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Review Article

A Comprehensive Review on Transmucosal Patch for Oral Ulcer

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ABSTRACT

Oral ulcers are frequently caused by trauma, systemic problems or idiosyncratic reasons, infections thus lead to more painful condition which impacts the mucosal lining of the mouth cavity. Major problems associated with traditional therapies comprises repeated dosage, inadequate retention rate as well as insufficient bioavailability. These consists of gel like formulation, mouthwashes and systemic therapies. Transmucosal films serves as a possibly efficient replacement for the oral delivery of medication for curing mouth ulcers. Defined release of medication, longer duration of contact, greater bioavailability and improved compliance among patient are some of the positives associated with these patches. The present article contains an in-depth discussion of transmucosal patches aimed for the treatment treating mouth ulcers, thus covers different methods of preparation of transmucosal patches, polymer types, Mucoadhesion mechanism and its theories, drug release mechanisms, and evaluation methods. The review paper additionally addresses possible potential futures regarding clinical use of this innovative treatment strategy along with latest advances in mucoadhesive techniques.

INTRODUCTION

Despite incredible advancements in drug delivery system, the oral route is persists as the most convenient way to administer drug since it is uncomplicated to administer, patient compliance is high, and it is affordable in cost.(1) Certain types of medication, specifically peptides and proteins are not able to administered orally due to the drawbacks of first-pass metabolism and enzymatic breakdown in the gastrointestinal tract.(2) For systemic drug distribution, transmucosal methods of administration have clear (comprehensible) advantages over peroral administration.(2) Recent progressions have led to increased exploration of mucosal drug delivery systems.(1) The oral mucosa is increasingly accepted as an effective site for drug administration due to its relative permeability, abundant blood supply, resilience, and quick recovery after injury (lesion).

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Additionally (although), the minimal presence(existence) of Langerhans cells makes the oral mucosa tolerant to potential allergens. Oral transmucosal delivery systems for systemic medication are generally intended to provide (i) rapid drug release for instant effects, (ii) pulsatile release for a swift increase of the drug in the bloodstream while sustaining therapeutic concentrations, or (iii) controlled release for extended durations.(1) Buccal administration presents a noteable alternative to the oral route for delivering drugs systemically.(9) In contrast to traditional pharmaceutical formulations, transmucosal patches have several benefits, such as fixed plasma concentrations, extended drug release, and minimized adverse effects.(3) Transmucosal patches designed for oral ulcers are an excellent method of avoiding first-pass hepatic metabolism, resulting in improved drug bioavailability. Since the medication is absorbed directly via mucous membranes in the mouth, it reaches the systemic circulation via jugular vein without initially bypassing the liver, thus avoiding enzymatic breakdown that often diminishes or decreases drug potency.(4) Drugs administration through the absorptive mucosa in to the accessible areas of the body—such as the buccal, ocular, nasal, rectal, and vaginal membranes—provides the benefit of avoiding the hepatic and gastrointestinal first-pass metabolism linked with oral intake.(5) Compared to oral drug delivery, the buccal region's mucosal lining provide various distinct advantages. Due to its high vascularization it exhibits reduced sensitivity, reduced enzymatic activity, Convenience of administration, and the ability to regurgitate the dosage form in the event of undesiarable consequences. It also prevents the hepatic first pass-effect and gastric acid hydrolysis. When compared to alternative non-oral drug delivery methods, buccal administration enhance superior patient adherence. The buccal route can also be used to distribute hydrophilic proteins and peptides that are vulnerable to acid and enzymes and have poor oral absorption. (6). In contrast to peroral administration, transmucosal drug distribution via the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities has several advantages for systemic effects. Among these routes, the buccal mucosa are particularly appropriate for controlled-release dose forms because of its smooth muscular surface, high accessibility, and relative immobility. In addition, patients acceptability is higher than other non-oral transmucosal techniques. By evading the gastrointestinal tract and preventing acid hydrolysis and first-pass metabolism, absorbed directly in to the blood stream through the internal jugular vein thus improves bioavailability. The buccal mucosa also presents quick cellular rebound. Nevertheless, a significant drawback of this method involves that the buccal membrane has poor permeability, particularly in contrast to the sublingual membrane has greater permeability, as well as its comparatively smaller(limited) surface area.(7) Mucoadhesion has acquired a lot of attention in the past 20th century due to its potential for both systemic and localized medication administration. For greater absorption of drug , it permits the prescribed drug form to be kept close to the absorption site (like the buccal cavity) or at the site of action (like the gastrointestinal system). Several types of mucoadhesive devices have been created, such as tablets, films, patches, disks, strips, ointments, and gels. Out of these mucoadhesive devices or formulation , buccal patches are more comfortable and flexible than sticky tablets. They also confront the issue of oral gels' such as brief duration of residence on mucosal surfaces, which are quickly removed (flushed out) by saliva. By evading the liver's first-pass metabolism and increasing bioavailability, the buccal route permits direct access to the systemic circulation across the jugular vein. Generally the bioadhesion defines

