



ORAL FAST DISSOLVING FILMS-AN INNOVATIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Oral dissolving films are formulated by incorporating the drug with selected oral cavity absorption enhancers in a specially designed oral dissolving film carriers. This facilitates the rapid absorption in the oral cavity for drugs with low GIT-bioavailability and intensive first-pass effects. This it offers shortening onset time, enhancing bioavailability and reducing the probability of first pass side effect. The current review focuses on the recent development in the oral dissolving film and discusses about its technique for preparation of film as well its evaluation.

KEYWORDS: Oral dissolving film, Film forming polymer,

Challenges, Evaluation.

ORAL DISSOLVING FILMS^[22,30,60,68]

It is a solid dosage forms that disperse or disintegrate quickly in the oral cavity, resulting in solution or suspension without need for the administration of water.

The delivery system simply placed on a patients tongue interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within in a minute without needing water or chewing. Recently oral dissolving films have been proposed which rapidly dissolves or disintegrate into buccal cavity. Alternative to fast dissolving tablets it definitely eliminates patients fear of choking. Oral dissolving films formulations are beneficial especially for the pediatrics but also for the geriatric population as swallowing high volumes of liquid can be avoided.

An important benefit of these dosage forms is accurate dosing as compared to liquid dosage form, no water is needed and there is no fear of choking as compared to tablets and capsules. Also, although oral disintegrating tablets disintegrate quickly, their disintegrated materials remain insoluble until swallowing. The rapidly dissolving dosage forms are referred by various means by researches like oral dissolving film, mouth dissolving, quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms. These are ultra thin postage stamp size with an active agent or pharmaceutical excipients. Since the sublingual mucosa is relatively permeable because of thin membrane and is highly perfused, rapid drug absorption and instant bioavailability is possible and this leads to quick onset of drug action. Since the drug is directly absorbed into the systemic circulation, degradation in the gastrointestinal tract (GIT) and first pass effect can be avoided.

Release Mechanism^[30,60,68]

The delivery system is simply placed on a patient's tongue or any oromucosal tissue. Instantly wet by saliva due to presence of hydrophilic polymer and other excipients, the film rapidly hydrates and adheres on to the site of application and dissolves to release the medication for oromucosal absorption. It rapidly disintegrates or dissolves to release the medicine for mucosal absorption or with modification, allows for oral GIT absorption with quick dissolving properties.

Special features^[9,10,30]

1. Available in various size and shapes.
2. Thin elegant film.
3. Un-obstructive.
4. Fast disintegration or dissolution.
5. Rapid release, Mucoadhesive and quick dissolving.
6. Criteria for Fast Dissolving Film.
7. Oral dissolving film should have a pleasant mouth feel.
8. Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of second.
9. Compatible with taste masking.
10. Leave minimum or no residue in the mouth after oral administration.
11. Exhibit low sensitivity to environmental conditions such as temperature and humidity.

Advantages

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. No risk of choking.
3. Convenient dosing and accurate.
4. No need of water to swallow or chew administered anywhere at any time.
5. Small size makes improved patient compliance.
6. Rapid onset of action.
7. Ease of handling and transportation.
8. Improve bioavailability for certain therapeutic ingredient and enhanced stability.
9. Taste masking can be achieved.
10. No special formulation setup required for industry.
11. The drug enters the systemic circulation with reduced hepatic first pass effect.
12. Can be loaded lower doses.
13. Minimal side effects.
14. Site specific and local action.
15. Non invasive.

Table. 1: Comparison between orodispersible film and orodispersible tablet. ^[12,13,31]

Orodispersible film	Orodispersible tablet
It is a film	It is a tablet
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area
Better durable than orodispersible tablets	Less durable as compared with orodispersible film
More patients compliance	Less patient compliance
Low dose can be incorporated	High dose can be incorporated
No risk of choking	It has a fear of choking

Disadvantages

1. Drugs which irritate the mucosa cannot be administered by this route.
2. Drug with small dose requirement can only be administered.
3. Most drugs have bitter taste, and need taste masking.
4. It is hygroscopic in nature so it must be kept in dry place.
5. It also shows the fragile and granule property.
6. They required special packaging for products stability and safety.
7. High dose cannot be incorporated into the oral film.
8. Drugs which are unstable at buccal pH cannot be administered

Limitations

1. Drugs with larger doses are difficult to formulate into ODF e.g. Rifampicin (600) Ethambutol (1000mg) etc. However, research has proven that the concentration level of active can be improved upto 50% per dose weight
2. Most bitter drugs should be avoided if used then co-administered of enzyme inhibition such as aprotinin, bestatin, puromycin etc.

