



ORALLY DISINTEGRATING FILMS- A RECENT MODIFICATION IN THE PHARMACEUTICAL DRUG DELIVERY SYSTEM

Deshmukh Saie^{1*}, Ghosh Amit², Karpe Manisha³, Kadam Vilasrao³

¹Department of Quality Assurance, Bharati Vidyapeeth's College Of Pharmacy, University of Mumbai, CBD-Belapur-Navi Mumbai, India

²Department of Pharmaceutics, Bharati Vidyapeeth's College Of Pharmacy, University of Mumbai, CBD-Belapur-Navi Mumbai, India

³Department of Pharmacy, Faculty of Bharati Vidyapeeth's College Of Pharmacy, University of Mumbai, CBD-Belapur-Navi Mumbai, India

Abstract: In recent years, there has been a significant increase in efforts to guarantee effectiveness, safety, and patient acceptance due to the trend towards new drug delivery technologies. The creation of novel drug delivery methods for currently available medications is becoming more popular as the research and development of new chemical agents is a difficult, expensive, and laborious process. Among them, orally disintegrating films are a popular medication delivery technique in paediatrics and geriatrics. The vital benefit of the dosage form is its rapid disintegration. ODFs are an innovative dosage form that breaks down and dissolves within the oral cavity. Intraoral absorption enables quick action and helps avoid first-pass effects, which lowers the unit dosage needed to deliver the anticipated therapeutic effect. These rapid-dissolving films are better than fast-disintegrating tablets since the latter have choking and friability issues. This drug delivery technology offers several benefits over traditional fast-disintegrating tablets, including the ability to be used for dysphasic and schizophrenic patients and the capacity to be taken without water due to their quick disintegration and rapid release of medicine in the mouth. This present review provides a brief summary of the benefits, composition, formulation methods, and evaluation parameters employed for oral disintegrating.

Keywords: Evaluation parameters, Formulation methods, Geriatric patient, Oral disintegrating films, Pediatric patient

I. INTRODUCTION

The oral route is the most preferred route by patients among the several routes of administration. Most pharmaceutical firms have focused their research efforts on finding feasible oral dosage form options for pediatric, geriatric, noncompliant, or nauseated patient¹. Orally disintegrating films provide an elegant means of systemic medication administration. Using transdermal patch's technology as a model, we developed orally disintegrating films as a new drug delivery technique for oral drug delivery. When placed on the tongue, these films exhibit the behaviour of either dissolving or disintegrating in salivary fluids without the need for water, making them an alternative to Rapidly Dissolving Tablets.² The improved systemic bioavailability is owing to the bypassing of the first pass effect and improved permeability as a result of well-supplied vascular and lymphatic drainage. OTFs are now in the early to mid-development phases for prescription drugs and are a well-established and widely accepted technology for the systemic administration of APIs for over-the-counter (OTC) treatments.

ADVANTAGES-

In comparison to traditional dosage forms and orally disintegrating tablets, fast dissolving oral films, an improved evolution of fast dissolving drug delivery methods, have several remarkable benefits.

1. Easy transportation.
2. Swallowing comfort for pediatric and geriatric.
3. Easy and precise dosage.
4. Water is not required for administration.
5. Convenient for dysphasic patients who have difficulty in swallowing capsules and tablets.
6. Stability and rapid onset of action with enhanced bioavailability by avoiding the hepatic first pass effect.³
7. These films can be produced using cost-effective non-sophisticated techniques and simple equipment.

DISADVANTAGES-

1. High doses cannot be assimilated.
2. It is not feasible to use drugs having unpleasant taste.
3. Maintaining dose consistency is difficult.
4. This method of delivery cannot be used for medications that irritate the oral mucosa.

IDEAL CHARACTERISTICS OF DRUG CANDIDATE FOR ODFs

1. The integrating API should have low dose of upto 40 mg.
2. It is preferable to use drugs with low molecular weight.
3. It must be capable of penetrating oral mucosal tissue.
4. The drug should have pleasant taste.
5. At the pH of the buccal cavity, it ought to be slightly unionized.
6. The drug should have appropriate stability and solubility in both water as well as saliva.

