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Review Article

Evaluation of Mouth Dissolving Films: Physical and Chemical Methods

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Abstract

Orodispersible is the term referred to dosage form which disperse or disintegrate into mouth i.e. oral cavity. The time required to disintegrate should be not more than 3 minutes. Dosage forms in which they are available are tablets and mouth dissolving films which when placed in oral cavity release drug instantaneously with rapid onset of action. An ideal ODF should exhibit adequate flexibility, elasticity, softness, resist the breakage, minimum disintegration time and taste compliance. All these parameters need to be evaluated during the formulation development stage and required standard protocols. The greatest challenge is to develop a high quality film which also necessitates constant evaluation and understanding the performance of the dosage form, the critical steps to achieve a successful product development. Despite the intense focus on film based drug delivery system, there are no official standardized methods for its evaluation. Significant efforts have been made to demonstrate and improve the efficacy, potency and safety of film using in vitro and in vivo assessments.

1. INTRODUCTION

Orodispersible is the term referred to the dosage form which disperse or disintegrate into mouth i.e. oral cavity. The time required to disintegrate should be not more than 3 minutes this is ideal requirement for orodispersible tablets according to monograph[1]. Oral route being the most patient complaint route for the administration, orodispersible dosage forms has further advantages in patients suffering from dysphagia(difficulty in swallowing), geriatric, pediatric and patients undertaking anti-cancer therapy. Dosage forms in which they are available are tablets and mouth dissolving films which when placed in oral cavity release drug instantaneously with rapid onset of action.

Orodispersible films are rectangular strips of thin polymeric films formulated to disintegrate or dissolve almost instantaneously when placed onto the tongue. Different terms can be found in the literature, for example, wafer, oral film, thin strip, orally dissolving film, flash release wafer, quick dissolve film and melt-away film[2-5]. ODFs recently became part of the monograph "oromucosal preparations" of the European Pharmacopoeia. However, no requirements limiting disintegration time have until now been specified[6].

An ideal ODF should exhibit adequate flexibility, elasticity, softness, resist the breakage, minimum disintegration time and taste compliance. All these parameters needs to be evaluated during the formulation development stage and required standard protocols. Several techniques can be applied to characterize and evaluate the orodispersible films and are based on methods ranging from physical and mechanical properties, *in vitro* disintegration to in vivo drug release in humans. This review outlines various *in vitro* and in vivo methods which are utilized in the pharmaceutical industries, regulatory agencies and drug delivery scientists to characterize the physical properties, and mechanical properties of ODFs.

2. IDEAL REQUIREMENTS

The ideal requirements for ODF are summarized below[7-9]:

- ODF should be thin and flexible, but stable to guarantee a robust manufacturing and packaging process and ease of handling and administration.
- The films should be transportable, not tacky and keep a plane form without rolling up.
- Ease of administration for patients who are mentally ill disabled and uncooperative.
- They should provide an acceptable taste and a pleasant mouth-feel.
- Require no water.
- Disintegration time should be as short as possible.
- They should exhibit low sensitivity to environmental conditions such as temperature and humidity.
- They should have ability to provide advantages of liquid medication in the form of solid preparation.
- Size of a unit FDF should not be too large that it will affect the patient's compliance.
- Surface of the FDF should be smooth and uniform.
- They should remain physically and chemically stable throughout its shelf life.
- Cost effective and ease of commercial production.

Table 1: Advantages and disadvantages of ODFs[9]

Advantages	Disadvantages
Rapid onset of action	Drug loading is limited
Patient complaint	Added cost for taste masking of bitter drugs
Used without water	Dose uniformity is technical challenge
Accurate dosing	Hygroscopic in nature
Avoids first pass metabolism	Require special packaging
Reduction in dose	

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Table 2: Percentage of various ingredients used in formulation of ODFs[8]

Sr. No.	Ingredients	Amount(w/w)
1	Drug(API)	5-30%
2	Water Soluble Polymer	45%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Surfactant	q.s
6	Sweeting agent	3-6%
7	Flavor, Color, Filler	q.s

Table 3: Examples of excipients used in formulation of ODTs[10]

