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Review on use of Natural Polymers in Buccal Patch

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ABSTRACT: The main focus of this study is the use of natural polymers in the mucoadhesive buccal patches. The buccal mucosa is an attractive site for systemic or local action due to rich blood supply and relatively permeable. Natural polymers are used as the mucoadhesive polymer in a buccal patch and have more advantages over synthetic polymers like they are chemically inert, nontoxic, low production cost, biocompatible and biodegradable. Natural gums are widely used in various dosage forms as a natural excipient and play a major role in the pharmaceutical formulations either directly or indirectly influence the absorption of drugs and the release of a drug. These natural polysaccharides form strong adhesion bonds with the mucin molecules due to the presence of hydroxyl and carboxyl groups in their structure hence it increases the contact time with the mucous membrane and controlled release of the drug can be achieved. This review article outlines the use of natural polymer in buccal drug delivery system, advantages, disadvantages, and natural gums source, properties anduses.

KEYWORDS: Mucosa, buccal drug delivery system, natural polymers, controlled release, buccal patch.

I. INTRODUCTION:

Most of the drugs in the pharmaceutical field formulated as oral solid dosage forms because of their low cost, self-medication, and ease of administration. But for the pediatric and geriatric and mentally ill patients are difficult to swallow the tablets and capsules and undergo hepatic first-pass metabolism. So, the recent advance in a novel drug delivery system has been made to increase patient compliance by formulating the dosage form that is convenient to the patient and also modifying the delivery of drugs. [1,2]

Amongst the various drug delivery systems, buccal drug delivery is the most convenient and easily accessible site for the administration of a drug. Because of the rich blood supply in buccal mucosa the drug enters directly into systemic circulation thereby increase in absorption of the drug by avoiding the first-pass metabolism and drug degradation in the gastrointestinal environment.[3] Various buccal dosage forms have been developed such as buccal tablets,buccal patches, buccal gels, buccal wafers, and ointments.[4] Among all these dosage forms buccal patches are easily administered and can be terminate the input of the drug by removing the patch from the applied site because of the flexibility of the patches.[5] Mucoadhesive polymers are may be natural polymers and synthetic polymers. But natural polymers have more advantages than synthetic polymers like biocompatibility, biodegradability, low cost, non-toxic, and easily available. [6]

Structure of the oral cavity:

Oral mucosa is a mucous membrane lining inside the mouth consist of the outmost layer oral epithelium contains stratified squamous epithelium, basement membrane beneath lamina propria the connective tissue, and innermost layer submucosa.[2]

Oral mucosa acts as a protecting barrier for the inner lining tissues from the harmful environment and prevents the entry of bacteria. The buccal cavity contains both keratinized and non-keratinized epithelium. Non-keratinized epithelium presents in the soft palate, inner cheeks, inner lips, and the anterior surface of the tongue, are most permeable and keratinized epithelium present in the gingival and hard palate, are less permeable. Permeability of buccal mucosa is more than the skin which differs in various regions and keratinization in these regions. Permeation of drugs into oral mucosa through passive diffusion either by transcellular and paracellular pathways depends on the nature of the drug. [2,7]

BUCCAL DRUG DELIVERY SYSTEM:

Buccal drug delivery system is defined as delivery of drug through the buccal mucosa lines and its lines in the inner region of the cheek. The drug should be placed in the mouth in between the gums and cheek. Delivery of drugs through this system can produce local and systemic action. [8]

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Classification of buccal drug delivery system:

1. Buccaltablets,
2. Buccalpatches
3. Buccalfilms
4. Buccalwafers
5. Buccalgels
6. Buccalspray
7. Buccal microspheres. [9,10]

Advantages of buccal drug delivery:

1) The administration of drugs through the buccal route is easy even for an unconscious patient.
2) The drug is transported through the facial vein after absorption and enters into blood circulation via the jugular vein and avoids first-pass metabolism by passing through theliver.
3) By placing the drug in the mouth for a prolonged period of time-controlled release of the drug can beachieved.
4) Drugs that show poor absorption through the oral route can be administrated by this route.
5) Termination of the drug from the applied site is easy in case of any toxicity even after the administration ofdrugs.
6) High patient compliance compared to non-oral routes.
7) Permeability of buccal mucosa is high when compared to the transdermal drug delivery via the skin.[2,11]

Disadvantages of buccal drug delivery:

