Review Article

Orally dissolving strips: A new approach to oral drug delivery system

Rajni Bala, Pravin Pawar, Sushil Khanna, Sandeep Arora

Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India

Abstract

Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients with fear of choking. Over-the-counter films for pain management and motion sickness are commercialized in the US markets. Many companies are utilizing transdermal drug delivery technology to develop thin film formats. In the present review, recent advancements regarding fast dissolving buccal film formulation and their evaluation parameters are compiled.

Key words: Fast dissolving films, oral mucosa, permeability, solvent casting, solvent casting and disintegration

INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing. Fast dissolving drug delivery systems were first invented [Figures 1 and 2] in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane.[1] It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine.[2] Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration.[3] The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 μm layer.[4] These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but are extremely sensitive to environmental moisture.[5] An ideal fast dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a pleasant taste. Therefore, they are very suitable for pediatric and geriatric patients; bedridden patients; or patients suffering from dysphagia, Parkinson's disease, mucositis, or vomiting. This novel drug delivery system can also be beneficial for meeting current needs of the industry. Rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for therapeutic benefits. The first of the kind of oral strips (OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were

Address for correspondence:
Assoc. Prof. Rajni Bala,
Chitkara College of Pharmacy, Chitkara University,
Chandigarh-Patiala National Highway,
Rajpura, Patiala - 140 401, Punjab, India.
E-mail: rajni.bala@chitkara.edu.in

Access this article online

Quick Response Code:

Website: www.jpionline.org

DOI: 10.4103/2230-973X.114897

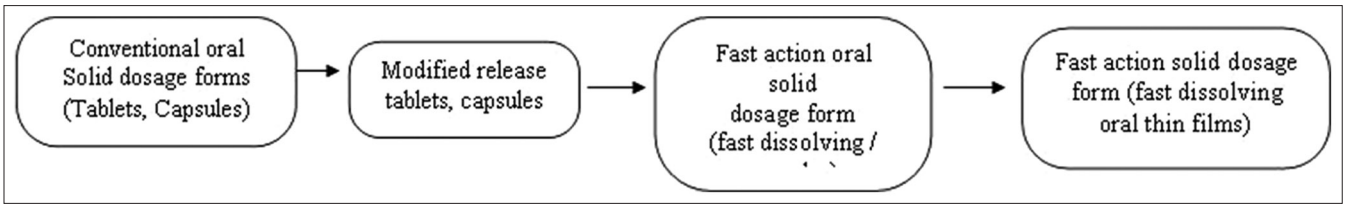

Figure 1: Stages in the development oral solid dosage forms

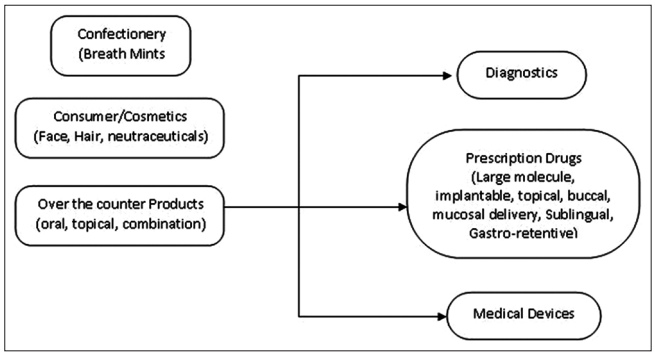

Figure 2: Evolution of oral thin films

used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films (OTF) which contained 7 benzocaine and were used for the treatment of sore throat. Formulation of fast dissolving buccal film involves material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and superdisintegrants. All the excipients used in the formulation of fast dissolving film should be approved for use in oral pharmaceutical dosage forms as per regulatory perspectives.

CLASSIFICATION OF FAST DISSOLVING TECHNOLOGY

For ease of description, fast dissolve technologies can be divided in to three broad groups.[6]

- Lyophilized systems.
- Compressed tablet-based systems.
- OTF.

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.

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 high density polyethylene (HDPE) bottles or blisters through to more specialists pack designs for product protection, for example, CIMA Labs, PackSolv. The speed of disintegration for fast dissolving tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or superdisintegrate 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 Fuisz Technology.[7] It uses the proprietary Shearform 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 inhouse development of line extension and generic fast dissolving dosage forms.

OTF

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable OTF or OS have evolved over the past few years from confection and oral care markets in the form of breath strips and become a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTF are a proven and accepted technology for systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs.

Table 1 gives the comparative account of three different fast dissolving technologies.

SPECIAL FEATURES OF FAST DISSOLVING FILMS[8]

- Film should be thin and elegant.
- Available in various size and shapes.
- Unobstructive.
- It should adhere to the oral cavity easily.
- Should processes fast disintegration without water.
- Rapid release.

