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Review Article

Fast Dissolving Oral Film Technology: An Innovative Buccal Drug Delivery System.

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ABSTRACT

The oral cavity is an attractive site for the delivery of drugs. Oral route has been the most convenient and commonly employed route of drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. The main obstacles that drugs meet when administered via the buccal route derive from the limited absorption area and the barrier properties of the mucosa. Oral films provide better drug utilization in by-passing the first pass metabolism, enhance drug bioavailability, mask the bitter taste of the drug and do not need water to swallow. In this article main focus is done on overview of Buccal drug delivery, anatomy of oral mucosa, different dosage forms, formulation aspects, evaluation methods, packaging; this will be useful to circumvent the difficulties associated with the formulation design.

KEYWORDS

Buccal drug delivery, Transmucosal, Oral mucosa, Innovative, Mucoadhesion, Barrier, Permeability.

1. INTRODUCTION

1.1.Oral Cavity

A drug can be administered via a many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The oral route of drug administration is the most important method of administering drugs for systemic effect. The parenteral route is not routinely used for self– administration of medication. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. [1] The oral cavity is an attractive site for the delivery of drugs either locally or directly into the systemic circulation. Its attractiveness based on the mucosal membranes, upon which drug delivery systems are located, is readily accessible to patients or their carriers. This means that the delivery system can be placed on the specific oral cavity membrane that is chosen as the site of absorption. Also if signs of adverse reactions are observed during treatment the delivery system can be removed in order to terminate delivery. The oral cavity represents a challenging area to develop an effective drug delivery system. This occurs due to the various intrinsic functions of the oral cavity such as eating, swallowing, speaking, chewing, as well as the presence of the fluid that is involved in all these activities, saliva. This fluid is continually secreted into, and then removed from, the mouth. Overall, however, it remains a viable option as a route for drug administration and has been extensively studied for that purpose. [2] Among the various routes of drug delivery, transmucosal drug delivery offer distinct advantages over per oral administration for systemic effect. Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs. The unique physiological features make the buccal mucosa as an ideal route for mucoadhesive drug delivery system. These advantages include bypass of hepatic first-pass effect and avoidance of pre systemic elimination within the gastrointestinal tract. The use of the oral cavity membranes as sites of drug administration has been the topic of increasing interest for the past decade. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation, both of which are associated with oral administration. [3]

For drug delivery purpose, the term bio adhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus membrane, the phenomenon is called as mucoadhesion. Hence a bacterial attachment is to tissue surfaces, and mucoadhesion can be modelled after the adherence of mucus on epithelial tissue. Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane.

By this definition, the mucosal routes for drug delivery are:

- Buccal/ Oral route
- Nasal route
- Ocular route
- Vaginal route
- Gastrointestinal route [4]

1.2. Anatomy of Oral Cavity

The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves. The mucosa can be divided into three types: Masticator mucosa, found on the gingiva and hard palate. Lining mucosa, found on the lips, cheeks, floor of mouth, under surface of the tongue and the soft palate. Specialized mucosa found on the upper surface of the tongue and parts of the lips. All consists of a squamous stratified epithelium, many cell layers (40-50 for Buccal mucosa) overlying a connective tissue, layer, the lamina propria. The total surface area of oral cavity = 170 cm^2.

Drug Delivery via Buccal Rout: Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. [5] The structure and anatomy of oral cavity is studied for understanding the environment provided for delivering drugs. The oral mucosa allows direct entry of drug to the systemic circulation and avoids first pass metabolism. The epithelium of the oral cavity is quite similar to that of the skin, with slight differences with regard to keratinisation, protective and lubricant mucous which is spread across its surface. The permeability of oral mucosa is 4–1000 times greater than the skin. The oral cavity is divided into two regions: outer is the oral vestibule bounded by the lips and cheeks; the hard and soft palates, the floor of the mouth and tonsils. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. [6]