that the bond forms between soft tissue and a polymer, whether it may be natural or manufactured.(7) Mucoadhesion refers to the formation of a bond among the polymer and the mucus membrane. Mucus is predominantly made up of the glycoprotein mucin, which is also secreted by goblet cells found in the mucus membrane. Mucoadhesive dosage forms can be placed over the buccal mucosa scince it offers a surface that is comparatively smooth and immovable. (7).

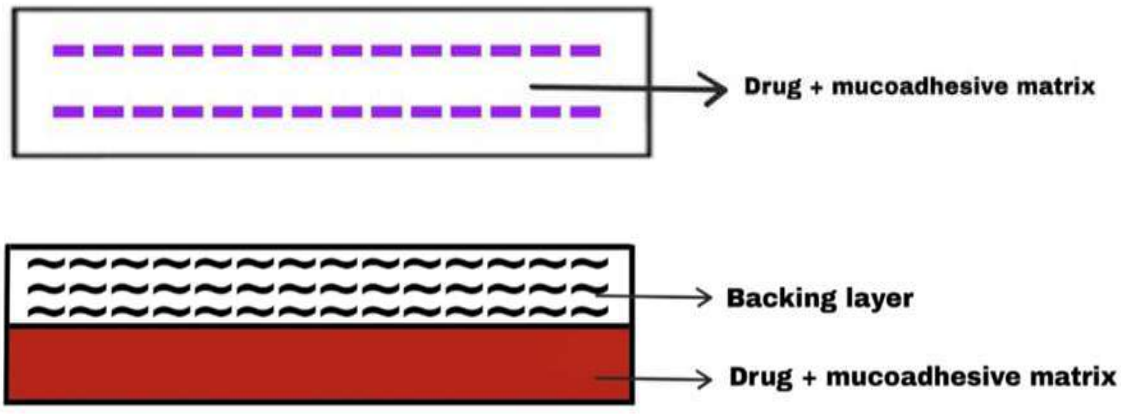
Buccal dosage form for buccal delivery:

Numerous medication delivery techniques for oral administration have been developed over this past few decades. Dosage forms such as Tablets and patches are the two most commonly used oral dose forms. Even after the dosage form hydrated in the oral cavity, the shape need to be smaller and have the appropriate geometry to prevent interfering with the mouth's internal processes. One of the criteria is that they not attached too excessively because it doesn't work if apply too much force to remove the formulation after usage since it has chance to harm the mucosa. An another approach is that by usage of formulation that can dissolve or disintegrate entirely during the course of application. In addition to that the drug release should be toward the mucosa and the release of drug in to the saliva should be prevented.(8)

3. Types:

Matrix type: A medication, adhesive, and additives are incorporated together to develop a formulation with an embeded design. The release of medication via bi directional patches into both mouth cavity and mucosa.[9] The pharmaceutical polymer is formed into a disc shape with a defined surface area after that the drug has been evenly distributed throughout a hydrophilic or lipophilic polymer matrix.[7]

Reservoir type: A cavity in the reservoir-system buccal patch retains the medication and additives separately from the adhesive. In order to avoid medication loss, minimize patch deformation and disintegration while in the mouth, and regulate the route of drug distribution, an impermeable backing is incorporated.[10] Furthermore, the patch can be designed to dissolve almost immediately or to degrade slightly in the oral environment.[11] There are two methods of drug delivery system for oral mucosa such as unidirectional or bidirectional. Unidirectional patches only release the medication into the mucous membrane, whereas bidirectional patches release the medication into the mouth as well as to the mucous membrane [12].



