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Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form

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Abstract : 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. 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. 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. 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 mid-development stages for prescription drugs.

Key words
Fast dissolving films • Solvent casting • Semisolid casting• Disintegration time • Contact angle

Introduction

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or non-compliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films[1].

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[2].

Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids,

tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices[3]. OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs[4].

Special features of mouth dissolving films[5]

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

Advantages

- Convenient dosing
- No water needed
- No risk of chocking
- Taste masking
- Enhanced stability
- Improved patient compliance

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[2].

A large number of drugs can be formulated as mouth dissolving films. Innovative products may increase the therapeutic possibilities in the following indications[3].
-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)

Composition of the system

Mouth dissolving film is a thin film with an area of 5-20 cm^2 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[2].

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. paracetamol, meloxicam, valdecoxib)[6,7,8,9].

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 cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGIT-RD10[8,9,10,11,12] .Polymerized rosin is a novel film forming polymer[13].

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[10].

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[14].

5) Flavour

Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors[15].

6) Colour

A full range of colors is available, including FD&C colors, EU Colours, Natural Colours and custom Pantone-matched colours[15].
*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[16].

Manufacturing Methods

One or combination of the following process can be used to manufacture the mouth dissolving films[17].

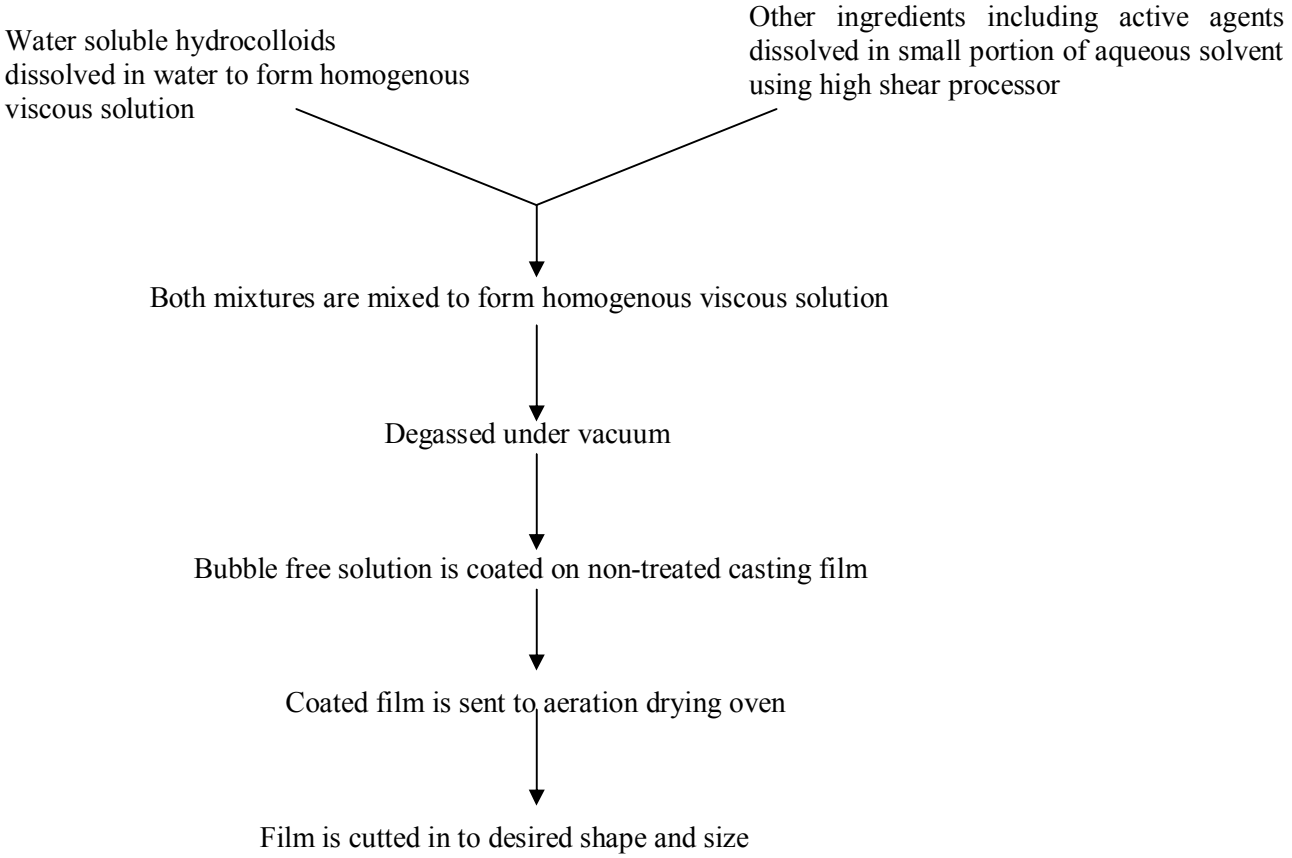
i) Solvent casting
ii) Semisolid casting
iii) Hot melt extrusion
iv) Solid dispersion extrusion
v) Rolling

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 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.



