MS.ID-IJPBS-5808
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2023) 13 (2): 213-222
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Fundamentals of Buccal Drug Delivery System with *in vitro* and *in vivo* Aspect

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Received: 10 Jan 2023 / Accepted: 8 March 2023/ Published online: 01 April 2023
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Abstract

The buccal region of the oral cavity is an alternative target for the delivery of the medicine of choice in order to overcome the limitation associated with the other route of administration. The significant pre systemic metabolism, instability in acidic medium, and insufficient absorption of the medications are the drawbacks of oral drug delivery. The transmucosal method offers the advantages of being simple to administer, patient-acceptable, and affordable. Buccal transmucosal administration, which provides immediate access to the systemic circulation via the internal jugular vein, aids in avoiding first-pass metabolism. The review article's objective is to provide a mechanism of bioadhesion, general overview of buccal drug delivery, oral mucosa anatomy, drug penetration mechanisms, and their in-vitro and in-vivo mucoadhesion testing methods and evaluation parameters of tablet of buccal drug delivery system.

Keywords

Buccal, Transmucosal, mucoadhesive, Experimental buccal permeation, Mechanism of bioadhesion

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INTRODUCTION

The oral route is likely the one that both patients and doctors prefer among the different drug delivery methods. However, there are drawbacks to intraoral [01] medication administrations, including hepatic first-pass metabolism and GI enzymatic degradation, which prevent the oral delivery of some drug classes. As a result, the absorptive mucosae are taken into consideration as prospective drug administration sites. Transmucosal medication delivery methods (i.e., mucosal linings of the nasal, rectal).

Fig. 01- Buccal route of drug administration

Fig 02. Drug delivery system

1.1 FUNDAMENTALS OF BIOADHESION

Development of an adhesive bond b/w a polymer and biological membrane or its coating can be visualized as a 2-step process. [02]

- Initial contact b/w the 2 surfaces
- Formation of secondary bonds due to non-covalent interaction.

The biological membrane surface, the adhesive surface, and the interfacial layer between the two surfaces are all involved in the bonding process. The characteristics of the polymer and membrane affect the molecular processes that happen in the interfacial layer.

Bioadhesive polymers

Bioadhesive polymers are classified into 2 main categories.

1- Polymers that are water soluble, linear and random polymer

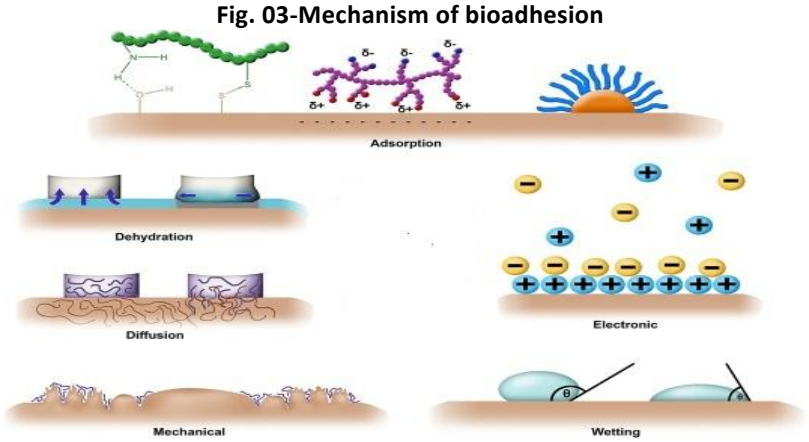
2- Water insoluble compounds that have swellable networks joined by cross-linking agents.

Numerous factors, such as molecular weight, chain length, and cross-linking density, are connected to polymers' bioadhesive characteristics. the ionization of charges, group hydrophilic and water Mobility of chains.

1.1 MECHANISM OF BIOADHESION

Several theories of bioadhesion have been proposed to explain fundamental mechanism of attachment.[03].

Fig. 03-Mechanism of bioadhesion



A. Electronics theory

When to surfaces come in contact, a double layer of electrical charges forms at the interface, and adhesion result forms.

B. Adsorption Theory

In the adsorption theory, bioadhesive polymer adheres to mucus because of two surface forces such

as Vander Waals' forces, hydrogen bonds or hydrophobic interactions.[04]

C. Wetting Theory

Wetting Theory analyzes adhesive and contact behavior in terms of the ability of a liquid or a paste to spread over a biological system and is primarily relevant to liquid bioadhesive systems.

