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A Review on Fast Dissolving Oral Films

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Kolhe Rohini C.*, Khot Suchita P., Gunjegaokar M.B.

SJVPM'S Rasiklal M. Dhariwal College of Pharmacy, Chinchwad-19, Maharashtra, India.

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ABSTRACT

Oral administration is the most broadly accepted route of delivery due to its ease of administration, convenience, usefulness and most importantly patient compliance. Several new technologies for oral delivery have recently been available to address the problems of a physicochemical and pharmacokinetic characteristic of drugs while improving patient compliance. One of these include fast dissolving technology which offers the advantages of both solids and liquids such as quick disintegration and dissolution of the formulation, no residue in the mouth, requires no water uptake, provides pleasant mouthfeel. Based on the available literature this review object to provide brief information about Fast dissolving films.

INTRODUCTION:

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bio-adhesive 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 oro-mucosal 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 an 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[3].

Special features of mouth dissolving films[4]

• Thin elegant film

• Available in various size and shapes

• Unobstructed

• Excellent mucoadhesive

• Fast disintegration

• Rapid release

Advantages of mouth dissolving films:

• 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 lyophilization process[1].
- A large number of drugs can be formulated as mouth dissolving films.
- Innovative products may increase the therapeutic possibilities in the following indications[2].
- Pediatrics (antitussives, expectorants, antiasthmatics)
- Geriatrics (antiepileptic, expectorants)
- Gastrointestinal diseases
- Nausea (e.g. due to cytostatic therapy)
- Pain (e.g. migraine)
- CNS (e.g. antiparkinsonism therapy)

Composition of the mouth dissolving film:

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 the glass transition temperature to lower temperature[1].

Table 1: A typical composition of Fast dissolving film contains

Drug	1-25%
Water-soluble polymer	40-50%
Plasticizers	0-20%
Fillers, colors, flavors etc.	0-40%

1) Drugs

Several classes of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthmatics (salbutamol sulfate), antitussives, expectorants, antihistaminics, and NSAID'S (e.g. paracetamol, meloxicam, valdecoxib) [5,6,7]

2) Water soluble polymers

Water-soluble polymers are used as film formers. The use of the 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, Methylcellulose A-3, A-6 and A-15, Pullulan, carboxymethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and Eudragit RD10[7,8,9]. Polymerized rosin is a novel film forming polymer[10].

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, dibutyl phthalate, and polyethylene glycols Etc[8].

4) Surfactants

Surfactants are used as solubilizing 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, benzethonium chloride, tweens etc. One of the most important surfactants is poloxamer 407 that is used as solubilizing, wetting and dispersing agent[11].

5) Flavour

Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors[12].

6) Colour

A full range of colors is available, including FD&C colors, EU Colours, Natural Colours and custom Pantone-matched colours[12]. Some saliva stimulating agents may also be added to enhance the disintegration and to get a rapid release. Some of these agents are citric acid, tartaric acid, malic acid, ascorbic acid and succinic acid[13].

Manufacturing Methods for preparation of mouth dissolving films:

One or combination of the following process can be used to manufacture the mouth dissolving films[14]

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 cast into the Petri plate and dried.

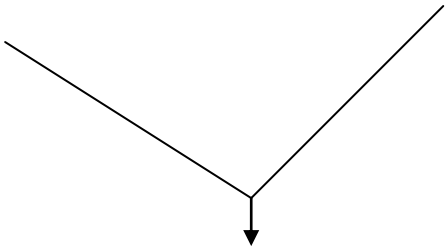
2) Semisolid casting

In semisolid casting method, a solution of water-soluble film forming polymer prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared with ammonium or sodium hydroxide. Then the appropriate amount of plasticizer is added so that a gel mass is obtained. Finally, the gel mass is cast into 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 a film forming polymer should be 1:4.

STEPS INVOLVED IN MANUFACTURING FAST DISSOLVING FILM

Water-soluble hydrocolloids dissolved in water to form homogenous viscous solution

other ingredients including active agents dissolved in small portion of aqueous solvents using high shear processor



Both mixtures are mixed to form homogeneous 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 cut into desired shape and size

3) Hot melt extrusion:

In hot melt extrusion method, the drug is mixed with carriers in solid form. The extruder having heaters melts the mixture. Finally, the melt is shaped into films using the dies. There are certain benefits of hot melt extrusion[15].

i) Fewer operation units

ii) Better content uniformity

iii) An anhydrous process

4) Solid dispersion extrusion

In this method, immiscible components are extruded with drug and then solid dispersions prepared. Finally, the solid dispersions are shaped into films by means of dies.

