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Buccal Patches: A Promising Buccal Bioadhesive Drug Delivery System - A Review

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ABSTRACT

Buccoadhesive drug delivery has gained considerable attention in recent years, especially for the formulation and development of oral patches**.** Buccal patch formulation helps target medication / drug delivery to remain in the appropriate area for longer period**.** The drug enters systemic circulation directly, avoiding hepatic first pass metabolism and presystemic gastric degradation, leading to improved drug bioavailability**.** Thus, buccal patch becomes the most suitable form of buccal drug delivery due to its flexibility, less thickness and high absorption owing to its large surface area and longer residence time**.** In this respect, this study covers the overview of buccal mucosa, permeation pathways and their barriers, novel manufacturing methods, prototypes, mucoadhesive polymers used in preparation, oral patch assessment parameters**.** In conclusion, this study offers proof of concept to young researchers that will be helpful in circumventing the difficulties associated with the development of buccal patches.

INTRODUCTION:

Recently, extensive efforts have been taken on targeting a drug or drug delivery system in a particular region of the body for a longer period of time to achieve desired benefits, not only for local drug targeting, but also for better control of systemic drug delivery. Conventional dosage forms are generally associated with difficulties in reaching the target site with a specified dose. While on oral administration many drugs are subjected to presystemic metabolism extensively in liver, which often leads to intolerance, poor absorption and bioavailability. Limitations to parenteral delivery are high production cost and poor patient compliance, thus it becomes necessary to explore other novel routes for drug delivery. In the early 1980s, the idea of mucosal adhesion or mucoadhesive was introduced, which in recent times has become an important part of the novel drug delivery system. Buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual path, and gastrointestinal area are isomer of the prospective sites for attachment of any mucoadhesive device (1). However among these, buccal route is the most preferred route of drug administration by the patients as well as physicians. Buccal mucosa has outstanding accessibility, a smooth muscle expanse and relatively immobile mucosa, making it suitable for retentive dosage types. Direct entry to the systemic circulation through the inner jugular vein bypasses drugs from the hepatic first pass metabolism, leading to high bioavailability (2). Adhesion between natural or synthetic polymer and tissues is called bio-adhesion and is recognized as mucoadhesion when between the mucus membrane and the polymer. Buccal mucosa exhibits a flat and steady surface for the placement of mucoadhesive dosage form. The quantity of medication that icon be integrated is limited ivy the size restriction of dosage form. Generally, for buccal delivery, a medication with a daily dose of 25 mg or less is acceptable. Short half-life drugs that require sustained or controlled release that have low aqueous solubility and are prone to enzymatic degradation can be successfully administered within the buccal mucosa. An effective delivery of oral drugs should be versatile and have good bio-adhesive properties along with the release of drugs in a regulated and consistent way to elicit the necessary therapeutic response (3). Thus, buccal patch becomes the most suitable form of buccal drug delivery due to its flexibility, less thickness and high absorption owing to its large surface area and longer residence time. Buccal patch is a modified release dosage form composed of one or more polymers, drug and other excipients with different designs (4). The objective of this review is to discuss buccal patches, their novel production processes, prototypes, mucoadhesive

polymers used in preparation, evaluation parameters and the difficulties faced by buccal patches etc.

ANATOMY AND PHYSIOLOGY OF ORAL CAVITY:

The oral cavity refers to the area of mouth formed by the lips, cheeks, the mouth floor, the soft palate and the hard palate as shown in figure 1. Oral mucosa comprises the buccal, sublingual, gingival, palatal and labial mucosa and is the general term for defining the lining of the oral cavity. (5).The oral mucosa has a surface area of 170 cm^2. And it is made up of an outermost layer of (about 40-50 cell layers thick) stratified squamous epithelium. Neath this is a basement membrane, a lamina propria, accompanied by the submucosa comprising the innermost layer of nerves and blood vessels, as shown in Figure 2.

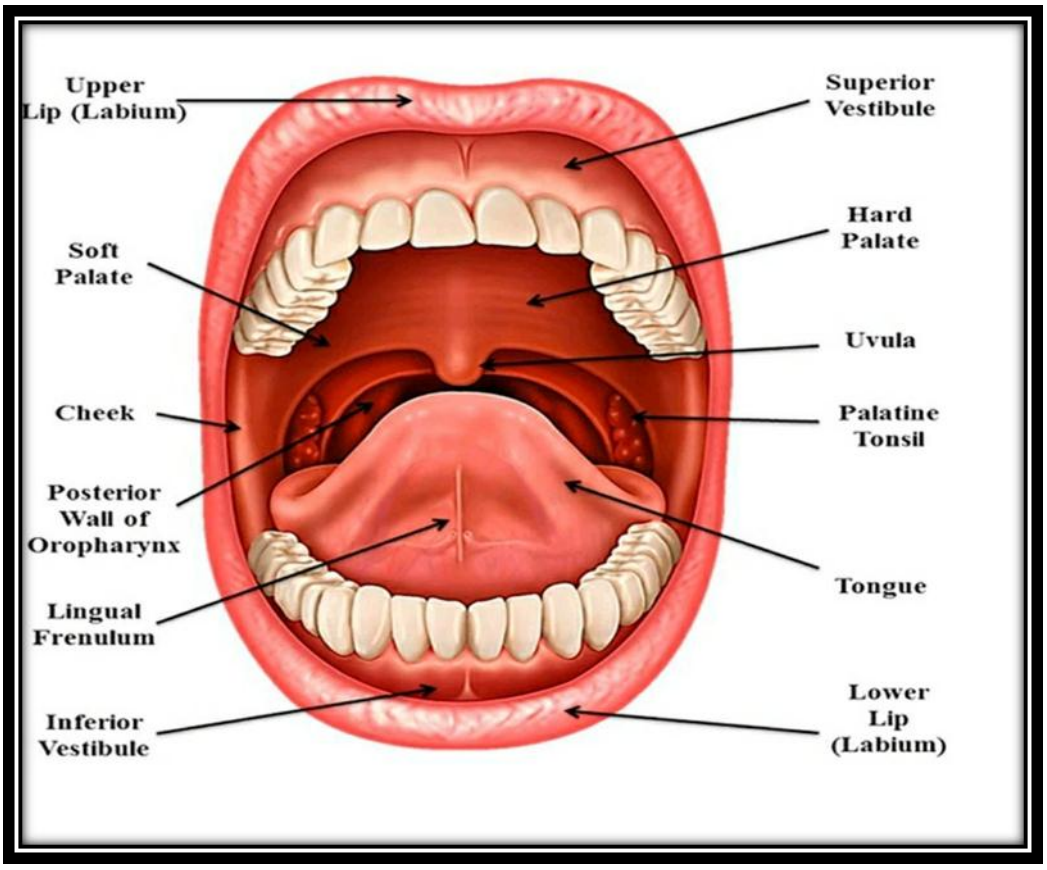

Figure no.1: Anatomy of the oral cavity [6]

The thickness depends upon the area. Buccal mucosa is 500-800 µm thick, while the thickness of the hard and soft palate mucosa, the floor of the mouth, the ventral tongue and the gingival is approximately 100-200µm. (6,7).When epithelial cells migrate from the basal layers to the superficial layers; they grow in size and become flatter. The buccal mucosal

epithelium has a thickness of approximately 40-50 cell layers. The turnaround period for the buccal epithelium has been stated to be 5-6 days, and this is possibly indicative of the entire oral mucosa. (8,9,10). Depending on the location in the oral cavity, the composition of the epithelium also differs. Masticatory mucosa, (25% of the overall oral mucosa) protects the keratinized gingiva and hard palate. Lining mucosa (60%) is non-keratinized, on the other hand, and protects the mouth, sublingual, soft palate and inner side of the lips. It has been found that non-keratinized epithelia are relatively more water-permeable than keratinized epithelia. Also, specialized mucosa (15%) protects the top surface of the tongue and contains characteristics of both masticatory and lining mucosa.

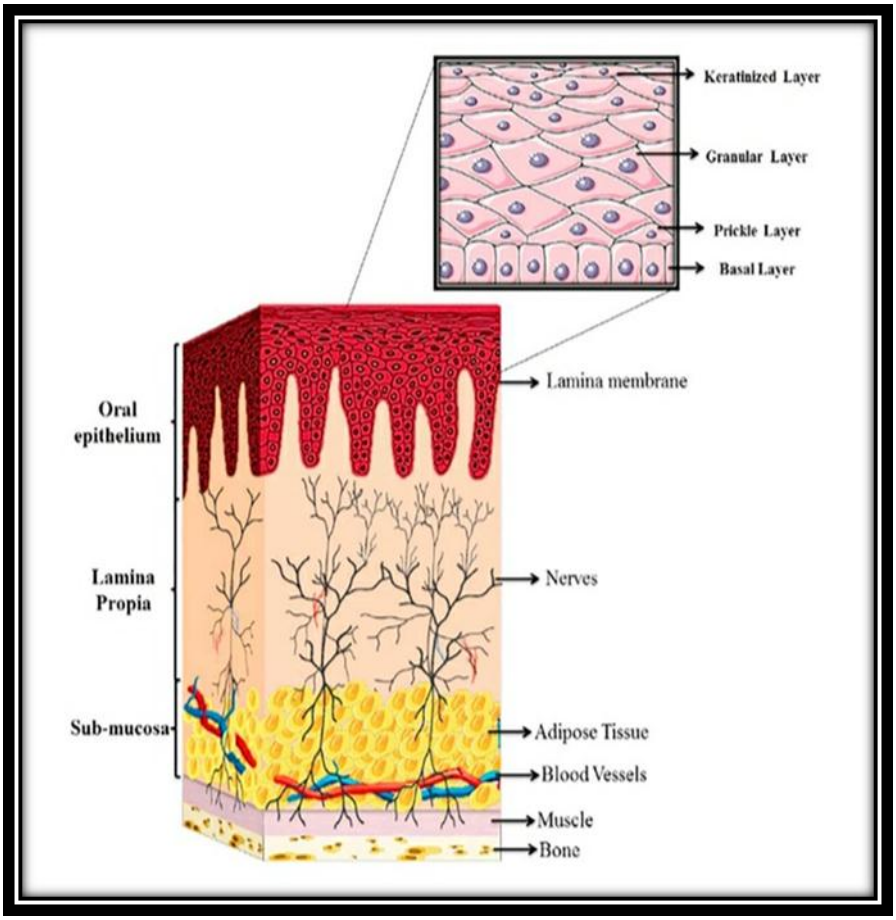

Figure No. 2: Layers of Oral Mucosa [6]

The most prominent oral transmucosal routes of administration are buccal and sublingual routes. The delivery of drugs through the oral mucosa is conditioned by the volume and flow rate of saliva, pH, enzyme activity, and oral mucosa permeability. Permeability, on the other hand, is influenced by the thickness of the mucosa, the composition of various epithelial cells and vascularization. There are small quantities of neutral and polar lipids such as cholesterol

sulphate and glucosyl ceramides in the non-keratinized epithelium of the buccal and sublingual mucosa; only small amounts of ceramides are present and acylceramides are missing. Buccal and sublingual routes, both are highly vascularized. The sublingual mucosa (100-200 mm thick) is comparatively thinner than the buccal mucosa (500-800 mm thick). Overall, sublingual mucosa is used mainly for the rapid onset of drug action, whereas buccal mucosa is ideal for the delivery of local and systemic drugs (11,12).

