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MUCOADHESIVE BUCCAL PATCHES - A REVIEW

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ABSTRACT

This article intends to audit the new advancements in the buccal adhesive drug conveyance frameworks to give essential standards to the youthful researchers, which will be valuable to bypass the challenges related with the formulation. The speedy improvements in the field of molecular science and gene innovation brought about age of numerous macromolecular medications including peptides, proteins, polysaccharides and nucleic acids in incredible number having predominant pharmacological viability with site explicitness and without undesirable and harmful impacts. The oral cavity is profoundly tolerable by patients. The mucosa is generally penetrable with a rich blood supply; it is tough and shows short recuperation times after stress or harm. The virtual absence of Langerhans cells makes the oral mucosa lenient to the expected allergens. Buccal drug conveyance leads direct admittance to the systemic circulation through the interiorly present jugular vein that circumvents drugs from the hepatic first pass digestion prompting high bioavailability. Buccal route is an alluring route to administer drugs for systemic drug conveyance. Buccal Bioadhesive films, delivering skin drugs in the oral space at a lethargic and programmed rate, give particular benefits over conventional systems for the treatment of numerous infections.

INTRODUCTION

Oral drug administration is the foremost favored and successfully utilized route for the controlled pharmaceutical conveyance among a few routes of drug conveyance system due to high patient compliance, possibility of self-medication, high flexibility, non-intrusive, pain evasion etc. When a drug administered orally its absorption, distribution, metabolism processes are interrupted at aimed location and might also exhibit following draw backs like hepatic first pass metabolism, enzymatic degradation with in gastro intestinal tract, delay between the line of administration and absorption. [1] 25% of populace thinks that It is hard to ingest tablets and capsules because of its hardness thus patients end up their treatment incomplete, which is recommended by their specialist. Especially, pediatrics and geriatrics feel difficulty while swallowing a drug, particularly those patients who have no access to water. To overcome all the drawbacks, parentral route of administration is established but the later have proven to be comparatively costly and possess least patient compliance when while required repeated administration. So, the various Trans and buccal mucosal routes have been evolved as an alternative for the oral drug administration.

The buccal region of oral cavity is an alternative for delivery of drugs owing to its ease of administration. Buccal drug delivery is an administration of desired drug through the buccal membrane lining of oral cavity.[2] This route is suitable for Tran's mucosal and mucosal drug administration which utilizes the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extensive period of time and exhibits both local as well as systemic impact.[3]

The use of mucoadhesive polymers in buccal drug delivery has greater application. The recently developed buccal patch offer greater flexibility and comfort over various mucoadhesive devices including tablets, films, patches, disk stripes, ointments and gels. Buccal patch has been well known for its good accessibility to the membrane that lines the oral cavity. Buccal patch is a non-dissolving, thin, matrix-modified release dosage form developed for administration into unconscious and less co-operative patients.[1]

Ideal characteristics: -

An ideal buccal adhesive system ought to have the accompanying attributes.

1. Fast adherence to the buccal mucosa and sufficient mechanical strength.
2. Should deliver the medication in a controlled way.
3. Should assist with the rate and degree of drug absorption.
4. Should hold good patient compliance.
5. Should not ruin typical functions like talking eating and drinking.
6. Should achieve unidirectional discharge of drug towards the mucosa.
7. Should not guide in growth of optional infections like dental caries.
8. Should hold a wide margin of safety both locally and systemically.
9. Should not induce salivation

Advantages [4]

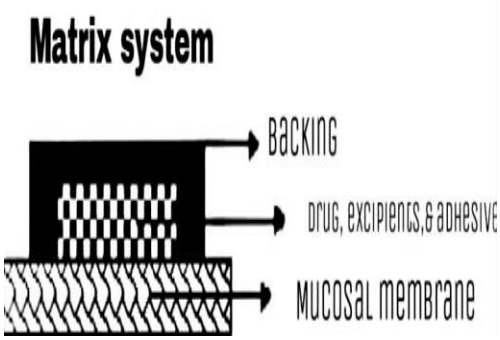
1. The buccal mucosa is all around vascularised and consequently medications can be quickly ingested
2. Circumvents the first pass effect and avoids the introduction of the drugs to the gastrointestinal fluids.
3. Patches can be applied, confined and taken out without any problem.
4. Close contact of the drug with the mucosa, improves its performance.
5. Enhanced patience compliance when compared to other routes of administration.
6. Dose-related side effects can be diminished because of the confinement of drug at the disease site.
7. It can be comfortably administered to unconscious patients.
8. Patients can handle the time of administration or end the treatment in the events of emergencies.