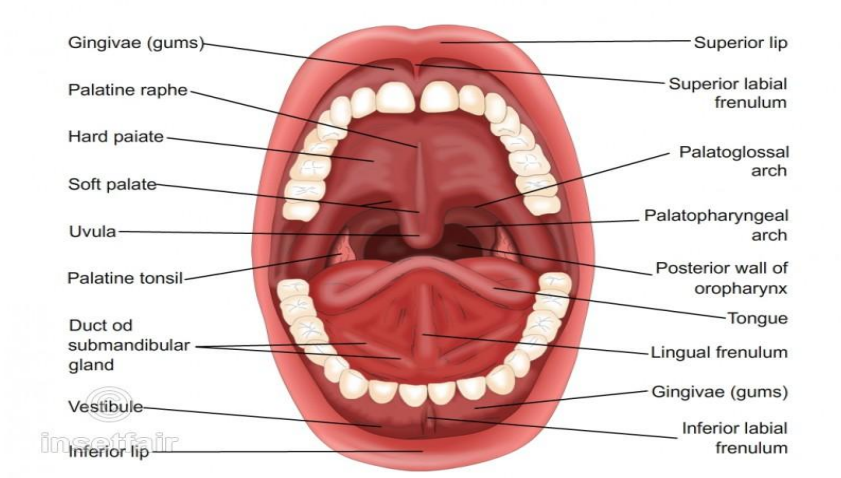

Fig. 1. Anatomy of Oral Cavity.

1.3 The Overview of the Oral Mucosa

1.3.1. Structure

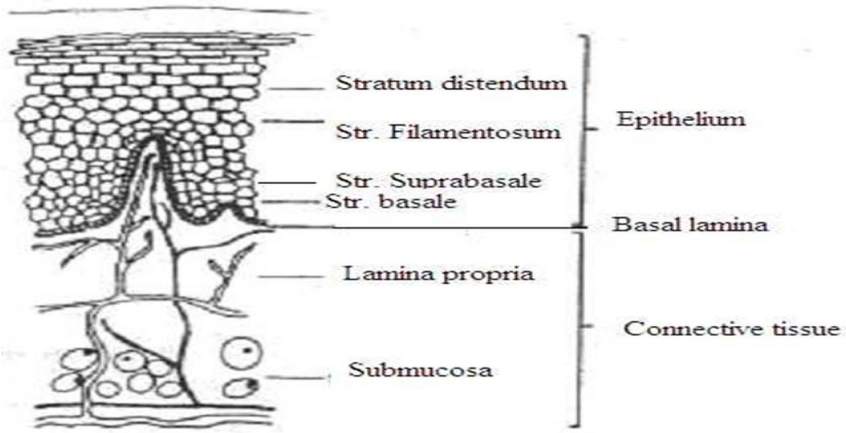

Fig. 2. schematic cross section through oral mucosa showing the epithelium, basal lamina, & connective tissue.

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

All covering and lining tissues of the body consist of a surface epithelium supported by a fibrous connective tissue. Epithelium, by virtue of the close packing and constant turnover of

Cells, is well adapted to protect underlying tissues and organs against mechanical and chemical insult, whereas the connective tissue, consisting of relatively few cells in an extensive matrix, provides mechanical support and nutrients for the epithelium. In comparing the structure of skin and oral mucosa to the gastrointestinal tract, a major difference emerges in the organization of the epithelium, which reflects the different functions of these regions. The lining of the stomach and small and large intestine consists of a simple epithelium composed of only a single layer of cells, which facilitates absorption across the tissue. Skin, oral mucosa, and oesophagus are covered by a stratified epithelium composed of multiple layers of cells that show various patterns of differentiation between the deepest cell layer and the surface. Features that differs the oral and oesophageal mucosa from skin are its moist surface and the absence of appendages. The skin contains numerous hair follicles, sebaceous glands, and sweat glands, whereas the glandular component of oral and oesophageal mucosa is represented primarily by the minor salivary glands. These glands are concentrated in the submucosa, and the secretions reach the mucosal surface via small ducts. The salivary glands have an important role in maintaining a moist surface containing mucins and a variety of antimicrobial substances as well as epidermal growth factor (EGF). In the oesophagus, the minor salivary glands can produce a secretion with high

bicarbonate concentration to neutralize refluxing stomach acid. Sebaceous glands are present in the upper lip and buccal mucosa in about three quarters of adults. [8]

