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Novel Oral Drug Delivery System: Fast Dissolving Buccal Films

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ABSTRACT

Fast dissolving buccal films is a novel oral drug delivery system offers new possibilities for drug delivery by providing the advantages of oral delivery coupled with the enhanced safety and efficacy of a drug molecule, enhanced onset of action, improved bioavailability by avoiding first pass metabolism and enzymatic degradation in the GI tract and convenience to special patient categories such as pediatrics, geriatrics and bedridden patients who experience difficulties in swallowing the conventional oral dosage form. This delivery system consists of a thin oral film, which is simply placed on the patient's tongue or any oral mucosal tissue (buccal/sublingual), instantly wet by saliva, rapidly hydrates and adhere onto site of application, where it disintegrates and dissolves to release the medication for oral mucosal absorption. More recently, fast dissolving films are gaining interest as an alternative to fast dissolving tablets to definitely eliminate patient's fear of chocking and overcome patient impediments. Fast dissolving films are formulated using polymers, plasticizers, sweeteners, flavours and colours. Fast dissolving films were prepared by solvent casting, rolling, extrusion and solid dispersion method. The films evaluated for disintegration, dissolution, tensile strength, thickness, folding endurance and elastic modulus. This article overview the advancements in oral dosage forms, formulation considerations, method of preparation, evaluation, marketed products and it also suggests that this delivery system can be adopted by various pharmaceutical companies in future at large scale.

Keywords: Fast dissolving buccal film, polymer, plasticizer, solvent casting, bioavailability enhancement.

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INTRODUCTION

Among the various routes, oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. About 60% of all the formulations are solid dosage form. The most popular oral solid dosage forms are tablets and capsules. Generally geriatric, pediatric and bedridden patient as well as travelling patients who may not have ready access to water experience difficulties in swallowing the conventional oral dosage form. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. To overcome this problem a novel formulation was developed i.e. oral fast dissolving films[1,2,3]. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention as it emerging new platform for pediatric and geriatric patients[4,5]. Fast dissolving buccal film (FDBF) is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch[1]. Fast dissolving buccal films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also large surface area of absorption, easy ingestion & pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery[6,7]. Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs. The unique physiological feature like better permeability due to a well supplied vascular and lymphatic drainage make the buccal mucosa as an ideal route for systemic drug delivery[8,9]. Even though the nasal, rectal, vaginal, and ocular mucosa all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration[10].

Benefits of buccal drug delivery[11-15]:

- It provides direct entry of drug into systemic circulation.
- Increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract
- Improved patient compliance due to the elimination of associated pain with injections
- Drug absorption can be terminated in case of emergency.
- It offers passive system, which does not require activation.
- Rapid cellular recovery following local stress or damage.
- Ability to withstand environmental extremes like change in pH, temperature etc.
- In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration.

Overview of Oral Mucosa[16-18]:

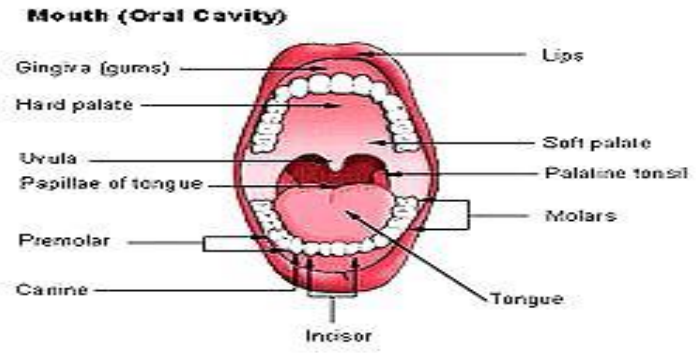

Figure 1: Structure of Oral cavity

Drug delivery via the oral mucosa is a promising route, when one wishes to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. 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 salivary glands secrete mucin as part of saliva. The pH of saliva ranges from 6.8 to 7. The permeability of buccal mucosa is found to be 4000 times greater than skin. The drug administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein[19,20]. Fast dissolving buccal film is new oral drug delivery system. This delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue (buccal/sublingual), instantly wet by saliva the film rapidly

hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption[16,21]. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment[3].