FORMULATION- ODFs are rapidly dissolving thin films with an area ranging from 5 to 20 cm² that contain a medication integrated as a matrix

utilising hydrophilic polymer. Up to 15 mg of active pharmaceutical ingredient can be combined with various excipients such as plasticizers, colorants, and preservatives. Sweeteners, flavour masking agents etc. Plasticizer improves workability, spreadability, and adhesion. Film flexibility increases by lowering the glass transition temperature of polymers.⁴

Active pharmaceutical ingredient-Several pharmacological classes can be incorporated into oral disintegrating films including anti-histamine, anti-depressant, vasodilator, anti-asthmatic, anti-emetic, etc. For flavour masking, dimenhydrinate can also be added to ODFs. Drugs including salbutamol sulphate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc⁵. are frequently included in ODFs. Additionally, an ODF containing a prochlorperazine an anti-emetic drug was developed using microcrystalline cellulose and other film-forming polymers.⁶

Hydrophilic polymers-In order to achieve the desired features, such as disintegration time, drug loading capacity, mechanical strength, and drug release profile, a variety of polymers can be utilised in the development of ODFs. Both individually and collectively, these polymers are used. The type and quantity of polymer in the formulation regulate the optimal formulation. ODFs, on the other hand, should dissolve within seconds of being placed in the mouth. As the drug-release matrices are the most essential and abundant component of the ODFs, the selection of the polymer or polymer mixtures may be the most critical phase in the development of ODFs; there is at least 45% w/w of polymeric matrix in the total weight of dry ODFs.

Ideal properties of polymer-

1. Polymer must have good spreadability
2. Non irritant
3. Non toxic
4. Should possess good mechanical strength
5. Polymer should have appropriate shelf life

ODF formulations are now developed using both natural and synthetic polymers. To regulate various film qualities, several polymers are used. Along with improving flexibility, pullulan has enhanced solubility. Pullulan- containing films also have good tensile strength and temperature stability. The qualities of produced films are influenced by the molecular weights of the gelatines, and a substantially more pleasing film can be made by utilising polymers with a higher average molecular weight.

Famotidine fast dissolving film with the appropriate physico-chemical characteristics was made using polyethylene glycol (PEG) and HPMC⁷. Maltodextrins (MDX) and similar low dosage dextrose were used to create fast-dissolving films, which included the medication piroxicam⁸.

Cetirizine fast dissolving films employing 2% w/v pullulan were thin and brittle, hence a slightly greater concentration was utilised⁹. The pharmacokinetic parameters (blood profile) of the reference (oral solution of pure drug) and the sample film of levocetirizine containing pullulan can be compared by testing on Sprague-Dawley rats¹⁰.

Plasticizers-In general, adding plasticizer to formulations improves mechanical properties including tensile strength and percent elongation¹¹. Plasticizer concentrations typically vary from 0 to 20% w/w. Plasticizers include PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate etc. When selecting a plasticizer for an ODF formulation, compatibility with the polymers and solvent type should be carefully studied.⁶

Surfactants-Surfactants are utilised as wetting, solubilizing, or dispersing agents, allowing the film to disintegrate in seconds and release the active ingredient instantly. Poloxamer 407, bezathonium chloride, sodium lauryl sulphate, tweens, benzalkonium chloride, and other common ingredients are used. The most often used surfactant among them is poloxamer 40¹².

Flavour- Flavors are essential to mask the bitter or nauseating taste of the drug that has been introduced. You may use any US-FDA authorised flavour, including mint, sour, and sweet⁽¹²⁾. Electronic tongues are used to assess the effectiveness of various taste masking agents. According to a study, the bitter taste of diclofenac sodium may be effectively covered up by a blend of the flavours by mint, liquorice, and sucralose.⁶

Sweetening agents- In the orally administered drugs to mask the taste of the API sweeteners are added. Especially, in pediatric this incorporation of sweeteners is highly beneficial. In the case of the paediatric population, the sweet flavour in the formulation is particularly significant. To improve the palatability of oral dissolving formulations, both natural and artificial sweeteners are employed. Artificial sweeteners are chosen over natural sugars since they demand less concentration and will not result in oral cavities in patients. Natural sweeteners are all in the saccharides family that is sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose are all examples of natural sugars. Saccharin, cyclamate, aspartame, acesulfame K, sucralose, alitame, and neotame are all artificial sweeteners.^{13,14}

Saliva stimulating agent-Saliva stimulation chemicals are used to boost saliva production, which helps the formulations for rapid disintegrating strip products dissolve more quickly. The substances that are most frequently utilised include citric acid, lactic acid, maleic acid, ascorbic acid, tartaric acid etc^{4,6}.

Colouring agent-As colouring agents, pigments are employed. ODFs and other medicinal preparations most frequently utilise titanium dioxide as a colorant. In addition to titanium dioxide, a broad spectrum of colours, such as FD and C, natural hues, and customised pantone-matched hues, are offered^{4,6}.