1.3.2. Permeability [9-10]

The oral mucosa is a protective tissue designed to prevent unwanted materials such as pathogens from entering the body and keeps the underlying tissue hydrated by preventing fluid loss. This means drugs cannot freely pass across the epithelium but are obstructed by the permeability barrier. The permeability barrier is predominantly found in the lipid rich upper layers of the epithelium (granular layer). The supra-basal cells have strong desmosomal junctions and form membrane coating granules, which release lipophilic materials into the extracellular space. This enhances keratinocyte adhesion but also slows the passage of hydrophilic materials. But, different areas of the mouth display different levels of permeability barrier and the area below the tongue (floor of mouth) has a thin epithelium that is significantly more permeable than other areas of the oral mucosa making it an ideal site for drug delivery. [9] This permeability feature of the oral mucosa is the most important factor that determines the appropriate drug formulations so that the drug gets absorbed and reaches the deeper layers of the oral mucosa. The movement of drug molecules mainly depends on the following features – local variations in mucosal thickness, epithelial keratinisation and lipid composition. These features are collectively known as the barrier region of the oral mucosa. The permeability of oral mucosa is attributed to intercellular materials derived from membrane coating granules, which are found in the intermediate cell layers of both keratinized and non keratinized epithelia (Shojaei, 1998). As there is a regional difference in the epithelial thickness of oral mucosa, it has been suggested that the permeability pattern decreases moderately from the sublingual mucosa to the buccal mucosa and palatal mucosa. [10]

1.3.3. Role of Saliva [11-12]

Saliva is a body fluid, secreted by three pairs of major salivary glands (parotid, submandibular and sublingual) and by many of minor salivary glands. Primary saliva is secreted in secretory end pieces of salivary glands. Primary saliva is modified by serum exudates via tight junctions between several glandular cells (ultra filtration) and via transcellular diffusion through these cells. Primary saliva is also modified in the intercalated, striated and excretory (collecting) ducts leading from the acini to the mouth. Entering the mouth, ductal saliva of several salivary glands are blended, and supplemented with many constituents that originate from intact or destroyed mucosal cells, immune cells, and oral microorganism. Blood constituents also enter the oral cavity via gingival crevicular fluid, via the mucosa as mucosal transudate, and via intraoral bleeding. Consequently, a complex mixture of a high variety of molecules is the result in the oral cavity, frequently called “mixed saliva” and/or “whole saliva” in the scientific literature. Whole saliva is a major determinant of the environment on all the oral surfaces. On tooth surfaces saliva plays an important role in acquired pellicle formation, which is a thin (*ca.* 0.5–1 μm) layer of several salivary proteins with calcium hydroxide binding properties [11]. In general, saliva helps us in eating, swallowing and also everyday activities like speaking. It helps keep the oral cavity hydrated, hence protecting teeth from microorganisms. Along with dental caries detection,

scientists have been pursuing interest in identifying salivary biomarkers that can be used to identify diseases and therefore monitor general health of people and detect diseases such as AIDS, diabetes, alcoholic cirrhosis, cystic fibrosis, diseases of the adrenal cortex, cardio vascular diseases, and in the early stage of onset [12].

1.3.4. The Mucus Layer [13]

Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans. 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 the pathophysiological state. However, it has the following general composition

1. Water - 95%
2. Glycoprotein's and Lipids - 0.5 to 5%
3. Mineral salts - 0.5 to 1%
4. Free Proteins - 0.5 to 1%

1.3.5. Functions of mucus layer

The Primary functions of the mucus layer are:

1. Protective

This is because its hydrophobicity and protecting the mucosa from the diffusion of hydrochloric acid from the lumen to the epithelial surface.

2. Barrier

The role of the mucus layer as a barrier in tissue absorption of drugs and other substrates is well known as it influences the bioavailability of drug.

3. Adhesion

Mucus has strong cohesional properties and firmly binds to the epithelial cell
Surface as a continuous gel layer.

4. Lubrication

Most important role of the mucus layer is to keep the mucosal membrane moist. Continuous secretion of mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and volatilization of mucin molecules. [13]

2. NOVEL BUCCAL DOSAGE FORMS

The novel type buccal dosage forms include buccal adhesive tablets, patches, films,
Semisolids (ointments and gels) and powders.

