



An Advanced Oral Solid Dosage Form: Oral Dissolving Film

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Abstract

Oral dissolving film has become very favoured and advanced form of oral solid dosage form due to highest acceptability of patients. The oral dissolving film fulfils all the needs of patients that's why it is the first priority of consumers over the other solid dosage forms. Improved patient compliance is a primary benefit of the fast dissolving drug delivery systems. Fast dissolving films are gaining interest as an alternative to other solid dosage form to definitely eliminate patients fear of choking and also for pediatric and geriatric patients who experience difficulties in swallowing. It disintegrates in mouth without chewing or drinking water. It is a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva and due to the presence of hydrophilic polymers film rapidly hydrates and dissolved to release the medication for oromucosal absorption. Oral dissolving films offer fast, accurate dosing in a safe, efficacious format that is convenient and portable. The film enables the drug to directly be delivered in the systemic circulation by avoiding the first pass metabolism.

Keywords

Fast dissolving films, Fast Disintegration, Oral strip.

INTRODUCTION [1,2,3,4,5]

Oral route of drug administration has wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance most importantly the patients compliance. The most popular solid dosage forms are being tablets and capsules. One important drawback of these dosage forms for some patients is difficulty in swallowing in common among all age groups. Travelling patients who may not have ready access to water are most in need of easy swallowing of oral dosage forms. oral drug delivery systems still need some advancements to be made because of some

drawbacks related to particular class of patients which includes geriatric, paediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many paediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. In this condition, oral fast dissolving drug delivery system is such a peculiar approach to increase patient compliance by its quality of rapid disintegration and self-administration without swallowing and chewing.

A strip or film can be defined as a dosage form that employs a water-dissolving polymer which allows the dosage form to quickly hydrate, adhere and dissolve

when placed on the tongue or in the oral cavity to provide rapid local and systemic drug delivery. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin. The

shelf life of film is 2-3 years, depending on the API. Oral fast dissolving films are useful for the patients suffering from emesis, diarrhoea, allergic attacks, cough, mental disorder, bedridden patients etc.

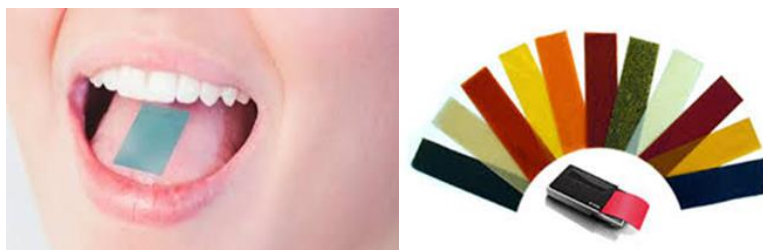


Fig:1 Pictures of oral Dissolving Film

Special features of oral dissolving films [6, 7]

- Thin elegant film
- Un-obstructive
- Fast disintegration
- Excellent mucoadhesive
- Should not leave residue in mouth
- Give a pleasant mouth feel
- Available in various size and shapes

Advantages [8, 9]

1. Rapid disintegrate within seconds when placed on tongue without the need of water and release one or more API.
2. Dose accuracy in comparison to syrup formulations.
3. Improved patient compliance
4. Enhanced stability.
5. By avoiding first pass metabolism, there can be reduction of the dose which can lead to reduction in side effects associated with molecule.
6. No risk of choking.
7. Taste masking
8. Films are flexible they are not fragile, so there is ease of transportation, handling and storage.
9. Provide good mouth feel.
10. Site specific and local action.
11. Controlled release of drug facilitates the rate and extent of absorption.
12. No need of water to swallow or chew.

13. Rapid onset of action.
14. Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
15. Enhanced safety and efficacy profile of medicament.
16. Beneficial in cases such as motion sickness, acute pain, episodes of allergic attack or coughing, where an ultra-rapid onset of action required.
17. Provide new business opportunity like product differentiation, product promotion, patent extension.
18. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation.
19. Patients suffering from dysphagia, repeated emesis, motion sickness and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

Disadvantages [10, 11]

- Restriction of eating and drinking.
- Not suitable for drugs which are unstable at buccal pH.
- Dose uniformity is a technical challenge.
- Packing requires special equipment So, difficult to pack.
- Only drugs with small dose can be administered.

