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Mucoadhesion: The Pathway for Buccal Drug Delivery System

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ABSTRACT

The ongoing research for increasing patient compliance and overcoming some disadvantages of Gastrointestinal tract (GIT) problems, like irritation to the gastric mucosa, drug degradation in the acidic gastrointestinal environment, and hepatic first-pass metabolism lead to the discovery of local mucoadhesive controlled drug delivery systems. The oral route is the most popular and is well accepted by the patient. Buccal route of drug delivery provides benefits of both and helps in local as well as systemic delivery of the drug. The delivery of drugs through the buccal route is known as Buccal Drug Delivery System (BDDS). Those drugs which undergo first-pass hepatic metabolism can be formulated into various types of liquid, solid, or semisolid dosage form and can be administered via buccal routes. Mucoadhesion, the attraction between dosage form and the mucous membrane is the basic principle involved in Buccal drug delivery systems. The present article consists of the review on Buccal Drug Delivery System (BDDS) for its advantages, disadvantages, site of administration and mechanism for the absorption by passive diffusion which is affected by various factors, the composition of the drugs and various approaches for formulation and evaluation of buccal dosage forms.

INTRODUCTION

There is continuous research going on in the pharmaceutical field that leads to drug discovery and the development of different delivery systems. Drug delivery refers to the process of administering a compound/drug to achieve the desired effect [1]. The various drug delivery systems employed can help in the study and control of the therapeutic profile, pharmacological actions, pharmacokinetics of the drugs and helps in overcoming the adverse effects [1]. Amongst the various routes of drug delivery, the oral route has the highest patient acceptability and convenience, but to give the desired action of the drug the oral route takes some time, as compared to the parenteral route [2] [3]. Thus, the development of various mucoadhesive drug delivery systems like buccal formulations offers the advantages of oral route as well as immediate release of medication at desired sites [4]. With the recent developments, the buccal drug delivery system has become one of the most favorable as compared to other drug delivery systems [5] [6]. Buccal drug delivery is very safe for delivery of the drug which helps to avoid the drug from entering the acidic environment of GIT [7]. The drugs can be delivered in the oral mucosal cavity by any one of the four regions, Buccal, Sublingual, Palatal, and Gingival [8] [9]. Amongst these, sublingual and buccal routes are most commonly used for delivery of drugs, and the sublingual region shows the highest permeability [6] and hence used for the therapeutic purpose of local and systemic diseases [8].

The buccal drug delivery system involves the administration of the desired drug through the lining of the oral cavity buccal mucosal membrane [10]. They lead to a rapid onset of action and prolonged delivery of the drugs through the mucous membrane [9]. Buccal cavity is an area that has a rich blood supply which helps to gain direct entry of the drug into the systemic circulation. These formulations are usually of small size and have suitable geometry to not interfere or block any physiological function of the mouth [1].

The mucoadhesive polymers are the main component of the BDDS and are used in buccal drug delivery formulations that have the greater application [1], they help to gain and form tight and close contact of the drug with the absorptive mucosa [11]. It also has the potential to retain the dosage forms at the site of action, by retaining the formulation in intimate contact with the site for a prolonged duration [12].

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

The buccal drug delivery system has several advantages which may be enlisted as

▪ The entry of the drug in the GIT is avoided, it helps to bypass the hepatic first-pass metabolism and the drug gains direct entry in the systemic circulation [13] [14] [15].

▪ The area of the buccal membrane is much sufficient, that can deliver the drug alternatively on any side of the buccal membrane (i.e left or right) [1] [4] [9].

▪ It has improved patient compliance, as it is easy to administer, non-invasive, and non-painful [12] [16] [17].

▪ It can be administered to unconscious patients and also those who are suffering from nausea, vomiting [3] [14] [16].

▪ Patients can involuntarily control the dose of administration or can even terminate the delivery if required [1] [13] [14].

▪ The formulation shows low/no enzymatic activity [12].

▪ The performance of the drug can be improved [16].

▪ The drug is protected from degradation in the acidic environment in the GIT [13].

▪ Faster onset of action is achieved due to the mucosal surface [18].

LIMITATIONS OF BUCCAL DRUG DELIVERY SYSTEM

The limitations associated with the buccal drug delivery systems may be enlisted as

▪ The oral mucosa has less surface area as compared to the gastric mucosa and has lesser permeability to the drugs [1] [3] [4].

▪ Saliva is continuously secreted in the oral cavity, which causes rapid dilution of the drugs which leads to elimination of the drug [13] [16] [19].

▪ Drugs that are to be given in smaller doses can only be administered [13] [16].

▪ There is a high restriction on eating and drinking, or the patient may swallow the tablet along with it [13] [20].

▪ Drugs that have an unpleasant taste, or may irritate the oral mucosa cannot be administered by this route [4] [17].

▪ The drugs which are not stable at the pH of the mucosal cavity cannot be administered by this route [3] [13].

▪ The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels [10].

SITES FOR ABSORPTION IN BUCCAL CAVITY

Within the oral mucosal cavity, absorption takes place at any of one of the 3 sites as shown in Figure No.1.

Figure No. 1: Absorption sites in the oral cavity

1. **Sublingual delivery**: It is the administration of the drug via the sublingual mucosa (the area in between the tongue and the floor of the mouth and then into the systemic circulation.

2. **Buccal delivery**: It is the administration of a drug via the buccal mucosa (the lining of the cheek) and then into the systemic circulation.

3. **Local delivery**: It is also used for the treatment of conditions of the oral cavity, major use is in mouth ulcers, fungal conditions [13] [17] [19].

METHODS TO INCREASE BUCCAL ABSORPTION

- Absorption enhancer
- Prodrugs
- Enzyme inhibitors

1. Absorption enhancers: Absorption enhancers are the agents that increase absorption by enhancing membrane permeation, rather than increasing solubility. They are also sometimes called Permeation enhancers. They increase the membrane permeation by different actions, like [22]

- Increasing the fluidity of the cell membrane,
- Extracting inter/intracellular lipids,
- Altering cellular proteins or
- Altering surface mucin

These are the agents that are capable of delivering the compounds that show a low buccal absorption rate. The commonly used Absorption enhancers are ozone, fatty acids, bile salts, and surfactants [21].

2. Prodrugs: Administration of some drugs which have low bioavailability in a prodrug form helps to increase the bioavailability of the marketed formulations to a great extent and also decrease the adverse effects [21] [22].

3. Enzyme inhibitors: Co-administration of a drug with enzyme inhibitors is another strategy to improve the buccal absorption of drugs, particularly peptides [9].

BUCCAL/ORAL CAVITY AND ITS ANATOMY:

To understand the different sites and approaches of buccal absorption, it is necessary to know the anatomy and physiology of the oral cavity. The anatomy of the oral cavity is shown in Figure No. 2.

