Oral Films - Patient Compliant Dosage Form For Pediatrics

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Abstract

Pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. Hence oral film drug delivery is a better alternative in such cases. The oral films are formulated using polymers, plasticizers, flavors, colors and sweeteners. The oral films are manufactured using solvent casting method, rolling method, extrusion method and solid dispersion method. The films are evaluated for dimensions, disintegration, dissolution, tensile strength and folding endurance. It has many applications like in taste masking, immediate release and sustained release formulation

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms.[1]Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking.[2]Hence orally dissolving tablets have come into existence. Even with these differences, most of the existing oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exists despite their short disintegration/dissolution times. Hence oral film drug delivery is a better alternative in such cases. The oral availability of many drugs is poor because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Traditionally, these drugs have been administered as parenteral drug delivery systems, which invariably lead to poor patient compliance. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery.

Oral film may be a fast dissolving film or a sustained release oral film. Sustained release oral films will release the drug in continuous manner in the oral cavity for a longer time.[3-4]

Intraoral fast-dissolving drug delivery system is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. This drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages. Lavipharm manufactured the dextromethorphan hydrobromide drug in the form of an orally-dissolving strip, also known as a oral thin film (OTF). Over 15 companies actively developing OTF delivery technologies have shifted from a tablet form to a fast-dissolving and highly water-soluble wafer or film. In addition, the report identifies: Nine launched OTF pharmaceutical products. Applied Pharma Research S.A. (APR), a leading Swiss R&D company focusing on innovative drug delivery. In conjunction with Labtec GmbH, APR has developed a novel OTF technology called Rapid Film (TM). Classes of drugs that can benefit from delivery via the Rapid Film system include hypnotics, anxiolytics, antiemetics, NSAIDs and pain killers, 5HT1 agonists for migraine treatment, antiallergics, antacids, vitamins, minerals, and treatments for the oral cavity. Oral film strips have hit the mainstream in the last few years as a new way of freshening the breath. The gel-like wafers are slipped into the mouth and dissolve quickly to release a minty flavor. Drug companies are now exploring this approach as a way of delivering over-the-counter and prescription pharmaceuticals.

ADVANTAGE OF FILM DRUG DELIVERY

SYSTEM

1. Oral Film is a drug delivery film that is placed on a mucosal or in oral cavity.
2. They provide suitability for a wide variety of drugs.
3. It has improved bio-availability for certain therapeutic ingredients.
4. It has small size for improved patient compliance.
5. Films has ability to dissolve rapidly without the need for water provides an alternative to patients with swallowing disorders and to patients suffering from nausea, such as those patients receiving chemotherapy.
6. It is also used for local and systemic delivery.
7. It provides dose removal possibility in emergency situations; and excellent content uniformity.
8. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
9. Film is more advantageous as it is stable, durable and quicker dissolving than other conventional dosage forms.
10. Film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain a precise amount of the drug.
11. Film not only ensures more accurate administration of drugs but also can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration.
12. These properties are especially beneficial for pediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult.
13. Sensitive drugs may degrade over time in an aqueous environment. Thin film formulations must ensure that the integrity of the drug remains constant over time.

FORMULATION CONSIDERATIONS FOR FILM

Active Ingredient: The active substance is may be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa, respectively. Pharmaceutically active substances are also to be understood as to include e.g. nicotine and salts and derivatives thereof as an aid for smoking cessation. Classes of pharmaceutically active substances that come into consideration are, for example, nicotine and salts and derivatives thereof, e.g. nicotine tartrate or nicotine polacrilex (=resin complex containing nicotine, e.g. 10 or 20 weight-% of nicotine), in particular nicotine tartrate; hormones, e.g. melatonin; fluoride supplements, e.g. sodium fluoride or others fluoride salts; local disinfectants, e.g. benzoxonium chloride, chlorhexidine or benzalkonium chloride; local anaesthetic agents etc. Preferred pharmaceutically active agents includes chlorpheniramine maleate, brompheniramine maleate, dexchlorpheniramine, triprolidine hydrochloride, acrivastine, azatadine maleate, loratidine, phenylephrine hydrochloride, dextromethorphan hydrochloride, ketoprofen, sumatriptan succinate, zolmitriptan, loperamide, famotidine, nicotine, caffeine, diphenhydramine hydrochloride, and pseudoephedrine hydrochloride, and their amounts per strip are well known in the art.