Table:1 Comparison between Oral Fast Dissolving Films and Oral Disintegrating. [12]

Oral Dissolving Films	Oral Dissolving Tablets
It is a film	It is a tablet
More patient compliance	Less patient compliance
No risk of choking	Risk of choking
Better durable and flexible than oral disintegrating tablets e.g. in transportation	Brittle and less durable as compared to oral films
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area

Low dose can only be incorporated

High dose can be incorporated

Table:2 Types of Films and their properties [13]

Property	Flash release	Mucoadhesive melt away wafer	Mucoadhesive sustained release wafer
Area(cm ²)	2-8	2-7	2-4
Thickness	20-70	50-500	50 -250
Structure	Film: Single layer	Single or multilayer system	Multi-layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble hydrophilic polymer	Low/non soluble polymers
Drug phase	Solid Solution	Solid solution suspended drug particles	Suspension and solid solutions
Application	Tongue	Gingival or buccal region	Gingival
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or oral	Systemic or local	Systemic or local

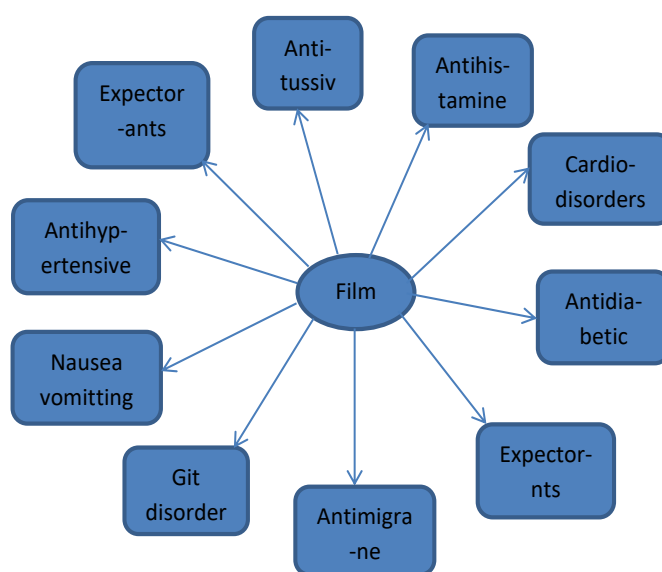


Fig:2 Applications of Film

Structure of oral mucosa-

The oral mucosa is composed of an outermost layer of stratified squamous epithelium, intermediate layer, 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 basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the epithelium and the underlying connective tissues,

and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa. The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole.

The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 μm . Oral mucosa can be categorized into sublingual, gingival, buccal and palatal mucosa through which oral transmucosal drug delivery can be achieved.

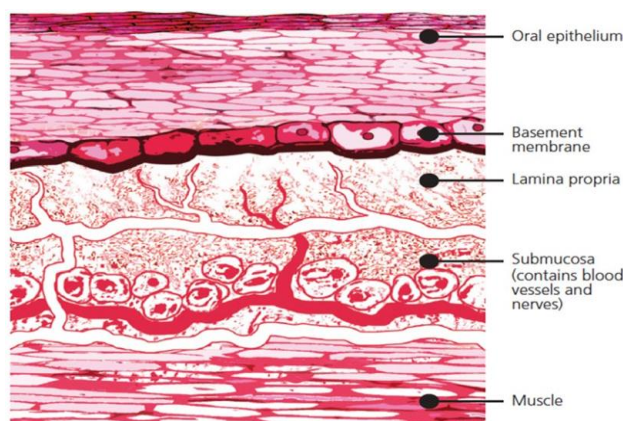


Fig:3 Structural features of oral cavity

Permeability-

The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa there is considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. The permeability of the buccal mucosa is 4-4000 times greater than that of the skin. The permeability coefficient of a drug is a measure of the ease with which the drug can permeate a membrane. The permeability coefficient is a function of the membrane thickness (i.e., inverse to its thickness) degree of keratinisation of these tissues, and the physicochemical properties of the drug (e.g.,

molecular weight, size, lipophilicity). Drug permeability appears to be highest in the sublingual area and lowest at the gingival site. For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer.

Composition of Oral Fast Dissolving Film-

All the excipients used in the formulation must be generally regarded as safe (i.e. GRAS-listed) and must be approved for use in oral pharmaceutical dosage forms. A typical formulation contains the following ingredients.