METHODS FOR FORMULATING ORAL DISINTEGRATING FILMS

1. Casting & drying method-

a. Solvent casting -For the API solubility, it is dissolved first in the aqueous media, the polymer solution is then produced. Organic solvents are used as they are favourably volatile and dry up easily. Prior to casting, any trapped air bubbles must be removed since uniformity of film qualities depends on this.¹⁵

Advantages-

1. Developing films using solvent casting method is popular and is useful.
2. An oral thin-film imparts relative standard deviation (RSD) in the range of 1.2% RSD.
3. heat-sensitive APIs are easily compatible by solvent casting method.
4. casting offers improved surface characteristics, great thickness and weight uniformity, as well as being simple to make and process at an affordable price.

Disadvantages-

1. Many countries have implemented restrictions regulating the use of organic solvents because solvent cast films may contain traces of residual solvents, which are usually organic in nature and can be harmful to patients and the environment^{16,17}.
3. The scale of commercial production may be impacted by the enormous investment necessary to optimise manufacturing units including mixing rates, drying times, and film thickness.

b. Semisolid casting-This approach involves mixing a water-soluble film forming polymer solution with an acid-insoluble polymer solution to produce a homogeneous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate). It is coated on casting film that has not been processed after sonication. The film should have a thickness of between 0.015 and 0.05 inches after drying. The ratio of the film-forming polymer to the acid-insoluble polymer should be 1:4¹³.

2. Extrusion-

a. Hot melt extrusion-In contrast to the solvent casting method, the HME process does not require solvent and forms the films using heat. A screw extruder heats and homogenises the excipients and API until they are thoroughly combined. When the mixture is The extrudate is forced into the required film shape after being run through a flat extrusion die, cooled, and then cut to the required size and packaged. The hopper, extruder, film die, and roller are the major elements of the HME apparatus.¹⁸

Advantages-

1. For the production of solid dosage forms intended for oral administration, HME offers a variety of different benefits over traditional manufacturing process.
2. It takes less time to create films and other compositions because there are fewer processing phases.
3. Due to the absence of organic solvents, it has also been demonstrated to be environmentally safe.

Disadvantages-

1. The main disadvantage of HME is the negative impact of high temperatures (thermal degradation) on APIs and other ingredients, particularly those that are thermolabile.
2. Because polymer rheology is critical to HME processing of films, the number of polymers that can be easily processed is constrained.
3. All HME constituents must be devoid of water or other solvents; otherwise, the heat required during production can cause it to boil and evaporate, causing voids in the final film product that can damage its uniformity, texture, and strength

b. Solid dispersion extrusion - solid dispersions in water soluble carriers have garnered a lot of attention as a way to increase the bioavailability and dissolution rate of hydrophobic medicines (19). Without removing the liquid solvent, solid dispersions can be produced from a suitable dispersion. One or more APIs are dispersed in a suitable solvent for the solid dispersion extrusion process, and then they are added to polyols such as melted PEG²⁰.

3. Rolling method - This technique involves creating a pre-mix, adding an active ingredient, and then forming a film. The solvent is primarily water or a water-alcohol mixture. The metering roller determined thickness of film. The film is cured on the rollers before being cut into the desired shapes and sizes.²¹

4. Spray technique -To produce a clear solution, the drug material, polymers, and other excipients are dissolved in a suitable solvent. This transparent solution is then sprayed onto a suitable substrate, such as glass, polyethylene film, non-siliconized Kraft paper, or Teflon sheet.⁶

EVALUATION PARAMETERS

1. **Organoleptic properties**

For this, specialised, regulated human taste panels are employed. This in vivo taste assessment is performed on human participants. Using taste sensors for screening, in-vitro taste evaluation of ODFs is carried out. High-throughput taste sensing of such dose formulations can be accomplished using in vitro technology and procedures. Analysis of the sweetness level and taste-masking properties of substances is done using both in vivo and in vitro methods.⁶

2. **Mechanical properties-**

•**Dryness test**-The purpose of this test is to determine a film's capacity to stick to a piece of paper pushed between strips. Tack describes the stubbornness with which a piece of paper or any other accessory is forced in between two films. Dry-to-touch, dry-to-recoat, dry hard, set-to-touch, dust-free, dry-through, tack-free, and dry print-free are the eight phases of the drying process for films that have been recognised. These tests can be used to evaluate oral fast-disintegrating films as well as the dryness of films used in the paint industry. With the use of certain recently developed devices, a dryness or tack test may also be carried out.^{4,6}