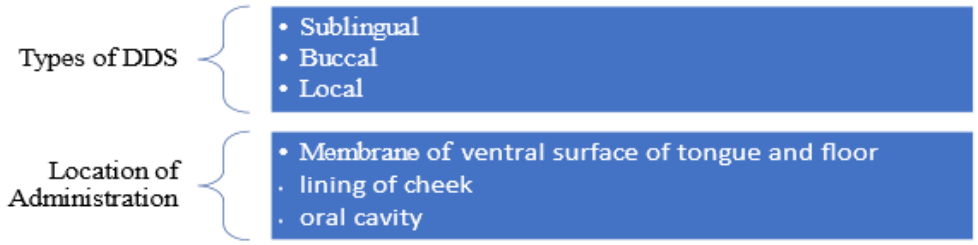
When a contact forms, it releases energy per square centimeter, which is known as the work of adhesion (or "Y"). Adhesion-related study is performed by:

Wa =YA+YB+YAB

Where, A=Biological membrane B=Bioadhesive formulation

D. Diffusion Theory

The fundamental principle behind this theory is that chains of the adhesive and substrate interpenetrate one another thoroughly enough to form a semi-permanent adhesive bond. The rate of penetration is dependent on the diffusion coefficients of both interacting polymers, and it is known that the diffusion coefficient depends on the molecular weight and cross-linking density.[05] Also, it's crucial to take into account aspects like segment mobility, bioadhesive polymer flexibility, mucus glycoprotein, and the extended nature of both networks. The following categories of drug distribution through the membrane of the oral cavity exist. [06-07]



1.1 ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

Drug administration via oral mucosae offers several advantages. [05,07,08,09]

- In buccal drug delivery system, there is ease of drug administration and the termination of therapy.
- Systemic absorption is rapid.
- Can be administered to unconscious patients.
- Permit localization of the drug to the oral cavity for a prolonged period of time.
- The drug's therapeutic return concentration can be attained more quickly.
- Provides an excellent route for the systemic administration of medications with fast first pass metabolism, improving bioavailability.
- A large dosage decrease can be achieved by reducing dose-dependent adverse effects.
- The drug's therapeutic return concentration can be attained more quickly.
- Drugs which are unstable in the acidic environment are destroyed by the enzymatic oral alkaline environment of the intestines can be administered by this route.
- The presence of saliva ensures relatively less amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- It enables local tissue permeability modification, protease inhibition, and immunogenic response decrease. Consequently, relative utilization of therapeutic substances such as peptides, proteins, and ionized species is possible.

1.1 LIMITATIONS OF BUCCAL DRUG ADMINISTRATION

Drug administration via this route has certain limitations [10,11,12]

- Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor, and the drugs which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Over hydration may lead to the formation of slippery surfaces and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.

- Only those drugs which are absorbed by the passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.

1.2 OVERVIEW OF THE ORAL MUCOSA

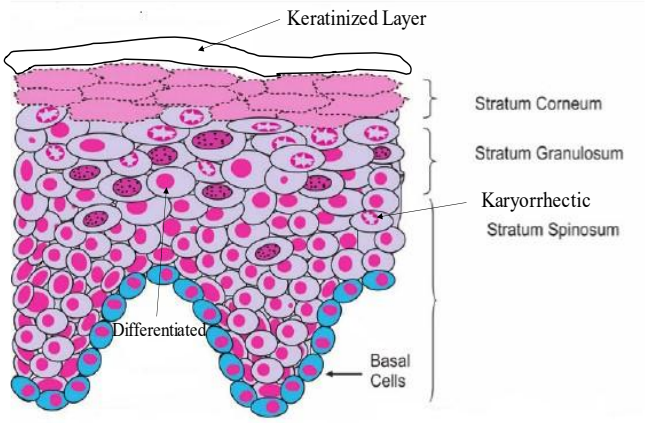


Fig04.Cross section view of buccal mucosa

The outermost layer of the oral mucosa is made up of stratified squamous epithelium. A basement membrane, a laminapropia, and the submucosa are the next layers down from here. The epithelia share characteristics with stratified squamous epithelia, which are located in the eastern part of the body, including a base cell layer that is actively mitotic. separating the intermediate layers from the superficial layers, where the epithelium's surface cells are shed. The sublingual epithelium includes slightly less cells than the buccal mucosa's epithelium, which has roughly 40–50 cell layers. As they move from the basal layers to the superficial layers, the epithelial cells get bigger and flatter. The buccal mucosa measures 500–800 m, while the mucosal thickness of the head and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at roughly 100–200 m. The oral mucosal thickness varies depending on the site. The mucosae of the gingivae and hard palate, which are prone to mechanical stress, are keratinized similarly to the epidermis. Nevertheless, the buccal, sublingual, and soft palate mucosae are not keratinized. [06,14] The floor of the mouth and buccal epithelia, which are not keratinized, do not contain acyl ceramides and only have trace amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosyl ceramides. These epithelia have been found to be considered permeable to water than keratinized epithelia. [15,16]

