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Examining the Buccal Patch, its Assembly, and its Performance as a Drug Delivery Method.

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ABSTRACT: The oral cavity is a desirable location for medication delivery because it is simple to administer and prevents drug degradation in the gastrointestinal tract and first-pass metabolism. The term "buccal drug delivery" appropriately describes the administration of medications through the buccal mucosa to influence systemic pharmacological effects.Buccalbioadhesive films offer obvious advantages over conventional dose forms for the treatment of numerous diseases since they release topical medications in the mouth cavity at a gradual and controlled rate.A non-dissolving thin matrix modified release dose form called a buccal patch was created to be applied to the less cooperative and flattened patient. Due to its accessible, smooth, relatively immobile surface, and accessibility, the buccal mucosa is an excellent candidate for a bioadhesion system. Consequently, medications possess a brief biological half-life. Flexible patches for oral usage have been created to address the shortcomings of tablets. This review article seeks to provide background knowledge on buccal patches and the buccal drug administration technology. Talk about the criteria used to assess buccal patches.

KEYWORDS: oral medicine delivery system, oral patch, oral patch application technique, and oral patch evaluation.

INTRODUCTION

Buccal drug delivery: The pharmaceutical industry has generated a great deal of attention, making it a significant player in the healthcare sector. The pharmaceutical sector has achieved significant strides in the treatment of sickness, which has improved people's quality of life. For systemic drug delivery, transmucosal routes—which include the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities—offer good options and possible benefits over peroral administration.[1]

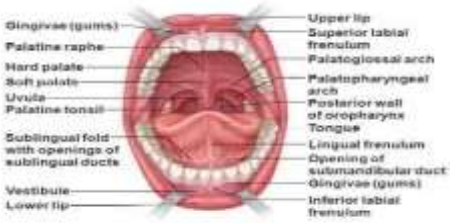

Fig :1oralcavity

mucoadhesivedrugdeliverysystem

By avoiding some of the body's natural defence mechanisms, mucoadhesive drug delivery systems enhance the bioavailability of therapeutic agents and offer advantages over conventional delivery methods in terms of extended residence time of the drug at the site of application, relatively large mucus membrane permeability that allows rapid uptake of a

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drug into the systemic circulation, and enhanced bioavailability of therapeutic agents.[2]These drug delivery systems' design heavily relies on mucoadhesion, which is the capacity to stick to the mucus gel layer. Since the buccal mucosa has a large blood supply and is moderately permeable, it is a

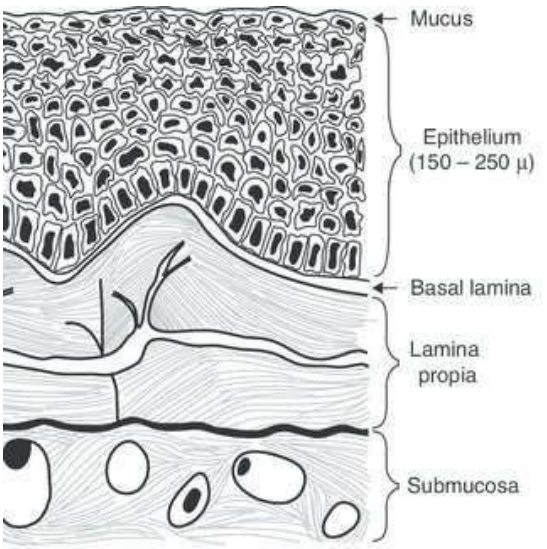
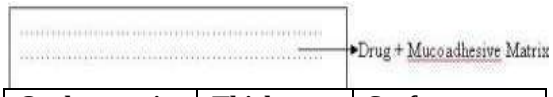


Fig:2 Oralmucosa

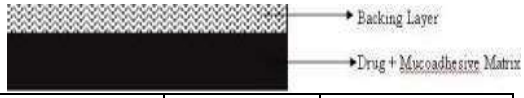
StructureofOralMucosa:

Theoralmucosaiscomprisedofsquamous stratified (layered) epithelium, basementmembrane, the lamina propria and submucosa. Italso contains many sensory receptors including thetastereceptorsofthetongue.[3]