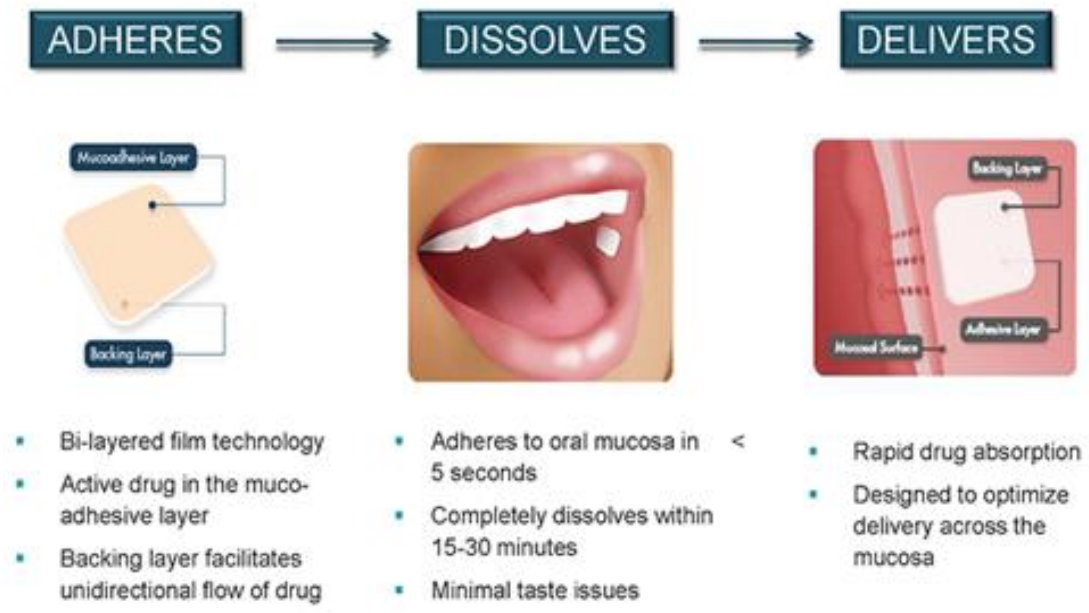

Figure 2: Fast dissolving buccal film

FDBF is prepared using hydrophilic polymer that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via buccal mucosa[22]. The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability[23]. This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. These films have potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also have been used for local action[24,25]. In recent application of fast dissolving buccal films it has been made possible that vaccines can be provided to infants in impoverished area against rotavirus[26].

Table 1: FDA approved Fast Dissolving Buccal Films[16,28,].

S.NO	Drug	Year	Use	Company
1.	Suboxone® (Buprenorphine and Naloxone	31/08/2010	Sublingual film indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.	Reckitt Benckiser Pharmaceuticals Inc.

2.	Zuplenz	January 2010	Prevention of postoperative, highly and moderately emetogenic cancer chemotherapy induced, and radiotherapy-induced nausea and vomiting.	PharmFilm®technology
3.	Ondansetron	23rd March 2010	Prevention and treatment of Chemotherapy and Radiotherapy Induced Nausea and Vomiting("CINV") in adults as well as children aged equal or above 6 months, and the prevention and treatment of Post Operative Nausea and Vomiting (PONV) in adults and children aged equal or above 4 years.	APR Applied Pharma Research s.a. ("APR") and Labtec GmbH ("Labtec")
4.	Zelapar	October 2005.	Treatment for Parkinson's disease.	Valeant Pharmaceuticals International Inc.

Special features of fast dissolving buccal films[1,22,29]:

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Quick dissolution
- Rapid release
- Leave minimal or no residue in the mouth
- Adaptable and amenable to existing processing and packaging machinery
- Cost effective

Advantage of FDBFs[1,3]:

- No need of water so, can be administered at anywhere, any time.
- Due to larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
- No risk of chocking so, ensure improved patient compliance.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing, mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.

