Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Introduction of a Novel Approach for Oral Drug Delivery: Fast Dissolving Films

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ARTICLE DETAILS

Article history:
Received on 31 July 2015
Modified on 20 September 2015
Accepted on 25 September 2015

Keywords:
Fast Dissolving,
Films,
Plasticizers,
Techniques

ABSTRACT

Fast-dissolving drug delivery systems have been developed as an alternative to conventional dosage form as an oral means of drug delivery in case of chronic conditions. Now a day's fast dissolving films are preferred over conventional tablets and capsules for masking the taste of bitter drugs to increase the patient compliance. Fast dissolving films consist of a very thin oral strip which dissolves in less than one minute when placed on the tongue. Dissolvable oral thin films are in the market since past few years in the form of breath strips and are widely accepted by consumers for delivering vitamins, vaccines and other drug products. The various manufacturing techniques for the preparation of films have also been detailed in the review. The present review details most of the patents on such fast dissolving films in recent years. A brief study has been made on various parameters which are used to evaluate such films. In case of chronic disorders these fast dissolving films are better for delivering drugs and obtaining faster therapeutic blood levels and superior in comparison to other oral conventional dosage forms.

INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and its ease of administration lead to high level of patient compliance. [1]Recently, fast-dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, which aim to enhance safety and efficacy of a drug molecule by formulating it into a convenient dosage form for administration and to achieve better patient compliance [2].

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastrointestinal tract [3].

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The development of a fast-dissolving film also provides an opportunity for a line extension in the market place; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form [4].

Ideal Characteristics of Fast Dissolving Films

- Require no water for oral administration, yet dissolve/disperse/disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Subsequent to oral administration, it should leave least or no residue in mouth.
- It should be compatible with the other ingredients [5, 6].

Advantages of Fast Dissolving Films

- No risk of choking and obstruction.
- Fast releasing and disintegration within minutes in the mouth.
- Reduction in first pass metabolism may lead to reduction in the dose
- The oral or buccal mucosa is highly vascularized; hence drugs can be absorbed directly and can enter the systemic

circulation without undergoing first-pass hepatic metabolism.
- Improved oral bioavailability of drugs
- Available in different size and shape.
- Improved patient compliance [6, 7].

Disadvantages of Fast Dissolving Films
- Drugs which are not stable at buccal pH cannot be administered
- Drug in large dose cannot be administered.
- It takes Special packaging due to fragile in nature and must be protected from water.
- Drugs which are irritate to the mucosa which cannot be administered by this route [8].

Formulation of Fast Dissolving Films
Ingredients require for formulation of fast dissolving films:
- Drug
- Film forming agent (polymers)
- Plasticizers
- Surfactant
- Flavoring and sweetening agent
- Saliva stimulating Agent
- Stabilizing and thickening agent

Drug
Drug can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day).

Ideal Characteristics of Drug Moiety for Fast Dissolving Film
- The incorporating active moiety should be not more than 40mg
- The drug should be unionized at the pH of buccal cavity.
- The drug should have pleasant taste.
- Drug should be stable and soluble in water like saliva.
- It should be able to able to permeate oral mucosal tissues.

Film Forming Agent
It is use as carrier for drug. The physiochemical and nature of film former polymer can be change. The mostly cellulose derivative polymer are use as film former like hydroxypropyl methyl cellulose, hydroxy propyl cellulose and sodium carboxy methyl cellulose in different grade and other i.e., sodium alginate, polyvinyl pyrrolidine, polyethylene glycol. The film should not be damage while handling or during transportation time. The tensile strength is depending on types of polymer and amount of polymer used in film. Mainly hydrophilic polymers are used as film former [9].

Plasticizers
Formulation considerations (Use of plasticizer) 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].

Surfactants
Surfactants act as solubilizing or wetting or dispersing agent in formulation so the film gets dissolved within seconds and releases active agent quickly. Some of the commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and Dispersing agent [11].