Table1:Thickness andsurfacearea oforalcavity



Oral cavity membrane	**Thickness (mm)**	**Surface area (cm^2)**
Buccalmucosa	500-600	5.2
Sublingual mucosa	100-200	26.5



Gingival mucosa	200	--
Palatal	250	20.1

The mucoadhesive drug delivery system in themucusmembraneoforalcavitycanbecategorized intothreedeliverysystems:

Sublingualdelivery

• Buccaldelivery

• Localdelivery

desirable route for systemic medication distribution. By administering the medication through the buccal route, issues like high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be avoided. In the event of toxicity, buccal drug absorption can also be quickly stopped by removing the dosage form from the buccal cavity.

These oral sites provide the high blood supply forthegreaterabsorptionofdrugwithsufficientpermeability.Fromthesethreesitesoforalmucoadhesivedrug deliverysystem,thebuccaldeliveryisthemostconvenientsite.

ADVANTAGESOFMUCOADHESIVEBUCCALDRUGDELIVERY SYSTEM

Mucoadhesiveviabuccalrouteoffersfollowingadvantages:-

- Ease of drug administration and termination ofdrugactioncanbeeasilyaccomplished.
- Permitslocalization or retention of the drug tothe specified area of oral cavity for extendedperiodoftime.
- Bypasshepaticfirstpassmetabolism.
- Drugs with poor bioavailability owing to thehigh first pass metabolism can be administeredconveniently.
- Easeofdrugadministrationtounconsciouspatients.
- Watercontentofsalivaisbeingcapabletoensuredrugdissolution.

STRUCTUREANDDESIGNOFBUCCALDOSAGEFORM:[3]

Matrixtype: Thebuccalpatchdesignedinamatrix configuration contains drug, adhesive, andadditivesmixedtogether.

Reservoirtype: Thebuccalpatchdesignedinareservoir systemcontains a cavity for the drug andadditivesseparatefromtheadhesive.Animpermeablebackingisappliedtocontrolthedirectionofdrugdelivery;toreducepatchdeformation and disintegration while in the mouth;andtopreventdrugloss.

Fig.3:Buccalpatchdesigned for bidirectionaldrug

Fig.4: Buccalpatchdesignedforunidirectionaldrug

TYPESOFBUCCALDOSAGEFORM:

1. Buccalbioadhesivetablets:Buccalbioadhesivetabletsaredrydosageformsthataretobemoistened prior to placing in contact with buccalmucosa.Doubleandmultilayeredtabletsarealr

eady formulated using bioadhesive polymers andexcipients.Thetwobuccalbioadhesivetabletsco mmerciallyavailablebuccoadhesivetabletsinUKare Bucastem(Nitroglycerine)andSuscardbuccaP(Proc hloroperazine).[10]

2. Buccalbioadhesivepatchesandfilms:Buccalbi oadhesivepatchesconsistsoftwopolylaminatesormu ltilayeredthinfilm

roundorovalasconsistingofbasicallyofbioadh esive

polymeric layer and impermeable backing layerto provide unidirectional flow of drug across buccalmucosa. Buccalbioadhesive films arc formulated

byincorporatingthedruginalcoholsolutionofbioadhe sivepolymer.[10]

Anidealpolymerforbuccoadhesivedrugdeliverys ystemsshouldhavefollowingCharacteristics.[4]

Itshouldbeinertandcompatiblewiththeenvironment.

• Thepolymeranditsdegradationproductsshouldben on-toxicabsorbablefrom themucouslayer.

• Itshouldadherequicklytomoisttissuesurfaceandsh ouldpossesssomesitespecificity.

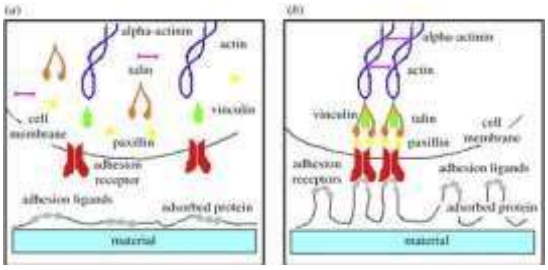
• Thepolymermustnotdecomposeonstorageordurin gtheshelflifeofthedosageform

Thepolymershouldbeeasilyavailableinthemarketand economical..

