ejpmr, 2021,8(12), 96-104

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON FAST DISSOLVING FILMS FOR ORAL DELIVERY OF DRUGS

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Article Received on 28/09/2021 **Article Revised on 17/10/2021** **Article Accepted on 08/11/2021**

ABSTRACT

The 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. These formulations are suitable for cold, allergic rhinitis, asthma attacks, CNS disorders where rapid onset of action is required for faster relief. The most popular oral solid dosage forms are tablets and capsules. Some companies introduced more robust forms of fast-dissolving drug delivery the film is placed on the top or the floor of the tongue. When put on the tongue, this film dissolves instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. It leads to enhancing drug bioavailability, No risk of chocking, Provide good mouth feel. Fast dissolving drug delivery system bypasses problems associated with difficulty in swallowing tablets/capsules etc. This review article emphasizes on the advancement in the oral dosage forms, application, formulation consideration, method of preparation, evaluation, marketed products and patented technologies of oral fast dissolving films.

KEYWORDS: Fast dissolving film, Onset of action, Bioavailability, Patients compliance.

INTRODUCTION

Fast Dissolving Film (FDF)/Oral Strip

Oral route is the most preferred route ofadministration for systemic effect. About 60% of all theformulations are solid dosage form. Tablet is the mostpreferred dosage form due to ease of transportation, manufacturing and more patient compliance Generally geriatric, pediatric and bedridden patientexperience difficulties in swallowing the conventional oraldosage form. To overcome this problem a novelformulation was developed i.e. oral fast dissolving films.

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the buccal cavity. The oral film systems are the third class, have been in existence for a number of years that is recently become the new area of attention in fast-dissolving pharmaceutical drug delivery. The fast dissolving oral thin film (OTFs) or oral strip (OS) developed in the past few years from the confection and oral care markets in the form of breath strips and developed a novel and widely accepted form by consumers for delivering vitamins and personal care products.

The companies' research from the polymer coatings containing active pharmaceutical ingredients (APIs) formulation for transdermal drug delivery capitalized on the opportunity to conversion this technology to OTF formulation.

Today, OTFs are a proven and accepted technology for the systemic delivery of API for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs.[1]

This is basically for their result of the success of the consumer breath freshener products such as Listerine Pocket Packs in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. In this film can be can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film are prepared big sheet then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats.[2]

Fast dissolving films are most advance form of solid dosage form due to its flexibility. It improves efficiency of active pharmaceutical ingredient (API) dissolving in the short duration oral cavity after the contact with less amount of saliva as compound to dissolving tablet.[3]

Fig. 1: Fast dissolving oral film.

a. Classification of Oral Film

There are three different subtypes

1. Flash release,
2. Mucoadhesive melt-away wafer,
3. Mucoadhesive sustained-release wafers.

These three types of oral films are differentiated from each other in following table 1.3.

Table 1: Type of Wafer/oral Film and their properties

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

b. Criteria for Fast Dissolving Film

Fast dissolving film should:

- Have a pleasant mouth feel.
- Not need water to swallow but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible by taste masking
- Leave minimum or no residue in the mouth after oral administration.

c. Advantages of FDF

- No risk of chocking.
- Convenient dosing or accurate.
- No need of water to swallow or chew.
- Small size for improved patient compliance.
- Fast onset of action.
- Easy of handling and transportation.
- Improve bioavailability for certain therapeutic ingredient.
- Enhanced stability.
- Taste masking.
- No special set required for industry.
- The drug enters the systemic circulation with reduced hepatic fires pass effect.
- Lower doses.

d. Disadvantages of FDF

- Drugs which are unstable on buccal pH cannot be administered.
- Drugs which irritate the oral mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.

e. Limitations

- Drugs with larger doses are difficult to formulate into FDF e.g. rifampicin (600mg), ethambutol (1000mg) etc. However, research has sure that the concentration level of active can be improved up to 50% per dose weight.
- Most bitter drugs should be avoided if used then co administration of enzyme inhibitors such as aprotinin, bestatin.

f. Criteria for selection of drug candidate for FDOF.

