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Lakshita Rathore, Narendra Gehalot, Vikas Jain
Mahakal Institute of Pharmaceutical Studies, Ujjain, Madhya Pradesh – 456664, India

Correspondence

Lakshita Rathore
Mahakal Institute of Pharmaceutical Studies, Ujjain, Madhya Pradesh – 456664, India

Email: lakshitasrathore@gmail.com

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A Short Review on Advancement in Fast Dissolving Oral Thin Films

Lakshita Rathore, Narendra Gehalot, Vikas Jain

ABSTRACT

The pharmaceutical industry is pursuing the development of thin films as a novel method of drug administration. Thin films as an alternative to standard dosage forms have been described. They are a very adaptable platform capable of producing immediate, local, or systemic effects. Additionally, these systems are self-administered, which is advantageous for patients with dysphagia, elderly, pediatric, or bedridden patients and those who cannot administer with water. Thin film drug delivery methods are available for oral, buccal, sublingual, ophthalmic, and transdermal administration. This review explores oral thin films in all of their elements from a contemporary standpoint and provides insight into the world's expanding market share due to the expansion of study areas and technical advancements. Simultaneously, it presents an overview of the essential parameters that affect formulation design that affects thin films, including thin-film design, anatomical and physiological constraints, and the selection of suitable manufacturing processes, characterization methodologies, and the physicochemical properties of polymers and drugs are all covered in this section. Additionally, it provides insight onto the most recent thin-films produced by various pharmaceutical companies.

Keywords: Fast dissolving films, patient compliance, dysphagia, oral, buccal, sublingual.

1. INTRODUCTION

Oral pharmaceutical formulations are available in the form of tablets, granules, powder, and liquid. Tablets are generally delivered to patients in a form that allows them to swallow or chew a specific dose of medication. However, certain patients, particularly the elderly and children, have trouble chewing or swallowing solid dose forms. [1] As a result, many youngsters and the elderly are fearful of asphyxiation when given these solid dose forms. Orally dissolving tablets (ODTs) have been developed to address this need. However, for some patient populations, despite fast dissolution/disintegration times, the anxiety of ingesting the solid dose form (tablet, capsule) and the risk of asphyxiation persist. Under these circumstances, oral thin film (OTF) drug delivery techniques are desirable. Numerous medicines have poor oral bioavailability due to enzymes, common first-pass metabolism, and stomach pH. [2] These traditional medications have been administered parenterally and have demonstrated low compliance among patients. These situations have paved the way for the pharmaceutical industry to develop alternate methods of medication conveyance by manufacturing thin dispersible/dissolving films for use in the mouth. Fear of drowning has been connected with several patient categories, which may be a danger with ODTs. Rapid dissolution/disintegration of OTF drug delivery systems is preferred over ODTs in patients with asphyxiation fears. OTFs are rapidly moistened with saliva upon placement on the tongue. As a result, they are disseminated and/or dissolved, allowing the medicine to be absorbed systemically and/or locally. ODTs are brittle and have been known to break during transit. As an alternative, oral rapid disintegrating/dissolving drug delivery methods are being developed. [3]

Oral fast dissolving films or strips are described as "drug delivery devices that rapidly release the active ingredient by dissolving or sticking in the mucosa with saliva within a few seconds when placed in the mouth cavity or on the tongue." Due to its thin membrane structure and high vascularization, the sublingual mucosa increases membrane permeability. It has a very high bioavailability due to its quick blood supply. [4] The increased systemic bioavailability is due to the absence of the first-pass effect, while the increased permeability is due to increased blood flow and lymphatic circulation. Additionally, due to the enormous surface area and simplicity of application for absorption, the oral mucosa is an extremely effective and selective route of systemic drug delivery. In general, OTFs are defined as a thin and flexible polymer layer that may or may not contain plasticizers. They can be believed to be less upsetting and more palatable to patients due to their inherent thin and flexible shape. Thin films are polymeric structures that meet a number of the criteria for a drug delivery device. [5] Thin films have been proven in trials to improve the initial effect and duration of the medicine, decrease the frequency of dose, and increase the treatment's effectiveness. Thin-film technology may enable the elimination of pharmacological side effects and the reduction of common metabolism mediated by proteolytic enzymes. Ideal thin films should exhibit the desired qualities of a drug delivery system, including a sufficient capacity for drug loading, fast dispersion/dissolution, or prolonged application, and adequate formulation stability. Additionally, they must be harmless, biodegradable, and biocompatible with living organisms. [6]