A. *Mucoadhesive Buccal Tablets*

Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. Example: a double layer tablet, consisting of adhesive matrix layer of hydroxy propyl, cellulose and polyacrylic acid with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

B. *Patches and Films*

Buccal patches consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape. A novel mucosal adhesive film called "Zilactin" –consisting of an alcoholic solution of hydroxypropyl cellulose and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids.

C. *Semisolid Preparations (Ointments and Gels)*

Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems –"orabase"– consists of finely ground pectin, gelatine and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.

D. *Powders*

Hydroxypropyl cellulose and beclomethasone in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.[14]

3. BUCCAL ABSORPTION

Buccal absorption leads systemic or local action via buccal mucosa.

3.1. 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 lipophilic 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. The linear relationship between salivary secretion and time is given as follows

dm/dt = Kc/ViVt ---Equation 1

Where,

M - Mass of drug in mouth at time ıtı

K - Proportionality constant

C - Concentration of drug in mouth at time

Vi - The volume of solution put into mouth cavity and

Vt - Salivary secretion rate [14]

4. STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM

Buccal dosage form can be of;

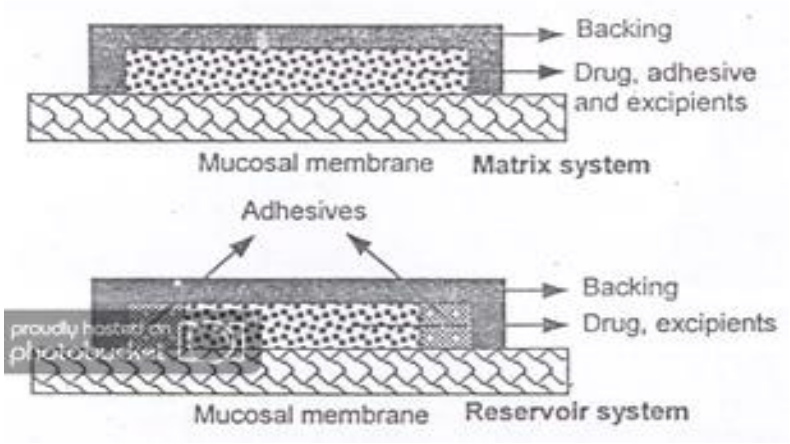

Fig. 3. Buccal patch design for matrix and reservoir type drug release.

4.1. Matrix type

The Buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.

4.2. 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. Buccal absorption: Buccal absorption leads systemic or local action via buccal mucosa [7]

5. RAPIDLY DISSOLVING DOSAGE FORMS(RDDF) [16-18]

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance.

5.1. Current Oral Fast-Dispersing Dosage Form Technologies

Although several technologies are available, few have reached commercial marketed products. Several methods are employed in the preparation of oral fast-dispersing tablets, such as modified tableting systems, floss, or Shear form. Formation by application of centrifugal force and controlled temperature, and freeze drying.

5.2. Classification of Fast Dissolve Technology

For ease of description, fast-dissolve technologies can be divided in to three broad groups:

1. Lyophilized systems,
2. Compressed tablet-based systems,

5.2.1. The lyophilized systems

This system has been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration.

Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems.

5.2.2. Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard HDPE bottles or blisters through to more specialists pack designs for product protection. CIMA Labs., PackSolv, for example. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail's Fuisz technology. It uses the proprietary Shear form system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms. [16]

6. FAST DISINTEGRATING ORAL FILMS

These are thin, flexible, elegant films of various sizes and shapes, typically the size of a postage stamp meant to be placed on patient's tongue. They rapidly disintegrate/disperse and release the drug when they come in contact with saliva[17]. Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for paediatrics, geriatrics, nauseous and non-compliance patients. Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are outcomes of technological development. Among various dosage forms, the use of polymeric films for delivering medication into buccal cavity has developed great potential in recent era. Orally disintegrating films (ODFs), when placed on tongue,

immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form. ODFs are kind of formulations which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are the typical examples of orally disintegrating drug delivery systems. These systems were developed in late 1970 to serve as an alternative to conventional dosage forms, for instance, fast disintegrating tablets and capsules for geriatrics and paediatric patients having difficulty in swallowing conventional dosage forms. A typical ODF is usually equal to the size of a postage stamp. In market place, the introduction of ODT was strongly associated with counselling of patients about the appropriate administration by giving instruction like ‘‘do not chew/do not swallow’’. However, in spite of these instructions, incidents regarding chewing and swallowing were often reported [18]