1) Drugs with a bitter taste, bad odor are not suitable for the buccal drug deliverysystem.
2) Due to the presence of saliva in the oral cavity the continuous loss of drugs due to dilution.
3) Drugs that are unstable in buccal p^H are cannot be administered by thisroute.
4) The patient feels uncomfortable or difficult for eating anddrinking.
5) The surface area of the buccal mucosa is less compared to the skin. Only drugs that have low doses can be formulated and administered by the buccal route.[2,11]

Buccal patch:

The buccal patch is a non-dissolving thin matrix modified release dosage form composed of one or more polymers containing the active ingredient and other excipients. This mucoadhesive polymer is used to adhere to the buccal mucosa and stays for a prolonged period in the mucosa for the controlled release of drugs. [9,10]

Composition of the buccal patch:

1. Activeingredient
2. Adhesive polymers: Polyvinylpyrrolidone, polyvinyl alcohol, Carbopol, hydroxypropylcellulose.
3. Plasticizers: Polyethylene glycol, glycerin, propylene glycol, diethylphthalate.
4. Sweetening agents: Aspartame, saccharin sodium,mannitol.
5. Backing layer: Polyethylene glycol, glycerin, propylene glycol, diethylphthalate.
6. Flavors: Menthol, Clove oil, vanillin.
7. Penetration enhancers: Sodium lauryl sulfate, chitosan.[9,12]

Bioadhesion:

Bioadhesion is defined as the ability of material adheres to a biological membrane for a prolonged period by interfacial molecular attractive forces.

Mucoadhesive system is defined as adhesion of natural or synthetic polymer attached to the mucous membrane and the system is designed to prolong the retention of the drug at the applied site for controlled drug release either systemic or local effect.[13]

Mechanism of Mucoadhesion:

In general, mucoadhesive must spread over the mucous membrane to initiate close contact and increase the surface area of contact. Mechanism of mucoadhesion involves mainly two stages:

- Contactstage
- Consolidationstage**.**

In a mucoadhesive drug delivery system, attractive and repulsive forces are very important to increase the contact between the adhesive and the mucous membrane. Therefore, in the first stage, the mucoadhesive comes contact with the mucous membrane causes wetting and swelling of the adhesive polymer due to components present within the mucoadhesive material have an affinity for water. Once the dosage form approaches the mucous membrane then it will come into contact with repulsive forces like electrostatic repulsion and attractive forces like Van der Waals forces and electrostatic attraction force. Attractive forces between the membrane and the adhesive are important to prolong the contacttime.

In the consolidation stage, a mucoadhesive material is activated in presence of moisture, and therefore the molecules in the mucoadhesive break free and cause the formation of weak chemical bonds between them like covalent bonds and weak

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interactions like Van der Waals and hydrogen bonds. [13,14]

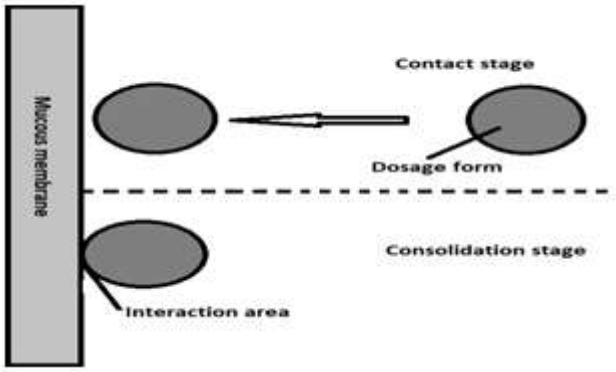

Fig. 1Mucoadhesion

Theories ofMucoadhesion:
There are six theories of mucoadhesion is classified depends on the biological material and the mucoadhesivepolymers:

- Adsorptiontheory
- Wettingtheory
- Electronictheory
- Fracturetheory
- Diffusiontheory
- Mechanicaltheory.[14]

Adsorption theory:
In the adsorption theory, the bioadhesive polymer adheres to the mucous membrane because of the forces present at the secondary surface, forces like hydrogen bonding, and van der Waals forces.[15]

Wettingtheory:
The wetting theory is only applied to the liquid system and considers surface and interfacial energies. The wetting theory is an ability of a liquid to spread over the mucous membrane and form strong adhesion and the affinity of liquid to the mucous membrane for spreading can be determined by the contact angle, with the general rule lower the contact angle then greater the affinity of liquid on the mucous membrane. [14,16]

