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An analytical assessment on Mucoadhesive Buccal Drug Delivery System for improving patient convenience and compliance

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ABSTRACT

In recent years, the novel mucoadhesive buccal drug delivery system has been developed over the conventional and systemic dosage forms. To bypass drugs from the hepatic first-pass metabolism and it enhances the bioavailability of drug at the site of administration. Absorption of a drug through the buccal mucosa reduces the degradation. Some of the enzyme activity and pH variation in the gastrointestinal tract reduces the absorption and active drug loss. To overcome this problem, the buccal route is preferred. Polymers are used in this formulation to improve the drug release rate over an extended period, and also, the therapeutic plasma level of the drug can be rapidly achieved. Overall this narrative review explains mechanism and theories, method of preparation, factors affecting mucoadhesion, advantages and limitations, applications, components used in the formulation, characterization and evaluation methods. Since the cytoplasm and intercellular spaces are hydrophilic. Lipophilic drugs have a low solubility in this environment. However, the cell membrane is rather lipophilic; it tends to difficulty permeating the hydrophilic solute through the cell membrane because of a low partition coefficient. Therefore, the cytoplasm and intercellular spaces act as a major barrier to penetration of lipophilic compounds and the cell membrane poses as an extensive transport barrier for hydrophilic compounds. Since the oral epithelial is stratified, the permeation of solute may involve these combination routes so that the route is more predictable.

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INTRODUCTION

Over the past few years, novel in drug formulations and advanced routes of administration have been developed. These advanced drug formulations enhance drug transport across tissues. The innovative formulation improves patient adherence to the therapeutic agent and improves pharmacologic response (Mahajan *et al.*, 2013). The administration of a drug by transmucosal route (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity). Especially, the mucoadhesive buccal drug delivery system is an ideal formulation compared to the other routes. It enhances sustained, controlled release drugs at a targeted

site for an extended period, and relatively being painless (Shinkar *et al.*, 2012). Additionally, buccal drug delivery has more patient acceptability than other non-oral transdermal routes of drug administration. It directly enters into the systemic circulation through the internal jugular vein. Controls acid hydrolysis in the gastrointestinal tract (GIT) and avoids drugs from the hepatic first-pass metabolism, hence leads to high bioavailability. However, fast cellular recovery of the buccal mucosa is another advantage of this route (Reddy *et al.*, 2011).

Mucoadhesive drug delivery systems can be delivered by various routes (Singh *et al.*, 2017)

1. Buccal delivery system
2. Oral delivery system
3. Rectal /Vaginal delivery system
4. Nasal delivery system
5. Ocular delivery system

Buccal delivery system

The buccal delivery system is similar to transdermal drug delivery systems (TDDS). Example of buccal delivery is buccal patches, films. Which consists of impermeable backing membrane and reservoir layer from which the drug is released in a controlled manner? It can be prepared either by solvent casting or direct milling. An impermeable backing membrane may also be applied to control the release of the drug, prevent drug loss, and minimize disintegration. Suitable bioadhesive buccal patches with desired permeability buccal delivery show good absorption and bioavailability compared to the oral solution. Buccal patches and films of sustained-release drugs bypass the extensive hepatic first-pass metabolism along with increased bioavailability (Sonawane *et al.*, 2017).

Oral delivery system

The oral delivery system has several advantages for the administration of macromolecules (i.e. proteins). It also avoids pain and discomfort related to injections as well as infections caused by the use of needles. Oral mucosa is highly permeable, rapid absorption convenient and shows adequate bioavailability of drugs. Delivery of the drug across the oral mucosa can be classified into three different types. They are,

1. Sublingual drug delivery: Administration of the drug through the mucosal membrane of the dorsal surface of the tongue and lining the floor of the mouth.
2. Buccal drug delivery: The administration of the drug through the buccal mucosa, mainly consists of the lining of the cheeks. In the human body oral cavity is the anterior part of the digestive system. It is also called a "buccal cavity".
3. Local drug delivery: Administration of the drug through all areas other than these two regions. These, site anatomically varies in their rate of drug delivery, permeability to drugs, and the ability to maintain a drug for a prolonged period.

Rectal /vaginal drug delivery

New rectal /vaginal drug delivery has been developed to improve the pharmacological effects of various classes of drugs like anti-inflammatory, analgesic and antiseptic drugs (Mansuri *et al.*, 2016). The drugs are given by rectal which do not undergo the first-pass metabolism in the GIT and the liver. It is an approved delivery system for infants, children, and unconscious patients. A suppository is a good example of the vaginal delivery system; it contains medicated solid dosage form which melts at body temperature.