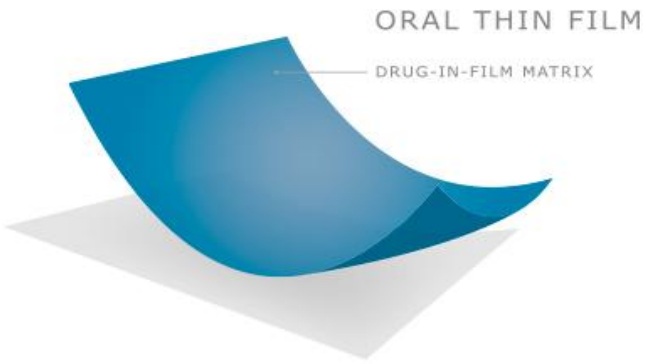

Fig. 4. Oral Thin Film.

6.1. Advantages

1. Rapidly dissolved and disintegrated in the oral cavity because of large surface area which lowers dosage interval, improves onset of action, efficacy and safety profile of therapy.
2. Oral films are more flexible, compliant and are not brittle as ODTS.
3. Easily handled, storage and transportation.
4. Accuracy in the administered dose is assured from every strip or film.
5. Pharmaceutical companies and customers practically accepted OTFs as an alternative of conventional OTC dosage forms such tablets and capsules etc. (Frey, 2006).
6. Oral film is desirable for patient suffering from motion sickness, dysphagia, repeated emesis and mental disorders.
7. From commercial point of view, oral films provide new business opportunity like product differentiation, promotion etc.[19]

6.2. Disadvantages

1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including buccal membrane.

2. The barriers such as saliva, mucus, membrane coating granules, basement membrane etc. retard the rate and extent of drug absorption through the buccal mucosa.
3. Continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
4. The hazard of choking by involuntarily swallowing the delivery system is a concern.
5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form[20]
6. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue[21]

7. FORMULATION CONSIDERATION

Mouth dissolving film is a thin film with an area of 5-20cm^2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water soluble polymers. Drug can be incorporated up to a single dose of 15mg. formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films, such as shifting the glass transition temperature to lower temperature.

Table 1. Composition of the patches [22]

Components	Concentration (%)
Active Pharmaceutical Ingredient	1-25
Hydrophilic Polymer	40-50
Plasticizer	0-20
Colour, Filler, Flavour	0-40

7.1. Active pharmaceutical ingredient

Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. It includes antiulcers, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal etc. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). Various categories of drugs such as antiemetic, neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorants and anitussive [12-19].

The ideal characteristics of a drug to be selected are as follows-

a. The drug should have pleasant taste.
b. The drug to be incorporated should have low dose generally less than 30mg.
c. The drugs with smaller and moderate molecular weight should be preferable.
d. The drug has should be stable and soluble in water as well as in saliva.
e. It should be partially unionized at the pH of oral cavity.
f. It should have the ability to permeate oral mucosal tissue [23]

7.2. Film forming polymer

Several polymers can be used for preparation of fast dissolving films (FDF) or oral strips (OS). To obtain the desired properties, polymers can be used alone or in combination. The film obtained should be of enough strength so that there won't be any damage while handling or during transportation, at the same time it should be thin and flexible and should have the property to disintegrate in seconds when placed in mouth to deliver the drug to the oral cavity promptly. As the strip forming polymer is the most crucial and main component of the OS, at least 45%w/w of polymer should be usually present based on the total weight of dry OS. [24] Properties of the commonly used film forming agents have discussed in following table 3.

7.3. Ideal properties of the film forming polymers

a. The polymer employed should be non-toxic, non-irritant.
b. It should be devoid of leachable impurities.
c. It should have good wetting and spreading properties.
d. The polymer should exhibit sufficient peel, shear and tensile
e. Strengths.
f. The polymer should be readily available and should not be very
g. Expensive.
h. It should have good shelf life.
i. It should not aid in cause secondary infections in the oral mucosa/dental region.
j. It should have a good mouth feel property.
k. It would be ideal to have a polymer that would have local enzyme
l. Inhibition action along with penetration enhancing property.
m. It should not be an obstacle in the disintegration time [25, 26].

