REVIEW ARTICLE

Orally Disintegrating Film: A Review of Its Formulation and Manufacturing Method

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ABSTRACT

Oral route drug delivery system is still considered as the most convenient and patient friendly drug delivery route. Over the decades, many research has been performed to improve the functionality oral dosage form. Orally disintegrating film (ODF) is a newer oral drug delivery system, which is in the form of a thin film that will disintegrate in the oral cavity within a matter of seconds. The aim of this review paper is to recap ODF, its benefits, formulation contents and manufacturing method. With more research and development work has been conducted on ODF, the dosage form is expected to be manufactured and scaled up to be commercializable products to be sold in the market.
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INTRODUCTION

The drug delivery sciences have been on the track of producing newer dosage forms that improving the safety, efficacy and compliance of patients towards the medication. In the late 1970, fast disintegrating tablet has been produced as a solution to improve the compliance of patients especially for children having difficulty to swallow pills, geriatric patients that having dysphagia (1). Out of the many inventions, drug delivery system being very eminent is orally disintegrating film (ODF).

There are 3 different subtypes of oral film, which are classified according to several factors including surface area, thickness, structure, excipients, and application area. For example, flash release wafer has a single layer film with thickness of approximately 7-20 micrometer, mucoadhesive melt-away film may either have single or multilayered film with thickness of 50-500 micrometer and mucoadhesive sustained release films have multi-layered films with thickness of 50-250 micrometer (2). An ideal ODF has a size approximately to a postage stamp and can be administered with or without water (3).

ADVANTAGES OF ODF

Since the rise in development of advance drug delivery system (ADDS), orally disintegrating film (ODF) stands as one of the most prominent ADDS due to its convenience as they are taken without water with fast disintegration time in mouth. ODFs can easily absorb saliva and hydrate when it is put on the tongue. The film then immediately disintegrates and dissolute to release its active pharmaceutical ingredient (4).

In addition, ODF has numerous of advantages such as ease of transportation due to small weight and size, easy to swallow for geriatrics and pediatrics, convenient dosage form, accurate dosing, can be taken with or without water, and eliminate the risk of choking (5).

CHALLENGES IN FORMULATING ODF

There is a vast amount of literature available today on formulation, development and evaluation of oral dissolving films. Despite this, developers may encounter challenges in creating these forms of medication, which must be addressed in order to further advance research

in this area and improve the overall formulation and development. The challenges that related to non-compliance towards medication need to be given priority to tackle it (6).

Taste Masking of Bitter Drugs

In the production of quick-dissolving oral films, it is necessary to mask the taste of bitter drugs in order to increase patient compliance, especially among the elderly population (7). Taste masking can be done by various methods such as incorporating sweeteners, flavors, complexing agents, bitterness inhibitors, and effervescent agents (8).

Long Duration of Drying

The drying time is a crucial factor in the formulation of oral films, as it affects the rate of production in industrial settings. In general, a hot air oven cannot be used to dry oral films that contain thermo-labile drugs; therefore, they are dried at room temperature instead, which would take even longer time to sufficiently dry (6).

There are several ways to reduce the drying time in the formulation of oral films which include:

1. Increasing the temperature without causing cracks in the film.
2. Choosing specific ingredients for the film, especially the type and concentration of the polymer and plasticizer. This may involve adding polymers and plasticizers that form less viscous solutions to minimize drying time, and avoiding those that form highly viscous solutions that increase drying time.
3. Using appropriate dryers.
4. Increasing the area of the film by exposing a larger surface area to the drying environment can also help to further reduce drying time.

Among factors that could increase drying time include (9):

1. Depth of solution in container exceeding 3.5mm. The depth however should not be less than 3.5mm as the solution would not spread evenly, which could also lead to longer drying time.
2. Using polymers that form highly viscous solution such as methylcellulose, moderate to high grades HPMC (E15, E50), carrageenan and guar gum.
3. Using too much plasticizer. Generally, plasticizer can be incorporated up to 20% of the formulation content. Using plasticizer at concentration above 30% form films that are sticky, difficult to handle and remove from the container, and shows problems during the drying stage.
4. Incorporating high dose of active ingredient. The highest dose of active ingredient that can be incorporated in oral film was found to be within the range of 2 to 62.5mg. The higher the dose of active ingredient needs to be incorporated, the larger the area of oral film should be.

