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A Review on Mucoadhesive Buccal Drug Delivery System

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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.

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. 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.[1] 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.[2]

Since the cytoplasm and intercellular spaces are hydrophilic. lipophilic drugs having 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. [3]

Mucoadhesive drug delivery systems can be delivered by various routes:[4]

- Buccal delivery system
- Oral delivery system
- Rectal /Vaginal delivery system
- Nasal delivery system
- Ocular delivery system

1.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.

2. Oral delivery system[5]

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,

a) 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.

b) 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".

c) 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.

3.Rectal /vaginal drug delivery[6]

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. 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.

4. Nasal delivery system [7]

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. 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.

5.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 adhesion of natural or synthetic material on biological membrane but in mucoadhesion, adhesion of materials to an epithelial membrane takes place.[8]

Mucoadhesion occurs in two stages. (Fig. 1) 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 or ocular formulations, the delivery system is established mechanically over the membrane. [9]

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.[10]

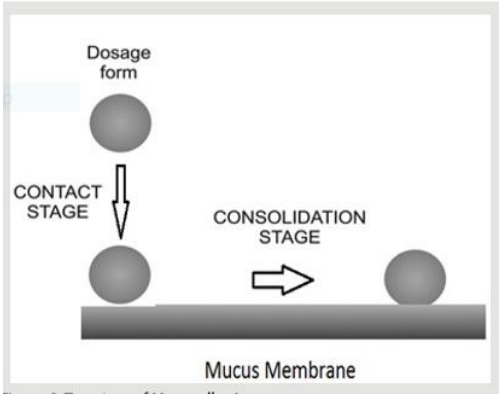

Figure No. 1: STAGES OF MUCOADHESION

Theories of mucoadhesion:[11]

To describe the mechanism of mucoadhesion several theories have been proposed, they are,

1. Wetting theory
2. Adsorption theory
3. Electronic theory
4. Fracture theory

5. Mechanical theory

6. diffusion interlocking theory

1. **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.[12]

2. **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. [12]

3. **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. [13]

4. **The fracture theory:** This fraction theory is necessary to explain, the force required to separate bonds of adhesion between two surfaces. Then fracture strength can be determined by using the following equation.[14]

$$\sigma = \sqrt{(E*\varepsilon)/L}$$

Where,

E=Young's modulus of elasticity, ε= the energy of fracture, and

L= the critical length of the crack.[15]

5. **Diffusion interlocking theory:** This theory explains mucoadhesive polymer chain diffuses into the mucous layer due to the breaking of the glycoprotein chain network. Fig.2. This diffusion is depending on diffusion co-efficient and time-dependent also concentration-dependent.[16]

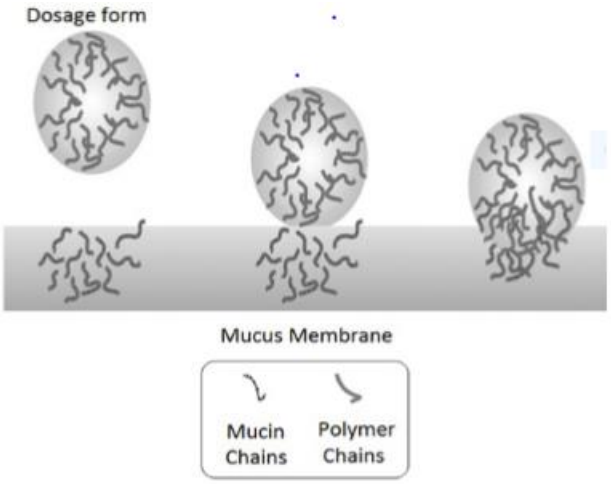

Figure No. 2 Diffusion interlocking theory

Importance of Mucoadhesive buccal Drug Delivery System: [17]

- It bypasses first-pass metabolism.
- Reduces fluctuation of plasma level at steady-state and increase the safety margin.
- Controlled release & Prolonged effect can improve.
- Target & localized drug delivery.
- Drug degradation can be avoided.
- It improves the permeability of drugs through the tissue.
- Better patient compliance and convenience, ease of drug administration
- Shorter treatment period and reduced dosing frequency.
- Rapid onset of action due to the mucous membranes.
- This route is an alternative system for the administration of various cardiovascular drugs, hormones, analgesics, narcotics, steroids, etc.
- Drugs that are unstable in the alkaline and acidic medium can be easily administered by this route.

