REVIEW ON MUCCOADHESIVE BUCCAL PATCH SYSTEM: FROMULATION ASPECTS AND EVALUATION

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Abstract : The muccoadhesive buccal drug delivery system of in view to improve bioavailability of drug, therapeutic efficacy and safety of drugs by specific sites within the body, thereby reducing both the size and number of doses. Mouth cavity in which absorption of the drug takes place and enters into systematic circulation over a period of time. The present article reviews the selection of drug candidates and polymers suitable to be formulated as Buccal drug delivery system, advantages, disadvantages of formulation design and the methods of evaluation.

Keywords : Buccal Drug delivery, Muccoadhesion , Bioavailability, permeation.

I. INTRODUCTION

The pharmaceutical industry has considerable interest to take part in healthcare industry. The progress made by pharmaceutical industry has greatly contributed in terms of treatment of disease, thereby enhancing the quality of life [1]. In the early 1980's, Professor Joseph R. Robinson at the University of Wisconsin pioneered the concept of mucoadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface. Over the years, mucoadhesive polymers were shown to be able to adhere to various other mucosal membranes. The capability to adhere to the mucus gel layer which covers epithelial tissues makes such polymers very useful excipients in drug delivery[3]. Researchers in the drug development industries are focusing on alternate routes to overcome the drawbacks of the oral route. It has been reasonably successful to to deliver drugs systemically via an alternate route of administration such as intranasal (IN), buccal/sublingual, pulmonary, or transdermal (TD) [2]. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival) [3]. However, when administered by the oral route, these agents suffer from problems such as poor absorption. To overcome these obstacles and for successful delivery of proteins and peptides, the buccal route of drug delivery has acquired significant attention [4]. Mucoadhesion is known to increase the intimacy and duration of contact between drug- containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The bioavailability of the drug is improved because of the combined effects of the direct drug absorption and the decrease in excretion rate. Increased residence time and adhesion may lead to lower API concentrations and lower administration frequency to achieve the desired therapeutically [5].

1.1. Advantages of Buccal Drug Delivery System [6]:

1. The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.
2. Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids
3. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
4. High patient acceptance compared to other non-oral routes of drug administration.
5. Increased residence time combined with controlled API release may lead to lower administration frequency.

As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment

1.2. Disadvantages of Buccal Drug Delivery System [7].

1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 of which ~50 cm^2 represents non-keratinized tissues, including buccal membrane.
2. Barrier properties of the mucosa.
3. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.

The hazard of choking by involuntarily swallowing the delivery system is a concern.

1.3. Anatomy and Physiology of the Oral Cavity

Oral cavity is the space bounded by the lips and cheeks interiorly and laterally, by palate above and by muscular floor of the given below

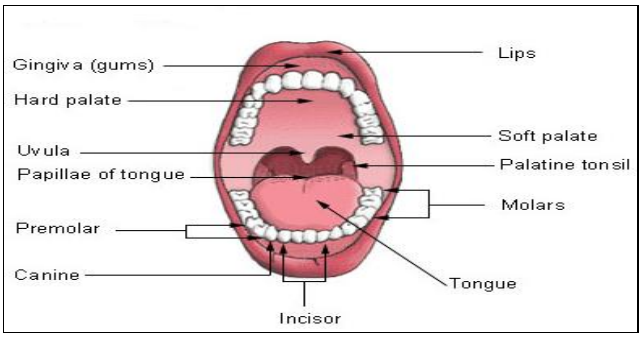

Fig. 1.3.1: Oral cavity.

The oral mucosa can be distinguished according to a number of major regions in the oral cavity: the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gum (gingival), the palatal mucosa, and the inner side of the lips.The mucous membrane having a total area of 100cm^2 and they show difference, in structure, thickness and blood flow depending on their location within the oral cavity. Fig.1 shows the different oral mucosal and their nature with respect to tissue keratinization[8].

1.3.1. Oral mucous membrane[8]

The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane of a highly vascularized nature. Drug penetrating into the membrane can find access to the systemic circulation via net of capillaries and arteries lying underneath.