• Itshouldalloweasyincorporationofdrugintothefor mulation.

AdvantagesofBuccal Patches: [5]

1. The oral mucosa has a rich blood supply. Drugsare absorbed from the oral cavity through



the

oralmucosa,andtransportedthroughthedeeplingual orfacialvein,internaljugularveinandbraciocep halicvein intothesystemiccirculation.

2. Buccaladministration,thedruggainsdirectentryi ntothesystemiccirculationtherebybypassingthefirst passeffect.Contactwith thedigestive fluids of gastrointestinal tract is avoidedwhichmightbeunsuitablefor stability ofmanydrugs like insulin or other proteins, peptides andsteroids. In addition, the rate of drug absorption isnotinfluencedbyfoodorgastric emptyingrate.

3. Theareaofbuccalmembraneissufficientlylarge to allow a delivery system to be placed atdifferentoccasions,additionally;therearetwoareas ofbuccalmembranespermouth,whichwouldallowb uccal drug delivery systemsto beplaced, alternatively on theleft and right buccalmembranes.

4. Buccalpatchhasbeenwellknownforitsgoodacces sibilitytothemembranesthatlinetheoralcavity, which makes application the oral cavity,whichmakesapplicationpainlessandwithco mfort.

5. Patients can control the period of administrationor terminate delivery in case of emergencies. Thebuccal drug delivery systems easily administeredinto thebuccal cavity.Thenovelbuccaldosageformsexhibitsbetterp atient compliance.

Limitation of buccal drug administration[6]

Thereiscertainlimitationviadrugadministeredthrou ghbuccalroute: -

- Drugs with ample dose are often difficult to beadministered.
- Possibilityofthe patientsto swallow thetabletsbeingforgotten.
- Eating and drinking may be restricted till theendofdrugrelease.
- Thisroute isunacceptable for those drugs,whichareunstableatpHofbuccalenviron ment.
- Thisroutecannotadministerdrugs,whichirritate themucosaorhaveabitterorunpleasanttaste.
- Limitedsurfaceareaisavailableforabsorption

Mechanism of bioadhesion: Bioadhesion is an interfacial phenomenon in which two materials, atleast one of which is biological, areheldtogetherbymeansofinterfacialforces.Theatt achmentcouldbebetweenanartificialmaterialandbio logicalsubstrate,suchasadhesionbetweenpolymera nd/orcopolymerandabiologicalmembrane.Incaseof polymerattachedtothemucinlayerofthemucosaltiss ue,theterm“mucoadhesion”isemployed.“Bioadhesi ve”isdefined as a substance that is capable of interactingwith biological material and being retained on themor holding them together for extended period of time [7]

Fig.5:bioadhesivemechanism

Characteristics of anIdealBuccoadhesiveSyst em:[8]

An ideal buccal adhesive system should possess thefollowingcharacteristics:

1. Quickadherencetothebuccalmucosaandsufficien tmechanicalstrength.
2. Drugreleaseinacontrolled fashion.
3. Facilitatestherateandextentofdrugabsorption.
4. Shouldhavegoodpatientcompliance.
5. Shouldnothindernormalfunctionssuchastalking, eatinganddrinking.
6. Shouldaccomplishunidirectionalreleaseofdrugto wardsthemucosa.
7. Shouldnotaidindevelopmentofsecondaryinfectio nssuchasdentalcaries.
8. Possessawidemarginofsafetybothlocallyandsyste

mically.
9. Shouldhavegoodresistancetotheflushingactionof saliva.