•**Tensile strength**-Maximum applied stress at which a film breaks is referred to as tensile strength. This test basically assesses the mechanical durability of films. It can be determined by dividing the applied load at rupture by the strip's cross-sectional area, as shown in the equation below.⁶

Tensile strength = (load at failure / strip thickness × strip width) × 10.⁶

•**Thickness test**-Using a calibrated digital micrometre, the thickness of a film is measured, and the mean average is then determined. Typically, the average of three measurements from all the batches is determined. By cutting the film and calculating the weight of each individual film, weight variation of a film is determined in triplicate. It is crucial to confirm thickness uniformity since it directly correlates with the film's dosage accuracy.⁴

•**Percent elongation**-When a film is stressed, the specimen expands, which is referred to as strain. The definition of strain is the change in film length divided by the film specimen's initial length. The percentage of elongation is quantitatively proportional to the plasticizer content of the film formulation. In general, increased plasticizer content in the film promotes strip elongation. It can be determined by formula given below.^{4,6}

Percentage elongation = (change in length / initial length) × 100.⁶

•**Tear resistance**-Film's tear resistance is a complicated function of its final resistance to rupture. The tear resistance value is the maximum force necessary to tear the film. This test is commonly associated with the plastics manufacturing. The loading rate used is 2 in/min, and it is intended to estimate the magnitude of force necessary to induce tearing in the film specimen. The tear resistance value is determined by the highest force required to cause tearing, which is often measured close to the tearing commencement.

•**Young's modulus**-It represents the rigidity of a film. It may be calculated as the ratio of applied stress to applied strain in the elastic deformation area. The formula below is used to determine it:

Young's modulus = (slope/strip thickness × cross head speed) × 100.⁶

Alternatively, it may be expressed as follows: **Young's modulus = force at corresponding strain / cross-sectional area corresponding strain.** In terms of Young's modulus and tensile strength, the films' qualities of hardness and brittleness are connected. The tensile strength and Young's modulus values of a hard, brittle film are greater, and the elongation is minimal.

•**Folding endurance**-Another method for determining a film's mechanical parameters is folding endurance. A film is folded at the same spot until it breaks in order to measure it. The number of times a film can be folded without breaking is its folding endurance value. Higher folding endurance values indicate a film's greater mechanical strength. Mechanical strength and film folding endurance are directly correlated. It is obvious that plasticizer concentration indirectly influences folding endurance value as plasticizer concentration governs mechanical strength.⁴

•**Swelling property**-The swelling studies of films are examined using simulated saliva. A stainless-steel wire mesh that has been pre-weighed and the initial weight of the film are both determined. The film holding the mesh is then submerged in an artificial saliva solution. And until there is no longer a rise in weight, the weight of the film is seen to increase at consistent predefined time intervals. These criteria define the swelling's degree.⁴

Degree of swelling = final weight (Wt) - initial weight(W0)/initial weight (W0).⁶

Wt = weight of film at time interval t; W0 = weight of film at time 0.

•**Transparency**-A UV spectrophotometer is used to determine a strip's transparency. The visual aspect of the formulation is tested in this test. The photometer cell's inner side is filled by rectangular-shaped film samples. At a wavelength of 600 nm, the film's transmittance is calculated.

Transparency = (log T600) / b = - εc T600 = transmittance at 600 nm, b stands for concentration, c for film thickness (mm).⁶

• **Contact angle**-With the use of a goniometer, contact angle of a film is typically determined at room temperature. A drop of double-distilled water is applied to the surface of the dried film. Within 10 seconds after the placing of the drop, images of water droplets are captured using a digital camera. Using image 1.28 V software, these digital photos are analysed to determine the contact angle. The mean of the contact angles measured on both sides of the droplets is determined. To get a better description of the characteristics of films, contact angle is measured at least five separate times at various points.

•**Disintegration time**-The disintegration period of a film is measured using disintegration apparatus that is specified in official pharmacopoeias. The disintegration period often varies depending on the content of the film and typically ranges from 5 to 30 seconds. For this test, the USP disintegration equipment is often utilised. For calculating the disintegration time of orally rapid dissolving films, there are no defined guidelines available. Slide frame method and petri dish methods are utilized for determining disintegration time of ODF.

•**Slide-frame technique**-On a petri dish with slide frames mounted onto it, distilled water is dropped onto the film. It is indicated how long it takes the film to disintegrate.

•**Petri dish method** - A film is placed on a petri dish with 2 mL of distilled water. The disintegration time is the amount of time it takes for the film to disintegrate completely.

