

Review Article

Fast Dissolving Film: Novel Drug Delivery System

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Received 15 June 2014; received in revised form 23 June 2014; accepted 23 June 2014

Available online 23 June 2014

Abstract

The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. The conventional oral solid dosage forms are tablets and capsules. Lots of patient find it difficult to swallow tablets and capsules particularly pediatric and geriatric patients and do not receive their medicine as prescribed. Hence many researchers are focusing on design and development of innovative drug delivery system for existing drugs. One such delivery system is fast dissolving oral film with lots of benefit of fast dissolving tablets by avoiding the friability and risk of choking. Choking problem is more in case of pediatrics patients. Formulation of fast dissolving film can be achieved by many techniques, but common methods used are the spraying and casting. This techniques use the hydrophilic film former in combination with suitable recipients, which disintegrate or dissolve the film within few seconds without need of water.

Keywords: Fast Dissolving Film, Spraying, Casting.**1. Introduction^{1,2}**

The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. The conventional oral solid dosage forms are tablets and capsules. Lots of patient find it difficult to swallow tablets and capsules particularly pediatric and geriatric patients and do not receive their medicine as prescribed. Hence 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 or mucosal absorption or with formula modifications, will maintain the

In contrast to other existing, rapid dissolving dosage forms, which consist of liophilisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets.

1.1. Overview of Oral Mucosa³**Fig. 1:** Overview of Oral Mucosa.

Drug given via the oral mucosa is a promising route, when one wants to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. Thus, there is a increasing interest in developing alternative dosage forms, i.e. orally fast

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disintegrating strip, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids.

1.2. Criteria for Fast Dissolving Film³

Fast dissolving film should,

- Have a pleasurable mouth feel.
- Not require water to swallow, but it should dissolve or disintegrate in the mouth within seconds.
- Be compatible with excipients.
- Depart no residue in the mouth after oral administration.

1.3. Advantages of Fast Dissolving Film^{3,4}

- Ease of administration to patients who cannot swallow the medicines like the bed-ridden, stroke victims and patients who refuse to swallow like geriatrics, pediatrics and psychiatrics.
- Good mouth feel.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an rapid onset of action required.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these films.

1.4. Disadvantages of Fast Dissolving Film³

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which cause irritation to the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Taste masking- Most drugs have bitter taste, and need taste masking.

1.5. Ideal characteristics of drug candidate⁵

- The incorporating APIs should have a low dose of up to 40 mg
- Drugs with low molecular weight are preferable
- The drug should possess pleasant taste
- The drug should have good solubility and stability both in water and saliva.
- It should have the ability to permeate oral mucosal tissue.

1.6. Composition of the system⁶

Fast dissolving film is a thin film with an area of 2-8 cm² containing an active ingredient. The immediate dissolution, in water or saliva is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 30mg. Formulation considerations have been reported as important factors affecting mechanical properties of the films. The excipients used in formulation of fast dissolving films are also discussed in detail. From the regulatory perspectives, all excipients used in the formulation should be generally regarded as safe (*i.e.* GRAS listed) and should be approved for use in oral pharmaceutical dosage forms⁷. Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. Like antiulcer, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal etc. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). Some of the examples of suitable drug molecule that can be incorporated in the FDF.

1.6.1. Water soluble polymers⁶:

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 mouth feel 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, carboxy methylcellulose,

cekol 30, Polyvinyl pyrrolidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hydroxy propylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGITRD10. Polymerized rosin is a novel film forming polymer.

Table 1: Composition of fast dissolving film.

Sr. No.	Category	Percentage amount%
1	Drug (API)	1-30%
2	Polymer	40-50%
3	Plasticizer	0-20%
4	Surfactant(Solubility Enhancer)	q.s
5	Saliva stimulating agent	2-6%
6	Sweetening agent	3-6%
7	Flavoring agent	0-10%
8	Coloring agent	q.s
9	Stabilizing agent or Thickening agent	0-5%

1.6.2. Plasticizers⁶

Plasticizers 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. Distinction in their concentration may affect these properties. The commonly used plasticizers are glycerol, di-butylphthalate, and polyethylene glycol etc.

1.6.3. Saliva stimulating agent⁶

The reason behind using saliva stimulating agents is to increase the rate of production of saliva that would help in the faster disintegration of the rapid dissolving film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. E.g. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used alone or in combination between 2 to 6% w/w of weight of the film.

1.6.4. Surfactants⁶

Surfactants are used as solubilising or wetting or dispersing agent so that the film is getting dissolved within seconds and liberate 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.

1.6.5. Sweetening agents⁶

Sweetening agents have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The conventional source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. The sweetness of fructose is apparent rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The artificial sweeteners have gained more popularity in pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose.

1.6.6. Flavoring agents⁶

Flavoring agents can be chosen from the synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Any flavor can be added such as essential oils 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 such as vanillin, chocolate, or fruit essence like apple, raspberry, cherry, pineapple. The sum of flavor needed to mask the taste depends on the flavor type and its strength.

2. Method of Preparation of fast dissolving film

Different methods for formulating fast dissolving film are given below.

1) Solvent casting Method⁷

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

2) Semisolid casting⁷

In this method at first a solution of water soluble film forming polymer is prepared. Then the resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate) which was prepared in ammonium or sodium hydroxide. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. A gel mass is obtained on addition of suitable amount of plasticizer. By the means of heat controlled drums, finally the gel mass is casted in to the films or ribbons.

