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FAST DISSOLVING FILMS: A UNIQUE STRATEGY FOR DRUG DELIVERY

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ABSTRACT

In the current scientific scenario the drug delivery technology has become highly competitive and rapidly evolving with ever increasing demand. Fast dissolving film (FDF) is one such type of an innovative and unique drug delivery system which is gaining much attention in the research field of rapid dissolving technology. FDFs are the most advanced form of oral solid dosage form due to more flexibility, comfort and acceptability. They improve the efficacy of APIs by instantly wetting with saliva due to presence of hydrophilic polymer; thereby the film rapidly gets hydrated and dissolves to release the medication within few seconds as compared to fast dissolving tablets, without chewing and no need of water for administration. These drug delivery systems allow the medication to bypass the hepatic first pass metabolism thereby increasing the bioavailability of the drug. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action. FDFs offers a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population thus can be considered as a versatile drug delivery system.

Key words: Fast Dissolving Film, Oral Cavity, Rapid Dissolving.

INTRODUCTION

Despite of so much of advancements in various delivery system developed for administration of various drugs through different routes such as oral, parental, transdermal and nasal etc., the oral route is considered as the preferred route of administration which includes painless, more patient compliance, ease of administration, patient friendly and so on [1,2]. Several new technologies had been developed for oral delivery is being available to address to improve the patient compliance [3]. Fast dissolving film is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration.

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Fast dissolving films (FDFs) are the most advanced form of oral solid dosage form as they improve the efficacy of APIs by dissolving within a minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin [4].

FDFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic, attacks, or coughing for those who have an active life style. It is also useful where local action is desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. Oral thin films (OTFs) also have an established shelf-life of 2-3years, depending on the API but are extremely sensitive to environmental moisture [5].

Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolves or disintegrates in the mouth within few seconds and eliminates the fear of chocking as an alternative to fast dissolving tablets [6,7]. Most fast dissolving films are having taste masked active

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ingredients which are swallowed by the saliva of patients along with the soluble and insoluble ingredients.

Among various approaches two are commonly used to diminish the bitter taste of drug [8]

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

Special Features [9]

- Thin elegant film
- Various sizes and shapes
- Unobstructive
- Mucoadhesion
- Fast disintegration
- Quick dissolving
- Rapid release

Advantage of orodispersible films [10, 11]

- Oral dissolving films can be administered without water, anywhere, any time.
- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated. Also in cases such as motion sickness, acute pain, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. As compared liquid formulations, precision in the administered dose is ensured from each strip of the film. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
- Provide new business opportunity like product differentiation, product promotion, and patent extension.

Disadvantages

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- These films are moisture sensitive and expensive packing of oral film is required.
- Limitations: Most bitter drugs should be avoided or taste masking is required. Proteinaceous drugs should be avoided if used then co-administration of enzyme inhibitors such as aprotinin bestatin, puromicin and bile salts required for the inhibition of proteolytic enzymes present in saliva.

COMPOSITION OF THE FORMULATION [12]

The area of drug loaded film should be between 1-20 cm^2 which depends on the amount of water-soluble polymers that are responsible for rapid disintegration.

FORMULATION ASPECTS FOR FAST DISSOLVING FILMS [12, 13]

Formulation of FDFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of oral strips should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

A. Drug Category

This technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose drugs are difficult to be incorporated in films. Less bitter, potent and highly lipophilic drug should be preferred for oral thin film as in case of fast dissolving tablets.

The ideal characteristics of a drug to be selected:

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

Film Forming Polymers

Water-soluble polymers are used as film formers as they provide quick disintegration, good mouth feel, and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations. A variety of polymers are available for preparation of films of which pullulan, gelatin and hypromellose are most commonly used. Examples of water-soluble polymers include: Pullulan, Gelatin, guar

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gum, xanthan gum, Hydroxyl propyl methyl cellulose, Modified starches, etc.

Ideal properties of the polymers used in the oral film [15]:

1. Polymers should be non toxic, non- irritant and non-bitter.
2. Polymers should be tasteless
3. It should be devoid of leachable impurities
4. It should be inexpensive and readily available
5. It should not be an obstacle in the disintegration time
6. It should have good wetting and spreadibility property
7. It should exhibit sufficient peel, shear and tensile strength
8. It should not cause secondary infection in the oral cavity and should have sufficient shelf life.

B. Plasticizers

Plasticizer is a vital ingredient of the oral films. The selection of plasticizer depends upon its compatibility with the polymer and also the type of solvent employed in the casting of film. It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. Typically the plasticizers are used in the concentration of 1 - 20%w/w of dry polymer weight. Examples include: Glycerol, Propylene glycol, Low molecular weight polyethylene glycols, Citrate derivatives like triacetin, acetyl citrate, Phthalate derivatives like dimethyl, diethyl, dibutyl derivatives, etc.

C. Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. Suitable sweeteners include:

(a) Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc.

(b) Water soluble artificial sweetener: sodium or calcium saccharin salts, acesulfame-k etc.