Advantages of Buccal Drug Delivery System:[9]Drugadministrationviabuccalmucosaoff ersseveraldistinctadvantages:
1. The buccal mucosais relatively permeable witha rich blood supply, robust in comparison to theothermucosaltissues.
2. Bypass the first-pass effect and non-exposure ofthedrugstothegastrointestinalfluids.
3. Easy access to the membrane sites so that thedeliverysystemcanbeapplied,localizedandremov edeasily.
4. Improvetheperformanceofmanydrugs,astheyareh avingprolongedcontacttimewiththemucosa.
5. High patient acceptance comparedto othernon-oralroutesofdrugadministration.
6. Tolerance(incomparisonwiththenasalmucosaand skin)topotentialsensitizers.
7. Increasedresidencetimecombinedwithcontroll edAPIreleasemayleadtoloweradministrationfreque ncy.
8. Additionally significant cost reductions may beachievedanddose-relatedsideeffectsmaybereducedduetoAPI localizationatthediseasesite.
9. As a result of adhesion and intimate contact, theformulationstayslongeratthedeliverysiteimprov ingAPIbioavailabilityusinglowerAPIconcentration sfordiseasetreatment.
10. Harsh environmental factors that exist in oraldelivery of a drug are circumvented by buccal drugdelivery.
11. It offers a passive system of drug absorptionanddoesnotrequireanyactivation.
12. The presence of saliva ensures relatively largeamount of water for drug dissolution unlike in caseofrectalortransdermalroutes.

Disadvantages of Buccal Drug Delivery System:[10]

Themainchallengesofbuccaladministratio n are: 1. Limited absorption area-thetotalsurfaceareaofthemembranesoftheoralcavit y available for drug absorption is 170 cm2 ofwhich ~50 cm2 represents non-keratinized tissues,includingbuccalmembrane.
2. Barrierpropertiesofthemucosa.
3. Thecontinuoussecretionofthesaliva(0.5-2/day)leadstosubsequentdilutionofthedrug.
4. Thehazardofchokingbyinvoluntarilyswallowin gthedeliverysystemisaconcern.
5. Swallowing of saliva can also potentially lead tothelossofdissolvedorsuspendeddrugandultimatel y the involuntary removal of the dosageform.

I. METHODOFPREPARATION

Twomethodsareusedtoprepareadhesivepatches.

1. Solventcasting [12]: 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 theprotective backing material is laminated onto thesheet of coated release liner to form a laminate thatis die-cut to form patches of the desired size andgeometryevaluated.

2. Direct milling: In this, patches are manufacturedwithout the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the result antmaterial is rolled on a release liner until the desired

thickness is achieved. The backing material is thenlaminated as previously described. While there areonlyminororevennodifferencesinpatchperformance between patches fabricated by the twoprocesses,thesolvent-freeprocessispreferredbecause there is no possibility of residual solventsand noassociatedsolvent-related healthissues.

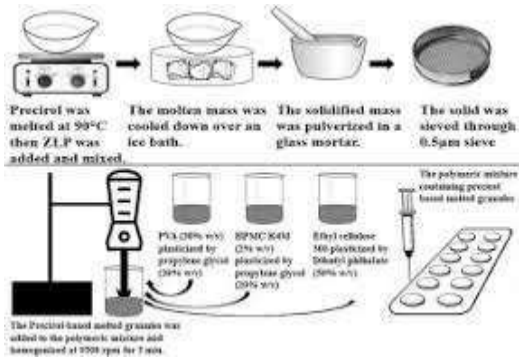


Fig:6preparationofbuccalpatch

CompositionofBuccalPatches:[13]

A. Activeingredient.

B. **Polymers(adhesivelayer):**Hydroxyethylcellulose,hydroxypropylcellulose,polyvinylpyrrolidone, polyvinyl alcohol, carbopol and othermucoadhesivepolymers.

C. **Diluents:** Lactose DC is selected as diluent foritshighaqueoussolubility,itsflavouringcharacteristics,anditsphysico-mechanicalproperties,whichmakeitsuitablefordirect compression.Otherexample:microcrystallinestarchandstarch.