However, suppositories often give the patients a feeling of discomfort, alien during insertion and refusal. The leakage of suppositories from the vagina gives itchy feelings to the patients.

Nasal delivery system

The nasal mucosa has a common administration site for systemic drug delivery an alternative route to parenteral drug delivery due to its self-medication and virtually painless. In modern pharmaceutics, the nose has been considered mainly as a route for local drug delivery particularly important in the management of difficult situations such as severe nausea and vomiting (Sangeetha *et al.*, 2010).

Nowadays, the nasal cavity is being particularly used for therapeutic agents like peptides and proteins for immunization purposes. Nasal drug delivery is essential for medications used in emergency medical situations.

Ocular delivery system

The mucoadhesive concept is now considered as a new approach to optimizing the ocular dosage form. There are so many disorders of the eye that can be treated by the topical application of the drug, and this administration is well accepted. Viscous semi-solid preparations, i.e. gel and ointments, provide sustained contact with the eye, but they lead sticky sensation, blurred vision, irritation and blinking due to discomfort.

Mechanism of mucoadhesion

The contact between the surface and pressure-sensitive adhesive substance is called adhesion; otherwise, it can be defined as two surfaces are attached because of their interlocking action or valence interfacial force or else both.

In this bio adhesion is the adhesion of natural or synthetic material on biological membrane but in mucoadhesion, adhesion of materials to an epithelial membrane takes place (Reineke *et al.*, 2013).

Mucoadhesion occurs in two stages. They are,

Stage-1(contact stage)

It is characterized by wetting, spreading, and swelling of the bioadhesive membrane, it creates close contact between a membrane and bioadhesive material. In some cases of vaginal in Figure 1 or ocular formulations, the delivery system is established mechanically over the membrane (Rajaram and Laxman, 2017).

Stage-2 (consolidation stage)

It is characterized by penetration of the mucoadhesive/ bioadhesive between two surfaces of the mucous membrane due to hydrogen bonding and hydrophobic interactions, Vander walls forces or electrostatic attractions. Consolidation step is explained by two theories:

Diffusion theory

It is a chemical as well as mechanical interaction. Here, mucus glycol protein reacts with the mucoadhesive moieties by interpenetrating their chains and forming secondary bonds.

Dehydration theory

Mucus and adhesive material are after contact with each other; they undergo dehydration until osmotic pressure reaches equilibrium. A mixture of mucus and material is obtained in the form of a gel (Verma, 2018).

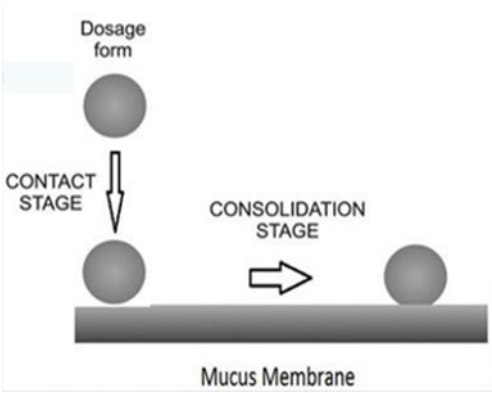

Figure 1: Stages of Mucoadhesion

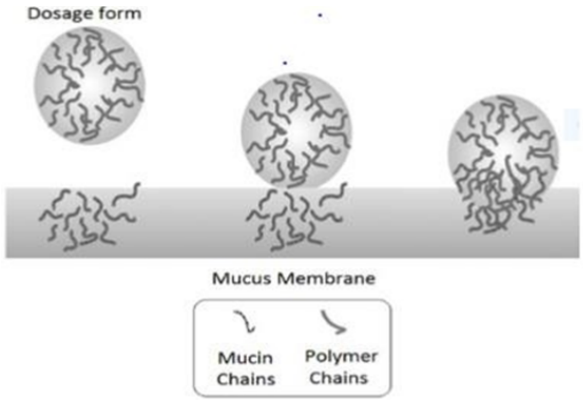

Figure 2: Diffusion interlocking theory

Theories of mucoadhesion

To describe the mechanism of mucoadhesion several theories have been proposed, they are (Mohanty *et al.*, 2018),

1. Wetting theory
2. Adsorption theory
3. Electronic theory
4. Fracture theory
5. Mechanical theory
6. diffusion interlocking theory

Wetting theory

This theory applicable to the liquid system. It explains the ability to spreadability of the polymer. Is having an affinity to the surface to spread over it. The affinity can be determined by using different techniques such as the contact angle. Affinity is indirectly proportional to the contact angle; it means, lower the contact angle greater the affinity (Caon and Jin, 2015).