Limitation of mucoadhesive buccal drug delivery system.[18]

- Drug having a bitter or unpleasant taste, the odor can irritate the oral mucosa which can't be administered by this route.
- Swallowing of the formulation may be occurred by the patient.
- Some of the drugs can't stable in the buccal pH.
- In this route only small dose drugs can be administered, which are absorbed by passive diffusion.
- Eating and drinking may become restricted.
- Overhydration may leads formulation to get disrupt and form a slippery surface.

Factor affecting much adhesion/ bio adhesion:[19]

1. Polymer-Related Factors: [19]

a. The molecular weight of the polymer:

The maximum adhesion/ mucoadhesion depends on the type of polymers. The forces of bioadhesive increase the molecular weight of the polymer**.**

b. Polymer chain length:

The active polymer molecule should have adequate chain length.

c. The concentration of polymer:

Polymer concentration is directly proportional to the bioadhesion. Higher concentration of polymer leads mucoadhesive strength significantly enhanced.

d. Molecular flexibility:

It is important for enlargement and interpenetration. As the mobility of the individual active polymer chain decreases, Due to the cross-linking of the water-soluble polymer. It facilitates the cross-linking density increases, they result from the penetration power of the active

polymer into the mucous layer decreases and also bioadhesion/ mucoadhesion strength is decreased.

2. Environmental factors:[20]

a.pH

pH shows a significant effect on mucoadhesion. It influences the charge on the surface of both the mucous membranes and polymers. Mucous will be having a various chart density due to the difference in their functional groups on the carbohydrate's moiety and amino acids of the polypeptide backbone. Ex. Polycarbophil shows the highest adhesive strength at pH 3, it decreases gradually when pH is increased up to 5.

b.Swelling (hydration)

Swelling is an important factor to expand mucoadhesive polymer and creates actual "macromolecular mesh" of adequate size, and also enhances mobility of the active polymer chain to enhance inter permeability process between mucous and polymer.

c.Selection of the Model Substrate Surface

During the testing of mucoadhesives, the handling and treatment of biological substrates is an important factor, under the experimental conditions, the formulation undergoes physical and biological changes in the mucous gels or tissues. The biological substrate changes can be identified by examining properties such as histology, permeability, and electrophysiology. These studies are may be necessary before and after conducting the in vitro tests using tissues.

a. Physiological factors:[21]

a. Disease state

Some of the disease state (i.e. common cold, fungal and bacterial infection, etc.) may alter the physicochemical property of mucous. this alteration may affect the bioadhesive property.

b. Mucin turnover

High mucin turnover is not suitable for the mucoadhesive property. Due to the high mucin turn over reduces the residence time of bioadhesive polymer. And also, large mucin turnover

may develop soluble mucin molecule, become thus molecule react with the polymer, before they interact with mucin membrane. Hence it leads the insufficient mucoadhesion**.**

c. Tissue movement

Tissue movement may affect the mucoadhesive system usually in case of gastro retentive dosage forms.

Table No. 1: The different components used in the Mucoadhesive buccal drug delivery system are as follows:[22]

Sl.no.	Components	Example	Uses
1	Polymers [23]	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 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[24]	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	Flavoring 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.

Methods of preparation of mucoadhesive drug delivery

1. Solvent casting: [25]

The solvent casting method is the widely preferred method for the preparation of buccal film/patches. In this method, all film/patch excipients including the polymer along with drug dispersed in an organic solvent. Above solvent mixture kept for overnight, and then triturated until to get a homogenous system then add glycerine and forms a gel. 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.

2. Direct milling:[26]

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.

3. Hot-melt extrusion of films:[27]

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.

Evaluation of mucoadhesive buccal films:

1. Surface pH:[28]

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.

2. Thickness measurement:[29]

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

3. Drug content:[30]

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.

4. Swelling studies:[31]

The films were cut into 3*2 cm^2 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 by using the following equation.

$$\text{Swelling Index} = \frac{W2 - W1}{W2} \text{ X } 100$$

5. Folding endurance:[32]

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.

6. Mucoadhesive strength:[33]

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.