Table 2. Some examples of drugs with Type of polymer used [27,28,29]

Oral films	**polymer used**
Amlodipin Besylate Sodium alginate	Amlodipin Besylate Sodium alginate
HPMC-E5	HPMC-E5
Famotidine HPMC, sodium carboxy methyl cellulose, PVA	Famotidine HPMC, sodium carboxy methyl cellulose, PVA
Ondansetron hydrochloride Polyvinylalcohol, polyvinyle pyrrolidone, Carbopol E5	Ondansetron hydrochloride Polyvinylalcohol, polyvinyle pyrrolidone, Carbopol E5
Glipizide HPMC, sodium carboxymethlcellulose, carbopol-934P and	Glipizide HPMC, sodium carboxymethlcellulose, carbopol-934P and
Domperidone PVA	Domperidone PVA
Valdecoxib HPMC, Eudragit EPO	Valdecoxib HPMC, Eudragit EPO

7.4. Plasticizers

Plasticizer used in the formulation should be compatible with the type of polymer used as it reduces the glass transition temperature and improves flow of the polymer. So, it helps to improve the flexibility of the strip and reduces the brittleness of the strip [30]. It is also reported that the use of particular plasticizer also affect the absorption rate of the drug. Various defects associated with the inappropriate use of the plasticizer are cracking, blooming, pilling and splitting of the strip [31].

7.5. Surfactants

Surfactants play a vital role as dispersing, wetting and solubilizing agent thus enabling films to disintegrate within seconds releasing the incorporated drug, speedily. Commonly used surfactants are benzalkonium chloride, tweens, and sodium lauryl sulfate. Often, polaxamer 407 is used due to its many advantages. [18]

7.6. Flavour

Flavours are needed to mask the bitter or nauseating taste of incorporated drug. Amount of flavour depends upon its nature and strength. Any US-FDA approved flavour can be used such as sweet, sour or mint flavour. One of the research work verified that mint, liquorice and sucralose mixture flavours appropriately mask the bitter taste of diclofenac Sodium. Electronic tongues are used to discriminate the effect of various taste masking agents (TMAs).[32]

7.7. Sweetening agents

Sweeteners have become important part of food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral unpalatable especially for paediatric preparations. Thus before incorporating the API in the OS, taste need to be masked. Various methods can be used to improve the palatability of the formulation.[33].

Table 3. Examples of some commonly used sweetening agents in ODFs.

Sweetening agent	Example
Natural	Glucose, fructose, dextrose, sucrose, and isomaltose
Artificial	Acesulfame-K, sucralose, and neotame

7.8. Saliva stimulating agent

Salivary stimulants are generally acidic in nature stimulating the production of saliva in buccal cavity, consequently, promoting the disintegrating of ODFs. Some commonly used saliva stimulating agents are citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid.[34]

7.9. Colouring agents

Pigments are used as colouring agents. Titanium dioxide is most widely used colorant in ODFs and various other pharmaceutical preparations. Apart from titanium dioxide, a full range of colours are available including FD and C, natural and custom pantone-matched colours.[35]

7.10. Methods of Preparation

The following process can be used:[35]

1) Solvent Casting Method
2) Semisolid Casting Method.
3) Hot Melt Extrusion Method
4) Solid Dispersion Extrusion Method
5) Rolling Methods