Adsorption theory

In this mucoadhesive device, different types of chemical bonding play an important role in the adhesion interaction, i.e. Hydrogen bonds, Vander walls, and electrostatic attraction (Dodou *et al.*, 2005).

Electronic theory

In this theory, the electron transfer between mucoadhesive and biological membrane leading to the formation of a double electronic layer at the interface of the mucoadhesive and membrane due to differences in their electronic structure. This results in attractive forces with the double layer and determines the strength of mucoadhesive (Ahagon and Gent, 1975).

Table 1: The different components used in the Mucoadhesive buccal drug delivery system are as follows

Sl.no.	Components	Example	Uses
1	Polymers (Smart, 2005)	Sodium carboxymethylcellulose, methylcellulose, Hydroxyethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol. etc.	Polymers control the rate of release of drug from the buccal mucoadhesive film.
2	Diluents	Lactose DC, microcrystalline starch and starch	To enhance the aqueous solubility improves its flavoring characteristics
3	Backing layer	Ethylcellulose, cellulose acetate, etc.	It should provide good flexibility and high tensile strength, and stabilizer
4	Penetration enhancer	Cyano acrylate, cyclodextrin cetylpyridium, etc.	Substances that help to enhance drug permeation through a buccal epithelium and absorption
5	Plasticizer (Averineni *et al.*, 2009)	PEG-100,400, propylene glycol glycerol, castor oil, etc.	The substance which is used to improves the softness and flexibility of the thin buccal film
6	Flavouring agents	Clove oil, menthol, peppermint oil, vanillin, etc.	To enhance the therapeutic effect.
7	Sweetening agents	Mannitol, sorbitol, glycerol, sucrose, aspartame, etc.	They are used to reduce the bitter taste of the formulation and increase the palatability of the therapeutic agents
8	Drug	Antibiotic (ofloxacin, cephalexin),antifungal (fluconazole, clotrimazole) NSAIDS, etc.	To exist therapeutic effectiveness at a specific site.

The fracture theory

This fraction theory is necessary to explain, the force required to separate bonds of adhesion between two surfaces (Gilhotra *et al.*, 2014).

Diffusion interlocking theory

This theory explains mucoadhesive polymer chain diffuses into the mucous layer due to the breaking of the glycoprotein chain network Figure 2. This diffusion is depending on diffusion co-efficient and time-dependent also concentration-dependent (Sharma *et al.*, 2012).

Methods of preparation of mucoadhesive drug delivery

Solvent casting

The solvent casting method is the widely preferred method for the preparation of buccal film/patches (Nagpal *et al.*, 2016). In this method, all film/patch excipients, including the polymer

along with drug dispersed in an organic solvent (Reena, 2018). Above solvent mixture kept for overnight, and then triturated until to get a homogenous system then add glycerine and forms a gel in a Table 1. To prevent entrapment of the air bubbles inside the patch/film, the entire gel was subjected to vacuum desiccators to remove bubbles. Then the gel was transferred into glass molds lined with an aluminium foil and allows gel casting for a period of 24 hr. The dried films are obtained, then remove from the glass molds, then patches are die-cut into the desired size and geometry. The patches were packed in aluminium foil and stored at room temperature then maintained the integrity and elasticity of the films (Ahuja *et al.*, 1997).

Direct milling

Drugs and excipients are mixed by kneading, usually without using any liquids. After the mixing process, the mixture is rolled on a release liner until the desired thickness is obtained. The backing material is then laminated. To characterize the film solvent-free process is selected because there is no possibility of residual solvents and no other solvent related health issue (Khan *et al.*, 2014).

Hot-melt extrusion of films

In the hot-melt extrusion method, shaping a polymer into a film through the heating process. A blend of all active pharmaceutical ingredients in a dry state. Then it is filled in the hopper, conveyor, mixer then subjected to the heating process. In the extruder, the mixture gets molted and form a molten state. The molten mass then used to cast the film. Casting and drying is a critical process in this method. This method has many advantages like it can be carried out at a lower temperature and less time consumption. Continuous operation possible, reducing the wastage, improves product quality (Venkatalakshmi *et al.*, 2012).