Content uniformity-The content of a film is assessed by a standard test technique prescribed for each drug in several pharmacopoeias. Analytical procedures are used to perform this test on 20 samples. According to Japanese pharmacopoeia, the test's acceptability value is less than 15%. The contents should range from 85% to 115%, with a standard deviation of less than or equal to 6%, according to USP27. For evaluating drug concentrations in individual films, content uniformity is determined.⁶

In-vitro dissolution test-For performing dissolution tests on films, standard official basket or paddle apparatus is employed. During dissolution, sink conditions should be maintained. Occasionally, when performing this procedure, film floats above the medium, making the necessary testing difficult. This issue is more likely to arise with the paddle approach, hence the basket equipment is often recommended. 6.8 pH phosphate buffer (300 mL) and 0.1 N HCl were employed as the media (900 ml). The temperature is normally kept around 37 ± 0.5 C, and the rotation speed is set at 50 rpm. Dissolved drug samples are collected at predetermined intervals and analysed using a UV-spectrophotometer. Despite its widespread usage, the dissolution test is nevertheless prone to significant error and test failure.

Surface pH-The pH value of a film is often determined by placing the prepared film in a petri dish, then wetting the film with distilled water and measuring the pH by touching the film surface with a pH meter electrode. The determination of surface pH is critical because acidic or basic pH might induce oral mucosal irritation.

Moisture uptake and moisture loss-Percent moisture loss is a measure that indicates a film's hygroscopicity. Typically, this metric is determined by first estimating the initial weight of the film and then placing it in a desiccator for three days. Strips are removed and weighed again after three days. The following formula is used to calculate moisture loss.

Initial weight - Final weight / Initial Weight x100 = percentage of moisture loss.⁶

Moisture uptake of a film is determined by first cutting the film with the dimension of 2×2 cm². Afterward these strips are exposed to environment with a relative humidity of 75% at room temperature for 7 days.

The percentage weight gain of the strips is used to estimate moisture uptake.

Percentage moisture uptake = final weight - initial weight / initial weight $\times 100$.⁶

Visual inspection- Colour, homogeneity, and transparency of a produced orodispersible film may be determined visually. Scanning electron microscopy is used to study surface morphology. The absence of pores and surface uniformity indicate that the film is of high grade.

APPLICATIONS OF ORAL DISINTEGRATING FILMS :

Oral mucosal delivery- For treatments requiring quick drug absorption, such as those used to treat pain, allergies, sleep disorders, and diseases of the central nervous system, oral mucosal administration via sublingual, buccal, and mucosal channels with the use of oral thin film may become the preferred delivery technique.⁶

Topical applications - It may be possible to deliver active ingredients like analgesics or antimicrobial ingredients for the treatment of wounds and other topical conditions using dissolvable films.¹³

Gastroenteric delivery system- Dissolvable films are being studied for dosage forms that incorporate molecules with a range of molecular weights that are both water-soluble and poorly soluble in a film format. The pH or enzyme secretions of the digestive tract may cause the films to dissolve, which could possibly be employed to treat digestive diseases.¹³

Diagnostic devices- Dissolvable films can be loaded with sensitive chemicals to permit controlled release when exposed to biological fluids or to construct isolation barriers for separating numerous reagents to enable a timed response inside a diagnostic device.¹³

PACKAGING OF ORAL DISINTEGRATING FILMS : - In the pharmaceutical industry, it is critical that the package used is appropriate for preserving the product's integrity. Orodispersible films are available in a range of packing configurations. Oral thin film packaging consists of foil paper or plastic pouches, single pouches, aluminium pouches, blister packaging with numerous units, and barrier films. Barrier films are most typically employed for medications that are particularly sensitive to moisture. The film should be packaged in an airtight container or pouch so that it does not retain moisture and degrades.^{13,21}

CONCLUSION - The current success and acceptance of oral disintegrating films in the worldwide market is simply due to the requirement to properly mask taste. In compared to traditional dose forms, they have increased acceptability and patient compliance, with no danger of choking and greater safety and efficacy. The fundamental purpose of ODFs is to help paediatric, geriatric, and psychiatric patients who have trouble swallowing conventional dose forms. ODFs are now widely accessible for hypertension, acidity, allergy, and pain, indicating their significance. The major advantage of such dosage forms is that they can be administered without the need of water, satisfying the requirement of the target population for convenience in medication administration while also avoiding hepatic metabolism, resulting in improved therapeutic response.

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The authors declare no conflict of interest, financial or otherwise.

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