ADVANTAGES OF FAST DISSOLVING FILMS[9]

- Convenient dosing.
- No water needed.
- No risk of chocking.
- Taste masking.
- Enhanced stability.
- Improved patient compliance.
- The drug enters the systemic circulation with reduced hepatic first pass effect.
- Site specific and local action.
- Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
- Dose accuracy in comparison to syrup.

DISADVANTAGE OF OS

- The disadvantage of OS is that high dose cannot be incorporated into the strip. The dose should be between 1-30 mg.
- There remain a number of technical limitations with use of film strips; the thickness while casting the film. Glass Petri plates cannot be used for casting.
- The other technical challenge with these dosage forms is achieving dose uniformity.
- Packaging of films requires special equipments and it is difficult to pack.

IDEAL CHARACTERISTICS OF A SUITABLE DRUG CANDIDATE[10]

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.

CLASSIFICATION OF OTF

There are three subtypes of oral fast dissolving films:[11]

- Flash release.
- Mucoadhesive melt-away wafer.
- Mucoadhesive sustained release wafers.

Table 2 lists three types of oral fast dissolving films along with their properties.

STANDARD COMPOSITION OF ORAL FAST DISSOLVING STRIP[13

Oral dissolving film is a thin film with an area of 1-20 cm^2 (depends on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30 mg. Formulation considerations (plasticizers, etc.) have been reported as important factors affecting mechanical properties of the films. Table 3 lists

Table 1: Classification of fast dissolving technologies

Properties	Lyophilized system	Compressed tablet based system	Oral thin films
Composition	Solution or suspension of drug with excipients	Active pharmaceutical ingredient with superdisintegrants	Hydrophilic polymers with drug and other excipients
Technology used	Lyophilization	Direct compression	Solvent casting, hot melt extrusion
Characteristics	High porosity which allow rapid water or saliva penetration and disintegration	Different levels of hardness and friability these result in varying disintegration and packaging needs	Large surface area leads to rapid disintegration
Packaging	Blister pack	High density polyethylene bottles	Blister cards with multiunits

Table 2: Types of oral thin films with their properties[12]

Properties	Flash release	Mucoadhesive melt-away wafers	Mucodhesive sustained released wafers
Area (cm^2)	2-8	2-7	2-4
Thickness (μm)	20-70	50-500	50-250
Structure	Single layer	Single or multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low/nonsoluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspension and/or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival, (other region in the oral cavity)
Dissolution	60 s	In few minutes forming gel	Maximum 8-10 h
Site of action	Systemic or local	Systemic or local	Systemic or local

the standard composition of fast dissolving strip along with the various ingredients used in the formulation of fast dissolving strips.

FILM FORMING POLYMERS

A variety of polymers are available for preparation of fast dissolving oral films.[14] The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of film forming polymers, is one of the most important and critical parameter for the successful development of film formulation. The polymers can be used alone or in combination to provide desired film properties. The polymers used in oral film formulation should be:

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spread ability property.
- Should have sufficient peel, shear, and tensile strength.
- Readily available.
- Inexpensive.
- Sufficient shelf life.
- Should not aid in causing secondary infections in oral mucosa.

Presently, both natural and synthetic polymers are used for the preparation of orally dissolving films. Table 4 represent various natural and synthetic polymers used for preparation of fast dissolving films. Tables 5 and 6 represent the quality parameters of natural and synthetic polymers, respectively.

APPROACHES USED FOR THE FORMULATION OF FAST DISSOLVING FILMS[18]

Conventional approaches

- Solvent casting method
- Hot-melt extrusion
- Semisolid casting
- Solid dispersion extrusion
- Rolling.

Solvent casting method

In this method, firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

Hot-melt extrusion

In hot melt extrusion method, the initial mass is formed with the help of carriers. To form initial mass, the drug is mixed with carriers and a solid mass is obtained and dried. Then dried granular material is introduced into the extruder. The extruder is divided into four zones having following degrees of temperature: 800 (zone 1), 1150 (zone 2), 1000 (zone 3), and 650°C (zone 4). The speed of extruder screw speed should be set at 15 rpm in order to process the granules inside the barrel of extruder for

Table 3: Standard composition of fast dissolving films[17]

Ingredients	Amount	Examples
Drug	5-30%w/w	Antiallergic, antiemetic, antiepileptic, antimigrant
Water soluble polymer	45%w/w	HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, polyvinylpyrollidone PVP K-90, pectin, gelatin, sodium, alginate, hdroxypropylcellulose, polyvinyl alcohol, maltodextrins
Plastisizers	0-20%w/w	Glycerol, dibutyl pthallate, polyethylene glycol, etc.,
Surfactants	q.s.	Sodium lauryl sulfate, benzalkonium chloride, Tween, etc.,
Sweetening agents	3-6%w/w	Saccharin, cyclamate, and aspartame
Saliva stimulating agents	2-6%w/w	Citric acid, malic acid, lactic acid, and ascorbic acid
Fillers, colors, flavors	q.s.	FD and C colors, US FDA approved flavors