The availability of several biocompatible polymers and a range of manufacturing technologies has enabled the development of a diverse range of OTFs. As a result, OTFs gain acceptance and appeal in pharmaceutical technology as a new drug carrier dosage form. A significant effort has been made to develop polymeric OTFs that can be administered orally, buccally, sublingually, ocularly, or transdermally. [7] Among these applications, the use of OTFs to distribute drugs through the buccal or sublingual mucosa has received considerable interest in recent years. Mechanical strength, related characteristics, mucoadhesive qualities, and drug release rate can also be modified by varying the amounts of polymers that make up thin films. Due to the appealing features of OTFs, the pharmaceutical industry is developing thin-film technology and is now patenting these formulations. [8]

According to the European Medicines Agency, an orodispersible film is a thin film that readily dissolves in the oral mucosa. Rapidly dissolving oral films are typically postage-stamp-sized OTFs that dissolve/disperse in the oral cavity within 1 minute of contact with saliva, resulting in rapid drug absorption and bioavailability. [9] These novel dosage forms are administered orally and do not require water for ingestion or absorption like conventional formulations.

According to the American Food and Drug Administration (FDA), OTF is defined as "a flexible and non-brittle strip containing one or more active pharmaceutical ingredients (APIs) that is placed on the tongue before entering the gastrointestinal tract, with the goal of rapid dissolution or disintegration in the saliva." Zuplenz (Ondansetron HCl, 4-8 mg) was the first OTF approved in 2010. According to statistics, four out of five patients prefer orally dissolving/disintegrating medication forms over standard oral solid dosage forms. [10] At the moment, OTFs are accessible in a wide variety of prescription and over-the-counter product categories, most notably cough, cold, sore throat, erectile dysfunction disorders, allergic responses, asthma, gastrointestinal disorders, pain, snoring complaints, and sleep problems, among others. Fast-dissolving oral films have several advantages over traditional solid dose forms, including enhanced API efficacy and flexibility. Additionally, compared to ODTs, oral films dissolve and disintegrate with relatively little saliva fluid in less than a minute. [11]

1.1 Advantages of fast dissolving film [12-13]

The fast dissolving film offer many advantages such as-

- Non-invasive
- Suitable for pediatric/geriatric patients
- No water and no chewing required for drug release and uptake resulting in a substantial improvement of patient compliance and convenience
- Fast dissolving films offers an elegant route for systemic drug delivery.
- The improved systemic bioavailability results from bypassing first-pass effect and permeability due to a well-supplied vascular and lymphatic drainage.
- The large surface area of absorption, easy ingestion and swallowing, pain avoidance make the oral mucosa a very attractive and selective site for systemic drug delivery.
- The demand for new dosage forms to meet the needs of the pediatric and geriatric population is rising.
- Improved stability for pH-sensitive drugs (mouth saliva pH ≈6.5)

1.2 Major limitations of thin films [14]

- Often the use of thin films is largely limited due to the low ability of drug charging for a less potent drug given at high doses.
- By fact, thin films appear to be hygroscopic. Special precautions should therefore be taken to protect them for a longer time.
- Combining more than one medication at the same time is a very challenging task in oral film formulation because the co-administration of a drug in oral films impedes both the speed of dissolution as well as the time of disintegration.
- The difficulty in obtaining a high degree of accuracy regarding the amount of medication in the individual film unit dose will

lead to therapeutic failure, non-reproductive effects and sometimes toxic effects.

