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REVIEW ARTICLE

FAST DISSOLVING ORAL FILM: CHALLENGES AND OPPORTUNITIES FOR DRUG DELIVERY

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ABSTRACT

Oral route is the most preferred route of drug administration for systemic effect. About 60% of all the formulations are solid dosage form, among this, tablets are the preferred due to ease of transportation, manufacturing and patient compliance. However, geriatric, pediatric and bedridden patient experience difficulties in swallowing the conventional oral dosage form. To overcome this problem oral fast dissolving films were developed. Oral strips are the new frontier of drug delivery technology that provides a very convenient means of taking medications and supplements, applicable both when systemic effect is required and local action in the mouth is desirable, such as local anesthetic for toothaches, oral ulcers, cold sores, or teething.

INTRODUCTION

Fast dissolving oral films (FDOFs) consist of non-bulky solid dosage form similar to postage stamp in their size, shape and thickness (50–150 μm). FDOFs are designed to be simply placed on the patient's tongue or mucosal tissue where dissolve and disintegrate within a minute after being in contact with the saliva, resulting in quick absorption and instant bioavailability of the drugs. FDOFs are considered the most advanced, innovative and promising drug delivery system due to the possibility to combine all the advantages of tablets (accurate dose, self administration) with those of liquid dosage forms (easy swallowing, quick bioavailability). However, thin films are not a recent invention as they were first introduced in 1970 to overcome swallowing difficulties exhibited by tablets and capsules. Dysphagia is a very common disorder associated with many medical conditions, including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy; in addition the problem of swallowing tablets is evident in geriatric, bedridden and pediatric population, as well as travelling patients who may not have ready access to water. Therefore, FDOFs offer a convenient way of dosing medications due to high flexibility and comfort.

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Furthermore, the oral mucosa is vascularized, drugs can be absorbed directly and can quickly enter the systemic circulation without first pass metabolism. Thereby FDOFs have great potential of delivering the medicinal agent systemically as well as locally and have several advantages over many conventional dosage forms. For these reasons FDOFs are gaining increasing attention in pharmaceutical industry. Oral films can be employed as delivery systems for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties and central nervous system disorders. The use of oral fast dissolvable films may be also feasible in the delivery of active agents such as analgesics or antimicrobials ingredients for wound care and other applications. Dissolution of the films could be trigged by the pH or enzyme secretions of the gastro-intestinal tract and could potentially be used to treat gastro-intestinal disorders. Finally, dissolvable devices may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

Advantages

Compared with the traditional dosage forms, FDOFs demonstrated their superiority in terms of enhanced bioavailability, high patient compliance, and patent extension of active pharmaceutical ingredients (API). Furthermore, thin film formulations offer several advantages, FDFOFs are:

- Available in various size and shape for improved patient compliance
- Un-obstructive (the risk of chocking is avoided)
- Fast disintegration/dissolution
- Rapid drug release and rapid onset of action
- Convenient dosing or accurate dosing
- No need of water to swallow or chew
- Ease of handling and transportation

Disadvantages

FDFOFs are very promising dosage form, however they suffer from several drawbacks which have to be carefully evaluated in order to take full advantage of them. FDOFs are hygroscopic in nature so they must be stored in dry places, therefore special packaging are imperative in order to assure products stability and safety. Single packaging is recommended so every dose can be taken out individually; usually an aluminum pouch is used as packaging format. High dose of API cannot be incorporated into the oral film. The area of drug loaded FDOFs should be between 1-20 cm^2 and the drug can be loaded up to a single dose of about 30-40 mg. Most bitter drugs should be avoided or taste masking is required. Proteinaceous drugs shouldn't be delivered, although co-administration of enzyme inhibitors such as aprotinin, bestatin, puromicin and bile salts is necessary to inhibit proteolytic salivary enzymes. Dose uniformity is a technical challenge. Even if the morphology of the film appears homogeneous and uniform distribution of drug is assured, the difficulty to obtain a high degree of accuracy with respect to the amount of drug in individual unit dose of the film can lead to therapeutic failure, non-reproducible effects and sometimes toxic effects to the patient.

Production planning

A typical FDOFs composition contains: drug 5 to 30 % w/w, water soluble polymer 45% w/w, plasticizers 0-20% w/w, sweetening agent 3-6% w/w, saliva stimulating agent 2-6% w/w, fillers, colors, flavors and surfactants. This technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose drugs are difficult to be incorporated in films. Less bitter, potent and highly lipophilic drug should be preferred for oral thin film as in case of fast dissolving tablets.