Classification of fast dissolving technology

1. Lyophilized system
2. Compressed tablet based system
3. Oral thin films/strips

Oral thin films/strips

These are the most convenient and advanced form of oral solid dosage form due to the efficiency of dissolving within minutes in oral cavity when it comes in contact of saliva. It neither requires chewing nor water for administration. It gives quick absorption and instant bioavailability of drugs due to the high blood flow and permeability of oral mucosa.

Classification of Oral Films^[8,9,10]

There are three different subtypes

- a) Flash release.
- b) Mucoadhesive melt-away wafer.
- c) Mucoadhesive sustained-release wafers.

Table. 2: Difference types of films.

Sub type	Flash release wafer	Mucoadhesive melt -away wafer	Mucoadhesive sustained release Wafer
Area (cm ²)	2-8	2-7	2-4
Thickness (µm)	20-7	50-500	50-250
Structure	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 and other region of oral cavity
Dissolution	Maximum 60 seconds Maximum 8-10 Hours	Disintegration in a few Minutes forming, gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Composition of the formulation^[4,20,30]

Formulation of oral dissolving film (ODF) involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance and mouth feel etc. The excipients used formulations of oral dissolving film are given below as per their categories. From the regulatory perspectives, all excipients used in the formulation of oral dissolving film should be generally regarded as safe (i.e. GRAS- listed) and should be approved for use in oral pharmaceutical dosage forms. Components of formulation are,

1. Drug.
2. Water soluble film forming polymers.
3. Plasticizers.
4. Saliva stimulating agent.
5. Sweetening agent.
6. Flavoring agent.
7. Surfactant.
8. Colours, Fillers.

Table. 3: Concentration of component.^[20,30]

S. No	Ingredients	Amounts
1	Drug	1-30%
2	Water soluble film forming polymers	40- 50%
3	Plasticizers	0-20%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Flavoring agent	Q.S
7	Surfactant	Q.S
8	Colours, Fillers	Q.S

Active Pharmaceutical Ingredient^[13,18,30]

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

Table. 4: Examples of suitable drug molecule and its category. ^[13,16,18,30]

Category	Examples
Anti-emetics	Ondansetron, Granisetron, Palonosetron, Dronabinol, Aprepitant, Ramosetron, metopimazine, nabilone, tropisetron, Metoclopramide, Prochlorperazine, Trimethobenzamide, Dimenhydrinate, Prochlorperazine and Dolasetron.
Serotonin inhibitors	Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram and Alaproclate.
5HT3 antagonists	Alosetron, Ondansetron, Granisetron, Palonosetron, Ramosetron and Tropisetron.
Anti- epileptics	Carbamazepine, Clonazepam, Diazepam, Divalporexosodium, Fosphenytoin, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenyloin, Pregabalin, Primidone, Tiagabine, Topiramate, Valproatesodium, Vigabatrin and Zonisamide.
Anti-migraines	Almotriptan, Dihydroergotamine Mesylate, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan,
Dopamine D1 and Dopamine D2 antagonist	Amisulpride, Bromperidol, Cabergoline, Domperidone, Fenoldopam, Haloperidol, Metoclopramide, Metopimazine, Pergolide Mesylate, Prochlorperazine, Quetiapine, Ropinirole Hydrochloride, Sulpiride, Tiapride and Zotepine.
No tropics	Almitrine Dimesylate and Raubasine, Cevimeline Hydrochloride, Codergocrine Mesylate, Donepezil, Galantamine, Ginkgo Biloba Extract (EGb 761), Memantine, Nicergoline, Piracetam, Rivastigmine, Sulbutiamine, Tacrine and Vinpocetine.
Statins	Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin and Simvastatin.

