DYNAMIC REVIEW OF MUCOADHESIVE PATCHES FOR BUCCAL ADMINISTRATION

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Abstract

The oral delivery is currently the gold standard within the pharmaceutical industry, where it's thought to be the foremost convenient, safest and economical route of drug delivery. When administration is taken under consideration, the rima are often cited jointly of the best sites for the delivery of drugs. Mucosal and transmucosal (local effect and systemic effect, respectively) drug administration could also be achieved through this route. The effect of the previous is specified a site-specific release of the drug on the mucosa is achieved, and within the latter, the drug reaches the circulation by the way of mucosal barrier and gets absorbed. The vascularization is high in oral mucosa, and enzymatic activity is minimal as that of nasal, intestinal, and rectal mucosa. On account of irritation and impairment, the oral mucosa may be a smaller amount sensitive than the nasal epithelium. The sublingual process is created use of within the treatment of acute disorders. Since it is a high permeability across the mucosa, it's generally administered for the delivery of medication. When never-ending release of the active substance becomes necessary as within the case of chronic disorders; the buccal process is typically employed. However, the sublingual process has pitfalls. The activity of the tongue hampers the contact of the dosage form with the mucosa, further worsened by the surface being incessantly washed by saliva (Gandhi et al., 2014). Buccal process is more suitable for the situation of control release system which the patient also receives well. as compared to sublingual, buccal mucosa is flush and has surface which is immovable.

Keyword: Mucoadhesive, Buccal, Oral Cavity

1.INTRODUCTION

The concept of mucosal adhesion or mucoadhesive was introduced into controlled drug delivery area within the first 1980's, which is become a big part of novel drug delivery system within the recent era. variety of the potential sites for attachment of any mucoadhesive system are include cavity, cavum, eyes, vagina, rectal area, sublingual route and gastrointestinal area. Amongst the various routes of administration tried to the current point for novel drug delivery systems localized delivery to tissue of the rima has been investigated for kind of applications including the treatment of toothaches, disease, bacterial and fungal infections, aphthous and dental stomatitis and facilitating tooth movement with prostaglandins (Semelty et al., 2018). Oral transmucosal drug delivery could even be of three types like sublingual, gingival, and buccal (Nagai et al., 2001). Absorption of therapeutic agents from the mouth provides a direct entry for such agents into the circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal degradation (Junginger et al., 2015). However, the buccal route of drug delivery gains superiority because of its unique advantages over the alternative oral transmucosal routes. form of mucoadhesive devices has been developed within the recent era includes tablet, films, patches, disks strips, ointments, and gels etc (shin et al., 2010). However, buccal films offer greater flexibility and luxury than adhesive tablets. additionally, films can circumvent the matter of the relatively short continuance of oral gels on mucosa. Since the gels are easily washed away by saliva. Again, it are often introduced to the wound surface which is able to control the healing more effectively. an ideal buccal coating must be flexible, elastic, and soft yet

tough enough to resist breakage because of stress from activities in the mouth. Moreover, it must also possess good mucoadhesive strength so as that it's retained within the mouth for the required duration (Patel et al., 2017).

1.1. History of Buccal Drug Development

Back in 1947, once attempts were prepared to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth, dental adhesive puffs for the employment of mucoadhesive polymers were used for the event of pharmaceutical formulations. Improved results were reported when carboxy methyl cellulose (CMC) and petrolatum were used for the event of formulation. Subsequent research resulted within the event of a mucoadhesive delivery vehicle which consisted of finely ground sodium CMC (SCMC), pectin, and gelatin. The formulation was later marketed as Orahesive R. A different formulation which arrived into the clinical trials is Orabase R which might be a mixture of polymethylene oil base. This was followed by the event of a system where polyethylene sheet was laminated with a combination of SCMC and polyisobutylene which provided an additional advantage of protecting the mucoadhesive coating by the polyethylene support from the physical interference of the external environment. (khairnar et al.,2012)

1.2 Adavantages of Buccal Patches

- Ease of administration to pediatric, geriatric, bedridden patients and psychiatric patients who refuse to swallow tablets.
- No need of water to swallow the dosage form, which is extremely convenient feature for patients who are traveling. (Harris et al., 2000)
- Some drugs are absorbed from the mouth, pharynx and esophagus because the saliva passes down into the stomach, which boosts bioavailability of drugs
- Pregastric absorption may find yourself in improved bioavailability and as a results of reduced dosage; improved clinical performance through a reduction of unwanted effects
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety (Silvia et al., 2015).
- Useful in cases where an rapid onset of action required like in nausea,
- Sudden episodes of allergic attack or coughing, bronchitis or asthma
- Convenient dosing or accurate dosing, small size for improved patient compliance,
- Enhanced stability
- Taste masking, more patient compliance.