The ideal characteristics of a drug to be selected:

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Combining more than one drug concomitantly is a very challenging task in oral film formulation because both the dissolution rate as well as the disintegration time are hindered by the co-administration of a drug in oral films.

Saliva stimulating agent are generally acids which are used in the preparation of food can be utilized as salivary stimulants, like citric acid, malic acid, lactic acid, ascorbic acid etc. Polymers are the backbone of film formulations and various polymers are available for the preparation of thin films, so polymer is an essential component while designing and formulating thin films. The polymers can be used alone or in combination to achieve the desired film properties. The polymers employed should be non-toxic, non-irritant, and absence of leachable impurities is required. Water-soluble polymers are used as film formers to produce a thin film with rapid disintegration, good mechanical strength, and good mouth feel effects. Both natural and synthetic polymers are used for film preparation. Knowing the features of polymers such as chemistry, rheology, and physicochemical properties seems to be of paramount importance for maximizing the use and development of a thin film. The selection of appropriate polymer during the development of polymeric thin films may be critical; thereby, several points should be considered according to the requirements. Therefore, it is imperative to consider the appropriate polymer for producing a thin film with a better performance that assures high therapeutic success.

Quality control tests

A FDOF should have adequate flexibility, softness, elasticity, and good physicochemical stability. Therefore, all these parameters should be considered carefully while developing film to ensure its efficient performance. Characterization of a film is a pre-requisite that may include assessing properties such as mechanical strength, hydration, *in vitro* release and surface morphology. Controlling physical and mechanical properties represents a very important task in order to assure the efficacy of this delivery system. Formulation considerations as well as the production technique have been reported as important factors which affected mechanical properties of the films.

Surface pH

The surface pH of the films is determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. So, it is determined to keep the surface pH as close to neutral as possible. The film to be tested is placed in a Petri dish and moistened with distilled water. The pH is noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating.

Assay of drug Content and Content Uniformity

Assay, drug content and drug content uniformity is determined by any standard assay method which is described for the particular API in any standard pharmacopoeia. Limit of content uniformity is 85-115%.

Folding endurance

The flexibility of thin film is important when considering that the films can be administered without breakage. The flexibility of the polymeric thin films can be measured with respect to its folding endurance.

The folding endurance is determined by folding the film repeatedly at 180° angle of the plane at the same place until it breaks. The film exhibiting folding endurance value of 300 or more is considered to have excellent flexibility

Percent elongation and elongation at break

Elongation, is a simple change in shape that any objects encounter under any applied stress. When the sample is subjected to tensile stress, deformation of the sample takes place resulting in stretching or elongation of sample. Elastic elongation or elongation at break of a sample can be measured by using a texture analyzer. The percent elongation indicates the stretch ability of material without being broken, whereas elongation at break means the point until which the film can be stretched when it is torn (or broken) by the applied probe. It is calculated as:

$$\%\ \text{Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

Elongation at break can also be calculated as:

$$\text{Elongation at break}\ (\%) = \left(\frac{\sqrt{a^2 + b^2 + r^2}}{a} - 1\right) \times 100$$

where a is the initial length of the film in the sample holding opening, a' is the length of the film not punctured by the probe, b is the penetration depth/vertical displacement by the probe, and r is the radius of the probe.

Young's modulus

Young's modulus or elastic modulus reflects the stiffness or elasticity of the films. This indicates resistance to deformation of the films, which can be calculated by plotting the stress strain curve, where slope indicates the modulus. The greater the slope, the greater is the tensile modulus. On the other side, the small slope means lesser tensile modulus and deformation. Young's modulus can be measured by a Texture analyzer. Slope is obtained from the stress strain curve and Young's modulus is represented as the ratio of applied stress over strain in the region of elastic deformation, which can be determined using the following formula:

$$\text{Young's modulus} = \frac{\text{Slope}}{\text{Film thickness} \times \text{Crosshead speed}} \times 100$$

Tear resistance

The property of the film to withstand the rupture is known as tear resistance. The measurement of tear resistance is done by allowing the film to undergo a constant rate of deformation. The maximum force or stress needed to tear the film is measured in Newton or pound-force. In a stress strain curve, the area of the plot measures the tear resistance. The relation of an area under the stress strain curve is directly proportional to the toughness of the film.