Water soluble film forming polymer ^[13,18,28,30]

Water soluble polymers are used as film formers. The use of film forming polymers in dispersible films has attracted considerable attention in medical and nutraceutical application. The water soluble polymers achieve rapid disintegration, good mouth feel effect and gives the mechanical property to the films. The disintegration rate of the polymers decreased by increasing the molecular weight of the polymer film bases. Some of the water soluble polymers used as film formers are hydroxypropyl methyl cellulose (HPMC), Hydroxypropyl cellulose (HPC), pullulan, carboxymethyl cellulose (CMC), pectin, starch, polyvinyl acetate (PVA), and sodium alginate these polymers can be used alone or in combination to obtain the desired strip properties. They comprise the physical structure of the films, affording their integrity. The robustness of the strip depends on the type of the polymer and amount in the formulation. Polymers are selected not only for the physical characteristics of the films but also for the rate at which they dissolve. The dissolution rate of the dissolving polymer inversely related to the molecular weight of the polymer. In formulation at least 45 % w/w of polymer should be present based on the total weight of the film.

Table 5: Type of polymers.

Natural Polymers	Synthetic Polymers
Pullulan	Hydroxyl propyl methyl cellulose (Hypromellose) (HPMC)
Gelatine	Polyvinyl pyrrolidone(PVP)
Modified starches	Polyvinyl alcohol (PVA)
Xanthan gum	Polyethylene oxide
Locust bean gum	Low viscosity grade of Hydroxy Propyl Cellulose(HPC)
Guar gum	Sodium carboxymethyl cellulose (SCMC)
Carrageenan	Hydroxyl ethyl cellulose (HEC)

Plasticizer^[9,10,30]

It improves the flexibility of film and decrease the brittleness of the polymer film. The selection of plasticizers depends on the compatibility with polymer, method of formulation and the nature of solvent. Plasticizers such as glycerin, sorbitol Propylene Glycol, Glycerol, castor oil, triacetin, triethylcitrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters can be added to the formulation to alter mechanical properties of final film. By lowering the glass transition temperature of the polymers more structurally pleasant, stronger and a flexible film can be prepared.

Salivary Stimulating Agents^[9,10,30]

The rationale of employing saliva stimulating agents is to increase the rate of production of saliva that would be aid in the faster disintegration of the fast dissolving film formulations. The salivary stimulating agents activate the salivary glands to produce saliva that helps in the rapid disintegration of the films. Generally acids which are used in the preparation of food can be utilized as salivary stimulations, like citric acid, malic acid, lactic acid, ascorbic acid etc. These are used alone or combination between concentration 2 to 6 % w/w of the film sweeteners is also act and as salivary stimulating agents.

Sweetening Agents^[9,10,30,33]

Sweeteners have become the essential part of the food products as well as pharmaceutical products intended to be disintegrated to be disintegrated or dissolved in the oral cavity. Sweeteners are used to mask the bad odour and bitter taste of the drugs. Both type of sweeteners are used natural and artificial sweeteners in the formulations and improves the palatability of the fast dissolving film i.e. Monosaccharide, Disaccharides and Polysaccharides can be used.

Table. 6: Type of sweetener.

Sweetener	Sweetness Factor
Aspartame	180 – 200
Sucralose	600
Neotame	7000 – 13000
Saccharin	300

Flavoring Agents^[9,10,30,33]

The flavors enhance the acceptance of the formulation and enhance the elegance properties of the film. Selection of flavor depends on which type of drug to be incorporated in the formulation. The flavoring agents can be selected from synthetic flavor oil, oleo resins, extracts derived from various parts of the plants like of leaves, flowers and fruits. Any flavor can be added such as essential oil or water soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary. Flavors are such as vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple etc. The amount of flavor required to mask the taste depend on the flavor type and its strength. Flavoring agent is used in the formulation in concentration of 10% w/w.

Basic taste and their taste masking agents^[11,30]

Salt: Butterscotch, maple, apricot, peach, vanilla, mint.

Bitter: Wild cherry, walnut, chocolate, mint, anise.

Sweet: Vanilla, fruit and berry.

Sour: Citrus flavor, licorice, root beer, raspberry.

