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Review Article

NOVEL APROACHES - MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT

Among novel drug delivery systems, Buccal mucoadhesive systems have attracted great attention in recent years due to their ability to adhere and remain on the oral mucosa and to release their drug content gradually. Mucoadhesion may be defined as the process where polymers attach to biological substrate or a synthetic or natural macromolecule, to mucus or an epithelial surface. Buccal mucoadhesive films can improve the therapeutic effect of drug by increasing the absorption of drug through oral mucosa which increases the drug bioavailability by reducing the hepatic first pass effect. Natural polymers have recently gained importance in pharmaceutical field. Mucoadhesive polymers are used to improve drug delivery by increasing the dosage form's contact time and residence time with the mucous membranes. This review article deals with the novel approaches use in the buccal drug delivery systems.

Keywords: Buccal delivery, permeation enhancers, Mucoadhesive, chitosan, Bioadhesive strength.

INTRODUCTION

Buccal drug delivery is one of the novel drug delivery systems. It localized the delivery of drug to tissues of the oral cavity for the treatment of bacterial and fungal infection as well as periodontal disease [1]. Buccal drug delivery also a safer mode of drug delivery system and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism [2]. The administration of drug through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism [3]. It is possible bypass of first pass effect and avoidance of pre-systemic elimination within the gastrointestinal tract. Buccal route is preferred the drugs having poor bioavailability because of high first pass metabolism [4]. Mucoadhesion is the phenomenon between two materials which are held together for prolong period of time by interfacial force. It is generally referred as mucoadhesion when interaction occurs between polymer and epithelial surface [5, 6]. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets [7]. Some of the potential sites for attachment of any mucoadhesive system include buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route and gastrointestinal area. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively [8].

Oral mucosa [9, 10]:

The total area of the oral cavity is 100cm^2. One third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The main role of oral mucosa is protection of tissue underlying. Lipid based permeability barriers in epithelium layer protect the tissues from fluid loss and also

from the attack of harmful environmental agents like microbial toxins, antigens, carcinogens, enzymes etc. Oral epithelium proliferation time is 5-6 days. Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions. Outer oral vestibule which is bounded by cheeks, lips, teeth and gingival (gums). Oral cavity proper which extends from teeth and gums back to the faucets (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

FUNCTIONS OF ORAL CAVITY [11]

- It helps in chewing, mastication and mixing of food stuff.
- It is Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water.
- To aid in speech and breathing process.

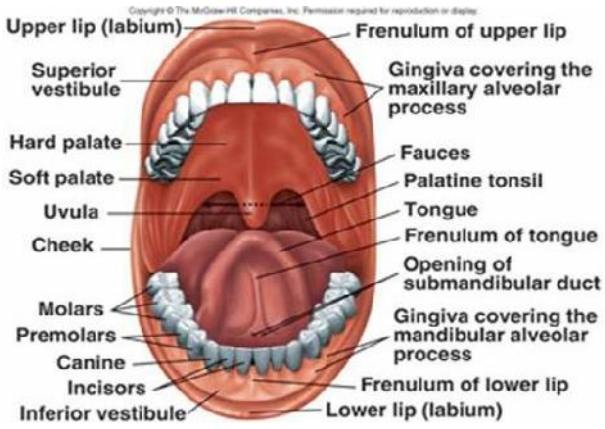

Figure 1: Structure of oral cavity

Methods to increase drug delivery via buccal route:

1. Permeation enhancers[12] **:**

The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

Mechanism [13]**:** Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

- Changing mucus rheology: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.
- Increasing the fluidity of lipid bilayer membrane: The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
- Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.
- By overcoming the enzymatic barrier: These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.
- Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption. Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. List of some permeation enhancer are listed in Table no 1 [14].

Table 1: Permeation Enhancers for Buccal Delivery

S. No	Permeation Enhancers	S. No	Permeation Enhancers
1	2,3-Lauryl ether	**12**	Phosphatidylcholine
2	Aprotinin	**13**	Polyoxyethylene
3	Azone	**14**	Polysorbate 80
4	Benzalkonium chloride	**15**	Polyoxyethylene
5	Cetylpyridinium chloride	**16**	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	**17**	Sodium EDTA
7	Cyclodextrin	**18**	Sodium glycocholate
8	Dextran sulfate	**19**	Sodium glycodeoxycholate
9	Glycol	**20**	Sodium lauryl sulfate
10	Lauric acid	**21**	Sodium salicylate
11	Lauric acid/Propylene	**22**	Sodium taurocholate

2. Prodrug [15]:

Nalbuphine and naloxone bitter drugs when administered to dogs via buccal mucosa causes excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds.

3. pH:

The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

NOVEL BUCCAL DOSAGE FORMS

The novel type buccal dosage forms include buccal adhesive patches, tablets, films, semisolids (ointments and gels) and powders [16].

1. Patches and Films:-

Patches consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape [17]. A novel mucosal adhesive film called "Zilactin" - consisting of an alcoholic solution of hydroxyl propyl cellulose and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids. E.g. buccal film of salbutamol.

2. Buccal mucoadhesive tablets:-

Mucoadhesive tablets are dry dosage forms and it is to be moistened prior to placing in contact with buccal mucosa [18]. It is double layer tablet, consisting of adhesive matrix layer of polyacrylic acid and hydroxy propyl, cellulose with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

3. Semisolid Preparations (Ointments and Gels):-

One of the original oral mucoadhesive delivery systems – "orabase"– consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes. Example: chitosan glutamate buccal hydrogel with local anaesthetics activity [19].