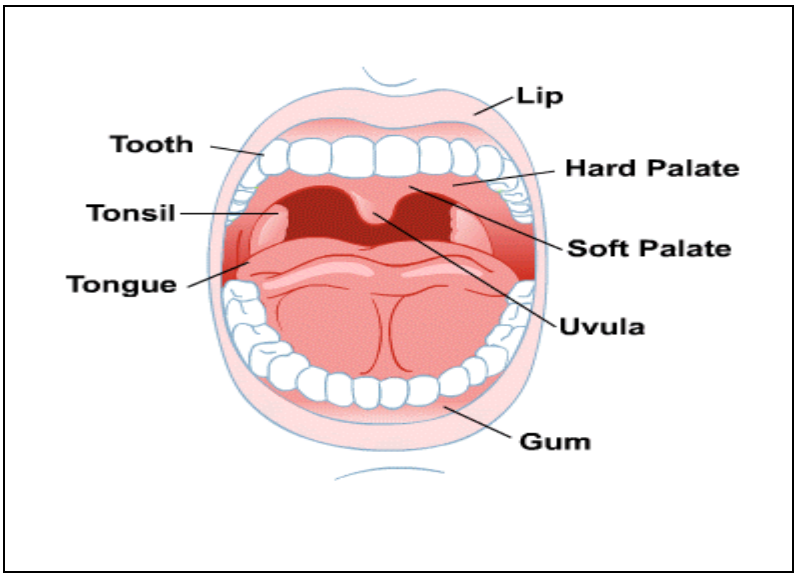

Figure No. 2: Anatomy of the oral cavity

The oral mucosa is the mucous membrane lining the inside of the mouth[17]. The buccal cavity is a component of the mouth, it is delined by lips, cheeks, teeth, and gums [19]. Oral cavity, extends from teeth and gums back to the fauces (which lead to pharynx) with the roof called the hard and soft palate. The tongue projects from the floor of the cavity.

The oral mucosa consists of three distinctive layers, as shown in Figure No. 3.

a. Epithelium,

b. Basement membrane and

c. Connective tissues.

In underlying tissues, the protective layer is stratified squamous epithelium which is divided into 2 parts;

1. Surface, it is a non-keratinized lining of the soft palate, tongue surface, lips, and vestibule, it is composed of polar lipids cholesterol sulfate and glaucocerinites [4] [8].

2. Hard palate and other non - flexible regions, they are keratinized epithelium present in the oral cavity, it is composed of neutral lipid ceramide [4] [8] [23].

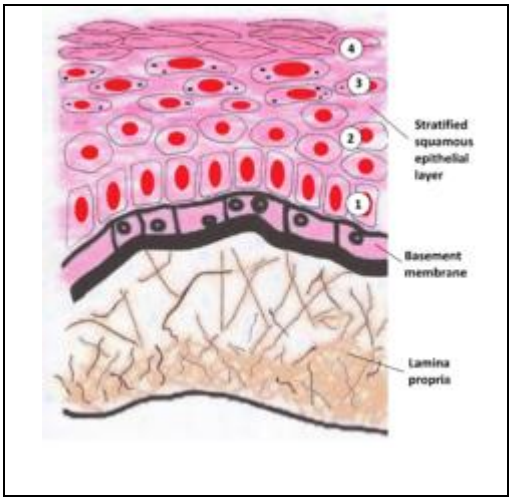

Figure No. 3: Histology of oral mucosa

The mucosa of the gingival and hard palate is keratinized, and the mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized [5]. The epithelial cells change their shape and increase in size while moving towards the surface. These layers help to protect the tissue from the fluid loads and also protect from the harmful environmental attack of toxic substances. The buccal cavity is delined with epithelium tissue; has the strong support of basement membrane.

1. The basement membrane is mechanical support for the epithelium and forms a distinctive layer between the connective tissues and the epithelium.

Buccal mucosa is more permeable and can tolerate allergens, toxic substances that can cause irreversible damage or irritation to the tissue [9].

2. The underlying connective tissues provide many of the mechanical properties of oral mucosa [5].

MUCOADHESION/ BIOADHESION REQUIRED FOR BDDS

Mucoadhesion can be defined as an attractive force between the adhesive/formulation and the mucous membrane [24]. The substance can be retained on the mucosal surface for a persistent time [9]. In the mucus membrane the goblet cells are present which help in the secretion of mucus which is composed of glycoprotein mucin [16] [25].

Along with the buccal drug delivery system, mucoadhesion is also involved in the following routes of drug delivery [11] [25]:

- Sublingual drug delivery systems [26]
- Rectal drug delivery systems [27]
- Vaginal drug delivery systems [28]
- Ocular drug delivery systems [29]
- Nasal drug delivery systems [30]

MECHANISM OF MUCOADHESION/BIOADHESION

The attractive and repulsive forces arise at the time of bioadhesion, where attractive forces play an important role [31]. For bioadhesion to occur, three steps are involved as displayed in Figure No. 4.

1. An intimate contact between a bioadhesive and membrane either from a good wetting property of the bioadhesive polymer and a membrane or from the swelling of bioadhesive.

2. There is a penetration of the bio-adhesive into the tissue.

3. Interpenetration of the polymer chains of the bioadhesive into the mucous membrane.

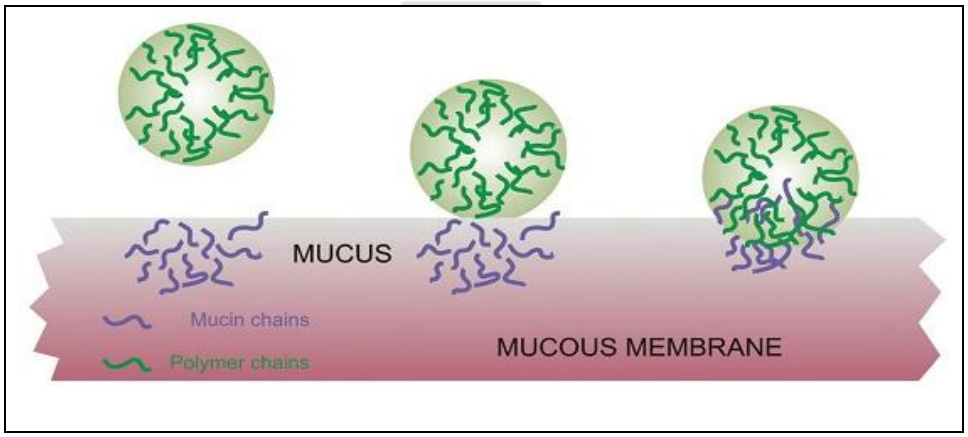

Figure No. 4: Penetration of the mucoadhesive through the membrane

The bonding between the mucus and the adhesive substance occurs chiefly through both physical and chemical processes involving electrostatic and hydrophobic interactions, hydrogen bonding and dispersion forces [11] [12] [23] [31].