Surfactants^[9,10,30,33]

These are used to enhance the solubility and wetting property of film to release within minute the drug. There are many surfactants which are used i.e. benzalkonium chloride, sodium lauryl sulfate, benzathonium chloride, tween and polaxamer.

Colouring Agents^[9,10,30,33]

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

Methods of Preparation^[10,30,33]

The manufacturing of orally dissolving films is done by various methods such as.

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

One or a combination of the following process can be used in the manufacturing of ODFs.

Solvent casting method^[10,30,33]

Solvent casting method is a century old making process. In pharmaceutical process two solutions is prepared the polymeric and drug solution. In polymeric solution the polymer added in the volatile solvents like ethanol and water after few minutes plasticizer are added, similarly in this solution other excipients are added. After mixing both solutions were stirring in a magnetic stirrer at suitable rpm. This material is known as film dope, it is spread out in classical solvent film casted methods. This solution poured into the Petri dish and covered with the inverted funnels to allow the evaporation of solvent.

The properties of the API play a critical role in the selection of a suitable solvent. The physicochemical properties of the API should be considered. These properties include compatibility of the API with other film-forming excipients, compatibility with solvents, the polymorphic nature of the API selected, and temperature sensitivity. Manufacturing and packaging ODFs requires special precaution to be taken to control the effect of moisture. Stability of the film and its mechanical properties are significantly affected by the presence of moisture. Another factor requiring strict control is temperature. Controlled temperature conditions are required for maintaining the viscosity of the solution and temperature sensitivity of the API. Specific types of equipment such as rollers are required for pouring the solution on an inert base. The clearance between the roller and the substrate determines the required thickness of the film. The final step, drying the film, removes the solvent and helps to obtain the finished product. Usually, glass, plastic, or teflon plates are used as an inert base for film casting. When the manufacturing technology is transferred from laboratory scale to production scale, several problems can be encountered. These problems include the casting of the film, obtaining uniform thickness of the film, and proper drying of the sample. The selection of the proper type of dryer is needed in the final step of drying. Once the films are dried, cutting, stripping, and packaging is done. Suitable size and shapes of films can be cut. The commonly available sizes of films are 3 x 2 cm² and 2 x 2 cm². Selection of the

packaging container is an equally important parameter for the ODF. The packaging container should provide sufficient mechanical strength to protect the film during shipping and from external factors such as temperature and humidity. Depending upon the characteristics of the film, single-unit containers and multiple-unit dispensers can be selected. The packaged films are inspected before being packed into a secondary packaging container

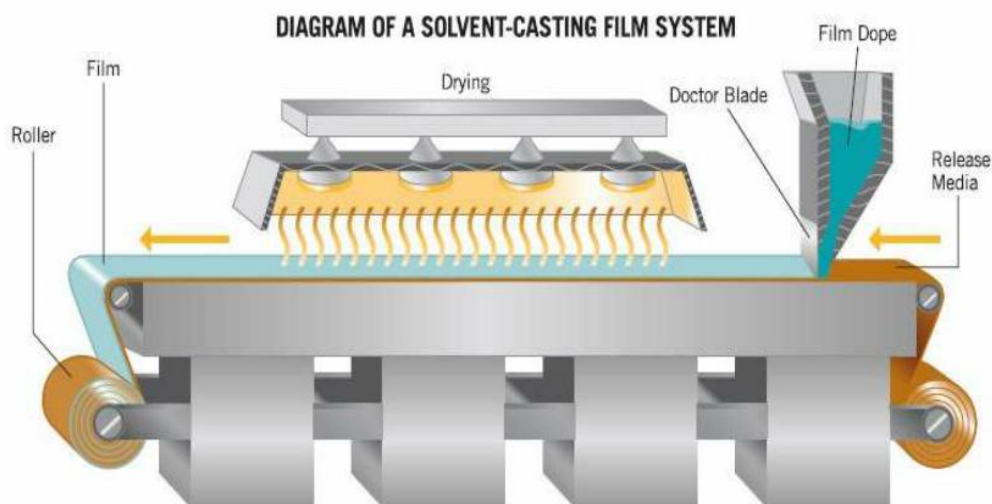


Figure. 1: Solvent casting method.