- Beneficial in cases where an ultra rapid onset of action required such as motion sickness, acute pain, suede episodes of allergic attack , coughing& asthma.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- Precision in the administered dose is ensured from each strip of the film as compared liquid formulations.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism so, improved oral bioavailability of molecules that undergo first passeffect[30].
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
- Usually contain a medicament in taste masked form so, provide good mouth feel.

Disadvantages of FDBFs[1,3]:

- Hygroscopic in nature so it must be kept in dry places.
- Shows the fragile, effervesces granule property.
- Require special packaging for the products stability and safety.
- High dose cannot be incorporated.
- Dose uniformity is a technical challenge.

Formulation Consideration

The area of drug loaded should be between1-20cm2. The drug can be loaded up to a single dose of 30mg. All excipients used in the fast dissolving film should be generally regarded as safe (GRAS-listed) and authorized for use in oral strip. Formulation considerations have been reported as important factors which affect mechanical properties of the films[31].

Table 2: A typical composition of fast dissolving buccal film contains following[3]

S. No	Ingredients	Amount (w/w)
1	Drug	1-30%
2	Film forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Flavoring agent	q.s
7	Surfactant	q.s

8	Colors, Filler	q.s

Active pharmaceutical ingredient:

A distinctive composition of the film contains 1-30%w/w of the active pharmaceutical ingredient[3]. The drugs which are potent, show high first pass metabolism and patient non-compliant are best candidates for fast dissolving buccal films[22]. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OFDFs. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste. This is often termed as obscuration technique[32-37].

Ideal characteristic of a drug to be selected[1].

- Drug should have pleasant taste.
- Should have low dose up to 40 mg.
- Drugs with smaller and moderate molecular weight are preferable.
- Drug should have good stability and solubility in water as well as in saliva.
- Should be partially unionized at the pH of oral cavity.
- Should have the ability to permeate oral mucosal tissue.

Table 3: list of few drugs that can be incorporated in FDBFs[38].

API	Therapeutic category	Dose
Nicotine	Smoking Cessation	1.0–15.0 mg
Nitroglycerin	Vasodilator	0.3–0.6 mg
Zolmitriptan	Anti migraine	2.5 mg
Loratidine	Antihistaminic	5–10 mg
Desloratidine	Antihistaminic	5.0 mg
Diphenhydramine Hcl	Antihistaminic	25.0 mg
Loperamide	Antidiarroheal	2.0 mg
Famotidine	Antacid	10.0 mg
Flurazepam	Anxiolytic, Anticonvulsant	15.0–30.0 mg
Chlorpherinamine maleate	Antihistaminic	4.0 mg
Acrivastine	Antihistaminic	8.0 mg
Oxycodone	Opoid Analgesic	2.5–10.0 mg
Diclyclomine	Muscle Relaxant	25.0 mg
Omeprazole	Proton pump inhibitor	10.0–20.0 mg
Cetrizine	Antihistaminic	5.0–10.0 mg
Ketoprofen	Anti–inflammatory	12.5–25.0 mg

Azatidine	Antihistaminic	1.0 mg
Sumatriptan succinate	Antimigraine	35.0–70.0 mg
Chlorhexidine gluconate	Antimicrobial	0.12%

Film forming polymers:

Polymers are the most important ingredient of the oral fast dissolving film. Robustness of the film depends on the amount and type of polymer. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. Generally 45% w/w of polymer is used which is based on total weight of dry film. Mainly hydrophilic polymers are used in the oral strip as they rapidly disintegrate in the oral cavity as they come in contact with saliva. The polymers can be used alone or in combination to obtain the desired film properties. Pullulan is a natural polymer obtained from non animal origin and does not require chemical modification. About 50 to 80 percent w/w of pullulan can be replaced by starch in the production of fast dissolving films without loss of required properties of Pullulan to decrease overall cost of the product. Combination of microcrystalline cellulose and maltodextrin has also been used to formulate fast dissolving films. The physicochemical characteristic of the Polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the film[1,39,40].