- The preparation of oral film formulation is concerned with the problems of prolonged drying time. This takes about one day to dry at room temperature, which significantly reduces the speed of film production. While the use of hot air oven for thermolabile drugs is not recommended, an alternative drying method should be explored.

1.3 Criteria for fast dissolving films [15]

- Have a pleasant mouth feel.
- It does not require water to drink, but in a matter of seconds it should dissolve or disintegrate into the mouth.
- Compatible with taste masking.
- Upon oral administration, leave a minimal or no residue in the mouth.
- High tolerance to conditions such as temperature and humidity.

2. FORMULATION CONSIDERATIONS FOR OTFs

Table 1. Formulation components of OTFs

Component	Amount
Drug	5-30%
Film-forming polymer	40-50%
Plasticizer	0-20%
Saliva stimulants	2-6%
Sweeteners	3-6%
Superdisintegrant	0-8%
Flavoring agents	Quantity sufficient
Surfactants	Quantity sufficient
Coloring agents	Quantity sufficient

2.1 Active ingredients used in OTFs

Absorption cannot occur unless the API is dissolved. If the active chemical is extremely lipophilic, it will be insoluble in water, resulting in inadequate absorption. As a result, there is a delicate balance between the drug's lipophilicity and solubility. Passive diffusion is the principal mode of medication absorption. As a result, the partition coefficient, degree of ionisation, and molecular weight of drugs all have a significant effect on their transit across oral mucosal membranes. When evaluating bioavailability, the pKa of the API and the degree of ionisation at ambient pH must be considered. Absorption is typically proportional to the API's lipophilicity or partition coefficient. However, the solubility of the drug is critical. The nonionized version of the drug is more lipid soluble and hence penetrates cellular membranes via diffusion. There are no issues with uniform dispersion of water-soluble APIs. However, in order to maintain an appropriate level of content homogeneity, water-insoluble APIs must be dispersed uniformly [11].

2.2 Desired properties of API to be used in OTFs

- Should be used in a low dosage
- The feeling and taste left in the mouth should be appropriate
- Must have low molecular weight
- Must be stable and soluble in saliva

Its potential and therapeutic effectiveness are also important in the selection of the API. The most suitable APIs for OTFs are anticancer drugs, antiasthmatic, antitussives, antihistamines, antiepileptics, antianginal drugs, antiemetics, cardiovascular drugs, neuroleptics, analgesics, anxiolytics, antiallergic drugs, hypnotics, sedatives, antibacterial drugs, anti-Alzheimer's drugs, and diuretics, and expectorants.

2.3 Film-forming polymers used in OTFs

Due to the tensile strength of polymers, which varies according to the kind and number of films employed, the selection of polymers is a vital and critical parameter in the successful manufacture of oral films. A minimum of 45 percent polymer by weight must be present in the dry film, but 60–65 percent polymer by weight is chosen to attain the desirable characteristics. To produce the necessary film qualities, polymers can be used alone or in combination. Due to the fast dispersion and dissolution of OTFs in the oral cavity, the polymers used to produce the film must be water soluble. Simultaneously, the films obtained must be sturdy and free of damage during travel and storage. OTFs have unique features due to the combination of several polymers. For example, gelatins have a range of molecular weights, allowing for the production of high-molecular-weight glossy and highly appealing films. Pullulan is frequently used to fabricate thin films with high tensile strength and solubility; it is also extremely stable across a wide temperature range. When high-methoxy pectin is combined with chitosan or low-methoxy pectin, a thin layer with ideal mechanical strength results. Film-forming polymers such as methylcellulose, hydroxypropyl cellulose, and carboxymethyl cellulose form a thin film that disperses and/or swells as a result of their hydrophilic properties, which aid in water absorption.

2.4 Plasticizers used in OTFs

Plasticizers aid in increasing the flexibility and decreasing the Tg of the polymer, hence reducing the film's friability. Additionally, plasticizers boost tensile strength. Plasticizers must be compatible with the medicine being used, the solvent being used, and the polymer being utilised. The most often used ingredients include

sorbitol, mannitol, glycerin, diethyl phthalate, triethyl citrate, tributyl citrate, macrogol, propylene glycol, and citric acid esters.