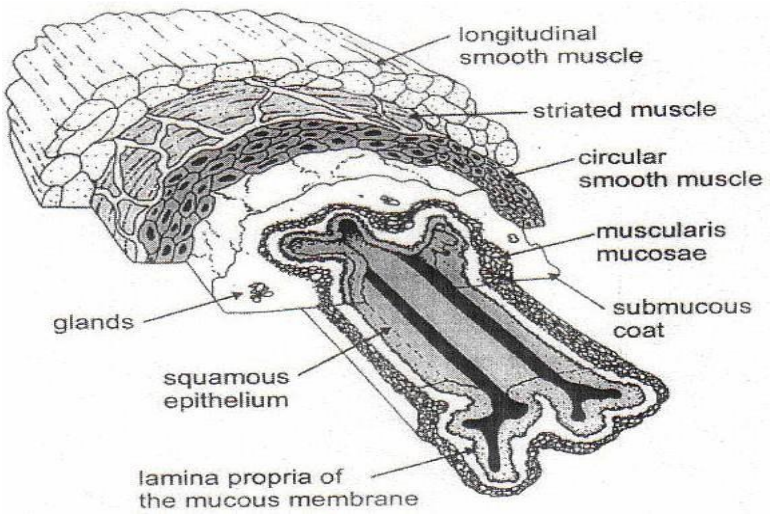


Fig-05. General structure of the oral mucosa

1.5 PERMEABILITY OF THE ORAL MUCOSA

Several areas of the oral cavity have significantly variable rates of permeability. In general, sublingual>buccal>palatal is the sequence in which the permeabilities of the oral mucosae decrease. The buccal and palatal mucosae are thicker, the sublingual mucosae are very thin, and the relative strength, however, is consistent with the physical properties of these tissues.

A. Mechanism of Transmucosal Permeation

Most medications travel across epithelial membranes, including the oral epithelium, by passive mechanisms that are essentially guided by diffusion rules. [17] The Paracellular and Transcellular pathways are two potential means of material transfer across the epithelium in the situation of simple diffusion (see fig 05). Although the transcellular route includes transporting into and through cells, the paracellular approach involves moving molecules through intercellular space. High lipid solubility compounds should be able to penetrate the lipid-rich plasma membranes of the epithelial cells more easily than water-soluble substances and ions, who will likely do so more through the intercellular gaps. Polar compounds, such as peptide-based drugs, may enter the mucosa through the paracellular pathway. Many obstacles do, however, stand in the way of paracellular penetration.