Advantages

1. Solvent-casting is ideal for manufacturing films containing heat-sensitive API's because the temperatures required to remove the solvents are relatively low compared to those needed for a hot-melt extrusion process.

Better uniformity of thickness and better clarity than extrusion.

2. Film has fine gloss and freedom from defects such as lines.

3. Film has more flexibility and better physical properties.

Disadvantages

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

2. The stable solution with reasonable minimum solid content & viscosity should be formed.

Hot melt extrusion^[10,30,33]

HME is commonly used to prepare granules, sustained-release tablets, and transdermal and transmucosal drug-delivery systems. The HME process recently has gained popularity in the pharmaceutical industry. Based on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers, and plasticizers into various final forms to achieve

desired drug-release profiles. In hot-melt extrusion, the dry ingredients for the film are heated and homogenized by the action of an extruder screw until they are molten and mixed. The melted material is forced through a flat extrusion die that presses extrudate into the desired film shape. The thickness and strength of the film can further be affected by elongation rollers while the material is still hot and pliable. The extruded film is then cooled, cut and packaged.

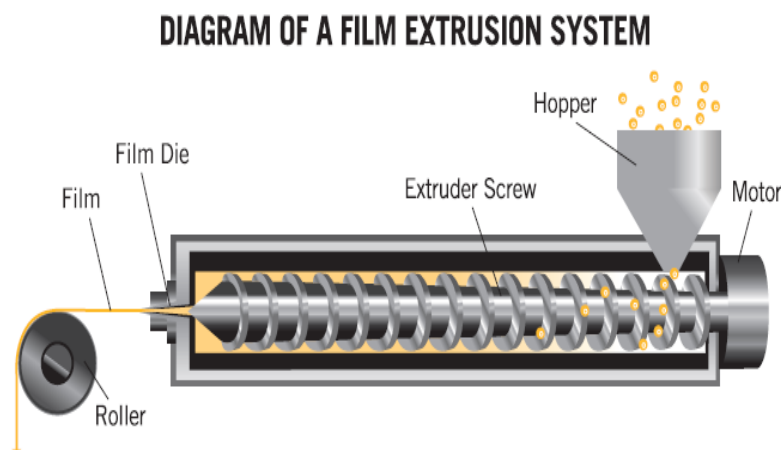


Figure. 2: Hot Melt Extrusion Method.

Advantages

1. Without use of any solvent or water.
2. Fewer processing steps.
3. Compressibility properties of the API may not be of importance.
4. Better alternative for poorly soluble drugs.
5. More uniform dispersion because of intense mixing and agitation.
6. Less energy compared with high shear methods.
7. Possibility of scale up.

Disadvantages

1. Thermal degradation due to use of high temperature.
2. Flow properties of the polymer are essential to processing.
3. Limited number of available polymers.
4. All excipients must be devoid of water or any other volatile solvent.

Table. 7: Different between Techniques Solvent Casting and Hot-melt extrusion.

Manufacturing technique	Solvent Casting	Hot-melt extrusion
API selected	Thermo labile, thermo stable	Thermostable
Solvent required	Yes	No
Process	Hydrous	Anhydrous
Equipment required	Rollers, coaters	Hot-melt extruder
Scale-up	May create problems	May not be difficult
Change of air entrapment	High chance	Low chance

Semi solid casting^[10,30,33]

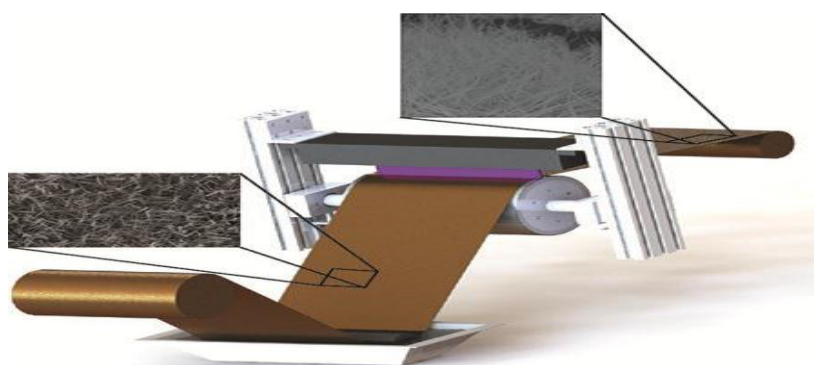
In semisolid casting method firstly solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Solid Dispersion Extrusion^[10,30,33]

The term solid dispersion refers to the dispersion of one or more APIs in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers using methods such as HME. In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.

