconscious and trauma patient's drug can be administered.
- Drug has high bioavailability because it bypass first pass metabolism.
- Some drugs are unstable in acidic environment of stomach can be administered by buccal delivery.
- Drug absorption occurs by passive diffusion.
- Due to close contact with the absorbing membrane surface, rate of absorption is high.
- Fast onset of action.

Limitations of buccoadhesive drug delivery [12]:

- Drugs which are unstable at buccal pH cannot be administered.
- Drug having unpleasant and bitter taste or an nauseating odor or causes irritation cannot be given by this route
- Drug having small quantity or dose can only be given by this route.
- Drugs which are required to be absorbed by passive diffusion only can be given by this route.
- Drinking and eating may be avoided.

Factors affecting mucoadhesion [13]:

- Polymer related factors: Several properties or characteristics of the active polymer play a vital role in mucoadhesion. Among them, concentration, swelling, polymer molecular weight, particular conformation and polymer chains flexibility that may affect the mucoadhesion.
- Environment associated factors: pH of the polymer-substrate interface, functional strength and first contact time is able to influence the mucoadhesion.

- Physiological factors: Disease state and mucin turn over are the important physiological factors, which can also affect mucoadhesion.

Basic components of buccal drug delivery system are:

a. DRUG SUBSTANCE:

Before formulating mucoadhesive drug delivery systems, one has to decide whether the intended, action is for local/systemic effect and for rapid or prolonged release. Pharmacokinetic properties play an important role for the selection of suitable drug for the design of buccoadhesive drug delivery systems.

The drug should have following characteristics [14].

- The conventional single dose of the drug should be very less.
- The drugs having biological half-life between 2-8 hrs are suitable candidates for controlled drug delivery.
- Tmax of the drug shows many changes or higher values when administered orally.
- Through oral route drug may exhibit first pass effect or presystemic drug elimination.
- When administered orally the drug absorption should be passive.

b. BIOADHESIVE POLYMER:

The first step in the formulation of buccoadhesive dosage forms is the characterization and selection of suitable bioadhesive polymers in the formulation. Bioadhesive polymers play a important role in buccoadhesive drug delivery systems. Polymers are also used in matrix devices in which the drug is enclosed in the polymer matrix, which control the period of release of drugs [15]. Bioadhesive polymers are from the most diverse class and they have considerable used upon patient health care and treatment. The drug is released into the mucous membrane by means of core layer or rate controlling layer. Bioadhesive polymers which adhere to the epithelial or mucin surface are effective and lead to significant improvement in the oral drug delivery system [16].

c. BACKING MEMBRANE:

Backing membrane plays an important role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert to the penetration enhancer and drug. This impermeable membrane on buccal bioadhesive patches prevent the loss of drug and provide good patient compliance. The various materials used in backing membrane are magnesium stearate, HPC, polycarbophil, HPMC, CMC, carbopol etc [17].

d. PERMEATION ENHANCERS:

Agents that allow the permeation via buccal mucosa are referred as permeation enhancers. Choice of permeation enhancer and its efficacy depends on the physicochemical properties of the drug,

nature of the vehicle, site of administration and other additives [18].

EVALUATION OF BUCCAL DRUG DELIVERY SYSTEMS:

Drug-excipients interaction studies

During the formulation and development of solid dosage form Drug-excipients interaction studies play a major role. To assess possible drug excipient interaction studies Differential scanning calorimeter (DSC), X Ray Diffraction (XRD), Fourier Transform Infra-Red Spectrum (FTIR) and thin layer chromatography can be used. Differential scanning calorimeter used as fast evaluation of possible incompatibilities, because it shows shift of melting endotherms and exotherms, changes in appearance, and variation in the corresponding enthalpies of the reaction [19].

Physical evaluation

It includes Content uniformity, Weight uniformity, and Thickness uniformity. Weight variation evaluation was performed by comparing the average weighed of ten randomly selected patches from each batch with individual patch. Thickness of the film should be evaluated at five locations (center and four corners), and the mean thickness is calculated. Sample with nicks or tears, having air bubbles and having mean thickness variation of greater than 5% are removed from analysis. Three patches having diameters 20 mm of each formulation were taken separately in 100 ml volumetric flasks, 100 ml phosphate buffer solution having pH 6.8 were added and stirred continuously for 24 hours. The solutions were filtered, diluted suitably and analyse by using UV spectrophotometer. The average of three patches was taken as final reading [20].

Surface pH

The surface pH of the buccal patch was determined in order to investigate the possibility of any side effects in in-vivo. As a basic or acidic pH may cause irritation to the buccal mucosa, so it is necessary to keep the surface pH as close to neutral as possible [21]. A combined glass electrode was used for this purpose. The buccal patches were kept in contact with 1 ml of distilled water (pH 6.5 ± 0.05) and allowed to swell for two hours at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute [22].

Swelling studies

Swelling increases the weight of patch:

A drug-loaded patch of $1 \times 1 \text{ cm}^2$ was kept and weighed on a pre weighed cover slip, and then 50 ml of phosphate buffer (pH 6.6) was added. The cover slip was removed after every five minutes and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch [23].