PERMEATION (ABSORPTION PATHWAY):

The oral mucosa, between the epidermis and the intestinal mucosa, is a very leaky epithelium. Owing to the difference in oral mucosal structure and function at different sites, the permeability in various regions of the oral cavity is different. For the buccal mucosa it found to be 4-4000 times greater than that of the skin. In general permeability order of oral mucosa is as, sublingual (thin & non-keratinized) > buccal (thick & non-keratinized)> palatal (intermediate thick & keratinized).The absorption or permeation of drug molecule through buccal mucosa follows passive diffusion which is classified as follows: (4)

◦ Transcellular or intracellular route (crossing the cell membrane and entering the cell)

◦ Paracellular or intercellular route (passing between the cells)

PERMEATION BARRIERS:

Barriers such as granules lining the squamous epithelium membrane, basement membrane, lamina propria, pathway of permeation, spit, mucus, enzyme, tongue, etc. There is a pause in the rate and length of drug absorption through the buccal mucosa. The highest penetration barrier exists in the outermost quarter to one third of the epithelium (13,14).

1. Squamous epithelium: An intercellular substance called MCG, i.e., membrane coating granules, is present in the outermost layer of squamous epithelium. The MCG present in nonkeratinizing epithelia are spherical, membrane-bounded in shape and around 0.2μm in diameter. In the membrane coated granules, an intracellular lipid component is packaged. MCGs begin to develop as cells go through differentiation and they merge with the plasma membrane at the apical cell surfaces and their lipid content is discharged into the intercellular spaces at the top one-third of the epithelium. This barrier occurs in the outermost 200μm superficial layer (15).A variety of very large molecular weight tracers, such as horseradish peroxidase and lanthanum nitrate, were used to conduct permeation tests. These tracers only

penetrate into the outermost layer or two of cells when added to the outer surface of the epithelium. According to these findings, it is evident that the key obstacle to permeation is flattened surface cell layers, whereas the more isodiametric cell layers are relatively permeable (16,17). It was found that the permeation of fentanyl citrate was increased significantly by removing lipids from the epithelial layer with a mixture of methanol and chloroform, which indicated that the epithelial layer's permeation resistance was linked to lipid substances in the intercellular domain. In both keratinized and non-keratinized epithelia, the same result was obtained; keratinization alone is not expected to play a significant role in the permeation barrier. Therefore, the rate limiting step in mucosal penetration is still considered to be the outer epithelium (8).

2. Basement Membrane: The basement membrane can also play a role in restricting the passage of materials through the epithelium-connective tissue junction. The rate of penetration of lipophilic compounds that can cross the superficial epithelial barrier relatively easily can be restricted by the charge on the constituents of the basal lamina (2).

3. Lamina Propria: Veuillez F et al. have used a lamina propria of porcine buccal mucosa as a permeation model to investigate the distribution during the permeation of a lipophilic myristoylated dipeptide at various mucosal depths. They found through the process that the drug was remained in the lamina propria in significant amounts, and was unable to move through it. This phenomenon suggests that a strongly lipophilic drug will not move through a hydrophilic lamina propria.

4. Permeation Pathway: Due to intracellular spaces in the cell membrane, intercellular spaces are hydrophilic, thus acting as a barrier to lipophilic drugs, while cell membranes are lipophilic in nature; they function as a barrier to hydrophilic drugs (18, 19).

5. Saliva The saliva is a biologic fluid present in the oral cavity produced by the submandibular, the parotid and the sublingual glands, along with other minor submucosa glands. It is continuously drained, dispersed and removed from the oral cavity**.** Saliva is a weak buffer system with a pH of 5.5-7 and regular salivary flow rate is approximately 0.5 mL min^{-1}, resulting in between 0.5 and 2 L of daily secretion, although the constant amount of saliva in the mouth is approximately 1 ml because of continuous swallowing**.** It has high shear during eating and swallowing. The renovation cycle of saliva induces dilution of drug thus affects the amount of drug present in the absorption site. Due to high turnover rate of saliva, the residence time of drug in oral cavity is short leading to poor drug absorption. The

saliva pH also influences the dissolution and concentration of drugs. The removal of the substance from the absorption site may also be caused by swallowing saliva or ingesting food. In addition, talking, eating and chewing can lead to poor distribution of drugs inside the oral cavity, affecting the delivery system's release rates. Thus, saliva is also the most important barrier element to drug penetration through the buccal mucosa (6, 21).

6. Mucus: The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus which is secreted by major and minor salivary glands as part of the saliva. The thickness of the mucus ranges from 40 μm to 300 μm. It is primarily composed of mucins and water-suspended inorganic salts. .Mucins is a family of large, highly glycosylated proteins made up of chains of oligosaccharides attached to a protein core.Three quarters of the protein core which are heavily glycosylated, impart a gel like characteristic to mucus. Mucins contain around 70-80% carbohydrate, 12-25% protein and up to 5% ester sulphate. Owing to the presence of sialic acids and ester sulphates, mucus is negatively charged at physiological salivary pH (22).

- By acting as a lubricant to cells, it allows cell movement with respect to each other, and also prevents destruction of cell junctions. This serves as an obstacle to penetration.
- By forming a highly cohesive gel structure that attaches to the epithelial cell surface as a gelatinous film, it helps adherence of mucoadhesive drug delivery systems. This property is capable of altering drug absorption (12).
- The heavy sugar coating of mucins gives them significant water holding ability and makes them resistant to proteolysis as well (2).

7. Enzyme: In the course of passage through the mucosa, some drugs are degraded by enzymes. These involve salivary enzymes like carbohydrases, esterases, etc. Different pharmaceutical methods may prevent this (for example, loading drugs into certain polymers). The degradation of the drug by salivary enzymes is, to this end, negligible. The function of the buccal mucosal enzyme is the lowest among all mucosa enzymes. Dehydrogenase, endopeptidases, carboxypeptidases, aminopeptidases, and dipeptidases are enzymes that are found in the buccal mucosa. Studies have revealed that aminopeptidase-N is the only active enzyme in the buccal mucosa. A variety of permeation enhancers such as cholates can restrict the activity of aminopeptidase. Therefore the barrier role of the enzyme in the transport of the drug by the buccal mucosal is not a major barrier (23).

8. Tongue: The tongue shaped by the skeletal muscle layered by the mucous membrane is another essential organ in the oral cavity, covering around 15% of the surface of the oral mucosa. During chewing, the tongue pushes the food in the mouth to aid in swallowing, and it is often an obstacle to drug absorption (6).

IDEAL CHARACTERISTICS OF BUCCAL DRUG DELIVERY SYSTEM: (24, 25,26)

- Safety and non-toxicity.
- Non-irritancy
- Biocompatible pH.
- Elevated flexibility.
- Instant adherence to buccal mucosa.
- Longer retention time.
- Optimum drug absorption rate and extent.
- Controlled release of a drug
- Unidirectional release of drug into the mucosa.
- No interference into normal functions such as talking and drinking.

LIMITATIONS OF BUCCAL DRUG DELIVERY: (27, 28, 29, 30)

Despite the advantages, the buccal delivery has restrictions that hamper the drug delivery such as:

- Drugs that are unstable at oral pH cannot be given.
- This route does not administer medications that have a bitter taste or bad taste or an obnoxious scent or irritate the mucosa.
- Drug required with small dose can only be administered.
- Drug dilution takes place due to saliva.
- Drugs may be swallowed along with the saliva and fail the benefits of buccal route.
- Those drugs which are absorbed by passive diffusion can only be administered by this route.
- Eating and drinking may become restricted.
- Lesser area of the oral cavity available for drug absorption.