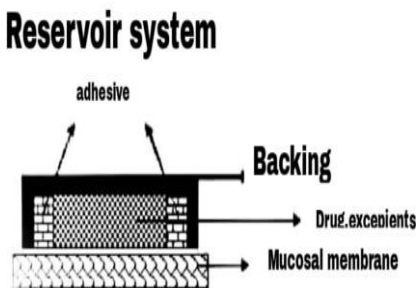
Disadvantages

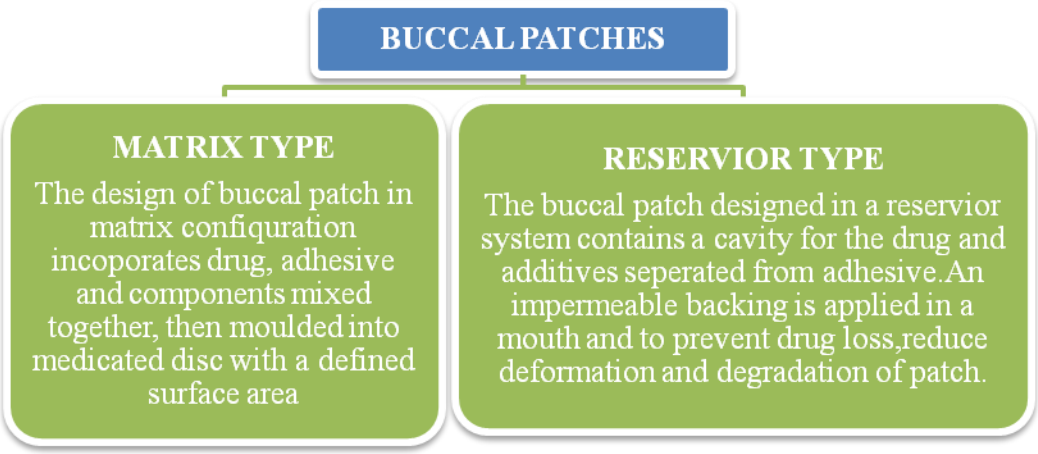
1. Drugs which bother mucosa and severe taste drugs can't be applied via buccal route.
2. Drugs with small dosage can be only administered.
3. Continuous discharge of saliva prompts quick elimination of drugs.
4. Little absorption area.
5. Involuntary gulping of salivation brings about a significant piece of disintegrated or suspended delivered drug being taken out from the site of retention. Besides, there is hazard that the delivery system itself would be gulped.

Types of buccal patches [5]

Buccal patches are of two types;







Structural features of oral cavity [6]