Swelling

Swelling properties of films are generally observed as the polymers employed for making films are hydrophilic. Swelling of the polymers is known to be the fundamental step required for bioadhesion. In many cases the degree and rate of swelling play a key role in controlling the release of the drug. Hence, these parameters can be considered as the indicator for bioadhesive or mucoadhesive potential and drug release profiles. The testing of swelling is done to measure polymer hydration. The swelling properties of films, i.e. water absorption capacities, are measured by evaluating the percentage of hydration. A piece of films is weighed (W1) and it is subjected to immersion in simulated physiological fluid for a predetermined time. After the predetermined time, the sample is taken out, wiped off to remove excessive water on the surface and weighed again (W2).

$$\text{Hydration}\ (\%) = \frac{W2 - W1}{W1} \times 100$$

Dissolution test

According to several studies, the release of the drug is markedly influenced by erosion of the film. The degradation rate of the film is also dependent on the types of plasticizer. To assure the drug penetration through biological membrane, the drug should be released from the delivery systems at an optimum rate. Assessing the drug release from the film is essential as it is the rate-determining step in the process of absorption. The dissolution of drugs and/or films can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed. Many authors have designed different dissolution apparatus to overcome this problem and better mimic the buccal environment.

Surface morphology

The morphology of the film should appear homogeneous and continuous to ensure the uniform distribution of drug throughout the polymeric mixture. Self-aggregation might take place during drying because of the intermolecular and convective forces leading to wrinkled surface in films. Additionally, interaction between drug and polymers, and the crystalline nature of the drug, may result in the formation of rough surface in the films. Hence, assessing the surface morphology and texture is of paramount importance to assure uniform distribution of drugs without any interaction with the polymers in the film formulation. Various surface characteristics such as surface texture (smooth or rough), thickness, and drug distribution (aggregated or scattered) of the film can be observed using light microscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM) and related imaging techniques.

Thickness and weight variation

The measurement of thickness is necessary as it directly correlates with the amount of drug in the film. In addition, an appropriate thickness is required for the comfortable administration of films. Generally, the thickness of the formed thin films is measured using Vernier caliper, electronic digital

micrometer, screw gauge, or scanning electron microscopy images.

Stability studies

Stability studies have to be carried out at accelerated condition (65% relative humidity and 35 °C temperature) in the humidity chamber.

***Ex-vivo* permeation study**

The modified Franz diffusion cell is used for permeation studies.

It consists of two compartments, one is donor compartment and another is receptor compartment of 18 mL capacity and having 0.785 cm^2 effective diffusion area. The receptor compartment was covered with water jacket to maintain 37°C. The porcine or rabbit buccal mucosa can be used for these studies. The buccal mucosa is carefully separated from fat and muscles using scalpel. The buccal epithelium is isolated from the underlying tissue. The buccal epithelium was used within 2 hrs upon removal. The separated buccal epithelium is mounted between two chambers and receptor chamber is filled with PBS pH 7.4. The buccal epithelium is allowed to stabilize for the period of 1 hr. After stabilization of buccal epithelium, the film is kept on buccal epithelium and periodically samples are withdrawn and some fresh volume is replaced. The aliquots are analyzed spectrophotometrically.

In vivo Methods

In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test.

Using this method, the kinetics of drug absorption were measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity. Various modifications of the buccal absorption test have been carried out correcting for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization. A feasible approach to achieve absorption site localization is to retain the drug on the buccal mucosa using a bioadhesive system. Pharmacokinetic parameters such as bioavailability can then be calculated from the plasma concentration vs. time profile. Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs.

Experimental Animal Species

Aside from the specific methodology employed to study buccal drug absorption/permeation characteristics, special attention is given to the choice of experimental animal species. For *in vivo* investigations, many researchers have used small animals including rats and hamsters for permeability studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory animals have an oral lining that is totally keratinized.

Conclusion

Fast dissolving oral films are non-bulky oral dosage forms that have several advantages over conventional ones which include the ease of administration with no need for water thus improving patient compliance particularly elderly and pediatrics. FDOFs are considered to be the most advanced, innovative and promising dosage forms as they have great potential of delivering the medicinal agent systemically as well as locally. This emerging drug delivery system help in the effective management of immediate attacked diseases. Bypassing the hepatic first pass metabolism, fast dissolving films increase the bioavailability of the medication. However, mechanical properties of FDOFs are strictly influenced by polymeric composition so strip design and characterization is of paramount importance in order to improve drug efficacy.

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