THEORIES OF MUCOADHESION/BIOADHESION:

Several theories are postulated to explain the mechanism of adhesion of the mucous

membrane and the buccal patch:

1.Wetting theory

2.Absorption theory

3.Electronic theory

4.Diffusion theory

5.Fracture theory

1. Wetting theory

The wetting theory is applicable for liquids, paste, or gels. It determines the ability of a liquid to remain in contact with a solid surface, because of intermolecular interactions when the two surfaces are brought together. Adhesion forces between a liquid and solid membrane cause a liquid to spread across the surface, and the contact between these two surfaces and the work of adhesion can be determined, by Dupre's equation as shown in Equation No. 1 [12] [25] [31].

$$W_A = \gamma_a + \gamma_b - \gamma_{ab}$$ ...**Equation No. 1**

Where

- W_A: specific thermodynamic work of adhesion
- γ_a: Surface tension of the bioadhesive membrane
- γ_b: Surface tension of the Substrate
- γ_{ab}: Interfacial tension

2. Absorption theory

Absorption theory is based upon the adhesion of liquid or pastes to the biological surface. As the contact between the 2 surfaces occurs, their materials adhere because of surface forces acting between the atoms in the two surfaces. This theory states that bioadhesion occurs because of the net result of the secondary surface forces such as Van der Waals forces, hydrogen bonds, or hydrophobic interactions. According to this theory, moderately wettable polymers show optimal adhesion, spreading, and proliferation (i.e polar molecules reorient at

the interface) [18 [21]] [31].

3. Electronic theory

As the name indicates, the electronic theory describes that the mucoadhesive and mucosal membrane comprises of opposite electrical charges. When both these surfaces come in contact, it leads to the transfer of electrons and forms a double electronic layer at their interface. The attractive forces are responsible for maintaining contact between the two layers and cause adhesion [20] [25].

4. Diffusion theory

Diffusion theory states that the bio-adhesives contain polymeric chains that penetrate glycoprotein mucin chains to the sufficient depth within the opposite matrix and form a semi-permanent bond [25]. The penetration rate depends on the diffusion coefficients and the diffusion coefficient is known to depend on molecular weight. And may decreases as the cross-linking density decreases [20] [21]. The theory has been depicted in Figure No. 5.

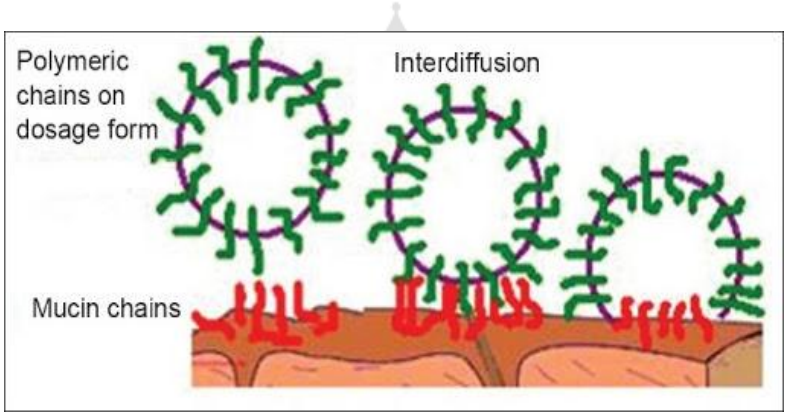

Figure No. 5: Penetration of polymeric chains

5. Fracture theory

Fracture theory is the major mechanism to determine the strength of a mucoadhesive, and the theory describes the force necessary to separate the two materials after muco-adhesion has occurred [25].

The fracture briefly indicates about the forces required to cause the fracture in the mucoadhesive and is not concerned with the diffusion or penetration of the polymers. The theory has been depicted in Figure No. 6.

The tensile strength is determined by the separating force and the total surface area of the

adhesion, and is given by Equation No. 2 [25].

$$\sigma = (E \times \varepsilon/L)^{1/2} \quad \ldots \textbf{Equation No. 2}$$

Where

- σ: fracture strength,
- E: young modulus of elasticity,
- ε: fracture energy,
- L: critical crack length

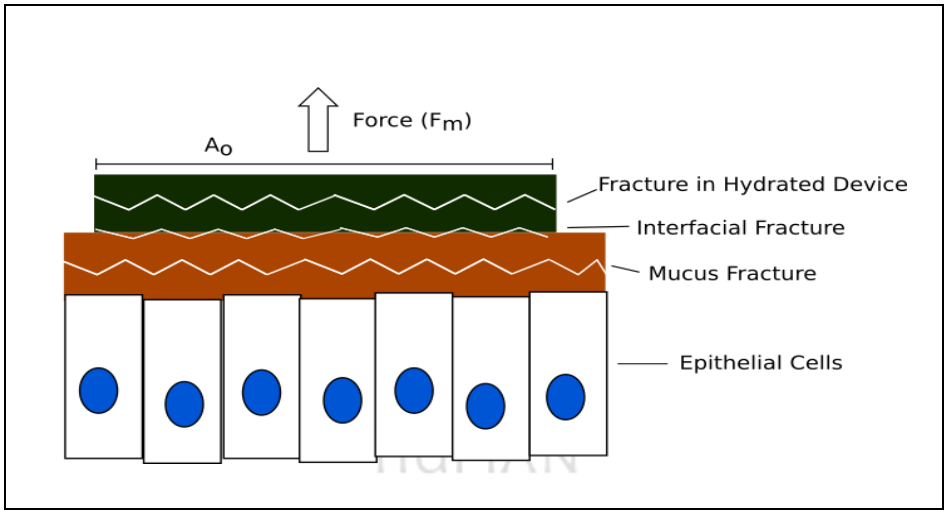

Figure No. 6: Places of fracture after the force is applied

TYPES OF BUCCAL DRUG DELIVERY FORMULATIONS:

They are usually of 2 types [13] [25] [31].