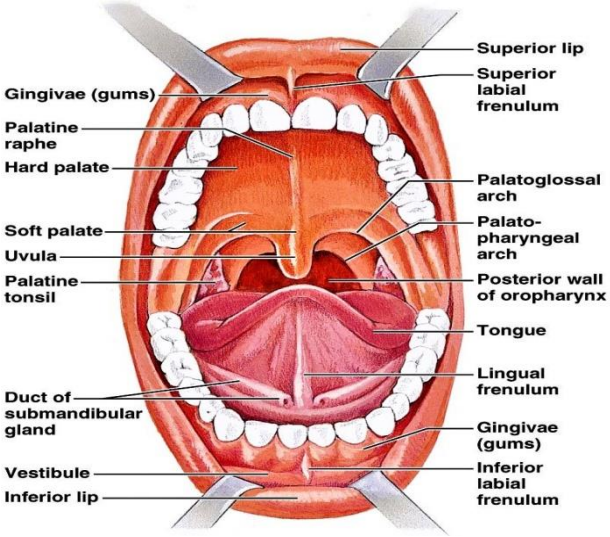


Figure 2: Structure of Oral Cavity

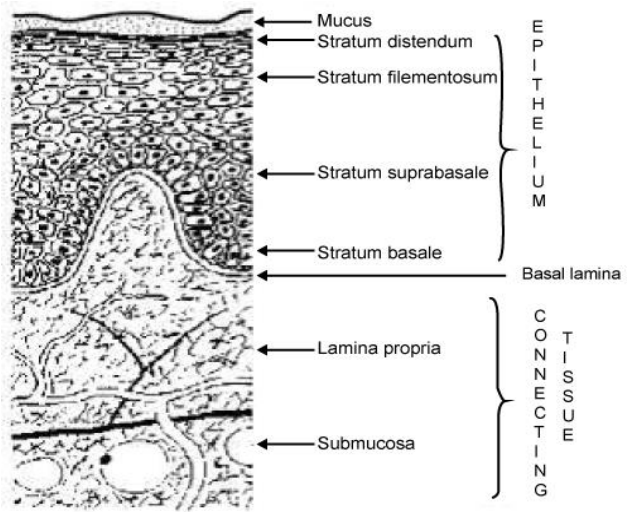


Figure 3: Cross Section of Buccal Mucosa

The oral cavity is a multi-layered mucous membrane, highly vascularized, relatively thick and dense. The drug penetrates into the systemic circulation via net of capillaries and arteries that lie under the mucosal membrane. There is a lining inside the cheeks is referred to as buccal mucosa.

Buccal drug delivery results when a dosage form is placed in the outer vestibule between the buccal mucosa and gingival, allowing the drug to be delivered.

Overview of buccal mucosa [7]

Buccal mucosa, like skin, has the primary function of protecting fundamental structures from foreign agents.

The oral mucosa is anatomically is divided into

1. Epithelium
2. Basement membrane and connective tissue

Epithelium

An undulating cellar film that isolates the stratified squamous epithelium of the buccal mucosa from the basic connective tissue. Keratinocytes in this delineated squamous epithelium change in size, shape and content as they relocate from the basal to the shallow areas, where the cells are shed. As a defensive layer for the tissues under, the epithelium is ordered into two kinds: (a) non-keratinized epithelium found in the mucosal covering of the delicate sense of taste, the floor of the mouth, ventral surface of the tongue, alveolar mucosa, vestibule, lips and cheeks.

(b)Keratinized epithelium is found in the hard sense of taste and non-adaptable districts of the oral cavity. While moving towards the surface, epithelial cells that begin from basal cells develop, change shape, and fill in size.

Basement membrane and connective tissue

The basement film is a ceaseless layer of extracellular materials that isolates the epithelium's basal layer from the connective tissues. While connective tissue and basement membrane are supposed to have even less impact on the dissemination of most pharmacologically significant compounds, they may limit the development of specific macromolecules and complexes.

Basic components of buccal drug delivery system

The basic components of buccal drug delivery system are;

1. Active pharmaceutical ingredient
2. Mucoadhesive polymer
3. Backing membrane
4. Penetration enhancers
5. Plasticizers

Active Pharmaceutical Ingredient

For buccal drug delivery, it is important to prolong and increase the contact between active pharmaceutical ingredient and mucosa to get the specified therapeutic effect. The selection of suitable drug for the mucoadhesive drug delivery system should be based on pharmacokinetic properties. The buccal patch delivery system distributes diverse kind of active pharmaceutical ingredients.

The drug should have following characteristics:

- ❖ The traditional single dose of the drug should be low.
- ❖ Drugs with a biological half life of 2-8 hours are ideal candidates for controlled drug delivery.
- ❖ When taken orally, drug absorption should passive.
- ❖ The drug should not have bad taste and be free from irritancy, discoloration or erosion of teeth, allergenicity.
- ❖ The drug's Tmax has wide fluctuations or higher value when given orally.

Mucoadhesive polymers

The selection and characterization of suitable mucoadhesive polymer is the first step in the development of mucoadhesive dosage forms. Bioadhesive polymers play a major role in buccoadhesive drug delivery system of drugs. Mucoadhesive are synthetic or natural polymers that interact with the mucus layer that covers the mucosal epithelial surface, as well as the main molecule that constitute the majority of mucus polymer s are also used in the matrix devices in which the drug is embedded in a polymer matrix that regulates the length of time the drug is released.

Backing membrane

The backing membrane is essential for Bioadhesive device to adhere the mucus membrane. The backing membrane materials used should be inert and impermeable to the drug and penetration enhancers.