1.3 Disadvantages of Buccal Patches

- The main drawback of fast dissolving film is that top dose cannot incorporate into the Patch.
- Dose uniformity may be a technical challenge. • Require special packaging for products stability and safety.
- Hygroscopic in nature.

Buccal mucosa is a horny route for systemic delivery of medication since it's relatively permeable with a fashionable blood supply. A drug may be easily applied and localized to the applying site and may be faraway from there if necessary. Try has been made earlier to formulate several Mucoadhesive buccal devices, with tablets, films, patch, disks gels and ointments. Buccal patches are highly flexible and thus rather more readily tolerated by the patient than tablets. Patches similarly ensure more precise dosing of the drug equaled to gel and ointment. Drug delivery via the oral mucosa may be a promising route, when one wishes to attain a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. Thus, there's a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating strip, which permit a rapidly dissolving drug to soak up directly into the circulation through the oral mucosa. These sorts of dosage forms are convenient for kids, elderly patients with swallowing difficulties, and within the absence of potable liquids.

1.4 Oral cavity: anatomic and physiologic features:

The oral fissure presents a expanse of about 100 cm the thickness of buccal mucosa is measured to be 500-800 µm. (Khan et al., 2016)

Two differing kinds of rima oris are recognized,

- Lining mucosa
- Masticatory mucosa

Lining mucosa (60% of total oral mucosa) is 500- 800µm in thickness and covers lips, cheeks, mouth, lower surface of tongue and floor of the rima oris Masticator mucosa representing 25% of total oral mucosa is 100-200 µm in thickness and covers the gingival and surface. it's tightly attached to underlying structure and subjected to abrasion and shear stress during mastication the specialized mucosa (15% of total oral mucosa) is found on dorsum of tongue and involved in taste.

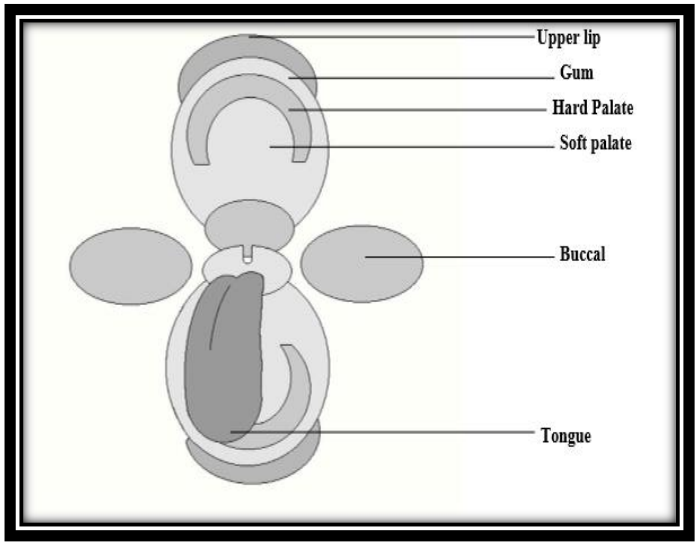

Figure 1: Schematic representation of oral mucosa

The term buccal refers to lining of cheek, upper and lower lips which represents one third of total oral mucosa surface. Buccal mucosa composed of several layers of various cells. The epithelia is comparable to stratified squamous epithelia found in remainder of body and is about 40-50 cell layers thick. Lining epithelium of buccal mucosa is that the non-keratinized stratified squamous epithelium has thickness of roughly 500-600 µ and area of fifty.2 cm Basement membrane lamina propria followed by submucosa is present below epithelial layer. Lamina propria is rich with blood vessels and capillaries that receptive internal vein.