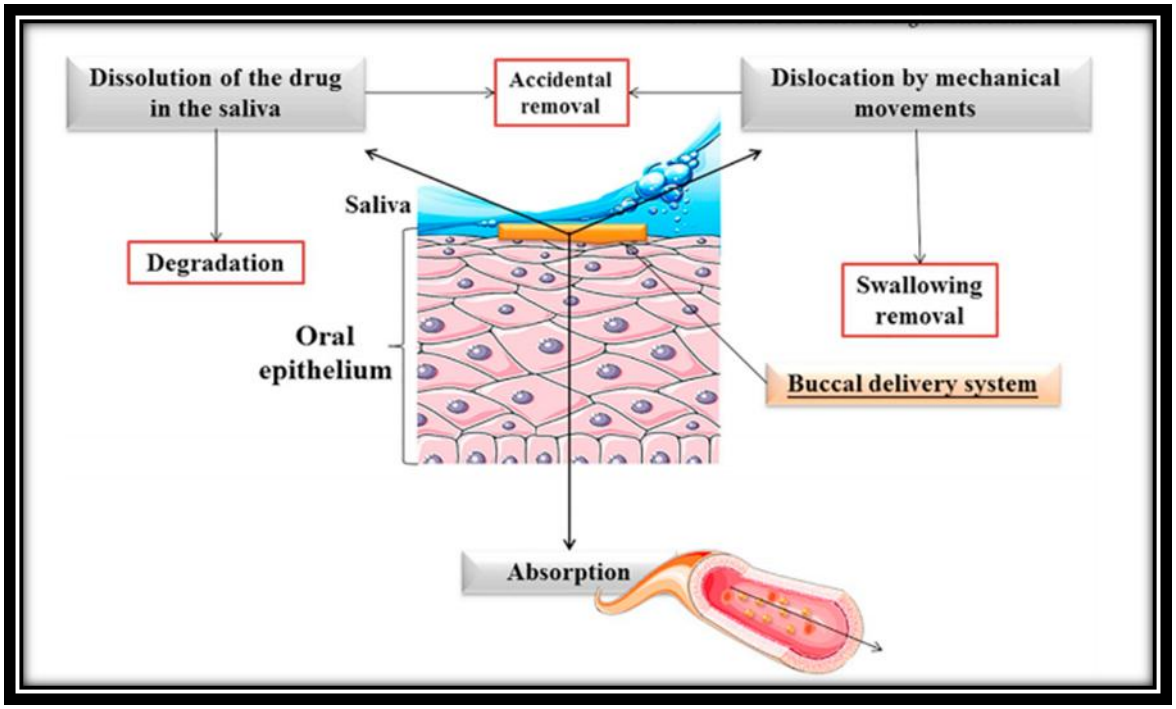

Figure No. 3: Factors hampering the buccal uptake of drugs. (6)

CLASSIFICATION OF BUCCAL DRUG DELIVERY SYSTEM (25) :

A. Solid dosage forms:

I. Buccal tablet

II. Lozenges

III. Wafers

IV. Buccal film and Patches

V. Buccal chewing gum

B. Semisolid dosage forms:

I. Ointments

II. Gels

C. Liquid dosage forms:

I. Spraying agents

II. Emulsions in the form of liposomes, nanoparticles

Buccal tablets: Buccal tablets are small, flat and oval, possibly 5-8 mm in diameter and around 2 mm thick, and have been shown to be excellent bioadhesive formulations that are mounted directly on the mucosal surface. Size is a drawback for tablets, however, as they need to have close mucosal contact. In the presence of saliva, these tablets cling to the buccal mucosa. They are designed to release the drug either unidirectionally or multidirectionally to the saliva (31, 32, 33).

Bioadhesive Micro/nanoparticles: Their physical properties allow them to make intimate contact with the larger mucosal surface area. These are usually administered as an aqueous suspension or are added into a paste or ointment or applied in the form of aerosols. They are more likely to be acceptable by the patients (34).

Wafers: A composite wafer with surface layers having adhesive properties is the delivery method, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers. A conceptually novel periodontal drug delivery system intended for the treatment of microbial infections associated with periodontitis has been reported (34). They are prepared by freeze drying polymeric gels or solutions that present a sponge-like structure due to fast hydration and gelation. Wafers preserve their swollen gel form for longer period when applied to the buccal mucosa than semisolid polymer gels, which easily flow after application (35).

Lozenges: Bioadhesive lozenges offer prolonged drug release with improved patient compliance compared to Conventional lozenges, thus avoiding multiple daily doses. They are suitable for local drug delivery including antimicrobials, corticosteroids, local anesthetics, antibiotics and antifungals.

Gels: By forming cross connected polyacrylic acid, bioadhesive polymers form gels. Gels remain bound to the surface of the mucosal to provide controlled drug release for a long period of time. The failure to administer a calculated dosage of medication to the site is a drawback of gel formulations (34).

Hydrogels: A modern controlled release method has incorporated multiple attractive aspects into one single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethylene oxide) to promote mucoadhesion. Natural or synthetic polymers form three-dimensional macromolecular networks to form mucoadhesive hydrogels and these contain a large fraction of water within

their structure. When placed in an aqueous medium, these hydrophilic matrices absorb water and, due to chain polymer relaxation, release the drug loaded through the spaces or channels within the hydrogel network (85).

Buccal patches and films: Patches are laminates that consist of a reservoir layer containing drugs and an impermeable backing layer. Drug is released in a controlled manner from the reservoir layer. Bioadhesive surface is for mucosal attachment. Mucoadhesive patches can be made up to 10-15 cm2 in size, but with an oval shape, they are typically 1-3 cm2 to fit comfortably into the middle of the buccal mucosa. The film attached to the oral mucosal should be kept in place for at least 12 hours (17, 33, 36).

Liquid oral adhesive dosage forms: The liquids used to cover the oral surface are viscous and act either as protecting agents or as drug vehicles to carry the drug to the surface of the mucosa. By supplying lubrication with artificial saliva solutions, dry mouth can be treated and maintain the drug on mucosal surfaces [8]. Novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been developed recently. Phospholipid deformable vesicles, transfersomes, have been recently used for the delivery of insulin in the buccal cavity (12).

Medicated chewing gums: The drug release can last about 20min–30min from a chewing gum in the oral cavity. Some commercial products are available in the market recently. Caffeine chewing gum, Stay Alert®, was developed for alleviation of sleepiness. Nicotine chewing gums (e.g., Nicorette® and Nicotinell®) marketed for smoking cessation (17).

ADVANTAGES OF BUCCAL PATCHES OVER OTHER BUCCAL DOSAGE FORM:

Various mucoadhesive formulations have been suggested for buccal drug delivery, including buccal mucoadhesive tablets, ointments, gels and films but buccal patches are superior than other forms.

1. Buccal patches are well tolerated by patients because of their high versatility and comfort as opposed to buccal tablets.

2. Compared to mucoadhesive ointments and gels, which have limited residence time in the buccal cavity, buccal patches ensure more precise dosing of the medication (37).

3. Higher contact surface area, and bitter drugs can be administered without taste masking. The patch's bilayered nature was chosen to achieve unidirectional drug release, Prerana D.

Navti, et al. studied on successful preparation of bilayered buccal patches with chitosan as a mucoadhesive polymer to ensure satisfactory unidirectional release of Carvedilol with adequate mucoadhesion (38).

4.Mucoadhesive buccal patches provide sufficient dosing, patient compliance, cost efficacy and decreased dosing frequency over metered dose inhalers (MDIs), nebulizers or other patented delivery devices (e.g. Rotahaler or Autohaler). For example, Salbutamol sulphate mucoadhesive buccal patch production used for asthma and chronic obstructive pulmonary disease by Ayarivan Puratchikody et al.(39).

5. Buccal patches preferred the method of oral controlled and sustained drug delivery, as the buccal mucosa is even and set, the patches are not washed by saliva (31).

6. Owing to the continuous secretion of saliva into the oral cavity, in the case of buccal film, dilute drugs at the absorption site, resulting in low drug concentrations at the surface of the absorbing membrane. The instinctive swallowing of saliva results in the removal from the absorption site of the maximum portion of the dissolved or suspended released substance. In addition, there is a possibility of swallowing the delivery system itself, but patches remain fixed at the absorption site.

7. The traditional form of oral drug delivery systems did not encourage the patient to eat, drink or speak at the same time (5).

DESIGNS OF BUCCAL PATCHES:

In general, different designs, based on the desired properties, are considered for the preparation of the buccal patch. Following Fig. shows several films of mucoadhesive drug delivery with various designs and features of drug delivery.

Matrix systems (Bi-directional): Drugs and other additives are dispersed or dissolved uniformly in a hydrophilic or lipophilic polymer matrix in these systems and their release properties are affected by the penetration of the polymer network. Bi-directional patches release drugs in both the mucosa and mouth site. Therefore, the most significant negative effects of a bi-directional design are partial absorption and lower drug bioavailability.

Reservoir systems (Unidirectional): In oral patches built into the reservoir or membrane structure, a film or sheet of polymer-containing drugs and additives as well as an impermeable backing layer are used to control the release rate of the drug and to prevent

patch deformation and degradation of the drug This style of design is usually used for both local and systemic drug releases. Various architectures may be used for drug delivery and treatment in membrane systems. In the first configuration, for example, a double layer system with a protective backing layer and a layer of drug-containing mucoadhesive polymer can be used as a needle-free mucosal vaccination. A membrane-based system consisting of two layers with fast and regulated release properties as well as an impermeable layer exists in another design. This is an effective design for managing oozing and relieving pain in the first treatment cycle. In the third form, a non-adherent drug-containing polymer and a mucoadhesive polymer matrix are used to build a controlled release system in addition to the presence of a non-penetrating protective layer (4).