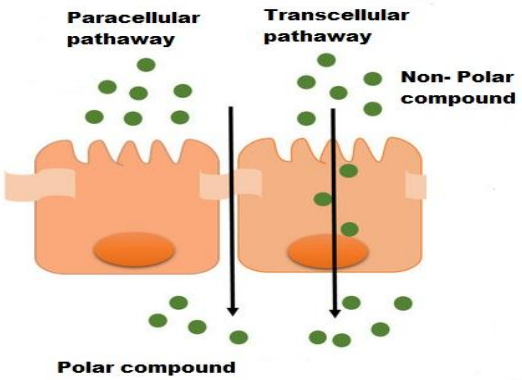
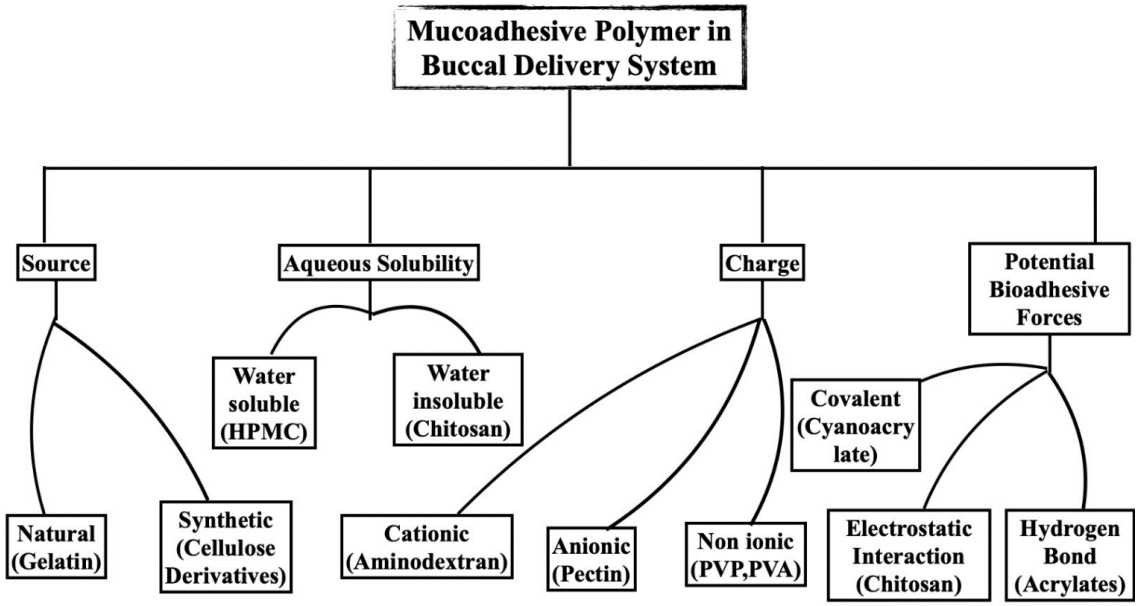


Fig 05 a. Mechanism of Transmucosal permeation

d. Mucoadhesive Polymers

Based on their adhesive properties, mucoadhesive polymers can be distinguished.



Bucco adhesive polymers used in the oral cavity [22]
The main benefits of bioadhesive systems are an extension of the drug-containing device's stay in the oral cavity and drug localization in a certain area. Theories related to electronics, adsorption, wetting, diffusion, and fracture have all been used to explain the bioadhesion process. The table's polymer classifications are nonspecific bio adhesives and are regarded as first-generation bio adhesives.

Lectins [21]
Lectins are naturally occurring proteins that are crucial to the biological processes of cell and protein recognition**.** These glycoproteins and proteins have a strong particular affinity for carbs. Despite the fact that lectins have a lot of benefits when it comes to site targeting, many of them are toxic or immunogenic, and the consequences of recurrent lectin exposure are largely unknown. The top epithelial layers of cut sections through human oral mucosa and to unprocessed, isolated human buccal cells have both shown lectin-binding. It is also possible that lectin-induced antibodies might stop adhesions between lectin delivery vehicles and mucosal epithelial cell surfaces in the future.

Table2. Mucoadhesive polymer classified according to their adhesive Performance.

Excellent bio adhesives	Fair performing polymers	Poor agents
Polycarbophil	Gum karaya	Pectis
Carbopol 934	Guar gum	Polyvinylpyrrolidone
Hydroxyethyl cellulose	Gelatin	Polyethylene glycol
Sodium alginate		Amberlite-200resin
Carboxymethyl cellulose		Psyllium
Polyacrylic acid		
Tragacanth		

Marketed buccal drug delivery product.
Marketed buccal drug delivery product mention in below table:

Manufacturer	Drug	Product	Available
Britannia Pharmaceuticals Ltd	Prochlorperazine	Buccal Tablet (Buccastem)	Commercially available
Cephalon, Inc	Fentanyl Citrate	Oral Transmucosal Solid Dosage Form (ACTIQ)	Commercially available
Columbia Laboratories Inc	Testosterone Desmopressin	Buccal Tablet (Straint) Buccal Tablet	Commercially available
Ciba-Geigy	Methyltestosterone	Buccal Tablets (Metandren)	Commercially available
Cytokine Pharma Sciences Inc	Pilocarpine	Buccal Tablet (PIOLOBUC)	Commercially available
Ergo Pharm	Androdiol Norandrodiol	Buccal Tablets (Cyclo-Diol SR) Buccal Tablets (Cyclo-Nordiol SR)	Commercially available
Generex Biotechnology Corporation	Insulin Heparin Fentanyl	Buccal Spray ORALGEN (US) ORALIN (Canada) Heparin Buccal Delivery System Fentanyl Buccal Delivery Systems	Commercially available Clinical Trials Completed
IVAX Corporation	Estrogen Buccal Tablet		Under Phase III clinical trials
Leo Pharmaceuticals	Nicotine	Mucoadhesive Tablet (Nicorette) Chewing Gum (Nicotinell)	Commercially available
Reckitt Benckiser	Prochlorperazine Buprenorphine HCl Naloxone HCl	Bioadhesive Buccal controlled release Tablet (Buccastem)	Commercially available
Regency Medical research	Vitamins Trans Buccal Spray		Commercially available
Rhone-Poulenc Rorer	Prochlorperazine	Bioadhesive Buccal Tablet (Tementil)	Commercially available