- The drug should have pleasant taste.
- The drug should preferably have a dose up to 40 mg.
- The drug should have small or moderate molecular weight.
- The drug should have good stability and solubility in water and in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should be the ability to permeate oral mucosal tissue.[3,4]

Formulation Considerations

The area of drug loaded FDF should be between1-20cm^2. The drug can be loaded up to a single dose of 30mg. All excipient used in the fast dissolving film should be commonly regarded as safe (GRAS-listed) and authorized for use in oral strip. Formulation considerations have been testified as important factors which affected mechanical properties of the film.

Table No.2: A typical composition contain following.

S.No	Ingredient	Amount (w/w)
1.	Drug	1-30%
2.	Film forming polymer	40-50%
3.	Plasticizer	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.

1. Active Pharmaceutical Ingredient

A unique composition of the film contains 1-30%w/w of the active pharmaceutical ingredient. Always use low dose of active pharmaceutical ingredients in the fast dissolving film because high dose of drug are difficult to incorporate in fast dissolving film micronized API is useful become it improve the texture of film and offer improved dissolution and uniformity in the fast dissolving film. A number of drugs can be used as fast dissolving oral film.

Table no. 3: List of drugs that can be incorporated in fast dissolving film.

Drug	Dose	Therapeutic class
Chlorpheniramine maleate	4 mg	Anti-allergic
Triplolidine hydrochloride	2.5 mg	Anti-histaminic
Loperramide	2 mg	Anti-diarrheal
Famotidine	10 mg	Antacid
Azatidine maleate	1 mg	Anti histamininic
Sumatriptan succinate	35-70 mg	Anti-migraine
Ketoprofen	12.5 mg	Analgesic

2. Film Forming Polymers

Formulation of film used most important ingredient is polymer which produce robustness of the film. Robustness is depended upon adding of polymer quantity. These polymers are generally attracted considerable attention by medical and neutraceuticals industry. Generally used 45% w/w polymer in film based on total weight of dry film. Mainly hydrophilic polymers are used in the oral strip as they quickly disintegrate in the oral cavity as they come in contact with saliva.

Ideal Properties of Film Forming Polymer

- It should be non-toxic and non-irritant.
- Polymer must be hydrophilic.
- It should have excellent film forming capacity.
- It should have good wetting and spread ability property.
- Polymer should be readily available & should not be very expensive.
- Polymer should have low molecular weight.

Currently, natural & synthetic polymers both are used in the preparation of fast dissolving film. The various natural & synthetic polymers are available in preparation of fast dissolving film.

Table No.4: Polymers used in preparation of fast dissolving film.

S.No.	Natural polymer	Synthetic polymer
1.	Pullulan	Hydroxy propyl methyl cellulose
2.	Starch gelatin	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 Hydroxy propyl cellulose
8.	Xanthan	Hydroxyl ethyl cellulose

3. Plasticizers

Plasticizer is a very essential ingredient of oral strip formulation. It is used &help in increase the flexibility and reduce the brittleness of the fast dissolving film and by addition of Plasticizers, tensile strength and elongation can be improved. Plasticizers selection is depending upon its compatibility with the polymer and various the type of solvent used in the casting of oral strip.

Example: Glycerol, Propylene glycol, Polyethylene glycol 400,200,600, Diethyl, Dicetyl, dibutyle Phthalate, Triacetrin, Castor oil, Citrate ether, Try ethyl citrate etc.