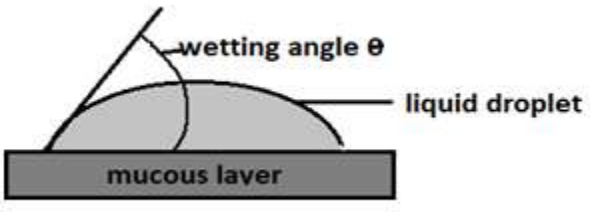

Fig. 2Influence of contact angle

If $\Theta \geq 90^0$ - incomplete wetting of the liquid system on the mucous layer.
If $\Theta \leq 90^0$ - wetting is good.
If $\Theta = 0$ - then the liquid system completely wets the mucous layer.

Electronic theory:
The electronic theory explains that when the adhesive layer contacts the mucous layer there will be a transfer of electrons between them because of opposite electrical charges. This results in the formation of an electrical double charge at the interface of the mucous membrane and adhesive layer due to the presence of attractive forces. [16,17]

Fracture theory:
The fracture theory is slightly different from other theories because it determines the measurement of mucoadhesion. It analyzes the force required to

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separate the two surfaces after the adhesion.[14]

Diffusion theory:

Diffusion theory explains the interpenetration of mucoadhesive polymer and mucin chains to a sufficient depth to create semi-permanent adhesive bond and adhesion force increases with the degree of penetration of polymer chains. Penetration mainly depends on the diffusion coefficient, mucoadhesive chains, mobility, and contact time. [14,16]

Mechanical theory:

The mechanical theory considers adhesion to be due to the filling of irregularities on a rough surface by mucoadhesive liquid. Due to roughness on the surface increase the surface area for interactions thereby aiding dissipating energy and can be considered as the most important phenomenon of this process. [17]

Mucoadhesive polymers:

The term mucoadhesive polymer indicates that the adhesion of the polymer to a mucous membrane and polymer may be a natural or synthetic polymer. Mucoadhesive polymers are used to improve the delivery of the drug by increasing the contact time and residence time in the mucous membrane so does control of the release of dosage form can be achieved. The polymers used may be water-soluble or water-insoluble.[18] These polymeric materials contain numerous hydrogen bonding forming groups such as carboxyl groups and hydroxyl groups from the secondary chemical bond with a mucous membrane containing functional groups.

Mucoadhesive polymers adhere to the mucous membrane divided into three classes:

- Polymers become sticky when in contact with the water and their Mucoadhesion is stickiness.
- Polymers that adhere through non-specific, non-covalent interactions areelectrostatic.
- Polymers that bind to a specific receptor site on a tile self-surface.[17]

Characteristics of ideal mucoadhesive polymers:

1. Should not decompose onstorage.
2. The flexibility of mucoadhesive polymer is very important in controlling interpenetration between the polymer and mucousmembranes.
3. The mucoadhesive polymer should be non-toxic and non-absorbable to the gastrointestinal tract. Polymers should be a non-irritant to the mucousmembrane.
4. Polymers that are water-soluble form stronger adhesive bonds with mucous membranes because the mucus layer contains a large amount ofwater.
5. It should adhere to the mucous membrane quickly and should possess site-specificity. Polymers should be compatible with the dosage form formulated should be no interactions.[17-19]

Classification of mucoadhesive polymers:

1) Based onsource

a) Natural polymers: Tragacanth, sodium alginate, guar gum, xanthan gum, karaya gum, soluble starch, cashew nut tree gum, chitosan, tamarind seedgum.

b) Synthetic polymers: Cellulose derivatives-Carboxymethylcellulose, methylcellulose, hydroxymethyl cellulose, thiolated Carboxymethylcellulose, Poly (acrylic acid) based polymers-polyvinylpyrrolidone.

2) Based onsolubility

a) Water-soluble: Sodium alginate,Hydroxypropylmethylcellulose.

b) Water insoluble:Chitosan.