Stability Against Temperature and Humidity During Handling and Storage

Obtaining film stability against humidity is challenging as film tend to absorb water from humid air and get liquefied.

Amorphous drugs commonly have lower physical stability during storage. Hydrophilic polymers used to formulate films can act as crystallization inhibitor, as they have the ability to reduce drug mobility, therefore reduces the driving force of crystallization. This however can only be achieved if the API is freely soluble in the polymer.

Nevertheless, if the polymer used is highly hygroscopic, it can form hydrogen bond with water molecules. In the presence of humidity, if the drug-polymer bond is weaker than polymer-water bond, amorphous drug may undergo phase separation and crystallize (10).

Dose Uniformity

Insoluble drug and excipients may form suspension, leading to fluctuations in API distribution. Insoluble materials may also degrade amorphous drug to form crystals, hence reduces dissolution rate of films. Several known methods to ensure dose uniformity include (11):

1. Avoid formulating solution with high viscosity. For example, incorporation of polymers that form highly viscous solution may cause uneven distribution and materials may lump together at one part of the container.
2. Use containers with flat surface. Rough surface reduces drug and thickness uniformity, as solution may remain more on one side of the container.
3. Use drying temperature that are below of melting point of drugs and excipients. High temperature during drying may degrade the chemicals in the films.
4. Conduct assay analysis based on specifications determined in pharmacopeia to estimate the API content in individual film. Generally, limit of content uniformity shall be between 85 to 115%.
5. Use water soluble drug and excipients or make the drug soluble in aqueous medium by suitable solubilizing techniques.
6. Option for semi-synthetic polymers such as HPMC and HPC or make a combination of both natural and semi-synthetic polymers to obtain less viscous solution.

METHODS OF MANUFACTURING

There are many methods used to formulate ODF such as solvent casting method, semisolid casting, rolling method, solid dispersion extrusion and spraying method. Different method has different advantages and disadvantages that can be considered before doing the film (12).

Solvent Casting Method

Solvent casting method the simplest yet the oldest

film-making method. The API is dissolved in a suitable solvent. Polymers, plasticizers and any other ingredients can be dissolved in another portion of solvent to prepare a polymeric solution. The mixture is referred as film dope and can be casted onto a continuous roll of release media, like plastic-impregnated paper or glass mould (13). Then, the media will be dried by using oven at temperature of 40°C-50°C and the dried film is then cut into desired size. The commonly available sizes of films are 3 x 2 cm^2 and 2 x 2 cm^2 and special storage is needed to protect the film from humidity as the film is highly affected by humid condition. Barrier films are most used for those drugs which is extremely moisture sensitive (13).

Solvent casting method is the most common technique to produce ODF due to fact that it is suitable for API's that are heat sensitive. The temperature used to remove the solvent is relatively low compared to the hot-melt extrusion process.

Spraying Method

Spraying method is not a commonly utilized method to produce ODF as not many researchers produce film by using this method. However, this method is simple as it does not require advance machine and complicated steps. The film forming polymer and other excipients are dissolved in a suitable solvent system and this mixture is sprayed on suitable carrier material, then dried and the film is peeled off. The examples of carrier materials are glass, non-siliconized Kraft paper or polyethylene film. This method may not be able to produce ODF with consistent thickness (14).

Hot Melt Extrusion (HME)

Polymers with low molecular weight and low viscosity are used in hot melt extrusion. The HME process has been applied frequently in pharmaceutical industry. Although the process is unsuitable for thermolabile API, the method offers plenty of advantages such as reduced chance of air entrapment, good suitability for scale up, more uniform dispersion of fine particles due to intense mixing and agitation, as well as good control of operating parameters. However, all the ingredients used in HME must contain no water or volatile solvents to prevent bubble formation, which can jeopardize its' uniformity, strength, and appearance. In HME, the dry ingredients for the films are heated and homogenized by extruder screw until they are molten and mixed. The melted material is forced through flat die that presses the extrudate into the desired film, which will be passed to elongation roller that controls thickness and strength of the film. The extruded film is the cooled, cut and packaged (13).