4. Sweetening agents

Sweetener is basic part of the food products as well as pharmaceutical products obtainable to be disintegrated or dissolved in the oral cavity. The sweet taste is usually more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to recover the palatability of the mouth dissolving formulations. Suitable sweeteners include.

a. **Water soluble natural sweetener:** Xylose, ribose, glucose, sucrose, maltose and stevioside.
b. **Water soluble artificial sweetener:** Sodium or calcium saccharin salts, cyclamate salts and acesulfame-k, etc
c. **Dipeptide based sweetener:** Aspartame
d. **Protein based sweeteners:** Thaumatin I and II.

5. Saliva stimulating agent

The saliva stimulating agents used for the improve the rate of production of saliva that is help in the faster disintegration of. Usually 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 Sweeteners also act & as saliva stimulating agent.

Example: Citric acid, Malic acid, lactic acid, ascorbic acid, Tatric acid.

6. Surfactant

Solubilizing or wetting or dispersing agent of film by using of Surfactant, therefore that the film gets dissolve within seconds and release the active agent immediately. One of the most important surfactant is Polaxamer 407 that is used a solubilizing, wetting and dispersing agent.

Example: Polaxamer 407, Sodium lauryl sulfate, Tweens, Spans, Benzalkonium chloride.

7. Flavoring Agent

Selection of flavor is depending on which type of drug is to be incorporated in the formulation. The recognition of the oral disintegrating/ dissolving formulation by an individual depend on the initial flavor quality which is observed in the first few seconds after the product has been consumed and the after taste of formulation continues for at least 10 min. The amount of flavor required to mask the taste depend on the flavor type and its strength. 10%w/w concentration of flavoring agent is used in the formulation.

Example: Peppermint oil, Cinnamon oil, Menthol etc.

8. Coloring Agent

In fast dissolving film used FD & C approved coloring agent. Generally coloring agent is not more than concentration a level of 1%w/w in formulation.
Example: Titanium dioxide, Sunset yellow etc. [5,6,7,8,9]

Methods of Preparation of FDF

Following methods are used for preparation of fast dissolving film such as:

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

1. Solvent Casting Method

In the solvents casting method water soluble polymer dissolved in suitable solvent and dissolved the drug and other excipient in suitable solvent. Then both solutions are mixed together and stirred and finally casted into the Petri plate and dried**.**

Polymer dissolved in suitable solvent + Drug & excipient

↓

Dissolved in suitable solvent

↓

To form solution

↓

Both solution are mixed with rapid stirring (1000 rpm, 60^0c)

↓

Homogenous solution is then spread on flat surface

↓

Dried

↓

Film formed

Fig no.2: Flow chart of solvent casting method.

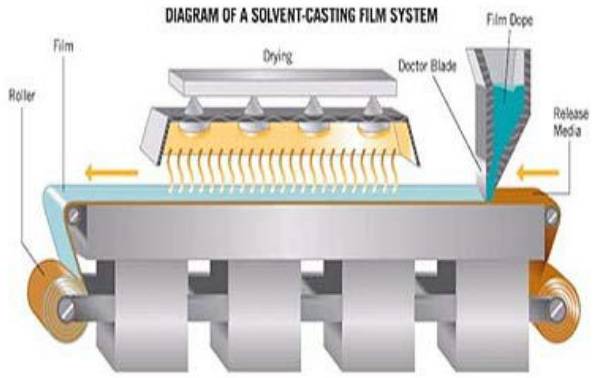

Fig no.3: Solvent casting film system.

Advantage

- 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

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

2. Semisolid Casting Method

Water soluble film forming polymer Solution is Prepared

↓

Ensuing solution is added to a solution of acid insoluble polymer
(E.g. cellulose acetate phthalate, cellulose acetate butyrate)

↓

Suitable amount of plasticizer is added to obtained gel mass

↓

casted gel mass into the films or ribbons using heat Controlled drums

↓

The thickness of the film should be about 0.015-0.05 inches.
Acid insoluble polymer to film forming polymer ratio is 1:4.

Figure 4: Flow chart of Semisolid casting method.