Table 3: Ingredients and their concentration

S:NO	Ingredients	Concentration
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	Flavouring agent	Q.S
7	Surfactant	Q.S
8	Colouring agent, Filler	Q.S

Active pharmaceutical ingredient [14, 15, 16]- A typical film contains 1-30% w/w of the active pharmaceutical ingredient. For the effective formulation, it is essential to incorporate micronized API since it enhances the texture of film and provide rapid dissolution and uniformity in the fast dissolving film. Several class of drugs can be formulated as mouth dissolving films including paediatrics (anti-tussive, expectorants, anti-asthmatics), geriatrics (antiepileptic, expectorants), gastrointestinal diseases, nausea (e.g. due to cytostatic therapy), pain. The selection of API depends on the potency of API, dose as well as therapeutic efficacy.

Strip forming polymer [17, 18]- Polymers can be used alone or in combination to get the desired film properties for the preparation of oral film to prevent damage during handling and transportation. Water-soluble polymers are used as film formers because they achieve rapid disintegration, good mouth feel and mechanical properties to the films. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive Polymer should be non-toxic and non-irritant. The thickness of the film depends upon the type and amount of the polymer.

Table:4 Examples of natural and artificial Polymers

S:NO	Polymer	Examples
1.	Natural polymers	Starch, Gelatin , Pectin , Pullulan , Xanthan , Sodium alginate , Sodium alginate , Maltodextrin
2.	Synthetic polymers	Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, Polyvinyl alcohol, Pyroli vinyl pyrrolidine

Plasticizer [19]- Plasticizer plays a very important role in the formulation of film as it imparts in flexibility to the strip by reducing its brittleness it also reduces the glass transition temperature of the polymer which results in the better film properties. The selection of plasticizer depends upon its compatibility with the polymer and solvent. Inappropriate use of the plasticizer results in the peeling, cracking, splitting of the film. The mechanical properties such as elongation, tensile strength to the film have also been improved by the addition of the plasticizer. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, propylene glycol, polyethylene glycol, dimethyl, dibutyl, diethyl phthalate, tributyl, triethyl, acetyl citrate, triacetin and castor oil.

Saliva stimulating agent [20,21]- The use of saliva stimulating agent results in faster disintegration of the film. This is because they increase the production of saliva as the name indicates. It can be used alone or in combination in the range of 2-6%. Commonly used saliva stimulating agents are citric acid, malic acid, lactic acid, ascorbic acid, tartaric acid. citric acid is the most preferred one among of all.

Sweetening agent [22]- Sweetening agents are used in the film formulation to mask the bitter taste of the drug. Generally, sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. Natural as well as artificial sweeteners are used to improve the taste as well as intended to be dissolve and disintegrate in the oral cavity.

Table:5 Examples of natural and artificial sweeteners

S:NO	Sweeteners	Examples
1	Natural sweeteners	Glucose, Mannose, Galactose, Fructose, Sucrose, Maltose, Starch
2	Artificial sweeteners	Saccharin, Cyclamate, Aspartame, Sucralose, Neotame, Alitame

Flavouring agents [34]- Flavouring agent added in the formulation to impart flavour in film formulation. The amount of flavour needed to mask the taste depends upon the flavour type and its strength.

There are different types of flavours used in pharmaceutical industry. The selection of flavour depends upon the age group of patients for which formulation is intended to be used.

Table:6 Examples of Flavouring agents

Flavour oils	Fruity flavours	Fruit essence type
Peppermint oil, Spearmint oil, Tulsi oil, Cinnamon oil	Vanilla, Citrus, Cocoa, Chocolate	Cherry, Apple, Pineapple, Raspberry

Surfactant [39]- Surfactants are used to increase the solubility, dispersability , wettability of the film so that the film gets dissolved within seconds and release the drug fastly.

Table:7 Examples of Surfactant

S: No	Name of surfactant
1	Sodium lauryl sulphate
2	Polaxmer 407
3	Benzalkonium chloride
4	Benzathonium chloride
5	Tweens (Tween 20, Tween 80, Tween 60)

Colours- Pigments like silicon dioxide, titanium oxide or FD&C approved colouring agents are most commonly used. The full range of colours are available, including FD and C colours, EU COLOURS,

Natural colours. Their concentration level should not exceed 1%.

Methods of preparation

- Solvent casting method
- Semisolid casting method
- Hot melt extrusion method

- Solid dispersion extrusion method
- Rolling method

From above given methods Solvent casting and Hot melt extrusion are most commonly used methods.