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[18].

-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 on the rollers and cutted in to desired shapes and sizes[3].

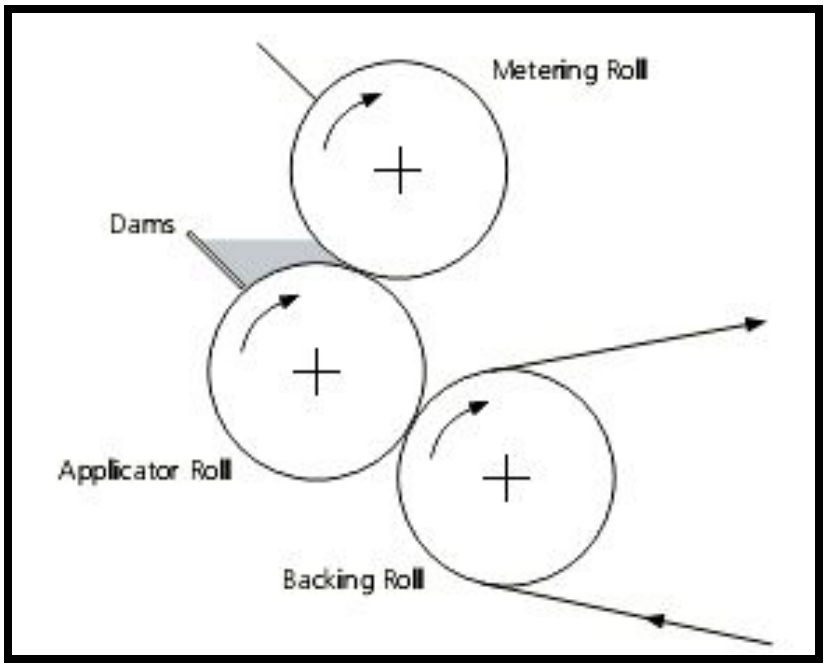


Figure1. Three roll coating unit.

TECHNOLOGIES[19]

1) SOLULEAVES™ technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

2) 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 flavoured for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release, or for use by patients who have difficulty swallowing.

3) 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. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.

4) 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, approved on religious grounds and is suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing platform. XGEL™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use.

All of the XGEL ingredients are well known and generally regarded as safe (GRAS).

Evaluating parameters

1) Mechanical properties

Mechanical properties of films are evaluated Instron using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Films are held between two clamps positioned between 3cm. During measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks.

Three mechanical properties namely tensile strength, elastic modulus and % elongation are calculated[20].

a) Tensile strength

Tensile strength is calculated by formula =

force at break/ initial cross sectional area of film in mm^2

b) Elastic modulus

Elastic modulus is calculated by formula

$$\text{Elastic modulus} = \frac{\text{force at corresponding strain}}{\text{Cross sectional area } (mm^2)} * \frac{1}{\text{Corresponding strain}}$$

c) % Elongation

It is calculated as =

$$\frac{\text{Increase in length}}{\text{Original length}} * 100$$

d) Folding endurance

Folding endurance is determined by folding the films of uniform cross sectional area and thickness until it breaks.

2) Morphology study

The morphology of the films is studied using scanning electron microscopy (SEM), at a definite magni fication[6].

3) Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed[20].

The degree of swelling was calculated using parameters $\mathbf{w_t\text{-}w_0/w_o}$, $\mathbf{w_t}$ is weight of film at time t, and $\mathbf{w_o}$ is weight of film at time zero.

4) Contact angle

Contact angle measurements is performed at room temperature with a goniometer (AB Lorentzen and Wettre, Germany). A drop of double distilled water was placed on the surface of the dry film. Images of the water droplet were recorded within 10 seconds of deposition by means of digital camera. Digital pictures were analyzed by imageJ 1.28v software (NIH, USA) for angle determination. A minimum of five measurements, taken at different positions of the film, was carried out. The contact angle was measured on both sides of the drop and averaged[21].

5) *In vitro* disintegration time

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates[10].

6) In vitro dissolution studies

The *in vitro* dissolution study is carried out in simulated saliva solution pH 6.4 phosphate buffer using USP paddle apparatus at 37±0.5°C. samples are withdrawn at regular time interval interval and analyzed by UV-Visible spectrophotometer[6].

