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Mucoadhesive Patch: A Novel Drug Delivery.

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Review Article

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ABSTRACT

During the past few decades, advances in drug formulations and innovative routes of administration have been made and simultaneously our understanding of drug transport across tissues has increased. Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed, to safely achieve its desired therapeutic effects. It is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products. It is a concept heavily integrated with dosage form and route of administration. Also these technologies and mode of administration modify the drug release profile, and other pharmacokinetics and dynamics. Oral mucous membrane being vascular, highly permeable and accessible, allows for the systemic uptake of drugs painlessly and at a steady rate of delivery also bypassing the stomach environment and first-pass liver metabolism. The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. This review enlightens about these novel drug delivery by mucoadhesive patches, their history, manufacturing, properties, advantages and disadvantages.

INTRODUCTION

Continued developments in the field of chemistry, molecular biology and genomics support the discovery and developments of new drugs and new drug delivery systems. The drug delivery system employed can control the pharmacological action of a drug, influencing its pharmacokinetic and subsequent therapeutic profile. During the past few decades, advances in drug formulations and innovative routes of administration have been made and simultaneously our understanding of drug transport across tissues has increased. These advances have often resulted in improved patient adherence to the therapeutic regimen and better pharmacologic response. The administration of drugs by transdermal or transmucosal routes offers the advantage of being relatively painless.

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed, to safely achieve its desired therapeutic effect. It may involve scientific site-targeting within the body, or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products. Drug delivery is a concept heavily integrated with dosage form and route of administration.

Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance.

Among the various transmucosal routes the oral mucosal lining has added advantages of being highly vascularized, accessible and easy control over the drug dosage administration. The permeability of the oral mucus membrane is estimated to be about 4000 times that of the epidermis; which allows for the systemic uptake of

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drugs painlessly and at a steady rate of delivery also bypassing the stomach environment and first-pass liver metabolism [1].

The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva.

Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.

Flexible films may be used to deliver drugs directly to a mucosal membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Buccal adhesive films are already in use commercially. They present a greater patient compliance compared with tablets owing to their physical flexibility that causes only minor discomfort to the patient. Patches are laminated and generally consist of an impermeable backing layer and a drug-containing layer that has mucoadhesive properties and from which the drug is released in a controlled manner.

Buccal dosage form for buccal delivery [2]

In the past decades, to till now, different drug delivery systems intended for buccal administration have been developed. The most common buccal dosage forms are tablets and patches. Such type of form must be of a small size and a suitable geometry so as to not interfere with physiological function of the mouth, even after their hydration in the oral cavity. One of the requirements is that they do not adhere too tightly because it is undesirable to exert too much force to remove the formulation/ dosage form after use, otherwise the mucosa could be injured. An alternative is the use of formulations that dissolve or disintegrate completely during the application period. Moreover, in the case of transmucosal administration, drug release should be unidirectional (towards the mucosa), and the release into the saliva should be avoided.

Types

Matrix type: This form consists of a matrix configuration of drug, adhesive and additive mixed together.

Reservoir type: This system consists of a reservoir which has a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth and to prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Following are the critical properties for candidature to Buccal Mucoadhesive Drug Delivery:

- The conventional single dose of drug should be low.
- Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
- The drug should not adversely affect the natural microbial flora or oral cavity.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

Design of Buccal Mucoadhesive Patches [3]

The different components of Buccal Mucoadhesive Patches are as following:

Drug: The important drug properties that affect its diffusion through the patch as well as the buccal include molecular weight, chemical functionality and melting point. The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on pharmacokinetic properties.

Polymers (Mucoadhesive polymers, polymers controlling rate of release and Polymers to prepare backing membrane):- As the contact between the formulation and the buccal mucosa is one of the key factors in successful buccal delivery, more emphasis is now given to the use of mucoadhesive polymers in the formulation of buccal drug delivery systems.

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Backing membrane: The polymer whose solution can be casted into thin poreless uniform water impermeable film can be used to prepare backing membrane of patches. It should have good flexibility and high tensile strength and low water permeation. They should be stable on long storage maintaining their initial physical properties per se. The cellulose acetate in concentration of 2.4% w/v in acetone with 10% of plasticizer (PEG 4000 or glycerol) of total polymer weight when air dried produces a thin film suitable for backing membrane purpose. Similarly, 2-4% w/v solution of ethyl cellulose in 1:4 mixture of alcohol: toluene and suitable plasticizer can be casted into film.

Plasticizer: - These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc.

Penetration enhancer: - Substances that help to promote drug permeation through the buccal epithelium are referred to as penetration enhancer, permeation promoters or absorption enhancer. Ideally chemical used as penetration enhancers should be safe, nontoxic, pharmacologically and chemically inert, nonirritant and non-allergenic. In addition, the tissue should revert to its normal integrity and barrier properties on removal of the chemical, surfactants, anions such as sodium laurate and sodium lauryl sulfate, cations such as cetylpyridium chloride.