The epithelium of the oral cavity is, in principle, similar to that of the skin, with interesting differences regarding keratinization and the protective, lubricant mucus spread across its surface. It can be divided into three functional zones:

1) The mucus-secreting regions consisting of soft palate, the floor of the mouth, the underside of the tongue and labial and buccal mucosa, which have a normally non-keratinized epithelium.
2) The hard palate and gingival are the regions of the masticatory mucosa and have a normally keratinized epidermis.
3) Specialized zone consisting of the borders of the lips and the dorsal surface of the tongue with its high selective keratinization.

As the stratum corneum is a potential barrier to mucosal penetration, drugs are traditionally placed at the non-keratinized sites like buccal and sublingual regions. The nature and functions of the mucus layer are described below.

The mucus layer:

Mucus is a translucent and viscid secretion, which forms a thin continuous gel blanket adherent to the mucosal epithelial surface. In humans the mean thickness of this layer varies from 50 to 450 mm. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathophysiological state. However, it has the following general composition.

I.	Water	95 %
II.	Glyco-proteins and lipids	0.5-5 %
III.	Mineral salts	1 %
IV.	Free proteins	0.5-1 %

Functions of mucus layer:

- Protective: Resulting particularly from its hydrophobicity.
- Barrier: The mucus constitutes a diffusion barrier for molecules and especially against drug absorption in tissue, thus influencing the bioavailability of drugs. Diffusion through the mucus layer depends largely on physicochemical characteristics of the active ingredient.
- Adhesion: Mucus has strong cohesion properties and firmly binds to the epithelial cell surface as a continuous gel layer.
- Lubrication: Mucus layer keeps the mucosal membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

At the physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues and this high charge density due to negative change contributes significantly to bioadhesion.

1.3.2. Structure of oral mucosa[9]

Oral mucosa is composed of two layers.

a) Epithelium: Epithelium of oral mucous membrane is made up of stratified squamous. It cells may be keratinized, parakeratinized or non-keratinized depending upon location.

b) Connective Tissue: The part of mucosa, which is constituted by connective tissue, is called laminapropria which is of variable thickness and supports epithelium. It carries blood vessels and nerves.

Two layers form an interface that is folded into corrugations. The protrusion of connective tissue into epithelium towards laminapropria and ridges, called as papillae, increases the contact area between laminapropria and epithelium. This additional area facilitates exchange of materials between epithelium and blood vessels of connective tissue. Epithelium and laminapropria are separated by basal lamina and basement membrane. This is the cell free zone and 1 to 4 µm wide. The submucosa is the layer

below mucosa, which contains glands, blood vessels and nerves. The major features influencing regional differences in drug absorption are the epithelial thickness and keratinization. Fig.2 shows the schematic cross section through oral mucosa showing epithelium, basal lamina and connective tissue

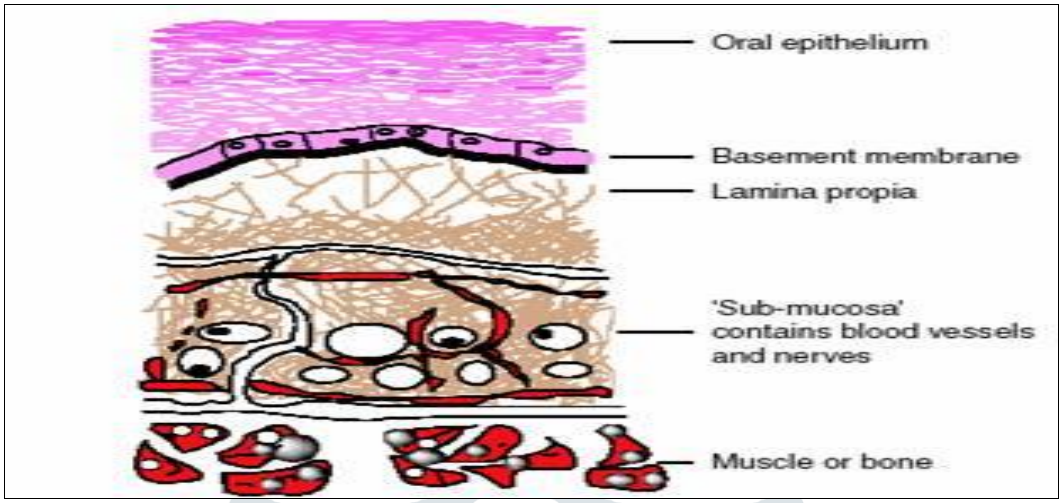

Fig. 1.3.2.1: Schematic cross section through oral mucosa showing epithelium basal lamina and connective tissue