2.5 Surfactants used in OTFs

Surfactants act as dispersing or wetting agents, assisting the film in dissolving swiftly and rapidly releasing the API. It is better to use poloxamer 407, sodium lauryl sulphate, and polysorbate.

2.6 Sweeteners used in OTFs

To ehance the flavour of OTFs, both natural and artificial sweeteners are employed. The most often used polyhydric alcohols are mannitol, sorbitol, maltitol, and isomalt. Additionally, polyhydric alcohols can be used in conjunction to impart a pleasant sensation and a cooling sensation in the mouth. Additionally, polyhydric alcohols have a less harsh aftertaste and are less carcinogenic. Except for xylitol and maltitol, the sweetness of the majority of polyols is less than half that of sucrose (both have a similar sweetness to sucrose). Aspartame and saccharin are frequently utilised as artificial sweeteners in OTFs.

2.7 Saliva stimulants used in OTFs

Saliva stimulating agents stimulate saliva production and aid in the breakdown of formulations. Additionally, acids commonly employed in food processing could be used as saliva stimulants. Saliva stimulating agents include ascorbic acid, malic acid, citric acid, tartaric acid, and lactic acid.

2.8 Superdisintegrants used in OTFs

When added to OTF formulations, superdisintegrants promote fast disintegration through the combined impact of water absorption and swelling. Superdisintegrants accelerate disintegration and breakdown by absorbing and swelling excess water. Disintegration requires a strong interaction with saliva [15].

2.9 Coloring agents used in OTFs

FD and C approved colorants, EU approved colorants, natural coloring agents, or pigments can be included in formulations up to 1% by weight.

2.10 Flavoring agents used in OTFs

The flavour to use is determined by the type of API being utilised. Acceptance of the dosage form by the patient as a result of oral disintegration or dissolution is contingent upon the taste perceived within the first few seconds following OTF consumption and for at least 10 minutes afterwards in the mouth. As a result, the choice of flavouring agent is critical.

3. PREPARATION METHODS OF OTFS [16]

One of the following methods or combinations could be utilized in the preparation of oral dissolving/disintegrating thin films:

3.1 Solvent casting method:

Among the various film manufacturing procedures, solvent casting is a practical, superior, and unquestionably extensively utilised technology, owing to its uncomplicated manufacturing process and inexpensive processing costs. It entails dissolving the medication, polymers, plasticizers, and other components in water, an appropriate solvent, or a solvent system. Solvents used to prepare solutions or suspensions should be classified according to the International Classification of Chemicals (ICH). The precipitated solution or suspension is cast onto a suitable surface in the required region and dried at an adequate temperature.

3.2 Hot-melt extrusion (HME)

HME is a flexible process that is used to make granules, tablets, pellets, and thin films. HME is a method that involves melting a mixture of polymers, drug ingredient, and other excipients into a film. At some point, the films are cut to a specific form and dimension. This process involves melting a combination of medicinal ingredients and then charging them through an aperture (the die) to produce homogeneous matrices.

3.3 Printing technologies

Polymeric thin films could be manufactured using novel methods such as 3D printing. Printing a medicine on a dosage form is the most recent intervention in the film preparation process, and it has developed into a highly effective method for producing dosage forms with exceptional consistency, speed, and stability. Inkjet printing and flexographic printing are two printing processes that have been utilised to make polymeric thin films (FPT).

4. CHARACTERIZATION OF OTFS

Numerous investigations and measurements are performed as part of the characterization studies of the generated OTFs. Among these are organoleptic and morphological control, moisture absorption, swelling ability, flexibility (elongation), folding ability, pH determination, weight variability, thickness, flavor, content uniformity, dispersion, dissolution rate, release kinetics, and degree of transparency, as well as analyses and measurements using a scanning electron microscope (SEM), X-ray powder diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry

According to the American Association of Pharmaceutical Scientists/International Pharmacy Federation, due to the brief duration of the disintegration and dissolution processes in OTFs, the disintegration test can be used in place of the dissolution test for

ODTs. If the API is molecularly dissolved in OTF, the rate at which it is released relies solely on the film's disintegration time. Simultaneously, if the API is spread in the film matrix in a particulate form, both dissolving rate and disintegration time tests are recommended.