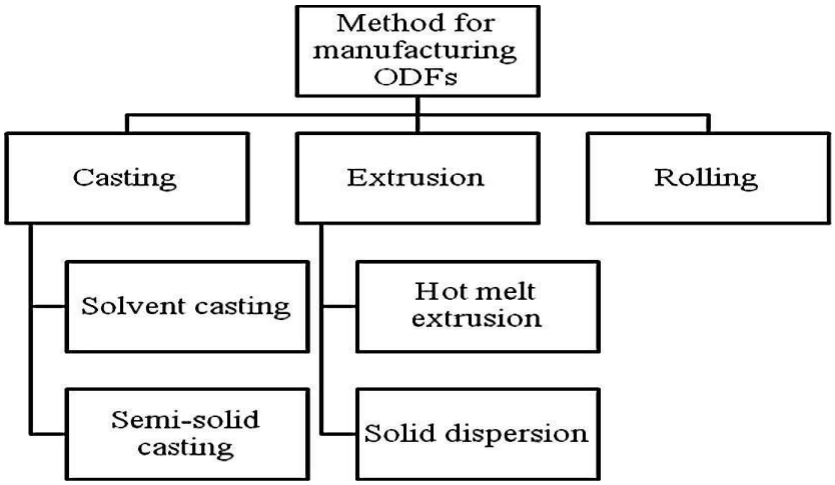

Fig. 5. Methods mainly employed for manufacturing ODFs.

7.11. Solvent Casting Method

Solvent casting is the most commonly used method for the preparation of ODFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor. Then, the prepared solution is poured onto petri plate and the solvent is allowed to dry by exposing it to high temperature in order to attain good quality films. [36,37]. In solvent casting technique, film forming polymer i usually soaked in an appropriate solvent for overnight. The type of API, which has to be incorporated in ODF, governs the selection of a suitable solvent depending on critical physico- chemical properties of API such as melting point, shear sensitivity and polymorphic form. Compatibility of drug with solvent and other excipients is also brought under consideration before finalizing a formulation. During formulation, entrapment of air bubbles can hinder the uniformity of prepared films. Thus, de aeration of the mixture is carried out with the help of a vacuum pump [38].

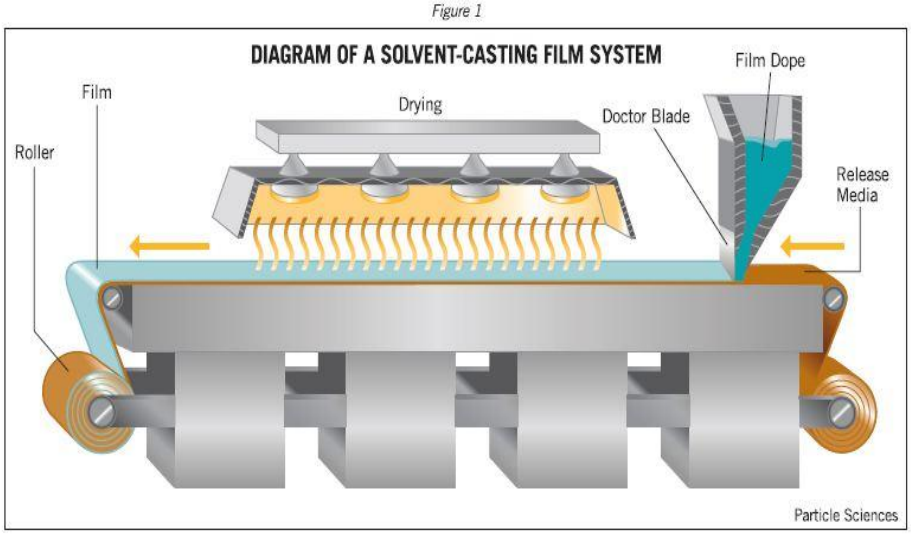

Fig. 6. Description of solvent casting technique.

7.12. Semisolid Casting

In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate) [39]. After sonication, it is coated on non-treated casting film. On drying the thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4[27].

7.13. 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 and finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion which includes-

- Fewer operation units
- Better content uniformity
- An anhydrous processing

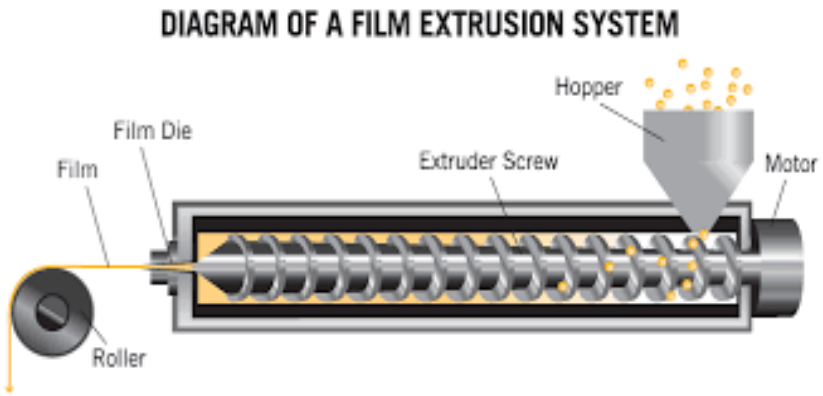

Fig. 7. Hot melt extrusion

7.14. 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 cutted in to desired shapes and sizes. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution [27].