1.Matrix type

2.Reservoir type

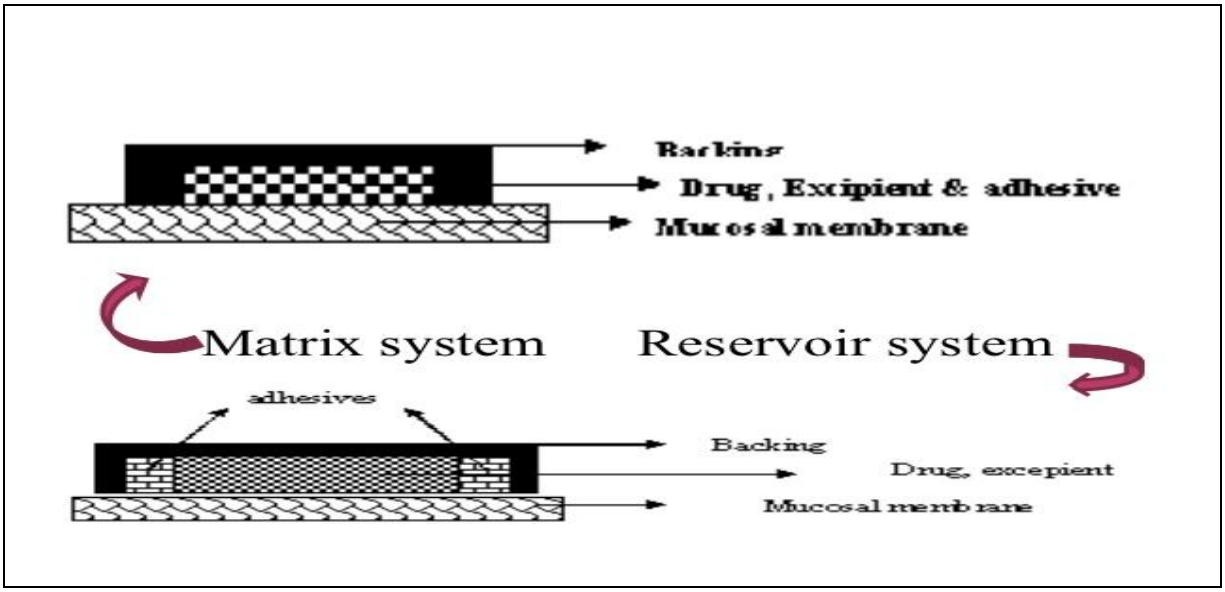

Figure No. 7: Buccal drug delivery systems

Matrix type: The buccal patch designed in a matrix configuration contains the drug, adhesive, and additives mixed, as shown in Figure No. 7.

Reservoir type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesives. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration when the drug dose is in the mouth, and prevent drug loss. Reservoir type BDDS is shown in Figure No. 7.

MECHANISM OF BUCCAL ABSORPTION

The primary mode of the mechanism is by passive diffusion, where the non-ionic species play a major role. The buccal mucosa acts as a lipoidal barrier to the passage of the drugs as like the other mucosal membrane, thus, the drug is more readily absorbed if it is more lipophilic [17]. The buccal absorption can be more adequately explained by the first-order rate process. Several potential barriers to buccal drug absorption have been identified.

Two scientists, Dearden and Tomlison (1971) revealed that the salivary secretion alters the kinetics of buccal absorption from drug solution by changing the concentration of drug in the mouth.

The linear relationship between salivary secretion and time as given in Equation No. 3 {17] [19] [32].

$$- dm/dt = KC/V_iV_t \qquad \textbf{Equation No. 3}$$

Where

- m: Mass of the drug in the mouth at time t
- K: Proportionality constant
- C: Concentration of drug in the mouth at a time
- V_i: The volume of the solution put into the mouth cavity and
- V_t: Salivary secretion rate

The equation revealed that there are certain barriers to penetration across buccal mucosa, and most of the area of the epithelium tissue consists of this barrier which is mainly useful for penetration. The barriers are [4],

- Membrane coating granules
- Basement membrane
- Mucus
- Saliva

FACTORS AFFECTING BUCCAL ABSORPTION

The oral cavity contains a complex environment for drug delivery where some independent or interdependent factors may affect/alter the absorbable concentration of the drug at the site of absorption.

Membrane Factor: They reduce the rate and amount of drug entering the systemic circulation. This happens because of the surface area available for absorption, mucus layer of saliva, lipoidal layer of epithelium, basement membrane, and lamina propria. Also, thickness, blood supply/ lymph drainage, cell renewal, and enzyme content of the absorptive membrane also affect drug delivery [5].

Salivary glands: They are located in the epithelial and/or in the deep epithelial region of the buccal mucosa. They constantly secrete mucus on the surface of the buccal mucosa, which acts as a potential barrier for drug penetration. The thickness (0.07-0.10mm), the composition of saliva, and the membrane activity and movement affect the drug absorption [5] [17].

Movement of buccal tissues: The buccal region has less active movement, the drug is to be held in this cavity and it must be able to withstand the actions, movements, or activity done by this region while eating, talking [5] [17] [32].

Related to drugs: Molecular size, Particle size, Chemical nature, Concentration, Dosage forms also affect the absorption of the drug in the oral cavity to an extent.

BUCCAL DRUG DELIVERY FORMULATIONS

The formulations available for delivery through buccal mucosa can be administered through various forms. They are summarized in Table No.1 [2] [9] [33] [34].

Table No. 1: Buccal formulations

Category		**Formulations**
Non-attached delivery system		▪ Fast dissolving tablets ▪ Microporous hollow fibers ▪ Chewing gum formulation
Mucoadhesive delivery system	Solids	▪ Tablets/lozenges ▪ Wafers ▪ Disc ▪ Powders
	Semisolids	▪ Adhesive gels ▪ Adhesive ointment ▪ Paste ▪ Sponges ▪ Emulsions with adhesive properties
	Patches/films	▪ Bi-layered films ▪ Multi-layered films
	Solutions	▪ Mouthwashes ▪ Aerosols/Spray

NON - ATTACHED DELIVERY SYSTEMS

Chewing gums: The medicated chewing gum formulation is used for controlled release drug

delivery which stands as an advantage. Medicated chewing gums are used in case of travel illness, pain relief. They provide great comfort and convenience to the patients, as the patients can voluntarily change and maintain the rate of chewing and can expel the gum whenever needed [20].

Fast dissolving tablets: Mouth dissolving films are placed on the tongue, and the continuous secretion of saliva in the mouth helps to hydrate the film and adhere tightly to the surface. These fast-dissolving formulation rapidly dissolves releasing the drug for absorption [35].

MUCOADHESIVE DELIVERY SYSTEMS

SOLID SYSTEMS

Buccal Tablets: These are a type of dry dosage form that is to be moistened after placing in the buccal cavity [32]. The tablets used for buccal drug delivery can be formulated by compression method or even wet granulation method is suitable, but as the tablet is to be held in the oral cavity it must dissolve properly, thus the force for compression should be appropriate only to give a moderately hard tablet [36]. These tablets are prepared by the direct compression of the powder using suitable type of excipients [2] [5].

Powders: These forms are a mixture of bio- adhesive polymers (hydroxyl propyl cellulose or beclomethasone) and the drug and are sprayed onto the buccal mucosa [5] [17].

Lozenges: Lozenge offers prolonged drug release and improves patient compliance [4]. Bio-adhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anesthetics, antibiotics [12]. They are thin and flexible so are well accepted by patients [34].

Wafers: These contain surface layers that have adhesive properties, and the bulk layer consists of antimicrobial agents, biodegradable polymers, and matrix polymers [18].

Microparticles: Microparticles are delivered as suspension, paste, or even by aerosols systems. The physical properties; the small size of this formulation help to create intimate contact with the mucosal membrane and can be administered to the sites like GI tract, and nasal cavity. They show less irritation, thus can prove to have advantages over buccal tablets, but their major drawback is that they show less resistance time at the surface of adhesion [34] [36].

SEMISOLID SYSTEMS

These are finely powdered natural or synthetic polymers dispersed in polyethylene or aqueous solution. They have less patient acceptability as compared to other mucoadhesive forms [5] [17].