Carbopol, magnesium stearate, hydroxyl propyl methyl cellulose, hydroxyl propyl cellulose, carboxy methyl cellulose, polycarbophil, and other materials are widely used in backing membranes.

Penetration enhancers [9]

Substances that facilitate the permeation buccal mucosa are referred as penetration enhancers. And which is used in buccal formulation to improve the release of the drug. The drugs physicochemical properties, site of administration, nature of vehicle and excipients all influence the enhancer selection and efficiency.

One of the major drawbacks associated with buccal drug delivery is the low flux of drugs through the mucosal epithelium, which results in low drug bioavailability. The use of various compounds as buccal penetration and absorption enhancers to improve drug flux through the mucosa has been studied.

Plasticizers

These are the materials that are used to make thin polymer or polymer mix films soft and flexible. Plasticizers help in the release of the drug from the polymer and act as penetration enhancers. The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymers and alters the polymer –polymer interaction. These materials have stability by relieving molecular rigidity when used in the proper proportion to the polymer.

Eg: glycerol, propylene glycol, poly ethylene glycol 200, poly ethylene glycol 400, castor oil.

Mechanism of buccal absorption [10]

Buccal drug absorption is mediated by passive diffusion of non- ionized species through the intercellular spaces of the epithelium, which is mainly regulated by a concentration gradient. The primary transport mechanism is the passive transport of non- ionic species through the

lipid membrane of the buccal cavity. The buccal mucosa, like many other mucosal membranes, has been defined as a lipoidal barrier to drug passage, with the more lipophilic the drug molecule, the more readily it is absorbed.

A first order rate process could better explain by the dynamics of drugs absorption in the mouth. Several possible barriers to drug absorption through the buccal mucosa have been established. Salivary secretion changes the buccal absorption kinetics from drug solution by adjusting the concentration of drug in the mouth, according to Dearden and Tomlison (1971). The following is the linear relationship between salivary secretion and time in which

$$-dm/dt=KC/ViVt$$

Where; M= mass of drug in mouth at time t
K=proportionality constant
C=concentration of drug in mouth at time
V_I= the volume of solution put into mouth cavity and VT= salivary secretion rate

Table 1: Mucoadhesive Polymers for Buccal Patches [8]

CRITERIA	CATEGORY	EXAMPLES
Source	Natural synthetic /semi-natural	**Natural polymers** Agarose, Chitosan, Gelatin, Hyaluronicacid, Various gums. **cellulose derivatives** CMC,ThiolatedCMC,sodium CMC, HEC, HPC,HPMC, MC, Methyl hydroxyl ethyl cellulose. **Poly(acrylic acid)-based polymers** CP,PC, PAA, , Poly(methyl vinyl ether-co-meth acrylic acid) Others Poly (N-2-hydroxy propyl methacrylamide) PVA, PVP.
Aqueous Solubility	Water soluble Water insoluble	CP, HEC, HPC (Water <38°C), HPMC, (Coldwater), PAA. Sodium alginate, Chitosan (soluble in dilute aqueous).
Charge	Cationic Anionic Non ionic	Amino dextran, Chitosan, trimethylated Chitosan Chitosan-EDTA, CP,CMC,pectin,PAA, PC,sodium alginate Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA,PVP
Potential bioadhesive forces	Covalent Hydrogen bonding Electrostatic interaction	Cyano acrylate Acrylates (hydroxylated methacrylate,Poly (methacrylic acid) Chitosan

Table 2: Example of Penetration Enhancers [8]

CATEGORY	EXAMPLES
Surfactants	IOINC: - sodium laurylsulfate, sodium laurate. NON IONIC: - Tween 80, sodium glycolate.
Bile Salts & Derivatives	Sodium deoxycholate, sodium glycocholate.
Fatty Acids & Derivatives	Oleic acid, caprylic acid, sodium caprate.
Chelating Agents	EDTA, citric acid, salicylates.
Sulfoxides	Dimethyl sulfoxide (DMSO), decyl methyl sulfoxide.
Polyols	Propylene glycol, poly ethylene glycol, glycerol.
Mono Hydric Alcohols	Ethanol, Iso propanol.

Mechanism of bioadhesion [5]

Number of theories proposed the mechanism of bioadhesion by the interaction of polymer and mucus and it is divided into two steps.

1) Contact step and,
2) Consolidation step.