(c) Dipeptide based sweetener: aspartame

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F. Cooling agents

Cooling agents like monomethyl succinate can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents like WS3, WS23 and Utracoll II can also be used in conjunction with flavors.

G. Flavoring agents

Perception for the flavor changes from individual to individual depending on the ethnicity and liking. Flavoring agents can be selected from synthetic flavor oils, oleo resins extract derived from various parts of the plants like leaves, fruits and flowers. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

H. Coloring agents

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in oral strips when some of the formulation ingredients or drugs are present in insoluble or suspension form.

I. Surfactants

Surfactants are used as solubilizing or wetting or dispersing agents so that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal films. E.g.: Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and spans etc.

J. Stabilizing and thickening agents

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Natural gums like xanthan gum, locust bean gum, carrageenan and cellulosic derivatives can be used.

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MANUFACTURING METHODS [18, 19, 20]

There are five methods for manufacturing purpose:

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

But the most commonly used industrial methods are Solvent-casting method and Hot melt extrusion.

Solvent-casting method

The OTF is preferably formulated using the solvent casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry.

E.g: A. Mahesh *et al.* formulated levocetirizine.2HCl oral film with pullulan polymer by using solvent casting method.

Advantages

- Better uniformity of thickness and better clarity than extrusion.
- Film has fine gloss and freedom from defects such as die lines.
- Film has more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 μm, although various thicknesses are possible to meet API loading and dissolution needs.

Disadvantages

- The polymer must be soluble in a volatile solvent or a stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

Hot Melt Extrusion

In present method the mass is prepared first under the control of temperature and steering speed. Afterwards, the film is coated and dried in a drying tunnel; once again the temperature, air circulation and line speed are controlled. Then follows a slitting and in the last step the films are punched, pouched and sealed.

Ex.: F. Cilurzo *et al*., formulated Piroxicam film with Maltodextrin plasticized by glycerin by using hot melt extrusion method.

Advantages

- Without use of any solvent or water and consists of fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages

- Thermal degradation due to use of high temperature
- Limited number of available polymers and flow properties of the polymer are essential for processing
- All excipients must be devoid of water or any other volatile solvent

Semisolid Casting

In semisolid casting method firstly a 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 film 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

Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method

In this 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 gives desired shape and sizes.

EVALUATION TESTS [21-28]

Thickness

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations.

Dryness test/tack tests

Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated

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by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below

$$\text{Tensile strength} = \frac{\text{Load at Failure X 100}}{\text{Strip thickness X Strip Width}}$$

Percent elongation

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

$$\% \text{ Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

Young's modulus

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

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

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

Tear resistance:

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm (2 in)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds-force).

Weight Variation

Weight variation is studied by individually weighing 10 randomly selected films and by calculating the average weight.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Surface pH of film

The surface pH of fast dissolving film was determined in order to investigate the possibility o any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. The pH was measured by bringing the electrode in contact with the surface of the oral film which was previously wet with the help of water.

Swelling property

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

$$\alpha = (wt - wo)/wo$$

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

Transparency

The transparency of the films can be determined using simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows:

$$\text{Transparency} = (\log T600)/b = - €c$$

Where T600 is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

Assay/ Content uniformity

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

Disintegration time

Disintegration of orally fast dissolving films requires US disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablet described in Centre for Drug Evaluation and Research (CDER) guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films strips.

Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

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Stability studies

Stability studies have to be carried out at accelerated condition (65% relative humidity and 35 ºC temperature) in the humidity chamber. After that films are to be evaluated for the

Packaging [28]

A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films. Which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. Applied Pharma Research (Switzerland)-Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the Mouth dissolving Films. The Rapid Card is exactly the same size as a credit card and holds three Mouth dissolving Films on each side. Every dose can be taken out individually, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet and have it readily available.

Table 1. Composition of fast dissolving film

S.No	Ingredients	Amount(w/w)
1.	Active pharmaceutical ingredient	5 to30%
2.	Water soluble polymer	45%
3.	Plasticizer	0 to20%
4.	Saliva stimulating agent	2 to 6%
5.	Surfactant	q.s.
6.	Sweetening agent	3 to 6%
7.	Flavors, colors, fillers	q.s.