1.4.1. Functions of Buccal Epithelium

- Protection of under lying tissue
- In non-keratinized regions, lipidbased permeability barriers in outer epithelial layers protect the underlying tissues against fluid loss (Michael et al., 2006)

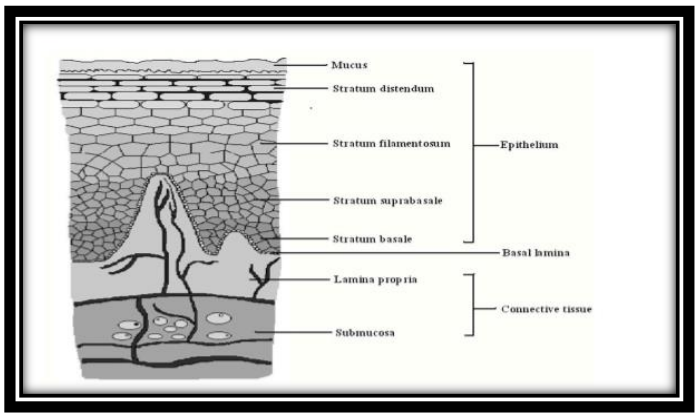

Figure 2: Cross section of oral mucosa

1.4.2 Functions of Oral Cavity (Khan et al., 2016)

- As a portal for intake of food material and water
- Identification of ingested material by taste buds of tongue
- To help in speech and breathing process
- Initiation of carbohydrates and metabolic process and absorption of catabolic products after metabolism catabolic products after metabolism
- To bring chewing, mastication and mixing of food stuff.

1.4.3 Secretions of Oral Cavity

Saliva: Saliva is complex fluid containing organic and inorganic materials. it's produced by three pairs of major glands viz, parotid, sub mandibular and sublingual glands situated in outside the rima oris and in minor salivary glands situated in tissues lining most of the rima. The surface of rima is continually bathed with a stream of saliva approximately 1litre/day by salivary glands. The pH of saliva varies from 6.5 to 7.5. it's a coffee buffering capacity and principal buffer of saliva being bicarbonate. Chemically saliva consists of 99.5% water 0.5% solute includes sodium, potassium, calcium, phosphate,

bicarbonate, chloride, urea, uric acid, albumen, mucin, enzymes and dissolved gases.

1.4.4 Physiological functions of saliva:

- Modulation of oral mucosa
- Remineralisation of teeth with orthophosphate salts
- Neutralization of acid in rima.
- Stimulation of epithelial proliferation Initiation of fat and starch digestion.
- Lubrication and cleansing if oral, pharyngeal and esophageal mucosa

Cervicular fluid: It is a fluid secreted from gingival glands of Mouth cavity.

Mucus: Mucus could be a thick fluid composed of mainly of water, electrolytes and a mix of several glycoproteins. Mucus is secreted in cavum which helps to supply saliva. It protects biological membranes and acts as excellent lubricant. The oral fissure could also be divided into two regions, the outer oral vestibule, bounded by the lips and cheeks and also the mouth itself the borders being, and formed by the hard and soft palates, the ground of the mouth and tonsils.

Table no 1: Regional variations in the composition of oral mucosa

Tissue	Structure	Epithelial thickness	Blood flow(ml/min/cm)
Buccal	Non-keratinized	500-600	2.40
Sublingual	Non-keratinized	100-200	0.97
Gingival	keratinized	200	1.47
Palatal	Keratinized	250	0.89

Although blood flow through oral mucosa of humans has not been reported, but it's generally considered that the blood flows through human oral mucosa, even during disease, is sufficiently fast as to not be rate limiting think about the absorption of medicine via the oral mucosa.

1.5 Muco/Bioadhesion

According to Longer and Robinson, the attachment of synthetic or natural macromolecule to mucus (Mucoadhesion) or an epithelial surface (Bio adhesion).

1.5.1 Theories of Muco/Bioadhesion (Lee and Park et al., 2010)

Many theories have been proposed to explain the forces that under in bioadhesion.

A) Electronic theory:
In this theory different electronic property of the mucoadhesive polymer and also the mucus glycoprotein, electron transfer between these two surfaces occurs. Electron transfer contributes to formation of a charged double layer at the interface of the mucus and also the polymer, which ends up in forces of attraction during this region and inters diffusion of the 2 surfaces.