HPMC: Hydroxypropyl methylcellulose, US FDA: United states food and drug administration, q.s.: Quantum satis

Table 4: Polymers used in the formulation fast dissolving film

Polymer	Examples
Natural polymer	Pullulan, starch, gelatin, pectin, sodium alginate, maltodextrins, polymerized rosin
Synthetic polymer	Hydroxypropyl methylcellulose, sodium carboxymethylcellulose, polyethylene oxide, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, ethyl cellulose

Table 5: Various types of synthetic polymers and their properties[15]

Polymer	Water solubility	pH	Moisture (% loss on drying)	Molecular weight (kDa)
Hrdroxypropyl cellulose	Soluble in water	5-8	1.6	50,000-1,250,000
Hrdroxypropyl methylcellulose	Soluble in cold water	5-8	1.6	50,000-1,250,000
Sodium carboxymethylcellulose	Viscous colloidal solution	6-8	10	90,000-700,000
Polyvinyl alcohol	Readily soluble	5-8	5	20,000-200,000
Polyethylene oxide	Readily soluble	8-10	<1	Variable
Kollicoat	>50% in water	6-7		About 45,000

Table 6: Various types of natural polymers and their properties[16]

Polymer	Water solubility	pH	Moisture (% loss on drying)	Molecular weight (kDa)
Pullulan	Readily soluble	5-7	6	100-250
Sodium alginate	Slowly soluble, forming viscous solution	7.2	15	
Pectin	Soluble in water	6-7.2	10	30,000-100,000
Gelatin	Swell in water and soften	3.8-6.0	10	15,000-250,000
Maltodextrine	Swell in water and soften	4-7	6	Variable

approximately 3-4 min so that mass should be properly melted. The extrudate (T = 650°C) obtained is then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion: Fewer operation units, minimum product wastage, possibility to scale up, an anhydrous process, absence of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix, and better content uniformity.[19]

Semi-solid casting

This method is mostly preferred when film ingredient involves acid insoluble polymer. In this firstly, the water soluble polymers are dissolved in water. The obtained solution is added to the acid insoluble polymer solution which is separately formed. Both the solutions are mixed properly. After mixing the two solutions, appropriate amount of plasticizer is added to the obtained final solution so that gel's mass can be obtained. At last, the gel mass is casted onto the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015-0.05". The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Examples of acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate.

Solid dispersion extrusion

Method involves the solid dispersion of drug incorporated in melted polymer solution so that drug can be loaded. The drug is dissolved in suitable liquid solvent and obtained solution is added to the melt of suitable polymer, obtainable below 70°C without removing the liquid solvent to obtain the solid dispersion. Finally the obtained solid dispersions are shaped into films by means of dyes.

Rolling method

In rolling method, both the drug solution and film forming polymer solution are mixed thoroughly and the resultant solution or suspension is subjected to the roller. The solution or suspension should have specific rheological consideration. The film is dried on rollers and cut into desired shapes and sizes.

Patented approaches[20]

XGel

XGel™ film provides unique product benefits for healthcare and pharmaceutical products: It is nonanimal derived, approved on religious grounds, and is suitable for vegetarians; the film is genetically modified organism (GMO) free and continuous production processing provides an economic and competitive manufacturing platform. XGel™ film can be taste masked, colored, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGel™ film systems can be made to encapsulate any oral dosage form and can be soluble in either cold or hot water. XGel™ film is comprised of a range of different water soluble polymers, specifically optimized for the intended use.

Soluleaves

This technology is used to produce a range of oral delivery films that can incorporate active ingredients, colors, and flavors. Soluleaves™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients, and flavors. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses, this method of administration is especially useful for pediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal, and pain therapeutic areas as well as delivering nutritional products. Soluleaves™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 min.

Wafertab

Wafertab™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The Wafertab™ filmstrip can be flavored for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a premanufactured XGel™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The Wafertab™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. Wafertab™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty in swallowing.

Foamburst

It is a special variant of the Soluleaves™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. Foamburst™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavors.

Micap

Micap plc signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress

water soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4 billion global market for smoking cessation products (SCPs).

EVALUATION PARAMETERS

Thickness

The thickness of film is measured by micrometer screw gauge or calibrated digital Vernier Calipers. The thickness of film should be in range 5-200 μm.[21] The thickness should be evaluated at five different locations (four corners and one at centre) and it is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film.