Polymers: The polymer may be water soluble, water insoluble, or a combination of one or more either water soluble or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, and combinations thereof.

Plasticizers: Plasticizers include glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters. plasticizer is added to improve flexibility of film.[5]

Flavoring agents: Flavoring agents, the essential oils or water soluble extracts of menthol, wintergreen, peppermint, sweet mint, spearmint, vanillin, cherry, chocolate, cinnamon, clove, lemon, orange etc.

Sweetening agents: Sweetening agent such as Sugar,

dextrose, lactose, mannitol, sucrose, xylitol, malitol, acesulfame potassium, talin, glycyrrhizin, sucralose, aspartame, saccharin etc.

Coloring agents: Coloring agents may include FD & C coloring agents, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc oxide.

METHODS OF MANUFACTURE OF FILMS

One (or a combination) of the following processes may be used to manufacture the oral films: [6]

- Solvent casting
- Hot-melt extrusion
- Solid dispersion extrusion
- Rolling.

Solvent Casting: The oral film is preferably formulated using the solvent-casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution, and combined with the bulk. This mixture is then added to the aqueous viscous solution. 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. Water-soluble hydrocolloids used to prepare films are: hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), pullulan, sodium alginate, pectin and carboxymethyl cellulose (CMC).[7]

Hotmelt extrusion: Hot melt extrusion (HME) is commonly used to prepare granules, sustained-release tablets, transdermal and transmucosal drug delivery systems.[8-9] Processing films by this technique, involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting method. Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. Since the turn of the century, many studies have been conducted on this process for the preparation of solid dispersion. Hot-melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained-release pellets. The drug carrier mix is filled in the hopper and is conveyed, mixed, and melted by the extruder. The die then shapes the melt in the required film form. Hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix (<2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters, and possibility to scale up. Repka et al. prepared chlorpheniramine maleate (CPM) topical HPC films by hot melt extrusion technique using hydroxy propyl cellulose as polymer.[8]

Solid dispersion extrusion: The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.[10]

Rolling method: In these method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film.[11] The pre-mix or master batch which includes the film -forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank .Then a pre-determined amount of the master batch is controllably fed via a first metering pump and control valve to either or both of the first and second mixers. The required amount of the drug is added to the desired mixer through an opening in each of the mixers. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan through the second metering pumps. The metering roller determines the thickness of the film and applies it to the application roller. The film is finally formed on the substrate and carried away via the support roller. The wet film is then dried using controlled bottom drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film.

QUALITY CONTROL OF FILMS

Disintegration Test: Disintegration time is defined as the time (second) at which a film breaks when brought into contact with water or saliva. The disintegration time is the time when a film starts to break or disintegrate.Thickness and mass play a role in determining the dissolvable film’s physical properties.[12-13]

Dissolution Test: Dissolution is defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Invitro method is carried out in modified USP XXIII apparatus (paddle over disk) and invivo dissoluition method is carried out in volunteers.[14]

Tensile strength: The "tensile strength" (psi) is the property of film that requires a load to cause load deformation failure of film. Tensile strength was evaluated according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02).[15] An electronic dynamometer AG/MC1 (Acquati, I) was used.[13] The tensile strength and elongation at break were calculated as below:

Tensile strength (N/mm^2) = Breaking force (N)/Cross-sectional area of sample (mm^2)

Percent elongation: The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit.

Elongation at break (%) = Increase in length at breaking point (mm)/Original length (mm) x 100%

Thickness: Thickness test is carried out using an electronic micrometer MI-1000 (Cheminstruments, USA).[14]The thickness of the film sample was measured using a micrometer (Digimatic Micrometer, Mitutoyo, Tokyo, Japan) at five locations (center and four corners), and the mean thickness calculated. Samples with air bubbles, nicks or tears and having mean thickness variations of greater than 5% were excluded from analysis.

Folding endurance: Folding endurance is determined by repeatedly folding a small strip of film at the same place till it breaks.