Ideal properties of film forming polymer[3]:

- Should be non-toxic and non irritant.
- Must be hydrophilic.
- Should have excellent film forming capacity.
- Should have good wetting and spread ability property.
- Should be readily available & should not be very expensive.
- Should have low molecular weight.
- Should have sufficient shelf-life.
- Must be tasteless, colourless.
- Should not cause any secondary infection in oral mucosa.
- Should exhibit adequate peel, shear and tensile strengths.

Currently, both natural & synthetic polymers are used for the preparation of fast dissolving buccal film.

Table4: List of polymers used in preparation of fast dissolving buccal film[41].

S.No	Natural polymers	Synthetic polymers
1	Pullulan	Hydroxypropylmethyl cellulose
2	Starch, gelatine	polyvinyl pyrrolidone
3	Pectin	Polyvinyl alcohol
4	Sodium alginate	Carboxy methyl cellulose
5	Maltodextrin	Poly ethylene oxide
6	Polymerized rosin	Kollicoat
7	Lycoat NG 73	Hydroxypropyl cellulose
8	Xanthan	Hydroxyl ethyl cellulose

Plasticizers:

Plasticizer is a very important ingredient of oral strip formulation and typically used in the concentration of 0–20% w/w of dry polymer weight. Plasticizer helps to improve the flexibility and reduces the brittleness of the films. By addition of Plasticizers, tensile strength and elongation can be improved. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of film. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug[42-44].

Sweetening agent:

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose[33,45].

Saliva stimulating agent:

The rationale of employing saliva stimulating agents is to increase the rate of production of saliva that would be aid in the faster disintegration of the fast dissolving film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants, like- citric acid, malic acid, lactic acid, ascorbic acid etc. These are used alone or in combination between concentration 2 to 6%w/w of the film[29].

Surfactant:

Surfactant are used as a solubilizing or wetting or dispersing agent so that the film gets dissolve within seconds and release the active agent instantly. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal films. Several numbers of surfactants are used in oral strip. One of the most important surfactant is poloxamer 407[23,31].

Flavoring agents:

Preferably up to 10%w/w flavours are added in the OFDF formulations. The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavour quality which is observed in first few seconds after the product has been consumed and after taste of the formulation which lasts for at least about 10 min. The selection of flavour is dependent on the type of drug to be incorporated in the formulation. Flavouring agents can be selected from synthetic flavour oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavours can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavour oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavours. Apple, raspberry, cherry, pineapple are few examples of fruit essencetype[29].

Coloring agent:

FD & C approved colouring agent is incorporated in fast dissolving buccal film. Generally colouring agent is not exceeding concentration a level of 1%w/w in fast dissolving film. Mainly titanium dioxide is used in the formulation[3].

Table 5: Different type of excipients used for preparation of fast dissolving buccal film[3].

Plasticizers	Sweating agent	Saliva stimulating agent	Surfactant	Flavouring agent	Colouring agent
Glycerol	Sorbitol	Citric acid	Polaxamer 407	Peppermint oil	Titanium dioxide
Propylene glycol	Sucrose	Tatric acid	SLS	Cinnamon oil	Sunset yellow
Polyethylene glycol(400,200,600)	Cyclamate	Malic acid	Tweens	Menthol	
Dimethyl, Dicetyl& dibutyle Phthalate	Erosin red	Lactic acid	Spans	Lemon oil	

Triacetrin	Aspartame	Ascorbic acid	Benzalkonium chloride
Castor oil	Neotame		
Citrate ether	Saccharin		
Try ethyle citrate	Mannitol		
	Acesulfame-K		

Method of Preparation

One or combination of the following methods can be used for preparation of the fast dissolving buccal films.

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling

Solvent casting method:

In solvent casting method excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried[46,47].