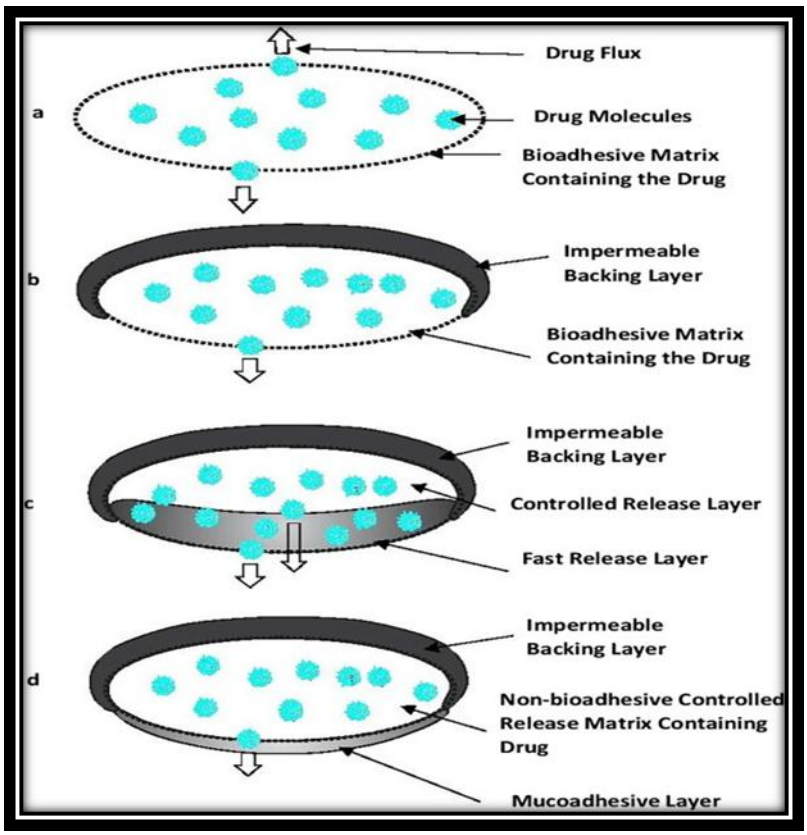

Figure no. 4: Oral Mucoadhesive Patches designs (4)

IDEAL DRUG CANDIDATES FOR BUCCAL DRUG DELIVERY:

Drug Substance Before formulating buccal drug delivery systems , it is important to determine if the action intended is for rapid release / prolonged release and local / systemic effects. The selection of appropriate drugs for the design of buccal drug delivery systems

should be focused on the pharmacokinetic properties of the drug. The drug should have following characteristics: (3)

- The conventional single dose of the drug should be minimal.
- Drugs with a biological half-life of 2-8 hours are strong candidates for controlled delivered medication.
- When orally administered, the medication Tmax displays larger fluctuations or higher values.
- First pass impact or pre-systemic drug removal can be shown by oral route drug.
- The absorption of drugs when administered orally should be passive.
- They should be odourless, tasteless, and have 200-500 Daltons molecular weight.

FORMULATION DESIGN OF BUCCAL PATCHES:

(1) Active Pharmaceutical Ingredient (API): Different types of active pharmaceutical ingredients are delivered through the buccal patch delivery system. As described above, they are primarily selected according to their pharmacokinetic properties.

(2) Mucoadhesive polymers: The selection of suitable mucoadhesive polymers plays a major role in drug delivery systems. The primary function may be polymer hydration and swelling properties. Polymers are also used in matrix devices where the drug is incorporated in the matrix of the polymer that regulates the duration of drug release. Mucoadhesive polymers are by far the most diverse class and have major advantages for patient health care and delivery of treatment (40).

(3) Diluents: lactose, microcrystalline starch, and starch are the diluents used in the buccal patch.

(4) Sweeteners: Sucralose, aspartame and mannitol are used for sweetening purposes.

(5) Flavoring agents: Menthol, vanillin, clove oil, peppermint oil, cinnamon oil, spearmint oil, vanilla, cocoa, coffee and chocolate are the flavoring agents used in the formulations.

(6) Backing layer: The backing membrane plays a major role in binding the mucus membrane to the bioadhesive devices. The materials used as the backing membrane should be inert and the drug and penetration enhancer should be impermeable. This impermeable layer on the oral bioadhesive patches prevents the loss of the drug and ensures improved compliance for

the patient. Carbopol, HPMC, HPC, CMC, Polycarbophil, Magnesium Stearate, etc. are the widely used materials in the backing membrane. R. Navamanisubramanian et al. formulated Repaglinide buccal tablets using Thiolated Chitosan as main mucoadhesive polymer and Sodium Carboxymethyl Cellulose (NaCMC), Ethyl Cellulose (EC), Micro Crystalline Cellulose (MCC) as backing layer (41).

(7) Penetration enhancer: The penetration enhancer is used to increase the release of the drug in oral formulations. They assist in the drug's systemic distribution by allowing the drug to reach the viable tissues more easily. The widely used penetration enhancers are Sodium lauryl sulphate, CPC, Polysorbate 80, Laureth 9, Sodium Fusidate, Sodium glycocholate, Dimethyl sulphide, etc. U. D. Shivhare et al. studies on preparation of mucoadhesive buccal patches containing Aceclofenac as API using polymers HPMC E-15 and Eudragit RL 100 and Dimethyl sulphide as penetration enhancer to improve the bioavailability (42).

An ideal polymer for buccal drug delivery systems should have following Characteristics:

- It should be inert and be environmentally compatible.
- The polymer and its degradation products should be absorbable from the mucous layer in a non-toxic way.
- It should bind easily to the surface of moist tissue and have some site specificity.
- In storage or during the shelf life of the dosage type, the polymer must not decompose.
- It should be non-toxic, economic, biocompatible and ideally biodegradable.
- It should make it easier to quickly integrate drugs into the formulation (43).

Selection Criteria followed in polymer selection:

- High molecular weight: To facilitate adhesion between the polymer and the mucus, the polymer must have a high molecular weight.
- Optimum chain length of polymer: The length of the polymer chain must be optimum. Long enough to enable adequate interpenetration and short enough to promote diffusion.
- High viscosity: Mucoadhesive polymers should have properties that, when applied around the site, make them viscous.
- Degree of cross linking: It affects the mobility of the chain and dissolution resistance. In the presence of water, strongly cross connected polymers swell and maintain their structure.

Swelling favors the drug's controlled release and raises the interpenetration of polymer / mucus. But as the cross connection increases, the mobility of the chain decreases, which decreases the strength of mucoadhesive (44).

- Charge and degree of ionization: After adding a few different chemical entities to chitosan, the effect of polymer charge on mucoadhesion was determined and mucoadhesive strength was then evaluated. In contrast to plain chitosan, the hydrochloride salt of chitosan showed marked adhesiveness. Ethylenediaminetetraacetic acid (EDTA) attachment as an anionic group greatly improved the strength of mucoadhesive.. The diethylenetriamine pentaacetic acid (DTPA) complex with chitosan showed lower mucoadhesive strength due to low charge compared to cationic chitosan and anionic EDTA chitosan complexes. Hence, on the basis of surface charge, the mucoadhesive strength get changed (45).
- Optimum hydration: Excessive hydration contributes to reduced mucoadhesive strength due to the formation of slippery mucilage.
- Optimum pH: At low pH conditions, mucoadhesion is optimum, but a change in conformation can occur at higher pH values, such as a rod like structure can make polymer more accessible for inter-diffusion and interpenetration. Positively charged polymers such as chitosan form mucus polyelectrolyte complexes and demonstrate strong mucoadhesive forces at very high pH values.
- Polymer chain flexibility: This facilitates the polymer's interpenetration within the mucus network.
- Polymer concentration: An optimal concentration is required to promote the strength of the mucoadhesive. For example, in the case of solid dosage form, the adhesive strength increases with the increase in polymer concentration, depending on the dosage form, while in the case of semi-solid dosage form, it increases vice versa. (46)

TYPES OF MUCOADHESIVE POLYMERS USED IN BUCCAL DRUG DELIVERY SYSTEM:

Natural /Semi natural Polymer: following natural/ semisynthetic polymers are reported to have been used in preparation of mucoadhesive buccal patches:-

Chitosan: Chitosan is a biopolymer of a derived type of chitin that occurs naturally. Chitosan is a linear polysaccharide comprised of randomly distributed β-(1-4)-linked D-glucosamine

(deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit).Commercial chitosan, like Pandalus borealis, is derived from shrimp shells and other sea crustaceans.

Properties of chitosan: 1. Good bioavailability and low toxicity. 2. Mucoadhesive nature. 3. Chitosan has ability to produce many different forms when combined with other chemical entities. 4. In drug delivery, it shows positive charge under acidic conditions. 5. Chitosan is insoluble in neutral and basic environments. 6. Chitosan may form many translational metal ions. 7. Ability to bind to other molecules by itself. 8. Power for target drugs to take particular cellular action. 9. It has fungistatic and bacteriostatic effects.

Pharmaceutical application: Different uses in the pharmaceutical field for chitosan and its derivatives: 1. It is a good thinner for the direct compression of the formulation of tablets. 2. It is used as a wet granulation binder. 3. Regulated release of drugs from tablets, granules and film is shown by chitosan. 4. It increases the viscosity during the processing of hydrogels in solutions. 5. Chitosan facilitates the dissolution of poorly soluble drugs and increases drug absorption in the delivery system of nasal and oral drugs.6. A novel mucoadhesive polymer used in the delivery system for transmucosal drugs. 7. Microcrystalline chitosan has a high water retention ability, so this is advantageous in developing the formulation of slow release gels that control the release of drugs. 8. The hydrophilic nature of microcrystalline chitosan aid in, controlling rate of drug release for mucoadhesive formulations in stomach. S.A. Agnihotri et al. have been done considerable research efforts directed towards developing safe and efficient chitosan-based particulate drug delivery systems (47).

Guar gum: Guar gum is a type of galactomannan that occurs naturally and is also called guaran. Around 80 % galactomannan, 12 % water, 5 % protein, 2 % acid soluble ash, and 0.7 % fat are found in guar gum. Guar gum's molecular weight is approximately 1 million. Due to its long chain structure and high molecular weight, guar gum has high viscosity. Guar gum is a polysaccharide that consists of galactose and mannose sugar.

Properties of Guar gum: 1.In cold and hot water, guar gum is easily soluble, but in many organic solvents it is insoluble. 2. Other excellent features, such as the emulsifying agent, thickening agent, stabilizing agent, and film forming agent. 3. It has the ability to monitor rheology by management of the water phase. 4. The temperature, pH, salts and other solids influence the viscosity of guar gum. 5. Due to its drug release retarding property, guar gum is used in colon delivery.6. Guar gum in the big intestine is also prone to microbial degradation.

Pharmaceutical application: Guar gum is used as a binder or as disintegrant in tablets in the pharmaceutical industry. It is used in some bulk-forming laxatives as well. Guar gum is used in the cosmetics and toiletries industry as a thickener in toothpastes and as a conditioner in shampoos.

Tragacanth: Tragacanth is a natural gum obtained as dried juice from many species of genus Astragalus, including A.adscenden, A. Gummifer's, and A. brachycalyx.

Properties of Tragacanth: Tragacanth gum is a viscous, odorless, tasteless and water-soluble mixture of polysaccharides.