1.3.3. The salivary secretion[10]

Besides the mucus, the mucosal layer of the oral cavity is kept moist by saliva secreted mainly by three parts of salivary glands namely the sub-maxillary, the parotid and sublingual glands. The pH of the salivary secretion ranges from about 6.2 to 7.4, with an average of 6.8, about 1.5 liters of saliva is secreted per day. There is considerable variation in individual salivary secretion. It ranges from 0.21 to 1.18ml /min with mean of 0.65 ml /min under resting condition and 0.56 to 2.70 ml /min with mean of 1.63 ml /min under exogenously stimulated conditions.

The saliva is composed of about 99.5% water and 0.5% solids. The solids consist of cellular constituents namely yeast cells, bacteria, polymorphonuclear leucocytes and desquamated epithelial cells, inorganic salts consisting of sodium chloride, potassium chloride, acid and alkaline sodium phosphate and calcium carbonate. The bicarbonates and phosphates acts as buffers, chlorides activate the enzyme amylase, organic matter includes enzymes, mucin, blood group substances, amino acids, cholesterol and vitamins. Human whole saliva contains number of antimicrobials.

1.4. Vascular system of oral mucosa[11].

The oral mucosa is highly perused with blood vessels. It has a high blood flow of 20-30ml/min for each 100g of tissue. The blood vessels are close to the surface and lymphatic drainage is also well developed. Hence therapeutic serum concentrations of a drug can be achieved rapidly. Drugs diffusing across the membranes have easy access to the systemic circulation via the internal jugular vein. The blood supply to the oral tissues is delivered principally via the external carotid artery which branches into the maxillary, the lingual and the facial arteries. The hard palate and cheeks are supplied with blood by maxillary artery. The lingual arteries supplies blood to tongue and sublingual and gingival areas, whereas the facial artery supplies blood to the soft palate and the lips. The three main veins collect blood from the capillary bed that finally flows into the internal Jugular vein.[15] The characteristics of the oral epithelium are shown in table no.1.4.1.

Tissue	Structure	Epithelia Thickness(μm)[a]	Flow (ml/min/cm^2)[b]
Buccal	Non-keratinized	500-600	2.40
Sublingual	Non-keratinized	100-200	3.14
Gingival (+)	Keratinzed	200	1.47
Palatal (–)	Keratinzed	250	0.89

Table 1.4.1: Oral Epithelium Characteristics

Where;

a Thickness of human oral epithelium.
b Blood flow in oral mucosa of Rhesus monkey.
+ Average value of maxillary and mandibular attached gingival mucosa.
– Average value of anterior and posterior hard palatal mucosa.

1.5. Pathways For Oral Mucosal Penetration[11,12]

Transmuccosal drug absorption can take place by two routes:
Transcellular / intracellular route, or
Intercellular / paracellular pathway.

Drug diffusing from one side of the oral cavity membrane to the other will not take the shortest route but the path of the lowest resistance. The path would be determined by physicochemical properties of diffusing substance and the composition and the

organization of phases observed during the penetration process. Both lipid soluble and water soluble drugs can penetrate the epithelium by either route.

Transcellular / Intracellular route

The mechanisms for Transcellular drug transport are:
1) Passive diffusion across lipid cell membranes.
2) Convective transport through aqueous pores in cell membranes.
3) Active or facilitated transport by means of carrier mediated systems.
4) Ion-pair transport after formation of neutral complexes of drug, e.g. bile salts.
5) Pinocytosis or phagocytosis.

Carrier-mediated, ion-pair transport and pinocytosis or phagocytosis have not been reported for buccal drug absorption, with the exception of some amino acids and small dipeptides and tripeptides. The Transport through aqueous pores is only relevant to compounds with low molecular weight of 400 Daltons. Most studies point to the absorption of compounds through the buccal mucosa, which is thought to be passive diffusion process through lipid membranes. The surface available for absorption is considerably greater for the intracellular route. For absorption, the drug should cross aqueous and lipid phases of the epithelial cells.