7) Determination of dissolution rate by conductivity method

In the past 5 years several personal care products formulated in quick release film form have entered the marketplace, of which fast-dissolve breath fresheners were first. The fast dissolve oral films completely dissolve in as little as 1 minute. The majority of oral films on the market today contain ionizable components. This work presents a method for high-resolution monitoring of the dissolution of fast dissolving oral films by measuring conductivity of the dissolution medium[22].

Equipment required

Equipment(Fig.2) includes the following:

- Variable speed stirrer motor: capable of 250 rpm.
- Analytical balance (medium weight): capable of weighing to the nearest 0.01g and having a range not less than 400g.
- Low-form beaker: 3×800 ml.
- Impeller: 2-inch diameter, 1 blade (stainless steel or monel metal).
- Conductivity probe: capable of measuring conductivity to 0.1 µ siemens (Hann 8033 conductivity meter).
- Laboratory equipment stand.
- Double-sided clear tape: 3/4 inch-wide.
- External stands to hold conductivity probe.
- Scissors
- Stopwatch with a second hand.

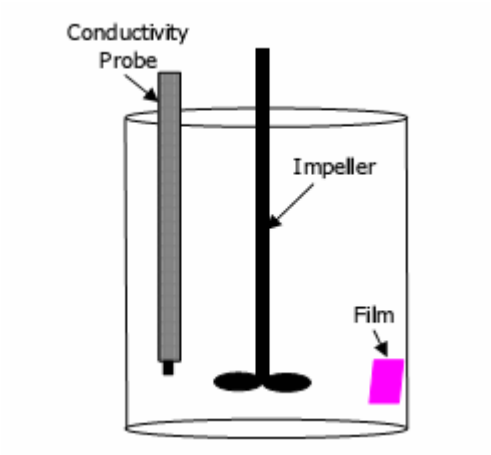


Figure. 2 Diagram of equipment set-up

Film Preparation

One side of the film is adhered to the double sided tape, and the double sided tape is cut to the dimensions of the film (Figure. 3).

Test Procedure

- Fill a clean beaker with 300 g (±0.05g) of the deionized water.
- Test the conductivity of the water to establish the background value.
- Adhere the film inside the dry, clean 800ml beaker so that the centre section is even with or slightly below the 100 ml line of the beaker. Arrange theConductivity probe and the impeller in the beaker.
- As quickly as possible pour the 300 ml of the water in the beaker containing the film, impeller and the conductivity probe. When the water completely covers the film, start the timer (approx 3sec). Then restart the impeller stirring at 250rpm.
- Take a data point at every 10 sec for the first minute. The take data as appropriate.

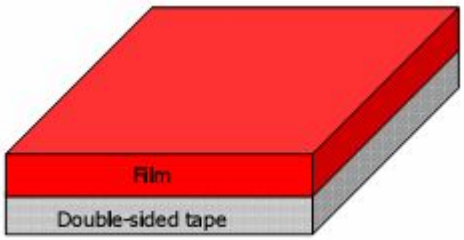


Figure 3. Diagram of prepared film

Packaging

A variety of packaging options are available for fast-dissolving films. 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, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually[2].

Marketed Films[23,24,25,26,27,28]

Table 1. List of marketed fast dissolving films

S.No.	Product	Manufactured By
1.	Dextromethorphan HBr (cough suppressant),Diphenhydramine Citrate (cough and cold),Breath Strips	MonoSolRx
2.	Doneprezil rapid dissolving films, Ondansatron rapid dissolving films	Labtec Pharma
3.	Life-saving rotavirus vaccine to infants	Johns Hopkins undergraduate biomedical engineering students.
4.	Methylcobalamin fast dissolving films, Diphemhydramine HCl fast dissolving films,Dextromethorphan fast dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films	Hughes medical corporation
5.	Altoid cinnamon strips, Boots vitamin c strips, Cool shock peppermint strips, Benzocaine films, Caffeine films	Dow chemical company

6.	Listerine Pocket Paks Breath Freshening Strips	Pfizer's Warner-Lambert consumer healthcare division
7.	Energy strips - Caffeine 20mg, Acetyl Salicylic Acid (ASA), Ondansetron HCl, Dexamethasone, Nitroglycerine, Risperidone Vitamin B12, melatonin, folic acid, biotin Benzocaine, Diphenhydramine HCl, Dextrometorphan	ODF Technologies Inc.

Conclusion

Fast dissolving oral films have several advantages over the conventional dosage forms. So they are of great importance during the emergency cases such as allergic reactions and astahmatic attacks whenever immediate onset of action is desired.

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