5) Rolling Method

In the rolling method, a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water or mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes[2]. Other ingredients including active agents dissolved in the small portion of aqueous solvent using a high shear processor. Water-soluble hydrocolloids dissolved in water to form a homogeneous viscous solution.

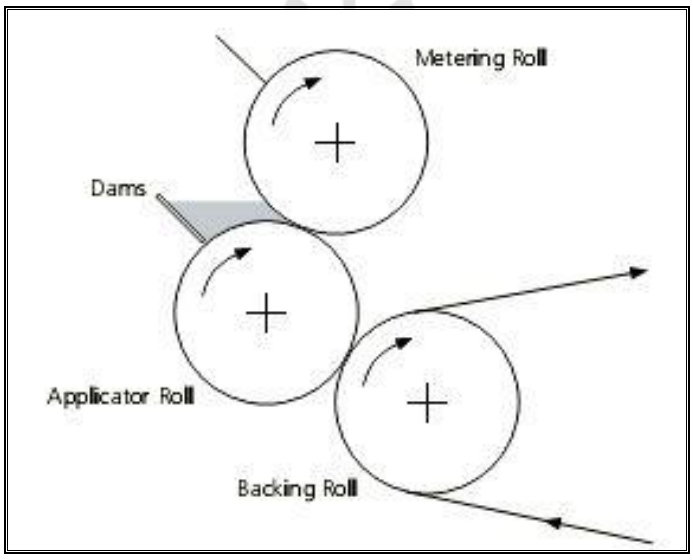


Figure 1: Three roll coating unit

NOVEL TECHNOLOGIES OF FAST DISSOLVING ORAL FILMS[16]:

1) SOLULEAVES™ technology is used to produce a range of oral delivery films that can incorporate active ingredients, colors and flavors. 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 requiring fast release in the mouth. For pharmaceutical uses, this method of administration is especially useful for pediatric 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 active ingredients into an ingestible filmstrip. The system provides rapid dissolution and release of active ingredients when the strip comes into contact with saliva in the mouth. The WAFERTAB™ filmstrip can be flavored 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 active ingredients 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 the 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 flavors.

4) XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is nonanimal derived, approved on religious grounds and is suitable for vegetarians; continuous production processing provides an economic and competitive manufacturing platform. XGEL™ film can be taste masked, colored, 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 optimized for the intended use. All of the XGEL ingredients are well known and generally regarded as safe (GRAS).

Characterization for fast dissolving films

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 3 cm. During measurement, the strips were pulled at the rate of 2mm/sec. The force and elongation were measured when the film breaks. Three mechanical properties namely tensile strength, elastic modulus, and % elongation are calculated[17].

a) Tensile strength

Tensile strength is calculated by formula = force at break/ initial cross-sectional area of film in mm^2

b) % Elongation

$$\text{It is calculated as} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

c) 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 magnification.

3) Swelling property

Film swelling studies are 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 the 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[17]. The degree of swelling was calculated using parameters **Wt- Wo /Wo, Wt** is a weight of film at time t, and **Wo** is a weight of film at time zero.

4) Contact angle

A contact angle measurement 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 the digital camera. Digital pictures were analyzed by image J1.28v 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.

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[8].

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 and analyzed by UV-Visible spectrophotometer[5].

PACKAGING OF MOUTH DISSOLVING FILMS:

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 the same size as a credit card and holds three raid films on each side. Every dose can be taken out individually[1].

Table 2: Marketed preparations of rapidly dissolving films

Brand name	Ingredients	Category
Listerine® pocket packs	Available in cool mint®, Fresh Citrus, Cinnamon, and fresh burst®. Pullulan is used as a film-forming polymer.	Mouth Freshener.
Onsolis™	Fentanyl buccal soluble film	Pain in opioid-tolerant patients.
Ondansetron Rapid film® Labtech Pharma Ltd.	Ondansetron	It is used in the prevention of chemotherapy and radiation-induced nausea and vomiting and prevention of postoperative nausea and vomiting.
Donepezil Rapid film®	Donepezil Hydrochloride 5 mg and 10 mg.	Treatment of mild to moderately severe dementia of the Alzheimer's type.
Paladin Labs (Bioenvelop)	Nicotine	To reduce the smoking habit
Triaminic Thin Strips®	Phenylephrine HCl 2.5 mg	It temporarily relieves nasal and sinus congestion.

CONCLUSION:

Drug delivery through oral cavity offers many advantages. The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of dosage forms Active substances can be administered locally to treat oral diseases like periodontal disease, bacterial and fungal infections. A systemic action can be achieved via permeation through the mucosal endothelium. For systemic drug absorption, various dosage forms and devices, e.g. buccal patches, buccoadhesive discs and mechatronic delivery devices have recently been developed. Mouth dissolving films seems to be promising dosage form as bioadhesive mucosal dosage form.

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