FAST DISSOLVING FILMS (FDF) : INNOVATIVE DRUG DELIVERY SYSTEM

Sandeep Saini*[1], Arun Nanda[1], Monika Hooda[1], Komal[1]

1.Department of Pharmaceutical Sciences,Maharshi Dayanand University Rohtak, Haryana -124001,India

Corresponding Author:
Sandeep Saini
Department of Pharmaceutical Sciences,
M.D. University,
Rohtak, Haryana-124001, India
Email:saini86pharma@gmail.com
Mob.No. +918901390127

Summary

Fast dissolving drug delivery system is a innovative drug delivery system in which the consumption of the dosage form without any use of water intaking.In this delivery system the dosage form is meant to put below the tongue or in the buccal cavity; then the dosage form get wetted and disintegrate with in seconds.In response to this need, a variety of orally disintegrating tablet (ODT) formats were commercialized.Most ODT products were formulated to dissolve in less than one minute when exposed to saliva to form a solution that could then be more easily swallowed.Fast dissolving films (FDF) evolved over the past few years from the consumers for delivering vitamins and personal care products.The objective of our review is to compile the recent advancements and literature regarding the fast dissolving films.

Keywords: ODTs, FDF, Fast dissolving, Solvent casting, Folding endurance, Bursting strength.

Introduction

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients.[1] Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms.[2]

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets.

Special features of mouth dissolving films

• Thin elegant film
• Available in various size and shapes
• Unobstructive
• Excellent mucoadhesion
• Fast disintegration
• Rapid release

The mouth dissolving films has also a clear advantage over the Oral dissolving tablets (ODTs):
-ODTs are sometimes difficult to carry, store and handle (fragility and friability).
-Many ODTs are prepared by using the expensive lyophillisation process.
A large number of drugs can be formulated as mouth dissolving films. Innovative products may increase the therapeutic possibilities in the following indications.
-Pediatrics (antitussives, expectorants, antiasthamatics)
- Geriatrics (antiepileptic, expectorants)
- Gastrointestinal diseases
- Nausea (e.g. due to cytostatic therapy)
- Pain (e.g. migraine)
- CNS (e.g. antiparkinsonism therapy).[1]

Improved patient compliance is a primary benefit of the fast-dissolving drug delivery systems. The main difference between the Quick-Dis™ (Example) drug delivery system and most conventional fast-dissolving dosage forms is that it is not a tablet. Rather, the Quick-Dis™ drug delivery system is a thin film that alleviates the fear of swallowing and the risk of choking commonly associated with a conventional tablet. This fast-dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment. These additional, superior benefits allow patients to take their medication anytime and anyplace under all circumstances.Quick-Dis™ however, comprises a tough, solid, soft, flexible film and does not require special packaging. It is thin and can be carried in a patient's pocket, wallet, or pocket book.

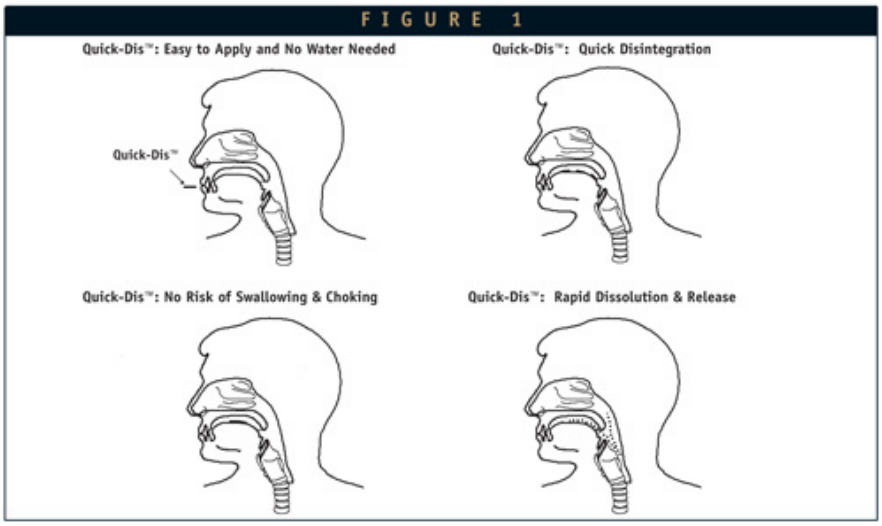
General properties & release mechanism

The Quick-Dis™ drug delivery system comprises a thin, printable, low-moisture, non-tacky film that is convenient for dosing, suitable for labeling, and flexible for easy packing, handling and application. The thickness of a typical film ranges from 1 to 10 mil and its surface area can be 1 to 20 cm^2 for any geometry. At the same time, the rapid hydration rate facilitates an almost immediate softening of the Quick-Dis™ film upon application in the oral cavity. The wet-tack and mucoadhesive properties of the system are designed to secure the film to the site of application. The flexibility and strength of the film may be selected/modified to facilitate automatic rewinding, die cutting, and packaging during manufacturing.

The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mil. The dissolving time, which is defined as the time at which not less than 80%

of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mil.