Semi Solid Casting Method

This method is preferred when acid insoluble polymers such as cellulose acetate phthalate and cellulose acetate butyrate are used in the preparation of ODF. Firstly, a solution of water-soluble polymers is prepared. This solution then added to a solution of acid insoluble polymer. Then, plasticizer is added in appropriate amount to form a gel mass that will be casted into films using heat-controlled drums. The thickness of the film is about 0.015 – 0.05 inches. Acid insoluble polymer and film forming polymer are mixed in 1:4 ratio (15).

Solid Dispersion Extrusion

Solid dispersion extrusion use HME-like method. One or more API is dispersed in an inert carrier in solid state in the presence of amorphous hydrophilic polymers. The immiscible components are then extruded with the drug, forming solid dispersions that finally shaped into films by dies (13).

Rolling Method

Rolling method require the solution or suspension to have specific rheological properties for rolling onto the drum. The solvent used is mainly water and a mixture of water and alcohol. In this method, the solution or suspension containing drug and other excipients is rolled on a carrier. The film is then evaporated or dried on the rollers and cut into desired shapes and sizes (13).

ODF FORMULATION AND AGENTS

Formulation is the drug delivery system that delivering the drug to appropriate site of absorption therefore it should be safe, effective and stable. The excipients used in ODF formulations should be Generally Regarded as Safe (GRAS listed) (12). General composition for ODF is shown in Table I.

Active Pharmaceutical Ingredient (API)

First agent needed is active pharmaceutical ingredient. API to be incorporated into ODF ideally should be low dose, non-bitter and have high water solubility (BSC class 1 such as paracetamol, propranolol and diltiazem) (1). API incorporated should be as low as possible.

Hydrophilic Polymer

Hydrophilic polymer is the main agent in forming the film. Hydrophilic polymer can dissolve in water easily. The lower the molecular weight of the polymer, the faster the dissolution rate (13).

Table I: General composition of ODF[1]

Components	Concentration (%)
API	5-30
Hydrophilic Polymer	40-50
Plasticizer	0-20
Saliva stimulating agent	2-6
Surfactant	Q.S
Sweetening agent	3-6
Flavours, colours, fillers	0-40

Plasticizer
Plasticizer is used to enhance spread ability, flexibility, elongation and tensile strength by reducing glass transition temperature of the polymers. Some of the most commonly used plasticizer include glycerol, propylene glycol, PEG, dimethyl, castor oil, etc (16).

Sweetening Agents
Sweetening agent is needed to mask the unpleasant taste and bad odor of active ingredient. Sweetening agent can be divided into two types, which are natural source and artificial source. Natural source agents like glucose, fructose and maltose are limited to diabetic patient while artificial source agents like mannitol, aspartame and saccharin, Neotame, acesulfame potassium are suitable in pharmaceutical. Sweeteners and flavors may also contribute to minor effects on the flexibility of the film (17).

Saliva Stimulating Agent
Saliva stimulating agent is used to improve the saliva secretion so that there is more fluid to dissolve ODF in the mouth. Examples of saliva stimulating agents are citric acid or ascorbic acid at 2-6% w/w used alone or in combination (1).

Flavouring Agent
Flavors play a significant role in masking the bitter and unpleasant taste of the API. Apart from taste and personal liking, the age of the target user can influence selection of flavors. Younger people prefer fruit punch, raspberry etc. whereas geriatric prefers orange, lemon and mint. Cooling agent can also be incorporated to elevate the flavor (16).

Coloring Agent
Coloring agent is needed to enhance the ODF elegance and agents like titanium oxide or food dye approved by FDA which can be incorporated up to 1% w/w (18).

Surfactant
Surfactant is used to enhance the solubility and wetting property of the film, allowing it to be released within minutes or less than that. There are many surfactants can be used, such as benzalkonium chloride and sodium lauryl sulfate. Lastly, coloring agent is needed to enhance the ODF elegance and agents like titanium oxide or food dye approved by FDA which can be incorporated up to 1% w/w (18).

SELECTION OF HYDROPHILIC POLYMERS

The choice of polymer is one of the most essential parameters for optimum film formation. Nowadays, both natural and synthetic polymers are utilized in the development of ODFs, however, natural polymer is appealing due to its' efficiency, accessibility, and safety. Ideally, polymers used for ODF should be non-toxic and non-irritant, non-bitter, tasteless, devoid of leachable impurities, allow for good disintegration time, good wetting and spread ability property, exhibit sufficient peel, shear and tensile strength, sufficient shelf life and do no cause secondary infection in oral cavity (1).