Adhesive patches and films:

Laminated patches and adhesive films buccal delivery devices are included in novel category that exhibits possibilities for both localized and systemic medication delivery. Identifying and defining a polymer that has suitable drug release control and bioadhesive characteristics, or combining polymers to do both, during the initial process of formulating a patch or film. A polymeric drug-loaded layer, an impermeable backing layer to undertake unidirectional drug release, and generally mucoadhesive components comprise the bioadhesive patches, which are laminated. It also consist of enzyme inhibitors, release retardants, or alterations like penetration enhancers. While designing patches to distribute distinct peptides, the scientist Anders et al. [82] researched a variety of polymers and geometries. The another scientist named as Veillard et al. [83] developed an unidirectional buccal patch which includes three separate layers an impermeable backing layer, a drug-carrying rate-limiting core membrane, and a mucoadhesive layer containing the bioadhesive polymer polycarbophil. The patch has not caused any visible discomfort when studied on the buccal mucosa of dogs, thus the patch has remained in place for up to 17 hours. [(13)] In contrast to sticky tablets, these buccal dose forms have greater flexibility, which increases patient comfort and adherence. In addition, they remain in mucosa for longer duration of time than oral gels, which are rapidly washed off by saliva. Moreover, for local distributed drug has polymeric adhesive coating which can protect the primary surface, minimizes the inflammation and increases the efficacy of treatment for oral health condition. But prolonged manufacturing processes as well as high expenses are remain as a major disadvantages of these dosage forms.[(13)] Mucoadhesive films ensure provide excellent adhesion throughout a wider range of surfaces via developing a effective bond with the mucosal membrane. This makes them suitable for local as well as systemic administration, dosing accuracy increases, and thus enhances systemic drug absorption.[(6)] Mucoadhesive drug delivery techniques utilizes the benefits of some polymers bioadhesive triats, which make the product tacky when hydrated. This property can permit these systems to guide a medication to a particular area of the organism and last it for a extended period. This ability is extreamly helpful for increasing absorption of systemic drug along with local treatment. [(7)]

Advantages of Buccal drug delivery system :

- Because of its broad vascularization, it is faster to remove a dosage form as well as to administer the dosage form.[(9)]
- In comparison to alternative non-oral drug administration methods, buccal administration of drug has a excellent acceptance among patients.[(9)]
- Buccal drug delivery prevents the challenging environmental circumstances that associated with oral drug administration.[(9)]
- Buccal drug administration method has mild adverse effects as well as fast commencement of action.[(4)]
- It helps to prevent or decrease the first-pass action and acid hydrolysis in the gastrointestinal tract.[(9)]
- In addition, the mucosa's smooth layer permits for fast regeneration of cell and the development of a localized position.[(9)]
- There is no possibility of chocking.[(4

- In contrast to liquid types buccal transmucosal patch has precise dosage.[4]
- Treatment termination is uncomplicated.[14]
- Drug administration is convenient.[14]
- Enables the medicine to stay in the oral cavity for a significant period.[14]
- It can be delivered to a patient who is unconscious.[14]
- These can also be given to people who have struggle in swallowing or who suffer from nausea and vomiting.[14]
- Convenient drug delivery can be achieved for medications with low level of bioavailability.[14]
- The patch has advantages such as flexibity in shape, size, surface and physical state.[10]
- In contrast huge amount of surface Accessibility thus an abundant supply of blood, along with that it has excellent long-term retention and low metabolic rate. The intestinal substitute Controlled release at zero order.[15]
- Controlling medication breakdown in the gastrointestinal tract.[15]
- The Mucous membrane lack a stratum corneum when compared to TDDS. Therefore, the transmucosal techniques for drug administration have no impact on the main barrier layer for transdermal drug transport. As a result compared to transdermal patches, transmucosal products shows more rapid initiation and drop of delivery.[2]
- Buccal patches are popular because of their excellent accessibility to the oral cavity's epithelial membranes, thus makes the administration convenient and painless.[16]
- At illness site the API localization can result to significant savings in cost as well as an overall reduction in dose-related adverse effects.[17]

6. Disadvantages of buccal drug delivery system:

- In contrast to the sublingual membrane, the buccal membrane has limited permeability.[9]
- The medication gets dilute subsequently because of constant production of saliva.[9]
- Patient acceptability is difficult when it comes to taste, irritability, and "mouth feel" thus it is an obstacle for both local as well as systemic therapy.[4]

