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MUCOADHESIVE BUCCAL FILM- REVIEW

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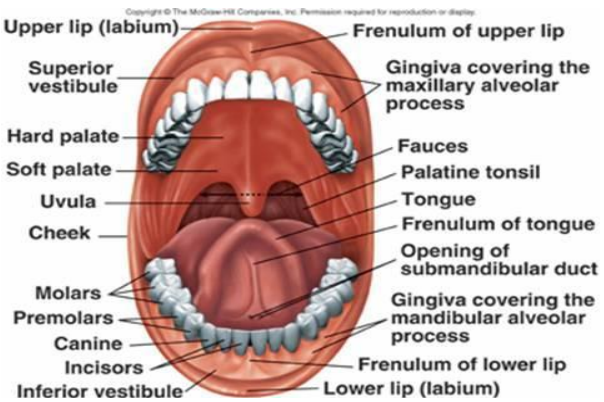
ABSTRACT

Buccal drug delivery leads direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Buccal route is an attractive route of administration for systemic drug delivery. Buccal bioadhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases. This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design. Drugs that are administered via the buccal mucosa directly enter the systemic circulation, thereby avoiding hepatic first pass metabolism therefore, this administration route is useful for improving the bioavailability of drugs that are subjected to an extensive first pass effect when delivered orally for oral mucosal route of administration, various types of dosage forms can be prepared. A sublingual tablet can afford rapid drug absorption and a prompt pharmacological effect, however, the duration of delivery is short owing the administered dose due to swallowing. To avoid such loses, a patch can be formulated that is located on the buccal mucosa of the oral cavity. The amount of drug reaching the systemic circulation is limited by the area of the mucosa that the patch covers, which for patient comfort reasons, is relatively small.

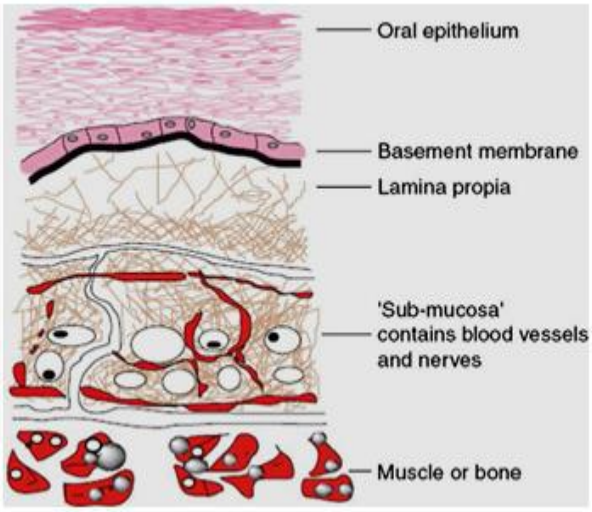
KEYWORDS: Mucoadhesive, Buccal drug delivery, films.

INTRODUCTION[1-2]

Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery. Buccal drug delivery is most advantageous because it abundant blood supply in buccal mucosa, bypassing the hepatic firstpass effect and accessibility. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Oral cavity has been investigated for number of applications including the treatment of periodontal disease bacterial and fungal infection, aphthous and dental stomatitis. Over the last two decades mucoadhesion has become of interest for its systemic delivery by retaining a formulation intimate contact with buccal cavity. The term bio adhesion has been used to define the attachment of a synthetic natural macromolecule to a biological tissue for an extended period of time. When a substrate is a mucosal system adheres and interacts primarily with the mucus layer, this phenomenon being referred to as mucoadhesion. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane. The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability.



Structure of oral cavity



Schematic diagram of buccal muccosa

ADVANTAGES[3-4]

- Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism.
- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients.
- Sustained drug delivery.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Increased ease of drug administration.
- Patient friendly, painless.
- Has the ease of self medication.
- Allows for a flexible and control dosing schedule in comparision to most other drug delivery system.
- Bypass of 1st pass effect.

DISADVANTAGES[5-6]

- Gastrointestinal enzymatic degradation.
- Delay between the time of administration and absorption.
- Rapid onset requirements.
- Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including buccal membrane.
- The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa.
- Continuous secretion of the saliva(0.5-2 l/day)leads to subsequent dilution of the drug.
- The hazard of choking by involuntarily swallowing the delivery system is a concern.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

MECHANISM OF ACTION

Mechanism of buccal absorption[6-7]

Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed.The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows

$$- dm/dt = Kc/ViVt$$

Where,
M - Mass of drug in mouth at time
K - Proportionality constant
C - Concentration of drug in mouth at time
Vi - The volume of solution put into mouth cavity and
Vt -Salivary secretion rate

EVALUATION TESTS[8,9]

*Evaluation Surface pH

The surface pH of the buccal patch was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and pH was note down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute.

* Swelling studies

Weight and area increase due to swelling were measured. Weight increase due to swelling: A drug-loaded patch of 1x1 cm2 was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every five minutes, the cover slip was removed and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch. Area increase due to swelling: A drug loaded patch size of 1x1 cm2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. 50ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at 5 min intervals for 60 min and area was calculated. The percent swelling, %S, was calculated using the following equation: Xt - Xo %S = x 100 Xo

Where Xt is the weight or area of the swollen patch after time t Xo is the original patch weight or area at zero time

***Thickness measurements**

The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.

*** Thermal analysis study**

Thermal analysis study is performed using differential scanning calorimeter (DSC).

*** Morphological characters**

Morphological characters are studied by using scanning electron microscope (SEM).

*** Palatability test**

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated 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 score two a geade then it would be considered as good and the one with all three A grade it would be the very good formulation.[30] Grades: A = very good, B = good, C = poor

***Folding endurance**

The test is performed by repeated folding of the film at the same place until film failure. A maximum of 300 times is sometimes reported as a limit to the test, and the value is reported as the number of times the film can be folded prior to rupture.

***In vitro drug release.[10-14]**

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug Release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release was performed at 37 0C ± 0.50 0C,with a rotation speed of 50 rpm. The backing layer of buccal patches attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm

In vitro drug permeation[15]

The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A one ml sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UVspectrophotometer.

Stability study in Human saliva[16]

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance. The stability study of optimized mucoadhesive patch formulation was performed at 400C, 37 ±50C & 75±5% RH for 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 8 hour which is considerable.

***Ex vivo mucoadhesive strength[17]**

A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 37^0C. The buccal mucosa cut into pieces and 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 sides of the balance made equal before the study, by keeping a 5 g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the righthand pan until the tablet detached from the mucosal surface. This detachment force gave the 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°C ±1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive.

CONCLUSION

Buccal region provides a convenient route of administration for both local and systemic drug actions. Controlled buccal drug delivery systems, where the drug delivery is directed towards buccal mucosa by protecting the local environment is also gaining interest. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many

issues are yet to be resolved before the safe and effective delivery through buccal mucosa. In mucoadhesive placebo buccal patches we can use any potent drugs which fulfill the criteria for buccal patch as drug delivery system.

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