PATCHES AND FILMS

These are the laminates consisting of an impermeable backing layer, a drug containing reservoir layer, and a bio-adhesive surface for mucosal attachment [17]. These are of unidirectional flow and are formulated by incorporating the drug in an alcohol solution of bio-adhesive polymer. Buccal films are suitable for both Geriatric and Pediatric diseases. These are widely used as they are non-toxic, biocompatible, and inexpensive and also have an appropriate peel, and tensile strength [8]. Also the films help to relieve pain by protecting the wound surface [36]. The film which is applied to the oral mucosa can be retained in the same place for a minimum of 12 hours [5].

COMPOSITION OF BUCCAL PATCHES:

1. ACTIVE PHARMACEUTICAL INGREDIENTS (API):

They are the important compound of the dose. The potent drugs which show high first-pass metabolism and patient noncompliance are best for formulating buccal formulations [33]. The molecular weight, chemistry, and melting point of the API affect the dissolution of the drug from the buccal mucosa [1]. Thus, the API should be selected properly by understanding the pharmacokinetics [13] [32].

The properties of API that should be considered while selection are [37]

1.It must not adversely affect the oral mucosal cavity.

2.It should not have a bad taste, must be non-irritating to the mucosal surface, and do not cause discoloration or harm to teeth.

3.It must undergo passive absorption.

4.It should have an appropriate half-life (2-8 hours).

2. MUCOADHESIVE POLYMERS:

They play an important role in controlling the rate of drug release and also in the dissolution of the drug [1]. The polymers can be used alone or in combination to obtain the desired film properties [33]. The contact between the buccal formulation and the buccal mucosa is an important factor to be studied for the buccal drug delivery, the polymers should be chosen properly, it should be of good quality, should have the good wetting, tough enough and spreadability property [19].

Bio-adhesive polymers used are classified depending upon their source. They are as follows [3]

- **Natural:**

Agarose, Chitosan, Gelatin, Hyaluronic Acid, Carrageenan, Pectin, and Sodium Alginate.

- **Synthetic:**

Cellulose derivatives: CMC, Na-CMC, Hydroxy ethyl cellulose, hydroxyl propyl cellulose, HPMC [5] [7] [38]

Others: polyoxyethylene, PVA, PVP, thiolated Polymers [9].

The use of different polymers that are used to formulate the BDDS formulation is shown in Table No. 2.

Table No. 2: Mucoadhesive polymers used in BDDS

Polymers	**Drugs**
Chitosan	Propranolol, Curcumin, Risperidone, Verapamil, Diclofenac sodium
Guar gum	Diltiazem hydrochloride, Lisinopril, Losartan, Timolol maleate
Sodium alginate	Propranolol hydrochloride, Losartan Metoprolol tartrate, Methotrexate
Xanthan gum	Tizanidine Hydrochloride

Desired characteristics of polymer to be used for BDDS [2] [25]:

- Nontoxic and non-absorbable, non-irritant.
- Form a strong non-covalent bond with the mucus or epithelial cell surface.
- Should adhere quickly to tissue.
- Should allow easy incorporation of the drug.
- Must have good properties like wetting, swelling, solubility, and biodegradability.
- Must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high so that the prepared.
- Should not produce a secondary infection in the dental cavity.

3. BACKING MEMBRANE: They should be flexible and have high tensile strength, low water permeation, and should remain stable even on long storage. The polymer which can be cast into a thin pore-less uniform water-impermeable film may be used to prepare backing membrane of patches [1]. The most commonly used polymers are Ethylcellulose, Polyvinyl alcohol, etc.[5] [9] [19].

4. PLASTICIZERS: Plasticizers are the common ingredients to be added to the formulations. These are the agents that are used to mix the polymers and help to gain softness and flexibility to thin films of polymer and reduces the brittleness of the strip [33].

Eg-PEG-100, propylene glycol [13].

5. PENETRATION ENHANCERS: These are substances that help to promote drug permeation/ penetration within the buccal epithelium and are also known as a permeation enhancers, permeation promoters, or absorption enhancers [1]. These chemicals are penetrated in mucosa and thus, should be safe, non-toxic, nonirritant, non- allergenic and pharmacologically as well as chemically inert. The most common penetration enhancers are bile salt, fatty acid, and a surfactant such as sodium dodecyl sulfate, chitosan [13] [19] [32].

The commonly used permeation enhancers are given in Table No.3.

Table No.3: Examples of permeation enhancers

Fatty acids	Oleic acid, propylene glycol
Bile salts	Sodium glycocholate, Sodium taurocholate
Surfactants	SLS, Benzalkonium chloride.
Chelators	Sodium salicylate, Methoxy salicylates, EDTA, Citric acid.
Other agents	Aprotinin, Azone, Menthol, Cyclodextrin, Dextran sulfate.
Thiolated polymers	Chitosan - 4 thiobutylamide, Chitosan – cysteine

Ideal Characteristics of Permeation Enhancers to be used in formulating BDDS [39]:

- It should be biocompatible.
- It should not induce toxicity.
- It should be compatible with the drug being given.
- It should not exhibit any adverse pharmacological activity inside the body.
- It should not have a high cost.
- It should possess good solvent properties.
- It should not have color, odor, and taste.
- It should be chemically and physically stable.
- It should not cause leakage of body fluids and endogenous materials

(unidirectional flow).

6. SWEETENING AND FLAVORING AGENTS: These are also added to the formulation to increase the patient's compliance [17].

- Sweeteners: Aspartame, Mannitol
- Flavors: Menthol, Vanillin, Cinnamon, and various fruits [8] [13].

Flavor is the sensory impression of food or other substances that is used in the dosage form for the taste and smell. These are usually essential oil or water-soluble extracts obtained from plants or animals.

7. Saliva stimulating agents:

The saliva stimulating agents are used to increase the rate of production of saliva which would result in faster disintegration and, rapid dissolving formulations.

Examples: Citric acid, Malic acid, Lactic acid, Ascorbic acid [15].

GENERAL METHODS OF PREPARATION OF BDDS

There are various methods for the preparation of BDDS, some are discussed below:

1.Solvent casting:

The solvent casting method is most widely preferred for manufacturing of the buccal formulation. The steps involved in solvent casting are shown in Figure No.8.

▪ Polymers are dissolved in water to form clear viscous solutions.

▪ The drug is mixed with other ingredients, which is then dissolved in suitable solvents to form clear, viscous solutions.

▪ Both these solutions are mixed, coated onto a sheet of the release liner. After the solvent is evaporated, a thin layer of the protective backing material is laminated onto the sheet of the coated release liner and is then allowed to dry [13] [19] [40].