3. Solid Dispersion Extrusion

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

Dissolved the Drug in a suitable liquid solvent

↓

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

↓

Solid dispersions are formed into the films by means Of Dies

Fig no.4: Flow chart of solid dispersion.

4. Hot Melt Extrusion

The drug &carriers mixed in solid form

↓

Extruder having heaters melts the mixture

↓

Finally the melted mixture is shaped in films by the dies

Fig no.6: Flow chart of hot melt extrusion.

Advantages

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

5. Rolling Method

A suspension containing drug is rolled on a carrier. The solvent is mostly water and water mixture and alcohol. The film is dried on the rollers and gives desired shape and size.[10,11]

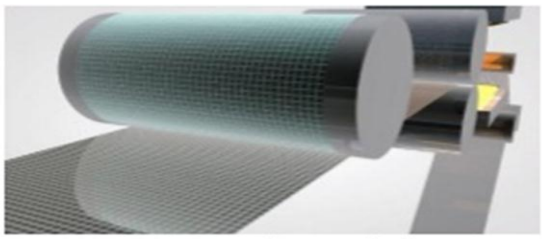

Fig no 7: Rolling Equipment.

Quality Control Test for Fast Dissolving Film

i. Morphology Study

The morphological study of fast dissolving strip is done by the scanning electron microscopy (SEM) at a definite magnification. Study mentions the differences between upper and lower side of the films. It also helps in determination of the distribution of API.

ii. Weight Variations

Weight variation is measured by individually weighting randomly selected 10 films. The average weight should not vary significantly from the average weight.

iii. Thickness

The film thickness is determined by micrometer screw gauge at 5 different points of the film i.e. central and the four angles and means thickness is calculated. It used for measurement of thickness Uniformity, the five film are randomly selected and thickness is measured on location of each formulation Maximum variation in the thickness of the films should be less than 5% mean±SD is calculated.

iv. Surface pH

The surface pH of oral strip is calculated in order to examine the risk of any adverse effect in vivo. Then irritation in the buccal mucosa may be cause by acidic or alkaline pH, it is determining to maintain the surface pH as close to neutral as possible. The surface pH of oral strip is determined by combined pH electrode.

v. Dryness Test/Track Tests

About eight stage of fast dissolving film drying process have been identified and they are set-to-touch, dust free, track free, dry to touch, dry hard, dry through, dry-to-recoat and dry print free. Dryness Test can be checked tack is the tenacity by which the film adheres to accessory which contact with the strip.

vi. Tensile Strength

Tensile strength of fast dissolving film is determined by applying the maximum stress to a point till the oral film breaks. It is calculated by the applied load at rupture divided by the cross section area of the oral film as given in the equation below.

$$\text{Tensile strength} = \frac{\text{Load at break}}{\text{Strip break} \times \text{Strip Width}}$$

vii. Percentage Elongation

Percentage elongation is determined by noting the distance travelled by pointer before breaking of the film on the graph paper. Normally elongation of oral strip increase as the plasticizer content increases.

$$\% \text{ Elongation} = \frac{L \times 100}{L^\circ}$$

L = Increase in the length of film,
L° = Initial length of film.

viii. Folding Endurance

Folding endurance is measured by manual repeated folding of film at the same place till it broke. The number of time the film is folded without breaking is known as the folding endurance value.

ix. Moisture Uptake

This test was carried out to check the physical stability and integrity of the films at high humid conditions. Film was placed in the desiccators containing standard

solution of aluminum chloride, keeping the humidity inside the desiccators at 79.55% RH. After 3 day films were taken and weighed the percentage moisture absorption of the films was found.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

x. Young's Modulus

Young's modulus is used to determine the stiffness of oral film. It is represented as the ratio of applied stress over strain in the region of elastic deformation. It is calculated as follows.