Pharmaceutical application: 1. It is used in tablets and pills as an adhesive agent. 2. Tragacanth is used in creams, pastes and lotions as an emulsifying oil droplet. 3. Used as an agent for thickening (30).

Sodium alginate: Alginic acid, or alginate, is an anionic polysaccharide, also referred to as algin, derived from brown algae cell walls. It has the ability to bind and form a viscous gum with water. In water, alginic acid can absorb 200-300 times its own weight when water is extracted from alginate. Mainly, alginate is derived from seaweed. Alginic acid is produced predominantly by two genera of bacteria, such as Pseudomonas and Azotobacter. They play an important role in the preparation of the pathway of biosynthesis. The sodium salt of alginic acid is .sodium alginate. $NaC_6H_7O_6$ is the formula. The gum derived from the cell walls of brown algae is sodium alginate. Sodium alginate is slowly soluble in water and insoluble in ethanol and ether.

Pharmaceutical application: 1. It is flavorless gum and used to increase viscosity in the food industry. 2. It is used as emulsifier. 3. Used in indigestion tablets and the preparation of dental impressions. 4. It is used for pulling radioactive toxins from the body because of their good chelating property. 5. It is also used in immobilizing enzymes by inclusion (48).

Hyaluronic acid (HA): It is a linear macromolecular acid mucopolysaccharide polymerized by the β-1,3-N-acetyl-D-glucosamine and β-1,4-D-glucuronic acid disaccharide polymerization unit. In different parts of the human body, they are widely distributed with strong biocompatibility. HA can form hydrogen bonds and interact with mucin electrostatically, and thus has outstanding mucoadhesive properties. It was confirmed that HA with various molecular weight could adhere to oral mucosa with different rates (49).

Lectins : Due to its natural ability to bind directly to free sugar or to sugar residues of polysaccharides, glycoproteins, or glycolipids that can be free or attached (as in cell membranes), Lectins have gained broad attention from biomedical scientists in the last few years. Because of their relatively strong resistance to acidic pH and enzymatic degradation, and the omnipresence of binding sites along the GIT, Lectins are good candidates for oral delivery. However, binding is only possible if the corresponding sugar moieties are available on the mucosal epithelium. As there is no homogeneous occurrence of corresponding specific sugar moieties along the GIT, interactions of lectins can be specific to some particular cellular type (e.g. M cells) or a specialized area (e.g. colon). Lectin was considered as a sugar binding protein having the ability to agglutinate cells and/or precipitate glycoconjugates (50).

Pectins: Specifically, it is an anionic polysaccharide, a heteropolysaccharide contained in most primary cell walls and often abundant in the nonwoody sections of terrestrial plants. Pectin is a normal component of the human diet but does not contribute substantially to nutrition. It is produced as a white to light brown powder commercially, primarily extracted from citrus fruits. Its mucoadhesiveness is due to large number of carboxyl groups in its structure is responsible for interaction with the mucus. Pectin gets to hydrate and form viscous hydrogel in contact with aqueous solution and hence facilitates the mucoadhesion.A texture analysis approach was used to test the mucoadhesive properties of various forms of pectin with varying degrees of esterification (DE) and molecular weights (MWs) against porcine GI mucosa. The mucoadhesion of pectin may be due to the mechanism of adsorption or electrostatic repulsion between pectin and mucin on the mucin molecules (51).

Starch: As a result of its biocompatibility and hydrophilic nature, polysaccharide has been widely used as mucoadhesive drug delivery systems. In particular, starch (amylum) consists of a large number of glucose units linked together by glycosidic bonds.Two native starches (maize starch and waxy maize starch) and one pre-gelatinized waxy maize starch have already been investigated for their muco-adhesive properties. Using the method of milling and spray-drying, the mucoadhesive properties of starches were induced or improved. The moisture absorbing property of starch makes it ideal to become a system-like mucoadhesive gel. The absorption causes the mucosal membrane to dehydrate, resulting in the drug moiety being channelled into paracellular close junctions.When combined with permeation enhancers [52], the increased release rate and higher surface area can simultaneously be greatly amplified. Amylose-rich cross-linked starch acetate, aminoethyl and carboxymethyl derivatives were evaluated for controlled drug release, and among these derivatives, amylose-

rich cross-linked starch carboxymethyl derivatives exhibited better mucoadhesion at neutral pH, making it more suitable for buccal delivery (53).

Table No.1: Buccal dosage form formulated using natural polymer

Sr.No.	Natural Polymer	Drug	Dosage form
1	Chitosan	Gambier (Uncaria gambir Roxb) Lidocaine HCL, Diltiazem HCL'	Muccoadhesive buccal patch (54) Muccoadhesive film composite (55) Muccoadhesive buccal patch (56)
2	Guar gum	Bitadistine dihydrochloride	Muccoadhesive buccal tablet(57)
3	Gelatin	Propranolol	Mucoadhesive buccal film (58)
4	Starch	Metformin HCL	Fast dissolving buccal film(59)
5	Sodium alginate	Ramipril, Hydrochlorothiazide and Atenolol	Muccoadhesive buccal patch (60) Muccoadhesive buccal patch(61)
6	Pectin	Triamcinolone and Acetonide	Muccoadhesive buccal film (62)
7	Jackfruit gum and Tamarind gum	Valsartan	Muccoadhesive buccal film (63)

Synthetic polymer: following synthetic polymers have been used in buccal drug delivery system:

Cellulose iderivatives: Cellulose derivatives are obtained by esterification, etherification or crosslink reaction between hydroxyl groups in cellulose with a chemical reagent. Hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (CMC-Na), hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC) are polymers widely used for mucoadhesive adherence. Flavia Laffleur et al. studied the preparation of buccal patches

with various cellulose derivatives such as carboxymethyl cellulose sodium salt (CMC) (medium viscosity), 2-hydroxyethyl cellulose (HEC) (average Mw 90,000 Da), (hydroxypropyl)methyl cellulose (HPMC) with solvent casting technique and evaluated their mucoadhesion and stability and this analysis showed that cellulose-based patches exhibit great and promising potential for various Buccal applications and intraoral cavity disorders (64). CMC-Na is an anionic adhesive substance with hydrogen bonding ability and strong mucous membrane adhesion. Singh et al. used CMC-Na as the key adhesive material to prepare the oral adhesive film of salbutamol sulphate, which had a strong coefficient of expansion, adhesion potential and *in vitro* release behavior. At the same time, for 4 hr, it had a calming effect on the bronchus that was longer than that of the solution of salbutamol sulphate (1.5 h) (65 Nonionic neutral cellulose derivatives such as HPMC have moderate adhesion as they are free of proton-donating carboxylic acid groups, which reduces the ability to form hydrogen bonds. While using HPMC K4M and carbomer 934P as mucoadhesive materials and ethyl cellulose as a backing material, Hiral Koradia et al., by direct compression, developed unidirectional buccal Mirtazapine tablets. Low drug release at the initial time point (1h) and full drug release at 6 h, optimum swelling and good bioadhesive strength were given by the prepared unidirectional oral tablets, suggesting a possible alternative drug delivery mechanism for Mirtazapine. [66] Acyclovir and polylactic acid-glycolic acid copolymer (PLGA) have been prepared into nanoparticles by Al-Dhubiab et al. Taking the HPMC as an adhesive material and Eudragit RL100 as a filmforming material, they made these materials into a film with oral biological adhesion. The drug penetrated the mucosa at a stable rate. Its bioavailability was increased by 8 times compared to oral dosage forms (67).

Acrylates: One of the best mucoadhesive polymers is known to be currant PAA in mucoadhesive materials. Its high solubility in water greatly limits its usage as a carrier for a drug's sustained release. To minimize the water solubility of PAA, interpolymer complexation of PAA with PEG, PEG macromer, poloxamer, and PVP has been observed. In this regard, Chun et al. stated that the water solubility of PAA decreased due to the complexation of PAA with these polymers to retain adhesive force. Interpolymer complexation between PVP/ PAA results in aggregation and precipitation in ethanol and water (68). Strong complexation due to strong hydrogen bonding between PAA and PVP could be utilized to prepare mucoadhesive microspheres. Both the polymers PAA and PVP are water soluble but, when they come close to each other they form a complex and

precipitate. Emulsification of PAA solution and PVP in solutions causes collision of droplets leading to complexation hardening to make microspheres (69).

Thiolated adhesive polymer materials: Thiolated polymers are modern polymers that have been built in recent years by pharmacists. In the cysteine-rich subdomain, which is more adhesive and cohesive, the thiol group of the thiolated polymer forms a disulfide bond with the sulfhydryl group. Its adhesion is less affected by changes in ionic strength and pH after covalent bonding. It can also inhibit the action of the extracellular drainage pump after thiolation. Via an amide bond, Laffleur et al. covalently connected carboxymethylcellulose (CMC) to Cys to form a thiolated carboxymethylcellulose (CMC-SH) that was then placed into a 2-mercapto nicotinic acid (MNA) reaction to produce activated carboxymethylcellulose (CMC-SS-MNA). Studies have shown that the CMC-S-S-MNA produced is toxin-free. The mucosal adhesion of CMC-S-S-MNA has been improved three times compared to unmodified CMC, and its adhesion potential has been optimized 8.8 times. [70]. Chitosan–TGA conjugate contains a large amount of immobilized thiol groups. For this reason, it shows improved viscoelasticity in comparison with unbound chitosan. Additionally, the covalent attachment of chitosan–TGA conjugate does not deteriorate the good swelling ability of its chitosan part. The stability of the protein conformation was not impacted by the whole thiolation process. *In vitro* tests have shown that the mucoadhesive properties of chitosan after thiolation are enhanced. Moreover, the dry gel was easy to hydrate and had good drug release properties, which could be used as a new dosage form for the oral administration of protein drugs (71).