Dryness/tack test

In all there have been eight stages identified for film drying and these 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. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with strip. Instruments are also available for this study.[22]

Tensile strength

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

Tensile strength = Load at failure × 100/Strip thickness × Strip width

Percent elongation

When stress is applied on a film (2 × 2 cm^2) sample it gets stretched, this is referred to strain. Strain is basically the deformation of strip before it gets broken due to stress. It is measured by using hounsfield universal testing machine.[23] Generally elongation of strip increases as the plasticizer content increases. It is calculated by the formula:

% Elongation = Increase in length of strip × 100/Initial length of strip

Tear resistance

Tear resistance is the resistance which a film offers when some load or force is applied on the film specimen. The load mainly applied is of very low rate 51 mm/min. The unit of tear resistance is Newton or pounds-force. In other words it is the maximum force required to tear the specimen.[24]

Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of strip.[25] It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's modulus = Slope × 100/Strip thickness × Cross head speed

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

Folding endurance

Folding endurance gives the brittleness of a film. The method followed to determine endurance value is that the film specimen (2 × 2 cm^2) are repeatedly folded at the same place until it breaks or a visible crack is observed. The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value.[26]

In vitro disintegration test

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30 s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time.[27] In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates.[28]

In vitro dissolution studies

Dissolution is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature, and solvent concentration. The standard basket or paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing. The selection of dissolution medium will essentially depend as per the sink conditions and highest dose of API. The temperature of dissolution medium should be maintained at 37 ± 0.5°C and rpm at 50. When the paddle apparatus is employed, it has a disadvantage that oral films have a tendency to float over the dissolution medium. Mashru *et al.*,[29] used stainless steel wire mesh with sieve opening of approximately 700 μm used to dip salbutamol fast dissolving film inside the dissolution medium.[30,31]

Drug content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%.[32]

Organoleptic test

The desired organoleptic properties a fast dissolving formulation should have are color, flavor, and taste. As the formulation will disintegrate in the oral cavity so it should provide acceptable organoleptic palatable characteristics. Color makes a formulation acceptable among the patients and moreover oral films should have attractive color as they are administered to children. Hence, color of formulation should be uniform and attractive. Color can be evaluated by visual inspection. The other organoleptic property is the odor. The flavor used in the formulation should provide good odor to the formulation. The odor of the polymer, drug, and any

other excipient should be masked with use of flavoring agent. Taste is also an important factor which has to be evaluated. To evaluate the taste, special human taste panels are used. Experiments using electronic tongue measurements have also been reported to distinguish between sweetness levels in taste masking formulation.[33] Electronic tongue technique works on the principle of potentiometric titration method. In this liquid samples can be analyzed directly, whereas solid samples need to be dissolved in a suitable solvent before analyzing. In this method, reference electrode and sensors are dipped in a beaker containing a test solution for 120 s and a potentiometric difference between each sensor and a reference electrode is measured and recorded by the E-tongue software.[34,35]

Surface pH test

The surface pH of fast dissolving strip can cause side effects to the oral mucosa, so it is necessary to evaluate the surface pH of film. The surface pH of film should be 7 or close to neutral. For this purpose, a combined pH electrode can be used. With the help of water, OS was made slightly wet and the pH was measured by bringing electrode in contact with surface of oral film. This study should be done on at least six films of each formulation and their mean ± SD can be calculated.[36] In another method to determine the surface pH, the films are placed on the 1.5%w/v agar gel and then the pH paper are placed on the film, change in color of pH paper gives surface pH of the film.

Contact angle

Contact angle measurement predicts the wetting behavior, disintegration time, and dissolution of oral film. These measurements are performed with help of goniometer (AB Lorentzen and Wettre, Germany) and the measurements should be done at room temperature. The water used to determine contact angle should be double distilled water.[37] A drop of double distilled water is placed on the surface of dry film. Images of water droplet are recorded within 10 s of deposition by means of digital camera. Digital pictures can be analyzed by imageJ 1.28v software (NIH, USA) for angle determination.