Drug	Polymer	Plasticizer	Sweetener
Nicotine	Pullulan	Glycerol	Dextrose
Nitroglycerine	Hydroxy propyl methyl cellulose	Propylene glycol	Fructose
Zolmitriptan	Poly (acrylic acid) derivatives	Dimethyl phthalate	Glucose
Loratidine	Sodium carboxy methyl cellulose	Diethyl phthalate	Maltose
Loperamide	Hydroxy ethyl cellulose	Dibuyl phthalate	Xylitol
Famotidine	Hyaluronic acid	Tributyl citrate	Maltitol
Flurazepam	Xanthan gum	Trietylcitrate	Mannitol
Acrivastine	Locust bean gum	Acetyl citrate	Sucralose
Dicyclomine	Guar gum	Triacetin	Aspartame
Omeprazole	Carragenan	Castor oil	Alitame
Cetrizine	Sodium alginate	Lanoline alcohol	Neotame

3. MANUFACTURING METHODS

3.1 Solvent Casting Method

Water soluble polymers are dissolved to form homogenous solution. Drug and other water soluble components are allowed to dissolve in small amount of water. Both solutions are mixed with each other with continuous stirring. Entrapped air bubbles are removed by applying vacuum. Solution formed is casted on non-treated surface. Subjected for drying and cut in pieces[11]. Figure: 1 (source: particle science) gives details about solvent casting method.

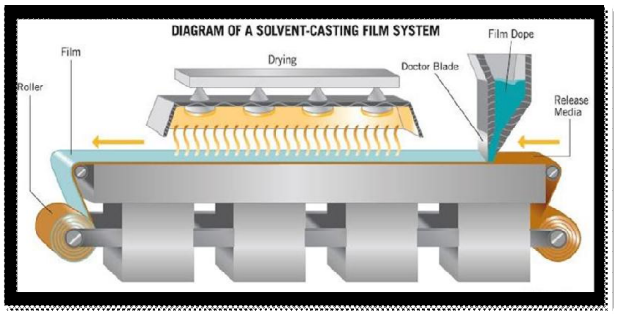

Figure 1: Solvent Casting Film system

3.2 Hot Melt Extrusion

In hot-melt extrusion, the dry ingredients for the film are heated and homogenized by the action of an extruder screw until they are molten and mixed. The melted material is forced through a flat extrusion die that presses the extrudate into the desired film shape. The thickness and strength of the film can further be affected by elongation rollers while the material is still hot and pliable. The extruded film is then cooled, cut and packaged[12]. Figure: 2 (source: particle science) gives details about hot melt extrusion technique.

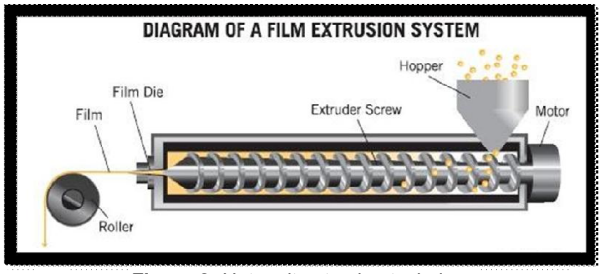

Figure 2: Hot melt extrusion technique

3.3 Semisolid Casting Method

Solution of water soluble film forming polymer is prepared. Resulting solution is added to a solution of acid insoluble polymer (*e.g.* cellulose acetate phthalate, cellulose acetate butyrate). Appropriate amount of plasticizer is added so that gels mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. 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[13].

3.4 Rolling Method

In this method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. Prepare pre-mix with film forming polymer, polar solvent and other additives except a drug add pre mix to master batch feed tank. Feed it via a 1st metering pump and control valve to either or both of the 1st and 2nd mixers. Add required amount of drug to the desired mixer. Blend the drug with master batch pre mix to give a uniform matrix. Then a specific amount of uniform matrix is then fed to the pan through 2nd metering pumps. 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. Solvent used is mainly water and mixture of water and alcohol[14].