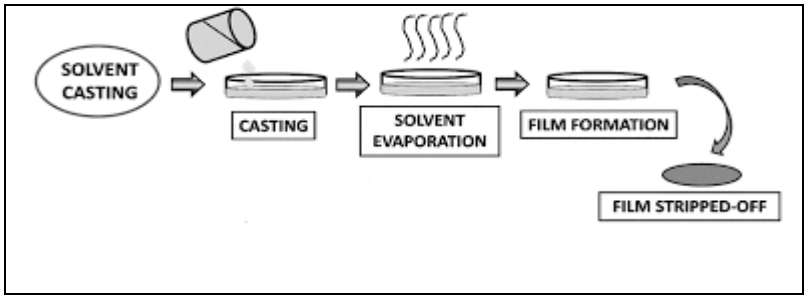

Figure No. 8: Steps involved in Solvent casting technique

2.Direct milling:

The manufacturing is done without the use of solvents. API and excipients are mechanically

mixed by milling/kneading, without the use of any liquids. After the mixing, the resultant mixture obtained is coated with a release liner until the desired thickness is achieved. The backing material is then laminated [17] [19]. The method is preferred as the solvent is not used and so there is no residual solvent [15].

3.Hot-melt extrusion:

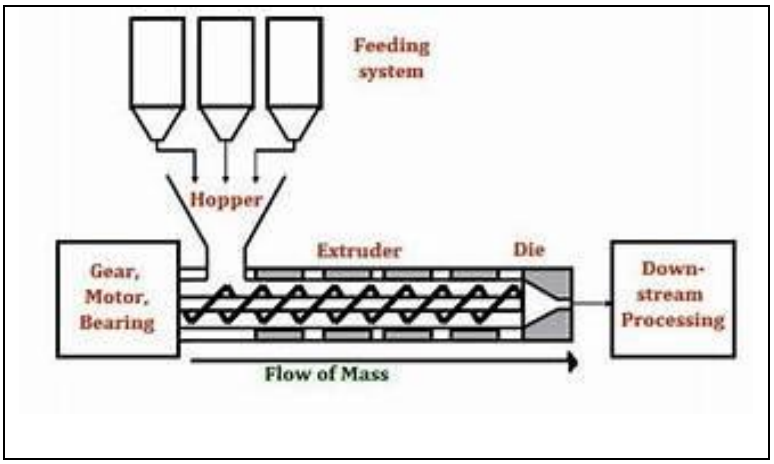

Figure No. 9: Hot melt extruder

The use of extruders is done in this process. It is a process that helps in shaping a polymer into a film with the help of the heating process. A mixture of excipients and the API is filled in the hopper, mixed properly, exposed to heating process, and then extruded out. The melted blend is shaped by using a die [1] [5]. The apparatus is depicted in Figure No. 9.

4.Rolling method:

In this rolling method, solution or suspension containing the drug is rolled on a carrier. The solvent is mainly water or a mixture of water and alcohol. The film is dried on rollers and cut into desired shapes and sizes. Other ingredients including active agents are dissolved in small portions of aqueous solvents using a high shear process [13].

5. Semisolid casting:

The water-soluble film-forming polymer is prepared, this solution is mixed with a solution of polymer (cellulose acetate phthalate, cellulose acetate butyrate), these polymers are usually acid-soluble. A suitable amount of plasticizer is added and blended properly, gel mass is obtained. Then, the gel mass is cast into films using heat-controlled drums. The thickness of the film should be maintained between 0.015-0.05 inches [3] [13].

DRUGS DELIVERED THROUGH BUCCAL ROUTE:

Many drugs are formulated to be given as BDDS for treating various diseases or disorders. They are summarized in Table No. 4.

Table No. 4: Drugs and various buccal formulations for different disorders

DRUGS	USE	FORMULATION	REFERENCES
Buprenorphine Fentanyl	Pain relief	Patches / Films Tablet / Lozenges	9, 20 12
Rizatripim	Migraine	Wafer / Film	8,20
Selegiline	Parkinson disease	Tablets	8,41
Glyceryl Trinitrate Nifedipine	Angina Pectoris	Tablets Patches / Films	9
Diltiazem	Hypertension	Tablets	9
Zolpidem	Insomnia	Tablets	9
Miconazole	Anti-fungal	Tablets	9, 12
Nicotine	Smoking cessation	Tablets	9
Ondansetron Prochlorperazine	Nausea, Vomiting	Films Tablets	15
Ondesartan	Antiemetic	Tablets	9
Ergotamine Tartarate	Analgesic	Tablets	9,34
Acyclovir	Viral Infection	Patches / Films	20
Lidocaine	Local anesthetic	Patches / Films	9, 20

EVALUATION PARAMETERS FOR BDD FORMULATIONS

Surface pH: The acidic/basic environment in the buccal cavity may cause irritation to the patient and even affect the pharmacokinetic properties of the drug, thus the pH should be always neutral [42]. To determine the pH of buccal patches, they are allowed to swell on the

surface of agar plate for 2 hours or kept in contact with water (pH: 6.5) for 60 min at room temperature[1]. After some time the pH is measured using a pH meter [32] [43].

The thickness of patch: Thickness is usually measured at 5 different spots, center, and 4 corners of a patch using an electronic digital micrometer or a gauze [40] [43] [44].

Swelling index: Initially the patches are weighed individually (W_1), and then placed in agar gel plates (2 %), for 3 hrs. After 3 hours excess of water content from the surface is removed using a filter paper by taking appropriate precautions; then they are again weighed (W_2). The swelling index is then calculated by the formula shown in Equation No. 4 [6] [43] [44].

$$SI= (W_2-W_1)/W_1\times 100 \quad \text{.... } \textbf{Equation No. 4}$$

Where

- SI: Swelling index
- W_1: Initial weight
- W_2: Final weight

Folding Endurance: The patches are continuously folded at 180º angles, till it is broken down [15] [40].

Palatability test: The palatability test depends upon the taste of the formulation, and is done after the test of physical appearance and bitterness is performed. All the batches are observed and then graded as A, B, or C according to the criteria they meet.

- A: very good
- B: good
- C: poor

If the formulation score only 1 A grade then it is said to be average/poor. If the formulation scores 2-A grade, it is said to be good, and if it scores all 3- A grades it is said to be good [45].

Water absorption capacity test: The patches are placed on the agar plates prepared in simulated saliva, and placed in an incubator. At various intervals, the patches are removed (0.5, 1, 2, 3 hours) and then weighed and allowed to dry in a desiccator for 7 days on

anhydrous calcium chloride, and then again weighed. The water uptake % is then calculated as shown in Equation No. 5 [5] [17].

$$\text{Water uptake (\%)} = (W_f - W_i)/W_f \times 100 \quad \textbf{… Equation No. 5}$$

Where

- W_f: Final wet weight
- W_i: Initial weight

In vitro drug release: The USP XXIII-B rotating paddle is used for the release study from the bilayered and multilayered patches which is set at 50 rpm. The release is performed at 37°C ± 0.5°C, using a phosphate buffer of pH 6.8. The backing layer of the buccal patch is attached to the glass disk. Samples (5 ml) are withdrawn at some intervals and then replaced with fresh medium. The withdrawn samples are filtered using a Whatman filter paper and then drug content is analyzed after proper dilution is done [11] [40] [43].