Transparency

To determine transparency of oral film, a simple ultraviolet (UV) spectrophotometer can be used. The film specimen is placed on the internal side of spectrophotometer cell. The transparency of films is calculated as follows:

$$\text{Transparency} = (\log T_{600})/b = -€c$$

Where T_{600} is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.[38]

Scanning electron microscopy

To study the surface morphology of film between different excipients and drug scanning, electron microscopy can be used. The film sample should be placed in sample holder and at ×1000 magnification, various photomicrographs can be taken using tungsten filament as an electron source.[39]

Permeation studies

Even though permeability of oral mucosa is 4-1000 times greater than that of skin, permeation studies should be carried out. To study the permeability, modified Franz diffusion cell can be used along with porcine buccal mucosa. The Franz diffusion cell consists of a donor and a receptor compartment. In between the two compartments, mucosa is mounted and the size of the mucosa should be of the same size as that of the head of receptor compartment. The receptor compartment is filled with buffer and maintained at 37 ± 0.2°C and to maintain thermodynamics a magnetic bead stirring at a speed of 50 rpm is used. A film specimen moistened with a few drops of simulated saliva should be kept in contact with mucosal surface. The donor compartment should consist of 1 ml simulated saliva fluid of pH 6.8. At particular interval, samples are withdrawn and replaced by same amount of fresh medium. By suitable analytical method, percentage of drug permeated can be determined.[40]

Percentage moisture loss

To determine percentage moisture loss films of area 2 × 2 cm^2 are cut and weighed accurately on an electronic balance. After weighing, the films were kept in desiccators containing fused anhydrous calcium chloride. The films should be kept for 72 h in the desiccator. After 72 h, they are taken out and again weighed and the percentage moisture loss of films was measured by using the formula:

Percent moisture loss = (Initial weight − Final weight)/Initial weight × 100

The percentage moisture loss studies are done to determine physical stability and integrity of the film.[41]

Determination of % yield of buccal patches[42]

Percentage yield of buccal patches can be calculated by the following formula:

% yield = Mass of the buccal patches obtained/Total weight of drug and polymer × 100

Stability study

Stability study should be carried out according to the International Conference on Harmonization (ICH) guidelines. The prepared formulation was wrapped in a special way. Firstly, it was wrapped in a butter paper then above it an aluminum foil was wrapped and the packing should be placed in an aluminum pouch and make it heat sealed. The storage conditions at which formulations are kept should be 30°C/60% relative humidity (RH) and 40°C/75% RH. After 3 months, the films were evaluated for drug content, disintegration time, and physical appearance observation.[43]

Storage and packaging of OS

Fast dissolving strips can be packed using single pouches, blister card with multiple units, multiple-unit dispenser, and continuous roll dispenser. There are certain patented packaging systems for fast dissolving films such as Rapidcard by Labtec and Core-peel by Amcor flexible. The rapid card is of same size as a credit card

and holds three films on each side. Every dose can be taken out individually.[44]

APPLICATIONS OF OTF IN DRUG DELIVERY SYSTEMS

- Oral mucosal delivery via sublingual, buccal, and mucosal routes by use of oral thin film could become preferential delivery method for therapies requiring rapid drug absorption, including those used to manage pain, allergies, sleep, and central nervous system disorders.[45]
- Topical applications: The use of dissolvable films may be feasible in delivery of active agents such as analgesic or antimicrobial agents in the wound care and other applications.
- Gastrorententive delivery system: Dissolvable films are being considered in the dosage form for which water soluble and poorly soluble molecules of various molecular weight are contained in film formate. Dissolution of film could be triggered by pH or enzyme secretion of gastrointestinal tract (GIT) and could potentially be used for treatment of gastrointestinal disorder.
- Diagnostic devices: Dissolvable films may be loaded with sensitive reagent to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

Clinical and regulatory aspects

In the US Food and Drug Administration (US FDA), if the product is bioequivalent to that of the existing oral product the drug, an Abbreviated New Drug Application (ANDA) route is followed. There is no clinical studies associated on this generic approval processes (section 505 (j) of the Food, Drug, and Cosmetic Act). The example of such case would be a comparative bioequivalence between an orally disintegrating tablet (ODT) formulation and orally dissolving film (ODF) product. However, developed oral film product may exhibit different pharmacokinetic profile compared to the existing marketed product. The ODF is categorized as 'new dosage form' and the section 505 (b) (2) approval process needs to be followed. In this case a new clinical study would be required. The advantage of new clinical study is that it would award 3 years of marketing exclusivity to the product. In Europe, marketing authorization approval is essential as per the European Medicine Evaluation Agency guidelines. Either of the two modes, that is, decentralization procedure or mutual recognition process can be adopted. The Ministry of Health, Labor and Welfare is responsible for product approval in Japan.[46] Many of the regulatory agencies lay special emphasis on the taste and palatability aspects, especially if the product is intended to target the pediatric population. Oral mucosa irritation testing is carried out in both animal models and humans. In case of animal studies, the most appropriate model is hamster cheek pouch, it is a reliable model for predicting irritation criteria prior to testing in humans. In clinical trials, the clinical endpoint is significant. Primary and secondary outcome measures are to be noted. The objective is to demonstrate the superiority and advantage of newly developed OS as against the existing traditional conventional dosage forms. The ICH has laid guidance on product development. According to the ICH Q8 guideline on pharmaceutical development, companies may choose either an empirical approach or a more systematic approach towards product development. This document is an integral part of regulatory document for USA, EU, and Japan. Clinical study protocol should define a clear objective; different problems should be tackled in separate well-defined studies. The planned study should have sufficient resolution power to pick up critical adverse health effect (including supporting rationale). Calculation of the study size(s) is dependent on type of study (e.g., effects on soft tissues and/or on hard tissues).