Typically, drug release from OTFs occurs in a 37°C environment (artificial saliva fluid or a pH 6.8 phosphate buffer) in accordance with the pharmacopoeia standards for solid oral dosage forms, using a pallet or basket system. However, there are significant downsides to the disintegration apparatus for OTFs. When the basket apparatus is used, OTFs may adhere to the edges and clog the basket pores; however, when the paddle apparatus is used, OTFs are likely to adhere to the bottom of the container or remain on the top of the container in the dissolution medium. Platinums and double-sided tapes are used to replicate in vivo adhesion and hinder the film from floating. Each film is adhered to the bottom of the dissolution media using a rectangular glass plate. As a result of the quick disintegration, the drug is released swiftly, and samples of the medium are collected in a short period.

5. EVALUATION OF FAST DISSOLVING TABLETS

5.1 Organoleptic properties

The color, homogeneity, transparency, smell, and texture of the OTFs are examined visually and sensually. They should be evaluated especially in terms of taste and flavor characteristics. [16]

5.2 Moisture absorption capacity

This test is conducted in high humidity conditions to ensure the films' physical stability and integrity. After individually weighing the samples, they are placed in desiccators containing aluminium chloride solution and left to dry for 3 days. The films are then weighed and their moisture absorption capabilities in percent are estimated using the formula below.

5.3 Weight variability

1x1 cm^2 films are cut from each formulation, and weight variability is calculated by weighing them individually on a sensitive scale.

5.4 Thickness

The film thickness was measured using a micrometer screw gauge at five points on the film to ensure the uniformity of the film thickness. The mean thickness was calculated from the five points.

5.5 Folding endurance test

Folding endurance values reflect the strength of the film prepared. The flexibility of thin films is determined by folding a film repeatedly at the same place at an angle of 180° until it breaks. The number of folds made before breaking is noted. The film that exhibits 300 times or more folding endurance is considered to have excellent flexibility. [15]

5.6 Weight variation

Ten films were randomly selected and their average was obtained. Individually films were weighed and compared with the average weight for the deviation.

5.7 Drug content

Drug content determination of the films is to ascertain whether the required amount of drug loaded in the polymer or not. Each film is filtered after being dissolved in a suitable solvent, and the drug content in each film is measured by the appropriate quantification method. It is expected that the relative standard deviation % is not more than 6%.

5.8 Disintegration test

To find out actual time required for disintegration of the film. The disintegration time is described as the time (seconds) that a film disperses when it comes into contact with saliva or water. The disintegration test apparatus specified in pharmacopoeias can also be used to determine the disintegration times of OTFs. Normally, the disintegration time of the film composition is usually 5-30 s.

5.9 *In vitro* dissolution test

Many research used Franz diffusion cells to assess drug release from polymeric films, whereas the apparatus used for dissolution rate testing was improved. The placing of film specimens is the most difficult challenge in the dissolution rate assay. Furthermore, several methods have been used in the literature in which the film's dissolution rate is bonded to the bottom of the glass container or the mixing device using a double-sided adhesive band.

6. CONCLUSION

OTFs have emerged as a breakthrough and most of the pharmaceutical companies continue to do research and development to adapt their products across multiple therapeutic categories to this technology. This device is a ground-breaking method of administering drugs to people with swallowing difficulties, particularly paediatric and geriatric patients. Additionally, it has several advantages over other dosage forms, including increased bioavailability and the faster onset of action. It is a critical dosage form that can be administered orally in emergencies and when an immediate onset impact is sought. As a result, it can be concluded

that OTFs with high patient compliance and numerous benefits provide novel futuristic potential.

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