7. Limitations of buccal drug delivery system:

- This method can be utilized to administer the drugs which are absorbed by passive diffusion.[5]
- Drugs which are unstable at buccal pH unable to be delivered via this method.[5]
- The outermost area of the absorptive membrane is significantly lower.[5]
- The formulation's structural strength or solidity may be distrupted because of development of a slippery coating due to the swelling and hydration of the buccal adhesive polymers.[5]
- Only low dose category drugs can be administered.[5]

- Not allowed to administer the drug which has unpleasant or bitter in taste or flavour.[15]

- This approach cannot applied in drug administration due to cause of irritation or discomfort to the mucosa or have an unpleasant odour.[15]

8. Mucoadhesion:

Mucoadhesive medicine delivery systems that make use of the bioadhesion of particular polymers, when it hydrated it become sticky and also it can target a medication to a specific area of the body for a prolonged time are commonly reffered to mucoadhesive drug delivery systems. If two different substances, among that one is biological in nature are bounded together by interfacial forces, this phenomenon is reffered as bioadhesion. While coming to mucoadhesion, this term described to a polymer or material or substance that is adhered to the mucosal fluid or layer of a mucous membrane. The substance or material's potential or capacity that may be synthetic or biological, to remain attached to a biological tissue over a longer duration of time this phenomenon is commonly reffered as mucoadhesion. For several drugs, taken by mouth or orally is the most frequently implemented method of medicine administration. Because of the rapid metabolic rate in the first pass and very strong acidic issues of stomach, some specific or particular medicines lacks bioavailability via this method. To work around these challenges different types of adhesive based mechanisms, which include buccal, nasal, and vaginal, are developed and administered via the following method apart from the oral route.(14) Although mucoadhesion is primarily used to define an attachment involving mucus or a mucosal surface, bioadhesion is frequently used to represent sticky relationship with any physiological or biologically achieved component.(17) At present, a numerous of recent research investigations on mucoadhesive drug delivery systems have been initiated. Numerous categories of medicines that comprises mucoadhesive systems, such as antihypertensive, antianginal, analgesic, anti-inflammatory, antihypertensive, ophthalmic, analgesic, anti-inflammatory, and hormonal medications.(14).

Mechanism of Mucoadhesion :

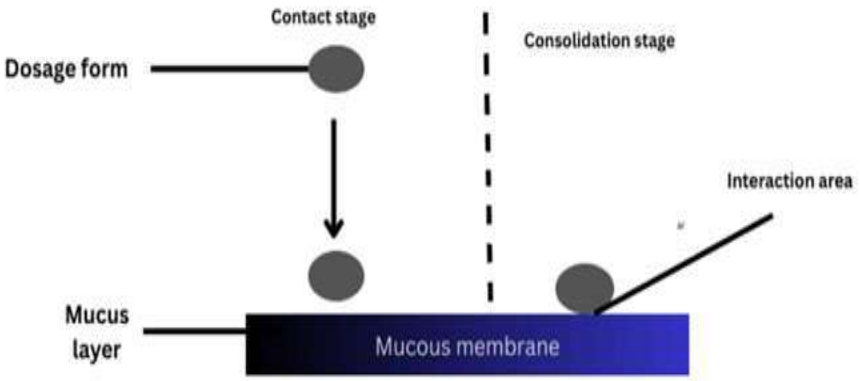
Interfacial forces retain two materials connected unless some of their properties is biological, this phenomenon is reffered as bioadhesion. Similarly the stickiness between a polymer-copolymer and membrane from a living organism, the connection may take place between a biological substrate and a synthetic product. On the other hand, mucoadhesion is the phenomenon that occurs when the polymer attaches to the mucosal tissue's mucin layer.

The Mucoadhesion mechanism is generally classified into two stages

1. Contact stage
2. Consolidation stage

Stage 1: Contact stage: The mucoadhesive and mucus membrane maintain close contact (wetting), either because of the bioadhesive swelling or an adequate wetness of the bioadhesive and a membrane itself.