4. EVALUATION OF ODFS

After the films are produced by one of the above manufacturing method, they are subjected to evaluation. Evaluation is very important and crucial step required to maintain inter and intra batch uniformity between films. Various parameters are studied which can be divided depending upon physical and chemical properties.

4.1 Physical Parameters

Physical parameters are important as they are performed on final dosage form which gives idea about the uniformity between batches and also to maintain aesthetic appeal of the final formulation. As the USP describes only a tensile strength test for surgical sutures and patches, technical regulations from other industries such as the plastic industry can be used as templates. Tensile tests according to the ASTM International Test Method for Thin Plastic Sheeting (D 882-02)[15] or tests described in the DIN EN ISO 527-1 and 527-3 regulations can be utilized.

4.1.1 Mechanical Parameters

a) Dryness / Tack test

Dryness can be described as the property to measure the solvent or water content present in the film whereas tack is the tenacity with which the film adheres to any piece of paper which is pressed into contact with the strip. Eight stages of film drying process have been recognized i.e. set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through; dry-to-recoat and dry print free. Various instruments are now available to measure these properties. At lab scale this can be done by using thumb and pressing it against the film[13].

b) Tensile strength

Tensile strength can also be defined as the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film from the following equation[16]. Table No.4 gives detail about various tensile testing instruments.

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

c) Percentage elongation
Elongation is a kind of deformation. It is a simple change in shape that anything undergoes when under stress, which can be measured using a texture analyzer. In other words, when a sample is put under tensile stress, the sample deforms, becomes longer or gets elongated[16]. It can be calculated by measuring the increase in length of the film after tensile measurement by using the following formulae[11]:

Percent Elongation = $[L-L_0]$ X 100 / L_0

Where L was the final length and L_0 was initial length.

d) Young's Modulus
Young's modulus or elastic modulus is the measure of stiffness of film[17]. The methods used for the measurement of tensile strength could be utilized here as well. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's Modulus= Slope x 100/ Film thickness x cross head speed

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation.

Table 4: Various tensile testing instruments

Instrument / Method	Procedure
A TA.XT2 texture analyzer	It is equipped with a 5 kg load cell to determine the tensile strength of the prepared film was. Briefly, film strips are held between two clamps positioned at a distance of 3 cm. Then the strips were pulled by the top clamp at a rate of 2 mm/s and the force was measured when the films breaks.
Palem et al. used a microprocessor based advanced force gauze with a motorized test stand	The strips from the patch are placed between two clamps to secure the patch. The lower clamp is held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/s until the strip breaks.
Tensiometer	The tensile strength of the film is determined by measuring the total weight loaded on the string to break the film
The Instron	Along with a 5-kilogram load cell. Film strips in special dimensions and free from air bubbles or physical imperfections are held between two clamps positioned at a distance of 3 cm. During measurement, the strips are pulled by the top clamp at a rate of 100 mm/min, and the force and elongation are measured in triplicate when the film breaks.

e) Tear Resistance
Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture[18]. Basically very low rate of loading 51 mm (2 in.) /min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required tearing the specimen is recorded as the tear resistance value in Newtons (or pounds-force).

f) Folding endurance
The flexibility of film is an important physical character needed for easy application on the site of administration. The flexibility of the film can be measured quantitatively in terms of folding endurance and is determined by repeatedly folding the film at 180° angle of the plane at the same plane until it breaks or folded to 300 times without breaking. The number of times the film is folded without breaking is computed as the folding endurance value[16].

4.1.2 Other physical parameters
a) Appearance
All prepared films can be checked for their appearances either they are transparent or opaque. Visual inspection is normally performed but instruments like microscope can also be used for determining surface properties.

b) Thickness
Thickness of the prepared film can be measured by micrometer screw gauge at different strategic locations. Film thickness should be measured at five points i.e. from the center and from all the four corners and then mean thickness is calculated. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip[16].

c) Weight variation
Individual film should be weighed and the average weights are calculated. Then the average weight of the films is subtracted from the individual weight of the film. A large variation in weight indicates the inefficiency of the method employed and is likely to have non-uniform drug content[16].