Solvent casting method [25, 26]

Water soluble polymers are dissolved in a suitable volatile solvent like methanol, ethanol or distilled water to form a viscous solution

The prepared solution is stirred for 2hrs on the magnetic stirrer and kept aside

API and other ingredients are dissolved in aqueous solvent and combined with the above prepared solution

Entrapped air bubbles are removed by applying vacuum

The final solution was casted into a petri plate and dried in an oven at 50°C for 24hr

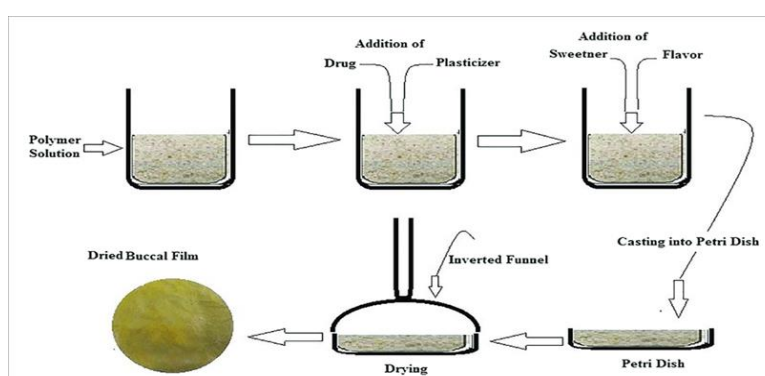


Fig:4 Solvent casting process for preparation of Oral Film

Advantages

1. Great uniformity of thickness and great clarity than extrusion.
2. Film has fine gloss and freedom from defects such as die lines.
3. Films have more flexibility and better physical properties.

Disadvantages

1. The polymer must be soluble in a volatile solvent or water.

2. Formation of a homogeneous film and release from the casting support must be possible.
3. A stable solution with a reasonable minimum solid content and viscosity should be formed.

Semi solvent casting method –

This method is preferably adopted when acid insoluble polymers are used in the preparation of the films. Acid insoluble polymers used to prepare films include cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and polymer should be used in the ratio of 1:4.

Firstly, water soluble polymers are dissolved in a water to form a solution

It is poured into the acid insoluble solution

Appropriate amount of plasticizer is added so that gel mass is obtained

Finally, the gel mass is casted as the films

Extrusion

(a) Hot-Melt Extrusion [27, 28]

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. Hot-

melt extrusion is commonly used to prepare granules, sustained release tablets, transdermal drug delivery systems.

Drug is mixed with carriers in solid form
 ↓
 The extruder having heaters melts the mixture
 ↓
 The extruder having heaters melts the mixture
 ↓
 Finally, the melt is shaped in films by the dies

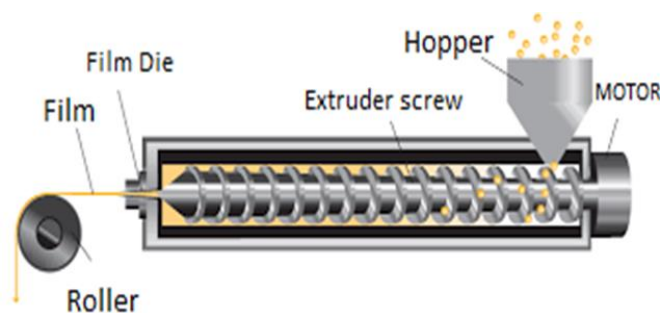


Fig:5 Diagram of Hot melt Extrusion system

Advantages

1. Fewer processing steps.
2. No need to use solvent or water.
3. Less energy compared with high shear methods.
4. More uniform dispersion of the fine particles because of intense mixing and agitation.

Disadvantages

1. Thermal process so drug/polymer stability problem.
2. Flow properties of the polymer are essential to processing.
3. Limited number of available polymers.

(b)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
 ↓
 Then solution is incorporated into melt of polyethylene glycol, obtained below 70°C
 ↓
 Finally, the solid dispersion is shaped into the films by means of dies

Rolling method

In this method the film is prepared by preparation of pre –mix, addition of an active and subsequent formation of a film.