Hybrid polymer: Hybrid bio adhesive polymers, mixing of different polymers is an approach to optimize the adhesion and mechanical properties of various polymers by adjusting their swelling behavior or improving their biocompatibility. Poloxamer 407 and carbomer 971P were mixed by De Souza Ferreira et al. to prepare new content. A sol-gel transition temperature was included in this newly developed material. That is to say, it was possible to obtain materials with different transformation temperatures, with different mixing proportions of the drug sites, and at the same time employed good mechanical properties and adhesion properties (72). It must be remembered that, due to the thermodynamic incompatibility of the two systems, mixing of different polymers frequently does not work due to phase separation. It is predicted that many water-soluble polymers with a combination of proton donor and proton acceptor groups are immiscible (73).

MANUFACTURING OF MUCOADHESIVE BUCCAL PATCHES

There are different methods for the preparation of mucoadhesive buccal patches divided mainly as traditional and novel methods; traditional includes solvent casting, direct milling, hot-melt extrusion, solid dispersion extrusion, semisolid casting and rolling process. While solvent casting is considered as the most popular method of preparation among others due to its simplicity and cost effectiveness .Recently, electrospinning, electrospraying and 3D printing methods have been used as novel techniques for the preparation of buccal patches. These methods are more efficient and do not have the problems associated with the solvent casting (4):

Traditional methods:

Solvent casting: In the process of solvent casting, a mucoadhesive polymer, drug and other excipients are dissolved under the magnet stirrer in a sufficient solvent to extract trapped air and form a homogeneous solution. The blend is then cast into a clean petri dish and dried in a hot air oven at 400^0C (5) Cast patches are placed in a desiccator before future evaluation continues. There are a lot of research studies on mucoadhesive patches created by the method of solvent casting.Dubey et. al used solvent casting technique to prepare mucoadhesive oral patches of hydrochlorothiazide (HCZ) and atenolol (ATN) using different concentrations of sodium alginate, hydroxyl propyl methyl cellulose, carbopol 934P and sodium carboxy methyl cellulose polymer and polyvinyl alcohol as a backing layer to achieve sustained release and enhanced bioavailability15 besides having short and simple method it has some limitation such as • Polymer must be dissolved in a volatile solvent. Moreover, a few amounts of solvent may remain in the final film. • Drug loading capacity in solvent casted films is low. • The synthesized film does not have a suitable uniformity (61).

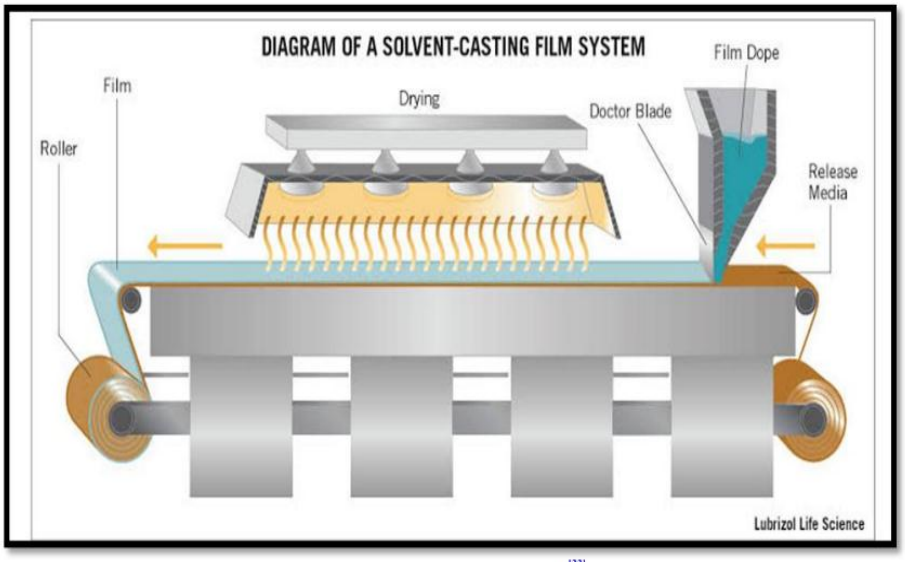

Figure. No. 5: Solvent casting method (5)

Direct milling: Patches are formed in this process, without the use of solvents. Without the presence of any liquefied solutions, indirect milling or kneading methods are used for motorized mixing of drugs and excipients. The desired thickness is achieved by rolling the resulting material. Then the backing material is laminated. The solvent-free process is selected because residual solvents and health concerns caused by solvents are not likely (18).

Hot melt extrusion: In hot melt extrusion method, blend of pharmaceutical ingredients is molten by the extruder having heater and different shapes yielded via die by forcing molten mixture through an orifice. hot melt extrusion has been used for the fabrication of controlled release matrix tablets, pellets, granules, oral disintegrating films dosage forms (3).Here are certain benefits such as molten polymers during the extrusion process can function as thermal binders and act as drug depots and/or drug release retardants upon cooling and solidification. Since it is anhydrous process, the numbers of processing and time-consuming drying steps are reduced. Independent of compression properties, a matrix may be massed into ia larger unit. De-aggregation of suspended particles in the molten polymer is caused by the extreme mixing and agitation forced by the spinning screw, resulting in a more uniform dispersion and the process is continuous and efficient. When solubilized or distributed at the molecular level in HME dosage types, the bioavailability of the drug substance may be increased. Pharmaceutical Hot-Melt Extrusion processes can be categorized as either ram extrusion or screw extrusion (74).

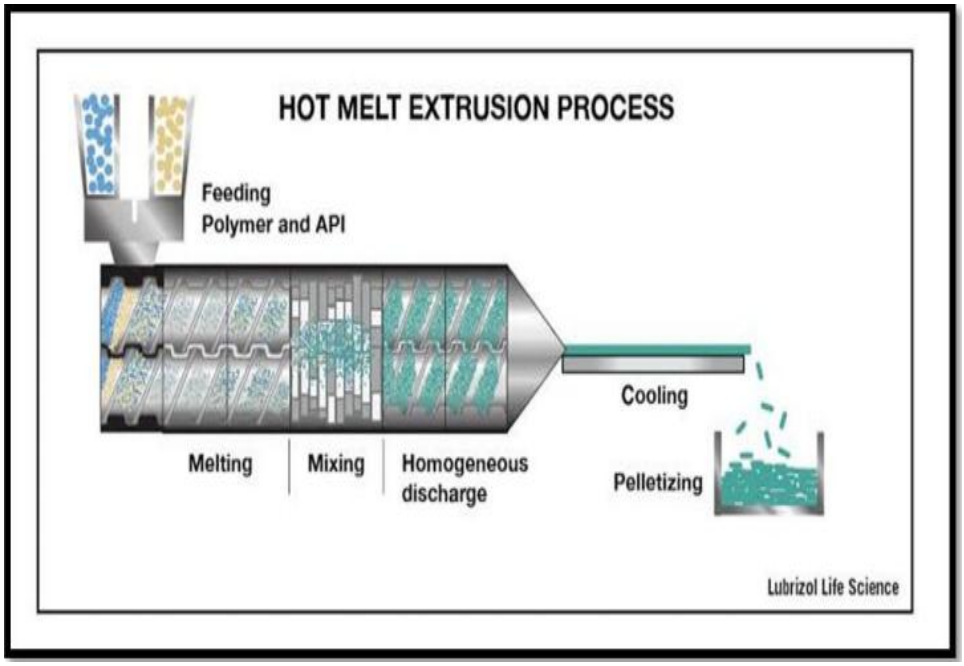

Figure. No. 6: Schematic representations of a single screw hot melt extruder (5)

Solid dispersion extrusion: In these immiscible materials, drugs are extruded and solid dispersions are prepared. Finally, the solid dispersions are created by dies in the films.

Semi-solid casting: First, a solution of water soluble film forming polymer is prepared in the semisolid casting process. The resulting solution is applied to a solution of polymer insoluble in acid (cellulose acetate phthalate, cellulose acetate butyrate) prepared in ammonium or sodium hydroxide. A sufficient amount of plasticizer is then applied is that a gel mass is obtained. Using heat-controlled drums, the gel mass is eventually cast into films or ribbons. The film's thickness is about 0.015-0.05 inches. The acid insoluble informing polymer should have a ratio of 1:4 (26).

Rolling method: The solution or suspension containing the substance is rolled into a carrier in this rolling method. In fact, the solvent is water and a combination of water and alcohol (29).

Novel approaches:

Electrospinning: Electrospinning is currently considered as a promising method for the preparation of oral patches. In fact, electrospinning is a simple, cost effective and versatile method that produces continuous nanofibers with unique properties including high porosity and large surface to volume ratio. These characteristics provide more loading capacity and

encapsulation efficiency, high dissolution rate, high biodegradability and multiple drug delivery. To enhance drug absorption through mucosa in the oral cavity, a high drug concentration is needed. Thus, by increasing drug concentration and rapid absorption, drug delivery efficiency will be increased. During the production of fibres in the electrospinning phase, the entanglement of polymer chains induces changes in the physicochemical properties of the formed nanofibers, such as drug release activity, patient acceptability and increased mucosal touch, leading to increased drug absorption. Therefore, this method can overcome the limitations and problems associated with the solvent casting method, which is mainly used in the preparation of oral films. In a research by Colley et al., electrospun polymeric mucoadhesive patches were produced. The results showed that Clobetasol-17-propionate incorporated into the patches was released in a sustained manner in both tissue-engineered oral mucosa and *ex vivo* porcine mucosa. Furthermore, electrospun patches were adherent to mucosal tissue without causing tissue damage, and could be successfully loaded and release clinically active drugs .[75] Chen et al. developed a novel delivery system consisted of an electrospun layer, an adhesive layer and a backing layer to improve the bioavailability of Carvedilol. The pharmacokinetic study demonstrated 154 % increase in the relative bioavailability and the electrospun fiber showed excellent drug permeation. This drug delivery system offered a novel platform for buccal drug delivery with high first-pass effect (76).