Cellulose Derived Film Forming Polymers
Cellulose derived film forming polymers produces films with lower resistance towards water vapor due to its hydrophilic nature. Hydroxypropyl methylcellulose (HPMC) however, is an excellent film former and comes in different grades such as Methocel E3, Methocel E5, Methocel E15 Premium LV, etc (3).

Polyvinyl Alcohol (PVA)
Polyvinyl alcohol (PVA) is a good film former and is characterized as having high tensile strength and flexibility, resistance towards oxygen, and prevents aroma from active ingredient escaping the film. The water, which serve as plasticizer, will reduce the tensile strength of the film, but increase elongation and tear strength. However, PVA have a high melting point at 230°C to fully hydrolyze and 180–190°C to partially hydrolyze, therefore increase the need for strong heating during the film preparation (19).

Polyvinyl Pyrrolidone (PVP)
Polyvinyl Pyrrolidone (PVP) is soluble in both water and polar solvent. One study that incorporates enrofloxacin into PVP ODF using solvent casting method and a mixture of methanol and chloroform as solvent, form film that exhibit excellent mechanical properties such as uniform thickness, high folding endurance, decent disintegration time and quick dissolution (20).

Polyethylene Glycol (PEG)
Polyethylene Glycol (PEG) has a good film forming property either alone or in combination with other polymers. PEG flexible films can be formed by by thermoplastic processing and solvent casting technique (19). A study that evaluates formulation of oro-flash release films containing anti-migraine drug produces films with good mechanical strength, uniformity of content, optimum surface pH, faster disintegration time and almost complete drug dissolution or release (21).

Pullulan Gum
Pullulan is an extracellular microbial polysaccharide produced by Aureobasidium pullulans. Pullulan has distinctive properties of structural flexibility and enhanced solubility. It also has adhesive properties, and a capability to form fibers and films that are oxygen impermeable. Pullulan comes in the form of powder that are write off-white in color, tasteless, odorless and form viscous non-hygroscopic solution when dissolved in water at 5-10%. Pullulan films are commonly prepared by rapid evaporation of 5-10% aqueous pullulan solution applied to smooth surface and dried. This process may involve the use of high temperature and pressure (19).

Guar gum
Guar gum is obtained from Cyamopsis tetragonolobus or C. psoraloide, a pod bearing plant that is resistant to drought. A study that incorporates telmisartan into guar gum films shows that the film produced has a good folding endurance (>200 times) and thickness (0.9mm – 1.2mm). However, in vitro release profile varies greatly and is proportional to the amount of sodium starch glycolate added (22).

Maltodextrin
Maltodextrin is an oligosaccharide produced from starch by partial hydrolysis and may have a taste of sweetness depending on the glucose chain length. It is a good carrier for sweetener and aromatizer. Maltodextrin has excellent fluidity, no smell and solubilize well in water. The powder is low in hygroscopicity and less likely to agglomerate. Polyethylene glycol 400 (PEG 400) and glycerin are the suitable plasticizers as they can provide good stability against crystallization (19). A study comparing the properties of maltodextrin film produced with glycerin and PEG 400 shows that both types give good in vivo and in vitro disintegration time. However, the films containing PEG 400 cause unpleasant taste and excess plasticizer may leak from the film, making the film sticky (23).

Gelatin
Gelatin is extracted from the collagen in animal skin, bones and fish skins by thermal denaturation. Type A gelatins are obtained by partial acid hydrolysis while type B gelatin are obtained by partial alkaline hydrolysis. Gelatins solubilize well and rapidly in water at above 40°C, forming viscous solution. It is also an excellent carrier for flavors and produce a pleasant mouth feel. Mammalian gelatins usually have better physical properties owning to their higher amino acid content that leads to higher molecular weight (24).

VALIDATION TESTS

There are several validation tests should be run to categorize the quality of the ODF film formed after using different techniques and different excipients specifically sweetening agents and polymers used (1).

Thickness Test
Thickness test is conducted by measuring film at few different locations for instance 1 central point and 4 corners measured using a calibrated digital vernier caliper. The reading should be triplicate to obtain the mean value. Uniformity of the thickness is essential to ensure dose accuracy of the film (2).