Different mechanisms of actions of penetration enhancers:

- Disruption of the intercellular lipid domain and protein domain integrity.
- Extraction of membrane fluidization and reverse micellisation in the membrane, creating aqueous channels.
- Increase the fluidity of phospholipids in the intercellular lipid domain.
- Neutralizing the charge of the mucosal surface and by opening the tight junctions.

Because of the similarities between buccal mucosa and the skin, chemical enhancers and vehicles that increase transdermal delivery have also been used on the buccal mucosa.

Method of Preparation of Mucoadhesive Patches [4]

Mucoadhesive buccal patches can be prepared by methods mentioned below:-

1. Solvent Casting Method
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling Method

Evaluation of Mucoadhesive Patches

Evaluation of mucoadhesive buccal patches can perform as mention below:

Weight variation: It is done by comparing the average weights of 10 different patches from each batch and individual patch.

Patch thickness: It is measured at 5 different randomly selected spots with the help of a screw gauge.

Volume entrapment efficiency %: It is volume uptake capacity of buccal patches after adhesion into the buccal cavity.

Measurement of the % elongation at break: It is measured by using the following formula. % Elongation at break = Increase in length×100/Initial length

Surface pH: The patches are allowed to swell in contact with 0.5 ml of distilled water (pH 6.5±0.5) for 60 min at room temperature and pH is noted down.

Folding endurance: It is determined by repeatedly folding one patch at 180 angle of plane at same plane till it broke or folded to 200 times without breaking.

Stability study: It is performed at 40^0C 37 ±50^0C & 75±5% relative humidity for three months.

The current research is more focused towards the mucoadhesive type of films or patches containing different mucoadhesive components to extend the residence time of dosage forms at the site of application.

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Mucoadhesive buccal patches formulations reported in the literature

Though there is ample of work done in this field of mucoadhesive patch development but clinical usage is flimsy. The reported mucoadhesive buccal patches drug delivery system are summarized here.

In 2000 experiments were carried out on design and evaluation of diltiazem hydrochloride buccal patches. Results indicate that formulation containing drug reservoir with 3% HPMC and 3% EC as rate controlling membrane has achieved the objective of prolong drug release, drug frequency of administration and thus improved patient compliance [5]. Also work on design and evaluation of mucoadhesive buccal patch containing metoprolol tartrate was carried out. Study concluded that drug release could be obtained up to 8 hours with a polymer combination of CP934 and HEC in ratio of 1: 2. [6]. Work on preparation and evaluation of buccoadhesive films of atenolol concluded that, the addition of carbopol 934P increased the viscosity and swelling of the films there by controling the release of drug and improving mucoadhesive properties [7].

Experiments on transbuccal delivery of chlorpheniramine maleate from mucoadhesive buccal patches showed that *in vitro* drug release and moisture absorbed were governed by HEC content and formulations exhibited good tensile and mucoadhesive properties. Bioavailability from optimized buccal patch was 1.46 times higher than the oral dosage form and the results showed statistically significant difference [8].

In 2008, development of mucoadhesive patches for buccal administration of prochlorperazine: evaluation of *in vitro* release and mechanical properties was carried out. Results have shown that prochlorperazine maleate could permeate through human buccal membrane and hence showing a scope for development of buccal dosage form for prochlorperazine maleate at industrial scale [9]. In the same year experiments on development of mucoadhesive buccal films of glipizide was carried out. The films containing 5mg glipizide in 4.9% w/v HPMC with 1.5% w/v SCMC (F2), show good swelling, a convenient residence time and promising controlled drug release, thus seems to be a good candidate for the development of buccal film for effective therapeutic use [10].

In 2010 work on development of bilayered mucoadhesive patches for buccal delivery of felodipine: *in vitro* and *ex vivo* characterization was carried out by a group of researchers. Bilayered buccoadhesive patches for buccal delivery of felodipine could be prepared. It showed significant bioadhesive properties with an optimum release profile and could be useful for buccal delivery [11].

Another group of scientists had done work on development of mucoadhesive patches for buccal administration of ibuprofen. Result indicates that this buccal film is very tolerable and comfortable because it is non-irritant and may be preferred over adhesive tablet in terms of elasticity, flexibility and capability to protect the wounded or inflamed surfaces [12].

In 2010 a study on ten clinically diagnosed OSMF patients was carried out to evaluate the efficacy of dexamethasone mucosal patch for oral submucous fibrosis. In this study 5 patients were given intralesional injection of steroids and other group was placed with the steroid patch. Both group showed equal response in terms of burning sensation reduction but the patch group had shown significant improvement in terms of mouth opening [13].

Another study was carried out in 2010 on formulation and evaluation of Levofloxacin dental patch for periodontitis, where they found that it could release 99.74% of drug at the end of tenth day. It was concluded that it could be incorporated in a slow release device for the treatment of periodontitis [14].

A study was conducted in 2011 carried out to evaluate the wound healing activity of Curcumin and Centella asiatica extract and comparision with to rhEGF (Epidermal growth Factor, human recombinant). Mucoadhesive patches were prepared of both the active agents. The patches were applied on 10 human volunteers with oral lesions of various sizes ranging from 0.3- 0.5 mm. Two tailed p-value was calculated as 0.0001 which is considered extremely statistically significant. It was also noted that on its application of MABP (mucoadhesive buccal patch) to the lesions or scar injury of buccal mucosa the healing takes place on consecutive replacement of patch after 6 hours' time interval [15].