Table 2. Some Examples of drugs and their categories that can be incorporated in the fast dissolving films

Category of drugs	Examples
Selective serotonin reuptake inhibitors	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram and alaproclate.
Anti-emetics	Ondansetron, granisetron, palonosetron, dronabinol, aprepitant, ramosetron, metopimazine, nabilone, , prochlorperazine, dimenhydrinate, prochlorperazine, etc.,
5HT3 antagonists	Alosetron, ondansetron, granisetron, palonosetron, ramosetron and tropisetron.
Anti-epileptics	Carbamazepine, clonazepam, diazepam, divalproex sodium, fosphenyloin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenyloin, primidone, tiagabine, topiramate, valproate s o d i u m , vigabatrin and zonisamide.
Anti-migraines	Almotriptan, dihydroergotamine mesylate, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan.
Dopamine D1 and D2 antagonists	Amisulpride, bromperidol, cabergoline, domperidone, fenoldopam, haloperidol, metoclopramide, metopimazine, pergolide mesylate, prochlorperazine, quetiapine, ropinirole hydrochloride, sulpiride, tiapride and zotepine.
Nootropics	Almitrine dimesylate and raubasine, cevimeline hydrochloride, codergocrine mesylate, donepezil, galantamine, ginkgo biloba extract (EGb 761), memantine, piracetam, rivastigmine, sulbutiamine, tacrine and vinpocetine.
Statins	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin

Table 3. List of FDA approved Non-Nutritive Sweeteners (Sweetness factor, Sucrose = 1) [17]

S.No.	Sweetener	Sweetness Factor
1.	Aspartame	180-200
2.	Sucralose	600
3.	Acesulfame K	200
4.	Neotame	7000-13000
5.	Saccharin	300

Table 4. Flavoring agents for taste masking [17]

Basic Taste	Masking agents
Salt	Butterscotch, maple, apricot, vanilla,wintergreen, mint.
Bitter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry
Sour	Citrus flavor, licorice, root beer, raspberry.

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Table 5. List of some marketed products available as Fast Dissolving Films [29]

Brand name	Manufacturer/Distributor	API (strength)	Uses
Klonopin Wafers	Solvay Pharmaceuticals	Clonazepam (0.125mg, 0.25mg, 0.5mg, 1mg and 2mg.)	Treatment of Anxiety
Listerine Cool Mint 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
Orajel	Del	Menthol/pectin (2mg/30mg)	Mouth ulcer
Gas-X	Novartis	Simethicone (62.5mg)	Anti Flatuating

Figure 1. Quick dissolving oral strip

Figure 2. Fast dissolving films using different polymers [16]

Figure 3. Solvent Casting Film Systems

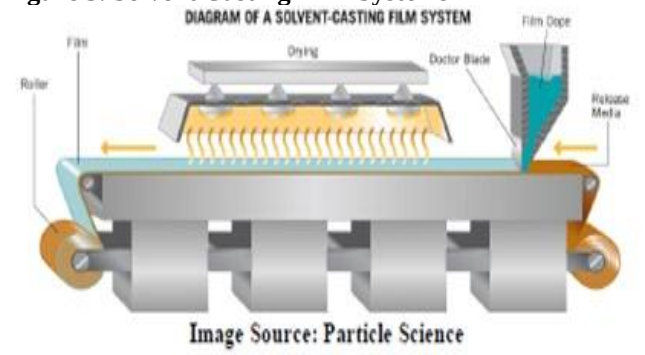

Figure 4. Film Extrusion system

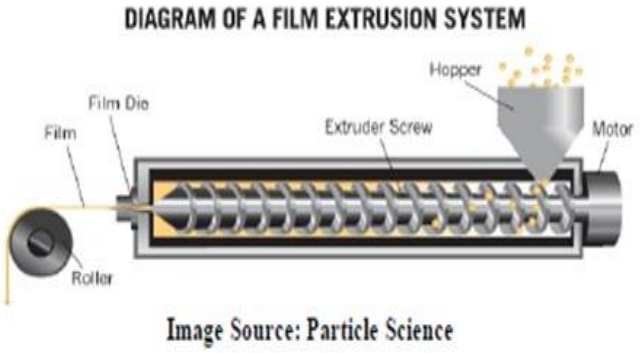

Figure 5. Three roll coating unit

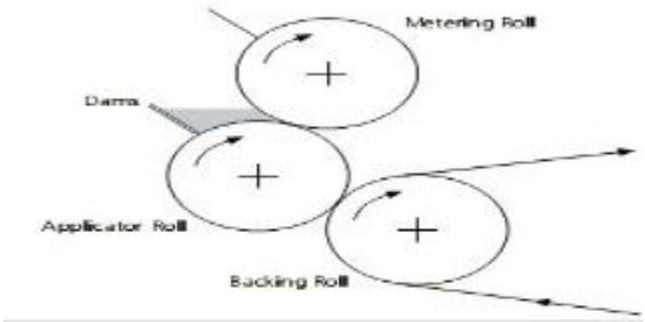

Figure 6. Rapid Card

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CONCLUSION

Fast dissolving films are considered to be the most advanced, innovative and promising dosage forms as they help in the effective management of immediate attacked diseases. Bypassing the hepatic first pass metabolism, fast dissolving films increase the bioavailability of the medication and moreover they are of more patient compliance. They have great potential of delivering the medicinal agent systemically as well as locally and have several advantages over many conventional dosage forms thus emerging as a new novel drug delivery system. As the future of fast dissolving films is expected to grow at a blistering pace day-by-day, more and more of scientific research work can be contributed for the further development in this particular arena of pharmaceutical drug delivery systems.

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