Intercellular/Paracellular route

The intercellular route would allow lipid soluble drugs to pass by diffusion through the lipid of intercellular matrix. Water-soluble drugs would transverse this route via the aqueous channels in the intercellular regions of the epithelium. For this route, the epithelium is required to have a sufficiently open matrix and the drug to have an appreciable affinity for, and diffusivity in intercellular fluids. Intercellular route appears to be the predominant route for most compounds of therapeutic interest. The major mechanism of drug transport across buccal mucosa appears to be by passive (simple Fickian) diffusion

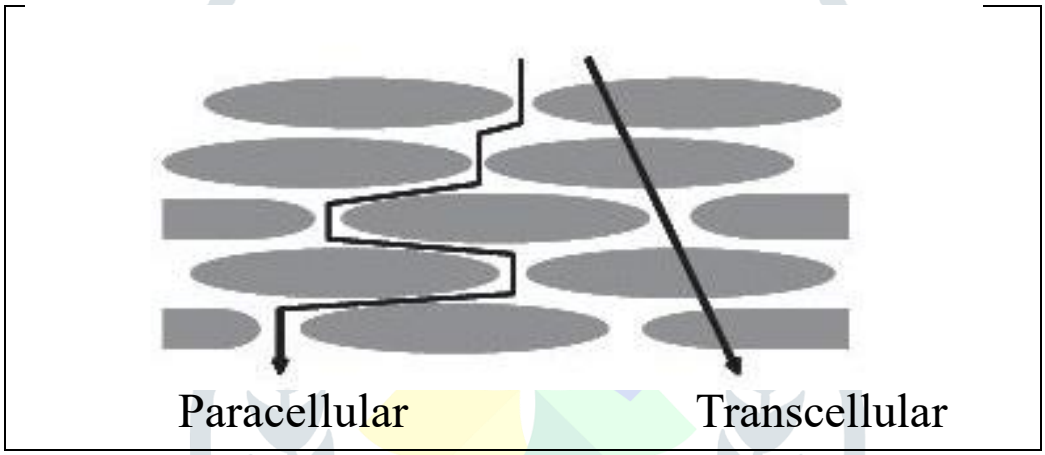

Fig.1.5.1: Paracellular and Transcellular routes of transport have been designated to the buccal mucosa.

II. PERMEABILITY OF DRUG THROUGH THE ORAL MUCOSA

The lipid membranes of the oral mucosa are resistant to the passage of large macromolecules; however, small un-ionized molecules tend to cross the membrane with relative ease.

a) Mechanism involved in drug absorption across the oral mucosa: The mechanism by which drugs cross biological lipid membranes are passive diffusion, facilitated diffusion, active transport and pinocytosis. Small water-soluble molecules may pass through small, water filled pores.

b) Membrane storage during buccal absorption of drugs: The absorption of a drug from mouth is not synonymous with drug entry into the systemic circulation. Instead, the drug appears to store in the buccal membranes due to drug binding in or on the oral epithelium.

2.1. Regional differences in mucosal permeability

The permeability of the oral mucosa in general is probably intermediate between that of the epidermis and that of the intestinal mucosa. Galey estimated the permeability of the buccal mucosa to be 4-4000 times greater than that of the skin. In general, the permeability of the oral mucosa decreases in the order sublingual > buccal> palatal.

2.2. Permeability barrier of the oral mucosa

For purpose of drug delivery, it is generally assumed that the non-keratinized lining mucosas are preferable to the keratinized regions. The permeability barrier of the oral mucosa is thought to reside within the superficial layers of the epithelium. Another barrier for large water-soluble molecules in both keratinized and non-keratinized epithelia is suspected to be the membrane. Coasting granules found in the intermediate cell layers of many stratified epithelia.

Other factors which may affect the permeability of molecules across the oral mucosa include exogenous substances placed in the mouth for their local effects such as mouth wash and toothpastes, which contain surface active agents, nutritional deficiencies, drugs which causes stomatitis and age changes.