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{Cross head speed}}$$

xi. Assay/drug Content and Content Uniformity

The Assay of drug, drug content and drug content uniformity is determined by any standard assay method which is described for the particular API in any standard pharmacopoeia. Limit of content uniformity is 85-115%.

xii. Disintegration Time

The disintegration time limit is of 30sec or less for orally disintegrating tablets, as described in CDER guideline and can be applied to fast dissolving oral film. No official guideline is available for oral films. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for film is 5-30 sec.

(1) Slide frame method

On the oral films one drop of distilled water was dropped by pipette. So the films were fixed into slide frames and were placed planar on a Petri dish. The time up until the film dissolved and caused a hole within the film was measured.

(2) Petri dish methods

2 ml of distilled water was placed in a Petri dish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely.

xiii. In-vitro Dissolution Test

In-vitro Dissolution study can be performed using the paddle or basket apparatus as described in the pharmacopoeia. The volume of dissolution medium will fundamentally be selected as per as the sink condition and highest dose of the API. the dissolution test of oral strip mainly paddle type of dissolution apparatus is used since sometimes the dissolution test can be difficult due to the tendency of the strip to float onto the dissolution medium.

xiv. Stability Testing

Stability testing of the oral film measurement is done by storing the of oral strip were stored 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.[12, 13,14]

Patented technologies of fast dissolving oral films

XGel

XGel film technology is recognized by Bio Progress which causes a revolution in the product offering and manufacturing methods which is now obtainable to the pharmaceutical industry. These films may be coloured or printed during manufacture for branding and coding which is quite helpful in product identification.

Soluleaves

In Soluleaves technology, saliva releases its active ingredients by the film on coming in contact with saliva, during this film adhere to the mucous membrane in oral cavity produce order to release the drug slowly in 15 min. This method is useful for those who have difficulty in swallowing conventional tablets. This technology is applied to flavoured products like mouth fresheners, confectionery and vitamins.

Wafertab

Wafertab is a patent technology that is known as drug delivery system which incorporates pharmaceutically active ingredients into an ingestible film strip. When film came in contact with saliva it offers rapid dissolution and release of active ingredient.

Foamburst

Foamburst is a novel patent technology granted in September 2004 which is for capsules made of formed film. During production an inert gas is blown into the film, results in a film with honeycomb structure as a capsule which dissolve quickly and causing a melt-in-the mouth sensation.

Micap

In 2004 Micapplc signed an agreement to combine its capability in micro encapsulation technology with the Bio Progress water soluble films. Their main aim is to provide new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs).

Rapid film™

It is a novel thin film technology advanced by Applied Pharma Research (APR), a leading Swiss R&D company whose main focusis innovative drug delivery, in conjugation with Labtec GmbH. Dr. Paulo Galfetti, Head of Licensing & Business Development states that this technology is of great importance when rapid onset of action is required. For example: Donepezil Rapidfilm®, Olanzapine Rapidfilm®

Table no. 5: Some patents on oral thin films.

Country	Patent Number	Title	Inventors
US	20110305768A1	Quick dissolving oral thin film for targeted delivery of therapeutic agents	Hai-Quan Mao et al[15]
WO	2012103464A2	Oral thin film vaccine preparation	Brian Pulliam[16]
WO	2013085224A1	Bitter taste masked oral thin film formulation of Sildenafil Citrate	Dae-Kun Song et al[17]
US	6177096B1	Water soluble film for oral administration with instant Wettability	Horst Georg Zerbe et al[18]
EP	1680079A2	Rapidly disintegrating films for delivery of pharmaceutical and cosmetic agents.	Scott D Bamhart et al[19]
EP	2509631A4	pH sensitive compounds in taste masking within oral thin film strips	A Mark Schobel et al[20]
WO	2012053006A2	Improved oral fast dissolving films comprising combination of polymers	Rajesh Jain et al[21]
US	6596298B2	Fast dissolving orally consumable films	Sau-Hung Spence Leung et al[22]
WO	2014183054A1	Thin film with high load of active ingredient	Eric Allen et al[23]
US	7579019B2	Pharmaceutical carrier device suitable for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al[24]

Packaging of fast dissolving oral films.