Teijin Ltd.	Triamcinolone acetonide	(Aftach)	Commercially available
Wyeth Pharmaceuticals	Lorazepam Oxazepam	Buccal Tablets (Temesta Expidet) (Seresta Expidet)	Commercially available

Bacterial adhesions

Recently, researchers have looked at the bacterial cells' ability to adhere. Fimbriae, unique cell-surface parts or appendages that promote adhesion to other cells or inanimate surfaces, are the foundation of bacteria's capacity to cling to a particular target.

According to research, Escherichia coli (*E. coli*) will only stick to the lymphoid follicular epithelium of the ileal Peyer's patch in rabbits. Furthermore, many staphylococci have the capacity to stick to the surface of mucus gel layers rather than to the mucus-free surface.

Thiolated Polymer

Thiolated polymers (thiomers) are hydrophilic polymers of the second generation mucoadhesive made from polyacrylates, chitosan, or deacetylated gellan gum. Thiol groups enable the creation of covalent connections with sub-domains of the mucus gel layer that are rich in cysteine, increasing residence duration and enhancing bioavailability. While second-generation systems' covalent bonding processes result in interactions that are less sensitive to variations in ionic strength and/or pH, first-generation mucoadhesive polymers nevertheless participate in non-covalent secondary contacts.

1.5 EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES [18]

To determine the viability of this method, buccal absorption/permeation tests must be carried out before developing a buccal drug delivery system. This research uses techniques to look at the drug's buccal permeability profile and absorption kinetics in vitro *and/or in vivo*.

***IN VITRO* METHODS**

The sacrifice of an animal occurs just before an experiment begins. When carefully removing the underlying connective tissue, the buccal mucosal membrane is separated when the buccal mucosa with connective tissue is surgically removed from the mouth cavity. The membranes are then installed between side-by-side diffusion cells for the in vitro permeation tests after being kept in ice-cold (4°C) buffers (typically Krebs buffer). However, ATP levels are not always a reliable predictor of tissue vitality. In the first six hours of the experiment found a 50% decrease in tissue ATP levels without a commensurate decrease in tissue permeability. Despite some modest modifications, the buccal tissue. Therefore, a decline in ATP levels does not automatically mean a change in the tissue's permeability properties. The most accurate way to determine if tissue is viable is to do the real permeation experiment; if, over the duration of the research, the drug permeability does not change under the experimental circumstances of pH and temperature, the tissue is deemed viable.

***IN VIVO* METHODS**

Beckett and Triggs were the first to invent in vivo techniques. The procedure entails human volunteers whirling a 25 ml sample of the test solution for up to 15 minutes before expelling the fluid. Salivary dilution of the medication is one of this method's negative aspects. There have been several changes made to the buccal absorption test to account for salivary dilution and accidental swallowing, however these variations equally suffer from the inability to localize the test location.

Using a tiny perfusion chamber fixed to the top lip of anaesthetized dogs is one example of an in vivo approach.

1.6 EXPERIMENTAL ANIMAL SPECIES

An extremely thick, keratinized surface layer covers the rat's buccal mucosa. Only the rabbit possesses non-keratinized mucosal linings in lab animals. Lining resembles human tissue, and it has been widely used in experimental research (48, 55, 58, 73, 74). It is challenging to separate the appropriate non-keratinized zone when employing rabbit oral mucosa because of the abrupt shift to keratinized tissue at the mucosal edges. The buccal mucosa is non-keratinized and closely resembles the buccal mucosa of humans.