Rolling Method^[10,28,30]

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes.

**Figure. 3: Rolling method.**

Various technologies used in oral film formulation^[4,10,30]**Soluleaves™**

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 require fast release in the mouth. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. **Soluleaves™** films can be designed to adhere to mucous membrane and to release the active ingredient slowly over 15 minutes.

Wafer tab™

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.

Foamburst™

FOAMBURST™ 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.

Xgel™

XGEL™ film is at the heart of Meldex International's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is non-animal-derived, the film is continuous production processing provides an economic and competitive manufacturing platform.

Packaging

Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR-Labtec has developed the Rapid card, a proprietary and patented packaging system. Single pouch: Soluble Film Drug Delivery Pouch is a peel able pouch for “quick dissolve” soluble films with high barrier properties. Blister card with multiple units: The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister.

Table. 8: List of some marketed products available as FDFs.^[10,24,45]

Brand name	Manufacturer/ Distributor	API (strength)	Uses
Klonopin Wafers®	Solvay Pharmaceuticals	Clonazepam (in five strengths: 0.125, 0.25, 0.5, 1 and 2 mg.)	Anti anxiety
Listerine® Pocket Paks	Pfizer, Inc.	Cool mint	Mouth Fresheners
Sudafed PE®	Wolters Kluwer Health, Inc.	Phenylephrine	Relieving Congestion
Suppress®	InnoZen® Inc.	Menthol (2.5 mg)	Cough Suppressants
Triaminic®	Novartis	Diphenhydramine HCL (12.5 mg)	Anti allergic
Theraflu®	Novartis	Dextromethorphan HBR (15 mg)	Cough Suppressant
Gas-X®	Novartis	Simethicone (62.5 mg)	Anti Flatuating
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
Donepezil Rapidfilm®	Labtec GmbH	Donepezil Hydrochloride (5, 10 mg)	Treatment of Dementia

Application^[9,30]: Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of ODFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. ODF evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products.

1. Gastro retentive dosage systems

Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.

2. Diagnostic devices: Dissolvable films may be loaded with sensitive reagents 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.

3. Taste masking: An important aspect of thin film drug delivery technology is the masking of the often bitter and poor taste of drug formulation.

4. Vaccination

Rotavirus vaccine is a room temperature stable quick-dissolving oral thin film delivery system for vaccines that will make vaccinations almost as simple as freshening your breath.

5. 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.

6. 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.

7. Vaginal drug delivery system: Films that are intended for vaginal administration can be applied manually, without mess or inconvenience of gel or cream applicator. Upon contact with vaginal fluid, the film forming ingredients hydrates to form an ad hoc hydrogel that functions as a normal vaginal product.

Challenging in Formulation Development of Fast Dissolving Oral Films^[9]

The following are some of the challenges in formulating fast dissolving oral film and trying to elaborate and solve these problems. These challenges are directly related to patient compliance.

These include

1. Insolubility of drug.
2. Taste masking of bitter and obnoxious drug.
3. Reduction in drying time of film.
4. High dose incorporation in film.
5. Co-administration of drugs.
6. Stability of film against humidity and temperature.
7. Need special packaging.
8. Dose uniformity.
9. Cost effectiveness.

Insolubility of drug^[9]: Solubility plays a rate limiting parameter to get desired concentration of drug of orally administered formulation in systemic circulation. Problem of solubility is a main challenge for formulation of oral film of BCS class II drugs having low solubility and high permeability.

Taste masking of bitter and obnoxious drug^[9]

Taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the pediatric and geriatric population. Taste is an important parameter in case of fast dissolving oral film. Oral film has to remain in contact with oral mucosa until it completely dissolves in saliva in oral cavity. For this, taste of bitter drugs should be masked. So, taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the pediatric and geriatric population.