In another study, an in-vitro and clinical evaluation of Indomethacin mucoadhesive patches was carried out. The film was evaluated in patients with oral pain. Indomethacin at concentration of 0.5% and 1% provided optimum analgesic effects and it was greatest in 1% group and therefore it was stated that this formulation could be used for local analgesic effect [16].

In dentistry mucosal patches are being tried for various oral problems e.g. anesthetic patches, corticosteroid patches, analgesic patches, anti-inflammatory patches for ulcers. A study was conducted in 2008 to evaluate the efficacy and tolerability of a mucoadhesive patch and compared with a pain relieving oral solution for the treatment of aphthous stomatitis. Patients with active aphthous stomatitis were randomly treated either once a

day with a mucoadhesive patch containing citrus oil and magnesium salts (n = 26) or three times a day with an oral solution containing benzocaine and compound benzoin tincture (n = 22). The mucoadhesive patch was found to be more effective than the oral solution in terms of healing time with statistically significant results. Local adverse effects 1 hour after treatment were significantly ($p < 0.01$) less frequent among the mucoadhesive patch patients compared with the oral solution patients and it was found that mucoadhesive patch were significantly more effective and better tolerated than the oral solution in the treatment of aphthous stomatitis [17].

A preliminary study was carried out in 2013 to study the effect of benzocaine mucoadhesive patches (20%) on orthodontic pain caused by elastomeric separators. In this split mouth design of 30 patient sample size, they were instructed to apply benzocaine and placebo patches randomly for right or left first permanent molars of maxillary/mandibular arches for 20 min and repeat this procedure every 6 h with a similar type patch. A 10 cm Visual Analogue Scale (VAS) was used for pain perception assessment in patients who were given benzocaine (benzocaine group) or placebo (placebo group) patches. Pain perception (VAS) was recorded immediately after separator placement and after 2, 6, 12, 18, 24, 48 and 72 hours. It was concluded that the benzocaine 20% patches significantly reduced the post-separation orthodontic pain [18].

Another study was conducted in 2003 to compare the efficacy of a local anesthetic-impregnated mucosal adhesive patch (DentiPatch) with topical anesthetic (Hurricaine Dry Handle Swab) for gingival anesthesia before rubber dam clamp placement in children. Twenty-eight children needing sealants on their posterior teeth were enrolled in this study. Topical anesthesia was provided using either the mucoadhesive patch (20% lidocaine) or topical anesthetic (20% benzocaine). Subjects were randomized using a split mouth model. Either the patch or topical anesthetic was applied to the gingiva for 5 minutes or 1 minute, respectively. Subjects used a visual analog scale to describe their pain during the procedure. The visual analog scale results (pain scores) showed no significant difference between treatments. The mean per-child patch-sticking fraction was 29.7%. Patch adherence to oral mucosa increased with age in girls ($P = .0045$), but not in boys. It was concluded that the DentiPatch was as effective as, although not superior to, the Hurricaine Dry Handle Swab for gingival anesthesia before rubber dam clamp placement in children. Although this study results did not support the use of the DentiPatch for gingival anesthesia in children because of poor adherence to oral mucosa and the extra time necessary to apply and retain the device [19].

Also water soluble mucoadhesive film of lycopene has been formulation to treat one of the most common premalignant lesion of the oral cavity predominantly associated with smoking; Leukoplakia. Ex-vivo evaluation of mucoadhesion time and force were the criteria to optimize the film formation using propylene glycol as plasticizer [20].

Advantages of buccal patches [21]

- Drugs are absorbed from the oral cavity through the oral mucosa due to rich blood supply, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation.
- Due to direct entry into the systemic circulation these drugs bypass the first pass effect. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate.
- The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.
- Buccal patch has been well known for its good accessibility to the membranes that line the oral cavity, which makes application painless and with comfort.
- Patients can control the period of administration or terminate delivery in case of emergencies.
- The buccal drug delivery systems easily administered into the buccal cavity.
- The novel buccal dosage forms exhibits better patient compliance.

Limitations in buccal patches:-

- The area of absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.
- One of the major hindrances faced is continuous secretion of saliva into the oral cavity leading to dilution and low drug concentrations at the site of absorption. Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.

- Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route.
- Movement of the tongue can cause dislodging of the patch from the site.
- It is difficult to carry out normal activities like eating, drinking and talking with the patch in the mouth.

Conventional type of buccal drug delivery systems did not allow the patient to concurrently eat, drink or in some cases, talk.

CONCLUSION

The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. From both a financial and global healthcare perspective, finding ways to administer injectable medications is costly and sometime leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailability are needed. Improved methods of drug release through trans-mucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated.

Also it should be noted that many drugs have been evaluated in patch form only in the labs and very few have been tried clinically. A note should be taken to take these experiments out of the lab setups and keeping in note of all the safety parameters and care of patient, tried clinically to get harvest the maximum benefits.

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