There are number of packaging collections available for oral thin films, it should be selected adequately to preserve the integrity of the product. Material selected for packaging must have following characteristics:

- They must be non-toxic
- They must protect the preparation from environmental conditions
- They must be FDA approved They must be non-reactive with the product They must not convey to the product taste and odours
- They must meet applicable temper resistant requirement

Various type of packaging

Foil, paper and plastic pouches

It delivers packaging which is temper-resistant. It provides high degree of environmental protection. During product filling operation a flexible pouch is formed by either vertical horizontal forming, filling and sealing equipment.

Single pouch or aluminum pouch

The soluble drug delivery pouch is a peelable pouch aimed at rapid dissolve % soluble films by high barrier properties Consuming a 2 structure combination allows for one side to be clear and further to use a cost effective foil lamination which has zero transmission of both gas and moisture The single dose pouch affords both product and dosage protection.

Blister card with multiple unit

Blister vessel consists of two components: first, the blister (plastic), which is the formed cavity which holds the product and second, the lid stock (aluminium), which is the material that seals the blister. The blister package is formed by heat softening by following method: A sheet of thermoplastic resin is softened by heating Softened sheet is vacuum dried into a countered mold Sheet is released from the mold after cooling Proceed to the packing station of filling machine Before formed semi rigid blister is filled with the product and lidded with the heat sealable backing material.

Marketing status and products available for oral thin film dosage form

The drug delivery sector of fast dissolve products has grown quickly from sales in 2002 of about $850 million to 2005 were estimated sales were around $1.4 billion (IMS Data). The market for these types of product is in excess of $15bn worldwide. Presently, fast dissolve technology are incorporate worldwide sales of drug are more than $1 billion and have an annual growth rate of more than 40 per cent. In 2001 and 2002 it was reported that several important therapeutic products would launch using this technology over the next two or three years. Whilst there has been a five-fold increase worldwide in the number of thin film strips since 2002, very few if any such products have arrived the ethical prescription market.[25]

Table 6: List of some marketed products available as FDFs			
Brand name	**Manufacturer/ Distributor**	**API(strength)**	**Uses**
Klonopin Wafers®	Solvay Pharmaceuticals	Clonazepam (in five strength; 0.125, 0.25, 0.5, 1 and 2 mg)	Anti-anxiety
Listerine® Pocket Packs	Pfizer, Inc.	Cool mint	Mouth fresheners
Sudafed PE ®	Walters Kluwer Health, Inc.	Phenylephrine	Relieving congestion
Suppress®	InnoZen Inc.	Menthol (2.5mg)	Cough suppressant
Gas-X®	Novartis	Simethicone (62.5 mg)	anti-Fluctuating
Chloraseptic®	Prestige	Benzocaine / menthol (3/3) mg	Sore throat
Benadryl®	Pfizer	Diphenhydramine HCL (12.5, 25 mg)	Anti-allergic
Ondansetron Rapidfilm®	Labtec GmbH	Ondansetron (4, 8 mg)	Anti-vomiting
Donezepil Rapidfilm®	Labtec GmbH	Donezepil Hydrochloride (5, 10 mg)	Treatment of dementia

CONCLUSION

The growing success and popularity of fast dissolving oral film recently in global market is evidence to the need for effective taste masked, "without water" pharmaceutical formulations. Fast dissolving oral films being a natural evolution of fast dissolving drug delivery systems have prominent advantages over conventional dosage forms and orally disintegrating tablets. Due to their immense importance during the emergency cases such as allergic reactions and high patient compliance, fast dissolving oral films have evolved as consumer friendly dosage forms. So many of the pharmaceutical companies are launching this technology as these films can be manufactured through non-sophisticated, uncomplicated equipment and procedures. Due to these, fast dissolving films have economically feasible developmental futuristic opportunities.

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