Reduction in drying time of film^[9]

Drying time plays an important role in oral film formulation and also in case of rate of production of oral film in industries. Generally, hot air oven is not used for drying of oral film of thermo labile drugs. So, oral film is dried at room temperature. But, it takes more time to dry (about one day).

Dose incorporation in film^[9]

Dose of drug in oral film formulation can be increased by increasing area of container. Only area should be increased keeping thickness of formulation solution constant so that volume of solution needed for formulation is also increased which help in incorporation of high dose and reduction in drying time also.

Co-administration of drugs^[9]

Use of more than one drug i.e. co-administration of drugs is a very difficult task in oral film formulation. Because, it may affect disintegration time as well as dissolution rate of formulation.

Stability of film against humidity and temperature^[9]

Fast dissolving oral film consists of about 45% of polymer which is hydrophilic in nature. In the humid atmosphere, film will absorb water and get liquefied due to dissolution of film in water. So, the stability of film against humidity is very difficult and challenging task. Amorphous drugs often have higher dissolution rates than their crystalline forms, but lower physical stability during storage. Addition of crystallization inhibitors such as hydrophilic polymers to the amorphous drug to form a film formulation is the best method to prevent drug crystallization.

Need of special packaging^[9]

In the pharmaceutical industry, it is vital that the package selected adequately preserve the integrity of the product. A variety of packaging options are available for fast dissolving films. An aluminum pouch is the most commonly used packaging material. APR- Labtec developed the Rapid card, patented packaging system designed for the Rapid films. The rapid card has same size as a credit card and holds three rapid films on each side. Every dose can be taken out individually.

Dose uniformity^[9]

Film which is to be made in a container has to cut into desired area containing required dose of drug. So, to get a uniform dose in all films which cut into desired area is a challenging task.

Evaluation of the Fast dissolving film^[30,38]

Fast dissolving film should be stiff, flat and should not curl on the edges. Mechanical property of the fast dissolving film plays an important role in deciding all these things. Therefore, the prepared mouth dissolving films were evaluated for the following parameters.

Physical characteristics observation^[30,38]

Characteristics such as homogeneity, colour, transparency, flexibility, brittleness and surface of the oral films were evaluated by visual inspection.

Folding Endurance^[30,38]

Folding endurance was determined by repeatedly folding the film at the same place till it break. The numbers of the times the film can be folded at the same place without breaking give the value of folding endurance.

Thickness of film^[30,38]

The thickness of the Mouth dissolving film (2×2 cm) was determined by using a screw gauge. The thickness of each film at three different places was determined and standard deviation was also calculated.

Surface pH^[30,33,34,38]

A film with too much acidic or basic pH affects the area of application and causes damages to oral mucosal membrane leading to patient discomfort. It is likely that the chemical nature of the drug and the excipients influences the pH of the prepared films. In this, the surface pH of

the prepared films was measured after allowing it to wet by keeping it in contact with distilled water for a short period at room temperature. It was measured by touching to bulb of pH meter.

Weight variations^[30,36, 38]

For weight variation, individual films are weighed and the average weights are calculated. Then the average weight of the films is subtracted from the individual weight of the films. A large variation in weight indicates the inefficiency of the method employed and is likely to have non-uniform drug content. This test was carried out for three films of size 2×2 cm in size cut from single film.

Tensile strength^[30,38]

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

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

Percent Elongation^[30, 38]

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

$$\% \text{ Elongation} = \frac{\text{Increase in Length of Strip}}{\text{Initial length of Strip}} \times 100$$

Drug content uniformity^[30,38]

The film unit of the dimensions 2 × 2 cm was placed in 100 ml of distilled water. After complete solubilization, the solution was diluted appropriately, filtered and analyzed by UV spectroscopic method. The average of three films was taken as the content of drug in one film unit.

In- Vitro Disintegration Time^[30,38]

The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER (Centre for Drug Evaluation and Research) guidance can be applied to oral dissolving films. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at

development stage. Typical disintegration time for films is 5–30 seconds. Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. The film as per the dimensions (2 x 2 cm) required for dose delivery was placed in a petridish containing 10 ml phosphate buffer (pH 6.8). Time required for the film to break was noted as *in-vitro* disintegration time. Petri dish was shaken with hands giving jerks. This test was performed on three films of each formulation and mean±S.D calculated.