1.7 EVALUATION OF BUCCAL DELIVERY SYSTEM [22]

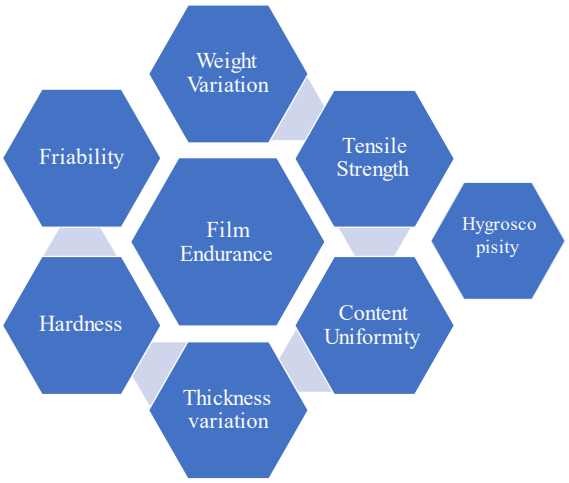


Fig. 06 evaluation parameter of buccal drug delivery system

Moisture absorption studies for buccal patches

Studies on the buccal patches' moisture absorption provide information on the relative moisture absorption capacity of several types of polymers. whether after absorbing moisture, the buccal patches retain their integrity.

$$\% \text{ Moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial Weigh}} \times 100$$

Swelling and erosion studies for buccal tablets

Swelling and erosion studies for buccal tablets were determined gravimetrically in phosphate buffer, of pH 6.6.

$$\text{Swelling index (\%)} = \frac{Ws - Wd}{Wd}$$

$$\text{Erosion (\% mass loss)} = \frac{\text{Original weight} - \text{remaining dry weight}}{\text{Original weight}} \times 100$$

Where Wd and Ws are, respectively, the weights of dry and swollen devices.

Study of the surface pH

After being coated with 1ml of distilled water, the bio adhesive buccal tablets were left to swell for 1-2 hours at room temperature. Putting the pH meter electrode in contact with the surface of the patches or pills and letting it equilibrate for a minute allowed us to determine the surface pH of the tablets or patches.

Measurement of Mechanical Properties

A automated test stand with a microprocessor-based sophisticated force gauze has been used to report on the mechanical characteristics of the films. equipped with a 25 kg load cell.

$$\text{Tensile strength (kg.mm-2)} = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm2)}}$$

$$\text{Erosion (\% mass loss)} = \frac{\text{Original weight} - \text{Remaining dry weight}}{\text{Original weight}} \times 100$$

***In vitro* bioadhesion measurement**

When evaluating the adhesive qualities of patches with a microprocessor based on sophisticated force gauze equipment and porcine buccal membrane as a model tissue under simulated buccal settings, in vitro bioadhesion measuring technique was first described.

Determination of the residence time

Ex vivo residence time

A modified USP disintegration device was used to calculate the ex vivo residence time.

Utilised this technique by using 800 ml of phosphate buffer with a pH of 6.6 maintained at 37 °C as the disintegration medium.

In vivo residence time

Eight adult male volunteers between the ages of 22 and 28 who were in good health participated in the trial. The duration of the film's stay on the buccal mucosa in the oral cavity was recorded by the volunteers, and that duration which was determined by the patch's and the backing membrane's continuous sensation was considered as the period during which the patch had entirely detached from the buccal mucosa. Time spent in each case's in vivo residence was noted.

Permeation studies

To determine the viability of this mode of administration for a drug candidate and to identify the kind of enhancer and its concentration that were to influence the rate of permeation of pharmaceuticals during the pre-formulation studies, buccal absorption/permeation experiments must be carried out.

This research use techniques to look at the buccal permeability profile and drug absorption kinetics in vitro, ex vivo, and/or in vivo.

Buccal absorption test

A technique was devised to determine the kinetics of drug absorption by having human volunteers spin a 25 ml sample of the test solution for 15 minutes before the fluid was expelled. The amount of medicine still present in the ejected volume is then calculated to determine how much drug was absorbed.

CONCLUSION

The buccal medication administration method offers a number of benefits for the drug delivery process. The buccal mucosa is rich in both vascular and lymphatic system, which prevents first-pass metabolism in the liver and pre-systemic clearance in the gastrointestinal tract and allows for direct drug drainage in systemic circulation. Also, buccal drug delivery is safe and simple because it can be stopped in the event of toxicity. The administration of powerful peptide and protein therapeutic molecules via the buccal cavity is a promising topic for future research with the goal of systemic distribution. Both in-vitro and in-vivo evaluation methods for buccal medicines are being developed. The expanded versions of the simple oral drug delivery system are mucoadhesive dosage forms.

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