B) Adsorption theory:
The primary and secondary chemical bonds of the covalent and non-covalent (electrostatic, Vander walls' forces, hydrogen and hydrophobic bonds) types are formed upon initial contact between the mucus and also the mucoadhesive polymer. Most of the initial interfacial bonding forces is attributed to non-covalent forces.

C) Wetting theory:
The ability of a bio adhesive polymer to spread biological surfaces. This theory is predominantly applicable to liquid bioadhesive systems moderately wettable polymers are shown to exhibit optimal adhesion to human endothelial cells.

D) Diffusion theory:
The basic involved during this theory is chain entanglement between glyco proteins of the mucus and

mucoadhesive polymer. Upon initial contact between these two polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the 2 polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and therefore the diffusion coefficient of the bioadhesive polymer are among the factor s which influence the inter diffusion of the macromolecule network (Khutoryanskiy et al., 2011). This theory is principally applicable to liquid mucoadhesive forms. Better ability of polymers to spread on the surface of mucosal tissues is typically related to excellent mucoadhesive performance.

E) Fracture theory:
It relates the force required for the detachment of polymer s from mucus to the strength of their adhesive bond. it's been found that job fracture is larger when the network strands are longer or the degree of cross-linking is reduced. 1.5.2 Factors Affecting Mucoadhesion in rima oris A variety of things affect the mucoadhesive properties of polymers, such a mass, flexibility, hydrogen bonding, charge, concentration and swelling of a polymer.

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A variety of factors affect the mucoadhesive properties of polymers, such a molecular weight, flexibility, hydrogen bonding, charge, concentration and swelling of a polymer.'

1.6 POLYMER RELATED FACTORS (Johnston et al., 2015)

1.6.1 Molecular weight:

In general, it's been shown that the bioadhesive strength of a polymer increases with molecular weights above 1, 00, 000

1.6.2 Flexibility:

Bioadhesion starts with the diffusion of the polymer chains within the interfacial region. Therefore, it's important that the polymer chains contain a considerable degree of flexibility so as to attain the required entanglement with the mucus. In general, mobility and adaptability of polymers may be associated with their viscosities and diffusion coefficients, where higher flexibility of a polymer causes

1.6.3 Charge:

Peppas and Buri have demonstrated that strong anionic charge on the polymer is one amongst the desired characteristics for Mucoadhesion. The nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers.

1.6.4 Hydrogen bonding:

It is another important think about Mucoadhesion of a polymer Park and Robinson found that so as for Mucoadhesion to occur, desired polymers must have functional groups that are ready to form hydrogen bonds. they need also confirmed that flexibility of the polymer is very important to boost this hydrogen bonding potential.

1.6.5 Concentration:

The importance of this factor involved within the development of a robust adhesive bond with the mucus, and might be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of them polymer is just too low, the quantity of penetrating polymer chains per unit volume of the mucus is tiny, and also the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would lead to a extended penetrating chain length and better adhesion. 1.6.6 Hydration Hydration is required for a polymer to expand and build a correct macromolecular mesh" of sufficient size, and also to induce mobility within the polymer chains so as to boost the interpretation process between polymer and mucin.

1.7 Environmental Factors

The Mucoadhesion of a polymer not only depends on its molecular properties, but also affects the behavior of the polymer. pH of the microenvironment nearby the mucoadhesive polymer can change the ionization state. Mucin employee turnover is another environmental factor. The continuance of dosage forms is proscribed by the mucin turnover time, which has been calculated

to range between 47 and 270 min in rats and 12-24 h in humans Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the rima. Movements within oral fissure continue even during sleep, and may potentially cause detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is important so as to avoid many of those interfering factors The Para cellular route is that the primary route for hydrophilic compounds. It involves passage between cells thro ugh cellular lipid material of intercellular spaces. This route could be a tortuous one, requiring the epithelium to own a sufficiently open matrix and drug to own an appreciable affinity and diffusivity within the intercellular fluids For lipophilic compounds, because the area for the trans cellular route is large, the partition coefficients are high, and therefore the path length for transcellular movement is comparatively short, the permeability of lipophilic compounds across the somatic cell membrane is usually high. during this case, drug molecules should move across lipophilic cytomembrane and hydrophilic cytoplasm also as intercellular space.