***In-Vitro* Dissolution Study^[30, 38]**

The dissolution study was carried out using USP paddle apparatus II (Thermonik Campbell Electronics, Mumbai, India), at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using 300 ml of phosphate buffer (pH 6.8) as a dissolution medium. The agitation rate of paddle was 50 rpm. In order to sink the film, each prepared film of the dimensions 2×2 cm was affixed to a paper clip and put into the vessel sampling was done after 30 seconds time interval. The sample was filtered through Whatmann filter paper, diluted suitably if required and analyzed by UV spectroscopic method. An equal volume of the fresh dissolution media, maintained at the same temperature was added after withdrawing the sample to maintain the volume.

Evaluation of Taste Masking^[30, 38]

In this work, Rivastigmine Tartrate having bitter taste so there is not much requirement of taste masking so just simply adding aspartame will solve the problem.

Evaluation of *in-vitro* release kinetics of optimized formulation^[42]

To study the kinetics, data obtained from *in-vitro* release were plotted in various kinetics models

Zero order equation

The graph was plotted as percentage drug released Vs time in hours.

$$C = K_0 t$$

Where K_0 ----- Zero order constant in conc / time

T ----- time in hours

The graph would yield a straight line with a slope equal to K_0 and intercept the origin of the axis. The results were tabulated and graph was shown.

First order equation

The graph was plotted as log % cumulative drug remaining Vs time in hours

$$\text{Log } C = \log C_0 - Kt / 2.303$$

Where C_0 – Initial concentration of drug

K – First order constant

T – Time

Higuchi Kinetics

The graph was plotted as percentage cumulative drug released Vs square root of time

$$Q = Kt^{1/2}$$

Where K = constant reflection design variable systems

t = Differential rate constant

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields as straight line and the slope is one, then the particular dosage form is considered to follow Higuchi Kinetics of drug release. The results were tabulated.

Hixson and Crowell Erosion Equation: To evaluate the drug release with changes in the surface area and the diameter of the particles, the data were plotted using the Hixson and Crowell Erosion rate equation. The graph was plotted by cube root of percentage drug remaining Vs time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} X_t$$

Where

Q_t - Amount of the drug released in time t .

Q_0 - Initial amount of drug

K_{HC} – Rate constant for Hixson and Crowell Erosion Equation

Korsmeyer – Peppas Equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log as cumulative percentage of drug release Vs time

$$M_t / M_\alpha = Kt^n$$

$$\text{Log } M_t / M_\alpha = \text{Log } K + n \log t$$

Where, M_t / M_α - Fraction of drug released at time t .

t – Release time.

K – Kinetic constant (incorporating structural and geometric characteristics of preparation)

α - Diffusional exponent indicative of the mechanism of drug release

If the values is 0.5 or less the release mechanism follows “Fickian Diffusion” and higher value of $0.5 < n < 1$ for mass transfer follow non – fickianmodel (anomalous transport). The drug release follows zero order drug release and case – II transport if the value is 1. For the values of n higher than 1 the mechanism of drug release is regarded as super case – II transport. This model is used to analyse the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The “ n ” value could be obtained from slope of the plot of long cumulative percentage of drug release Vs log time. The results were tabulated.

CONCLUSION

Oral dosage forms remain the primary delivery route for pharmaceuticals because of ease of administration and beneficial release characteristics. There are problem of tablets and painful parenteral dosage forms. Fast dissolving oral film has many advantages related to disintegration, dissolution and bioavailability over these existing dosage forms. In addition to this, film avoids first pass metabolism due to pre-gastric absorption and fast onset of action. Patient compliance is high in all age groups patients especially paediatrics and geriatrics. The rapidly dissolving film drug delivery vehicle bridges the gap between the two ideas, incorporating positive elements from both solid and liquid dosage forms into an elegant, stable, and effective delivery vehicle. But, this film dosage form has come across some obstacles during its formulation and development. So, there is need to address such challenges which may help in future to explore the particular area in research and that may help in overall formulation and development and large scale manufacturing.

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