Evaluation of mucoadhesive buccal films

Surface pH

For determination of the surface pH, the buccal patch is allowed to swell for 2 hr by keeping them in contact with 1 ml of distilled water at room temperature. The pH was recorded by using pH meter, placing the electrode in contact with the surface of the patch and allows equilibrating for 2 minutes (Yamsani *et al.*, 2007).

Thickness measurement

The thickness of each film/ patches was determined using an electronic digital micrometre. Usually, thickness measured at different locations (i.e. centre and four corners) (Smart, 2005).

Drug content

The prepared film/patch was analyzed for drug content. Five mucoadhesive films were taken and the contents are dissolved in suitable solvent phosphate buffer 6.8 in 100 ml volumetric flask. Shake well, the drug content was determined by measuring the absorbance at respective wavelength using UV-spectrophotometer (Averineni *et al.*, 2009).

Swelling studies

The films were cut into 3*2 cm2 pieces. Then calculate the primary weight of the film (W1), the swelling properties of patch/films was determined by placing films in phosphate buffer solution (pH 6.8) at 37°C.

At specified time intervals of 5 min, then films were removed from the solution and the swollen films were weighed (W2) and the swelling ratio was calculated (Reddy *et al.*, 2013).

Folding endurance

The folding endurance of the film/patches was determined by continuous folding a patch at the same place until it breaks or is folded up to 250 times without breaking (Madhavi *et al.*, 2013).

Mucoadhesive strength

Mucoadhesion studies are performed by using the physical balance. The porcine buccal mucosa membrane was collected from slaughterhouse excised and washed, then tied tightly to the upper part of glass vials, which contains PBS (pH 6.8) to keep the mucosal surface moisten.

The patch was then fixed with a little moist on to the surface of lower rubber closure hanging from then brought in contact with the mucosa. The balance is kept in this position for 5 min and then gradually weigh until the patch separated from the mucosal membrane surface (Castán *et al.*, 2015).

Tensile strength and percentage elongation to break

Tensile strength (TS) is the maximum stress applied to a specific part of patch/films without tearing. Elongation to break (EB) is the maximum deformation of patch/films length without tearing. TS and EB% were calculated by using the following equations (Salehi and Boddohi, 2017).

Morphological Characterization

Scanning electron microscope

The surface morphology of the selected films was studied by using a scanning electron microscope. after the film was gold-sputtered under vacuum visualize the film at an acceleration voltage of 80kV (Obaidat *et al.*, 2010).

Differential scanning calorimeter

This study was carried out to identify the arrangement of crystal on a pure drug, excipients, polymer, physical mixtures, and selected drug-loaded films. Accurately weighed samples were placed in aluminium pan and scans were performed under nitrogen stream (Anil and Preethi, 2018).

In-vitro Release Study

The *in-vitro* drug release study was performed by using a Franz diffusion cell, using commercially available dialysis membrane (Manivannan *et al.*, 2008). The receptor compartment was filled with phosphate buffer solution (pH 6.8.) The patches were placed on the dialysis membrane is fitted between the donor and receptor compartments of the cell. The drug release was carried out at 37±0.5°C, with continuous stirring using a magnetic stirrer (Nautiyal, 2013). The sample was withdrawn from the receptor medium at specific intervals. The amount of drug released into the receptor medium was determined by using UV–visible spectrophotometer at a specific wavelength against a blank (El-Kamel *et al.*, 2007).

Ex-vivo permeation study

The *ex-vivo* permeation studies of buccal films were carried out using an excised layer of the porcine buccal mucosa (Adhikari *et al.*, 2010). The study was carried out using the modified Franz diffusion cell. A piece of the patch was placed in intimate contact between excised porcine buccal mucosa and the top of the assembly was closed with aluminium foil. The receptor compartment was filled with phosphate buffer then stirred with a magnetic stirrer. The temperature of the instrument was maintained at 37±10C. The samples were withdrawn at a specified time of interval, then analyzed using a UV spectrophotometer at the respective wavelength (Labib *et al.*, 2014).

CONCLUSIONS

Now, innovative drug delivery systems designed to improve patient compliance and convenience. Therefore, massive work is going on to develop mucoadhesive buccal dosage forms to satisfy patient demands than conventional dosage forms. Buccal mucosa delivery improved a convenient way of dosing medication and controlled the release of drugs for a prolonged period. This formulation is economy, high patient compliance, and ease of administration. Mucoadhesive polymers improve bioavailability and residence time of the active agent. Mucoadhesion buccal film provides satisfactory treatment than other drug delivery systems.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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