Tensile Strength Test
Tensile strength test is used to measure the maximum stress that a film can withstand before it breaks by using machine such as texture analyser (14). It can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below:

$$\text{Tensile strength} = \frac{\text{(load at failure x 100)}}{\text{strip thickness x strip width}}$$

Young's Modulus Test
Young's modulus or elastic modulus is the measure of stiffness of the strip (18). It is represented as the ratio of applied stress to the strain in elastic deformation regions as follows:

Young's Modulus = (slope/strip thickness x cross head speed) x 100

Percentage of Elongation
Film is placed in between specimen grips and load cell. Then, force will be applied to the film gradually until the film breaks. The original length (mm) and the increase in length (mm) of the film after subjected to force will be recorded and calculated using the equation below:

Folding Endurance Test
Folding endurance test is conducted by repeatedly folding at the same place of the film until the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value. High folding endurance value indicates stronger mechanical strength (2).

Content Uniformity Test
Content uniformity should be evaluated based on the standard assay method stated for specific API in pharmacopeia. Content uniformity is determined by estimating the API content in individual strip. The limit of content uniformity is 90–110 percent. US pharmacopeia suggested to use Gas Chamber (GC) Chromatography for determinination.

Disintegration Time Test
Disintegration test is the test to measure the time required for an ODF to completely disintegrate in a disintegration solvent such as distilled water. The disintegration time test of ODF is not specified in any compendia yet up-to-date. Normally, the disintegration time for the film is within seconds to 3 minutes which varies based on the formulation and composition of the ingredients in the production of the film (2).

In Vitro Dissolution Test
As films tend to float over the medium, standard official paddle apparatus is preferred over basket apparatus to maintain sink conditions during dissolution. Temperature shall be maintained at 37 ± 0.5 C while rotation at the speed of 50 rpm (3).

Moisture Uptake Test
To determine moisture uptake, 2 x 2cm^2 film are exposed to environment with relative humidity of 75% at room temperature for 7 days (25). Moisture uptake

is determined as percent weight gain calculated by the following formula:

$$\% \text{ moisture uptake} = \frac{[\text{final weight} - \text{initial weight}]}{\text{initial weight}} \times 100$$

Moisture Loss Test

Percent moisture loss determines the hygroscopicity of the film. This parameter is determined by measuring the initial weight of the film, then placing the film in a desiccator containing calcium carbonate. After 3 days, films are taken out and weighed again (25). Moisture loss is determined by the following formula:

$$\% \text{ moisture loss} = \frac{[\text{initial weight} - \text{final weight}\}}{\text{initial weight}} \times 100$$

In Vivo Organoleptic Test

Organoleptic test will evaluate the ability of the sweetening agent to mask the unpleasant taste of the drug. Organoleptic test is an essential step for most oral formulation due to more residence time in the oral cavity. The product should possess the desired features of sweetness and flavor which is acceptable to large mass of population. There are several methods to test the efficiency of the sweetening agents to mask the unpleasant taste of the ADB such as E-tongue evaluation and human taste panel sensory/in vivo taste masking evaluation (1).

Despite wide use of E-tongue in taste evaluation, the in vivo test the most definitive way to evaluate the efficiency of taste masking components in the drug. This test is usually performed on small group of 4–15 people. The testers must be of healthy volunteers in the age group of 18 to 30 years of both sexes. The volunteers are required to sign an agreement approved from Human Ethic Committee (5).

In- vivo organoleptic test can be further divided into bitter taste threshold and gustatory evaluation test. Bitter taste threshold is determined by the minimum average concentration of drug that triggers bitter taste on volunteers' tongue. The most definitive way to measure efficacy of taste masking agent is the gustatory evaluation test as it provides direct taste evaluation from human volunteers. This test is conducted by placing the masked drug on the tongue of each volunteer separately for 30 seconds and the taste is then evaluated. The degree of bitterness is recorded immediately as a bitterness scale ranging from 0 to 5 with being the taste of pure drug as the highest bitter taste (26).

CONCLUSION

ODF formulations are gaining popularity and industry starts to look into the possibility to manufacture commercializable product. Due to its convenience and patient friendly properties, this dosage form has potential to be a main stream dosage form in the market in future.

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