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A Review on study of Buccal Drug Delivery System

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ABSTRACT

Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. Buccal nitroglycerin, can use for acute therapy for an animal attack as well as for chronic prophylaxis Novel liquid aerosol formulation of insulin Development of suitable delivery devices, permeation enhancement, and Buccal delivery of drugs that undergo a first-pass effect, such as cardiovascular drugs, analgesics, and peptides Research yield some successes Promote further research; more companies Rest depend on delivery technology

Key word : Buccal, first-pass effect, suitable delivery devices, permeation enhancement.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, 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.

The nasal cavity as a site for systemic drug delivery has been investigated by many research groups[1-7] and the route has already reached commercial status with several drugs including LHRH [8-9] and

calcitonin[10-12] However, the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms, as well as the large intra- and inter-subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal, and ocular mucosa all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration.. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. Within the oral mucosal cavity, delivery of drugs is classified into three categories: (i) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (ii) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and (iii) local delivery, which is drug delivery into the oral cavity.

1.1) ADVANTAGES OF BUCCAL DRUG DELIVERY[13-17]

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract
2. Improved patient compliance due to the elimination of associated pain with injections;
3. 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.
4. Increased ease of drug administration
5. Though less permeable than the sublingual area, the buccal mucosa is well vascularized**,** and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
6. In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration.

1.2) OVERVIEW OF THE ORAL MUCOSA

A. **Structure**

The oral mucosa is composed of outermost layer of stratified epithelium.Below lies a basement membrane, a lamina prairie followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium[18.] The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium.It has been estimated at 5-6 days[2], and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200 µm.

B. Role of Saliva

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

C. Role of Mucus

- Made up of proteins and carbohydrates.
- Made up of proteins and carbohydrates.
- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery systems

D**. Permeability**

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin[20] In general, the perm abilities of the oral mucosa decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

E. Structure And Design Of Buccal Dosage Form [23]

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together

2. Reserviour type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

F. Permeability Of Drugs Through Buccal Mucosa [24]

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

i.Transcellular (intracellular, passing through the cell)

ii.Paracellular (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the Para cellular route through the intercellular lipids produced by membrane-coating granules.

G. Buccal Drug Delivery And Mucoadhesivity [25]

In the development of these buccal drug delivery systems, mucoadhesion of the device is a key element. The term ‘mucoadhesive’ is commonly used for materials that bind to the mucin layer of a biological membrane These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as

1. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups

2. Suitable surface property for wetting mucus/mucosal tissue surfaces and

H. Factors Affecting Drug Delivery via Buccal Route [26]

The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules.

I. Toxicity And Irritancy Associated With Buccal Drug Delivery[27]

Formulations that produce local damage at the site of application, such as ulceration of the mucosa, would preclude their widespread usage as a result of the associated pain and discomfort. This is articularly important in buccal drug delivery where the formulation is in contact with the mucosa for extended periods. Toxic effects can arise from the drug itself, the bioadhesive or from other components of the formulation

J. Methods to Increase Drug Delivery via Buccal Route

(1) Absorption enhancers [26]

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates.

Sr. no	Permeation Enhancers	Sr. no	Permeation Enhancers
1	2,3-Lauryl ether	9	Phosphatidylcholine
2	Aprotinin	10	Polyoxyethylene
3	Azone	11	Polysorbate 80
4	Benzalkonium chloride	12	Polyoxyethylene
5	Cetylpyridinium chloride	13	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	14	Sodium EDTA
7	Cyclodextrin	15	Sodium glycocholate
8	Dextran sulfate	16	Sodium glycodeoxycholate

Table 1: List of Permeation Enhancers

(2) Prodrugs [26]

Hussein et al delivered opioid agonists and antagonists in bitterness prodrug forms and found that the drug exhibited low bioavailability as prodrug.

Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability

(3) PH [26]

Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. 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).

(4) Patch design [26]

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated.
Also, the drug release pattern was different between single-layered and multi-layered patches.

1.3) CLASSIFICATION OF BUCCAL BIOADHESIVE DOSAGE FORMS

1. Buccal Bioadhesive Tablets.
2. Buccal Bioadhesive semisolids
3. Buccal Bioadhesive patch and films
4. Buccal Bioadhesive Powders

BUCCAL BIOADHESIVE TABLETS

Buccal bioadhesive tablets are dry dosage forms that are to be moistened prior to placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. The two buccal bioadhesive tablets commercially available buccoadhcsive tablets in UK are "Bucastem" and" Suscard buccaP'.

BUCCAL BIOADHESIVC SEMISOLID DOSAGE FORMS

Buccal bioadhesive semisolid dosage forms consists of finally powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution, Example: Arabase.21

BUCCAL BIOADHESIVE PATCHES AND FILMS

Buccal bioadhesive patches consists of two ply laminates or multilayered thin film round or oval as consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films arc formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

BUCCAL BIOADHESIVE POWDER DOSAGE FORMS

Buccal bioadhesive powder dosage forms are a mixture of Bioadhesive polymers and the drug and are sprayed onto the buccal mucosa the reduction in diastolic B.P after the administration of buccal tablet and buccal film of Nifedipine.

1.4) BASIC COMPONENTS OF BUCCAL BIOADHESIVE DRUG DELIVERY SYSTEM

The basic components of buccal bioadhesive drug delivery system are

- Drug substance
- Bioadhesive polymers
- Backing membrane
- Penetration enhancers
- Adhesives

1. DRUG SUBSTANCE

Before formulating buccoadhcsive drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect The drug should have following characteristics[29]

1. The conventional single dose of the drug should be small.
The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.

2. T_{max} of the drug shows wider-fluctuations or higher values when given orally.[30]

3. The drug absorption should be passive when given orally.

2. BIOADHESIVE POLYMERS

The first step in the development of buccoadhcsive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation." Bioadhesive polymers play a major role in buccoadhcsive drug delivery systems of drugs. Polymers arc also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs An ideal polymer for buccoadhcsive drug delivery systems should have following Characteristics.