Stage 2: Consolidation stage: In order to strengthen or consolidate and solidify the adhesive connection and also to enhance long-term adhesion, a several type of physical and chemical interactions, which include forces of dispersion, hydrogen bonding, and hydrophobic reactions, take place.[4]



Theories of Mucoadhesion: Several proposal are being put forward to better understand the underlying principles associated with Mucoadhesion, thus it is a complex procedure. They can be described as follows:[4]

1. The theory of wetting
2. The theory of diffusion
3. The theory of electronics
4. The theory of fracture
5. Theory of Adsorption

1.Wetting theory : Wetting theory evaluates the adhesion and interface affinity of a paste or fluid to dispersed over a living system and is primarily utilized in liquid bioadhesive systems. The angle of contact may be applied to determine affinity. As a general principle, the contact angle decreases with increase in affinity. The angle of contact needs to be zero or near to that of zero for appropriate Spreadability.

The calculation that follows to determine the Spreadability coefficient (SAB):

SAB = γB-γA-γAB.

Where

- γB stands for surface energy.
- γA stands for interfacial energy.

Energy or the Adhesion work WA required to differentiate both the stages, thus it will be higher if interfacial energy is higher when compared to individual energy at the surface.

Adhesion work = γA + γB – Γab[4,17]

2.Diffusion theory: This concept proposes the fact that the mucus and polymer chain molecules connect effectively enough to produce a partially permanent adhesion bond. The contact period and rate of diffusion define how extent the polymer chains permeate to the mucus. In addition, this rate of diffusion is impacted with the weight of the molecule among cross-links thus greatly declines with increasing linking density. [4,17] The literature suggests that in favour to achieve an efficient bio adhesive link, the level of penetration should fall within 0.2 to 0.5 µm. The formula that follows to calculate the level of mucin and polyer chain interpenetration:

L = (t Db)½

Where,

T, stands for time period for contact. Db, stands for mucoadhesive material's rate of diffusion in Mucus. It's very crucial that the mucus and the bioadhesive substances associated maintain robust relative solubility, identical chemical properties, to permit or allow for

diffusion. If the similarities in structure is greater than the mucoadhesive bond is better.(4)

3. Electronic theory: Derjaguin and Smigla introduced the electrical theory of adhesion. This concept suggests that the transfer of electron takes place when both the adhesive polymer and the mucus glycoprotein structure come into contact precisely because of the contrast in their electrical properties. This eventually leads to the invention of a double layer of electricity at the point of contact. The attractive forces within the two distinct layers create adhesion. Based on this concept, adhesion develops whenever the electrons within the mucoadhesive layer and mucus migrate due to the deviations in their electronic properties. (4,10,17)

4. Fracture theory: This proposed theory suggests that the connection among the systems and adhesive is correlates to the pressure required for the separation of both the surfaces. Such the "fracture theory" connects the effectiveness of the polymer's adhesive attached to the force thus required to breakdown it from the mucus. The work fracture increases along with the dimension of the chain of polymer strands. On the other hand, there is rise in the work fracture while the level of cross-linking in such a system is decreased. The formula that follows to calculate the fracture length:

r = (E x e / L) ½

Where,

- R refer to the fracture strength.
- E refer to the elasticity of Young's modulus, and e implies fracture energy.
- L refers to the extreamly important length of the fracture.

5.Adsorption theory: This concept proposes that the retains or attaches the material following initial interaction amongst two separate surfaces results from the surface tension generated across the atoms of the two interfaces.

The resulting forces generate two separate kinds of chemical bonds, namely:

• The covalent fundamental chemical bonds.

• Intermediate chemical bonds involving numerous kinds of forces of interactions, such as bonds of hydrophobic and hydrogen, forces of Vander Waals and electrostatic. (17)

9. Techniques for preparation of patches:

a) Solvent casting method: This technique develops a solution that is uniformly distributed via polymers that dissolve in water. Following dissolvation in an aqueous solvent, the medicinal elements which are in active and including additional components that are attached to a release liner sheet. For the purpose to develop a surface which is laminated that is capable of being die-cut towards the patches which have suitable dimension and shape, a tiny amount of protective covering backing material has been attached to the release liner sheet which contains coating thus subsequently follows solvent evaporation. It has improved physical attributes, increased flexibility, outstanding thickness consistency, greater adaptability, simple and affordable manufacturing are some of the few benefits.(4) Even though the procedure of solvent casting is easy to manufacturing the patches, it comes with certain limitations, which includes substantial expenses, prolong period for manufacturing process lengthy production time, high costs, and problems of environment caused by utilization of solvents. The another patch manufacturing procedure named as

hot-melt extrusion prevents the above constraints.(9)