D. **Sweeteningagents:**Sucralose,aspartame,mannitol,etc.

E. **Flavouringagents:**Menthol,vanillin,cloveoil,etc.

F. **Backinglayer:**Ethylcellulose,Polyvinylalcohol etc.

G. **Penetrationenhancer:**Cyanoacrylate,etc.

H. **Plasticizers:**PEG-100,400,propyleneglycol,etc

II. EVALUATION PARAMETERS [14]

The following tests are used to evaluate the Buccal Patches:

DrugContentUniformity,Ex-VivoResidenceTime, Thickness Testing, In-vitro drug permeationstudies,In-vitroreleasestudies,Moistureabsorptionstudies,SurfacepHstudy,In-vitrobioadhesionmeasurement,In-vitropermeationthroughporcinebuccalmembrane,Stabilityinhumansaliva,FTIRstudiesetcwater(15:85,v/v).

The flow rate was 2.0 ml/min and the run time 15min. The retention time of TPL was 3.1 min. TheTPLcalibrationcurve,atconcentrationsvaryingfrom5_g/mlto100_g/ml.

1. Surface pH: Buccal patches are left to swell for2 hr on the surface of an agar plate. The surface pHis measured by means of a pH paper placed on thesurfaceoftheswollenpatch.

2. Thicknessmeasurements: Thethicknessofeach filmismeasured at five different locations(centre and four corners) using an electronic digitalmicrometer.

3. Swellingstudy: Buccalpatchesareweighedindividually(designatedasW1),andplacedseparatelyin2 %agargelplates,incubatedat37°C ± 1°C, and examined for any physical changes. Atregular 1-hour time intervals until 3 hours, patchesare removed from the gel plates and excess surfacewater isremovedcarefullyusingthefilterpaper.

$$SI = \frac{(W2-W1) \times 100}{W1}$$

4. Waterabsorptioncapacitytest: CircularPatches, with a surface area of 2.3 cm2 are allowedto swell on the surface of agar plates prepared insimulatedsaliva(2.38gNa2HPO4,0.19gKH2PO4, and 8 g NaCl per litter of distilled wateradjusted with phosphoric acid to pH 6.7), and keptin an incubatormaintained at 37°C ± 0.5°C.Atvarioustimeintervals(0.25,0.5,1,2,3and4hours), samples are weighed (wet weight) and thenleft to dry for 7 days in a desiccator over anhydrouscalcium chloride at room temperature then the finalconstant weights are recorded. Water uptake (%) iscalculatedusingthefollowingequation,

$$\text{Water uptake (\%)} = \frac{(W_w - W_f) \times 100}{W_f}$$

Where, Ww is the wet weight and Wf is the finalweight.Theswellingofeachfilm ismeasured.[27]

5. Ex-vivo bioadhesion test[15]: The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in theopen mouth of a glass vial, filled with phosphatebuffer(pH6.8).Thisglassvialistightlyfitted intoa 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

rubberstopperwithcyanoacrylateadhesive.Twopans ofthe balance are balanced with a 5-g weight. The 5-gweightisremovedfromthelefthandsidepan,which loaded the pan attached with the patch overthe mucosa. The balance is kept in this position for5minutesofcontacttime.

The water is added slowly at 100 drops/min to theright-hand side pan until the patch detached fromthe mucosal surface. The weight, in grams, requiredtodetachthepatchfromthemucosalsurfaceprovidedthemeasure ofmucoadhesivestrength.

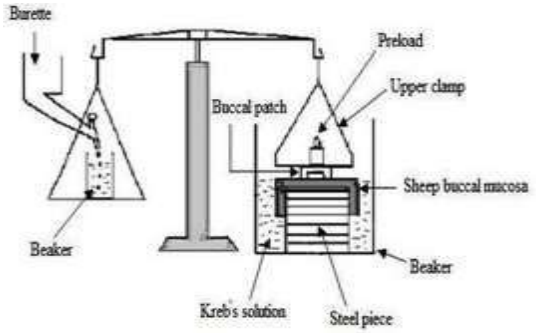


FIG.7: Measurementofmucoadhesive

6. InvitroDrugRelease [16] : The United States Pharmacopeia(USP)XXIII-Brotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolutionmedium consisted of phosphate buffer pH 6.8. Thereleaseisperformedat37°C±0.5°C,witharotation speedof 50rpm.Thebackinglayerofbuccalpatchisattachedtotheglassdiskwithinstant adhesive material. The disk is allocated tothe bottom ofthe dissolutionvessel. Samples(5ml) are withdrawn at predetermined time intervalsandreplacedwithfreshmedium.Thesamples filtered through whatman filter paper and analyzedfordrugcontentafterappropriatedilution.