7. Tensile strength and percentage elongation to break:[34]

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.

$$\mathrm{TS}\left(\frac{N}{\mathrm{cm}^2}\right) = F \times \frac{100}{t \times w}$$

$$\mathrm{EB\%\ (cm\%)} = \frac{((L - L_0) \times 100)}{L_0}.$$

8. Morphological Characterization:[35]

a. 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.

b. Differential scanning calorimeter [36]

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.

9. *In-vitro* Release Study: [37]

The *in-vitro* drug release study was performed by using a Franz diffusion cell, using commercially available dialysis membrane. 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. 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.

10. *Ex-vivo* permeation study: [38]

The *ex-vivo* permeation studies of buccal films were carried out using an excised layer of the porcine buccal mucosa. 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.

CONCLUSION

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 improves 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.

REFERENCES

1. Shankar DM, Dhake AS, Setty CM. Drug Delivery from the Oral Cavity: A Focus on Mucoadhesive. PDA J. Pharm. Sci. Technol. 2012;66:466-500.
2. Reddy PC, Chaitanya KS, Rao YM. A review of bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences. 2011;19(6):385.

3. Singh A, Prajapati UK. A review on Mucoadhesive Buccal Patches. IJRDPL.;6:2654-60.
4. Mahajan P, Kaur A, Aggarwal G, Harikumar SL. Mucoadhesive drug delivery system: a review. Int J Drug Dev Res. 2013 Jan;5(1):11-20.
5. Sonawane M, Dattatrey S, Ravindrasaudagar, Mucoadhesive buccal drug delivery system: review article; Int j curr pharm res, vol 9, issue 4, 1-4.
6. Mansuri S, Kesharwani P, Jain K, Tekade RK, Jain NK. Mucoadhesion: a promising approach in the drug delivery system. Reactive and functional polymers. 2016 Mar 1;100:151-72.
7. Khan S, Verma M, Aggarwal G, and Kumar S. L. Hari. MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW. World Jour.of Pharmacy and Pharmaceutical Sciences. 2016; Vol.5(5), 392-405
8. Sangeetha S, Nagasamy Venkatesh D, Krishan P, Saraswathi R. Mucosa as a route for systemic drug delivery. Res J Pharm Biol Chem Sci. 2010;1(3):178-87.
9. Reineke J, Cho DY, Dingle YL, Cheifetz P, Laulicht B, Lavin D, Furtado S, Mathiowitz E. Can bioadhesive nanoparticles allow for more effective particle uptake from the small intestine. Journal of controlled release. 2013 Sep 28;170(3):477-84.
10. Rajaram DM, Laxman SD. Buccal Mucoadhesive Films: A Review. Systematic Reviews in Pharmacy. 2017;8(1):31.
11. Verma S. Polymers in designing the mucoadhesive films: A comprehensive review. International Journal of Green Pharmacy (IJGP). 2018 Aug 3;12(02).
12. Mohanty D, Gurulatha C, Bakshi V, Maya B. Novel approaches on buccal mucoadhesive drug delivery system. Indo American Journal of Pharmaceutical Sciences. 2018 Apr 1;5(4):2131
13. Caon T, Jin L, Simões CM, Norton RS, Nicolazzo JA. Enhancing the buccal mucosal delivery of peptide and protein therapeutics. Pharmaceutical Research. 2015 Jan 1;32(1):1-21.
14. Dodou D, Breedveld P, Wieringa PA. Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications. European Journal of Pharmaceutics and Biopharmaceutics. 2005 May 1;60(1):1-6.
15. Ahagon, A. N. Gen. Effect of Interfacial Bonding on the Strength of Adhesion. journal of polymer science: (1976) vol. 13,1285-1300.
16. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. Journal of biomedical research. 2014 Mar;28(2):81.
17. Sharma D, Singh M, Kumar D, Singh G. Novel paradigms in mucoadhesive drug delivery system. Int J Pharm Sci Res. 2012;3:2455e2471.
18. Navneet N, Jaideep B, Garima S, Lovepreet K, Karan S, Manisha A, Mucoadhesion: a new polymeric approach. Bulletin of Pharmaceutical Research 2016;6(3):74-82
19. Reena S, Buccal Drug Delivery System: A Review. Int. J. Pharm. Sci. Rev. Res., 50(1), May - June 2018; Article No. 07, Pages: 40-46.
20. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Development and industrial pharmacy. 1997 Jan 1;23(5):489-515.
21. Khan AB, Mahamana R, Pal E. Review on mucoadhesive drug delivery system: novel approaches in modern era. Rajiv Gandhi Univ Heal Sci J Pharm Sci. 2015;4:128-41.
22. Venkata Lakshmi R, Sudhakar Y, Chetty MC, Sasikala C, Varma MM. Buccal drug delivery using adhesive polymeric patches. International Journal of Pharmaceutical Sciences and Research. 2012 Jan 1;3(1):35.
23. Yamsani V, Gannu R, Kolli C, Rao M, Yamsani M. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharmaceutica. 2007 Jun 1;57(2):185-97.
24. Smart JD. Buccal drug delivery. Expert opinion on drug delivery. 2005 May 1;2(3):507-17.
25. Averineni RK, Sunderajan SG, Mutalik S, Nayak U, Shavi G, Armugam K, Meka SR, Pandey S, Nayanabhirama U. Development of mucoadhesive buccal films for the treatment of oral sub-mucous fibrosis: a preliminary study. Pharmaceutical development and technology. 2009 Apr 1;14(2):199-207.
26. Reddy RJ, Anjum M, Hussain MA. A comprehensive review on buccal drug delivery system. Am J Advan Drug Deliv. 2013;1:300-12.
27. Madhavi BR, Murthy VS, Rani AP, Kumar GD. Buccal film drug delivery system-an innovative and emerging technology. J Mol Pharm Org Process Res. 2013;1(107):2.

