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An Overview on : Orally Fast Dissolving Film

Kadbhane N.S[1]*, Shinkar D.M[2], Saudagar R.B[3]

[1,2]Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.
[3]Department of Pharmaceutical Chemistry, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik- 422213, Maharashtra, India.

Abstract : This review represents importance of mouth dissolving films as compared to other oral dosage forms. Fast dissolving oral drug delivery system are solid dosage form which disintegrate or dissolve within seconds when placed in the mouth without need of water or chewing. This facilitates the rapid absorption in the oral cavity and reduces first-pass effects. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. Fast dissolving oral drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer, better patient compliance, rapid drug absorption and sudden-onset of drug action with instant bioavailability is possible.
Keywords : Fast dissolving oral film, film forming polymers, patient compliance, disintegration, geriatrics and paediatrics patient.

Introduction

Among the different routes, the most agreeable route for the patients is oral route. Most of thepharmaceutical companies have directed their research activity in developing viable dosagealternatives from oral route for pediatrics, geriatric, noncompliant or nauseous patients. Research in the oral drug delivery segment has led to evolution of dosage forms from simple conventional

Tablets/capsules to modified release tablets/capsules to oral disintegrating tablet to wafer to the recent development of fast dissolving oral films1**.**Fast dissolving drug delivery systems were first invented in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. It provide the direct entry into the systemic circulation thereby avoiding the hepatic first pass Effect and ease of administration.2Fast dissolving films are very similar to ultra-thin strip of postage stamp in their shape, size and thickness. Fast dissolving films are formulated using polymers, active pharmaceutical ingredients (API), plasticizers, saliva stimulating agents, sweeteners, flavors, preservatives and colors. These fast dissolving oral films have persistent to extend in sales and launched as patient compliant and convenient products effectively addressing issues for pharmaceuticals as well as nutraceuticals that have been traditionally administered as oral solid dosages.

Special features of orally fast dissolving films[(5,6)]

1. Thin elegant film
2. Available in various size and shape

3. Unobstructive
4. Excellent mucoadhesion
5. Fast disintegration
6. Rapid release

Criteria for orally fast dissolving film[(7)]:

Fast dissolving film should:

1. Have a pleasant mouth feel
2. Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
3. Compatible with taste masking
4. Leave minimum or no residue in the mouth after oral administration.
5. Exhibit low sensitivity to environmental conditions such as temperature and humidity.

Advantages

Fast dissolving oral films being an advanced evolution of fast dissolving drug delivery systems have some outstanding advantages over conventional dosage forms and orally disintegrating tablets. They are:

1. No risk of choking.
2. Improved patient compliance.
3. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
4. Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
5. Water is not needed for administering, so problem encountered in swallowing of tablets or capsules can be evaded.
6. Good mouth feels property helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.

Disadvantages

1. Dose uniformity is a technical challenge
2. Hygroscopic in nature
3. High doses cannot be incorporated
4. Require special packaging for products stability and safety[(4,6)].

Criteria for selection of drug candidate for Orally Fast Dissolving Film's:

1. The drug should have pleasant taste
2. The drug should preferably have a dose up to 40 mg
3. The drug should have small or moderate molecular weight
4. The drug should have good stability and solubility in water and in saliva
5. It should be partially unionized at the pH of oral cavity
6. It should have the ability to permeate oral mucosal tissue.

Challenges for preparing Fast Dissolving Oral Film:

1. Palatability
2. Mechanical strength
3. Hygroscopicity
4. Amount of drug
5. Aqueous solubility's
6. Cost-effectiveness

Film Forming Polymers

The polymers used in oral film formulation should be:

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spread ability property.
- Should have sufficient peel, shear, and tensile strength.
- Readily available.
- Inexpensive.
- Sufficient shelf life.
- Should not aid in causing secondary infections in oralmucosa.

Active Pharmaceutical agents (1-25%)

Several class of drugs can be formulated as mouth dissolving films including antiasthamatics (Salbutamol sulphate), antiulcer (Omeprazole), expectorants, antitussives, NSAID'S (Valdecoxib, Meloxicam) 5,6,7.The drugs selected for oral films should possess good stability in saliva and water with low dose. The film should consist of 1-25% w/w of the drug. Small dose molecules are the best candidates to be incorporated in Oral fast dissolving film.

Water Soluble Polymers (40-50%)

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 base. Both natural as well as synthetic polymers can be used in the formulation of sublingual films. In order to prepare a film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity.19.Polymers frequently used as film formers are water soluble grades of cellulose ethers, polyvinyl alcohol, polysaccharides, polyvinylpyrrolidone K-90, polyethylene glycols, pullulan, gelatin, carboxmethylcellulosecekol 30, hydroxypropylmethyl cellulose E-3 and K-3, methyl cellulose A-3, A-6 and A-15, pectin, sodium alginate,hydroxypropyl.

Plasticizers (0-20%)

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation tothe films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers areglycerol, di-butylpthallate, and polyethylene glycols etc. Some of the commonly employed plasticizers are phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and glycerol. Improper use of plasticizer may lead to blooming, film cracking, splitting and peeling of the strip[8,11,12,13].