Thein- vitro buccal permeation throughthe buccal mucosa (sheep and rabbit) is performedusingKeshary-Chien/Franztypeglassdiffusioncellat37°C±0.2°C.Freshbuccalmucosaismountedbetweenthedonorandreceptorcompartments. The buccal patch is placed with thecorefacingthemucosaandthecompartmentsclamped together. The donor compartment is filledwithbuffer

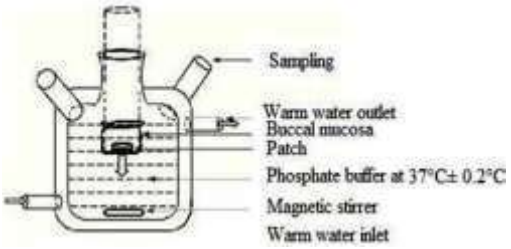


Fig.8: Schematicchematicdiagramoffranzdiffusioncellforbuccalpatch

7. Permeationstudyofbuccalpatch: Thereceptor compartmentisfilledwithphosphatebufferpH6.8,anddthehydrodynamicsinthereceptorcompartmentismaintainedbystirringwithamagneticbeadat50rpm.Samplesarewithdrawnatpredeterminedtimeintervalsandanalyzedfordrugcontent.

8. Ex-vivo Muco adhesion Time [17]: The ex-vivo muco adhesion time performed after application ofthebuccalpatchonfreshlycutbuccalmucosa(sheep and rabbit). The fresh buccal mucosa is tiedon the glass slide,andamucoadhesivepatchiswetted with 1 drop of phosphate buffer pH 6.8 andpasted to the buccal mucosa by applying a lightforce with afingertipfor 30 seconds. The glassslide is then put in the beaker, which is filled with200 ml of the phosphate buffer pH 6.8, is kept at37°C ± 1°C. After 2 minutes, a 50-rpm stirring rateisappliedtosimulatethebuccalcavityenvironment, and patch adhesion is monitored for12 hours.[15] The time for changes in colour, shape,collapsing ofthepatchand drugcontentisnoted.

9. Measurementofmechanicalproperties [18]: Mechanicalpropertiesofthefilms(patches)include tensile strength and elongation at break isevaluated using a tensile tester. Film strip with thedimensions of 60 x 10 mm and without any visualdefectscutandpositionedbetweentwoclampsseparated by a distanceof 3 cm. Clamps designedto secure the patch without crushing it during thetest, the lower clamp held stationary and the stripsare pulledapart by the upper clampmovingat arate of 2 mm/sec until the strip break, the force andelongation of the film at the point when the tripbreakis recorded.[15]

III. CONCLUSION

Thebuccalmucosaoffersseveraladvantages forcontrolleddrugdeliveryforextendedperiodsoftime.Themucosaiswellsupplied with both vascular and lymphatic drainageandfirst-passmetabolismintheliverandpre-systemic elimination in the gastrointestinal tract areavoided.Theareaiswellsuitedforaretentivedevice and appears to be acceptable to the patient.With the right dosage form design and formulation,the permeability and the local environment of themucosa can be controlled and manipulated in ordertoaccommodatedrugpermeation.Buccaldrugdelivery is a promising area for continued researchwiththeaimofsystemicdeliveryoforallyinefficient drugs as well as a feasible and attractivealternativefornon-invasivedeliveryofpotentpeptide andprotein drugmolecules. A lot of workisstillgoingonallaroundtheworldonmucoadhesivebuccal patches using various naturalpolymer. This review is an effort to summarize thework done till date and to show the future pathwayof mucoadhesivebuccal patches preparation usingnaturalpolymer.Theareaiswellsuitedforaretentive device and appears to be acceptable to thepatient.Withtherightdosageformdesignandformulation,thepermeabilityandthelocalenvironment of the mucosa can be controlled andmanipulatedinordertoaccommodatedrugpermeation.

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