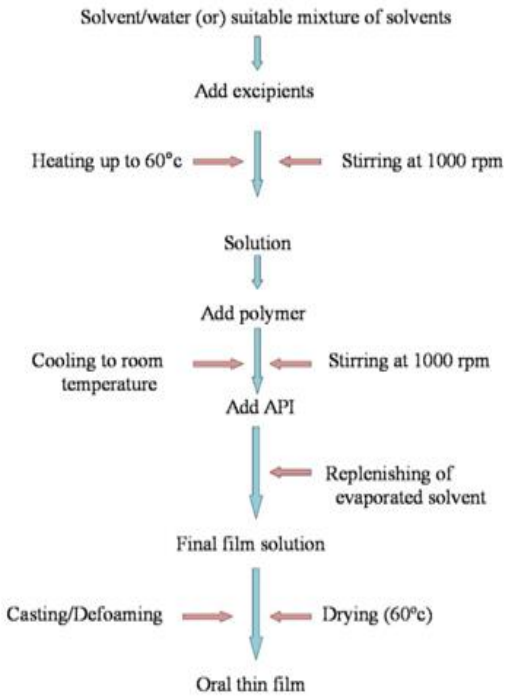

Figure 3: Preparation of film by solvent casting method

Advantages[3]:

- Great uniformity of thickness & great clarity than extrusion.
- Films have fine gloss & freedom from defect such a die lines.
- Films have more flexibility & better physical properties.

Disadvantage[3]:

- The polymer must be soluble in a volatile solvent or water.
- The stable solution with reasonable minimum solid content & viscosity should be formed.

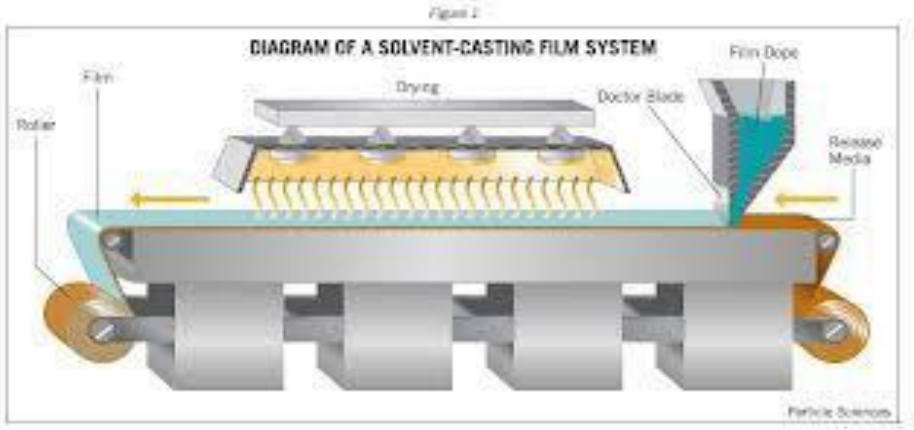

Figure 4: Solvent casting film system[48]

Semisolid casting method[49,50]:

Solution of water soluble film forming polymer is prepared

⇓

Resulting solution is added to a solution of acidinsoluble polymer

(*E.g.* cellulose acetate phthalate, cellulose acetate butyrate)

⇓

Appropriate amount of plasticizer is added to obtained gel mass

⇓

Gel mass is casted into the films or ribbons using heat controlled drums

⇓

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.