Film flexibility: Film flexibility was determined by adapting the ASTM bend mandrel test (D 4338-97). Film was bended over a mandrel and examined for cracks over the area of the bend in a strong light.

PACKAGING OF ORAL FILM

Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast-dissolving dosage forms. Unlike these other quick-dispersing and/or dissolving oral delivery systems, the Quick-Dis™ system can be packaged using various options, such as single pouch, blister card with multiple units, and continuous roll dispenser, depending on the application and marketing objectives

Single pouch: Soluble Film Drug Delivery Pouch is a peelable pouch for "quick dissolve" soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutriceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection.

Blister card with multiple units: The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

Polyvinyl Chloride - The most commonly used blister material is polyvinyl chloride (PVC). This material, which provides a nominal or zero barriers to moisture, is used when the product does not require effective moisture protection.

Barrier Films - Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. Several materials may be used to provide moisture protection such as Polychlorotrifluoroethylene (PCTFE) film, Polypropylene.[16]

Continuous roll dispenser: An automatic drug tape dispensing and metering device and a disposable cassette containing a roll of drug tape housed in a small reusable portable dispenser unit. The dispenser contains a measurement device for carefully measuring the length of tape as it is dispensed. A counter monitors the remaining doses of drug tape remaining within the dispenser. A timer device may be provided to alert the patient that it is time for the medicament to be dispensed. As the lid of the dispenser unit is opened, the measured length of drug tape is severed from the roll by a cutter blade incorporated into the lid. The dosage and administration of the medicament to be given a patient may be set by adjusting the tape length released for each single dose and selecting the time intervals between dosages. The invention comprises also ingestible tapes of medicament.

APPLICATIONS OF FILM DELIVERY SYSTEM

Taste masking: Oral film systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.[16] An important aspect of thin film drug delivery technology is the masking of the often bitter and poor taste of drug formulations. One method of taste-masking is encapsulation, the coating of drug particles with a polymeric covering sufficient to mask the taste of the drug particle while maintaining the ability to release the drug for absorption.

Orally disintegrating films: Orally disintegrating thin film based on a water-soluble polymer. The film disintegrates rapidly within seconds in contact with water or saliva, releases the drug in the mouth and promotes gastrointestinal absorption.[17-22]

Figure 1

Table 1. Advantage of oral dissolving film over oral disintegrating tablets.

Oral dissolving film	Oral disintegrating tablets
It is a film	It is a tablet
Greater dissolution due to greater surface area	Lesser dissolution due to less surface area
Better durable as compared to disintegrating tablet	Less durable as compared to oral film
More patient compliance	Less patient compliance as compared to film
Low dose can only be incorporated in film	Higher dose can be incorporated in tablet
No fear of choking	It has fear of choking

Vaccination: Oral thin film is delivered in the form of vaccine which is stable at room temperature so that is quickly dissolve in mouth and in saliva.[23] Rotavirus vaccine is prepared in United States by Johns Hopkins University in 2006. Rotavirus vaccine is a room temperature stable quick-dissolving oral thin film delivery system for vaccines that will make vaccinations almost as simple as freshening your breath. This delivery system exhibits many advantages not available in current products: improved patient compliance, improved bioavailability, reduction in the costs associated with storage, distribution, handling and administration.

Sustained release film: Sustained release oral film is applicable in hospital preparations and drug carriers by polymer Chitin and chitosan derivatives are used as excipients and drug carriers in the pharmaceutical field. Their derivatization contributed to expansion of application and decrease toxicity. Chitosan is used as an excipient in oral dosage form. Films prepared using chitin or chitosan have been developed as wound dressings, oral mucoadhesive and water-resisting adhesive by virtue of their release characteristics and adhesion.[24]

CONCLUSION

Oral films are becoming important film drug delivery system because of their rapid disintegration and possibly improved dissolution characteristics especially in pediatric and geriatric patient category,. Most of the commercially existing rapid dissolving dosage forms are in the form of oral disintegrating tablets. Oral film, have gained more popularity because of their portability, patient compliance, faster absorption and ease of administration. They can be applied by oral and buccal routes and can be used in breath fresheners, local anaesthetics, vitamin supplements and in cold-allergy remedies. In the future, more pharmaceutical companies could be interested in film for delivering a wide range of active pharmaceutical ingredients.

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