3) Based oncharge

a) Anionic polymers: sodium alginate, xanthangum.

b) Cationic polymers: Chitosan,Aminodextran.

c) Non-ionic polymers: Hydroxypropylcellulose, Polyvinyl alcohol.[20]

Natural polymers:

Natural polymers are obtained from plant origin, animal origin, and microbial origin. For example, guar gum is of plant origin and alginate from microbial origin, and chitosan from animal origin. [21]

These natural polymers are gained attention in the pharmaceutical field as an excipient for various drug delivery systems. Natural polymers have various advantages over systemic polymers like low production cost, non-toxic, biocompatible, and biodegradable. Natural polymers are readily available and have multiple applications in pharmaceutical formulations as a thickening agent, disintegrating agent, diluents, mucoadhesive polymer, emulsifying agent, suspending agent, and as a binder. Almost all the natural polymers have sugar units which contain hydroxyl and carboxyl group in their structure due to this a strong non-covalent bond form between the polymer and the mucin molecules. [17]

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Advantages:

1. Biodegradable – biodegradable polymers are produced by living organisms and they show no adverse effects for the humanbeing.
2. Non-toxic and biocompatible – because natural polymer contains the sugar units i.e., monosaccharide hence they arenon-toxic.
3. Low cost – they are readily available and the production cost is less compared to syntheticpolymers.
4. Fewer side effects as compared to synthetic polymers and an easily available and renewablesource.
5. Natural polymers have high molecular weight hence suitable for the mucoadhesive system.[17]

Disadvantages:

1. Generally, natural polymers prone to microbial contamination during production because of the presence of moisture content and they arecarbohydrates.
2. Batch to batch variation occurs because of the collection of these natural polymers at a different time in differentregions.
3. Heavy metalcontamination.
4. Reduced viscosity on storage due to the complex nature of the natural polymers reduces viscosity onstorage.
5. Uncontrolled rate of hydration due to the collection of material at the different climatic conditions and different regions and species.[17,19]

There are various gums and mucilage's obtained from a natural source that is used in the formulation of a buccal drug delivery system either in combination with synthetic polymers or only the natural polymer as a mucoadhesive polymer.

Tamarind seed polysaccharide:

Tamarind seed polysaccharide is obtained from the kernel seeds of Tamarindus indica. TSP is a galactoxyloglucan with an average molecular weight of 52,350 Daltons. TSP contains the monomers of glucose, galactose, and xylose sugar units present in the molar ratio of 3:1:2, which constitutes 65% of seed components. [22,23]

Properties:

TSP is soluble in hot water at a temperature above 85^0C and insoluble in organic solvents like ethanol, methanol, acetone, ether, and TSP is insoluble in cold water.TSP has broad p^H tolerance, high viscosity, non-toxic, non-irritant, and biocompatible. Tamarind seed polysaccharide has a high drug holding capacity, high thermal stability, and high swelling index. [22]

Applications:

- Used as a binder in the solid dosageform.
- Used in the mucoadhesive drug delivery system as an adhesivepolymer.
- Used as a suspending and emulsifying agent in the liquidorals.
- TSP has good mucoadhesive strength so it can hold the drug on the applied site for a prolonged time hence controlled release of the dosage form is achieved in the ocular drug delivery system.[22]

In a literature review, TSP and sodium alginate blend is used as the mucoadhesive polymer in the preparation of mucoadhesive microspheres for oral gliclazide delivery (Dilipkumar Pal, Nayak, 2012). [25]

Cross-linked TSP and Carbopol are used as the mucoadhesive polymer in the formulation of the Metoprolol Succinate buccal tablet (Surawase, Maru, Kothawade, Lunkad, Kanade, 2011).
[26]

Sodium alginate:

Alginate is an anionic polysaccharide that is obtained from brown algae which contain a large amount of alginate in their cell wall. These are the linear polymers composed of (1 →4)–α-L-guluronic acid, (1→4)–β-D-mannuronic acid is linked by glycosidic bonds. Bacterial alginates are mainly synthesized from two bacterial genera i.e**.** Pseudomonas aeruginosa and Azotobacter vinelandii**.** Sodium alginate is the sodium salt of alginic acid or alginate. And sodium alginate is insoluble in organic solvents like ethanol, methanol and slowly soluble in water.[26,27]

Applications of sodium alginate:

- Sodium alginate is used as a gelling agent in many pharmaceuticalpreparations.
- In the food industry, used as a thickening agent, stabilizer, and emulsifyingagent.
- It is also used in the buccal drug delivery system as a mucoadhesive polymer by combination with synthetic polymers.[26]

In a literature review, sodium alginate and TSP blend is used as the mucoadhesive polymer in the preparation of mucoadhesive microspheres for oral gliclazide delivery (Dilipkumar Pal, Nayak, 2012). [25]