1.8 Drug transport across the oral mucosa

Since the main resistance of this route is the cell membrane, drug movement in the cytoplasm and intercellular space is relatively rap id and assumed as instantaneous the oral mucosal drug absorption process

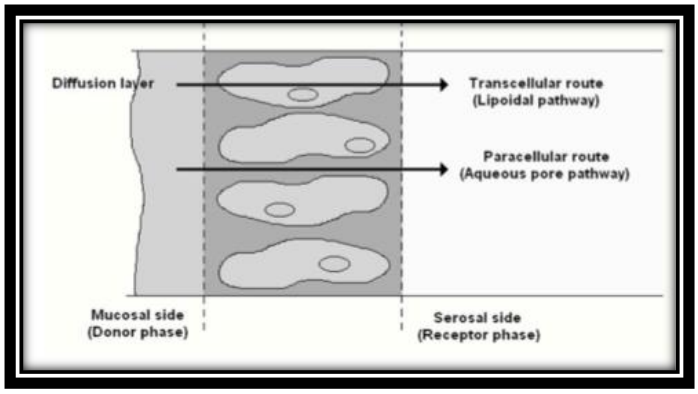

Figure 3: Drug absorption pathways across buccal mucosa

From a dynamic point of view, drug molecules par cellular and transcellular routes depicted here are a simplified version of the will preferentially move through the route which offers the least resistance. Since the movement of drug molecules may involve a mixture of these two routes, i.e., using one route in one region and other route in the other region.

1.9 Buccal mucoadhesive dosage form

Buccal adhesive dosage forms can deliver the drug either locally to treat condition within the buccal cavity or systemically via the mucosa. It is often a requirement that buccal adhesive dosage forms should adhere and allows controlled delivery of drug for prolonged periods. This dosage form can be divided into following.

1.9.1 Buccal Tablets:

Buccal approximately 5-8 mm. Unlike conventional tablets, buccal mucoadhesive tablets are small, flat, and oval with a diameter of allow for drinking and speaking without major discomfort the saliva softens the buccal tablets which is adheres to mucosa, and is retained imposition until dissolution or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and gum. Successive tablets can be applied to alternate sides of the mouth. The main drawback of buccal bioadhesive tablets is their absence of physical flexibility, prominent to poor patient compliance for long time and frequent use. (John et al., 2003)

1.9.2 Semisolid preparation

Bioadhesive gels or ointments have less patient acceptability than solid dosage adhesive forms and most are used only for localized drug therapy within oral cavity. One of the original oral mucosal adhesive delivery system- "Orabase" consists of finely ground pectin, gelatin and sodium CMC dispersed in poly(ethylene) and mineral oil gel base, which can be keep up at its site of application for 15-150 min. (James et al., 2012)

1.9.3 Powders

A hydroxypropyl cellulose and beclomethasone dipropionate containing powder that was sprayed onto oral mucosa of rats. A significant increase in residence time relative to an oral solution was seen and 2.5% of

beclomethasone was retained on buccal mucosa for over 4 h.

1.9.4 Buccal Mucoadhesive Patches

These are two ply aminates or multilayered thin film, round or oval consistently basically of bioadhesive polymeric layer and impermeable basically layer to provide unidirectional flow of drug across buccal mucosa.

1.10 Design of buccal mucoadheisve patches (Dixit et al., 2009)

The following considerations are taken while designing buccal mucoadhesive patches:

- Convenient to apply and unobtrusive when in place.
- Not to incorporate a bitter tasting drug. It should have smooth surface rather than textured surface preferably it should achieve unidirectional release of drug.
- It should not irritate buccal mucosa.
- The different components of buccal mucoadhesive patches are,

1.10.1 Drug:

The important drug properties that affect its diffusion through the patch as well as buccal mucosa include molecular weight partition coefficient, dissociation constant of drug. The choice of appropriate drug to design buccal drug delivery systemic based on pharmacokinetic properties. Following are the properties for candidature to mucoadhesive buccal drug delivery system. Conventional dose of drug should be less. The drug should not adversely affect the natural microbial flora of oral cavity Drug should not have bad taste and free from irritancy, allerginicity, discoloration or erosion of teeth.