III. PHYSICOCHEMICAL CHARACTERISTICS OF THE DRUG FOR BUCCAL DRUG DELIVERY [14.15]

a) Molecular weight and size: In general, molecules penetrate the oral mucosa rapidly than ions and small molecules (<75-100 Daltons) more rapidly than larger molecules. For hydrophilic substances, the rate of absorption is a function of the molecular size. High molecular weight substances e.g. mucopolysaccharide like heparin and protein like insulin are not well absorbed.

b) Degree of ionization: The degree of ionization of a drug is a function of both pKa of the drug and pH in the oral cavity. The average pH of saliva is 6 to 7 and it is relatively constant. In absence of buffer, pKa plays the major role to the state of the

ionization. For absorption from the oral mucosa, pKa should be greater than two for acid and at less than 10 for basic drug. Absorption is observed to be highest pH values when the drug is predominantly in the unionized form. The degree of ionization of a drug at specific pH can be calculated using the Henderson-Hasselbalch equation as follows.
For acid,

$$PH = pka + 10 \frac{\text{(Ionized species)}}{\text{(Un-ionized species)}}$$

For a base,

$$PH = pka + 10 \frac{\text{(Ionized species)}}{\text{(Un-ionized species)}}$$

c) Lipid solubility: A common way of assessing the lipid solubility is to measure oil/water partition coefficient. Compounds with favorable partition coefficient (in range of 40-2500) are readily absorbed through the oral mucosa. The un-dissociated form of a drug has higher lipid solubility and hence more absorption of drug takes place.
Along with the physicochemical properties of the drug, other factors, not related to absorption properties of the drug need to be considered. These include Organoleptic properties of the drug and excipients, texture of the delivery system, irritation and allergenic properties, other adverse effects such as discoloration of teeth, potential to alter the natural microflora. Any of these properties may limit the drug candidate for its use.

IV. THEORIES OF BUCCAL DRUG DELIVERY SYSTEM [12,15.]

1. Electronic Theory

The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical charge forms at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.

2. Adsorption Theory

A bioadhesive polymer adheres to mucus because of secondary surface forces such as Van der Waal's forces, hydrogen bonds, or hydrophobic interactions. For a bioadhesive polymer with a carboxyl group, hydrogen bonding is considered to be the dominant force at the interface. On the other hand, hydrophobic interactions can explain the fact that a bioadhesive may bind to a hydrophobic substrate more tightly than to a hydrophilic surface

3. Wetting Theory

Primarily applicable to liquid bioadhesive systems, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetted surface is controlled by structural similarity, degree of cross-linking of the adhesive polymer, or use of a surfactant.

4. Diffusion Theory

The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi-permanent adhesive bond. The penetration rate depends on the diffusion coefficients of both interacting polymers, and the diffusion coefficient is known to depend on molecular weight and cross linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both networks are important parameters that need to be considered.
These general theories are not particularly useful in establishing a mechanistic base to modern bioadhesive but they do identify variables that are important to the bioadhesive process.

4.1. Bioadhesive Polymer For Buccal Drug Delivery [16-18]

Muccoadhesive polymers are water-soluble and water insoluble which are swellable. It should possess optimal polarity to make sure that it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus.
Polymers that adhere to the mucin-epithelial surface can be divided into three broad categories:
a) Polymer that becomes sticky when placed in water and owes their bioadhesion to stickiness.
b) Polymer that adhere through nonspecific, non-covalent interactions, which are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
c) Polymer that bind to specific receptor site on the cell surface.
An ideal polymer for muccoadhesive drug system should have the following characteristics.
1. The polymer and its degradation products should be nontoxic and nonabsorbent from gastro-intestinal tract.
2. It should be non-irritant to the mucous membrane.
3. It should be preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to moist tissue and should possess site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of dosage from
Robinson and his group, using fluorescence tech., concluded that.
1. Cationic and anionic polymers bind more effectively than neutral polymer.
2. Polyanions are better that polycations in terms of binding or potential toxicity; and further, that water insoluble polymers give greater flexibility in dosage form design compared to rapidly or slowly dissolving water soluble polymers.
3. Anionic polymer with sulfate groups bind more effectively that those with carboxylic group.
4. Degree of binding is proportional to charge density on the polymer.
5. Highly binding polymers include carboxy methyl cellulose, gelatin, hyaluronic acid, carbopol and polycarbophil.
Role of pH on bioadhesion is of most importance with maximum adhesion being observed from pH 5 to 6