In the first step the mucus layer come in contact with mucoadhesion and mucus membrane and formulation swell and spread over mucus membrane.

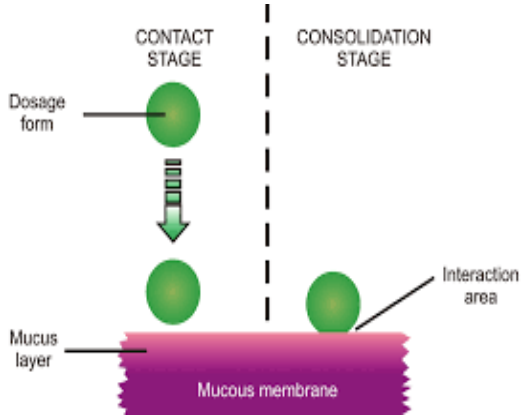


Figure 4: Two Steps Of Mucoadhesionprocess

In second consolidation step the moisture activates the mucoadhesive material, this plasticizes the system, this allow to mucoadhesive molecules to break free and link up by weak Vander walls and hydrogen bonds. The diffusion and dehydration theory explain the consolidation step.

The diffusion theory is the mutually interacting of Bioadhesive molecules and glycoprotein of mucus and building of secondary bonds by interpenetration of their chains. According to dehydration theory the material get gelify when it come in contact with the mucus in the aqueous environment. The drawing of water into the formulation due to concentration gradient until the osmotic balance is reached. This process increases the contact time of mucous membrane with the mixture of formulation and mucus. So it is not the interpenetration of macromolecule chains, it is the water motion that leads to the consolidation of adhesion bond.

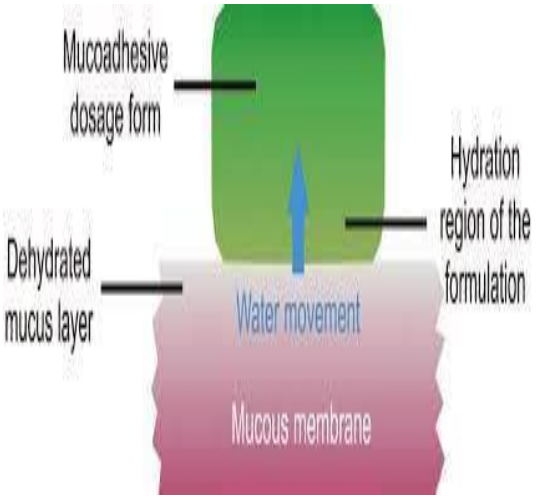


Figure 5: Diffusion Theory

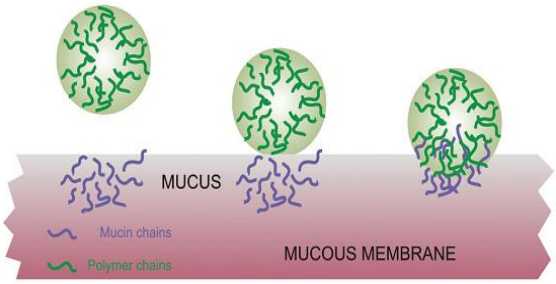


Figure 6: Dehydration Theory

Theories of bioadhesion [11]

To describe the fundamental mechanism of adhesion, some theories have been proposed.

Electronic theory

According to this theory, due to variation in their electronic structures, electron transfer occurs when an adhesive polymer comes into contact with mucus glycoprotein network. An electrical double layer forms at the interface as a result of this. Attractive forces through the double layer cause adhesion.

Adsorption theory

According to this theory, after initial contact between the buccal mucosal surface and the material adheres to it has their own surface energy. Two types of chemical bonds resulting from these forces are:

1) Primary chemical bonds of covalent nature.
2) Secondary chemical bonds having many different forces of attraction including electrostatic forces, Vander Waals forces, hydrogen and hydrophobic bonds.

Wetting theory

This theory applies to liquid or low-viscosity Bioadhesive which presents affinity to the surface in order to spread over it. This theory is based on the mechanism for drug dosage form spreadability through the biological layer. It is a general route that greater be the affinity lower the contact angle. For the adequate spreadability the contact angle must be equal or close to zero the spreadability coefficient (SAB) is calculated by the equation:

$$SAB = \gamma B - \gamma a - \gamma AB$$

Where γ B is Surface energy and γ A is Interfacial energy.