1. It should be inert and compatible with the environment
2. The polymer and its degradation products should be non-toxic absorbable from the Mucous layer.
3. It should adhere quickly to moist tissue surface and should possess some site Specificity.
4. The polymer must not decompose on storage or during the shelf life of the dosage form.
5. The polymer should be easily available in the market and economical.

Criteria followed in polymer selection

- It should form a strong non covalent bond with the mucin/epithclial surface
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

The polymers that are commonly used as bioadhesive in pharmaceutical applications are:

1. Natural polymers
Ex.: Gelatin, sodium alginate.
2. Synthetic and scmisynthctic polymers
Ex.: PVA, PEG, HPMC, PVP, carbomers etc[31]

1. BACKING MEMBRANE

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer.The commonly used materials in backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc.

4. PENETRATION ENHANCERS

Penetration enhancers arc used in buccoadhcsive formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues.[32]

5. BIOADHESIVES

Bioadhesive are the substances that are capable of interacting with the biological material and being retained on them or holding them together for extended period of time.Bioadhesive can be used to apply to any mucous or no mucous membranes and it also increases intimacy and duration of contact of the drug with the absorbing membrane. The commonly used bioadhesive are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

The bioadhesive should have the following characters,

1. It should not produce any residue on mucosa layer.
2. It should be inert and compatible with biological environment.
3. It should adhere to the mucus membrane aggressively
4. It should preferably form a strong non-covalent bond with mucin/ epithelial ceil Surface.

1.5) LIST OF DRUGS DELIVERED VIA BUCCAL ROUTE [33]

In an effort to determine the feasibility of buccal route as a novel route of drug delivery, several drugs have been studied. The variation in class of compounds illustrates that the pharmaceutical industries have an alternative and novel routes of administration for existing drugs.

Sr. No.	Active Ingredients	Sr. No.	Active Ingredients
1.	Acitretin	19	Metronidazole
2	Acyclovir	20	Melatonin
3	Arecoline	21	Metoprolol tartrate
4	Buprenorpine	22	Morphine sulphate
5	Carbamazepine	23	Nalbuphine
6	Cetyl Pyridinium chloride	24	Nicotine
7	Chlorhexidine diacetate	25	Nifedipine
8	Chitosan	26	Omeprazole

9	Chlorpheniramine maleate	27	Oxytocin
10	Cyanocobalamin	28	Pentazocine
11	Danazol	29	Protirelin
12	Denbufylline	30	Pindolol
13	Diclofenac sodium	31	Piroxicam
14	Diltiazem Hydrochloride	32	Propranolol
15	Ergotamine tartrate	33	Propolis
16	Fluride	34	Recombinant human epidermal growth factor (Rh EFG)
17	Flurbiprofen	35	Salmon calcitonin
18	Glucagon-like peptide (GLP)-1	36	Sodium fluoride

1.6) LIMITATIONS OF BUCCAL DRUG DELIVERY [34-37]

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows.

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.

2. The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels

.3.For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.

1.7) BUCCAL ROUTES OF DRUG ABSORPTION

The are two permeation pathways for passive drug transport across the oral mucosa: Para cellular and Tran cellular routes. Permeates can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusion. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility's in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes.

2.1) EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES

Before a buccal drug delivery system can be formulated; buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

A. In vitro Methods

At the present time, most of the *in vitro* studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments

B. In vivo Methods

In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. Various modifications of the buccal absorption test have been carried out correcting for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization.

C. Experimental Animal Species

Aside from the specific methodology employed to study buccal drug absorption/permeation characteristics, special attention is warranted to the choice of experimental animal species for such experiments. For *in vivo* investigations, many researchers have used small animals including rats and hamsters) or permeability studies.

2.2) DEVELOPMENT & IN VITRO EVALUATION TASTE MASKED BUCCAL DOSAGE FORM OF AN ANTIMIGRAINE AGENT

Introduction

Taste masked buccal dosage form of Sumatriptan_Succinate (SS) was prepared by wet granulation method. Initially placebo buccal tablets were prepared by using combination of various bioadhesive polymers and normal tablet excipients & optimized on the basis of bioadhesive strength. Various taste masking trials were carried out and finally taste masking was done by complexation with ion - exchange resin. Drug - resin complex was then loaded in the optimized formulations. The final formulation was optimized on the basis of pharmacopoeial tablet tests, bioadhesive strength & *in-vitro* release studies.

1. Development of Placebo buccal tablets - Placebo buccal tablets were prepared by wet granulation method; using PVP K 30 as binder

2. Taste masking of the drug - It was done by completion with ion - exchange resin. Complex formation was confirmed by FT-IR spectroscopy & DS*C* studies.

3. Development of drug loaded tablets - Taste masked complex was loaded in the optimized placebo tablet and these tablets evaluated for pharmacopoeial Tablet tests bioadhesive strength & *in-vitro* release studies.

2.3) RECENT & FUTURE OF BDDS:

Buccal nitroglycerin, can use for acute therapy for an animal attack as well as for chronic prophylaxis Novel liquid aerosol formulation of insulin Development of suitable delivery devices, permeation enhancement, and Buccal delivery of drugs that undergo a first-pass effect, such as cardiovascular drugs, analgesics, and peptides Research yield some successes Promote further research; more companies Rest depend on delivery technology

2.4) *CONCLUSION*

The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. 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 are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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