3) **Hot melt extrusion[40-42]:**

The drug is mixed with carriers in solid form

⇓

Extruder having heaters melts the mixture

⇩

Finally the melted mixture is shaped in films by the dies

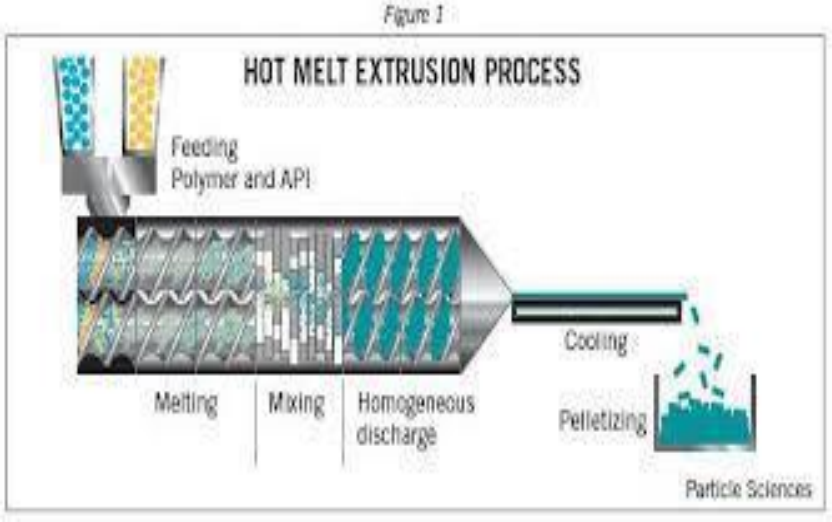

Figure 5: Hot melt extrusion process[48]

Advantages[3]:

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

Solid dispersion extrusion: The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers.

Drug is dissolved in a suitable liquid solvent

⇩

Incorporated solution into the melt of polyethylene glycol, below 70ºC

⇩

Solid dispersions are shaped into the films by means of dies[43,51]

Precautions while preparing sold dispersions[22]:

The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol and polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

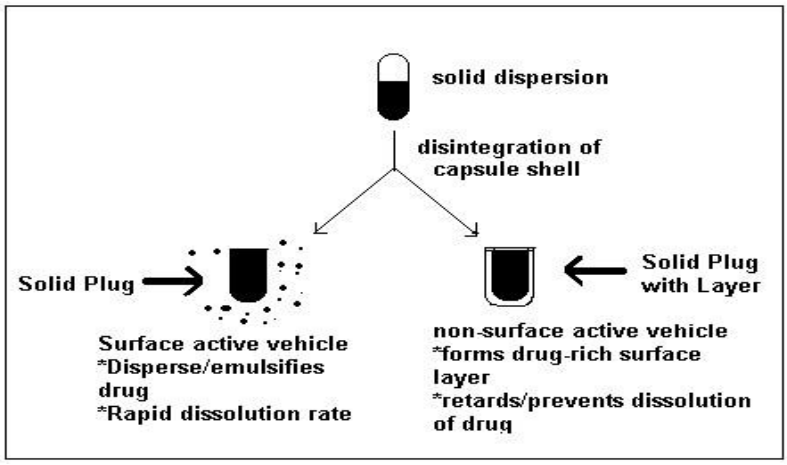

Figure 6. Solid dispersion extrusion method[48]

Rolling method:

A 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 into desired shape and size[3].

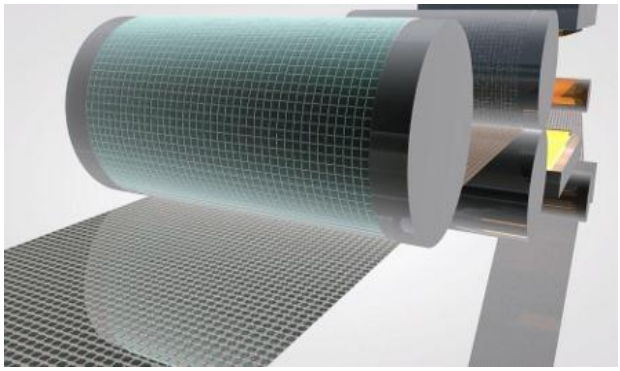

Figure 7: Rolling method[48]

Evaluation

- Drug - Excipient Compatibility Study
- Visual inspection
- Morphology study
- Weight variation
- Thickness
- Surface pH test
- Mechanical properties
  - Tensile strength
  - Percentage elongation
  - Folding endurance

- Young's modulus
- Dryness/ tack test

- Swelling test
- Percent moisture uptake
- Assay/drug content
- Taste evaluation
- Disintegration time
- ***In vitro*** release studies
- ***Ex vivo*** permeation studies
- Stability studies

Drug-excipient compatibility studies:

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients. In order to develop stable, safe and effective dosage forms the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances. During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form was considered. Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra Red Spectrum (FTIR), Differential scanning calorimeter (DSC), Thin layer chromatography and X Ray Diffraction (X-RD) can be used to assess possible drug excipient interaction. The film was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 400 and 4000 cm-1. The physical state of the drug in the formulation was characterized by using differential scanning calorimeter. The analysis was performed by heating 10 mg of sample on aluminium crimp pans at a rate of 100c/min in a nitrogen atmosphere (50ml, min-1)[22,52,53].