In a literature review, sodium alginate is used in the formulation of Ramipril buccal films.[29] (Hyma, Kumar, Damayanthi, 2016). [26]

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Cashew nut tree gum (Anacardium occidentale):

Cashew nut tree gum is obtained from the incised trunk of the tree Anacardium occidentale. It is a branched and complex polysaccharide that contains glucose, galactose, rhamnose, D-mannose, and D-glucuronic acid, and 4-O-methyl-glucuronic acid. [29]

Uses of cashew nut tree gum:

- Initially, it is used as adhesive for envelopes, labels, stamps,posters.
- Used as an additive in the manufacture of chewing gum because of its thickening power.[29]

A literature survey reveals that the gelling property of cashew gum of Aceclofenac gel had been studied (Kumar, Patil, Patil, Paschapur, 2009). [30]

The use of cashew gum as a sustained release and mucoadhesive in the formulation of the buccal tablet for curcumin had been studied (Gowthamarajan, Jawahar, Wake, Jain, Sood, 2012). [31]

Cashew nut tree gum is used as a binder in the formulation of paracetamol tablets (Gowthamarajan, Kumar, Gaikwad, Suresh, 2011). [32]

Xanthan gum:

Xanthan gum is a microbial polysaccharide obtained from bacterium Xanthomonas campestris found on cabbage plants that produces an extracellular polysaccharide with exceptional rheological properties. Xanthan gum consists of 1, 4-linked β-D-glucose residues having a trisaccharide side chain attached to alternate D-glucosyl residues. Xanthan gum is soluble in hot and cold water and insoluble in alcohol. [27,33]

Applications of xanthan gum:

- Xanthan gum is used in cosmetic products as a thickener and stabilizer in creams, eye contour gel. It is also used in toothpaste as athickener.
- In emulsions and suspensions, xanthan gum prevents the separation of insoluble ingredients.
- Used in the food industry as a thickener and stabilizing agent mainly in salad dressings.[33]

In a literature review cross-linked starch and xanthan gum hydrogels used as film-forming material for control, the release had been studied (Shalviri, Liu, Abdekhodaie, Xiao Yu Wu, 2009). [34]

Xanthan gum is used as a drug release modifier and mucoadhesive polymer in the formulation of zolmitriptan bilayered buccal patches (Shiledar, Tagalpallewar, Kokare, 2014).

Table 1: - Buccal dosage forms formulated using natural polymers:

S.No	Natural Polymer	Drug	Dosage form
1.	Tamarind seed polysaccharide	Gliclazide Metoprolol Succinate Rizatriptanbenzoate	Mucoadhesive microspheres.[24] Mucoadhesive buccaltablet.[25] Mucoadhesive buccal film.[35]
2.	Sodium alginate	Ramipril Diltiazem Hydrochloride Methotrexate	Mucoadhesive buccal film.[28] Mucoadhesive buccal tablet.[36] Mucoadhesive buccal patch.[37]
3.	Cashew nut tree gum	Curcumin	Mucoadhesive buccal Tablet.[31]
4.	Xanthan gum	Zolmitriptan Tizanidine Hydrochloride	Bilayered buccal patch.[3] Mucoadhesive buccal Tablet.[38]
5.	Chitosan	Carvedilol Ondansetron Hydrochloride Verapamil Hydrochloride Propranolol Hydrochloride	Mucoadhesivebuccal Patch.[39] Mucoadhesive buccal Film.[40] Mucoadhesive buccalPatch.[41] Mucoadhesive buccalPatch.[42]

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II. CONCLUSION:

The use of natural polysaccharides in the buccal drug delivery system recently gained attention because they are safe, readily available, chemically inert, biodegradable, non-toxic, biocompatible, and low production cost. Natural polymers are used as mucoadhesive polymers to help in improving bioavailability by increasing the contact time at the applied site hence controlled release of the drug can be achieved. And buccal drug delivery system has advantages over conventional drugs like avoiding hepatic first-pass metabolism, reduction in dose frequencies, and improvingbioavailability.

From the above study, one can conclude that natural polymer-based mucoadhesive buccal patches provide good adhesion between polymer and the mucous membrane and it is necessary to confirm the residence time and permeation of natural polymer-based mucoadhesive buccal patches by in-vivo studies. So, we can expect that the addition of naturalmucoadhesive polymer in the buccal patch may be one of the important dosage forms in future pharmaceuticalformulations.

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