b) Direct milling method: In this method, avoids the usage of solvents while manufacturing process of patches. Generally due to the absence of liquids usage, the excipients and the medication are mechanically homogenized by kneading or immediate grinding process. After the completion of mixing, the end product is then rolled across a release liner before it has attained the required or necessary thickness.(16) For regulating the rate of medicinal product release, minimize drug loss and reduces deformation in the instruments and disintegration all over the course of use, an impenetrable underlying membrane can be additionally used. The free of solvent approach is generally preferred thus there has been no possibility of remaining solvents as well as minimal hazards to health where associated, eventhough there may be minimal or absence of deviations in patch functionality among the patches manufactured via two techniques.(18)

c) Hot melt extrusion: This method includes moulding a combined or combination medication containing drug, polymeric material and additives are extruded over high temperature in order to produce an evenly distributed mass which is there after casted to achieve a smooth film. Hot melt extrusion was previously applied for manufacturing regulated release matrix tablets, granules, pellets and orally dispersing patches as dosage forms.(4,19) The most significant disadvantage associated with the solvent-free procedure involves the fact that thermolabile components are not possible to incorporate because of the usage of extreamly highest temperature used throughout the extrusion process.(20) Offering multiple benefits above convectional pharmaceutical processing methods, the hot-melted extrusion (HME) technology is a optional process for typical formulation process. Throughtout the procedure of extrusion, the molten state polymer compounds may act as a thermal energy binders and, as well as whenever at the cool and solid state, thus provide as a release of drug retardants. There are significantly fewer manufacturing procedure as well as less time taking procedures steps consideringly solvents and water are not required.(21) Irrespective of its compressive features, the elements of matrix being organized or packed into a bigger entity. Thus the procedure is extreamly productive and consistent since the revolving screw's leads to rapid mixing and vigorous agitation or stirring generates the particles that are suspended within the polymer’s melting state to dis-aggregate, leads to a more evenly distributed dispersion.(21) While the active ingredient in the medication is dispersed or dissolved molecularly in the use of hot melt extrusion forms of dosage, thus the absorption of drug into the body might be enhanced. The Ram extrusion and screw extrusion are two distinct kinds of pharmaceutical hot-melt extrusion techniques. In fact there are two distict types of screw extruders such as one screw extruder and extruders with twin screws.(21)

d) Rolling method: The process of rolling techniques consists of rolling or laying a drug-containing suspension or solution on an appropriate carrier. The fresh water as well as fresh water-alcohol combination constitutes the more than half of the solvents. Subsequently after cure process, the patch is cutted into suitable dimensions and lengths.(2)

e) Solid dispersion extrusion: While performing this method, solvent is not necessary for this technique, thus no excess solvent remains after formulation, along with that concern’s with stability can be minimized at the duration of product's shelf life. The drugs active component is

blended along with the various immiscible solid or thick ingredients, and for formulation improvement solid dispersed particles are created. A mixture of more than one insoluble components are commonly known as solid dispersion. After preparation, the liquid is placed into the dye, kept for drying and then collected and finally separated into the requisite quantities for use.(15)

f) Semisolid casting: In this technique a solution that consist of film-forming polymeric material which is soluble in water is initially manufactured in the semisolid casting procedure. A solution that consists of insoluble polymers which is acidic in condition such as cellulose acetate butyrate, cellulose acetate phthalate thus synthesized via sodium hydroxide or ammonium is incorporated with the obtained solution. A sufficient quantity of plasticizing agent has been incorporated in order to achieve a gel like mass. In the end, heat-controlled containers have been utilized to form the gel like mass in to ribbons or films. Film thickness is ranges from 0.015 and 0.05 inches. The acid-insoluble producing polymer must have a ratio of 1:4.(7)

10. Evaluation of transmucosal patches:

1. Physical appearance and surface texture of patches: These standards have been evaluated easily with the help of visual examination of patches either via sensation or touch. The examination indicates that the films possess smoother surfaces and as such they are sufficiently elegant to be observed. (22)

2. Film thickness: The film thickness can be observed with the help of an adjustable screw gauge or calibrated digital vernier calipers. Every single film's thickness has been determined at five distict points, which includes the core and its four central regions. The mean ± standard deviation across five replicate readings has been employed for calculating the thickness.(4)