Visual inspection

Properties such as homogeneity, colour, transparency and surface of the oral films were evaluated for all the prepared oral films[54].

Morphology Study:

The surface morphology of oral strip is done by the scanning electron microscopy (SEM) at a definite magnification. The film sample was placed in the sample holder and the

photomicrographs were taken using tungsten filament as electron source and GSE detector at 65x and 350x magnification. It also helps in determination of the distribution of API[3,52].

Weight variation:

The weight variation of the oral film was done by weighting twenty films individually and the average weight was calculated. For the film to be accepted, the weights of not more than two films deviate from the average weight by no more than 7.5%and no film deviates by more than 15%[55].

Thickness:

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Callipers. For measurement of thickness, 5 films are randomly selected and thickness is measured at 5 different points of the film i.e. central and the four corners and means thickness is calculated. Maximum variation in the thickness of the films should be less than 5% and mean± S.D is calculated[1, 16,29].

Surface pH Measurement:

The surface pH oral dissolving film is determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to neutral as possible. A combined pH electrode is used for this purpose. Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation and mean ± S.D was calculated[17].

Measurement of mechanical properties of the film

Tensile strength: Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It also known as stress at rupture, is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below and is expressed in force per unit area.

Tensile strength =Load at breakage/ Strip thickness × Strip Width

To measure, the film formulations were cut into dumbbell-shaped specimens using appropriate punching dies with a width of 4 mm and a neck length of 15 mm. The film specimens were tested at a crosshead speed of 50 mm/min, with a load cell of 10–20 N[16,56].

Percent elongation:

The percent elongation also known as strain at rupture is calculated according to the following equation:

$$E\% = L - L0 / L0 \times 100$$

Where L0 is the initial length of the specimen and L is the length at the moment of rupture.

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases[16,56].

Folding endurance:

This gives an indication of brittleness of the film. Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value [57, 58]

Young's modulus:

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's modulus} = \frac{\text{Force at corresponding strain}}{\text{Cross sectional area}} \times \frac{1}{\text{Corresponding strain}}$$

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation[16].

Dryness test/tack tests:

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-to touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OFDF. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study[16].

Swelling property:

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a pre-weighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed. The degree of swelling was calculated using parameters[57,58]

$$\alpha = Wt - Wo/Wo$$

Wt is weight of film at time t, and Wo is weight of film at time zero.

Percent moisture uptake:

The test was carried out to check the physical stability of the film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 79.5 %. After 72 hours the films were removed, weighed and percentage moisture absorption was calculated by using the following formulae[59].

% Moisture uptake= Final weight-Initial weight /Initial weight ×100

Assay / Drug content:

A film of size 3 × 2 cm2 is cut and put in 30 ml of volumetric flask containing solvent. This is then shaken in a mechanical shaker for 1 hr to get a homogeneous solution and filtered. The drug is determined spectroscopically after appropriate dilution. Limit of content uniformity is 85-115%[3,60].

Taste evaluation:

Taste acceptability was measured by a taste panel(n=5) with 3 mg drug and subsequently film sample containing 3 mg drug held in mouth until disintegration, then spat out and the bitterness level was then recorded. The volunteers were asked to gargle with distilled water between the drug and film sample administration. The scale for the bitterness study was as follows[61]

+ = very bitter

++ = moderate to bitter

+++ = slightly bitter

++++ = tasteless/taste masked

+++++ = excellent taste masking

Disintegration time:

The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films strips. Disintegration time study was slightly modified to mimic the in-vitro and in-vivo conditions. The low volume of the liquid medium as well as the relatively low agitation employed during the test closely resemble the volume of saliva and the relatively static environment in the buccal cavity, respectively. For the study, film as per the dimensions (3 x 2 cm2)required for dose delivery were placed in a glass Petri dish containing 25 ml of distilled water at37°C, with swirling every 10 s. The disintegration time was recorded as the time at which the film starts to break ordisintegrate[16.61].