Table 7: Recent patents on fast dissolving strips/films[48-58]

Title	Patent number	Inventor	Issued	Assignee
Water soluble film for oral administration with instant wettability	5,948,430	Zerbe *et al*.	Sep 7, 1999	LTS Lohman Therapie-systeme GmbH
Bioerodable films for delivery of pharmaceutical compounds to mucosal surface	6159498	Tapolsky *et al*.	Dec 12, 2000	-
Fast dissolving orally consumable films containing sweetner	2003/0211136	Lori *et al*.	Nov 13, 2003	Warner Lambert company LLC
Fast dissolving films for oral administration of drug	2004/0208931	Friend *et al*.	Oct 21, 2004	William Squire, Esq.
Fast dissolving consumable films containing a modified starch for improved heat and moisture resistance	2004/0247648	David *et al*.	Dec 9, 2004	Pfizer, Inc.
Fast dissolving orally consumable films	7,025,983	Leung *et al*.	April 11, 2006	Warner Lambert company LLC
Dissolving thin film xanthone supplement	7182964B2	Kupper *et al*.	Feb 27, 2007	-
Thin film strips	7,241,411	Berry *et al*.	Jul 10, 2007	Acupac packaging, Inc.
Disintegratable films for diagnostic devices	7,470,397	Meathrel *et al*.	Dec 30, 2008	Adhesive research, Inc.
Pharmaceutical carrier devices suitable for delivery of pharmaceutical compounds to mucosal surface	7579019B2	Tapolsky *et al*.	Aug 25, 2009	-
Film comprising nitroglycerin	20100215774	Maibach and Todd	Aug. 26, 2010	-
Dissolvable tobacco film strips and method of making the same	7946296B2	Wern *et al*.	May 24, 2011	-

LTS: Lohman therapie-systeme

Table 8: List of some marketed products available as fast dissolving strips

Product	API	Manufacturer	Use
Listerine®	Cool mint	Pfizer, Inc.	Mouth ulcer
Benadryl	Diphenyhydramine HCL	Pfizer	Antiallergic
Suppress®	Menthol	InnoZen®, Inc.	Cough suppressant
Klonopin wafers	Clonazepam	Solvay pharmaceuticals	Antianxiety
Theraflu	Dextormethorphan	Novartis	Antiallergic
Orajel	Menthol/pectin	Del	Mouth freshner
Gas-X	Simethicone	Novartis	Antiflatuating
Chloraseptic	Benzocain/menthol	Prestige	Sore throat
Sudafed PE	Phenylepinephrine	Wolters Kluwer Health, Inc.	Congestion
Triaminic	Diphenhydramine	Novartis	Antiallergic

API: Active pharmaceutical ingredient, PE: Polyethylene

Specification of all endpoints should be determined. Description of usage pattern(s) (single/multiple application) is to be included. Follow-up during a relevant period after treatment (e.g., single application with follow-up periods of 1, 3, 6, and 12 months; multiple applications with longer follow-up, etc.) should be mentioned. There should be an inclusion of confounders and effect modifiers along with description of subject source(s), selection criteria, and methodology with appropriate analytical details. Due to the modified drug dissolution characteristics, clinical effect and drug bioavailability may be very different than conventional dosage forms. Being a noninvasive delivery system, it bypasses the first-pass effect to a large extent which can alter the clinical profile. The safety profiles can be improved as toxic metabolites that result from hepatic metabolism can be lowered in the case of drug being majorly absorbed from buccal mucosa. Another aspect is its faster onset of action which leads to rapid signs of clinical end-point. Since every strip ideally contains precise amounts of the drug and the dosage form is independent of physiological variability of gastrointestinal tract, the intersubject variability in clinical response is fairly reduced. On the other hand, the absorption of drugs through oral mucosa would be much rapid than the conventional counterparts that have to disintegrate and then solubilize the active, there is a possibility of dose dumping phenomena. Its clinical implications need to be studied. Due to this rapid response characteristic, the safety aspects of dosage form should be closely monitored.[47]

PATENT REVIEW ON MOUTH DISSOLVING STRIPS

Table 7 lists some of the recent patents on fast dissolving strips.

MARKETED PRODUCTS OF ORAL FILMS

A review of marketed products and patents of fast dissolving films are compiled in the Table 8.