3. Weight Variation: The main objective of the weight variation test was to examine the consistency of the patch weight consistency along with that batch-to-batch variability also been examined. The weight variation test procedure involves, three samples of each patch are selected randomly (1.5 cm x 1.9 cm) thus separately weighed with the help of electronic balance, and the mean weights were then calculated . (2, 7)

4. Folding Endurance: The procedure involved in folding endurance, single patch has been folded frequently until it breaks to determine the robustness of folding of the patches.(7) The film is about 2cmsquare in size has taken to test folding endurance. By constantly folding the patch at the same spot until its breaks down, thus the folding endurance can be calculated. The films has folded above 200 folds should not cause the film to break, thus patches considered as good quality characteristics. While during the trial 3 films were utilized thus average results are calculated.(4) The folding endurance test shows how flexible when the films are placed in the buccal area as well as to what extent films can resist mechanical handling. The folding endurance value indicates that the total number of times the film could have been folded at the same spot continuously without breaks down of patch.(23)

5. Surface pH: In order to inquire any potential adverse reaction in in-vivo, thus buccal patch's surface pH was taken in to consideration. So the product was established to maintain the surface pH as almost near to neutral as can be achieved since an alkaline or an acidic pH level might cause irritation to the oral mucosa.(24) For this, electrode composed of glass had been used to evaluate the surface pH. The surface pH procedure involves, lasting the patches for two hours at room

or ambient temperature, the patches were permitted to immersed in 1 milliliter of distilled water (pH 6.5 ± 0.05) to allow them to expand. The electrode was setup over the patch's surface while pH was monitored shortly after a minute of equilibrium.(25)

6. Tensile Strength: Here tensile tester is used thus its helps to assess the mechanical features of patches which includes, elongation properties and tensile strength. A film strip with 60 x 10 mm of dimension and without the presence of any evident imperfections is cut or divided and laid within two clamps which are positioned or placed 3 cm apart. Thus clamps have been developed in order to keep the hold patch firmly in place with no crushing meanwhile during the testing, the higher clamp pushes the strips away at an average rate of 2 milli meters for each second unless the strip breaks down, whereas the bottom clamp stays stationary. The film's stretching and force at the precise time that represents the breakage of strip being monitored. The below equation is employed to determine the elongation and the tensile strength at breakdown values. (2).

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

$$\text{Elongation at break (\%.mm}^{-2}) = \frac{\text{Increase in the length (mm)}}{\text{Original length}} \times 100$$

7. Moisture absorption: The buccal film's moisture absorption tests provides information regarding the relative moisture absorbing abilities among the polymers alongside offering information towards the buccal patches whether it retain their structural integrity upon moisture absorption.[10] The films were stored in desiccators which contains anhydrous calcium chloride shortly after being precisely weighed. The films had been removed and then measured the weight after three consecutive days. The formula utilized for calculating the loss of moisture (%) thus the aim is to determine the moisture content (%).[1,17]

$$\text{Moisture content (\%)} = \frac{\text{Initial weight - Final weight x 100}}{\text{Final weight}}$$ [1,17]

8. Drug Content Uniformity: Each one of the film about 1cm2 in size has to dissolve in 10 ml of solvent in order to assess the content or concentraton of drug. Here the Whatman filter paper (0.45 µm) has been employed to remove the unwanted particles from the solution. When the filtrate has been evaporated, thus the drug residual is allowed to dissolve in 100 milliliters and a phosphate buffer with a pH of 6.8. The 0.45-µm Whatman filter paper has been employed to remove contaminants from 5 ml of the previously mentioned solution once it has been thoroughly diluted with buffer containing phosphate (pH 6.8) to 20 ml. Here phosphate buffer solution with pH 6.8 is used as a blank, thus the absorbance can be determined at a suitable wavelength via UV Spectrophotometer. The experiments are carried out in three replicates, thus the average outcomes are calculated.(4)

9. In- Vitro Drug Release Studies: The release of drug via multilayered and bilayered patches has been examined with the help of rotational paddle technique according to the instruction in the United States Pharmacopeia (USP) XXIII. A phosphate buffer solution which contains a pH of 6.8 serves as the dissolving media. The release has been carried out via at a rotational rate of 50 rpm and an ambient temperature at 37 degree Celcius ± 0.50 degree celcius. Applying an instantaneous adhesive such as cyanoacrylate glue, thus the oral patch supporting material had been affixed to the surface of the glass disk. In the dissolution container, the disk had been placed towards the bottom. During particular intervals, 5ml of samples were collected and replaced with a freshly prepared media. Later the withdrawned samples

were then filtered via whatman filter paper as well as upon suitable dilution analysed absorbance with the help of UV spectrophotometry at the appropriate wavelength nm.(18)