3) Hot melt extrusion⁸

In the hot melt extrusion drug mixed with carrier in the solid form. Extruder having extra facility with heater it melt the solid form carrier and drug then this melt is place in the dies and cut in to specific shape. E.g. Maltodextrin can be used to produce fast-dissolving films with a high drug loading capacity by hot-melt extrusion technology.

4) Rolling method⁹

In the rolling method, film is prepared by premixing of an active ingredients and excipients followed by subsequent addition of vehicles. The pre mix includes the film forming agent polar solvents, and other excipients. Then required amount of drug is added to pre mix batch through opening in each mixer. After the drug is blended with pre mix batch. Then this mixer is fed to the pan through second metering pump. The film is finally formed on the inert substance and carried away via support roller. Thus wet film is then dried.

5) Solid dispersion extrusion¹⁰

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

3. Novel techniques for preparation of fast dissolving film¹¹

1) Soluleaves

In this technology the film is produced in order to release the active ingredients on coming in contact with saliva. This method is especially useful for pediatric and geriatric patients who may have difficulty swallowing conventional tablets. SOLULEAVES are designed in such a way that they adhere to mucous membrane in order to release the drug slowly in 15mins

2) Foam burst

FOAMBURST is a new patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt-in-the mouth sensation.

3) XGEL

XGel film Technology produced by Bio Progress was causing a revolution in the product offerings and manufacturing methods, which was now available to the pharmaceutical industry. XGel film, potentially enhance the product stability. The films may be colored or printed during manufacture for branding and coding which is a useful mechanism to enhance product identification and has also been developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices.

4. Evaluation of fast dissolving film^{12,13,14,15,16}

4.1. Appearance, Size, Shape and Thickness

The formulated films should be checked for their appearance, shape and thickness. The thickness of the films should be determined at five different places using a micrometer for each formulation and mean value is calculated.

4.2. Weight variation

The film is subjected to mass variation study by individually weighing randomly selected films. The average of five observations of each

batch was calculated. Such determinations were carried out for each batch.

4.3. Drug Content

The film of specified area (2x2cm) is to be cut and put in a volumetric flask containing 100 ml of phosphate buffer pH 6.8. The medium should be stirred on a magnetic stirrer for proper dissolution for 6 hours. The contents should filtered using Whatman filter paper and the filtrate is analyzed by UV spectrophotometer (Pharmaspec-1700S, Shimadzu, Japan) at 206 nm. The experiments should perform in triplicate.

4.4. Hydration Study (water uptake/ swelling study)

The film sample is weighed and placed on a pre weighed stainless steel wire mesh. The wire mesh is then submerged in a petridish containing 20 ml distilled water. Increase in weight of the film is determined at regular time intervals until a constant weight is obtained the hydration ratio of the film is calculated using following formula,

$$\text{Hydration ratio} = \frac{W_t - W_0}{W_0}$$

Where W_t = weight of film at time t and W_0 = weight of film at zero time.

4.5. Moisture Loss (Moisture Vapor Transmission)

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using following formula

$$\text{Moisture loss} = \frac{W_0 - W_t}{W_0} \times 100$$

Where W_0 = initial weight W_t = final weight

4.6. Drug content uniformity

Three films are taken in separate flasks. 100 ml of 0.01 N HCl (pH 2.0) is added and continuously stirred for 2 hrs. The solutions should be filtered, suitably diluted and analyzed at 217 nm UV-visible spectrophotometer.

4.7. Stability Studies

Stability studies should be conducted on matrix films to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing them at 40° C/75 % RH for 6 months.

Samples should withdraw at 0, 30, 90 and 180 days.

4.8. pH of film

pH of film is measured by keeping the film in contact with distilled water and after 1 hr pH of solution is measured.

4.9. Measurement of folding endurance

The folding endurance is carried out by folding the strip repeatedly at the same place until it breaks. The number of times the film is folded at the same place prior to breaking gives the folding endurance.

4.10. Disintegration time

DT is the time at which the film begins to break down when break in to contact with water. It can be determined by placing the film in Petri dish containing water and note down the time it takes to break down.

4.11. *In-vitro* dissolution studies

The *in-vitro* dissolution studies can be conducted using simulated saliva (300 mL). The dissolution studies should be carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37 ± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (3 x 2 cm²) should be placed on a stainless steel wire mesh with sieve opening 700µm. The film sample placed on the sieve is submerged into dissolution media. Samples should withdraw at 0, 15, 30 and 60 sec. time intervals and filter through 0.45µm whatman filter paper and analyze spectrophotometrically at respective wavelength. To maintain the volume, an equal volume of fresh dissolution medium should maintain at same temperature should added after withdrawing samples.

5. Compatibility study of fast dissolving film¹⁷

5.1. FT-IR spectroscopy

The FT-IR of pure drug and prepared film should be carried out to check the compatibility bet the drug and other excipients used.

5.2. Differential Scanning Calorimetry (DSC)

The DSC thermo grams of pure drug and film should be carried out to check the compatibility between the drug and excipients.

Conclusion

Fast dissolving film have several advantages over the conventional dosage forms, hence they are of great importance. Fast dissolving films are very useful in emergency cases such as motion sickness, asthmatics attacks whenever rapid onset of action is required. It can be prepared by using various techniques and can be evaluated for effectiveness.

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Source of Support: Nil. Conflict of Interest: None declared