Permeation study of the buccal patch: The receptor compartment is filled with phosphate buffer pH 6.8, the stirring is maintained in the compartment with a magnetic bead at 50 rpm. Samples are withdrawn at time intervals and analyzed for drug content [3] [17].

Stability in human saliva: The human saliva is collected from humans from different age groups. The patches are placed in separate Petri - dishes containing 5 ml of human saliva and the temperature is controlled. At the regular time, the dose formulations with better bioavailability are observed [13] [17].

Measurement of mechanical properties: The mechanical properties include the tensile strength and elongation at the time of break. These are evaluated using a tensile tester. The film strip is placed between two clamps separated by a distance of 3 cm. Clamps are designed in such a way that they secure the patch without crushing it during the test. The lower clamp stays stationary and the strips are pulled apart by the upper clamp moving until the strip break. The force and elongation of the film at the point when the strip break is recorded. The tensile strength is calculated as shown in Equation No. 6 [5] [32].

$$T = m \times g / b \times T \ Kg/mm^2 \quad \text{… } \textbf{Equation No. 6}$$

Where

- m = Mass (gm)
- g = Acceleration due to gravity
- b = breadth
- T = Thickness (cm)

Weight Variation: The patches are weight individually on electronic balance for the weight variation test, and the average weights were calculated [3].

Ex-vivo muco-adhesion time: It is performed after application of the buccal patch on freshly cut buccal mucosa. The fresh buccal mucosa is tied on the glass slide and a mucoadhesive patch is wetted with 1 drop of phosphate buffer (pH 6.8) and a light force is applied with a fingertip so that the mucosa is properly moist and adhere tightly. The glass slide is then put in the beaker which is filled with 200 ml of the phosphate buffer (pH 6.8). After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment and the patch is monitored for 12 hours and the time for any change in color, the shape of the patch is noticed and then drug content is noted [13].

Drug content uniformity: Three buccal film/tablets with suitable dimensions are taken and allowed to dissolve in simulated saliva (approximately 100 ml) separately for 24 hours with occasional stirring. After 24 hours the fluid is filtered to remove excess undissolved part of the drug. Then 1ml filtrate is diluted with 10ml simulated saliva, and the absorbance is measured using UV spectrometer [19] [36].

Ex-vivo diffusion studies: Here, the phosphate buffer is used as a medium and the goat mucosa is used as a barrier membrane. The drug release is determined using Franz diffusion cell. The diffusion cell is then placed in simulated saliva, the film is placed on the mucosal membrane and the receptor compartment is filled with phosphate buffer of pH 6.8. The magnetic stirring is maintained at 50 rpm. Within the time intervals, 1ml solution is withdrawn and the sink condition is maintained by adding 1ml of fresh medium [15].

RECENT APPROACHES IN BUCCAL DRUG DELIVERY SYSTEM

Many drug formulations or vaccines given by the buccal route have shown good results in treating various diseases and disorders and also are well accepted by the patients. Various

investigations and research are ongoing for reducing any damage to the buccal cavity and particularly the mucosa which may happen due to acidic/basic nature of drug and for improving the taste of the formulation for gaining better results. Globally, studies are carried out to discover new ways to improve the buccal adhesion properties and absorption, probably by trying to improve the bioavailability of orally less/ inefficient drugs by using pH modifiers, enzyme inhibitors, permeation enhances, etc. The buccal drug delivery is a vast topic to study and also has some obstacles. Various ways for upcoming these obstacles are carried on like use of nanocarriers, use of enhanced polymers, delivery of proteins, peptide, penetration enhancers, etc. Nanocarriers system like multiple emulsions, liposomes, polymeric nanoparticles, dendrimers are considered for the future of the buccal delivery. Studies on polymers with enhanced properties are carried out which show good hydrophilicity/ hydrophobicity interactions. Further, this route is found to be emerging in use and getting quick and better results.

CONCLUSION

The buccal route has several advantages for the efficient delivery of the drugs. It has proved to be feasible and attractive to target and treat a local disorder, which is related to the oral cavity, as well as they can also be used for systemic disorders since they release drug directly into the systemic circulation by absorption through buccal mucosa by-passing the first -pass effect. Thus, it can be said that BDDS is a promising area in the global health care system in discovering many medications that may help in effectively treating the disorder, with patient compliance. Although being suitable for administration, the buccal drug delivery system has some challenging concept, and obstacles to study and overcome with the drug delivery. Thus, strategies are made and the detailed study and research are going on globally to overcome these barriers. Development in this area is widely increased and recent studies are going on to deliver even proteins and peptides through Buccal drug delivery systems.

REFERENCES:

1. Annigeri, R.G., Jadhav, M. Mucoadhesive Patch : A Novel Drug Delivery. *Res. Rev. J. Pharm. Pharmaceutical Sci.* **3**, 56–62 (2014).
2. Gandhi, P. A. A Review Article on Mucoadhesive Buccal Delivery System. *Int. J. Pharm. Res. Dev.* **3**, 159–173 (2011).
3. Srivastava, N. & Monga, M. G. Current Status of Buccal Drug Delivery System: a Review. *J. Drug Deliv. Ther.* **5**, 34–40 (2015).
4. Tangri, P., Jawla, S., Jakhmola, V., Mishra, R. Highlights of Mucoadhesive Drug Delivery Systems: A review. *Indo Global J. Pharm. Res.*, 7(2), 112–125 (2017).
5. Ramesh, B. *et al.* A review on buccal drug delivery system. *Int. J. Res. Pharm. Sci.* **5**, 200–204 (2014).