Electrospraying: Electrospray technique has been studied extensively in the last few years due to its simple experimental setup, broad applications and cost effective trait. Electrospraying as a modified version of the electrospinning process can be used for the preparation of micro and nanoparticles which can be used as oral, injectable, inhalable, topical, and local drug-delivery systems in drug-delivery systems. In addition, electrospraying can overcome the disadvantages associated with traditional particle-producing techniques (solvent evaporation, single and double emulsion, spray-drying, emulsification of porous glass membrane, and coacervation) such as low efficiency of drug loading, scale-up limitations, poly-dispersity of particle size , low capacity to produce small particles, and integration difficulties to hydrophilic druds. In electrospraying process, a solution including mucoadhesive polymer, drug and suitable solvent is prepared and by changing the solution and processing parameters such as concentration, flow rate and applied voltage, a continuous and charged jet can be broken down into droplets, resulting in different particle size and shapes. Unlike the traditional methods, in electrospraying technique, a

desired drug is incorporated into a polymeric carrier in a single step. Adequate physical interactions between the polymer and the drug are vital for getting sustained and prolonged drug delivery properties. In a research study by Subramanian et al. (77) two types of films made by electrospray technique were prepared and their physicochemical properties of the oral films and *in-vitro* drug release profiles were evaluated. The obtained results were analyzed and compared with the oral film made by solvent casting. The results showed that the oral film made by electrospray technique has higher drug encapsulation inefficiency up to 99.3 %. For the electrospray oral film, the cumulative drug released within an hour and their disintegration time was 2.5 times faster than the oral film made by the solvent casting. In summary, electrospray technique was highly recommended to fabricate oral films for drug delivery applications.

Simultaneous electro spinning and electro spraying: Both electro spinning and electro spraying techniques may also be used at the same time. Simultaneous electro spinning of polymer solution and electro spraying of colloidal suspension is carried out in this process from two separate capillary nozzles. A non-woven Nano composite fabric can be made from a polymer material with nanoparticles deposited on a fiber surface using this method (78). Electro spraying can be considered as an ideal method for producing multi-layer membrane mucoadhesive patch containing droplets formed by electro spraying method that can be imbedded into the electro spun mats according to the aforementioned advantages. It primarily improves the efficiency of the drug loading and facilitates the production process of a multi-layer reservoir system in a single-step (7).

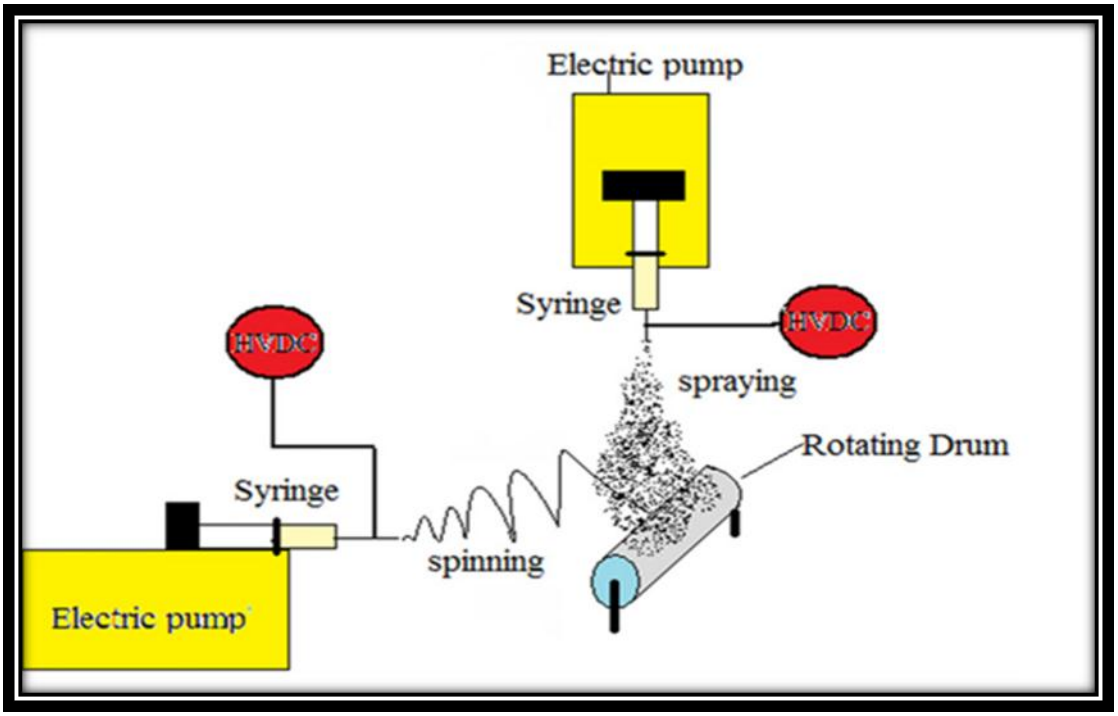

Figure. No. 7: Laboratory set up for simultaneous electrospin – electrospraying (78)

3D printing: In most cases, electrospinning is limited to the construction of arbitrary 2D structures. There is also inadequate control on porosity and pore size within fibrous electrospun films. In addition, electrospun drug polymer films need to be cut or formed into the geometry of the desired dosage type. To create mucoadhesive oral films, recent technologies such as 3D printing can be used. This technique is also highly versatile and cost-effective. As a novel 3D printing technique, electrohydrodynamic (EHD) jet printing offers greater control over fibre shaping and deposition. Drug loading can also be improved and it is possible to customize and personalize dosage forms. In fact, in a single step, the geometry of a dosage form is printed to fit the patient's anatomical position or age. High resolution, ambient temperature operation, one-step fabrication and complex 3D structure preparation are provided by the EHD printing process. Compared to electrospinning process, EHD printing deposits single fibers to fabricate predetermined 3D structures on a layer-by-layer basis, and is made possible by shortening the deposition distance from greater than 10 cm to < 10 mm. These fibrous drug-loaded patches have been developed for buccal drug delivery. Therefore, the potential to develop 3D printed fibrous patch systems (for various anatomical and age groups) with greater control on drug loading, release and patch geometry is immense. Wang et al. used EHD printing technique to fabricate aligned fiber antibiotic (tetracycline hydrochloride, TE-HCL) patches using polycaprolactone (PCL), polyvinyl pyrrolidone (PVP)

and their composite (PVP-PCL). In aligned fibres, FTIR showed good TE-HCL encapsulation. Enhanced hydrophobicity showed patches prepared using PVP and TE-HCL. The antibiotic release from the dosage types of PCL-PVP was observed over 5 days and was slower compared to pure PCL or PVP [79]. Various fast-dissolving oral films, prepared by Ehtezazi et al., consist of PEO, PVA, ibuprofen and paracetamol via 3D FDM. The single-layer and multi-layer films had thicknesses of about 197 ± 21 mm and 298 ± 15 mm, respectively, based on the results. Disintegration period was also shown to be as short as 42±7 s and 48±5 s , respectively. This study provides proof-of - concept for the use of 3D printing to create quick dissolving oral films. As such, the latest advance in film production is the printing of a drug on dosage form, which has proven to be a powerful method for processing dosage form with excellent uniformity, specific speed and high stability (80).

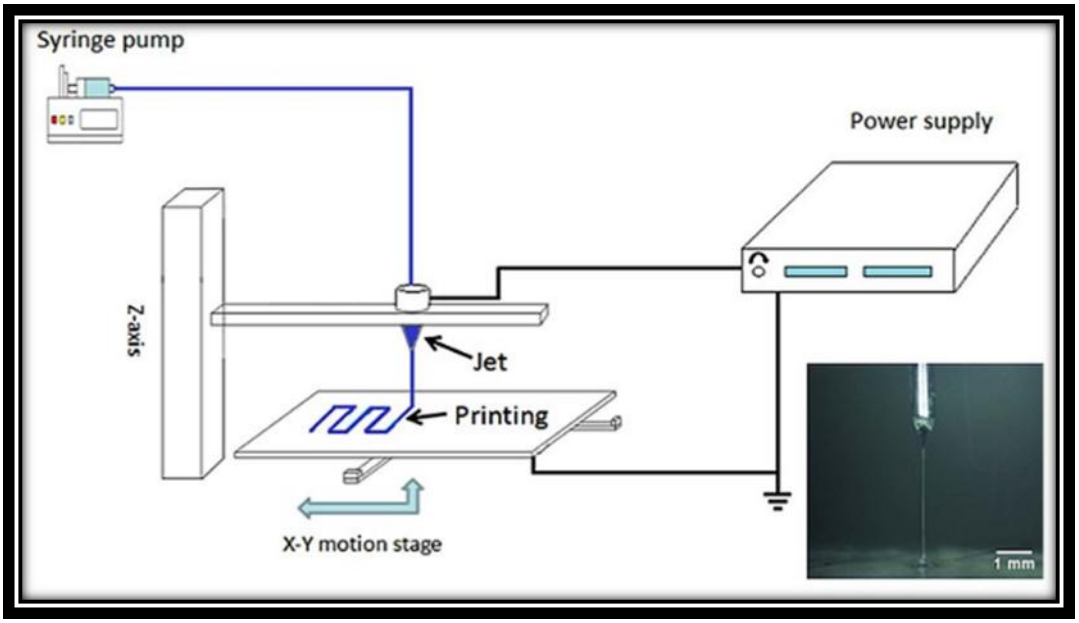

Figure. No. 8: Schematic representation of electrohydrodynamic (EHD) jet printer (80) system (54)

Table No.2: Marketed buccal patches/films (81,4)

Sr. No.	Drug	Product name	Company	Indications
1	Lidocaine	Dentipatch	Noven	Topical Anesthesia
2	Amlexanox	Oradisc	Access Pharmaceuticals	Apthous ulcer
3	Natural ingredients	Snoreeze	PFL healthcare	Eliminate snoring
4	Vitamin and natural ingredients	Soluleaves	Bioprogress	Cold treatment, Vitamin supplement
5	Diphenhydramine HCl	Triaminic	Novartis	Antiallergic
6	Dextromethorphan HBr	Theraflu	Novartis	Antiallergic
7	Simethicone	Gas-x itongue twisters	Gas-x	Flatulence, Nausea
8	Diphenhydramine	Benadryl	Pfizer	Antiallergic
9	Menthol	Suppress	Innozen INC.	Mouth Freshener
10	Menthol/Pectin	Orajel		Canker sore pain
11	Cool mint	Listerine pocket packs	Pfizer	Mouth freshener
12	Ferric oxide, Folic acid	Hemoramin	C.L. Pharm	Iron deficiency anemia
13	Nicotine	NiQuitine	GSK	Nicotine withdrawal
14	Ondansetron	Setofilm Zuplenz	Norgine/tesa labtec Galena Biopharm	Chemotherapy induced nausea, vomitting
15	Zolmitriptan	Zolmitriptan Renantos	Renantos	Migraine
16	Risperidone	Risperidon HEXAL SF	Hexal/Sandoz	Schizophrenia
17	Donepezil hydrochloride	Donepezil-HCl HEXAL SF	Hexal/Sandoz	Alzheimer's disease
18	Sildenafil citrate	Sildenafil Sandoz, Sedera	Sandoz C.L.Pharm	Erectile dysfunction

EVALUATION PARAMETER OF BUCCAL PATCHES:

Weight variation: Three films of each formulation are randomly selected for film weight assessment and individual weights of each 1x1 cm patch are taken ion digital imbalance. The test was carried out to verify the uniformity of weight and batch to batch variation. The average weight was determined.