CONCLUSION

Fast dissolving films are the novel approach in oral drug delivery systems. It promises patient compliance especially in case of pediatrics and geriatrics patients. They can also be used when quick action is required. They possess many advantages over conventional dosage form and can also be used in cases of dysphagia, Parkinson's disease, mucositis, or vomiting.

REFERENCES

1. Siddiqui MD, Garg G, Sharma P. A short review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and their Patents". Adv Biol Res 2011;5:291-303.
2. Galey WR, Lonsdale HK, Nacht S. The *in vitro* permeability of skin and buccal mucosa to selected drugs and tritiated water. J Invest Dermatol 1976;67:713-7.
3. Malke M, Shidhaye S, KadamVJ. Formulation and evaluation of oxcarbazepine fast dissolve tablets. Indian J Pharm Sci 2007;69:211-4.
4. Mishra R, Amin A. Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as a film forming agent. Indian J Pharm Educ Res 2011;45:71-7.
5. Mahajan A, Chabra N, Aggarwal G. Formulation and characterization of fast dissolving buccal films: A review. Sch Res Libr Der Pharm Lett 2011;3:152-65.
6. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. Int J Chem Tech Res 2010;2:576-83.
7. Chemical Market Reporter. Fuisz sign deal for drug delivery. Chem Mark Report 1998;253:17.
8. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Int J Pharm Sci Rev Res 2011;9:50-6.
9. Bhura N, Sanghivi K, Patel U, Parmar B. A review on fast dissolving film. Int J Res Bio Sci 2012;3:66-9.
10. Fulzele SV, Satturwar PM, Dorle AK. Polymerized rosin: Novel film forming polymer for drug delivery. Int J Pharm 2002;249:175-84.
11. Barnhart SD, Sloboda MS. The future of dissolvable films. Drug Deliv Technol 2007;7:34-7.
12. Hariharn M, Bogue A. Orally dissolving film strips (ODFS): The final evolution of orally dissolving dosage forms. Drug Deliv Technol 2009;9:24-9.
13. Nagar P, Chauhan I, Yasir M. Insight into polymers: Film formers in mouth dissolving films. Drug Invent Today 2011;3:280-9.
14. Dixit RP, Puthli SP, Oral strip technology: Overview and future potential. J Control Release 2009;139:94-107.
15. Saurabh R, Malviya R, Sharma PK. Trends in buccal film: Formulation characteristics, recent studies and patents. Eur J Appl Sci 2011;3:93-101.
16. Gauri S, Kumar G. Fast dissolving drug delivery and its technologies. Pharm Innov 2012;1:34-9.