d) Contact angle
Contact angle can be measured by Goniometer (AB Lorentz and wettre, Germny) at room temperature. This can be done by taking a dry film and placing a drop of distilled water on the surface of the dry film. Images of water droplet are recorded with in 10 seconds of deposition by means of digital camera. The contact angle can be measured on both side of drop and average is taken[19].

e) Transparency
The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film in the rectangular shape and placed inside the spectrophotometer cell. Determine the transparency of the film at 600nm.The transparency of the film can be calculated as follows[17]:

Transparency= (log T_{600})/b = —εC

Where,
T_{600}= transmittance at 600nm
b= film thickness (mm)
C= concentration

f) Moisture content:
The amount of moisture affects the brittleness and friability of films. Basically, the contents in the product regulate the degree of moisture in a particular film. The amount of moisture present in the film can generally be determined using moisture content testing equipment, Karl fisher titration method or by weighing method[16]. Typically, a specific size of pre-weighed film is heated to 100–120 °C until it attains constant weight and the difference in weight gives the amount or degree of moisture present in the film.

Moisture content can be calculated as:

% Moisture content= [(Initial weight – Final weight) ×100/Initial weight].

The moisture content in an ideal film should be <5%.

4.2 Chemical Parameters

a) Surface pH test
Surface pH of the film can be determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the color of pH paper is observed and reported[20-21].

b) Disintegration time
Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The required size of film (2×2 cm^2) is placed in a stainless steel wire mesh containing 25 ml of pH 6.8 simulated salivary fluid. Time taken by film to break and dissolve is measured as in-vitro disintegration time[11].

c) *In vitro* dissolution test
Dissolution testing 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[18].

d) Thermal analysis
Thermo-grams of the samples can be recorded using a differential scanning calorimeter, which provides insight into the state of the drug molecules inside the film. Any shift in the endothermic or exothermic peak or widening of peak area directly represents phase transition, recrystallization or molecular interaction of the drug molecule entrapped inside the film. This can be assessed by heating the sample in an aluminum pan from room temperature to elevated temperature (~500 °C) at a specified heating rate (~10 °C/min)[16].

e) Crystallinity
The physical form (crystalline or amorphous) of the drug molecule inside the film can be easily determined by X-ray crystallographic analyses using X-ray diffractometer. The films can be placed in the sample holder and the XRD transmission diffractograms can be acquired with a specific X-ray source over a start to end diffraction angle, scan range and scan speed[16].

f) Assay / Content uniformity
This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%[17].

4.3 *In Vivo* test
Efforts have been made to simulate the in vivo disintegration, such as contact angle measurements and thermo-mechanical analysis of the swelling behavior of the films[4].
In vivo testing mainly involves tasting of the films and their in-vivo disintegration time with help of the tasting panel and human volunteers. Electronic tongue tester is also used to evaluate taste of the films.

4.4 Other tests
Other methods for characterization and quality control of ODFs include viscosity measurement of the polymer solution, content uniformity and determination of residual solvents[22,23]. Garsuch and Breitkreutz found caffeine recrystallization in ODFs varying between the upper and lower surface by scanning electron microscopy, X-ray diffraction and near-infrared chemical imaging[4].Near-infrared spectroscopy and Raman spectroscopy are suitable technologies to qualify and quantify APIs within the films[7]. Differential scanning calorimetry, thermo-mechanical analysis and X-ray diffraction are used to investigate crystallinity and glass transition temperature[23,24]. Gaisford et al. monitored crystallization of drugs from ODFs with isothermal calorimetry[7].Hygroscopic and residual water content are investigated by dynamic vapor sorption or by weight[7, 24]. Further, microbiological studies and stability tests should be investigated regarding common guidelines[7, 22].

5. CONCLUSION
Delivery of drug through oral thin film provides several advantages. ODFs are a very suitable dosage form for children and the elderly, because they are easy to swallow and involve no risk of choking. They usually consist of film-forming polymers, plasticizers and further excipients, for example, for improvement of taste. The main disadvantage of ODFs is the limited drug load. ODFs are commonly manufactured by solvent casting. Basic characterization methods are determination of mechanical properties and disintegration behavior.

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