6. Hua, S. Advances in Nanoparticulate Drug Delivery Approaches for sublingual and buccal adminstration. *Front Pharmacol*, **10,** 1328 (2019).
7. Attama, A. A., Akpa, P. A., Onugwu, L. E. & Igwilo, G. Novel buccoadhesive delivery system of hydrochlorothiazide formulated with ethyl cellulose-hydroxypropyl methylcellulose interpolymer complex. *Sci. Res. Essays* **3**, 343–347 (2008).
8. Panchal, P., Parvez, N. & Srivastav, S. Buccal Film: Insight for Treatment of Various Disease. *Int. J. ChemTech Res.* **12**, 97–107 (2019).
9. V, S., Reddy, S. S., K, Y. D. B., T, P. & Kar, A. Buccal Drug Delivery- the Road Less Travelled: a Review. *Indian J. Med. Res. Pharm. Sci.* **5**, 48–60 (2018).
10. Mahajan, P., Kaur, A., Aggarwal, G. & Harikumar, S. L. Mucoadhesive drug delivery system: A review. *Int. J. Drug Dev. Res.* **5**, 11–20 (2013).
11. Roy, S. K. & Prabhakar, B. Bioadhesive polymeric platforms for transmucosal drug delivery systems - A review. *Trop. J. Pharm. Res.* **9**, 91–104 (2010).
12. Puratchikody, A., Prasanth, V. V., Mathew, S. T. & Kumar, A. B. Buccal drug delivery: Past, present, and future - A review. *Int. J. Drug Deliv.* **1**, 171–184 (2011).
13. Singh, C.L., Srivastav, N., Monga, M.G., *et al.* A review : Buccal buccoadhesive drug delivery system World J. Pharma. Sci. (2014).
14. Dodla, S. & Velmurugan, S. Buccal penetration enhancers-An overview. *Asian J. Pharm. Clin. Res.* **6**, 39–47 (2013).
15. Jagtap, V. D. Buccal Film - A Review on Novel Drug Delivery System. *Int. J. Res. Rev.* **7**, 17–28 (2020).
16. Bases, S., Azetidinone, I. T. S. & Derivatives, T. International Journal of Innovative Pharmaceutical Sciences and Research ACTIVITY OF NOVEL 2-SUBSTITUTED BENZIMIDAZOLE. **3**, 574–583 (2015).
17. Mishra, S., Kumar, G. & Kothiyal, P. A Review Article : Recent Approaches in Buccal Patches. *pharma Innov.* **1**, 87–92 (2012).
18. Lokhande, S. D. & Lahoti, S. S. Buccoadhesive Drug Delivery System: Need 1. *Asian J. Biomed. Pharm. Sci.* **2**, 29–36 (2012).
19. Prasad, N. & Kakkar, S. A review: on buccal patches. *Int. J. Recent Adv. Sci. Technol.* **2**, 8–15 (2015).
20. Mitul, P., Asif, K., Pratik, S., MV, R. & Ashwini, D. Buccal drug delivery system: the current interest. *Res. J. Pharm.* **2**, 2011 (2011).
21. Ramesh, B. *et al.* A review on buccal drug delivery system. *Int. J. Res. Pharm. Sci.* **5**, 200–204 (2014).
22. Hooda, R., Tripathi, M. & Kapoor, K. A Review on Oral Mucosal Drug Delivery System. *Pharma Innov.* **1**, 14–21 (2012).
23. Tangri, P. Recent Advances in Oral Mucoadhesive Drug Delivery Systems: A Review. *Int. J. Pharma Res. Dev.* **3**, 151–162 (2011).
24. Carvalho, F. C., Bruschi, M. L., Evangelista, R. C. & Gremião, M. P. D. Mucoadhesive drug delivery systems. *Brazilian J. Pharm. Sci.* **46**, 1–17 (2010).
25. Shaikh, R., Raj Singh, T., Garland, M., Woolfson, A. & Donnelly, R. Mucoadhesive drug delivery systems. *J. Pharm. Bioallied Sci.* **3**, 89–100 (2011).
26. Nayak, B. S., Sourajit, S., Limited, M. P. & Behera, S. Sublingual drug delivery system : A. (2017).
27. Baviskar, P., Bedse, A., Sadique, S., Kunde, V. & Jaiswal, S. Drug Delivery on Rectal Absorption : Suppositories. **21**, 70–76 (2013).
28. Chatterjee, A. A review on vaginal drug delivery systems. Int. J. Bio. Pharm., Allied Sci. (2015).
29. Gupta, S. & Kesarla, R. Ophthalmic Drug Delivery Systems with Emphasis on In-Situ Hydrogels Ophthalmic Drug Delivery Systems with Emphasis on In-Situ Hydrogels, *Pharmagene*, 1(2), 80-87 (2013)
30. Gupta S, Kesarla R, Omri AW. Approaches for CNS delivery of drugs - Nose to brain targeting of anti-retroviral agents as a potential attempt for complete elimination of major reservoir site of HIV to aid AIDS treatment. Expert Opinion on drug delivery, 16:3,287-300, (2019)
31. Kumari, N., Aggarwal, G. & Harikumar, S. L. Mucoadhesive Microspheres: a Review. *J. Drug Deliv. Ther.* **4**, 48–54 (2014).
32. Koyi, P.K. and Khan A.B., Buccal Patches: A review., Int. J. Pharm. Sci. Res.,**4**, 83–89 (2013).
33. Mahajan, A., Chhabra, N. & Aggarwal, G. Formulation and characterization of fast dissolving buccal films: A review. *Der Pharm. Lett.* **3**, 152–165 (2011).

34. Arun, J. L., Rani, S. & Manoj Kumar, P. Buccal drug delivery system: History and recent developments. *Asian J. Pharm. Clin. Res.* **9**, 36–42 (2016).
35. Arya, A., Chandra, A., Sharma, V. & Pathak, K. Fast dissolving oral films: An innovative drug delivery system and dosage form. *Int. J. ChemTech Res.* **2**, 576–583 (2010).
36. Gawas, S. M., Dev, A., Deshmukh, G. & Rathod, S. Evaluations Current approaches in buccal drug delivery system. *Pharm. Biol. Eval.* **3**, 165–177 (2016).
37. Bhalodia, R., Basu, B., Garala, K., Joshi, B. & Mehta, K. Buccoadhesive drug delivery systems: A review. *Int. J. Pharma Bio Sci.* **1**, (2010).
38. Gupta, S. et al. "Formulation, optimization and evaluation of colon targeted delivery system for Isradipine". World Journal of Pharmacy and Pharmaceutical Sciences, 5 (5), 632-649, (2016)
39. Absorption, P., Permeation, T., Metabolism, F. P. & Pradesh, U. No Title. **8**, 1001–1011 (2017).
40. Yadav, A. V. & Urade, M. N. Formulation and evaluation of chitosan based transdermal patches of lornoxicam for prolonged drug release and to study the effect of permeation enhancer. *Indian J. Pharm. Educ. Res.* **53**, 88–96 (2019).
41. Poojar, B. *et al.* Methodology Used in the Study. *Asian J. Pharm. Clin. Res.* **7**, 1–5 (2017).
42. M. Muthukumaran, D. Dhachinamoorthi & et. al. In-Vitro And In-Vivo Evaluation Of Novel Mucoadhesive Buccal Drug Delivery Systems-A Review. *Int. Res. J. Pharm. Appl. Sci.* **3**, 56–59 (2013).
43. Okorochukwu, N. Development and Characterization of Mucoadhesive Patches for Buccal Delivery of Pregabalin. *Univers. J. Pharm. Res.* **2**, 6–10 (2017).
44. Castán, H., Ruiz, M. A., Clares, B. & Morales, M. E. Design, development and characterization of buccal bioadhesive films of Doxepin for treatment of odontalgia. *Drug Deliv.* **22**, 869–876 (2015).
45. Singh, P. K., Singh, D. & Bijauliya, R. K. A Comprehensive Review on Buccal DrugDelivery System. *Int. J. Res. Dev. Pharm. Life Sci.* **6**, 2606–2618 (2017).

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