10. Stability studies: Here human saliva has been employed to determine the stability of the oral patches. Saliva from humans is obtained from adults within the ages of 18 to 50. The procedure involves in stability test follows 5ml of individual saliva's have been placed into individual petri dishes which contains buccal patches, these are heated in temperature controlled oven at 37°C ± 0.2°C for a duration of six hours. Dosage formulations with improved bioavailability are required at regular intervals (0, 1, 2, 3, and 6 hours), and the medicated patches are undergone examination for variations in shape, color, and amount of drug as well as formulations should contain greater bioavailability at periodic intervals such as 0, 2, 3, and 6 hours.(11)

11. Ex-vivo mucoadhesive strength: The freshly sliced buccal tissues of sheep or rabbit, has been employed to conduct the ex-vivo mucoadhesive study thus the ex-vivo mucoadhesion time has been recorded shortly after the oral patch has been placed. The freshly cleaned buccal tissue was attached on the glass slide, as well as adhesive film has been moistened via a single drop of phosphate buffer solution at pH 6.8, thus complied to the buccal tissue with the help of mild force by using fingertip for 30 seconds. Once the glass slide gets placed in a container or beaker which holds 200 milliliters of phosphate buffer solution with pH level 6.8 which keeps temperature at 37°C ± 1°C. In an attempt to accurately represent the environment of oral cavity, a 50 rpm stirring rate has been applied within couple of minutes, whereas adhesion of patch has been recorded over a period of twelve hours. The period of time it usually takes to transform the shape, color and drug content of the film's.(15)

12. Ex-vivo permeation study: Here modified Franz glass diffusion cell has been employed for ex-vivo permeation study, thus the ex-vivo buccal absorption via the porcine buccal tissue is carried out. The Porcine buccal tissue should be within couple shortly after slaying and can be bought from a nearby slaughterhouse. A fresh buccal tissue collected from a pig thus has been embedded among the receptor and donor compartments. The compartments are clasped together once the patch is gently pressed into the mucosa's smooth surface. The divided compartments are connected together tightly while the patch has been pressed gently against the mucosa's smooth outer layer. A single milliliter of simulated saliva with a pH level of 6.2 has been employed to hydrate or moisten the donor compartment, while 100 milliliters of ethanol and isotonic buffer with phosphate solution and its ration involves (20:80) are then added to the receiver compartment till it meets the membrane surface. Here magnetic stirrer has been used thus rotating with the help of magnetic bead at 50 rpm retains the fluid flowing inside the receptor compartment. The water jacket enclose the container regulates the ambient temperature at 37±0.2 °C. Thus a 2 milliliter of sample has been collected thus which was replaced with a new media further analysed with the help of spectrophotometer analysis at predetermined intervals. The permeation research has been conducted within three replicates.(17)

11. CONCLUSION:

A exciting innovation in administration of medication, thus the transmucosal patches for mouth ulcers minimizes the challengers associated with traditional dosing forms such mouthwashes, gels, and systemic remedies. They work around significant challenges includes metabolism in first

pass as well as rapid clearance of medication via sustained drug release, higher drug distribution, greater absorption and ease of patients to use. The review emphasizes h buccal films mucoadhesive qualities guarantee site-specific activity while also improving systemic medication absorption when necessary. The review article emphasizes the way buccal fims adhesive features provide particular site yet enhancing absorption of medication systematically whenever desired. Although approaches of assessement maintains effectiveness, safety and compliance among patient, thus various kinds of methods of manufacturing which includes hot-melt extrusion method, solvent casting method and direct milling, which offers flexibility in formulation development. Since there are existence of some issues with masking of flavour, inadequate loading of drugs, and stability of the product, these systems merits significantly exceed their disadvantages they pose. Though the transmucosal patches offers an abudance of promises as a patient-friendly and efficient treatment approach for curing mouth ulcers, thus according to the current development in the science of polymers, integration of nanocarrier, and membrane adhesive technology, thus they could possibly improve therapeutic outcomes.

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