Surfactants

Role of Surfactants is for solubilising or wetting or dispersing agent, so that the film isgetting dissolved within seconds & release active agent immediately. Example of the commonly used is sodium lauryl sulphate, benzalkonium chloride, bezthonium chloride, tweens, etc. One of the most important surfactant is poloxamer 407 that is used as solubilizing, wetting & dispersing agent[14].

Sweetening agents

Sweeteners are the important part of the formulations intended to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 % w/w either alone or in combination. Some of the commonly employed sweeteners are dextrose, sucrose, fructose, glucose, isomaltose, polyhydric

alcohols (sorbitol, mannitol), etc. Artificial sweeteners like saccharin, cyclamate, aspartame (first generation) and acesulfame-K, sucralose, alitame, neotame (second generation) can also be used[15].

Saliva stimulating agents

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Examples of salivary stimulants are citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. Among these the most preferred one is citric acid[16].

Flavouring agents

Preferably up to 10%w/w flavours are added in the fast dissolving film formulations. The acceptance of the oral disintegrating or dissolving formulation has been consumed and the after taste of the formulation which lasts for at least about 10 min. Commonly employed are fruity flavours(vanilla, cocoa, coffee, chocolate, citrus), flavor oils (peppermint oil, cinnamon oil, oil of nutmeg). Flavours can also be chosen from oleo resins, synthetic flavour oils and extract derived from various parts of the plants like fruits, flowers etc.

Colouring agents

Generally incorporated colouring agents are FD&C colours, natural colours, pigments such as titanium dioxide etc[17].

Manufacturing Of Orally Fast Dissolving Film[23,24,25,26]

Following processes can be used to manufacture fast dissolving films:

1. Solvent casting
2. Semi solid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

1. Solvent casting method

In this method, firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

2.Semi solid casting

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[18].

3.Hot melt extrusion

Hot metal extrusion is commonly used to prepare granules, sustained release tablets, transdermal and transmucosal drug delivery systems. Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971 [15,16].approximately 3-4 min so that mass should be properly melted. The extrudate (T = 650°C) obtained is then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion: Fewer operation units, minimum product wastage, possibility to scale up, an anhydrous process, absence of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix, and better content uniformity[19]

4.Solid dispersion extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70◦ C Finally the solid dispersions are shaped into the films by means of dies.

5.Rolling method

Solvents mainly used in this method are water and mixture of water and alcohol. By the means of high shear processor, active agent and other ingredients are dissolved in small portion of aqueous solvent. Water soluble hydrocolloids are dissolved in water to form homogenous viscous solution. Then the resultant solution or suspension containing drug is rolled on a carrier. Finally the obtained film is cut in to desired shapes and sizes[19].

Characterization of fast dissolving films:

Drug-excipients interaction studies:

Fourier Transformer Infra Red Spectrum Differential scanning calorimeter thin layer chromatography& X Ray Diffraction can be used to assess possible drug excipient interaction.

Thickness

The thickness of film is measured by micrometer screw gauge or calibrated digital Vernier Calipers. The thickness of film should be in range 5-200 μm[21]. The thickness should be evaluated at five different locations (four corners and one at centre) and it is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film.

Morphology study

The morphology of the films is studied using Scanning Electron Microscopy (SEM), at a definite Magnification[5].

pH value

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH value.

Folding endurance

Folding endurance gives the brittleness of a film. The method followed to determine endurance value is that the film specimens (2 × 2 cm2) are repeatedly folded at the same place until it breaks or a visible crack is observed. The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value[26].

Content Uniformity

Drug content can be determined by dissolving the film in 100 ml of suitable solution to get 20 μg/ml solutions. An aliquot of 2ml sample can withdraw and diluted to 10 ml with solution. Then solution can be filtered through whatman filter and solution analyzed spectrophotometrically.

Tensile strength

The tensile strength (Psi) is the property of the film that requires a load tocause load deformation failure of film using is measured by Instrontester[22].

Tensile strength (N/mm2) = breaking force (N) / cross-sectional area of sample (mm2)

Percent elongation

The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation can be obtained by following equation:

$$\% \text{ Elongation} = \frac{\text{Increase in length at breaking point (mm)}}{\text{Original length (mm)}} \times 100$$

Disintegration time

Disintegration test is done by using Disintegration apparatus

Dissolution test

Dissolution testing can be performed in simulated saliva solution or pH 6.4 phosphate buffer using the standard basket or paddle apparatus described in any of the pharmacopoeia at 37±0.5°C. Samples are withdrawn at regular time intervals and analyzed by UV-Visible spectrophotometer[5,24].

Permeation studies

Permeation studies are carried using the modified Franz diffusion cell by using porcine buccal mucosa. The mucosa is mounted between the donor & receptor compartment of Franz diffusion cell. The receptor compartment is filled with buffer & maintained at 37 °C ± 0.2 °C& the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One previously weighed film is placed in intimate contact with the mucosal surface of the membrane that should be previously moistened with a few drops of simulated saliva. The donor compartment is filled with 1 ml of simulated saliva of pH 6.8. Samples are withdrawn at suitable interval, replacing the same amount with the fresh medium. The percentage of drug permeated is determined by measuring the absorbance by selected analytical method.

Stability study

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance[19,23].

Palatability test

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade it would be the very good formulation.

Grades: A= very good, B= good, C=poor.

Packaging of fast dissolving film

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. 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.

The material selected must have the following characteristics

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement

- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product tastes or odors.

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