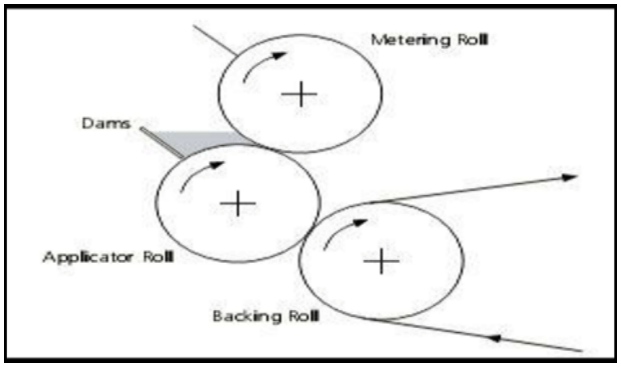

Fig. 8. Rolling method

8. EVALUATION OF FAST DISSOLVING FILM

8.1. Physical characterization

Physical characterization can be carried out by visual inspection for characteristics such as colour, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity [40].

8.2. Film thickness

The film thickness can be measured by micrometer screw gauge (Mitutoyo, Japan) at 5 different locations and the average value was calculated. This is essential to determine uniformity in the film thickness which is subsequently related to the accuracy of dose in the film [41].

8.3. Surface pH of films

For determination of surface pH, three films of each formulation are allowed to swell for 2 h on the surface of an agar plate. The surface pH is to be measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings is to be recorded [42].

8.4. Folding endurance

Three films of each formulation of required size are cut by using sharp blade. Folding endurance is to be determined by repeatedly folding the film at the same place, till it is broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance [43].

8.5. Moisture content

The prepared films are to be weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are to be weighed again after a specified interval, until they show a constant weight. The percent moisture content is to be calculated by using following formula [44].

% Moisture content= [Initial weight–Final weight/Final weight] ×100 --- Formula 1

8.6. Palatability test

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two a grade then it would be considered as good and the one with all three a grade it would be the very good formulation. [45]

Specifications Grades: A = very good, B = good, C = poor

8.7. Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. No official guidance is available about this. Pharmacopeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30s. [46]

Drop Method. In this method one drop of distilled water is dropped by a pipette onto the oral films. The films are placed on a glass slide and then the glass slide is placed planar on a petri dish. The time until the film dissolved and caused a hole within the film is measured as disintegration time. [47]

Petri dish Method. In this method 2mL of distilled water is placed in a petri dish and film was added on the surface of the water and the time required until the oral film dissolved completely was measured. [47]

8.8. In vitro drug release

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug Release from the bilayer and multi-layered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release was performed at 37 0C ± 0.50 0C, with a rotation speed of 50 rpm. The backing layer of buccal patches attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through what man filter paper and analysed after appropriate dilution by UV spectrophotometry at suitable nm. [48]

8.9. In vitro drug permeation

The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A one ml sample can be withdrawn at predetermined time intervals and analysed for drug content at suitable nm using a Spectrophotometer. [49]

9. PACKAGING

Many options are available for buccal films packing, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roller dispenser. Single packaging is mandatory for films. An aluminium pouch is the most commonly used packaging system. There are some patented packaging systems for oral films. Labtec Company has patented packaging technology called Rapid card and Amcor Flexibilities Company has patented Core-peel technology. [50]

Fig. 9. Blister card

10. CONCLUSION

The present review concludes that the buccal film is the most accurate and acceptable dosage form, which bypasses the hepatic first pass effect and shows good bioavailability. This is the most promising and innovative technology, which is useful to all the age groups, specifically paediatric, geriatric patients and also to the patients with swallowing difficulties. Buccal films can replace the conventional dosage forms, including fast disintegrating tablets due to its advantages over the conventional dosage forms, and they can be manufactured with low cost.

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