If greater the interfacial energy in relating to the individual surface energy, greater the adhesion work WA, i.e., greater the energy needed to separate the two phases.

$$WA = \gamma a + \gamma B - \gamma AB$$

Diffusion theory

According to this theory, to establish a semi-permanent adhesive bond, the polymer chains and mucus must combine to an appropriate depth. The diffusion coefficient and the time of contact influence the exact depth to which the polymer chains to penetrate the mucus. This diffusion coefficient, in turn, is affected by the value of molecular weight difference between cross-links and decreases as the linking density increases.

Fracture theory

For measurement of the mucoadhesion mechanism, this is most studied theory. The difficulty of separating two surfaces after adhesion is related to adhesive bond strength according to the fracture theory of bioadhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E \varepsilon / L)^{1/2}$$

Where is Young's modules of elasticity; E is fracture energy and L is critical length when two surfaces are separated.

Manufacturing methods of buccal patches [12,13]

In order to produce mucoadhesive buccal patches, the following manufacturing methods are used: solvent casting, direct milling, solid dispersion extrusion, semi solid casting, and hot melt extrusion.

Solvent casting

Patch excipients, including the drug, are dispersed in an organic solvent and coated on to a sheet of release liner in this process. After the solvent has evaporated a thin layer of protective backing material is laminated to the coated release liner sheet, resulting in a laminate that can be die - cut into patches of the desire size and geometry.

Direct milling

Patches are made without the use of solvents in direct milling. Direct milling or Kneading are used to mechanically combine the drug and excipients, typically without the use of liquids. Following the mixing step, the resulting material is rolled out on a release liner until it reaches the appropriate thickness. After that, the backing material is laminated as mentioned previously. Despite the fact that there are only small to no variations in patch performance between the two systems, the solvent free process is favoured because there are no residual solvents and no associated solvent related health problems.

Solid dispersion extrusion

This process involves extruding immiscible components with drug and then preparing solid dispersions. Finally, dies are used to form the solid dispersions into films.

Semi solid casting

Semisolid casting involves the preparation of a solution of a water soluble film forming polymer. The resulting solution is mixed with an ammonium or sodium hydroxide solution of acid insoluble polymer (cellulose acetate pthalate, cellulose acetate butyrate).The required amount of plasticizer is then added, resulting in a gel mass. Finally, heat controlled drums are used to cast the gel mass into films or ribbons. The film is between 0.015-0.05inches thick. The acid insoluble forming polymer should be used.

Hot melt extrusion

The drug is first blended with carriers in solid form before being extruded using the hot melt extrusion process. The mixture is then melted in an extruder with heaters. Finally, dies are used to form the melts into films. Hot melt extrusion has a range of advantages, including fewer operation units, greater material uniformity, and anhydrous process.

Evaluation of buccal patch [14,15,16]

Thickness measurement

The patch's thickness was measured with vernier calipers with a count of at least 0.001mm. The uniformity of the thickness was calculated at five different locations, with the average reading taken.

Swelling study

Buccal patches are weighed separately (W1)and placed in 2% agar gel plates, incubated at 37°±1°c,and examined for any physical changes. Patches are removed from the gel plates at regular 1-hour time intervals until 3hours, and excess surface water is carefully removed using the filter paper. Following that, the swollen patches are reweighed (W2) and the swelling index is determined by using the formula below

$$SI= W2-W1/W1 X100$$

Folding endurance

The patch's folding durability was measured by repeatedly folding it in the same spot before it break. The folding endurance was determined by the amount of times the patch could be folded in the same position without splitting.

Ex-vivo bioadhesion test

The mouth of a young sheep was isolated and washed in phosphate buffer (PH6.8). A fragment of gingival mucosa is inserted into the open mouth of a glass vial filled with phosphate buffer PH6.8, 37±1°c until it only touches the mucosal surface. A cyano acrylate adhesive is used to adhere the patch to the lower side of a rubber stopper. With a 5g weight, two pans of the balance are balanced. The 5g weight from the left hand pan is removed, which filled the pan with the patch over the mucosa. For a total of 5 minutes of contact time, the balance kept in this position. Water is steadily applied at a rate of 100 drops per mile. Pan to the right before the patch separates from the mucosal surface. The weight, in grams, required to detach from the mucosal surface was used to determine mucoadhesive strength.