Thickness: Using Vermeer calipers with a least count of i0.001 mm, the thickness of the patch was calculated. The thickness uniformity was calculated at five different points and the average reading was taken.

Surface pH study: A combined glass electrode or pH paper may be used for this purpose. Every patch was allowed to swell for 2 hours at room temperature by holding it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) and the pH was noted by bringing the electrode or pH paper into contact with the surface of the patch and allowing it to balance for 1 minute. A mean reading of three is reported.

Folding endurance: For the patch, the folding endurance was measured by folding the patch repeatedly at the same position before it splits. For this test randomly three patches were selected from formulation. It was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.

Drug content uniformity: Drug content uniformity determined by dissolving 1cm^2 patch in (5% of methanol contained) 100 ml of simulated salivary fluid (pH 6.8), then it is shaken for 24 hr. at room temperature. The solution is then filtered through Whitman filter paper in. 42 and analyzed at specified nm using a UV spectrophotometer. The experiments were carried out in triplicate (25, 26, 27).

Mechanical properties (Percent elongation at break and tensile strength): the mechanical properties of the films have been recorded and carried out using an advanced force gauze biased on a microprocessor fitted with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), fitted with a load cell of 25 kg. The 60 x 10 mm film strips were held between two clamps placed at a distance of 3 cm. To avoid the film from being cut by the groves of the clamp, a carton was stuck to the surface of the clamp. Clamp.The strips were pulled by the top clamp at a pace of 2.0 mm / s at a distance before the film broke during the calculation reported by 'Tehran University of Medical Sciences' (www.tums.ac.ir). As the films were fractured, the force and elongation were measured. Film sample findings that were split at the end and not present between the clamps were not included in the observations. Six replicates of the measurements were carried out for each formulation (82).

Tensile strength (kg.mm-2) = Force at break (kg) /Initial cross sectional area of the sample (mm^2)

Elongation at break (%.mm-2) = Increase in the length (mm)/ Original length × 100 /Cross sectional area (mm^2)

Moisture absorption: The moisture absorption studies for buccal patches provide an indicator if the relative ability of polymers to absorb moisture and an idea of whether the buccal patches preserve their integrity after moisture absorption. Moisture absorption experiment is carried out in 5 % iw/v agar in distilled water and put in a desiccator to extract moisture if any and laminated with water impermeable backing membrane on one side. Put on the surface of the agar plate and incubated in the incubator at 37 °C or 2 hours. The patches were again weighed and the percentage of the moisture absorbed was determined using the formula: (83):

% Moisture absorbed = Final weight – Initial weight / Initial weight ×100

Swelling index: Individually weighed (designated as W1) and put separately in 2% agar gel plates, incubated at 37 ^{0}C±1 ^{0}C, and examined for any physical changes, the swelling index of buccal patches was determined. Patches were removed from the gel plates at daily 1-hour intervals for up to 3 hours, and excess surface water was carefully removed using the filter paper. The swollen patches then reweighed (W2) and the swelling index (SI) were calculated using formula:

Swelling index = (W2-W1)/W1× 100.

***In vitro* drug release :** The rotating paddle system used by the US Pharmacopeia XXIII was used to research drug release from buccal patches of 200 mL of phosphate buffer (pH 6.8) used as a dissolution medium at 37.0 ± 0.50C and paddle rotation speed was 50 rpm. An instant adhesive (cyanoacrylate adhesive) was applied to the glass disc on one side of the oral patch. 24 aliquots (5 mL) were removed at half-hour intervals and replaced with fresh medium at the bottom of the dissolution vessel. The samples were filtered through 0.45-µm Whatmann filter paper and analyzed using UV spectrophotometer. The cumulative percentage drug release was calculated (25).

In vitro residence/mucoadhesion time: In a well stirred beaker filled with 500 ml phosphate buffer pH 6.8 at 37 ° C, the in vitro adhesion period of the patch was measured by measuring the period for the patch to detach from the goat buccal mucosa. The mucosal membrane was fixed with cyanoacrylate glue on the side of the beaker. By applying light force with a fingertip for 60 s, the patch was applied to the membrane. To mimic oral and saliva motion,

the beaker was then magnetically stirred at an approximate rate of 150 rpm. The time necessary for complete erosion or detachment of the films from the mucosal membrane was taken as an indication of the in vitro adhesion time.

Effect of temperature and humidity: The optimization formulation effect of temperature and humidity was achieved for one month at 40 ° C ± 2 ° C, 75 percent ± 5 percent RH preserved in the environmental stability chamber. The patches were wrapped and exposed to the said conditions in aluminum foil. At 0, 7, 14, 21 and 28 days, samples were evaluated for parameters such as i. Occurrence ii. Surface pH iii. Folding Endurance iv. Drug release (%) (84).

RECENT TRENDS IN BUCCAL DDS:

The use of lipophilic gel, oral spray and phospholipid vesicles to deliver peptides through the oral route involves revolutionary drug delivery systems (86).It has also been proposed to use glyceryl monooleate cubic and laminar illiquid crystalline phases as the oral drug carrier for peptide drugs. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) (87) has recently been developed and is now in phase III clinical trials. This approach allows specific insulin doses to be administered in the form of fine aerosolized droplets into the mouth via a metered dose inhaler. The levels of drugs in the mouth have risen considerably relative to conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium and provides the plasma insulin levels needed to regulate the postprandial increase in the glucose in diabetic patients. This new, pain-free, oral insulin formulation has IA number of advantages, including rapid absorption, a simple (user-friendly) administration process, imprecise dosing control (comparable to single-unit injection) and bolus delivery of drugs. Phospholipid deformable vesicles, transferases, have recently been developed for oral cavity insulin delivery (88). They are morphologically similar to liposomes, but differ due to function. Transferosomes respond to external stresses by rapid shape transformations requiring low energy. This high deformability allows item, across epithelial barriers, to deliver medication. It prepare these vesicles, surfactants, such as sodium cholate or sodiumideoxycholate, are injected into the vesicular membrane. In rabbits, insulin administration exceeds that seen with traditional liposomes: the bioavailability of deformable vesicles relative to subcutaneous insulin solution administration is superior to that of conventional liposomes (89).

Table No. 3: Current IPR status in buccal drug delivery system (90,91)

Sr. No.	Patent No.	Title of Patent	Types iof idelivery isystem	Investor
1	US20110028431	Oral mucoadhesive dosage form	Tablets	Zerbe et al.(2011)
2	WO/2006/069911	Mucoadhesive pharmaceutical compositions comprising chemoattractant	Gels	Herman et al.(2006)
3	US20140056949	Controlled release mucoadhesive systems	Toothpaste, Mouthwash, Mouth rinse, gel, paste, spray, chewing-gum, lozenge.	Mallery et al.(2014)
4	US8529939	Mucoadhesive drug delivery tools and methods of preparing and utilizing thereof	Wafer, Tablet, Cylinder, Sheet, Particles or Sphere.	Masters et al.(2013)
5	WO/2013/188979	Mucoadhesive nanoparticle delivery system	Injectable Preparations, Ointments, Pastes, Creams, and Gels, Powders and Sprays	GU, Frank et al.(2013)
6	US20150174076	Mucoadhesive tools for release of active agents	Wafers	Harris et al.(2015)
7	US20090098203	Mucoadhesive Tetracycline Formulations	Mouth rinse or Tablet	Lawter (2009)
8	US20100144618	Constituents including an trefoil peptide of intestine as well as of a mucoadhesive	Oral spray, Oral rinse, Ointment, Paste, Cream, Gel, Chewing gum, Chewable Tablet, Lozenge, Bioerodable film.	Podolsky (2010)
9	US8703177	Abuse-impervious mucoadhesive tools for release of buprenorphine	Patches	Finn et al.(2014)

CONCLUSION:

Through vascular and lymphatic drainage, the buccal mucosa is well perfused, preventing first-past metabolism and presystemic removal in the gastrointestinal tract. Due to the countless advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy and high patient compliance, some recently proposed systems such as oral patches have gained growing attention in the pharmaceutical sector. The delivery of buccal drugs is a promising field for going research with the goal of systemic delivery of orally efficient drugs as well as a viable and desirable option for the non-invasive delivery of impotent molecules such as peptides and protein drugs. In theory, mucoadhesive buccal patch is a novel and promising drug delivery method with various informs, including mono/multi-layered I(matrix or reservoir) designs. For the production of buccal mucoadhesive patches, various polymeric systems can be used. In the development of an oral film, various new techniques are involved, such as electrospinning, electro spraying and 3D printing technology, which have their own advantages and characteristics. Due to the perticular characteristics of the delivery of oral drugs, it is predictable that buccal patches will improve one of the critical dosage types in the pharmaceutical and healthcare sectors in the incoming years.

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