↓
 Prepare pre-mix with film forming polymer, polar solvent and other additives except a drug
 ↓
 Fed it via a first metering pumps and control valve to either or both of 1st and 2nd mixer
 ↓
 Add required amount of drug to the desired mixer
 ↓
 Blend the drug with master batch premix to give uniform matrix
 ↓
 Specific amount of uniform matrix is then fed to the pan through 2nd metering pumps
 ↓
 The film is finally forced on the substrate and carried away via the support roller
 ↓
 The wet film is then dried using controlled bottom drying

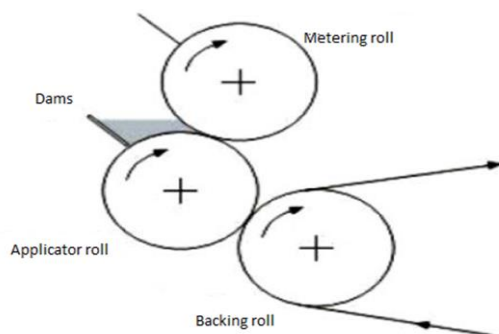


Fig:6 Preparation of film by Rolling Method

Evaluation of oral dissolving Films

Organoleptic test [23, 24]

As the formulation will disintegrate in the oral cavity so it should provide acceptable organoleptic palatable characteristics. Colour makes a formulation acceptable among the patients and moreover oral films should have attractive colour as they are administered to children. Hence, colour of formulation should be uniform and attractive. Colour can be evaluated by visual inspection. The other organoleptic property is the odour. The flavour used in the formulation should provide good odour to the formulation. The odour of the polymer, drug, and any other excipient should be masked with use of flavouring agent. Taste is an important factor in patient acceptance. Specially controlled taste panels are used.

Weight determination [41, 42]

Three films were randomly selected and weighed individually. Then the mean weight and standard deviation of films was calculated. It is desired that films have nearly constant weight. It is useful to ensure that a film contain the proper amount of excipients and API.

Thickness [40]

A thickness of film was calculated by using digital vernier caliper. Film was measured at five positions i.e; central and corners and the mean thickness was calculated. Variation in thickness of the films should be less than 5% and mean $\pm$ SD was calculated. This is essential to ascertain uniformity in the thickness of the film that is directly related with drug content uniformity, it is necessary to ascertain uniformity in the thickness of the film.

Folding Endurance [31, 32]

Folding endurance of film is essential to study the elasticity of the film during storage and handling. Folding endurance of film was measured by repeatedly folding one film at same place till it breaks. The number of times the film is folded

without breaking is known as the folding endurance value. The folding endurance of prepared films was measured in triplicate and average with SD was calculated.

In-vitro Disintegration Time [37, 38]

No specific details of disintegration test for films were specified in any pharmacopoeia, so a house manual method have been devised in which film was placed in a petri dish containing 6ml of phosphate buffer 6ml and swirling is done every 10 sec. The disintegration time is the time when a film starts to break or disintegrates. The disintegration time of prepared films was measured in triplicate and average with SD was calculated.

Drug content [35, 36]

A simple UV-spectrophotometric method is used to check the drug content. For this cut 2x2 cm² strip from the full-sized film and dissolve in 10ml of 6.8 pH phosphate buffer. Then dilute the 1ml of this solution upto 10ml, filter and record the absorption on UV-spectrometer.

Surface pH Measurement [44, 45]

Firstly, place the film in a petri dish and moistened with 1ml of distilled water and kept for 30s. Note the pH after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. This test is applied on at least 6 films and the mean $\pm$ SD can be calculated which is the final value.

Moisture loss studies

The percent moisture loss study is carrying out to check the physical stability and integrity of the films. In the present study the moisture loss capacity of the films is determine by placing the known weight and predetermined size of the films in desiccator containing anhydrous calcium chloride for three days. Remove the films and reweighed and measure the percentage moisture loss of the films by using formula:

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}}$$

Tensile strength [46]

It is the maximum stress applied to a point of film at which the strip specimen breaks. A film should have good tensile strength. Weight at which the film breaks is known as load failure. Tensile strength is calculated by following formula

$$\text{Tensile strength} = \frac{\text{Applied load at rupture}}{\text{strip thickness} \times \text{strip width}} \times 100$$

Percent elongation [33]

It depends upon the concentration of the plasticizer. As the concentration of the plasticizer increases, percentage elongation of the film also increases.

$$\text{Percent elongation} = \frac{\text{Increase in length of film}}{\text{Initial length of film}} \times 100$$

Contact angle

This test gives the information about wetting behaviour, disintegration time and dissolution of oral film. For this test double distilled water is used. Take a dry film and place a drop of double distilled water on the surface of dry film. Take images of water droplet by a digital camera within 10 sec of deposition. Analyse the digital pictures by image j 1.28v software for angle determination.