Polymer	Bioadhesive property
Carboxy methyl cellulose	+++
Cabopol 934	+++
Polycarbophil	+++
Tragacanth	+++
Poly (acrylic acid/divinyl benzene)	+++
Sodium alginate	+++
Hydroxy ethyl cellulose	+++
Gum Karaya	++
Gelatin	++
Guar gum	++
Thermally modified starch	+
Pectin	+
Polyvinyl pyrrolidone	+
Acacia	+
Polyethylene glycol	+
Psyllium	+
Amberlite-200	+
Hydroxy propyl cellulose	+
Chitosan	+

(+++) Excellent (++) Fair (+) Poor

Table 4.1.1: Muccoadhesive Polymers

V. STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM.

Buccal Dosage form can be

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.
2. Reservoir type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.
3. Buccal absorption: Buccal absorption leads systemic or local action via buccal mucosa.

5.1. Mechanism of buccal absorption

Buccal drug absorption occurs by passive diffusion of the non ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophillic the drug molecule, the more readily it is absorbed. The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth.[13].

VI. VARIOUS METHODS FOR PREPARATION OF ORAL PATCHES[22]

One or combination of the following process can be used to manufacture the mouth dissolving films:

i) Solvent casting
ii) Semisolid casting
iii) Hot melt extrusion
iv) Solid dispersion extrusion
v) Rolling

I. Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the petri plate and dried.

II. Semisolid casting

In semisolid casting method firstly a solution of water soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel

mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

III. Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion,-Fewer operation units,-Better content uniformity, an anhydrous process.

IV. Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

V. Rolling Method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and sizes.

VII. METHODS OF EVALUATION

1. **Surface pH**
   Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch [16].
2. **Thickness measurements:**
   The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer [17].
3. **Folding endurance**
   The folding endurance is accomplished by number of times patches could be doubled repetitively till it broke contributed the assessment of the folding endurance[18]
4. **Swelling study:**
   Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper.The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula.[19]
5. **Water absorption capacity test**
   Circular Patches, with a surface area of 2.3 cm^2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na_2HPO_4, 0.19 gKH_2PO_4, and 8 g NaCl per litter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3 and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccator over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured [20].
6. ***Ex-vivo* bioadhesion test:**
   The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time.The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength [21,22,23] .

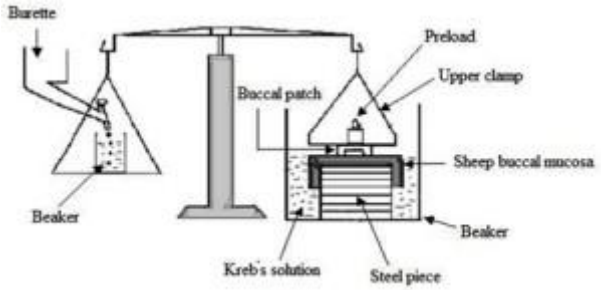

Fig. 6.1: Measurement of mucoadhesive strength.

7. **In-vitro drug release studies**
   For in-vitro release of patches paddle apparatus used. The phosphate buffer pH 6.8 used as dissolution media and temperature maintained at 37°C ± 0.5°C and paddle rotate at 50 rpm. The adhesive material used to attach patch backing layer. The disk is allocated to the bottom of the dissolution vessel. After predetermined time intermissions, fresh medium changed with earlier taken sample. The samples evaluated for drug content after appropriate dilution[20].
8. **Permeation evaluation of buccal patch**
   For permeation study the receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is sustained by mixing with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intermissions and evaluated for drug content[24].
9. **In-vivo techniques for buccal patches**
   The following approaches are used in-vivo determination of buccal patches
   (1) Use of radioisotopes. (2) Use of gamma scintigraphy. (3) Use of pharmacoscintigraphy (4) Use of electron paramagnetic resonance (EPR) oximetry. (5) X-ray studies. (6) Isolated loop technique[26].

10. Stability study in human saliva

The stability study of optimized bilayered and multi-layered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate petridishes containing 5ml of human saliva and placed in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3 and 6 hours), the dose formulations with better bioavailability are needed.

Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated[28].

VIII. CONCLUSION

The buccal mucosa offers many advantages for controlled drug delivery for longer periods of time. Buccal drug delivery is an effective area for continued research with the purpose of systemic delivery of orally not suitable drugs. The buccal drug delivery is well suited for a retentive device and appears to be acceptable to the patient because it is non-invasive. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled.

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