Flavoring and Sweetening Agent
The flavors enhance the acceptance of the formulation and enhance the elegance properties of film. Some flavors i.e. menthol, peppermint, essential oils such as methyl salicylate, eucalyptol, thymol, vanilla, cinnamon etc. Sweeteners use to mask the bad odour and bitter taste of the drugs. Both type of sweeteners are used, natural and synthetic sweeteners i.e. monosaccharide's, disaccharides and polysaccharides such as galactose glucose, mannose, fructose, xylose, ribose, dextrose, maltose, sucrose, , sugar , sorbitol, xylitol, mannitol and soluble saccharin salts, saccharin, cyclamate salts, acesulfam-K, Aspartame, Neotame respectively [8,12,].

Saliva Stimulating Agent
More saliva production helps in the faster disintegration of the fast dissolving film formulations. So the formulations should contain acids which are used in the preparation of food as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them [10].

Stabilizing and thickening agent

The stabilizing and thickening agents are employed for the improvement of viscosity and consistency of dispersion or solution of the strip preparation. Natural gums such as xanthum gum, locust bean gum, carragenan and cellulose derivatives can be used in concentrations up to 5%w/w as stabilizing and thickening agent [13].

Techniques Used in preparation of Fast Dissolving Films

One or more of the following process can be used to manufacture the Fast dissolving films:

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

Solvent casting Method

In solvent casting method, excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried [14].

Semisolid casting Method

In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate).After sonication, it is coated on non-treated casting film. On drying the thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4 [10].

Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min The processing temperatures should be 800C (zone 1), 1150C (zone 2), 1000C (zone 3) and 650C (zone 4). The extrudate (T = 650C) then pressed into a cylindrical calendar in order to obtain a film **[15]**. There are certain benefits of hot melt extrusion:

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

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 [16].

Rolling methods

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. 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 [15].

Evaluation Parameters [17, 18, 19]

Morphology Study

The morphological study of oral strip is done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API.

Folding endurance

The folding endurance candetermine by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Weight variation

For weight variation three films of every formulation should take weighed individually on digital balance then average weight can calculate.

Surface pH

The film to be tested should place in a petridish and moistened with 0.5 ml of distilled water and kept for 1hr. The pH cab noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

Wetting time

Wetting time of dosage form is associated to the contact angle. It needs to be assessed to give an insight to the disintegration properties; less wetting time implies a quicker disintegration of film.

Percentage elongation:
Percentage elongation is determined by noting the distance travelled by pointer before breaking of the film on the graph paper. Generally elongation of oral strip increase as the plasticizer content increases.

$$\% \text{ Elongation} = \frac{L}{L^\circ} \times 100$$

L = Increase in the length of film,
L° = Initial length of film

Young's Modulus
Young's modulus is used to determine the stiffness of oral film. It is represented as the ratio of applied stress over strain in the region of elastic deformation. It is calculated as follows:

$$\text{Young's modulus} = \frac{\text{Slope}}{\text{Strip thickness} \times \text{Cross head speed}} \times 100$$

***In-vitro* Dissolution Test**
In-vitro Dissolution study can be performed using the paddle or basket apparatus as described in the pharmacopoeia. The volume of dissolution medium will essentially be selected as per as the sink condition and highest dose of the API. Mainly paddle type dissolution apparatus is used for the dissolution test of oral strip because sometimes the dissolution test can be difficult due to the tendency of the strip to float onto the dissolution medium

Content Uniformity
Drug content can be determined by dissolving the film in 100 ml of suitable solution to get 20µg/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.

Challenges [20, 21]
Fast dissolving films face many challenges as given below, these challenges are related to new technologies and products.

- Most of the drugs need taste masking
- Need protection from humidity which demands a specialized product packaging.
- Amount of drug that can be incorporated into each unit dose
- A novel manufacturing process is a challenge, due to new equipment, technology and process.
- Limited drug loading due to technology limitation, taste masking and tablet size.
- Need more clinical trials to study more clinical/medical benefits.

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