4. Powders:-

Beclomethasone and Hydroxpropyl cellulose in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours [20].

5. Buccal sprays:-

Generex bio technologies have been introduced insulin spray [21]. This technology is being used to develop a formulation for buccal delivery of insulin for the treatment of type -1 diabetes Buccal spray delivers a mist of fine droplets onto mucosal membrane probably on to mucin layer. e.g. Estradiol sprays [22].

Methods of preparation [23]

1. Solvent casting [24]

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

Flow chart of Solvent casting Method [25]

Water soluble ingredient is dissolve in water (H_2O) and API and other agent are dissolving in suitable solvent so as to form a clear solution.

↓

Followed by both the solution are mixed

↓

Resulting solution in cast as a film is and allowed to dry

↓

Film is coated

2. Direct milling

Drug and excipients are mixed by kneading, usually without the presence of any liquids. After the mixing process, material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described [26]. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues [27].

Flow chart of Solvent casting Method

API and excipient are blended by direct milling

↓

Blended mixture is rolled with the help of roler

↓

Followed material is laminated

↓

Finally film is collected

Hot melt extrusion of films: In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films.

Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films. However, only hand full articles have reported the use of hot melt extrusion for manufacturing mucoadhesive buccal films.

Table 2 : Drugs administered by Buccal route

S. No	Drug	Dose of drug as per IP
1	Morphine sulphate	
2	Pantoprazole	40mg
3	Nicotin	Prophylactic 15-30mg, therapeutic 50-250mg
4	Nifedipine	5-20mg
5	Omeprazole	20-40mg
6	Oxytocin	Enhancement of labour Intravenous infusion of a 5% dextrose solution count 1unit.
7	Piroxicam	10-20mg
8	Acitretin	25-30mg
9	Aciclovir	200-800mg 4-5time daily, By Intravenous infusion 5-10mg per kg of body weight
10	Buprenorpine Hydrochloride	Slow I.V equivalent 300-600µg, Sublingually equivalent upto 400µg
11	Carbamazepine	200mg
12	Chlorpheniramine maleate	4-6mg
13	Metronidazole	200mg
14	Ergotamine tartrate	1-2mg by subcutaneous or I.V injection 250µg-500µg.

EVALUATION OF BUCCAL DRUG DELIVERY SYSTEMS

1. **Surface pH** [29]**:-** Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.
2. **Thickness measurements** [30]**:-** The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.
3. **Swelling study** [31]**:-** Weighed the buccal patches individually (W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper. The swollen patches are then reweighed (W2) and the swelling index (SI) were calculated using the following formula.

$$\left[SI = \frac{(z2 - W1)}{W1} \times 100\right]$$

4. **Folding endurance** [32]:- Folding endurance can be done by folding the patches upto200 times with our breaking.
5. **Thermal analysis study:-** Thermal analysis study is performed using differential scanning calorimeter (DSC).
6. **Morphological characterization** [33]:- Morphological characters are studied by using scanning electron microscope (SEM).
7. **Water absorption capacity test [34]:-** Circular Patches, with a surface area of 2.3 cm^2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na_2HPO4, 0.19 g KH_2PO_4, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccators over anhydrous calcium chloride [35] at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation [36].

$$\left[water\ uptake\ (\%) = \frac{(Ww - Wf)}{Wf} \times 100\right]$$

Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured.

8. **Ex-vivo bioadhesion test** [37]:- A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive [38]. Two pans of the balance are balanced with a 5g weight. The 5g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa [39]. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface.
9. **In vitro drug release:-** The dissolution medium consisted of phosphate buffer pH 6.8 maintaining a temperature at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material [40]. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution in a UV spectrophotometer [41]. The in-vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using KesharyChien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with suitable buffer.
10. **Permeation study of buccal patch** [42]:- The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content.
11. **Ex-vivo mucoadhesion time** [43]:- The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit) [44]. The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours [45]. The time for changes in color, shape, collapsing of the patch and drug content is noted.
12. **Measurement of mechanical properties:-** Mechanical properties of the films (patches) include tensile strength

and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break. Force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula.

$$\left[T = \frac{m \times g}{b \times t} Kg/mm^2\right]$$

Where, M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec^2, B - is the breadth of the specimen in cm, T - is the thickness of specimen in cm. Tensile strength (kg/mm2) is the force at break (kg) per initial cross- sectional area of the specimen (mm^2).

13. **Stability study in human saliva:-** The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate petridishes containing 5ml of human saliva and placed in a temperature controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the dose formulations with better bioavailability are needed.
14. **Animal Models for Permeability Measurement:-** The most commonly used animal models are dogs, rabbits, and pigs. A general criterion for selecting an in vivo animal model is the resemblance of the animal mucosa to the oral mucosa of human beings in both ultra structure and enzyme activity, which represent the physical and metabolic barriers of the oral mucosa.

CONCLUSION:-

Mucoadhesive buccal patches have gained importance in drug delivery. The use of Natural polymers is increasing in the formulation of buccal patches. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract is avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. This review focuses on the preparation of novel drug delivery systems which will provide least adverse effects and maximal therapeutic response.

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