28. Obaidat RM, Bader A, Al-Rajab W, ABU SHEIKHA G, Obaidat AA. Preparation of mucoadhesive oral patches containing tetracycline hydrochloride and carvacrol for treatment of local mouth bacterial infections and candidiasis. Scientia Pharmaceutica. 2010 Dec 14;79(1):197-212.
29. Castán H, Ruiz MA, Clares B, Morales ME. Design, development, and characterization of buccal bioadhesive films of Doxepin for treatment of odontalgia. Drug delivery. 2015 Aug 18;22(6):869-76.
30. Haranath C, Khan KA, Reddy CS, Kumar BP, Bhadrappa KV. Formulation and In-vitro Evaluation of Mucoadhesive Buccal Tablets of Anti-migraine Drug.
31. Salehi S, Boddohi S. New formulation and approach for mucoadhesive buccal film of rizatriptan benzoate. Progress in biomaterials. 2017 Dec 1;6(4):175-87.
32. Obaidat RM, Bader A, Al-Rajab W, ABU SHEIKHA G, Obaidat AA. Preparation of mucoadhesive oral patches containing tetracycline hydrochloride and carvacrol for treatment of local mouth bacterial infections and candidiasis. Scientia Pharmaceutica. 2010 Dec 14;79(1):197-212.
33. Anjana Anil, Preethi S. Design and Evaluation of Mucoadhesive Buccal Patch of Ramipril, Int. J. Pharm. Sci. Rev. Res., 50(2), May - June 2018; Article No. 18, Pages: 121-129.
34. Manivannan R, Balasubramaniam A, Anand DC, Sandeep G, Rajkumar N. Formulation and in-vitro evaluation of mucoadhesive buccal tablets of Diltiazem Hydrochloride. Research Journal of Pharmacy and Technology. 2008;1(4):478-80.
35. El-Kamel AH, Ashri LY, Alsarra IA. Micromatricial metronidazole benzoate film as a local mucoadhesive delivery system for treatment of periodontal diseases. AAPS Pharmscitech. 2007 Sep 1;8(3): E184-94.
36. Labib GS, Aldawsari HM, Badr-Eldin SM. Metronidazole and Pentoxifylline films for the local treatment of chronic periodontal pockets: preparation, in vitro evaluation and clinical assessment. Expert opinion on drug delivery. 2014 Jun 1;11(6):855-65.
37. Adhikari SN, Nayak BS, Nayak AK, Mohanty B. Formulation and evaluation of buccal patches for delivery of atenolol. Aaps Pharmscitech. 2010 Sep 1;11(3):1038-44.
38. Nautiyal U. Development and evaluation of buccal film.International Journal of Pharmaceutical and Medicinal Research, 2013; 1:39-43.