***In vitro* drug release study:**

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. Mainly paddle type dissolution apparatus is used for the dissolution test of oral strip because many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium. The USP dissolution apparatus was set at the temperature of 37±10C and stirring speed of 60 rpm. Each film was fixed on a glass slide with the help of adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessels containing 300 ml of phosphate buffer solution (pH 6.8).The Samples of 5 ml were withdrawn at the definite time intervals. The samples were filtered through a 0.45-µm membrane filter and analyzed spectrophotometrically. The same volume was replenished with fresh buffer, Sink conditions were maintained throughout the study. Cumulative drug release was calculated at various time intervals[3,59].

***Ex vivo* permeation study:**

Permeation studies are carried using the modified Franz diffusion cell by using porcine buccal mucosa. The mucosa is mounted between the donor and receptor compartment of Franz diffusion cell. The receptor compartment is filled with buffer and maintained at 37 °C ± 0.2 °C and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One previously weighed film is placed in intimate contact with the mucosal surface of the membrane that should be previously moistened with a few drops of simulated saliva. The donor compartment is filled with 1 ml of simulated saliva of pH 6.8. Samples are withdrawn at suitable interval, replacing the same amount with the fresh medium. The percentage of drug permeated is determined by measuring the absorbance by selected analytical method[62].

Stability studies:

Stability of a drug has been defined as the ability of a particular formulation in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Recommended storage conditions, re-test periods and shelf-lives are to be established. ICH specifies the length of study and storage conditions.

Long-term testing: - 25 0C ± 2 0C / 60 % RH ± 5% for 12 months.

Accelerated testing: - 40 0C ± 2 0C/ 75 % RH ± 5% for 6 months.

Stability measurement is done by storing the oral strip under controlled conditions of 25ºC/60%RH as well as 40°C/75% over a period of 12 months in stability chamber according to

the ICH guideline [48, 49].During storage period various evaluating parameter like, morphological properties, tensile strength, drug content and dissolution behaviour are checked[3,62].

Table 3: List of some marketed products available as fast dissolving film[3]:

Product	Manufacturer	API	Use
Listerine	Pfizer	Cool mint	Mouth fresheners
Triaminic	Novartis	Dextromethorphan HBr	Cough suppressants
Suppress®	InnoZen®, Inc	Menthol	Mouth fresheners
Chloraseptic	Prestige	Benzocaine Menthol	Local anesthetic
Gas-X	Novartis	Simethicone	Anti Flatuating
Theraflu	Novartis	Dextromethorphan HBr	Anti allergic
Setofilm	BioalliancePharma	Ondansetron	Prevention of Nausea and Vomiting
Zuplenz(R)	MonoSol Rx	Ondansetron	Prevention of Nausea and Vomiting
Donepezil Rapid film	Labtec	Donepezil	Alzheimer's disease
Sudafed PE	Wolters Kluwer Health Inc.	Phenyleprine	Relieving Congestion
Klonopin Wafer	Solvay Pharmaceuticals	Clonazepam	Treatment of anxiety

Impact in Industry

The first of this kind of oral strips were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Recently, Rotavirus vaccine is prepared in United States by Johns Hopkins University in 2006.Rotavirus vaccine is a room temperature stable quick-dissolving oral thin film delivery system for vaccines that will make vaccinations almost as simple as freshening your breath. Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip[16,29]. Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of $500 million in 2007and could reach $2 billion in 2012. Based on upward global growth trends of the past decade, the fast dissolving dosage market could produce revenues of $13billion by 2015[51,63].

CONCLUSION

Fast dissolving buccal films have gained popularity because of better patient compliance, rapid drug delivery and drug is directly absorbed into systemic circulation. Hence, fast dissolving buccal films can be a better option to optimize therapeutic efficacy of various active pharmaceutical ingredients which have extensive first pass metabolism. Offers several advantages over many dosage forms even over the fast disintegrating tablets, this explains the extensive research actively going on this technology.

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