In-Vitro Drug Dissolution study

No specific details of dissolution test are mentioned in pharmacopoeia regarding fast dissolving film so In-vitro release study is carried out manually. The amount of saliva is less than 6ml in mouth and conventional dissolution apparatus used 900 ml of solution will not be representative of actual dissolution rate *in vivo*. So, a manual method is developed and carry out in the Kershary chain Diffusion cell containing 6ml of the phosphate buffer (pH 6.8) as a dissolution medium maintain at $37 \pm 0.5^\circ\text{C}$. Place the film in the receptor compartment of cell. The medium is stirred at 75 rpm. Withdraw the aliquots(1ml) of the dissolution medium at 15, 30, 45, 60, 75, 90, 105, 120, 135 and 150 sec time intervals from donor compartment and replace the same amount with fresh dissolution medium. Dilute the samples and assayed spectrophotometrically at desired wavelength using UV- VIS spectrophotometer. Perform the procedure in triplicate for all samples and calculate the average value with standard deviation.

Stability studies [47]

Stability studies are important to perform to check whether the product is stable or not. Store the formulations at 45°C / 75% RH for 3 months. During the stability studies, triplicate samples are taken at three sampling intervals i.e 0, 1 and 3 month and films should be evaluated for physical changes and drug content.

Transparency [29, 30]

Film is taken and placed on the internal side of spectrophotometer cell and analysed at 600 nm. Transparency can be calculated by

$$\text{Transparency} = \frac{\log T_{600}}{B} = -\epsilon c$$

Where

T600 = Transmittance at 600 nm

B = Film thickness (mm)

C = Concentration

Packaging (48)

There are many packaging options are available for fast dissolving films. An aluminium pouch is the most commonly used packaging format. APR-Labtec has developed the rapid card, a patented packaging system, which is specially designed for the rapid films. The rapid card has same size as a credit card and holds three rapid films on each side. Each dose can be taken out individually, allowing patient to carry 6 single, packaged dosage of his medication in his purse or wallet and is readily available.

The material selected for packaging must have following characteristics:

- They must protect the package from environmental conditions.
- They must be FDA approved.
- They must meet applicable temper resistant requirements.
- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product taste or odour.

Foil, paper or plastic pouches

A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling or sealing equipment. The pouches can be single pouches or aluminium pouches. Soluble film drug delivery pouch is a peelable pouch for "quick dissolve" soluble films with high barrier properties. The pouch is transparent for product

display. Using a two-structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceuticals and pharmaceutical applications.

Blister card with multiple units

The blister container consists of two components: the blister, which is formed cavity that holds the product and the lids stock, which is a material that

seals to the blister. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

Barrier film

These are used where drug preparations are extremely sensitive to moisture. Several materials may be used to provide moisture protection such as poly chloro trifluoro ethylene (PCTFE) film, polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapour barrier.

Table:8 Marketed products

Product	Manufacturer	Active pharmaceutical ingredients	Strength(mg)
Theraflu	Novartis	Dextromethorphan HBr	15
Sudafed	Pfizer	Phenylephrine HCl	10
Triaminic	Novartis	Diphenhydramine HCl	12.5
Orajel	Del	Menthol/Pectin	2/30
Ondansteron	Labtec GmbH	Ondansetron	4/8
Suppress	InnoZen	Menthol	2.5
Chloraseptic	Prestige	Benzocaine/Menthol	3/3
Donezepil	Labtec GmbH	Donezepil HCl	5/10

CONCLUSION

The present review concluded that Oral dissolving film is the most effective dosage form for quick release and accurate dose. It is the most promising drug delivery system today because of their rapid disintegration and improved dissolution properties. Other properties that increase the popularity of this dosage form now days are easy portability, improved patient compliance and ease of administration. Due to pregastric absorption the bioavailability of drug is improved, and first pass effect can be avoided, there can be reduction of the dose which can lead to reduction in side effects associated with the molecule. The dosage form can be consumed at any time as per convenience of the individual. The pharmaceutical companies prefer this dosage form.

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