1.10.2 Buccal adhesive polymers:

Polymer is a very long molecule consisting of structural u nits connected by covalent chemical bonds. Bioadhesive formulations use polymers as adhesive component. These formulations are often water soluble and when in dry form attract water from bio logical surface and this water transfer leads to strong interaction. These polymers also form viscous liquids when mixed with water. Bioadhesive polymers should possess certain physicochemical feature including hydrophilicity, hydrogen bonding and visco-elastic properties.

1.10.3 Plasticizer:

The role of Plasticizer is beneficial for preparation of Buccal film. Plasticizer helps to increase the flexibility of the film and decreases the fragility of the film. The plasticizer should be compatible with polymer and solvent the flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer These are the materials used to achieve smoothness and elasticity of thin films of polymer or mixture of polymers. The plasticizer which helps in release of drug from polymer base as well as it acts as penetration enhancer. Usually the concentration of polymer will be the 10-50% of the total polymer weight. Ex: glycerol, Propylene glycol, PEG-200, PEG-400. (Dahiya et al., 2009)

1.10.4 Permeation enhancer:

The substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Most of the permeation enhancers were designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be priority in drug delivery. The selection of enhancer and its efficacy depends on physicochemical properties of drug, site of administration, nature of vehicle and other excipients.

1.10.5 The different permeation enhancers available are

- Chelators: EDTA, citric acid, sodium salicylates, methoxy salicylates
- Surfactants: sodium lauryl sulphate, polyoxyethylene.
- Bile salts: sodium glycoholate, sodium deoxycholate, sodium taurocholate.
- Fatty acids: oleic acid, capric acid, lauric acid, propylene glycol, methyloleate.
- Non-surfactants: unsaturated cyclic ureas
- Inclusion complex

1.11 Method of preparation of buccal patches / film

The following processes can be used to manufacture the Mucoadhesive Buccal Patches:

- Solvent Casting Method
- Hot-melt Extrusion Method
- Semisolid casting
- Rolling method

1.11.1 Solvent Casting Method:

The oral fast dissolving films are prepared by dissolving strip forming agents, plasticizer and saliva stimulating agent in the distilled water, then solution is continuous aroused to 4 hrs. on magnetic stirrer and kept for 1 hour to get rid of all the air bubbles entrapped. Meanwhile, within the separate container remaining water soluble excipients i.e. sweetening agent, disintegrating agent, saliva stimulating agent, flavor and drug are dissolved with constant stirring for 45 min.. Then keep the answer stationary for 1 hrs. to let the foams quiet down. The resulting formulation is casted on an acceptable platform and is dried to create a movie. The film is rather air-dried or dried in oven then the film is cautiously removed. (Dahiya et al., 2019)

1.11.2 Hot-melt Extrusion Method:

Drug and polymers are blended into a sigma blade mixer for 10 min, so plasticizer is slowly added. The mixture is granulated within the presence of an anti-sticking agent. Granules are stored overnight at temperature then sieved through a 250µm sieve so as to get rid of the surplus of powder and standardize the particle size. The dry granular material is nourished into the extruder. At the tip of the preparation processes, the films are cut consistent with the dimensions required.

1.11.3 Semisolid casting

- Water soluble polymers are dissolved in water
- Solution added to solution of acid insoluble polymer (CAP, CAB)
- Plasticizer is added to get gel mass.
- The prepared gel mass is cast into films.

1.11.4 Rolling method

- A solution or suspension containing the drug is rolled on a carrier
- Solvent : water or water and alcohol

The film is dried on the rollers and takes desired size

2. CONCLUSION

The goal was to Dynamic Review buccal mucoadhesive patches. The film were evaluated for physical appearance and surface texture, thickness, drug content uniformity, swelling index, mucoadhesive time and in vitro drug release study. Buccal patches were prepared to retain in rima oris thus increase bioavailability, reduces drug waste and side effect like gastric irritation and nausea and also facilitate administration to patients littered with nausea or vomiting and with and upper digestive tube disease or surgery which affects GIT absorption and having difficulty in swallowing oral medication. Buccal drug delivery has lately become a vital route of drug administration, various bioadhesive mucosal dosage forms are being developed.

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