Swelling increases patch area:

A drug-loaded patch size of 1x1cm² was cut and kept on a petridish. Beneath the petridish a graph paper was placed to measure the increase area of the patch. 50 ml of phosphate buffer (pH 6.6) was poured into the petridish. An increase in length and breadth of the patch was noted every five minute intervals upto 60 minutes and area was calculated. The percentage swelling (% S) was calculated using the following equation [24].

$$\% = \frac{X_t - X_o}{X_o} \times 100$$

Where,

X_t is the weight or area of the swollen patch after time t.

X_o is the original patch weight or area at zero time.

Palatability test

On the basis of taste after bitterness and its physical appearance palatability test is conducted.

All the batches are named A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade would be the very good formulation [25].

Grades:

A = very good,

B = good,

C = poor.

Ex vivo mucoadhesive strength

For determining ex vivo mucoadhesive strength a modified balance method is used. Fresh buccal mucosa of rabbit or sheep obtained and used within 2 hours of slaughter. The mucosal membrane separated by separating underlying fat and loose tissues. The mucosal membrane were washed with distilled water and then with phosphate buffer (pH 6.8) at 37^o C. The buccal mucosa cut into small pieces and again washed with phosphate buffer (pH 6.8). A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two side of the modified balance was made equal before the study, by putting a 5 g weight on the right-hand side of pan. A weight of 5 g was removed from the right-hand side of pan, which lowered the pan along with the tablet over the mucosa. The balance was kept for 5 minutes contact time in this position. Equivalent to weight, the water was added at a slow rate with an infusion set of 100 drops per minute to the right-hand side of pan until the tablet detached from the mucosal surface. This detachment force gave the knowledge

of mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8) at $37\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$ due to which it only touch the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive [26].

Ex- vivo mucoadhesive time

The ex vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa of sheep or rabbit. The fresh buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer (pH 6.8) and pasted to the sheep buccal mucosa by applying a light force with a finger tip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer having pH 6.8, and kept at $37\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$. A 50 rpm stirring rate was applied after two minute to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time taken for the tablet to detach from the buccal mucosa was noted as the mucoadhesion time [27].

In vitro drug release

United States Pharmacopoeia (USP) XXIII rotating paddle method used to study the drug release rate from the bilayered and multilayered tablets. The dissolution medium consist of phosphate buffer pH 6.8. The study was performed at $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$, with a rotation speed of 50 rpm. The backing layer membrane of buccal tablet attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. At a predetermined interval of time 5 ml sample were withdrawn and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm [28].

In vitro drug permeation

Using Keshary-Chien or Franz type glass diffusion cell, the in vitro buccal drug permeation study of Drugs through the buccal mucosa of sheep or rabbit is performed at $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$. It includes the donor and receptor compartments in which a fresh buccal mucosa was tied. The core side of the buccal tablet was facing the mucosa and the compartments clamped together. One ml phosphate buffer (pH 6.8) is placed in donor compartment and phosphate buffer (pH 7.4) is placed receptor compartment. The hydrodynamics condition was maintained in receptor compartment by stirring with a magnetic bead at 50 rpm. At a predetermined interval of time one ml sample can be withdrawn and test for drug content at suitable nm using a UV spectrophotometer [29].

Stability study in Human saliva

According to ICH guidelines stability study of fast dissolving films is carried out for all the batches.

After predetermined interval of time, the films were evaluated for the disintegration time, drug content and physical appearance. The stability study of optimized mucoadhesive patch formulation was performed at 40 °C, 37 ± 5 °C & 75 ± 5 % RH upto three months. The value of all parameter after three months remain same as their values and minor changes occur in value of volume entrapment efficiency, % elongation & % drug release after eight hours which was considerable [30].

Measurement of mechanical properties

Mechanical properties of the patches were tested by using a microprocessor based advanced force gauge equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25kg load cell. Film strip with the dimensions 60 x 10 mm and without any visual defects were cut and positioned between two clamps separated by a distance of 3 cm. Clamps were designed to secure the patch without crushing it during the evaluation, the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke whereas the lower clamp was held non-moving. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and elongation at break values was calculated using the formula [31].

Tensile strength (kg. mm⁻²) =

$$\frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

Elongation at break (%. mm⁻²) =

$$\frac{\text{Increase in length (mm)}}{\text{Original length Cross sectional area (mm}^2\text{)}} \times 100$$

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance. This test is done on five patches [32].

Viscosity

Aqueous solutions containing both plasticizer and polymer prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number four is used. The viscosity was measured at 20 rpm at room temperature. The recorded values the mean of three determinations [33].

Ageing

Bioadhesive patches were packed in petri dish lined with aluminum foil and placed in an incubator maintained at 37 ± 0.5 °C and 75 ± 5 % RH for six months. Changes in the release behavior,

residence time, appearance, and drug content of the stored patches tested after 1, 2, 3, 4, 5 and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, investigated using scanning electron microscope [34].

CONCLUSION:

This review about mucoadhesive buccal drug delivery system is probably a useful article for the proficient design of newer or novel mucoadhesive dosage form. Mucoadhesive dosage form has applications from various edges, including advancement of novel mucoadhesives, layout of the device, permeation enhancement and mechanisms of mucoadhesion. With the introduction of an enormous number of latest drug molecules because of medication revelation, mucoadhesive drug delivery will play a much progressively significant function in delivering these molecules.

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