The drug is released from the dosage form upon disintegration and dissolution. The disintegration and dissolving times are prolonged as the film thickness increases as shown in the Figure 1. The disintegration and dissolving times may be further influenced, by varying the formulation composition of the film.[3]



Composition of the system[1]

Mouth dissolving film is a thin film with an area of 5- 20 cm2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 15mg. formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films, such as shifting shifting the glass transition temperature to lower temperature.
A typical composition contains the following
Drug 1-25%
Water soluble polymer 40-50%
Plasticizers 0-20%
Fillers, colours, flavours etc. 0-40%

1. Drugs

Several class of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. Dexamethacone, salbutamol, Ondansterone).[4,5,6]

2. Water soluble polymers

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application.

The water-soluble polymers achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol30,Hdroxypropylcellulose,Polyvinylalcohol,Maltodextrin.

3. Plasticizers

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, di-butylpthallate, and polyethylene glycols etc.

4. Surfactants

Surfactants are used as solublising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

5. Flavour

Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors.

6. Colour

A full range of colors is available, including FD&C colors, EU Colours, Natural Colours and custom Pantone-matched colours.

*Some saliva stimulating agents may also be added to enhance the disintegration and to get rapid release. Some of these agents are citric acid, tartaric acid, malic acid, ascorbic acid and succinic acid.

Classification Of Fast Dissolve Technology[7]

For ease of description, fast-dissolve technologies can be divided in to three broad groups:.

Lyophilized systems,

Compressed tablet-based systems,

Thin film strips.

The lyophilized systems

The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems.

Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients.

Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard HDPE bottles or blisters through to more specialist pack designs for product protection The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail.s Fuisz technology. It uses the proprietary Shearform system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms.

Oral Thin Films (OTF)

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) 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. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to middevelopment stages for prescription drugs. This is largely as a result of the success of the consumer breath freshener products such as Listerine PocketPaks in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats**.**

Advantages and disadvantages of oral formulations such as[8]

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. The disadvantage of most ODT is that they are fragile and brittle, which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.
3. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
4. No need of water has led to better acceptability amongst the dysphagic patients. The difficulty encountered in swallowing tablets or capsules is circumvented. The large surface area available in the strip dosage form allows rapid wetting in the moist buccal environment. The dosage form can be consumed at anyplace and anytime as per convenience of the individual.

5. 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 .
6. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
7. Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

Disadvantage of Oral Strip[7]

The disadvantage of OS is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip **.**
There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly
limits the range of compatible drug products. The other technical challenge with these dosage forms is achieving Dose Uniformity .

Application of Oral Strip in Drug Delivery[7]

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs 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. Dissolvable oral thin films (OTFs) 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.Topical applications

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

2.Gastro retentive dosage systems

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. 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.

3.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 **.**

Manufacturing Methods[1]

One or combination of the following process can be used to manufacture the mouth dissolving films.

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

1. Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

2. Semisolid casting

In semisolid casting method firstly a solution of watersoluble 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. Both mixtures are mixed to form homogenous viscous solution .Degassed under vacuum Bubble free solution is coated on non-treated casting film Coated film is sent to aeration drying oven Film is cutted in to desired shape and size.

3. Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion.

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

4. Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5. Rolling Method

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 onthe rollers and cutted in to desired shapes and sizes.

Compounds suitable for this system

- Compounds should have good aqueous solubility.
- They must have good solubility at salivary pH.

- They must have low dose so that could be incorporated into oral film.
- They must be stable in aqueous or basic ph.
- Compounds with problem of first pass metabolism are suitable for this system.
- Compounds with gastric irritating property are suitable for this system.

Quality control tests

Thickness

It can be measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

Dryness test/tack tests

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-totouch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OS as well.[9] The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. 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 .[10] It is calculated 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.[11]

$$\%\ \text{Elongation} = \frac{\text{Increase in length of strip X 100}}{\text{Initial length of strip}}$$

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 Newtons (or pounds-force).[12]

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.[13]

Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. 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. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s.[14]

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.

Assay/drug content and 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 percent.

Table 1: Some marketed product of oral fast dissolving film[1,2,8]

Distributor	Brand	API	Strength
Del	Orazel	Menthol/pectin	2mg/30 mg
InnoZen	Suppress	Menthol	2.5 mg
Novartis	Gas-X	Simethicone	62.5 mg
Novartis	Theraflu	Phenylepherine HCl/Dextromethorphan HBr	10 mg/20 mg
Novartis	Theraflu	Phenylepherine HCl/Diphenhydramine HCl	10 mg/25 mg
Novartis	Theraflu	Dextromethorphan HBr	15 mg
Novartis	Theraflu	Diphenhydramine HCl	25 mg
Novartis	Triaminic	Diphenhydramine HCl	12.5 mg
Novartis	Triaminic	Phenylepherine HCl	2.5 mg
Novartis	Triaminic	Phenylepherine HCl/Diphenhydramine HCl	5 mg/12.5 mg
Novartis	Triaminic	Dextromethorphan HBr	7.5 mg
Novartis	Benadryl	Diphenylhydramine HCl	12.5 mg

Pfizer	Benadryl	Diphenylhydramine HCl	25 mg
Pfizer	Suldafed	Phenylephrine HCl	10 mg
Prestige	Chloraseptic	Benzocaine/menthol	3mg/3mg
Labtec GmbH	Ondansterone Rapdifilm	Ondensterone	4mg/8 mg
Labtec GmbH	Donepzil Rapdifilm	Donepzil HCl	5mg/10 mg

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