17. Deshmane SV, Joshi UM, Channwar MA, Biyani KR, Chandewar AV. Design and characterization of carbopol-HPMC-ethyl cellulose based buccal compact containing propranolol HCl. Indian J Pharm Educ Res 2010;44:67-78.
18. Khairnar A, Jain P, Bhaviskar D, Jain D. Development of mucoadhesive buccal patches containing aceclofenac: *In vitro* evaluation. Int J Pharm Sci 2009;1:91-5.
19. Shinde AJ, Garala KC, More HN. Development and characterization of transdermal therapeutics system of tramadol hydrochloride. Asian J Pharm 2008;2:265-9.
20. Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: Swelling, mechanical, and bioadhesive properties. J Pharm Pharm Sci 1999;2:53-61.
21. Sani S, Nanda A, Hooda M, Komal. Fast dissolving films (FDF): Innovative drug delivery system. Pharmacologyonline 2011;2:919-28.
22. Okabe H, Suzuki E, Sugiura Y, Yanagimoto K, Tkanashi Y, Hoshi M, *et al*. Development of an easily swallowed film formulation. Int J Pharm 2008;355:62-6.
23. Borsadia SB, O'Halloran D, Osborne JL. Quick dissolving films-a novel approach to drug delivery. Drug Deliv Technol 2003;3:63-7.
24. Ali S, Quadir A. High molecular weight povidone polymer-based films for fast-dissolving drug delivery applications. Drug Deliv Technol 2007;7:36-43.
25. Mashru RC, Sutariya VB, Sankalia MG, Parikh PP. Development and evaluation of fast dissolving films of salbutamol sulphate Drug Dev Ind Pharm 2005;31:25
26. Kalyan S, Bansal S. Recent trends in the development of oral dissolving film. Int J PharmTech Res 2012;4:725-33.
27. Dahiya M, Saha S, Sahiwala AF. A review on mouth dissolving films. Curr Drug Deliv 2009;6:469-76.
28. Vishwkarma DK, Tripathi AK, Yogesh P, Maddheshiyab B. Review article on mouth dissolving film. J Glob Pharm Technol 2011;3:1-8.
29. Mahajan A. Formulation and evaluation of fast dissolving buccal films of sertraline. Int J Drug Dev Res 2012;4:220-6.
30. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS Pharm Sci Tech 2008;9:349-56.
31. Rathi V, Senthil V, Kammili L, Hans R. A brief review on oral film technology. Int J Res Ayurveda Pharm 2011;2:1138-47.
32. Sharma R, Parikh RK, Gohel MC, Soniwala MM. Development of taste masked film of valdecoxib for oral use. Indian J Pharm Sci 2007;69:320-3.
33. El-Setouhy DA, Abd El-Malak NS. Formulation of a novel tianeptine sodium orodispersible films. AAPS PharmSciTech 2010;11:1018-25.
34. Tomar A, Sharma K, Chauhan NS, Mittal A, Bajaj U. Formulation and evaluation dissolving oral film of dicyclomine as potential route of buccal delivery. Int J Drug Dev Res 2012;4:408-17.
35. Kumar SV, Gavaskar B, Sharan G, Rao YM. Overview on fast dissolving films. Int J Pharm Pharm Sci 2010;2:29-33.
36. Parmar D, Patel U, Bhimni B, Tripathi A, Daslaniya D, Patel G. Orally fast dissolving films as dominant dosage form for quick release. Int J Pharm Res Bio Sci 2012;1:27-41.
37. Meathrel B, Moritz C. Dissolvable films and their potential in IVDs. IVD Technol 2007;13:53-8.
38. Corniellio C. Quick dissolving strips: From concept to commercialization. Drug Deliv Technol 2006;6:68-71.
39. World Health Organization Working document 2008, QAS/08.257.
40. Patel AR, Prajapati DS, Raval JA. Fast dissolving films (FDFs) as a newer venture in fast dissolving dosage forms. Int J Drug Dev Res 2010;2:232-46.
41. Kulkarni AS, Deokule HA, Mane MS, Gadhe DM. Exploration of different polymers for use in the formulation of oral fast dissolving strips. J Curr Pharm Res 2010;2:33-5.
42. Peppas NA, Buri PA. Surface, interfacial, molecular aspects of polymer bioadhesion to soft tissues. J Control Release 1985;2:257-75.
43. Sakellariou P, Rowe RC. Interactions in cellulose derivative films for oral drug delivery. Prog Polym Sci 1995;20:889-942.
44. Browhn GL. Formation of film from polymer dispersions. J Polym Sci 1956;22:423-34.
45. Brown D. Orally disintegrating tablets-taste over speed. Drug Deliv Technol 2003;3:58-61.
46. Zerbe H, Guo J. Water soluble films for oral administration with instant wettability. US Patent 5948430, Sep 7, 1999.
47. Tapolsky G, Osborne D. Bioerodable film for delivery of pharmaceutical compounds to mucosal surface. US Patent 6159498, Dec 12, 2000.
48. Lori D. Fast dissolving orally consumable films containing sweetners. US Patent 2003/0211136 Nov 13, 2003.
49. Friend DR, Levine AW, Ziegler KL, Manna E. Fast dissolving films for oral administration of drugs. US Patent 2004/0208931 A1, 2004.
50. Fadden DJ, Kulkarni N, Sorg AF. Fast dissolving oral consumable film containing modified starch for improved heat and moisture resistance. US Patent 2004/0247648 May 3, 2003.
51. Leung SS, Leone RS, Kumar LD, Kulkarni N, Sorg AF. Fast dissolving orally consumable film. US Patent 7025983, Apr 11, 2006.
52. Kupper R, Smothers M, Dissolving thin film xanthone supplement, US Patent 7182964 B2, Feb, 27, 2007.
53. Berry CJ, Clauser W. Thin film strips US Patent 7241411B2 July 10, 2007.
54. Meathrel WG, Meyer NA, Barnhart SD, Moritz CM, Full AP, Newsom SR, *et al*. Disintegrable films for diagnostic devices. US Patent 7,470,497 Dec 30, 2008.
55. Tapolsky G, Osborne D. Pharmaceutical carrier device sutiable for delivery of pharmaceutical compounds to mucosal surfaces. US Patent 7579019B2 Aug 25, 2009.
56. Maibach T. Film comprising nitroglycerin. US Patent 20100215774 Aug 26, 2010.
57. Wrenn S, Marun M. Dissolvable tobacco film strips and method of making the same. US Patent 7946296B2 May 24, 2011.
58. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. Drug Dev Ind Pharm 2004;30:429-48.

How to cite this article: Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharma Investig 2013;3:67-76.
Source of Support: Nil. **Conflict of Interest:** None declared.