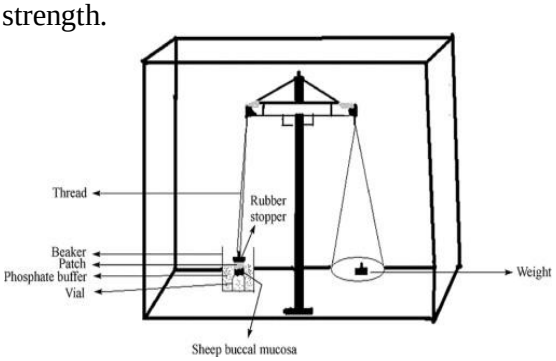


Figure 7: Measurement Of Mucoadhesive Strength

Invitro drug release

The revolving paddle system of the *United States pharmacopeia XXIII-B* is used to investigate drug release from bilayered and multilayered patches. Phosphate buffer PH6.8 was used as the dissolution medium. The release is carried out at a temperature of 37°c ± 0.5°c and a rotational speed of 50 rpm. The buccal patch's backing layer is adhered to the glass disc using instant adhesive material. The disc is assigned to the dissolution vessel's rim. At fixed time intervals, samples (5ml) are extracted and replaced with fresh medium. After sufficient dilution, the samples were filtered through whatman filter paper and analysed for drug content.

The *invitro* buccal permeation through the buccal mucosa (sheep and rabbit) is done in a keshary-chien / Franz style glass diffusion cell at 37°c ± 0.2°c.Between the donar and receptor compartment, fresh buccal mucosa is placed .The core of the buccal patch is positioned against the mucosa, and the compartments are clamped together. Buffer is stored in the donar compartments.

Permeation study of buccal patch

The receptor compartment is filled with phosphate buffer PH6.8, and the hydrodynamics are maintained in the receptor compartment by stirring at 50 rpm with a magnetic bead. At fixed intervals, samples are taken and tested for drug material.

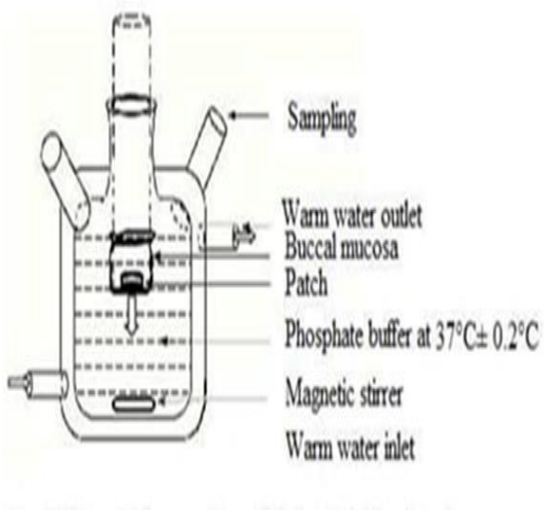


Figure 8: Franz Diffusion Cell for Buccal Patch

Ex vivo mucoadhesion time

The ex-vivo mucoadhesion time was assessed after the buccal patch was applied to freshly cut buccal mucosa. A mucoadhesive patch is wetted with 1 drop of phosphate buffer PH6.8 and pasted to the buccal mucosa with a light force with finger tip for 30 seconds. After that, the glass slide is mounted in the beaker, which is loaded with 200ml of phosphate buffer PH6.8 and held at 37°c ±1°c.

After 2 minutes, a 50 rpm stirring rate is used to mimic the condition in the buccal cavity, and patch adhesion is controlled for 12 hours. Changes in colour, form, patch collapsing, and drug content, are tracked over time.

CONCLUSION

The buccal mucosa is abundant in both vascular and lymphatic system through which drugs are straightforwardly delivered systematically. Also, patches avoid the first-pass digestion in liver and pre-systemic end in gastrointestinal tract. Furthermore, buccal medication can be ended at any point of time in cases of toxicity enabling patches a safe and simple method of application of drugs in the buccal space. Thus, buccal drug delivery has emerged to be assuring area for continued research with the aim of systemic delivery and attractive alternative for delivery of potent peptide and protein drug molecules.

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